Studies on the Enantioselective Total Synthesis of Diarylheptanoid and Furylhydroquinone-Derived Natural Products, and Eugenol Derivatives as Potential Antidiabetic Agents

by

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Under the supervision of

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Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled, *"Studies on the Enantioselective Total Synthesis of Diarylheptanoid and Furylhydroquinone-Derived Natural Products, and Eugenol Derivatives as Potential Antidiabetic Agents"*, submitted by *Ms. Priyanka Kataria* to the Academy of Scientific and Innovative Research (AcSIR), in partial fulfillment of the requirements for the award of the Degree of *Doctor of Philosophy in Science*, embodies original research work carried-out by the student. We, further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material(s) obtained from other source(s) and used in this research work has/have been duly acknowledged in the thesis. Image(s), illustration(s), figure(s), table(s) *etc*., used in the thesis from other source(s), have also been duly cited and acknowledged.

Ms. Priyanka Kataria
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Dr. Ravindar Kontham
Research Supervisor
Date: 07-12-2022

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I Ms. Priyanka Kataria, a Ph.D. student of the Academy of Scientific and Innovative Research (AcSIR) with Registration No. 10CC16J26018 hereby undertake that, the thesis entitled "*Studies on the Enantioselective Total Synthesis of Diarylheptanoid and Furylhydroquinone-Derived Natural Products, and Eugenol Derivatives as Potential Antidiabetic Agents*" has been prepared by me and that the document reports original work carried out by me and is free of any plagiarism in compliance with the UGC Regulations on *"Promotion of Academic Integrity and Prevention of Plagiarism in Higher Educational Institutions (2018)"* and the CSIR Guidelines for "*Ethics in Research and in Governance (2020)".*

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Date: 07-12-2022
Place: Pune, Inida

This dissertation is dedicated to

-My beloved family members-

Whose constant love, trust, and

support helped me to reach this stage of

my life

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Chapter-3

Design, Synthesis, and Biological Evaluation of Eugenol Derivatives as Potential Antidiabetic Agents

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Finally, I express my gratitude to the Almighty for the blessings and the great scientific community whose achievements are a constant source of inspiration for me.

With many thanks,

Priyanka Kataria

Units	
°C	Degree centigrade
g	Gram
mg	Milligram
h	Hour (s)
Hz	Hertz
µg	Microgram
µM	Micromolar
mL	Millilitre
min	Minutes
MHz	Megahertz
mmol	Millimole
nM	Nanometre
ppm	Parts per million
ɗ	Delta
m/z	Mass to charge ratio
cm	Centimetre
Chemical Notations	
Ac_2O	Acetic anhydride
AuCl	Aurum chloride
AgOTf	Silver trifluoromethanesulfonate
BBr_3	Boron tribromide
n-BuLi	*n*-Butyl lithium
BH_3	Borane
t-BuOH	*tert*-Butyl alcohol
BCl_3	Boron trichloride
$BF_3.OEt_2$	Boron trifluoride etherate
$Bi(OTf)_3$	Bismuth(III) trifluoromethanesulfonate
$Bi(NO_3)_3.5H_2O$	Bismuth(III) nitrate pentahydrate
CD_3OD	Deuterated Methanol
$CHCl_3$	Chloroform

CBr_4	Tetra bromo methane
COSY	Correlation Spectroscopy
CH_2Cl_2	Dichloromethane
$CDCl_3$	Deuterated Chloroform
CD	Circular dichroism
CBS	Corey–Bakshi–Shibata
$CeCl_3.7H_2O$	Cerium(III) chloride heptahydrate
CCl_4	Carbon tetrachloride
$(CH_2)_2Cl_2$ (DCE)	Dichloroethane
Conc.	Concentrated
DAH	Diarylheptanoid
2D	Two Dimensional
3D	Three Dimensional
DMAP	4-Dimethylaminopyridine
DCC	N,N′-Dicyclohexylcarbodiimide
DMF	N, N'-Dimethylformamide
DIBAL-H	Diisobutylaluminium hydride
DMP	Dess–Martin periodinane
DET	Diethyl tartrate
EDC.HCl	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EtOH	Ethanol
EtOAc	Ethyl Acetate
ESI	Electrospray ionization Mass spectrometry
eq.	Equation
$Fe(OTf)_3$	Iron (III) trifluoromethanesulfonate
$FeSO_4.7H_2O$	Ferrous sulphate heptahydrate
$Fe(ClO_4)_2$	Iron (II) perchlorate
HSQC	Heteronuclear Single Quantum Coherence
HMBC	Heteronuclear Multiple Bond Coherence
HRMS	High Resolution Mass Spectrometry

HCl	Hydrochloric acid
H_2O	Water
H_2O_2	Hydrogen peroxide
HBPin	Pinacol borane
IC_{50}	Inhibitory Concentration required for 50% inhibition
IR	Infra-Red
I_2	Iodine
J	Coupling constant (in NMR)
$KMnO_4$	Potassium permanganate
K_2CO_3	Potassium carbonate
LiHMDS	Lithium bis(trimethylsilyl)amide
LiCl	Lithium chloride
LDA	Lithium diisopropylamide
m-CPBA	meta-Chloroperbenzoic acid
Mg	Magnesium
MeONHMe.HCl	N,O-Dimethylhydroxylamine hydrochloride
$MgBr_2.OEt_2$	Magnisium bromide diethyl etherate
MeI	Methyl Iodide
MeCN	Acetonitrile
$Ni(OTf)_2$	Nickel (II) trifluoromethanesulfonate
$NiCl_2.6H_2O$	Nickel (II) chloride hexahydrate
NMR	Nuclear magnetic Resonance
$NaIO_4$	Sodium metaperiodate
NOESY	Nuclear Overhausser Effect Spectroscopy
Na_2SO_4	Sodium sulphate
NH_4Cl	Ammonium chloride
$NaHCO_3$	Sodium bicarbonate
$Na_2S_2O_3$	Sodium thiosulphate
$NaBH_4$	Sodium borohydride
NMO	N-Methylmorpholine-N-Oxide

NaOH	Sodium hydroxide
OsO_4	Osmium tetroxide
PMB-TCAI	*p*-methoxybenzyl 2,2,2-Trichloroacetimidates
PPh_3AuCl	Chloro(triphenylphosphine)gold(I)
Pd/C	Palladium on charcoal
PPTS	Pyridinium *p*-toluenesulfonate
PTSA	*p*-toluenesulfonic acid
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium (0)
$Pd(OH)_2/C$	Palladium hydroxide on charcoal
i-Pr_2NEt	N,N-Diisopropylethylamine
rt	Room temperature
R_f	Retention factor
SiO_2	Silica
SAR	Structure-Activity Relationship
$Sc(OTf)_3$	Scandium triflate
$SOCl_2$	Thionyl chloride
TEA (Et_3N)	Triethylamine
TBHP	tert-Butyl hydroperoxide
TPP	Triphenyl phosphine
THF	Tetrahydrofuran
THP	Tetrahydropyran
TLC	Thin Layer Chromatography
TsCl	Tosyl chloride
TBS	tert-butyldimethylsilyl
p-TSA	*p*-Toluenesulfonic acid
tert	Tertiary
TBSOTf	tert-butyldimethylsilyl trifluoromethanesulfonate
TFA	Trifluoro acetic acid
TfOH	Triflic acid

- Independent compound and reference numbering have been used for each chapter as well as for sections of the chapters.
- All reagents and solvents were purchased from commercial suppliers and used as such without any further purification. Starting materials were obtained from commercial suppliers or prepared using known procedures.
- All the known compounds reported in literature were characterized by their NMR spectra.
- Solvents were distilled and dried following standard procedures. Petroleum ether used for column chromatography was of 60-80 °C boiling range.
- Column chromatographic separations were carried out on silica gel (100-200 or 230-400 mesh size).
- All reactions were monitored by TLC with 0.25 mm pre-coated E-Merck silica gel plates (60 F254) and TLC spots were made visible by exposing to UV light, Iodine adsorbed on silica gel or by immersion into an ethanolic solution of phosphomolybdic acid (PMA), *p*-anisaldehyde, ninhydrin or $KMnO_4$ followed by heating with a heat gun for ~15sec.
- NMR spectra were recorded on Bruker AV200 (200.13 MHz for ^1H NMR and 50.03 MHz for ^{13}C NMR), AV 400 (400 MHz for ^1H NMR and 101 MHz for ^{13}C NMR), Jeol-400 (400 MHz for ^1H NMR and 101 MHz for ^{13}C NMR), DRX 500 (500 MHz for ^1H NMR and 126 MHz for ^{13}C NMR) and AV 700 (700 MHz for ^1H NMR and 176 MHz for ^{13}C NMR) spectrometers.
- Chemical shifts (δ) have been expressed in ppm units relative to tetramethylsilane (TMS) as an internal standard and coupling constants (J) were measured in Hertz.
- The following abbreviations were used for ^1H NMR: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet, dd = doublet of doublet, dt = doublet of triplet, td = triplet of doublet and ddd = doublet of doublet of doublet.
- Optical rotations were recorded on a JASCO P-1020 polarimeter at 589 nm (sodium D-line). Specific rotations $[\alpha]_D$ are reported in deg/dm, and the concentration (c) is given in g/100 mL in the specific solvent.
- Structures and IUPAC nomenclature were generated using ChemBioDraw Ultra 14.0 software.
- High-resolution mass spectra (HRMS) (ESI) were recorded on an Orbitrap (quadrupole plus ion trap) and TOF mass analyzer.

AcSIR	**Synopsis of the thesis to be submitted to the Academy of Scientific and Innovative Research for the award of the degree of Doctor of Philosophy in Chemical Science**
Name of the Candidate	Ms. Priyanka Kataria
Enrollment No. and Date	Ph.D. in Chemical Sciences (10CC16J26018); January 2016
Title of the Thesis	Studies on the Enantioselective Total Synthesis of Diarylheptanoid and Furylhydroquinone-Derived Natural Products, and Eugenol Derivatives as Potential Antidiabetic Agents
Research Supervisor	Dr. Ravindar Kontham

1. <u>Introduction:</u> The current thesis describes the studies directed toward the enantioselective total synthesis of diarylheptanoid and furylhydroquinone-derived bioactive natural products and derivatives of eugenol as potential antidiabetic agents. This thesis is categorized into three chapters. The *first chapter* describes two distinct synthetic strategies to access hedycoropyrans A and B, which led us to establish a facile synthetic route for *des*-hydroxy (–)-hedycoropyran B (*ent*-rhoiptelol B) from simple and readily accessible building blocks of 4-allylanisole and vanillin, employing Sharpless asymmetric epoxidation, CBS reduction, and an intramolecular AgOTf-catalyzed oxa-Michael reaction of hydroxy-ynone as key transformations. The *second chapter* deals with the first enantioselective total synthesis and establishment of the absolute stereochemistry of furylhydroquinone-derived natural products shikonofuran J, D, E, C, and their enantiomers employing an unprecedented $Bi(OTf)_3$-catalyzed construction of 2,4-disubstituted furans from α-hydroxy oxetane-tethered ketones, followed by chiral-phosphoric acid (TRIP)-catalyzed asymmetric prenylation, and the *third chapter* describes the design, synthesis, and *in vitro* biological activity profile of diverse eugenol derivatives as antidiabetic agents.

2. <u>Statement of the problem</u>: Natural products are a diverse group of chemical substances produced by nature. Living organisms, including bacteria, fungi, insects, animals, and plants produce these compounds, which have evolved over time to serve different purposes of human needs, such as life-saving drugs, vitamins, colors, tastes, scents, etc. However, these molecules are often produced in minimal quantities, which creates supply issues and hamper systematic chemical and biochemical investigations and utilization. Hence, the development of efficient, facile, and sustainable synthetic methodologies and their application in devising concise and

practical synthetic routes for biologically potent natural and unnatural molecules is one of the pivotal objectives for synthetic organic chemists worldwide. Despite remarkable advances made in the field of total synthesis of natural products, the exploration of concise and more efficient methods to synthesize these molecules is still in demand.

3. Objectives: Inspired by the interesting biological profile of natural products possessing oxygen heterocyclic motifs, we aimed to develop a practical, concise, and enantioselective synthetic routes for diarylheptanoid-derived natural product hedycoropyran B utilizing a Sharpless asymmetric epoxidation, CBS reduction, and an intramolecular AgOTf-catalyzed oxa-Michael reaction of hydroxy-ynone as key transformations and allyl anisole and vanillin as affordable building blocks. To develop a concise asymmetric synthetic route and establish the absolute configuration for anti-inflammatory and antibacterial natural products shikonofurans J, D, E, C and their enantiomers possessing furylhydroquinone scaffold as a key structural unit, using an unprecedented $Bi(OTf)_3$-catalyzed furan construction from acyl-hydroxy oxetanes, followed by chiral-phosphoric acid (TRIP)-mediated asymmetric prenylation reactions as key steps. Further, aimed at the design, synthesis, and *in vitro* antidiabetic activity evaluation of natural product eugenol and its derivatives having improved bioavailability.

4. Methodology and Result:

Chapter 1: Enantioselective Total Synthesis of Diarylheptanoid *ent*-Rhoiptelol B (*des*-Hydroxy Hedycoropyran B):

Diarylheptanoids (DAHs) is an emerging structural class of natural products with interesting biological properties like anti-inflammatory, antioxidant, anticancer, NO inhibition, etc.[1] Structurally, DAH's have two aryl units connected with a heptanoid linker at C1-C7 positions, and they can be cyclic or acyclic [containing a tetrahydropyran (THP) or tetrahydrofuran (THF) ring system]. Among several subclasses of DAH's, THP-derived natural products are ubiquitous and known to display a wide range of biological activities and triggered the interest among synthetic and medicinal chemistry research groups, particularly, centrolobines, calyxins, diospongins, hedycoropyrans, and rhoiptelols are notable examples of this category (Figure 1).

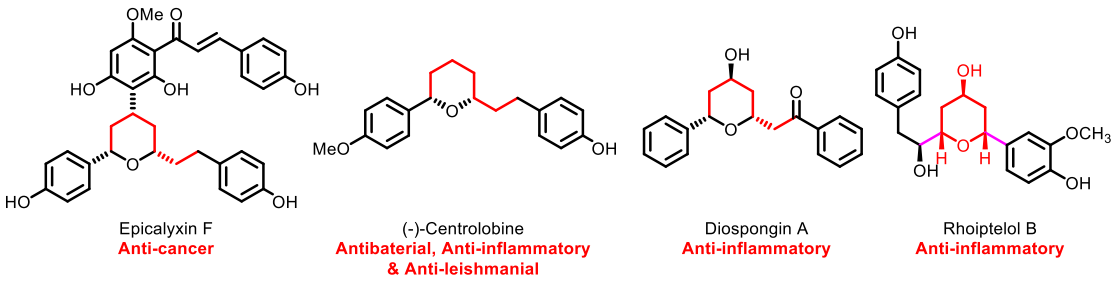


Figure 1. Chemical structures of representative diarylheptanoid-derived natural products.

Two new DAHs, hedycoropyran A (**1**) and B (**2**) were isolated by Lee and co-workers in 2015, from the *n*-BuOH soluble fraction of the rhizome of *Hedychium coronarium*, which possesses 2,6-*trans* and 2,6-*cis* configured THP-DAHs, respectively, along with hedycorofurans and several cytotoxic labdane-type diterpenoids (Figure 2).[2]

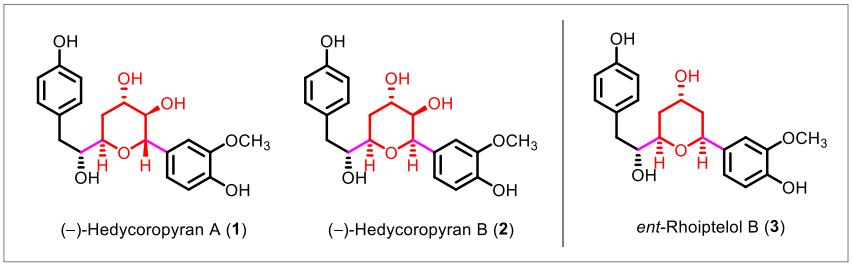
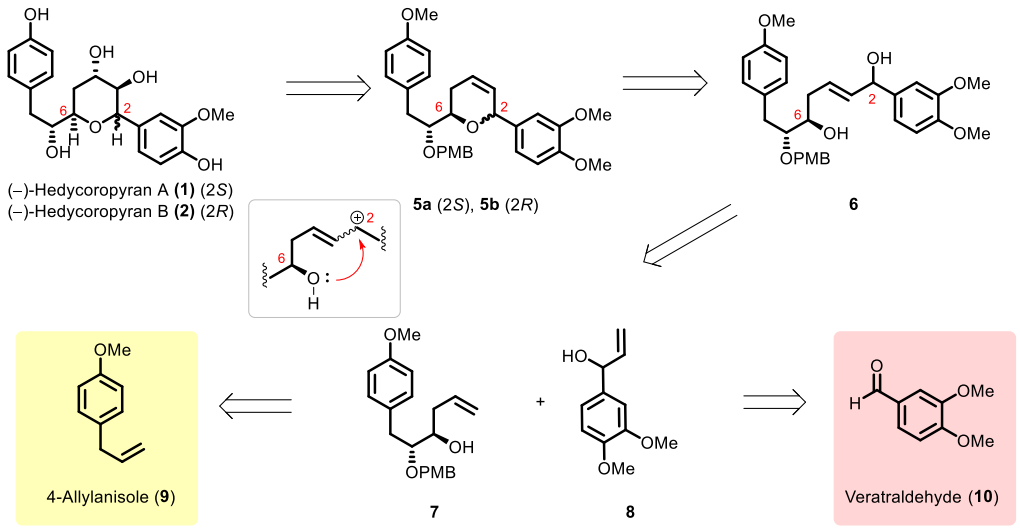


Figure 2. Chemical structures of hedycoropyran A and B.

In continuation of our interest in the stereoselective total synthesis of THP-containing biologically potent natural products, we planned an efficient and concise chemical synthetic route for hedycoropyrans (**1**, **2**) that led us to showcase very interesting synthetic transformations and establish a facile synthetic route for *des*-hydroxy-hedycoropyran B, which is *ent*-rhoiptelol B (**3**), from the readily accessible building blocks of 4-allylanisole (**9**) and vanillin (**10**) using Sharpless asymmetric epoxidation, Corey–Bakshi–Shibata reduction and an AgOTf-catalyzed oxa-Michael reaction of hydroxyl alkyl-tethered ynone as key steps.

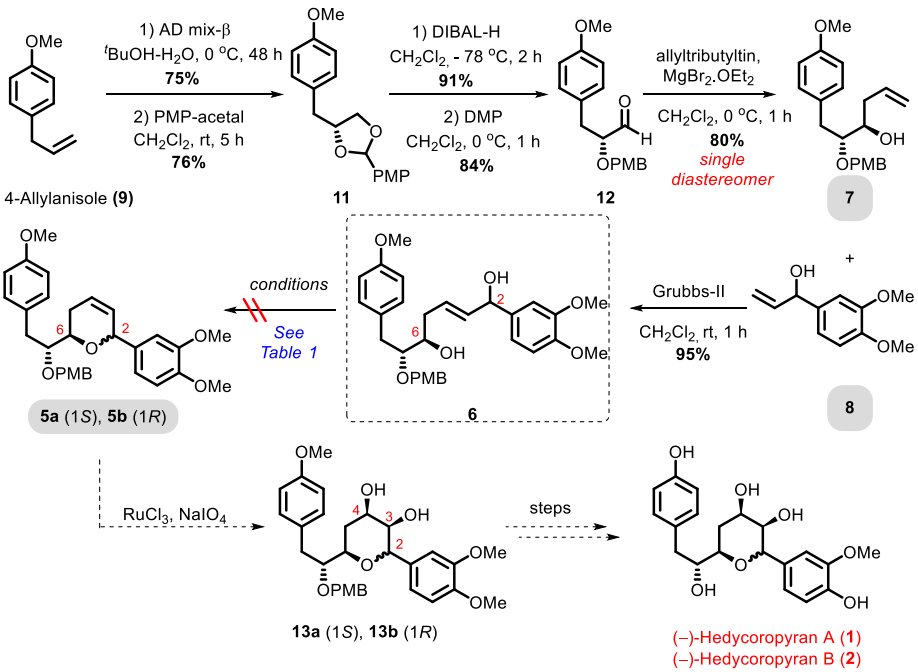
In the initial retrosynthetic analysis, we envisioned a unified approach for the synthesis of hedycoropyrans A (**1**) and B (**2**) from a suitably functionalized dihydroxy alkene intermediate **6** (containing allylic and homoallylic alcohol functionalities) *via* allylic carbocation-mediated ring-closure that would deliver advanced 2,6-*trans*/2,6-*cis* dihydropyran intermediate **5a**/**5b** as shown in Scheme 1. A cross-metathesis reaction of homoallylic alcohol **7** and allylic alcohol **8** was planned to obtain intermediate **6**. Alkenols **7** and **8** would be synthe-



Scheme 1: Initial retrosynthetic analysis of hedycoropyrans A (**1**) and B (**2**).

sized from commercially available and cost-effective building blocks 4-allylanisole (estragole, **9**) and veratraldehyde (**10**) using an interesting sequence of reactions (Scheme 1).

To explore the feasibility of this retrosynthetic analysis, we initially focused on synthesizing the key DAH-derived dihydroxy alkene intermediate **6** starting from building blocks **9** and **10** *via* intermediates **7** and **8**. Accordingly, the synthesis of allyl alcohol **7** was initiated from **9**. Sharpless asymmetric dihydroxylation of **9** using AD-mix-β/ $MeSO_2NH_2$ followed by subsequent protection of 1,2-diol using PMP-acetal gave *p*-methoxy benzylidene acetal **11**. The regioselective reductive opening of acetal **11** using DIBAL-H followed by Dess–Martin periodinane oxidation delivered the aldehyde **12**. Subsequent substrate-controlled addition of allyltributyltin onto the aldehyde **12** in the presence of $MgBr_2$•OEt_2 delivered the requisite homoallylic alcohol **7** with complete diastereoselection. Then, the cross-metathesis reaction of **7** and **8** (prepared from the vinylation of veratraldehyde (**10**) using the Grubbs 2nd-generation catalyst furnished the desired DAH-derived dihydroxy alkene intermediate **6** (exclusively *trans*-olefin) in an excellent yield of 95%, which was the precursor for our anticipated allylic carbocation-mediated ring-closure reaction. To realize this hypothesis, well-established reaction conditions of BF_3•OEt_2/CH_2Cl_2,[3] $PdCl_2(PPh_3)_2/CH_2Cl_2$[3] and $Pd(CH_3CN)_2Cl_2/CH_2Cl_2$[3] at low to ambient (−78 °C to rt) temperatures were attempted, which proved to be unsuccessful, in all cases starting material **6** was decomposed. If this proposed transformation to access **5a**/**5b** from **6** had worked well, our following sequence of reactions

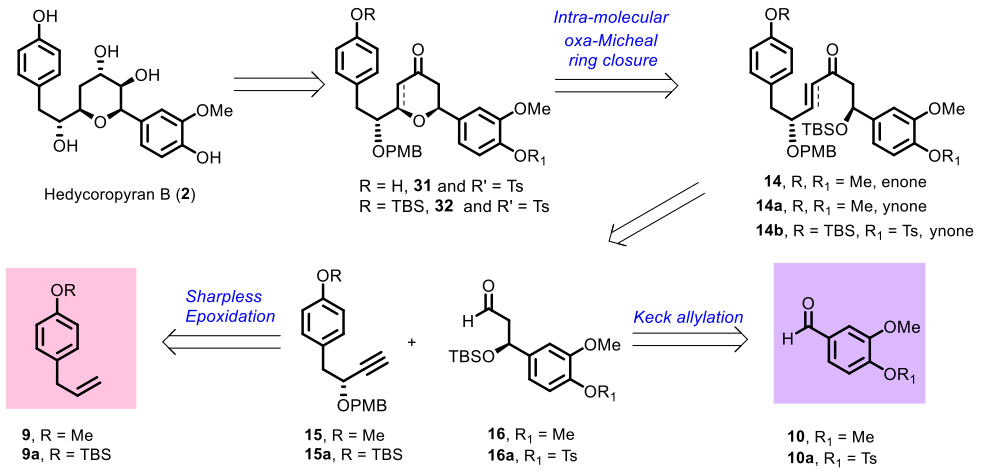


Scheme 2: Efforts directed toward the synthesis of hedycoropyrans A (**1**) and B (**2**) *via* allylic carbocation-mediated ring-closure.

(as reported by Li and Tong) as described describe in Scheme 2 (*via* diols **13a**/**13b**) would have led to the total synthesis of hedycoropyrans A (**1**) and B (**2**) (Scheme 2).

After these unsuccessful efforts to access natural products **1** and/or **2** following our initial retrosynthetic analysis and synthetic sequence, we explored a new retrosynthetic analysis based on the intra-molecular oxa-Michael reaction, which enables access to the THP ring system with desired stereochemistry, as shown in Scheme 3. We hypothesized synthesizing hedycoropyran B (**2**) *via* intra-molecular oxa-Michael reaction induced ring-closure of suitably constructed enone **14** or ynone **14a**/**14b** intermediates with varying O-substituents. In this scenario, we envisioned a convergent strategy involving the addition of Li-acetylide (derived from **15**/**15a**) to the chiral-aldehydes **16**/**16a**, followed by the oxidation to obtain the enone/ynone intermediates (**14**/**14a**, **14b**). Intermediates **15**/**15a** and **16**/**16a** could be synthesized from commercially accessible 4-allylanisole (**9**) and veratraldehyde (**10**) or their analogs (**9a** and vanillin) (Scheme 3).

Hence, the proposed alternate route began with the synthesis of alkyne intermediate **15** from 4-allylanisole (**9**) in two divergent pathways. In the first route, aldehyde **12** (prepared

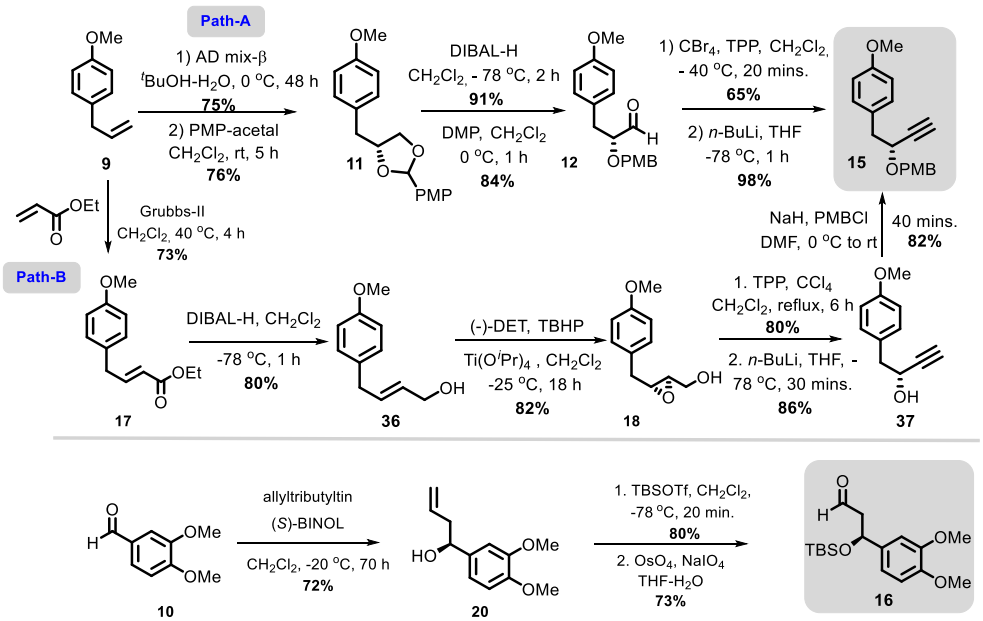


Scheme 3: New retrosynthetic analysis of hedycoropyran B (**2**) based on the oxa-Michael reaction of hydroxy-enone or hydroxy-ynone.

from **9** in Scheme 2) was subjected to Corey–Fuchs olefination and subsequently treated with *n*-BuLi to afford the desired alkyne fragment **15** (path A, Scheme 4). Furthermore, an alternate route to synthesize the key intermediate **15** started from allyl anisole **9**, which was converted into *α,β*-unsaturated ester **17** employing a cross-metathesis reaction, and was then reduced using DIBAL-H to afford allylic alcohol **36**, which was subsequently converted into chiral epoxy alcohol **18** under Sharpless conditions, then the chiral epoxy alcohol **18** was converted to propargylic alcohol **37** *via* chlorination and base (*n*-BuLi)-mediated rearrangement reactions, which was protected as its PMB-ether to get the required key intermediate **15** (path B, Scheme 4).

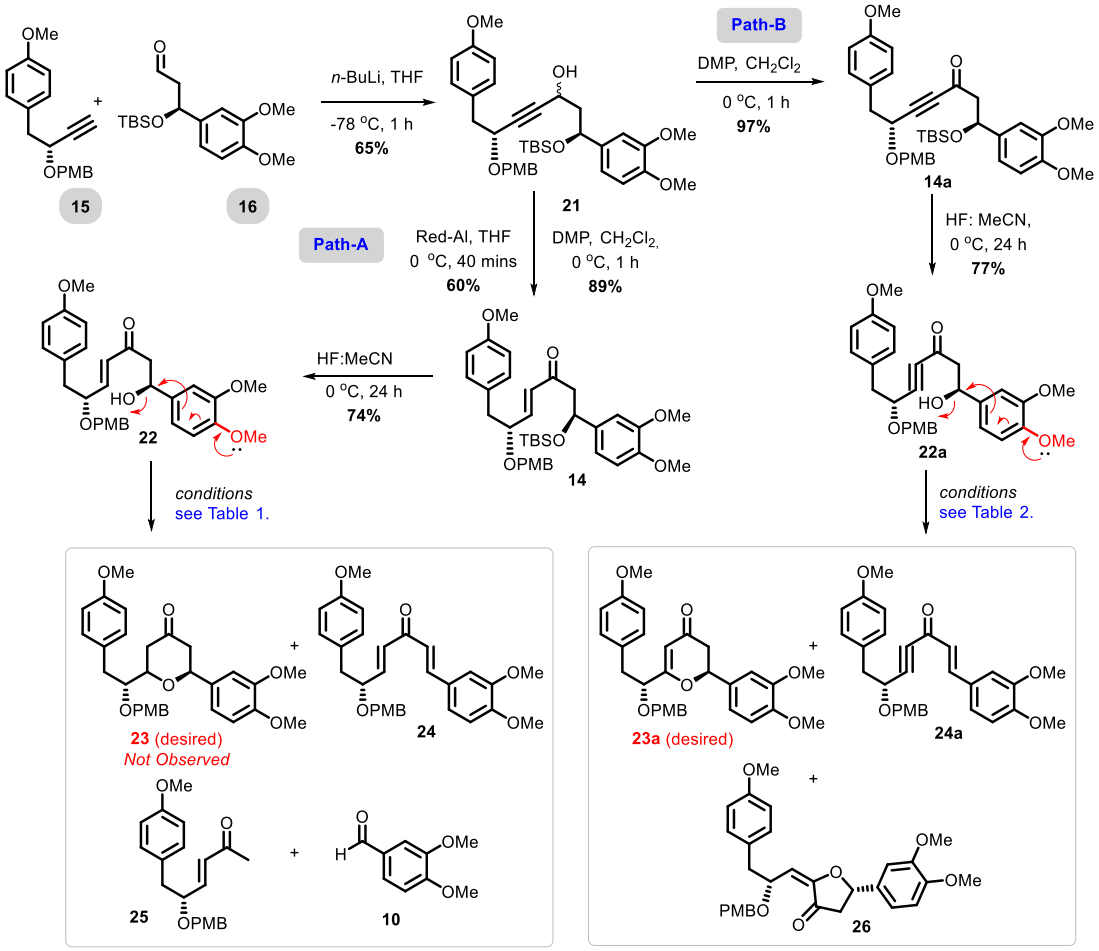
After successfully establishing a reliable synthetic route for **15**, then we moved towards the synthesis of aldehyde coupling partner **16** from veratraldehyde **10**. Asymmetric Keck allylation of **10** [using (*S*)-BINOL, $Ti(O^iPr)_4$, and allyltributyltin] to give allyl alcohol **20**, followed by TBS protection and dihydroxylative cleavage (OsO_4, 2,6-lutidine, and $NaIO_4$) steps, cleanly delivered aldehyde **16** (Scheme 4).

After successful synthesis of required key fragments **15** and **16** on a gram scale, next our target was to verify our hypothesis of an intramolecular oxa-Michael reaction. For that purpose, both fragments of alkyne **15** and aldehyde **16** were coupled using *n*-BuLi to get propargylic alcohol **21** which was partially reduced with Red-Al followed by DMP-oxidation to get enone **14**. Further TBS deprotection of **14** using HF-CH_3CN gave hydroxy-alkyl tethered



Scheme 4: Synthesis of alkyne fragment **15** and aldehyde fragment **16**

enone **22**. Unfortunately, the crucial oxa-Michael reaction of the hydroxy-enone **22** to give pyranone **23** was proved to be insurmountable, under base (KO^{t}Bu, NaH, DBU), acid (Amberlyst-15) and Pd(II)-catalyzed reaction conditions, leading to either the corresponding dehydrated product **24** or *retro*-aldol products **10** and **25** (path A, Scheme 5; Table 1). Therefore, we slightly altered the strategy by replacing enone **22** with the corresponding ynone **22a** as an oxa-Michael addition precursor to verify the reactivity patterns, as shown in path B of Scheme 5. Hence, ynone **22a** was prepared from **21** through Dess–Martin periodinane oxidation, and HF-CH_3CN-mediated TBS deprotection steps, and was evaluated for the intramolecular oxa-Michael reaction using reported procedures (Table 2). Initial conditions of using $Pd(CH_3CN)_2Cl_2$-mediated cyclization[4a] led to the decomposition of the starting material. Cyclization using NaH[4b] and/or mild Lewis acid (catalytic AgOTf)[4c] resulted in the undesired dehydrated product **24a**, whereas, AuCl-catalyzed[4d] cyclization was found to be non-selective towards this oxa-Michael reaction by providing an inseparable mixture (1:1 ratio) of desired pyranone **23a** (through the 6-*exo*-*dig* mode of cyclization) and furanone **26** (through the 5-*endo*-*dig* mode of cyclization) (path-B, Scheme 5). These unfruitful results (except for the AuCl reaction of entry4, Table 2) reveal the sensitivity of the benzylic hydroxyl group (of **22** and **22a**) toward basic or acidic conditions, which could be due to the stabilization of the benzylic carbocation through the mesomeric effect of the *p*-OMe group of the phenyl ring (path A and path B, Scheme 5).



Scheme 5: Efforts toward the synthesis of hedycoropyran B (**2**) *via* an oxa-Michael reaction of hydroxy-enone/hydroxy-ynone.

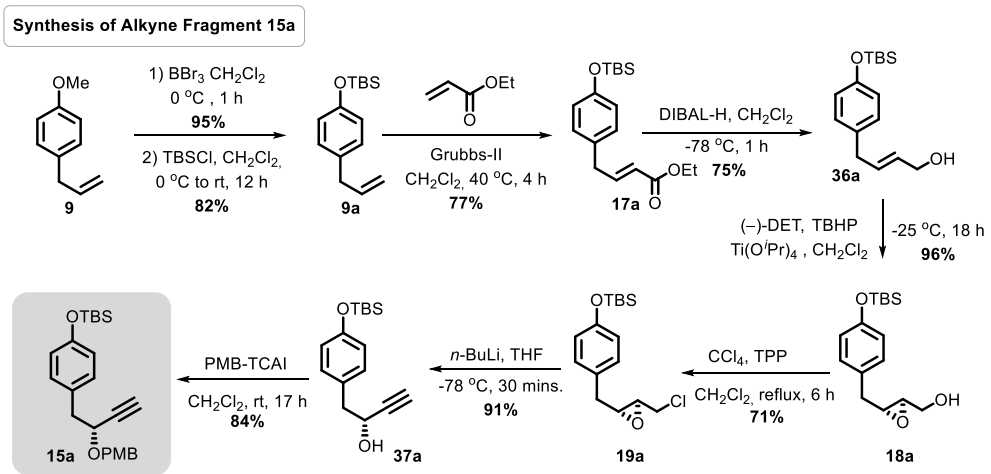
Table 1. Efforts toward the synthesis of pyranone **23**.

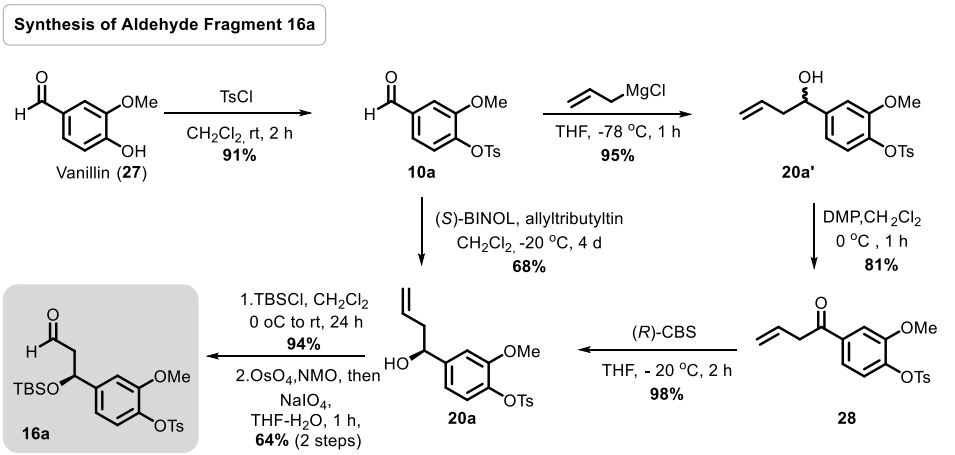
Entry	Conditions	Result
1	KO^{t}Bu (0.1 equiv), EtOH, 0 °C to rt	**24**, 13%; **25**, 60% and **10**, 26%
2	NaH (2.2 equiv), -78 °C, THF	**24**, 8%; **25**, 49% and **10**, 32%
3	DBU (4 equiv), DCM, 0 °C	**24**, 68%
4	Amberlyst-15 (2 equiv) CH_2Cl_2, rt	**24**, 74%
5	$Pd(MeCN)_2Cl_2$ (0.1 equiv) CH_2Cl_2, rt	**22**, recovered

Table 2. Efforts toward the synthesis of dihydropyranone **23a**.

Entry	Conditions	Result
1	$Pd(CH_3CN)_2Cl_2$ (0.1 equiv), $Cu(OAc)_2.H_2O$ (0.1 equiv), PPh_3, DME, 65 °C, 24 h	**22a** decomposed
2	NaH (1 equiv), THF, 0 °C, 1 h	**24a**, 78 %
3	AgOTf (0.1 equiv), CH_2Cl_2, rt, 18 h	**24a**, 72%
4	AuCl (0.02 equiv), $NaHCO_3$, MS-4 Å, 5 h	**23a** and **26** (1:1), 90%, inseparable

Suspecting the role of the *p*-OMe group (of **22** and **22a**, Scheme 5) in the failure of the above intramolecular oxa- Michael reactions and the literature precedence of a successful survival of similar benzylic hydroxyl groups in the presence of *p*-OAc and *p*-OTs substituents. We further modified our strategy by replacing the *p*-OMe group with *p*-OTs (replacing alkyne **15** and **16a** with **15a** (having *p*-OTBS) and **16a** (having *p*-OTs) respectively). These revised intermediates alkyne **15a,** and aldehyde **16a** were synthesized using sequences similar to that described in Scheme 4. In addition, an alternative route to synthesize intermediate **16a** *via* allylic ketone **28** (prepared from aldehyde **10a** through the initial addition of allyl magnesium chloride followed by oxidation). Subsequent Corey–Bakshi–Shibata reduction (using (*R*)-CBS catalyst) of **28** gave the common precursor **20a** (Scheme 6).

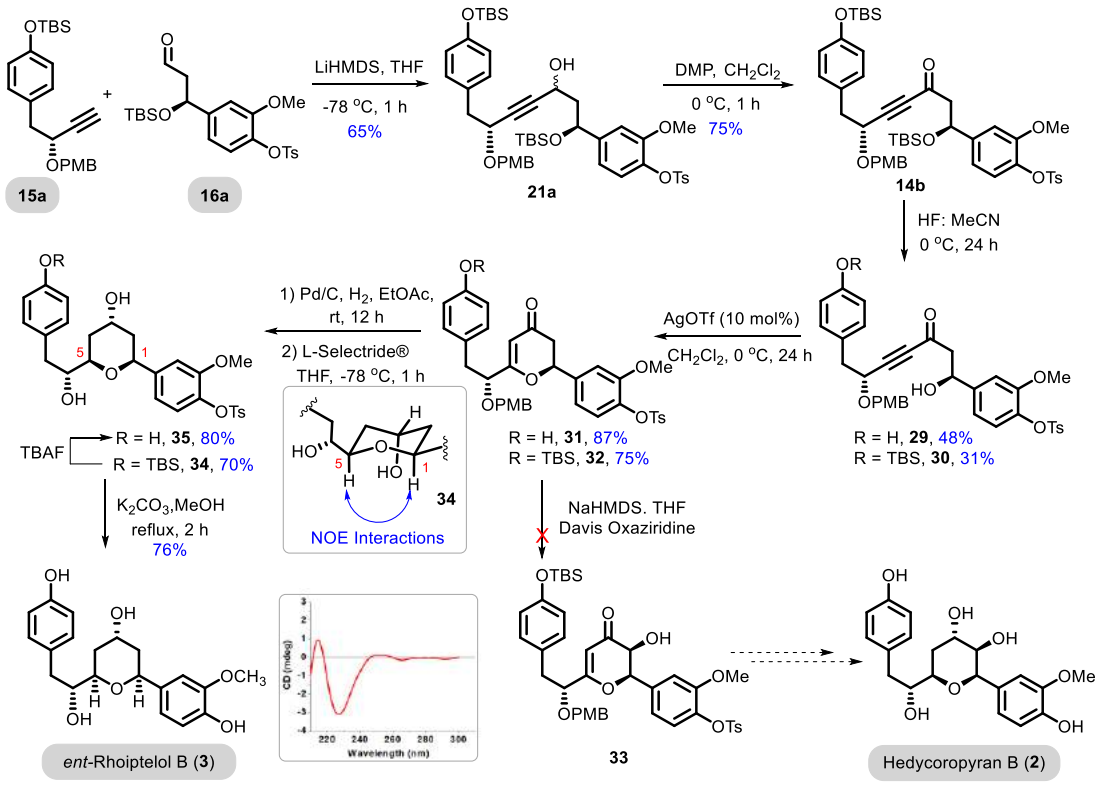




Scheme 6: Synthesis of alkyne fragment **15a** and aldehyde fragment **16a**.

Now, the stage was set to verify our envisioned ultimate strategy to access hedycoropyrans. Accordingly, we coupled both fragments **15a** and **16a** to get the coupled propargylic alcohol **21a**, subsequent DMP oxidation gave ynone **14b**. As expected, HF-CH_3CN-mediated TBS deprecation **14b** led to the fully and partially deprotected alcohols **29** and **30**. Then we tested the subsequent intramolecular oxa-Michael reaction of **29**/**30** using 10 mol% of AgOTf at 0 °C. To our delight, pyranones **31**/**32** were obtained in good yields without anticipated retro-aldol by-products. At this stage, the TBS-protected dihydro-pyranone **32** was subjected to *α*-hydroxylation using diverse conditions of NaHMDS, Davis oxaziridine, and PIDA, which failed to provide the desired product **33** and hampered the possibility to access hedycoropyran B (**2**) (Scheme 7).

As we had a sufficient quantity of intermediates **31** and **32** in hand, we embarked on accessing the structurally close diarylheptanoid *ent*-rhoiptelol B (*des*-hydroxy hedycoropyran B, **3**). Rhoiptelol B (**3a**) was isolated from the fruits of *Rhoiptelea chiliantha* and also from the bark of *Alnus hirsuta* in 1996 and 2007 and is known to display inhibitory activities against LPS-induced NF-KB activation, NO, and TNF-α production, and HIF-1 in AGS cells. Thus, dihydropyranones **31** and **32** were subjected to hydrogenation (Pd/C, H_2) of the olefin followed by *L*-selectride reduction of the carbonyl group, which cleanly delivered the respective pyrans **35** and **34** (**34** was subjected to TBS deprotection to get **35**; NOE analyses confirmed 2,6-*cis* stereochemistry of THP **34**). Finally, K_2CO_3 in MeOH-mediated detosylation of **35** delivered *des*-hydroxy hedycoropyran B (*ent*-rhoiptelol B, **3**)[5] which was confirmed by comparing ^{1}H,



Scheme 7: Completion of the total synthesis of *des*-hydroxy hedycoropyran B.

^{13}C NMR, and ESI-MS (HRMS) data with the reported data. The optical rotation value of **3** ($[\alpha]_D^{26:6}$ = −81.04 (c = 0.1, MeOH), this work) was found to be opposite to the reported value of natural product (+)-rhoiptelol B (**3a**) ($[\alpha]_D^{12}$ = +97 (c = 0.3, MeOH), literature data). The assigned absolute configuration of **3** was further supported by electronic circular dichroism (ECD) analyses; the ECD spectrum of **3** showed a negative Cotton effect (CE) at 227.10 nm (CD, 0.4 × 10^{-3} M, EtOH), λmax (Δε) 214.44 (+0.91), 227.10 (−3.09) (nm) which was similar to data reported for structurally close DAH, hedycoropyran B (Scheme 7).

Conclusion: In this Chapter, a couple of synthetic strategies for the total synthesis of the diarylheptanoid natural products hedycoropyrans were attempted, which were unfruitful, but led us to showcase some interesting synthetic organic chemistry and the development of a total synthetic route for *des*-hydroxy hedycoropyran B (*ent*-rhoiptelol B) in 19 steps using the commercially available and affordable building blocks 4-allylanisole (estragole), veratraldehyde and vanillin. The key steps involved in this work were cross-metathesis, Sharpless asymmetric epoxidation, CBS-reduction/Keck asymmetric allylation, and AgOTf-mediated intramolecular oxa-Michael addition of hydroxy-ynone.

Chapter 2: Development of a Facile Synthetic Strategy for Substituted Furans from Keto-Oxetanes Using Bi(III) Catalysis: Application to Unified Total Synthesis of Furylhydroquinone-Derived Natural Products Shikonofuran J, D, E and C

Furylhydroquinones are a class of natural products having structural diversity and are known to show interesting biological activities. Recently, Kim and co-workers isolated a novel member of the furylhydroquinone family along with six known compounds from *Lithospermum erythrorhizon* Sieb. et Zucc (*Boraginaceae*) as shown in Figure 1. Among the isolates, five compounds have shown potential inhibition of Interleukin-6 (IL-6) production[6a] and three compounds (**2-4**) have shown inhibitory activity towards GH33 sialidases[6b] (antibacterial) with lower IC_{50} values (Figure 1).

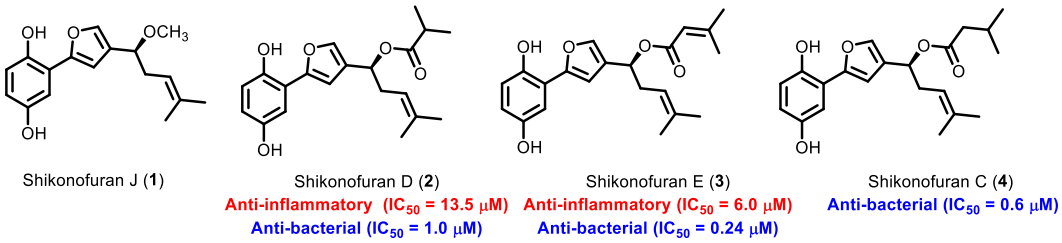
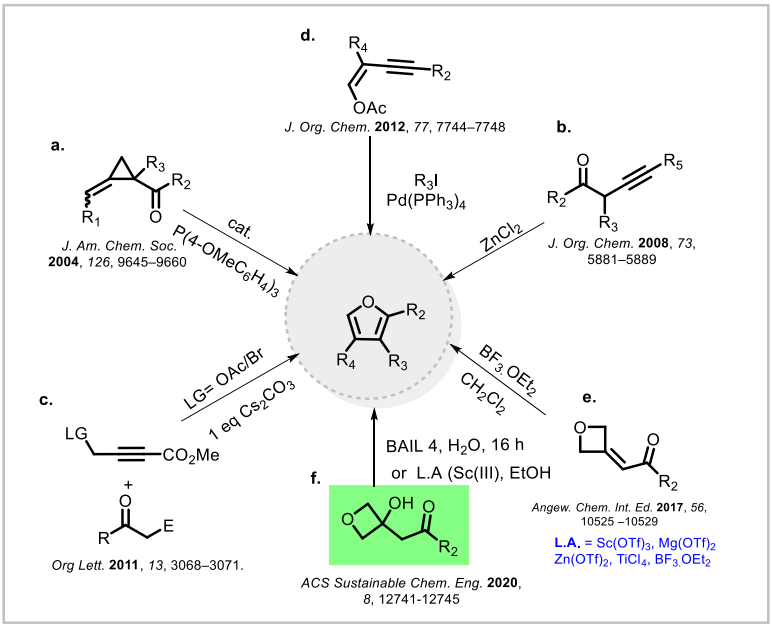


Figure 1. Chemical structures and biological activities of shikonofuran J, D, E, and C.

Structurally these natural products contain an ester chiral center adjacent to the furan ring (at C4), which is connected to hydroquinone (at C2 of furan) and mainly varies in the ester part of the molecule. Inspired by these interesting structural features, the biological profile of furyl-hydroquinones, and our interest in the chemistry of oxygen-containing heterocyclic compounds, we have initiated a research project to establish unified and enantioselective total synthesis routes for shikonofurans J, D, E, and C.

After an extensive literature survey, we found that very few synthetic methods are reported in the literature to access 2,4-disubstituted furans (particularly C4 hydroxymethyl substituted), which are required for this work. Notable examples include phosphine-catalyzed rearrangement of cyclopropyl ketones, Zn(II)-catalyzed cycloisomerization of homopropargylic ketones, PPh_3-Cs_2CO_3 induced annulation of ketones and propiolates, Pd(0)-catalyzed alkylative ring-closure of propargylic vinyl acetates (entries a-d, Scheme 1).

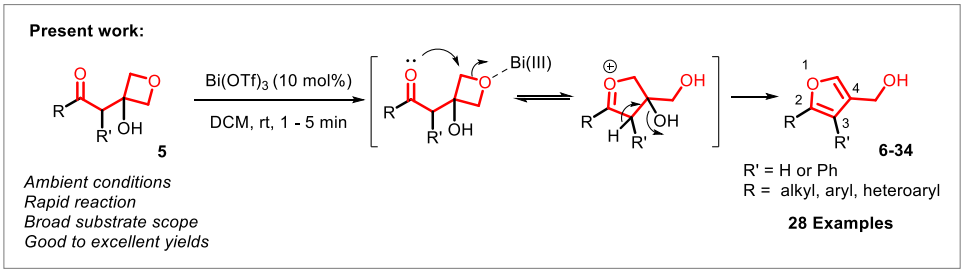


Scheme 1: Know-how methodologies for the synthesis of tri-substituted furans.

Recently, an interesting Lewis acid-mediated mediated cycloisomerization of α-hydroxy oxetane-tethered ketone was disclosed by Vanderwal and co-workers, which was also studied using ionic liquid (BAIL 4 in water) by Ni and co-workers (entry e and f, Scheme 1).[7] However, these two later strategies have disadvantages of using a stoichiometric amount of strong acid as the promoter, expensive catalytic systems (like Scandium-based catalysts), incompatible solvent systems, harsh reaction conditions, and longer reaction times. Keeping in mind these disadvantages of know-how methodologies, we aimed at developing a facile and rapid methodology to construct 2,4-disubstituted furans using acyl-oxetane as a building block and its subsequent application in enantioselective total synthesis of shikonofurans (Scheme 1).

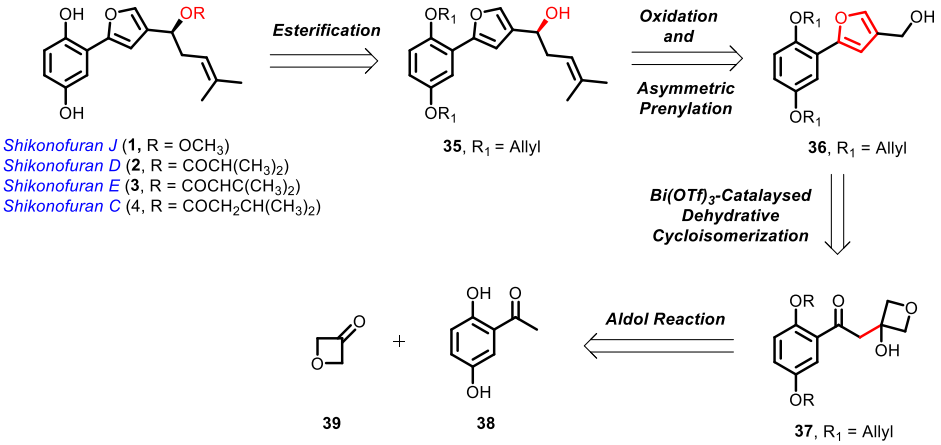
The feasibility of our projected hypothesis was initially tested using α-hydroxy oxetane-tethered ketone **5** as starting material, various Lewis acids (Ni(II), Ag(I), Fe(II), Fe(III), Bi(II), Bi(III), $BF_3.OEt_2$, etc.) and Brønsted acids (TfOH, TFA, PTSA, etc.) as catalysts in different solvents. To our delight, 10 mol% of $Bi(OTf)_3$ in DCM at room temperature delivered the desired product **6** (3-hydroxymethyl-derived furan). Employing these optimized conditions, we have accomplished the synthesis of 2,4-disubstituted and 2,3,4-trisubstituted furans possessing C2-alkyl, aryl, and heteroaryl; C3-H, aryl substituents, in good to excellent isolated (62-99%), in short reaction time (1-5 min). Aryl or heteroaryl substituents (at C2 of

the furan) containing electron-withdrawing (CF_3, Cl, NO_2) and/or electron-donating (MeO, alkyl, BnO, Allyl-O-) groups, and diverse protecting groups (-OTIPS, -OTBS, -OTBDPS, -OBn, -OPMB) were found to be compatible under these optimized conditions. The substrate scope of this transformation is high and demonstrated through the preparation of 28 diverse hydroxymethyl furans (Scheme 2).



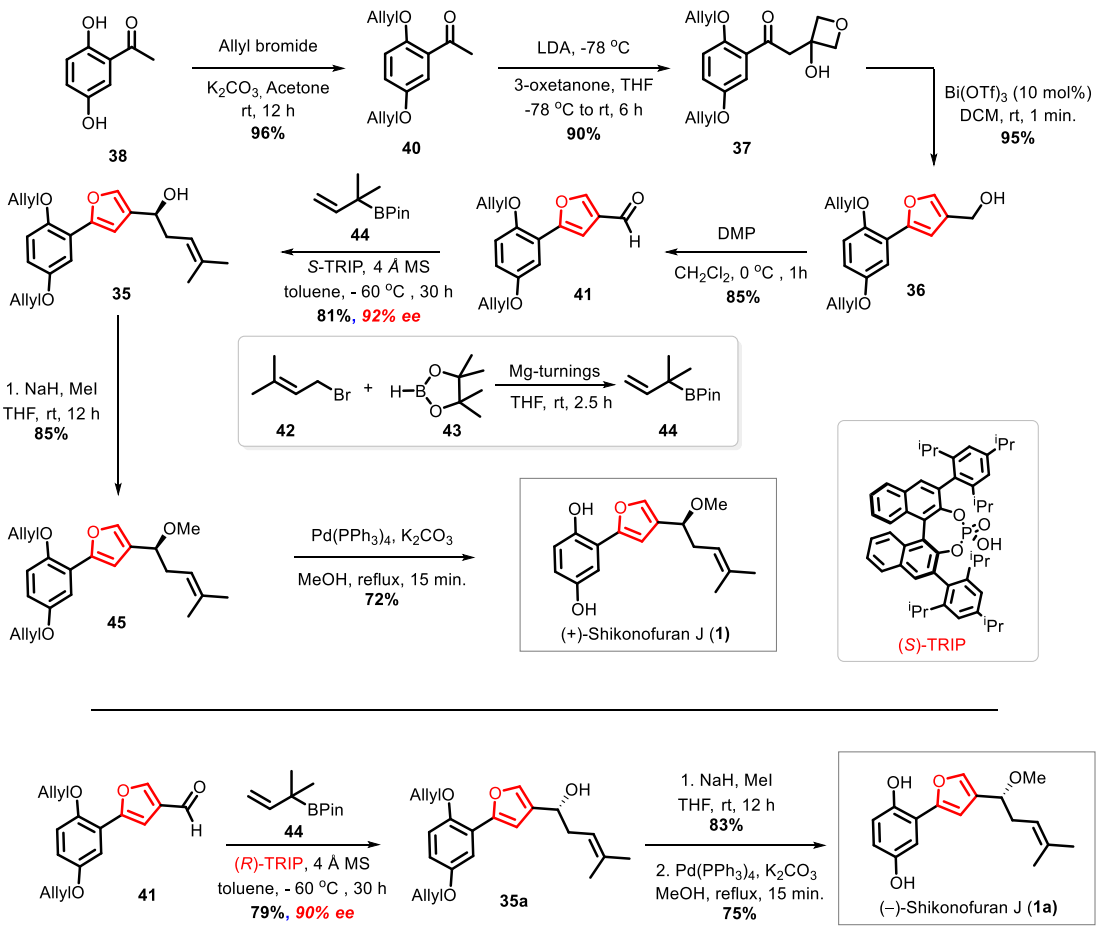
Scheme 2: Present work: Synthesis of di- and tri-substituted furans.

After exploration of the substrate scope of this methodology, we hypothesized a common retrosynthetic analysis for the enantioselective total synthesis of shikonofurans. Shikonofurans J, D, E, and C (**1**-**4**, with varying ester groups) could be prepared from hydroxyalkyl furan **35** *via* esterification using suitable carboxylic acids followed by deprotection of protected arene. Intermediate **35** could be readily accessed from 2,4-disubstituted furan **36** using TRIP-catalyzed asymmetric prenylation reaction, which can be constructed employing the above-disclosed Bi(III)-catalyzed dehydrative-cycloisomerization of α-hydroxy oxetane-tethered ketone **37**. The intermediate **37** could in turn be prepared employing the aldol reaction of acetophenone **38** and oxetanone **39** (Scheme 3).



Scheme 3: Retrosynthetic analyses of shikonofurans J, D, E and C.

Our studies started with enantioselective total synthesis of the reported structure of shikonofuran J (**1**) starting from commercially available 2,5-dihydroxy acetophenone (**38**). Allyl protection of **38** using allyl bromide in presence of K_2CO_3 gave **40**, which was subjected to LDA-mediated aldol reaction with 3-oxetanone (**39**) to give the requisite aldol product **37**. Next, aldol **37** was subjected to our in-house developed methodology of $Bi(OTf)_3$-catalyzed dehydrative cycloisomerization reaction, which cleanly furnished the desired hydroxy-methylated furan **36** in 95% yield in 1.0 min. Then, **36** was oxidized to aldehyde **41** using Dess–Martin periodinane (DMP), and subsequently subjected to asymmetric prenylation[8] reaction using chiral phosphoric acid [(*S*)-TRIP] and prenyl-pinacol-boronate to get the anticipated chiral alcohol **35**, which was used as a common intermediate for all shikonofurans. Then methylation of alcohol **35** using NaH and MeI to give **45**, followed by $Pd(PPh_3)_4$-catalyzed allyl deprotection of both allyl groups delivered shikonofuran J (**1**) in 72% yield (Scheme 4).



Scheme 4: Enantioselective total synthesis of shikonofuran J (**1**) and its enantiomer (**1a**).

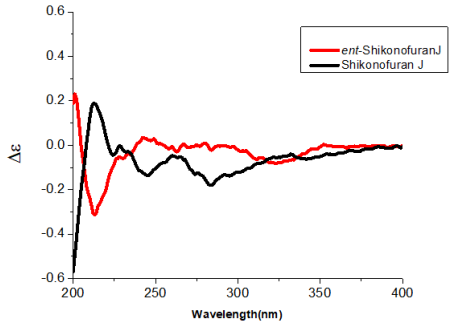
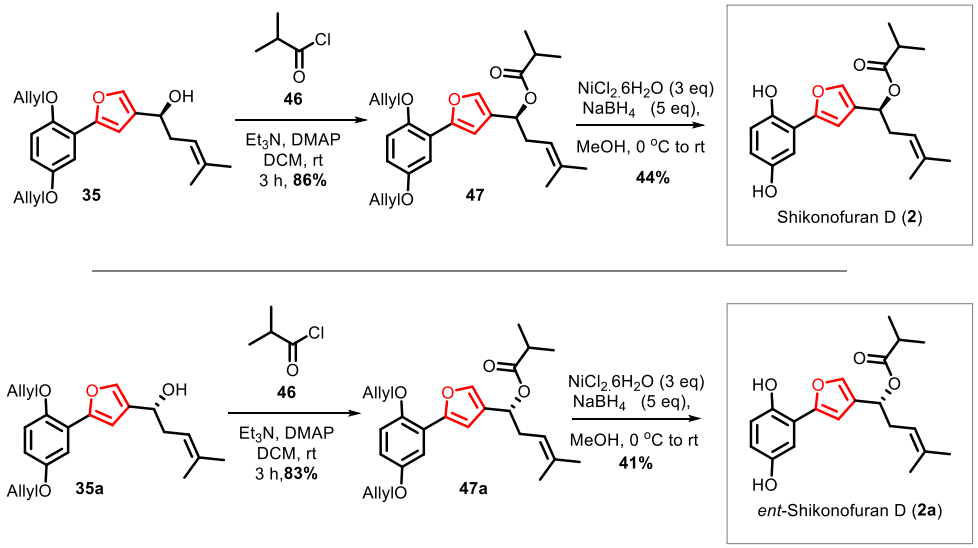


Figure 2: ECD spectra of Shikonofuran J (**1**) and *ent*-Shikonofuran J (**1a**).

^{1}H and ^{13}C NMR data of synthesized **1** was in full agreement with that of the literature data (isolated natural product **1**). To our surprise, the optical rotation value of **1** ($[\alpha]^{26:6}{}_{D}$ = +7.07 (*c* = 0.5, MeOH), our work) was found to be opposite to the reported value of natural shikonofuran J (**1**) ($[\alpha]^{12}{}_{D}$ = –11.3 (*c* = 0.3, MeOH), reported earlier). Hence, we synthesized the enantiomer of **1** (**1a**) by using (*R*)-TRIP as a ligand in the asymmetric prenylation step *via* **35a**, and compared the ECD data (Scheme 4). (*S*)-(+)-Shikonofuran J (**1**, this work) structure) showed a negative Cotton effect (CE; CD, 4.3 x 10^{-4} M, MeOH) at λmax 283 nm (Δε −0.180), 245 nm (Δε −0.134), and a positive cotton effect at λmax 213 nm (Δε +0.187), which was in agreement with the data reported for (*S*-isomer) of shikonofuran J (**1**, isolated). While the (*R*)-isomer **1a** showed anticipated opposite ECD data compared to **1** (CD, 4.3 x 10^{-4} M, MeOH, λmax (Δε) 283 (−0.018), 245 (+0.026) and 213 (−0.312) nm) (Figure 2).

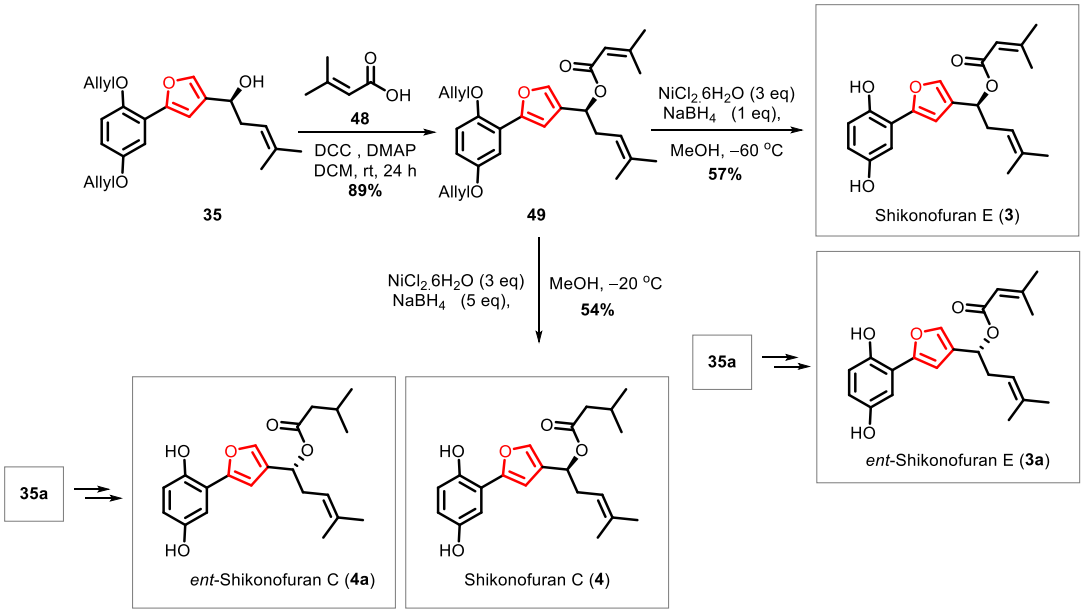
After successful synthesis and establishment of the absolute configuration of shikonofuran J (**1**) and its enantiomer (**1a**), we embarked on the total synthesis of shikonofurans D, E, and C, and their antipodes utilizing common intermediates **35** and **35a**. Thus, the hydroxyalkyl furan intermediate **35** (possessing the desired stereochemistry of natural products) was treated with isobutyryl chloride **46** in presence of Et_3N, and DMAP to afford the corresponding ester **47** in 86% yield. The subsequent bis-allyl deprotection of **47** was found to be difficult under well-established conditions using $Pd(PPh_3)_4$ / $Pd(OH)_2$ and diverse bases, $BiCl_3$-$NaBH_4$, LiCl-$NaBH_4$, and $CeCl_3.7H_2O$-NaI, which led to the ester hydrolysis and non-selectively deprotected products. After extensive experimentation, $NiCl_2.6H_2O$ (3 eq), $NaBH_4$ (5 eq), MeOH, 0 ºC to rt conditions[9] were found to be fruitful by providing the desired shikonofuran D (**2**, reported structure) in a moderate yield of 44%, along with a few unidentified and inseparable products (Scheme 5). A similar strategy was employed to

synthesize the enantiomer (**2a,** *ent*-shikonofuran D) of shikonofuran D (**2**) from **35a** (Scheme 5).



Scheme 5: Enantioselective total synthesis of shikonofuran D (**2**) and its enantiomer (**2a**).

Next, the alcohol **35** was subjected to esterification using commercially available 3-methylbut-2-enoic acid (**48**) under DCC and DMAP conditions to get ester **49**, which served as a common precursor for both the natural products shikonofuran E and C. Phenolic allyl de-



Scheme 6: Enantioselective total synthesis of shikonofuran E and C (**3** and **4**), and their enantiomers (**3a** and **4a**).

protection using $NiCl_2.6H_2O$ and $NaBH_4$ in MeOH at −60 °C delivered shikonofuran E (**3**) in 57% yield. While optimizing this allyl deprotection of **49** at various temperatures, we observed the reduction of the butenoic-ester segment at −20 °C, which led to the formation of shikonofuran C (**4**). Utilizing a strategy similar to this, synthesized *ent*-shikonofuran E (**3a**) and *ent*-shikonofuran C (**4a**) from **35a** (Scheme 6).

Conclusion: We have developed a mild, efficient, and facile methodology for the synthesis of hydroxy methyl-derived polysubstituted furans employing an unprecedented Bi(III)-catalyzed dehydrative cycloisomerization of α-hydroxy oxetane-tethered ketones. Moreover, we have successfully applied this protocol in the first enantioselective total synthesis of furyl-hydroquinone-derived antimicrobial natural products shikonofurans J, D, E, and C in 7 linear steps with 34.6 %, 21.4 %, 28.6%, 27.1% overall yield respectively, and also synthesized their enantiomers to establish the absolute stereochemistry. This work may find immediate applications in the synthesis of related furan-derived bioactive natural products and medicinal chemistry investigations.

Chapter 3: Design, Synthesis, and Biological Evaluation of Eugenol Derivatives as Potential Antidiabetic Agents

Diabetes mellitus is a severe & chronic disorder that occurs when the human body is incapable of producing or ineffectively uses the hormone insulin, resulting in an elevation of blood glucose level (hyperglycaemia). According to the International Diabetic Federation, 537 million people in the world had diabetes in the last year, expected to rise to 643 million by 2030 and 783 million by 2045. Presently, oral anti-diabetic medications are used in the pharmacological treatment of diabetes to help control hyperglycaemia. These medications either increase insulin secretion and sensitivity, lower hepatic glucose production, or help with glucose absorption. However, due to limited effects and unwanted side effects, the efficacies of these medications are debatable. On the other hand, α-glucosidase inhibitors are found beneficial in treating diabetes. They regulate blood glucose levels by inhibiting the digestion of oligosaccharides/carbohydrates (like maltose, maltotriose, dextrins, sucrose, etc.) into glucose. In addition to these drugs, inhibition of advanced glycation end products (AGEs) is

also considered a proper therapeutic strategy in managing diabetes-associated complications.

Eugenol is a natural monoterpene molecule that is very cheap, readily available, and has various biological properties like antihypertensive, anticarcinogenic, antiparasitic, antifungal, antibacterial, antimicrobial, antiseptic, dental analgesic, and antiviral. It has attracted the attention of researchers in past decades because of its chemical versatility and its biological profile. Therefore, we have investigated the major Ocimum metabolite eugenol and its role in a multifactorial effect in diabetic conditions. Our studies have focused mainly on the inhibition of α-amylase, α-glucosidase, glycation inhibition, and antioxidant properties of the eugenol molecule.[10] These activities are further optimized by derivatization of functional groups of eugenol because eugenol is an oily compound and it is not water-soluble, hence it should be administered into the body by the intra-peritoneal route, and we cannot use it orally (in *in vivo* and *preclinical* investigations). Hence, there is a desperate need for the design, synthesis, and biological evaluation of water-soluble derivatives of eugenol.

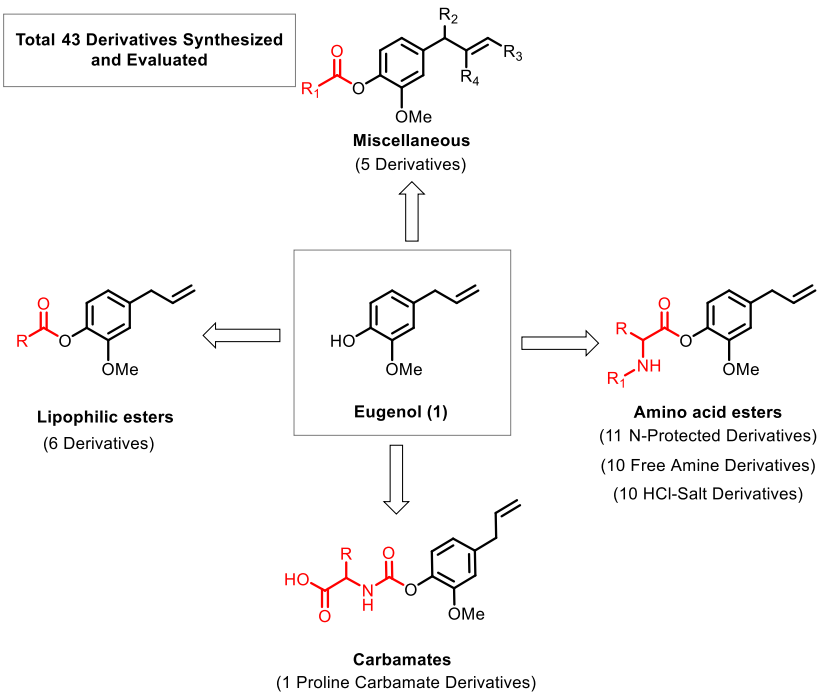
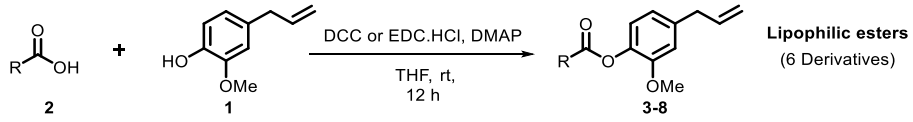


Figure 1: General classification of eugenol derivatives synthesized and evaluated in the present work.

Herein, we reported the synthesis and biological studies of various eugenol derivatives of lipophilic esters, amino acid conjugates, and carbamates, based on a prodrug concept, and

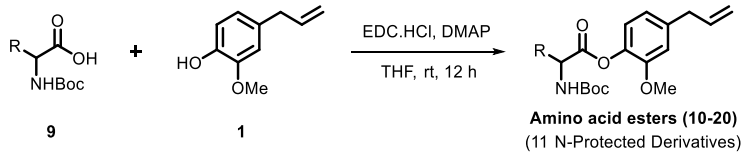
other miscellaneous known analogs (which were studied earlier for other therapeutic effects) (Figure 1). This approach may open the opportunity for a flexible and wide therapeutic window for the treatment of diabetes, and further show better solubility, bioavailability, permeability, adsorption, and anti-diabetic activity.

Category 1. Lipophilic ester derivatives of eugenol: Lipophilic esters were used as prodrugs due to their known capability of intracellular enzymatic hydrolysis and delivering corresponding acid or alcohol-containing drug molecule, and also facilitates cell-membrane permeability due to the lipophilic cellular membrane interactions. Based on this hypothesis, we have designed and synthesized diverse six lipophilic esters **3-8** using well-established DCC/EDC.HCl-coupling reaction conditions in good scale and yields (Scheme 1).[11]

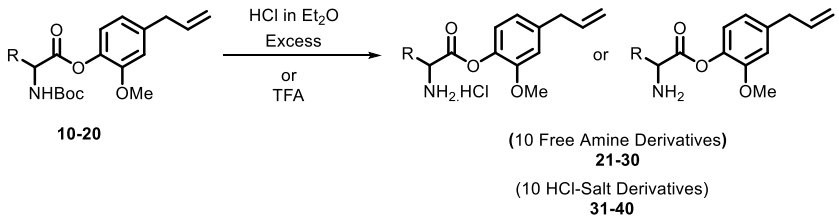


Scheme 1: General synthetic route for lipophilic derivatives of eugenol.

Category 2. Amino acid ester derivatives of eugenol: To increase the solubility and bioavailability of eugenol (**1**), we connected polar amino acids (**9**, Boc protected, prepared from natural amino acids) to eugenol *via* ester linkage using EDC.HCl as a coupling reagent. Synthesized 11 N-protected amino acid conjugates **10**-**20** of eugenol, which were used as a building blocks for their 10 free-amine derivatives **21**-**30** and 10 corresponding HCl salts **31**-**40** (Scheme 2, and Scheme 3).

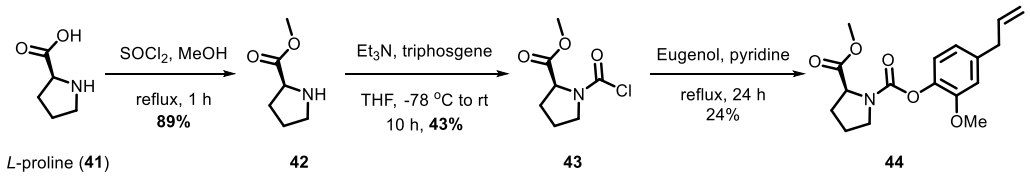


Scheme 2: General synthetic route for amino acid derivatives of eugenol.



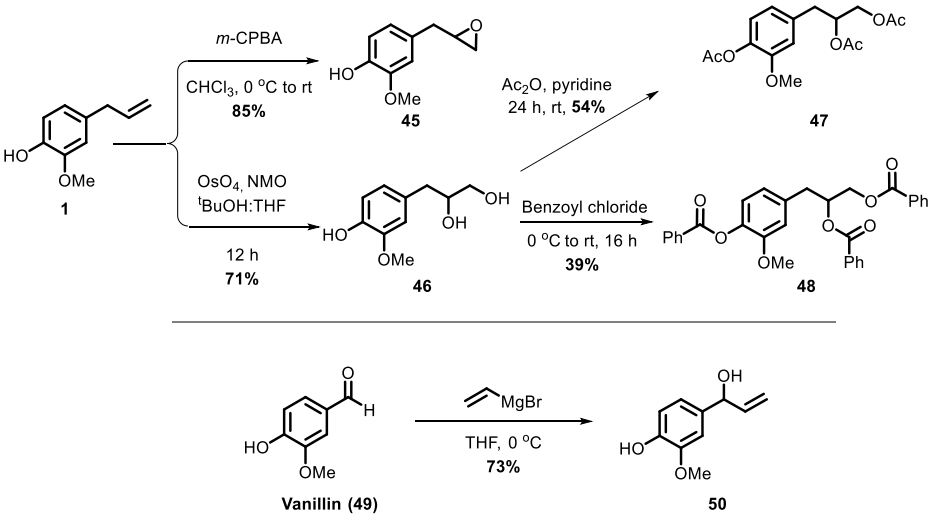
Scheme 3: General synthetic route for HCl salt and free amine derivative of amino acid derivatives of Eugenol

Category 3. Carbamate derivative of eugenol: Carbamates are well-known to serve as prodrugs. Hence, we prepared one such carbamate derivative from natural amino acid proline and eugenol. *L*-proline (**41**) was converted into its methyl ester **42** using $SOCl_2$, MeOH, then subsequently treated with triphosgene to get corresponding carbamoyl chloride **43**. The reaction between carbamoyl chloride **43** and eugenol (**1**) in the presence of pyridine under reflux conditions delivered the desired carbamate **44** (Scheme 4).[12]



Scheme 4: Synthesis of carbamate derivative of eugenol.

Category 4. Miscellaneous derivatives: In addition to these novel derivatives of eugenol (Schemes 1-4), we also synthesized some known miscellaneous analogs of eugenol *via* modification of its functional groups based on known literature protocols. Epoxidation[13] of eugenol (**1**) using *m*-CPBA delivered the corresponding epoxide **45**, whereas, dihydroxylation[14] using OsO_4, NMO gave the diol derivative **46**, which was used as a precursor for two more acetate **47** and benzoate **48** analogs.[15] The reaction of vinyl magnesium chloride with vanillin (**49**) furnished the hydroxy vinyl derivative **50** of eugenol (Scheme 5).



Scheme 5: Synthesis of miscellaneous derivatives of eugenol.

All these synthesized 43 derivatives of eugenol were evaluated for their *in vitro* radical scavenging (DPPH assay), *α*-amylase inhibition, *α*-glucosidase inhibition, and BSA-AGE glycation inhibition activities. To our delight, seven derivatives (A, B, C, D, E, F, and G) were found to be better active compared to the parent molecule eugenol (Figure 2).

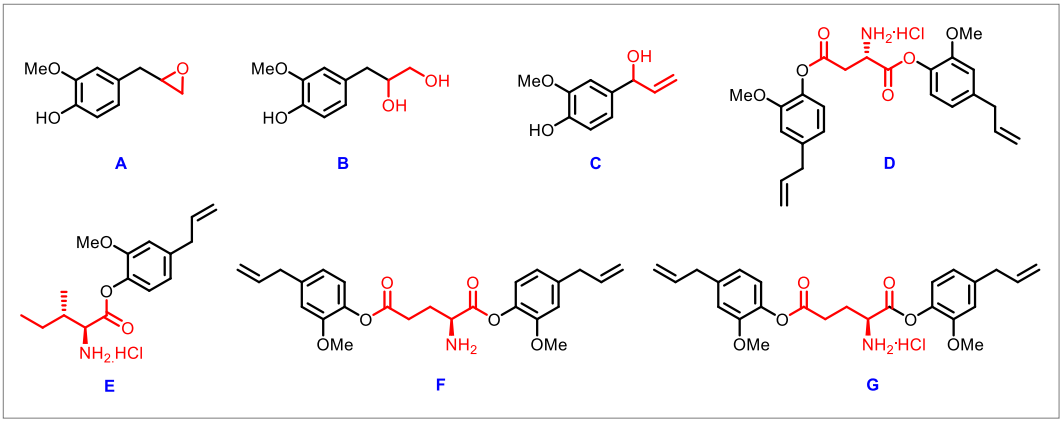


Figure 2: Potential eugenol derivatives identified in this present work.

Conclusion: We have synthesized forty-three derivatives of eugenol which are more soluble and bioavailable than eugenol (except lipophilic ester derivatives), and we found that seven derivatives (A, B, C, D, E, F, and G) were more active toward *in vitro α*-amylase inhibition, *α*-glucosidase inhibition, and BSA-AGE glycation inhibition compared to the parent molecule eugenol. Moreover, these molecules showed significant *in vitro* radical scavenging activity as well (evaluated using DPPH assay). These results may find applications in the field of antidia-

betic drug discovery based on the natural product eugenol as a pharmacophore. However, to prove our pro-drug concept of eugenol derivatives, further *in vitro* and *in vivo prodrug assays* are needed, which are in progress.

5. <u>Summary</u>: *Chapter 1* comprised investigations directed toward the total synthesis of diarylheptanoid natural products hedycoropyran, which led us to establish a novel synthetic route for *ent*-rhoiptelol B from the commercially available building block of 4-allylanisole, veratraldehyde and vanillin. The synthetic chemistry utilized in this endeavor and our critical observations of stereo-electronic effects may help synthetic organic chemists to devise practical synthetic routes for these classes of molecules. In *Chapter 2*, we have developed an unprecedented, rapid, and facile Bi(III)-catalyzed cascade dehydrative cycloisomerization reaction to access hydroxy methyl-tethered polysubstituted furans, and we have successfully demonstrated the utility of this strategy through the enantioselective total synthesis of antibacterial natural products shikonofurans J, D, E and C and their enantiomers in 7 linear steps and in good overall yields. These investigations provide solutions to access related natural products in sufficient quantities, which in turn facilitate comprehensive biochemical investigations of natural product-based drug discovery. *Chapter 3* showcased the design, synthesis, and biological evaluation of diverse eugenol analogs with improved bioavailability and *in vitro* α-amylase inhibition, α-glucosidase inhibition, and BSA-AGE glycation inhibition activities. These studies suggested that the solubility of the eugenol derivatives has a pivotal impact on their inhibitory properties, further *in vitro* and *in vivo* analyses of all these pro-drug-based derivatives may lead to the identification of efficient antidiabetic agents with multiple activity profiles.

6. <u>Future directions:</u> Natural product rhoiptelol B is known to possess significant *in vitro* inhibitory activities against LPS-induced NF-KB activation, NO and TNF-α production, and HIF-1 in AGS cells. Since we established a total synthesis route for its enantiomer (*ent*-rhoiptelol) in *Chapter 1*, the synthesis of natural rhoiptelol and its structurally close analogs in a multi-gram scale and systematic structure-activity-relationship (SAR) studies are the future considerations of this work. In *Chapter 2*, diverse hydroxymethyl-tethered polysubstituted furans were synthesized in very good quantities, and many of them were new chemical entities, hence, *in vitro* / *in vivo* antibacterial activity screening can be taken up as a future project.

In addition, *Chapter 2* comprises the concise synthesis of furyl-hydroquinone-derived natural products shikonofuran J, D, E, and C and their enantiomers, the scale-up of these natural products and enantiomers and structure-activity relationship (SAR) studies may be considered in future research. Studies incorporated in *Chapter 3* suggested that the solubility of the eugenol derivatives has a pivotal impact on their inhibitory properties, further *in vitro* and *in vivo* analyses of all these pro-drug-based derivatives may be considered for the antidiabetic lead optimization.

7. Publications:

1. Studies directed toward the synthesis of hedycoropyrans: total synthesis of *des*-hydroxyl (−)-hedycoropyran B (*ent*-rhoiptelol B).
   Kataria, P.; Nomula, R. and Kontham R., *Org. Biomol. Chem*., **2022,** *20*, 444–463.
2. Synthesis of Furo[2,3-b]pyran-2-ones through Ag(I)- or Ag(I)−Au(I)-Catalyzed Cascade Annulation of Alkynols and α-Ketoesters
   Thorat, S. S.; **Kataria. P**.; Kontham, R. *Org. Lett*. **2018**, *20*, 872-875.
3. Development of a Facile Synthetic Strategy for Substituted Furans from Keto-Oxetanes Using Bi(III) Catalysis: Application to Unified Total Synthesis of Furylhydroquinone-Derived Natural Products Shikonofuran J, D, E, and C.
   Kataria, P.; Sahoo S. S.; Kontham, R. (*Manuscript under preparation)*
4. Design, Synthesis and Biological Evaluation of Eugenol Derivatives as Potential Antidiabetic Agents
   Kataria, P.; Kontham, R.; Kulkarni M. J.; Giri A. P.; Agawane S. B. (*Manuscript under preparation*)
5. Eugenol derivatives with improved anti-diabetic and related activitives, **Kataria. P**.; Kontham, R. Kulkarni M. J.; Giri A. P.; Agawane S. B.
   NCLI-INV-2019-031 (*Patent submitted*)

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CHAPTER-1

Enantioselective Total Synthesis of Diarylheptanoid *ent*-Rhoiptelol B (*des*-Hydroxy Hedycoropyran B)

Chapter-1, Section-A: Introduction and previous approaches

1.1 Introduction

Natural products are a diverse group of chemical substances produced by nature. Living organisms, including bacteria, fungi, insects, animals, and plants, produce these compounds, which have evolved to serve human needs, such as life-saving drugs, vitamins, colors, tastes, scents, etc. Natural products (NPs) are the most successful source of drug leads. Despite spending decades in the shadow of drug discovery using synthetic molecules, the development of drugs from natural sources is currently experiencing a revival. It consumes a lot more chemical space than those produced by synthetic chemistry. In 2020, Newman and Cragg described all therapeutic agents approved by the FDA covering nearly four decades, January 1981 to September 2019, for all diseases worldwide in a survey. According to this, 346 biological molecules (B, 18%), 71 unaltered natural products (N, 4%), 14 botanical drugs (NB, 1%), 356 natural product derivatives (ND, 19%), 463 synthetic drugs (S, 25%), 217 natural product mimics (S/NM, 11%), 65 synthetic drugs (S*, with NP pharmacophore, 3%), 207 natural product mimics (S*/NM, 11%) and 142 vaccines (V, 8%) were sharing respective percentages (Figure 1.1) [1] which clearly shows that natural product-based drug discovery still plays a vital role for treating various diseases (Figure 1.1).

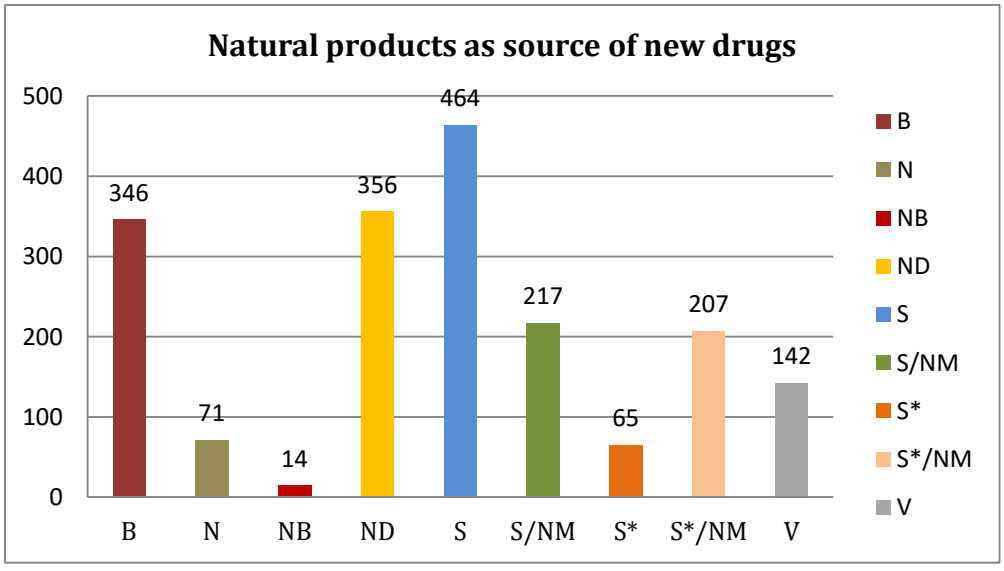


Figure 1.1. Natural product-based new drugs over four decades.

Among various sources of natural products, plant-based natural products are mainly used for treatment as traditional or folk medicine by our ancestors. Here some natural product-based drugs are listed, which are approved by FDA for curing many diseases. Morphine is the first active ingredient isolated from plants by Friedrich Sertürner in 1804 and commercialized by Merck in 1827, it is used to treat severe pain. Aspirin is the first synthetic drug that Bayer synthesized in 1899. It is used as a pain reliever. Quinine is initially isolated from the bark of *chinchona* in 1820 and is used to treat malaria caused by *Plasmodium falciparum* which is resist to chloroquine. Subsequently, many natural product-based drugs were developed in the 19th century (Figure 1.2).

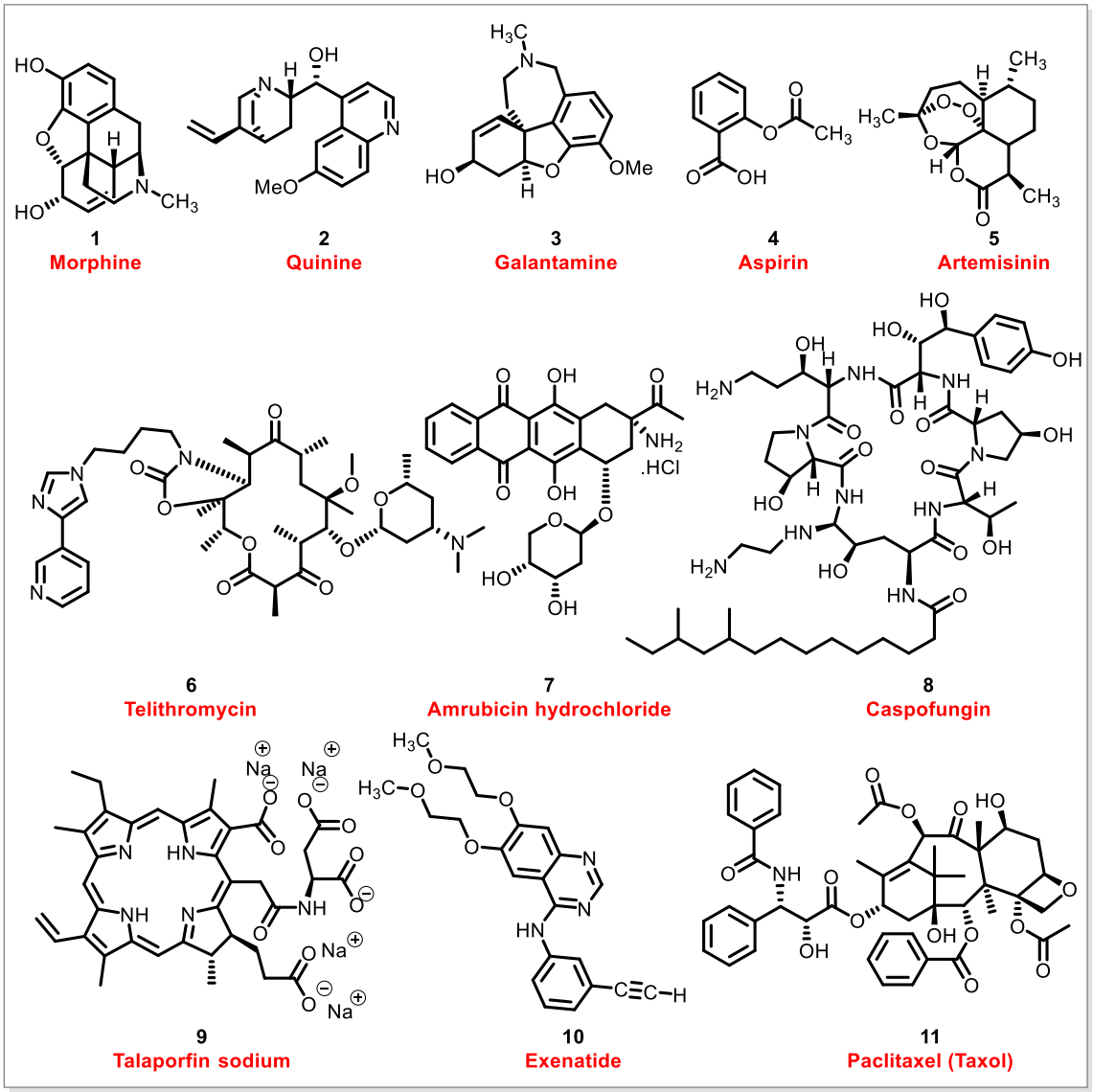


Figure 1.2. Representative plant-based natural products developed as drugs.

Galantamine is a natural alkaloid isolated from bulb and flowers of *Galanthus nivalis* used to treat Alzheimer's disease. Artemisnin, a semi-synthetic drug used to treat malaria, was first discovered by Tu Youyou in 1972 for this she got the Nobel prize in Physiology or Medicine in 2015. The other natural product-based drugs are telithromycin a semisynthetic erythromycin derivative (used for the treatment of pneumonia). Amrubicin hydrochloride is a synthetic anthracycline agent based on a doxorubicin natural product used for lung cancer treatment. Talaporfin sodium is an anticancer agent derived from chlorophyll and *L*-aspatic acid with photosensitizing activity. Exenatide an antidiabetic agent, based on incretin which is used to treat diabetes mellitus type-2. The next plant-based natural product is paclitaxel (taxol) which is widely used as an anticancer agent to treat various types of cancers (Figure 1.2).[2]

Even though natural goods are a reliable source of therapeutic leads, most large pharmaceutical companies have curtailed or even stopped their natural product research efforts. Consequently, what caused natural products to fall into obscurity in the 1990s? In the 1990s, the development of new technologies that could aid in the endeavor to discover medications derived from natural products has not kept pace with the demands of the market. Another problem for natural products was that many pharmaceutical businesses lacked focus; there are so many different natural product sources, and by focusing on too many things, they spread themselves too thin. Because of these issues, there was a belief within the industry that looking for a potential natural therapy for any ailment was an expensive and difficult process that wasn't worth the time, money, and effort. There are several drawbacks when comparing the drug discovery process for natural products to that of synthetic chemicals, such as the fact that natural products are frequently produced in very small quantities and found mixed together in extracts, necessitating labor-intensive and time-consuming purification procedures and It is uncommon for industry professionals to possess the skill set required to create and maintain a high-quality natural product library. Typically, the structures of natural products are extremely complicated. Organic chemistry modification of complex natural compounds is frequently difficult. The reason that medicinal and combinatorial chemists avoid working with complicated natural products is because of the compounds' enormous size and complexity, which contain too many functional groups to protect. It is tough

to prepare as many natural product analogues as synthetic molecules in the same period of time.[3]

To overcome these problems, the screening of natural products has been remolded by current technical advancements to develop new methodologies, and this presents a unique chance to reestablish natural products as a lead source of therapeutic leads. The advanced improvements involved efficient screening process, good organic synthetic routes, good natural sources etc. The most recent advancement in hyphenated methods combines separation technologies like solid phase extraction (SPE) with NMR, HPLC, and mass spectrometry. Spectrometry has significantly decreased the timeline for determining the structure and isolation of natural products in the crude extracts. The majority of the plant-based drug discovery research included bioassay-guided fractionation and isolation of natural compounds, which were then thoroughly investigated *in vitro*, *in vivo*, in preclinical studies, and in humans.[4]

Chirality is a feature of any molecule with asymmetrically substituted carbon that is non-superimposable on each other. The Chiral property of a compound plays an important role in biological activity by determining the specific binding and pharmacological action of a drug. Louis Pasteur, a French scientist, and biologist, first discovered chiral chemistry in 1848 when he first manually separated the two isomers of sodium ammonium tartrate (Figure 1.3).[5]

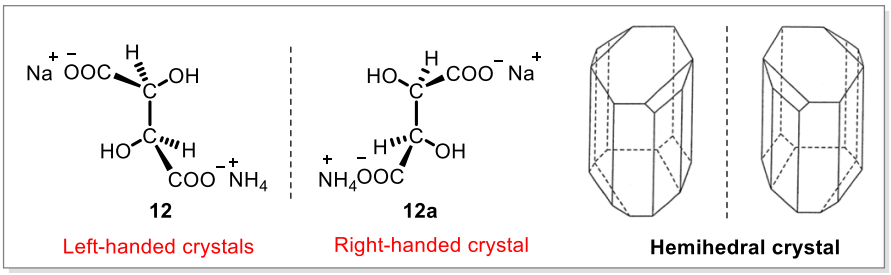


Figure 1.3. Separation of (+)– and (–)– sodium ammonium tartrate.

The study of the interaction between a drug molecule and a living organism is called pharmacology. The Chiral property of a compound plays an important role in biological activity by determining a drug's specific binding and pharmacological action. The drug molecule and receptors interaction is based on the lock and key

model. In industries, only 56% of all drugs are chiral, and 88% are in racemic form. Generally, all-natural compounds are present in single enantiomeric form (chiral) compared to synthesized ones. For example, all amino acids are in Levorotatory (*L*-form), and all sugars are dextrorotatory (*D*-form). Selected information on chirality versus pharmacological effect is described below:

i) Most racemic compounds have one active enantiomer called eutomer and another inactive or less toxic, called distomer. For example (*S*)-(–)-propranolol is a β-blocker which is 100 times more effective as a than its opposite isomer, and (*R*)-methadone is around 50 times more active than its (*S*)-antipode as an analgesic.
ii) Racemic compound where both the enantiomers are equally active and have the same pharmacologic properties. Few drugs are reported in this category, such as flecainide as an antiarrhythmic, cyclophosphamide as an antineoplastic, and fluoxetine as an antidepressant.
iii) The last one is with only one active enantiomer (eutomer), and the inactive isomer (distomer) is changed to eutomer when it gets into the body by chiral inversion. For example (*S*)-(+)-ibuprofen is more active enantiomer than (*R*)-(–)-ibuprofen. In our body inactive (*R*)-isomer is converted to its active (*S*)-isomer by chiral inversion using hepatic enzyme not (*S*)-antipode to (*R*). (*S*)-(+)-oxazepam is 100-200 fold more potent than (*R*)-(–)-oxazepam as a tranquilizer.
iv) Another examples are (*S*)-(+)-dexchlorpheniramine (antihistamine) is almost 200 times more potent than (*R*)-(–)-dexchlorpheniramine. (*S*)-(+)-Ketamine is more potent as an anesthetic agent, and it may have less side effects compared to (*R*)-(–)-ketamine (Figure 1.4).

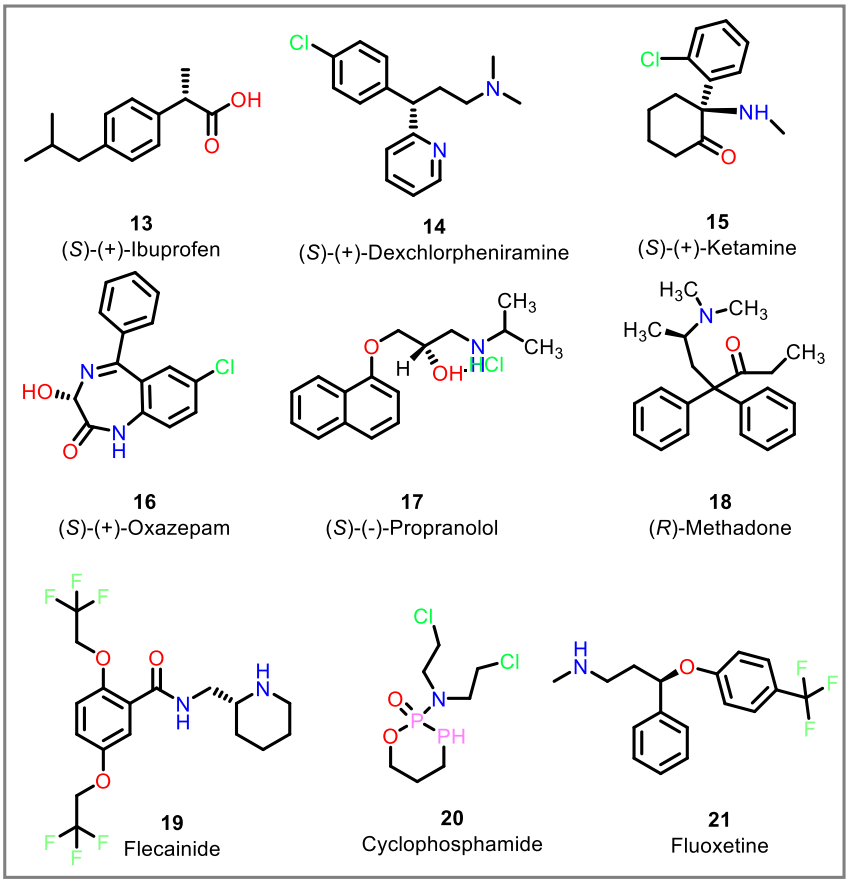


Figure 1.4. FDA-approved Chiral Drugs

In all the above cases, only one enantiomer from their racemic mixture is active, hence, avoiding unnecessary isomers is warranted, which could be addressed using various chiral separation techniques. The "racemate-versus-enantiomer" issue has also given rise to a new marketing technique in industries called the racemic switch. A racemic switch refers to the transformation of a drug into its pure single enantiomer, which was previously approved as its racemic form. There are two types of techniques used for chiral separation. The common method is the synthesis of diastereomeric salt of enantiomers using reactions with chiral acids or chiral bases, which would form a set of diastereomers having different physical and chemical properties. So they can easily be separated by simply crystallization or filtration if one isomer is soluble in a particular solvent and another is not. The other classical method is enzymatic or kinetic resolution, in which we can achieve one of the enantiomers in its pure form using some microorganism like yeast, bacteria etc. Modern techniques like chiral high-performance liquid chromatography (HPLC),

capillary electrophoresis, liquid-liquid extraction, etc are used for the purification of optically active compounds.[6]

Even though several technologies are available in the market to access chiral molecules, still pharmaceutical industries rely only on small molecule-based drugs due to their low production cost, easy determination, quick timelines, and also the problems with natural products like complex structure, difficult isolation process, low abundance, finally the issue in supply. Hence there is an urgent need to develop sustainable and practical synthetic routes or techniques to synthesize natural products in a stereoselective manner. So keeping these points in mind, we aimed to develop efficient stereoselective synthetic routes for biologically relevant diarylheptanoid-containing natural products.

Diarylheptanoids (DAHs) belong to one of the emerging structural classes of natural products known to display interesting biological profiles of anti-inflammatory, antioxidation, anticancer, inhibition of NO production, DPPH-radical scavenging activity, and others. Structurally these natural products possess two aryl rings connected with seven carbons chain at the C1 and C7 positions. Curcumin was the first diarylheptanoid isolated from turmeric's rhizomes by Vogel and Pelletier in 1815, which is a yellow-colored matter. After that various diarylheptanoids were isolated from a number of plants family including *Zingiberaceae*, *Myricaceae*, *Burseraceae*, *Actinidiaceae*, *Casuarinaceae*, *Juglandaceae*, *Leguminosae*, *Aceraceae*, and *Betulaceae*, from leaves, fruits, roots, seeds, rhizomes, and barks. As of today, more than 400 diarylheptanoid natural products are identified in nature.

Diarylheptanoids are classified as linear and cyclic respectively. Linear diarylheptanoids are mostly rich in plant species of *Curcuma*, *Zingiber*, *Zingiberaceae*, and *Betulaceae* families. Natural product curcumin (**22**) falls under this category. Cyclic diarylheptanoids are generally found in *Myricaceae*, *Aceraceae*, *Garuga Burseraceae*, *Betulaceae*, and *Juglandaceae* species, these are further divided into two classes: biaryl type possessing tetrahydrofuran and tetrahydropyran rings (**23**-**25**) and diarylether type having macrocyclic ring-systems (**26** and **27**) (Figure 1.5)[7]

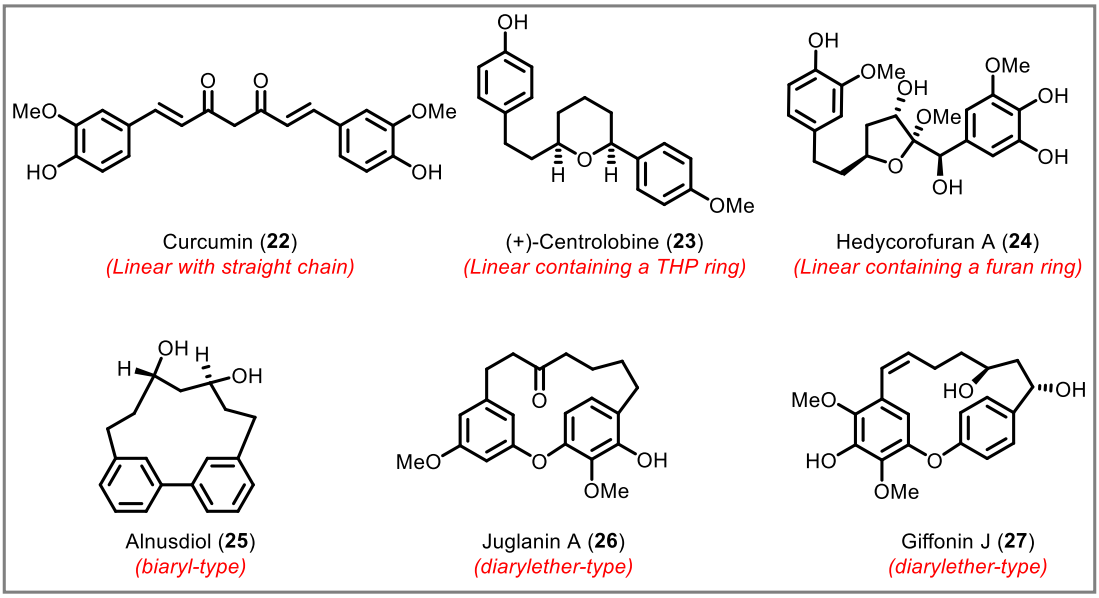
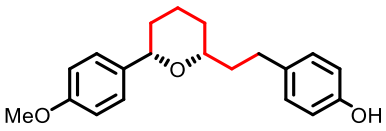
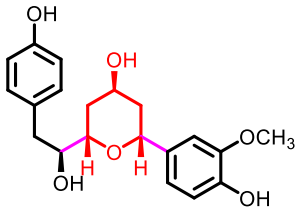
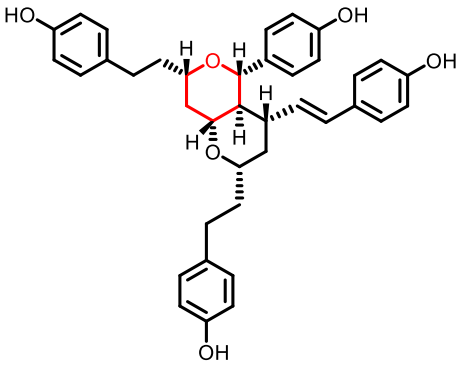
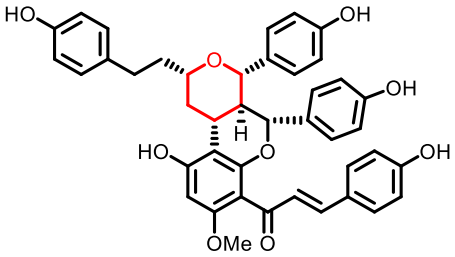
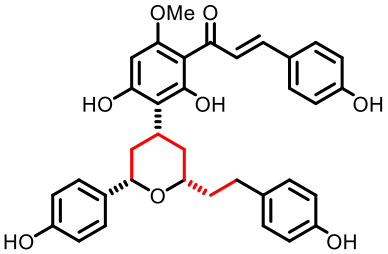


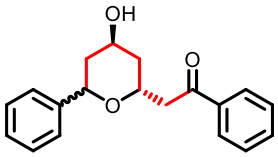
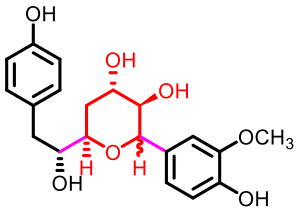
Figure 1.5 Diarylheptanoid natural products with the linear and cyclic skeleton.

A significant number of tetrahydropyran diarylheptanoids (THP-DAHs) with complex structures were isolated from many plant species having various biological activities. Particularly, centrolobines, calyxins, diospongins, rhoiptelol B, and others, have led to a substantial interest in medicinal and synthetic organic chemistry. As part of our investigations on the development of novel and practical synthetic approaches for diarylheptanoid with THP ring containing natural products (hedycoropyran A & B), we performed an extensive literature survey on known synthetic methodologies to access these THP ring and the list of THP derived diarylheptanoids, and the details are presented below (Table 1.1).

Table1.1 Representative examples for THP-DAHs natural products.

S. No	Structure	Isolation and activity
1.	 (–)-Centrolobine (**28**)	In 1964, De Albuquerque, I. L isolated (–)-centrolobine (**28**) from the heartwood of C*entrolobine robustum,* later from the stem of *Brosinium potabile.* It exhibits anti-inflammatory, antibacterial, and anti-leishmanial activity[8]

2.	 (+)-Rhoiptelol B (**29**)	In 1996, Kouno and coworkers isolated Rhoiptelol B (**29**) from the fruits of *Rhoiptelea chiliantha,* and in 2007, Bae and coworkers also isolated it from the bark of *Alnus hirsute* and is known to display inhibitory activities against LPS induced NF-KB activation, NO and TNF-α production, and HIF-1 in AGS cells.[9]
3.	 Blepharocalyxin D (**30**)	In 2000, Kadota and coworkers isolated Blepharocalyxin D (**30**) from an EtOH extract of seeds of *Alpinia blepharocalyx.* It shows potent antiproliferative activity against murine colon 26-L5 carcinoma and human HT-1080 ®brosarcoma cells, with ED_{50} values of 3.61 μM.[10]
4.	 Calyxin I (**31**)	In 2001, Kadota and co-workers isolated Calyxin I (**31**) from an EtOH extract of the seeds of *Alpinia blepharocalyx.* It shows significant cytotoxicity against murine colon 26-L5 carcinoma and human HT-1080 fibrosarcoma cells.[11]
5.	 Epicalyxin F (**32**)	In 2001, Kadota and co-workers isolated epicalyxin F (**32**) from an EtOH extract of the seeds of *Alpinia blepharocalyx.* It also shows significant cytotoxicity against both the cell lines of murine colon 26-L5 carcinoma and human HT-1080 fibrosarcoma cells.[11]

6.	 Diospongin A (**33**), Ph = α Diospongin B (**34**), Ph = β	In 2004, Kadota and coworkers isolated Diospongins A (**33**) and B (**34**) from rhizomes of *Dioscorea spongiosa.* Diospongin A shows significant activity against NO production (anti-inflammatory) and Diospongin B shows inhibitory activity against bone resorption.[12]
7.	 Hedycoropyran A (**35**) H = β Hedycoropyran B (**36**) H = α	In 2015, Lee and co-workers isolated hedycoropyran A (**35**) and B (**36**) from an *n*-BuOH-soluble fraction of the rhizome of *Hedychium coronarium*. The biological activity of these compounds has not yet been evaluated due to less abundance.[13]

Inspired by the interesting biological profile and structural features of these diarylheptanoid natural products, and the lowest natural abundance of hedycoropyrans (**35**, **36**), and our continues interest in the THP containing stereoselective total synthesis biologically potent natural products, we aimed to develop concise chemical synthetic routes for two THP-diarylheptanoid natural products (–)-hedycoropyran A and B. Introduction, earlier synthetic approaches documented in the literature toward the total synthesis of hedycoropyran A and B are discussed in subsequent sections of this chapter.

1.1.1 Isolation and biological activity of (–)-hedycoropyran A and B:

(–)-Hedycoropyran A and B are two novel compounds possessing a unusual diarylheptanoid with a *trans*- and a *cis*-2-aryl-6-alkyl-THP core respectively. In 2015, Lee and co-workers isolated two new DAHs, hedycoropyrans A (**35**) and B (**36**), along with other hedycorofurans and several cytotoxic labdane-type diterpenoids from the rhizome of *Hedychium coronarium* in *n*-BuOH soluble fraction. The biological activity of these compounds is not yet evaluated due to the very less abundance in

nature which is 1.0 mg of hedycoropyarn A and 0.4 mg of hedycoropyran B respectively from 14.5 kg powdered dry rhizomes (Figure 1.6).[13]

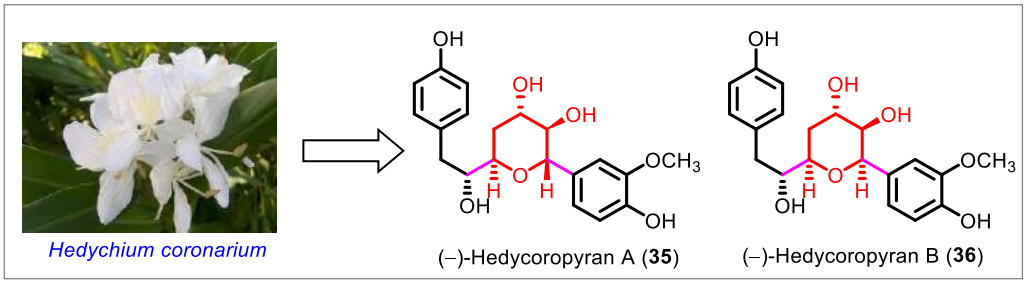


Figure1.6 | Structures of (–)-hedycoropyran A & B.

Hedycoropyran A (**35**) and B (**36**) were obtained as a solid (amorphous) having specific optical rotation $[\alpha]_D^{22}$ −86 (*c* 0.04, MeOH) and −100 (*c* 0.02, MeOH) respectively. The (–)-hedycoropyran A (**35**) and B (**36**) have molecular formula $C_{20}H_{24}O_7$, which displays seven degrees of unsaturation as determined from HRESIMS analysis, which displays the ion peak at 375.1445 $[M-H]^-$ for compound **35**, for which calcd formula is $C_{20}H_{23}O_7$ and molecular mass is 375.1449 and HRESIMS *m/z* 375.1442 $[M-H]^-$ for compound **36**, for which calcd formula for $C_{20}H_{23}O_7$ and mass is 375.1449 respectively. The proton NMR spectrum of **35** displayed seven protons, δ 7.06, and 6.69 *J* = 8.5 Hz (AA'XX' pattern) and δ 7.02 (d, *J* = 1.8 Hz) (ABX pattern) δ 6.89 (dd, *J* = 8.2, 1.8 Hz) and 6.76 (d, *J* = 8.2 Hz), which indicated the existence of a 1,4-di and 1,3,4-trisubstituted aromatic ring. One -OCH_3 group at δ 3.86, five (-OCH) protons at δ 4.48, (d, *J* = 9.2 Hz), 4.04, (ddd, *J* = 7.8, 6.6, 4.9 Hz), 3.98, (ddd, *J* = 10.9, 8.3, 5.1 Hz), 3.77, (ddd, *J* = 6.6, 6.5, 2.0 Hz) and 3.38, (dd, *J* = 9.2, 8.3 Hz) and two (-CH_2) groups at δ 2.82, (dd, *J* = 13.9, 4.9 Hz), 2.16, (ddd, *J* = 13.6, 5.1, 2.0 Hz) and 1.85, (ddd, *J* = 13.6, 10.9, 6.5 Hz). The carbon NMR spectrum displayed seven aromatic carbon at δ 116.0 and 131.5 ppm for 1,4-disubstituted phenyl group and δ 115.7, 122.1, and 112.6 ppm for 1,3,4-trisubstituted phenyl group and five quaternary aromatic carbon at δ 156.8, 148.7, 147.3, 133.0 and 130.9. One methoxy (-OCH_3) carbon at δ 56.4, five oxymethine carbon (-CH) at δ 78.6, 73.9, 70.7, 76.5, and 77.9. The two methylene carbon (-CH_2) at δ 35.2 and 40.6 ppm. The corresponding stereochemistry of **35** was assigned using 2D-NMR analysis. The (*S*) absolute stereochemistry of **35** was assigned by electronic circular dichroism analysis (ECD).

It exhibited a positive Cotton effect at 230 nm, opposite to adrenaline and niacicoside, allowing the assignment of **35** (2S) configurations.

Hedycoropyran B (**36**): The NMR spectral data is extremely similar to hedycoropyran A. The relative stereochemistry of hedycoropyran A and B (**35** and **36**) was tentatively established based on 2D NMR analysis and the (*R*) absolute stereochemistry was assigned by electronic circular dichroism analysis (ECD) which exhibited a negative Cotton effect at 230 nm, this is the exact opposite of **35**, thus allowing the assignment of **36** (2R) configurations.[13]

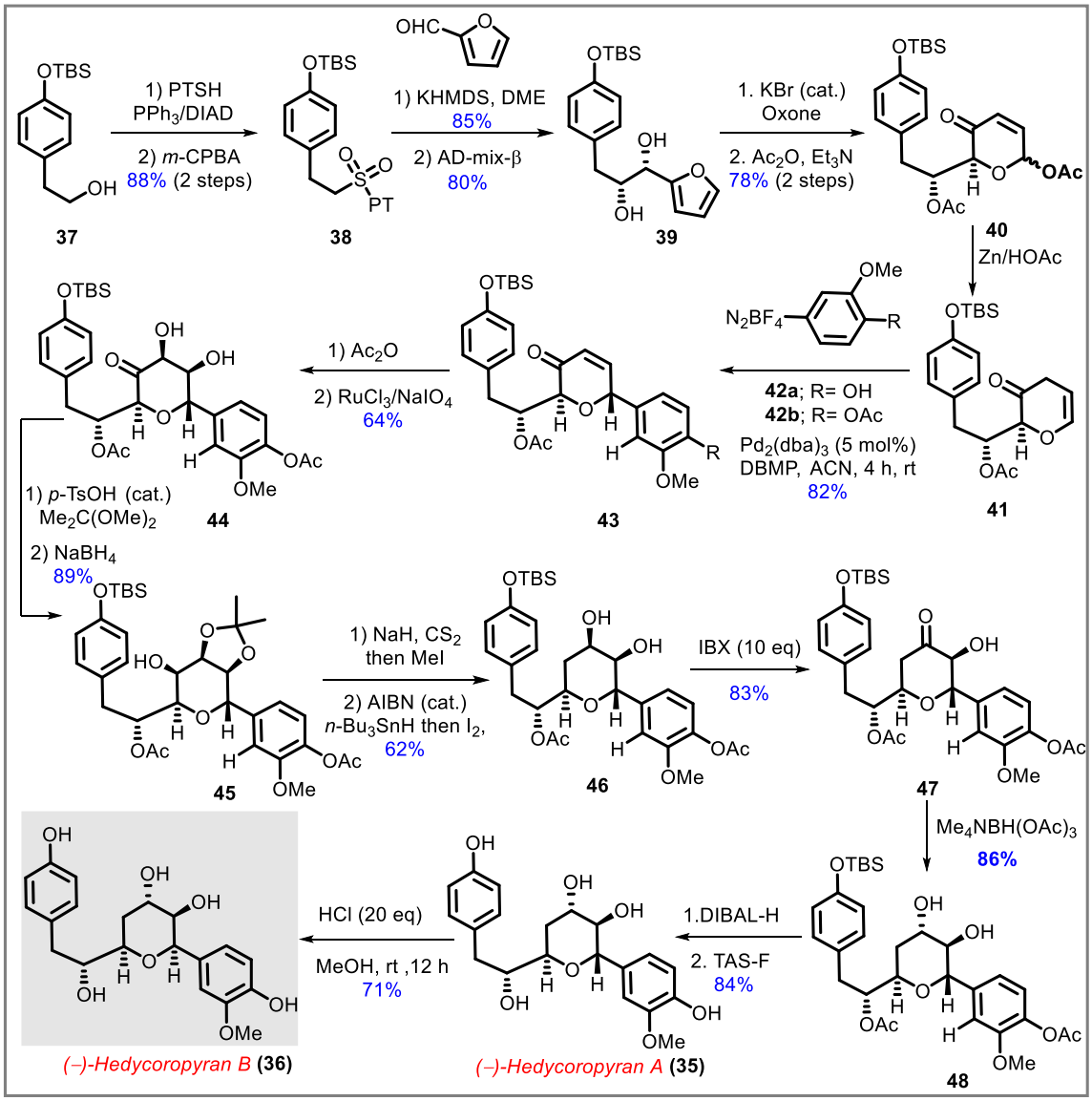
Bioactivity: Due to very less natural abundance that is (1 mg for **35** and 0.4 mg for **36** from powdered dried rhizomes (14.2 Kg), the biological activity of these compounds has not been evaluated yet.

1.1.2 Previous approaches

1.1.2.1 First total synthesis by Tong and co-workers (2017)[14]

The first asymmetric total synthesis is done by Tong *et al*. after immediate isolation of hedycoropyran A (**35**) and B (**36**) with 5.4% and 3.9 % overall yield in a total of 18 and 19 steps respectively. They employed their in-house-developed Achmatowicz rearrangement as a key transformation for the construction of pyran intermediate **40** using KBr and oxone from furyl alcohol **39** which was prepared from commercially available tyrosol in 5 steps. Next Zn-catalysed reductive deoxygenation followed by coupling reactions (Heck–Matsuda) were used to construct an unusual and thermodynamically disfavored 2,6-trans THP (**43**) moiety using $Pd_2(dba)_3$ and 2,6-tert-butyl-4-methyl-pyridine (DBMP). Then acylation followed by dihydroxylation using $RuCl_3/NaIO_4$ delivered the required *cis*-diol intermediate **44**. Next compound 45 was obtained through a two step reaction process which involve acetonide protection followed ketone reduction by $NaBH_4$, and subsequent Barton–McCombie deoxygenation conditions gave diol **46** by removal of carbonyl group and acetonoid protection. IBX oxidation followed by Evans–Saksena reaction delivered the inverted chiral center at C4 position and gave 3,4-anti diol **48**. Finally the deprotection of acetyl group of **48** using DIBAL-H reduction followed be TBS deprotection sing TAS-F furnished hedycoropyran A (**35**) in 84% yield as a single

isomer, and subsequenr C2 epimerization of **35** using HCl in methanol delivered another natural product hedycoropyran B (**36**) in 71% yield (Scheme 1.1).[14]



Scheme 1.1 | Total synthesis of hedycoropyran A and B by Rongbiao Tong.

1.1.3 Isolation and biological activity of (+)-Rhoiptelol B:

The first isolation of (+)-Rhoiptelol B (**29**) along with two other diarylheptanoids was done by Kouno and coworkers in 1996 from the fruits and leaves of *Rhoiptelea chiliantha* and then from *Alnus hirsuta's* bark in 2007 (Formerly used in traditional medicine in Korea and China as an anti-inflammatory agent) by Bae and co-workers. It examined for the inhibitory actions against TNF-α production, NO, HIF-1 in AGS cells and LPS induced NF-KB activation. The structural features

involved 1,4-di and 1,3,4-trisubstituted aryl ring along with a chiral hydroxy group on THP ring and another hydroxyl group adjacent carbon to the THP ring (Figure 1.7).

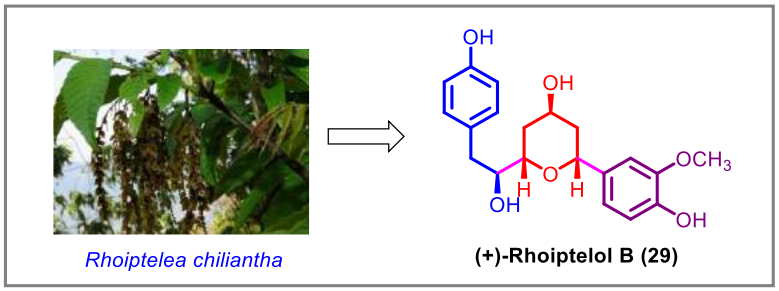


Figure1.7 | Structures of (+)-rhoiptelol B (**29**)

(+)-Rhoiptelol B (**29**) was obtained as an amorphous powder having $[\alpha]_D^{12}$ +97 (*c* = 0.3, MeOH). It has molecular formula $C_{20}H_{24}O_6$. It showed positive FAB-MS *m/z* calcd for $C_{20}H_{24}O_6Na$ $[M + Na]^+$, 383 and $[M]^+$ 360. The (+)-rhoiptelol B (**29**) structure was determined by 1D and 2D NMR spectroscopy. The whole proton-carbon connectivity of the molecule was established with the help of ^1H NMR, ^{13}C NMR, and HSQC techniques. The proton spectrum of **29** displyed seven protons at δ 6.69, (d, *J* = 8) and 7.03, (d, *J* = 8 Hz) (AA′XX′ pattern) and δ 6.77 (d, *J* = 8 Hz), δ 6.84 (dd, *J* = 2, 8 Hz), 7.04 (br, s) (ABX pattern) which indicated the existence of a 1,4-di- and a 1,3,4-trisubstituted phenyl group. One methoxy group showed at δ 3.87 and methoxy group position was estabilished through NOESY correlation to be at C-3' of the trisubstituted benzene ring. The two phenolic groups and two alcoholic hydroxy groups presence were determined through acetylation with Ac_2O in pyridine and methylation with diazomethane of **29** which gave **29a** and **29b**, respectively. Four oxymethine protons at δ 4.69, (dd, *J* = 3, 11 Hz), 4.27, (t, *J* = 3 Hz), 3.82, (dt, *J* = 13, 3 Hz) and 3.60, (dt, *J* = 3, 7 Hz) and three methylene group ($-CH_2$) at δ 1.75, (ddd, *J* = 3, 11, 12 Hz, *ax*), 1.84, (dd, *J* = 3, 12 Hz, *eq*), 1.57, (dd, *J* = 2, 13 Hz, *eq*), 1.89, (dt, *J* = 3, 13 Hz, *ax*) and 2.70, (dd, *J* = 7, 13 Hz), 2.89, (dd, *J* = 7, 13 Hz). The carbon NMR spectrum showed seven carbon (-CH) at δ 116.0 and 131.4 ppm for 1,4-disubstituted phenyl group and δ 115.8, 119.8, and 111.1 ppm for 1,3,4-trisubstituted phenyl group and five quaternary aromatic carbon at δ 136.1, 148.8, 146.7, 131.1 and 156.6. One methoxy ($-OCH_3$) carbon at δ 56.4, four oxymethine carbon (-CH) at δ 75.2, 65.6, 74.3, and 76.3. The three methylene carbon ($-CH_2$) at δ 41.3, 34.9 and 39.7ppm. The

absolute configurations of **29** was determined using modified Mosher's method to **29b** (Figure 1.4). According to this both C4 and C7 determined to be *S*, and hence C2 and C6 are *R* and *S* compatibly. So the combined data revealed the structure of rhoiptelol B (**29**) (Figure 1.8)[9]

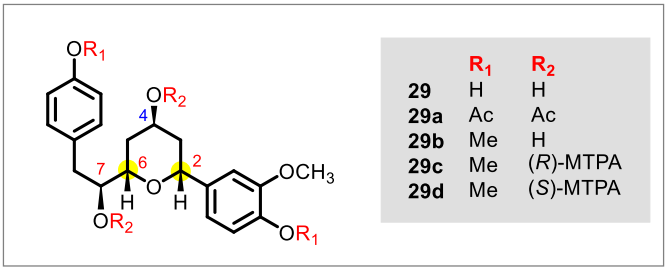
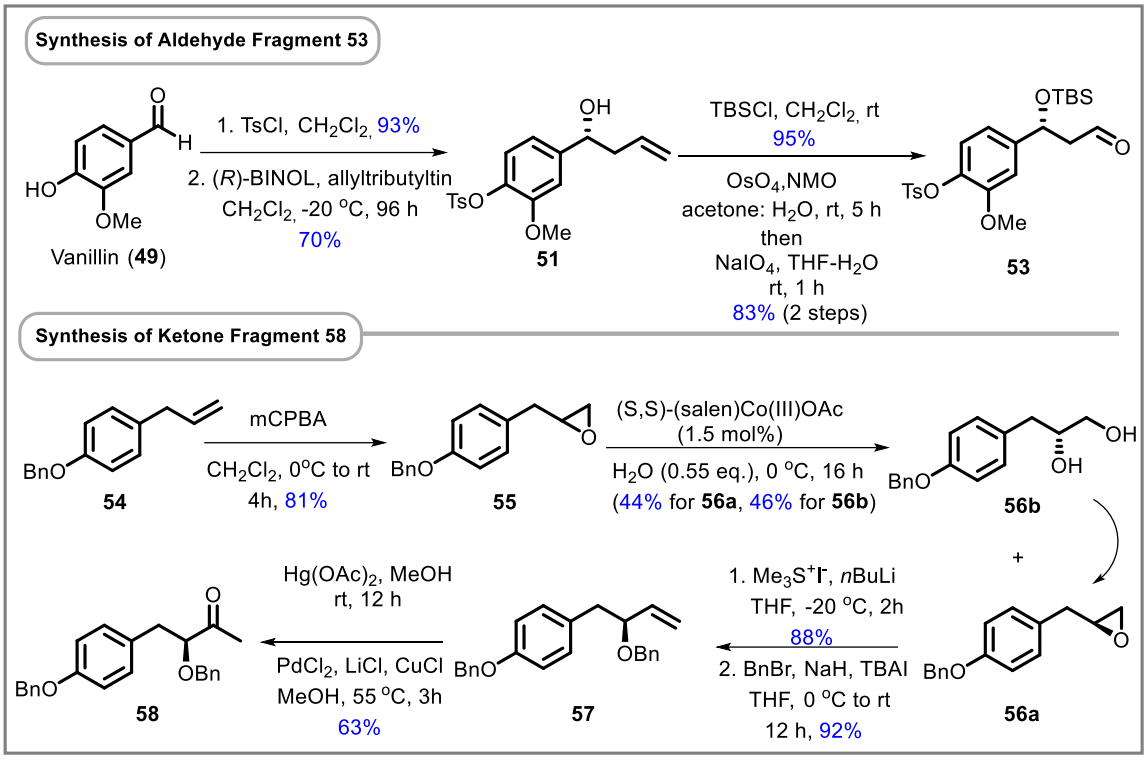


Figure1.8 | Structures of (+)-rhoiptelol B (**29**), acyl **29a**, methyl **29b** and its MTPA ester **29c** and **29d**.

1.1.4 Previous approaches

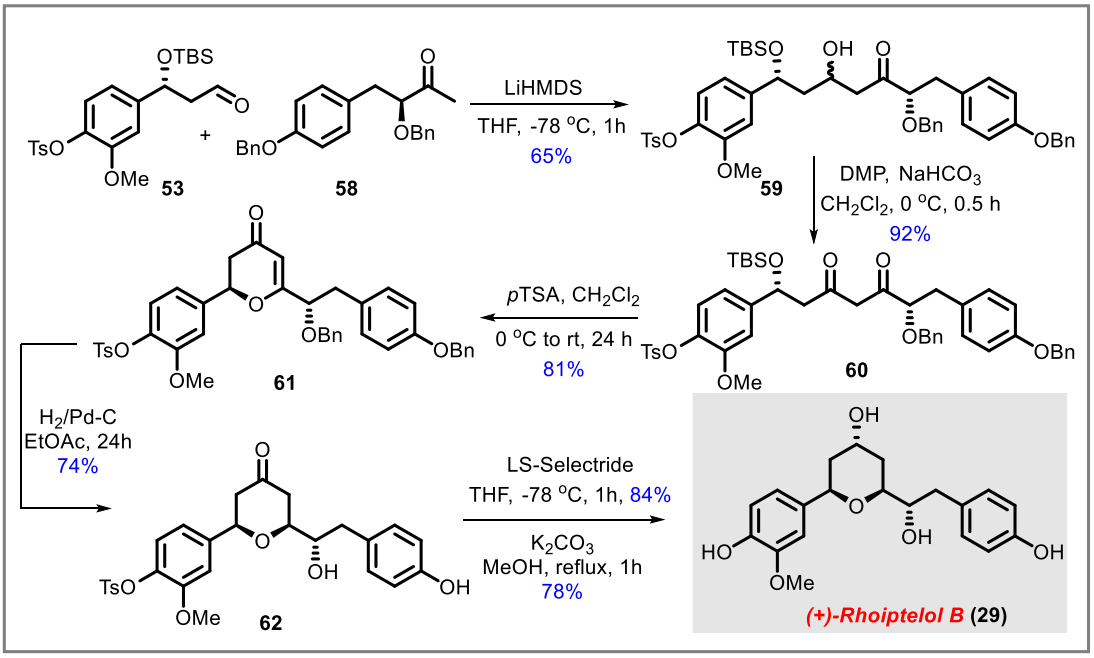
1.1.4.1 First asymmetric total synthesis by Raji Reddy's group (2010)[15]

The first asymmetric total synthesis of rhoiptelol B (**29**) was reported by Raji Reddy *et al.* in 2010 in a total of 15 steps using simple building blocks vanillin (**49**) and benzyl chavicol (**54**) using various key transformation. Their synthetic strategy started with tosyl protection followed by asymmetric Keck allylation of vanillin (**49**) using allyltributyltin and (*R*)-BINOL to get the chiral allylic alcohol **51**. Then TBS protection of alcohol **51** followed by oxidative cleavage of the olefinic bond using OsO_4 and $NaIO_4$ delivered the required key fragment aldehyde **53** in 83% yield. Next, the synthesis of ketone fragment **58** began with epoxidation of benzyl chavicol **54** using *m*-CPBA followed by chiral resolution using the Jacobson method gave chiral epoxide **56a** along with diol **56b** which can again be converted into **56a** using the known procedure. Then the reaction of chiral epoxide **56a** with trimethyl sulfonium iodide in presence of *n*-BuLi delivered the allyl alcohol which was further protected as its benzyl ether using NaH and BnBr to get **57**. Then allyl benzyl ether **57** was used for Wacker oxidation to get the required product **58** in 63% yield (Scheme 1.2).



Scheme 1.2 | Synthesis of key aldehyde **53** and ketone **58** fragments.

After the successful synthesis of both key fragments, both fragments were coupled by aldol reaction using LiHMDS at –78 °C to get the corresponding aldol **59**. Dess-Martin periodinane oxidation of 59 gave the 1,3-diketone intermediate **60** in 92% yield. Next, *p*-TSA mediated cyclisation of hydroxy diketone gave dihydropyranone intermediate **61** via TBS-deprotection followed by cyclisation and dehydration cascade. Olefin reduction of pyranone **61** followed by debenzylation uisng hydrogenation delivered tetrahydropyranone **62** in 74% yield. Next, selective reduction of tetrahydropyranone **62** using *LS*-selectride followed by detosylation using K_2CO_3 in MeOH delivered the desired natural product (+)-rhoiptelol B (**29**) in 78% yield. They found that ^1H, ^{13}C, HRMS and optical rotation of **29** {$[\alpha]_D^{28}$ = +77.2 (c = 0.2, MeOH) } was comparable to the reported data (Scheme 1.3),



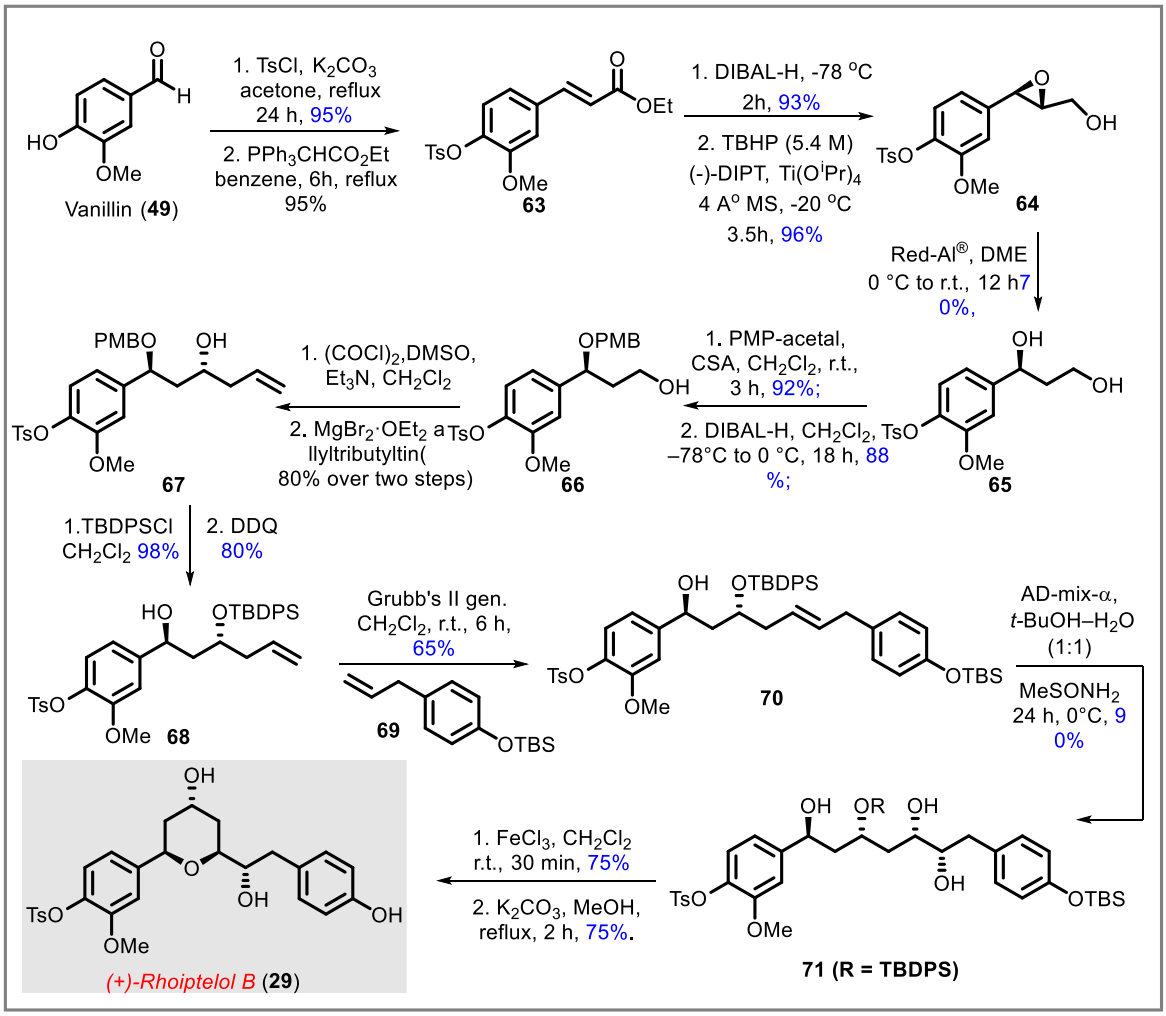
Scheme 1.3| First total synthesis of (+)-rhoiptelol B by Raji Reddy's group.

1.1.4.2 Second total synthesis by J. S. Yadav's group (2010)[16]

In 2010, J. S. Yadav and co-workers reported the second total synthesis of rhoiptelol B (**29**) in a total of 14 steps.[16] The synthesis started with tosylation followed by witting olefination of vanillin (**49**) to get olefin **63**, which was subjected to DIBAL-H reduction to reduced ester followed by Sharpless asymmetric epoxidation condition using (–)-DIPT, TBHP and $Ti(O^iPr)_4$ to deliver the chiral epoxide **64** in 96% yield. Next, the reductive ring opening of **64** by Red-Al gave the desired 1,3-diol **65**, which was protected as its benzylidene acetal using PMP-acetal and CSA, then subjected to the regioselective opening of the acetal using DIBAL-H at -78 °C to 0 °C to obtain the alcohol **66** which was oxidised using Swern oxidation followed by $MgBr_2.OEt_2$ mediated chelation-controlled addition of allyltributyltin delivered the *trans*-allylic alcohol **67** majorly with a 9:1 diastereomeric ratio. This product **67** was protected as its TBDPS ether and subjected to PMB-deprotection with DDQ to deliver the required alcohol **68** in 80% yield cross-metathesis

The cross-metathesis between alkenes **68** and **69** in presence of Grubb's second-generation catalyst gave the *E-Z* mixture of **70** with a 6:1 ratio. Next, Sharpless asymmetric dihydroxylation with AD-mix α in a 1:1 ratio of *tert*-butanol

and H_2O gave dihydroxylated product **71**, which was further cyclized to form pyran ring with concomitant deprotection of TBS and TBDPS group to give **71** under $FeCl_3$ catalysis. Finally deprotection of tosyl group of **71** using K_2CO_3, MeOH in reflux conditions gave the desired natural product rhoiptelol B (**29**) in 75% yield. (Scheme 1.4)

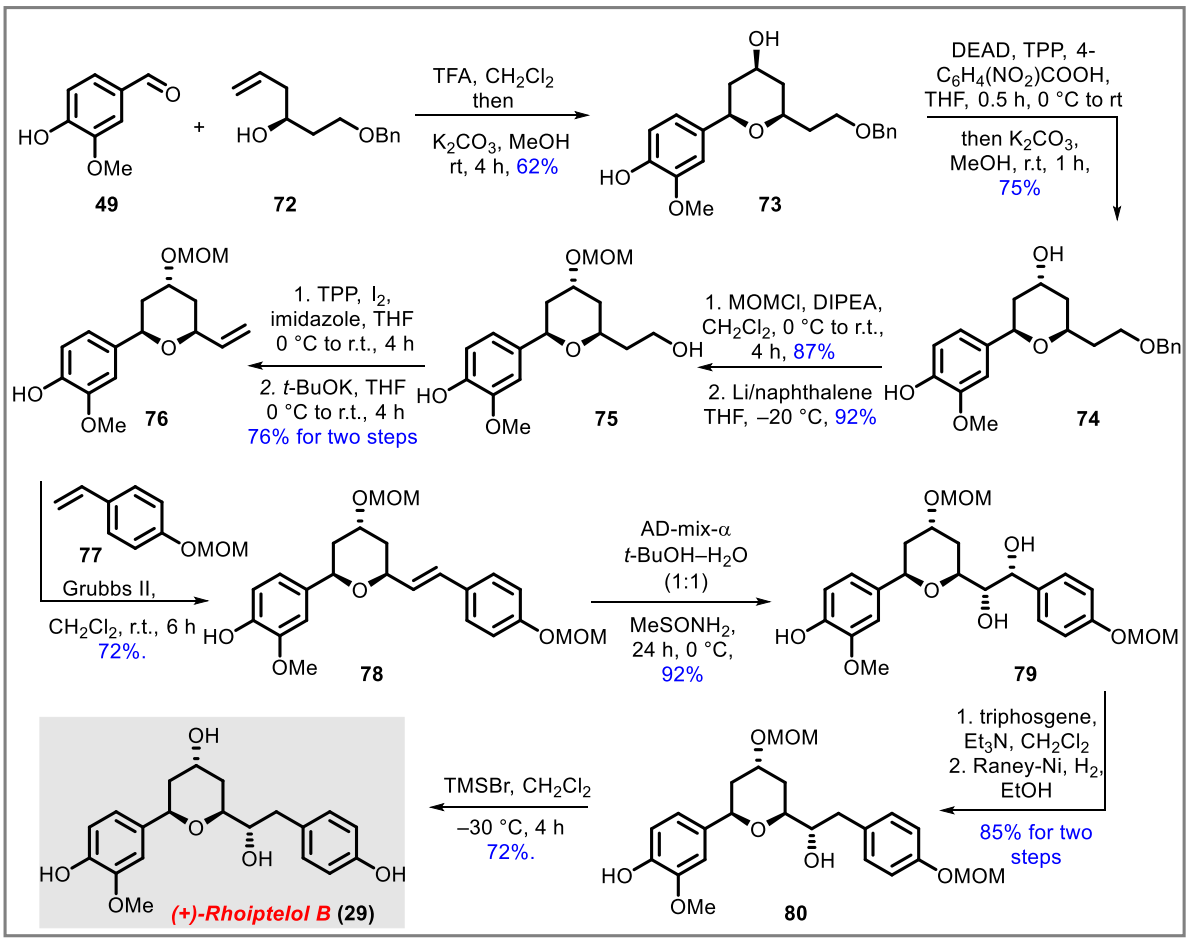


Scheme 1.4 | Second total synthesis of (+)-rhoiptelol B by J. S. Yadav's group

1.1.4.3 Third total synthesis of rhoiptelol B via Prins cyclization by J. S. Yadav's group (2014)[17]

In 2014, another stereoselective total synthesis of rhoiptelol B (**29**) was reported by J. S. Yadav and co-workers using Prins cyclization as key step. The synthesis began with TFA-mediated Prins cyclization between vanillin (**49**) and homoallylic alcohol **72** followed by treatment with K_2CO_3, MOH to deliver the

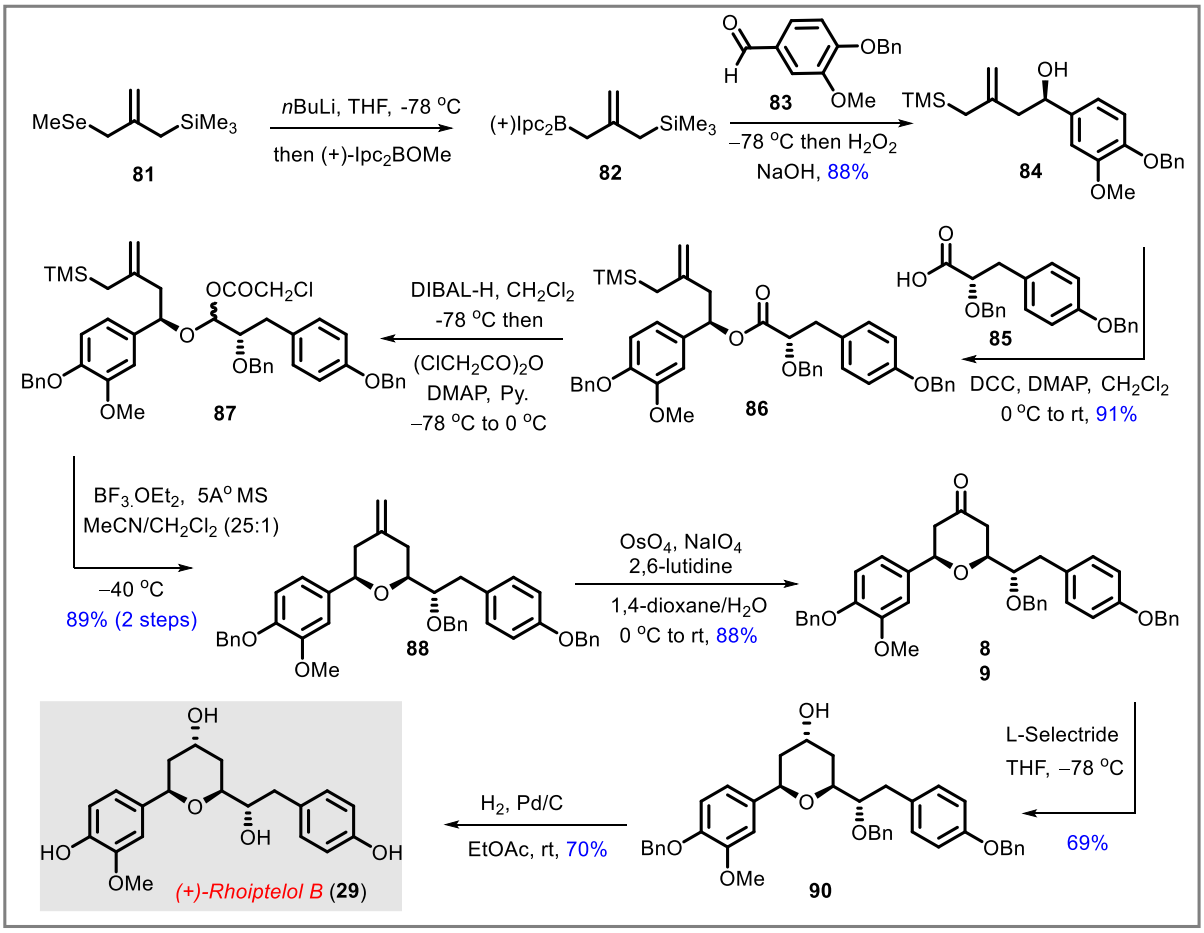
pyranonol **73**. The secondary hydroxyl group's stereochemistry in the pyran ring was inverted using the Mitsunobu conditions to get pyranol **74** in 75% yield. Next, then MOM protection of hydroxyl group of **74** using MOMCl and subsequent benzyl deprotection using Li/naphthalene gave alcohol **75**. The primary alcohol was knocked out using iodination followed by treatment with *tert*-butoxide delivered alkene **76**. Cross-metathesis between alkene **76** and **77** in presence of Grubb's II generation catalyst delivered alkene **78** in 72% yield. Next, Asymmetric Sharpless dihydroxylation of **78** by using AD-mix-α gave the diol **79**, followed by cyclic carbonate protection using triphosgene and then subjected to hydrogenolysis with Raney- Ni to get alcohol **80**. Finally, MOM-deprotection by TMSBr delivered (+)-rhoiptelol B (**29**).(Scheme 1.5).[17]



Scheme 1.5 | Stereoselective total synthesis of (+)-rhoiptelol B by J. S. Yadav's group.

1.1.4.4 Fourth total synthesis of rhoiptelol B by Kadota's group (2018)[18]

The fourth total synthesis of (+)-rhoiptelol B (**29**) was reported by Kadota and co-workers in 2018 via intramolecular allylation of α-acetoxy ether as a key strategy.



Scheme 1.6 | Stereoselective total synthesis of (+)-rhoiptelol B by Kadota's group.

The synthesis began with the construction of allyl borane **82** by known allyl selenide **81** with *n*-BuLi followed by treatment with (+)-Ipc2BOMe providing the chiral allyl borane **82** which was used for the reaction with benzyl-protected vanillin **83** to deliver alcohol **84** in 88% yield. Esterification of alcohol **84** with acid **85** in the presence of DCC, DMAP gave ester **86** in 91% yield. Then partial reduction of **86** with DIBAL-H followed by treatment with chloroacetic anhydride gave α-acetoxy ether **87**. $BF_3.OEt_2$-mediated cyclization of α-acetoxy ether **87** delivers the *exo*-methylene THP intermediate **88** as a single stereoisomer. then, the oxidative cleavage of *exo*-olefin **88** gave the pyranone **89** in 88% yield by using OsO_4, 2,6-lutidne and $NaIO_4$. Stereoselective reduction of pyranone **89** with L-Selectride provided pyranol **90**

(69%) and its stereoisomer (19%). Finally, the deprotection of the benzyl group of **90** using Pd/C catalyzed hydrogenation reaction delivered the desired natural product rhoiptelol B (**29**) in 70% yield (Scheme 1.6).[18]

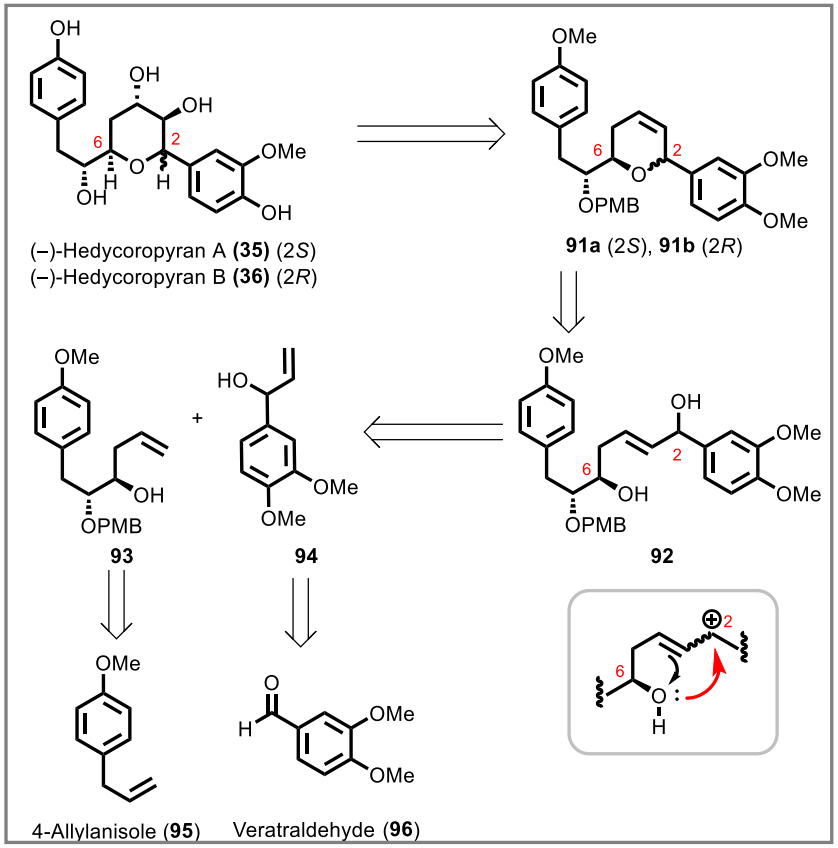
Chapter-1, Section-B: Present work

1.2. Result and Discussions

The First Approach:

1.2.1 Retrosynthetic analysis

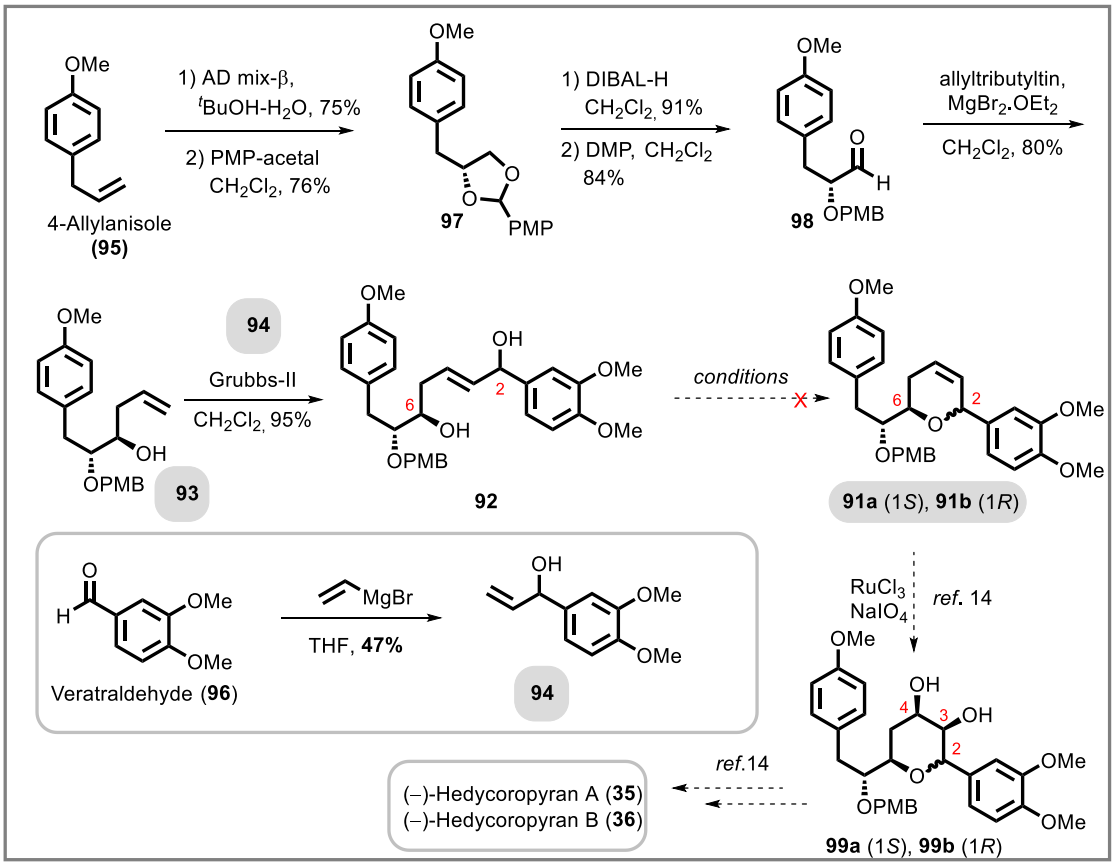
In the initial retrosynthetic analysis, as described in Scheme 2, we envisioned a unified route for the synthesis of hedycoropyrans A (**35**) and B (**36**) by a suitably functionalized dihydroxy alkene intermediate **92** (containing allylic and homoallylic alcohol functionalities) via allylic carbocation-mediated ring-closure that would deliver advanced 2,6-*trans*/2,6-*cis* dihydropyran intermediate **91**a/**91**b. This key intermediate **92** could be obtained through cross-metathesis reaction of homoallylic alcohol **93** and allylic alcohol **94**. Alkenols **93** and **94** would be synthesized from commercially available and cost-effective building blocks 4-allylanisole (estragole, **95**) and veratraldehyde (**96**) employing interesting synthetic manipulations (Scheme 1.7).



Scheme 1.7. Initial retrosynthetic analysis of hedycoropyrans A (**35**) and B (**36**).

1.2.2 Synthesis of of hedycoropyrans A (35) and B (36) via allylic carbocation-mediated ring-closure.

Our efforts began to access the key DAH-derived dihydroxy alkene intermediate **92** starting from building blocks **95** and **96**. 4-Allylanisole (estragole, **95**) was subjected to Sharpless asymmetric dihydroxylation[19] using AD mix-β/$MeSO_2NH_2$ to obtain the corresponding 1,2-diol, which was subsequently protected as its *p*-methoxy benzylidene acetal **97**.[20] The regioselective reductive opening[21] of the 1,2-acetal **97** using DIBAL-H followed by Dess-Martin periodinane oxidation[22] delivered aldehyde **98**. Substrate-controlled addition of allyltributyltin onto aldehyde **98** in the presence of $MgBr_2.OEt_2$ delivered requisite homoallylic alcohol **93** as only a diastereomer.[23] Then, cross-metathesis reaction[24] of **93** and **94** (prepared from vinylation of veratraldehyde 10)[25] using Grubbs 2nd generation catalyst furnished the desired DAH-derived dihydroxy alkene intermediate **92** (exclusively *trans*-olefin) in excellent yield of 95%.



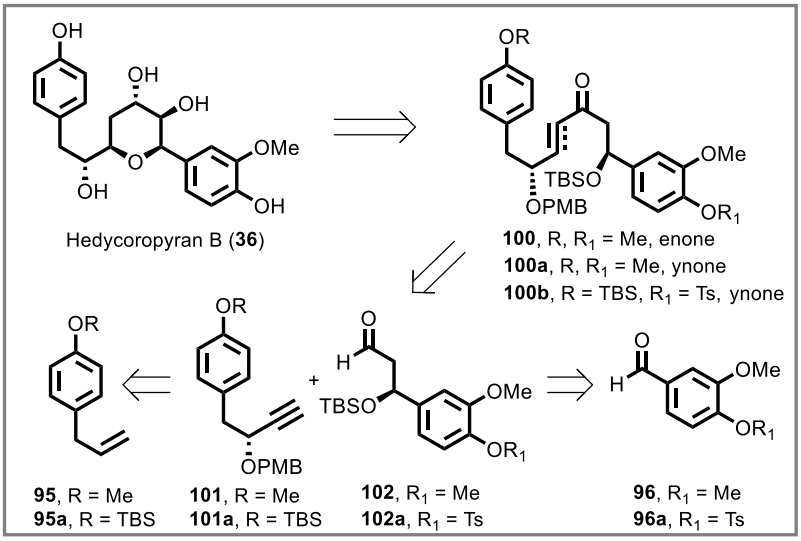
Scheme 1.8. Efforts toward the synthesis of hedycoropyrans A (**35**) and B (**36**) via allylic carbocation-mediated ring-closure.

Next, the crucial allylic carbocation induced ring-closure reaction of alkene-diol **92** was attempted using well-established reaction conditions of $BF_3.OEt_2/CH_2Cl_2$[24], $PdCl_2(PPh_3)_2/CH_2Cl_2$[24] and $Pd(CH_3CN)_2Cl_2/CH_2Cl_2$[24] at low to ambient (-78 ^oC to rt) temperatures, which proved to be unsuccessful, and starting material **92** was decomposed in all cases. If this proposed transformation to access **91a/91b** from **92** worked well, our next sequence of reactions (as reported by Li and Tong)[14] as described via diols **99a/99b**, would have led to the total synthesis of hedycoropyrans A (**35**) and B (**36**) (Scheme 1.8).

The Second Approach:

1.2.3 Retrosynthetic analysis

Since this initially designed strategy was unsuccessful, we were required to seek a distinct approach to access natural products **35** and/or **36**, and we considered a new retrosynthetic analysis based on the intramolecular oxa-Michael reaction that provides access to the THP ring system with desired stereochemistry as depicted in Scheme 1.9. Thus, we envisioned the construction of hedycoropyrans B (**36**) via intramolecular oxa-Michael induced ring closure of suitably constructed enone **100** or ynone **100a/100b** intermediates with varying O-substituents. In this context, we

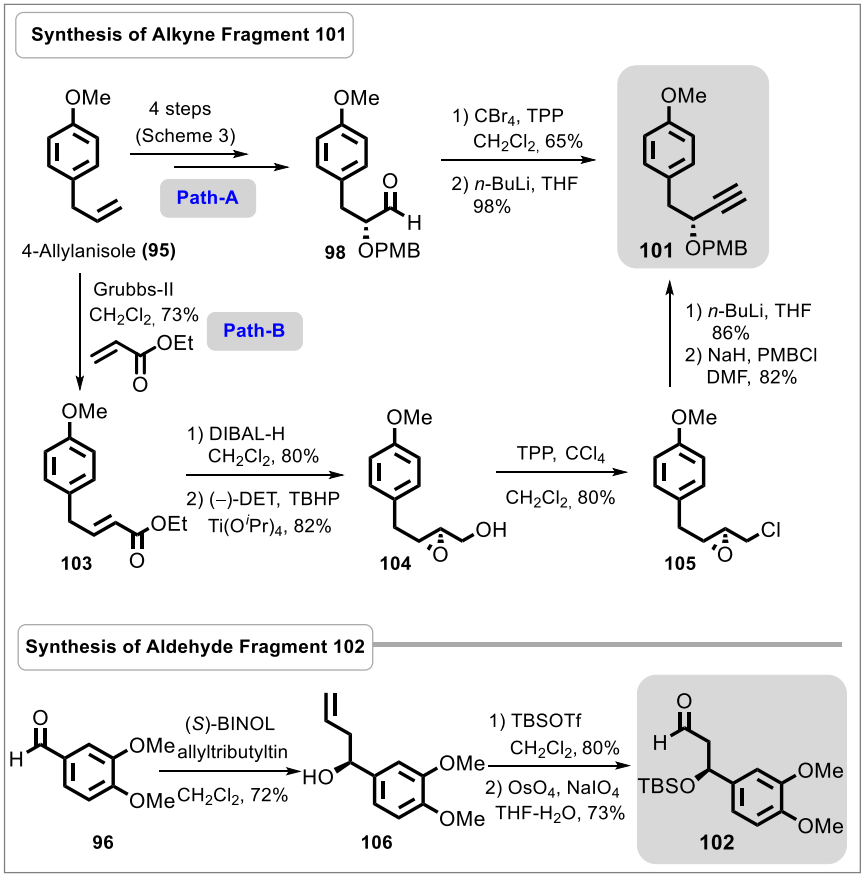


Scheme 1.9. New retrosynthetic analysis of hedycoropyran B (**36**) based on the oxa-Michael reaction of hydroxy-enone or hydroxy-ynone.

anticipated a convergent approach comprising Li-acetylide (generated from **101/101a**) addition onto the chiral-aldehydes **102/102a** followed by oxidation to access the enone/ynones intermediates (**100/100a**, **100b**). Intermediates **101/101a** and **102/102a** could be obtained from commercially available 4-allylanisole (**95**) and veratraldehyde (**96**) or their congeners (**95a** and vanillin **49**) respectively (Scheme 1.9).

1.2.4 Synthesis of alkyne fragment 101 and aldehyde fragment 102

Hence, this alternate route began with the synthesis of alkyne intermediate **101** from 4-allylanisole (**95**) in two distinct pathways. In the first route, aldehyde **98** (prepared from **95** in Scheme 3) was subjected to Corey-Fuchs olefination[26] and subsequently treated with *n*-BuLi[26] to afford the desired alkyne fragment **101** (Path A, Scheme 1.10). Further, an alternate route for **101** was also evaluated via epoxy alcohol **104**. Thus, allylanisole **95** was converted into α,β-unsaturated ester **103** employing cross-metathesis reaction,[24] which was then reduced using DIBAL-H to aff-



Scheme 1.10. Synthesis of alkyne fragment **101** and aldehyde fragment **102**.

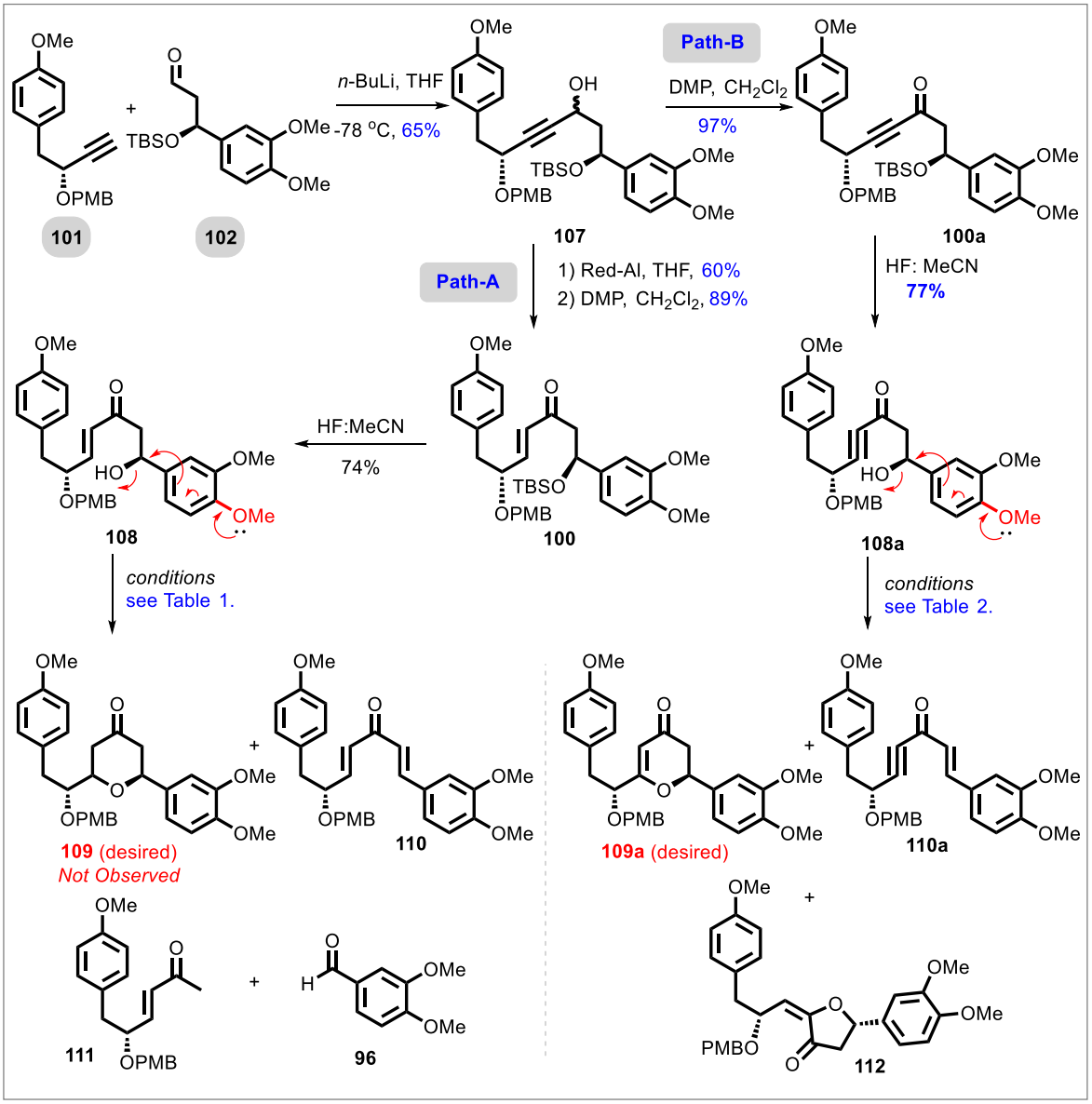
ord allylic alcohol and subsequently converted into chiral epoxy alcohol **104** under Sharpless conditions.[27] Next, epoxy alcohol **104** was transformed into chloride **105** using TPP, CCl_4.[28] It was subjected to base-mediated (*n*-BuLi) rearrangement reaction to obtain propargylic alcohol, which was subsequently protected as its PMB ether to get the desired alkyne fragment **101** (Path B, Scheme 1.10).[29]

After establishing a reliable synthetic route for **101**, we synthesized aldehyde coupling partner **102** from veratraldehyde **96**. Asymmetric Keck allylation of **96** to give allyl alcohol **106** by using $Ti(O^iPr)_4$, (*S*)-BINOL, allyltributyltin,[30] followed by TBS protection[31] and dihydroxylative cleavage (OsO_4, NMO then $NaIO_4$)[32] steps cleanly delivered aldehyde **102** (Scheme 1.10).

Having synthesized alkyne **101** and aldehyde **102** fragments on a gram-scale, the stage was set for the coupling and to verify our hypothesis of intra-molecular oxa-Michael reaction. Initially, we wanted to evaluate the oxa-Michael reaction using enone **100** as a substrate (Path-A, Scheme 1.11). Thus, alkyne **101** and aldehyde **102** were coupled using *n*-BuLi in THF to obtain propargylic alcohol **107**.[33] Next, partial reduction of alkyne **107** using Red-Al[34] followed by Dess-Martin periodinane oxidation,[22] cleanly delivered enone **100** in a good yield. TBS deprotection[35] of **100** using HF in CH_3CN gave hydroxy-alkyl tethered enone **108** in 74% yield. Next, the crucial oxa-Michael reaction of the hydroxy-enone **108** to give pyranone **109** proved to be insurmountable, under base (KO^tBu,[36a] NaH,[36b,c] DBU[36d]), acid (Amberlyst-15)[36e,f] and Pd(II) catalyzed[36g,h] reaction conditions, leading to either the corresponding dehydrated product **110** or retro-aldol products **96** and **111** (Path A, Scheme 1.11; Table 1).

Hence, we slightly altered the strategy by replacing enone **100** with the corresponding ynone **100a** as oxa-Michael addition precursor to verify reactivity patterns as shown in Path B of Scheme 1.11. Therefore, ynone **100a** was prepared from **107** through Dess-Martin periodinane oxidation,[22] HF-CH_3CN-mediated TBS deprotection[35] steps, and evaluated for the intramolecular oxa-Michael reaction using well-reported procedures (Table 2). Initial conditions of using $Pd(CH_3CN)_2Cl_2$-mediated cyclization[37a] led to the decomposition of starting material. Cyclization using NaH[37b] and/or mild Lewis acid (AgOTf, catalytic)[37c] resulted in undesired dehydrated product **110a**. Whereas, AuCl-catalyzed cyclization[38] was found to be

non-selective towards this oxa-Michael by providing an inseparable mixture (1:1 ratio) of desired pyranone **23a** (through the 6-*exo*-dig mode of cyclization) and furanone **26** (Path-B, Scheme 1.11) through the 5-*endo*-dig mode of cyclization. These unfruitful results (except AuCl reaction of entry 4, Table 2) reveal the sensitivity of the benzylic hydroxyl group (of **108** and **108a**) toward basic or acidic conditions, which could be due to the stabilization of benzylic carbocation through the mesomeric effect of the *p*-OMe group of phenyl ring (Path A and Path B, Scheme 1.11).



Scheme 1.11. Efforts toward the synthesis of hedycoropyrans B (**36**) via oxa-Michael reaction of hydroxy-enone/hydroxy-ynone

Suspecting the role of *p*-OMe group (of **108** and **108a**, Scheme 1.11) in failure of above intramolecular oxa-Michael reactions and the literature precedence of successful survival of similar benzylic hydroxyl groups in presence of *p*-OAc and *p*-

Table 1. Efforts toward the synthesis of pyranone **109**.

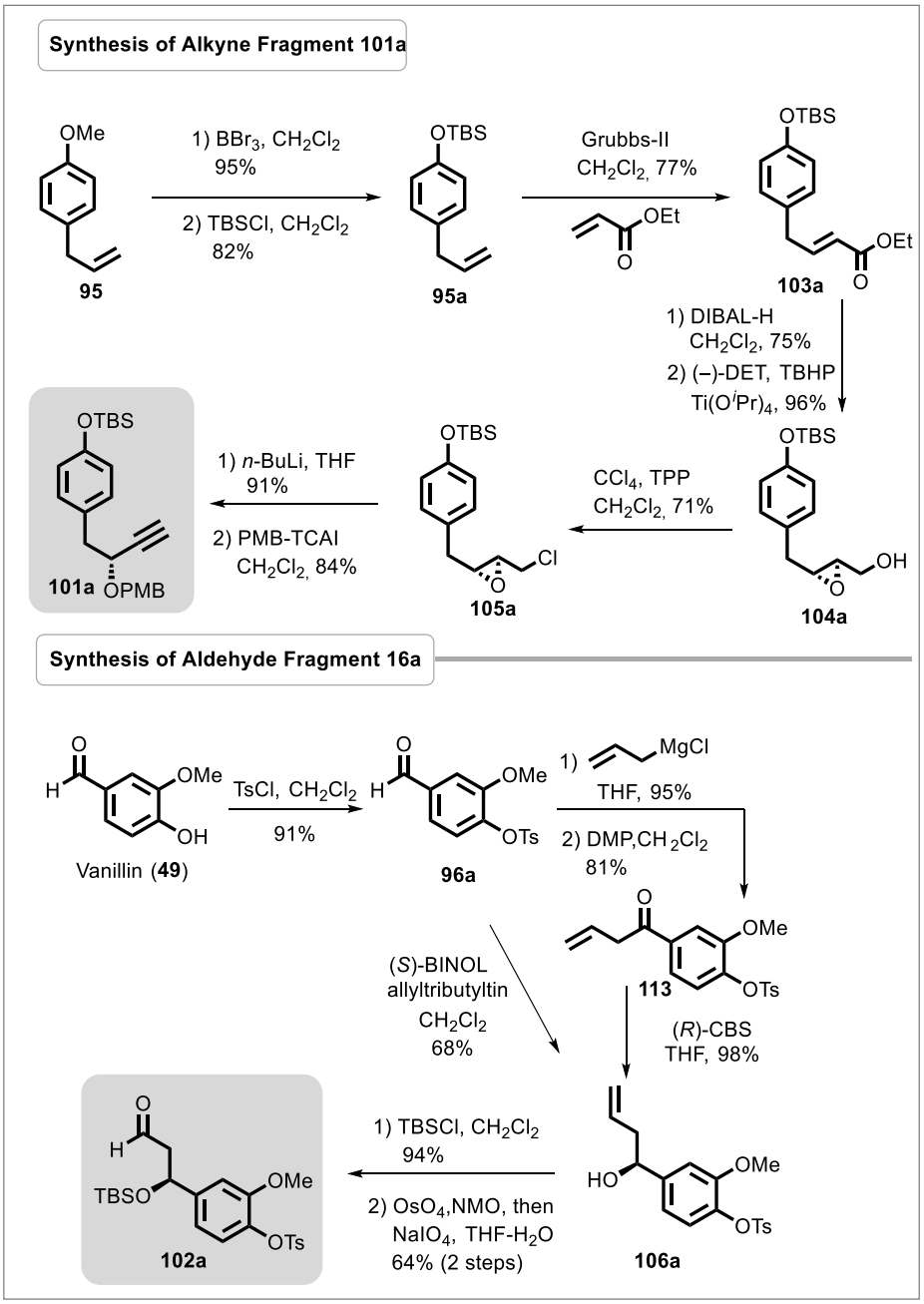
Entry	Conditions	Result
1	KO^tBu (0.1 equiv) EtOH, 0 °C to rt	**110**, 13%;**111**, 60% and **96**, 26%
2	NaH (2.2 equiv) -78 °C, THF	**110**, 8%; **111**, 49% and **96**, 32%
3	DBU (4 equiv) DCM, 0 °C	**110**, 68%
4	Amberlyst-15 (2 equiv) CH_2Cl_2, rt	**110**, 74%
5	$Pd(MeCN)_2Cl_2$ (0.1 equiv) CH_2Cl_2, rt	**108**, recovered

Table 2. Efforts toward the synthesis of dihydropyranone **109a**.

Entry	Conditions	Result
1	$Pd(CH_3CN)_2Cl_2$ (0.1 equiv), $Cu(OAc)_2.H_2O$ (0.1 equiv), PPh_3, DME, 65 °C, 24 h	**108a** decomposed
2	NaH (1 equiv), THF, 0 °C, 1 h	**110a**, 78 %
3	AgOTf (0.1 equiv), CH_2Cl_2, rt, 18 h	**110a**, 72%
4	AuCl (0.02 equiv), $NaHCO_3$, MS-4 Å, 5 h	**109a** and **112** (1:1), 90%, inseparable

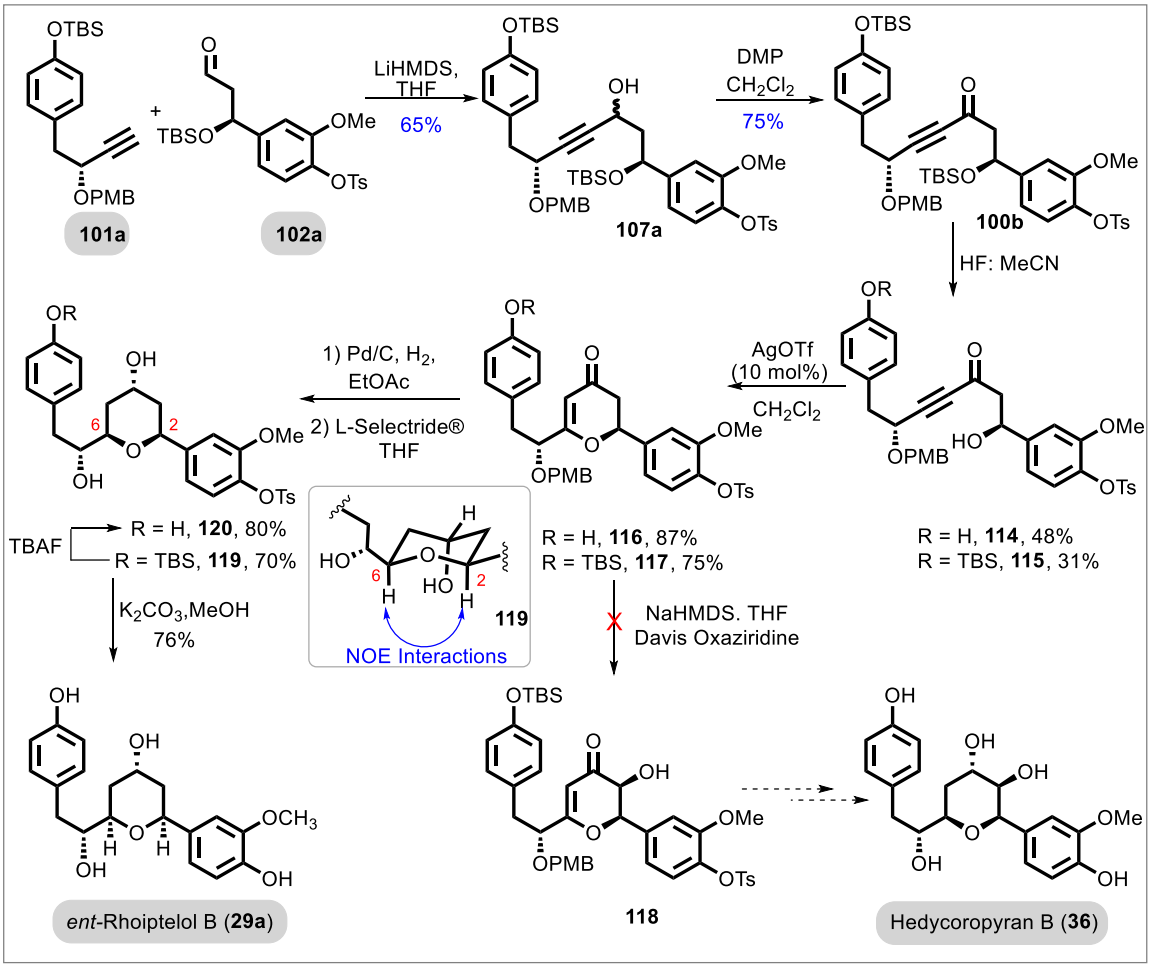
OTs substituents,[15,16] we intended to verify the fate of our endeavor by replacing the *p*-OMe group with *p*-OTs (replacing alkyne **101** and aldehyde **102** fragments with **101a** (having *p*-OTBS) and **102a** (having *p*-OTs) respectively as described in Scheme 1.12. Demethylation[39] of 4-allylanisole (**95**) using BBr_3 followed by TBS protection gave allylbenzene **95a**. Next, the cross-metathesis reaction[24] of **95a** with ethyl acrylate delivered α,β-unsaturated ester **103a.** The DIBAL-H reduction of **103a** followed by Sharpless epoxidation using (−)-DET, TBHP, $Ti(O^iPr)_4$ resulted in epoxy alcohol **104a**. We then used a similar reaction sequence employed for the preparation **101** (of Scheme 1.12) to obtain alkyne fragment **101a** from **104a**. Next, the aldehyde coupling partner **102a** containing *p*-OTs group was obtained from vanillin (**49**). A

four-step sequence comprising tosylation, Keck asymmetric allylation, TBS protection followed dihydroxylative cleavage of olefin (OsO_4, NMO then $NaIO_4$) delivered the desired fragment **102a** (**49→96a→106a→102a**). In an alternative route, allylic alcohol **106a** was obtained from a common tosylate intermediate **96a**, in which **96a** was subjected to vinylation, Dess-Martin periodinane oxidation steps to obtain ketone **113**. Subsequent Corey-Bakshi-Shibata reduction[40] (using (R)-CBS catalyst) of **113** gave the common precursor **106a** (**49→96a→113→102a**; Scheme 1.12).



Scheme 1.12 | Synthesis of alkyne fragment **101a** and aldehyde fragment **102a**.

1.2.5 Completion of total synthesis of des-hydroxy hedycoropyran B (*ent*-rhoiptelol B): Now, the stage was set to verify our envisioned ultimate strategy to access hedycoropyrans using *p*-OTs substituted intermediates. Accordingly, lithiated alkyne **101a** was coupled with aldehyde **102a** to obtain propargylic alcohol **107a** as a mixture of diastereomers in a good yield of 65%, Then DMP oxidation of **107a** furnished the desired ynone **100b**. As expected, HF-CH_3CN mediated TBS deprecation led to the fully and partially deprotected alcohols **114** and **115**. Then we tested the subsequent intramolecular oxa-Michael reaction of **114/115** using 10 mol% of AgOTf at 0 °C. To our delight, pyranones **116/117** were obtained in good yields without anticipated retro-aldol by-products. At this stage, the TBS-protected dihydro-pyranone **117** was subjected to α-hydroxylation using diverse conditions of NaHMDS, Davis- oxaziridine,[41] and PIDA,[42] which failed to provide the desired product **118** and hampered the possibility to access hedycoropyran B (**36**) (Scheme 1.13).



Scheme 1.13 | Completion of total synthesis of des-hydroxy hedycoropyran B (*ent*-rhoiptelol B).

As we had a sufficient quantity of intermediates **116** and **117** in hand, we embarked on to access structurally close diarylheptanoid *ent*-rhoiptelol B (des-hydroxy hedycoropyran B, **29a**). (+)-Rhoiptelol B (**29**) was isolated along with two other diarylheptanoids was done by Kouno and coworkers in 1996 from the fruits and leaves of *Rhoiptelea chiliantha* and then from Alnus hirsuta's bark in 2007 (Formerly used in traditional medicine in Korea and China as an anti-inflammatory agent) by Bae and co-workers. It examined for the inhibitory actions against TNF-α production, NO, HIF-1 in AGS cells and LPS induced NF-KB activation.[9] Thus, dihydropyranones **116** and **117** were subjected to hydrogenation (Pd/C, H_2) of the olefin followed L-Selectride reduction of the carbonyl group, which cleanly delivered respective pyrans **119** and **120** (**119** was deprotected to get **120**; NOE analyses confirmed 2.6-*cis* stereochemistry of THP **119**). Finally, K_2CO_3 in MeOH-mediated detosylation of **120** delivered des-hydroxy hedycoropyran B (*ent*-rhoiptelol B, **29a**) (Scheme 1.13).

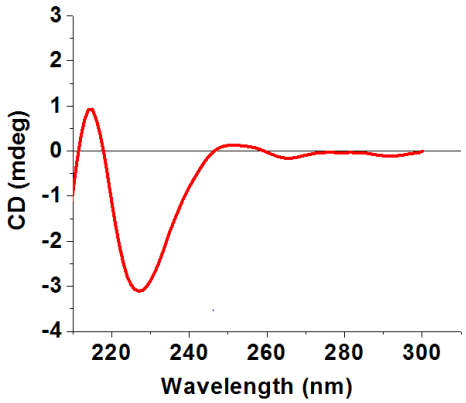


Figure 1.9 | ECD spectrum of *ent*-rhoiptelol (**29a**)

ent-Rhoiptelol B (**29a**) was confirmed by comparing ^{1}H, ^{13}C NMR, and ESI-MS (HRMS) data with the reported data. As expected, optical rotation value of **29a** ($[\alpha]_D^{26.6}$= -81.04 (c = 0.1, MeOH), this work) was found opposite to the reported value of natural product (+)-rhoiptelol B (**29**) ($[\alpha]_D^{12}$ = +97 (c = 0.3, MeOH), literature data). The assigned absolute configuration of **29a** was further supported by electronic circular dichroism (ECD) analyses, the ECD spectrum of **29a** displyed a negative Cotton effect (CE) at 227.10 nm (CD, 0.4 × 10^{-3} M, EtOH) λmax (Δε) 214.44 (+0.91), 227.10 (-3.09) nm), which was similar to the data reported for structurally and

stereochemically closer hedycoropyran B (**36**) (showed a negative CE at 230 nm) (Figure 1.9).[9]

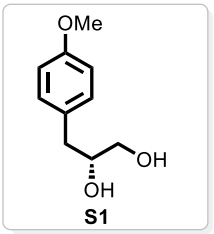
1.3. Conclusion

In conclusion, we have attempted a couple of synthetic routes for the diarylheptanoid natural products hedycoropyrans synthesis, which were unfruitful, but led us to showcase some efficient synthetic organic chemistry and the development of synthetic route for *des*-hydroxy hedycoropyran B (*ent*-rhoiptelol B) in 19 steps using commercially available and affordable starting materials of 4-allylanisole (estragole), veratraldehyde and vanillin. Cross-metathesis, Sharpless asymmetric epoxidation, Keck asymmetric allylation/CBS-reduction, AgOTf-mediated intramolecular oxa-Michael addition of hydroxy-ynone were used as key steps in this work. Based on the investigations described in this work various novel synthetic routes for THP-DAH-derived natural products can be designed. Further study of the structure-activity relationships of rhoiptelol B and its congeners is in progress and will be published in due course.

1.4 Experimental Procedures and Analytical Data:

1.4.1. Experimental Procedure & Spectroscopic Data of Synthesised Products:

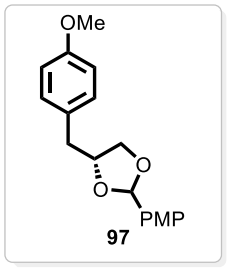
(*R*)-3-(4-Methoxyphenyl)propane-1,2-diol (S1): To a stirred solution of ^{t}BuOH :H_2O (1:1, 20 mL), were added AD mix-β (6.74 g, 13.4 mmol) and $CH_3SO_2NH_2$ (1.28 g, 13.4 mmol) at room temperature. The mixture were vigorously stirred at room temperature until both the phases were clear and then cooled to 0 °C. A solution of *p*-allylanisole **95** (2 g, 13.4 mmol) in *t*-BuOH was added at 0 °C. The reaction was stirred at the same temperature for about 48 h. The reaction was quenched at 0 °C by addition of solid sodium sulphite, warmed to rt and further stirred for 1 h at rt. The reaction mixture was extracted with EtOAc and the combined layers were washed with 2N KOH solution, water and brine. The organic layer was dried over Na_2SO_4, filtered, concentrated and subjected to column chromatography (using 40 % EtOAc in hexanes) to afford **S1** (1.84 g, 75%) as white solid. R_f = 0.6 (SiO_2, 100% EtOAc in



S1

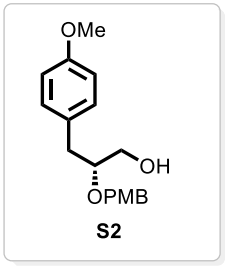
hexanes); Reported $[\alpha]_D^{25}$ = +12.90 (*c* = 2, $CHCl_3$), Observed $[\alpha]_D^{26.30}$ = +5.495 (*c* = 1.8, $CHCl_3$); FTIR (cm^{-1}): 3682, 3614, 3444, 2402, 1612, 1515, 1427, 1036, 927; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.13 (d, *J* = 7.9 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 3.95-3.85 (m, 1H), 3.79 (s, 3H), 3.71-3.64 (m, 1H), 3.53-3.47 (m, 1H), 2.80-2.63 (m, 2H), 2.19 (br. s, 2H); $^{13}C\{H\}$ NMR ($CDCl_3$, 101 MHz): δ 158.5, 130.4, 129.7, 114.2, 73.3, 66.2, 55.4, 39.0; HRMS (ESI): *m/z* calcd for $C_{10}H_{14}O_3Na$ $[M+Na]^+$ 205.0835, found 205.0835.

(4*R*)-4-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-1,3-dioxolane (97): To a solution of **S1** (1.96 g, 10.75 mmol) in CH_2Cl_2 were added the 1-(dimethoxymethyl)-4-methoxybenzene (2.93 g, 16.13 mmol) and PPTS (270 mg, 1.07mmol) at rt. The resulting mixture was stirred at rt for 5 h, then the reaction was quenched with aq. NH_4Cl and extracted with EtOAc (3x10 mL). The organic layer was dried over Na_2SO_4, filtered, concentrated under reduced pressure and subjected to silica gel column chromatography (using 12% EtOAc in hexanes) to afford **97** (2.6 g, 76%) as white solid. TLC: R_f = 0.6 (SiO_2, 30% EtOAc/hexanes); FTIR (cm^{-1}): 3425, 2973, 2402, 1622, 1516, 1430, 1299, 1078, 1037, 927; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.49-7.34(m, 2H), 7.20-7.13 (m, 2H), 6.95-6.82 (m, 4H), 5.84 (d,1H), 4.48-4.36 (m, 1H), 4.20-3.96 (m, 1H), 3.85-3.79 (m, 6H), 3.79-3.64 (m, 1H), 3.11-3.01 (m, 1H), 2.89-2.73(m, 1H); $^{13}C\{H\}$ NMR ($CDCl_3$, 50 MHz): δ 160.4, 158.5, 130.6, 130.3, 129.3, 128.2, 127.9, 114.1, 113.9, 104.3, 103.5, 70.3, 69.6, 55.4, 39.2, 38.7; HRMS (ESI): *m/z* calcd for $C_{18}H_{20}O_4Na$ $[M+Na]^+$323.1254, found 323.1251.



97

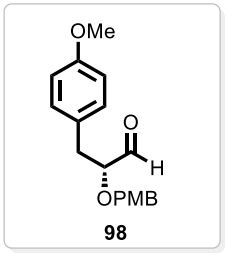
(*R*)-2-((4-Methoxybenzyl)oxy)-3-(4-methoxy-phenyl)propan-1-ol (S2): To a solution of (4*R*)-4-(4-methoxybenzyl)-2-(4-methoxyphenyl)-1,3-dioxolane (**97**) (2.6 g, 8.27 mmol) in CH_2Cl_2 and stirred at -78 ℃, added DIBAL-H (13.72 mL, 13.70 mmol) to it drop wise and stirred about 2 h. Monitored the reaction by TLC. After completion of the reaction, it was quenched with saturated solution of sodium potassium tartarate (Na^+-K^+ tartarate) and extracted the reaction mass with EtOAc (3x20 mL) and filtered through celite. The filtrate containing organic compound is filtered through Na_2SO_4, concentrated and crude was subjected to silica gel column chromatography (using 30% EtOAc in hexanes) to afford **S2** (2.28 g, 91%) as a yellow



S2

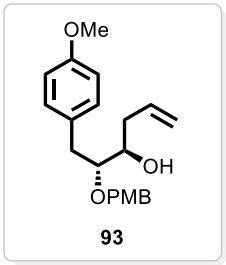
liquid. TLC: R_f= 0.4 (SiO_2, 40% EtOAc/hexanes); $[\alpha]_D^{26.30}$ = +2.93 (*c* = 1.3, $CHCl_3$); FTIR (cm^{-1}): 3417, 1638, 1381, 1249, 1072, 805, 743; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.21 (d, *J* = 8.46 Hz, 2H), 7.13 (d, *J* = 8.59 Hz, 2H), 6.91-6.80(m, 4H), 4.55-4.38 (m, 2H), 3.85-3.77 (m, 6H), 3.71-3.58 (m, 2H), 3.54-3.41(m, 1H), 2.94-2.80 (m, 1H), 2.80-2.66 (m, 1H),, 2.10 (br.s, 1H); $^{13}C\{H\}$ NMR ($CDCl_3$, 50 MHz): δ 159.3, 158.2, 130.4, 130.3, 129.5, 113.9, 80.7, 71.6, 63.7, 55.3, 36.6; HRMS (ESI): *m/z* calcd for $C_{18}H_{22}O_4Na$ $[M+Na]^+$ 325.1410, found 325.140.

(*R*)-2-((4-Methoxybenzyl)oxy)-3-(4-methoxy-phenyl)propanal (98): To a solution of (*R*)-2-((4-methoxybenzyl)oxy)-3-(4-methoxyphenyl)propan-1-ol (**S2**) (846 mg, 2.81 mmol) in CH_2Cl_2 was added Dess-Martin Periodinane (DMP) (1.79 g, 4.22 mmol) at 0 ℃ under inert atmosphere. The reaction progress was monitored by TLC. After the completion conversion, added aqueous $NaHCO_3$ and sodium thiosulphate (1:1). Turbidity was removed and is extracted with DCM using a separating funnel. The combined organic layer is dried over anhydrous Na_2SO_4, filtered, concentrated and the crude was subjected to silica gel column chromatography (using 15% EtOAc in hexanes) to afford **98** (712 mg, 84%) as colorless oil. TLC: R_f = 0.6 (SiO_2, 30% EtOAc/hexanes); $[\alpha]_D^{26.23}$ = +4.36 (*c* = 1.2, $CHCl_3$); FTIR (cm^{-1}): 3686, 3618, 3455, 2975, 2402, 1721, 1603, 1518, 1426, 1039, 927; ^1H NMR (200 MHz, $CDCl_3$) δ 9.64 (d, *J* = 1.98 Hz, 1H), 7.14 (d, *J* = 7.72 Hz, 4H), 6.92-6.72 (m, 4H), 4.58-4.35(m, 2H), 4.00-3.85(m, 1H), 3.80 (s, 6H), 3.07-2.70(m, 2H);$^{13}C\{H\}$NMR (50 MHz, $CDCl_3$) δ 203.6, 191.1, 142.1, 133.6, 132.2, 130.6, 129.8, 128.2, 114.5, 114.0, 84.2, 72.7, 55.7, 55.4, 36.0; HRMS (ESI): *m/z* calcd for $C_{18}H_{20}O_4Na$ $[M+Na]^+$323.1254, found 323.1249.



98

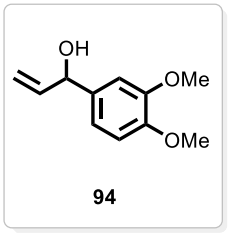
(2*R*,3*R*)-2-((4-Methoxybenzyl)oxy)-1-(4-methoxyphenyl)hex-5-ene-3-ol (93): To a solution of aldehyde **98** (500 mg, 1.66 mmol) in Et_2O in 100 mL round bottom flask at 0 ℃, $MgBr_2.OEt_2$ (687 mg, 2.66 mmol) was added in one portion. After 10 min, allyltributyltin (0.87 mL, 2.82 mmol) was added dropwise over 10 min. After completion of addition reaction was stirred for 3h at 0 ℃ and reaction was monitored by TLC. After completion of reaction it was quenched by aq. sat. $NaHCO_3$



93

and the layers were separated and the aqueous layer was extracted with EtOAc (3x10 mL) and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography (using 15% EtOAc in hexanes) to afford **93** (456 mg, 80%) as a colorless liquid. TLC: R_f = 0.5 (SiO_2, 30% EtOAc/hexanes); $[\alpha]_D^{25.23}$ = +4.49 (*c* = 1.9, $CHCl_3$); FTIR (cm^{-1}) : 3680, 3620, 2975, 2399, 1611, 1512, 1476, 1423, 1300, 1035, 928, 877, 849; ^1H NMR (200 MHz, $CDCl_3$) δ 7.23-7.08 (m, 4H), 6.94-6.76(m, 5H), 5.95-5.67 (m, 1H), 5.18-4.98 (m, 2H), 4.52-4.23 (m, 2H), 3.82-3.78 (m, 6H), 3.57-3.40 (m, 2H), 2.97-2.74 (m, 2H), 2.36-2.15 (m, 3H); $^{13}C\{H\}$ NMR (126 MHz, $CDCl_3$) δ 159.4, 158.2, 135.0, 130.6, 130.3, 129.7, 129.7, 117.3, 113.9, 113.9, 82.0, 72.6, 71.5, 55.3, 38.5, 36.2; HRMS (ESI): *m/z* calcd for $C_{21}H_{26}O_4Na$ $[M+Na]^+$ 365.1723, found 365.1728.

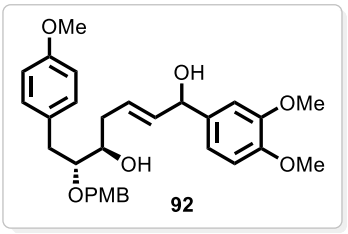
1-(3,4-Dimethoxyphenyl)prop-2-en-1-ol (94): To a solution of aldehyde **96** (2 g, 12.0 mmol) in dry THF, vinyl magnesium bromide (1 M in THF, 14.44 mL, 14.4 mmol) was added at -78 °C and the reaction mixture stirred for 1 h at the same temperature. After completion of reaction, reaction was quenched with sat. aq. solution of NH_4Cl. The layers were separated and the aqueous layer was extracted with ethyl acetate (3x15 mL) and the combined organic layer were washed with brine and dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo and the crude product was purified by silica gel column chromatography (using 30% EtOAc in hexanes) to afford **94** (1.05 g, 47%) as colorless liquid, TLC: R_f = 0.4 (SiO_2, 40% EtOAc/hexanes); FTIR (cm^{-1}) : 3673, 3490, 2841, 2598, 2410, 2054, 1847, 1729, 1648, 1598, 1512, 1457, 1423, 1374, 1146, 1036, 928, 858; ^1H NMR (200 MHz, $CDCl_3$): δ 6.97-6.75 (m, 3H), 6.15-5.90 (m, 1H), 5.31 (d, *J* = 17.05 Hz, 1H), 5.23-5.03 (m, 2H), 3.95-3.75 (m, 6H), 2.28 (br. s., 1H); $^{13}C\{H\}$ NMR (50 MHz, $CDCl_3$): δ 149.3, 148.8, 140.4, 135.4, 118.8, 115.1, 111.2, 109.6, 75.2, 56.1, 56.0; HRMS (ESI): *m/z* calcd for $C_{11}H_{14}O_3Na$ $[M+Na]^+$ 217.0835, found 217.0835.



94

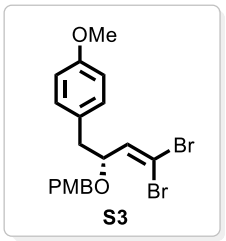
(5*R*,6*R*,*E*)-1-(3,4-Dimethoxyphenyl)-6-((4-methoxybenzyl)oxy)-7-(4-methoxyphenyl)hept-2-ene-1,5-diol (92): To a solution of **93** (450 mg, 2.33 mmol) and **94** (100 mg, 0.292 mmol) in CH_2Cl_2 (1 mL) was added G-II generation catalyst (20 mg,

0.05 mmol) and was stirred at rt for 1 h. The solvent was evaporated in vacuum and the residue was purified by silica gel column chromatography (using 40% EtOAc in hexanes) to afford **92** (637 mg, 95%) as yellow liquid. TLC: *Rf* = 0.8 (SiO_2, 50% EtOAc/hexanes); FTIR (cm^{-1}): 3685, 3618, 2974, 2403, 1674, 1596, 1516, 1426, 1149, 1034, 927; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.20-7.12 (m, 3H), 7.09 (d, *J* = 3.16 Hz, 1H), 6.91 (s, 1H), 6.88-6.78 (m, 6H), 5.77-5.62 (m, 2H), 5.10 (d, *J* = 4.04 Hz, 1H), 4.47-4.20 (m, 2H), 3.98-3.92 (m, 1H), 3.89 (br. s., 1H), 3.87 (s, 6H), 3.79 (s, 6H), 3.57-3.37 (m, 2H), 2.84 (dd, *J* = 2.78, 5.81 Hz, 2H), 2.34-2.24 (m, 2H)); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$): δ 159.5, 158.4, 149.3, 148.6, 135.4, 130.6, 130.3, 129.9, 118.5, 114.0, 111.2, 109.5, 82.1, 74.9, 72.6, 56.0, 55.4, 36.3; HRMS (ESI): *m/z* calcd for $C_{30}H_{36}O_7Na$ $[M+Na]^+$ 531.2353, found 531.2367.



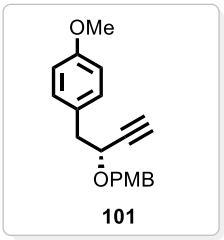
92

(*R*)-1-(((4,4-Dibromo-1-(4-methoxyphenyl)but-3-en-2-yl)oxy)methyl)-4-methoxybenzene (S3): To a solution of CBr_4 (4.86 g, 14.6 mmol) in CH_2Cl_2 at -40 °C, TPP ((7.70 g, 29.3 mmol) dissolved in minimum amount of CH_2Cl_2) under inert atmosphere was added. After stirred for 20 min, added a cold solution of **98** (1.47 g, 4.89 mmol) contained Et_3N (0.68 mL, 4.89 mmol) dropwise to the reaction mixture. Reaction was monitored by TLC. After completion of reaction, added Et_3N and MeOH successively at the same temperature then solvent was evaporated and diethyl ether was added then filtered the reaction mass through a sintered funnel containing celite. Collected the filtrate, concentrated and subjected to column chromatography (using 7% EtOAc in hexanes) to afford **S3** (1.45 g, 65% yield) as white solid. TLC: R_f = 0.6 (SiO_2, 20% EtOAc/hexanes); FTIR (cm^{-1}): 3685, 3619, 3453, 2975, 2402, 1608, 1518, 1427, 1049, 927; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.23-7.05 (m, 4H), 6.91-6.76 (m, 4H), 6.43 (d, *J* = 8.34 Hz, 1H), 4.51 (d, *J* = 11.49 Hz, 1H), 4.30 (d, *J* = 11.49 Hz, 1H), 4.26-4.13 (m, 1H), 3.84-3.78 (m, 6H), 2.99-2.67 (m, 2H); $^{13}C\{H\}$ NMR ($CDCl_3$, 126 MHz): δ 159.3, 158.4, 139.6, 130.8, 130.2, 129.4, 129.3, 113.8, 113.8, 91.4, 80.1, 70.9, 55.4, 40.0; HRMS (ESI): *m/z* calcd for $C_{19}H_{20}O_3Br_2Na$ $[M+Na]^+$ 478.9651, found 478.9646.



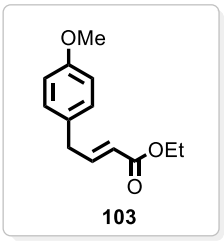
S3

(*R*)-1-Methoxy-4-(2-((4-methoxybenzyl)oxy)but-3-yn-1-yl)benzene (101): To a solution of (*R*)-1-(((4,4-dibromo-1-(4-methoxyphenyl)but-3-en-2-yl)oxy)methyl)-4-methoxybenzene (**S3**) (1.45 g, 3.17 mmol) in anhydrous tetrahydrofuran at -78 ℃ was added *n*-BuLi (1.6 M, 4.3 mL, 6.99 mmol) dropwise at the same temperature. The reaction is kept monitoring with TLC for about an hour. After the completion of reaction, saturated aqueous NH_4Cl was added to quench the reaction mass and was extracted with EtOAc (3x20 mL). The combined organic layer was dried over Na_2SO_4, concentrated under reduced pressure and subjected to a silica gel column chromatography (using 10% EtOAc in hexanes) to afford **101** (800 mg, 98% yield) as colorless oil. TLC: R_f = 0.5 (SiO_2, 20% EtOAc/hexanes); $[\alpha]_D^{26.20}$ = +20.0 (*c* = 1.4, $CHCl_3$); FTIR (cm^{-1}): 3685, 3415, 2927, 2402, 1610, 1516, 1428, 1036, 927; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.25-7.14 (m, 4H), 6.90-6.79 (m, 4H), 4.75 (d, *J* = 11.49 Hz, 1H), 4.45 (d, *J* = 11.49 Hz, 1H), 4.21 (dt, *J* = 2.02, 6.82 Hz, 1H), 3.83-3.77 (m, 6H), 3.11-2.87 (m, 2H), 2.49 (d, *J* = 2.02 Hz, 1H); $^{13}C\{H\}$ NMR ($CDCl_3$, 126 MHz): δ 159.3, 158.5, 130.8, 129.9, 129.6, 129.3, 113.9, 113.7, 82.7, 74.7, 70.4, 69.5, 55.4, 55.3, 41.3; HRMS (ESI): *m/z* calcd for $C_{19}H_{20}O_3Na$ $[M+Na]^+$ 319.1305, found 319.1302.



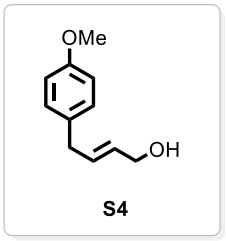
101

Ethyl (*E*)-4-(4-methoxyphenyl)but-2-enoate (103): To a solution of Grubb's 2nd generation catalyst (21 mg, 0.03 mmol), *p*-allylanisole **95** (500 mg, 3.37 mmol) and ethyl acrylate (0.71 mL, 6.74 mmol) were added simultaneously via syringe. The resulting mixture was heated at 40 ℃ until consumption of starting material occurred as determined by TLC analysis. The reaction cooled to rt, concentrated and residue was purified by column chromatography using 10% EtOAc in hexanes) to afford **103** (540 mg, 73%) as colorless liquid. TLC: R_f = 0.6 (SiO_2, 20% EtOAc/hexanes); FTIR (cm^{-1}) : 3681, 3427, 2842, 2403, 1711, 1651, 1611, 1513, 1432, 1376, 1037, 984, 926; ^1H NMR (200 MHz, $CDCl_3$): δ 7.18-6.96 (m, 3H), 6.91-6.77 (m, 2H), 5.78 (td, *J* = 1.64, 15.54 Hz, 1H), 4.17 (q, *J* = 7.20 Hz, 2H), 3.79 (s, 3H), 3.46 (dd, *J* = 1.39, 6.69 Hz, 2H), 1.27 (t, *J* = 7.07 Hz, 3H); $^{13}C\{H\}$NMR (101 MHz $CDCl_3$): δ 166.2, 158.2, 147.6, 132.1, 132.0, 131.4, 131.3, 129.6, 129.4, 128.4, 128.3, 127.2, 121.8, 113.9, 113.7, 60.0, 54.9, 37.3, 14.1; HRMS (ESI): *m/z* calcd for $C_{13}H_{16}O_3Na$ $[M+Na]^+$ 243.0992, found 243.0990.



103

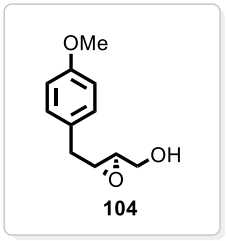
(*E*)-4-(4-Methoxyphenyl)but-2-en-1-ol (S4): To a solution of corresponding ester



S4

103 (1.08 g, 4.9 mmol) in DCM (10 mL) at -78 °C was added DIBAL-H (1M in toluene, 10.30 mL, 10.3 mmol) dropwise. The solution was stirred at this temperature until consumption of starting material was observed by TLC at which point the reaction was quenched by careful addition of methanol. The reaction was allowed to warm at rt whereupon sat. aq. Na^+-K^+ tartarate and EtOAc were added and the mixture was stirred vigorously for 1h. The phases were then separated and the aqueous phase was extracted with EtOAc (3x10 mL). The organic phases were combined washed with sat. aq. Na^+-K^+tartarate, water and brine, dried over Na_2SO_4, filtered and concentrated and crude product was purified by silica gel column chromatography (using 20% EtOAc in hexanes) to afford **S4** (703 mg, 80%) as colorless liquid. TLC: R_f = 0.3 (SiO_2, 30% EtOAc/hexanes) FTIR (cm^{-1}): 3686, 3619, 3444, 2973, 2402, 1766, 1600, 1521, 1426, 1041, 927; ^1H NMR (400 MHz, $CDCl_3$): δ 7.10 (d, *J* = 8.54 Hz, 2H), 6.84 (d, *J* = 8.54 Hz, 2H), 5.88-5.77 (m, 1H), 5.74-5.62 (m, 1H), 4.10 (d, *J* = 5.49 Hz, 2H), 3.79 (s, 3H), 3.32 (d, *J* = 6.10 Hz, 2H), 1.79 (br. s., 1H); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$): δ 158.1, 132.2, 132.0, 130.1, 129.6, 114.0, 63.5, 55.4, 37.8; HRMS (ESI): *m/z* calcd for $C_{11}H_{14}O_2Na$ $[M+Na]^+$ 201.0886, found 201.0886.

((2*R*,3*R*)-3-(4-Methoxybenzyl)oxiran-2-yl)methanol (104): M.S. (4 Å) were dried

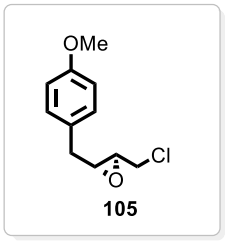


104

in a flask and allowed to rt, dry DCM and (-)-DET (0.09 mL, 0.561 mmol) were added and the suspension was cooled to -25 °C. To this $Ti(O^iPr)_4$ (0.24 mL, 0.084 mmol) and TBHP (2.46 mL, 1.23 mmol) were added and the mixture was stirred at -25 °C for 30 min. A solution of allylic alcohol **S4** (1 g, 5.61 mmol) in dry DCM was added to the above mixture and it was kept in freezer at about -25 °C for 18 h. To the reaction mixture water was added and stirred at 0 °C for 30 min. A solution of 10% aq. NaOH was then added and the mixture was warmed to rt for 1h. The product was extracted with DCM (3x10 mL), dried over Na_2SO_4, filtered and concentrated in vacuum and purified by silica gel column chromatography (using 25% EtOAc in hexanes) to afford **104** (980 mg, 82%). as colorless liquid. TLC: R_f = 0.4 (SiO_2, 40% EtOAc/hexanes); $[\alpha]_D^{25.27}$ = +15.71 (*c* = 2.9, $CHCl_3$); FTIR (cm^{-1}): 3415, 2404, 1615, 1515, 1432, 1035, 927; ^1H NMR (500 MHz, $CDCl_3$): 7.15 (d, *J* = 8.39 Hz, 2H), 6.85 (d, *J*

= 8.77 Hz, 2H), 3.93-3.85 (m, 1H), 3.79 (s, 3H), 3.66-3.59 (m, 1H), 3.17 (dt, *J* = 2.29, 5.34 Hz, 1H), 3.02-2.94 (m, 1H), 2.92-2.78 (m, 2H), 1.81 (t, *J* = 6.10 Hz, 1H); ^{13}C{H}NMR (126 MHz, $CDCl_3$): δ 158.6, 130.1, 129.0, 114.1, 61.6, 58.3, 56.2, 55.4, 37.0; HRMS (ESI): *m/z* calcd for $C_{11}H_{14}O_3Na$ $[M+Na]^+$ 217.0835, found 217.083.

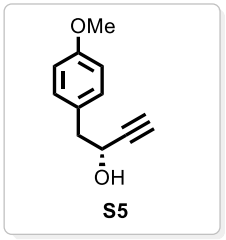
(2*S*,3*R*)-2-(Chloromethyl)-3-(4-methoxybenzyl)oxirane (105): To a solution of



105

epoxy alcohol **104** (1.68 g, 8.64 mmol) in DCM, CCl_4 (1.67 mL, 17.2 mmol) and triphenylphosphine (3.01 g, 14.9 mmol) were added at 0 ℃ and the refluxed for 6 h. after completion of reaction, it was diluted with hexane and filtered through celite. The filtrate was concentrated to give a residue which was purified by silica gel column chromatography (using 5% EtOAc in hexanes) to afford **105** (1.48 g, 80%) as yellowish liquid. TLC: R_f = 0.8 (SiO_2, 20% EtOAc/hexanes); $[\alpha]_D^{25.30}$ = +9.46 (*c* = 1.9, CHCl3); FTIR (cm^{-1}): 3415, 2402, 1611, 1516, 1432, 1038, 928; ^{1}H NMR (400 MHz $CDCl_3$): δ 7.20-7.13 (m, *J* = 8.70 Hz, 2H), 6.91-6.81 (m, *J* = 8.70 Hz, 2H), 3.80 (s, 3H), 3.60-3.49 (m, 2H), 3.12-3.01 (m, 2H), 2.95-2.79 (m, 2H); ^{13}C{H} NMR (101 MHz, $CDCl_3$): δ 158.6, 130.1, 128.6, 114.1, 59.2, 57.0, 55.4, 44.6, 36.9; HRMS (ESI): *m/z* calcd for $C_{11}H_{14}O_2Cl$ $[M+H]^+$ 213.0677, found 213.0679.

(*R*)-1-(4-Methoxyphenyl)but-3-yn-2-ol (S5): To a solution of chloride **105** (1.48 g,

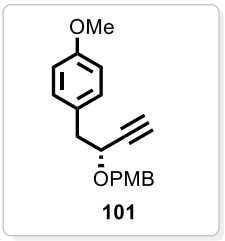


S5

6.97 mmol) in dry THF (20 mL), *n*-BuLi (15.25 mL, 24.3 mmol) was added dropwise at -78 ℃. The reaction mixture was stirred at the same temperature for 30 min. after completion of reaction; reaction was quenched with aq. sat. NH_4Cl at 0 ℃. The organic phase was separated and the aqueous phase was extracted with EtOAc (3x20 mL). The combine organic layers were dried over Na_2SO_4, filtered and concentrated in vacuum and crude product was purified by silica gel column chromatography(using 12% EtOAc in hexanes) to afford **S5** (1.05 g, 86%) as yellow liquid . TLC: R_f = 0.4 (SiO_2, 20% EtOAc/hexanes); $[\alpha]_D^{25.32}$ = +3.50 (*c* = 2.9, CHCl3); FTIR (cm^{-1}): 3683, 3303, 2926, 2850, 2403, 1728, 1609, 1511, 1455, 1298, 1036, 925; ^{1}H NMR (400 MHz $CDCl_3$): 7.24-7.17 (m, 2H), 6.91-6.81 (m, 2H), 4.53 (br. s., 1H), 3.79 (s, 3H), 3.03-2.88 (m, 2H), 2.49 (d, *J* = 1.83 Hz, 1H), 2.13 (br. s., 1H); ^{13}C{H} NMR (101

MHz, $CDCl_3$): δ 158.7, 130.9, 128.3, 114.0, 84.4, 73.9, 63.2, 55.3, 43.0; HRMS (ESI): *m/z* calcd for $C_{11}H_{12}O_2Na$ $[M+Na]^+$ 199.0730, found 199.0727.

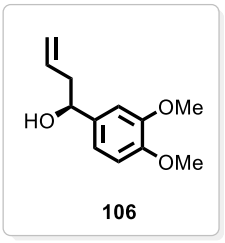
(*R*)-1-Methoxy-4-(2-((4-methoxybenzyl)oxy)but-3-yn-1-yl)benzene (101): To a



101

suspension of NaH (0.1 g, 4.19 mmol) in DMF (2 mL) at 0 °C was added a solution of alcohol **S5** (369 mg, 2.09 mmol) in DMF (3 mL). After that the reaction mixture was stirred for 1h at 0 °C then PMBCl (0.313 mL, 2.29 mmol) and TBAI (43 mg, 0.209 mmol) were added at 0 oC. The reaction mixture was stirred for 40 min. at rt. After completion of reaction saturated aqueous $NaHCO_3$ was added at 0 °C. The mixture was extracted with diethyl ether (3x5 mL) and the organic layer was dried over Na_2SO_4, filtered and solvent was evaporated then crude product was purified by silica gel column chromatography (using 10% EtOAc in hexanes) to afford **101** (510 mg, 82%) as yellow oil. TLC: R_f = 0.5 (SiO_2, 20% EtOAc/hexanes); $[\alpha]_D^{26.19}$ = +22.10 (*c* = 1.4, $CHCl_3$); FTIR (cm^{-1}): 3684, 3619, 3454, 3304, 2964, 2403, 1612, 1514, 1456, 1298, 1039, 928; ^1H NMR (500 MHz $CDCl_3$): δ 7.18 (d, *J* = 8.39 Hz, 2H), 7.21 (d, *J* = 8.39 Hz, 2H), 6.85 (t, *J* = 8.39 Hz, 4H), 4.75 (d, *J* = 11.44 Hz, 1H), 4.44 (d, *J* = 11.44 Hz, 1H), 4.20 (dt, *J* = 1.91, 6.87 Hz, 1H), 3.86-3.76 (m, 6H), 3.08-2.92 (m, 2H), 2.48 (d, *J* = 1.91 Hz, 1H); $^{13}C\{H\}$ NMR (50 MHz, $CDCl_3$): δ 159.3, 158.5, 130.8, 129.9, 129.6, 129.3, 113.9, 113.7, 82.7, 74.7, 70.4, 69.5, 55.4, 55.3, 41.3.

(*S*)-1-(3,4-Dimethoxyphenyl)but-3-en-1-ol (106): To a 50 mL round bottom flask,

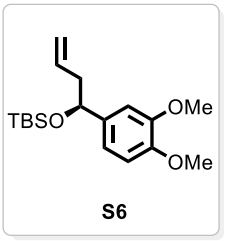


106

a mixture of (*S*)-BINOL (861 mg, 3.00 mmol), 1.0 M $Ti(O^iPr)_4$ (3 mL, 3.00 mmol) in DCM and freshly activated 4 Å MS powder in DCM was refluxed for 1h. The red brown mixture was cooled to rt and then aldehyde **96** (5 g, 30.08 mmol) was added. After being stirred for 10 min. the contents were cooled to -78 °C and allyltributyltin (10.95 mL, 33.08 mmol) was added. The reaction mixture was stirred for 10 min. and then replaced in -20 °C freezer. After 70 h saturated $NaHCO_3$, 1.5 mL was then added and contents were stirred for 1 h, dried with anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (using 20% EtOAc in hexanes) to afford **106** (4.52 g, 72%) as white solid. TLC: R_f = 0.5 (SiO_2, 40% EtOAc/hexanes); $[\alpha]_D^{26.07}$ = −4.13 (c = 0.3, $CHCl_3$); FTIR (cm^{-1}): 3686, 3616, 2974,

2402, 1599, 1517, 1426, 1146, 1036, 926, 860; ^{1}H NMR (200 MHz $CDCl_3$): δ 6.93 (s, 1H), 6.91-6.82 (m, 2H), 5.96-5.67 (m, 1H), 5.19 (d, *J* = 7.96 Hz, 1H), 5.12 (s, 1H), 4.69 (dt, *J* = 2.78, 6.69 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 2.51 (t, *J* = 6.95 Hz, 2H), 1.99 (d, *J* = 2.91 Hz, 1H); ^{13}C {H} NMR (50 MHz, $CDCl_3$): δ 149.2, 148.6, 136.7, 134.7, 118.5, 118.2, 111.1, 109.1, 73.3, 56.1, 56.0, 44.0; HRMS (ESI): *m/z* calcd for $C_{12}H_{16}O_3Na$ $[M+Na]^+$ 231.0992, found 231.0991.

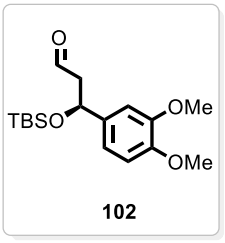
(*S*)-*Tert*-butyl((1-(3,4-dimethoxyphenyl)but-3-en-1-yl)oxy)dimethylsilane(S6):



S6

2,6-lutidine (2.97 mL, 25.58 mmol) was added to a solution of alcohol **106** (3.6 g, 17.28 mmol) in dry DCM (30 mL) at -78 ℃. After 10 min. TBSOTf (3.97 mL, 17.28 mmol) was added and the reaction mixture was stirred for 20 min. at this temperature. The reaction mixture was diluted with DCM and the organic layers were washed with water and saturated aqueous NH_4Cl. The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuum. The crude product was purified by silica gel column chromatography (using 5% EtOAc in hexanes) to afford **S6** (4.5 g, 80%) as yellow liquid. TLC: R_f = 0.5 (SiO_2, 30% EtOAc/hexanes); $[\alpha]_D^{26.11}$ = -34.53 (c = 2.8, CHCl3); FTIR (cm^{-1}): 3775, 3685, 3619, 3456, 2966, 2402, 2358, 1600, 1516, 1466, 1425, 1148, 1079, 1037, 925; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.90 (s, 1H), 6.83-6.72 (m, 2H), 5.91-5.63 (m, 1H), 5.04 (d, *J* = 3.79 Hz, 1H), 4.98 (s, 1H), 4.62 (dd, *J* = 5.43, 7.07 Hz, 1H), 3.87 (m, 6H), 2.54-2.25 (m, 2H), 0.92-0.83 (m, 9H), 0.02 (s, 3H), -0.09--0.16 (m, 3H); ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 148.8, 148.0, 138.1, 135.5, 118.1, 116.9, 110.6, 109.2, 74.9, 56.0, 55.9, 45.8, 26.0, 18.4, -4.5, -4.8; HRMS (ESI): *m/z* calcd for $C_{18}H_{30}O_3NaSi$ $[M+Na]^+$ 345.1856, found 345.1855.

(*S*)-3-((*Tert*-butyldimethylsilyl)oxy)-3-(3,4-dimethoxyphenyl)-propanal (102):

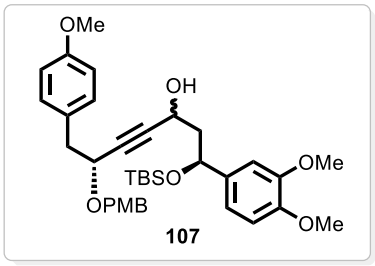


102

To a solution of olefin **S6** (1.29 g, 4.00 mmol) in THF:H_2O (3:1, 7.5 mL: 2.5 mL) were added 2,6-lutidine (1.86 mL, 16.02 mmol), OsO_4 (0.02 g, 0.08 mmol) and $NaIO_4$ (1.70 g, 8.00 mmol). The reaction mixture was stirred for 2 h at rt. After completion of reaction, reaction was quenched with solid Na_2SO_3 and then filtered through celite using EtOAc. The filtrate was concentrated in vacuum and the crude product was purified by silica gel column chromatography (using 10% EtOAc in hexanes) to

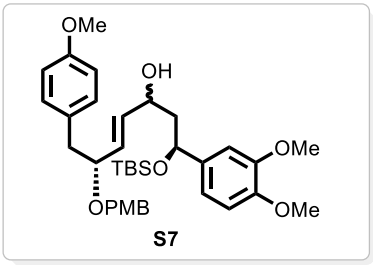
afford the desired product **102** (938 mg, 73%) as yellowish liquid. TLC: R_f= 0.6 (SiO_2, 20% EtOAc/hexanes); $[\alpha]_D^{26.13}$ = – 32.98 (c = 0.2, $CHCl_3$); FTIR (cm^{-1}): 3683, 3615, 3433, 2976, 2402, 2357, 1637, 1520, 1426, 1041, 927; ^1H NMR (400 MHz, $CDCl_3$): δ 9.76 (dd, *J* = 2.13, 2.75 Hz, 1H), 6.90 (d, *J* = 1.75 Hz, 1H), 6.86-6.76 (m, 2H), 5.15 (dd, *J* = 4.13, 8.25 Hz, 1H), 3.85 (s, 3H), 3.86 (s, 3H), 2.82 (ddd, *J* = 2.88, 8.25, 15.76 Hz, 1H), 2.60 (ddd, *J* = 2.00, 4.13, 15.76 Hz, 1H), 0.85 (s, 9H), 0.03 (s, 3H), -0.14 (s, 3H); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$): δ 201.5, 149.1, 148.4, 136.6, 117.8, 110.9, 108.8, 70.6, 56.0, 55.9, 54.2, 25.8, 18.2, -4.5, -5.1; HRMS (ESI): *m/z* calcd for $C_{17}H_{28}O_4NaSi$ $[M+Na]^+$ 347.1649, found 347.1645.

(1*S*,6*R*)-1-((*Tert*-butyldimethylsilyl)oxy)-1-(3,4-dimethoxyphenyl)-6-((4-methoxybenzyl)-oxy)-7-(4-methoxyphenyl)hept-4-yn-3-ol (107): To the alkyne **101** (482 mg, 1.62 mmol) in dry THF (5 mL), *n*-BuLi (1.1 g, 1.78 mmol) was added at -78 °C and stirred for 1h at the same temperature. After that aldehyde **102** (263 mg, 0.81 mmol) was added in one shot and reaction was stirred for 2 h. After completion of reaction, reaction was quenched with sat. aq. NH_4Cl and extracted with EtOAc (3x 10 mL), dried over Na_2SO_4, filtered and concentrated and subjected to silica gel column chromatography to afford the desired product **107** (650 mg, 65%)as yellowish liquid. TLC: R_f = 0.5 (SiO_2, 30% EtOAc/hexanes; $[\alpha]_D^{26.11}$ = +4.85 (c = 3.7, $CHCl_3$); FTIR (cm^{-1}): 3685, 3618, 2972, 2402, 1604, 1517, 1426, 1216, 1040, 927; ^1H NMR (400 MHz $CDCl_3$): δ 7.24-7.12 (m, 4H), 6.93-6.72 (m, 7H), 5.02 (ddd, *J* = 3.05, 7.93, 15.87 Hz, 1H), 4.76-4.66 (m, 1H), 4.59 (br. s., 1H), 4.41 (d, *J* = 11.60 Hz, 1H), 4.24 (t, *J* = 6.10 Hz, 1H), 3.88 (s, 6H), 3.84-3.74 (m, 6H), 3.08-2.88 (m, 2H), 2.27-2.04 (m, 1H), 2.04-1.86 (m, 1H), 0.94-0.87 (m, 9H), 0.10-0.01 (m, 3H), -0.15- -0.23 (m, 3H); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$): δ 159.3, 158.5, 149.0, 148.4, 136.8, 130.8, 130.0, 129.5, 118.3, 118.1, 113.8, 113.6, 110.8, 109.1, 87.5, 83.5, 72.9, 70.4, 69.7, 60.2, 56.0, 55.9, 55.4, 55.3, 48.6, 47.1, 46.9, 41.5, 25.9, 18.2, -4.3, -4.4, -4.9; HRMS (ESI): *m/z* calcd for $C_{36}H_{48}O_7NaSi$ $[M+Na]^+$ 643.3062, found 643.3053.



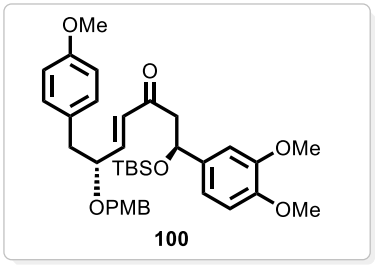
(1*S*,6*R*,*E*)-1-((*Tert*-butyldimethylsilyl)oxy)-1-(3,4-dimethoxyphenyl)-6-((4-methoxybenzyl)-oxy)-7-(4-methoxyphenyl)hept-4-en-3-ol (S7): To a stirred

solution of alcohol **107** (50 mg, 0.048mmol) in dry THF, Red-Al (0.031 mL, 0.161 mmol) was added at 0 ℃ under argon. The reaction mixture was stirred at the same temperature for 40 minutes. After completion of reaction, quenched with sat. aq. Rochelle salt and the whole reaction was stirred at rt for 30 min. and extracted with EtOAc (3x5 mL), the combined organic layer was washed with water and brine, dried over Na_2SO_4, filtered and concentrated and the crude product was purified by silica gel column chromatography using (10% EtOAc in hexanes) to afford **S7** (30 mg, 60%) as yellow liquid.; TLC: R_f = 0.5 (SiO_2, 20% EtOAc/hexanes). $[\alpha]_D^{29.77}$ =−10.48 (*c* = 0.1, $CHCl_3$); FTIR (cm^{-1}): 3685, 3619, 3461, 2971, 2402, 1728, 1604, 1515, 1426, 1040, 925; ^1H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, *J* = 8.39 Hz, 1H), 7.12-7.05 (m, 3H), 6.91-6.87 (m, 1H), 6.82-6.75 (m, 6H), 5.69-5.52 (m, 2H), 4.90-4.77 (m, 1H), 4.61 (s, 1H), 4.52-4.43 (m, 1H), 4.37-4.29 (m, 1H), 4.25-4.19 (m, 1H), 3.89-3.87 (m, 6H), 3.81-3.76 (m, 6H), 2.89-2.81(m, 1H), 2.74-2.66 (m, 1H), 2.01-1.74 (m, 2H), 1.69-1.63 (m, 1H), 0.93-0.89 (m, 9H), 0.09-0.05 (m, 3H), -0.10--0.14 (m, 1H), -0.22 (s, 2H); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$): δ 159.0, 158.1, 149.1, 148.4, 137.4, 135.5, 130.8, 130.7, 130.3, 129.2, 129.2, 128.8, 118.2, 114.0, 113.7, 113.5, 110.8, 110.7, 109.0, 80.4, 80.4, 76.1, 71.6, 70.0, 65.1, 56.0, 55.9, 55.4, 55.3, 55.3, 47.7, 41.7, 31.1, 25.9, 18.1, -4.2, -4.5, -4.9; HRMS (ESI): *m/z* calcd for $C_{36}H_{50}O_7NaSi$ $[M+Na]^+$ 645.3218 found 645.3210.



S7

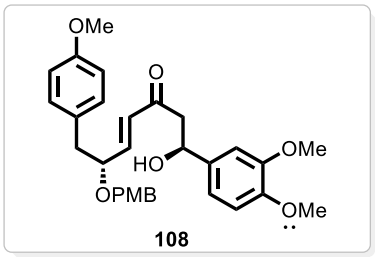
(1*S*,6*R*,*E*)-1-((*Tert*-butyldimethylsilyl)oxy)-1-(3,4-dimethoxyphenyl)-6-((4-mehoxybenzyl)-oxy)-7-(4-methoxyphenyl)hept-4-en-3-one (100): To a stirred solution of alcohol **S7** (104 mg, 0.167 mmol) in dry DCM, DMP (212 mg, 0.501 mmol) was added at 0 ℃ and the reaction mixture was stirred for 1h at the same temperature. After completion of reaction, reaction mixture was quenched with hypo solution (sat. aq. Solution of $NaHCO_3$ and sat. aq. solution of $Na_2S_2O_3$ (1:1)) and the aqueous layer was extracted with DCM (3x10 mL) and the combined organic layer was washed with brine and dried over Na_2SO_4, filtered and concentrated and the crude product was purified by silica gel column chromatography (using 10% EtOAc in hexanes) to afford **100** (92 mg, 89%) as a yellow liquid. TLC: R_f = 0.6 (SiO_2, 20% EtOAc/hexanes);



100

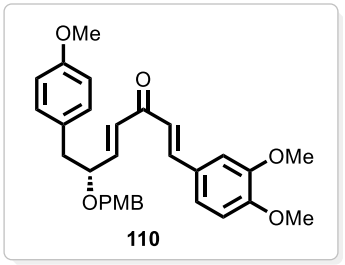
$[\alpha]_D^{28.93}$ =–12.33 (c = 1.6, $CHCl_3$); FTIR (cm^{-1}): 3425, 2967, 2403, 1614, 1513, 1464, 1426, 1079, 1036, 927; ^1H NMR (400 MHz, $CDCl_3$): δ 7.13-7.05 (m, 4H), 6.96-6.90 (m, 1H), 6.89-6.78 (m, 6H), 6.75-6.62 (m, 1H), 6.28-6.16 (m, 1H), 5.17 (ddd, *J* = 1.75, 3.88, 8.38 Hz, 1H), 4.49-4.38 (m, 1H), 4.26-4.19 (m, 1H), 4.13-4.04 (m, 1H), 3.82 - 3.91 (m, 6H), 3.82-3.76 (m, 6H), 3.06 (dd, *J* = 8.76, 14.88 Hz, 1H), 2.92-2.81 (m, 1H), 2.79-2.70 (m, 1H), 2.62 (dd, *J* = 4.13, 14.76 Hz, 1H), 0.91-0.76 (m, 9H), 0.0- -0.02 (m, 3H), -0.11- -0.18 (m, 3H); $^{13}C\{H\}$ NMR (101 MHz $CDCl_3$): δ 198.6, 159.3, 158.4, 149.0, 148.3, 146.6, 137.5, 131.2, 130.6, 130.1, 129.6, 129.4, 118.0, 113.9, 113.8, 110.8, 109.0, 79.3, 72.0, 71.1, 71.1, 56.0, 55.4, 55.4, 51.5, 41.0, 25.9, 18.3, -4.5, -5.0; HRMS (ESI): *m/z* calcd for $C_{36}H_{48}O_7NaSi$ $[M+Na]^+$ 643.3062, found 643.3051.

(1*S*,6*R*,*E*)-1-(3,4-Dimethoxyphenyl)-1-hydroxy-6-((4-methoxybenzyl)oxy)-7-(4-methoxyphenyl)-hept-4-en-3-one (108): To the TBS-alcohol **100** (77 mg, 0.12 mmol), HF: MeCN (5:95, 4 mL) was added at 0 °C. The reaction mixture was stirred at the same temperature for 24 h. after completion of reaction; reaction mixture was quenched with sat. aq. $NaHCO_3$. Both aqueous and organic layers were separated and the aqueous layer was extracted with EtOAc (3x5 mL) and combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated and the crude product was purified by silica gel chromatography (using 25% EtOAc in hexanes) to afford **108** (46 mg, 74%) as a yellow viscous liquid. TLC R_f = 0.2 (SiO_2, 30% EtOAc/hexanes). $[\alpha]_D^{28.56}$ = +4.35 (*c* = 1.5, $CHCl_3$).; FTIR (cm^{-1}): 3687, 3402, 1600, 1518, 1426, 1026, 922; ^1H NMR (400 MHz, $CDCl_3$): δ 7.13-7.02 (m, 4H), 6.95 (d, *J* = 1.75 Hz, 1H), 6.91-6.79 (m, 6H), 6.72 (ddd, *J* = 1.75, 6.00, 16.01 Hz, 1H), 6.20 (ddd, *J* = 1.13, 3.13, 16.01 Hz, 1H), 5.13 (dd, *J* = 2.75, 8.50 Hz, 1H), 4.45 (dd, *J* = 1.88, 11.51 Hz, 1H), 4.29 (d, *J* = 11.38 Hz, 1H), 4.17-4.06 (m, 1H), 3.94-3.86 (m, 6H), 3.84-3.75 (m, 6H), 3.41 (br. s., 1H), 3.01-2.85 (m, 3H), 2.76 (dd, *J* = 6.00, 13.88 Hz, 1H); $^{13}C\{H\}$ NMR (126 MHz, $CDCl_3$): δ 200.2, 159.4, 158.5, 149.3, 148.7, 147.5, 135.7, 130.6, 130.2, 130.0, 129.4, 129.3, 118.0, 113.9, 113.9, 111.2, 109.1, 79.3, 79.2, 71.3, 70.0, 56.1, 56.0, 55.4, 55.4, 48.9, 48.8, 40.8; HRMS (ESI): *m/z* calcd for $C_{30}H_{34}O_7Na$ $[M+Na]^+$ 529.2197, found 529.2197.



108

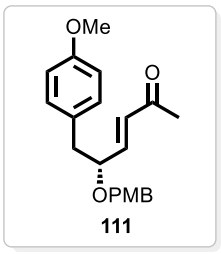
(*R*,1*E*,4*E*)-1-(3,4-Dimethoxyphenyl)-6-((4-methoxybenzyl)oxy)-7-(4-methoxyphenyl)hepta-1,4-dien-3-one (110): To the alcohol **108** (46 mg, 0.090 mmol) in



110

EtOH at 0 °C, KO^{t}Bu (1.0 mg, 0.013 mmol) in EtOH (2 mL) was added and reaction was monitored by TLC. After completion of reaction, solvent was evaporated in vacuum then sat. aq. solution of NH_4Cl was added and the aqueous layer was extracted with EtOAc (3x5 mL), dried over Na_2SO_4, filtered and concentrated and the crude product was purified by silica gel column chromatography to afford **110** as a yellow liquid (6 mg, 13%); TLC R_f = 0.5 (SiO_2, 50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 16.01 Hz, 1H), 7.20-7.06 (m, 5H), 6.93-6.76 (m, 7H), 6.54 (d, *J* = 15.76 Hz, 1H), 4.53 (d, *J* = 11.38 Hz, 1H), 4.33 (d, *J* = 11.51 Hz, 1H), 4.13-4.14 (m, 1H), 3.97-3.86 (m, 6H), 3.79 (s, 3H), 3.80 (s, 3H), 2.94 (dd, *J* = 7.25, 13.88 Hz, 1H), 2.83 (dd, *J* = 5.88, 13.76 Hz, 1H); ^{13}C{H} NMR (101 MHz, $CDCl_3$): δ 189.1, 159.4, 158.4, 151.6, 149.4, 145.9, 144.0, 130.8, 130.2, 129.7, 129.4, 129.1, 127.8, 123.4, 123.3, 113.9, 113.8, 111.2, 109.9, 79.7, 71.2, 56.2, 56.1, 55.4, 55.4, 41.1; HRMS (ESI): *m/z* calcd for $C_{30}H_{33}O_6$ $[M+H]^+$ 489.2272, found 489.2273.

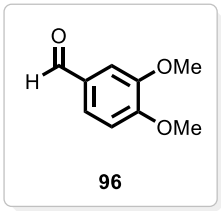
(*R*,*E*)-5-((4-Methoxybenzyl)oxy)-6-(4-methoxyphenyl)hex-3-en-2-one (111):



111

colorless oil (18 mg, 60%). TLC R_f = 0.7 (SiO_2, 50% EtOAc/hexanes); $[\alpha]_D^{29.80}$ = +8.76 (c = 1.1, $CHCl_3$).; ^{1}H NMR (400 MHz, $CDCl_3$): 7.15-7.04 (m, 4H), 6.88-6.79 (m, 4H), 6.65 (dd, *J* = 6.38, 16.13 Hz, 1H), 6.15 (dd, *J* = 1.13, 16.13 Hz, 1H), 4.47 (d, *J* = 11.51 Hz, 1H), 4.29 (d, *J* = 11.51 Hz, 1H), 4.10 (q, *J* = 7.00 Hz, 1H), 3.80 (s, 6H), 2.92 (dd, *J* = 7.25, 13.88 Hz, 1H), 2.78 (dd, *J* = 5.88, 13.88 Hz, 1H), 2.24 (s, 3H); ^{13}C {H} NMR (101 MHz, $CDCl_3$): δ 198.5, 159.4, 158.5, 146.7, 131.3, 130.7, 130.1, 129.4, 129.4, 113.9, 113.9, 79.3, 71.2, 55.4, 55.4, 41.0, 27.4; HRMS (ESI): *m/z* calcd for $C_{21}H_{24}O_4Na$ $[M+Na]^+$ 363.1567, found 363.1573.

3,4-Dimethoxybenzaldehyde (10): Off white solid; (4 mg, 26%); TLC R_f = 0.6 (SiO_2,

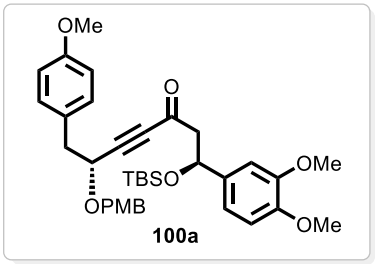


96

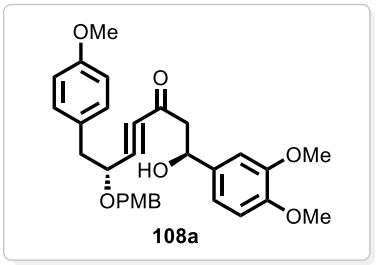
50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.85- 9.82 (m, 1H), 7.47-7.42 (m, 1H), 7.41-7.37 (m, 1H), 7.00-6.93 (m, 1H), 3.97-3.94 (m, 3H), 3.93-3.90 (m, 3H); ^{13}C{H} NMR (101 MHz, $CDCl_3$): δ 191.0, 154.6, 149.7, 130.2, 127.0, 110.5, 109.0, 56.3, 56.1; HRMS

(ESI): *m/z* calcd for $C_9H_{11}O_3$ $[M+H]^+$ 167.0703, found 167.0703.

(1*S*,6*R*)-1-((*Tert*-butyldimethylsilyl)oxy)-1-(3,4-dimethoxyphenyl)-6-((4-methoxybenzyl)-oxy)-7-(4-methoxyphenyl)hept-4-yn-3-one (100a): To the alcohol **107** (395 mg, 0.63 mmol) in dry DCM (5 mL), Dess-Martin-Periodinane (DMP) (405 mg, 0.95 mmol) was added at 0 °C and stirred for 1h. After completion of reaction, reaction was quenched with hypo solution 1:1 (aq. $NaHCO_3$: aq. $Na_2S_2O_3$), extracted with DCM (3x5 mL), dried over Na_2SO_4, filtered, concentrated and crude product was purified by silica gel column chromatography (using 12% EtOAc in hexanes) to afford **100a** (395 mg, 97%)as yellow liquid; TLC: R_f = 0.6 (SiO_2, 30% EtOAc/hexanes; $[\alpha]_D^{26.12}$ = +16.41 (*c* = 0.7, $CHCl_3$); FTIR (cm^{-1}): 3424, 2974, 2402, 1622, 1517, 1428, 1039, 927; ^1H NMR (500 MHz $CDCl_3$): δ 7.20-7.13 (m, 4H), 6.90 (s, 1H), 6.86-6.78 (m, 6H), 5.17 (ddd, *J* = 3.81, 9.16, 17.93 Hz, 1H), 4.71 (dd, *J* = 7.63, 11.44 Hz, 1H), 4.41 (dd, *J* = 5.34, 11.44 Hz, 1H), 4.33 (dt, *J* = 1.53, 6.87 Hz, 1H), 3.87 (s, 3H), 3.88 (s, 3H), 3.80 (m, 3H), 3.78 (s, 3H), 3.09-2.94 (m, 3H), 2.69 (ddd, *J* = 3.81, 7.25, 14.88 Hz, 1H), 0.85- 0.83 (m, 9H), 0.02 (d, *J* = 10.68 Hz, 3H), -0.16 (d, *J* = 9.16 Hz, 3H)); $^{13}C\{H\}$ NMR (126 MHz, $CDCl_3$) 185.2, 159.5, 158.7, 149.1, 148.5, 136.7, 130.8, 129.7, 129.3, 128.6, 118.1, 114.0, 113.9, 110.9, 109.0, 91.0, 86.0, 71.4, 71.0, 69.7, 69.5, 56.8, 56.0, 56.0, 55.4, 55.4, 40.7, 31.7, 25.9, -4.5, -5.0; HRMS (ESI): *m/z* calcd for $C_{36}H_{46}O_7NaSi$ $[M+Na]^+$ 641.2905, found 641.2895.

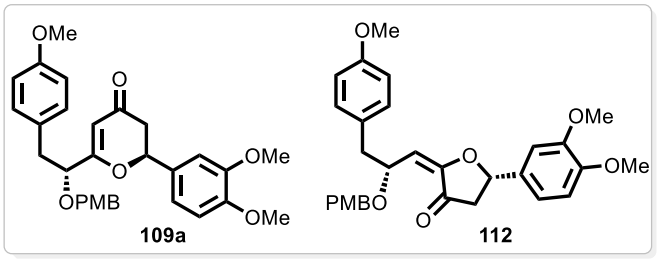


(1*S*,6*R*)-1-(3,4-Dimethoxyphenyl)-1-hydroxy-6-((4-methoxybenzyl)oxy)-7-(4-methoxyphenyl)hept-4-yn-3-one (108a): To the TBS-alcohol **100a** (50 mg, 0.08 mmol), HF:MeCN (5:95, 2 mL) was added and stirred at 0 °C until starting material was completely consumed (24 h). After completion of reaction, reaction was quenched with sat. aq. $NaHCO_3$, extracted with EtOAc (3x 5 mL), dried over Na_2SO_4, filtered, concentrated and subjected to column chromatography (using 30 % EtOAc in hexanes) to afford **108a** (31 mg, 77%)as yellow liquid. TLC: R_f = 0.4 (SiO_2, 40% EtOAc/hexanes; $[\alpha]_D^{26.13}$ = +16.97 (c = 1.6, $CHCl_3$). FTIR (cm^{-1}): 3686, 3618, 3444, 2974, 2403, 1605, 1518,



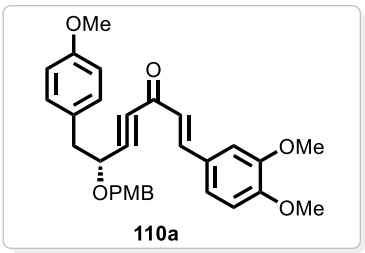
1427, 1039, 927; ^{1}H NMR (500 MHz $CDCl_3$): δ 7.18 (d, *J* = 8.77 Hz, 2H), 7.16-7.12 (m, 2H), 6.93-6.89 (m, 1H), 6.87-6.79 (m, 6H), 5.13 (d, *J* = 8.01 Hz, 1H), 4.69 (d, *J* = 11.83 Hz, 1H), 4.43 (d, *J* = 11.44 Hz, 1H), 4.35 (t, *J* = 6.49 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.79 (s, 3H), 3.77-3.74 (m, 3H), 3.09-2.94 (m, 3H), 2.91-2.84 (m, 1H), 2.76 (br. s., 1H); ^{13}C{H} NMR (126 MHz, $CDCl_3$) δ 186.2, 159.5, 158.8, 149.3, 148.8, 135.1, 130.8, 129.7, 129.2, 128.4, 118.0, 114.0, 113.8, 111.2, 109.0, 92.1, 85.3, 71.2, 69.7, 69.5, 56.1, 56.0, 55.4, 55.3, 54.3, 40.6; HRMS (ESI): *m/z* calcd for $C_{30}H_{32}O_7Na$ $[M+Na]^+$527.2040, found 527.2045.

(*S*)-2-(3,4-Dimethoxyphenyl)-6-((*R*)-1-((4-methoxybenzyl)oxy)-2-(4-methoxyphenyl)ethyl)-2,3-dihydro-4*H*-pyran-4-one (109a), and (*S*,*E*)-5-(3,4-Dimethoxyphenyl)-2-((*R*)-2-((4-methoxybenzyl)oxy)-3-(4-methoxyphenyl)propylidene)-dihydrofuran-3(2*H*)-one (112): AuCl (1.0 mg) was taken in DCM in 10 mL round



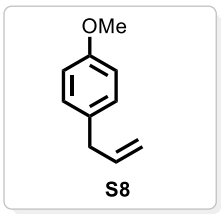
bottom flask then activated molecular sieves was added to this and the mixture was stirred for 15 min., then hydroxy-ynone **108a** (11 mg, 0.021 mmol) in DCM was added to AuCl mixture dropwise then $NaHCO_3$ was added to the reaction mixture and mixture was stirred for 1h at rt. After completion of reaction the mixture was filtered through celite and the filtrate was concentrated and crude product was purified by silica gel column chromatography (using 30% EtOAc in hexanes) to afford the inseparable mixture **109a** and **112** (10 mg, 90%); as yellow oil. TLC: R_f = 0.5 (SiO_2, 40% EtOAc/hexanes; $[\alpha]_D^{26.12}$ =–2.31 (c = 0.6, $CHCl_3$).; FTIR (cm^{-1}) : 3686, 3620, 3455, 2975, 2403, 1600, 1521, 1427, 1041, 927; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15-7.07 (m, 4H), 6.89 (s, 2H), 6.86-6.78 (m, 5H), 5.66 (d, *J* = 15.57 Hz, 1H), 5.33 (dd, *J* = 3.66, 13.28 Hz, 1H), 5.11 (dd, *J* = 2.75, 14.20 Hz, 1H), 4.51 (dd, *J* = 11.45, 16.49 Hz, 1H), 4.39-4.23 (m, 1H), 4.09-4.00 (m, 1H), 3.93-3.86 (m, 7H), 3.81-3.76 (m, 6H), 3.02-2.88 (m, 2H), 2.87-2.74 (m, 1H), 2.65-2.54 (m, 1H); ^{13}C{H} NMR (101 MHz, $CDCl_3$): δ 192.9, 192.7, 176.4, 175.4, 159.4, 158.5, 149.6, 149.3, 130.6, 130.5, 130.2, 129.5, 129.1, 119.1, 119.1, 113.9, 113.8, 111.2, 109.8, 109.6, 104.1, 104.0, 81.1, 79.8, 79.7, 71.9, 71.8, 56.1, 55.4, 55.3, 42.8, 42.6, 39.9, 39.5; HRMS (ESI): *m/z* calcd for $C_{30}H_{33}O_7$ $[M+H]^+$ 505.2221, found 505.2217.

(*R*,*E*)-1-(3,4-Dimethoxyphenyl)-6-((4-methoxyben-zyl)oxy)-7-(4-methoxyphe-nyl)hept-1-en-4-yn-3-one (110a): To the solution of alcohol **108a** (40 mg, 0.079 mmol), NaH (1 mg, 0.079 mmol, 55-60% in mineral oil) was added in one portion at 0 °C. The reaction was stirred for 15 min. after completion of reaction, it was quenched with water and extracted with EtOAc (3x5 mL) , dried over Na_2SO_4, filtered, concentrated and subjected to column chromatography(using 15 % EtOAc in hexanes) to afford **110a** (30.4 mg, 78%) as yellow viscous liquid; TLC: R_f = 0.4 (SiO_2, 30% EtOAc in hexanes); FTIR (cm-1): 3433, 2974, 2402, 2361, 2104, 1630, 1518, 1427, 1340, 1040, 927; ^{1}H NMR (400 MHz $CDCl_3$): δ 7.48 (d, *J* = 16.01 Hz, 1H), 7.25-7.19 (m, 4H), 7.05 (dd, *J* = 1.88, 8.25 Hz, 1H), 6.99 (d, *J* = 1.75 Hz, 1H), 6.91-6.81 (m, 5H), 6.64 (d, *J* = 16.01 Hz, 1H), 4.80 (d, *J* = 11.51 Hz, 1H), 4.52 (d, *J* = 11.51 Hz, 1H), 4.46 (t, *J* = 6.88 Hz, 1H), 3.95-3.93 (m, 3H), 3.92 (s, 3H), 3.80 (s, 3H), 3.73 (s, 3H), 3.12(dd, *J* = 6.63, 13.76 Hz, 1H), 3.06 (dd, *J* = 7.00, 13.63 Hz, 1H); ^{13}C{H} NMR (101 MHz $CDCl_3$): δ 177.9, 159.5, 158.7, 152.2, 149.5, 149.2, 130.9, 129.8, 129.4, 128.6, 127.1, 126.6, 123.9, 114.0, 113.9, 111.2, 110.1, 90.9, 84.2, 71.1, 69.8, 56.2, 56.1, 55.4, 55.3, 40.8; HRMS (ESI): m/z calcd for C30H32O6 [M+H]+ 487.2115, found 487.2132.



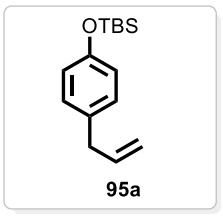
110a

4-Allylphenol (S8): Allyl anisole (5 g, 33.7 mmol) was dissolved in DCM (50 mL) and BBr_3 (3.52 mL, 37.1mmol) was added at 0 °C. Then reaction mixture was stirred for 1h at the same temperature. After completion of reaction, it was quenched with water and extracted with DCM (3x20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (using 8% EtOAc in hexanes) to afford 4-allylphenol (**S8**) (4.3 g, 95%) as colorless liquid. TLC: R_f = 0.2 (SiO_2, 10% EtOAc/hexanes); FTIR (cm^{-1}): 3944, 3687, 3583, 2986, 2685, 2521, 2410, 2304, 1605, 1546, 1512, 1428, 1171, 995, 898; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.11-7.03 (m, 2H), 6.86-6.72 (m, 2H), 6.07-5.89 (m, 1H), 5.42 (br. s., 1H), 5.16-5.03 (m, 2H), 3.34 (d, *J* = 6.63 Hz, 2H); ^{13}C{H}NMR ($CDCl_3$, 101 MHz): δ 153.8, 138.0, 132.4, 129.8, 115.6, 115.4, 39.4; HRMS (ESI): *m/z* calcd for $C_9H_{11}O$ $[M+H]^+$ 135.0804, found 135.0809.



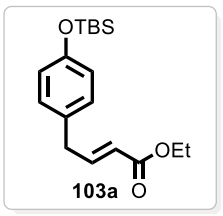
S8

(4-Allylphenoxy)(*tert*-butyl)dimethylsilane (95a): To the allyphenol **S8** (4.3 g, 32.0 mmol) in dry DCM, (tert-butyl)dimethylsilylchloride (5.79 g, 38 mmol) and imidazole (4.35 g, 64 mmol) was added at 0 °C and reaction mixture was stirred for overnight. After completion of reaction, reaction was quenched with sat. NH_4Cl and the aqueous layer were extracted with DCM (3x20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (using 3% EtOAc in hexanes) to afford **95a** (6.5 g, 82%) as colorless liquid. TLC: R_f = 0.8 (SiO_2, 20% EtOAc/hexanes); FTIR (cm^{-1}): 3685, 3620, 2940, 2894, 2861, 2403, 1887, 1609, 1511, 1446, 1426, 1258, 1101, 1043, 915, 834; ^1H NMR , ($CDCl_3$, 400 MHz): δ 7.08-7.01 (m, 2H), 6.83-6.73 (m, 2H), 6.03-5.89 (m, 1H), 5.12-5.01 (m, 2H), 3.33 (d, *J* = 6.63 Hz, 2H), 0.99 (s, 9H), 0.20 (s, 6H); $^{13}C\{H\}$NMR ($CDCl_3$, 101 MHz): δ 154.0, 138.1, 132.8, 129.6, 120.1, 115.5, 39.6, 25.9, 25.8, 18.3, -4.3; HRMS (ESI): *m/z* calcd for $C_{15}H_{25}OSi$ $[M+H]^+$ 249.1669, found 249.1670.



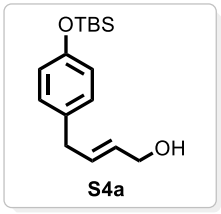
95a

Ethyl-(*E*)-4-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)but-2-enoate (103a): To a solution of Grubb's 2nd generation catalyst (123 mg, 0.1 mmol) (4-allylphenoxy)(tert-butyl)dimethylsilane (**95a**) (4.89 g, 19.7 mmol) and ethyl acrylate (4.33 mL, 39.4 mmol) were added simultaneously via syringe. The resulting mixture was heated at 40 °C until consumption of starting material occurred as determined by TLC analysis. The reaction cooled to rt, concentrated and residue was purified by column chromatography using 10% EtOAc in hexanes) to afford **103a** (4.88 g, 77%) as yellowish liquid. TLC: *Rf* = 0.6 (SiO_2, 20% EtOAc/hexanes); FTIR (cm^{-1}): 3531, 2985, 2481, 2254, 2090, 2015, 1887, 1742, 1561, 1449, 1374, 1232, 1165, 1099, 1046, 914, 847;^1H NMR ($CDCl_3$, 400 MHz): δ 7.07 (d, *J* = 15.51 Hz, 1H), 7.04-6.99 (m, 2H), 6.83-6.73 (m, 2H), 5.78 (td, *J* = 1.75, 15.63 Hz, 1H), 4.18 (q, *J* = 7.13 Hz, 2H), 3.44 (dd, *J* = 1.50, 6.88 Hz, 2H), 1.27 (t, *J* = 7.13 Hz, 4H), 0.98 (s, 9H), 0.19 (s, 6H); $^{13}C\{H\}$NMR ($CDCl_3$, 101 MHz): δ 166.8, 154.5, 147.9, 130.4, 129.9, 122.2, 120.4, 60.4, 37.9, 25.8, 18.3, 14.4, -4.3 ; HRMS (ESI): *m/z* calcd for $C_{18}H_{28}O_3NaSi$ $[M+Na]^+$ 343.1700, found 343.1709.



103a

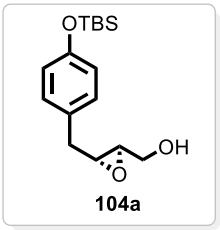
(*E*)-4-(4-((*Tert*-butyldimethylsilyl)oxy)phenyl)but-2-en-1-ol (S4a): To a solution



S4a

of corresponding ester **103a** (4.88 g, 15.2 mmol) in DCM at -78 ℃ was added DIBAL-H (1M in toluene, 12.99 mL, 22.8 mmol)) dropwise. The solution was stirred at this temperature until consumption of starting material was observed by TLC at which point the reaction was quenched by careful addition of methanol. The reaction was allowed to warm at rt where upon sat. aq. Na^+-K^+ tartarate and EtOAc were added and the mixture was stirred vigorously for 1h. The phases were then separated and the aqueous phase was extracted with EtOAc (3x20 mL). The organic phases were combined washed with sat. aq. Na^+-K^+ tartarate, water and brine, dried over Na_2SO_4, filtered and concentrated and crude product was purified by silica gel column chromatography (using 20% EtOAc in hexanes) to afford **S4a** (3.2 g, 75%) as yellow liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/hexanes); FTIR (cm^{-1}): 3944, 3424, 3056, 2987, 2685, 2522, 2410, 2304, 1764, 1640, 1552, 1427, 1263, 1159, 1055, 901; ^1H NMR ($CDCl_3$, 400MHz): δ 7.08-6.98 (m, 2H), 6.81-6.71 (m, 2H), 5.90-5.78 (m, 1H), 5.75-5.61 (m, 1H), 4.17-4.09 (m, 2H), 3.31 (d, J = 6.50 Hz, 2H), 0.98 (s, 9H), 0.18 (s, 6H); $^{13}C\{H\}$ NMR ($CDCl_3$, 101 MHz): δ 154.1, 132.7, 132.2, 130.1, 129.6, 120.1, 63.7, 38.0, 25.8, 18.3, -4.3; HRMS (ESI): *m/z* calcd for $C_{16}H_{27}O_2Si$ $[M+H]^+$ 279.1775, found 279.1773.

((2*R*,3*R*)-3-(4-((*Tert*-butyldimethylsilyl)oxy)benzyl)oxiran-2-yl)methanol

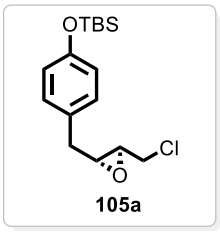


104a

(104a): MS-4 Å were dried in a flask and allowed to rt, dry DCM (10 mL) and (-)-DET (0.27 mL, 1.59 mmol) were added and the suspension was cooled to -25 ℃. To this $Ti(O^iPr)_4$ (0.70 mL, 2.39 mmol) and TBHP (5 M in DCM, 7.02 mL, 35.1 mmol) were added and the mixture was stirred at -25 ℃ for 30 min. A solution of allylic alcohol **S4a** (4.45 g, 15.97 mmol) in dry DCM was added to the above mixture and it was kept in freezer at about -25 ℃ for 18 h. To the reaction mixture water was added and stirred at 0 ℃ for 30 min. A solution of 10% aq. NaOH was then added and the mixture was warmed to rt for 1h. The product was extracted with DCM (3x20 mL), dried over Na_2SO_4, filtered and concentrated in vacuum and purified by silica gel column chromatography using (20% EtOAc in hexanes) to afford **104a** (4.53 g, 96%) as yellow liquid. TLC: R_f = 0.5 (SiO_2, 40% EtOAc/hexanes); $[\alpha]_D^{26.49}$ = +15.31 (c = 2.1, $CHCl_3$); FTIR (cm^{-1}): 3434, 2964, 2865, 2403, 2361, 2086, 1763, 1614, 1513, 1471,

1425, 1257, 1216, 1043, 917, 838; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.12-7.03 (m, 2H), 6.84-6.71(m, 2H), 3.96-3.84 (m, 1H), 3.68-3.57 (m, 1H), 3.17 (dt, *J* = 2.25, 5.50 Hz, 1H), 3.00-2.94 (m, 1H), 2.91-2.75 (m, 2H), 1.69 (t, *J* = 6.25 Hz, 1H), 0.98 (s, 9H), 0.19 (s, 6H); ^{13}C{H} NMR ($CDCl_3$, 101 MHz): δ 154.6, 130.0, 129.7, 120.3, 61.6, 58.3, 56.2, 37.2, 25.8, 18.3, -4.3; HRMS (ESI): *m/z* calcd for $C_{16}H_{27}O_3Si$ $[M+H]^+$ 295.1724, found 295.1716.

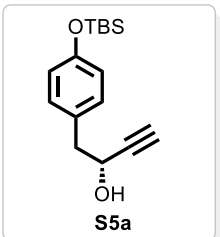
***Tert*-butyl(4-(((2*R*,3*S*)-3-(chloromethyl)oxiran-2-yl)methyl)phenoxy)dimethyl-**



105a

silane (105a): To a solution of epoxy alcohol **104a** (5 g, 17.9 mmol) in DCM (50 mL), CCl_4 (3.47 mL, 35.9 mmol) and triphenylphosphine (6.57g, 25.06 mmol) were added at 0 ℃ and the refluxed for 6h. After completion of reaction, it was diluted with hexane and filtered through celite. The filtrate was concentrated to give a residue which was purified by silica gel column chromatography (using 3 % EtOAc in hexanes) to afford **105a** (4.01 g, 71%) as yellow liquid. TLC: R_f = 0.6 (SiO_2, 20% EtOAc/hexanes; $[\alpha]_D^{26.51}$ = +22.24 (c = 1.4, $CHCl_3$); FTIR (cm^{-1}): 3679, 3426, 2971, 2402, 2361, 2096, 1764, 1640, 1516, 1478, 1426, 1043, 921; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.11-7.06 (m, 2H), 6.80-6.76 (m, 2H), 3.62-3.49 (m, 2H), 3.13-3.02 (m, 2H), 2.96-2.74 (m, 2H), 0.98 (s, 9H), 0.19 (s, 6H); ^{13}C{H} NMR ($CDCl_3$, 101 MHz): δ 154.7, 130.3, 130.1, 129.3, 120.5, 120.3, 59.3, 57.1, 44.7, 37.1, 25.8, 25.8, 18.3, -4.3; HRMS (ESI): *m/z* calcd for $C_{16}H_{26}O_2ClSi$ $[M+H]^+$313.1385, found 313.1385.

(*R*)-1-(4-((*Tert*-butyldimethylsilyl)oxy)phenyl)but-3-yn-2-ol (S5a): To a solution

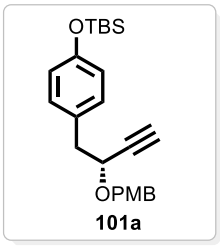


S5a

of chloride **105a** (4 g, 12.7 mmol) in dry THF, *n*-BuLi (2.5 M in hexane, 17.78 mL, 44.7 mmol) was added dropwise at -78 ℃. The reaction mixture was stirred at the same temperature for 30 min. after completion of reaction; reaction was quenched with aq. sat. NH_4Cl at 0 ℃. The organic phase was separated and the aqueous phase was extracted with EtOAc (3x20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuum and crude product was purified by silica gel column chromatography (using 5% EtOAc in hexanes) to afford **S5a** (3.2 g, 91%) as yellow liquid. TLC: R_f = 0.6 (SiO_2, 20% EtOAc/hexanes; $[\alpha]_D^{26.20}$ = +1.87 (*c* =

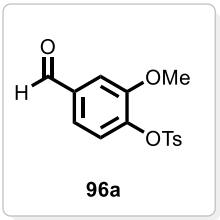
1.2, $CHCl_3$); FTIR (cm^{-1}): 3685, 3615, 3305, 2965, 2893, 2402, 1606, 1513, 1473, 1426, 1257, 1216, 1041, 919; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.06-7.12 (m, 2H), 6.81-6.77 (m, 2H), 4.54 (dq, *J* = 1.91, 6.10 Hz, 1H), 3.00-2.90 (m, 2H), 2.48 (d, *J* = 1.91 Hz, 1H), 1.92 (d, *J* = 5.72 Hz, 1H), 0.98 (s, 9H), 0.19 (s, 6H); $^{13}C\{H\}$ NMR ($CDCl_3$, 125 MHz): δ 154.9, 130.9, 128.9, 120.2, 84.4, 73.8, 63.2, 43.2, 25.8, 18.3, -4.3; HRMS (ESI): *m/z* calcd for $C_{16}H_{25}O_2Si$ $[M+H]^+$277.1618, found 277.1618.

(*R*)-*Tert*-butyl(4-(2-((4-methoxybenzyl)oxy)but-3-yn-1-yl)phenoxy)dimethyl-silane (101a): PMB-TCAI in CH_2Cl_2 (20 mL) was added via cannula to a solution of (*R*)-1-(4-((tert-butyldimethyl-silyl)oxy)phenyl)but-3-yn-2-ol **S5a** (3.421 g, 10.87 mmol) in anhydrous CH_2Cl_2 (200 mL) under N_2 at room temperature. PPTS (856 mg, 3.372 mmol) were then added and the resultant mixture was stirred for 17 h. After addition of a saturated solution of $NaHCO_3$ (50 mL), the phases were separated and the organic layer was washed with brine (50 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (using 5% EtOAc in hexanes) to afford **101a** (3.0 g, 84%) as yellow liquid. TLC: R_f = 0.7 (SiO_2, 20% EtOAc/hexanes); $[\alpha]_D^{26.51}$ = +17.0 (c = 2.6, $CHCl_3$); FTIR (cm^{-1}): 3425, 2976, 2402, 1640, 1519, 1427, 1041, 927; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.18 (d, *J* = 8.39 Hz, 2H), 7.10 (d, *J* = 8.39 Hz, 2H), 6.84 (d, *J* = 9.16 Hz, 2H), 6.77 (d, *J* = 8.39 Hz, 2H), 4.74 (d, *J* = 11.44 Hz, 1H), 4.44 (d, *J* = 11.44 Hz, 1H), 4.19 (dt, *J* = 1.53, 6.87 Hz, 1H), 3.80 (s, 3H), 3.05-2.91 (m, 2H), 2.47 (d, *J* = 2.29 Hz, 1H), 0.99 (s, 9H), 0.20 (s, 6H); $^{13}C\{H\}$NMR ($CDCl_3$, 101 MHz): δ 159.3, 154.5, 130.7, 130.0, 129.9, 129.6, 119.8, 113.8, 82.7, 74.6, 70.4, 69.4, 55.4, 41.5, 25.8, 18.3, -4.3; HRMS (ESI): *m/z* calcd for $C_{24}H_{33}O_3Si$ $[M+H]^+$ 397.2193, found 397.2193.



101a

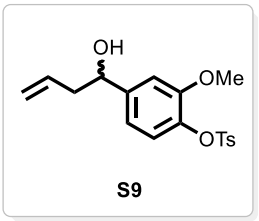
4-Formyl-2-methoxyphenyl-4-methylbenzenesulfonate (96a): To a stirred solution of vanillin (5 g, 32.86 mmol) in DCM at 0 °C was added Et_3N (4.5 mL, 32.86 mmol) followed by *p*-toluene sulphonylchloride (6.26 g, 32.86 mmol) then the reaction temperature raised to 25 °C and stirred for 2h. The reaction was diluted with 1N HCl and the layers were separated. The organic layer was further washed with 1N HCl followed by sat. aq. $NaHCO_3$ and brine. The combined organic



96a

layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (using 8% EtOAc in hexanes) to afford **96a** (9.2 g, 91%) as white solid; TLC: R_f = 0.7 SiO_2, 20% EtOAc/hexanes; FTIR (cm^{-1}): 3859, 3425, 2926, 2856, 1694, 1502, 1379, 1276, 1214, 1103, 1035, 855; ^1H NMR (500 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.74 (d, *J* = 8.01 Hz, 2H), 7.40 (s, 1H), 7.36-7.33 (m, 2H), 7.30 (m, 2H), 3.62 (s, 3H), 2.44 (s, 3H); $^{13}C\{H\}$ NMR (126 MHz, $CDCl_3$) δ 190.9, 152.7, 145.6, 143.1, 135.9, 133.0, 129.6, 128.7, 124.6, 124.4, 111.2, 55.9, 21.8; HRMS (ESI): *m/z* calcd for $C_{15}H_{15}O_5S$ $[M+H]^+$ 307.0635, found 307.0634.

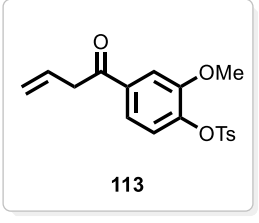
4-(1-Hydroxybut-3-en-1-yl)-2-methoxyphenyl-4-methylbenzenesulphonate



S9

(S9): To a solution of aldehyde **96a** (9.2 g, 30.2 mmol) in dry THF (100 mL), allyl magnesium chloride (2 M in THF, 22.71 mL, 45.4 mmol) was added at -78 ℃ and the reaction mixture stirred for 1 h at the same temperature. After completion of reaction, reaction was quenched with sat. aq. solution of NH_4Cl. The layers were separated and the aqueous layer was extracted with ethyl acetate (3x50 mL) and the combined organic layer were washed with brine and dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuum and the crude product was purified by silica gel column chromatography (using 15% EtOAc in hexanes) to afford **S9** (10 g, 95%) as colorless oil. TLC: R_f = 0.4 (SiO_2, 30% EtOAc/hexanes, FTIR (cm^{-1}): 3434, 2971, 2927, 2860, 2403, 2068, 1640, 1606, 1507, 1460, 1372, 1273, 1104, 1039, 927, 854; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78-7.73 (m, 2H), 7.32-7.27 (m, 2H), 7.10 (d, *J* = 8.26 Hz, 1H), 6.89 (d, *J* = 1.88 Hz, 1H), 6.86-6.81 (m, 1H), 5.85-5.73 (m, 1H), 5.20-5.13 (m, 2H), 4.69 (dd, *J* = 4.75, 8.00 Hz, 1H), 3.57 (s, 3H), 2.54-2.46 (m, 1H), 2.44 (s, 3H), 2.43-2.35 (m, 1H), 2.12-2.06 (br. s, 1H); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$) δ 151.9, 145.1, 144.2, 137.6, 134.2, 133.4, 129.5, 128.7, 123.9, 119.0, 117.9, 110.1, 72.8, 55.7, 44.1, 21.8.

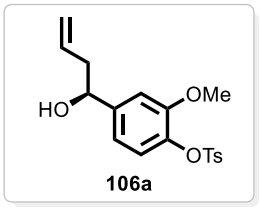
4-(But-3-enoyl)-2-methoxyphenyl-4-methylbenzenesulfonate (113): To the allyl alcohol **S9** (10 g, 28.7 mmol) in dry DCM (100 mL) at 0 ℃, DMP (18.26 g, 43.0 mmol) was added and the reaction mixture was stirred up to starting material completely consumed (1 h). After completion of reaction, reaction was quenched with hypo



113

solution (1: 1 ratio of Sat. $NaHCO_3$ and Sat. $Na_2S_2O_3$) and the aqueous layer was extracted with DCM (3x50 mL) and the combined organic layers were washed with brine and dried with anhydrous Na_2SO_4, filtered and concentrated and crude product was purified by silica gel column (using 15 % EtOAc in hexanes) chromatography to afford **113** (8.1 g, 81%) as yellow liquid. TLC: R_f = 0.5 (SiO_2, 30% EtOAc/hexanes), FTIR (cm^{-1}): 3680, 3517, 2970, 2928, 2858, 2625, 2405, 1917, 1674, 1596, 1502, 1455, 1409, 1374, 1281, 1167, 1119, 1032, 962, 914, 847; ^1H NMR (400 MHz, , $CDCl_3$) δ 7.74 (d, *J* = 8.00 Hz, 2H), 7.50 (dd, *J* = 1.75, 8.25 Hz, 1H), 7.47-7.40 (m, 1H), 7.30 (d, *J* = 8.13 Hz, 2H), 7.26 (d, *J* = 8.26 Hz, 1H), 6.14-5.92 (m, 1H), 5.26-5.16 (m, 2H), 3.71 (d, *J* = 6.75 Hz, 2H), 3.60 (s, 3H), 2.44 (s, 3H); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$) δ 196.9, 152.2, 145.5, 142.2, 136.2, 133.1, 130.8, 129.6, 128.7, 124.1, 121.5, 119.1, 112.0, 55.8, 43.5, 21.8; HRMS (ESI): *m/z* calcd for $C_{18}H_{19}O_5S$ $[M+H]^+$ 347.0948, found 347.0948.

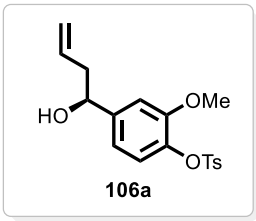
(*S*)-4-(1-Hydroxybut-3-en-1-yl)-2-methoxyphenyl-4-methylbenzenesulphonate



106a

(106a): (*R*)-CBS (23.40 mL, 23.4 mmol) reagent was added to a solution of BH_3-Me_2S (2.21 mL, 23.4 mmol) in dry THF (10 mL) and stirred for 15 min. at rt, then cooled to -20 ℃. After that a solution of 4-(but-3-enoyl)-2-methoxyphenyl-4-methylbenzenesulfonate **113** (8.1 g, 23.4 mmol) in dry THF (60 mL) was added to this dropwise. Then the reaction mixture was stirred for 2h at the same temperature then quenched with MeOH and warmed to rt for 1h then the solvent was removed in vacuum and the crude product was purified by silica gel column chromatography (using 15% EtOAc in hexanes) to afford **106a** (8 g, 98%) as colorless oil; TLC: R_f = 0.4 (SiO_2, 30% EtOAc/hexanes); Reported $[\alpha]_D^{25}$ = +17.0 (*c* = 1.0, $CHCl_3$) for (*R*)-20a, observed $[\alpha]_D^{26.27}$ = −11.038 (c = 2.3, $CHCl_3$); FTIR (cm^{-1}): 3433, 2976, 2402, 2361, 2100, 1640, 1515, 1423, 1376, 1084, 1041, 926, 850; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76-7.69 (m, 2H), 7.29-7.26 (m, 2H), 7.07 (d, *J* = 8.25 Hz, 1H), 6.87 (d, *J* = 1.88 Hz, 1H), 6.86-6.77 (m, 1H), 5.82-5.70 (m, 1H), 5.18-5.08 (m, 2H), 4.67 (dd, *J* = 4.75, 7.88 Hz, 1H), 3.54 (s, 3H), 2.52-2.44 (m, 1H), 2.43 (s, 3H), 2.42-2.36 (m, 1H), 2.13 (br. s., 1H); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$) δ 151.9, 145.1, 144.2, 137.6, 134.2, 133.4, 129.5, 128.7, 123.9, 119.0, 117.9, 110.1, 72.8, 55.7, 44.1, 21.8; HRMS (ESI): *m/z* calcd for $C_{18}H_{21}O_5S$ $[M+H]^+$ 349.1104, found 349.1320.

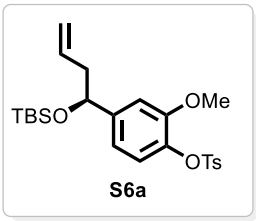
(*S*)-4-(1-Hydroxybut-3-en-1-yl)-2-methoxyphenyl-4-methylbenzenesulphonate (106a): To the stirred solution of oven dried MS 4Å in DCM under N_2 atmosphere



106a

was added *S*-BINOL (953 mg, 3.32 mmol) a 1.0 M solution of $Ti(O^iPr)_4$ (1.66 mL, 1.66 mmol) in DCM and a freshly prepared 1 M solution of TFA (0.09 mL, 0.099 mmol) in DCM. The reaction mixture was heated at reflux for a period of 3h and then cooled to rt, a solution of tosyl aldehyde **96a** (5.1 g, 16.64 mmol) in DCM was added to the reaction mixture stirred for 0.5 h at rt then cooled to -78 ℃, allyltributyltin (7.16 mL, 21.64 mmol) was slowly added and the reaction mixture was stirred for addition 10 min. at -78 ℃ and then kept in a -20 ℃ freezer. After 4 d, the reaction was filtered through a pad of celite into a 500 mL flask that contained a stirring sat. aq. $NaHCO_3$ solution and the resulting mixture were stirred for 1h then the layers were separated. The aq. layer was extracted with DCM. The combined layers were washed with brine dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. The crude product was purified by silica gel column chromatography to afford **106a** (3.97 g, 68%) as colorless oil. TLC: R_f = 0.4 (SiO_2, 30% EtOAc/hexanes); $[\alpha]_D^{25.89}$ =−13.50 (c = 2.2, $CHCl_3$); FTIR (cm^{-1}): 3607, 3434, 3019, 2403, 2360, 2067, 1638, 1608, 1508, 1461, 1419, 1376, 1123, 1085, 1041, 938, 853; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.39 Hz, 2H), 7.28 (d, *J* = 8.01 Hz, 2H), 7.09 (d, *J* = 8.01 Hz, 1H), 6.88 (s, 1H), 6.86-6.80 (m, 1H), 5.82-5.72 (m, 1H), 5.18-5.11 (m, 2H), 4.68 (dd, *J* = 4.96, 7.63 Hz, 1H), 3.56 (s, 3H), 2.51-2.45 (m, 1H), 2.43 (s, 3H), 2.42-2.37 (m, 1H), 2.18 (br. s., 1H); $^{13}C\{H\}$ NMR (126 MHz, $CDCl_3$) δ 151.9, 145.1, 144.2, 137.6, 134.2, 133.4, 129.4, 128.7, 123.9, 118.9, 117.9, 110.2, 72.8, 55.7, 44.0, 21.8; HRMS (ESI): *m/z* calcd for $C_{18}H_{20}O_5NaS$ $[M+Na]^+$ 371.0924, found 371.0923.

(*S*)-4-(1-((*Tert*-butyldimethylsilyl)oxy)but-3-en-1-yl)-2-methoxyphenyl-4-methylbenzenesulphonate (S6a): To a solution of (*S*)-4-(1-hydroxybut-3-en-1-yl)-

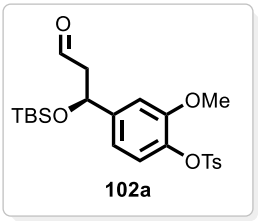


S6a

2-methoxyphenyl-4-methyl-benzenesulphonate 20a (8 g, 22.96 mmol) in dry DCM (50 mL), imidazole (2.34 g, 34.44 mmol) and DMAP (280 mg, 2.29 mmol) was added at 0 ℃ and the reaction mixture was stirred for 10 min. After that TBSCl (3.97 g, 26.4 mmol) was added to this reaction mixture and it was stirred for 24 h. After completion of reaction it was quenched with sat. aq. NH_4Cl and aqueous layer was

extracted with DCM (3x50 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuum and the crude product was purified with silica gel column chromatography to afford **S6a** (10 g, 94%) as colorless oil. TLC: R_f= 0.8 (SiO_2, 20% EtOAc/hexanes; $[\alpha]_D^{26.26}$ = –25.92 (c = 2.6, $CHCl_3$); FTIR (cm^{-1}): 3426, 2937, 2860, 2403, 1640, 1604, 1504, 1462, 1418, 1370, 1088, 1039, 925, 845; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.39 Hz, 2H), 7.24 (d, *J* = 8.39 Hz, 2H), 7.10 (d, *J* = 8.01 Hz, 1H), 6.81 (d, *J* = 1.91 Hz, 1H), 6.76 (dd, *J* = 1.53, 8.01 Hz, 1H), 5.76-5.67 (m, 1H), 5.02-4.95 (m, 2H), 4.62 (dd, *J* = 5.34, 7.25 Hz, 1H), 3.49 (s, 3H), 2.41 (s, 3H), 2.40-2.29 (m, 2H), 0.86 (s, 9H), 0.01 (s, 3H), -0.15 (s, 3H); $^{13}C\{H\}$ NMR (126 MHz, $CDCl_3$) δ 151.5, 145.6, 145.0, 137.2, 134.8, 133.1, 129.2, 128.8, 123.5, 117.9, 117.3, 110.1, 74.5, 55.5, 45.4, 25.9, 21.7, 18.3, -4.6, -4.8; HRMS (ESI): *m/z* calcd for $C_{24}H_{34}O_5NaSSi$ $[M+Na]^+$ 485.1788, found 485.2017.

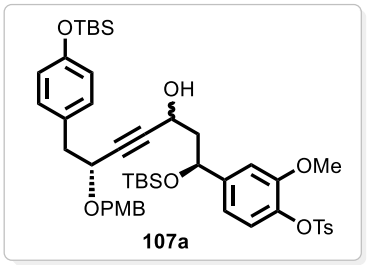
(*S*)-4-(1-((*Tert*-butyldimethylsilyl)oxy)-3-oxopropyl)-2-methoxyphenyl-4-methylbenzenesulfonate (102a): To a solution of (*S*)-4-(1-((tert-butyldimethylsilyl)oxy)but-3-en-1-yl)-2-methoxyphenyl-4-methylbenzene sulphonate **S6a** (10 g, 21.6 mmol) in 30 mL of acetone : water (3:1, 45 mL : 5 mL) was added OsO_4 (54 mg, 2.16 mmol) and NMO (5.52 g (50% solution), 25.9 mmol) at rt and stirred for 5 h. After that solvent was evaporated and the residue was extracted with EtOAc (3x50 mL). Organic layers were washed with brine and dried over Na_2SO_4 and concentrated in a vacuum. To a solution of the above crude diol in 20 mL of THF: water (4: 1) was added $NaIO_4$ (9.21 g, 43.2 mmol) and the reaction mixture was stirred 1h at rt then solid was removed by filtration, and the filtrate was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4 and concentrated in vacuum. And the crude aldehyde was purified by silica gel column chromatography to afford **102a** (6.4 g, 64%) yield as colorless oil. TLC: R_f = 0.6 (SiO_2, 20% EtOAc/hexanes); $[\alpha]_D^{26.27}$ = – 39.398 (*c*= 3.7, $CHCl_3$); FTIR (cm^{-1}): 3425, 2942, 2859, 2403, 1719, 1672, 1605, 1505, 1462, 1417, 1372, 1263, 1096, 1037, 933, 847; ^1H NMR (500 MHz, $CDCl_3$) δ 9.74 (dd, *J* = 1.88, 2.50 Hz, 1H), 7.70 (d, *J* = 8.25 Hz, 2H), 7.28-7.25 (m, 2H), 7.11 (d, *J* = 8.13 Hz, 1H), 6.85 (d, *J* = 1.88 Hz, 1H), 6.83-6.80 (m, 1H), 5.15 (dd, *J* = 4.13, 8.25 Hz, 1H), 3.52 (s, 3H), 2.80 (ddd, *J* = 2.63, 8.13, 15.88 Hz, 1H), 2.60 (ddd, *J* = 1.75, 4.00, 16.01 Hz, 1H), 2.42 (s, 3H), 0.84 (s, 9H),



102a

0.03 (s, 3H), -0.15 (s, 3H); $^{13}C\{H\}$NMR (126 MHz, $CDCl_3$) δ 200.8, 151.9, 145.1, 144.3, 137.6, 133.1, 129.4, 128.8, 124.1, 117.7, 110.0, 70.2, 55.6, 54.0, 25.8, 21.8, 18.1, -4.6, -5.0; HRMS (ESI): *m/z* calcd for $C_{23}H_{33}O_6SSi$ $[M+H]^+$ 465.1762, found 465.3765.

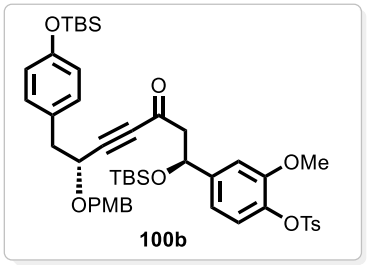
4-((1*S*,6*R*)-1-((*Tert*-butyldimethylsilyl)oxy)-7-(4-((*tert*-butyldimethylsilyl)-oxy)phenyl)-3-hydroxy-6-((4-methoxybenzyl)oxy)hept-4-yn-1-yl)-2-methoxy-phenyl-4-methylbenzene-sulfonate (107a): To the alkyne **101a** (2.76 g, 6.95 mmol) in dry THF (20 mL), LiHMDS (1.0 M in THF, 9.75 mL, 9.7 mmol) was added at -78 ℃ and stirred for 1h at the same temperature. After that aldehyde **102a** (3.23 g, 6.97 mmol) was added in one shot and reaction was stirred for 2 h. After completion of reaction, reaction was quenched with sat. aq. NH_4Cl and extracted with EtOAc (3x 30 mL), dried over Na_2SO_4, filtered and concentrated and subjected to silica gel column chromatography (using 15% EtOAc in hexanes) to afford **107a** (3.9 g, 65%) as yellow liquid. TLC: R_f = 0.5 (SiO_2, 30% EtOAc/hexanes); $[\alpha]_D^{26.26}$ =–4.74 (c = 2.6, $CHCl_3$); FTIR (cm^{-1}): 3684, 3615, 2968, 2403, 1730, 1599, 1413, 1468, 1424, 1374, 1085, 1040, 922; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74-7.69 (m, 2H), 7.32-7.27 (m, 2H), 7.17-7.10 (m, 3H), 7.09-7.05 (m, 2H), 6.93-6.88 (m, 1H), 6.84-6.80 (m, 3H), 6.78-6.72 (m, 2H), 4.98 (dd, *J* = 3.15, 8.83 Hz, 0.5H), 4.78 (dd, *J* = 4.10, 9.46, 0.5H), 4.69 (dd, *J* = 5.67, 11.66 Hz, 1H), 4.63 (s, 1H), 4.54 (m, 1H), 4.40 (dd, *J* = 2.21, 11.66 Hz, 1H), 4.26-4.19 (m, 1H), 3.81-3.79(m, 3H), 3.52-3.48 (m, 3H), 3.02-2.95 (m, 1H), 2.94-2.87 (m, 1H), 2.43 (s, 3H), 0.97 (s, 9H), 0.88 (s, 9H), 0.17 (s, 4H), 0.05 (d, *J* = 16.71 Hz, 3H), 0.00 (s, 3H), -0.19—0.25 (m, 3H); $^{13}C\{H\}$ NMR (126 MHz, $CDCl_3$) δ 163.4, 159.3, 154.5, 151.9, 145.1, 144.9, 144.8, 137.7, 137.6, 133.3, 130.7, 130.2, 130.1, 130.0, 129.5, 129.4, 128.9, 124.0, 119.9, 118.1, 118.0, 114.1, 113.9, 110.2, 91.9, 87.2, 87.0, 84.4, 83.9, 73.4, 72.3, 70.5, 69.7, 65.3, 61.1, 59.8, 55.6, 55.4, 48.5, 47.2, 41.7, 25.9, 25.9, 21.8, 18.4, 18.2, -4.3, -4.4, -4.9; HRMS (ESI): *m/z* calcd for $C_{47}H_{65}O_9SSi_2$ $[M+H]^+$ 861.3882, found 861.3925.



107a

4-((1*S*,6*R*)-1-((*Tert*-butyldimethylsilyl)oxy)-7-(4-((*tert*-butyldimethylsilyl)-oxy)phenyl)-6-((4-methoxybenzyl)oxy)-3-oxohept-4-yn-1-yl)-2-methoxy-phenyl-4-methylbenzenesulfonate (100b): To the alcohol **107a** (1.6 g, 1.8 mmol) in dry DCM (15 mL), DMP (1.18 g, 2.7 mmol) was added at 0 ℃ and stirred for 1h.

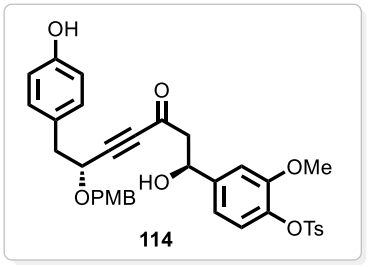
After completion of reaction, reaction was quenched with hypo solution 1:1 (saturated aq. $NaHCO_3$: saturated aq. $Na_2S_2O_3$), extracted with DCM (3x15 mL), dried over Na_2SO_4, filtered, concentrated and crude product was purified by silica gel column chromatography (using 10% EtOAc in hexanes) to afford the desired product **100b** (1.2 g, 75%) as yellow viscous liquid. TLC: R_f = 0.6 (SiO_2, 30% EtOAc/hexanes); $[\alpha]_D^{26.26}$ = +1.69 (c = 2.5, $CHCl_3$); FTIR (cm^{-1}): 3681, 3613, 3409, 2973, 2402, 2360, 1729, 1612, 1516, 1425, 1042, 926; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75-7.68 (m, 2H), 7.28-7.25 (m, 2H), 7.17-7.05 (m, 5H), 6.87-6.71 (m, 6H), 5.18 (dd, *J* = 3.88, 9.13 Hz, 1H), 4.73-4.65 (m, 1H), 4.43-4.37 (m, 1H), 4.35-4.30 (m, 1H), 3.81-3.77 (m, 3H), 3.54-3.50 (m, 3H), 3.07-2.91 (m, 3H), 2.72-2.64 (m, 1H), 2.43 (s, 3H), 0.98 (s, 9H), 0.84 (s, 9H), 0.18 (s, 6H), 0.05 - 0.01 (m, 3H), -0.15- -0.20 (m, 3H); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$) δ 184.6, 159.5, 154.8, 151.9, 145.1, 144.3, 137.7, 133.2, 130.7, 129.6, 129.4, 129.2, 129.2, 128.8, 124.0, 120.0, 117.9, 113.9, 110.1, 91.4, 85.7, 71.1, 71.0, 69.5, 56.4, 55.6, 55.4, 40.8, 25.8, 21.8, 18.3, 18.2, -4.3, -4.5, -5.0; HRMS (ESI): *m/z* calcd for $C_{47}H_{62}O_9NaSSi_2$ $[M+Na]^+$ 881.3545, found 881.3540.



100b

4-((1*S*,6*R*)-1-Hydroxy-7-(4-hydroxyphenyl)-6-((4-methoxybenzyl)oxy)-3-oxo-hept-4-yn-1-yl)-2-methoxyphenyl 4-methylbenzenesulfonate (114) and 4-((1*S*,6*R*)-7-(4-((*Tert*-butyldimethylsilyl)oxy)phenyl)-1-hydroxy-6-((4-methoxy-benzyl)oxy)-3-oxohept-4-yn-1-yl)-2-methoxyphenyl 4-methylbenzenesulfonate (115): To the TBS-keto intermediate **100b** (248 mg, 0.28 mmol), HF:MeCN (5:95, 6 mL) was added and stirred at 0 ℃ up to starting material was completely consumed. After completion of reaction, reaction was quenched with sat. aq. $NaHCO_3$, extracted with EtOAc (3x5 mL), dried over Na_2SO_4, filtered, concentrated and subjected to column chromatography to afford **114** and **115**.

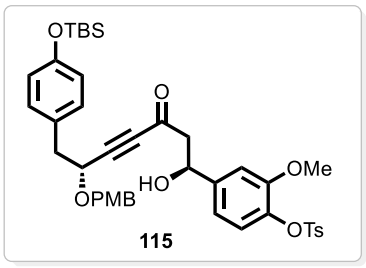
114: yellow liquid, (88 mg, 48%), TLC: *Rf* = 0.2 (SiO_2, 40% EtOAc/hexanes); $[\alpha]_D^{26.22}$ = +24.531 (c = 0.2, $CHCl_3$); FTIR (cm^{-1}): 3685, 3617, 3444, 2975, 2928, 2402, 1603, 1519, 1426, 1041, 927; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84-7.74 (m, 2H), 7.35-7.30 (m, *J* = 8.00 Hz, 2H), 7.23-7.17 (m, 2H), 7.13-7.04 (m, 3H), 6.90 (d, *J* = 1.75 Hz, 1H), 6.88-6.83 (m, 2H), 6.79 (dd, *J* = 1.81,



114

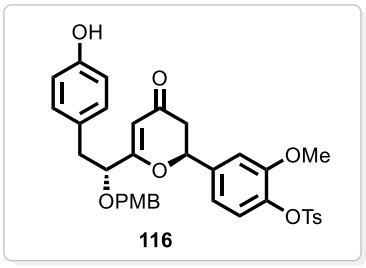
8.32 Hz, 1H), 6.7-6.65 (m, 2H), 5.17 (s, 1H), 5.10 (d, *J* = 7.88 Hz, 1H), 4.69 (d, *J* = 11.51 Hz, 1H), 4.43 (d, *J* = 11.51 Hz, 1H), 4.39-4.33 (m, 1H), 3.79 (s, 3H), 3.61 (s, 3H), 3.08-3.00 (m, 1H), 2.98-2.89 (m, 2H), 2.87-2.80 (m, 2H), 2.45 (s, 3H); $^{13}C\{H\}$ NMR ((101 MHz, $CDCl_3$) δ 186.0, 159.6, 155.0, 152.2, 145.3, 142.7, 137.8, 133.4, 131.0, 129.7, 129.6, 129.1, 128.7, 128.2, 124.1, 117.7, 115.3, 114.0, 110.2, 93.1, 85.3, 71.3, 69.6, 69.3, 55.8, 55.4, 54.5, 40.6, 21.8; HRMS (ESI): *m/z* calcd for $C_{35}H_{34}O_9NaS$ $[M+Na]^+$ 653.1816, found 653.1830.

115: yellow liquid, (68 mg, 31%); TLC: R_f = 0.5 (SiO_2, 40% EtOAc/hexanes); $[\alpha]_D^{26.25}$ = +5.11 (*c* = 0.5, $CHCl_3$); FTIR (cm^{-1}): 3425, 2976, 2402, 2359, 1640, 1520, 1426, 1041, 927; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.38 Hz, 2H), 7.30 (d, *J* = 7.88 Hz, 2H), 7.18-7.14 (m, 2H), 7.12-7.09 (m, 2H), 7.08-7.04 (m, 3H), 6.90 (d, *J* = 1.88 Hz, 1H), 6.85-6.82 (m, 2H), 6.77-6.74 (m, 2H), 5.18-5.11 (m, 1H), 4.68 (d, *J* = 11.51 Hz, 1H), 4.42 (d, *J* = 11.51 Hz, 1H), 4.34 (t, *J* = 6.63 Hz, 1H), 3.79 (s, 3H), 3.07-3.00 (m, 1H), 2.99-2.96 (m, 1H), 2.92-2.88 (m, 2H), 2.44 (s, 3H), 0.97 (s, 9H), 0.17 (s, 6H); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$) δ 186.0, 159.6, 154.8, 152.1, 145.1, 142.5, 137.9, 133.5, 131.1, 130.7, 129.7, 129.6, 129.5, 129.2, 129.0, 128.7, 124.1, 120.1, 117.7, 115.0, 114.0, 113.9, 110.2, 92.6, 71.3, 69.5, 69.3, 55.8, 55.4, 54.2, 40.8, 25.8, 21.8, 18.3, -4.3; HRMS (ESI): *m/z* calcd for $C_{41}H_{49}O_9SSi$ $[M+H]^+$745.2861, found 745.2863.



115

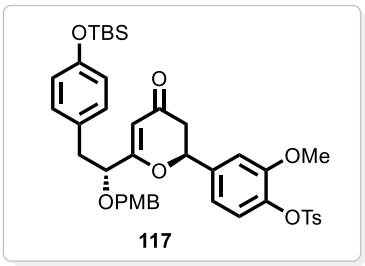
4-((*S*)-6-((*R*)-2-(4-Hydroxyphenyl)-1-((4-methoxybenzyl)oxy)ethyl)-4-oxo-3,4-dihydro-2*H*-pyran-2-yl)-2-methoxyphenyl 4-methylbenzenesulfonate (116): To the hydroxy-ynone **114** (25 mg g, 0.03mmol) in dry DCM (2 mL), AgOTf (1.0 mg, 0.003 mmol) was added at 0 °C and stirred at the same temperature for 24 h. After completion of reaction, reaction was quenched with brine, extracted with DCM (3x5 mL), dried over Na_2SO_4, filtered, concentrated in vacuum and the crude product was purified by silica gel column chromatography (using 30% EtOAc in hexanes) **116** (21 mg, 87%) as yellow liquid. TLC: R_f = 0.4 (SiO_2, 60% EtOAc/hexanes); $[\alpha]_D^{26.20}$ = +8.20 (*c* = 2.7, $CHCl_3$); FTIR (cm^{-1}): 3414, 2988, 2307, 1641, 1430, 1266, 1219, 1024, 897; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82-7.77 (m, 2H), 7.36-7.30 (m, 2H), 7.16-7.10 (m, 3H), 7.05-6.98 (m,



116

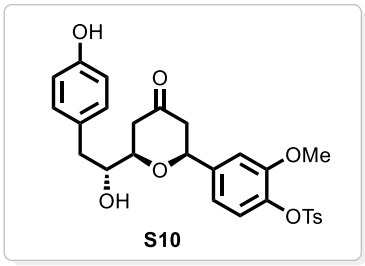
2H), 6.86-6.80 (m, 3H), 6.80-6.77 (m, 1H), 6.75-6.68 (m, 2H), 5.68-5.63 (m, 1H), 5.30 (dd, *J* = 4.13, 13.01 Hz, 1H), 5.11-5.01 (m, 1H), 4.49 (d, *J* = 11.38 Hz, 1H), 4.30 (d, *J* = 11.51 Hz, 1H), 4.02 (t, *J* = 6.50 Hz, 1H), 3.80 (s, 3H), 3.63-3.58 (m, 3H), 3.00-2.87 (m, 2H), 2.76-2.55 (m, 2H), 2.50-2.43 (m, 3H); $^{13}C\{H\}$ NMR ((101 MHz, $CDCl_3$) δ 192.1, 175.3, 159.5, 154.7, 152.3, 145.4, 138.7, 138.1, 133.5, 130.8, 129.6, 129.6, 129.4, 128.9, 128.7, 124.4, 118.4, 115.3, 114.0, 110.7, 104.3, 80.4, 79.7, 72.0, 55.9, 55.5, 42.8, 39.7, 21.9; HRMS (ESI): *m/z* calcd for $C_{35}H_{35}O_9S$ $[M+H]^+$631.1996, found 631.1995.

4-((*S*)-6-((*R*)-2-(4-((*Tert*-butyldimethylsilyl)oxy)phenyl)-1-((4-methoxybenzyl-)oxy)ethyl)-4-oxo-3,4-dihydro-2*H*-pyran-2-yl)-2-methoxyphenyl-4-methylbenzenesulfonate (117): To the hydroxyl-ynone **115** (116 mg, 0.155 mmol) in dry DCM



117

(4 mL), AgOTf (3 mg, 0.0015mmol) was added at 0 °C and stirred at the same temperature for 24 h at the same temperature. After completion of reaction, brine was added to the reaction and extracted with DCM (3x5 mL), dried over Na_2SO_4, filtered, concentrated in vacuum and the crude product was purified by silica gel column chromatography (using 20% EtOAc in hexanes) to afford **117** (87 mg, 75%)as yellow liquid. TLC: R_f = 0.4 (SiO_2, 40% EtOAc/hexanes); $[\alpha]_D^{26.22}$ = +7.15 (*c* = 0.9, $CHCl_3$); FTIR (cm^{-1}): 3686, 3619, 3457, 2972, 2928, 2402, 1721, 1602, 1519, 1426, 1041, 927; ^1H NMR (500 MHz, $CDCl_3$) δ 7.82-7.75 (m, 2H), 7.37-7.29 (m, 2H), 7.19-7.07 (m, 3H), 7.06-7.00 (m, 2H), 6.87-6.78 (m, 4H), 6.78-6.70 (m, 2H), 5.67-5.61 (m, 1H), 5.31 (dd, *J* = 4.10, 13.24 Hz, 1H), 4.47 (d, *J* = 11.35 Hz, 1H), 4.28 (d, *J* = 11.35 Hz, 1H), 4.06-3.99 (m, 1H), 3.79 (s, 3H), 3.60 (s, 3H), 3.03-2.89 (m, 2H), 2.76-2.64 (m, 1H), 2.64-2.54 (m, 1H), 2.51-2.43 (m, 3H), 0.98 (s, 9H), 0.18 (s, 6H); $^{13}C\{H\}$NMR (126 MHz, $CDCl_3$) δ 191.9, 175.1, 159.5, 154.7, 152.3, 145.3, 138.8, 138.2, 133.6, 130.6, 129.6, 129.5, 128.7, 124.4, 120.1, 118.4, 114.0, 110.6, 104.5, 80.5, 79.8, 72.0, 55.9, 55.4, 43.0, 39.7, 25.8, 21.9, 18.4, -4.3; HRMS (ESI): *m/z* calcd for $C_{41}H_{48}O_9NaSSi$ $[M+Na]^+$767.2681, found 767.2701.

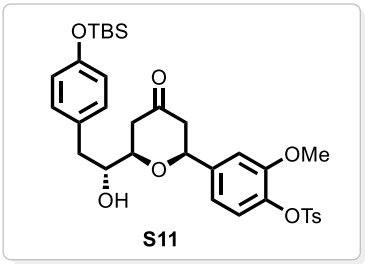


S10

4-((2*S*,6*R*)-6-((*R*)-1-Hydroxy-2-(4-hydroxyphenyl)-ethyl)-4-oxotetrahydro-2*H*-pyran-2-yl)-2-methoxyphenyl 4-methylbenzenesulfonate (S10): To the dihydropyranone **116** (89 mg, 0.14 mmol) in dry ethyl

acetate (4 mL), Pd/C (40 mg, 10% wet weight) was added and the reaction mixture was stirred overnight under hydrogen atmosphere. After completion of reaction, the mixture was filtered through celite and the resulting filtrate was concentrated in vacuum. The crude product was purified by silica gel column chromatography (using 50% ethyl acetate in hexane) to afford **S10** (50 mg, 69%) as a amorphous solid. TLC: R_f = 0.3 (SiO_2, 60% EtOAc/hexanes); $[\alpha]_D^{24.29}$ =−17.64 (c = 0.8, $CHCl_3$); FTIR (cm^{-1}): 3687, 3599, 2927, 2402, 1600, 1519, 1426, 1022, 927; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.38 Hz, 2H), 7.33 (d, *J* = 8.13 Hz, 2H), 7.13 (d, *J* = 8.25 Hz, 1H), 7.07 (d, *J* = 8.51 Hz, 2H), 6.89-6.84 (m, 2H), 6.75 (d, *J* = 8.38 Hz, 2H), 4.95 (br. s., 1H), 4.58 (dd, *J* = 2.75, 11.51 Hz, 1H), 3.82-3.75 (m, 2H), 3.73-3.66 (m, 1H), 3.62 (s, 3H), 2.89 (dd, *J* = 5.88, 14.01 Hz, 1H), 2.87-2.80 (m, 1H), 2.79-2.66 (m, 2H), 2.64-2.59 (m, 1H), 2.56-2.50 (m, 1H), 2.46 (s, 3H); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$) δ 206.0, 154.6, 152.2, 145.3, 140.6, 138.2, 133.5, 130.6, 129.7, 129.6, 129.5, 128.7, 124.3, 117.8, 115.6, 110.2, 78.4, 78.2, 74.5, 55.9, 49.4, 43.9, 38.8, 21.9; HRMS (ESI): *m/z* calcd for $C_{27}H_{28}O_8NaS$ $[M+Na]^+$ 535.1397, found 535.1392.

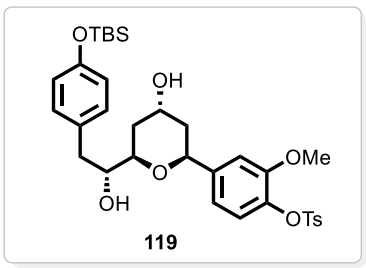
4-((2*S*,6*R*)-6-((*R*)-2-(4-((*Tert*-butyldimethylsilyl)oxy)phenyl)-1-hydroxyethyl)-4-oxotetrahydro-2*H*-pyran-2-yl)-2-methoxyphenyl 4-methylbenzenesulfonate (S11): To the dihydropyranone **117** (18 mg, 0.0241 mmol) in dry ethyl acetate, Pd/C (10 mg) was added and the reaction mixture was stirred overnight under hydrogen atmosphere. After completion of reaction, the mixture was filtered through celite and the resulting filtrate was concentrated in vacuum. The crude product was purified by silica gel column chromatography using 50% ethyl acetate in hexanes to afford **S11** (11 mg, 73%) as amorphous solid. TLC: R_f = 0.3 (SiO_2, 40% EtOAc/hexanes); $[\alpha]_D^{26.32}$ =−24.18 (c = 0.7, $CHCl_3$); FTIR (cm^{-1}): 3411, 3157, 2858, 2256, 1802, 1603, 1468, 1381, 1266, 1166, 1097, 908; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.39 Hz, 2H), 7.32 (d, *J* = 8.39 Hz, 2H), 7.13 (d, *J* = 8.39 Hz, 1H), 7.06 (d, *J* = 8.39 Hz, 2H), 6.91-6.86 (m, 2H), 6.80-6.75 (m, 2H), 4.59 (dd, *J* = 3.05, 11.44 Hz, 1H), 3.78 (br. s., 1H), 3.71-3.66 (m, 1H), 3.62 (s, 3H), 3.61-3.54 (m, 1H), 2.91-2.80 (m, 2H), 2.78-2.66 (m, 2H), 2.66-2.58 (m, 1H), 2.57-2.51 (m, 1H), 2.47-2.45 (m, 3H), 2.43-2.37 (m, 1H), 2.22 (br. s., 1H), 0.97 (s, 9H), 0.18 (s, 6H); $^{13}C\{H\}$ NMR ((101 MHz, $CDCl_3$) δ 206.1, 154.6, 152.2, 145.2,



S11

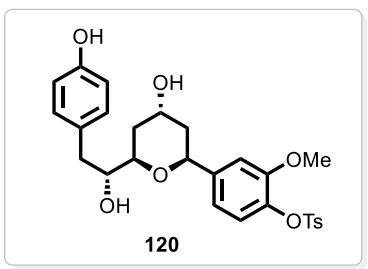
140.6, 138.2, 133.5, 130.4, 130.0, 129.6, 128.7, 124.3, 120.3, 117.8, 110.1, 78.2, 78.2, 74.6, 58.7, 55.9, 49.3, 43.9, 38.9, 25.8, 21.9, 18.6, 18.3, 1.2, 0.1, -4.3; HRMS (ESI): *m/z* calcd for $C_{33}H_{42}O_8NaSSi$ $[M+Na]^+$649.2262, found 649.2269.

4-((2*S*,4*R*,6*R*)-6-((*R*)-2-(4-((*Tert*-butyldimethylsilyl)oxy)phenyl)-1-hydroxyethyl)-4-hydroxytetrahydro-2*H*-pyran-2-yl)-2-methoxyphenyl 4-methylbenzenesulfonate (119): To a stirred solution of tetra-hydro-pyranone **S11** (12 mg, 0.019 mmol) in THF at -78 ℃ was added *LS*-selectride (0.02 mL, 0.021 mmol). The reaction mixture was stirred for 1 h at the same temperature. After completion of reaction it was quenched with saturated aq. NH_4Cl and warmed to rt. The organic layer was separated and aqueous layer was extracted with EtOAc (3x3 mL) and combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuum and crude product was purified by silica gel column chromatography (using 70% EtOAc in hexanes) to afford **119** (8.5 mg, 70%) as thick liquid. TLC: R_f = 0.3 (SiO_2, 70% EtOAc/hexanes); $[\alpha]_D^{23.96}$ =−22.12 (c = 0.8, $CHCl_3$); FTIR (cm^{-1}): 3687, 2928, 2402, 2358, 2255, 1599, 1518, 1426, 1024, 911; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.39 Hz, 2H), 7.30 (d, *J* = 8.01 Hz, 2H), 7.08 (d, *J* = 8.77 Hz, 3H), 6.88-6.84 (m, 2H), 6.76 (d, *J* = 8.77 Hz, 2H), 4.83 (d, *J* = 1.53, 11.83 Hz, 1H), 4.40-4.35 (m, 1H), 3.88 (ddd, *J* = 1.91, 4.96, 11.83 Hz, 1H),, 3.72 (q, *J* = 6.87 Hz, 2H), 3.58 (s, 3H), 2.84 (dd, *J* = 5.34, 13.73 Hz, 1H), 2.75 (dd, *J* = 8.01, 14.11 Hz, 1H), 2.45 (s, 3H), 1.93-1.87 (m, 1H), 1.85-1.77 (m, 2H), 1.70-1.65 (m, 2H), 0.97 (s, 9H), 0.18 (s, 6H); ^{13}C{H} NMR (126 MHz, $CDCl_3$) δ 154.3, 151.9, 145.1, 143.0, 137.6, 133.6, 130.4, 129.5, 128.8, 123.9, 120.1, 117.9, 110.4, 75.2, 73.9, 73.3, 64.7, 55.8, 40.7, 38.8, 34.5, 25.8, 21.8, 18.6, 1.2, -4.3; HRMS (ESI): *m/z* calcd for $C_{33}H_{44}O_8NaSSi$ $[M+Na]^+$ 651.2418, found 651.2418.



119

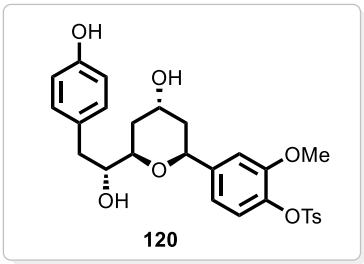
4-((2*S*,4*R*,6*R*)-4-Hydroxy-6-((*R*)-1-hydroxy-2-(4-hydroxyphenyl)ethyl)-tetrahydro-2*H*-pyran-2-yl)-2-methoxyphenyl 4-methylbenzenesulfonate (120): To a stirred solution of tetrahydro-pyranone **S10** (15 mg, 0.02 mmol) in THF at -78 ℃ was added *LS*-Selectride (0.03 mL, 0.03 mmol) dropwise. Then the reaction was stirred for 1 h at the



120

same temperature. After completion of reaction it was quenched with saturated aq. NH_4Cl and warmed to rt. The organic layer was separated and aqueous layer was extracted with EtOAc (3x3 mL) and combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuum and crude product was purified by silica gel column chromatography (using 70% EtOAc in hexanes) to afford **120** (12 mg, 80%) as colorless thick liquid. TLC: R_f = 0.2 (SiO_2, 60% EtOAc/hexanes); $[\alpha]_D^{25.22}$ =–15.45 (c = 0.3, $CHCl_3$); FTIR (cm^{-1}): 3687, 2402, 1600, 1519, 1426, 1022, 927; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82-7.72 (m, 2H), 7.31 (d, *J* = 8.00 Hz, 2H), 7.12-7.04 (m, 3H), 6.86-6.81 (m, 2H), 6.76-6.70 (m, 2H), 4.82 (dd, *J* = 1.88, 11.76 Hz, 1H), 4.38 (t, *J* = 2.75 Hz, 1H), 3.88 (ddd, *J* = 2.25, 4.88, 11.88 Hz, 1H), 3.74-3.69 (m, 1H), 3.59-3.55 (m, 3H), 2.85 (dd, *J* = 5.38, 13.88 Hz, 1H), 2.74 (dd, *J* = 7.75, 13.88 Hz, 1H), 2.45 (s, 3H), 1.92-1.86 (m, 1H), 1.84-1.78 (m, 1H), 1.71-1.64 (m, 2H); $^{13}C\{H\}$ NMR ((101 MHz, $CDCl_3$) δ 154.4, 151.9, 145.1, 142.9, 137.6, 133.5, 130.6, 130.2, 129.5, 128.7, 123.9, 117.9, 115.5, 110.4, 75.2, 73.9, 73.3, 64.7, 55.8, 40.6, 38.7, 34.5, 21.8; HRMS (ESI): *m/z* calcd for $C_{27}H_{30}O_8NaS$ $[M+Na]^+$ 537.1554, found 537.1563.

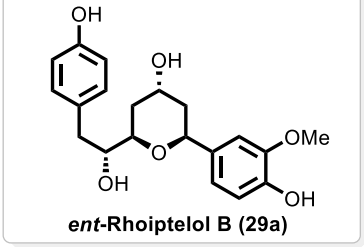
4-((2*S*,4*R*,6*R*)-4-Hydroxy-6-((*R*)-1-hydroxy-2-(4-hydroxyphenyl)ethyl)-tetrahydro-2*H*-pyran-2-yl)-2-methoxyphenyl 4-methylbenzenesulfonate (120): To a solution of benzenesulfonate **119** (15 mg, 0.023 mmol) in dry THF at 0 °C , TBAF (0.02 mL, 0.028 mmol) was added dropwise and the reaction mixture was stirred for 30 min. at the same temperature. The reaction was monitored by TLC and after completion of reaction, it was quenched with H_2O. The organic layer was separated and aqueous layer was extracted with EtOAc (3x3 mL) and combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuum and crude product was purified by silica gel column chromatography (using 70% EtOAc in hexanes) to afford **120** (7 mg, 87%) as colorless thick liquid. TLC: R_f = 0.2 (SiO_2, 60% EtOAc/hexanes); FTIR (cm^{-1}): 3686, 3425, 2402, 1611, 1519, 1426, 1023, 927, 672; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.38 Hz, 2H), 7.31 (d, *J* = 8.13 Hz, 2H), 7.12-7.06 (m, 3H), 6.87-6.83 (m, 2H), 6.77-6.72 (m, 2H), 4.82 (dd, *J* = 1.88, 11.26 Hz, 1H), 4.41-4.35 (m, 1H), 4.14-4.09 (m, 1H), 3.88-3.83 (m, 1H), 3.60-3.57 (m, 3H), 2.90-



120

2.82 (m, 1H), 2.78-2.70 (m, 1H), 2.45 (s, 3H), 1.94-1.86 (m, 1H), 1.85-1.78 (m, 1H), 1.72-1.65 (m, 2H).

***ent*-Rhoiptelol B (29a):** To a solution of **120** (9 mg, 0.017 mmol) in MeOH (2 mL) was added K_2CO_3 (12 mg, 0.08 mmol) and the mixture was heated at reflux for 2h. After completion of reaction the reaction mixture was cooled to 0 °C and acidified with 1 N HCl until pH of the solution reached to 2. The combined aqueous/MeOH solution was extracted with ethyl acetate (3x3 mL). The organic layers were washed with brine, dried with Na_2SO_4, filtered and concentrated in vacuum. The crude product was purified by silica gel column chromatography (using 70% EtOAc in hexanes) to get *ent*-rhoiptelol (**29a**) as amorphous solid (4.6 mg, 76%); TLC: R_f = 0.3 (SiO_2, 70% EtOAc/hexanes); $[\alpha]_D^{26.63}$ =–81.04 (c = 0.1, MeOH); FTIR (cm^{-1}): 3687, 2968, 2402, 1722, 1520, 1427, 1025, 927, 672; ^{1}H NMR (400 MHz, CD_3OD) δ 7.05 (s, 2H), 7.03 (s, 1H), 6.84 (dd, *J* = 1.88, 8.38 Hz, 1H), 6.77 (d, *J* = 8.13 Hz, 1H), 6.71-6.68 (m, 2H), 4.69 (dd, 1H), 4.28 (m, 1H), 3.88 (s, 3H), 3.85-3.82 (m, 1H), 3.82-3.79 (m, 1H), 3.60-3.57 (m, 1H), 2.89 (dd, *J* = 7.00, 13.66 Hz, 1H), 2.71 (dd, *J* = 7.25, 13.26 Hz, 1H), 1.92-1.89 (m, 1H), 1.84-1.80 (m, 1H), 1.76 (d, *J* = 2.88 Hz, 1H), 1.57-1.54 (m, 1H); 13C NMR (101 MHz, CD_3OD) δ 156.6, 148.8, 146.7, 136.2, 131.4, 131.2, 129.9, 119.9, 116.0, 115.8, 111.1, 76.4, 75.2, 74.3, 65.7, 56.4, 49.8, 49.6, 49.4, 49.2, 48.8, 48.6, 48.4, 41.3, 39.7, 34.9; HRMS (ESI): *m/z* calcd for $C_{20}H_{24}O_6Na$ $[M+Na]^+$ 383.1465, found 383.1462.



***ent*-Rhoiptelol B (29a)**

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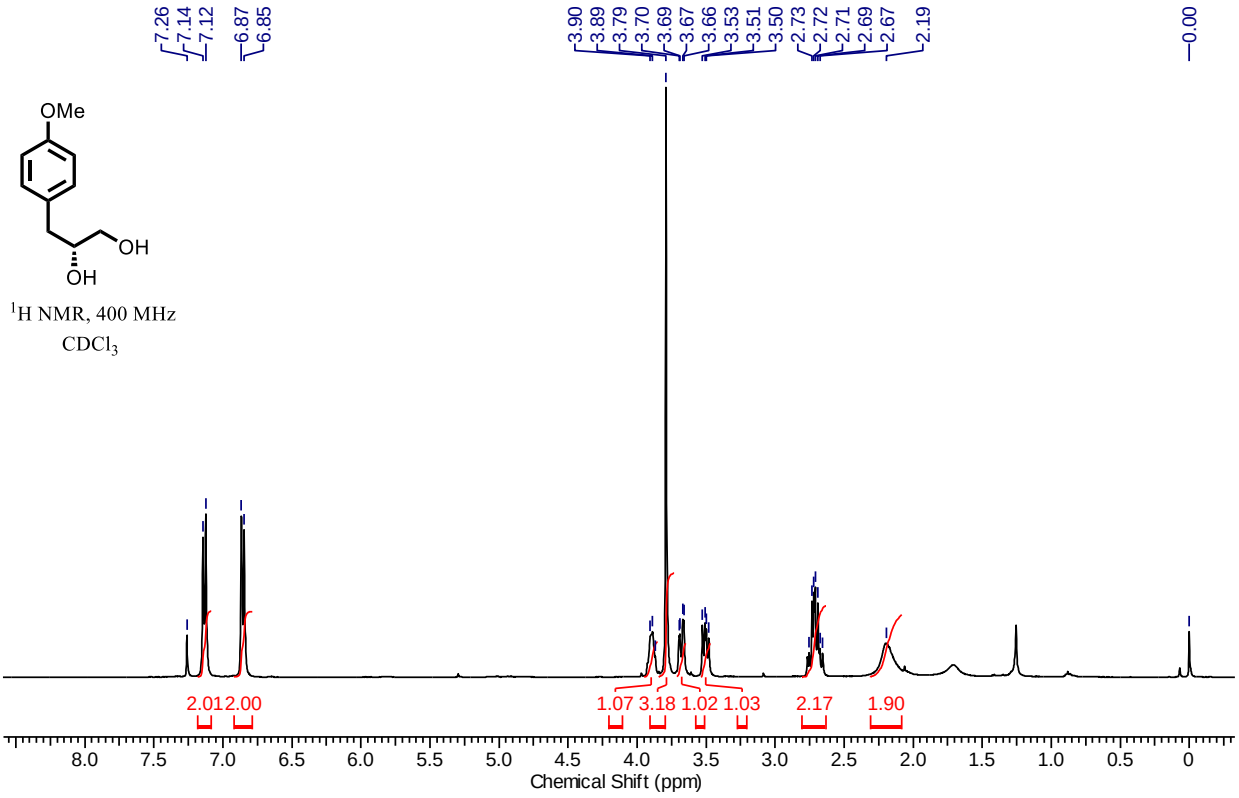
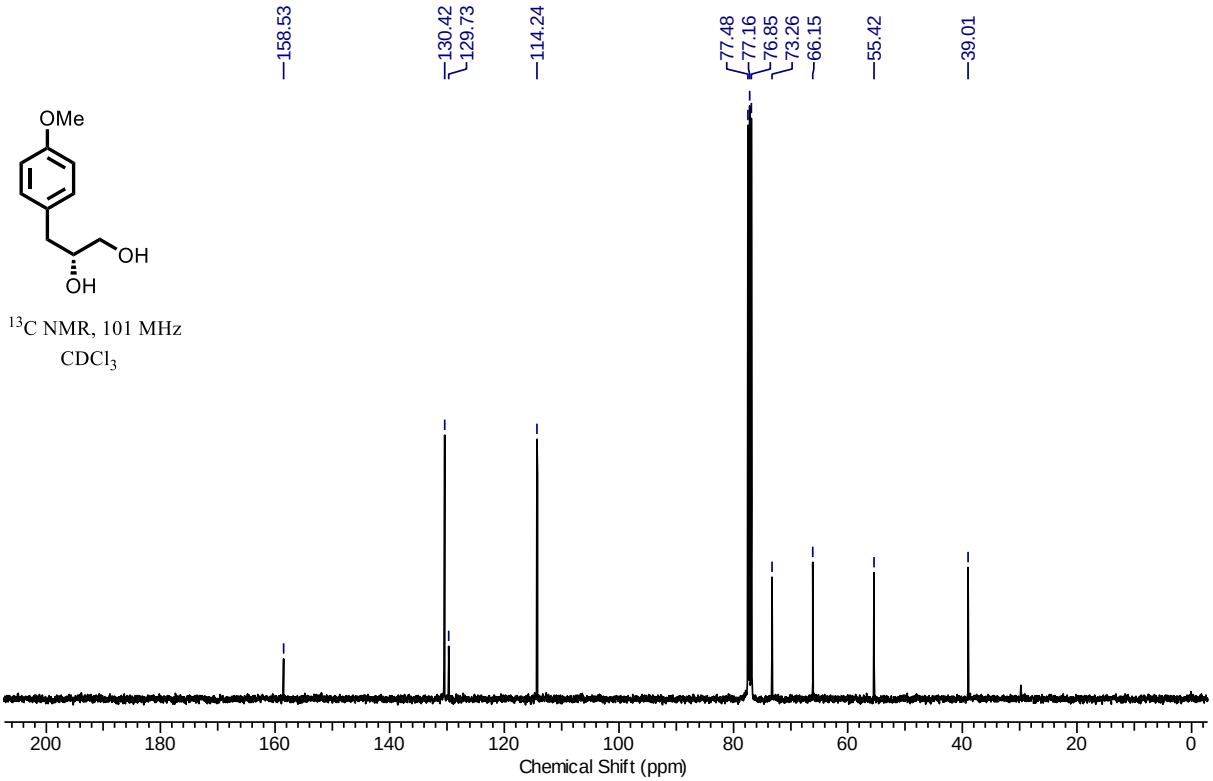
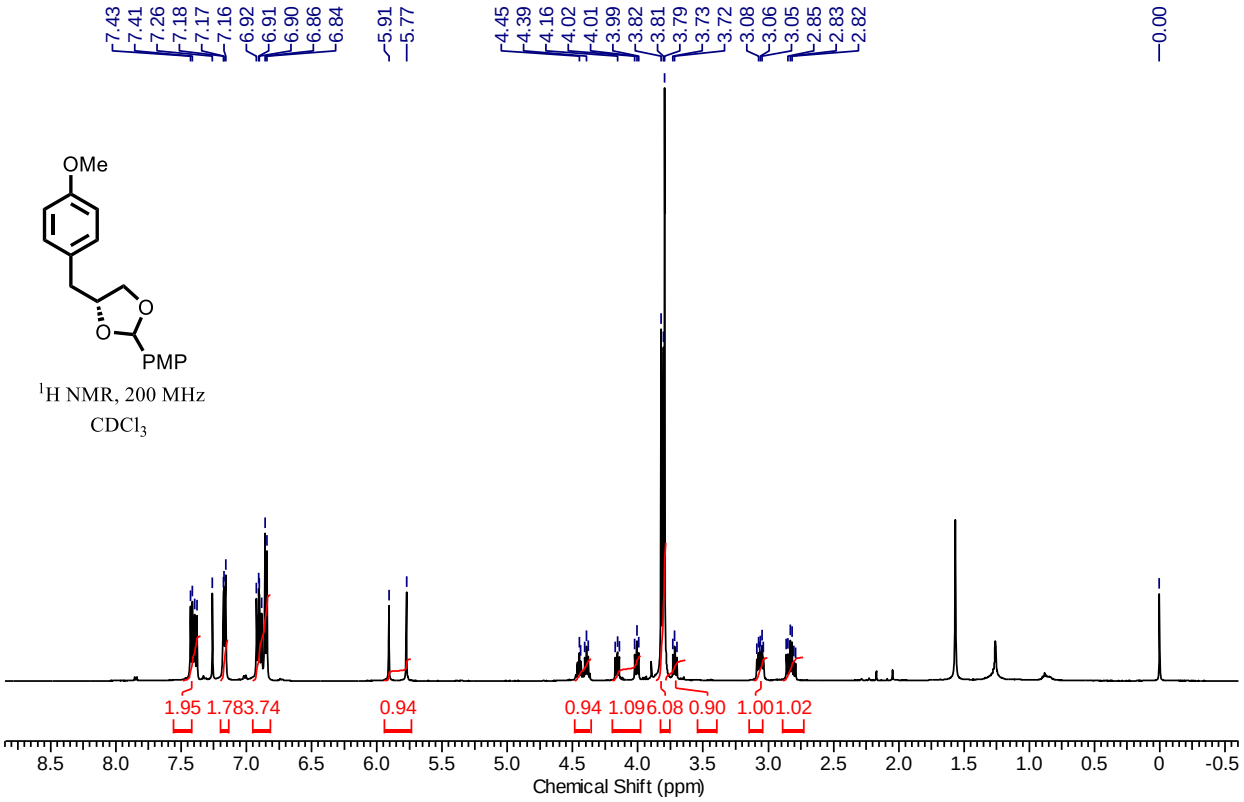
(*R*)-3-(4-Methoxyphenyl)propane-1,2-diol (**S1**):



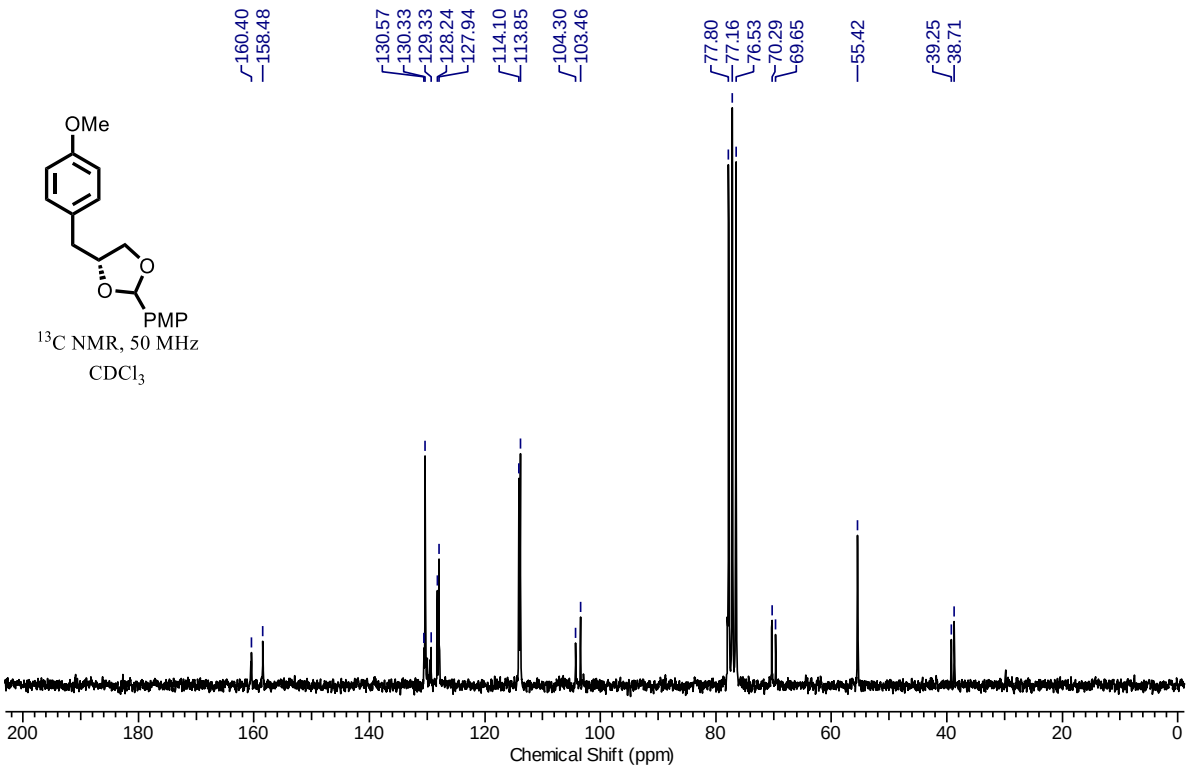
(*R*)-3-(4-Methoxyphenyl)propane-1,2-diol (**S1**):



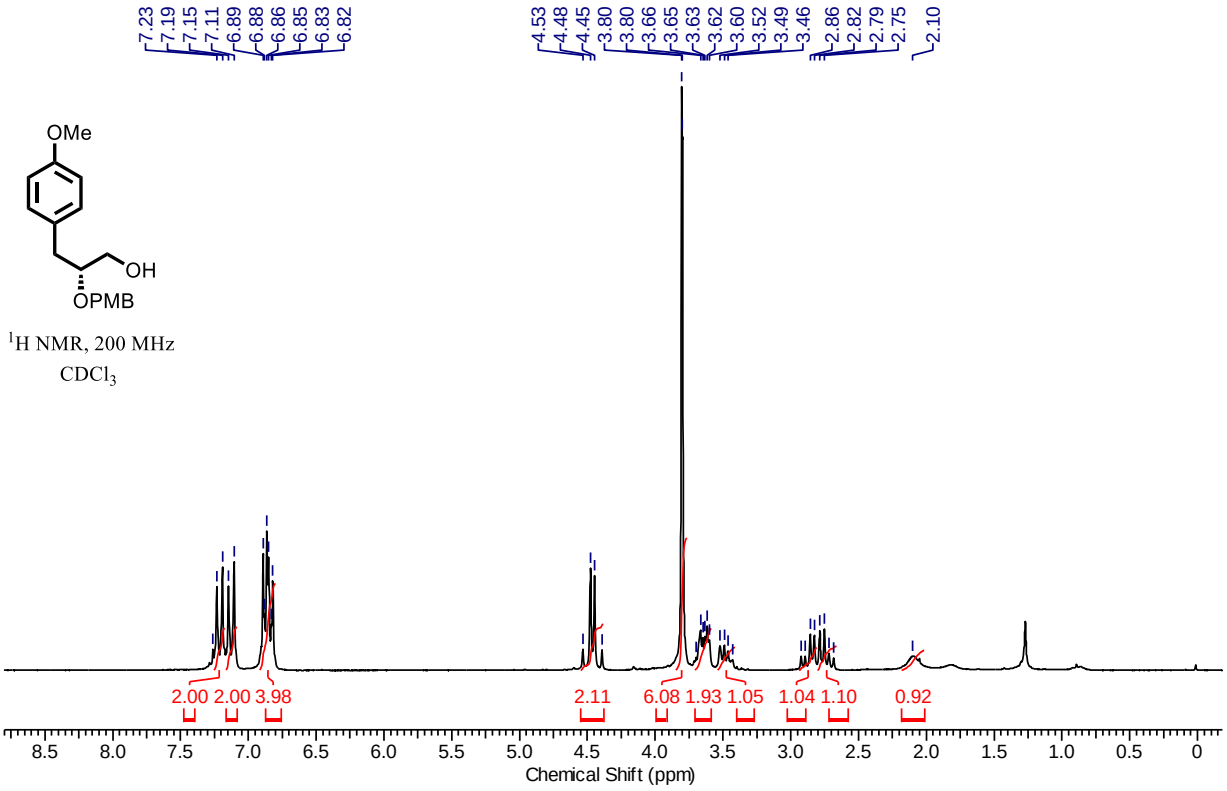
(4*R*)-4-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-1,3-dioxolane (**97**):



(4*R*)-4-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-1,3-dioxolane (**97**):



(*R*)-2-((4-Methoxybenzyl)oxy)-3-(4-methoxyphenyl)propan-1-ol (**S2**):



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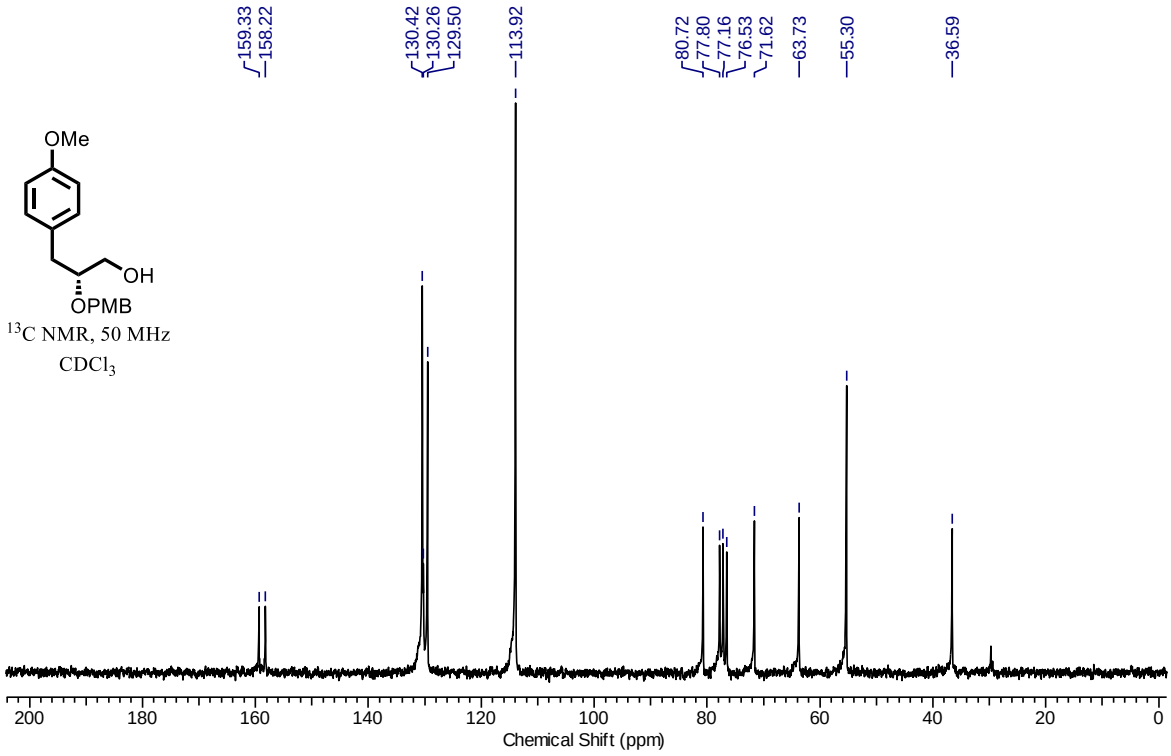
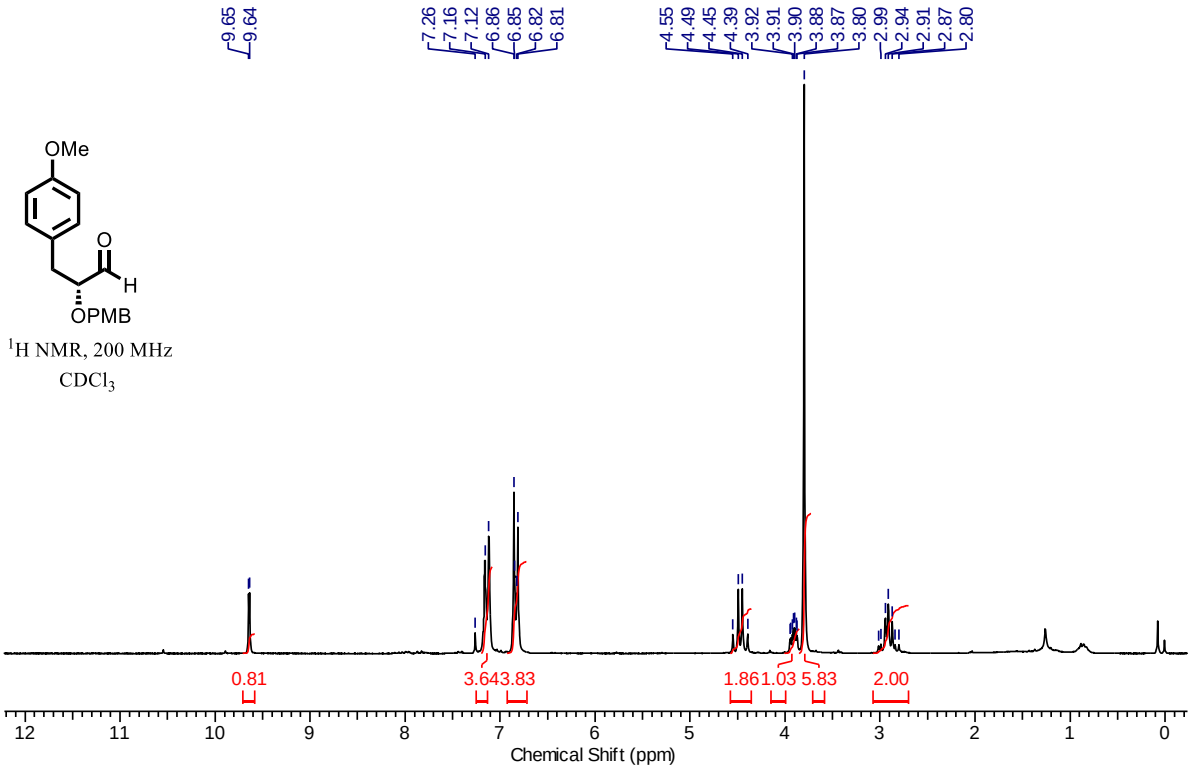
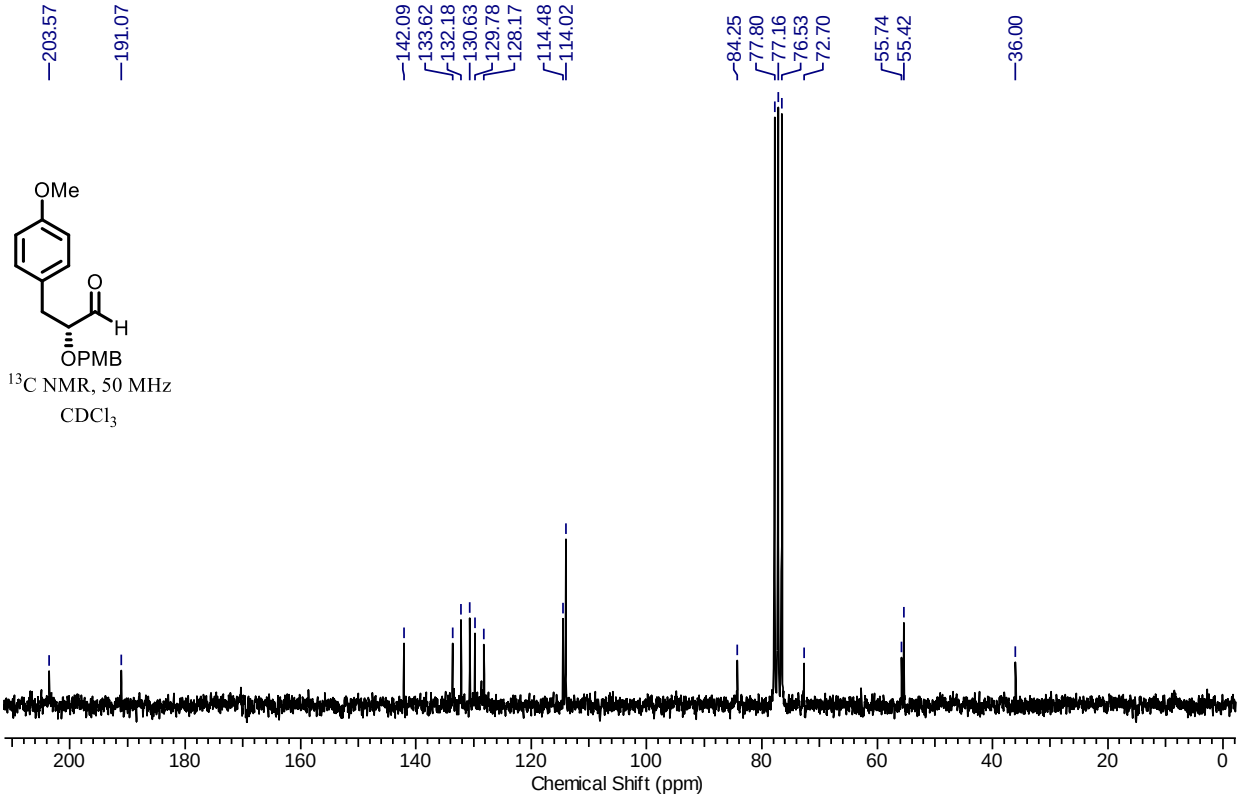


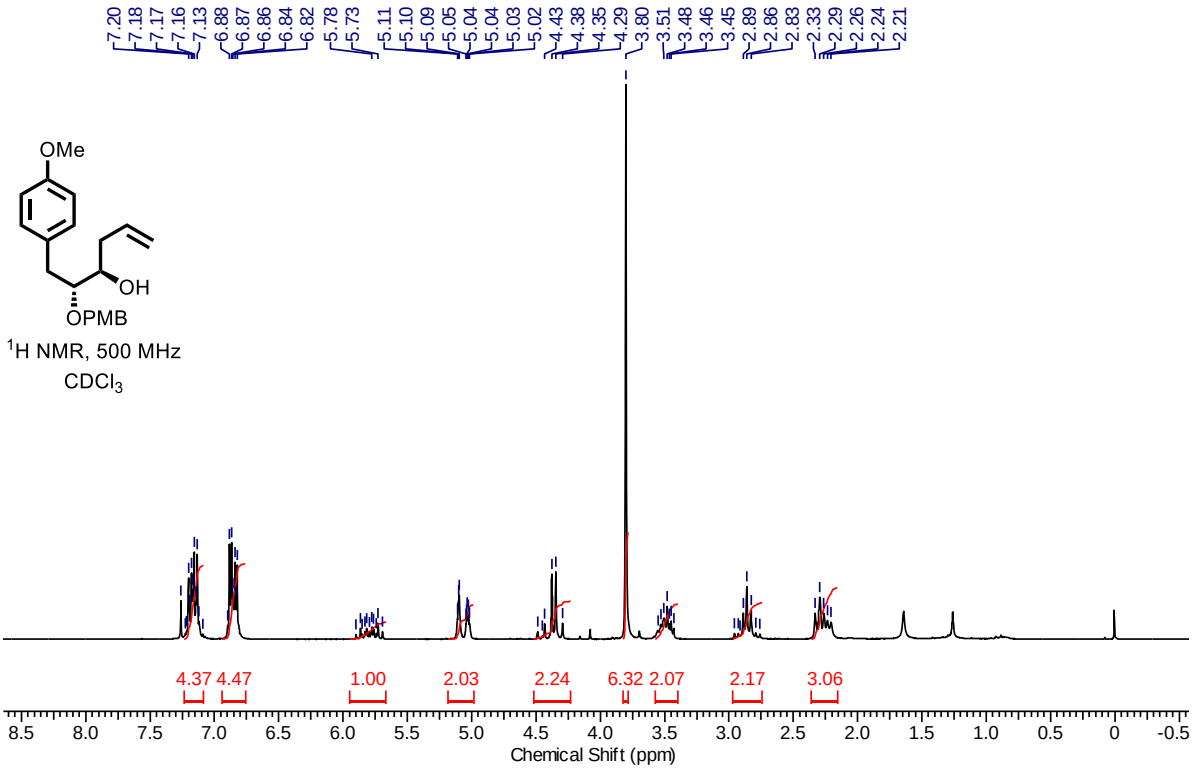
(*R*)-2-((4-Methoxybenzyl)oxy)-3-(4-methoxyphenyl)propanal (**98**):



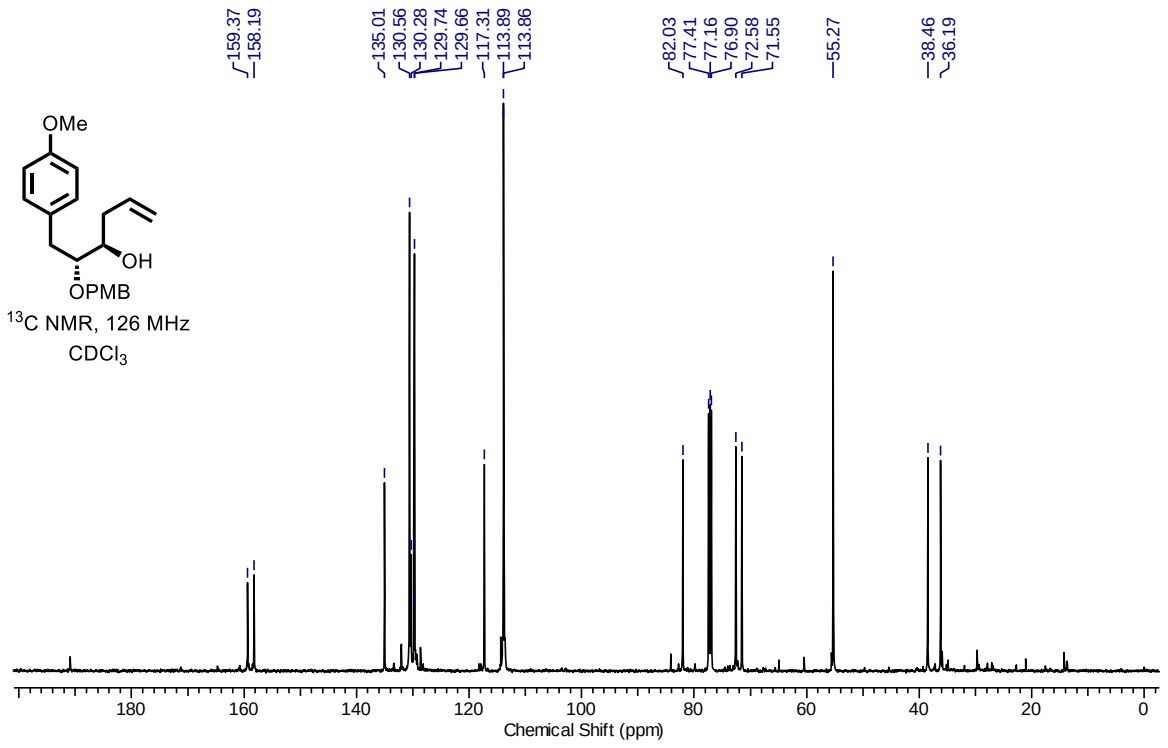
(*R*)-2-((4-Methoxybenzyl)oxy)-3-(4-methoxyphenyl)propanal (**98**):



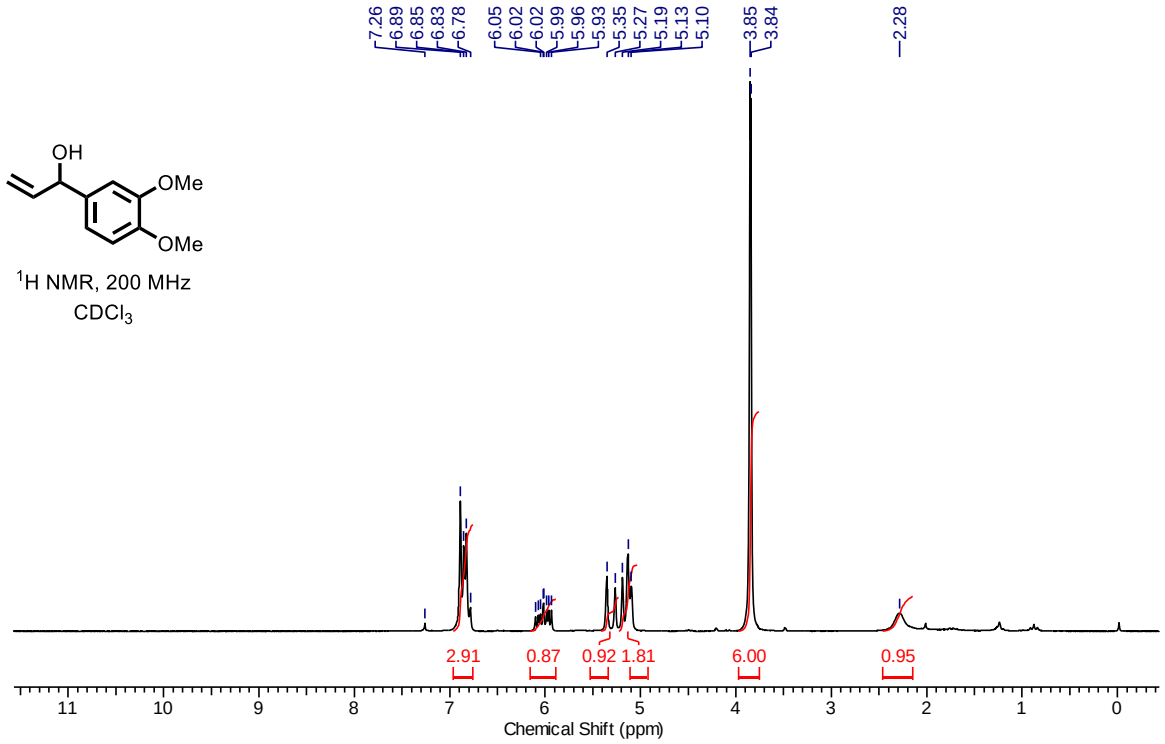
(*2R,3R*)-2-((4-Methoxybenzyl)oxy)-1-(4-methoxyphenyl)hex-5-ene-3-ol (**93**):



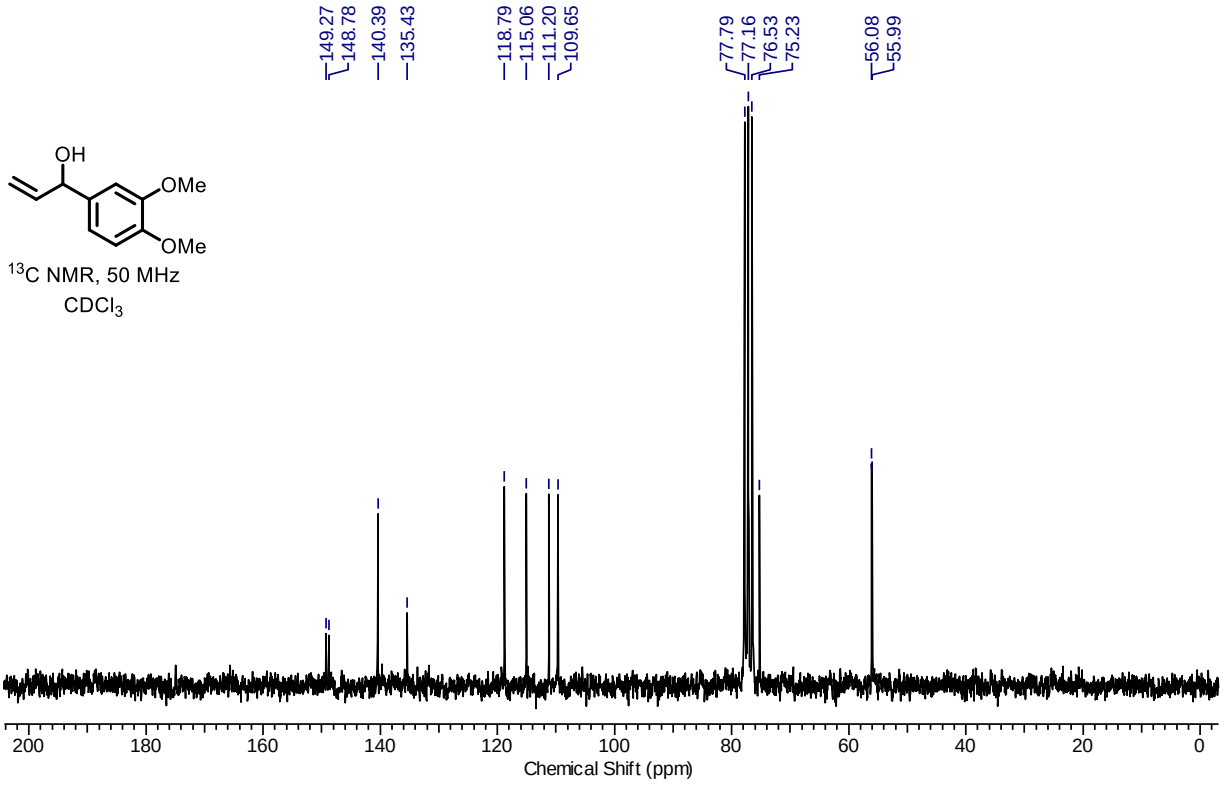
(*2R,3R*)-2-((4-Methoxybenzyl)oxy)-1-(4-methoxyphenyl)hex-5-ene-3-ol (**93**):



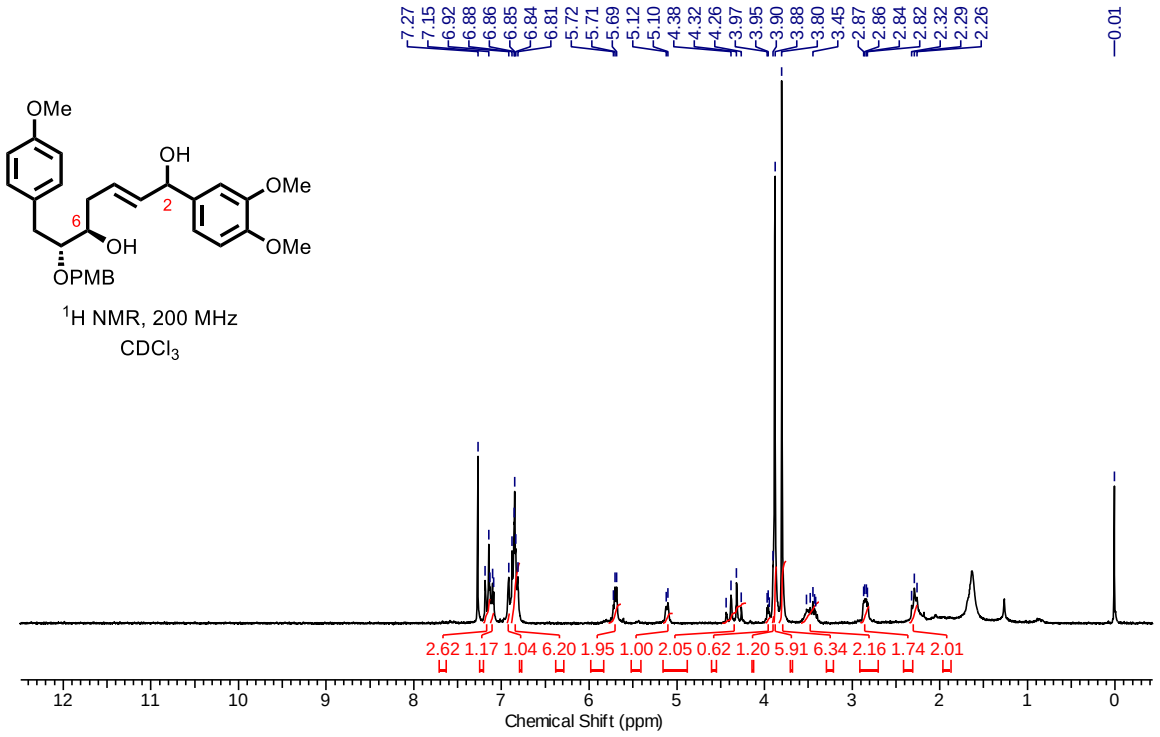
1-(3,4-Dimethoxyphenyl)prop-2-en-1-ol (**94**):



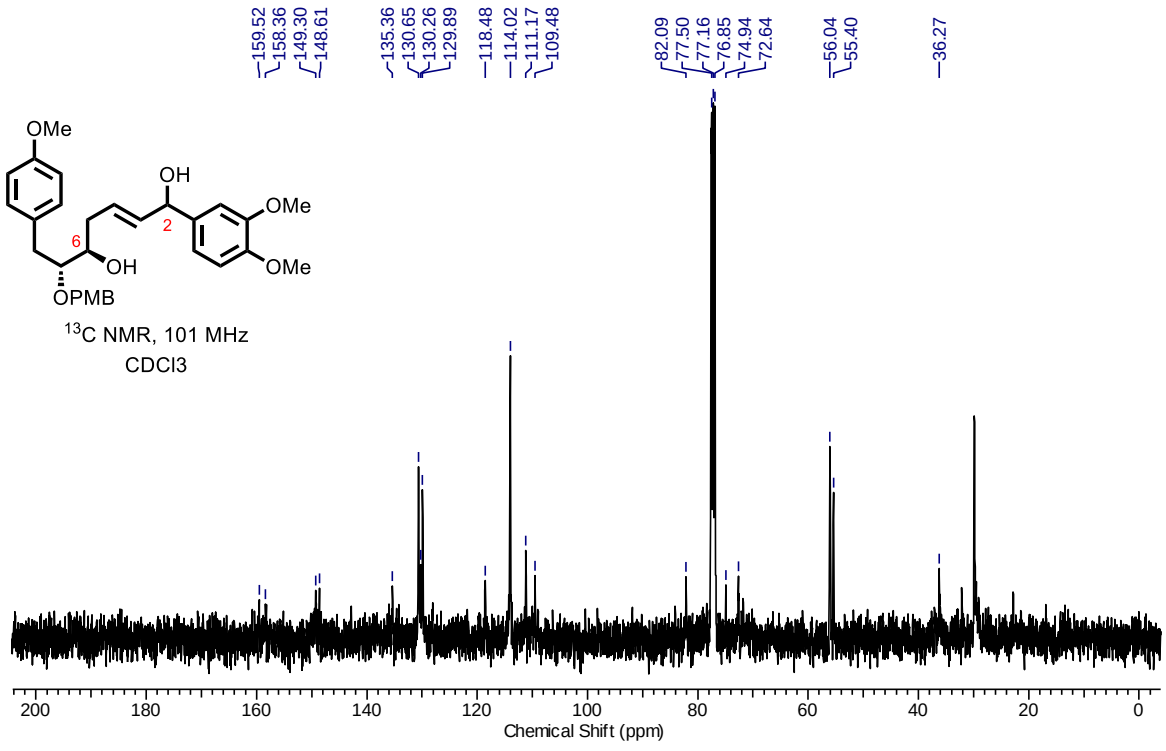
1-(3,4-Dimethoxyphenyl)prop-2-en-1-ol (**94**):



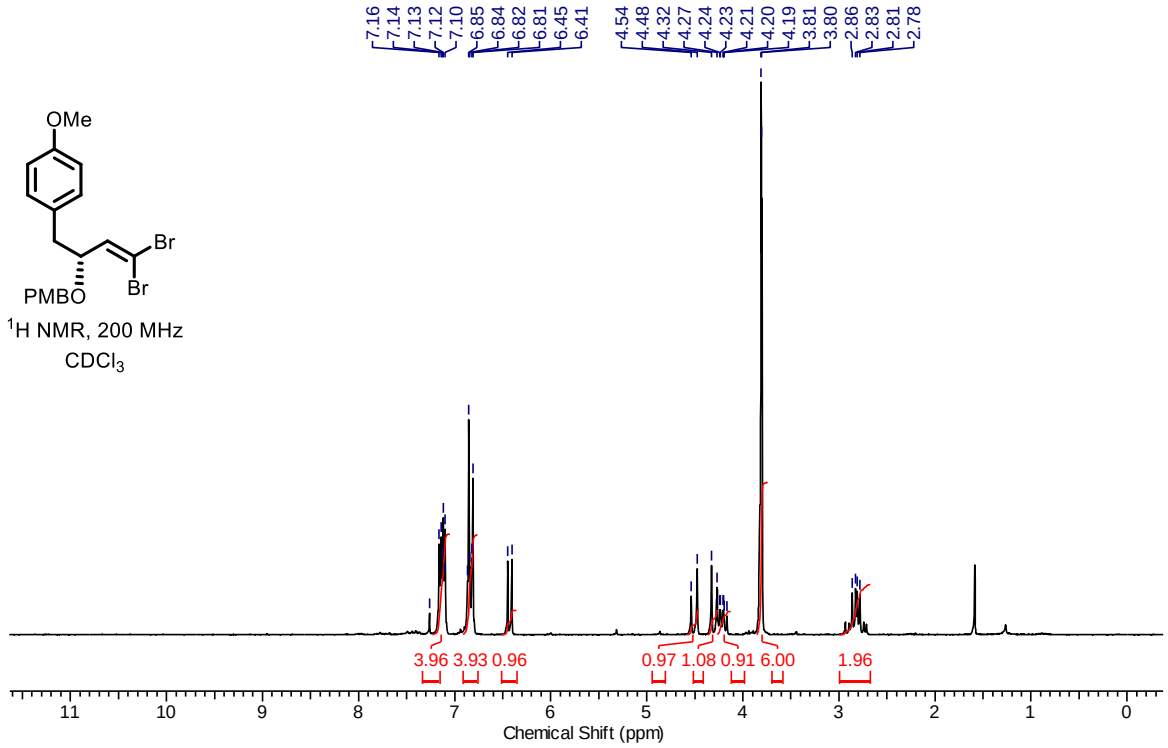
(*5R,6R,E*)-1-(3,4-Dimethoxyphenyl)-6-((4-methoxybenzyl)oxy)-7-(4-methoxyphenyl)hept-2-ene-1,5-diol (**92**):



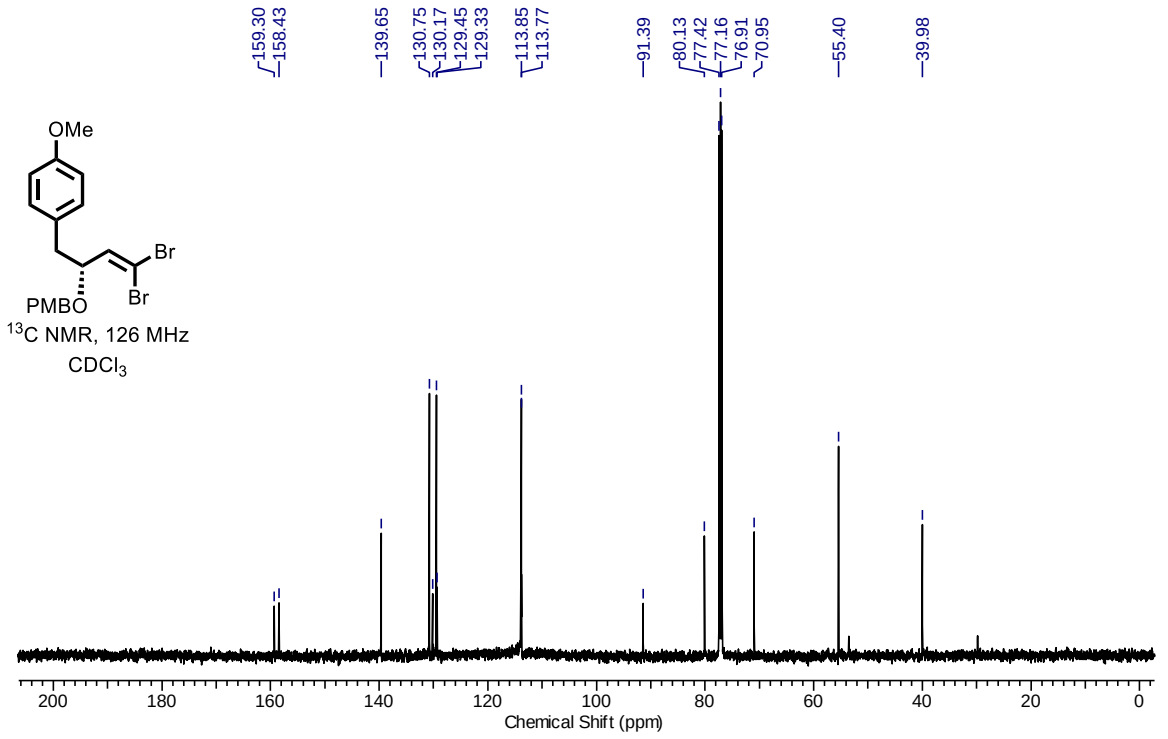
(*5R,6R,E*)-1-(3,4-Dimethoxyphenyl)-6-((4-methoxybenzyl)oxy)-7-(4-methoxyphenyl)hept-2-ene-1,5-diol (**92**):



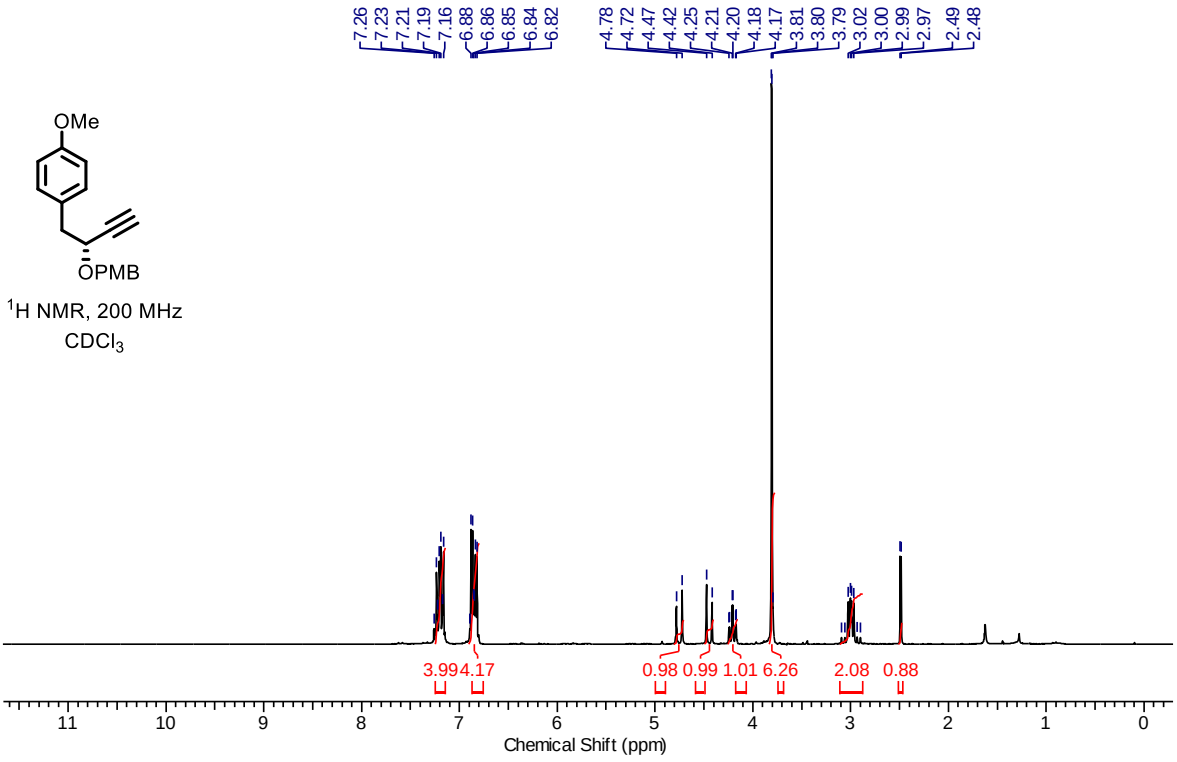
(*R*)-1-(((4,4-Dibromo-1-(4-methoxyphenyl)but-3-en-2-yl)oxy)methyl)-4-methoxybenzene (**S3**):



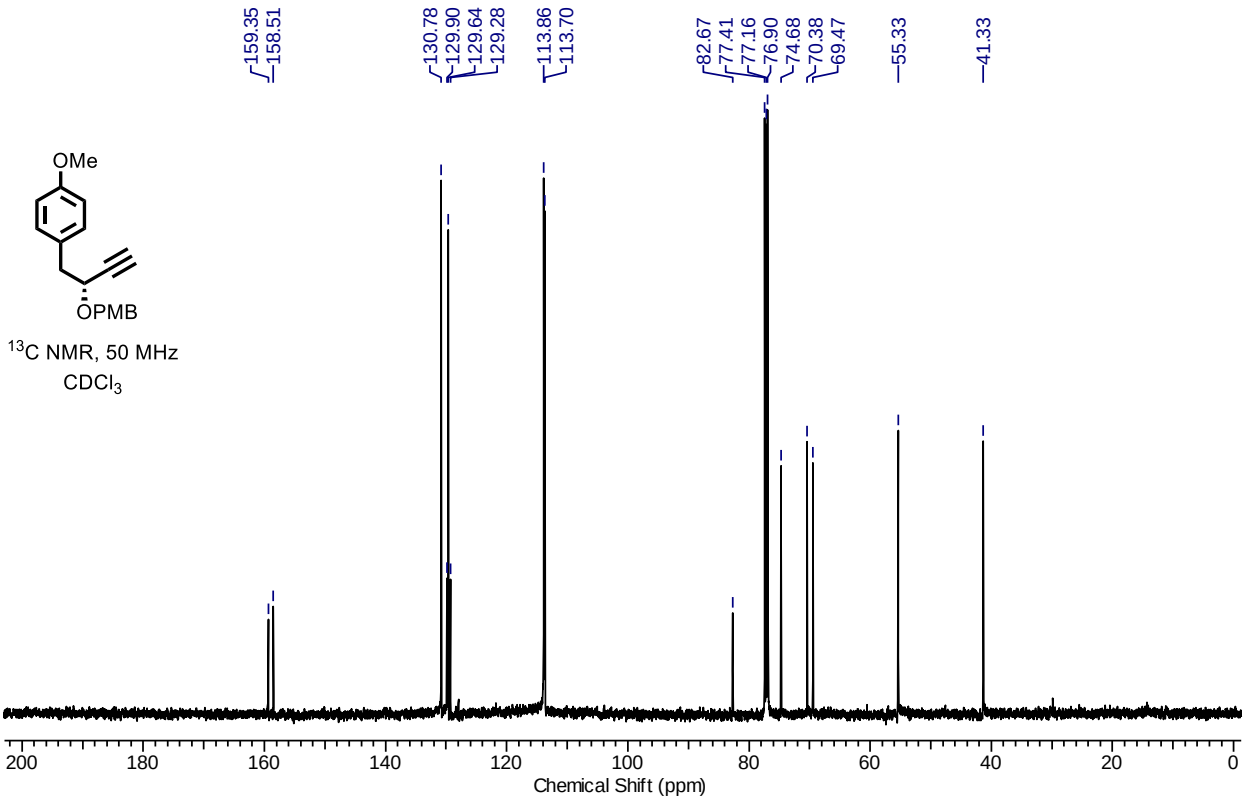
(*R*)-1-(((4,4-Dibromo-1-(4-methoxyphenyl)but-3-en-2-yl)oxy)methyl)-4-methoxybenzene (**S3**):



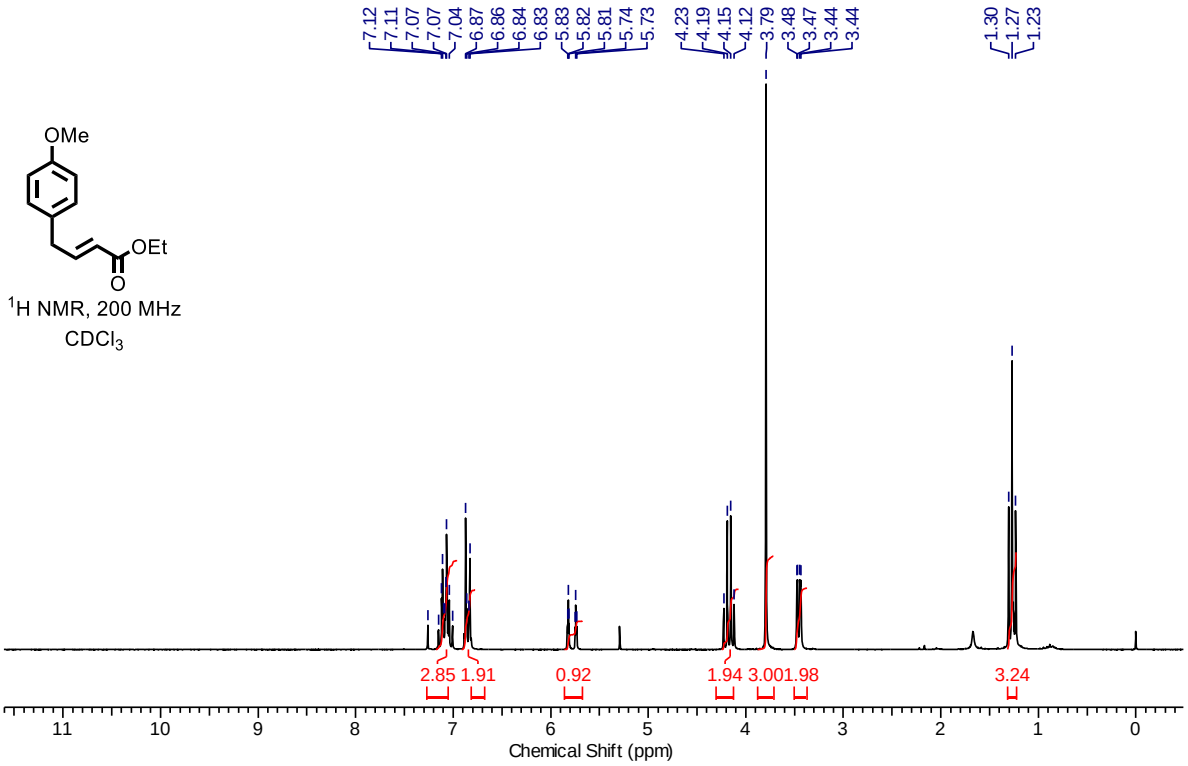
(*R*)-1-Methoxy-4-(2-((4-methoxybenzyl)oxy)but-3-yn-1-yl)benzene (**101**):



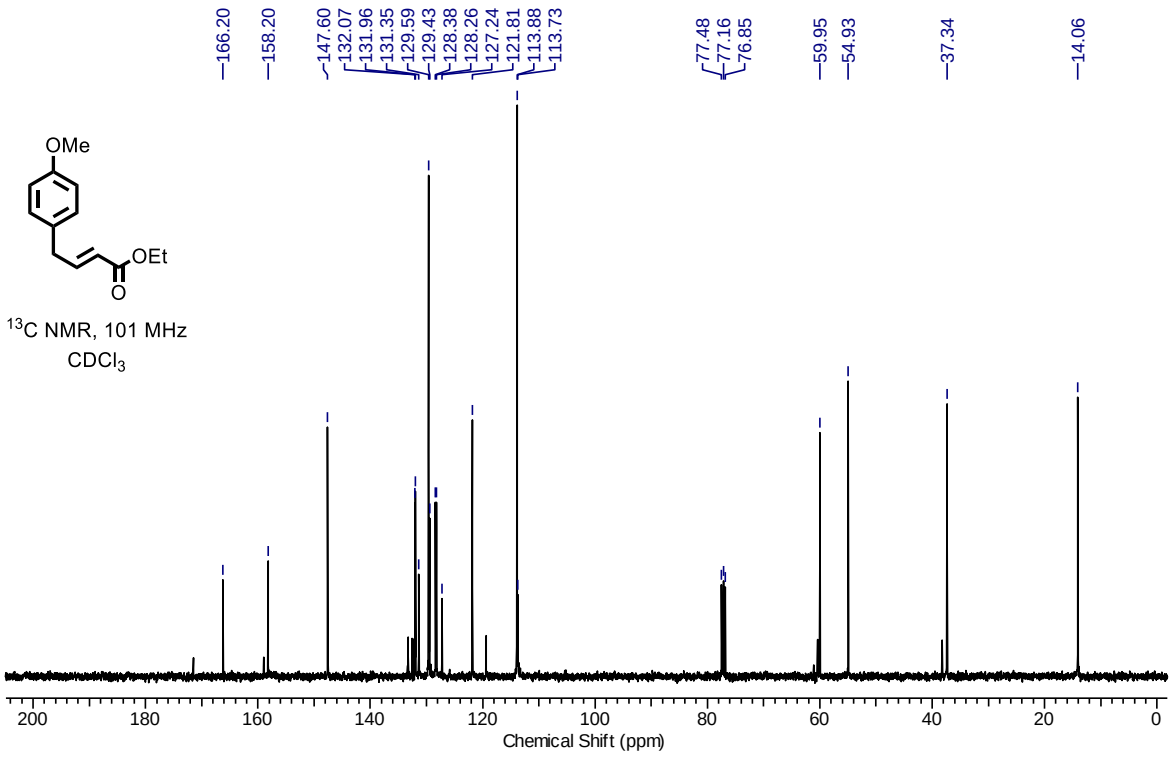
(*R*)-1-Methoxy-4-(2-((4-methoxybenzyl)oxy)but-3-yn-1-yl)benzene (**101**):



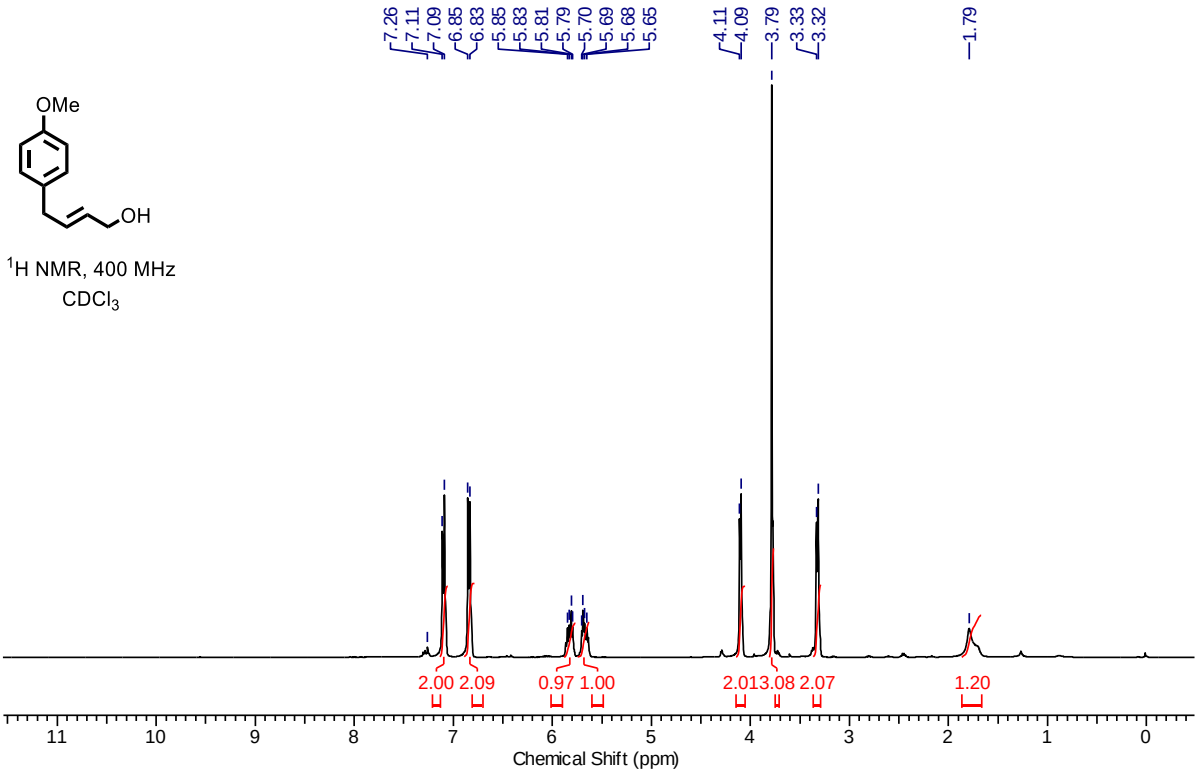
Ethyl (*E*)-4-(4-methoxyphenyl)but-2-enoate (**103**):



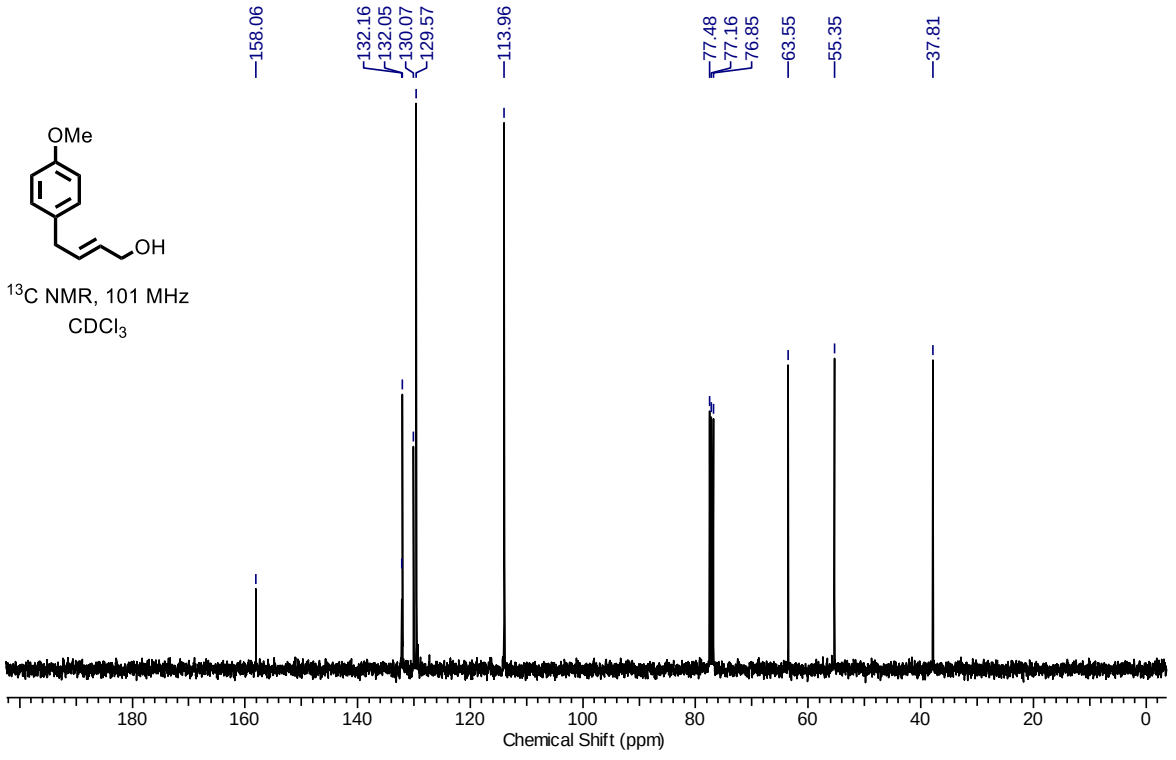
Ethyl (*E*)-4-(4-methoxyphenyl)but-2-enoate (**103**):



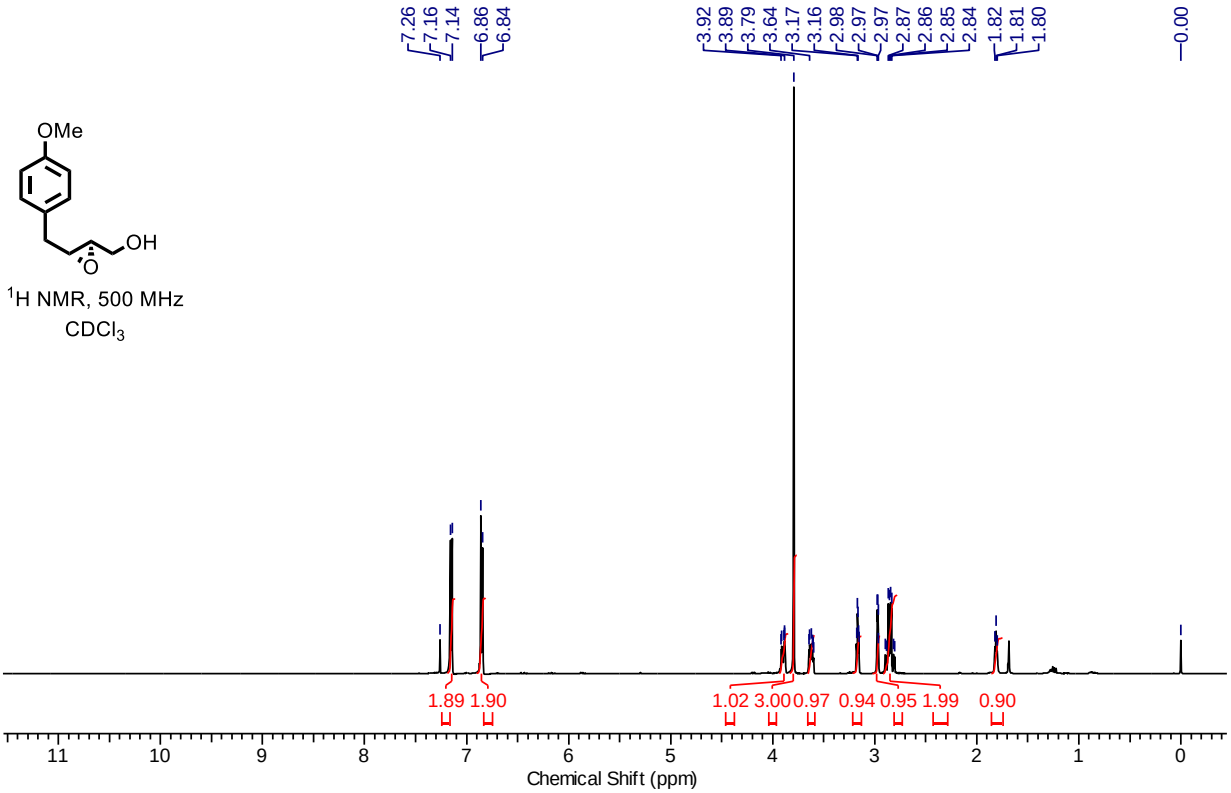
(*E*)-4-(4-Methoxyphenyl)but-2-en-1-ol (**S4**):



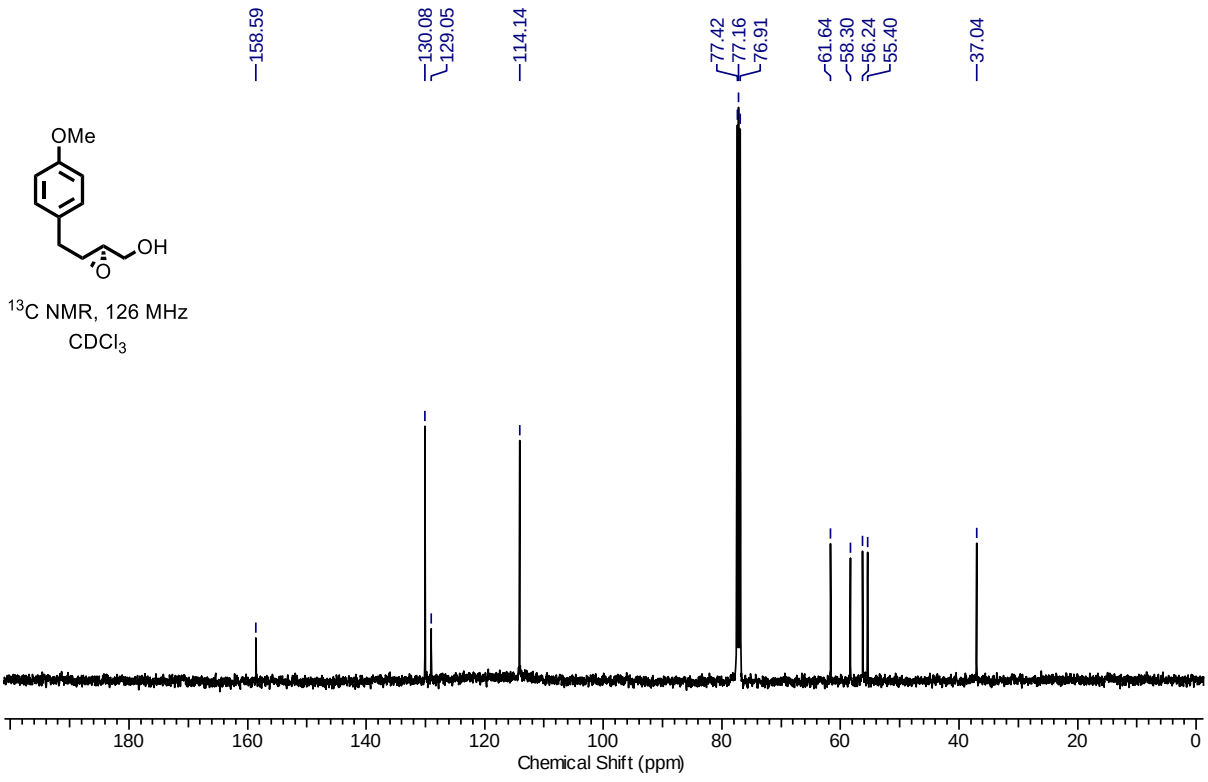
(*E*)-4-(4-Methoxyphenyl)but-2-en-1-ol (**S4**):



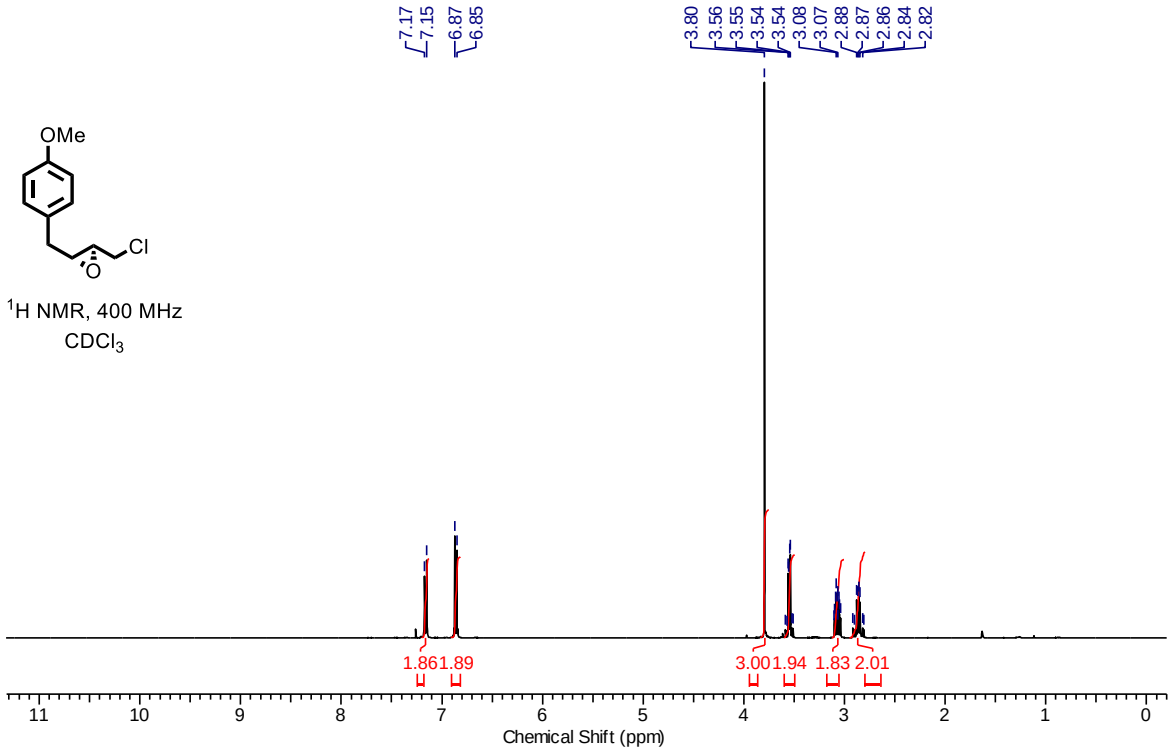
((*2R,3R*)-3-(4-Methoxybenzyl)oxiran-2-yl)methanol (**104**):



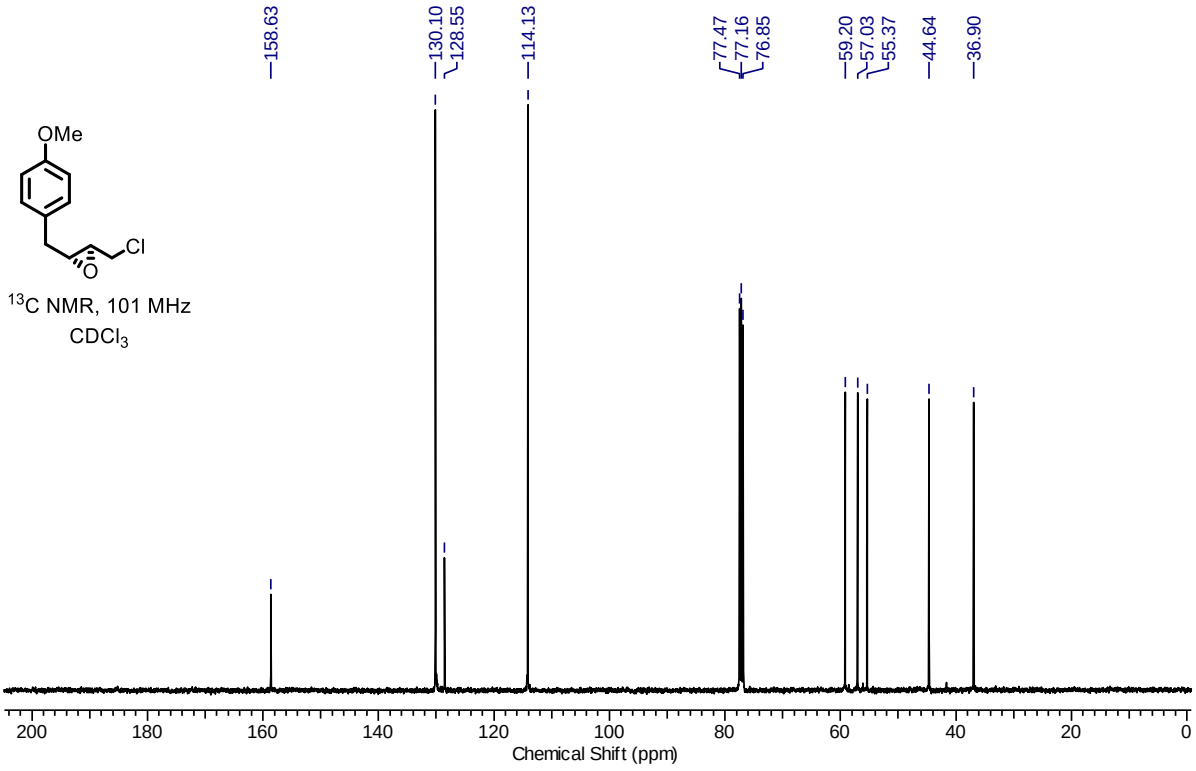
((*2R,3R*)-3-(4-Methoxybenzyl)oxiran-2-yl)methanol (**104**):



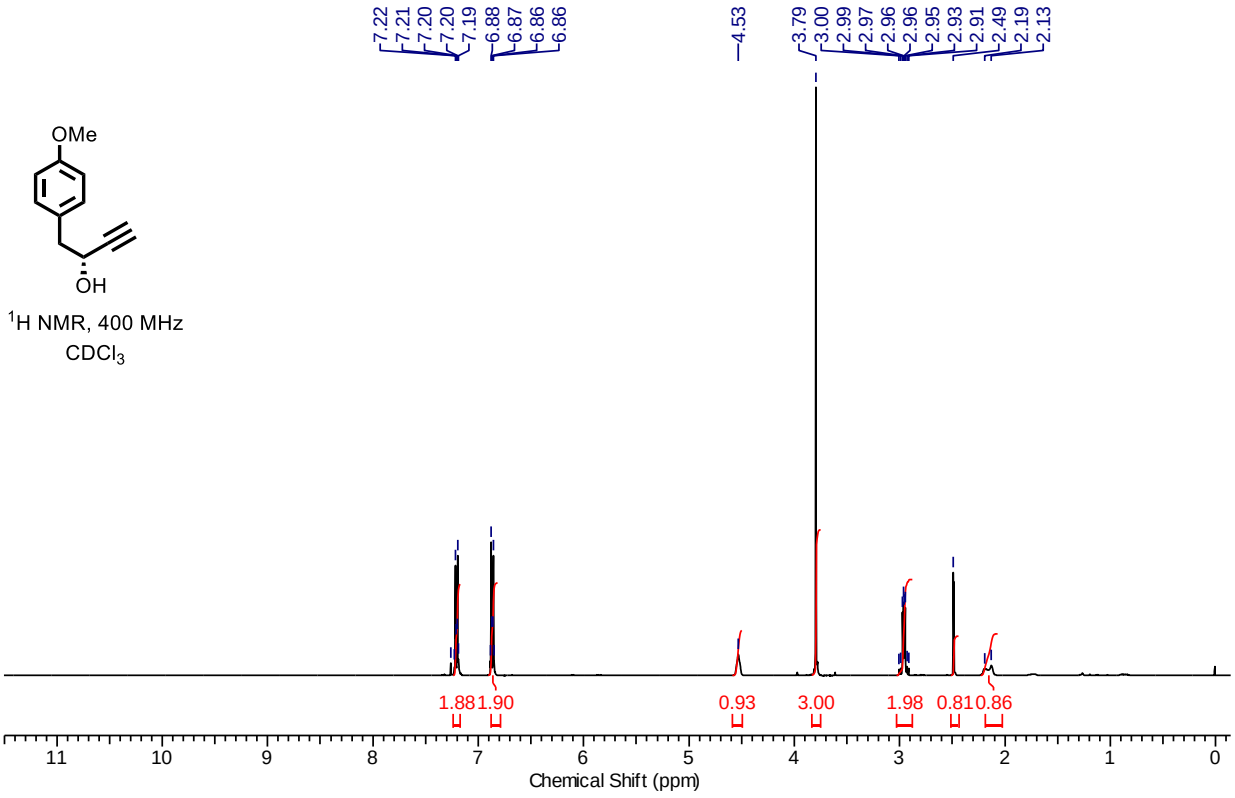
(*2S,3R*)-2-(Chloromethyl)-3-(4-methoxybenzyl)oxirane (**105**):



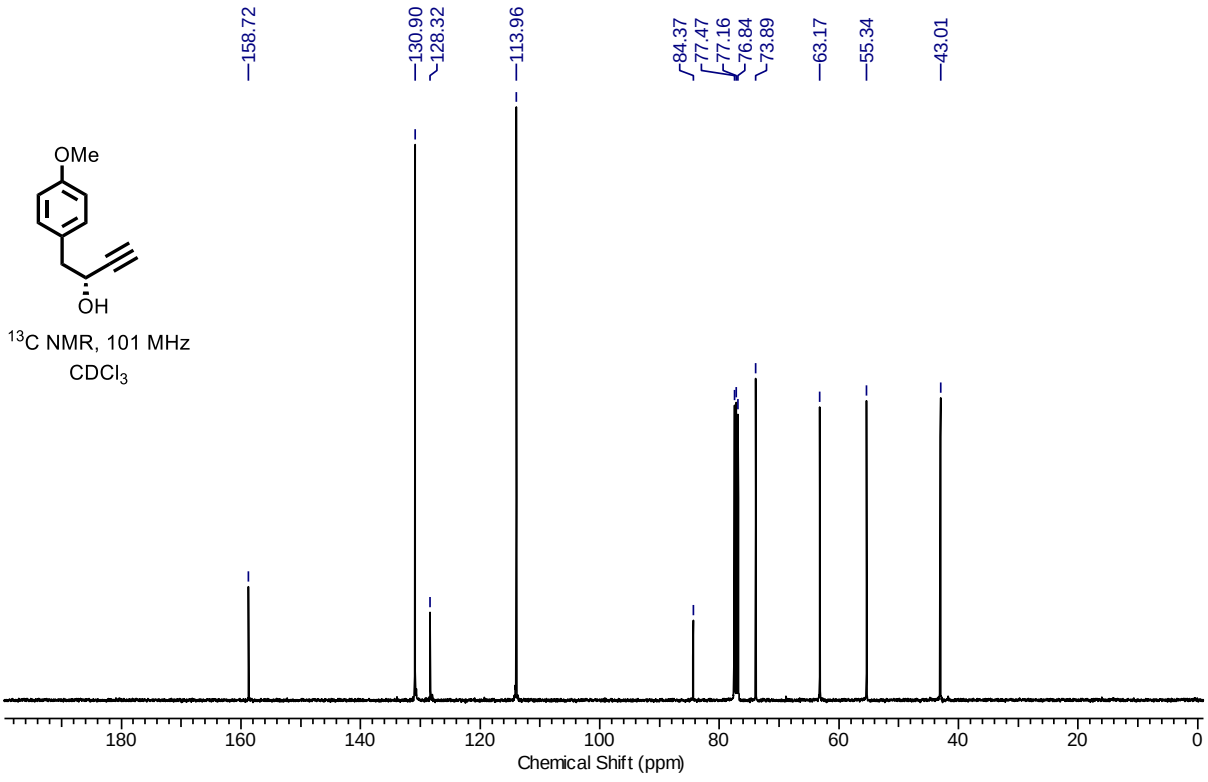
(*2S,3R*)-2-(Chloromethyl)-3-(4-methoxybenzyl)oxirane (**105**):



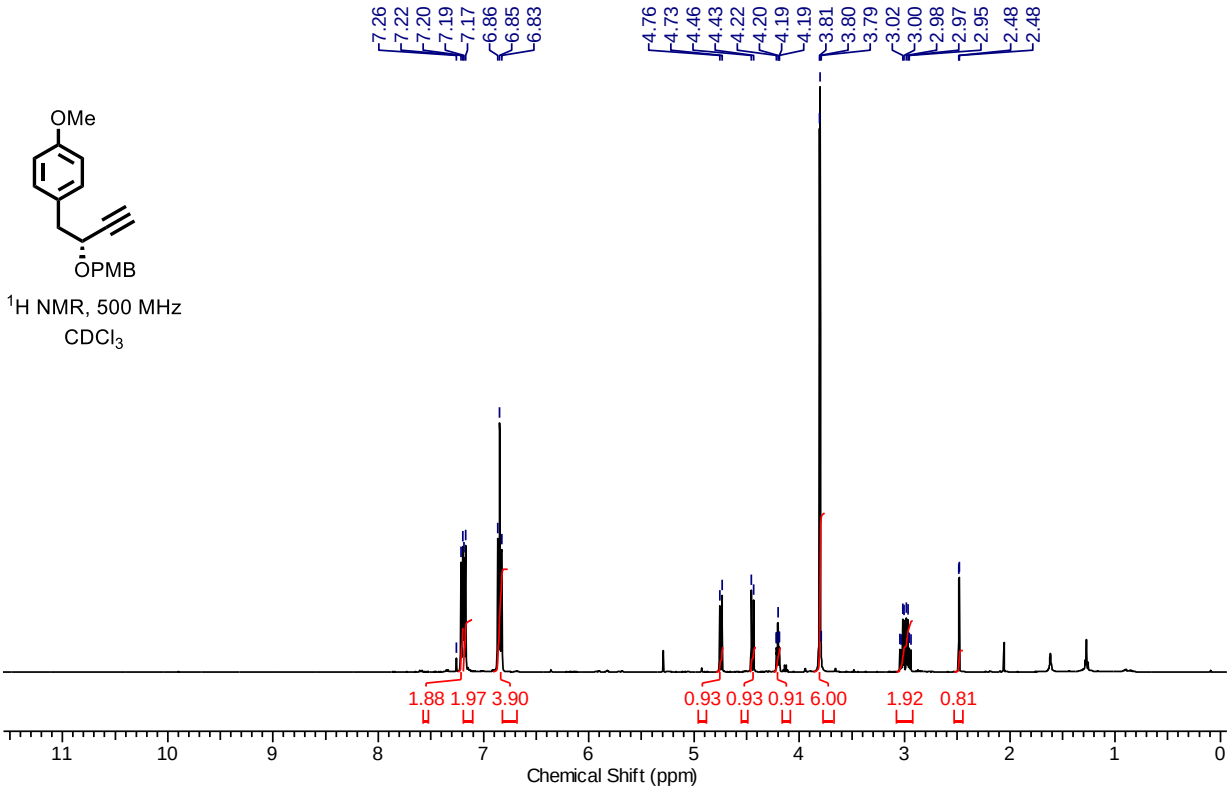
(*R*)-1-(4-Methoxyphenyl)but-3-yn-2-ol (**S5**):



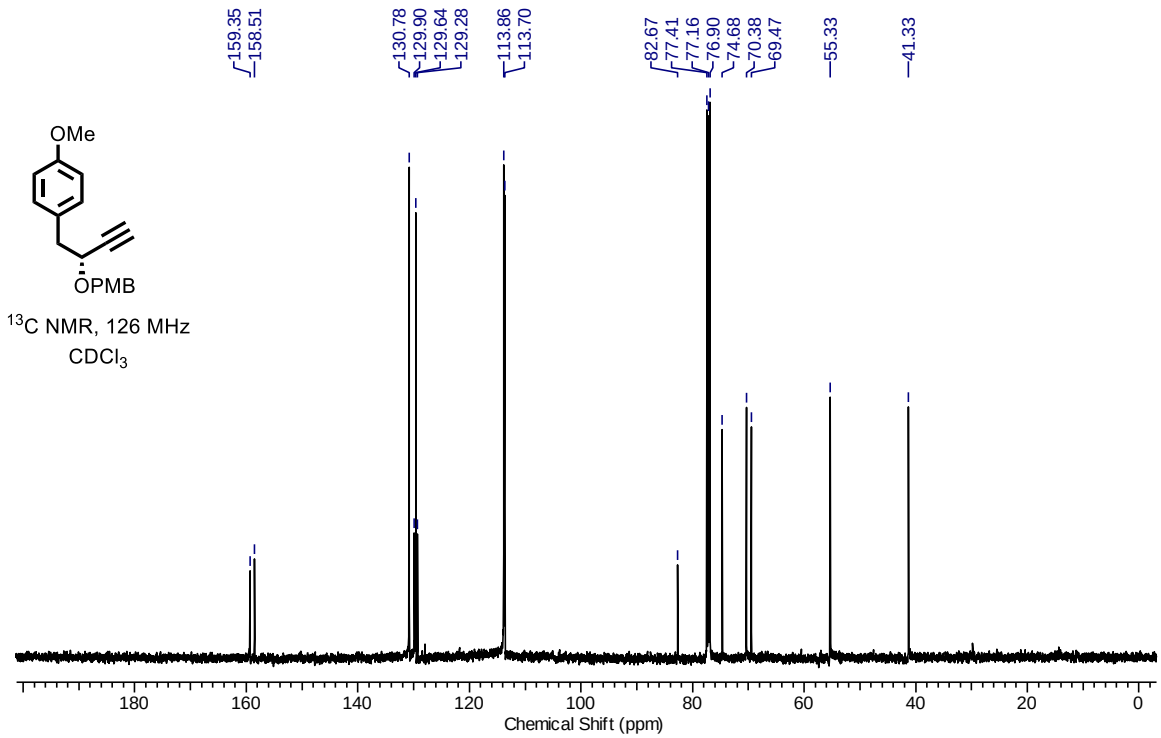
(*R*)-1-(4-Methoxyphenyl)but-3-yn-2-ol (**S5**):



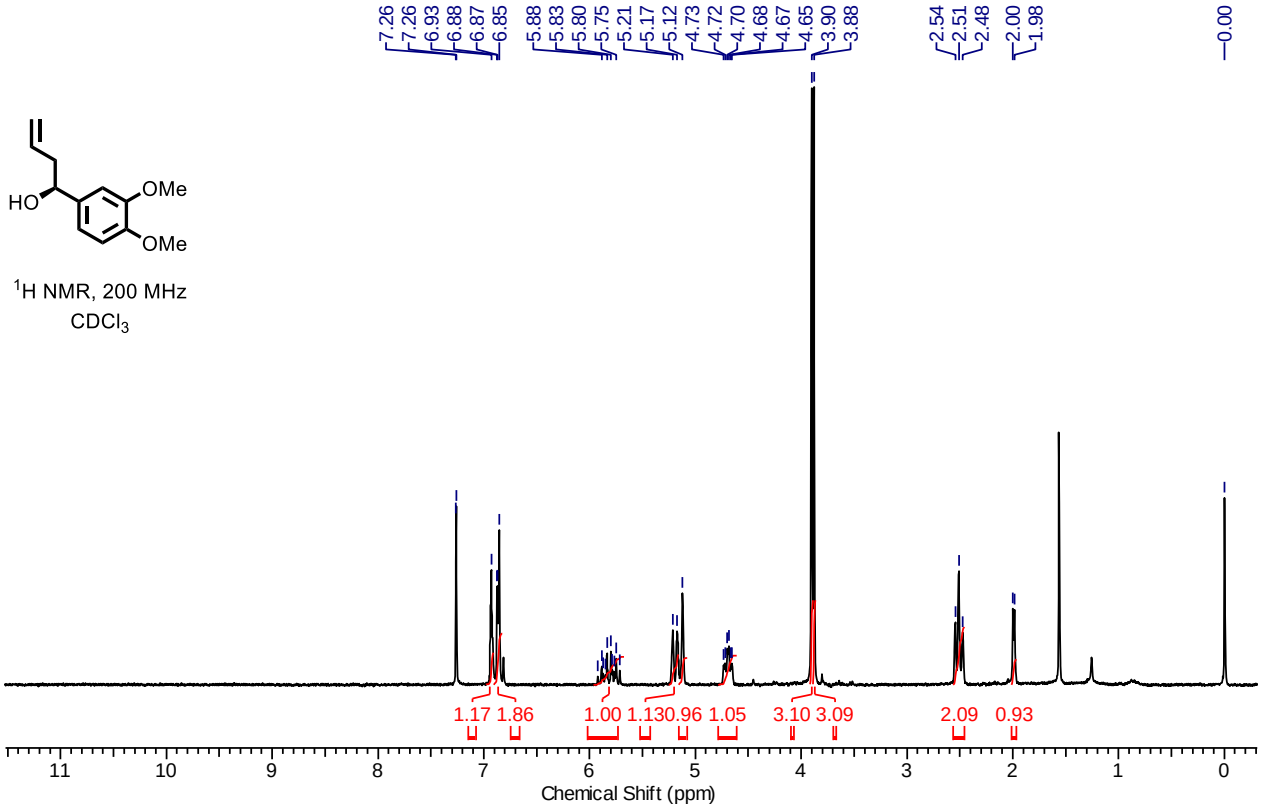
(*R*)-1-Methoxy-4-(2-((4-methoxybenzyl)oxy)but-3-yn-1-yl)benzene (**101**):



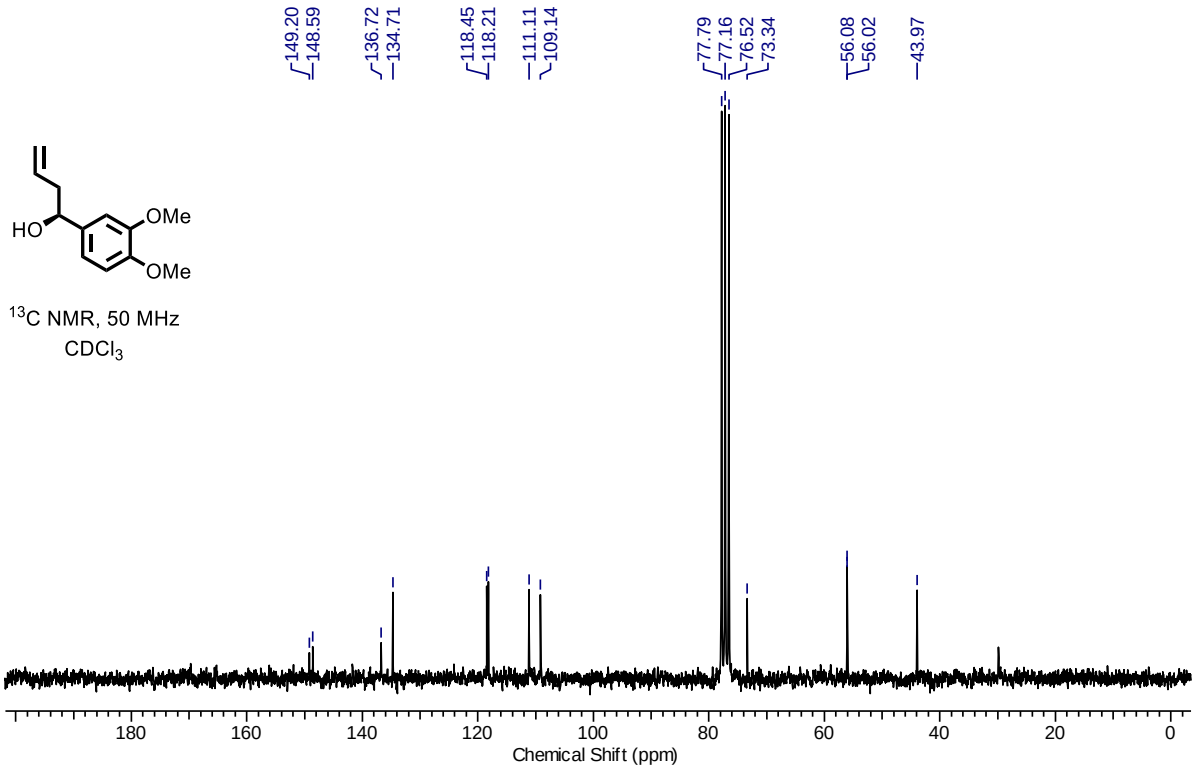
(*R*)-1-Methoxy-4-(2-((4-methoxybenzyl)oxy)but-3-yn-1-yl)benzene (**101**):



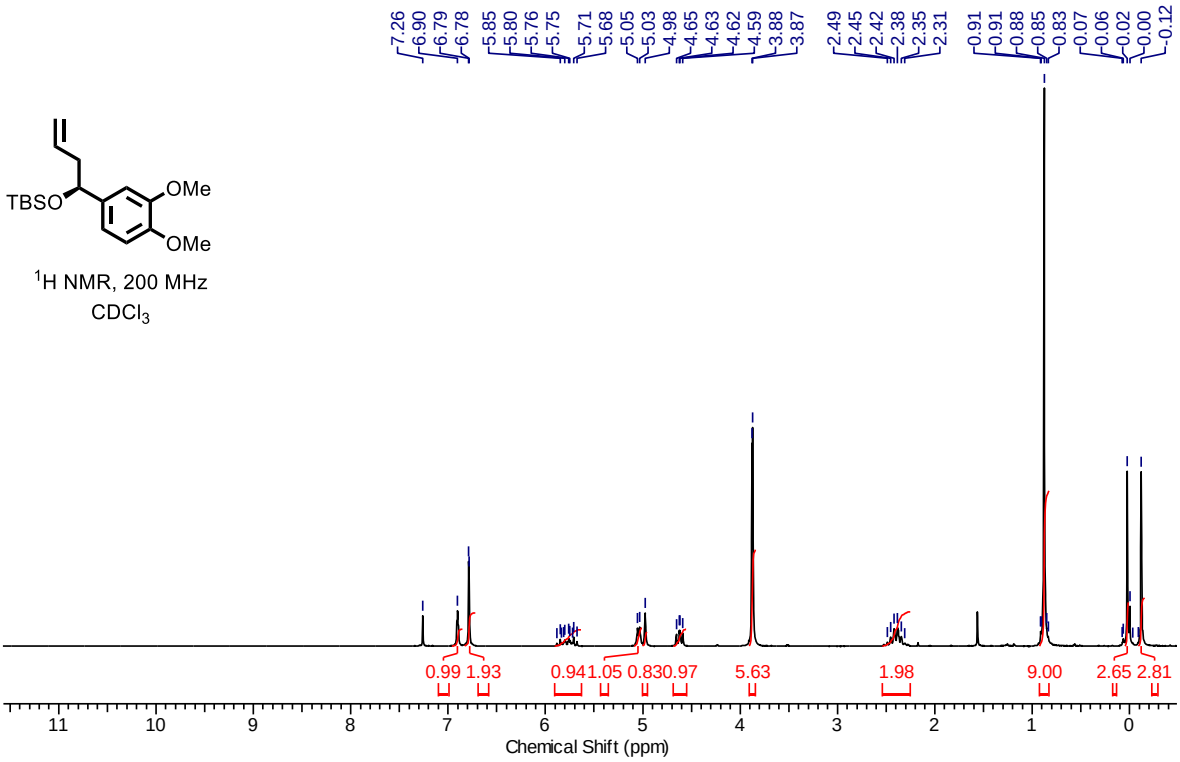
(*S*)-1-(3,4-Dimethoxyphenyl)but-3-en-1-ol (**106**):



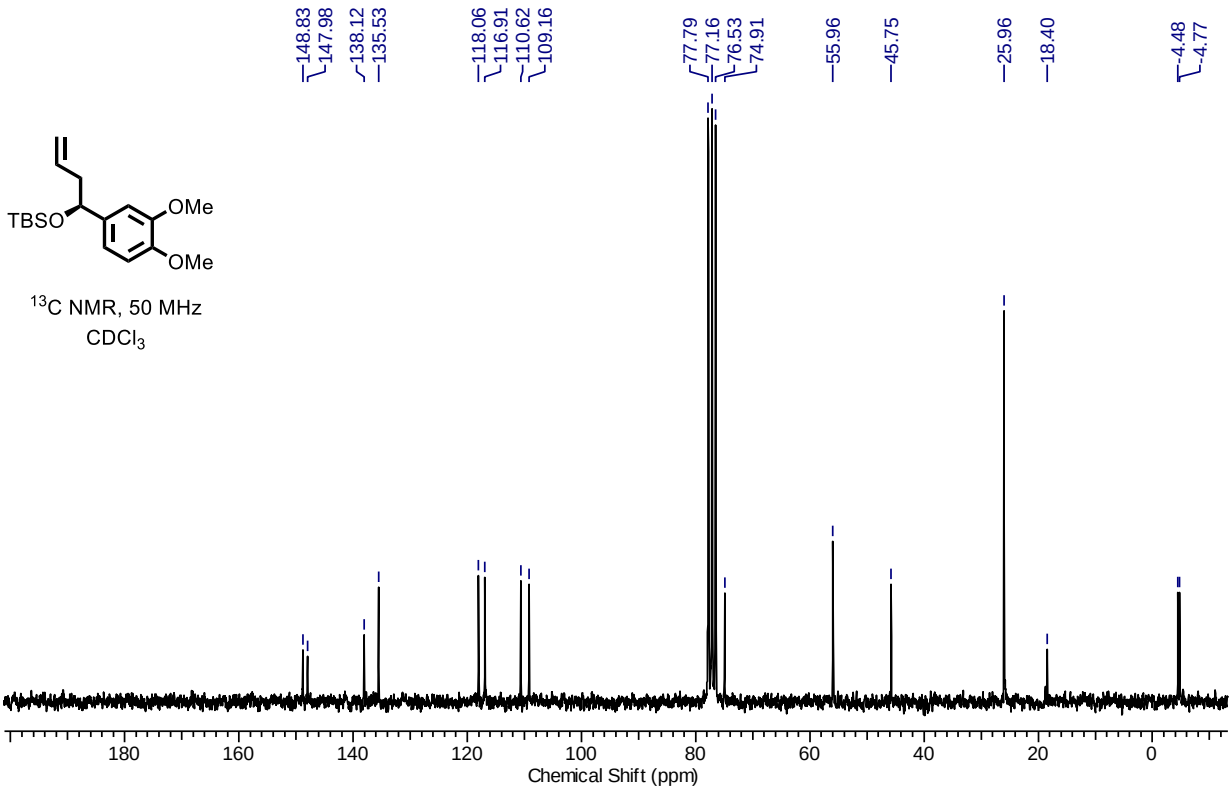
(*S*)-1-(3,4-Dimethoxyphenyl)but-3-en-1-ol (**106**):



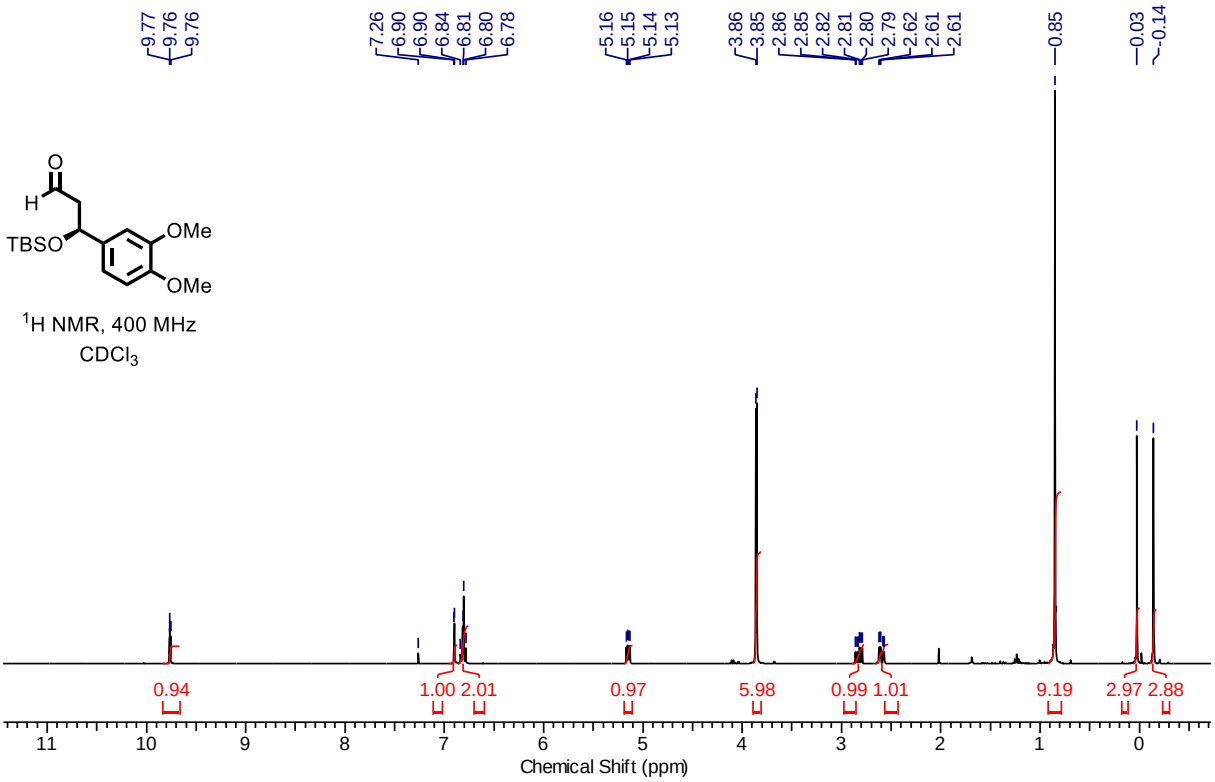
(*S*)-*Tert*-butyl((1-(3,4-dimethoxyphenyl)but-3-en-1-yl)oxy)dimethylsilane (**S6**):



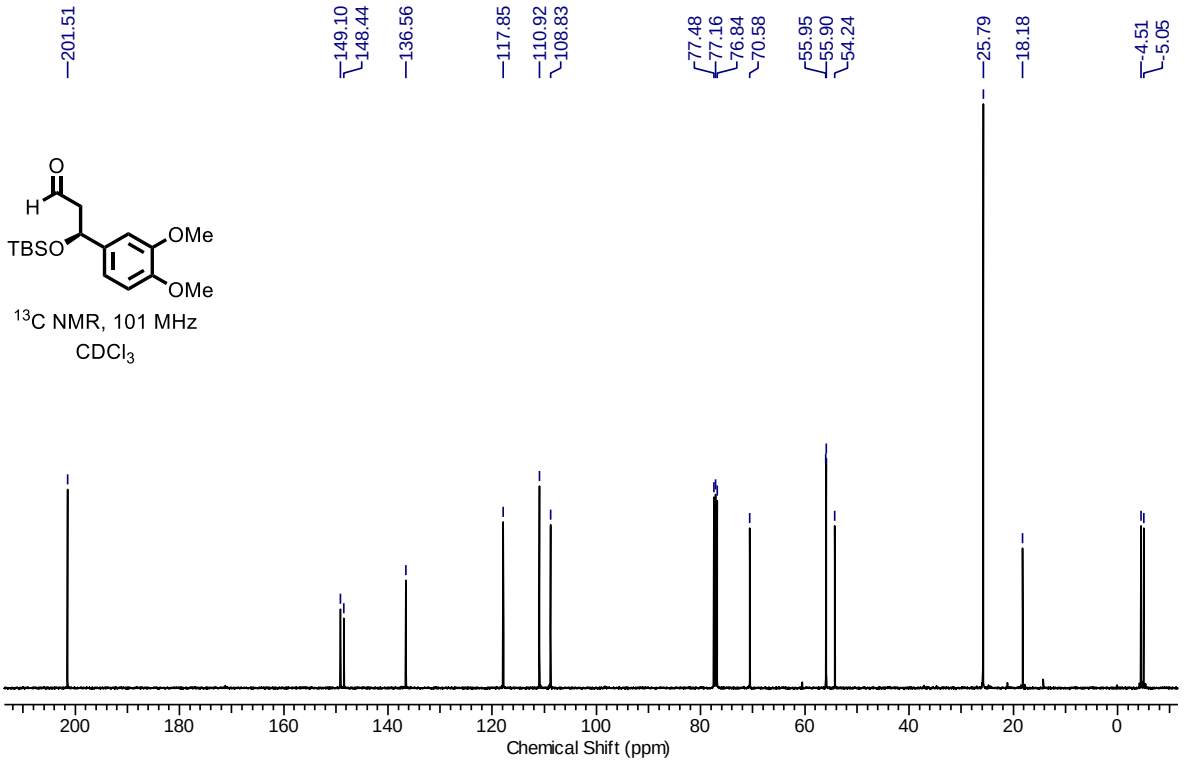
(*S*)-*Tert*-butyl((1-(3,4-dimethoxyphenyl)but-3-en-1-yl)oxy)dimethylsilane (**S6**):



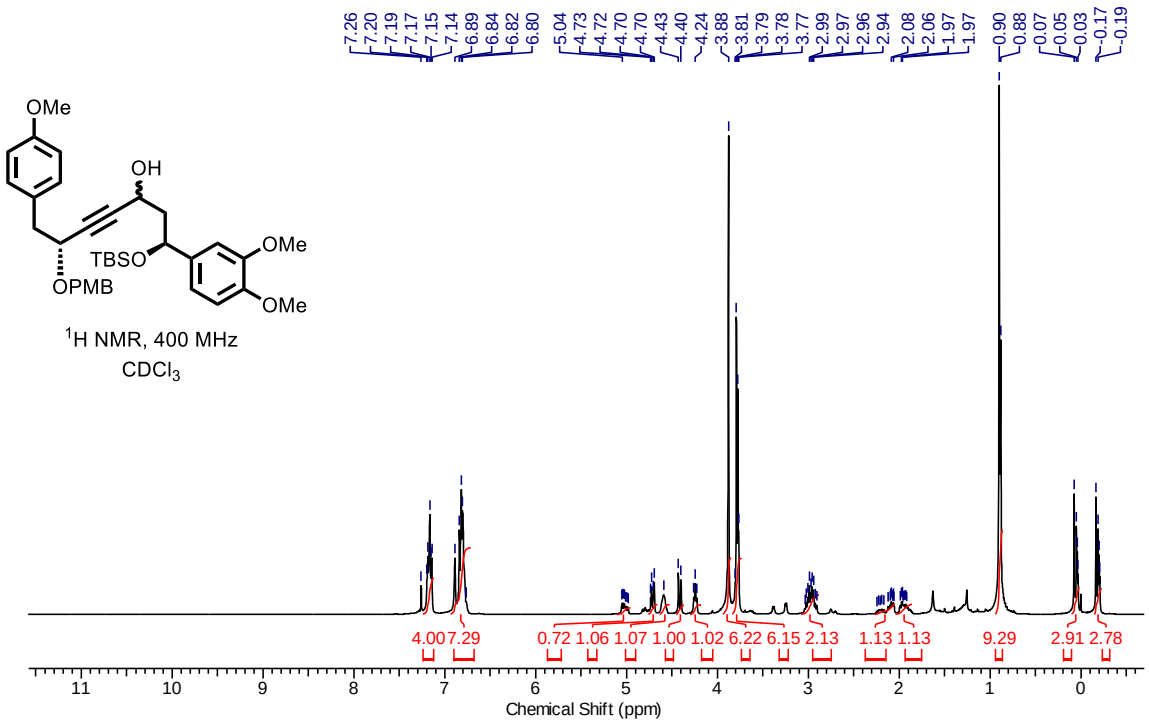
(*S*)-3-((*Tert*-butyldimethylsilyl)oxy)-3-(3,4-dimethoxyphenyl)propanal (**102**):



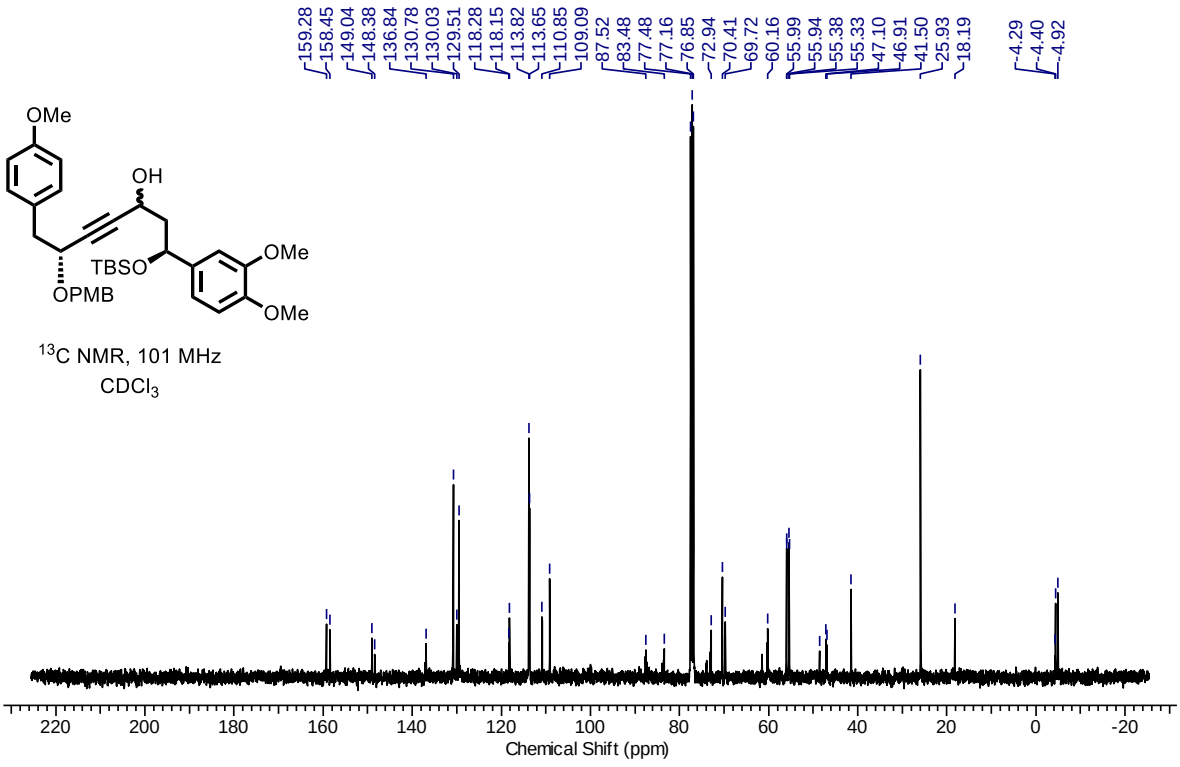
(*S*)-3-((*Tert*-butyldimethylsilyl)oxy)-3-(3,4-dimethoxyphenyl)propanal (**102**):



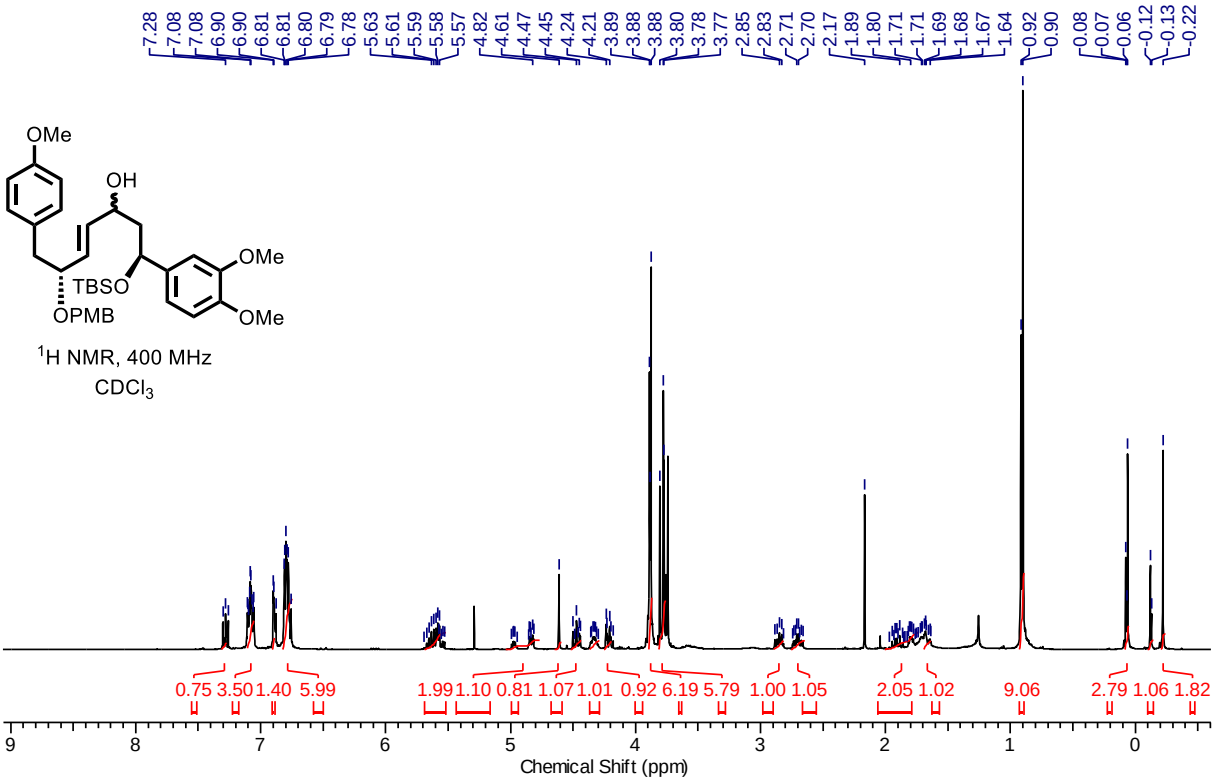
(*1S,6R*)-1-((*Tert*-butyldimethylsilyl)oxy)-1-(3,4-dimethoxyphenyl)-6-((4-methoxybenzyl)-oxy)-7-(4-methoxyphenyl)hept-4-yn-3-ol (**107**):



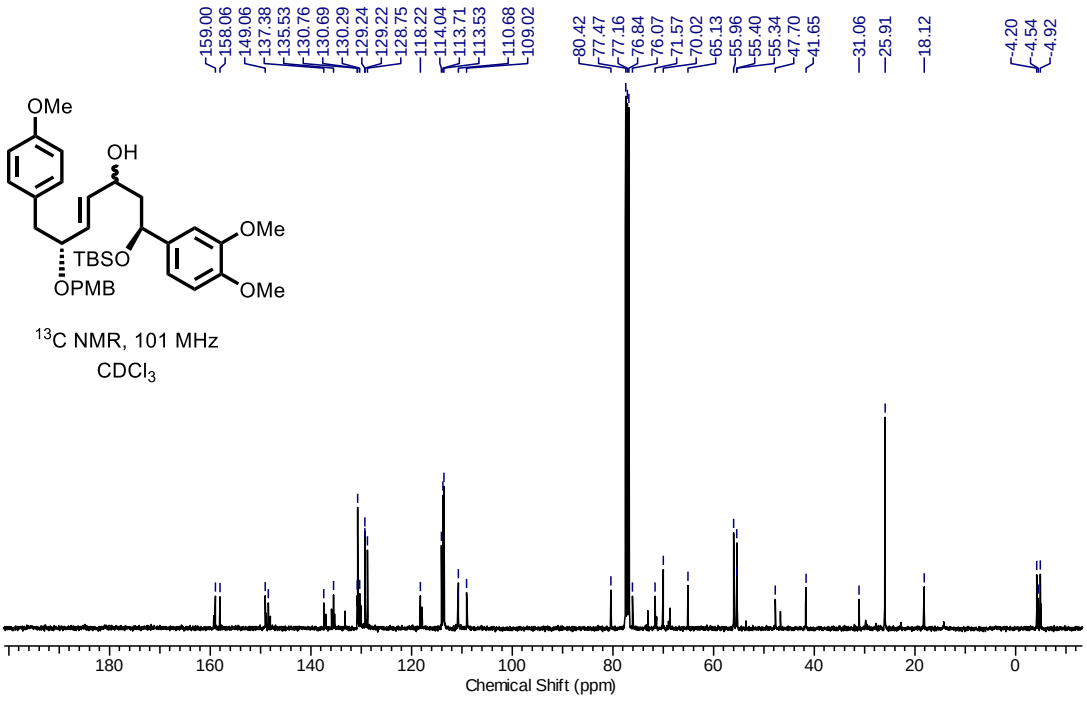
(*1S,6R*)-1-((*Tert*-butyldimethylsilyl)oxy)-1-(3,4-dimethoxyphenyl)-6-((4-methoxybenzyl)-oxy)-7-(4-methoxyphenyl)hept-4-yn-3-ol (**107**):



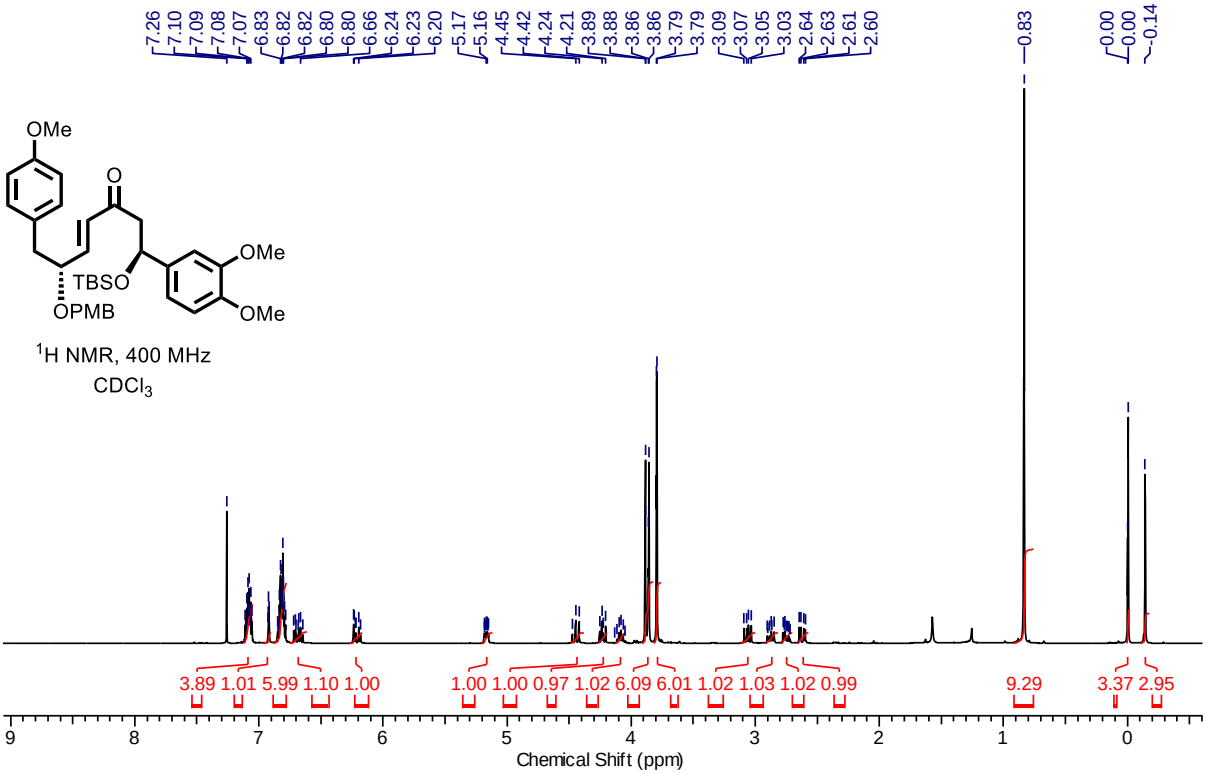
(*1S,6R,E*)-1-((*Tert*-butyldimethylsilyl)oxy)-1-(3,4-dimethoxyphenyl)-6-((4-methoxybenzyl)-oxy)-7-(4-methoxyphenyl)hept-4-en-3-ol (**S7**):



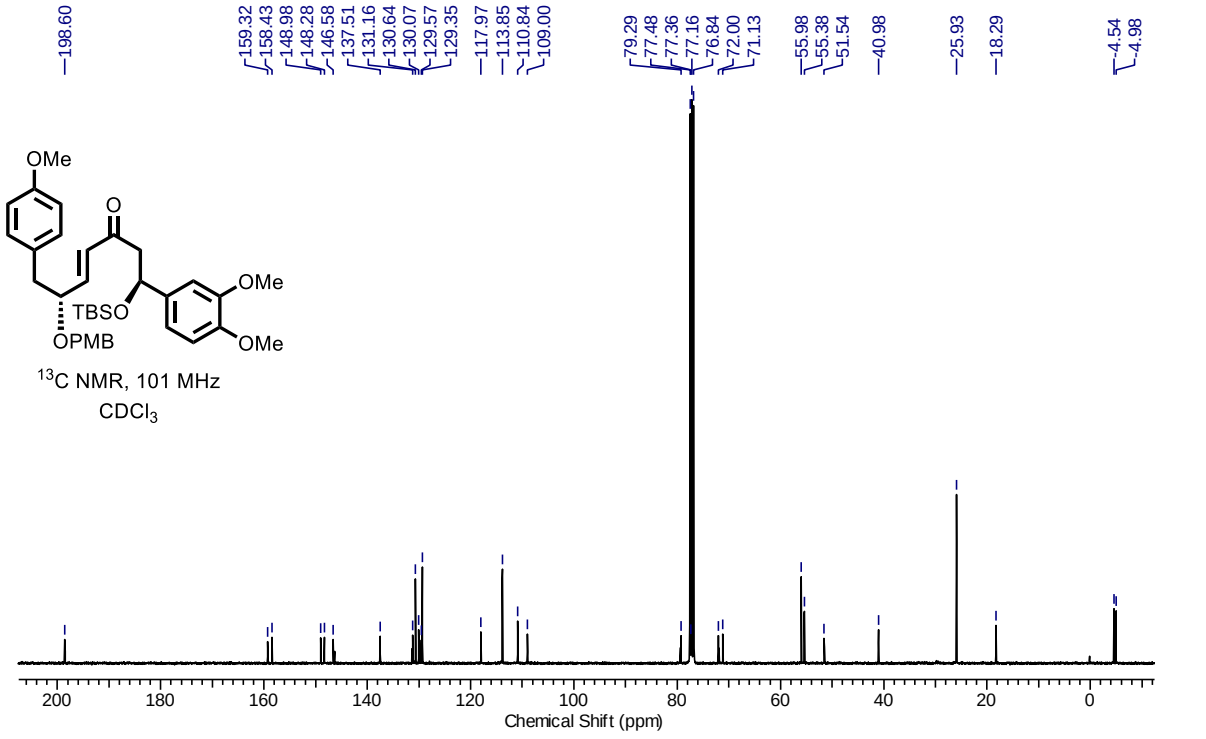
(*1S,6R,E*)-1-((*Tert*-butyldimethylsilyl)oxy)-1-(3,4-dimethoxyphenyl)-6-((4-methoxybenzyl)-oxy)-7-(4-methoxyphenyl)hept-4-en-3-ol (**S7**):



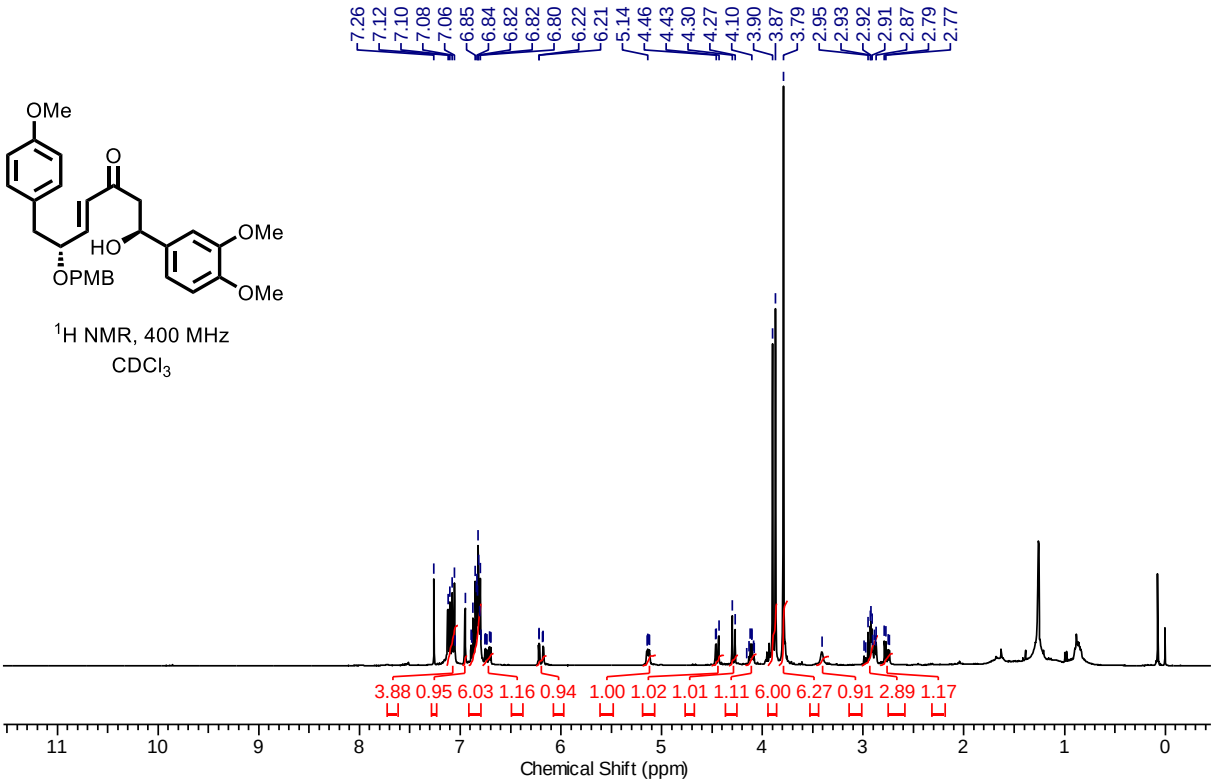
(*1S,6R,E*)-1-((*Tert*-butyldimethylsilyl)oxy)-1-(3,4-dimethoxyphenyl)-6-((4-mehoxybenzyl)-oxy)-7-(4-methoxyphenyl)hept-4-en-3-one (**100**):



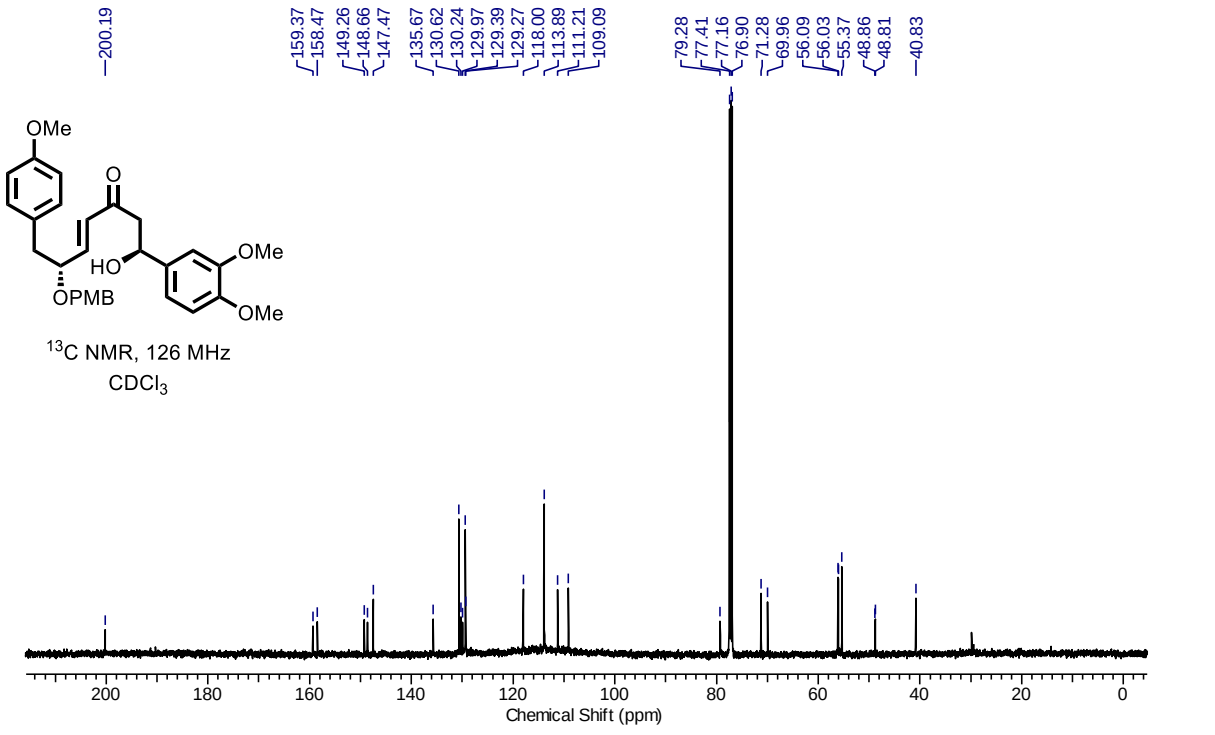
(*1S,6R,E*)-1-((*Tert*-butyldimethylsilyl)oxy)-1-(3,4-dimethoxyphenyl)-6-((4-mehoxybenzyl)-oxy)-7-(4-methoxyphenyl)hept-4-en-3-one (**100**):



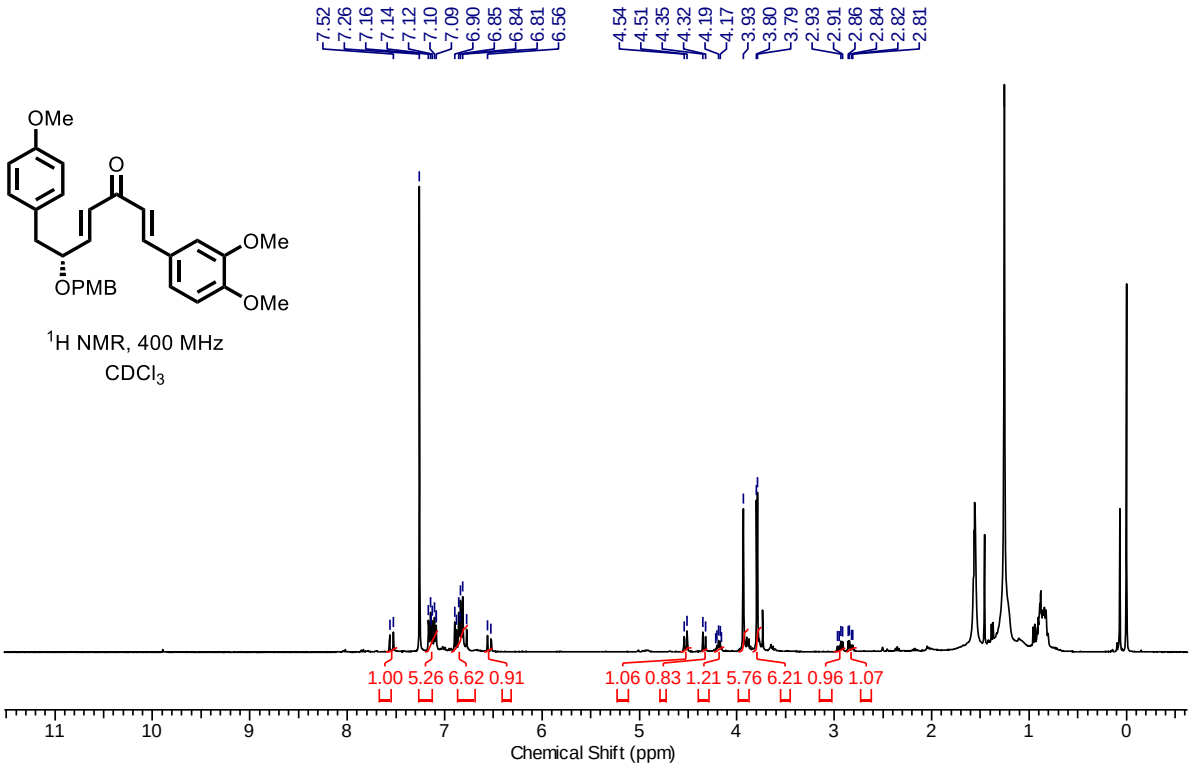
(*1S,6R,E*)-1-(3,4-Dimethoxyphenyl)-1-hydroxy-6-((4-methoxybenzyl)oxy)-7-(4-methoxyphenyl)-hept-4-en-3-one (**108**):



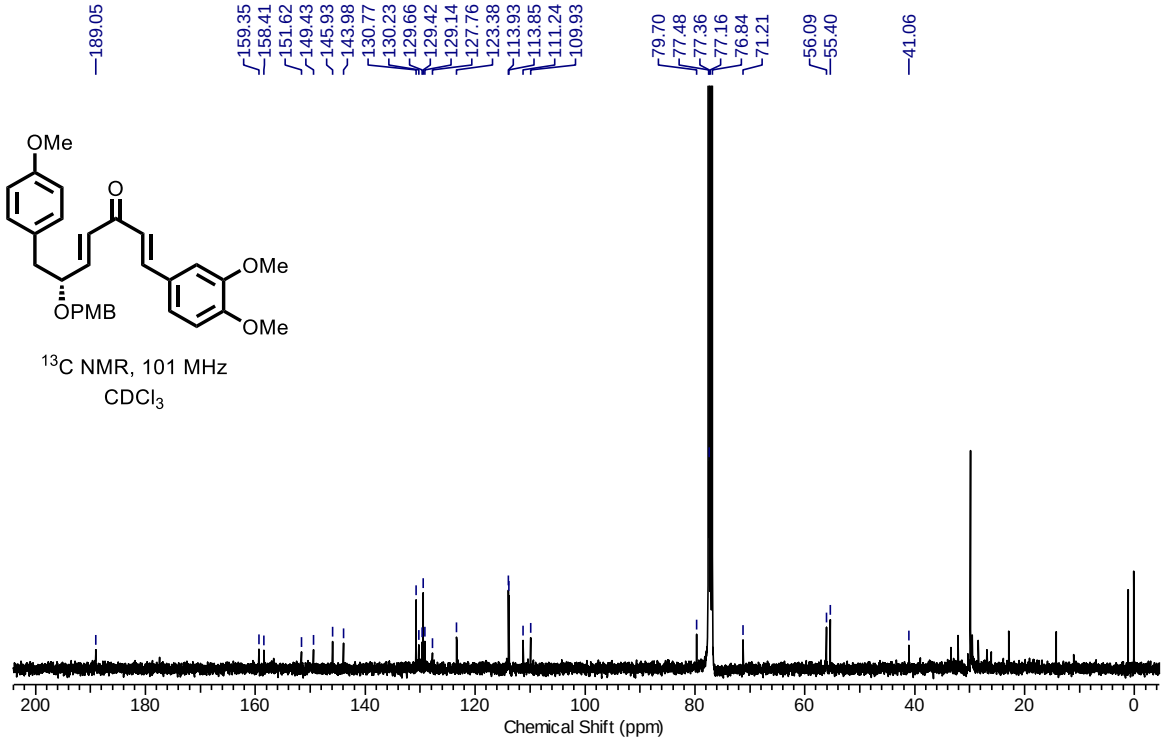
(*1S,6R,E*)-1-(3,4-Dimethoxyphenyl)-1-hydroxy-6-((4-methoxybenzyl)oxy)-7-(4-methoxyphenyl)-hept-4-en-3-one (**108**):



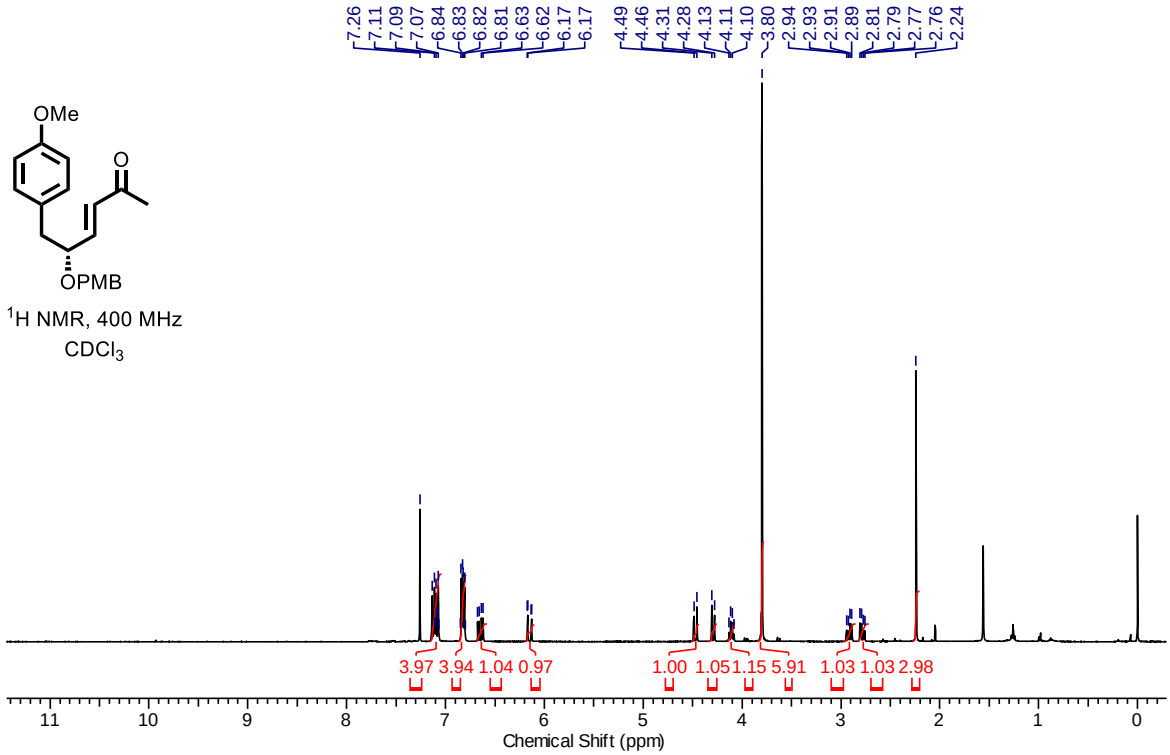
(*R,1E,4E*)-1-(3,4-Dimethoxyphenyl)-6-((4-methoxybenzyl)oxy)-7-(4-methoxyphenyl)hepta-1,4-dien-3-one (**110**):



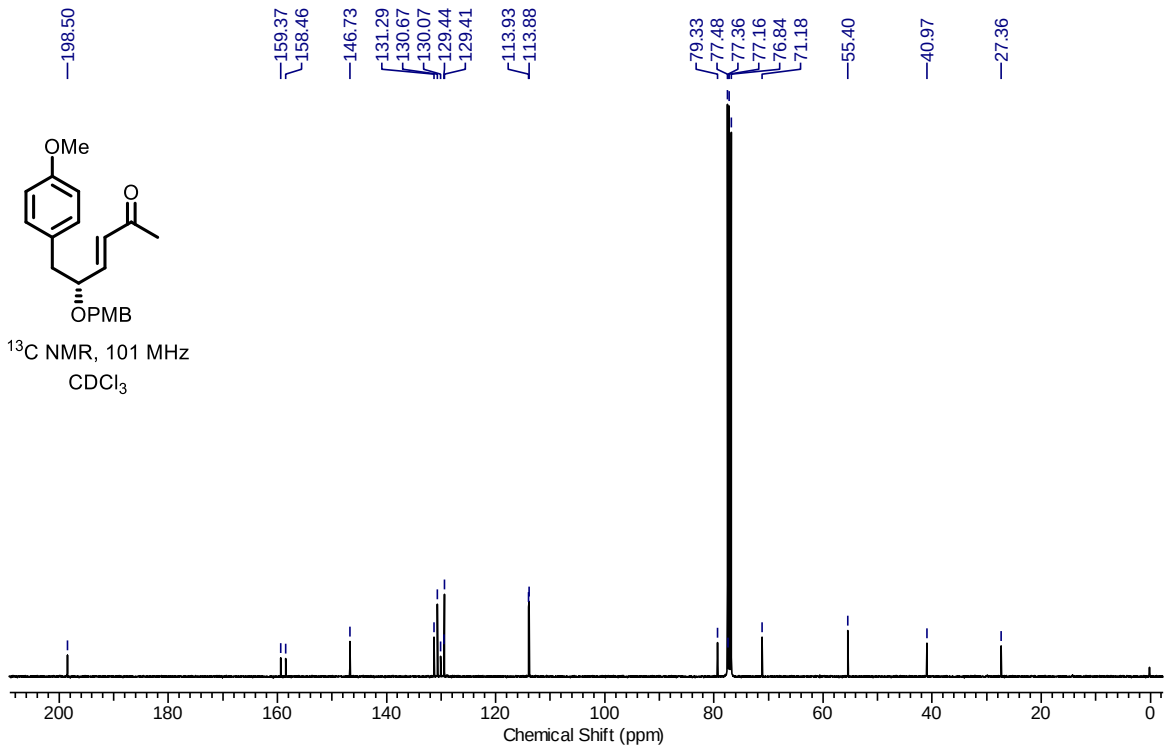
(*R,1E,4E*)-1-(3,4-Dimethoxyphenyl)-6-((4-methoxybenzyl)oxy)-7-(4-methoxyphenyl)hepta-1,4-dien-3-one (**110**):



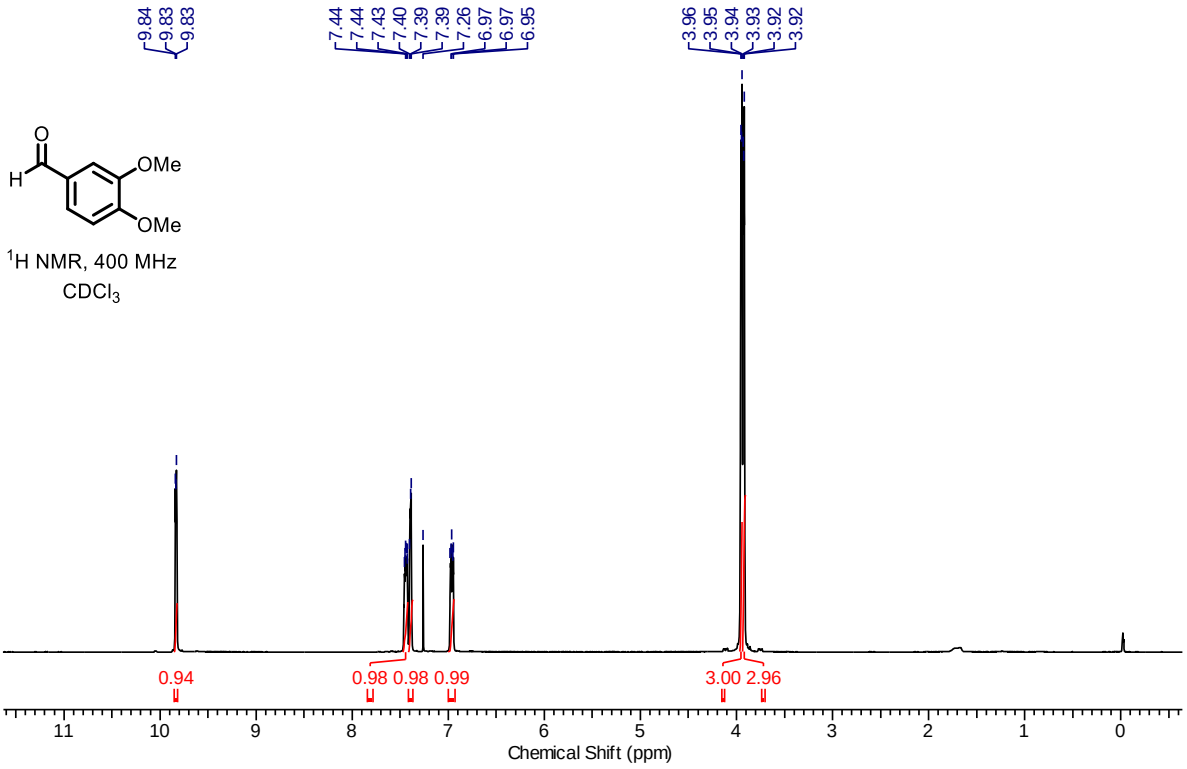
(*R,E*)-5-((4-Methoxybenzyl)oxy)-6-(4-methoxyphenyl)hex-3-en-2-one (**111**):



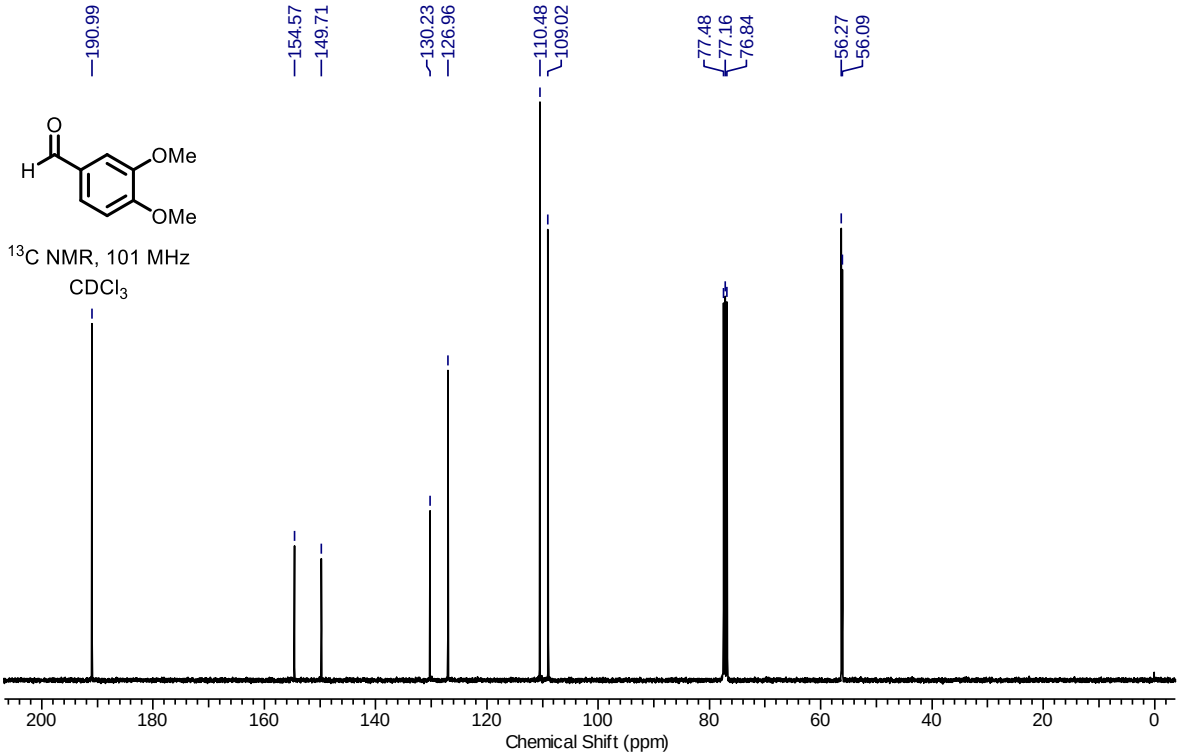
(*R,E*)-5-((4-Methoxybenzyl)oxy)-6-(4-methoxyphenyl)hex-3-en-2-one (**111**):



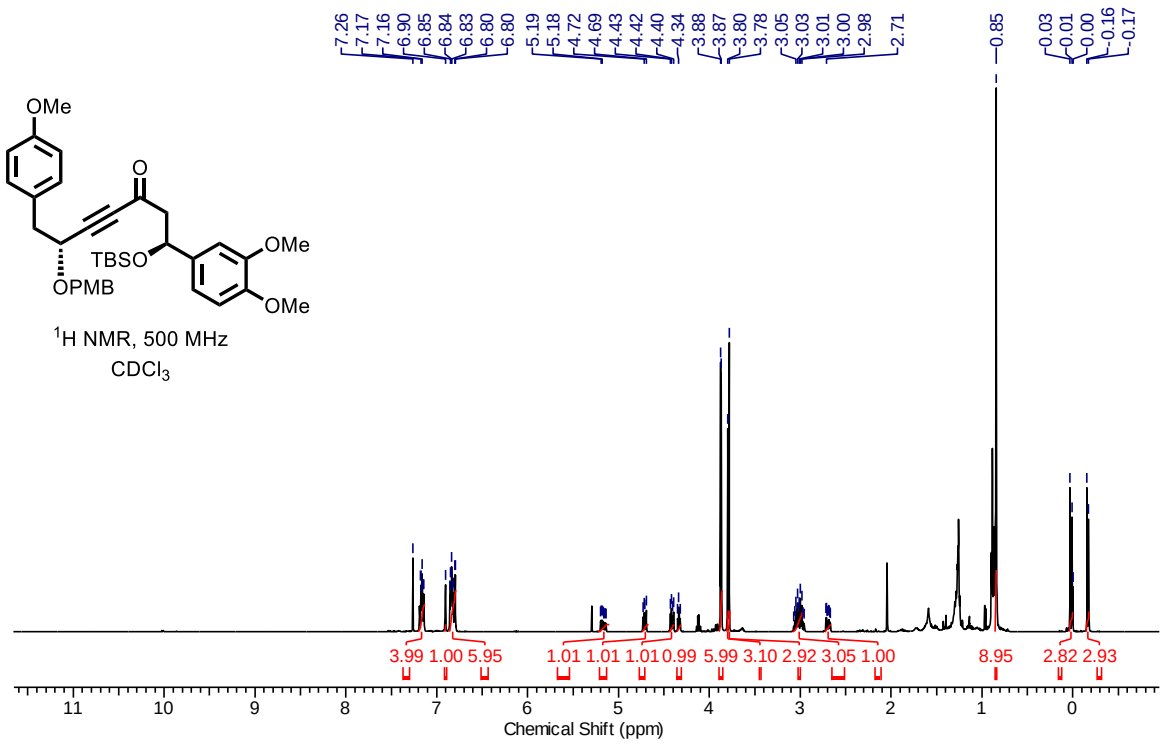
3,4-Dimethoxybenzaldehyde (**96**):



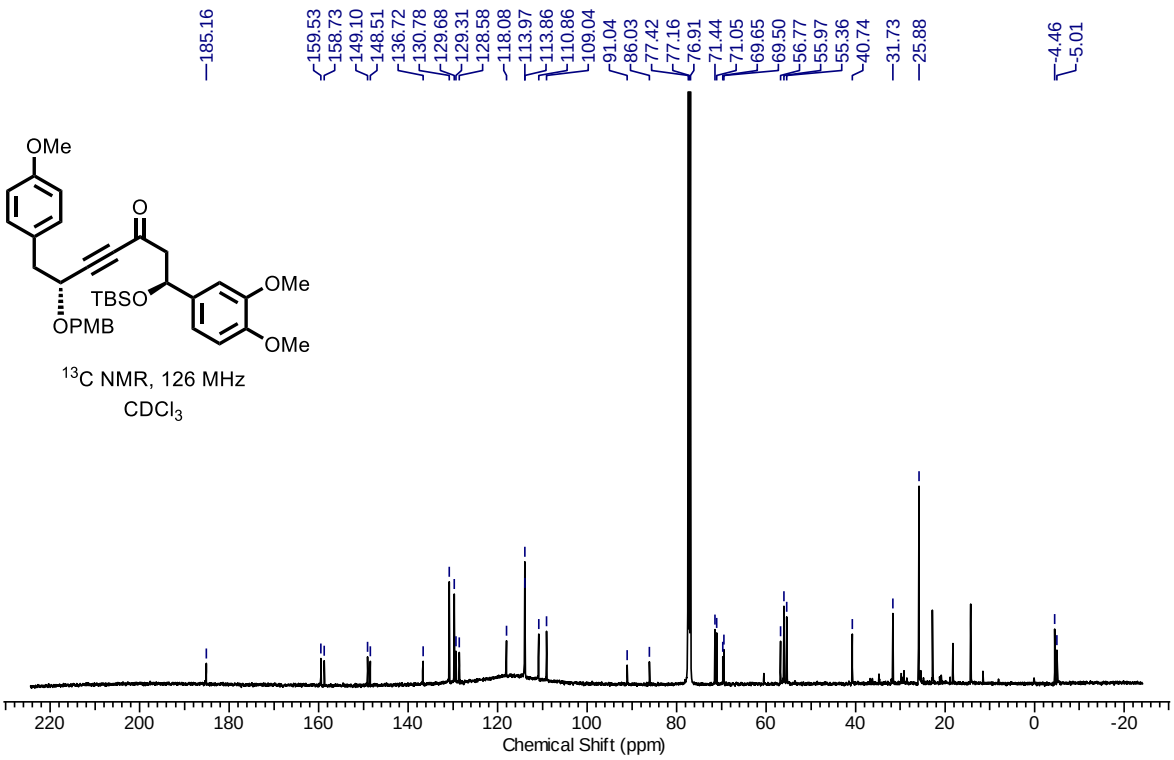
3,4-Dimethoxybenzaldehyde (**96**):



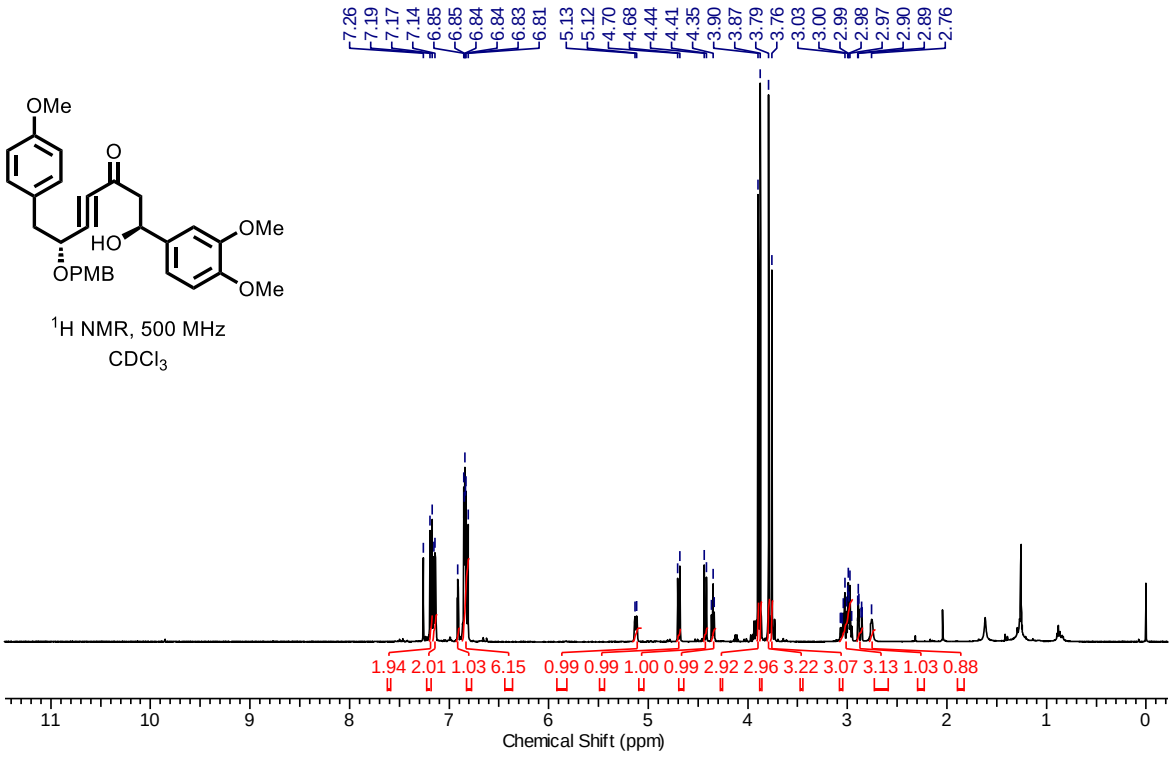
(*1S,6R*)-1-((*Tert*-butyldimethylsilyl)oxy)-1-(3,4-dimethoxyphenyl)-6-((4-methoxybenzyl)-oxy)-7-(4-methoxyphenyl)hept-4-yn-3-one (**100a**):



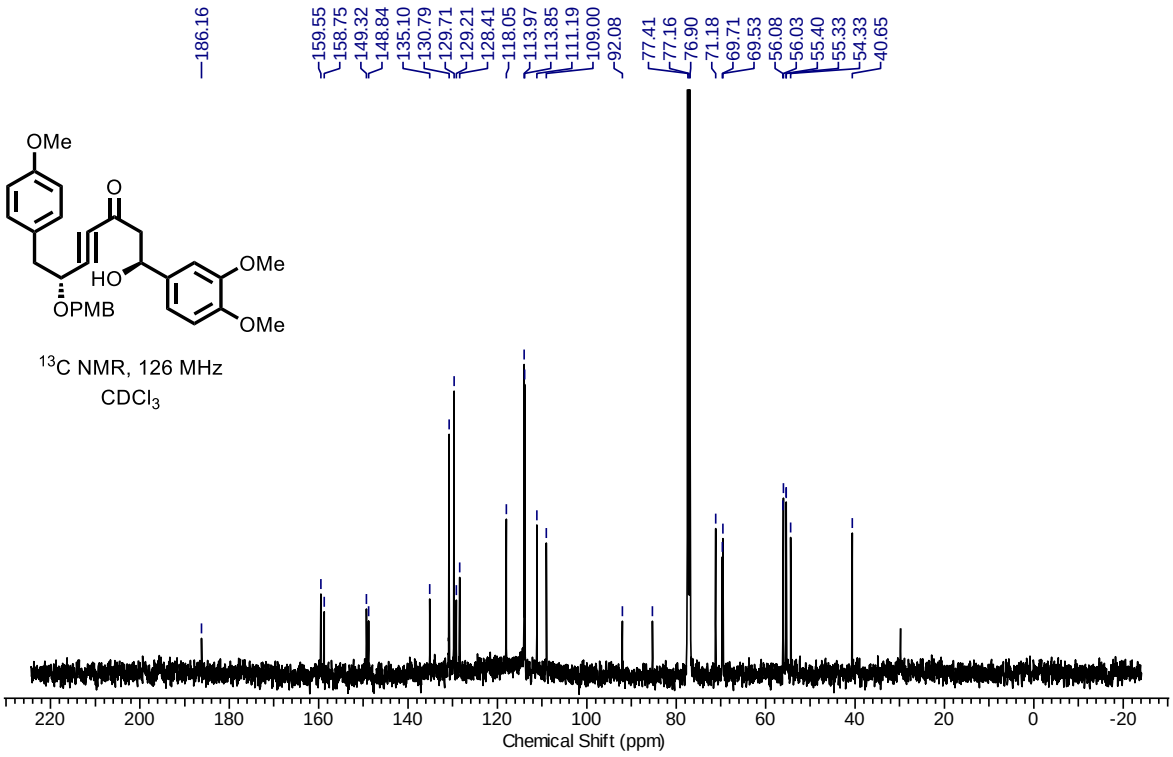
(*1S,6R*)-1-((*Tert*-butyldimethylsilyl)oxy)-1-(3,4-dimethoxyphenyl)-6-((4-methoxybenzyl)-oxy)-7-(4-methoxyphenyl)hept-4-yn-3-one (**100a**):



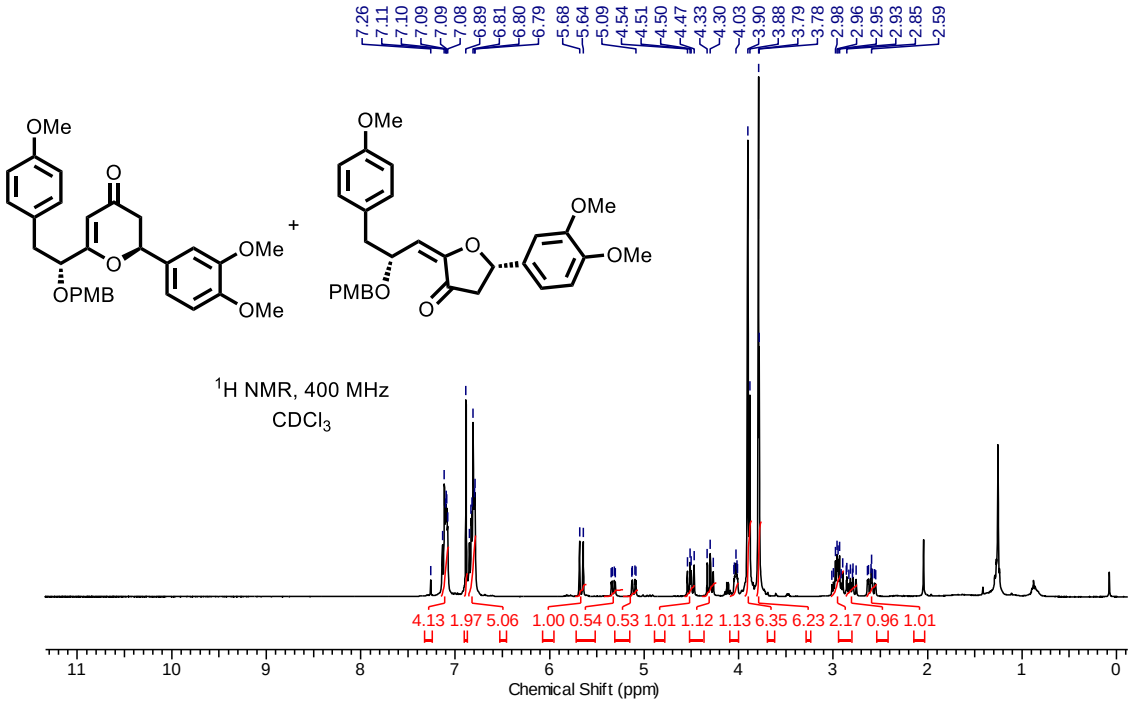
(*1S,6R*)-1-(3,4-Dimethoxyphenyl)-1-hydroxy-6-((4-methoxybenzyl)oxy)-7-(4-methoxyphenyl)hept-4-yn-3-one (**108a**):



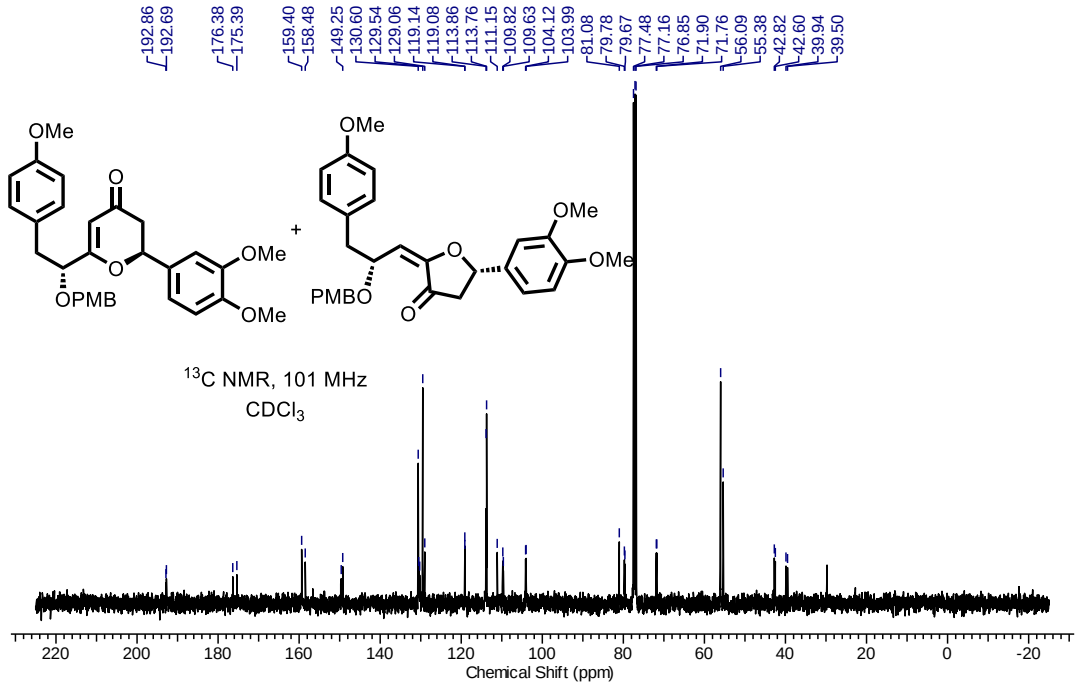
(*1S,6R*)-1-(3,4-Dimethoxyphenyl)-1-hydroxy-6-((4-methoxybenzyl)oxy)-7-(4-methoxyphenyl)hept-4-yn-3-one (**108a**):



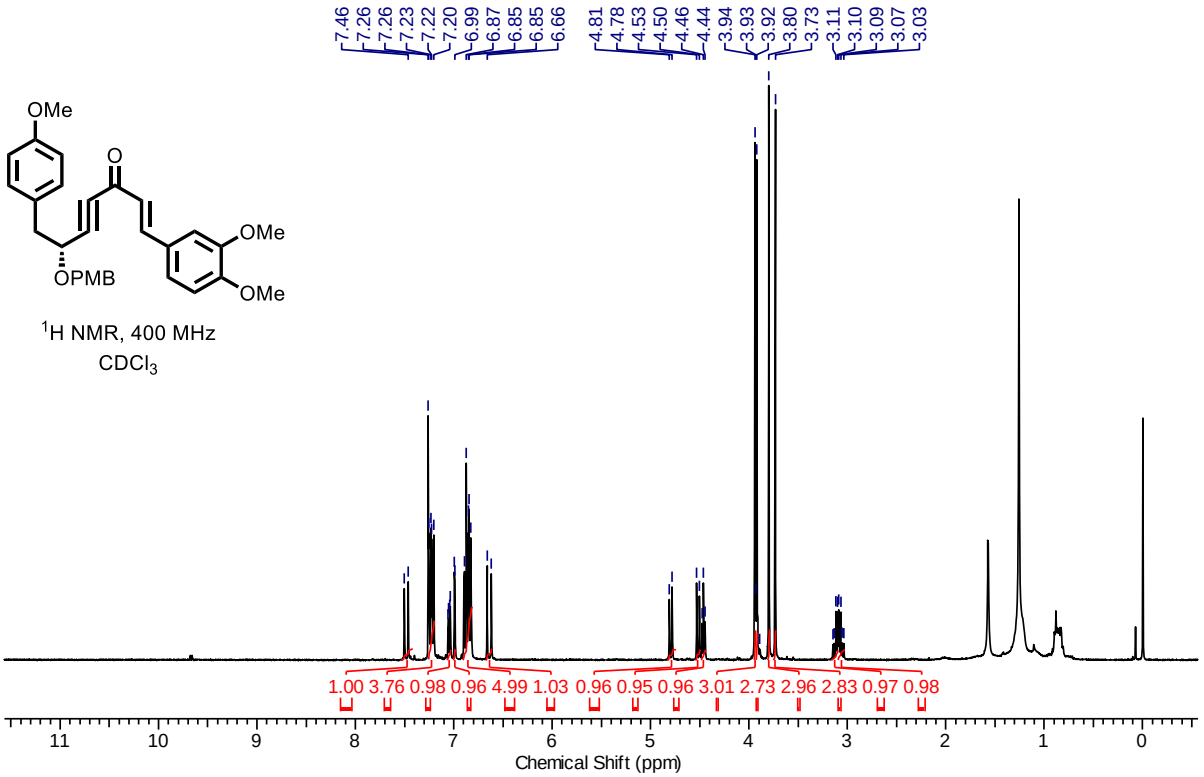
(*S*)-2-(3,4-Dimethoxyphenyl)-6-((R)-1-((4-methoxybenzyl)oxy)-2-(4-methoxy-phenyl)ethyl)-2,3-dihydro-*4H*-pyran-4-one (**109a**) and (*S,E*)-5-(3,4-dimethoxyphenyl)-2-((*R*)-2-((4-methoxybenzyl)oxy)-3-(4-methoxyphenyl)propylidene)dihydrofuran-3(*2H*)-one (**112**):



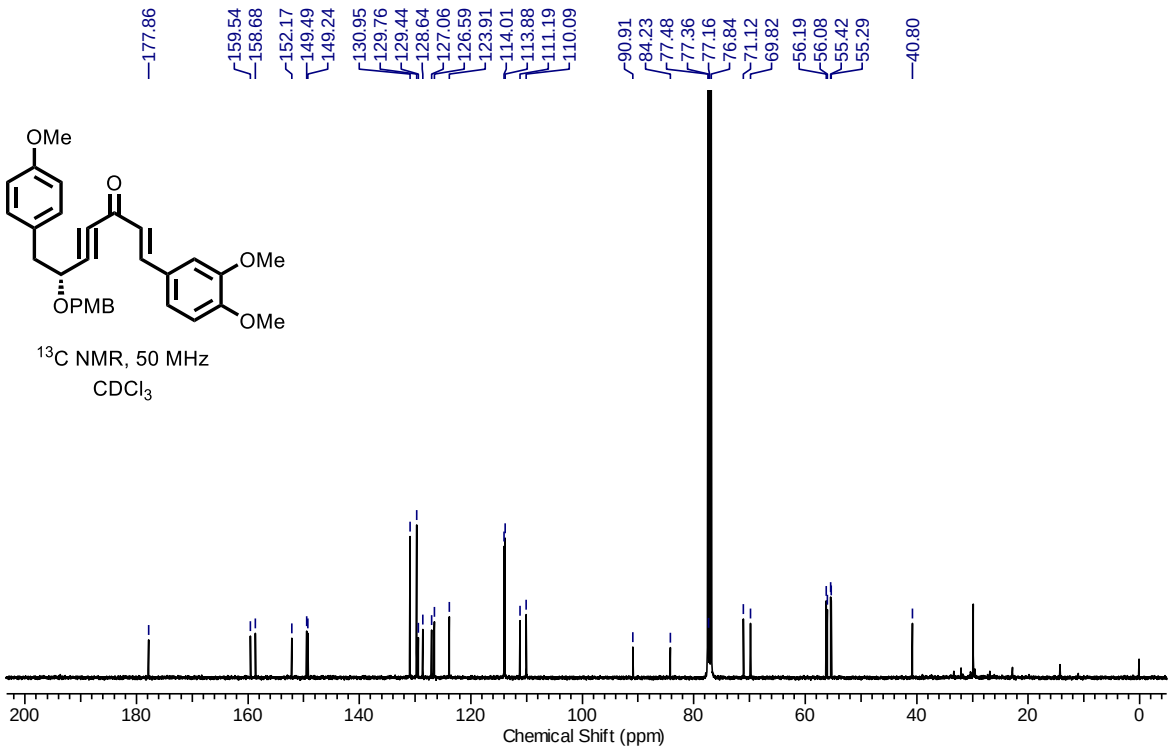
(*S*)-2-(3,4-Dimethoxyphenyl)-6-((R)-1-((4-methoxybenzyl)oxy)-2-(4-methoxy-phenyl)ethyl)-2,3-dihydro-*4H*-pyran-4-one (**109a**) and (*S,E*)-5-(3,4-dimethoxyphenyl)-2-((*R*)-2-((4-methoxybenzyl)oxy)-3-(4-methoxyphenyl)propylidene)dihydrofuran-3(*2H*)-one (**112**):



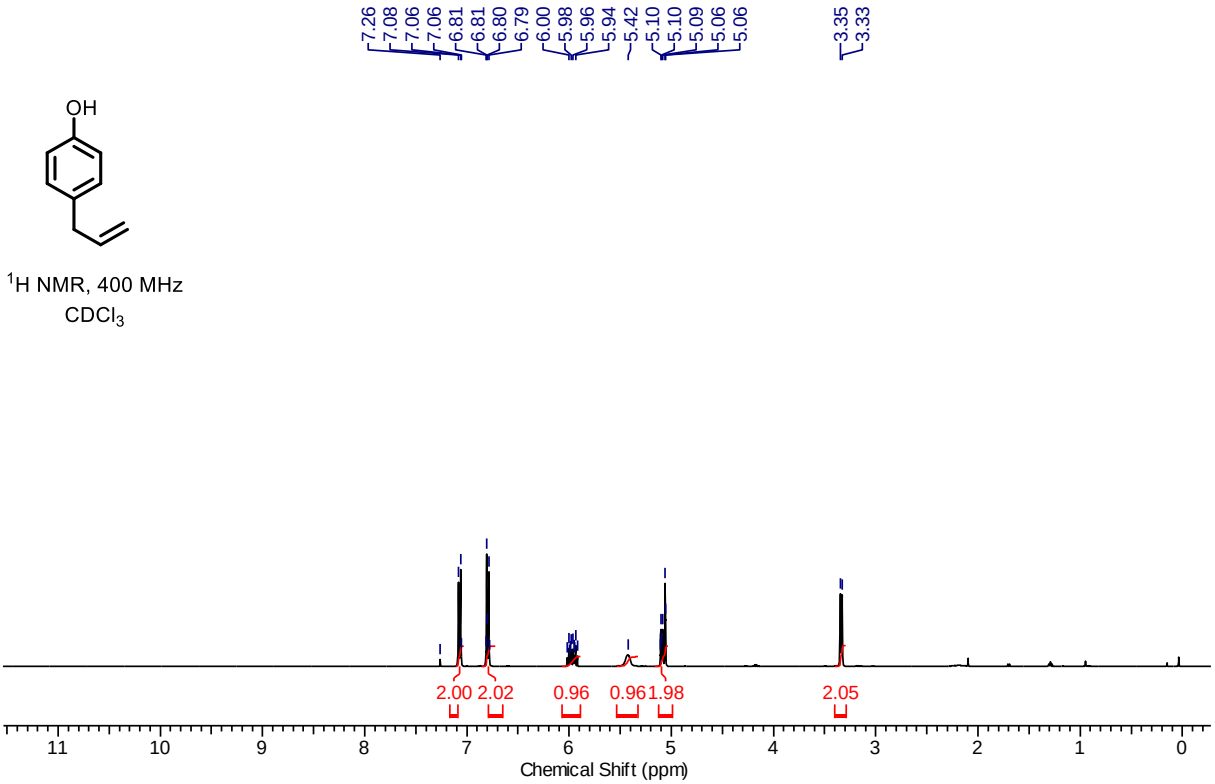
(*R,E*)-1-(3,4-Dimethoxyphenyl)-6-((4-methoxybenzyl)oxy)-7-(4-methoxyphenyl)hept-1-en-4-yn-3-one (**110a**):



(*R,E*)-1-(3,4-Dimethoxyphenyl)-6-((4-methoxybenzyl)oxy)-7-(4-methoxyphenyl)hept-1-en-4-yn-3-one (**110a**):

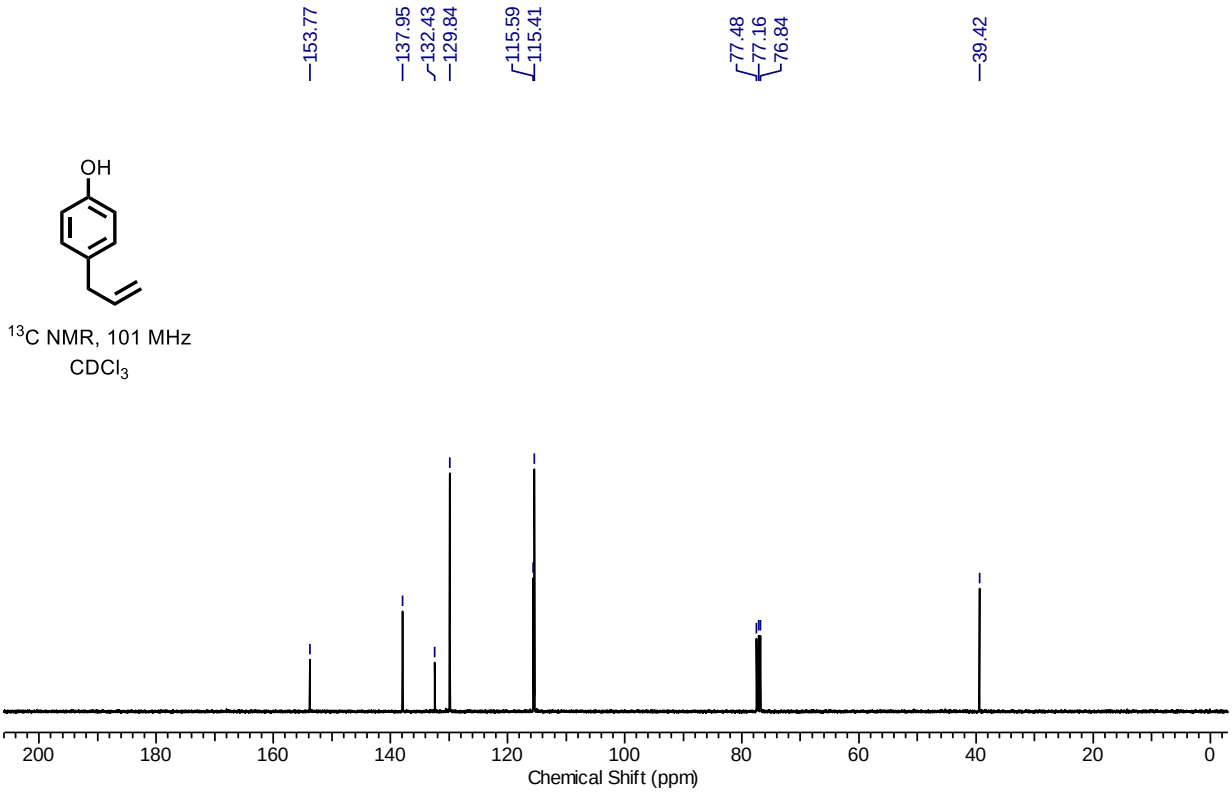


4-Allylphenol (**S8**)



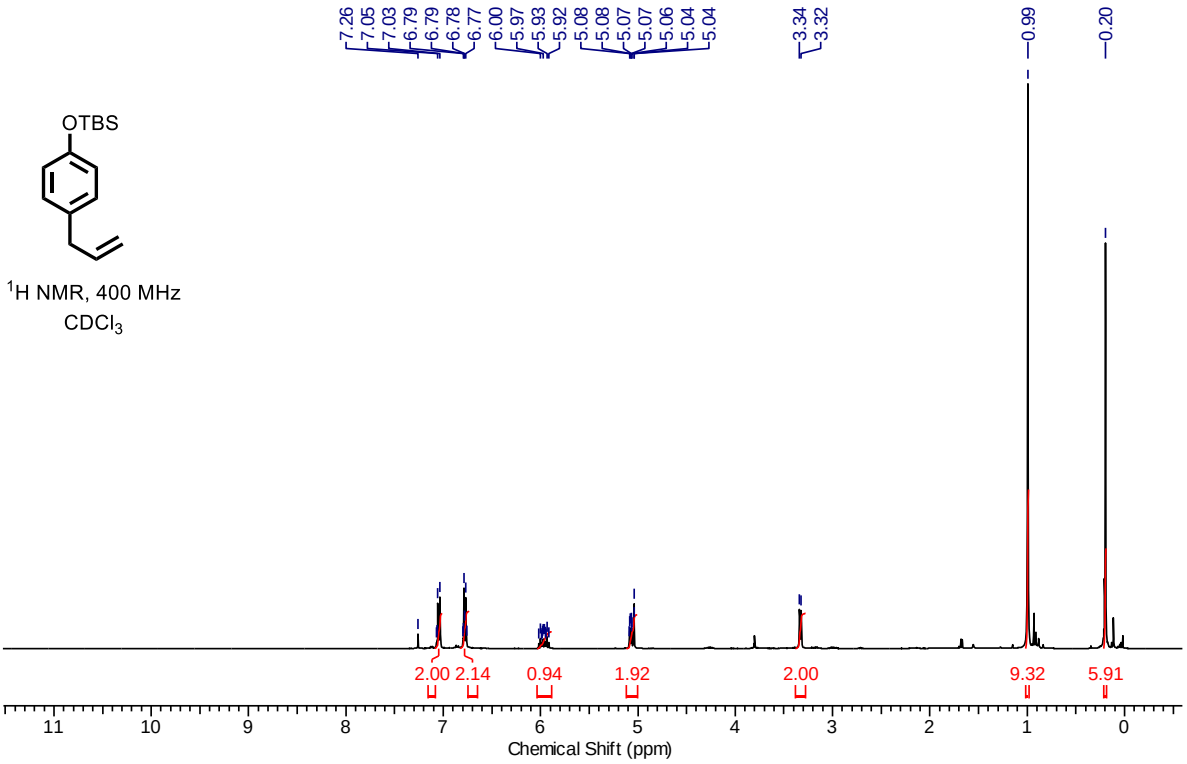
^{1}H NMR, 400 MHz
$CDCl_3$

4-Allylphenol (**S8**)

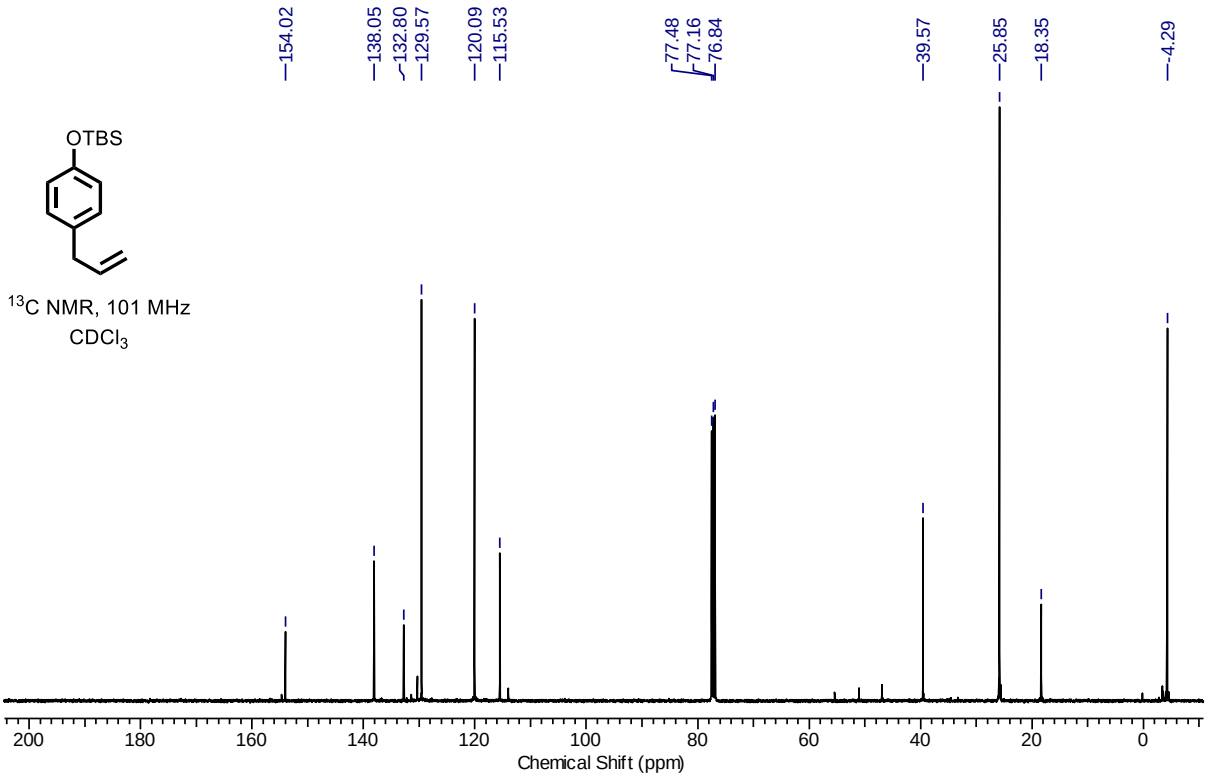


^{13}C NMR, 101 MHz
$CDCl_3$

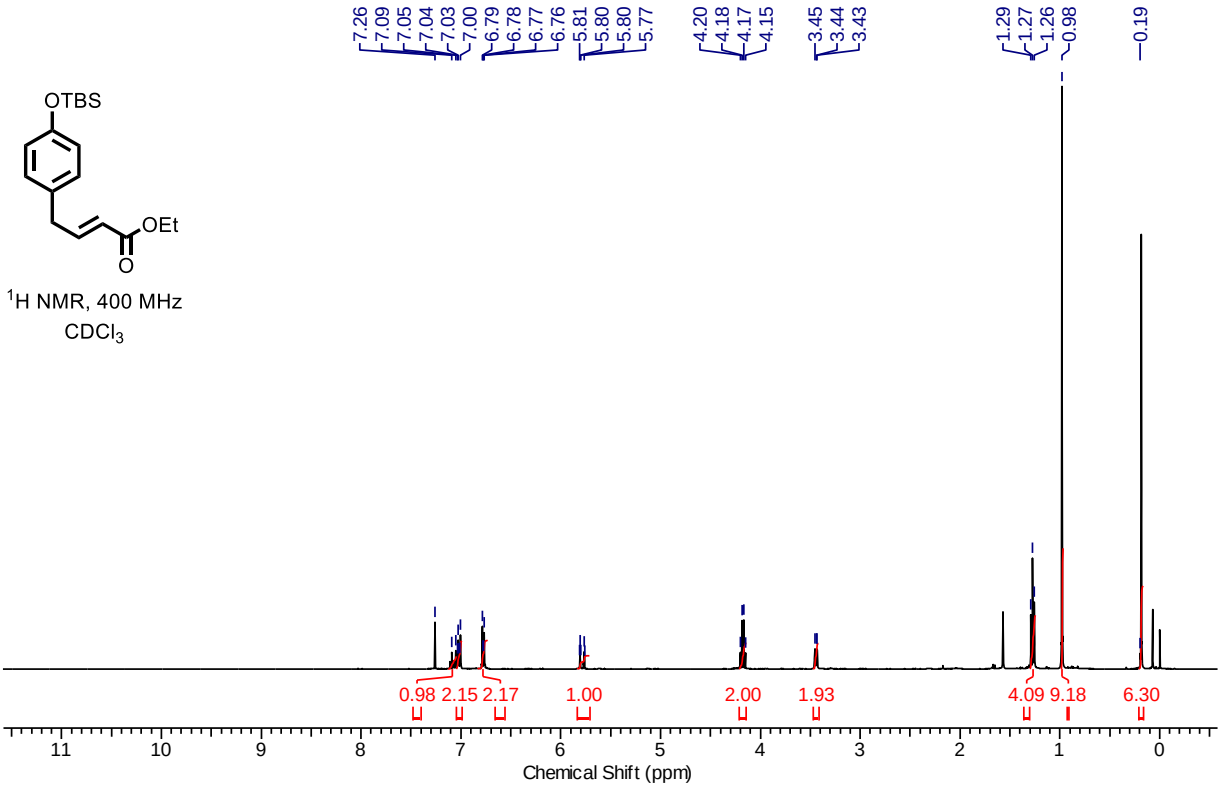
(4-Allylphenoxy)(*tert*-butyl)dimethylsilane (**95a**):



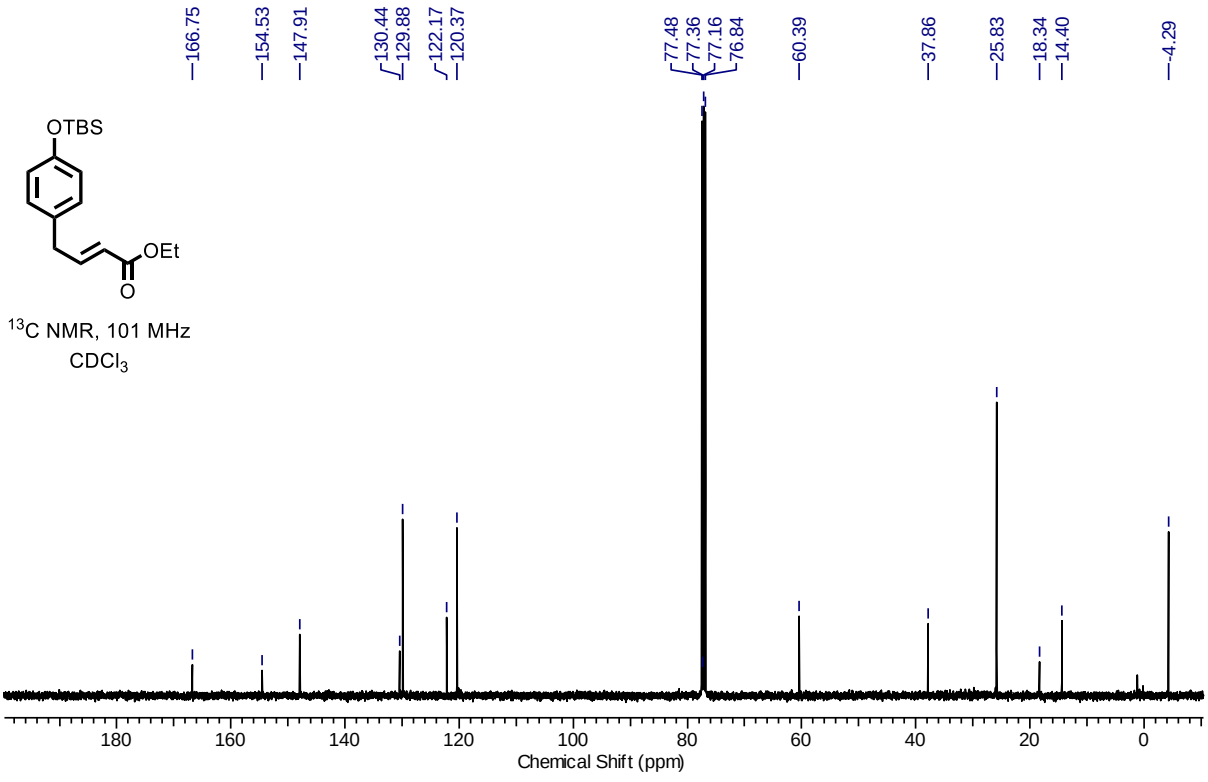
(4-Allylphenoxy)(*tert*-butyl)dimethylsilane (**95a**):



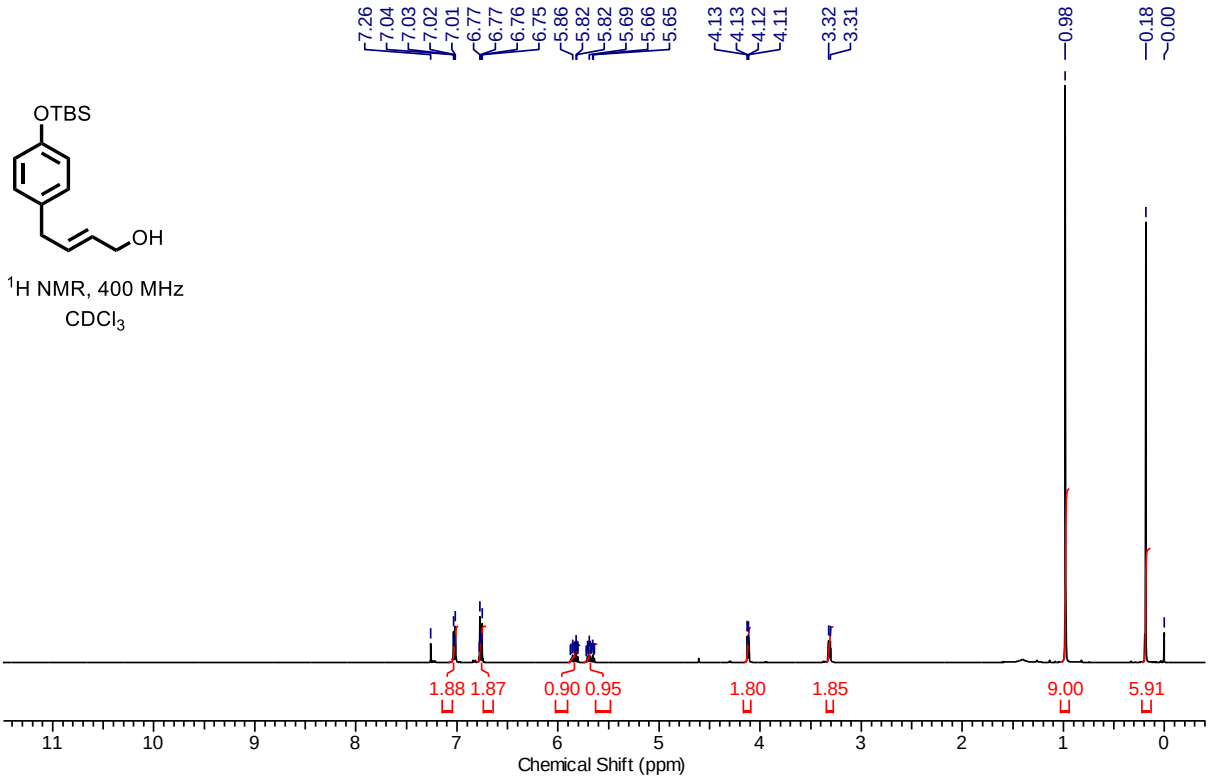
Ethyl-(*E*)-4-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)but-2-enoate (**103a**):



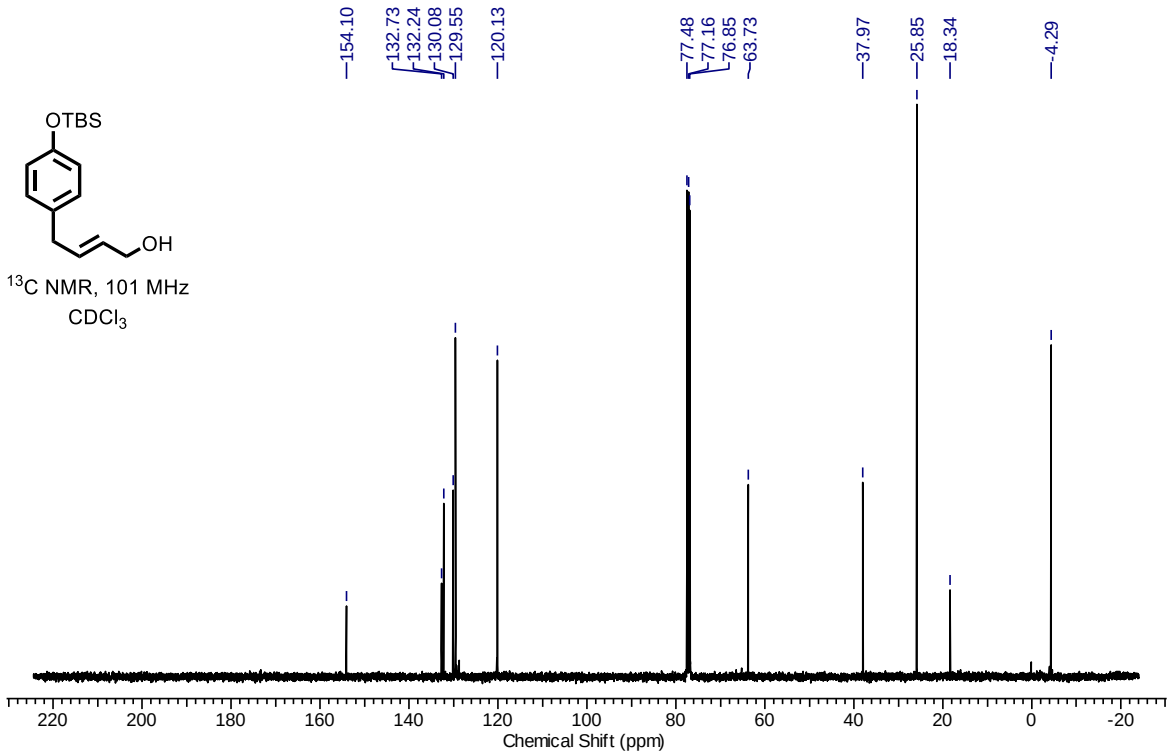
Ethyl-(*E*)-4-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)but-2-enoate (**103a**):



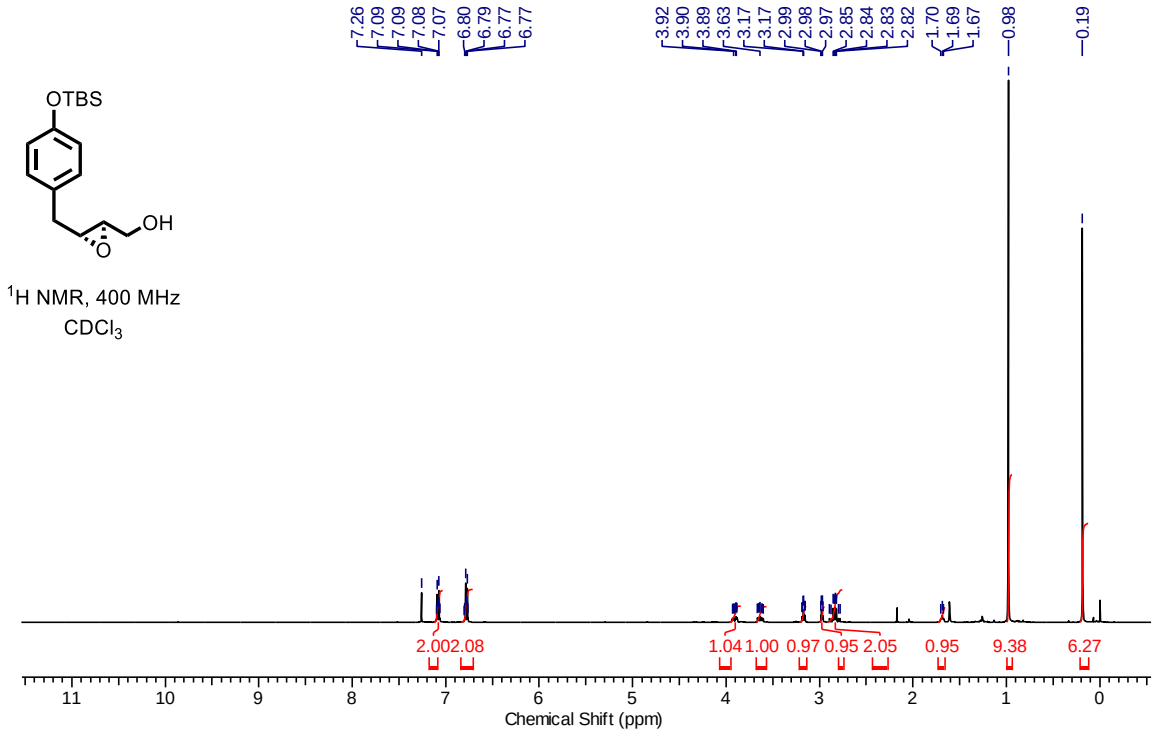
(*E*)-4-(4-((*Tert*-butyldimethylsilyl)oxy)phenyl)but-2-en-1-ol (**S4a**):



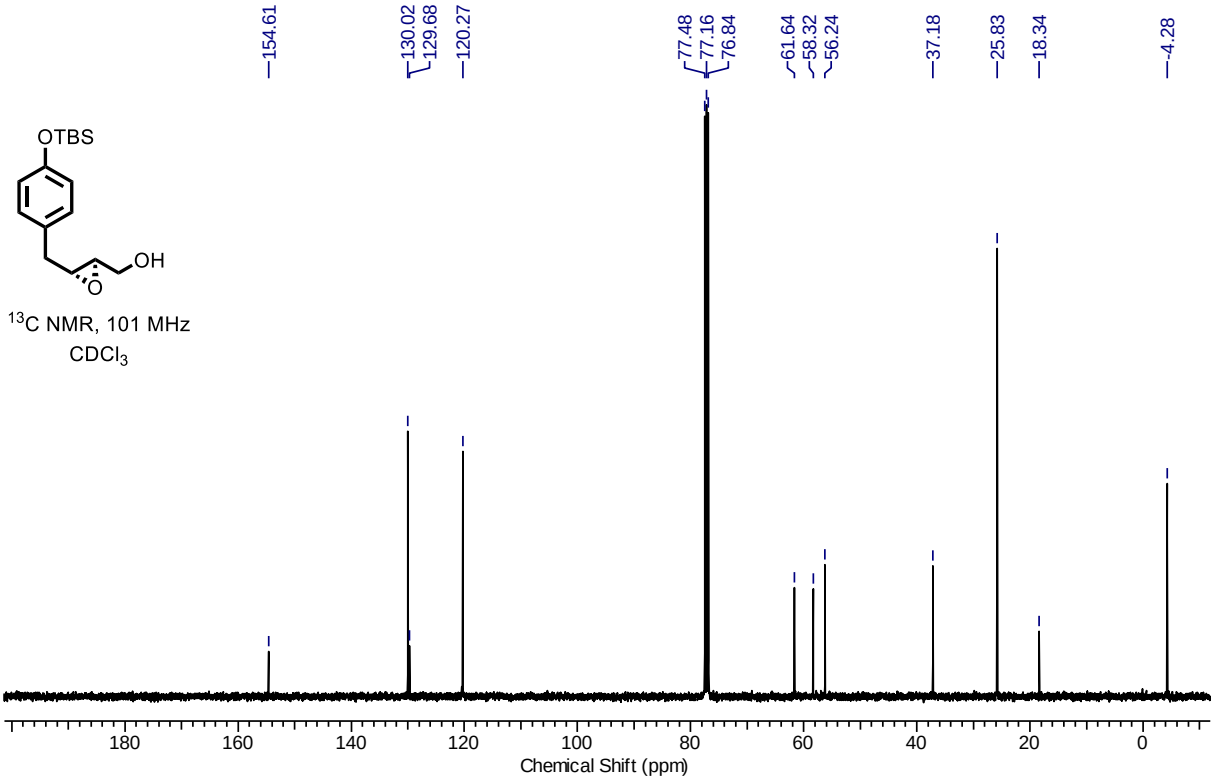
(*E*)-4-(4-((*Tert*-butyldimethylsilyl)oxy)phenyl)but-2-en-1-ol (**S4a**):



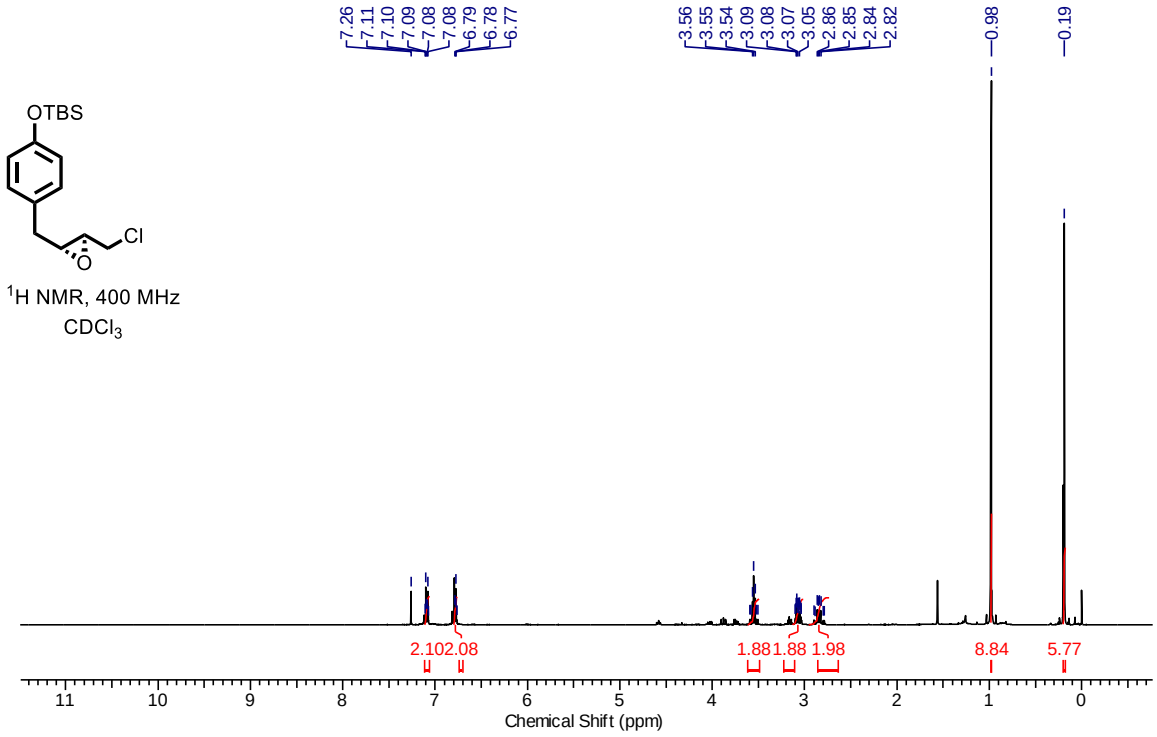
((*2R,3R*)-3-(4-((*Tert*-butyldimethylsilyl)oxy)benzyl)oxiran-2-yl)methanol (**104a**):



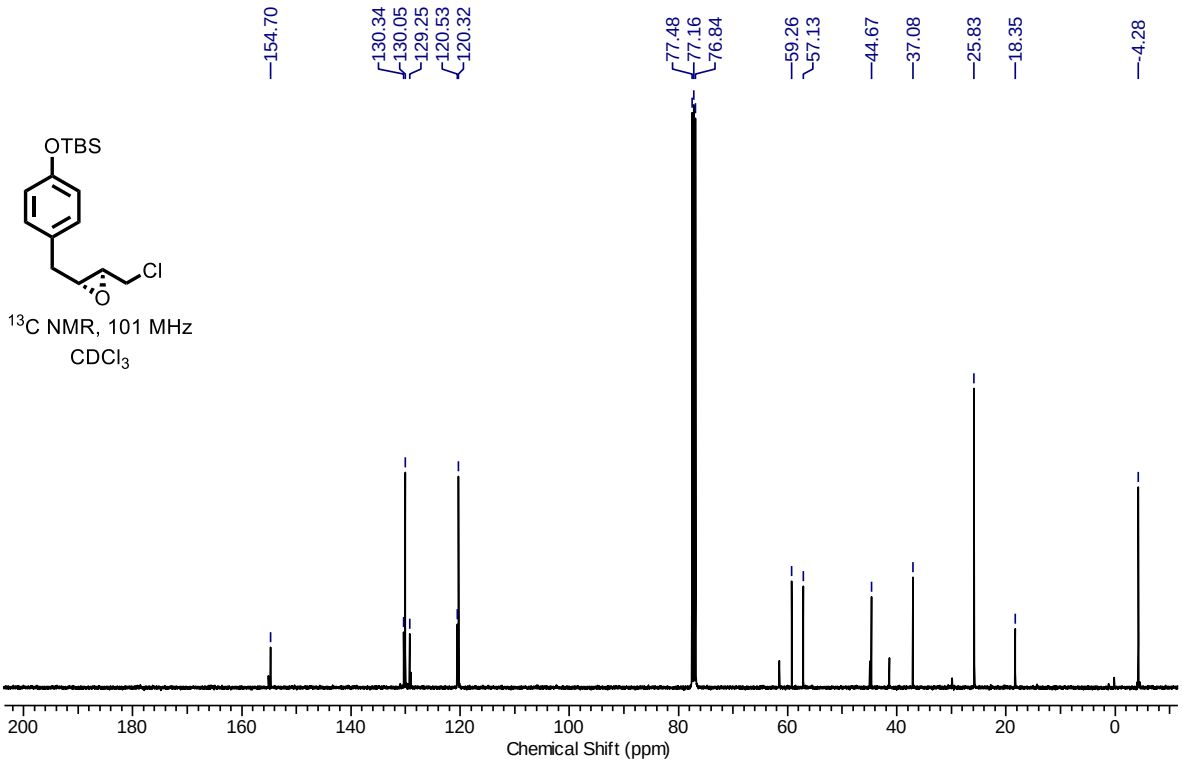
((*2R,3R*)-3-(4-((*Tert*-butyldimethylsilyl)oxy)benzyl)oxiran-2-yl)methanol (**104a**):



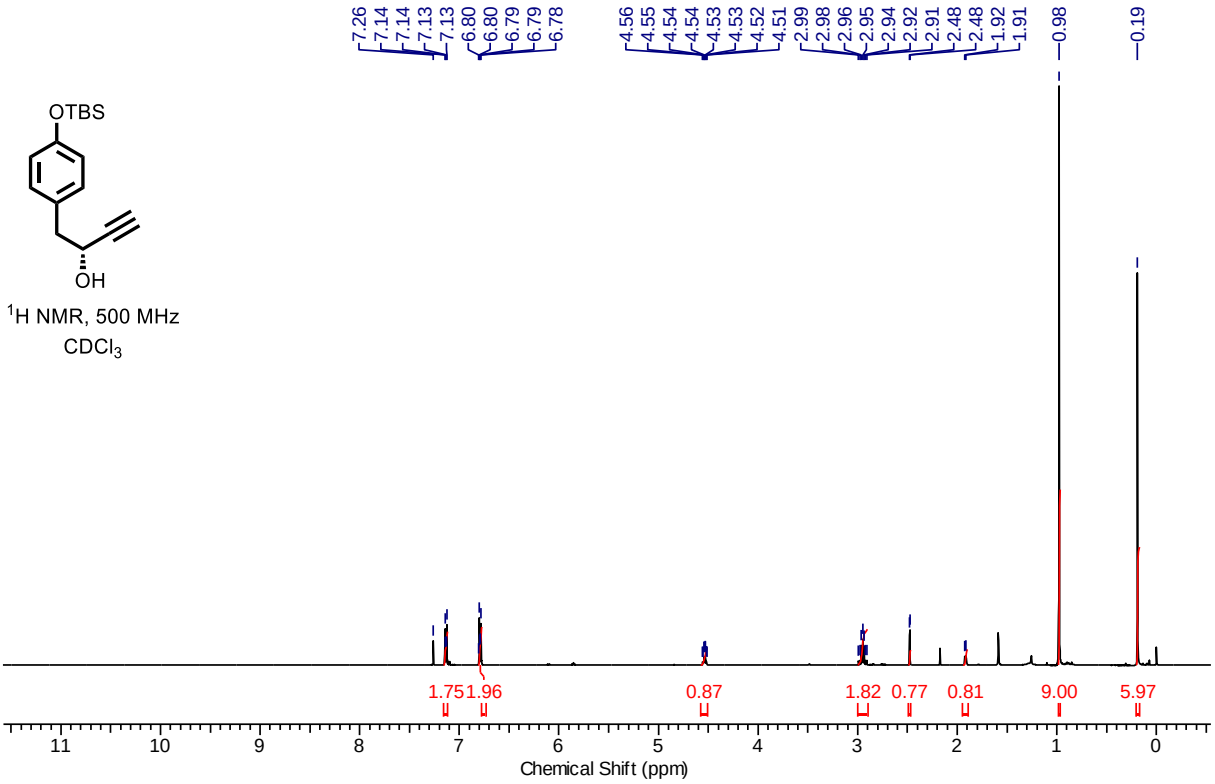
Tert-butyl(4-(((*2R,3S*)-3-(chloromethyl)oxiran-2-yl)methyl)phenoxy)dimethylsilane (**105a**):



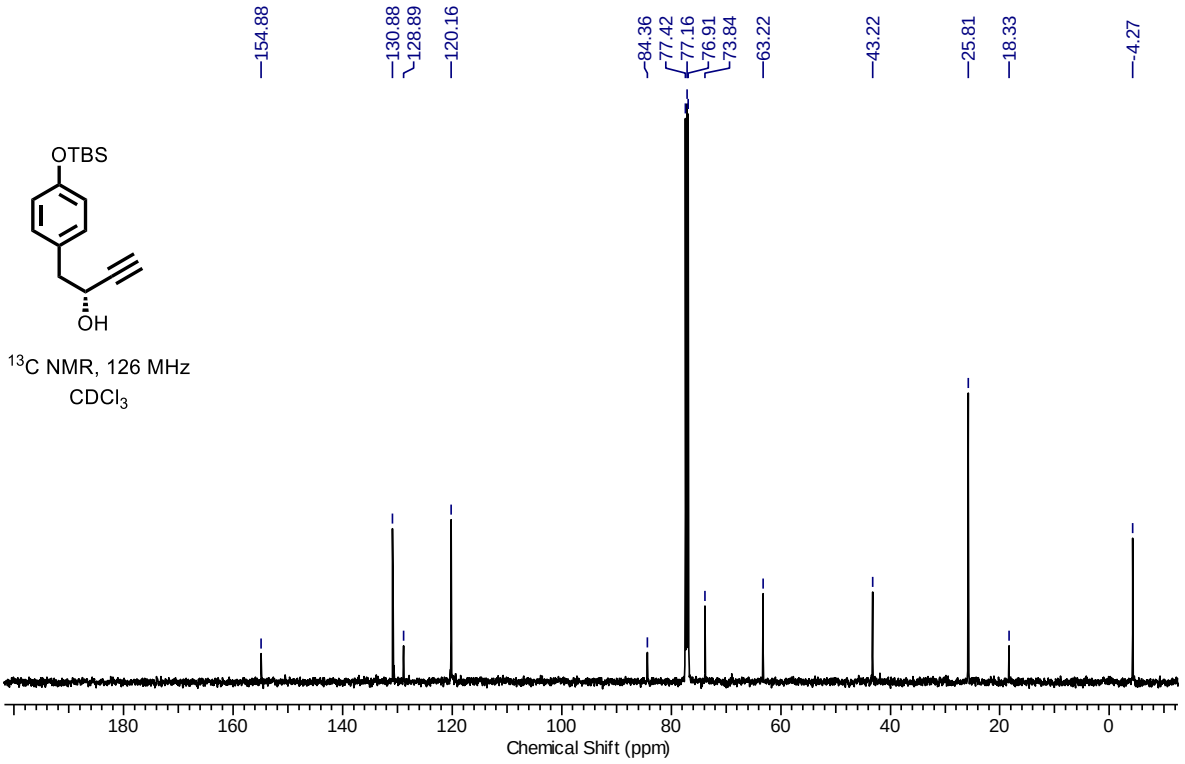
Tert-butyl(4-(((*2R,3S*)-3-(chloromethyl)oxiran-2-yl)methyl)phenoxy)dimethylsilane (**105a**):



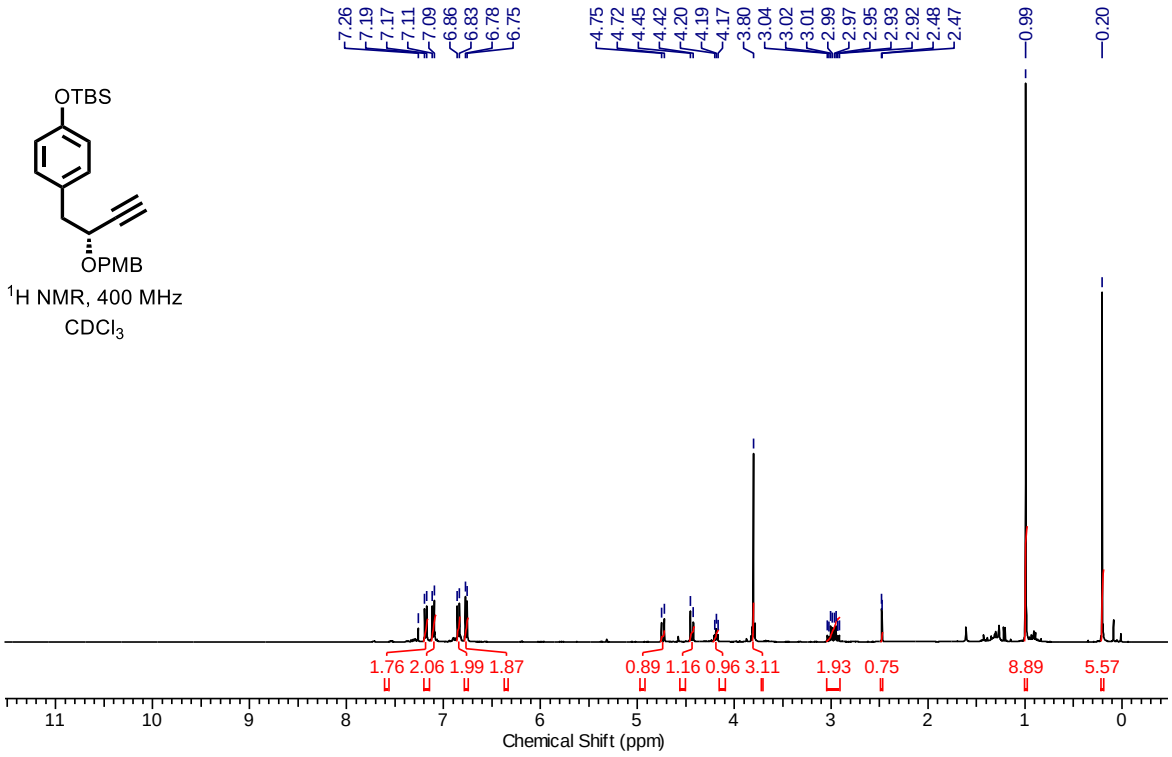
(*R*)-1-(4-((*Tert*-butyldimethylsilyl)oxy)phenyl)but-3-yn-2-ol (**S5a**):



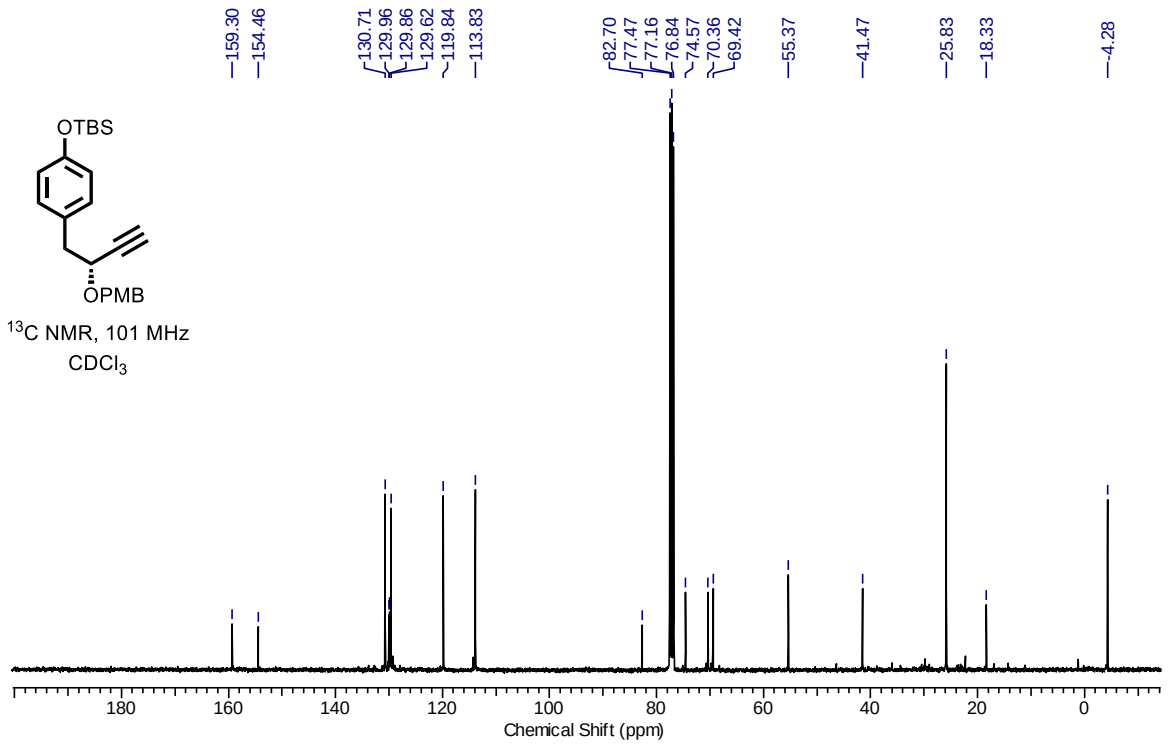
(*R*)-1-(4-((*Tert*-butyldimethylsilyl)oxy)phenyl)but-3-yn-2-ol (**S5a**):



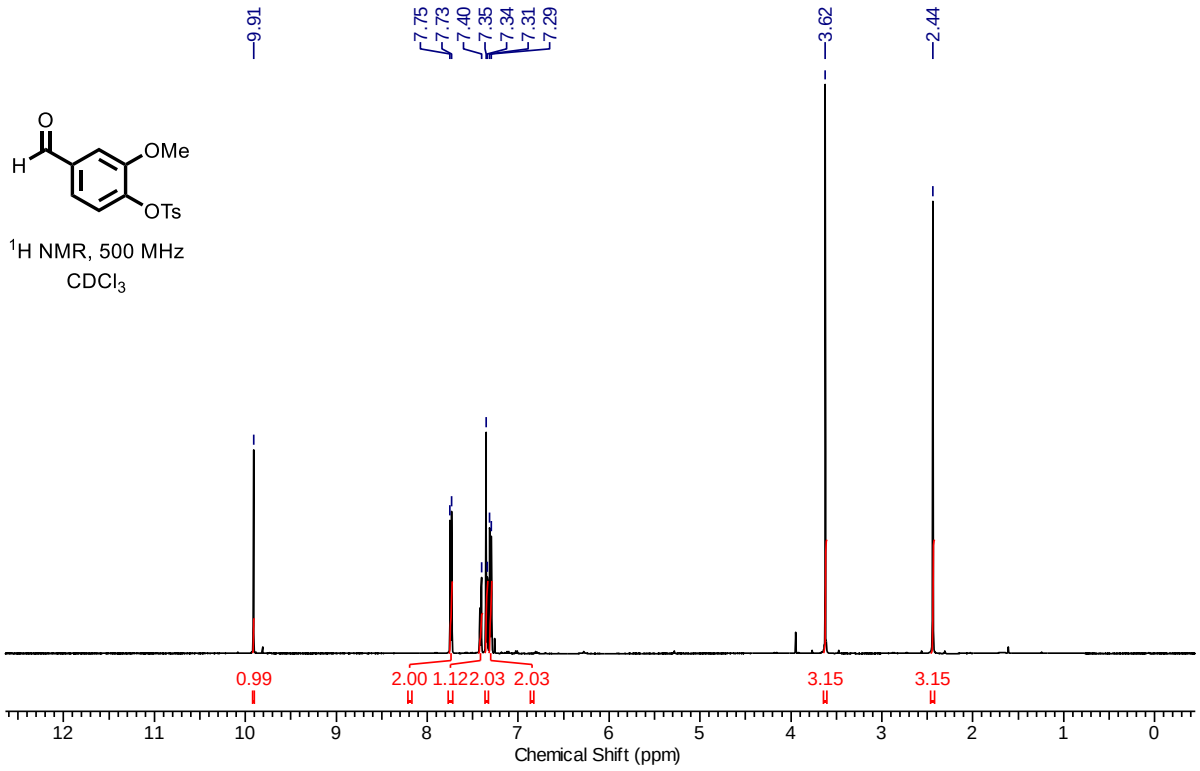
(*R*)-*Tert*-butyl(4-(2-((4-methoxybenzyl)oxy)but-3-yn-1-yl)phenoxy)dimethylsilane (**101a**):



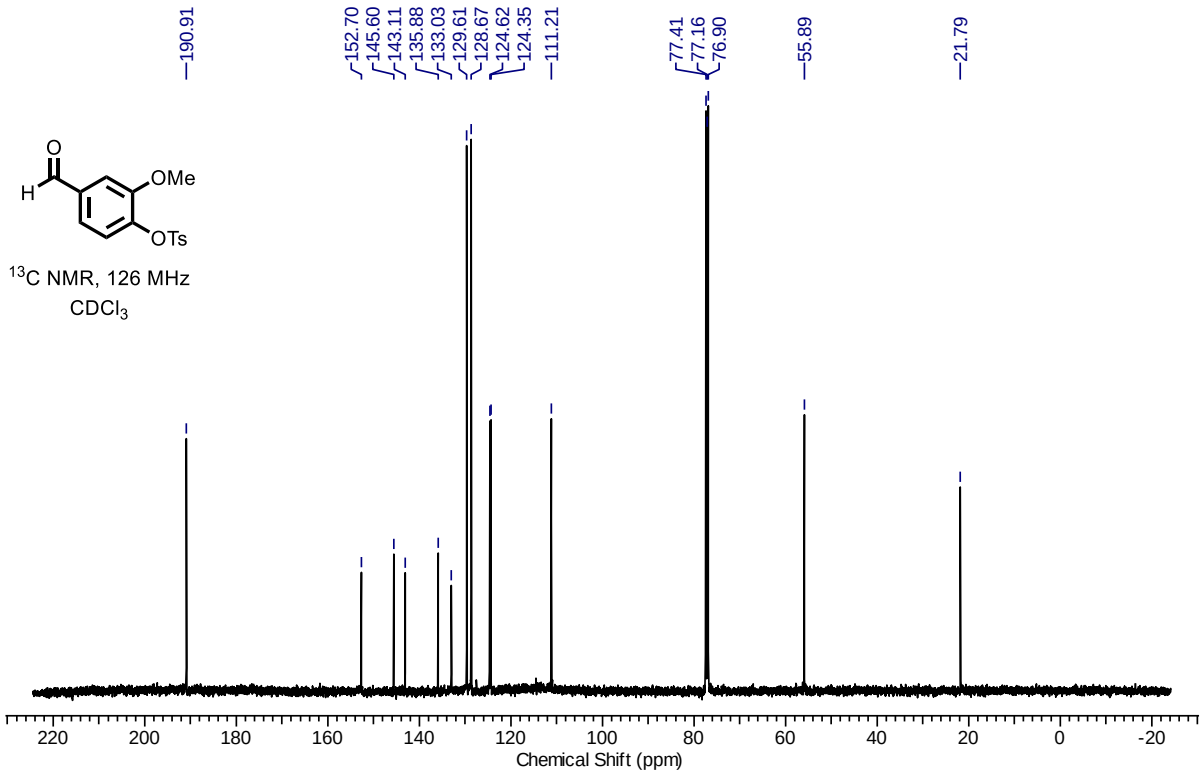
(*R*)-*Tert*-butyl(4-(2-((4-methoxybenzyl)oxy)but-3-yn-1-yl)phenoxy)dimethylsilane (**101a**):



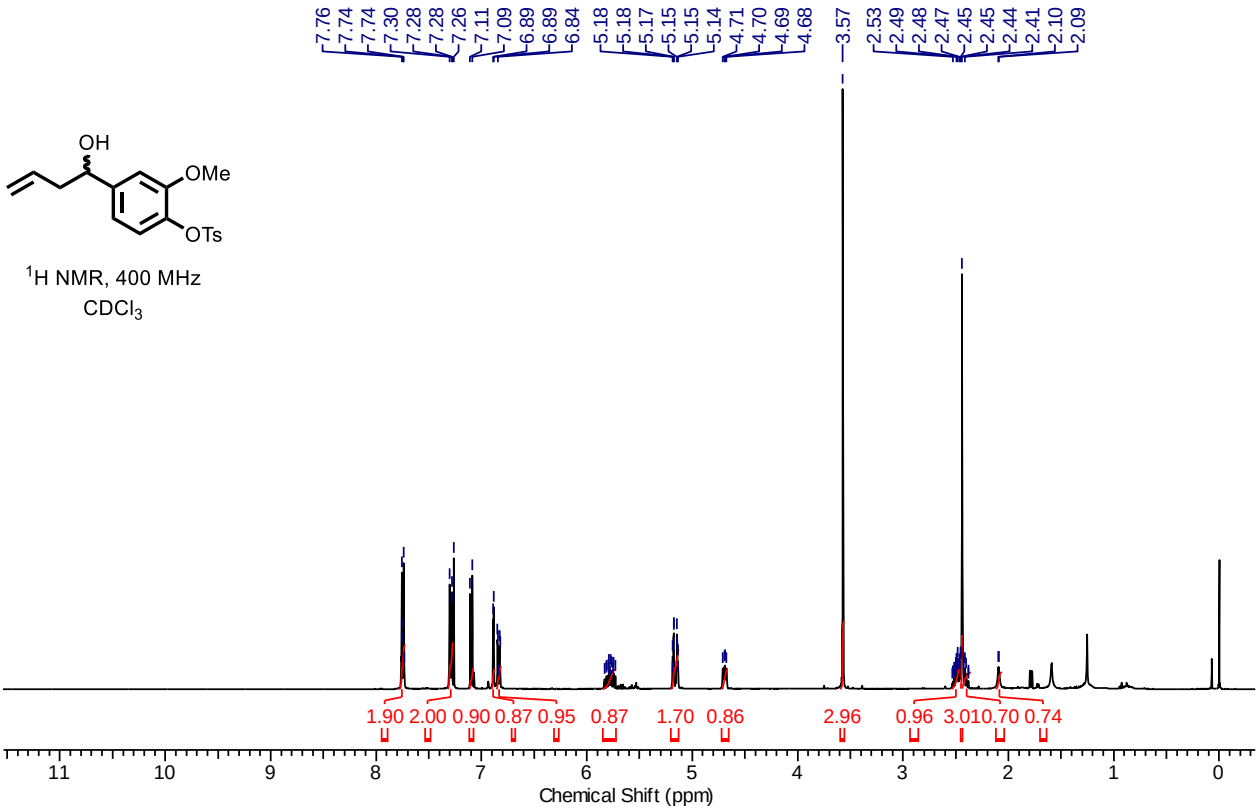
4-Formyl-2-methoxyphenyl-4-methylbenzenesulfonate (**96a**):



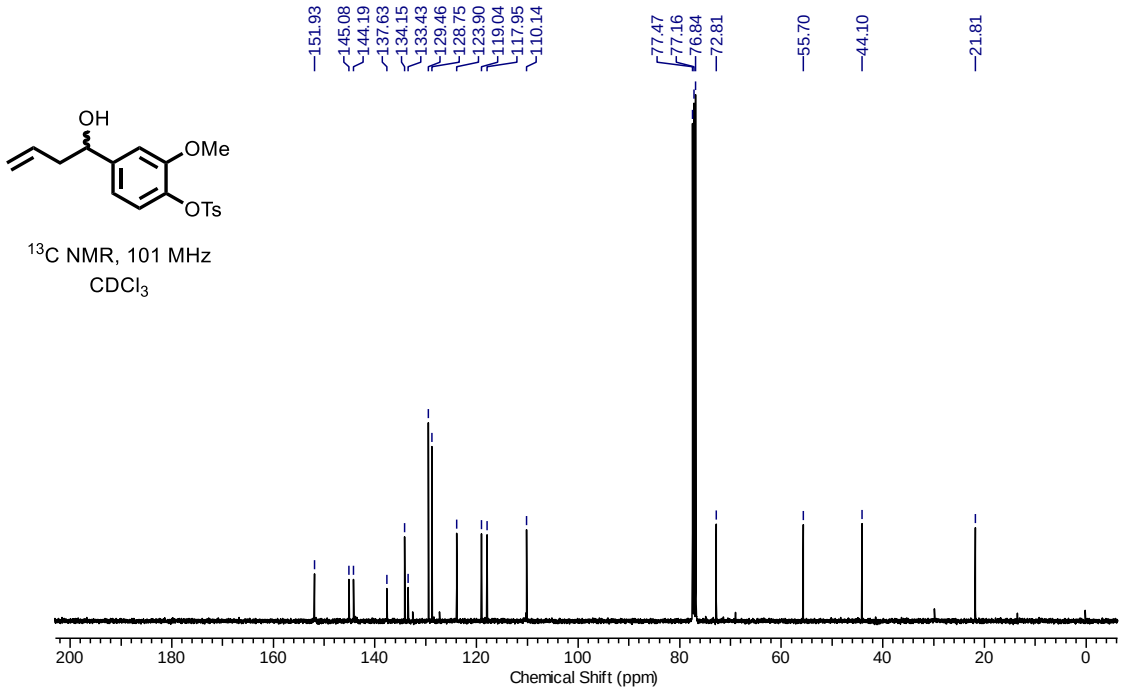
4-Formyl-2-methoxyphenyl-4-methylbenzenesulfonate (**96a**):



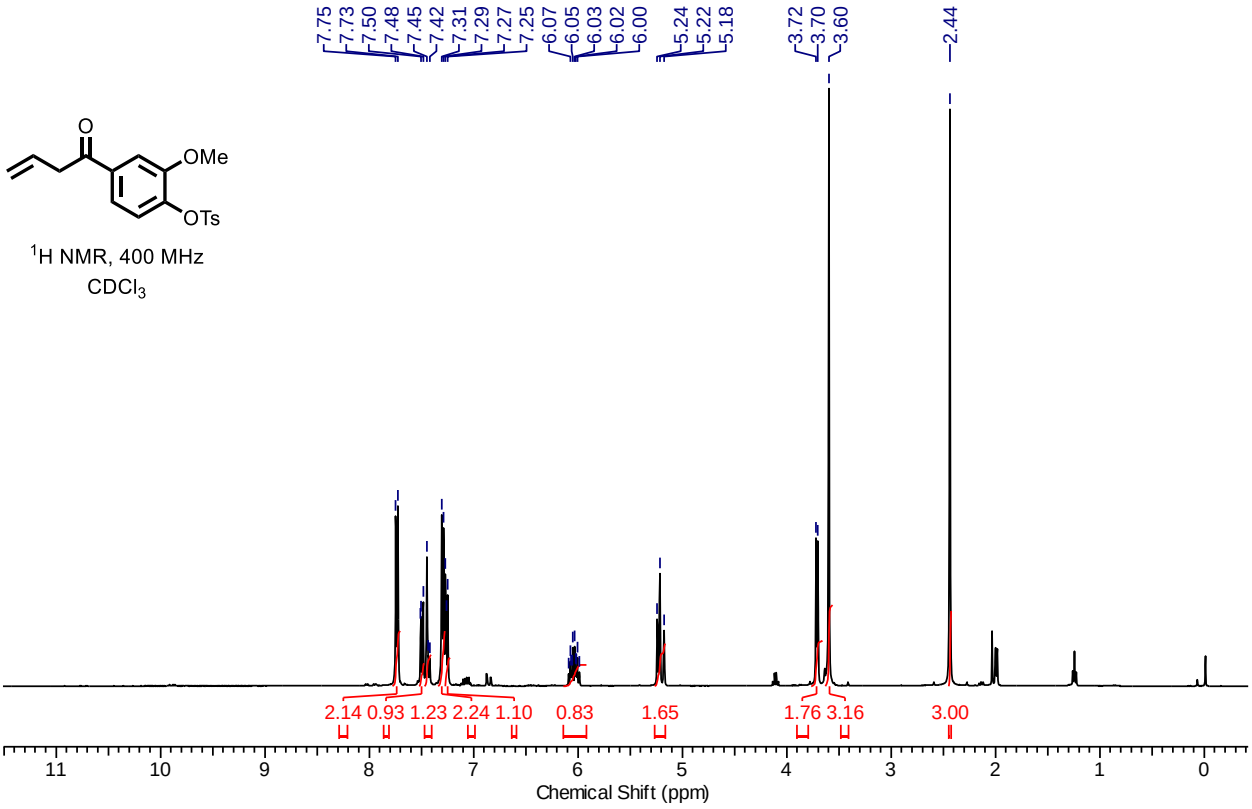
4-(1-Hydroxybut-3-en-1-yl)-2-methoxyphenyl 4-methylbenzenesulphonate (**S9**):



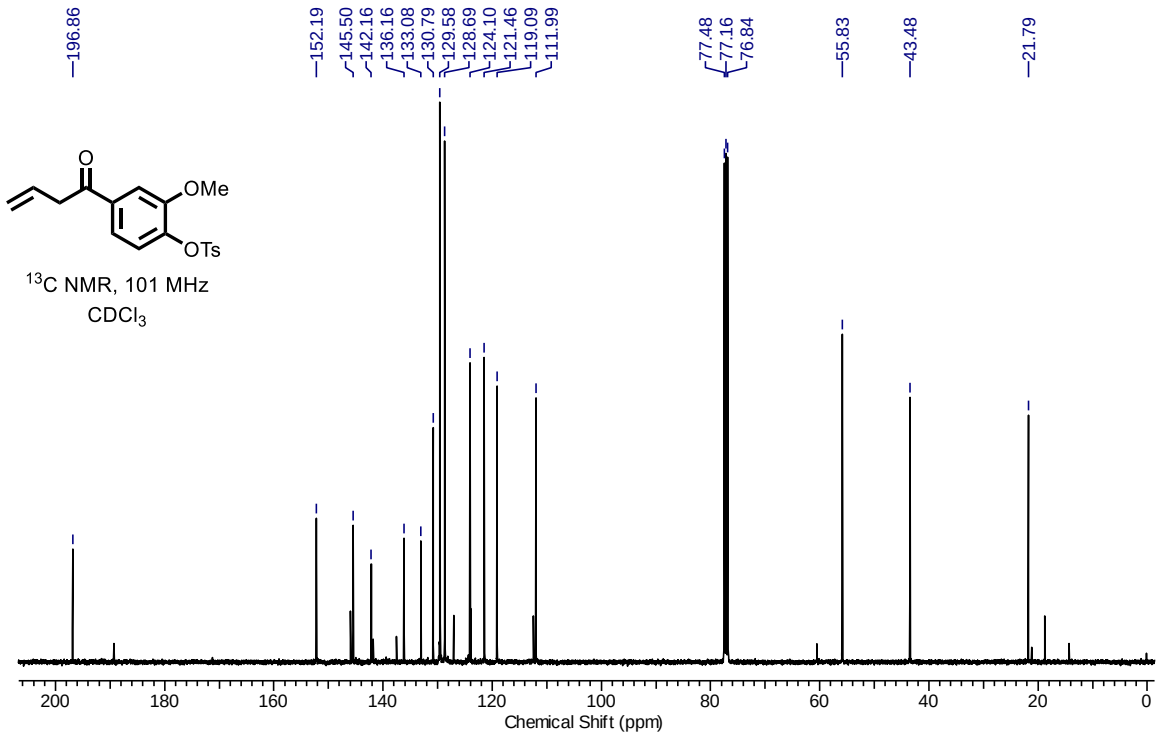
4-(1-Hydroxybut-3-en-1-yl)-2-methoxyphenyl 4-methylbenzenesulphonate (**S9**):



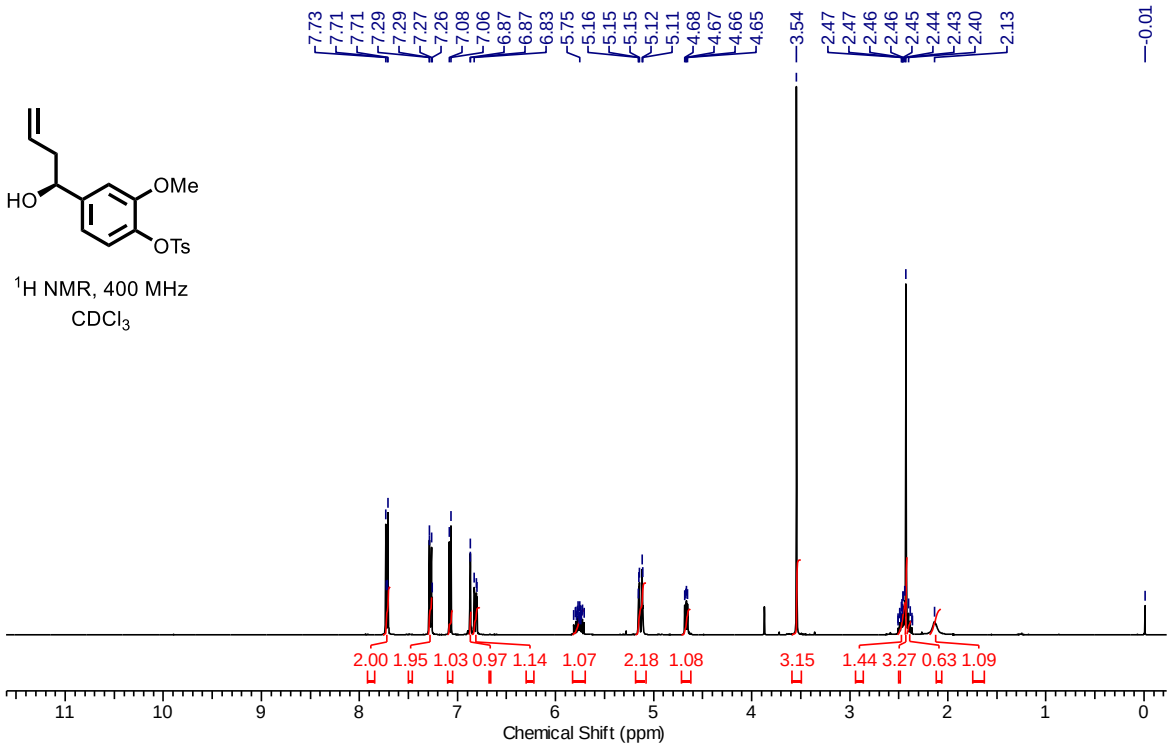
4-(But-3-enoyl)-2-methoxyphenyl-4-methylbenzenesulfonate (**113**):



4-(But-3-enoyl)-2-methoxyphenyl-4-methylbenzenesulfonate (**113**):

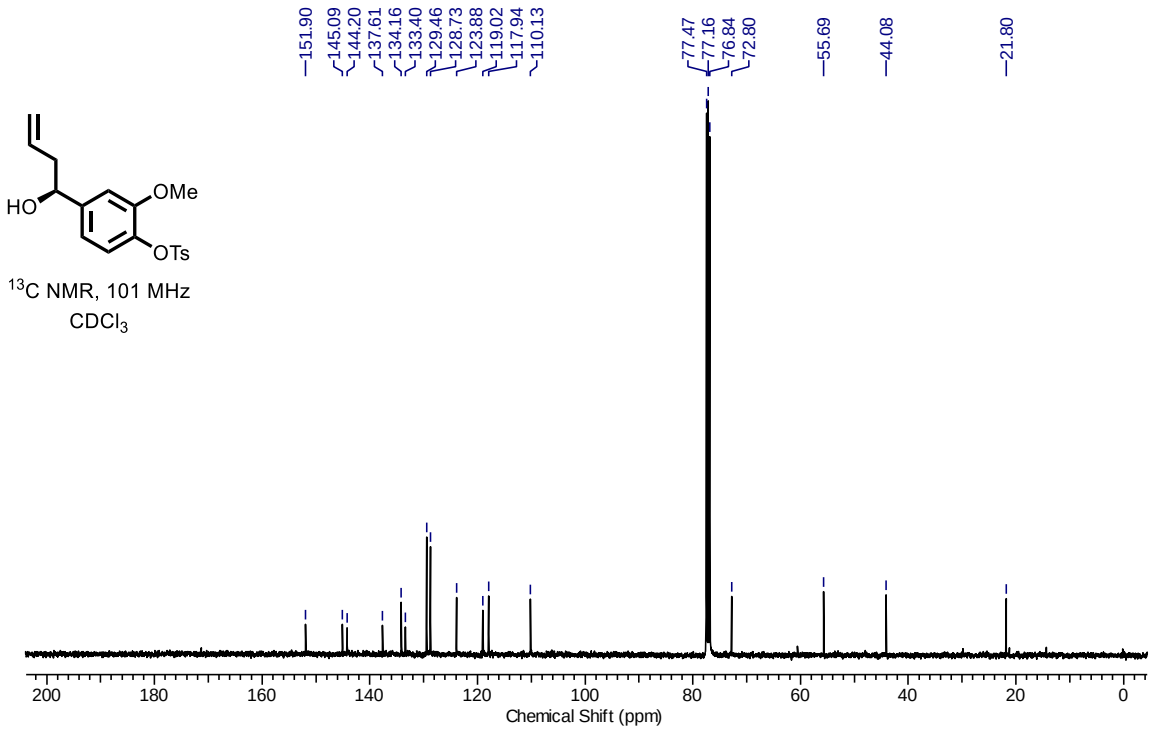


(*S*)-4-(1-Hydroxybut-3-en-1-yl)-2-methoxyphenyl-4-methylbenzenesulphonate (**106a**) *(prepared from* **113***)*



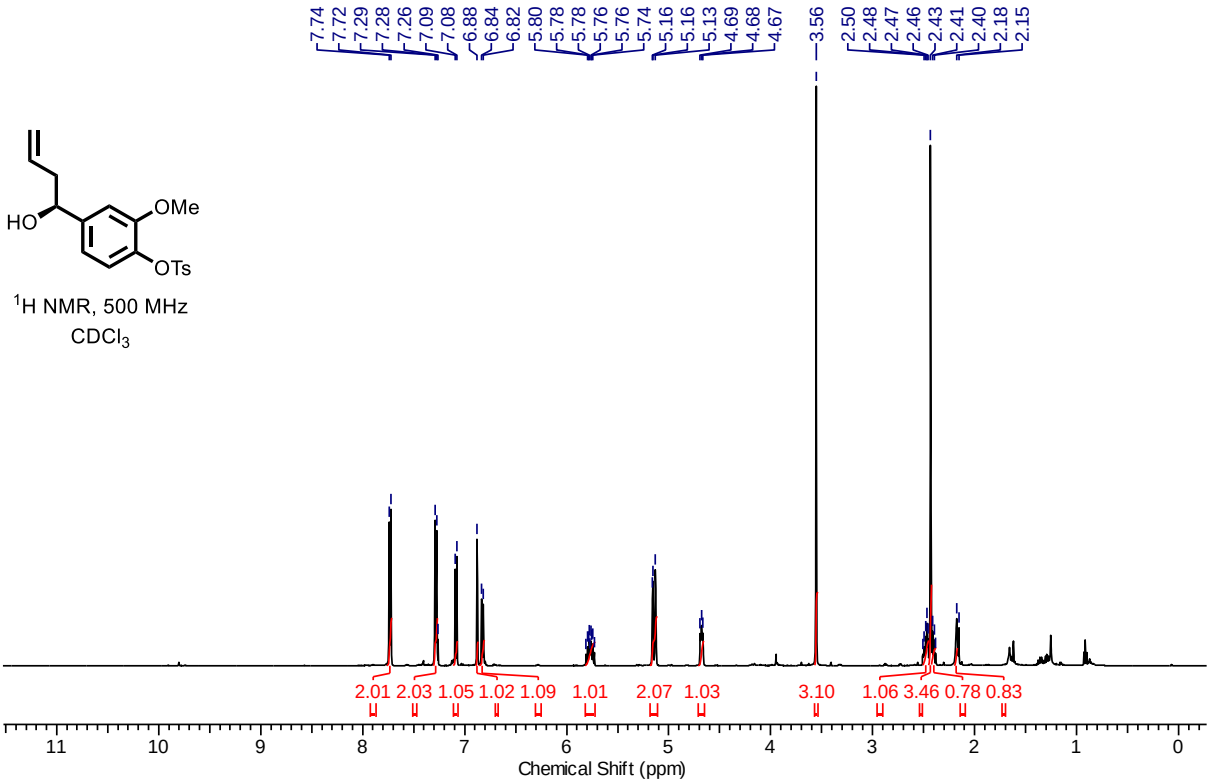
^{1}H NMR, 400 MHz
$CDCl_3$

(*S*)-4-(1-Hydroxybut-3-en-1-yl)-2-methoxyphenyl-4-methylbenzenesulphonate (**106a**) *(prepared from* **113***)*

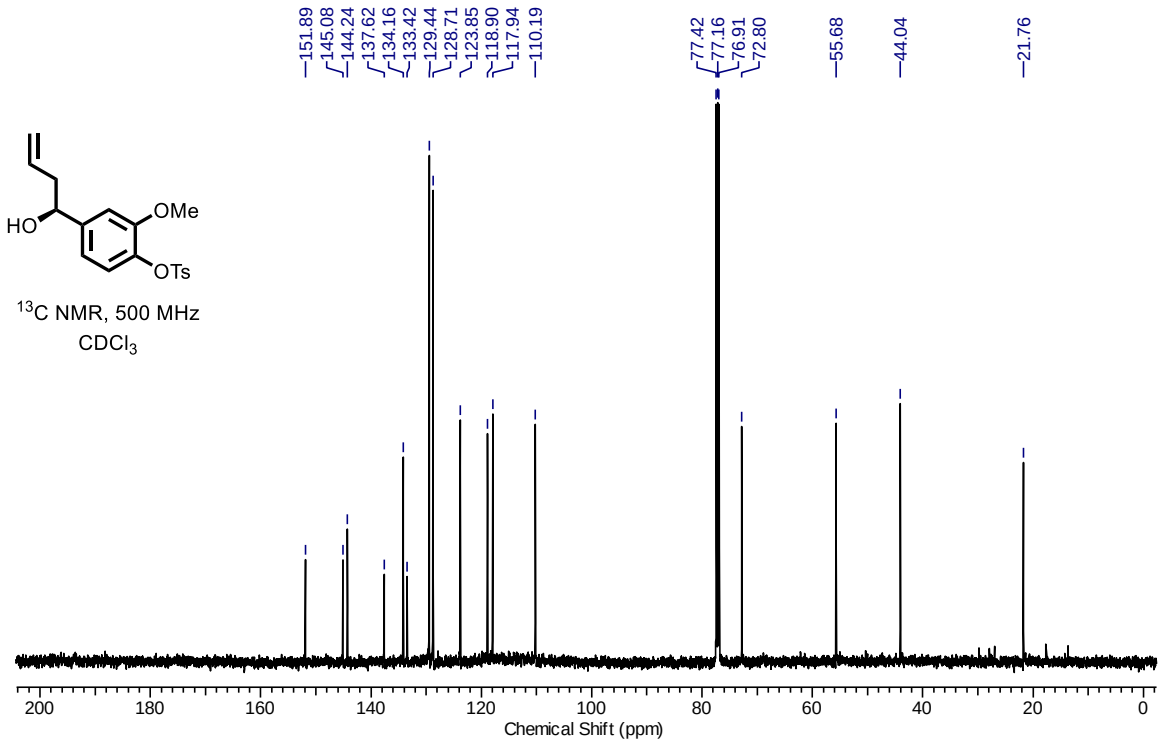


^{13}C NMR, 101 MHz
$CDCl_3$

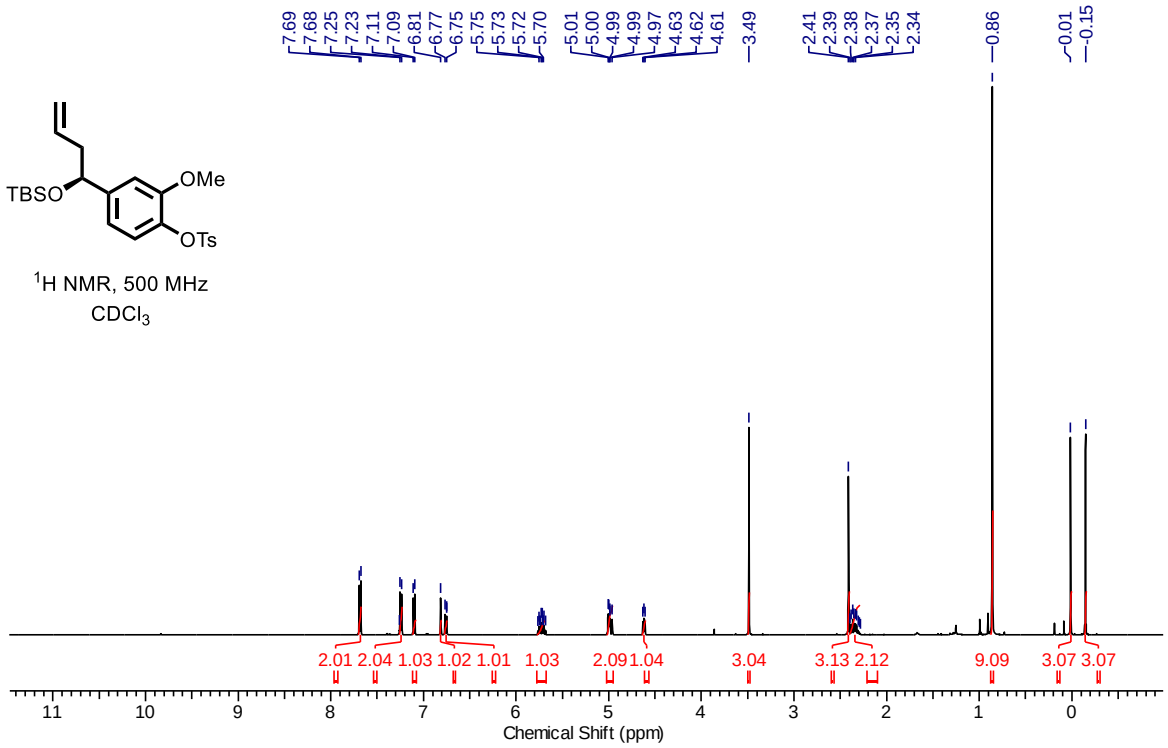
(*S*)-4-(1-Hydroxybut-3-en-1-yl)-2-methoxyphenyl-4-methylbenzenesulphonate (**106a**) (prepared from **96a**):



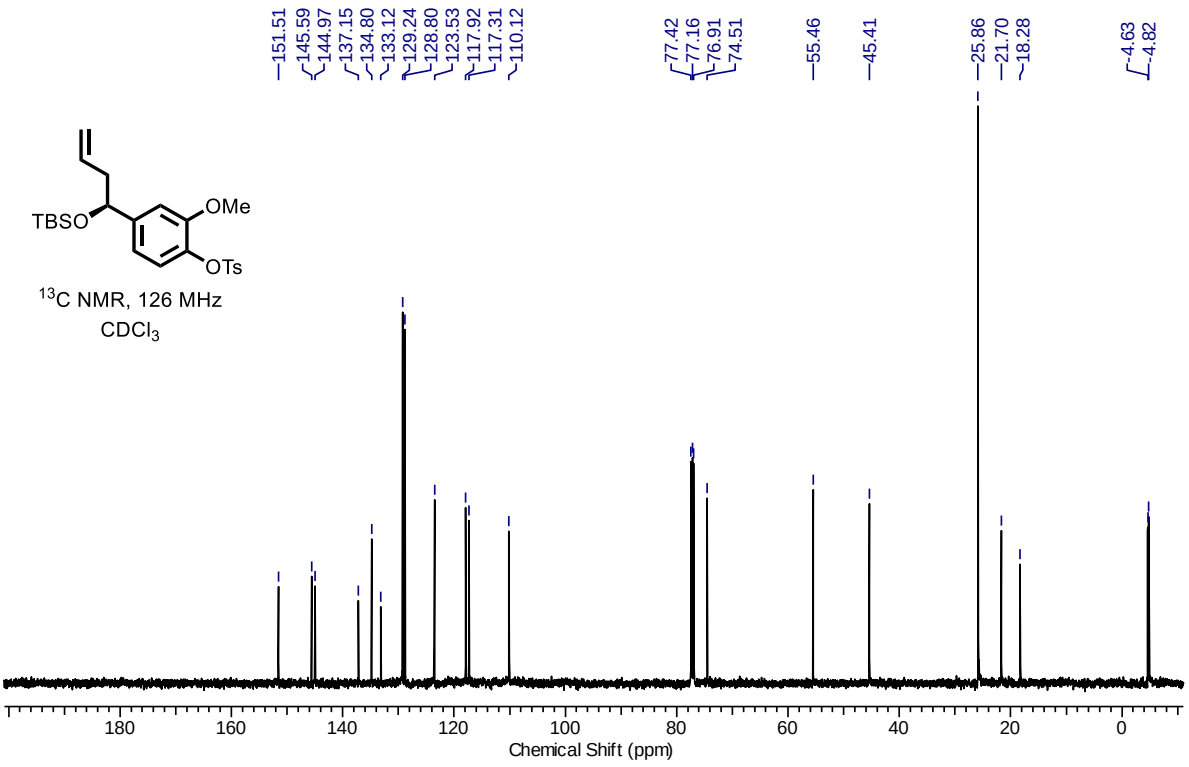
(*S*)-4-(1-Hydroxybut-3-en-1-yl)-2-methoxyphenyl-4-methylbenzenesulphonate (**106a**) (prepared from **96a**):



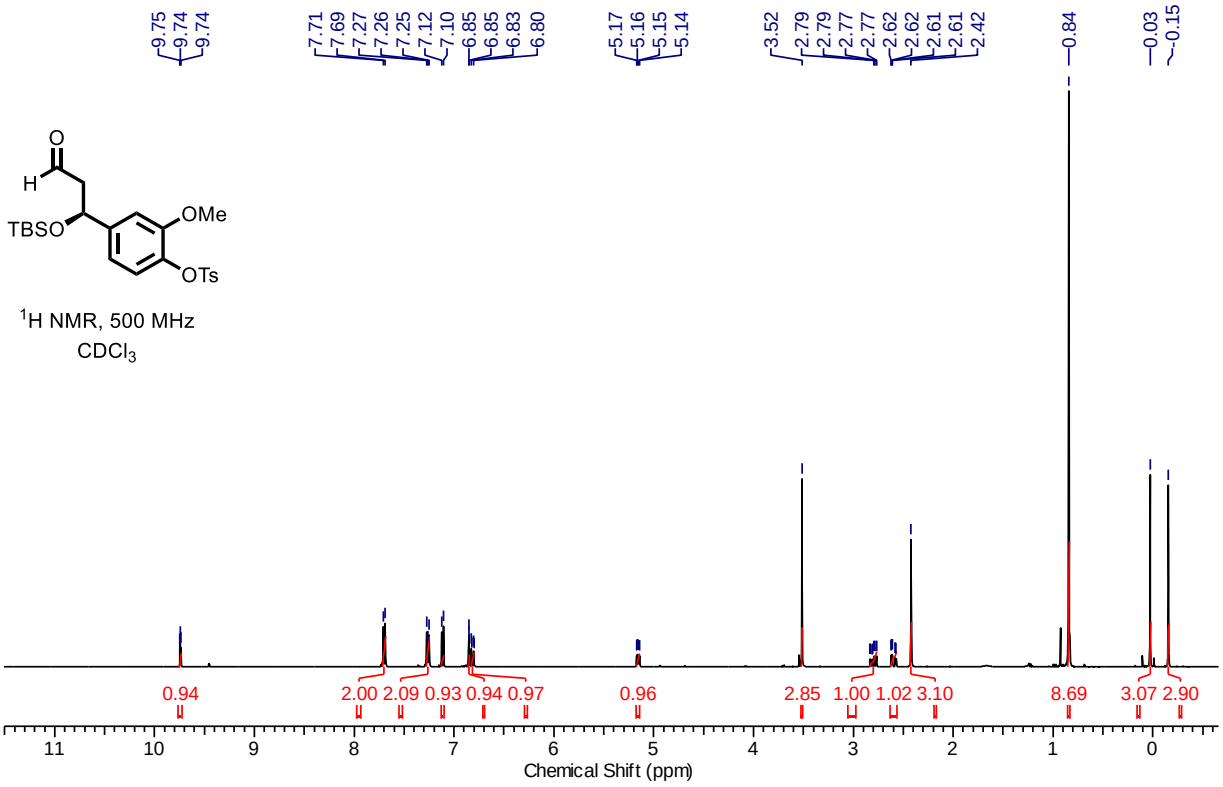
(*S*)-4-(1-((*Tert*-butyldimethylsilyl)oxy)but-3-en-1-yl)-2-methoxyphenyl-4-methylbenzene-sulphonate (**S6a**):



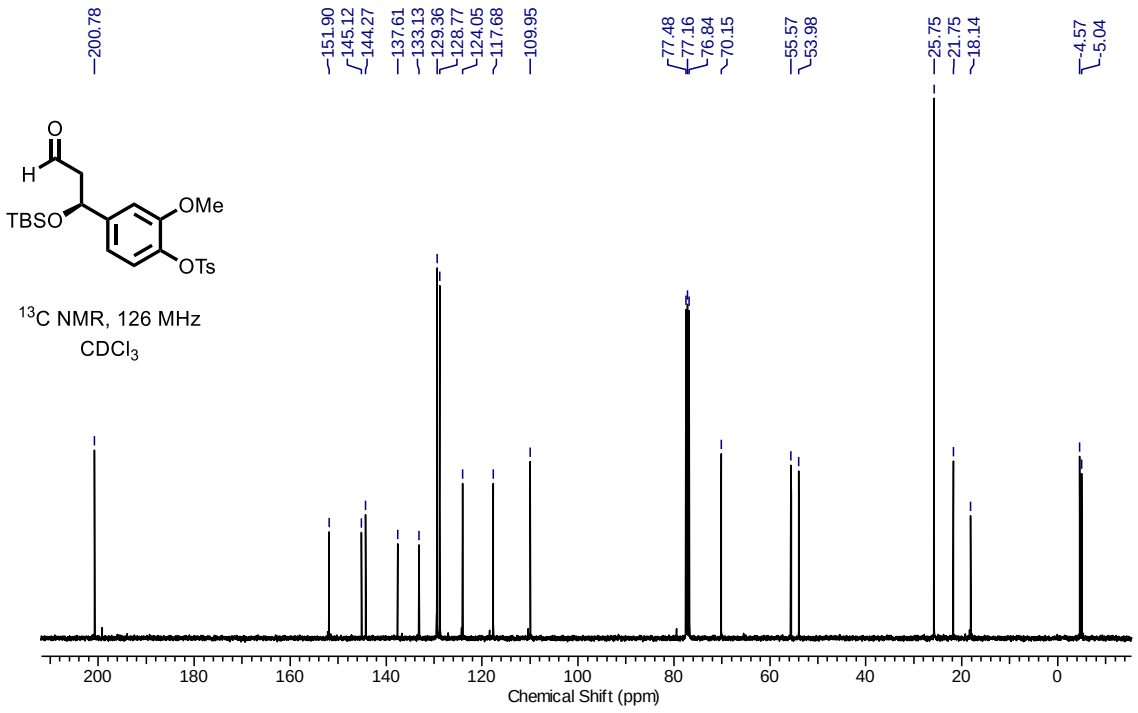
(*S*)-4-(1-((*Tert*-butyldimethylsilyl)oxy)but-3-en-1-yl)-2-methoxyphenyl-4-methylbenzene-sulphonate (**S6a**):



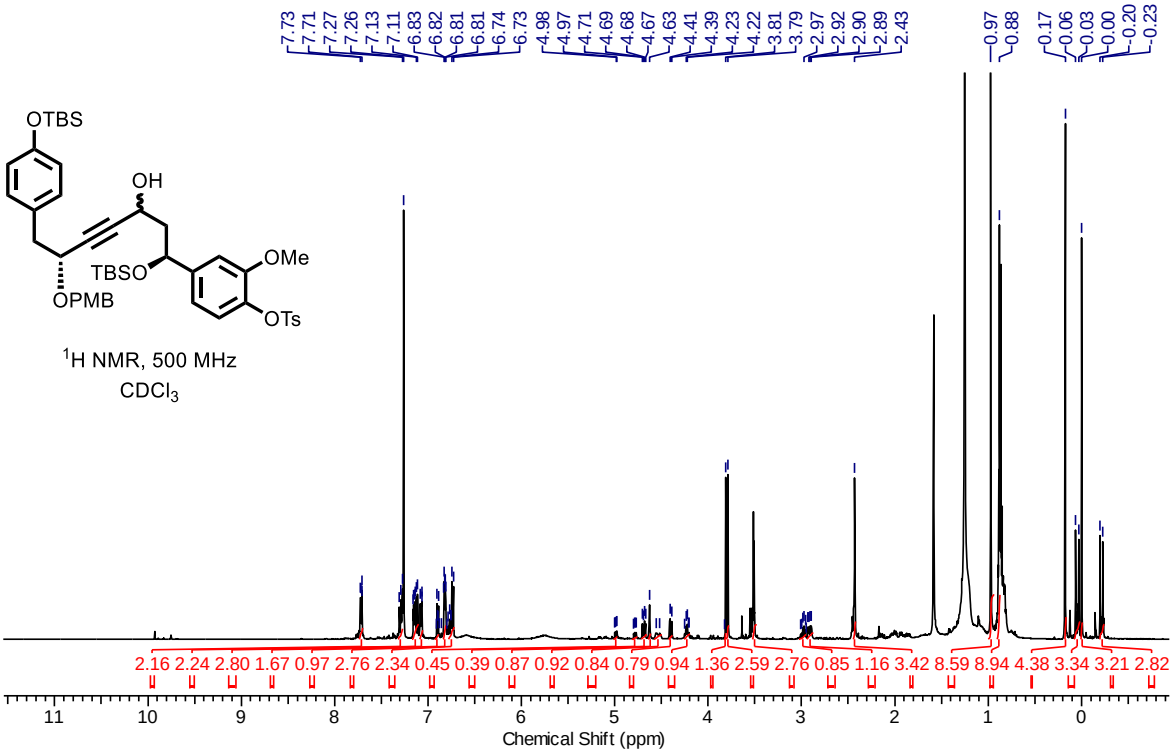
(*S*)-4-(1-((*Tert*-butyldimethylsilyl)oxy)-3-oxopropyl)-2-methoxyphenyl-4-methylbenzene-sulfonate (**102a**):



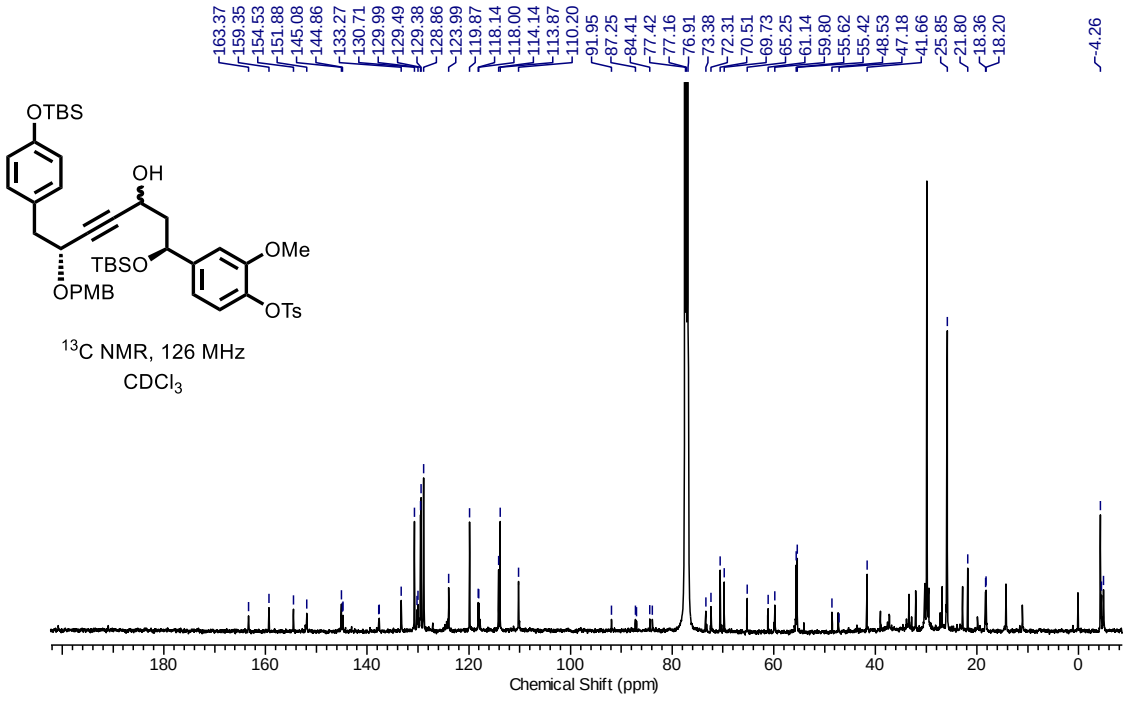
(*S*)-4-(1-((*Tert*-butyldimethylsilyl)oxy)-3-oxopropyl)-2-methoxyphenyl-4-methylbenzene-sulfonate (**102a**):



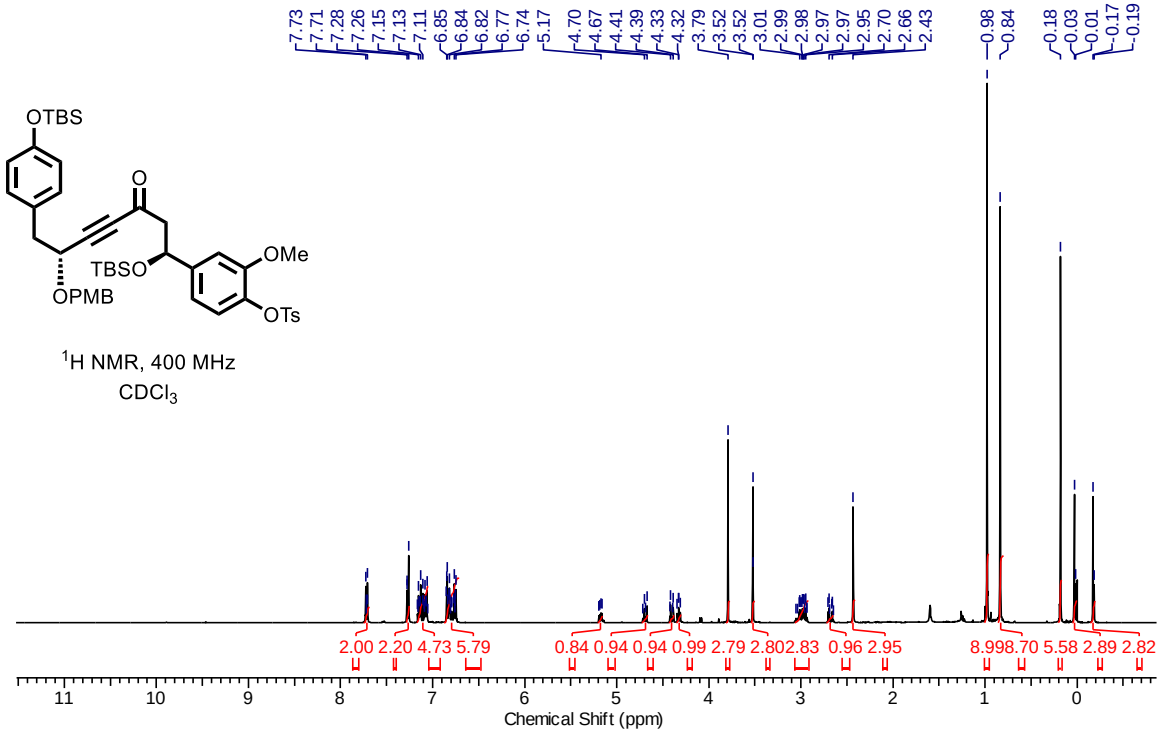
4-((*1S,6R*)-1-((*Tert*-butyldimethylsilyl)oxy)-7-(4-((*tert*-butyldimethylsilyl)oxy)-phenyl)-3-hydroxy-6-((4-methoxybenzyl)oxy)hept-4-yn-1-yl)-2-methoxyphenyl-4-methylbenzene-sulfonate (**107a**):



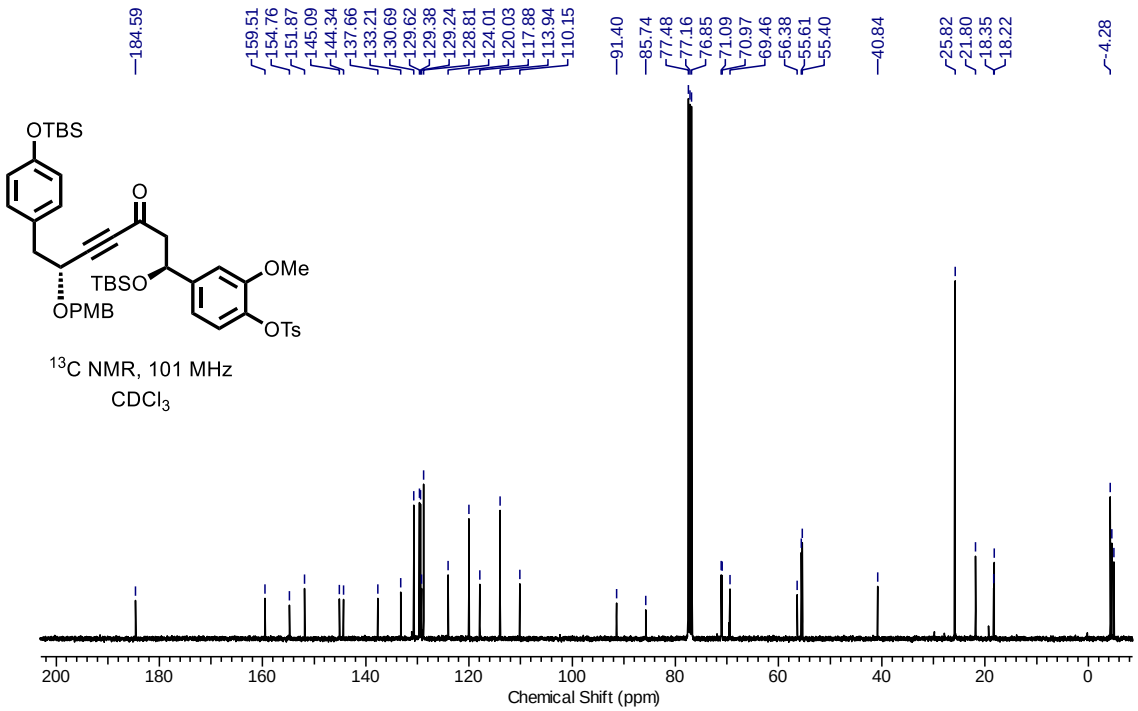
4-((*1S,6R*)-1-((*Tert*-butyldimethylsilyl)oxy)-7-(4-((*tert*-butyldimethylsilyl)oxy)-phenyl)-3-hydroxy-6-((4-methoxybenzyl)oxy)hept-4-yn-1-yl)-2-methoxyphenyl-4-methylbenzene-sulfonate (**107a**):



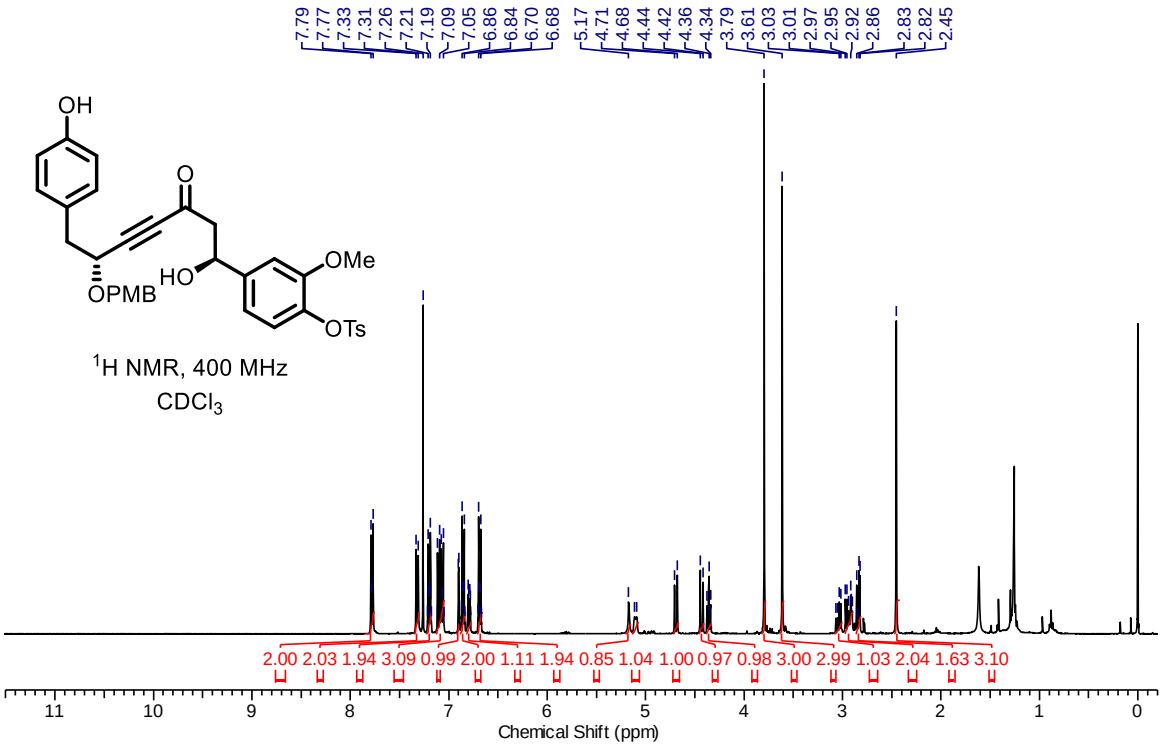
4-((*1S,6R*)-1-((*Tert*-butyldimethylsilyl)oxy)-7-(4-((*tert*-butyldimethylsilyl)oxy)-phenyl)-6-((4-methoxybenzyl)oxy)-3-oxohept-4-yn-1-yl)-2-methoxyphenyl-4-methylbenzenesulfonate (**100b**):



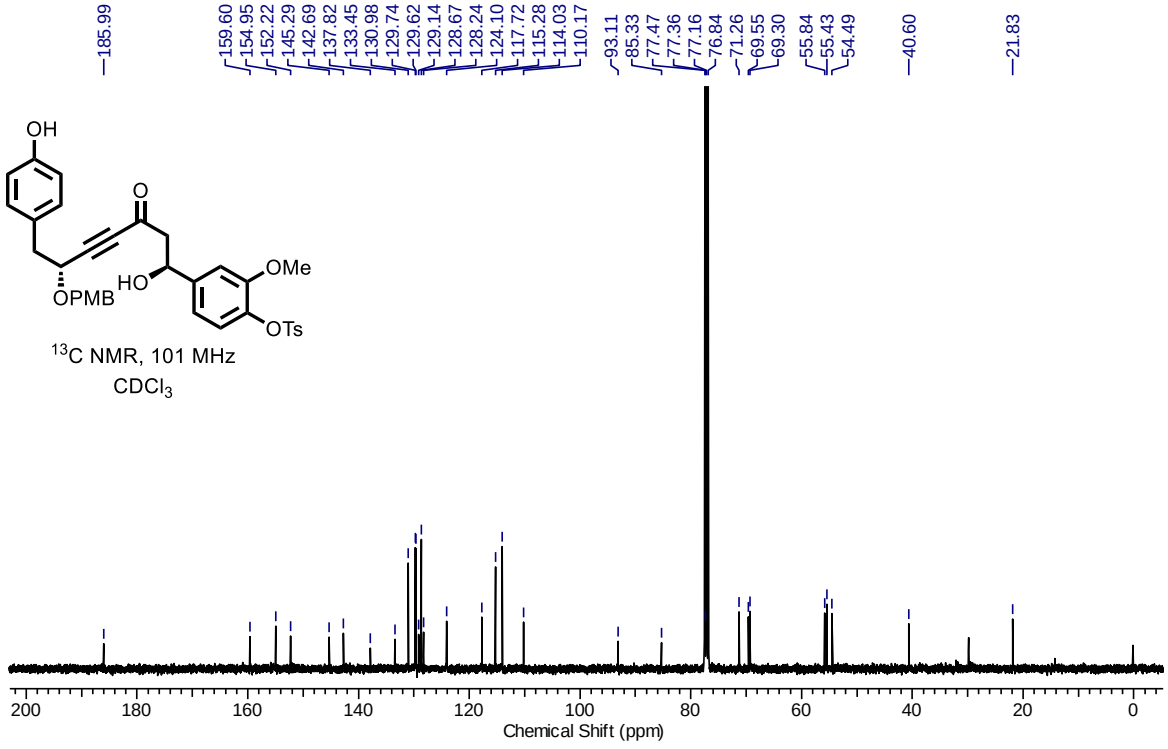
4-((*1S,6R*)-1-((*Tert*-butyldimethylsilyl)oxy)-7-(4-((*tert*-butyldimethylsilyl)oxy)-phenyl)-6-((4-methoxybenzyl)oxy)-3-oxohept-4-yn-1-yl)-2-methoxyphenyl-4-methylbenzenesulfonate (**100b**):



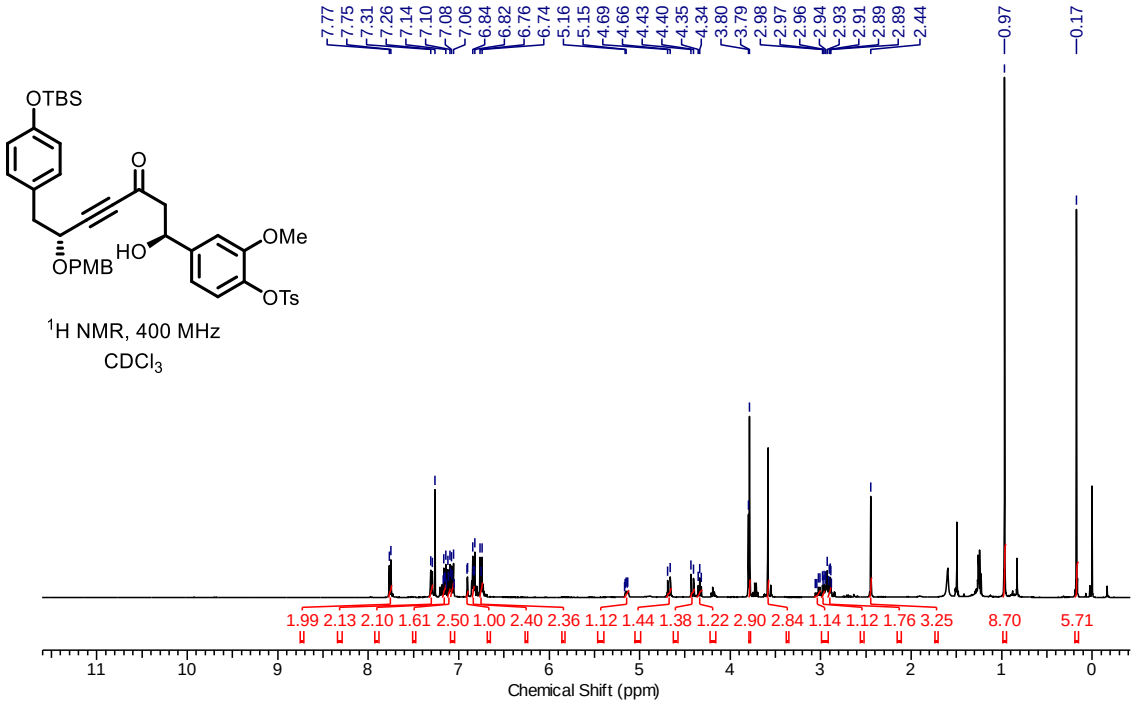
4-((*1S,6R*)-7-(4-((*Tert*-butyldimethylsilyl)oxy)phenyl)-1-hydroxy-6-((4-methoxy-benzyl)oxy)-3-oxohept-4-yn-1-yl)-2-methoxyphenyl-4-methylbenzenesulfonate (**114**):



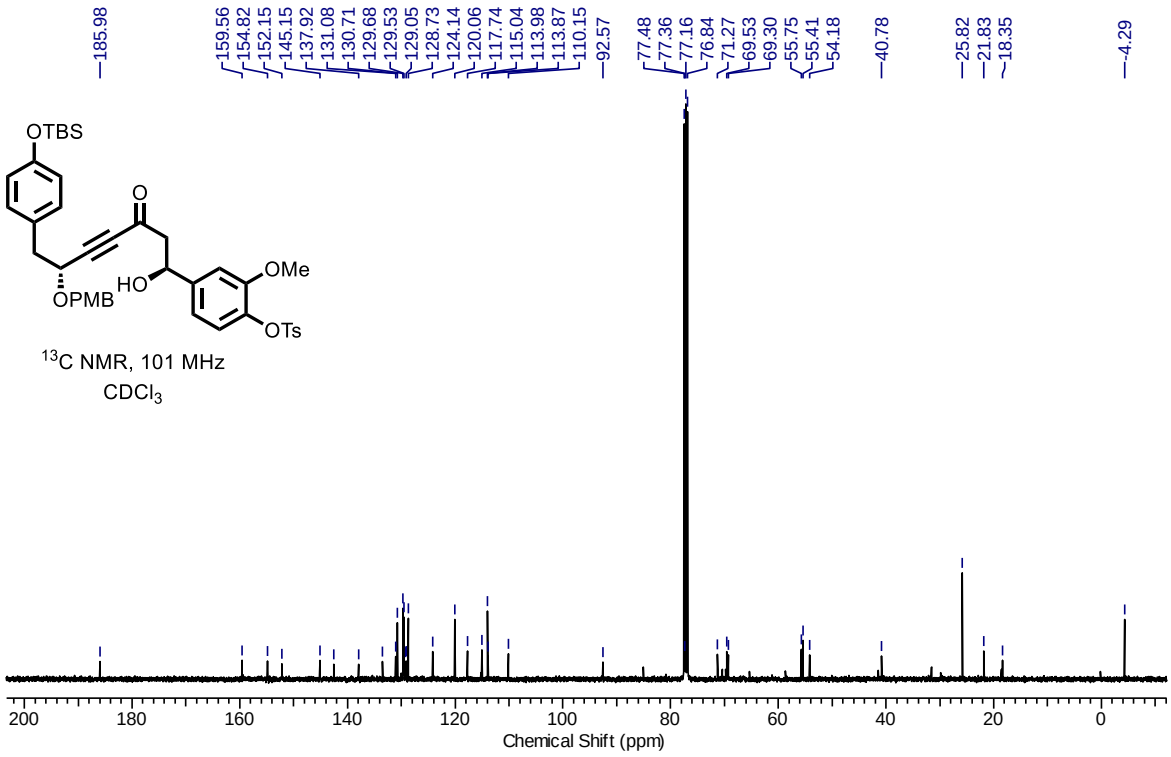
4-((*1S,6R*)-7-(4-((*Tert*-butyldimethylsilyl)oxy)phenyl)-1-hydroxy-6-((4-methoxy-benzyl)oxy)-3-oxohept-4-yn-1-yl)-2-methoxyphenyl-4-methylbenzenesulfonate (**114**):



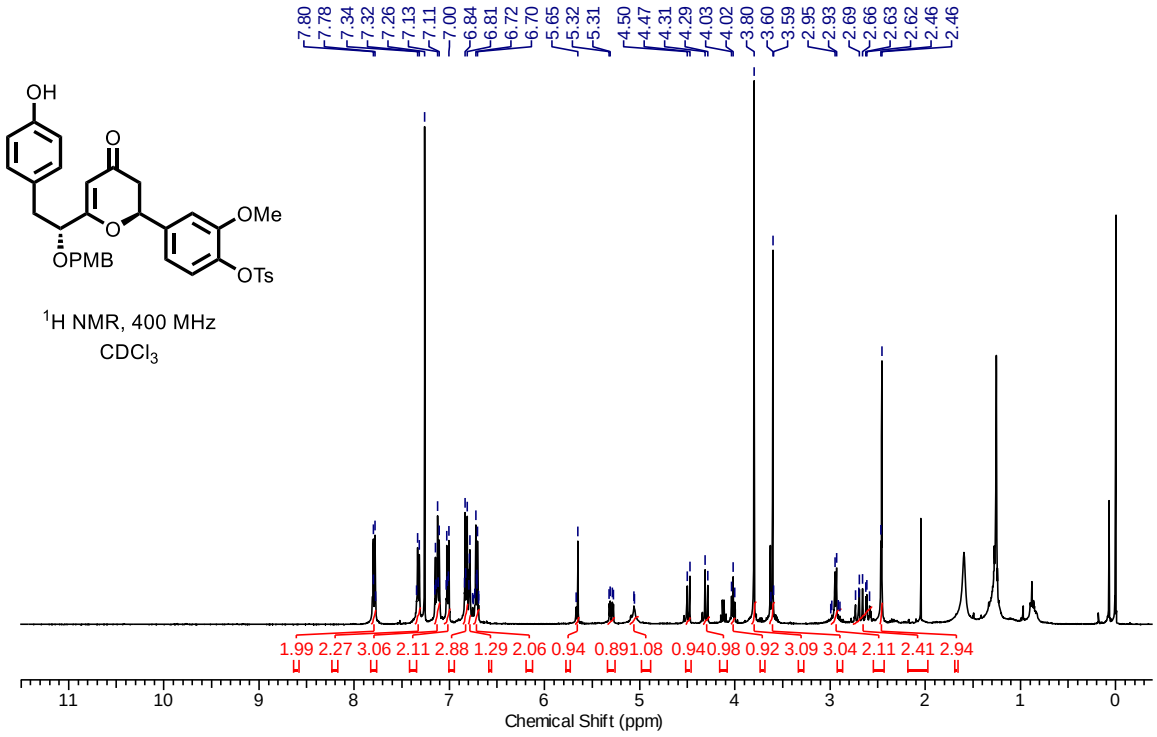
4-((*1S,6R*)-1-Hydroxy-7-(4-hydroxyphenyl)-6-((4-methoxybenzyl)oxy)-3-oxohept-4-yn-1-yl)-2-methoxyphenyl 4-methylbenzenesulfonate (**115**):



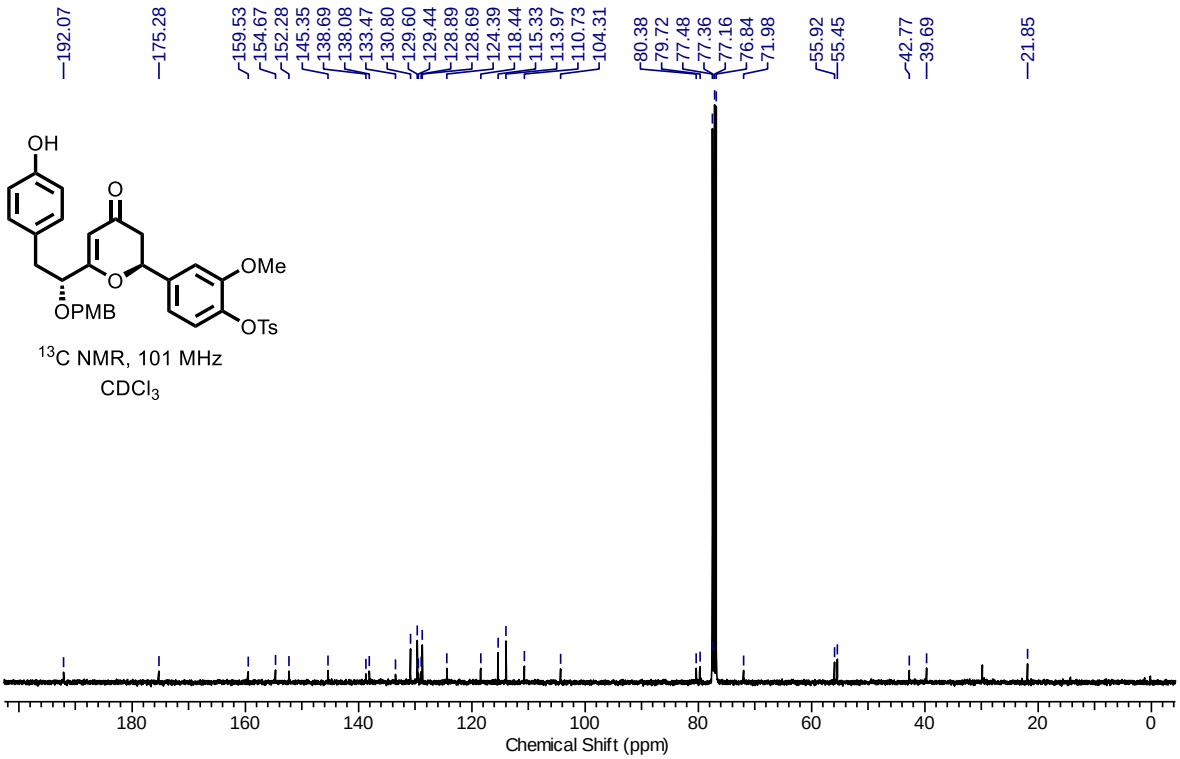
4-((*1S,6R*)-1-Hydroxy-7-(4-hydroxyphenyl)-6-((4-methoxybenzyl)oxy)-3-oxohept-4-yn-1-yl)-2-methoxyphenyl 4-methylbenzenesulfonate (**115**):



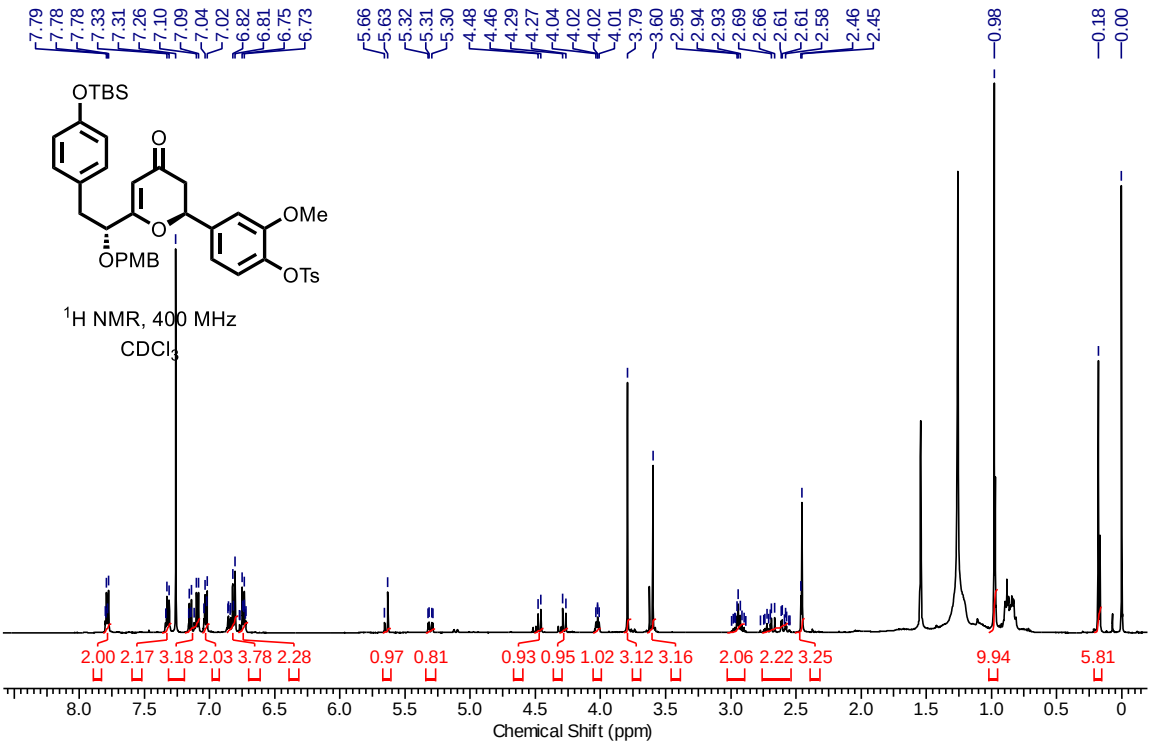
4-((*S*)-6-((*R*)-2-(4-Hydroxyphenyl)-1-((4-methoxybenzyl)oxy)ethyl)-4-oxo-3,4-dihydro-2*H*-pyran-2-yl)-2-methoxyphenyl 4-methylbenzenesulfonate (**116**):



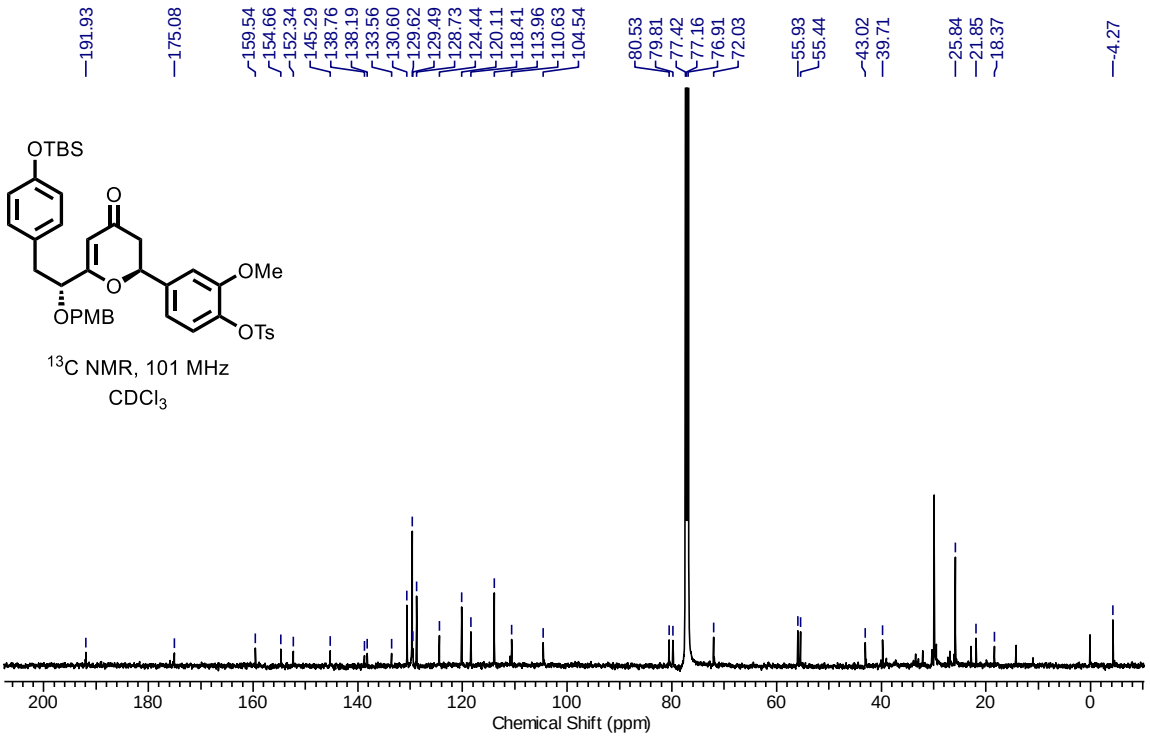
4-((*S*)-6-((*R*)-2-(4-Hydroxyphenyl)-1-((4-methoxybenzyl)oxy)ethyl)-4-oxo-3,4-dihydro-2*H*-pyran-2-yl)-2-methoxyphenyl 4-methylbenzenesulfonate (**116**):



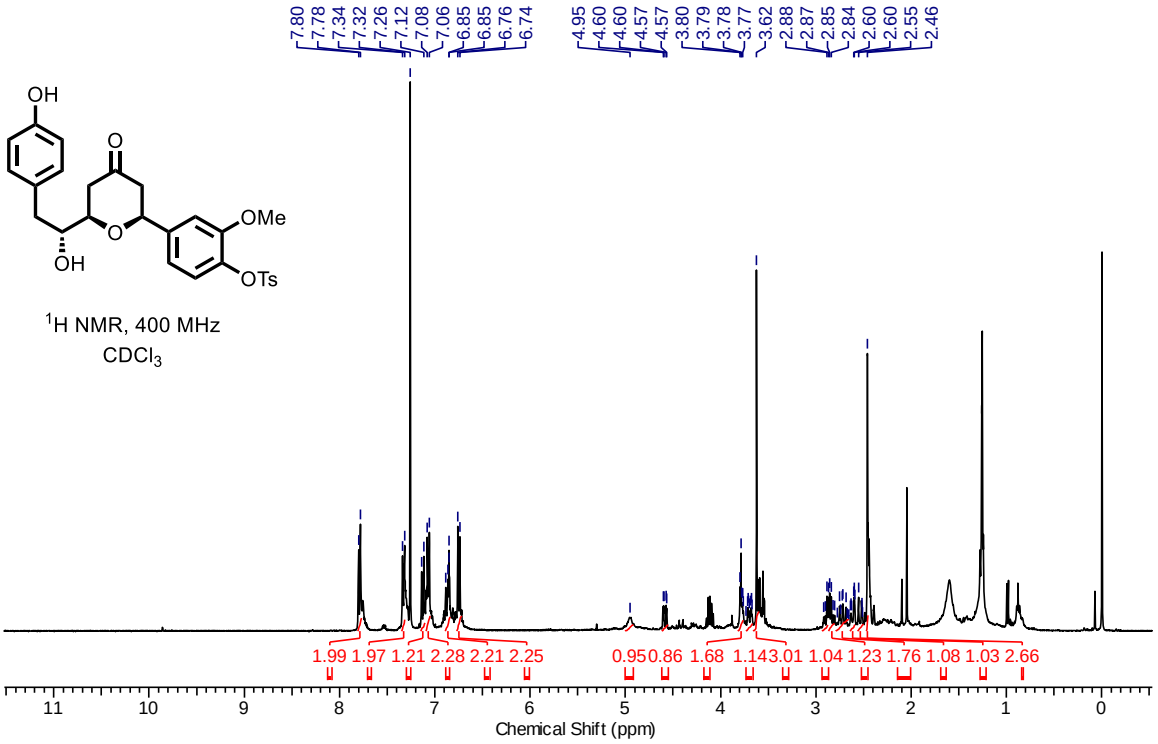
4-((*S*)-6-((*R*)-2-(4-((*Tert*-butyldimethylsilyl)oxy)phenyl)-1-((4-methoxybenzyl)-oxy)ethyl)-4-oxo-3,4-dihydro-2*H*-pyran-2-yl)-2-methoxyphenyl-4-methylbenzenesulfonate (**117**):



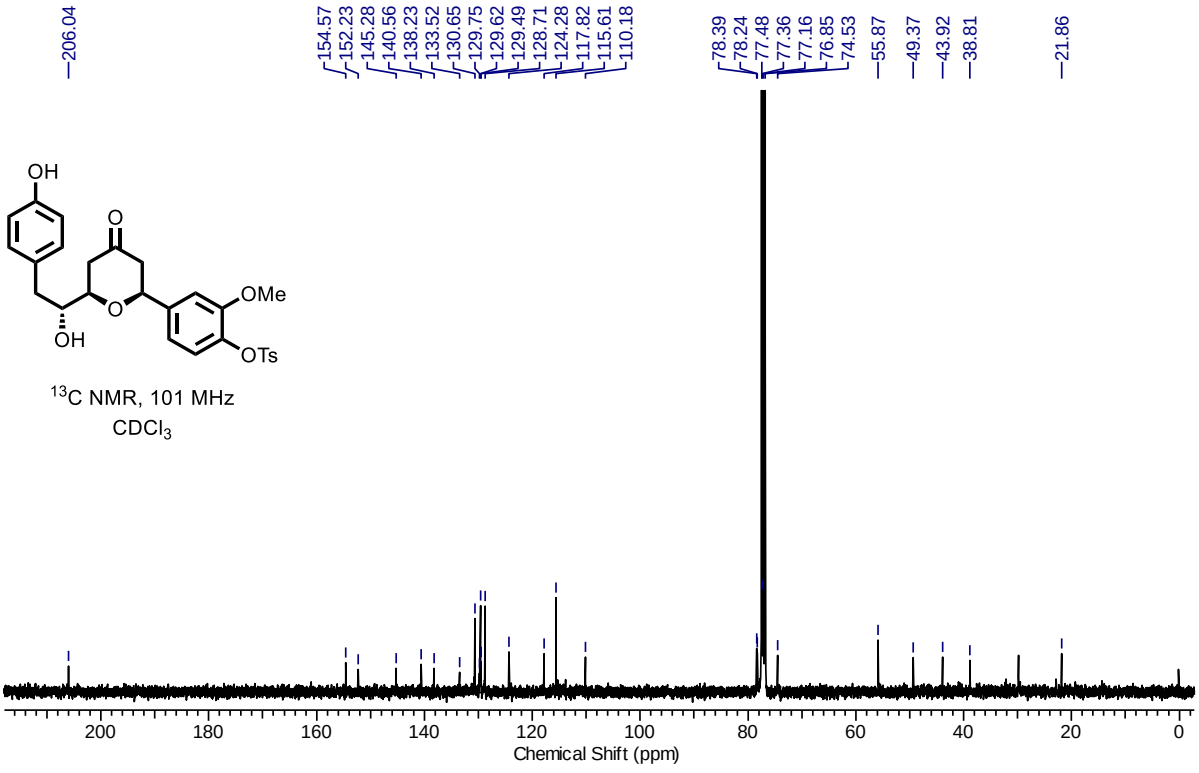
4-((*S*)-6-((*R*)-2-(4-((*Tert*-butyldimethylsilyl)oxy)phenyl)-1-((4-methoxybenzyl)-oxy)ethyl)-4-oxo-3,4-dihydro-2*H*-pyran-2-yl)-2-methoxyphenyl-4-methylbenzenesulfonate (**117**):



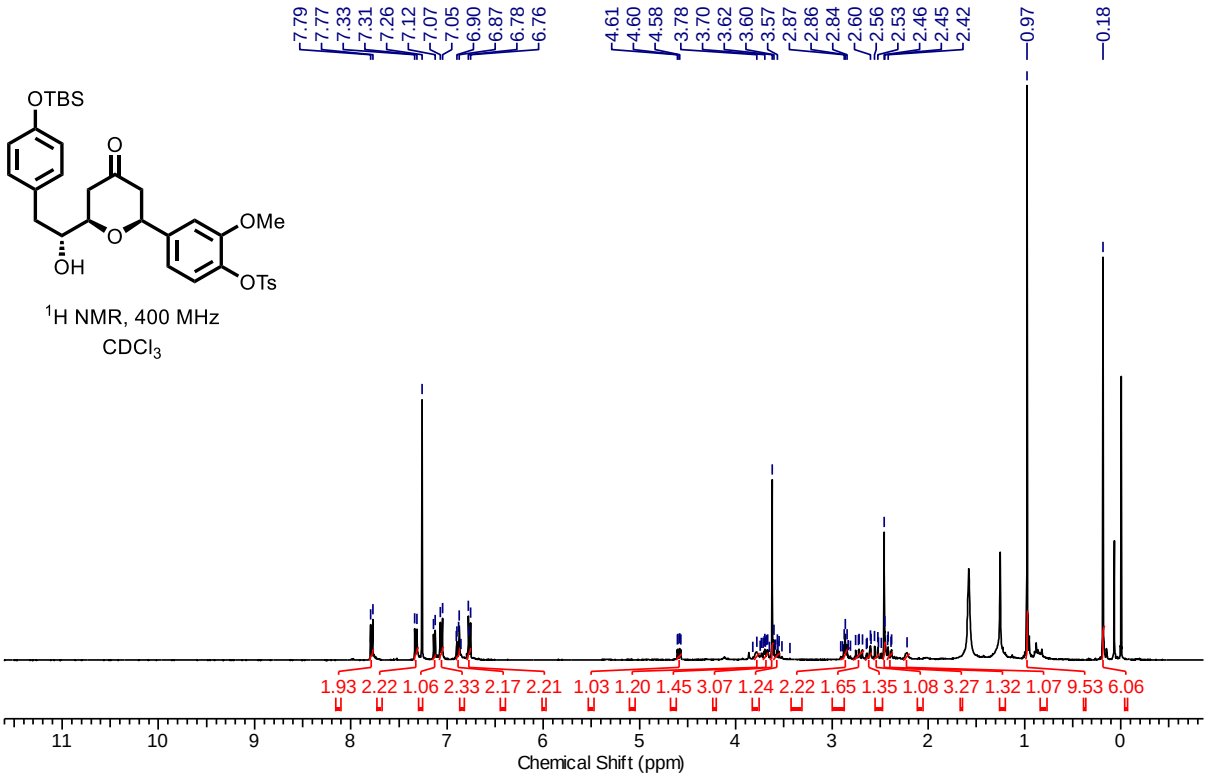
4-((*2S,6R*)-6-((*R*)-1-Hydroxy-2-(4-hydroxyphenyl)ethyl)-4-oxotetrahydro-2*H*-pyran-2-yl)-2-methoxyphenyl 4-methylbenzenesulfonate (**S10**):



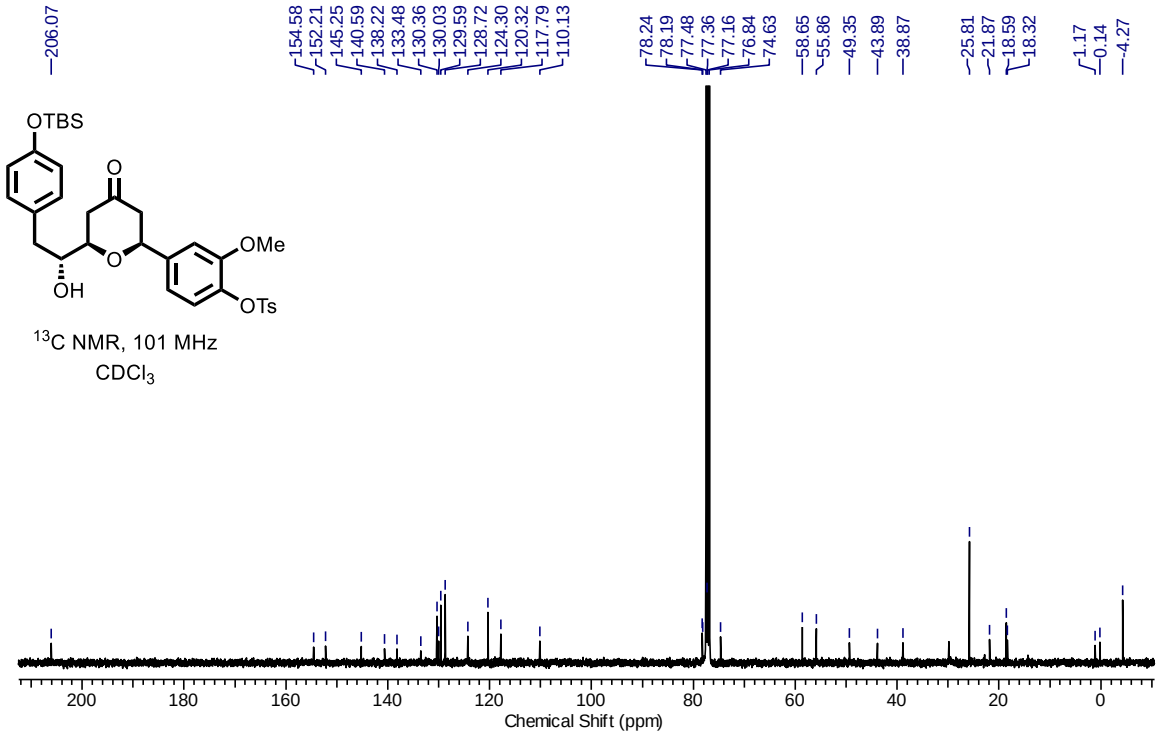
4-((*2S,6R*)-6-((*R*)-1-Hydroxy-2-(4-hydroxyphenyl)ethyl)-4-oxotetrahydro-2*H*-pyran-2-yl)-2-methoxyphenyl 4-methylbenzenesulfonate (**S10**):



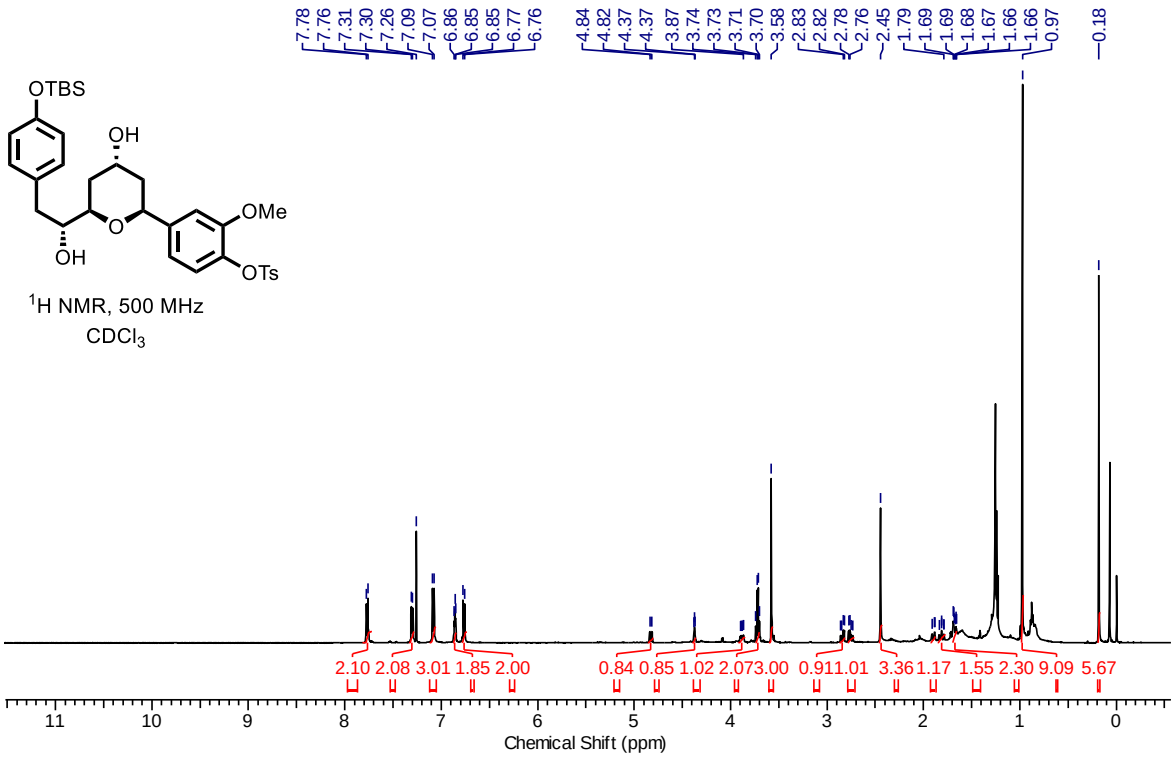
4-((*2S,6R*)-6-((*R*)-2-(4-((*Tert*-butyldimethylsilyl)oxy)phenyl)-1-hydroxyethyl)-4-oxotetrahydro-2*H*-pyran-2-yl)-2-methoxyphenyl 4-methylbenzenesulfonate (**S11**):



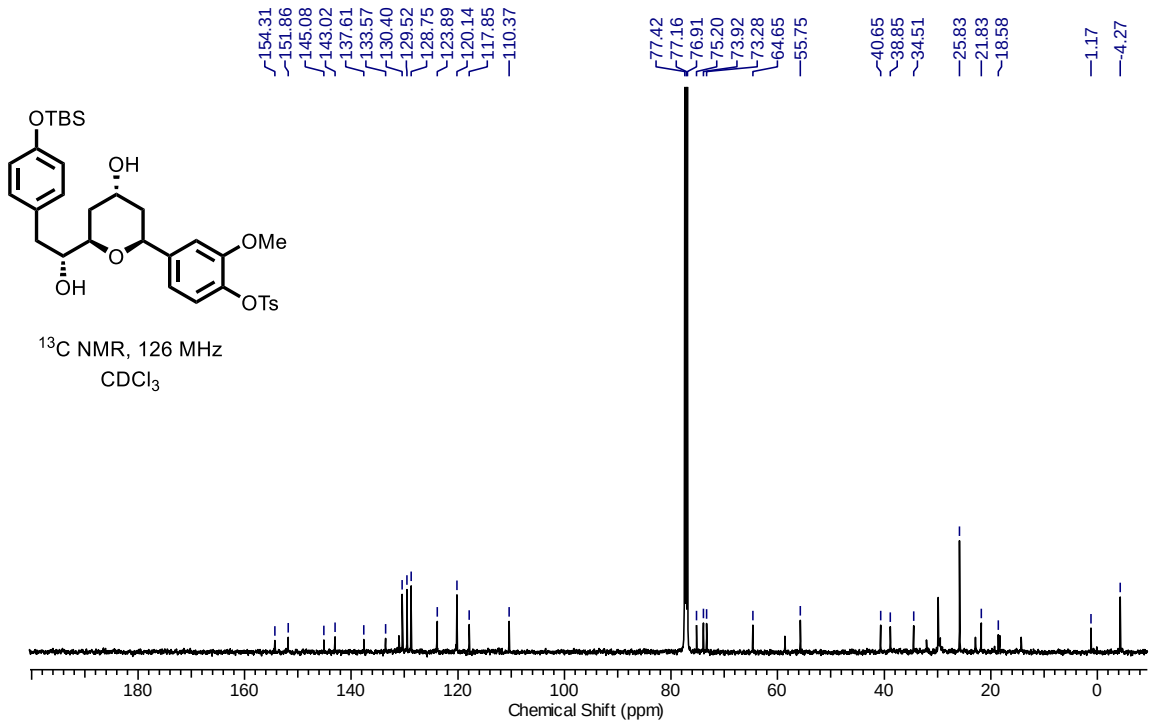
4-((*2S,6R*)-6-((*R*)-2-(4-((*Tert*-butyldimethylsilyl)oxy)phenyl)-1-hydroxyethyl)-4-oxotetrahydro-2*H*-pyran-2-yl)-2-methoxyphenyl 4-methylbenzenesulfonate (**S11**):



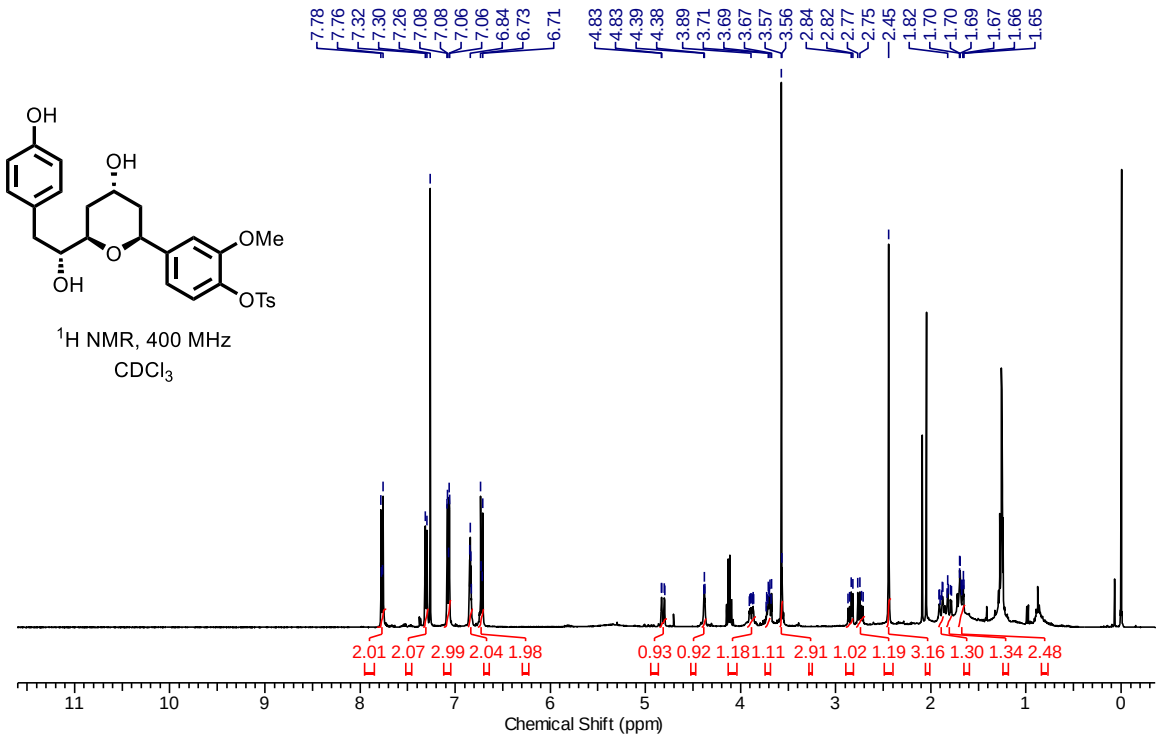
4-((*2S,4R,6R*)-6-((*R*)-2-(4-((*Tert*-butyldimethylsilyl)oxy)phenyl)-1-hydroxyethyl)-4-hydroxytetra-hydro-2*H*-pyran-2-yl)-2-methoxyphenyl-4-methylbenzenesulfonate (**119**):



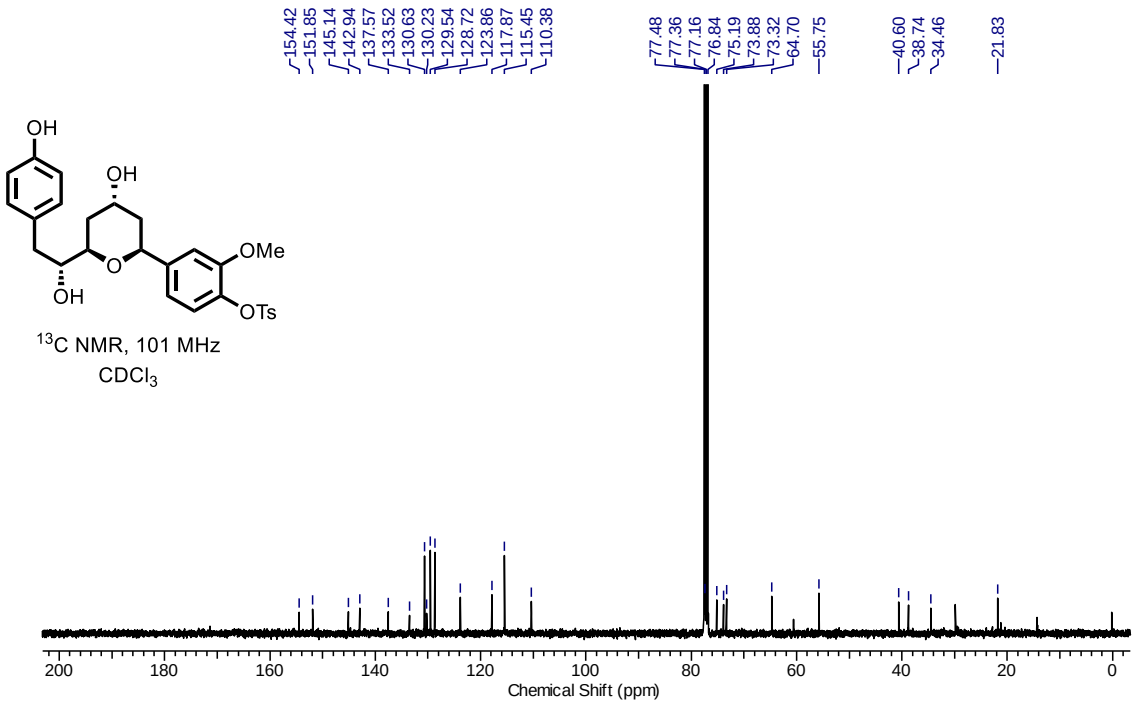
4-((*2S,4R,6R*)-6-((*R*)-2-(4-((*Tert*-butyldimethylsilyl)oxy)phenyl)-1-hydroxyethyl)-4-hydroxytetra-hydro-2*H*-pyran-2-yl)-2-methoxyphenyl-4-methylbenzenesulfonate (**119**):



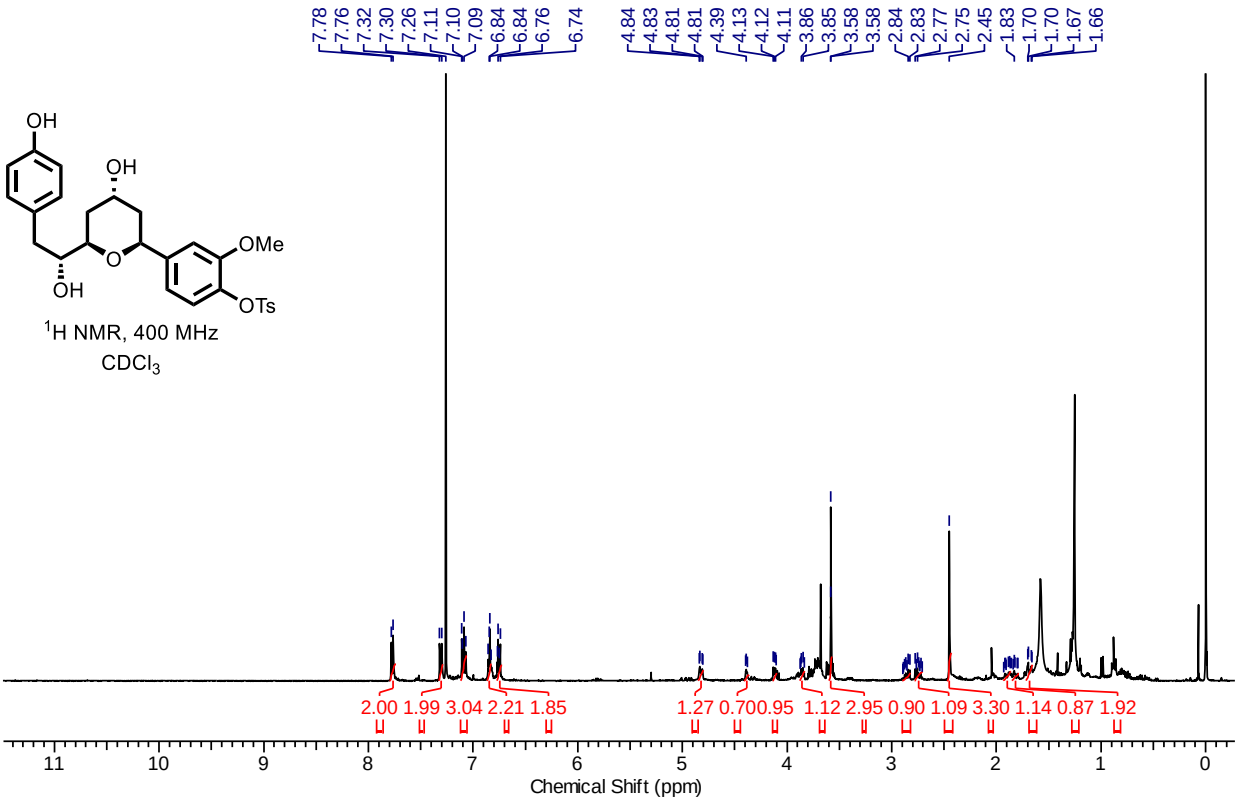
4-((*2S,4R,6R*)-4-Hydroxy-6-((*R*)-1-hydroxy-2-(4-hydroxyphenyl)ethyl)tetrahydro-2*H*-pyran-2-yl)-2-methoxyphenyl 4-methylbenzenesulfonate (**120**) (using *LS-Selectride*):



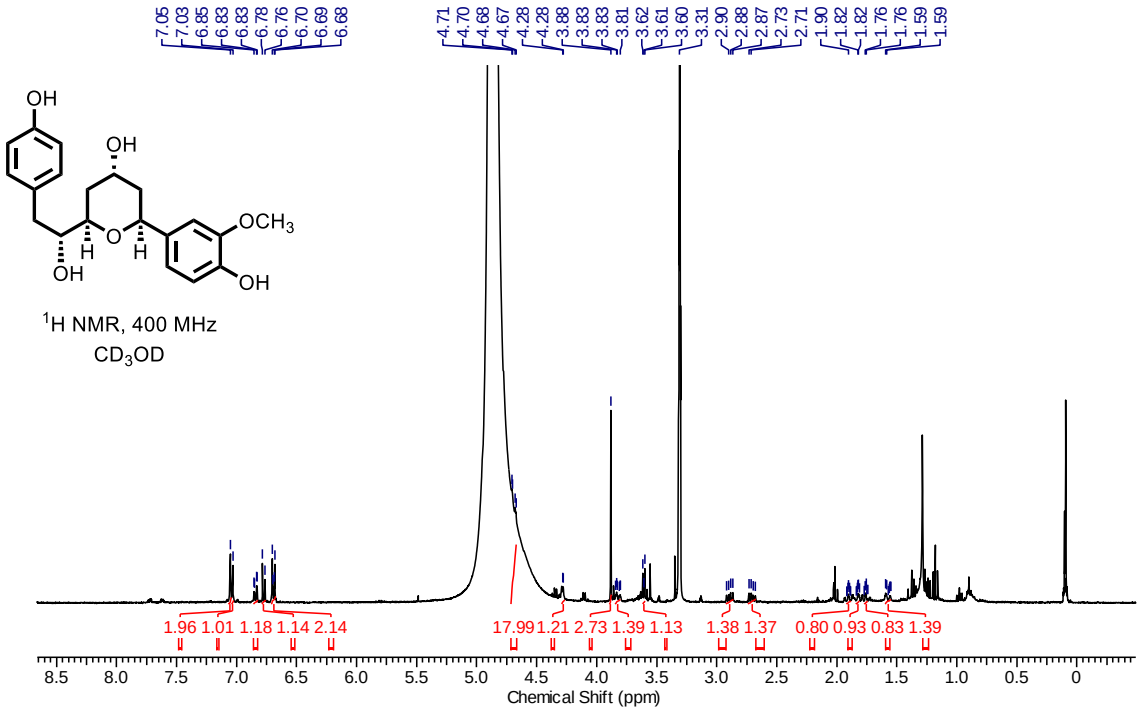
4-((*2S,4R,6R*)-4-Hydroxy-6-((*R*)-1-hydroxy-2-(4-hydroxyphenyl)ethyl)tetrahydro-2*H*-pyran-2-yl)-2-methoxyphenyl 4-methylbenzenesulfonate (**120**) (using *LS-Selectride*):



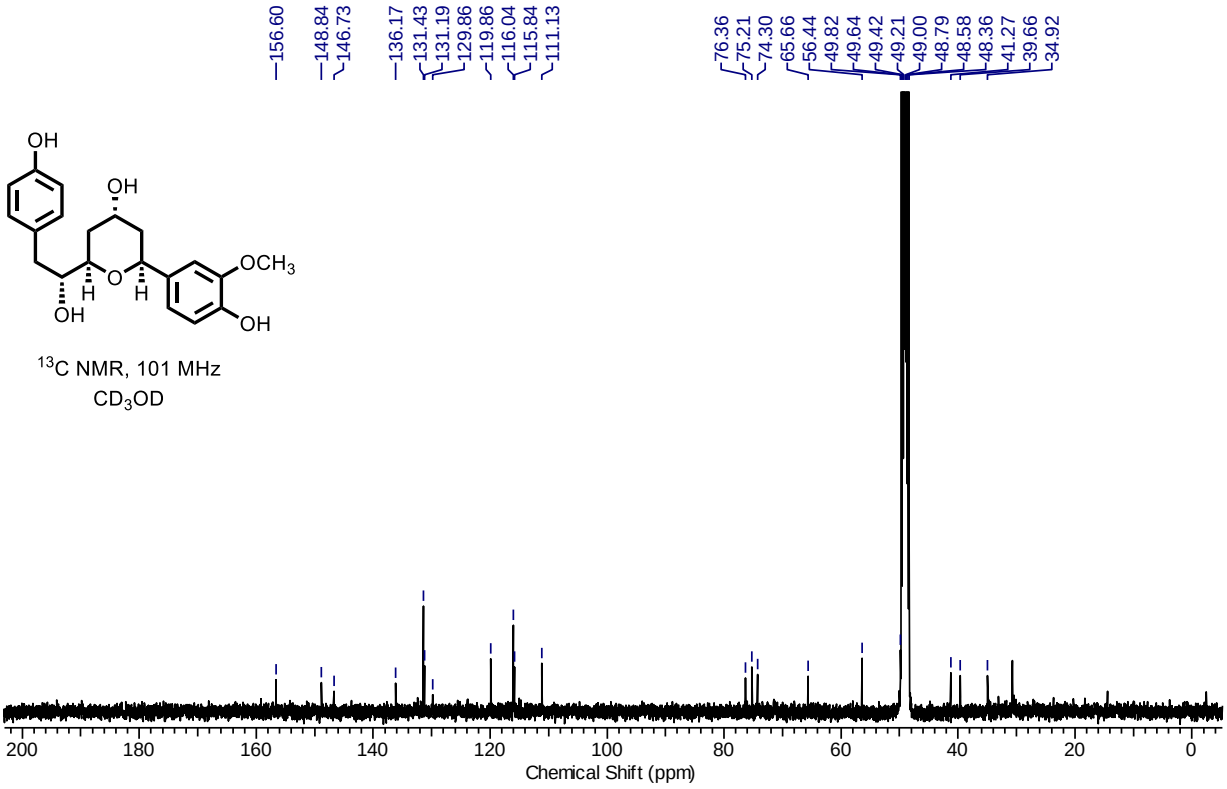
4-((*2S,4R,6R*)-4-Hydroxy-6-((*R*)-1-hydroxy-2-(4-hydroxyphenyl)ethyl)tetrahydro-2*H*-pyran-2-yl)-2-methoxyphenyl 4-methylbenzenesulfonate (**120**) (*using TBAF*)*:*



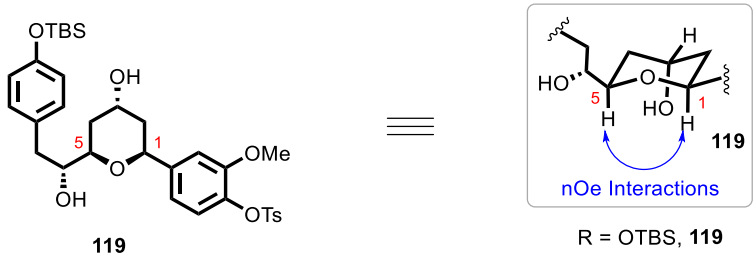
ent-Rhoiptelol B (**29a**):



ent-Rhoiptelol B (**29a**):

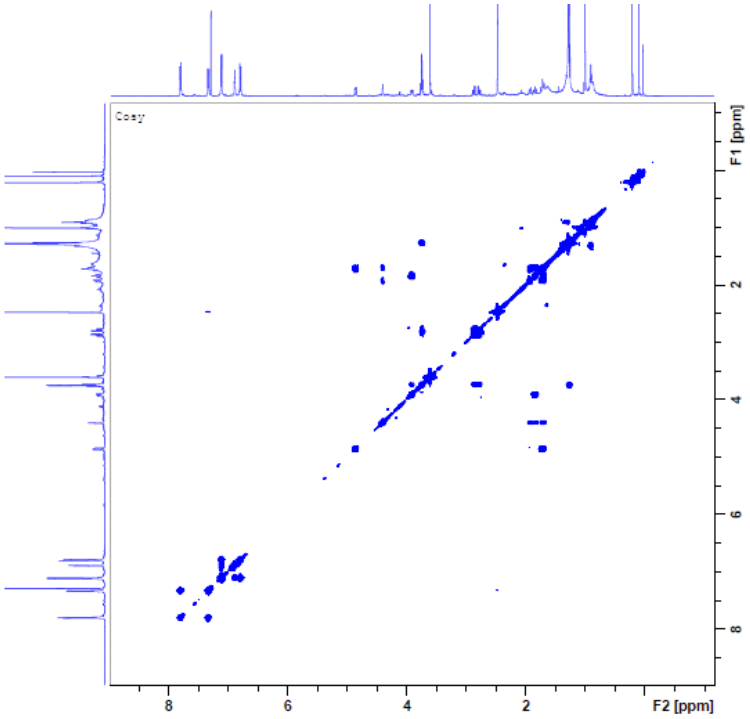


2. *2D-NMR Spectra of 4-((2S,4R,6R)-6-((R)-2-(4-((tert-butyldimethyl-silyl)oxy)phenyl)-1-hydroxyethyl)-4-hydroxytetrahydro-2H-pyran-2-yl)-2-methoxyphenyl 4-methylbenzenesulfonate* (**119**):

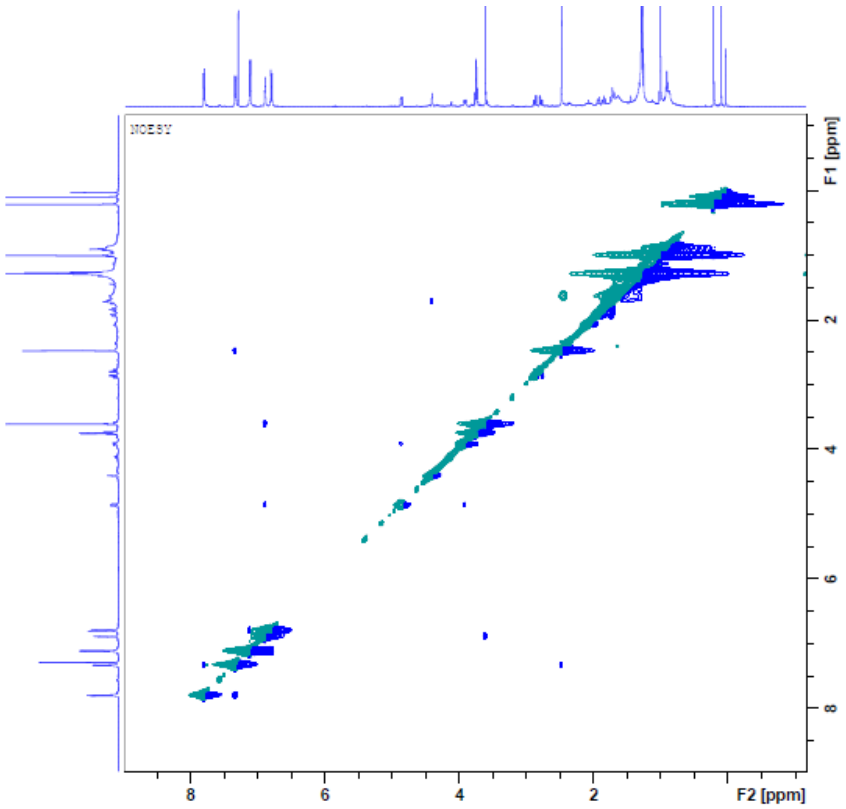


R = OTBS, **119**

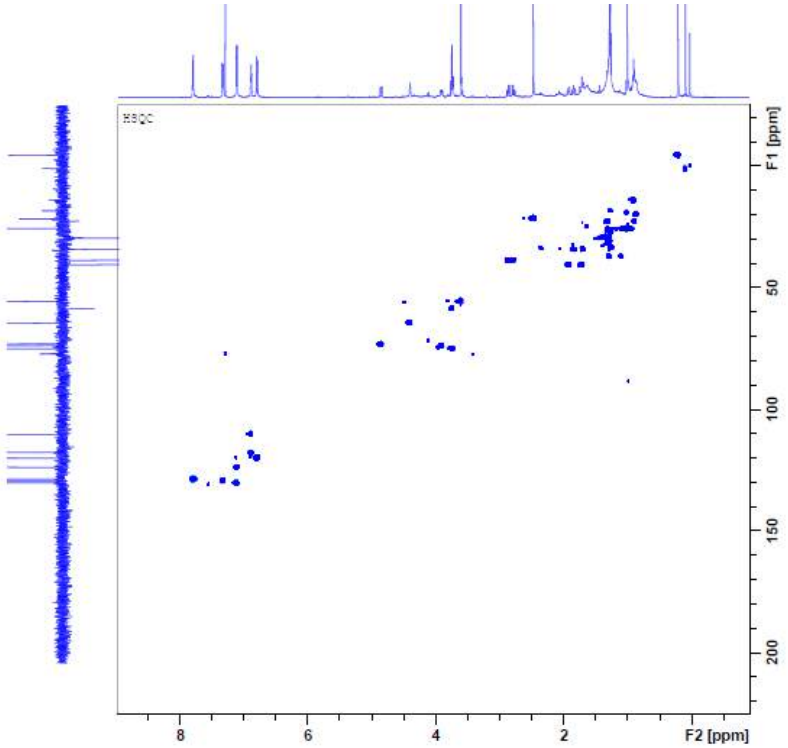
a) COSY spectra:



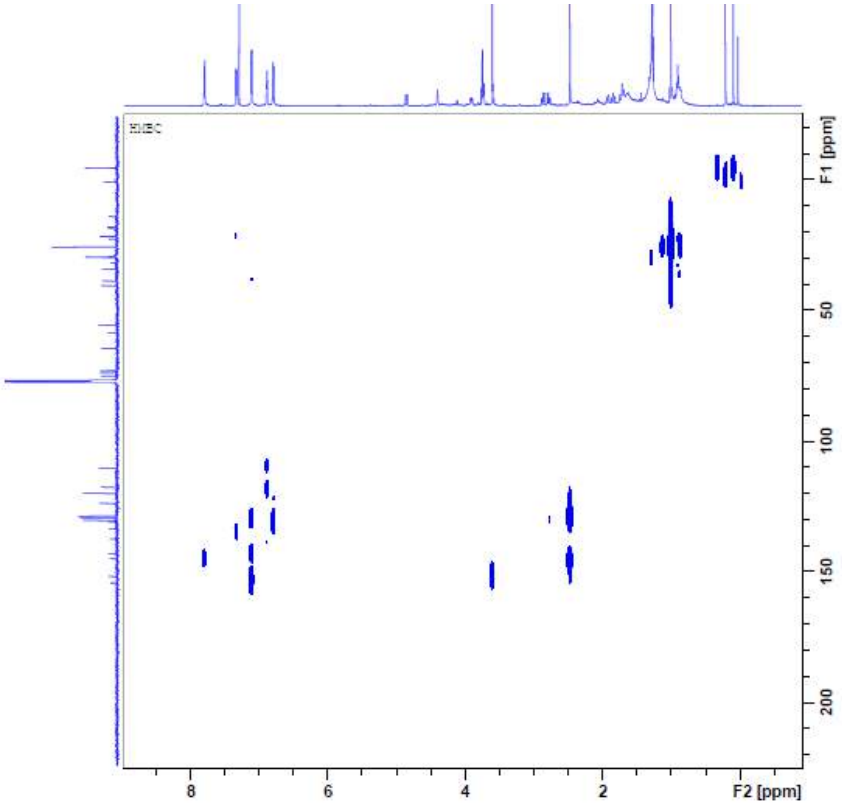
b) NOESY spectra:



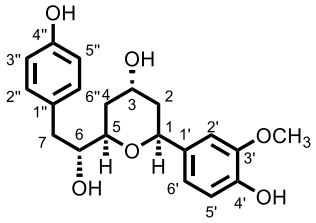
c) HSQC spectra



d) HMBC spectra:



3. Table S1. Comparison of NMR data of rhoiptelol B (**29a**) (Our work, Natural (Isolated) and First synthesised)



ent-Rhioptelol B(3a)

Position	Our Work (*ent*-Rhoiptelol B)		Natural Rhoiptelol B (Isolated)		First Synthesis of Rhoiptelol B	
	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
1	4.69 (1H, *dd,J*= 2.25, 11.51 Hz)	75.2	4.69 (1H, *dd,J*=3, 11 Hz)	75.2 d	4.69 (1H, dd, *J* = 11.1, 3.0 Hz)	75.2
2	1.76 (1H, d, *J* = 2.88 Hz) 1.84-1.80 (1H, m)	41.3	1.75 (1H, *ddd*, *J*=3, 11, 12 Hz, *ax*) 1.84 (1H, *dd*, *J*=3, 12 Hz, *eq*)	41.3 t	1.74 (1H, ddd, *J* = 13.9, 11.3, 3.0 Hz) 1.83 (1H, dd, *J* = 14.5, 2.6 Hz)	41.3
3	4.28 (1H, m)	65.7	4.27 (1H, *t*, *J*=3 Hz)	65.6 d	4.27 (1H, t, *J* = 3.0 Hz)	65.7
4	1.57-1.54 (1H, m) 1.92-1.89 (1H, m)	34.9	1.57 (1H, *dd*, *J*=2, 13 Hz, *eq*) 1.89 (1H, *dt*, *J*=3, 13 Hz, *ax*)	34.9 t	1.55 (1H, dd, *J* = 13.4, 2.0 Hz) 1.92 (1H, dd, *J* = 13.5, 3.0 Hz)	35.0
5	3.85-3.82 (1H, m)	74.3	3.82 (1H, *dt*, *J*=13, 3 Hz)	74.3 d	3.81 (1H, dt, *J* = 12.5, 2.89 Hz)	74.3
6	3.60-3.57 (1H, m)	76.4	3.60, (1H, dt, *J* =3, 7 Hz)	76.3d	3.59 (1H, dt, *J* = 7.0, 3.2 Hz)	76.4
7	2.71 (1H, dd, *J* = 7.25, 13.26 Hz) 2.89 (1H, dd, *J* = 7.00, 13.66 Hz)	39.7	2.70 (1H, dd, *J*= 7, 13 Hz) 2.89 (1H, dd, *J*= 7, 13 Hz)	39.7 t	2.69 (1H, dd, *J* = 13.4, 7.3 Hz) 2.89 (1H, dd, *J* = 13.4, 6.8 Hz)	39.7
1'		136.2		136.1 s		136.2
2'	7.05 (2H, br. s)	111.1	7.04 (1H, br s)	111.1 d	7.04 (1H, br. s)	111.1
3'		148.8		148.8 s		148.8
4'		146.7		146.7 s		146.8

5’	6.77 (1H, d, *J* = 8.13 Hz)	115.8	6.77 (1H, d, *J* = 8 Hz)	115.8 d	6.76 (1H, d, *J* = 8.1 Hz)	115.9
6’	6.84 (1H, dd, *J* = 1.88, 8.38 Hz)	119.9	6.84 (1H, dd, *J*= 2, 8 Hz)	119.8 d	6.83 (1H, dd, *J* = 8.1, 1.9 Hz)	119.8
1’’		129.9		131.1 s		131.2
2’’	7.03 (1H, s)	131.4	7.03 (1H, d, *J*= 8 Hz)	131.4 d	7.03 (2H, d, *J* = 8.1 Hz)	131.4
3’’	6.71-6.68 (2H, m)	116.0	6.69 (1H, d, *J* = 8 Hz)	116.0 d	6.68 (2H, d, *J* = 8.1 Hz)	116.0
4’’		156.6		156.6 s		156.7
5’’		115.8	6.69 (1H, d, *J* = 8 Hz)	116.0 d		116.0
6’’		131.4	7.03 (1H, d, *J* = 8 Hz)	131.4 d		131.5
OMe	3.88 (3H, s)	56.4	3.87 (3H, s)	56.4 q	3.87 (1H, s)	56.4

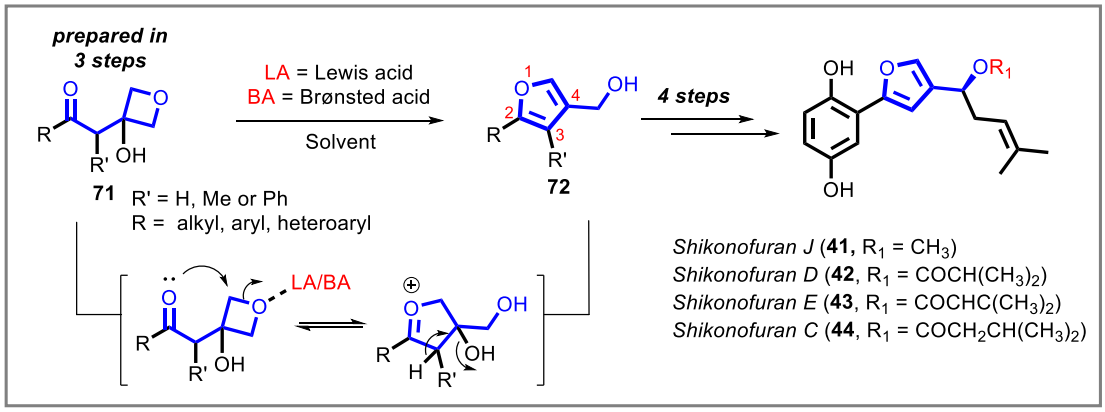
CHAPTER-2

Enantioselective Total Synthesis of Furylhydroquinone-derived Natural Products: Shikonofuran J, D, E and C

Chapter-2, Section-B: Present work

2.2.1. Hypothesis

Inspired by the interesting biological profile and structural features of shikonofurans J, D, E, and C (**41-44**) and our curiosity in stereoselective total synthesis of furan-containing biologically potent natural products, we embarked on the development of efficient and practical stereoselective synthetic routes for these natural products. As discussed in the previous section of this Chapter 2, we have chosen the known construction strategy of 2,4-disubstituted furan moiety **72** (used as a key intermediate for the total synthesis of shikonofurans) from acyl-tethered 3-hydroxy oxetane building blocks **71** using Lewis- or Brønsted acid catalysis. As described in the below synthetic strategy (Scheme 2.12), this method proceeds through the initial activation of the strained oxetane ring with the aid of Lewis- or Brønsted acid, which triggers the intramolecular carbonyl (nucleophile-mediated) ring-closure (5-membered), and ring-opening (4-membered) sequence, and generates cyclic oxacarbenium. Subsequent dehydrative aromatization results in hydroxymethylated-furan intermediate **72**. This hydroxy-methylated furan **72** can be used as a key and divergent building block for the construction of all shikonofurans in a maximum number of 7 steps (Scheme 2.12).



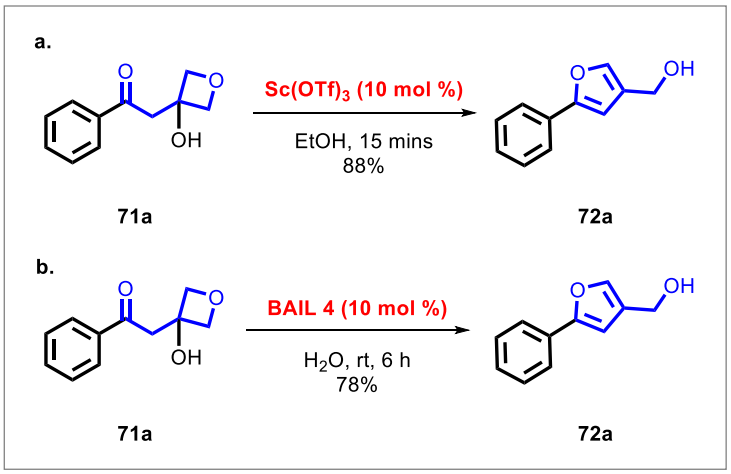
Scheme 2.12 | Concept of polysubstitutedfuran formation from Lewis- or Brønsted-catalyzed dehydrative cycloisomerization of α-hydroxy oxetane-tethered ketones.

2.2.2. Result and discussions

To realize our projected hypothesis, we synthesized a known α-hydroxy oxetane-tethered ketone **71a** building block. We performed the reaction using previously reported $Sc(OTf)_3$ (10 mol %) as a catalyst in EtOH, which delivered the

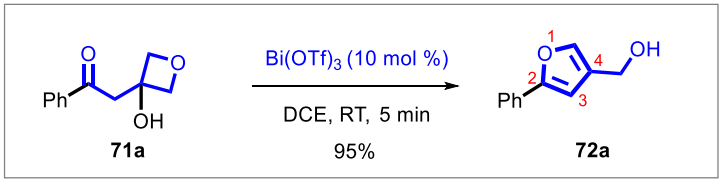
product **72a** in 88% yield in 15 minutes (entry a, Scheme 2.13). Next, we tested the reaction profile using ionic liquid BAIL-4 in water, this reaction was very sluggish and gave the hydroxymethylated product **72a** in 78% in 6 h (entry b. Scheme 2.13).

Taking into consideration of drawbacks of these strategies, like expensive Scandium catalysis, tedious work-up procedures using BAIL-4 in water, and longer reaction times, we aimed at developing a facile and rapid methodology to construct 2,4-disubstituted furans using acyl-oxetane as a building block utilizing cost-effective and efficient catalytic systems and its subsequent application in enantioselective total synthesis of shikonofurans (Scheme 2.13).



Scheme 2.13 | Initial synthesis of the 2,4-disubstituted furan **72a** using known protocols.

Inspired by the suitable catalytic property of $Sc(OTf)_3$ for this transformation (however limited to a single example) and our group's continuing interest in bismuth catalysis, we intended to verify the catalytic profile of $Bi(OTf)_3$ in this reaction. To our delight, the expected 2,4-disubstituted furan **72a** was isolated in an excellent yield (99%) from **71a** within five minutes using 10 mol % of $Bi(OTf)_3$ in dichloromethane at room temperature. The structure of **72a** was unambiguously determined by proton, carbon NMR, and mass spectrometry (Scheme 2.14).



Scheme 2.14 | Initial synthesis of 2,4-disubstituted furan **72a** using bismuth triflate.

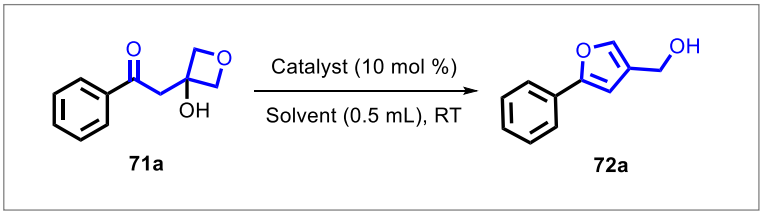
2.2.3. Further optimization of reaction conditions

We further explored the feasibility of this transformation using other Lewis acid and Brønsted acid catalysts. Considering the wide range of organic small molecules solubility in dichloromethane (DCM), dichloroethane (DCE), and methanol, all shortlisted catalysts were screened using these solvents. Since excellent results were obtained using $Bi(OTf)_3$, tested the reaction using other bismuth salts $BiCl_3$, $Bi(NO_3)_3.5H_2O$ in DCE, which delivered the desired product in good yields albeit in a little longer reaction time of 2 h. The reaction using the AgOTf catalyst was very slow, giving the product a 44% yield even after 6 h. Next, tested the efficiency of iron salts [$Fe(OTf)_3$, $Fe(ClO_4)_2$, $FeSO_4.7H_2O$] as catalysts, which was found to be moderately active toward this transformation, whereas, $Ni(OTf)_2$ was unable to promote the reaction. $BF_3.Et_2O$ delivered the product in 75% yield after 6 h. Then screened the reaction using Brønsted acid catalysts *p*-TSA, TFA, and TfOH in DCE, all of them were found to facilitating the reaction, TfOH delivered the product in excellent yield of 91% in 5 min with little decomposition.

Next, we screened same set of Lewis acid catalysts using polar and proteic solvent MeOH, in which reactions found to be faster compared to DCE, still, little decomposition was observed on TLC, which led to moderately compromising yields. Similarly, Brønsted acid catalysts pTSA, TFA, and TfOH in MeOH delivered the desired product **72**a in moderate to good yields.

TfOH is a usual contaminant associated with triflate-based Lewis acid catalysts and is solely responsible for the catalytic activity in some instances (Entry 19 vs 23), and is known to be responsible for side reactions owing to its (TfOH) high acidity. Due to the rapid reaction (within ~1 min), clean reaction profile, and excellent isolated yields using $Bi(OTf)_3$ as the catalyst, we strongly believe in the role of bismuth in this transformation, and owing to its great natural abundance, and non-toxic nature, we have chosen $Bi(OTf)_3$ as a reliable catalytic system for this work instead of closely potent TfOH and other Lewis acids.

Table 2.2 | Optimization of reaction conditions[a,b]



71a **72a**

Entry	Catalyst	Solvent	Time	Yield[b]
A	Screening of Lewis acids catalysts in DCE			
1)	$Bi(OTf)_3$	DCE	5 min	95
2)	$BiCl_3$	DCE	2 h	93
3)	$Bi(NO_3)_3.5H_2O$	DCE	2 h	87
4)	AgOTf	DCE	6 h	44
5)	$Fe(OTf)_3$	DCE	6 h	80
6)	$Fe(ClO_4)_2$	DCE	8 h	45
7)	$FeSO_4.7H_2O$	DCE	1 h	77
8)	$Ni(OTf)_2$	DCE	24 h	N.R[c]
9)	$BF_3.Et_2O$	DCE	6 h	75
B	Screening of Brønsted acid catalysts in DCE			
10)	*p*-TSA	DCE	40 mins	91
11)	TFA	DCE	6 h	88
12)	TfOH	DCE	5 min	91
C	Screening of Lewis acids catalysts in MeOH			
13)	$Bi(OTf)_3$	MeOH	5 min	95
14)	$BiCl_3$	MeOH	30 mins	90
15)	$Bi(NO_3)_3.5H_2O$	MeOH	3 h	85
16)	$BF_3.Et_2O$	MeOH	1 h	71
17)	$Fe(OTf)_3$	MeOH	15 mins	89
18)	$Fe(OTf)_2$	MeOH	16 h	41
19)	$FeSO_4.7H_2O$	MeOH	3 h	73
20)	$Ni(OTf)_2$	MeOH	24 h	N.R[c]
21)	$BF_3.Et_2O$	MeOH	1 h	71
D	Screening of Brønsted acid catalysts in MeOH			
22)	*p*-TSA	MeOH	40 mins	86
23)	TFA	MeOH	12 h	75
24)	TfOH	MeOH	15 min	93

[a]Reaction conditions unless otherwise specified: **71a** (0.5 mmol) and catalyst (10 mol%) solvent (0.5 mL) at room temperature (RT). [b]Isolated yields of **72a**. [c]N.R = No Reaction. Tf = triflate (CF_3SO_2).

In subsequent optimization studies, the compatibility of various solvents, THF, DMSO, DMF, toluene, and diethyl ether, delightfully was investigated, in which many solvents were found to be reliable for this transformation except DMF & DMSO. However, a very clean reaction profile and isolated yields were observed using DCM (Table 2.2.1). Next, altered the mol % (loading) of $Bi(OTf)_3$ (using optimized solvent (DCM)), where a decrease in the catalyst loading led to an increase in reaction time and a low isolated yield of the product (Table 2.2.2).

Table 2.2.1 | Solvent screening using $Bi(OTf)_3$ (10 mol%)[a,b]

Entry	Solvent	Time	Yield of 72a (%)
1)	MeOH	5 min	95

2)	DCE	5min	95
3)	DCM	5 min	99
4)	THF	15 min	96
5)	DMSO	6 h	N.R[c]
6)	DMF	6 h	N.R[c]
7)	Toluene	5 min	93
8)	Et_2O	15 min	95

[a]Reaction conditions unless otherwise specified: **71a** (0.5 mmol) and catalyst (10 mol%) solvent (0.5 mL) at room temperature (RT). [b]Isolated yields of **72a**. [c]N.R = No Reaction.

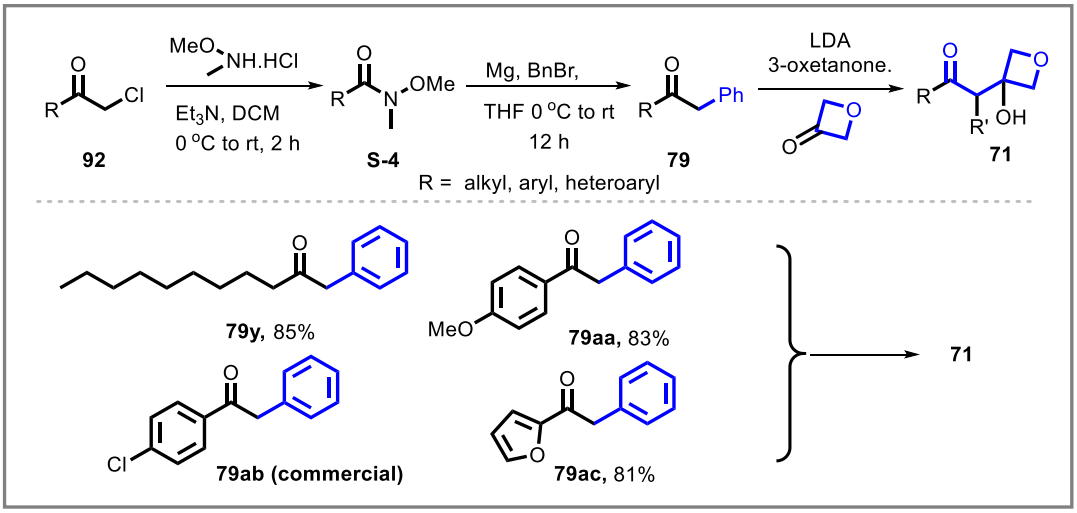
Table 2.2.2 | Screening of $Bi(OTf)_3$ loading using DCM as an optimal solvent [a,b]

Entry	$Bi(OTf)_3$ loading	Time	Yield of 72a (%)
1)	10 mol%	5 min	99
2)	5 mol%	30 min	85
3)	2 mol%	3 h	65
4)	1 mol%	24 h	30

[a]Reaction conditions unless otherwise specified: **71a** (0.5 mmol) and DCM (0.5 mL) at room temperature (RT). [b]Isolated yields of **72a**. [c]N.R = No Reaction.

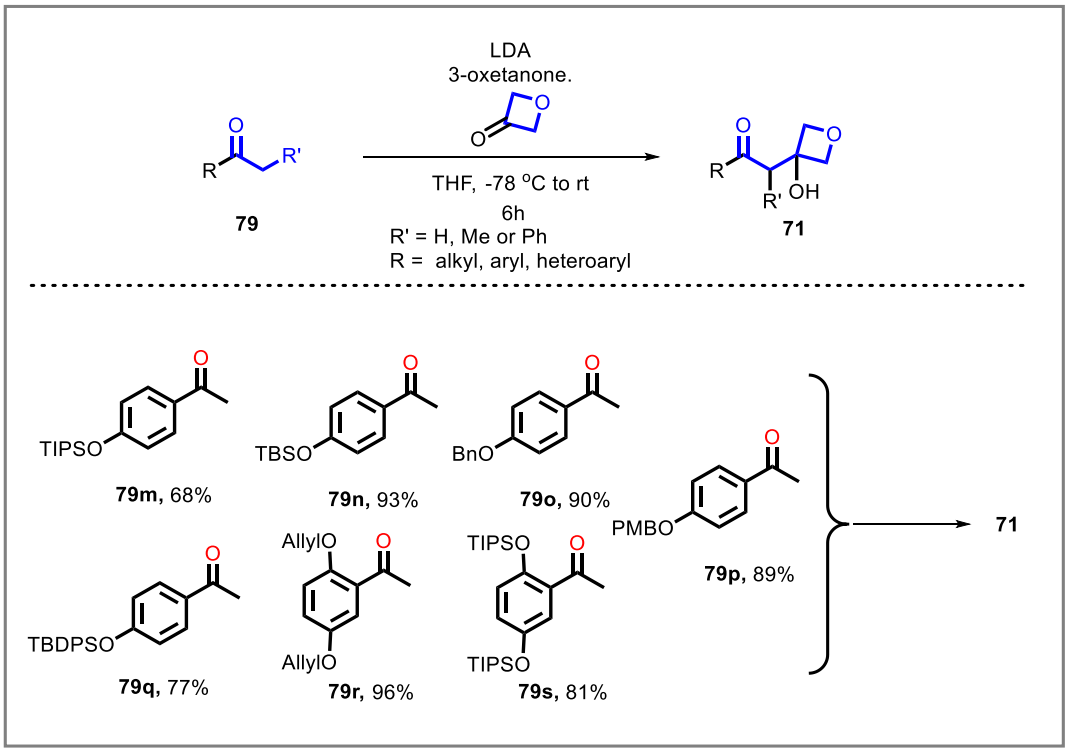
2.2.4. Synthesis of α-hydroxy oxetane-tethered ketone building blocks (71):

a) From acid chlorides (92): To investigate the generality of this methodology, synthesized diverse α-hydroxy oxetane-tethered ketones **71** (substrates of this methodology) in a three-step sequence starting from acyl-halides **92**. Acyl-halide **92** was treated with NMe(OMe).HCl salt in the presence of Et_3N in DCM solvent to form its Weinreb amide salt, which was in situ treated with diverse Grignard reagents to obtain their alkyl-ketone analogs **79**. Next, an LDA-mediated aldol reaction of **79** with commercially available 3-oxetanone gave desired α-hydroxy oxetane-tethered ketones **71** (Scheme 2.15).

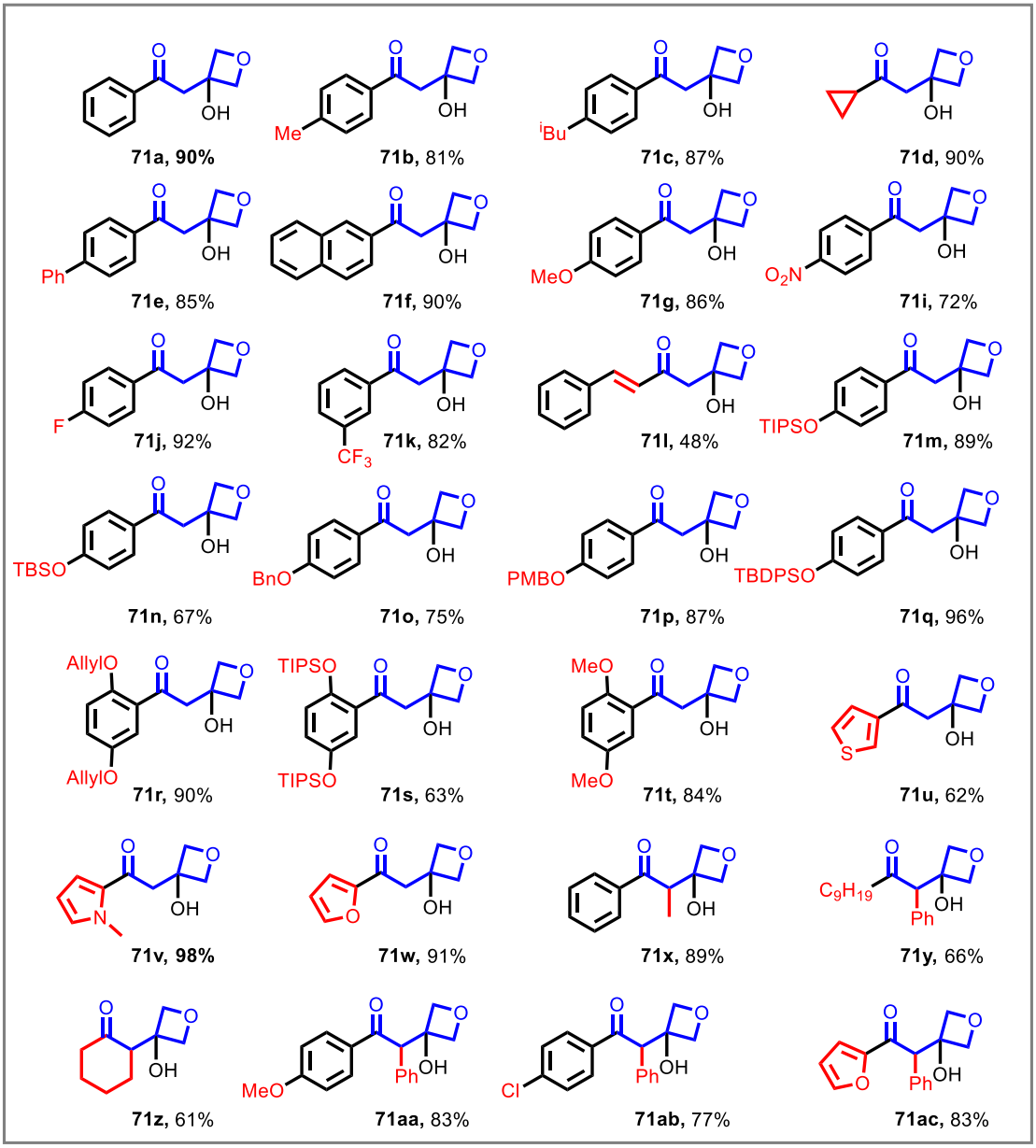


Scheme 2.15

b) From ketones (79): Several commercially available ketones were converted into corresponding α- hydroxy oxetane-tethered ketones **71** through L-enolate addition to the oxetanone. Using this strategy, diverse protected acetophenones (with TIPS, TBS, TBDPS, benzyl, PMB, and allyl groups) were prepared from 4-hydroxy acetophenone and 2,5-dihydroxy acetophenones and used to obtain corresponding α-hydroxy oxetane-tethered ketones **71** (Scheme 2.16 and 2.17).



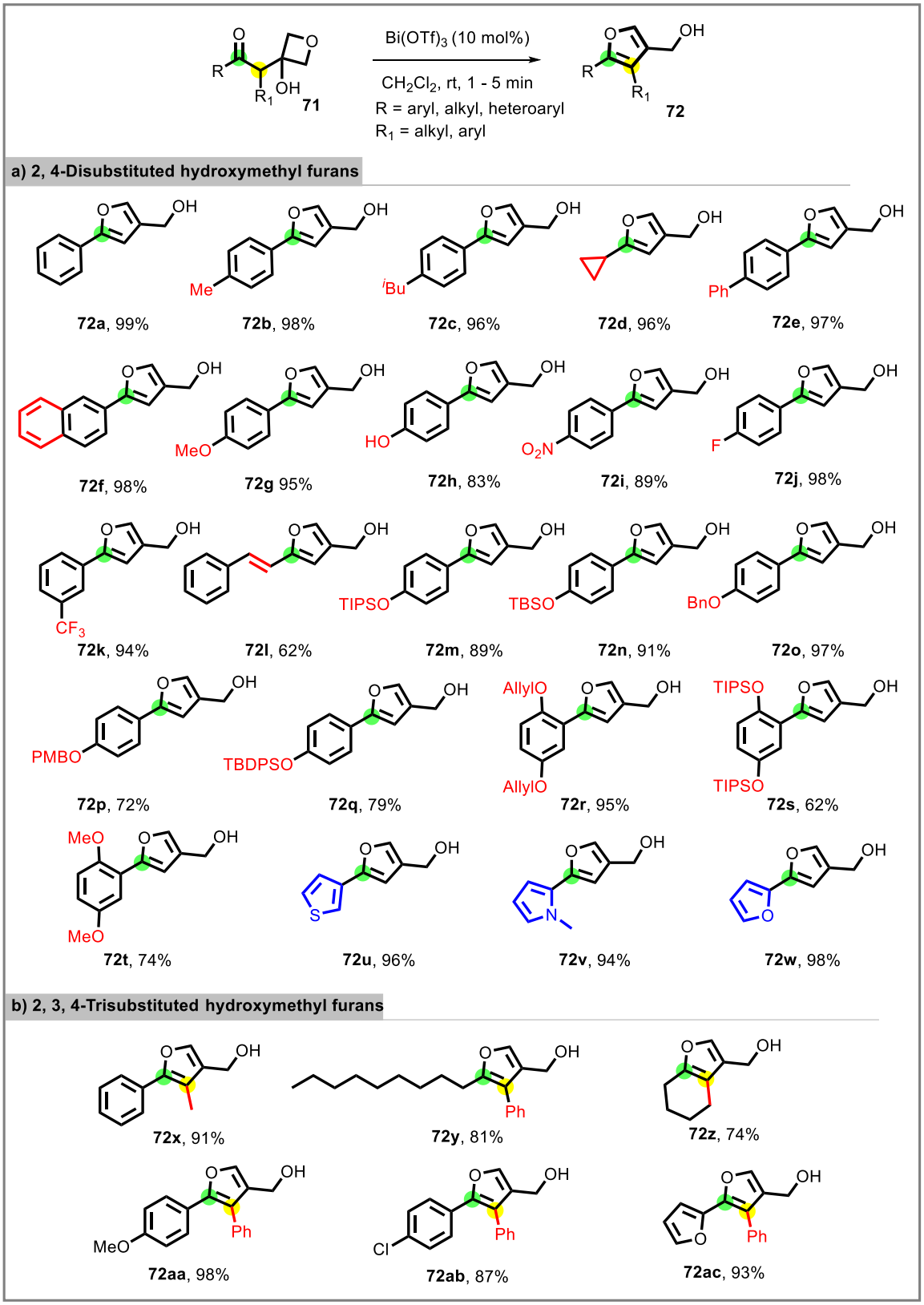
Scheme 2.16



Scheme 2.17. List of α- hydroxy oxetane-tethered ketones **71** synthesized.

2.2.5. Scope and generality of the reaction (Furan 72 synthesis):

With the optimal conditions established, the substrate scope concerning the construction of 2,4 disubstituted and 2,3,4-trisubstituted furans **72** from α-hydroxy oxetane-tethered ketones **71** is described in Scheme 2.18. Substrates having substituted aryl-ketone moiety (**71**, *t*-Bu, cyclopropyl substituted phenyl, and biphenyl, naphthyl and OMe) furnished the corresponding disubstituted furan **72a-72g**) in good to moderate yields (97-98%). Substrates possessing electron-withdrawing groups (OH, NO_2, F and CF_3,) also delivered desired products (**72h-72k**)



Scheme 2.18. Synthesis of 2,4-disubstituted and 2,3,4-trisubstituted furans

in good yields of 83%, 89%, 98% and 94% respectively. Styrene-derived substrate was also found to be a suitable substrate for this reaction and delivered corresponding furan 72l in a good yield of 62% (entry 12, Scheme 2.18).

Next, the compatibility of aryl ketone-derived substrates having diverse protecting groups (-OTIPS, -OTBS, -OBn, -OPMB, -OTBDPS, -OAllyl and -OMe) were tested, delightfully, all delivered respective furans (**72m**-**72t**) in good to excellent yields. diverse protecting groups were found to be compatible under these optimized conditions (entry 13-20, Scheme 2.18).

To our delight, substrates consisting of heteroaryl-ketone (thiophene, N-methyl pyrrole, and furan-derived) gave corresponding bis-heterocycles **72u**-**72w** in very good yields (entry 21-23, Scheme 2.18).

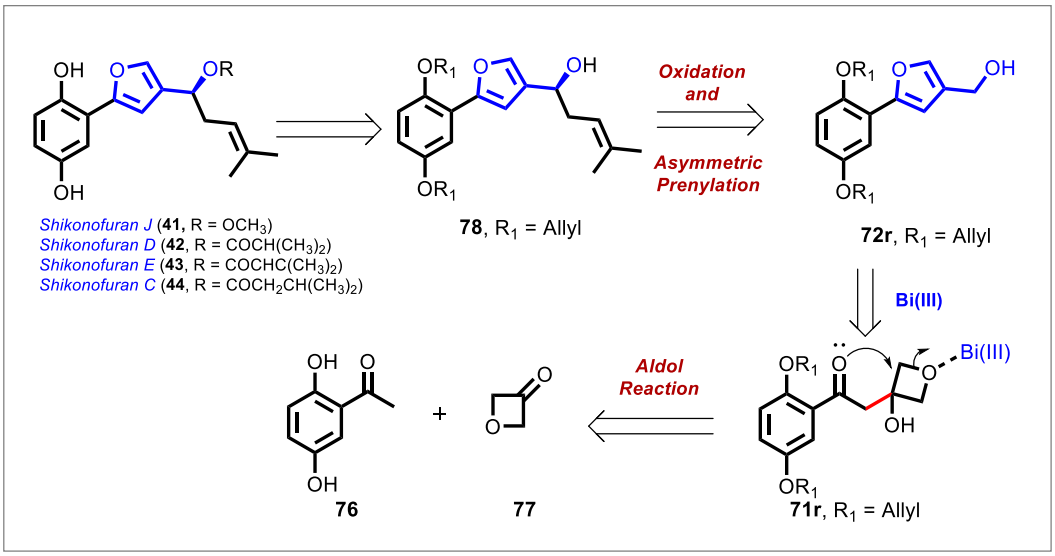
Then, we focused on the preparation of 2,3,4-trisubstituted furans **72** under optimal reaction conditions. To our delight, all these reactions delivered products containing C2-alkyl, aryl, and heteroaryl & C3-H, aryl substituents (**72x**-**72ac**) in good to excellent yields (74-98%) in shorter reaction time (1-5 min) (entry 24-29, Scheme 2.18).

In conclusion, we have established a rapid, efficient, and operationally simple synthetic strategy for the construction of hydroxymethyl-tethered di- or trisubstituted furans using environmentally benign and cost-effective $Bi(OTf)_3$ as a catalytic system. The generality of this method was showcased through the construction of diverse furans containing, alkyl, cycloalkyl, aryl, and heteroaryl substituents. Moreover, diverse acid-sensitive protecting groups were found to be extremely stable under optimized reaction conditions. As we hypothesized, this methodology was effectively employed in the total synthesis of bioactive natural products, shikonofurans (*vide infra*).

2.2.6. Retrosynthetic analysis of shikonofurans (41-44)

After the successful establishment of the general synthetic strategy for the construction of hydroxymethyl-tethered furans, we turned our interest toward the stereoselective total synthesis shikonofurans J, D, E, and C (**41**-**44**, with varying oxygen-substituents of ether/ester groups) based on the retrosynthetic analyses described in Scheme 2.19. Shikonofurans could be accessed from substituted arene

containing hydroxyalkyl furan **78** via methylation (for shikonofuran J) or esterification (for shikonofuran C-E) using suitable carboxylic acids followed by deprotection steps. Intermediate **78** could be obtained from 2,4-disubstituted furan **72r** through initial oxidation to give the corresponding aldehyde followed by TRIP-catalyzed asymmetric prenylation. This key intermediate **72r** (hydroxymethyl-tethered furan) synthesized as part of our investigation in the previous section (Bi(III)-catalyzed dehydrative-cycloisomerization of α-hydroxy oxetane-tethered ketone **71r**) (Scheme 2.19).

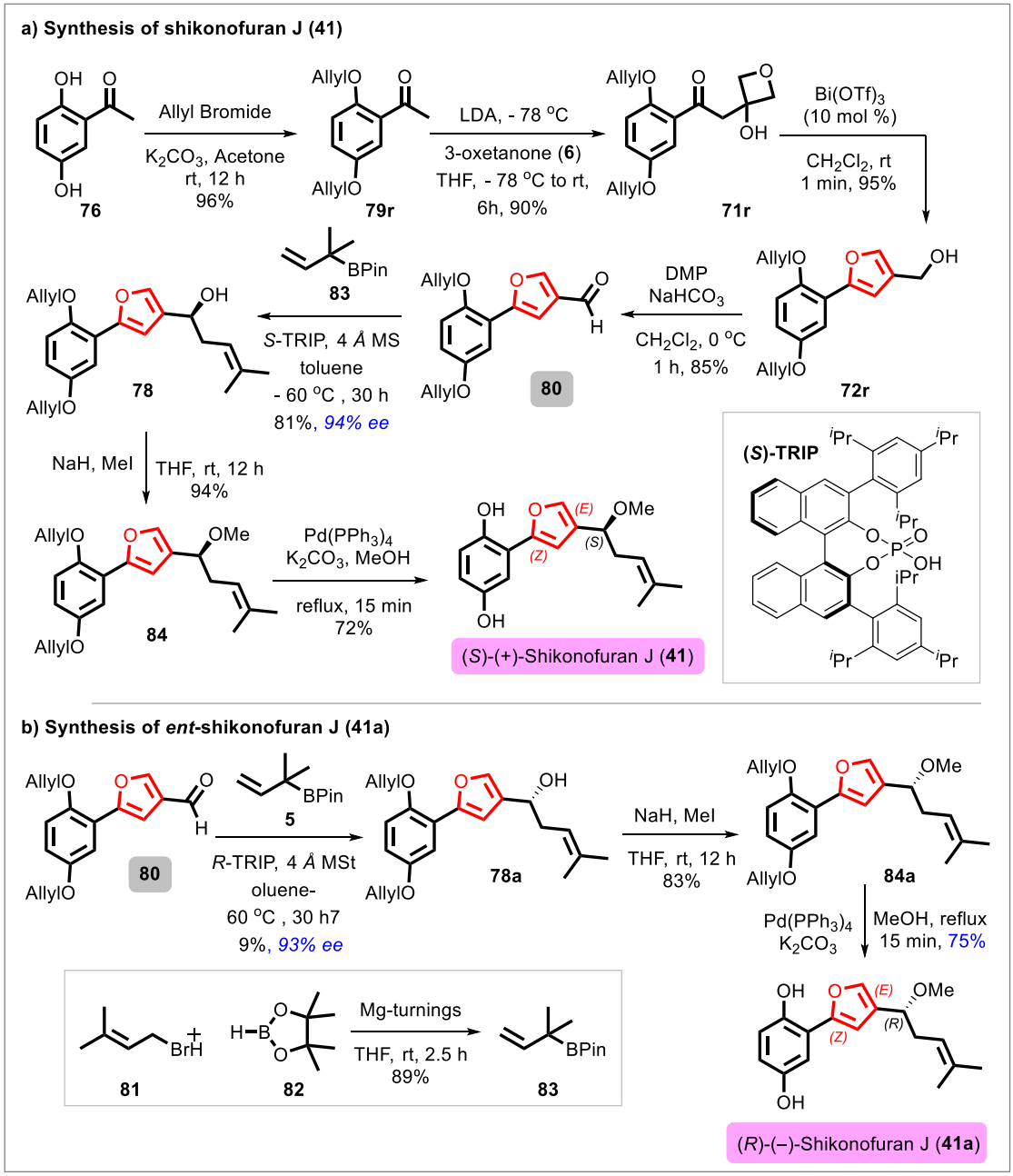


Scheme 2.19 | Common retrosynthetic analysis of shikonofurans **41**-**44**.

2.2.6.1. Synthesis and absolute configuration of shikonofuran J (41):

Our studies started with enantioselective total synthesis of the reported structure of shikonofuran J (**41**), starting from commercially available 2,5-dihydroxy acetophenone (**76**). Allyl protection[37] of **76** using allyl bromide in the presence of K_2CO_3 gave **79r**, and subsequent LDA-mediated aldol reaction with 3-oxetanone (**77**) gave the requisite aldol product **71r** in 90% yield. Next, the oxetane intermediate **71r** was subjected to our in-house developed methodology of $Bi(OTf)_3$-catalyzed dehydrative cycloisomerization reaction, which cleanly furnished the desired hydroxy-methylated furan **72r** in 95% yield in 5 min. Then, **72r** was oxidized to aldehyde **80** using Dess–Martin periodinane (DMP),[35] and subsequently subjected to asymmetric prenylation reaction using chiral phosphoric acid[38] [(*S*)-TRIP] and prenyl-pinacol-boronate **83** to get the anticipated chiral alcohol **78**, which was used

as a common intermediate for all shikonofurans. Then methylation[39] of alcohol **78** using NaH and MeI to give **84**. Ultimately, $Pd(PPh_3)_4$-catalyzed allyl deprotection[40] of both allyl groups of 84 delivered shikonofuran J (**41**) in 72% yield (entry a, Scheme 2.20).



Scheme 2.20 | Total synthesis of shikonofuran J (**41**) and its enantiomer **41a**.

^1H and ^{13}C NMR data of synthesized shikonofuran J (**41**) was in complete agreement with that of the reported data (isolated natural product **41**). To our surprise, the optical rotation value of **41** [$[\alpha]^{26.6}{}_D$ = +7.07 (*c* = 0.5, MeOH), this work]

was found to be opposite to the reported value of natural shikonofuran J (**41**) [$[\alpha]^{12}{}_{D}$ =−11.3 (*c* = 0.3, MeOH)].

Hence, utilizing a similar strategy that was used for the synthesis of (+)-shikonofuran J (**41**), we have obtained its enantiomer (*ent*-shikonofuran J; **41a**) using [(*R*)-TRIP] ligand in the conversion of common intermediate **80** into its prenylated product **78a**, and its subsequent methylation and allyl deprotection steps.

Surprisingly, the optical rotation data of **41a** [$[\alpha]_D^{27.13}$= –7.63 (*c* = 0.5, MeOH)] was found to be very close to the reported data (entry b, Scheme 2.20). To further verify the authenticity of the reported optical rotation data and absolute stereochemistry of shikonofuran J [**(*S*)-41**], we further carried out ECD analyses of [**(*S*)-41**] and **(*R*)-41a** and compared them with the reported ECD data. Where (*S*)-(+)-shikonofuran J ([**(*S*)-41**], this work) showed a negative Cotton effect (CE; CD, 4.3 x 10-4 M, MeOH) and a positive Cotton effect at λmax 213 nm (Δε = +0.187), which was in agreement with the data reported for (*S*)-isomer) of shikonofuran J (**41**, isolated), while the **(*R*)-41a** showed opposite ECD data compared to **41** (CD, 4.3 x 10-4 M, MeOH, λmax (Δε) 283 (−0.018), 245 (+0.026) and 213 (−0.312) nm) (Figure 2.4). These investigations established the absolute stereochemistry of shikonofuran J as (*S*)-(+)-shikonofuram J (**41**) (Figure 2.4).

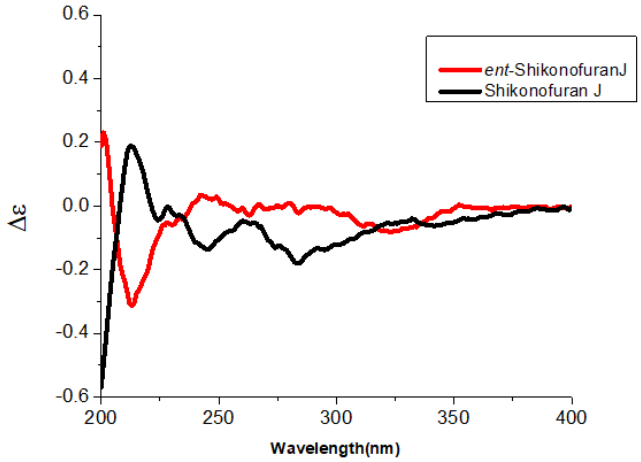


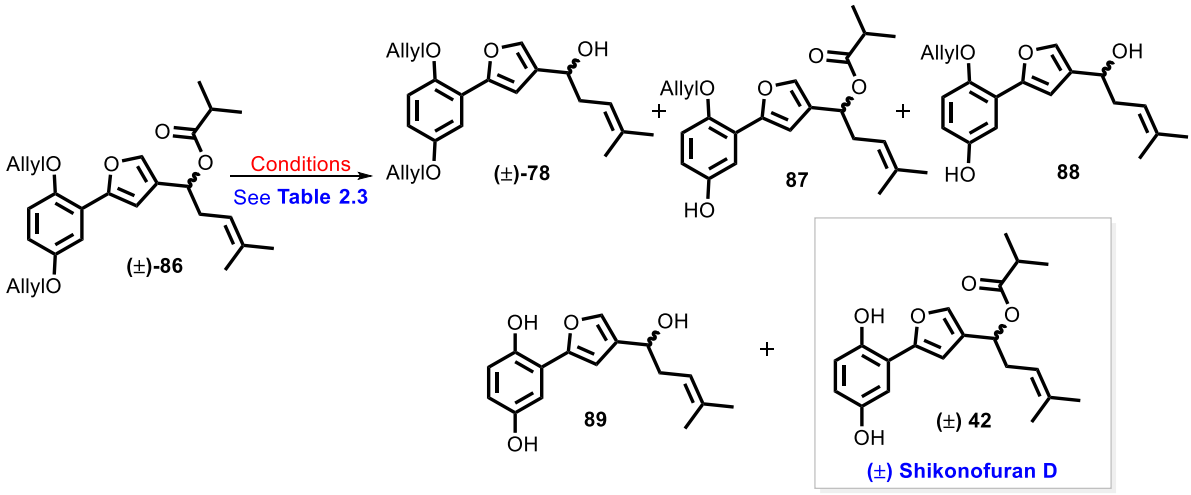
Figure 2.4: | ECD spectra of Shikonofuran J [**(*S*)-41**] and *ent*-Shikonofuran J [**(*R*)-41a**].

2.2.6.2. Synthesis and absolute configuration of shikonofuran D (42):

After the successful synthesis and establishing the absolute configuration of shikonofuran J (**41**), we embarked on the total synthesis of shikonofurans D, E, and C,

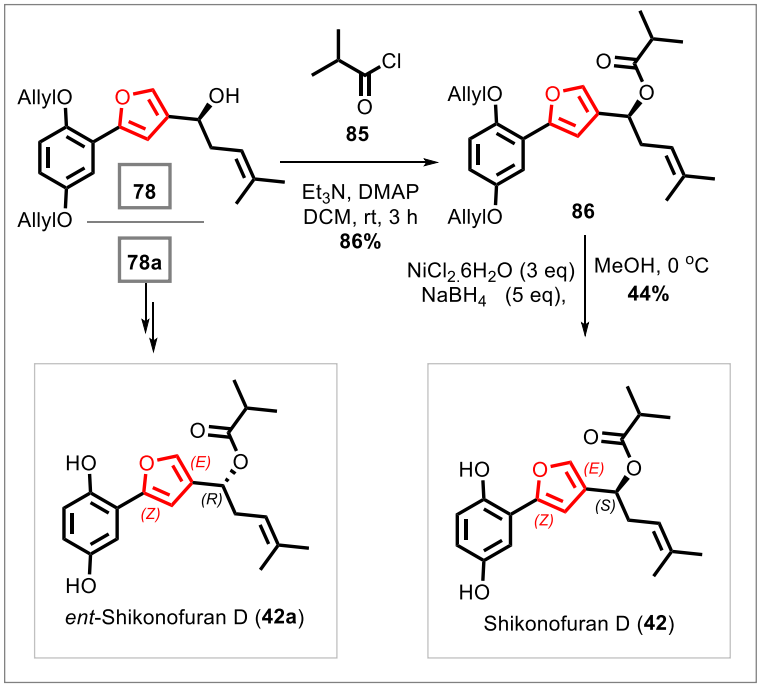
and their antipodes utilizing common intermediates **78** and **78a**. Thus, the hydroxyalkyl furan intermediate **78** (possessing the desired stereochemistry of natural products; reported data) was treated with isobutyryl chloride **85** in the presence of Et_3N, and DMAP to afford the corresponding ester **86** in 86% yield.

Table 2.3. Optimization of reaction conditions for allyl deprotection



Entry	Conditions	(±)-78	87	88	89	(±) -42	SM (±) -(86)
1.	$Pd(PPh_3)_4$ (10 mol%), K_2CO_3, MeOH, reflux , 15 min	-	-	-	90%	-	-
2.	$Pd(PPh_3)_4$ (10 mol%), K_2CO_3 (3 eq), MeOH, rt, 3 h	60%	-	40%	-	-	-
3.	$Pd(PPh_3)_4$ (10 mol%), pyrrolidine (1 eq), DCE, rt, 5 h	5%	20%	-	-	-	75%
4.	$BiCl_3$ (1 eq) + $NaBH_4$ (1 eq), THF, 0 °C to rt, 2 h	10%	-	-	-	-	90%
5.	$CeCl_3.7H_2O$ (1.5 eq), NaI (1.5 eq), MeCN, rt, 24 h	-	5%	-	-	-	95%
6.	$Pd(PPh_3)_4$ (20 mol%), $NaBH_4$ (1.5 eq), THF, 0 °C to rt, 1 h	20%	20%	-	-	-	60%
7.	LiCl (1 eq), $NaBH_4$ (1 eq), THF, 0 °C to rt, 24 h	50%	10%	10%	-	-	trace
8.	$Pd(PPh_3)_4$ (10 mol%), K_2CO_3 (3 eq), dioxane, rt, 48 h	-	-	-	-	-	100%
9.	$NiCl_2.6H_2O$ (3 eq), $NaBH_4$ (5 eq), MeOH, 0 °C to rt, 10 min	10%	10%	-	-	40%	-
10.	$Pd(OH)_2/C$ (10 mol%), Pd/C (10 mol%), iPrOH, 80 °C, 12 h	50%	10%	-	-	-	40%
11.	Cs_2CO_3 (1 eq), $Pd(PPh_3)_4$ (10 mol%), THF, rt, 48 h	-	-	-	-	-	100%

Then our next target was to deprotect the allyl groups in **86** employing well-established reaction conditions of $Pd(PPh_3)_4$, K_2CO_3, MeOH at various temperatures, unfortunately, all attempts in this line were proved to be unsuccessful (Scheme 2.22). Hence, synthesized *racemic*-**86**, and optimized reaction conditions for the allyl deprotection as described in Table 2.23. Reactions using $Pd(PPh_3)_4$ /$Pd(OH)_2$[41] and diverse bases[42], $Pd(PPh_3)_4$-$NaBH_4$[43], LiCl-$NaBH_4$[44], and $CeCl_3.7H_2O$-NaI[45], led to the ester hydrolysis and non-selective deprotected products. After extensive experimentation, $NiCl_2.6H_2O$ (3 eq), $NaBH_4$ (5 eq), MeOH, 0 °C to rt conditions[46] were found to be fruitful by providing the desired shikonofuran D (*rac*-**42**, in a moderate yield of 44%, along with a few unidentified and inseparable products (Table 2.3).



Scheme 2.21 | Efforts towards the total synthesis of shikonofuran D (**42**) and its enantiomer **42a**.

Employing these optimal reaction conditions for allyl deprotection, shikonofuran D (**42**, reported structure) was obtained form **86**. Similarly, common intermediate **78a** (an enantiomer of **78**, that was used in the synthesis of ent-shikonofuran J) was converted into *ent*-shikonofuran D (**42a**) in two steps (Scheme 2.21).

Surprisingly, the optical rotation data of **42a** $[[\alpha]_D^{26.54}$ = +26.19 (*c* = 1.3, $CHCl_3$)] was found to be very close to the reported data which is $[[\alpha]_D^{20}$ = +56 (c = 0.1, $CHCl_3$) (Scheme 2.21). To further verify the authenticity of the reported optical

rotation data and absolute stereochemistry of shikonofuran D [**(*S*)-42**], we further carried out ECD analyses of [**(*S*)-42**] and **(*R*)-42a**, where (*S*)-(+)-shikonofuran D ([**(*S*)-42**], this work) showed a negative Cotton effect (CE; CD, 4.3 x 10-4 M, MeOH) at λmax 322 nm (Δε = -1.10), 274 nm (-1.29) and 204 nm (-3.23) while the **(*R*)-42a** showed opposite ECD data compared to **42** (CD, 4.3 x 10-4 M, MeOH, λmax (Δε) 323 nm (+1.39), 267 nm (+6.00) and 207 nm (+2.50) (Figure 2.5).

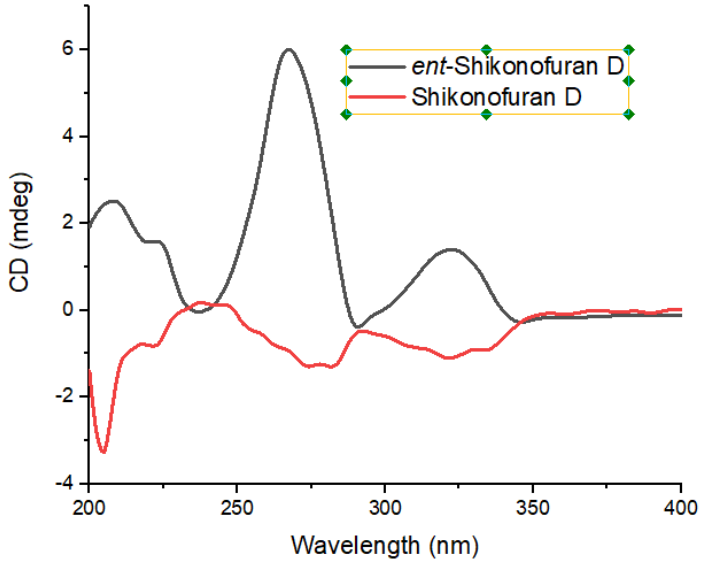
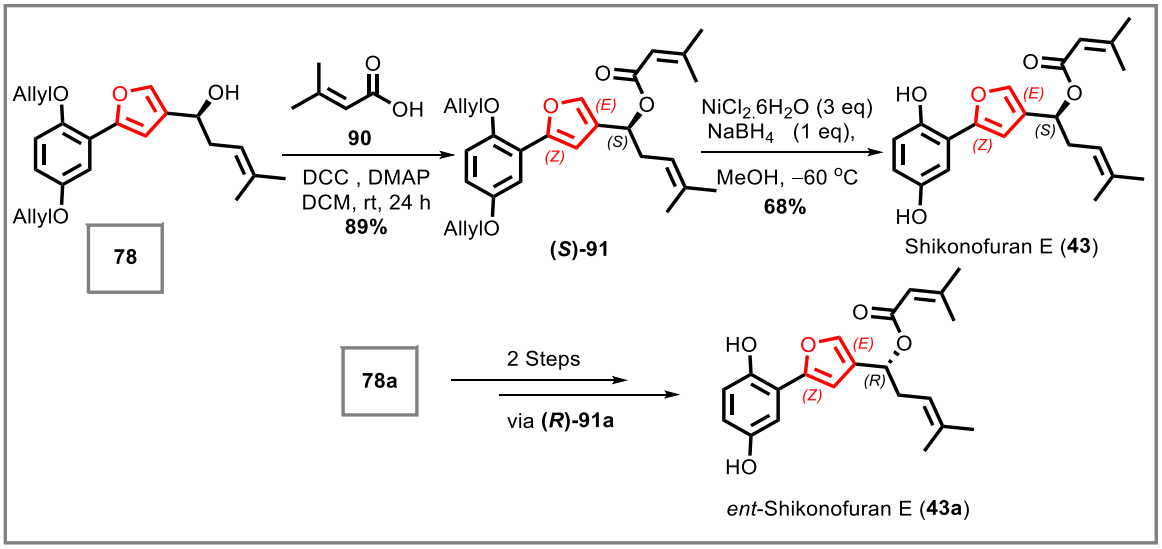


Figure 2.5. | ECD spectra of Shikonofuran D [**(*S*)-42**] and *ent*-Shikonofuran D [**(*R*)-42a**].

2.2.6.3. Synthesis and absolute configuration of shikonofuran E (43):

To synthesize the reported structure of shikonofuran E (**43**), the alcohol **78** was subjected to esterification using commercially available 3-methylbut-2-enoic acid (**90**) under DCC and DMAP conditions to get the corresponding ester **91**, which served as a common precursor for both the natural products shikonofuran E and C. Subsequent phenolic allyl deprotection using $NiCl_2.6H_2O$ and $NaBH_4$ in MeOH at –60 °C delivered shikonofuran E (**43**, reported structure) in 57% yield. Similarly, common intermediate **78a** (an enantiomer of **78**, that was used in the synthesis of ent-shikonofuran J) was converted into *ent*-shikonofuran E (**43a**) in two steps of esterification and allyl deprotection. (Scheme 2.22).



Scheme 2.22 | Enantioselective total synthesis of shikonofuran E (**43**), and its enantiomers (**43a**).

The optical rotation data of [**(*S*)-43**] [$[\alpha]_D^{30.49}$ = -62.40 (*c* = 0.1, $CHCl_3$)] was found to be very close to the reported data which is [$[\alpha]_D^{20}$ = -69 (c = 0.5, $CHCl_3$) (Scheme 2.2). To further verify the authenticity of the reported optical rotation data and absolute stereochemistry of shikonofuran E [**(*S*)-43**], we further carried out ECD analyses of [**(*S*)-43**] and **(*R*)-43a**, where (*S*)-(+)-shikonofuran E ([**(*S*)-43**], this work) showed a negative Cotton effect (CE; CD, 4.3 x 10-4 M, MeOH) at λmax 316 nm (Δε = -

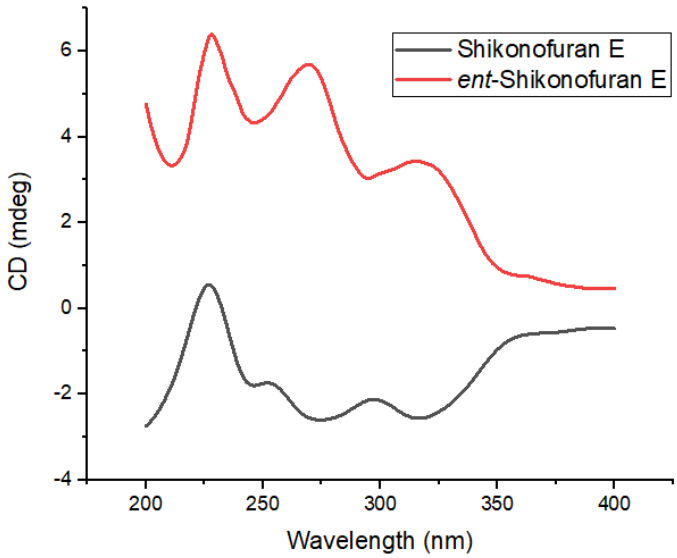
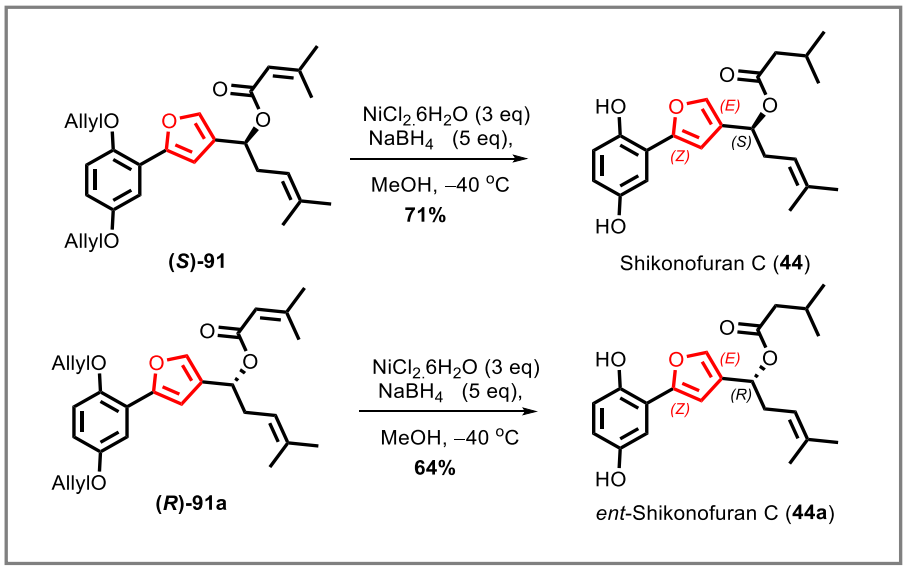


Figure 2.6. | ECD spectra of Shikonofuran E [**(*S*)-43**] and *ent*-Shikonofuran E [**(*R*)-43a**].

2.56), 274 nm (-2.59), 245 nm (-1.79) and a positive Cotton effect at 227 nm (+0.549) while the **(*R*)-43a** showed opposite ECD data compared to **43** (CD, 4.3 x 10-4 M, MeOH, λmax (Δε) 319 nm (+3.39), 270 nm (+5.69), 227 nm (+6.33) and 212 nm (+3.34) (Figure 2.6).

2.2.6.4. Synthesis and absolute configuration of shikonofuran C (44):

While optimizing the allyl deprotection of **91** at various temperatures using $NiCl_2$ and $NaBH_4$, we observed the reduction of the butenoic ester segment at –40 °C, which led to the formation of shikonofuran C (**44**). Utilizing a strategy similar to this, synthesized *ent*-shikonofuran C (**44a**) from **78a** (Scheme 2.23).



Scheme 2.23 | Enantioselective total synthesis of shikonofuran C (**44**), and their enantiomers (**44a**).

Surprisingly, the optical rotation data of **44a** [$[\alpha]_D^{27.96}$ = +57.56 (*c* = 1.1, $CHCl_3$)] was found to be very close to the reported data which is [$[\alpha]_D^{20}$ = +64 (*c* = 0.1, $CHCl_3$) (Scheme 2.23). To further verify the authenticity of the reported optical rota tion data and absolute stereochemistry of shikonofuran C [**(*S*)-44**], we further carried out ECD analyses of [**(*S*)-44**] and **(*R*)-44a**, where (*S*)-(+)-shikonofuran C ([**(*S*)-44**], this work) showed a negative Cotton effect (CE; CD, 4.3 x 10^{-4} M, MeOH) at λmax 321 nm (Δε = -1.76), 283 nm (-1.68), 260 nm (-1.19) and 224 nm (-3.02) while the **(*R*)-44a** showed opposite ECD data compared to **44** (CD, 4.3 x 10^{-4} M, MeOH, λmax (Δε) 321 nm (0.79), 277 nm (+2.82), 269 nm (+4.07) and 220 nm (+2.28) (Figure 2.7).

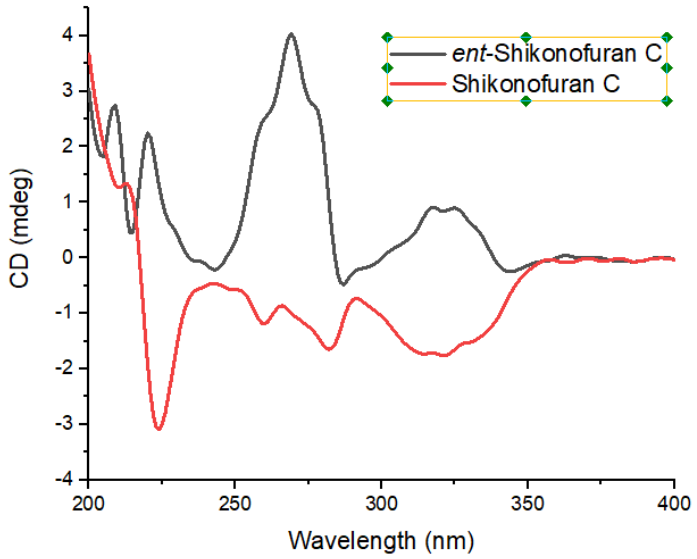


Figure 2.7. | ECD spectra of Shikonofuran C [**(*S*)-44**] and *ent*-Shikonofuran C [**(*R*)-44a**].

In addition to analytical studies like NMR (^{1}H and ^{13}C), MS, optical rotation, ECD, chiral-HPLC data also supported our conclusions on this work.

2.2.7. Conclusion

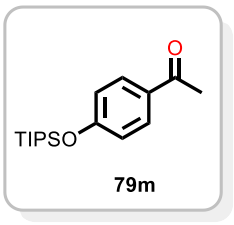
In conclusion, employing a novel methodology developed as part of this work, i.e, Bi(III)-catalyzed dehydrative cycloisomerization of α-hydroxy oxetane-tethered ketones to access hydroxy methyl-tethered furans, we have successfully completed the first enantioselective total synthesis of furyl-hydroquinone-derived antimicrobial natural products, shikonofurans J, D, E, and C in 7 linear steps with 38.24%, 21.4 %, 34.20%, 35.70% overall yield respectively. The absolute stereochemistry of all these natural products was established on the basis of comparison of optical rotation and ECD (electric circular dichroism) analyses. Biological activity investigations of all-natural products and their enantiomers are in progress.

2.2.8. Experimental procedures and data:

General Information: All reactions were performed under an argon atmosphere with an oven (80 °C) or flame-dried glassware with a septum seal. Tetrahydrofuran (THF) was distilled from sodium benzo-phenone under an argon atmosphere immediately prior to use. Anhydrous toluene and dichloromethane were purchased

from commercial sources. Reaction temperatures are reported as the temperature of the bath surrounding the reaction vessel. Analytical thin layer chromatography (TLC) was performed on TLC Silica gel 60 F254. Visualization was accomplished with short-wave UV light, anisaldehyde, or $KMnO_4$ staining solutions, followed by heating. chromatography was performed on silica gel (100-200 mesh) by standard techniques eluting with solvents as indicated. ^1H and ^{13}C NMR spectra were recorded on Bruker AV 200, 400, and 500 in solvents as indicated. Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δ H = 7.26 ppm, δ C = 77.16 ppm), the following abbreviations were used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublet; td, triplet of doublet; and br, broad. HRMS data were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump. . ECD spectra were recorded on a JACSO J-815 CD spectrometer. Chiral HPLC separations were achieved using an Agilent 1260 Infinity series normal phase HPLC unit and HP Chemstation software with Chiralpak Diacel columns (250 mm × 4.6 mm). Experimental procedures for all new compounds and known compounds without published experimental procedures are described below.

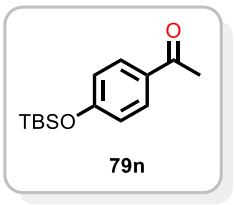
1-(4-((Triisopropylsilyl)oxy)phenyl)ethan-1-one (79m). To the 4'-hydroxy acetophenone (1 g, 7.34 mmol) in dry dichloromethane (10 mL) imidazole (1.24 g, 18.3 mmol) were added, and the reaction was stirred for 10 minutes. Then TIPSCl (1.88 g, 8.81 mmol) were added dropwise and the reaction was stirred up to starting material was completely consumed (5h). After completion of the reaction, it was quenched with water, the aqueous layer was extracted with DCM (10 mL x 3), dried over Na_2SO_4, filtered, and concentrated and the crude product was purified using silica gel column chromatography to afford the desired product **79m** (1.45 g, 68%) as a colourless liquid. (TLC: R_f = 0.8 (SiO_2, 10% EtOAc/ hexanes). IR (neat) 3891, 3777, 3665, 3441, 3359, 3175, 2961, 2883, 2388, 2336, 1823, 1678, 1600, 1524, 1469, 1373, 1274, 1174, 1077, 1008, 900, 833, 673 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91-7.81 (m, 2H), 6.95-6.85 (m, 2H), 2.54 (s, 3H), 1.35-1.21 (m, 3H), 1.11 (s, 9H), 1.05 - 1.10 (m, 9H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 197.0, 160.8, 130.7, 130.7, 119.8,



79m

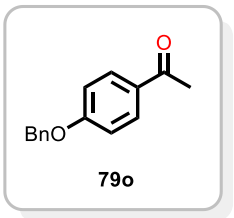
119.8, 26.5, 18.0, 17.8, 12.8; HRMS (ESI): *m/z* calcd for $C_{17}H_{29}O_2Si$ $[M+H]^+$ 293.1931, found 293.1933.

1-(4-((*Tert*-butyldimethylsilyl)oxy)phenyl)ethan-1-one (79n). To the 4'-hydroxy acetophenone (1 g, 7.34 mmol) in dry DMF (10 mL), imidazole (1.49 g, 22.0 mmol) was added, and the reaction was stirred for 10 minutes. Then TBSCl (1.90 g, 11.0 mmol) was added, and the reaction was stirred overnight at room temperature. The reaction progress was monitored by TLC. After completion of the reaction, it was quenched with water, the aqueous layer was extracted with DCM (10 mL x 3), dried over Na_2SO_4, filtered, and concentrated and the crude product was purified using silica gel column chromatography to afford the desired product **79n** (1.7 g, 93%) as white solid. (TLC: R_f = 0.8 (SiO_2, 10% EtOAc/ hexanes). IR (neat) 3682, 2949, 2862, 1673, 1596, 1513, 1472, 1363, 1266, 1112, 1015, 918, 672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93-7.84 (m, 2H), 6.91-6.82 (m, 2H), 2.55 (s, 3H), 0.98 (s, 10H), 0.23 (s, 6H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 197.0, 160.4, 131.0, 130.6, 120.0, 26.5, 25.7, 18.4, -4.2; HRMS (ESI): *m/z* calcd for $C_{14}H_{23}O_2Si$ $[M+H]^+$ 251.1462, found 251.1461.



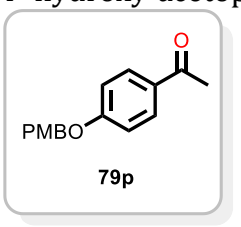
79n

1-(4-(Benzyloxy)phenyl)ethan-1-one (79o). To the 4'-hydroxy acetophenone (1 g, 7.34 mmol) in dry acetone (10 mL), K_2CO_3 (2.03 g, 14.6 mmol) and benzyl bromide (1.30 mL, 11.0 mmol) were added, and the reaction was refluxed for 24 h. After completion of the reaction, it was diluted with water, the aqueous layer was extracted with Et_2O (10 mL x 3), dried over Na_2SO_4, filtered, and concentrated, and the crude product was purified using silica gel column chromatography to afford the desired product **79o** (1.5 g, 90 %) as colorles liquid. (TLC: R_f = 0.8 (SiO_2, 10% EtOAc/ hexanes). IR (neat) 3683, 3332, 2878, 1960, 1888, 1673, 1597, 1510, 1423, 1365, 1312, 1261, 1174, 1118, 1078, 959, 922, 834, 771, 674 cm-1; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.88 Hz, 2H), 7.46-7.32 (m, 5H), 7.01 (d, *J* = 8.88 Hz, 2H), 5.12 (s, 2H), 2.55 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 196.8, 162.7, 136.2, 130.7, 130.6, 128.8, 128.3, 127.5, 114.6, 70.2, 26.4; HRMS (ESI): *m/z* calcd for $C_{15}H_{15}O_2$ $[M+H]^+$ 227.1067, found 227.1067.



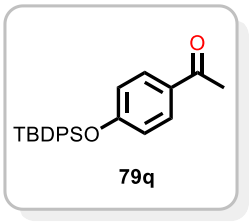
79o

1-(4-((4-Methoxybenzyl)oxy)phenyl)ethan-1-one (79p). To a stirred solution of 4'-hydroxy acetophenone (1 g, 7.34 mmol) in dry DMF (10 mL), K_2CO_3 (2.03 g, 14.6 mmol) and PMBCl (0.98 mL, 7.34 mmol) were added, and the reaction was stirred for 5 h at room temperature. After completion of the reaction it was quenched with ice water, the aqueous layer was extracted with ethyl acetate (10 mL x 3), then the combined organic layer was washed with brine (20 mL),), dried over Na_2SO_4, filtered, and concentrated and the crude product was purified using silica gel column chromatography to afford the desired product **79p** (1.68 g, 89%) as a colorless liquid. (TLC: R_f = 0.8 (SiO_2, 10% EtOAc/ hexanes). IR (neat) 3686, 2952, 2842, 1673, 1602, 1515, 1467, 1365, 1307, 1242, 1218, 1175, 1113, 1027, 927, 795, 746, 642 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.98-7.89 (m, 2H), 7.42-7.32 (m, 2H), 7.05-6.95 (m, 2H), 6.95-6.89 (m, 2H), 5.06 (s, 2H), 3.82 (s, 3H), 2.55 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 196.9, 162.9, 159.8, 130.7, 130.6, 129.4, 128.3, 114.7, 114.3, 70.1, 55.5, 26.5; HRMS (ESI): *m/z* calcd for $C_{16}H_{17}O_3$ $[M+H]^+$ 257.1172, found 257.1169.



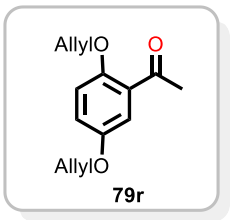
79p

1-(4-((*Tert*-butyldiphenylsilyl)oxy)phenyl)ethan-1-one (79q): To the 4'-hydroxy acetophenone (1 g, 7.34 mmol) in dry DMF (10 mL), imidazole (1.24 g, 18.3 mmol) were added, and the reaction was stirred for 10 minutes. Then TBDPSCl (3.02 mL, 11.0 mmol) were added, and reaction was stirred for 5h at room temperature. The reaction progress was monitored by TLC. After completion of the reaction it was quenched with water, the aqueous layer was extract-ed with DCM (10 mL x 3), dried over Na_2SO_4, filtered, and concentrated in vacuo and the crude product was purified using silica gel column chromatography to afford the desired product **79q** (2.1 g, 77%) as white solid. (TLC: R_f = 0.8 (SiO_2, 10% EtOAc/ hex-anes). IR (neat) cm^{-1} 3674, 3468, 2945, 2893, 2860, 1965, 1892, 1670, 1597, 1515, 1472, 1363, 1265, 1110, 1014, 919, 749, 673; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75-7.69 (m, 7H), 7.42-7.35 (m, 6H), 6.81- 6.77 (m, 2H), 2.48 (s, 3H), 1.11 (s, 9H); ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 197.1, 160.2, 135.5, 135.4, 134.9, 132.3, 130.8, 130.5, 130.3, 129.8, 128.1, 127.9, 119.8, 26.7, 26.5, 26.4, 19.6; HRMS (ESI): *m/z* calcd for $C_{24}H_{27}O_2Si$ $[M+H]^+$ 375.1775, found 375.1776.



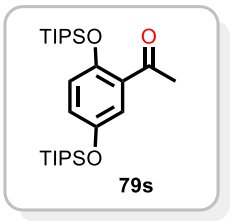
79q

1-(2,5-Bis(allyloxy)phenyl)ethan-1-one (79r): To the 4'-hydroxy acetophenone (5 g, 32.8 mmol) in dry acetone (50 mL), K_2CO_3 (18.17 g, 131.5 mmol) and allyl bromide (8.52 mL, 98.6 mmol) were added, and the reaction was stirred at room temperature for 24 h. After completion of the reaction, it was filtered through celite. The residue was washed with DCM. The filtrate was evaporated in vacuo and the crude product was purified using silica gel column chromatography to afford the desired product **79r** (7.3 g, 96%) as a white solid. TLC: R_f = 0.6 (SiO_2, 10% EtOAc/ hexanes). IR (neat) 3948, 3767, 3702, 3633, 3536, 3317, 3166, 3103, 2885, 2554, 2390, 2031, 1944, 1680, 1494, 1422, 1207, 1016, 927, 811, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 3.25 Hz, 1 H), 7.02 (dd, *J* = 3.25, 9.01 Hz, 1 H), 6.88 (d, *J* = 9.01 Hz, 1 H), 6.11-5.98 (m, 1 H), 5.44-5.41 (m, 1 H), 5.39-5.37 (m, 1 H), 5.31-5.25 (m, 2 H), 4.58 (td, *J* = 1.38, 5.38 Hz, 2 H), 4.51 (td, *J* = 1.38, 5.38 Hz, 2 H), 2.63 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 199.5, 152.7, 152.6, 133.3, 133.0, 128.9, 121.2, 118.2, 117.9, 115.0, 114.7, 70.2, 69.5, 32.1; HRMS (ESI): *m/z* calcd for $C_{14}H_{16}O_3Na$ $[M+Na]^+$ 255.0992 found 255.0991.



79r

1-(2,5-Bis((triisopropylsilyl)oxy)phenyl)ethan-1-one (79s). To the 4'-hydroxy acetophenone (1 g, 6.57 mmol) in dry DMF (10 mL), Et_3N (2.75 mL, 19.7 mmol) and DMAP (0.08 g, 0.65 mmol) were added at 0 °C and the reaction was stirred for 15 minutes then TIPSCl (4.11 mL, 16.4 mmol) was added dropwise to this. The reaction was stirred at room temperature for 5h. After completion of the reaction the mixture was filtered through celite, the filtrate was diluted with dichloromethane (30 mL) and washed consecutively with water (2 x 40 mL) and brine (50 mL) then dried over Na_2SO_4, the solvent was removed in vacuo and the crude product was purified using silica gel column chromatography to afford the desired product **79s** (2.46 g, 81%) as white solid. (TLC: R_f = 0.8 (SiO_2, 10% EtOAc/ hexanes). IR (neat) cm^{-1} 3429, 2953, 2867, 1674, 1480, 1413, 1272, 1067, 1002, 896; ^1H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, *J* = 3.13 Hz, 1H), 6.85 (dd, *J* = 3.25, 8.88 Hz, 1H), 6.72 (d, *J* = 8.76 Hz, 1H), 2.60 (s, 3H), 1.38-1.17 (m, 7H), 1.14-1.04 (m, 36H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 200.5, 149.8, 149.6, 131.2, 124.5, 120.4, 120.3, 31.4, 18.1, 18.1, 18.0, 13.4, 12.7; HRMS (ESI): *m/z* calcd for $C_{26}H_{49}O_3Si_2$ $[M+H]^+$ 465.3215, found 465.3230.

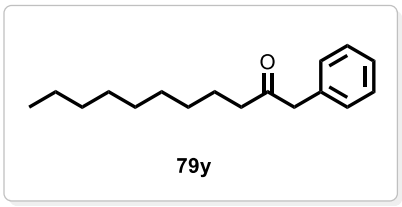


79s

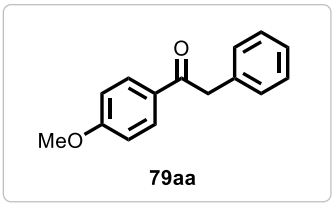
General procedure B for 1-(alkyl/aryl)-2-phenylethan-1-one (A)

To the 100 mL RBF, Mg turnings (1.2 equiv) were taken in dry THF (10 mL) was taken and BnBr (1 equiv) was added dropwise at 0 °C. The reaction was stirred for 1 h at room temperature until the Grignard was generated. The freshly prepared Grignard reagent was added dropwise to a solution of Weinreb amide (1 equiv) in dry THF at 0 °C. The reaction mixture was allowed to room temperature and stirred for 12 h. After completion of the reaction, it was quenched with a saturated aqueous solution of NH_4Cl. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (20 mL x 3), dried over Na_2SO_4, filtered, and concentrated in vacuo, and the crude product was purified using silica gel column chromatography to afford the desired product.

1-Phenylundecan-2-one (79y). The title compound was prepared following general procedure A, using N-methoxy-N-methyldecanamide (1 g, 4.64 mmol)), Mg (0.133 g, 5.57 mmol) and BnBr (0.55 mL, 4.64 mmol), THF (20 mL). Yield (0.97 g, 85 %) as colorless liquid. (TLC: R_f = 0.4 (SiO_2, 40% EtOAc/ hexanes). IR (neat) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (m, 2H), 7.23-7.15 (m, 3H), 3.68 (s, 2H), 2.43 (t, J = 7.38 Hz, 2H), 1.22 (s, 12H), 0.89-0.85 (m, 3H); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$) δ 208.9, 134.5, 129.5, 128.8, 128.6, 128.5, 127.1, 50.3, 42.2, 38.1, 32.0, 29.8, 29.5, 29.5, 29.4, 29.2, 23.9, 22.8, 14.3; HRMS (ESI): *m/z* calcd for $C_{17}H_{27}O$ $[M+H]^+$ 247.2056, found 247.2056.

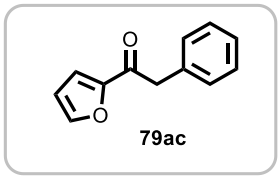


1-(4-Methoxyphenyl)-2-phenylethan-1-one (79aa). The title compound was prepared following general procedure A, using N-4-dimethoxy-N-methylbenzamide (1 g, 5.12 mmol)), Mg (0.147 g, 6.14 mmol) and BnBr (0.68 mL, 5.12 mmol), THF (20 mL). Yield (0.95 g, 83%) as a yellowish liquid. (TLC: R_f = 0.4 (SiO_2, 40% EtOAc/ hexanes). IR (neat) 2942, 2842, 2574, 2409, 1919, 1674, 1600, 1507, 1454, 1425, 1318, 1260, 1170, 1113, 1026, 927, 835, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.88 Hz, 2H), 7.38-7.22 (m, 5H), 6.93 (d, J = 9.01 Hz, 2H), 4.23 (s, 2H), 3.86 (s, 3H); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$) δ 196.4, 163.7, 135.1,



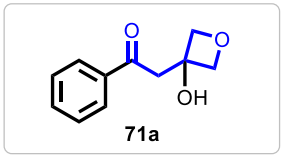
131.1, 129.8, 129.5, 128.8, 126.9, 113.9, 55.6, 45.4; HRMS (ESI): *m/z* calcd for $C_{15}H_{15}O_2$ $[M+H]^+$ 227.1067, found 227.1064.

1-(Furan-2-yl)-2-phenylethan-1-one (79ac). The title compound was prepared following general procedure A, using N-methoxy-N-methylfuran-2-carboxamide (1 g, 6.44 mmol)), Mg (0.185 g, 7.72 mmol) and BnBr (0.74 mL, 6.44 mmol), THF (20 mL).): Yield (0.96 g, 81%) as a colorless liquid. (TLC: R_f = 0.4 (SiO_2, 40% EtOAc/ hexanes). IR (neat) 3777, 3573, 3341, 2938, 1743, 1674, 1579, 1468, 1399, 1307, 1250, 1164, 1084, 1037, 910, 837, 717 cm-1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.53 (m, 1 H), 7.33-7.27 (m, 4 H), 7.25-7.19 (m, 1 H), 7.18 (d, *J* = 3.63 Hz, 1 H), 6.48 (dd, *J* = 1.63, 3.5 Hz, 1 H), 4.08 (s, 2 H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 186.7, 152.4, 146.7, 134.1, 129.6, 128.7, 127.1, 118.0, 112.5, 45.5; HRMS (ESI): *m/z* calcd for $C_{12}H_{11}O_2$ $[M+H]^+$ 187.0754, found 187.0754.



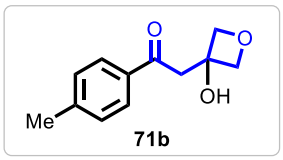
General Procedure B for the synthesis of α-hydroxy oxetane-tethered ketone: To a 100 mL two necked round bottom flask were added DIPA (1.2 equiv.) in anhydrous THF (mL) at 0 °C with stirring. To it, *n*-BuLi (1.2 equiv.) was added dropwise, and the reaction was stirred for 45 min at the same temperature. Then it was cooled to -78 °C, to this freshly prepared LDA enolate solution of acetophenone derivatives (equiv.) in anhydrous THF was added dropwise. The mixture was stirred for 1 hour at -78 °C followed by slow addition of 3-oxetanone (1 equiv.). Then the reaction was slowly warmed to room temperature and stirred for additional four hours. Then, reaction progress was monitored by TLC. Then, the reaction was quenched with saturated NH_4Cl (50mL), and the aqueous layer was extracted with EtOAc (3 x 50 mL), dried over Na_2SO_4, filtered, and concentrated under vaccuo and the resulting crude product was purified by silica gel column chromatography (SiO_2, 20% EtOAc/hexane) to afford desired product in high to moderate yields.

2-(3-Hydroxyoxetan-3-yl)-1-phenylethan-1-one (71a). The titled compound was prepared following general procedure B, using acetophenone (**79a**) (3 g, 24.96 mmol), 3-oxetanone (**77**) (1.46 mL, 24.96 mmol), *n*-BuLi (2.5 M, 11.98 mL, 29.95 mmol) and DIPA (3.5 mL, 29.95 mmol) and anhydrous THF (50 mL): yield (4.3 g, 90%) as a white solid.



(TLC: Rf = 0.4 (SiO_2, 40% EtOAc/ hexanes). IR (neat) 3684, 3539, 2958, 2880, 1674, 1593, 1519, 1442, 1397, 1338, 1115, 1036, 970, 926, 676, 633 cm-1; ^1H NMR (400 MHz, $CDCl_3$): δ 8.01-7.95 (m, 2H), 7.67-7.60 (m, 1H), 7.54-7.47 (m, 2H), 4.78 (d, *J* = 7.25 Hz, 2H), 4.49 (d, *J* = 7.38 Hz, 2H), 4.03 (s, 1 H), 3.64 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$): δ 200.3, 136.3, 134.3, 129.0, 128.3, 83.3, 72.4, 45.7; HRMS (ESI): *m/z* calcd for $C_{11}H_{13}O_3$ $[M+H]^+$ 193.0859, found 193.0860.

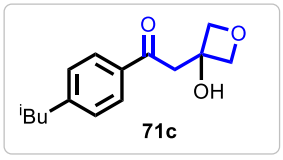
2-(3-Hydroxyoxetan-3-yl)-1-(*p*-tolyl)ethan-1-one (71b). The title compound was



71b

prepared following general procedure B, using acetophenone (**79b**) (3 g, 22.35 mmol), 3-oxetanone (**77**) (1.30 mL, 22.35 mmol), *n*-BuLi (2.5 M, 10.73 mL, 26.82 mmol) and DIPA (3.7 mL, 26.82 mmol) and anhydrous THF (50 mL): yield (3.74 g, 81.12%) as a white solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3755, 3636, 3421, 3365, 2970, 2690, 2393, 2303, 1680, 1617, 1419, 1342, 1226, 1119, 1034, 972, 812, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ : 7.88 (d, *J* = 8.25 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 4.78 (d, *J* = 7.25 Hz, 2H), 4.47 (d, *J* = 7.25 Hz, 2H), 4.10 (s, 1H), 3.60 (s, 2H), 2.44 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ : 199.9, 145.4, 133.9, 129.7, 128.5, 83.4, 72.4, 45.5, 21.9; HRMS (ESI): *m/z* calcd for $C_{12}H_{15}O_3$ $[M+H]^+$ 207.1016, found 207.1015.

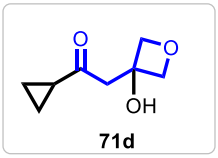
2-(3-Hydroxyoxetan-3-yl)-1-(4-isobutylphenyl)ethan-1-one (71c). The title



71c

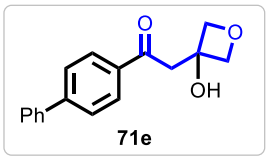
compound was prepared following general procedure B, using acetophenone (**79c**) (0.3 g, 1.70 mmol), 3-oxetanone (**77**) (0.09 mL, 1.70 mmol), *n*-BuLi (1.6 M, 1.27 mL, 2.04 mmol) and DIPA (0.28 mL, 2.04 mmol) and anhydrous THF (5 mL): yield (0.36 g, 87%) as a white solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3861, 3763, 3648, 3527, 3443, 3356, 2967, 2770, 2663, 2337, 1682, 1615, 1410, 1226, 1120, 973, 849, 755 cm-1; ^1H NMR (400 MHz, $CDCl_3$) δ : 7.89 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.76 Hz, 2H), 4.78 (d, *J* = 6.75 Hz, 2H), 4.47 (d, *J* = 6.75 Hz, 2H), 4.09 (s, 1 H), 3.61 (s, 2 H), 2.55 (d, *J* = 7.25 Hz, 2H), 1.91 (quind, *J* = 6.8, 13.5 Hz, 1 H), 0.92 (s, 3 H), 0.91 (s, 3 H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ : 200.0, 149.1, 134.2, 129.7, 128.4, 83.4, 77.5, 77.4, 76.8, 72.4, 45.6, 45.6, 30.3, 22.5; HRMS (ESI): *m/z* calcd for $C_{15}H_{21}O_3$ $[M+H]^+$ 249.1485, found 249.1486.

Cyclopropyl(3-hydroxyoxetan-3-yl)methanone (71d): The title compound was prepared following general procedure B, using acetophenone (**79d**) (0.5 g, 5.94 mmol), 3-oxetanone (**77**) (0.34 mL, 5.94 mmol), *n*-BuLi (1.6 M, 4.45 mL, 7.13 mmol) and DIPA (0.99 mL, 7.13 mmol) and anhydrous THF (5 mL): yield (0.839 g, 90%) as a yellowish liquid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3423, 3012, 2957, 2878, 2090, 1913, 1825, 1688, 1395, 1328, 1260, 1116, 1080, 1031, 967, 833 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.64 (d, *J* = 6.88 Hz, 2H), 4.37 (d, *J* = 7.00 Hz, 2H), 4.05 (s, 1H), 3.19 (s, 2H), 2.01-1.90 (m, 1H), 1.10-1.03 (m, 2H), 0.98-0.92 (m, 2H); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$) δ 211.4, 83.2, 72.0, 50.0, 21.5, 11.8; HRMS (ESI): *m/z* calcd for $C_8H_{13}O_2$ $[M+H]^+$ 157.0864, found 157.0855.



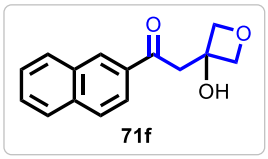
71d

1-([1,1'-Biphenyl]-4-yl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (71e). The title compound was prepared following general procedure B, using acetophenone (**79e**) (0.5 g, 2.54 mmol), 3-oxetanone (**77**) (0.14 mL, 2.54 mmol), *n*-BuLi (1.6 M, 1.6 mL, 3.05 mmol) and DIPA (0.43 mL, 3.05 mmol) and anhydrous THF (8 mL): yield (0.58 g, 85%) as a white solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3925, 3874, 3690, 3398, 3040, 2762, 2373, 1591, 1221, 745, 672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ : 8.09-8.03 (d, *J* = 8.38 Hz, 2H), 7.76-7.71 (d, *J* = 8.38 Hz, 2H), 7.67-7.61 (m, 2H), 7.53-7.40 (m, 3H), 4.81 (d, *J* = 7.0 Hz, 2H), 4.51 (d, *J* = 7.25 Hz, 2H), 4.09 (s, 1H), 3.67 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ : 199.9, 147.0, 139.6, 134.9, 129.2, 129.0, 128.7, 127.6, 127.4, 83.4, 72.4, 45.7; HRMS (ESI): *m/z* calcd for $C_{17}H_{17}O_3$ $[M+H]^+$ 269.1172 found 269.1171.



71e

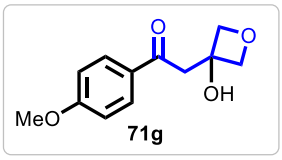
2-(3-Hydroxyoxetan-3-yl)-1-(naphthalen-2-yl)ethan-1-one (71f). The title compound was prepared following general procedure B, using acetophenone (**79f**) (3 g, 17.62 mmol), 3-oxetanone (**77**) (1.46 mL, 17.62 mmol), *n*-BuLi (2.5 M, 8.4 mL, 21.15 mmol) and DIPA (2.98 mL, 21.15 mmol) and anhydrous THF (50 mL): yield (3.85 g, 90%) as a white solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat): 3858, 3742, 2960, 2880, 2405, 2313, 1669, 1517, 1396, 1119, 966, 672, 623 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ : 8.52 (s, 1H), 8.05-7.97 (m, 2H), 7.96-7.88 (m, 2H), 7.68-7.57 (m, 2H), 4.82 (d, *J* = 7.25 Hz, 2H), 4.54 (d, *J* = 7.38 Hz, 2H), 4.10 (s, 1 H), 3.78 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz,



71f

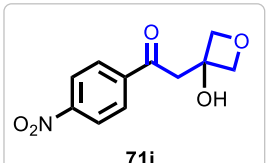
$CDCl_3$) δ : 200.3, 136.2, 133.7, 132.6, 130.6, 129.9, 129.3, 129.0, 128.0, 127.3, 123.4, 83.4, 72.5, 45.7; HRMS (ESI): *m/z* calcd for $C_{15}H_{15}O_3$ $[M+H]^+$ 243.1016, found 243.1016.

2-(3-Hydroxyoxetan-3-yl)-1-(4-methoxyphenyl)ethan-1-one (71g). The title compound was prepared following general procedure B, using acetophenone (**79g**) (3 g, 19.97 mmol), 3-oxetanone (**77**) (1.17 mL, 19.97 mmol), *n*-BuLi (2.5 M, 9.5 mL, 23.96 mmol) and DIPA (3.37 mL, 23.96 mmol) and anhydrous THF (50 mL): yield (3.82 g, 86%) as a white solid. (TLC: R_f = 0.4 (SiO_2, 40% EtOAc/ hexanes). IR (neat) 3860, 3517, 2957, 2880, 2312, 1664, 1601, 1514, 1414, 1342, 1259, 1172, 1114, 1028, 966, 835, 671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ : 7.95-7.90 (m, 2H), 6.96-6.91 (m, 2H), 4.74 (d, *J* = 6.88 Hz, 2H), 4.46 (d, *J* = 7.38 Hz, 2H), 4.24 (s, 1H), 3.86 (s, 3H), 3.54 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ : 198.5, 164.4, 130.6, 129.4, 114.1, 83.4, 72.4, 55.6, 45.1; HRMS (ESI): *m/z* calcd for $C_{12}H_{15}O_4$ $[M+H]^+$ 223.0965, found 223.0964.



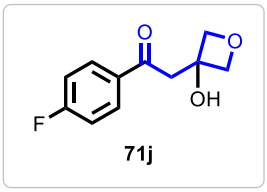
71g

2-(3-Hydroxyoxetan-3-yl)-1-(4-nitrophenyl)ethan-1-one (71i). The title compound was prepared following general procedure B, using acetophenone (**79i**) (3 g, 18.16 mmol), 3-oxetanone (**77**) (1.06 mL, 18.16 mmol), *n*-BuLi (2.5 M, 8.7 mL, 21.79 mmol) and DIPA (3.07 mL, 21.79 mmol) and anhydrous THF (50 mL): yield (3.10 g, 72%) as a yellow solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3686, 3560, 2960, 2880, 1686, 1600, 1528, 1415, 1346, 1114, 1011, 971, 927, 850, 673 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.75 Hz, 2H), 8.15-8.09 (m, 2H), 4.75 (d, *J* = 7.13 Hz, 2H), 4.52 (d, *J* = 7.63 Hz, 2H), 3.66 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ : 198.4, 151.0, 140.6, 129.4, 124.2, 83.2, 72.3, 46.4; HRMS (ESI): *m/z* calcd for $C_{11}H_{12}O_5N$ $[M+H]^+$ 238.0710, found 238.0710.



71i

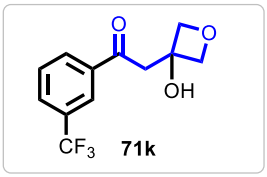
1-(4-Fluorophenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (71j). The title compound was prepared following general procedure B, using acetophenone (**79j**) (3 g, 21.71 mmol), 3-oxetanone (**77**) (1.27 mL, 21.71 mmol), *n*-BuLi (2.5 M, 10.40 mL, 26.06 mmol) and DIPA (3.67 mL, 26.06 mmol) and anhydrous THF (50 mL): yield (4.2 g, 92%) as a white solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat)



71j

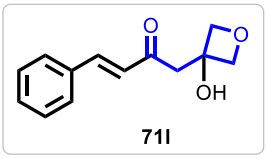
3858, 3669, 3455, 2957, 2880, 1676, 1598, 1509, 1407, 1342, 1157, 1114, 1043, 968, 924, 837, 669, 624 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ : 8.02-7.95 (m, 2H), 7.18-7.11 (m, 2 H), 4.74 (d, *J* = 7.13 Hz, 2H), 4.47 (d, *J* = 7.38 Hz, 2H), 4.05 (s, 1H), 3.58 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ : 198.3, 167.6, 165.1, 132.8, 131.1, 131.0, 116.2, 116.0, 83.3, 72.3, 45.6; HRMS (ESI): *m/z* calcd for $C_{11}H_{12}O_3F$ $[M+H]^+$ 211.0765, found 211.0764.

2-(3-Hydroxyoxetan-3-yl)-1-(3-(trifluoromethyl)phenyl)-ethan-1-one (71k).

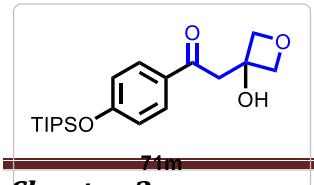


The title compound was prepared following general procedure B, using acetophenone (**79k**) (0.3 g, 1.59 mmol), 3-oxetanone (**77**) (0.08 mL, 1.59 mmol), *n*-BuLi (1.6 M, 1.19 mL, 1.91 mmol) and DIPA (0.26 mL, 1.91 mmol) and anhydrous THF (5 mL): yield (0.34 g, 82%) as a white solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3832, 3785, 3674, 3510, 3350, 3284, 3192, 2975, 2898, 2762, 2347, 1833, 1695, 1619, 1330, 1178, 1126, 1078, 967, 811, 661 cm^{-1}; ^1H NMR (400 MHz ,$CDCl_3$) δ : 8.22 (s, 1H), 8.16 (d, *J* = 7.88 Hz, 1H), 7.89 (d, *J* = 7.75 Hz, 1H), 7.66 (t, *J* = 7.75 Hz, 1H), 4.78 (d, *J* = 7.38 Hz, 2H), 4.51 (d, *J* = 7.5 Hz, 2H), 3.84 (s, 1 H), 3.66 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ : 198.7, 136.8, 131.9, 131.6, 131.4, 130.6, 129.8, 125.2, 125.0, 83.2, 72.3, 46.0; HRMS (ESI): *m/z* calcd for $C_{12}H_{12}O_3F_3$ $[M+H]^+$ 261.0733 found 261.0733.

(*E*)-1-(3-Hydroxyoxetan-3-yl)-4-phenylbut-3-en-2-one (71l). The title compound



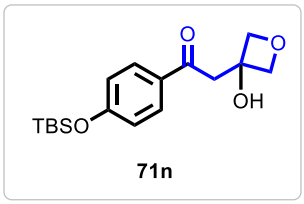
was prepared following general procedure B, using acetophenone (**79l**) (0.3 g, 2.05 mmol), 3-oxetanone (**77**) (0.14 mL, 2.05 mmol), *n*-BuLi (1.6 M, 1.53 mL, 2.46 mmol) and DIPA (0.34 mL, 2.46 mmol) and anhydrous THF (5 mL): yield (0.21 g, 48%) as a white solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3918, 3829, 3690, 3578, 3462, 3397, 3338, 3279, 3093, 2938, 2881, 2601, 2349, 1833, 1728, 1454, 966, 758, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ : 7.69-7.52 (m, 3H), 7.49-7.38 (m, 3H), 6.76 (d, *J* = 16.26 Hz, 1H), 4.75 (d, *J* = 6.88 Hz, 2H), 4.45 (d, *J* = 7.0 Hz, 2H), 4.10 (s, 1H), 3.35 (s, 2H); $^{13}C\{1H\}$NMR (101 MHz, $CDCl_3$) δ : 200.3, 145.0, 134.0, 131.3, 129.2, 128.7, 126.0, 83.4, 72.4, 47.1; HRMS (ESI): *m/z* calcd for $C_{13}H_{15}O_3$ $[M+H]^+$ 219.1021found 219.1017.



2-(3-Hydroxyoxetan-3-yl)-1-(4-((triisopropylsilyl)oxy)phenyl)ethan-1-one (71m). The

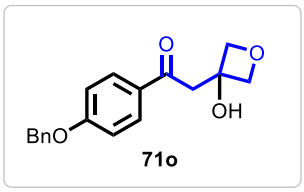
title compound was prepared following general procedure B, using acetophenone (**79m**) (1.45 g, 4.96 mmol), 3-oxetanone (**77**) (0.29 mL, 4.96 mmol), *n*-BuLi (1.6 M, 3.72 mL, 5.95 mmol) and DIPA (0.84 mL, 5.95 mmol) and anhydrous THF (30 mL): yield (1.61 g, 89%) as a colorless liquid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3541, 2954, 2873, 1660, 1597, 1515, 1473, 1420, 1280, 1113, 1009, 917, 632 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95-7.86 (m, 2H), 6.97-6.89 (m, 2H), 4.76 (d, *J* = 7.13 Hz, 2H), 4.47 (d, *J* = 7.25 Hz, 2H), 4.21 (s, 1H), 3.56 (s, 2H), 1.33 - 1.23 (m, 3H), 1.10 (d, *J* = 7.38 Hz, 18H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 198.8, 161.8, 130.7, 129.7, 120.1, 83.4, 72.4, 45.2, 18.0, 12.8; HRMS (ESI): *m/z* calcd for $C_{20}H_{33}O_4Si$ $[M+H]^+$ 365.2143, found 365.2141.

1-(4-((*Tert*-butyldimethylsilyl)oxy)phenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (71n). The title compound was prepared following general procedure B, using acetophenone (**79n**) (1.5 g, 5.99 mmol), 3-oxetanone (**77**) (0.43 mL, 5.99 mmol), *n*-BuLi (1.6 M, 4.5 mL, 7.18 mmol) and DIPA (1.01mL, 7.18 mmol) and anhydrous THF (20 mL): yield (1.79 g, 67.04%) as a white solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3685, 3385, 2947, 2867, 1665, 1599, 1512, 1473, 1422, 1355, 1265, 1173, 1109, 1015, 916, 839, 747, 672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.76 Hz, 2H), 6.91 (d, *J* = 8.75 Hz, 2H), 4.78 (d, *J* = 7.13 Hz, 2H), 4.48 (d, *J* = 7.25 Hz, 2H), 4.19 (s, 1H), 0.99 (s, 9H), 0.25 (s, 6H); ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 198.9, 161.5, 131.1, 130.7, 126.9, 120.5, 120.4, 115.4, 83.4, 72.5, 45.2, 25.7, 18.4, -4.2; HRMS (ESI): *m/z* calcd for $C_{17}H_{27}O_4Si$ $[M+H]^+$ 323.1673, found 323.1671.



71n

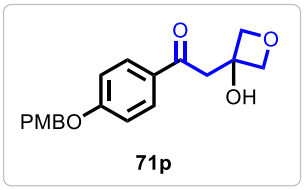
1-(4-(Benzyloxy)phenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (71o). The title compound was prepared following general procedure B, using acetophenone (**79o**) (1.2 g, 5.30 mmol), 3-oxetanone (**77**) (0.38 mL, 5.30 mmol), *n*-BuLi (1.6 M, 3.98 mL, 6.37 mmol) and DIPA (0.89 mL, 6.37 mmol) and anhydrous THF (15 mL): yield (1.19 g, 75%) as a white solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3606, 3541, 2956, 2880, 1661, 1600, 1508, 1420, 1316, 1174, 1116, 1011, 925, 672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.88 Hz, 2H), 7.49-7.34 (m, 5H), 7.04 (d, *J* = 8.88 Hz, 2H), 5.15 (s, 2H), 4.77 (d, *J* = 6.88 Hz, 2H), 4.47 (d, *J*



71o

= 7.00 Hz, 2H), 4.20 (s, 1H), 3.57 (s, 2H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 198.7, 163.6, 136.0, 130.7, 129.6, 128.9, 128.5, 127.6, 115.0, 83.4, 72.4, 70.4, 45.2; HRMS (ESI): *m/z* calcd for $C_{18}H_{19}O_4$ $[M+H]^+$ 299.1278, found 299.1277.

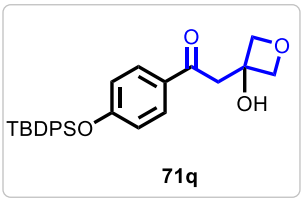
2-(3-Hydroxyoxetan-3-yl)-1-(4-((4-methoxybenzyl)oxy)phenyl)ethan-1-one



71p

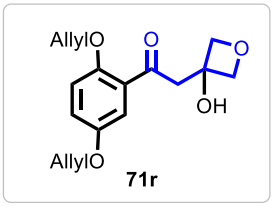
(71p). The title compound was prepared following general procedure B, using acetophenone (**79p**) (0.772 g, 3.01mmol), 3-oxetanone (**77**) (0.17 mL, 3.01 mmol), *n*-BuLi (1.6 M, 2.25 mL, 3.61 mmol) and DIPA (0.51mL, 3.61mmol) and anhydrous THF (10 mL): yield (0.856 g, 87%) as a white solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3686, 3399, 2929, 2858, 2360, 1626, 1515, 1471, 1367, 1102, 1025, 927, 739, 674, 630 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.88 Hz, 2H), 7.36 (d, *J* = 8.63 Hz, 2H), 7.03 (d, *J* = 8.88 Hz, 2H), 6.93 (d, *J* = 8.76 Hz, 2H), 5.08 (s, 2H), 4.77 (d, *J* = 7.13 Hz, 2H), 4.47 (d, *J* = 7.25 Hz, 2H), 4.18 (br. s., 1H), 3.82 (s, 3H), 3.57 (s, 2H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 198.7, 163.7, 159.9, 130.7, 129.5, 129.5, 128.0, 115.0, 114.3, 83.4, 72.5, 70.3, 55.5, 45.2; HRMS (ESI): *m/z* calcd for $C_{19}H_{21}O_5$ $[M+H]^+$ 329.1384, found 329.1380.

1-(4-((*Tert*-butyldiphenylsilyl)oxy)phenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (72q). The title compound was prepared following general procedure B, using acetophenone (**79q**) (2.1 g, 5.61 mmol), 3-oxetanone (**77**) (0.39 mL, 5.61 mmol), *n*-BuLi (1.6 M, 4.2 mL, 6.73 mmol) and DIPA (0.95 mL, 6.73 mmol) and anhydrous THF (30 mL): yield (2.41 g, 96%) as a white solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3905, 3853, 3781, 3641, 3568, 3445, 3366, 3088, 3047, 2957, 2879, 2691, 2624, 2558, 2389, 2336, 1019, 1954, 1801, 1628, 1516, 1267, 1177, 1144, 920, 838, 704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81-7.74 (m, 2H), 7.73-7.67 (m, 4H), 7.49-7.43 (m, 2H), 7.42-7.36 (m, 4H), 6.86-6.79 (m, 2H), 4.74 (d, *J* = 7.00 Hz, 2H), 4.43 (d, *J* = 7.13 Hz, 2H), 4.18 (s, 1H), 3.50 (s, 2H), 1.13 (s, 9H); ^{13}C{H} NMR (101 MHz, $CDCl_3$) δ 198.7, 161.1, 135.5, 132.0, 130.4, 130.4, 129.7, 128.1, 120.1, 83.3, 77.5, 76.8, 72.4, 45.2, 26.5, 19.6; HRMS (ESI): *m/z* calcd for $C_{27}H_{31}O_4Si$ $[M+H]^+$ 447.1986, found 447.1987.



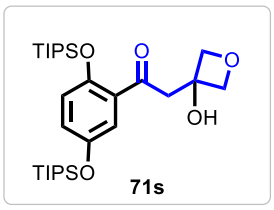
71q

1-(2,5-Bis(allyloxy)phenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (71r). The



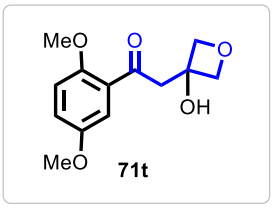
title compound was prepared following general procedure B, using acetophenone (**79r**) (5 g, 21.5 mmol), 3-oxetanone (**77**) (1.55 mL, 21.5 mmol), *n*-BuLi (2.5 M, 10.33 mL, 25.8 mmol) and DIPA (3.68 mL, 25.8 mmol) and anhydrous THF (100 mL): yield (5.9 g, 90%) as a white solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3795, 3643, 3434, 3315, 3170, 2940, 2795, 2689, 1672, 1493, 1420, 1270, 1220, 1178, 1116, 1011, 956, 819, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 3.00 Hz, 1H), 7.13-7.06 (m, 1H), 6.92 (d, *J* = 9.01 Hz, 1H), 6.13-5.95 (m, 2H), 5.49-5.20 (m, 4H), 4.73 (d, *J* = 6.63 Hz, 2H), 4.63 (d, *J* = 5.50 Hz, 2H), 4.53-4.49 (m, 2H), 4.46 (d, *J* = 7.13 Hz, 2H), 4.04 (br. s., 1H), 3.68 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 201.1, 153.3, 152.7, 133.1, 132.6, 127.2, 122.6, 118.7, 118.0, 114.8, 114.7, 83.5, 72.6, 70.2, 69.5, 51.6; HRMS (ESI): *m/z* calcd for $C_{17}H_{21}O_5$ $[M+H]^+$ 305.1384, found 305.1380.

1-(2,5-Bis((triisopropylsilyl)oxy)phenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one



(71s). The title compound was prepared following general procedure B, using acetophenone (**79s**) (2.6 g, 5.59 mmol), 3-oxetanone (**77**) (0.40 mL, 5.59 mmol), *n*-BuLi (1.6 M, 4.19 mL, 6.71 mmol) and DIPA (0.94 mL, 6.71 mmol) and anhydrous THF (8 mL): yield (1.9 g, 63%) as a white solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 2953, 2870, 1657, 1483, 1413, 1268, 1172, 1113, 1008, 896 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 3.25 Hz, 1H), 6.94 (dd, *J* = 3.13, 8.76 Hz, 1H), 6.76 (d, *J* = 8.88 Hz, 1H), 4.74 (d, *J* = 7.00 Hz, 2H), 4.43 (d, *J* = 7.13 Hz, 2H), 4.03 (s, 1H), 3.69 (s, 2H), 1.40-1.31 (m, 3H), 1.28-1.19 (m, 3H), 1.13 (d, *J* = 7.38 Hz, 18H), 1.08 (d, *J* = 7.13 Hz, 18H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 201.5, 150.7, 150.0, 128.8, 126.3, 120.8, 120.2, 83.4, 72.6, 51.0, 18.1, 18.0, 13.6, 12.7; HRMS (ESI): *m/z* calcd for $C_{29}H_{53}O_5Si_2$ $[M+H]^+$ 537.3426, found 537.3419.

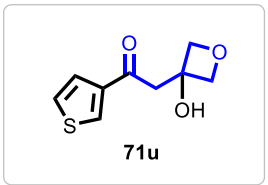
1-(2,5-Dimethoxyphenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (71t). The title



compound was prepared following general procedure B, using acetophenone (**79t**) (0.70 g, 3.88 mmol), 3-oxetanone (**77**) (0.22 mL, 3.88 mmol), *n*-BuLi (1.6 M, 2.91 mL, 4.66 mmol) and DIPA (0.65 mL, 4.66 mmol) and anhydrous THF (8 mL): yield (0.82 g, 84%) as a white solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat)

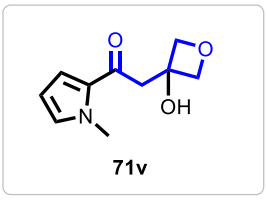
3605, 3444, 3018, 2950, 2840, 2404, 1759, 1603, 1502, 1456, 1275, 1172, 1040, 974, 936, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 3.38 Hz, 1H), 7.10 (dd, *J* = 3.25, 9.13 Hz, 1H), 6.95 (d, *J* = 9.13 Hz, 1H), 4.75 (d, *J* = 6.88 Hz, 2H), 4.48 (d, *J* = 7.25 Hz, 2H), 3.91 (s, 3H), 3.80 (s, 3H), 3.66 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 201.3, 154.2, 153.6, 126.8, 122.0, 113.6, 113.4, 83.5, 72.7, 56.1, 56.0, 51.4; HRMS (ESI): *m/z* calcd for $C_{13}H_{17}O_5$ $[M+H]^+$ 253.1071, found 253.1066.

2-(3-Hydroxyoxetan-3-yl)-1-(thiophen-3-yl)ethan-1-one (71u). The title compound was prepared following general procedure B, using acetophenone (**79u**) (3 g, 23.77 mmol), 3-oxetanone (**6**) (1.71 mL, 23.77 mmol), *n*-BuLi (2.5 M, 11.41 mL, 28.53 mmol) and DIPA (4.0 mL, 28.53 mmol) and anhydrous THF (50 mL): yield (2.91 g, 62%) as a white solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3806, 3740, 3684, 3600, 3337, 3116, 2975, 2898, 2758, 2353, 1666, 1412, 1338, 1238, 1104, 962, 881, 809, 683 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ : 8.15 (dd, *J* = 1.25, 2.88 Hz, 1H), 7.56 (dd, *J* = 1.13, 5.13 Hz, 1H), 7.37 (dd, *J* = 2.88, 5.13 Hz, 1H), 4.76 (d, *J* = 7.3 Hz, 2H), 4.47 (d, *J* = 7.3 Hz, 2H), 4.07 (s, 1H), 3.54 (s, 2H); $^{13}C\{1H\}$ NMR (101MHz, $CDCl_3$) δ : 194.3, 141.8, 133.6, 127.2, 126.7, 83.3, 72.4, 46.7; HRMS (ESI): *m/z* calcd for $C_9H_{11}O_3S$ $[M+H]^+$ 199.0423, found 199.0424.



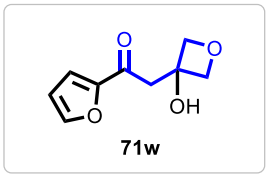
71u

2-(3-Hydroxyoxetan-3-yl)-1-(1-methyl-1H-pyrrol-2-yl)ethan-1-one (71v). The title compound was prepared following general procedure C, using acetophenone (**79v**) (3 g, 24.36 mmol), 3-oxetanone (**77**) (1.42 mL, 24.36 mmol), *n*-BuLi (2.5 M, 11.69 mL, 29.20 mmol) and DIPA (4.12 mL, 29.20 mmol) and anhydrous THF (50 mL): yield (4.64 g, 98%) as a white solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3687, 3456, 2958, 2879, 1630, 1521, 1475, 1410, 1107, 1060, 1026, 971, 927, 672, 624 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ : 7.07-7.02 (m, 1H), 6.86 (s, 1H), 6.16 (d, *J* = 2.38 Hz, 1H), 4.71 (d, *J* = 6.63 Hz, 2H), 4.57 (br. s., 1 H), 4.46 (d, *J* = 6.38 Hz, 2H), 3.90 (s, 3H), 3.39 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ : 189.8, 132.5, 130.3, 121.1, 108.8, 83.5, 72.7, 45.0, 37.8; HRMS (ESI): *m/z* calcd for $C_{10}H_{14}NO_3$ $[M+H]^+$ 196.0968 found 196.0968.



71v

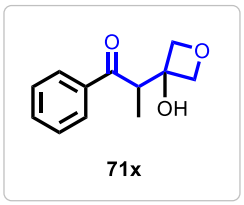
1-(Furan-2-yl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (71w). The title compound



71w

was prepared following general procedure B, using acetophenone (**79w**) (0.5 g, 4.54 mmol), 3-oxetanone (6) (0.25 mL, 4.54 mmol), *n*-BuLi (1.6 M, 3.40 mL, 5.44 mmol) and DIPA (0.75 mL, 5.44 mmol) and anhydrous THF (8 mL): yield (0.67 g, 91%) as a white solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3685, 3427, 2959, 2880, 2402, 1661, 1566, 1519, 1469, 1416, 1327, 1118, 1021, 969, 928, 891, 672, 624 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ : 7.64 (dd, *J* = 0.63, 1.63 Hz, 1H), 7.29 (dd, *J* = 0.75, 3.63 Hz, 1H), 6.59 (dd, *J* = 1.63, 3.63 Hz, 1H), 4.74 (s, 1H), 4.72 (s, 1H), 4.48 (d, *J* = 7.38 Hz, 2H), 4.04 (s, 1 H), 3.48 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ : 188.6, 152.3, 147.5, 118.7, 112.9, 83.3, 77.5, 76.8, 72.4, 45.2; HRMS (ESI): *m/z* calcd for $C_9H_{11}O_4$ $[M+H]^+$ 183.0652, found 183.0652.

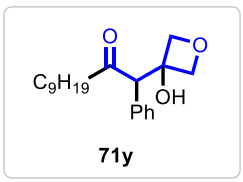
2-(3-Hydroxyoxetan-3-yl)-1-phenylpropan-1-one (71x). The title compound was



71x

prepared following general procedure B, using acetophenone (**79x**) (0.3 g, 2.23 mmol), 3-oxetanone (**77**) (0.12 mL, 2.23 mmol), *n*-BuLi (1.6 M, 1.67 mL, 2.68 mmol) and DIPA (0.37 mL, 2.68 mmol) and anhydrous THF (5 mL): yield (0.412 g, 89%) as a white solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3905, 3785, 3421, 2961, 2889, 2374, 1676, 1600, 1459, 1395, 1342, 1287, 1221, 1074, 971, 893, 762, 700, 651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01-7.95 (m, 2H), 7.66-7.59 (m, 1H), 7.55-7.47 (m, 2H), 4.70 (dd, *J* = 6.8, 8.38 Hz, 2H), 4.56-4.50 (m, 1H), 4.32 (d, *J* = 6.75 Hz, 1H), 4.26 (d, *J* = 0.88 Hz, 1H), 4.12 (q, *J* = 7.25 Hz, 1H), 1.32 (d, *J* = 7.38 Hz, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 205.7, 135.4, 134.3, 129.1, 128.7, 83.8, 81.6, 75.3, 46.0, 12.7; HRMS (ESI): *m/z* calcd for $C_{12}H_{15}O_3$ $[M+H]^+$ 207.1016, found 207.1015.

1-(3-Hydroxyoxetan-3-yl)-1-phenylundecan-2-one (71y). The title compound

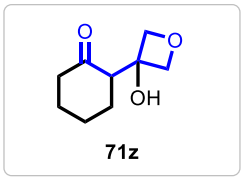


71y

was prepared following general procedure B, using acetophenone (**79y**) (0.5 g, 2.02 mmol), 3-oxetanone (**77**) (0.11 mL, 2.02 mmol), *n*-BuLi (1.6 M, 1.52 mL, 2.43 mmol) and DIPA (0.33 mL, 2.43 mmol) and anhydrous THF (8 mL): yield (0.427 g, 66 %) as a colorless liquid. TLC: *Rf* = 0.3 (SiO_2, 40% EtOAc/ hexanes). IR (neat) 3922, 3873, 3788, 3696, 3573, 3486, 3337, 3268, 2939, 2872, 2763, 1769, 1744, 1608, 1460, 1271, 991, 773, 705, 654 cm^{-1}; ^1H NMR (400 MHz ,$CDCl_3$) δ 8.01-7.95 (m, 2H),

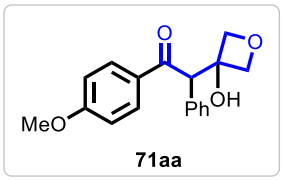
7.66-7.59 (m, 1H), 7.55-7.47 (m, 2H), 4.70 (dd, *J* = 6.8, 8.38 Hz, 2H), 4.56-4.50 (m, 1H), 4.32 (d, *J* = 6.75 Hz, 1H), 4.26 (d, *J* = 0.88 Hz, 1H), 4.12 (q, *J* = 7.25 Hz, 1H), 1.32 (d, *J* = 7.38 Hz, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 205.7, 135.4, 134.3, 129.1, 128.7, 83.8, 81.6, 75.3, 46.0, 12.7; HRMS (ESI): m/z calcd for $C_{20}H_{31}O_3$ $[M+H]^+$ 319.2268, found 319.2269.

2-(3-Hydroxyoxetan-3-yl)cyclohexan-1-one (71z). The title compound was prepared following general procedure B, using cyclohexanone (**79z**) (0.432 g, 2.13 mmol), 3-oxetanone (**77**) (0.12 mL, 2.13 mmol), *n*-BuLi (1.6 M, 1.6 mL, 2.56 mmol) and DIPA (0.35 mL, 2.56 mmol) and anhydrous THF (5 mL): yield (0.358 g, 61%) as a colorless liquid. TLC: R_f = 0.3 (SiO_2, 40% EtOAc/ hexanes). IR (neat) 3432, 3022, 2953, 2402, 2352, 2101, 1642, 1523, 1428, 1018, 926, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.67 (d, *J* = 7.13 Hz, 1H), 4.57 (d, *J* = 7.00 Hz, 1H), 4.42 (d, *J* = 7.13 Hz, 2H), 3.35 (s, 1H), 2.99-2.87 (m, 1H), 2.44-2.30 (m, 2H), 2.19-2.05 (m, 2H), 2.00-1.90 (m, 1H), 1.79-1.56 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.1, 83.5, 80.8, 74.1, 57.1, 42.6, 28.0, 27.8, 24.9; HRMS (ESI): *m/z* calcd for $C_9H_{15}O_3$ $[M+H]+$ 171.1021, found 171.1020.



71z

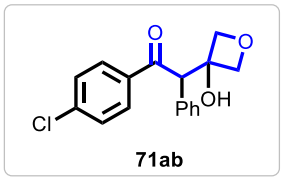
2-(3-Hydroxyoxetan-3-yl)-1-(4-methoxyphenyl)-2-phenylethan-1-one (71aa). The title compound was prepared following general procedure B, using acetophenone (**79aa**) (0.32 g, 1.41 mmol), 3-oxetanone (**77**) (0.08 mL, 1.41 mmol), *n*-BuLi (1.6 M, 1.06 mL, 1.69 mmol) and DIPA (0.23 mL, 1.69 mmol) and anhydrous THF (5 mL): yield (0.348 g, 83%) as a yellow liquid. TLC: R_f = 0.3 (SiO_2, 40% EtOAc/ hexanes). IR (neat) 3896, 3782, 3701, 3643, 3514, 3434, 3314, 2954, 2889, 2487, 2396, 2324, 2124, 1669, 1603, 1465, 1326, 1258, 1177, 973, 839, 715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95-7.89 (m, 2H), 7.37-7.27 (m, 5H), 6.88-6.82 (m, 2H), 5.16 (s, 1H), 4.80 (d, *J* = 6.63 Hz, 1H), 4.60 (d, *J* = 7.13 Hz, 1H), 4.46 (dd, *J* = 7.13, 10.76 Hz, 2H), 3.81 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 200.0, 164.3, 134.3, 131.7, 129.6, 129.1, 128.7, 128.0, 114.1, 84.2, 80.8, 75.7, 58.1, 55.6; HRMS (ESI): *m/z* calcd for $C_{18}H_{19}O_4$ $[M+H]^+$ 299.1278, found 299.1272.



71aa

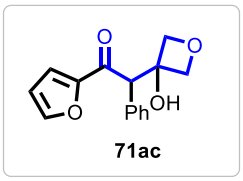
1-(4-Chlorophenyl)-2-(3-hydroxyoxetan-3-yl)-2-phenylethan-1-one (71ab). The title compound was prepared following general procedure B, using acetophenone

(**79ab**) (0.5 g, 2.16 mmol), 3-oxetanone (**77**) (0.12 mL, 2.16 mmol), *n*-BuLi (1.6 M, 1.62 mL, 2.60 mmol) and DIPA (0.36 mL, 2.60 mmol) and anhydrous THF (8 mL): yield (0.502 g, 77%) as a yellow liquid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3945, 3881, 3764, 3636, 3422, 3338, 2965, 2892, 2486, 2394, 1680, 1592, 1482, 1399, 1253, 1101, 973, 827, 717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91-7.79 (m, 2H), 7.40-7.27 (m, 7H), 5.13 (s, 1H), 4.81 (d, *J* = 6.75 Hz, 1H), 4.60 (d, *J* = 7.13 Hz, 1H), 4.48 (d, *J* = 7.25 Hz, 1H), 4.44 (d, *J* = 6.75 Hz, 1H), 4.39 (br. s., 1H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 200.2, 140.7, 134.0, 133.6, 130.6, 129.6, 129.3, 129.3, 128.4, 83.9, 80.7, 75.6, 58.9; HRMS (ESI): *m/z* calcd for $C_{17}H_{16}O_3Cl$ $[M+H]^+$ 303.0782, found 303.0777.



71ab

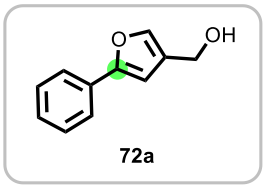
1-(Furan-2-yl)-2-(3-hydroxyoxetan-3-yl)-2-phenylethan-1-one (71ac). The title compound was prepared following general procedure B, using acetophenone (**79ac**) (0.594 g, 3.18 mmol), 3-oxetanone (**77**) (0.18 mL, 3.18 mmol), *n*-BuLi (1.6 M, 2.39 mL, 3.82 mmol) and DIPA (0.53 mL, 3.82 mmol) and anhydrous THF (8 mL): yield (0.685 g, 83%) as a colorless liquid. TLC: R_f = 0.3 (SiO_2, 40% EtOAc/ hexanes). IR (neat) 3686, 3433, 3023, 2959, 2402, 2351, 1676, 1603, 1522, 1473, 1423, 1023, 928, 672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57-5.55 (m, 1H), 7.42-7.37 (m, 2H), 7.37-7.29 (m, 3H), 7.20 (d, *J* = 3.63 Hz, 1H), 6.49 (dd, *J* = 1.63, 3.63 Hz, 1H), 5.01 (s, 1H), 4.78 (d, *J* = 6.75 Hz, 1H), 4.59-4.49 (m, 2H), 4.49-4.41 (m, 2H); $^{13}C\{H\}$NMR (101 MHz $CDCl_3$) δ 189.8, 151.8, 147.8, 133.6, 129.7, 129.0, 128.3, 120.2, 112.9, 84.0, 80.8, 75.6, 58.3; HRMS (ESI): *m/z* calcd for $C_{15}H_{15}O_4$ $[M+H]^+$ 259.0965, found 259.0974.



71ac

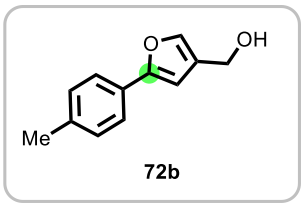
***General Procedure C* for the synthesis of 5-phenylfuran-3-yl)methanol:** To the α-hydroxy oxetane-tethered ketone **71a-71ac**(1 equiv) in anhydrous DCM, $Bi(OTf)_3$ (10 mol%) were added at room temperature and the reaction was stirred up to starting material was completely consumed (1 minute). After completion of the reaction, it was quenched with saturated aqueous solution of $NaHCO_3$ and the aqueous layer was extracted with DCM (3 x 10 mL), dried over Na_2SO_4, filtered, and concentrated in vaccuo, and the resulting crude product was purified by silica gel column chromatography (SiO_2, 20% EtOAc/hexane) to afford desired product in high to moderate yields.

(5-Phenylfuran-3-yl)methanol (72a): The title compound was prepared following general procedure C using 2-(3-hydroxyoxetan-3-yl)-1-phenylethan-1-one (**71a**, 0.05 g, 0.26 mmol), $Bi(OTf)_3$ (0.017 g, 0.026 mmol) and DCM (0.5 mL): yield (0.0448 g, 99%) as white solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3687, 3602, 1769, 1601, 1520, 1426, 1020, 927, 678, 624 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66-7.59 (m, 2H), 7.44-7.39 (m, 1H), 7.39-7.32 (m, 2H), 7.25-7.21 (m, 1H), 6.67 (s, 1H), 4.56 (d, *J* = 2.6 Hz, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 154.9, 139.4, 130.8, 128.8, 127.7, 127.3, 123.9, 105.2, 56.9; HRMS (ESI): *m/z* calcd for $C_{11}H_{11}O_2$ $[M+H]^+$ 175.0754, found 175.0753.



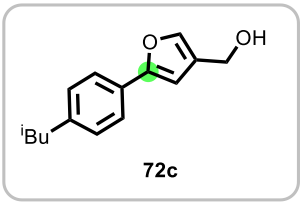
72a

(5-(*p*-Tolyl)furan-3-yl)methanol (72b): The title compound was prepared following general procedure C using 2-(3-hydroxyoxetan-3-yl)-1-(*p*-tolyl)ethan-1-one (**71b**, 0.05 g, 0.242 mmol), $Bi(OTf)_3$ (0.015 g, 0.024 mmol) and DCM (0.5 mL): yield (0.044 g, 98%) as white solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3685, 3610, 3451, 2931, 2880, 1901, 1757, 1600, 1498, 1423, 1021, 971, 923, 672, 624 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57-7.53 (m, 2H), 7.42 (d, *J* = 0.88 Hz, 1H), 7.21-7.17 (m, 2H), 6.64 (s, 1H), 4.59 (s, 2H), 2.36 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 155.2, 139.1, 137.6, 129.5, 128.1, 127.2, 123.9, 104.5, 57.0, 21.4; HRMS (ESI): *m/z* calcd for $C_{12}H_{13}O_2$ $[M+H]^+$ 189.0910, found 189.0909.



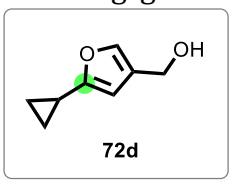
72b

(5-(4-Isobutylphenyl)furan-3-yl)methanol (72c): The title compound was prepared following general procedure C using 2-(3-hydroxyoxetan-3-yl)-1-(4-isobutylphenyl)ethan-1-one (**71c**, 0.05 g, 0.201 mmol), $Bi(OTf)_3$ (0.013 g, 0.020 mmol) and DCM (0.5 mL): yield (0.044 g, 96%) as white solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3625, 3363, 3008, 2945, 2832, 2513, 2040, 1638, 1456, 1112, 1026, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.13 Hz, 2H), 7.43 (s, 1H), 7.16 (d, *J* = 8.25 Hz, 2H), 6.65 (s, 1H), 4.59 (s, 2H), 2.48 (d, *J* = 7.13 Hz, 2H), 1.87 (quind, *J* = 6.63, 13.38 Hz, 1H), 0.92 (s, 3H), 0.90 (s, 3H); 13C NMR (101 MHz, $CDCl_3$) δ 155.2, 141.5, 139.1, 129.6, 128.4, 127.2, 123.8, 114.2, 104.5, 57.1, 45.3, 30.4, 22.5; HRMS (ESI): m/z calcd for $C_{15}H_{19}O_2$ [M+H]+ 231.1380, found 231.1380.



72c

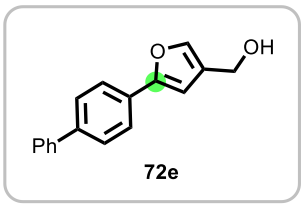
(5-Cyclopropylfuran-3-yl)methanol (72d). The title compound was prepared following general procedure C using cyclopropyl(3-hydroxyoxetan-3-yl)methanone



72d

(**71d**, 0.05 g, 0.201 mmol), $Bi(OTf)_3$ (0.013 g, 0.020 mmol) and DCM (0.5 mL): yield (0.045 g, 94%) as colorless liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3427, 3022, 2956, 2402, 1641, 1426, 1023, 932, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (s, 1H), 6.00 (s, 1H), 4.48 (s, 2H), 1.90-1.79 (m, 1H), 0.88-0.83 (m, 3H), 0.77-0.72 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 137.8, 125.9, 103.8, 57.0, 8.9, 6.7; HRMS (ESI): m/z calcd for $C_8H_{11}O_2$ [M+H]+ 139.0754, found 139.0755.

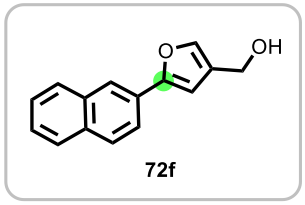
(5-([1,1'-Biphenyl]-4-yl)furan-3-yl)methanol (72e): The title com-pound was



72e

prepared following general procedure C using 1-([1,1'-biphenyl]-4-yl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (**71e,** 0.05 g, 0.186 mmol), $Bi(OTf)_3$ (0.012 g, 0.018 mmol) and DCM (0.5 mL): yield (0.0448 g, 97%) as white solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3023, 2927, 2402, 1727, 1604, 1414, 1044, 850, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76-7.70 (m, 2H), 7.65-7.60 (m, 4H), 7.49-7.42 (m, 3H), 7.38-7.33 (m, 1H), 6.75 (s, 1H), 4.62 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz , $CDCl_3$) δ 154.7, 140.4, 139.6, 129.8, 129.0, 127.6, 127.5, 127.1, 124.4, 105.3, 57.0; HRMS (ESI): *m/z* calcd for $C_{17}H_{15}O_2$ $[M+H]^+$ 251.1067, found 251.1066.

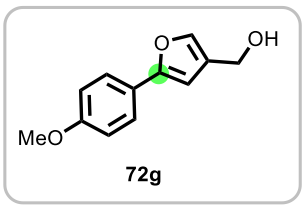
(5-(Naphthalen-2-yl)furan-3-yl)methanol (72f): The title compound was



72f

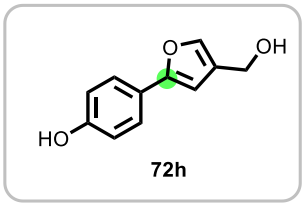
prepared following general procedure C using 2-(3-hydroxyoxetan-3-yl)-1-(naphthalen-2-yl)ethan-1-one (**71f**, 0.05 g, 0.206 mmol), $Bi(OTf)_3$ (0.013 g, 0.020 mmol) and DCM (0.5 mL): yield (0.0453 g, 98%) as white solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3021, 1518, 1216, 1022, 769, 671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.88-7.79 (m, 3H), 7.74 (dd, *J* = 1.75, 8.63 Hz, 1H), 7.53-7.42 (m, 3H), 6.82 (s, 1H), 4.62 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 155.0, 139.7, 133.6, 132.9, 128.6, 128.3, 128.1, 127.9, 127.5, 126.7, 126.2, 122.4, 122.4, 105.8, 57.0; HRMS (ESI): *m/z* calcd for $C_{15}H_{13}O_2$ $[M+H]^+$ 225.0910, found 225.0909.

(5-(4-Methoxyphenyl)furan-3-yl)methanol (72g): The title compound was prepared following general procedure C using 2-(3-hydroxyoxetan-3-yl)-1-(4-methoxyphenyl)ethan-1-one (**71g**, 0.05 g, 0.224 mmol), $Bi(OTf)_3$ (0.014 g, 0.0224 mmol) and DCM (0.5 mL): yield (0.043 g, 95%) as white solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3864, 3736, 3257, 2953, 2842, 2315, 2042, 1893, 1611, 1537, 1497, 1290, 1179, 1108, 1034, 914, 835, 670, 624 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61-7.56 (m, 2H), 7.40 (s, 1H), 6.94-6.90 (m, 2H), 6.56 (s, 1H), 4.58 (s, 2H), 3.83 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 159.3, 155.0, 138.8, 127.3, 125.4, 123.9, 114.3, 103.6, 57.1, 55.5; HRMS (ESI): *m/z* calcd for $C_{12}H_{13}O_3$ $[M+H]^+$ 205.0859, found 205.0859.



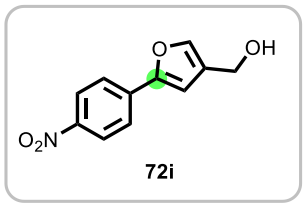
72g

4-(4-(Hydroxymethyl)furan-2-yl)phenol (72h): To a solution of (5-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-furan-3-yl)methanol (**72n**) (0.03 g, 0.098 mmol) in dry THF at 0 °C , TBAF (1 M in THF, 0.11 mL, 0.118 mmol) were added dropwise and the reaction mixture was stirred for 30 min. at the same temperature. The reaction was monitored by TLC and After completion of the reaction, it was quenched with H_2O. The organic layer was separated and aqueous layer was extracted with EtOAc (3x3 mL) and combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuum and crude product was purified by silica gel column chromatography (using 60% EtOAc in hexanes) to afford **72h** (15 mg, 83%) as white solid. TLC: R_f = 0.3 (SiO_2, 60% EtOAc/hexanes); FTIR: 3949, 3870, 3762, 3700, 3639, 3540, 3323, 3173, 2975, 2862, 2687, 2493, 2376, 2231, 2084, 1914, 1665, 1532, 1466, 1120, 1029, 977, 771, 683 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.53-7.45 (m, 2H), 7.42 (s, 1H), 6.83-6.74 (m, 2H), 6.57 (s, 1H), 4.48 (s, 2H); $^{13}C\{H\}$ NMR (101 MHz, CD_3OD) δ 158.4, 156.5, 139.7, 129.0, 126.4, 124.4, 116.6, 104.3, 56.9; HRMS (ESI): *m/z* calcd for $C_{11}H_{11}O_3$ $[M+H]^+$ 191.0703, found 191.0704.



72h

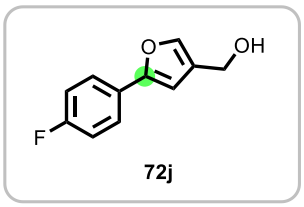
(5-(4-Nitrophenyl)furan-3-yl)methanol (72i): The title compound was prepared following general procedure C using 2-(3-hydroxyoxetan-3-yl)-1-(4-nitrophenyl)ethan-1-one (**71i**, 0.05 g, 0.210 mmol), $Bi(OTf)_3$ (0.013 g, 0.021 mmol) and DCM (0.5 mL): yield (0.042 g, 89%) as yellow solid. TLC: R_f = 0.4 (SiO_2, 20%



72i

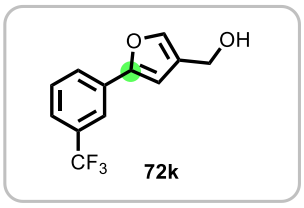
EtOAc/ hexanes). IR (neat) 3862, 3738, 3615, 2936, 2404, 2313, 1600, 1518, 1433, 1341, 1217, 1107, 1022, 924, 856, 672, 624 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.63 Hz, 2H), 7.76 (d, *J* = 8.63 Hz, 2H), 7.54 (s, 1H), 6.92 (s, 1H), 4.62 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 152.5, 146.7, 141.4, 136.4, 128.1, 124.5, 124.1, 109.1, 56.7; HRMS (ESI): *m/z* calcd for $C_{11}H_{10}O_4N$ $[M+H]^+$ 220.0604, found 220.0605.

(5-(4-Fluorophenyl)furan-3-yl)methanol (72j): The title compound was prepared following general procedure C using 1-(4-fluorophenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (**71j**, 0.05 g, 0.237 mmol), $Bi(OTf)_3$ (0.015 g, 0.023 mmol) and DCM (0.5 mL): yield (0.044 g, 98%) as white solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3686, 3601, 2926, 1708, 1612, 1518, 1424, 1310, 1047, 925, 672, 624 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65-7.58 (m, 2H), 7.43 (s, 1H), 7.07 (t, *J* = 8.63 Hz, 2H), 6.63 (s, 1H), 4.58 (s, 2H), 1.70 (br. s., 1H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 163.6, 161.2, 154.1, 139.4, 127.3, 127.2, 125.8, 125.7, 116.0, 115.8, 104.9, 56.9; HRMS (ESI): *m/z* calcd for $C_{11}H_{10}O_2F$ $[M+H]^+$ 193.0659, found 193.0659.



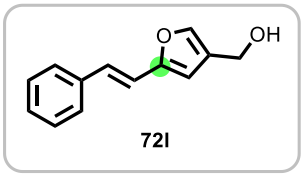
72j

(5-(3-(Trifluoromethyl)phenyl)furan-3-yl)methanol (72k): The title compound was prepared following general procedure C using 2-(3-hydroxyoxetan-3-yl)-1-(3-(trifluoromethyl)phenyl)ethan-1-one (**71k**, 0.05 g, 0.192 mmol), $Bi(OTf)_3$ (0.0126 g, 0.019 mmol) and DCM (0.5 mL): yield (0.0434 g, 94%) as white solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3627, 3378, 3016, 2946, 2835, 2407, 1768, 1708, 1623, 1440, 1332, 1173, 1132, 1078, 1024, 926, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.82 - 7.78 (m, 1H), 7.51 - 7.47 (m, 3H), 6.79 (s, 1H), 4.61 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz , $CDCl_3$) δ 153.4, 140.1, 131.5, 129.4, 127.6, 126.9, 124.2, 124.1, 120.7, 120.68, 106.5, 56.9; HRMS (ESI): *m/z* calcd for $C_{12}H_{10}O_2F_3$ $[M+H]^+$ 243.0627, found 243.0623.



72k

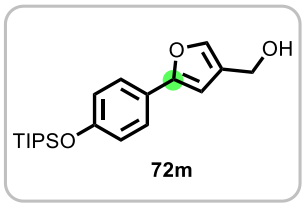
(*E*)-(5-Styrylfuran-3-yl)methanol (72l): The title compound was prepared following general procedure C using (*E*)-1-(3-hydroxyoxetan-3-yl)-4-phenylbut-3-en-2-one (**71l**, 0.05 g, 0.229 mmol), $Bi(OTf)_3$ (0.015 g, 0.022 mmol) and DCM (0.5 mL): yield (0.028 g, 62%) as off white solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat)



72l

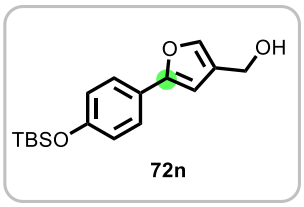
3627, 3375, 3013, 2946, 2883, 2407, 2037, 1632, 1415, 1110, 1025, 929, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.38 Hz, 2H), 7.39 (s, 1H), 7.34 (t, *J* = 7.13 Hz, 3H), 7.04 (d, *J* = 16.88 Hz, 1H), 6.86 (d, *J* = 16.38 Hz, 1H), 6.40 (s, 1H), 4.57 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 154.2, 139.5, 137.0, 128.9, 127.8, 127.4, 126.5, 116.5, 108.6, 57.0. HRMS (ESI): *m/z* calcd for

(5-(4-((Triisopropylsilyl)oxy)phenyl)furan-3-yl)methanol (72m): The title compound was prepared following general procedure C using 2-(3-hydroxyoxetan-3-yl)-1-(4-((triisopropylsilyl)oxy)-phnyl)ethan-1-one (**71m**, 0.05 g, 0.137 mmol), $Bi(OTf)_3$ (0.008 g, 0.013 mmol) and DCM (0.5 mL): yield (0.042 g, 89%) as yellow solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3899, 3767, 3643, 3426, 3320, 2956, 2885, 2694, 2633, 2379, 1919, 1609, 1503, 1272, 1176, 1009, 909, 837, 746, 682 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.63 Hz, 2H), 7.40 (s, 1H), 6.89 (d, *J* = 8.75 Hz, 3H), 6.56 (s, 1H), 4.58 (s, 2H), 1.29-1.24 (m, 3H), 1.12 (s, 9H), 1.10 (s, 9H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 156.0, 155.2, 138.7, 127.3, 125.3, 124.1, 120.3, 103.6, 57.1, 18.1, 12.8; HRMS (ESI): *m/z* calcd for $C_{20}H_{31}O_3Si$ $[M+H]^+$ 347.2037, found 347.2036.



72m

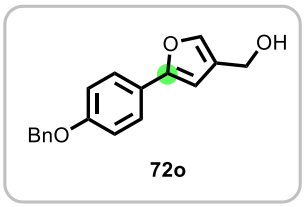
(5-(4-((*Tert*-butyldimethylsilyl)oxy)phenyl)furan-3-yl)methanol (72n): The title compound was prepared following general procedure C using 1-(4-((tert-butyldimethylsilyl)oxy)phenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (**71n**, 0.05 g, 0.155 mmol), $Bi(OTf)_3$ (0.010 g, 0.015 mmol) and DCM (0.5 mL): yield (0.043 g, 91%) as white solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3876, 3798, 3671, 3566, 3474, 3390, 2938, 2875, 2758, 2644, 2102, 1598, 1468, 1372, 1276, 913, 779, 661 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54-7.49 (m, 2H), 7.42-7.38 (m, 1H), 6.87-6.83 (m, 2H), 6.57-6.54 (m, 1H), 4.58 (s, 2H), 0.99 (s, 9H), 0.21 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6, 153.0, 138.8, 130.7, 127.3, 125.4, 125.3, 120.5, 120.3, 103.7, 57.1, 25.8, 18.1, -4.3; HRMS (ESI): m/z calcd for $C_{17}H_{25}O_3Si$ $[M+H]^+$ 305.1567, found 305.1567.



72n

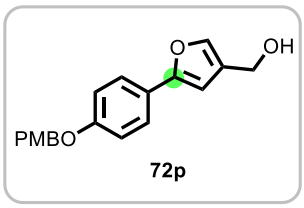
(5-(4-(Benzyloxy)phenyl)furan-3-yl)methanol (72o): The title com-pound was prepared following general procedure C using 1-(4-(benzyloxy)phenyl)-2-(3-

hydroxyoxetan-3-yl)ethan-1-one (**71o**, 0.05 g, 0.167 mmol), $Bi(OTf)_3$ (0.011 g, 0.016 mmol) and DCM (0.5 mL): yield (0.045 g, 97%) as white solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3931, 3878, 3806, 3769, 3680, 3603, 3398, 3333, 3272, 3203, 2764, 2349, 1603, 1501, 1383, 1308, 1256, 1180, 1112, 1041,819, 735, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62-7.55 (m, 2H), 7.46-7.36 (m, 5H), 7.03-6.95 (m, 2H), 6.57 (s, 1H), 5.09 (s, 2H), 4.58 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 158.5, 155.0, 138.8, 137.0, 128.8, 128.2, 127.6, 127.3, 125.4, 124.2, 115.2, 103.7, 70.2, 57.1; HRMS (ESI): *m/z* calcd for $C_{18}H_{17}O_3$ $[M+H]^+$ 281.1172, found 281.1167.



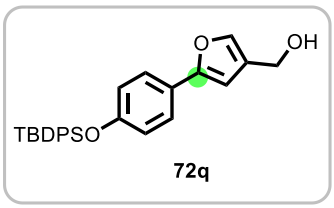
72o

(5-(4-((4-Methoxybenzyl)oxy)phenyl)furan-3-yl)metha-nol (72p): The title compound was prepared following general procedure C using 2-(3-hydroxyoxetan-3-yl)-1-(4-((4-methoxybenzyl)-oxy)phenyl)ethan-1-one (**71p**, 0.05 g, 0.152 mmol), $Bi(OTf)_3$ (0.009 g, 0.015 mmol) and DCM (0.5 mL): yield (0.034 g, 72%) as white solid TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3952, 3854, 3780, 3700, 3608, 3430, 3293, 3170, 3056, 2999, 2937, 2879, 2770, 2680, 2396, 2338, 1923, 1713, 1520, 1383, 1255, 1183, 1117, 1030, 912, 838, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.88 Hz, 2H), 7.41 (m, 1H), 7.36 (d, *J* = 8.75 Hz, 2H), 6.98 (d, *J* = 8.88 Hz, 2H), 6.92 (d, *J* = 8.63 Hz, 2H), 6.56 (s, 1H), 5.01 (s, 2H), 4.58 (s, 2H), 3.82 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 159.7, 158.6, 155.0, 138.8, 129.4, 129.0, 127.3, 125.4, 124.1, 115.3, 114.2, 103.7, 70.0, 57.1, 55.5; HRMS (ESI): *m/z* calcd for $C_{19}H_{19}O_4$ $[M+H]^+$ 311.1278, found 311.1275.



72p

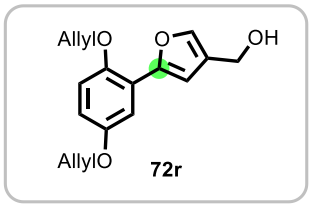
(5-(4-((*Tert*-butyldiphenylsilyl)oxy)phenyl)furan-3-yl)methanol (72q): The title compound was prepared following general procedure C using 1-(4-((*tert*-butyldiphenylsilyl)oxy)phenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (**71q**, 0.05 g, 0.111 mmol), $Bi(OTf)_3$ (0.007 g, 0.011 mmol) and DCM (0.5 mL): yield (0.037 g, 79%) as white solid TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3892, 3822, 3747, 3681, 3278, 3082, 2955, 2876, 2762, 2352, 1625, 1509, 1263, 1180, 1110, 920, 838, 751, 706 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75-7.68 (m, 4H), 7.47-7.33 (m, 9H), 6.77 (d, *J* = 8.75 Hz, 2H), 6.49 (s, 1H), 4.55 (s, 2H), 1.10 (s, 9H);



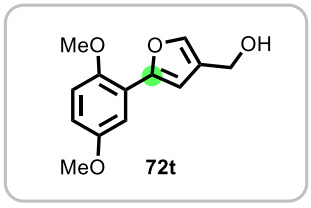
72q

$^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$) δ 155.4, 155.1, 138.7, 135.6, 132.8, 130.1, 128.0, 127.2, 125.2, 124.1, 120.1, 103.6, 57.1, 26.6, 19.6; HRMS (ESI): *m/z* calcd for $C_{27}H_{29}O_3Si$ $[M+H]^+$ 429.1880, found 429.1881.

(5-(2,5-Bis(allyloxy)phenyl)furan-3-yl)methanol (72r): The title compound was prepared following general procedure C using 1-(2,5-bis(allyloxy)phenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (**71r**, 0.05 g, 0.164 mmol), $Bi(OTf)_3$ (0.010 g, 0.016 mmol) and DCM (0.5 mL): yield (0.044 g, 95%) as white solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3923, 3800, 3545, 3438, 3095, 2936, 2881, 1767, 1653, 1610, 1503, 1431, 1284, 1218, 1013, 932, 809, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.42 (d, *J* = 3.00 Hz, 1H),, 7.04 (s, 1H), 6.87 (d, *J* = 8.88 Hz, 1H), 6.79 (dd, *J* = 3.00, 8.88 Hz, 1H), 6.21-5.99 (m, 2H), 5.43 (td, *J* = 1.50, 17.14 Hz, 2H), 5.36-5.25 (m, 2H), 4.64-4.59 (m, 4H), 4.55 (d, *J* = 5.38 Hz, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 153.0, 151.0, 149.0, 138.6, 133.6, 133.6, 127.4, 118.1, 117.7, 114.8, 114.0, 112.2, 110.5, 77.5, 77.4, 76.8, 70.1, 69.6, 57.2; HRMS (ESI): *m/z* calcd for $C_{17}H_{19}O_4$ $[M+H]^+$ 287.1278 found 287.1277.



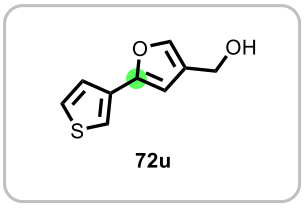
(5-(2,5-Bis((triisopropylsilyl)oxy)phenyl)furan-3-yl)methanol (72s): The title compound was prepared following general procedure C using 1-(2,5-bis((triisopropylsilyl)oxy)phenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (**71s**, 0.05 g, 0.0931 mmol), $Bi(OTf)_3$ (0.006 g, 0.0093 mmol) and DCM (0.5 mL): yield (0.03 g, 62%) as colorless liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3894, 3793, 3706, 3645, 3313, 3166, 2958, 2881, 1491, 1390, 1221, 1012, 899, 824, 766, 672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.27 (d, *J* = 1.63 Hz, 1H), 6.93 (s, 1H), 6.75 (d, *J* = 8.76 Hz, 1H), 6.67 (dd, *J* = 3.00, 8.75 Hz, 1H), 4.59 (s, 2H), 1.35-1.23 (m, 6H), 1.13-1.10 (m, 36H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 151.8, 149.9, 146.6, 138.5, 127.2, 122.2, 119.8, 119.5, 117.7, 109.5, 57.2, 18.1, 18.1, 13.5, 12.7; HRMS (ESI): *m/z* calcd for $C_{29}H_{51}O_4Si_2$ $[M+H]^+$ 519.3320 found 519.3326.



(5-(2,5-Dimethoxyphenyl)furan-3-yl)methanol (72t): The title com-pound was prepared following general procedure C using 1-(2,5-dimethoxyphenyl)-2-(3-

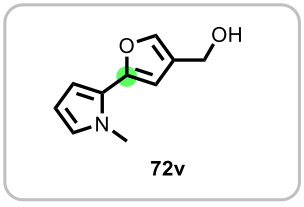
hydroxyoxetan-3-yl)ethan-1-one (**71t**, 0.05 g, 0.198 mmol), $Bi(OTf)_3$ (0.013 g, 0.019 mmol) and DCM (0.5 mL): yield (0.034 g, 74%) as yellow liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3021, 2943, 2403, 1765, 1601, 1503, 1456, 1042, 931, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.43 (m, 1H), 7.39 (d, *J* = 3.13 Hz, 1H), 7.02 (s, 1H), 6.88 (d, *J* = 9.01 Hz, 1H), 6.79 (dd, *J* = 3.13, 9.01 Hz, 1H), 4.60 (s, 2H), 3.89 (s, 3H), 3.82 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 153.8, 151.0, 150.0, 138.6, 127.4, 120.3, 113.8, 112.4, 111.1, 110.4, 57.2, 56.0, 56.0; HRMS (ESI): *m/z* calcd for $C_{13}H_{15}O_4$ $[M+H]^+$ 235.0965, found 235.0963.

(5-(Thiophen-3-yl)furan-3-yl)methanol (72u): The title compound was prepared following general procedure C using 2-(3-hydroxyoxetan-3-yl)-1-(thiophen-3-yl)ethan-1-one (**71u**, 0.05 g, 0.252 mmol), $Bi(OTf)_3$ (0.016 g, 0.025 mmol) and DCM (0.5 mL): yield (0.0432 g, 96%) as yellow solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3863, 3736, 3601, 3391, 3112, 2938, 2880, 1723, 1566, 1482, 1413, 1025, 975, 941, 856, 674 cm^{-1}; ^1H NMR (400 MHz ,$CDCl_3$) δ 7.46 (dd, *J* = 1.25, 2.88 Hz, 1H), 7.39-7.37 (m, 1H), 7.33 (dd, *J* = 2.88, 5.0 Hz, 1H), 7.29 (dd, *J* = 1.38, 5.13 Hz, 1H), 6.52 (s, 1H), 4.57 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz , $CDCl_3$) δ 151.9, 138.7, 132.5, 127.0, 126.4, 124.7, 119.4, 104.9, 56.9; HRMS (ESI): *m/z* calcd for $C_9H_9O_2S$ $[M+H]^+$ 181.0318, found 181.0319.



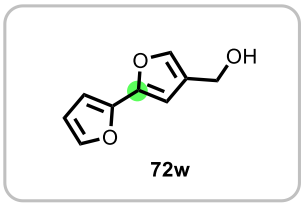
72u

(5-(1-Methyl-1*H*-pyrrol-2-yl)furan-3-yl)methanol (72v): The title compound was prepared following general procedure C using 2-(3-hydroxyoxetan-3-yl)-1-(1-methyl-1H-pyrrol-2-yl)ethan-1-one (**71v**, 0.05 g, 0.256 mmol), $Bi(OTf)_3$ (0.016 g, 0.025 mmol) and DCM (0.5 mL): yield (0.042 g, 94%) as yellow solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3884, 3830, 3787, 3670, 3543, 3334, 3131, 2969, 2754, 2499, 2383, 2346, 2125, 1630, 1469, 1317, 1266, 1175, 1030, 917, 794, 719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1H), 6.66 (s, 1H), 6.45-6.41 (m, 1H), 6.38 (s, 1H), 6.18-6.14 (m, 1H), 4.55 (s, 2H), 3.75 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 148.8, 138.3, 126.7, 124.8, 124.3, 108.9, 107.9, 105.3, 56.7, 35.8; HRMS (ESI): *m/z* calcd for $C_{10}H_{12}O_2N$ $[M+H]^+$ 178.0863, found 178.0862.



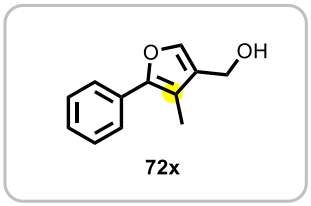
72v

[2,2'-Bifuran]-4-ylmethanol (72w): The title compound was prepared following general procedure C using 1-(furan-2-yl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (**71w**, 0.05 g, 0.274 mmol), $Bi(OTf)_3$ (0.018 g, 0.027 mmol) and DCM (0.5 mL): yield (0.044 g, 98%) as yellow solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3880, 3790, 3689, 3555, 3422, 3340, 3285, 2937, 2878, 2762, 2362, 2049, 1672, 1601, 1459, 1394, 1303, 1182, 1013, 883, 805, 785, 667 cm^{-1}; 1H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 0.75, 1.75 Hz, 1H), 7.38 (d, *J* = 0.88 Hz, 1H), 6.58 (s, 1H), 6.55 (d, *J* = 3.38 Hz, 1H), 6.45 (dd, *J* = 1.75, 3.38 Hz, 1H), 4.58-4.56 (m, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 147.5, 146.4, 142.1, 139.1, 127.1, 111.5, 105.6, 105.2, 56.8; HRMS (ESI): *m/z* calcd for $C_9H_9O_3$ $[M+H]^+$ 165.0546, found 165.0546.



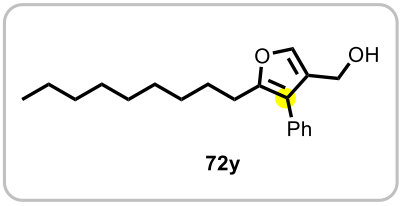
72w

(4-Methyl-5-phenylfuran-3-yl)methanol (72x): The title compound was prepared following general procedure C using 2-(3-hydroxyoxetan-3-yl)-1-phenylpropan-1-one (**71x**, 0.05 g, 0.242 mmol), $Bi(OTf)_3$ (0.015 g, 0.024 mmol) and DCM (0.5 mL): yield (0.041 g, 91%) as white solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3413, 3022, 2928, 2403, 1761, 1677, 1436, 1017, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 1.38, 8.5 Hz, 2H), 7.45-7.39 (m, 3H), 7.31-7.27 (m, 1H), 4.58 (s, 2H), 2.29 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 150.0, 139.2, 131.8, 128.7, 127.5, 127.1, 125.7, 115.8, 55.9, 9.7; HRMS (ESI): *m/z* calcd for $C_{12}H_{13}O_2$ $[M+H]^+$ 189.0910, found 189.0908.



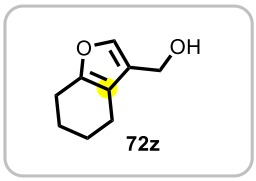
72x

(5-Nonyl-4-phenylfuran-3-yl)methanol (72y): The title compound was prepared following general procedure C using 1-(3-hydroxyoxetan-3-yl)-1-phenylundecan-2-one (**71y**, 0.05 g, 0.157 mmol), $Bi(OTf)_3$ (0.010 g, 0.015 mmol) and DCM (0.5 mL): yield (0.038 g, 81%) as white solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44-7.31 (m, 6H), 4.51 (s, 2H), 2.68-2.57 (m, 2H), 1.67-1.61 (m, 2H), 1.26-1.22 (m, 10H), 0.87 (t, *J* = 7.00 Hz, 3 H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 153.7, 138.9, 130.1, 129.5, 128.7, 127.0, 125.2, 120.8, 56.0, 32.0, 29.4, 29.4, 28.6, 26.6, 22.8, 14.3.



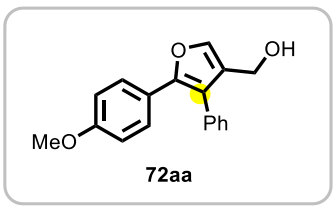
72y

(4,5,6,7-Tetrahydrobenzofuran-3-yl)methanol (72z): The title compound was prepared following general procedure C using 2-(3-hydroxyoxetan-3-yl)cyclohexan-1-one (**71z**, 0.05 g, 0.193 mmol), $Bi(OTf)_3$ (0.012 g, 0.019 mmol) and DCM (0.5 mL): yield (0.043 g, 93%) as colorless liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3432, 3024, 2348, 2097, 1642, 1428, 1018, 669 cm^{-1}; 1H NMR (400 MHz, $CDCl_3$) δ 7.24 (s, 1H), 4.48 (s, 2H), 2.56 (t, *J* = 6.00 Hz, 3H), 2.47-2.41 (m, 3H), 1.82 (dt, *J* = 3.75, 5.82 Hz, 2H), 1.77-1.70 (m, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 152.0, 138.0, 124.6, 116.6, 77.5, 76.8, 56.1, 23.3, 23.0, 22.9, 20.7; HRMS (ESI): *m/z* calcd for $C_9H_{13}O_2$ $[M+H]^+$ 153.0915, found 153.0905.



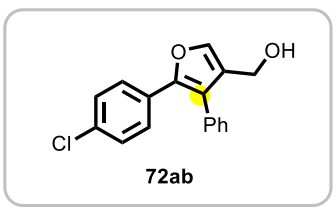
72z

(5-(4-Methoxyphenyl)-4-phenylfuran-3-yl)methanol (72aa): The title compound was prepared following general procedure C using 2-(3-hydroxyoxetan-3-yl)-1-(4-methoxyphenyl)-2-phenylethan-1-one (**71aa**, 0.05 g, 0.167 mmol), $Bi(OTf)_3$ (0.010 g, 0.016 mmol) and DCM (0.5 mL): yield (0.045 g, 98%) as white solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3870, 3782, 3665, 3550, 3465, 3334, 3273, 3081, 2938, 2876, 2760, 2548, 2400, 2053, 1754, 1608, 1454, 1258, 1183, 1031, 842, 780, 671 cm-1; 1H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.44-7.36 (m, 5H), 7.36-7.32 (m, 3H), 6.84-6.74 (m, 2H), 4.48 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 149.9, 139.2, 133.4, 130.0, 129.0, 127.6, 127.4, 127.2, 123.8, 120.5, 113.9, 55.8, 55.4; HRMS (ESI): m/z calcd for C18H17O3 [M+H]+ 281.1172, found 281.1167.



72aa

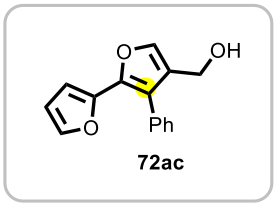
(5-(4-Chlorophenyl)-4-phenylfuran-3-yl)methanol (72ab): The title compound was prepared following general procedure C using 1-(4-chlorophenyl)-2-(3-hydroxyoxetan-3-yl)-2-phenylethan-1-one (**71ab**, 0.05 g, 0.165 mmol), $Bi(OTf)_3$ (0.010 g, 0.016 mmol) and DCM (0.5 mL): yield (0.041 g, 87%) as white solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3900, 3799, 3753, 3635, 3434, 3304, 3063, 2942, 2881, 2703, 2546, 2421, 2335, 2136, 1961, 1766, 1601, 1488, 1265, 1093, 1018, 835, 769, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56-7.54 (m, 1H), 7.46-7.30 (m, 7H), 7.22-7.17 (m, 2H), 4.47 (d, *J* = 0.75 Hz, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 148.8, 140.0, 133.3, 132.9, 129.9, 129.5, 129.2, 128.7, 128.0,



72ab

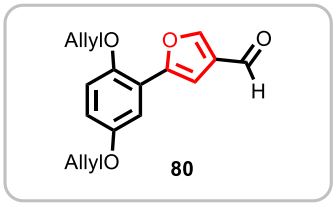
127.5, 127.0, 122.5, 55.7; HRMS (ESI): m/z calcd for C17H14O2Cl [M+H]+ 285.0677, found 285.0673.

(3-Phenyl-[2,2'-bifuran]-4-yl)methanol (72ac): The title compound was prepared following general procedure C using 1-(furan-2-yl)-2-(3-hydroxyoxetan-3-yl)-2-phenylethan-1-one (**71ac**, 0.05 g, 0.193 mmol), $Bi(OTf)_3$ (0.012 g, 0.019 mmol) and DCM (0.5 mL): yield (0.043 g, 93%) as colorless liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat)3426, 3022, 2402, 2350, 1641, 1523, 1426, 1022, 927, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.47-7.33 (m, 6H), 6.35 (dd, *J* = 1.75, 3.38 Hz, 1H), 6.30 (d, *J* = 3.00 Hz, 1H), 4.51 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 146.0, 142.7, 142.1, 140.0, 132.0, 129.9, 128.7, 127.9, 126.9, 121.7, 111.3, 107.0, 55.7; HRMS (ESI): *m/z* calcd for $C_{15}H_{13}O_3$ $[M+H]^+$ 241.0859, found 241.0863.



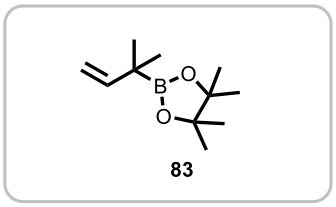
72ac

5-(2,5-Bis(allyloxy)phenyl)furan-3-carbaldehyde (80): To the furyl alcohol **72r** (2.1 g, 7.33 mmol) in dry DCM, Dess Martin Periodinane (DMP, 6.22 g, 14.6 mmol) were added at 0 ℃ and the reac-tion mixture was stirred for 1h at the same temperature. The reac-tion progress was monitored by TLC. After completion of the reaction it was quenched with 1:1 ratio of saturated aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$ and and the aqueous layer was extracted with DCM (3 x 50 mL), then the combined organic layer was washed with brine and dried over Na_2SO_4, filtered, and concentrated in vaccuo and the resulting crude product was purified by silica gel column chromatography to afford the desired product **80** (1.77g, 85%). TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3885, 3806, 3664, 3598, 3443, 3354, 2934, 2877, 2761, 2606, 2351, 2214, 2047, 1690, 1606, 1504, 1427, 1382, 1283, 1227, 1146, 1029, 933, 811, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1H), 8.07 (s, 1H), 7.42 (d, *J* = 3.00 Hz, 1H), 7.32 (s, 1H), 6.94-6.87 (m, 1H), 6.87-6.80 (m, 1H), 6.17-6.01 (m, 2H), 5.47-5.38 (m, 2H), 5.34-5.26 (m, 2H), 4.63 (d, *J* = 5.38 Hz, 2H), 4.54 (d, *J* = 5.38 Hz, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 184.9, 152.8, 149.9, 149.4, 133.5, 133.2, 130.6, 119.3, 118.4, 117.8, 115.7, 113.9, 112.6, 106.6, 77.5, 76.8, 70.0, 69.6; HRMS (ESI): *m/z* calcd for $C_{17}H_{17}O_4$ $[M+H]^+$ 285.1121, found 285.1120.



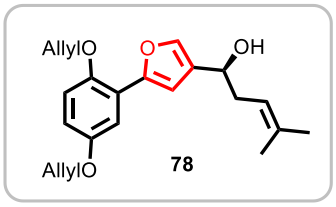
80

4,4,5,5-Tetramethyl-2-(2-methylbut-3-en-2-yl)-1,3,2-dioxaborolane (83): To a suspension of Mg turnings (1.03 g, 39.3 mmol) in THF, pinacol borane (**82**, 5 g, 43.2 mmol) and prenyl bromide (**81**, 9.09 mL, 78.7 mmol) were added dropwise and th reaction was stirred for 0.5 h at room temperature and then another equivalent of prenyl bromide were added to the reaction mixture. The reaction was stirred for additional 2h at room temperature then diluted with hexane and quenched with 0.1 N HCl solution at 0 °C. After that the organic layer was separated and aqueous layer was extracted with hexane. Then the combined organic layer was washed with brine and dried over Na_2SO_4, filtered, and concentrated in vaccuo and used for next step without purification. TLC: R_f = 0.9 (SiO_2, 10% EtOAc/ hexanes). IR (neat) 3891, 3782, 3632, 3431, 3293, 2955, 2387, 2321, 2133, 1469, 1389, 1264, 1023, 803, 686 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{11}H_{22}O_2B$ $[M+H]^+$ 197.1707, found 197.1707.



83

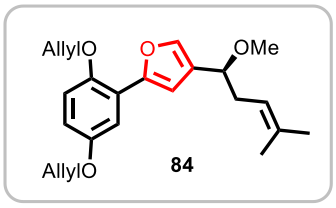
(*S*)-1-(5-(2,5-Bis(allyloxy)phenyl)furan-3-yl)-4-methylpent-3-en-1-ol (78): To an oven dried 100 ml RBF with a stirring bar (*S*)-TRIP (0.264 g, 5.27 mmol) and 4 Å MS were added in N_2 atmosphere. Then aldehyde **80** in dry toluene were added to this mixture drop-wise at room temperature. The reaction mixture was cooled to -60 °C and a solution of borane ester **83** (1.03 g, 5.77 mmol) in dry toluene were added dropwise over 20 minutes. The reaction mixture was stirred at the same temperature for 30 h. then After completion of the reaction, it was filtered through sintered funnel and solvent was evaporated under vacuum. The crude product was purified using silica gel column chromatography to afford the desired product prenyl alcohol **78** (1.01 g, 81%, 94% ee) as yellow liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). The enantiomeric purity was determined by HPLC (CHIRALPAK AD-H column, n-hexane: *i*PrOH = 90:10, flow rate = 1 mL/min, λ = 254 nm, t_{major} = 11.18 min, t_{minor} = 13.22 min), *ee* = 94%, $[\alpha]_D^{28.73}$= -12.81 (*c* = 2.1, $CHCl_3$). IR (neat) 3894, 3791, 3601, 3542, 3426, 3320, 2942, 2559, 2490, 2343, 1716, 1489, 1283, 1214, 1015, 927, 805, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 3.00 Hz, 1H), 7.40 (t, *J* = 0.88 Hz, 1H), 7.03-7.01 (m, 1H), 6.87 (d, *J* = 9.01 Hz, 1H), 6.78 (dd, *J* = 3.13, 9.01 Hz, 1H), 6.17-6.01 (m, 2H), 5.43 (qdd, *J* = 1.63, 4.88, 17.26 Hz, 2H), 5.29



78

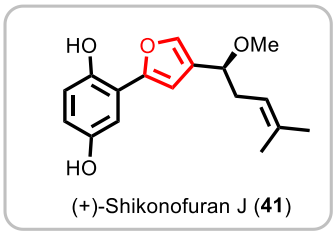
(qdd, *J* = 1.38, 9.13, 10.51 Hz, 2H), 5.23-5.17 (m, 1H), 4.69 (t, *J* = 6.50 Hz, 1H), 4.60 (td, *J* = 1.50, 5.38 Hz, 2H), 4.54 (td, *J* = 1.50, 5.38 Hz, 2H), 2.56-2.46 (m, 2H), 1.75-1.73 (m, 3H), 1.66 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 153.0, 150.6, 149.0, 137.7, 135.8, 133.7, 133.6, 131.0, 121.0, 119.7, 117.9, 117.7, 114.7, 114.1, 112.1, 109.4, 70.1, 69.6, 67.2, 36.9, 26.1, 18.2; HRMS (ESI): *m/z* calcd for $C_{22}H_{27}O_4$ $[M+H]^+$ 355.1904 found 355.1902.

(*S*)-2-(2,5-Bis(allyloxy)phenyl)-4-(1-methoxy-4-methylpent-3-en-1-yl)furan



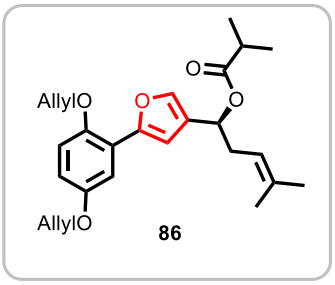
(84): To the suspension of NaH (0.006 g, 0.028 mmol) in dry THF (1 mL), alcohol **78** (0.1 g, 0.028 mmol) in dry THF (2 mL) were added dropwise at 0 °C and the reaction was stirred for 10 minutes at the same temperature. After that MeI (0.02 mL, 0.042 mmol) dissolved in THF (0.5 mL) were added to this dropwise and the reaction was stirred for overnight at room temperature. After completion of the reaction, it was quenched with water and the aqueous layer was extracted with EtOAc (3 x 10 mL), then the combined organic layer was washed with brine and dried over Na_2SO_4, fil-tered and concentrated in vaccuo and the resulting crude product was purified by silica gel column chromatography to afford the desired product **84** (0.097 g, 94%) as yellow liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). The enantiomeric purity was deter-mined by HPLC (CHIRALPAK AD-H column, *n*-hexane:*i*-PrOH = 95:5, flow rate = 1 mL/min, λ = 254 nm, t_{major} = 4.74 min, t_{minor} = 5.06 min), *ee* = 90%, $[\alpha]_D^{28.73}$= -+1.27 (*c* = 0.5, $CHCl_3$). IR (neat) 3929, 3789, 3670, 3600, 3555, 3460, 3392, 3332, 3216, 2938, 2760, 2363, 1775, 1502, 1441, 1379, 1286, 1225, 1106, 1016, 940, 816, 663 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 3.00 Hz, 1H), 7.37 (s, 1H), 7.02-6.98 (m, 1H), 6.87 (d, *J* = 9.01 Hz, 1H), 6.78 (dd, *J* = 3.13, 9.01 Hz, 1H), 6.09 (dtd, *J* = 2.13, 5.25, 10.51 Hz, 1H), 6.17-6.02 (m, 2H), 5.47-5.39 (m, 2H), 5.33-5.25 (m, 2H), 5.18-5.11 (m, 1H), 4.60 (td, *J* = 1.50, 5.38 Hz, 2H), 4.55 (td, *J* = 1.50, 5.38 Hz, 2H), 4.13 (t, *J* = 6.75 Hz, 1H), 3.29 (s, 3H), 2.61-2.51 (m, 1H), 2.47-2.37 (m, 1H), 1.71-1.68 (m, 3H), 1.59 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 153.0, 150.7, 149.0, 138.9, 133.8, 133.7, 133.6, 128.1, 121.0, 120.1, 117.9, 117.7, 114.6, 114.1, 112.1, 109.7, 76.2, 70.1, 69.6, 56.4, 35.2, 25.9, 18.1; HRMS (ESI): *m/z* calcd for $C_{23}H_{29}O_4$ $[M+H]^+$ 369.2060, found 369.2062.

Shikonofuran J (41): To the methoxy furan **84** (0.075 g, 0.20 mmol), in dry MeOH (2 mL) $Pd(PPh_3)_4$ (0.023 g, 0.020 mmol) were added at room temperature and the reaction was stirred for 5 minutes then activated K_2CO_3 (0.168 g, 1.21 mmol) were added to the reaction mixture and the reaction was refluxed for 15 minutes. After completion of reaction, MeOH was removed under vaccum and the residue was treated with 2 N HCl, and the aqueous layer was ex-tracted with EtOAc (3 x 10 mL), then the combined organic layer was washed with brine and dried over Na_2SO_4, filtered, and concentrated in vaccuo and the resulting crude product was purified by silica gel column chromatography to afford the desired product **41** (0.042 g, 72%) as yellow liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). The enantiomeric purity was determined by HPLC (CHIRALPAK AD-H column, n-hexane:i-PrOH = 90:10, flow rate = 1 mL/min, λ = 254 nm, t_{minor} = 21.09 min, t_{major} = 21.90 min), *ee* = 90%, $[\alpha]_D^{28.73}$= -+7.07 (*c* = 0.5, MeOH). ECD (4.3 x 10-4 M, MeOH) (Δε) λ_{max} at 283 (-0.180), 245 (−0.134) and 213 (+0.187); IR (neat) 3869, 3775, 3638, 3446, 3352, 3176, 2941, 2768, 2635, 2562, 2396, 2328, 1957, 1522, 1459, 1360, 1205, 1086, 806, 690 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.42 (s, 1H), 7.17 (d, *J* = 3.05 Hz, 1H), 6.95 (s, 1H), 6.71 (d, *J* = 8.54 Hz, 1H), 6.55 (dd, *J* = 3.05, 8.85 Hz, 1H), 5.16-5.12 (m, 1H), 4.16 (t, *J* = 6.71 Hz, 1H), 3.27 (s, 3H), 2.58-2.49 (m, 1H), 2.44-2.36 (m, 1H), 1.68 (s, 3H), 1.59 (s, 3H); $^{13}C\{1H\}$ NMR (126 MHz, CD_3OD) δ 153.0, 151.2, 148.2, 140.0, 134.7, 129.0, 121.4, 119.9, 117.7, 116.1, 112.7, 109.6, 77.7, 56.5, 36.1, 26.1, 18.2; HRMS (ESI): *m/z* calcd for $C_{17}H_{21}O_4$ $[M+H]^+$ 289.1434, found 289.1432.



(+)-Shikonofuran J (**41**)

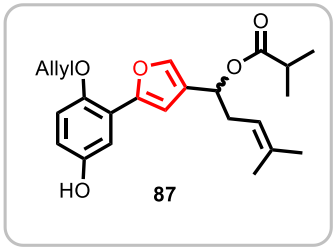
(*S*)-1-(5-(2,5-Bis(allyloxy)phenyl)furan-3-yl)-4-methylpent-3-en-1-yl isobutyrate (86): To the prenyl alcohol **78** (0.2 g, 0.56 mmol) in dry DCM (2 mL), DMAP (0.006 g, 0.0056 mmol) and then Et_3N (0.15 mL, 1.12 mmol) were added at 0 °C. then isobutyryl chloride **85** (0.07 mL, 0.67 mmol) were added dropwise at the same temper-ature. The reaction mixture was stirred for 3h at room temperature. After completion of the reaction, water were added, and the aqueous layer was extracted with DCM (3 x 50 mL), then the combined organic layer was washed with aq. 2 M NaOH and dried over Na_2SO_4, filtered, and concentrated in vaccuo and the resulting crude product was purified by



86

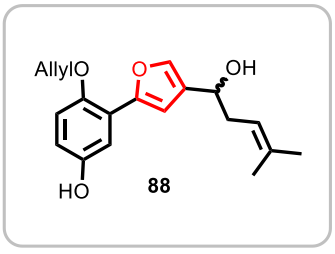
silica gel column chromatography to afford the desired product **86** (0.206 g, 86%) as yellow liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). The enantiomeric purity was determined by HPLC (CHIRALART Cellulose-SC column, n-hexane: *i*PrOH = 95:5, flow rate = 1 mL/min, λ = 254 nm, tmajor = 5.24 min, tminor = 6.36 min), *ee* = 92%, $[\alpha]_D^{26.65}$= -29.96 (*c* = 1.85, $CHCl_3$). IR (neat) 3904, 3795, 3696, 3435, 3315, 2935, 2882, 2646, 2492, 2330, 2132, 1738, 1503, 1211, 1023, 935, 809, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44-7.37 (m, 2H), 7.03-6.96 (m, 1H), 6.87 (d, *J* = 9.01 Hz, 1H), 6.78 (dd, *J* = 3.13, 8.88 Hz, 1H), 6.16-6.02 (m, 2H), 5.78 (t, *J* = 6.75 Hz, 1H), 5.43 (qdd, *J* = 1.63, 9.25, 17.26 Hz, 2H), 5.34-5.25 (m, 2H), 5.11 (tt, *J* = 1.38, 7.13 Hz, 1H), 4.59 (td, *J* = 1.50, 5.25 Hz, 2H), 4.54 (td, *J* = 1.50, 5.25 Hz, 2H), 2.66-2.47 (m, 3H), 1.71-1.67 (m, 3H), 1.63 (s, 3H), 1.17 (d, *J* = 7.13 Hz, 3H), 1.15 (d, *J* = 7.00 Hz, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 176.6, 153.0, 150.5, 149.0, 138.7, 134.8, 133.7, 133.6, 127.3, 120.9, 119.1, 117.9, 117.7, 114.7, 114.2, 112.1, 109.7, 70.2, 69.6, 68.5, 34.3, 33.8, 25.9, 19.1, 19.0, 18.1; HRMS (ESI): *m/z* calcd for $C_{26}H_{33}O_5$ $[M+H]^+$ 425.2323, found 425.2319.

1-(5-(2-(Allyloxy)-5-hydroxyphenyl)furan-3-yl)-4-methylpent-3-en-1-yl isobutyrate (87): yellow colored liquid. TLC: R_f = 0.4 (SiO_2, 30% EtOAc/ hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.07 (d, *J* = 3.00 Hz, 1H), 6.86 (d, *J* = 8.88 Hz, 1H), 6.79 (dd, *J* = 3.00, 8.88 Hz, 1H), 6.70 (s, 1H), 6.44 (br. s., 1H), 6.11-6.00 (m, 1H), 5.77 (t, *J* = 6.88 Hz, 1H), 5.41 (qd, *J* = 1.50, 17.26 Hz, 1H), 5.28 (dd, *J* = 1.38, 10.51 Hz, 1H), 5.09 (t, *J* = 7.00 Hz, 1H), 4.51 (td, *J* = 1.50, 5.38 Hz, 2H), 2.67-2.47 (m, 3H), 1.69 (s, 3H), 1.63 (s, 3H), 1.17 (d, *J* = 7.00 Hz, 3H), 1.15 (d, *J* = 7.00 Hz, 3H); HRMS (ESI): *m/z* calcd for $C_{23}H_{29}O_5$ $[M+H]^+$ 385.2010, found 385.2011.



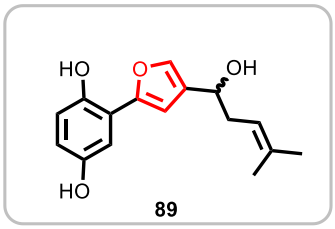
87

4-(Allyloxy)-3-(4-(1-hydroxy-4-methylpent-3-en-1-yl)furan-2-yl)phenol (88): yellow colored liquid. TLC: R_f = 0.3 (SiO_2, 30% EtOAc/ hexanes). ^1H NMR (500 MHz, CD_3OD) δ 7.41 (d, *J* = 2.93 Hz, 1H), 7.29-7.22 (m, 1H), 7.04-6.99 (m, 1H), 6.78 (d, *J* = 8.80 Hz, 1H), 6.72-6.63 (m, 1H), 6.19-6.02 (m, 1H), 5.47-5.37 (m, 1H), 5.30-5.22 (m, 1H), 5.22-5.16 (m, 1H), 4.63-4.57 (m, 2H), 4.50 (td, *J* = 1.49, 5.19 Hz, 1H), 2.53-2.40 (m, 2H), 1.70 (s, 3H), 1.63 (s, 3H); HRMS (ESI): *m/z* calcd for $C_{19}H_{23}O_4$ $[M+H]^+$ 315.1591, found 315.1585.



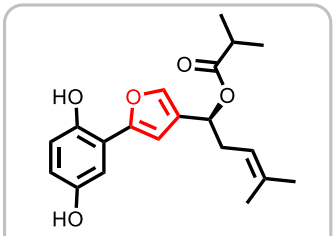
88

2-(4-(1-Hydroxy-4-methylpent-3-en-1-yl)furan-2-yl)benzene-1,4-diol (89): Red colored liquid. TLC: R_f = 0.2 (SiO_2, 30% EtOAc/ hexanes). IR (neat) 3022, 2929, 2402, 1721, 1517, 1432, 1021, 929, 670 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.39 (s, 1H), 7.16 (d, *J* = 3.00 Hz, 1H), 7.00 - 7.02 (m, 1H), 6.70 (d, *J* = 8.63 Hz, 1H), 6.55 (dd, *J* = 3.00, 8.63 Hz, 1H), 5.20 (tt, *J* = 1.36, 7.14 Hz, 1H), 4.59 (t, *J* = 6.69 Hz, 1H), 2.42-2.53 (m, 2H), 1.69-1.72 (m, 4H), 1.63 (s, 3H); HRMS (ESI): *m/z* calcd for $C_{16}H_{19}O_4$ $[M+H]^+$ 275.1278, found 275.1275.



89

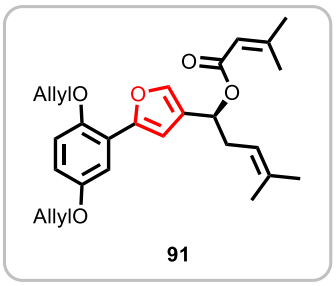
Shikonofuran D (42): To the isobutyryl ester **86** (0.073 g, 0.17 mmol) in dry MeOH (2 mL), $NiCl_2.6H_2O$ (0.122 g, 0.51 mmol) were added at 0 °C. Then $NaBH_4$ (0.032 g, 0.85 mmol) were added at the same temperature. The reaction was stirred for 10 minutes. After completion of the reaction, it was quenched with MeOH and stirred for another 20 minutes. Then it was filtered through celite and the filtrate was concentrated and the crude product was purified by silica gel column chromatography to afford the desired product **42** (0.026 g, 44%) as reddish liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). The enantiomeric purity was determined by HPLC (CHIRALART Cellulose-SC column, *n*-hexane:*i*PrOH = 95:5, flow rate = 1 mL/min, λ = 254 nm, t_{major} = 15.32 min, t_{minor} = 17.51 min), *ee* = 92%, $[\alpha]_D^{31.77}$ = -25.32 (*c* = 0.2, $CHCl_3$). ECD (4.3 x 10-4 M, MeOH) λ_{max} (Δε) at 322 nm (-1.10), 274 nm (-1.29) and 204 nm (-3.23); IR (neat) 3778, 3645 3528, 3269, 3167, 2936, 2872, 2701, 2387, 2129, 1752, 1468, 1267, 1184, 861, 809, 737, 625 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.01 (d, *J* = 3.00 Hz, 1H), 6.81 (d, *J* = 8.63 Hz 1H), 6.72-6.65 (m, 2H), 6.44 (br. s., 1H), 5.77 (t, *J* = 6.75 Hz, 1H), 5.14-5.03 (m, 1H), 4.89 (br. s., 1H), 2.71-2.45 (m, 3H), 1.71-1.67 (m, 3H), 1.62 (s, 3H), 1.19-1.17 (m, 3H), 1.15 (d, *J* = 7.00 Hz, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 176.8, 152.5, 149.3, 146.7, 138.9, 135.2, 127.3, 118.7, 118.2, 117.0, 116.6, 112.2, 106.8, 68.3, 34.3, 33.7, 25.9, 19.1, 19.0, 18.1; HRMS (ESI): *m/z* calcd for $C_{20}H_{25}O_5$ $[M+H]^+$ 345.1697, found 345.1692.



Shikonofuran D (**42**)

(*S*)-1-(5-(2,5-Bis(allyloxy)phenyl)furan-3-yl)-4-methylpent-3-en-1-yl-3-methylbut-2-enoate (91): To the stirred solution of prenyl alcohol **78** (0.2 g, 0.56 mmol) in dry DCM (4 mL) DCC (0.186 g, 0.090 mmol) and DMAP (0.006 g, 0.056

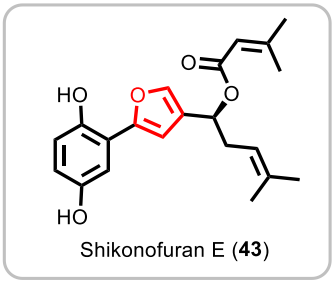
mmol) were added at 0 °C and the reaction mixture was stirred for 10 minutes. After



91

that 3-methylbut-2-enoic acid **90** (0.067 g, 0.067 mmol) were added to this. The reaction was stirred for 12 h at room temperature. After completion of the reaction it was quenched with water and the aqueous layer was extracted with DCM (3 x 10 mL) and dried over Na_2SO_4, filtered, and concentrated in vaccuo and the resulting crude product was purified by silica gel column chromatography to afford the desired product **91** (0.22 g, 89%) as yellow liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). The enantiomeric purity was determined by HPLC (CHIRALPAK AD-H column, *n*-hexane:*i*PrOH = 95:5, flow rate = 1 mL/min, λ = 254 nm, t_{minor} = 5.43 min, t_{major} = 5.95 min), *ee* =88%, $[\alpha]_D^{28.73}$= -14.35 (*c* = 0.5, $CHCl_3$). IR (neat) 3905, 3804, 3763, 3650, 3572, 3433, 3316, 2962, 2923, 2861, 1721, 1647, 1497, 1452, 1376, 1273, 1222, 1137, 1026, 804, 672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.40 (d, *J* = 3.00 Hz, 1H), 7.03-7.01 (m, 1H), 6.86 (d, *J* = 9.01 Hz, 1H), 6.77 (dd, *J* = 3.00, 8.88, 1H), 6.17-6.01 (m, 2H), 5.81 (t, *J* = 6.88 Hz, 1H), 5.72-5.69(m, 1H), 5.43 (qdd, *J* = 1.63, 9.76, 17.26 Hz, 2H), 5.29 (qt, *J* = 1.25, 10.26 Hz, 2H), 5.15-5.09 (m, 1H), 4.59 (td, *J* = 1.38, 5.25 Hz, 2H), 4.54 (td, *J* = 1.50, 5.25 Hz, 2H), 2.69-2.49 (m, 2H), 2.17 (d, *J* = 1.25 Hz, 3H), 1.89 (d, *J* = 1.25 Hz, 3H), 1.70-1.67 (m, 3H), 1.62 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.1, 156.8, 153.0, 150.4, 149.0, 138.9, 134.8, 133.6, 133.6, 127.3, 121.0, 119.1, 117.8, 117.7, 116.4, 114.6, 114.1, 112.1, 109.9, 70.1, 69.6, 67.8, 33.8, 27.6, 25.9, 20.4, 18.1; HRMS (ESI): *m/z* calcd for $C_{27}H_{33}O_5$ $[M+H]^+$ 437.2323, found 437.2317.

Shikonofuran E (43): To the ester **91** (0.15 g, 0.343 mmol) in dry MeOH (2 mL),

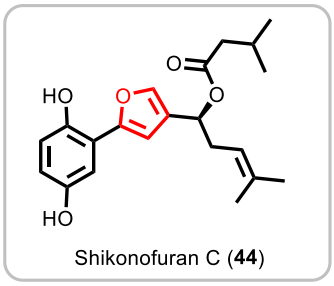


Shikonofuran E (**43**)

$NiCl_2.6H_2O$ (0.245 g, 1.03 mmol) were added at -60 °C. Then $NaBH_4$ (0.013 g, 0.343 mmol) were added at the same temperature. The reaction was stirred for 10 minutes. After completion of the reaction, it was quenched with MeOH and stirred for another 20 minutes. Then it was filtered through celite and the filtrate was concentrated and the crude product was purified by silica gel column chromatography to afford the desired product **43** (0.083 g, 68%) as reddish liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). The enantiomeric purity was determined by HPLC (CHIRALPAK AD-H column, n-hexane:*i*PrOH = 80:20, flow rate = 1 mL/min, λ = 254 nm, t_{minor} = 6.74 min,

t_{major} = 7.68 min), *ee* = 66%, %, $[\alpha]_D^{30.49}$ = -62.40 (*c* = 0.1, $CHCl_3$); ECD (4.3 x 10-4 M, MeOH) λ_{max} ($\Delta\varepsilon$) at 316 nm -2.56), 274 nm (-2.59), 245 nm (-1.79) and a positive Cotton effect at 227 nm (+0.549); IR (neat) 3894, 3841, 3784, 3652, 3544, 3422, 3379, 3327, 2986, 2937, 2777, 2706, 2632, 2551, 2334, 2053, 1952, 1845, 1697, 1457, 1230, 1161, 1085, 1022, 768, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 6.98 (d, *J* = 3.00 Hz, 1H), 6.80 (d, *J* = 8.63 Hz, 1H), 6.69 (s, 1H), 6.69-6.66 (m, 1H), 6.51 (s, 1H), 5.79 (t, *J* = 6.88 Hz, 1H), 5.73-5.69 (m, 1H), 5.12-5.07 (m, 1H), 2.67-2.48 (m, 2H),, 2.17 (d, *J* = 1.25 Hz, 3H), 1.90 (d, *J* = 1.25 Hz, 3H), 1.68 (s, 3H), 1.61 (s, 3H); $^{13}C\{1H\}$NMR (101 MHz, $CDCl_3$) δ 166.3, 157.7, 152.5, 149.3, 146.6, 139.0, 135.2, 127.4, 118.8, 118.2, 117.0, 116.6, 116.1, 112.2, 106.8, 67.7, 33.8, 27.6, 25.9, 20.5, 18.1; HRMS (ESI): *m/z* calcd for $C_{21}H_{25}O_5$ $[M+H]^+$ 357.1697, found 357.1691

Shikonofuran C (44): To the ester **91** (0.10 g, 0.229 mmol) in dry MeOH (2 mL),

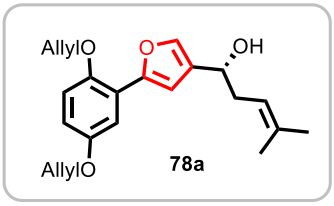


Shikonofuran C (**44**)

$NiCl_2.6H_2O$ (0.163 g, 0.687 mmol) were added at -40 °C. Then $NaBH_4$ (0.043 g, 1.14 mmol) were added at the same temperature. The reaction was stirred for 10 minutes. After completion of the reaction, it was quenched with MeOH and stirred for another 20 minutes. Then it was filtered through celite and the filtrate was concentrated and the crude product was purified by silica gel column chromatography to afford the desired product **44** (0.059 g, 71%) as reddish liquid. TLC: R_f= 0.4 (SiO_2, 20% EtOAc/ hexanes). The enantiomeric purity was determined by HPLC (CHIRALPAK AD-H column, n-hexane:^{i}PrOH = 80:20, flow rate = 1 mL/min, λ = 254 nm, tminor = 7.89 min, tmajor = 9.10 min), *ee* = 94%, $[\alpha]_D^{27.51}$= -58.05 (c = 0.5, $CHCl_3$); ECD (4.3 x 10-4 M, MeOH) λ_{max} ($\Delta\varepsilon$) at 321 nm (-1.76), 283 nm (-1.68), 260 nm (-1.19) and 224 nm (-3.02); IR (neat) 3863, 3780, 3710, 3611, 3548, 3442, 3352, 3274, 3198, 3136, 3094, 2978, 2936, 2884, 2764, 2628, 2552, 2505, 2431, 2373, 2326, 2209, 2109, 2049, 1998, 1891, 1717, 1509, 1452, 1360, 1291, 1202, 1110, 1038, 989, 875, 817, 753, 708, 671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ; 7.45 (s, 1H), 7.01 (d, *J* = 2.88 Hz, 1H), 6.81 (d, *J* = 8.63 Hz, 1H), 6.74-6.64 (m, 2H), 6.43 (s, 1H), 5.79 (t, *J* = 6.88 Hz, 1H), 5.09 (t, *J* = 7.13 Hz, 1H), 4.99 (br. s., 1H), 2.68-2.57 (m, 1H), 2.56-2.44 (m, 1H), 2.23-2.17 (m, 2H), 2.17-2.02 (m, 1H), 1.69 (s, 3H), 1.62 (s, 3H), 0.94 (dd, *J* = 1.13, 6.63 Hz, 6H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 172.9, 152.5, 149.4, 146.6, 139.1, 135.3, 127.2, 118.7, 118.2, 117.1, 116.6, 112.2,

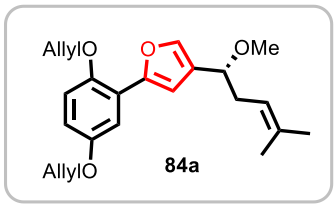
106.9, 68.3, 43.9, 33.7, 26.0, 25.9, 22.5, 18.1; HRMS (ESI): *m/z* calcd for $C_{21}H_{27}O_5$ $[M+H]^+$ 359.1853, found 359.1848.

(*R*)-1-(5-(2,5-Bis(allyloxy)phenyl)furan-3-yl)-4-methylpent-3-en-1-ol (78a): To



an oven dried 100 ml RBF with a stirring bar (*R*)-TRIP (0.264 g, 5.27 mmol) and 4 Å MS were added in N_2 atmosphere. Then aldehyde **80** (1 g, 3.51 mmol) in dry toluene were added to this mixture drop-wise at room temperature. The reaction mixture was cooled to -60 °C and a solution of borane ester **83** (1.03 g, 5.77 mmol) in dry toluene were added dropwise over 20 minutes. The reaction mixture was stirred at the same temperature for 30 h. then After completion of the reaction, it was filtered through sintered funnel and solvent was evaporated under vacuum. The crude product was purified using silica gel column chromatography to afford the desired product prenyl alcohol **78a** (0.97 g, 79%, 94% ee) as yellow liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). The enantiomeric purity was determined by HPLC (CHIRALPAK AD-H column, n-hexane: *i*PrOH = 90:10, flow rate = 1 mL/min, λ = 254 nm, t_{minor} = 11.32 min, t_{major} = 13.20 min), *ee* = 93%, $[\alpha]_D^{32.24}$= +13.38 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 3.13 Hz, 1H), 7.40 (s, 1H), 7.04-6.98 (m, 1H), 6.87 (d, *J* = 9.01 Hz, 1H), 6.78 (dd, *J* = 3.00, 8.88 Hz, 1H), 6.17-6.01 (m, 2H), 5.46-5.40 (m, 2H), 5.22-5.18 (m, 2H), 5.17 - 5.24 (m, 1H), 4.69 (t, *J* = 6.38 Hz, 1H), 4.60 (td, *J* = 1.50, 5.25 Hz, 2H), 4.54 (td, *J* = 1.50, 5.25 Hz, 2H), 2.57-2.45 (m, 2H), 1.77-1.72 (m, 3H), 1.66 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.0, 150.6, 149.0, 137.7, 135.8, 133.7, 133.6, 131.0, 121.0, 119.7, 117.9, 117.7, 114.7, 114.1, 112.1, 109.4, 70.1, 69.6, 67.2, 36.9, 26.1, 18.2;

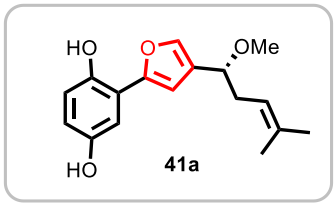
(*R*)-2-(2,5-Bis(allyloxy)phenyl)-4-(1-methoxy-4-methylpent-3-en-1-yl)furan



(84a): To the suspension of NaH (0.006 g, 0.028 mmol) in dry THF (1 mL), alcohol **78a** (0.1 g, 0.028 mmol) in dry THF (2 mL) were added dropwise at 0 °C and the reaction was stirred for 10 minutes at the same temperature. After that MeI (0.02 mL, 0.042 mmol) dissolved in THF (0.5 mL) were added to this dropwise and the reaction was stirred for overnight at room temperature. After completion of the reaction, it was quenched with water and the aqueous layer was extracted with EtOAc (3 x 10 mL), then the combined organic layer was washed with

brine and dried over Na_2SO_4, fil-tered and concentrated in vaccuo and the resulting crude product was purified by silica gel column chromatography to afford the desired product **84a** (0.097 g, 94%) as yellow liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). The enantiomeric purity was deter-mined by HPLC (CHIRALPAK AD-H column, n-hexane:*i*-PrOH = 95:5, flow rate = 1 mL/min, λ = 254 nm, t_{minor} = 4.70 min, t_{major} = 5.01 min), *ee* = 90%, $[\alpha]_D^{28.73}$= -1.94 (*c* = 1.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 3.00 Hz, 1H), 7.37 (s, 1H), 7.00 (s, 1H), 6.87 (d, *J* = 9.01 Hz, 1H), 6.78 (dd, *J* = 3.00, 8.88 Hz, 1H), 6.15-6.04 (m, 2H), 5.43 (td, *J* = 1.75, 17.26 Hz, 2H), 5.31-5.27 (m, 2H), 5.15 (t, *J* = 6.88 Hz, 1H), 4.60 (d, *J* = 5.25 Hz, 2H), 4.55 (d, *J* = 5.25 Hz, 2H), 4.13 (t, *J* = 6.75 Hz, 1H), 3.29 (s, 3H), 2.61-2.51 (m, 1H), 2.48-2.36 (m, 1H), 1.69 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.0, 150.7, 149.0, 138.9, 133.8, 133.7, 133.6, 128.1, 121.0, 120.2, 117.9, 117.7, 114.6, 114.1, 112.1, 109.7, 77.5, 76.8, 76.2, 70.1, 69.6, 56.4, 35.2, 25.9, 18.1

***ent*-Shikonofuran J (41a):** To the methoxy furan **84a** (0.026 g, 0.0705 mmol), in dry

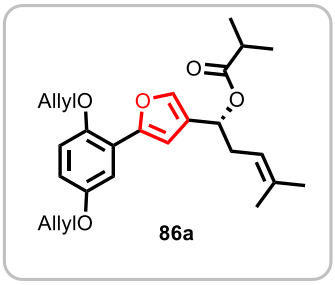


41a

MeOH (1 mL) $Pd(PPh_3)_4$ (0.008 g, 0.00705 mmol) were added at room temperature and the reaction was stirred for 5 minutes then activated K_2CO_3 (0.058 g, 0.423 mmol) were added to the reaction mixture and the reaction was refluxed for 15 minutes. After completion of the reaction, MeOH was removed under vaccum and the residue was treated with 2 N HCl, and the aqueous layer was ex-tracted with EtOAc (3 x 5 mL), then the combined organic layer was washed with brine and dried over Na_2SO_4, filtered, and concentrated in vaccuo and the resulting crude product was purified by silica gel column chromatography to afford the desired product **41a** (0.015 g, 75%) as yellow liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). The enantiomeric purity was determined by HPLC (CHIRALPAK AD-H column, n-hexane:*i*-PrOH = 90:10, flow rate = 1 mL/min, λ = 254 nm, t_{major} = 31.46 min, t_{minor} = 34.06 min), *ee* = 90%, $[\alpha]_D^{27.13}$= -7.63 (*c* = 0.5, MeOH); ECD (4.3 x 10-4 M, MeOH) λ_{max} (Δε) at 283 (−0.018), 245 (+0.026) and 213 (−0.312) nm); ^{1}H NMR (500 MHz, CD_3OD) δ 7.42 (s, 1H), 7.17 (d, *J* = 3.05 Hz, 1H), 6.95 (s, 1H), 6.71 (d, *J* = 8.54 Hz, 1H), 6.56 (dd, *J* = 3.05, 8.54 Hz, 1H), 5.17-5.11 (m, 1H), 4.15 (t, *J* = 6.71 Hz, 1H), 3.26 (s, 3H), 2.58-2.49 (m, 1H), 2.44-2.36 (m, 1H), 1.70-1.66 (m, 3H), 1.59 (s, 3H); ^{13}C NMR

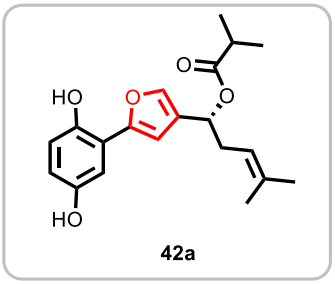
(126 MHz, CD_3OD) δ 153.0, 151.2, 148.2, 140.0, 134.7, 129.0, 121.4, 119.9, 117.7, 116.1, 112.7, 109.6, 77.6, 56.5, 36.1, 26.1, 18.2

(*R*)-1-(5-(2,5-Bis(allyloxy)phenyl)furan-3-yl)-4-methylpent-3-en-1-yl isobutyrate (86a): To the prenyl alcohol **78a** (0.2 g, 0.56 mmol) in dry DCM (2 mL), DMAP (0.006 g, 0.0056 mmol) and then Et_3N (0.15 mL, 1.12 mmol) were added at 0 °C. then isobutyryl chloride **85** (0.07 mL, 0.67 mmol) were added dropwise at the same temper-ature. The reaction mixture was stirred for 3h at room temperature. After completion of the reaction, water were added, and the aqueous layer was extracted with DCM (3 x 50 mL), then the combined organic layer was washed with aq. 2 M NaOH and dried over Na_2SO_4, filtered, and concentrated in vaccuo and the resulting crude product was purified by silica gel column chromatography to afford the desired product **86a** (0.198 g, 83%) as yellow liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). The enantiomeric purity was determined by HPLC (CHIRALART Cellulose-SC column, n-hexane: *i*PrOH = 95:5, flow rate = 1 mL/min, λ = 254 nm, t_{minor} = 5.27 min, t_{major} = 6.36 min), *ee* = 92%, $[\alpha]_D^{26.72}$ = +30.84 (*c* = 0.3, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.38 (m, 2H), 7.00 (s, 1H), 6.87 (d, *J* = 9.01 Hz, 1H), 6.78 (dd, *J* = 3.13, 9.01 Hz, 1H), 6.16-6.02 (m, 2H), 5.79 (t, *J* = 6.75 Hz, 1H), 5.43 (qdd, *J* = 1.63, 9.76, 17.26 Hz, 2H), 5.34-5.24 (m, 2H), 5.16-5.09 (m, 1H), 4.59 (td, *J* = 1.38, 6.75 Hz, 2H), 4.54 (td, *J* = 1.50, 6.75 Hz, 2H), 2.68-2.47 (m, 3H), 1.71-1.67 (m, 3H), 1.63 (s, 3H), 1.17 (d, *J* = 7.00 Hz, 3H), 1.15 (d, *J* = 7.00 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.5, 153.0, 150.5, 149.0, 138.7, 134.8, 133.6, 133.6, 127.2, 120.9, 119.0, 117.9, 117.7, 114.7, 114.1, 112.1, 109.7, 70.1, 69.6, 68.4, 34.3, 33.8, 25.9, 19.1, 19.0, 18.1



86a

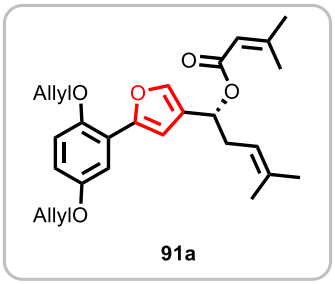
***ent*-Shikonofuran D (42a):** To the isobutyryl ester **86a** (0.062 g, 0.146 mmol) in dry MeOH (2 mL), $NiCl_2.6H_2O$ (0.104 g, 0.438 mmol) were added at 0 °C. Then $NaBH_4$ (0.027 g, 0.73 mmol) were added at the same temperature. The reaction was stirred for 10 minutes. After completion of the reaction, it was quenched with MeOH and stirred for another 20 minutes. Then it was filtered through celite and the filtrate was



42a

concentrated and the crude product was purified by silica gel column chromatography to afford the desired product **42a** (0.023 g, 46%) as reddish liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). The enantiomeric purity was determined by HPLC (CHIRALART Cellulose-SC column, *n*-hexane:*i*PrOH = 95:5, flow rate = 1 mL/min, λ = 254 nm, t_{minor} = 15.52 min, t_{major} = 17.30 min), *ee* = 92%, $[\alpha]_D^{26.54}$= +26.19 (*c* = 1.3, $CHCl_3$); ECD (4.3 x 10-4 M, MeOH) λ_{max} (Δε) at 323 nm (+1.39), 267 nm (+6.00) and 207 nm (+2.50); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.00 (d, *J* = 3.00 Hz, 1H), 6.82 (d, *J* = 8.75 Hz, 1H), 6.72-6.65 (m, 2H), 6.39 (s, 1H), 5.77 (t, *J* = 6.82 Hz, 1H), 5.12-5.06 (m, 1H), 4.53 (br. s., 1H), 2.67-2.47 (m, 3H), 1.69 (s, 3H), 1.63 (s, 4H), 1.18 (d, *J* = 7.00 Hz, 3H), 1.15 (d, *J* = 7.00 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.6, 152.5, 149.3, 146.7, 138.9, 135.2, 127.3, 118.7, 118.2, 117.0, 116.6, 112.2, 106.8, 68.1, 34.3, 33.7, 25.9, 19.1, 19.0, 18.1.

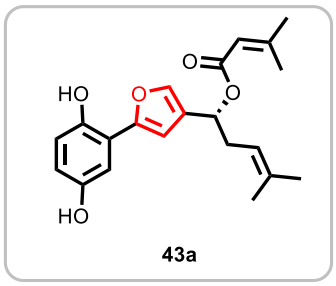
(*R*)-1-(5-(2,5-Bis(allyloxy)phenyl)furan-3-yl)-4-methylpent-3-en-1-yl-3-methylbut-2-enoate (91a): To the stirred solution of prenyl alcohol **78a** (0.287 g, 0.809 mmol) in dry DCM (4 mL) DCC (0.267 g, 1.29 mmol) and DMAP (0.009 g, 0.080 mmol) were added at 0 °C and the reaction mixture was stirred for 10 minutes. After that 3-methylbut-2-enoic acid **90** (0.067 g, 0.067 mmol) were added to this. The reaction was stirred for 12 h at room temperature. After completion of the reaction it was quenched with water and the aqueous layer was extracted with DCM (3 x 10 mL) and dried over Na_2SO_4, filtered, and concentrated in vaccuo and the resulting crude product was purified by silica gel column chromatography to afford the desired product **91a** (0.298 g, 84%) as yellow liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). The enantiomeric purity was determined by HPLC (CHIRALPAK AD-H column, n-hexane:^{i}PrOH = 95:5, flow rate = 1 mL/min, λ = 254 nm, t_{major} = 5.22 min, t_{minor} = 5.96 min), *ee* =92%, $[\alpha]_D^{31.57}$ = +53.23 (*c* = 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.36 (m, 2H), 7.01 (s, 1H), 6.86 (d, *J* = 8.88 Hz, 1H), 6.77 (dd, *J* = 3.00, 8.88 Hz, 1H), 6.16-6.02 (m, 2H), 5.80 (t, *J* = 6.75 Hz, 1H), 5.72-5.66 (m, 1H), 5.43 (qdd, *J* = 1.63, 9.38, 17.26 Hz, 2H), 5.34-5.24 (m, 2H), 5.17-5.09 (m, 1H), 4.59 (td, *J* = 1.50, 5.38 Hz, 2H), 4.54 (td, *J* = 1.50, 5.25 Hz, 2H), 2.67-2.48 (m, 2H), 2.17 (d, *J* = 1.13 Hz, 3H), 1.89 (d, *J* = 1.25 Hz, 3H), 1.72-1.66 (m, 3H), 1.62 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 156.8, 153.0, 150.4, 149.0,



91a

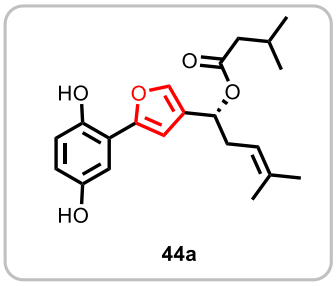
138.9, 134.8, 133.7, 133.6, 127.4, 119.2, 117.8, 117.7, 116.5, 114.7, 114.2, 112.1, 109.9, 70.2, 69.6, 67.9, 33.8, 27.6, 25.9, 20.4, 18.1

***ent*-Shikonofuran E (43a):** To the ester **91a** (0.251 g, 0.574 mmol) in dry MeOH (4 mL), $NiCl_2.6H_2O$ (0.409 g, 1.72 mmol) were added at -60 °C. Then $NaBH_4$ (0.022 g, 0.574 mmol) were added at the same temperature. The reaction was stirred for 10 minutes. After completion of the reaction, it was quenched with MeOH and stirred for another 20 minutes. Then it was filtered through celite and the filtrate was concentrated and the crude product was purified by silica gel column chromatography to afford the desired product **43a** (0.113 g, 55%) as reddish liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). The enantiomeric purity was determined by HPLC (CHIRALPAK AD-H column, n-hexane:*i*PrOH = 80:20, flow rate = 1 mL/min, λ = 254 nm, t_{major} = 6.82 min, t_{minor} = 7.70 min), *ee* = 92%, $[\alpha]_D^{30.40}$= +68.26 (c = 1.4, $CHCl_3$); ECD (4.3 x 10-4 M, MeOH) λ_{max} (Δε) at 319 nm (+3.39), 270 nm (+5.69), 227 nm (+6.33) and 212 nm (+3.34); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 6.99 (d, *J* = 2.88 Hz, 1H), 6.79 (d, *J* = 8.75 Hz, 1H), 6.70 (s, 1H), 6.67 (dd, *J* = 2.88, 8.63 Hz, 1H), 5.78 (t, *J* = 6.75 Hz, 1H), 5.72-5.68 (m, 1H), 5.13-5.05 (m, 1H), 2.67-2.57 (m, 1H), 2.57-2.48 (m, 1H), 2.19-2.15 (m, 3H), 1.92-1.87 (m, 3H), 1.68 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 157.7, 152.4, 149.3, 146.6, 139.0, 135.2, 127.4, 118.8, 118.2, 117.1, 116.6, 116.2, 112.2, 106.9, 67.7, 33.8, 27.6, 25.9, 20.5, 18.2



43a

***ent*-Shikonofuran C (44a):** To the ester **91a** (0.150 g, 0.343 mmol) in dry MeOH (4 mL), $NiCl_2.6H_2O$ (0.245 g, 1.03 mmol) were added at -40 °C. Then $NaBH_4$ (0.052 g, 1.37 mmol) were added at the same temperature. The reaction was stirred for 10 minutes. After completion of the reaction, it was quenched with MeOH and stirred for another 20 minutes. Then it was filtered through celite and the filtrate was concentrated and the crude product was purified by silica gel column chromatography to afford the desired product **44a** (0.078 g, 64%) as reddish liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). The enantiomeric purity was determined by HPLC (CHIRALPAK AD-H column, n-hexane:^{i}PrOH = 80:20, flow rate = 1 mL/min, λ = 254 nm, t_{major} = 7.92 min,



44a

t_{minor} = 9.14 min), *ee* = 92%, $[\alpha]_D^{27.96}$ = +57.56 (c = 1.1, $CHCl_3$); ECD (4.3 x 10-4 M, MeOH) λ_{max} ($\Delta\varepsilon$) at 321 nm (0.79), 277 nm (+2.82), 269 nm (+4.07) and 220 nm (+2.28); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.01 (d, *J* = 3.00 Hz, 1H), 6.81 (d, *J* = 8.76 Hz, 1H), 6.72-6.66 (m, 2H), 6.43 (br. s, 1H), 5.79 (t, *J* = 6.88 Hz, 1H), 5.14-5.05 (m, 1H), 2.66-2.59 (m, 1H), 2.54-2.47 (m, 1H), 2.22-2.17 (m, 2H), 2.15-2.05 (m, 1H), 1.69 (s, 3H), 1.62 (s, 3H), 0.95 (d, *J* = 1.38 Hz, 3H), 0.93 (d, *J* = 1.25 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 152.5, 149.3, 146.7, 139.0, 135.3, 127.2, 118.7, 118.2, 117.1, 116.6, 112.2, 106.9, 68.3, 43.8, 33.7, 26.0, 25.9, 22.5, 18.1

2.2.9. References

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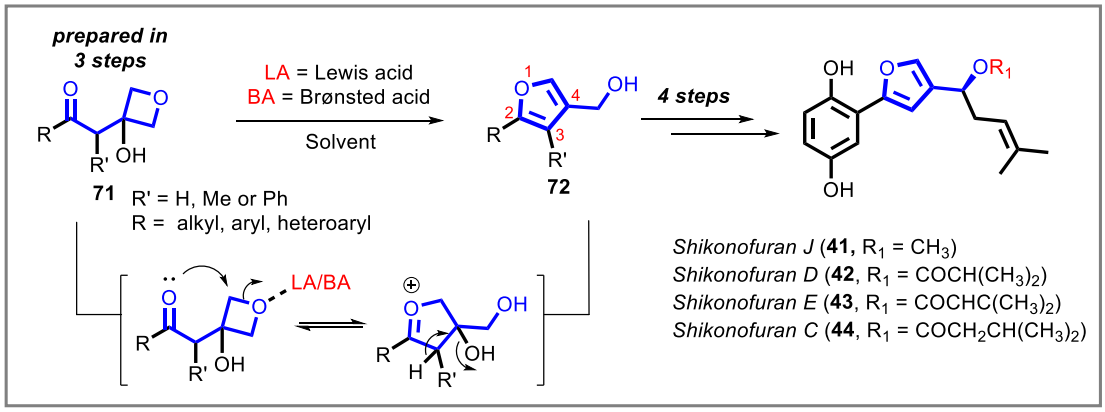
Chapter-2, Section-B: Present work

2.2.1. Hypothesis

Inspired by the interesting biological profile and structural features of shikonofurans J, D, E, and C (**41-44**) and our curiosity in stereoselective total synthesis of furan-containing biologically potent natural products, we embarked on the development of efficient and practical stereoselective synthetic routes for these natural products. As discussed in the previous section of this Chapter 2, we have chosen the known construction strategy of 2,4-disubstituted furan moiety **72** (used as a key intermediate for the total synthesis of shikonofurans) from acyl-tethered 3-hydroxy oxetane building blocks **71** using Lewis- or Brønsted acid catalysis. As described in the below synthetic strategy (Scheme 2.12), this method proceeds through the initial activation of the strained oxetane ring with the aid of Lewis- or Brønsted acid, which triggers the intramolecular carbonyl (nucleophile-mediated) ring-closure (5-membered), and ring-opening (4-membered) sequence, and generates cyclic oxacarbenium. Subsequent dehydrative aromatization results in hydroxymethylated-furan intermediate **72**. This hydroxy-methylated furan **72** can be used as a key and divergent building block for the construction of all shikonofurans in a maximum number of 7 steps (Scheme 2.12).



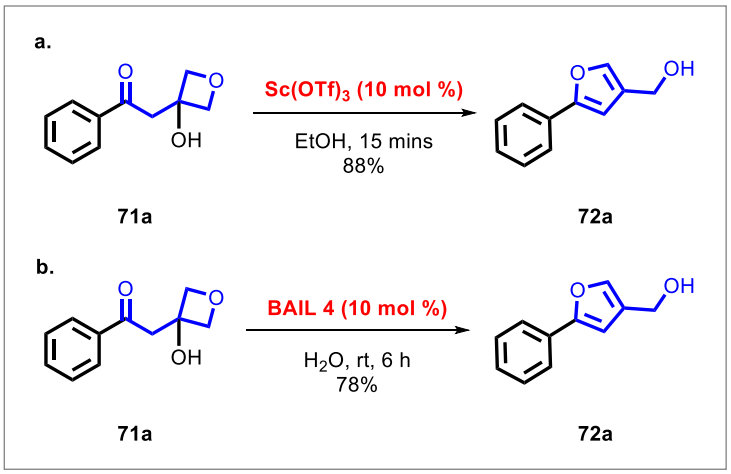
Scheme 2.12 | Concept of polysubstitutedfuran formation from Lewis- or Brønsted-catalyzed dehydrative cycloisomerization of α-hydroxy oxetane-tethered ketones.

2.2.2. Result and discussions

To realize our projected hypothesis, we synthesized a known α-hydroxy oxetane-tethered ketone **71a** building block. We performed the reaction using previously reported $Sc(OTf)_3$ (10 mol %) as a catalyst in EtOH, which delivered the

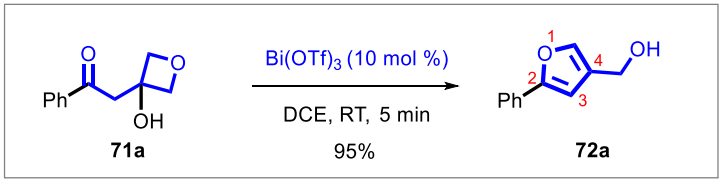
product **72a** in 88% yield in 15 minutes (entry a, Scheme 2.13). Next, we tested the reaction profile using ionic liquid BAIL-4 in water, this reaction was very sluggish and gave the hydroxymethylated product **72a** in 78% in 6 h (entry b. Scheme 2.13).

Taking into consideration of drawbacks of these strategies, like expensive Scandium catalysis, tedious work-up procedures using BAIL-4 in water, and longer reaction times, we aimed at developing a facile and rapid methodology to construct 2,4-disubstituted furans using acyl-oxetane as a building block utilizing cost-effective and efficient catalytic systems and its subsequent application in enantioselective total synthesis of shikonofurans (Scheme 2.13).



Scheme 2.13 | Initial synthesis of the 2,4-disubstituted furan **72a** using known protocols.

Inspired by the suitable catalytic property of $Sc(OTf)_3$ for this transformation (however limited to a single example) and our group's continuing interest in bismuth catalysis, we intended to verify the catalytic profile of $Bi(OTf)_3$ in this reaction. To our delight, the expected 2,4-disubstituted furan **72a** was isolated in an excellent yield (99%) from **71a** within five minutes using 10 mol % of $Bi(OTf)_3$ in dichloromethane at room temperature. The structure of **72a** was unambiguously determined by proton, carbon NMR, and mass spectrometry (Scheme 2.14).



Scheme 2.14 | Initial synthesis of 2,4-disubstituted furan **72a** using bismuth triflate.

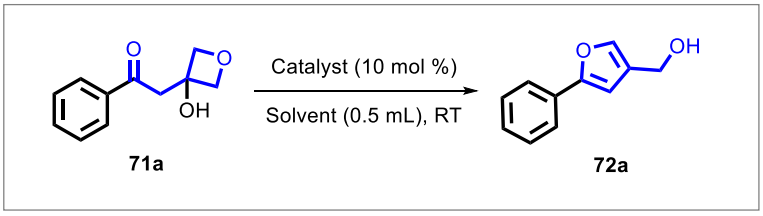
2.2.3. Further optimization of reaction conditions

We further explored the feasibility of this transformation using other Lewis acid and Brønsted acid catalysts. Considering the wide range of organic small molecules solubility in dichloromethane (DCM), dichloroethane (DCE), and methanol, all shortlisted catalysts were screened using these solvents. Since excellent results were obtained using $Bi(OTf)_3$, tested the reaction using other bismuth salts $BiCl_3$, $Bi(NO_3)_3.5H_2O$ in DCE, which delivered the desired product in good yields albeit in a little longer reaction time of 2 h. The reaction using the AgOTf catalyst was very slow, giving the product a 44% yield even after 6 h. Next, tested the efficiency of iron salts [$Fe(OTf)_3$, $Fe(ClO_4)_2$, $FeSO_4.7H_2O$] as catalysts, which was found to be moderately active toward this transformation, whereas, $Ni(OTf)_2$ was unable to promote the reaction. $BF_3.Et_2O$ delivered the product in 75% yield after 6 h. Then screened the reaction using Brønsted acid catalysts *p*-TSA, TFA, and TfOH in DCE, all of them were found to facilitating the reaction, TfOH delivered the product in excellent yield of 91% in 5 min with little decomposition.

Next, we screened same set of Lewis acid catalysts using polar and proteic solvent MeOH, in which reactions found to be faster compared to DCE, still, little decomposition was observed on TLC, which led to moderately compromising yields. Similarly, Brønsted acid catalysts pTSA, TFA, and TfOH in MeOH delivered the desired product **72**a in moderate to good yields.

TfOH is a usual contaminant associated with triflate-based Lewis acid catalysts and is solely responsible for the catalytic activity in some instances (Entry 19 vs 23), and is known to be responsible for side reactions owing to its (TfOH) high acidity. Due to the rapid reaction (within ~1 min), clean reaction profile, and excellent isolated yields using $Bi(OTf)_3$ as the catalyst, we strongly believe in the role of bismuth in this transformation, and owing to its great natural abundance, and non-toxic nature, we have chosen $Bi(OTf)_3$ as a reliable catalytic system for this work instead of closely potent TfOH and other Lewis acids.

Table 2.2 | Optimization of reaction conditions[a,b]



71a 72a

Entry	Catalyst	Solvent	Time	Yield[b]
A	Screening of Lewis acids catalysts in DCE			
1)	$Bi(OTf)_3$	DCE	5 min	95
2)	$BiCl_3$	DCE	2 h	93
3)	$Bi(NO_3)_3.5H_2O$	DCE	2 h	87
4)	AgOTf	DCE	6 h	44
5)	$Fe(OTf)_3$	DCE	6 h	80
6)	$Fe(ClO_4)_2$	DCE	8 h	45
7)	$FeSO_4.7H_2O$	DCE	1 h	77
8)	$Ni(OTf)_2$	DCE	24 h	N.R[c]
9)	$BF_3.Et_2O$	DCE	6 h	75
B	Screening of Brønsted acid catalysts in DCE			
10)	*p*-TSA	DCE	40 mins	91
11)	TFA	DCE	6 h	88
12)	TfOH	DCE	5 min	91
C	Screening of Lewis acids catalysts in MeOH			
13)	$Bi(OTf)_3$	MeOH	5 min	95
14)	$BiCl_3$	MeOH	30 mins	90
15)	$Bi(NO_3)_3.5H_2O$	MeOH	3 h	85
16)	$BF_3.Et_2O$	MeOH	1 h	71
17)	$Fe(OTf)_3$	MeOH	15 mins	89
18)	$Fe(OTf)_2$	MeOH	16 h	41
19)	$FeSO_4.7H_2O$	MeOH	3 h	73
20)	$Ni(OTf)_2$	MeOH	24 h	N.R[c]
21)	$BF_3.Et_2O$	MeOH	1 h	71
D	Screening of Brønsted acid catalysts in MeOH			
22)	*p*-TSA	MeOH	40 mins	86
23)	TFA	MeOH	12 h	75
24)	TfOH	MeOH	15 min	93

[a]Reaction conditions unless otherwise specified: **71a** (0.5 mmol) and catalyst (10 mol%) solvent (0.5 mL) at room temperature (RT). [b]Isolated yields of **72a**. [c]N.R = No Reaction. Tf = triflate (CF_3SO_2).

In subsequent optimization studies, the compatibility of various solvents, THF, DMSO, DMF, toluene, and diethyl ether, delightfully was investigated, in which many solvents were found to be reliable for this transformation except DMF & DMSO. However, a very clean reaction profile and isolated yields were observed using DCM (Table 2.2.1). Next, altered the mol % (loading) of $Bi(OTf)_3$ (using optimized solvent (DCM)), where a decrease in the catalyst loading led to an increase in reaction time and a low isolated yield of the product (Table 2.2.2).

Table 2.2.1 | Solvent screening using $Bi(OTf)_3$ (10 mol%)[a,b]

Entry	Solvent	Time	Yield of 72a (%)
1)	MeOH	5 min	95

2)	DCE	5min	95
3)	DCM	5 min	99
4)	THF	15 min	96
5)	DMSO	6 h	N.R[c]
6)	DMF	6 h	N.R[c]
7)	Toluene	5 min	93
8)	Et_2O	15 min	95

[a]Reaction conditions unless otherwise specified: **71a** (0.5 mmol) and catalyst (10 mol%) solvent (0.5 mL) at room temperature (RT). [b]Isolated yields of **72a**. [c]N.R = No Reaction.

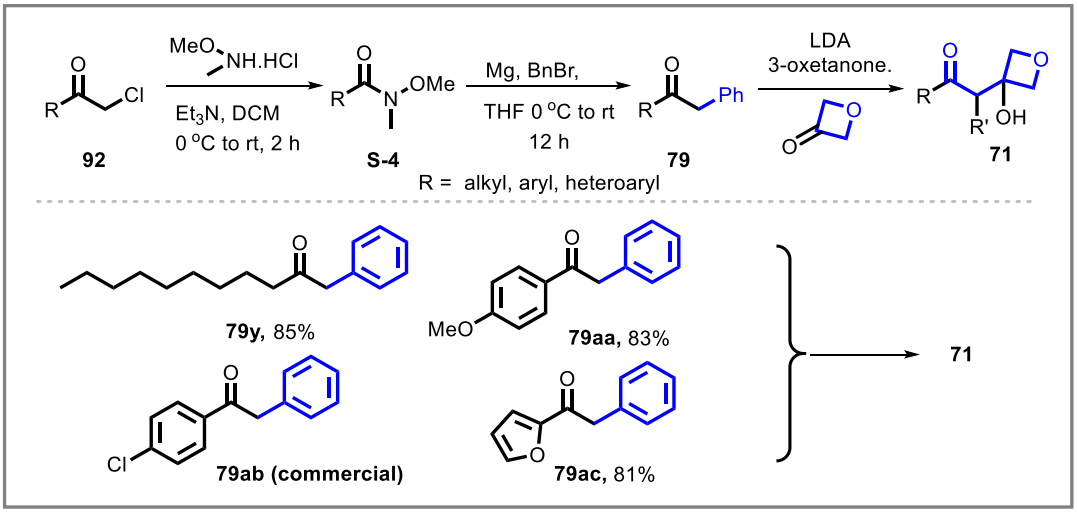
Table 2.2.2 | Screening of $Bi(OTf)_3$ loading using DCM as an optimal solvent [a,b]

Entry	$Bi(OTf)_3$ loading	Time	Yield of 72a (%)
1)	10 mol%	5 min	99
2)	5 mol%	30 min	85
3)	2 mol%	3 h	65
4)	1 mol%	24 h	30

[a]Reaction conditions unless otherwise specified: **71a** (0.5 mmol) and DCM (0.5 mL) at room temperature (RT). [b]Isolated yields of **72a**. [c]N.R = No Reaction.

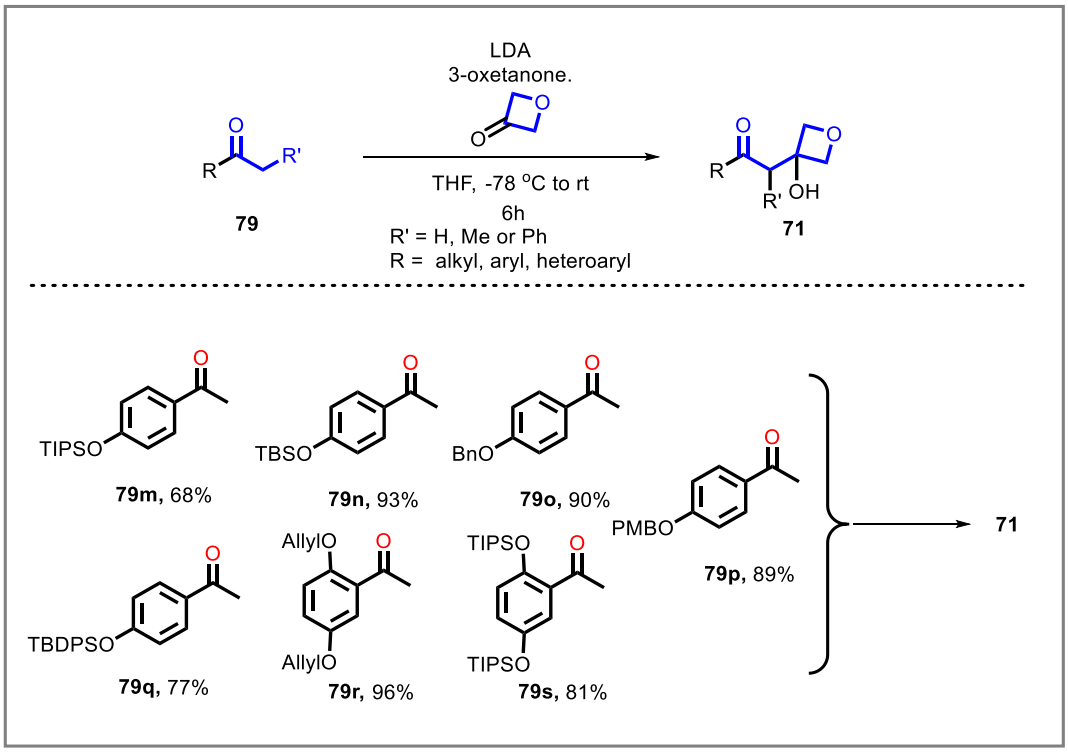
2.2.4. Synthesis of α-hydroxy oxetane-tethered ketone building blocks (71):

a) From acid chlorides (92): To investigate the generality of this methodology, synthesized diverse α-hydroxy oxetane-tethered ketones **71** (substrates of this methodology) in a three-step sequence starting from acyl-halides **92**. Acyl-halide **92** was treated with NMe(OMe).HCl salt in the presence of Et_3N in DCM solvent to form its Weinreb amide salt, which was in situ treated with diverse Grignard reagents to obtain their alkyl-ketone analogs **79**. Next, an LDA-mediated aldol reaction of **79** with commercially available 3-oxetanone gave desired α-hydroxy oxetane-tethered ketones **71** (Scheme 2.15).

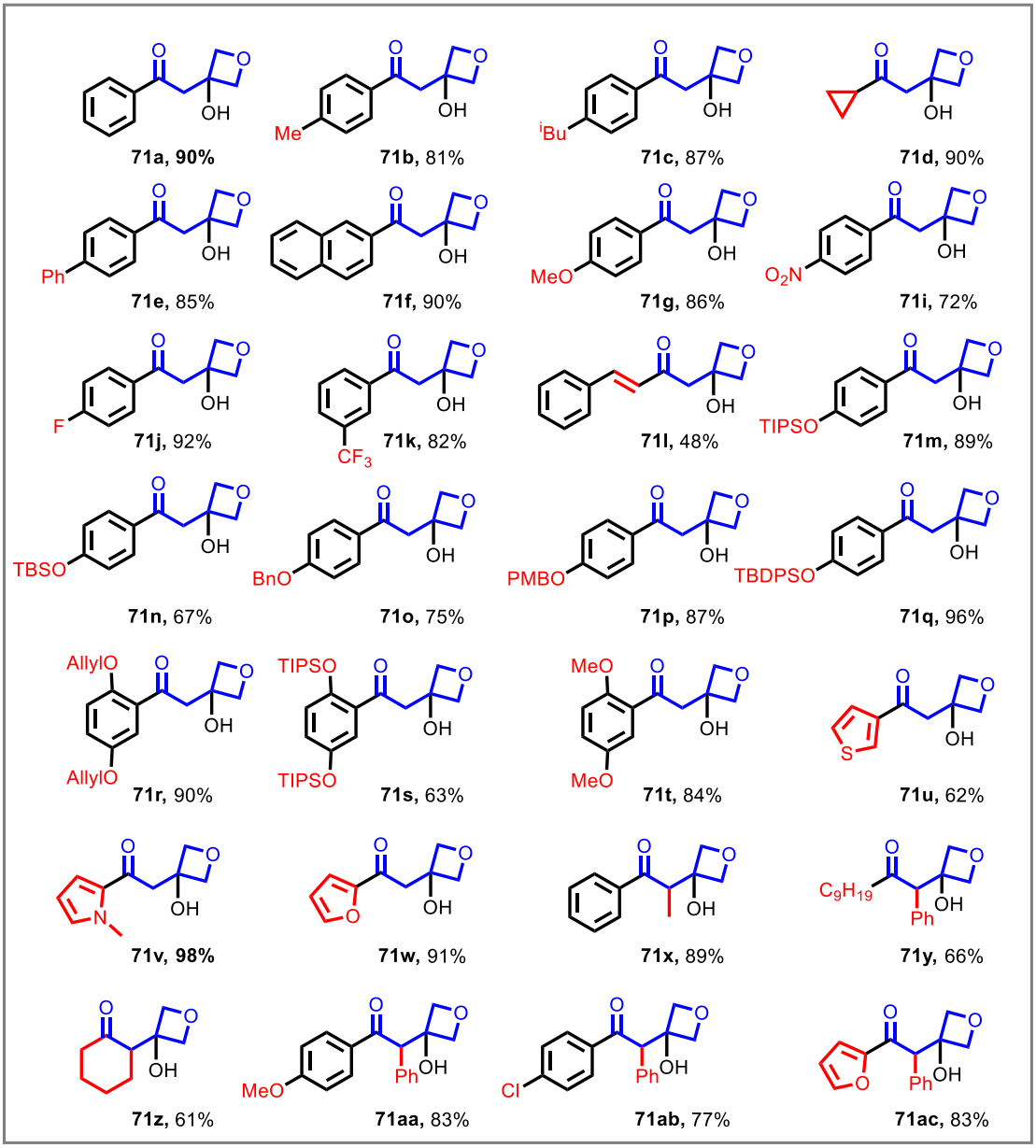


Scheme 2.15

b) From ketones (79): Several commercially available ketones were converted into corresponding α- hydroxy oxetane-tethered ketones **71** through L-enolate addition to the oxetanone. Using this strategy, diverse protected acetophenones (with TIPS, TBS, TBDPS, benzyl, PMB, and allyl groups) were prepared from 4-hydroxy acetophenone and 2,5-dihydroxy acetophenones and used to obtain corresponding α-hydroxy oxetane-tethered ketones **71** (Scheme 2.16 and 2.17).



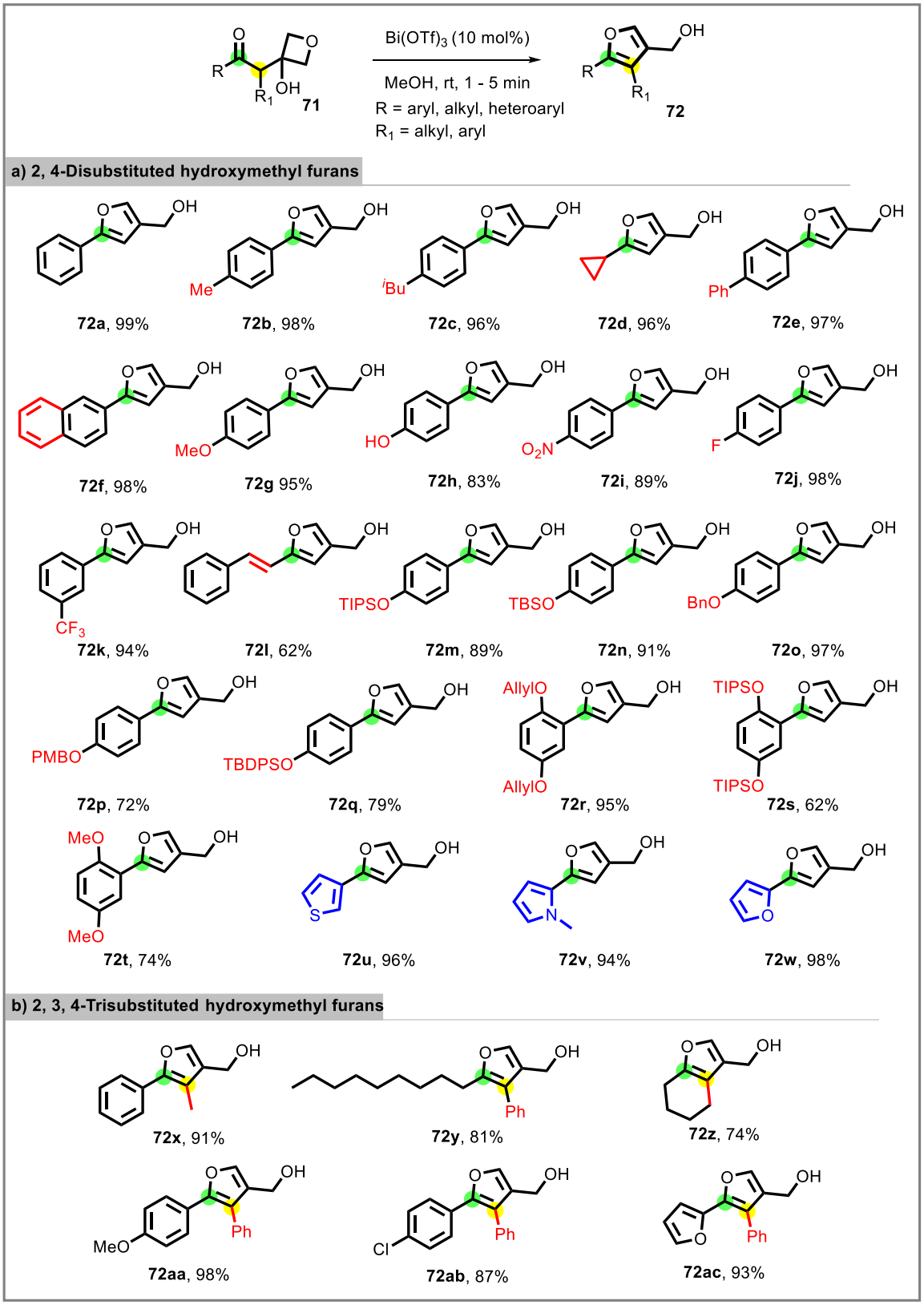
Scheme 2.16



Scheme 2.17. List of α- hydroxy oxetane-tethered ketones **71** synthesized.

2.2.5. Scope and generality of the reaction (Furan 72 synthesis):

With the optimal conditions established, the substrate scope concerning the construction of 2,4 disubstituted and 2,3,4-trisubstituted furans **72** from α-hydroxy oxetane-tethered ketones **71** is described in Scheme 2.18. Substrates having substituted aryl-ketone moiety (**71**, *t*-Bu, cyclopropyl substituted phenyl, and biphenyl, naphthyl and OMe) furnished the corresponding disubstituted furan **72a-72g**) in good to moderate yields (97-98%). Substrates possessing electron-withdrawing groups (OH, NO_2, F and CF_3,) also delivered desired products (**72h-72k**)



Scheme 2.18. Synthesis of 2,4-disubstituted and 2,3,4-trisubstituted furans

in good yields of 83%, 89%, 98% and 94% respectively. Styrene-derived substrate was also found to be a suitable substrate for this reaction and delivered corresponding furan 72l in a good yield of 62% (entry 12, Scheme 2.18).

Next, the compatibility of aryl ketone-derived substrates having diverse protecting groups (-OTIPS, -OTBS, -OBn, -OPMB, -OTBDPS, -OAllyl and -OMe) were tested, delightfully, all delivered respective furans (**72m**-**72t**) in good to excellent yields. diverse protecting groups were found to be compatible under these optimized conditions (entry 13-20, Scheme 2.18).

To our delight, substrates consisting of heteroaryl-ketone (thiophene, N-methyl pyrrole, and furan-derived) gave corresponding bis-heterocycles **72u**-**72w** in very good yields (entry 21-23, Scheme 2.18).

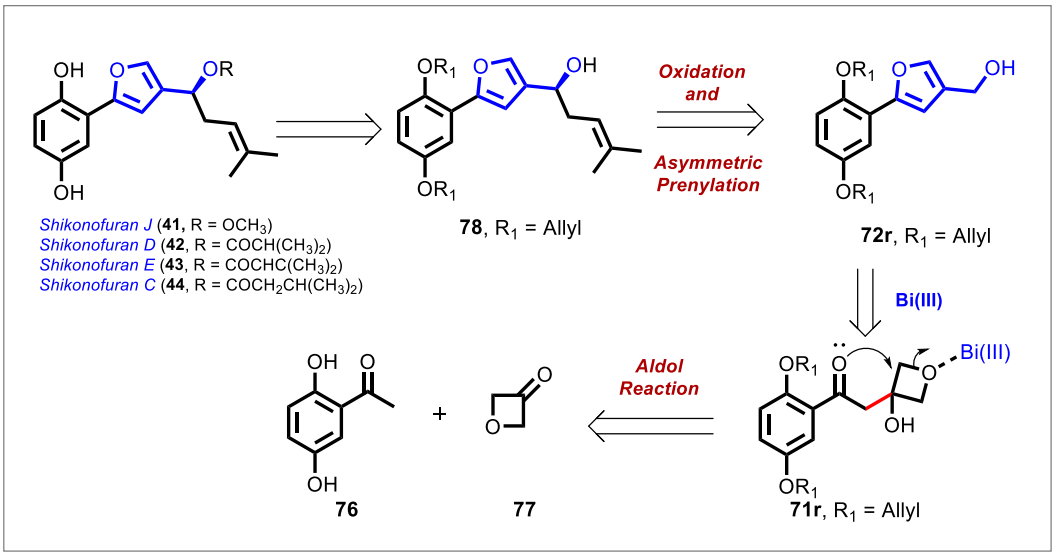
Then, we focused on the preparation of 2,3,4-trisubstituted furans **72** under optimal reaction conditions. To our delight, all these reactions delivered products containing C2-alkyl, aryl, and heteroaryl & C3-H, aryl substituents (**72x**-**72ac**) in good to excellent yields (74-98%) in shorter reaction time (1-5 min) (entry 24-29, Scheme 2.18).

In conclusion, we have established a rapid, efficient, and operationally simple synthetic strategy for the construction of hydroxymethyl-tethered di- or trisubstituted furans using environmentally benign and cost-effective $Bi(OTf)_3$ as a catalytic system. The generality of this method was showcased through the construction of diverse furans containing, alkyl, cycloalkyl, aryl, and heteroaryl substituents. Moreover, diverse acid-sensitive protecting groups were found to be extremely stable under optimized reaction conditions. As we hypothesized, this methodology was effectively employed in the total synthesis of bioactive natural products, shikonofurans (*vide infra*).

2.2.6. Retrosynthetic analysis of shikonofurans (41-44)

After the successful establishment of the general synthetic strategy for the construction of hydroxymethyl-tethered furans, we turned our interest toward the stereoselective total synthesis shikonofurans J, D, E, and C (**41**-**44**, with varying oxygen-substituents of ether/ester groups) based on the retrosynthetic analyses described in Scheme 2.19. Shikonofurans could be accessed from substituted arene

containing hydroxyalkyl furan **78** via methylation (for shikonofuran J) or esterification (for shikonofuran C-E) using suitable carboxylic acids followed by deprotection steps. Intermediate **78** could be obtained from 2,4-disubstituted furan **72r** through initial oxidation to give the corresponding aldehyde followed by TRIP-catalyzed asymmetric prenylation. This key intermediate **72r** (hydroxymethyl-tethered furan) synthesized as part of our investigation in the previous section (Bi(III)-catalyzed dehydrative-cycloisomerization of α-hydroxy oxetane-tethered ketone **71r**) (Scheme 2.19).

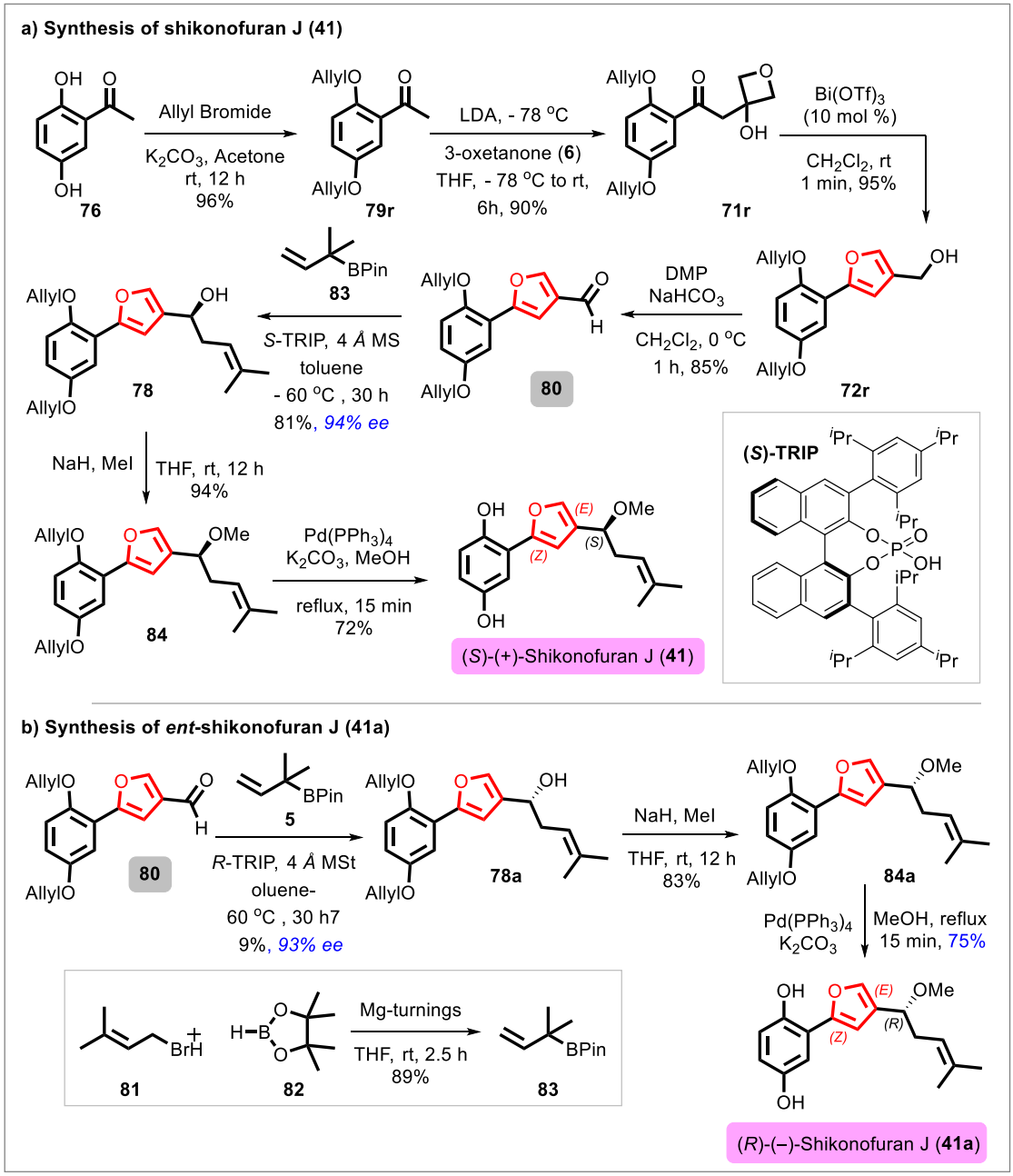


Scheme 2.19 | Common retrosynthetic analysis of shikonofurans **41**-**44**.

2.2.6.1. Synthesis and absolute configuration of shikonofuran J (41):

Our studies started with enantioselective total synthesis of the reported structure of shikonofuran J (**41**), starting from commercially available 2,5-dihydroxy acetophenone (**76**). Allyl protection[37] of **76** using allyl bromide in the presence of K_2CO_3 gave **79r**, and subsequent LDA-mediated aldol reaction with 3-oxetanone (**77**) gave the requisite aldol product **71r** in 90% yield. Next, the oxetane intermediate **71r** was subjected to our in-house developed methodology of $Bi(OTf)_3$-catalyzed dehydrative cycloisomerization reaction, which cleanly furnished the desired hydroxy-methylated furan **72r** in 95% yield in 5 min. Then, **72r** was oxidized to aldehyde **80** using Dess–Martin periodinane (DMP),[35] and subsequently subjected to asymmetric prenylation reaction using chiral phosphoric acid[38] [(*S*)-TRIP] and prenyl-pinacol-boronate **83** to get the anticipated chiral alcohol **78**, which was used

as a common intermediate for all shikonofurans. Then methylation[39] of alcohol **78** using NaH and MeI to give **84**. Ultimately, $Pd(PPh_3)_4$-catalyzed allyl deprotection[40] of both allyl groups of 84 delivered shikonofuran J (**41**) in 72% yield (entry a, Scheme 2.20).



Scheme 2.20 | Total synthesis of shikonofuran J (**41**) and its enantiomer **41a**.

^1H and ^{13}C NMR data of synthesized shikonofuran J (**41**) was in complete agreement with that of the reported data (isolated natural product **41**). To our surprise, the optical rotation value of **41** [$[\alpha]^{26.6}{}_D$ = +7.07 (*c* = 0.5, MeOH), this work]

was found to be opposite to the reported value of natural shikonofuran J (**41**) [$[\alpha]^{12}{}_{D}$ =−11.3 (*c* = 0.3, MeOH)].

Hence, utilizing a similar strategy that was used for the synthesis of (+)-shikonofuran J (**41**), we have obtained its enantiomer (*ent*-shikonofuran J; **41a**) using [(*R*)-TRIP] ligand in the conversion of common intermediate **80** into its prenylated product **78a**, and its subsequent methylation and allyl deprotection steps.

Surprisingly, the optical rotation data of **41a** [$[\alpha]_D^{27.13}$= −7.63 (*c* = 0.5, MeOH)] was found to be very close to the reported data (entry b, Scheme 2.20). To further verify the authenticity of the reported optical rotation data and absolute stereochemistry of shikonofuran J [**(*S*)-41**], we further carried out ECD analyses of [**(*S*)-41**] and **(*R*)-41a** and compared them with the reported ECD data. Where (*S*)-(+)-shikonofuran J ([**(*S*)-41**], this work) showed a negative Cotton effect (CE; CD, 4.3 x 10-4 M, MeOH) and a positive Cotton effect at λmax 213 nm (Δε = +0.187), which was in agreement with the data reported for (*S*)-isomer) of shikonofuran J (**41**, isolated), while the **(*R*)-41a** showed opposite ECD data compared to **41** (CD, 4.3 x 10-4 M, MeOH, λmax (Δε) 283 (−0.018), 245 (+0.026) and 213 (−0.312) nm) (Figure 2.4). These investigations established the absolute stereochemistry of shikonofuran J as (*S*)-(+)-shikonofuram J (**41**) (Figure 2.4).

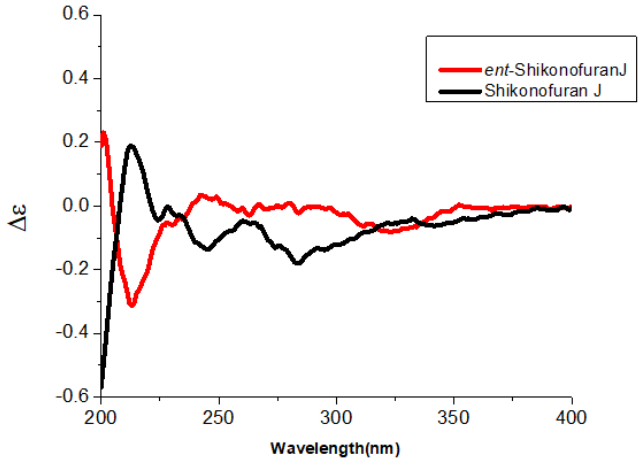


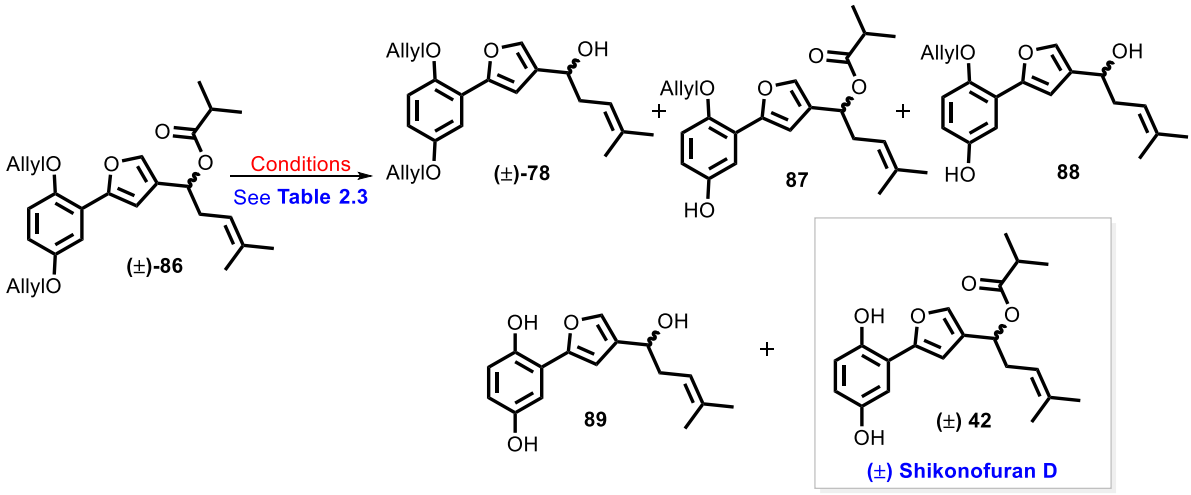
Figure 2.4: | ECD spectra of Shikonofuran J [**(*S*)-41**] and *ent*-Shikonofuran J [**(*R*)-41a**].

2.2.6.2. Synthesis and absolute configuration of shikonofuran D (42):

After the successful synthesis and establishing the absolute configuration of shikonofuran J (**41**), we embarked on the total synthesis of shikonofurans D, E, and C,

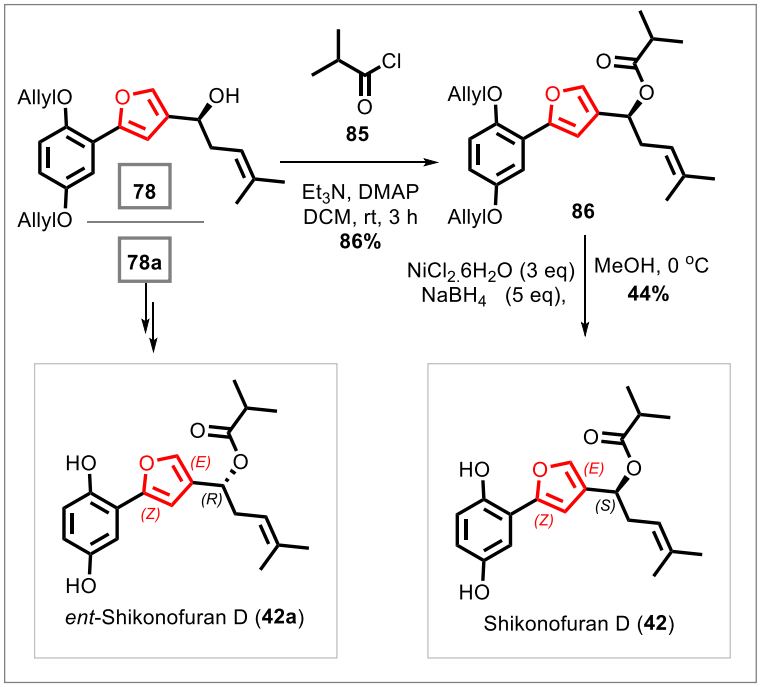
and their antipodes utilizing common intermediates **78** and **78a**. Thus, the hydroxyalkyl furan intermediate **78** (possessing the desired stereochemistry of natural products; reported data) was treated with isobutyryl chloride **85** in the presence of Et_3N, and DMAP to afford the corresponding ester **86** in 86% yield.

Table 2.3. Optimization of reaction conditions for allyl deprotection



Entry	Conditions	(±)-78	87	88	89	(±) -42	SM (±) -(86)
1.	$Pd(PPh_3)_4$ (10 mol%), K_2CO_3, MeOH, reflux , 15 min	-	-	-	90%	-	-
2.	$Pd(PPh_3)_4$ (10 mol%), K_2CO_3 (3 eq), MeOH, rt, 3 h	60%	-	40%	-	-	-
3.	$Pd(PPh_3)_4$ (10 mol%), pyrrolidine (1 eq), DCE, rt, 5 h	5%	20%	-	-	-	75%
4.	$BiCl_3$ (1 eq) + $NaBH_4$ (1 eq), THF, 0 °C to rt, 2 h	10%	-	-	-	-	90%
5.	$CeCl_3.7H_2O$ (1.5 eq), NaI (1.5 eq), MeCN, rt, 24 h	-	5%	-	-	-	95%
6.	$Pd(PPh_3)_4$ (20 mol%), $NaBH_4$ (1.5 eq), THF, 0 °C to rt, 1 h	20%	20%	-	-	-	60%
7.	LiCl (1 eq), $NaBH_4$ (1 eq), THF, 0 °C to rt, 24 h	50%	10%	10%	-	-	trace
8.	$Pd(PPh_3)_4$ (10 mol%), K_2CO_3 (3 eq), dioxane, rt, 48 h	-	-	-	-	-	100%
9.	$NiCl_2.6H_2O$ (3 eq), $NaBH_4$ (5 eq), MeOH, 0 °C to rt, 10 min	10%	10%	-	-	40%	-
10.	$Pd(OH)_2/C$ (10 mol%), Pd/C (10 mol%), iPrOH, 80 °C, 12 h	50%	10%	-	-	-	40%
11.	Cs_2CO_3 (1 eq), $Pd(PPh_3)_4$ (10 mol%), THF, rt, 48 h	-	-	-	-	-	100%

Then our next target was to deprotect the allyl groups in **86** employing well-established reaction conditions of $Pd(PPh_3)_4$, K_2CO_3, MeOH at various temperatures, unfortunately, all attempts in this line were proved to be unsuccessful (Scheme 2.22). Hence, synthesized *racemic*-**86**, and optimized reaction conditions for the allyl deprotection as described in Table 2.23. Reactions using $Pd(PPh_3)_4$ /$Pd(OH)_2$[41] and diverse bases[42], $Pd(PPh_3)_4$-$NaBH_4$[43], LiCl-$NaBH_4$[44], and $CeCl_3.7H_2O$-NaI[45], led to the ester hydrolysis and non-selective deprotected products. After extensive experimentation, $NiCl_2.6H_2O$ (3 eq), $NaBH_4$ (5 eq), MeOH, 0 °C to rt conditions[46] were found to be fruitful by providing the desired shikonofuran D (*rac*-**42**, in a moderate yield of 44%, along with a few unidentified and inseparable products (Table 2.3).



Scheme 2.21 | Efforts towards the total synthesis of shikonofuran D (**42**) and its enantiomer **42a**.

Employing these optimal reaction conditions for allyl deprotection, shikonofuran D (**42**, reported structure) was obtained form **86**. Similarly, common intermediate **78a** (an enantiomer of **78**, that was used in the synthesis of ent-shikonofuran J) was converted into *ent*-shikonofuran D (**42a**) in two steps (Scheme 2.21).

Surprisingly, the optical rotation data of **42a** $[[\alpha]_D^{26.54}$ = +26.19 (*c* = 1.3, $CHCl_3$)] was found to be very close to the reported data which is $[[\alpha]_D^{20}$ = +56 (c = 0.1, $CHCl_3$) (Scheme 2.21). To further verify the authenticity of the reported optical

rotation data and absolute stereochemistry of shikonofuran D [**(*S*)-42**], we further carried out ECD analyses of [**(*S*)-42**] and **(*R*)-42a**, where (*S*)-(+)-shikonofuran D ([**(*S*)-42**], this work) showed a negative Cotton effect (CE; CD, 4.3 x 10-4 M, MeOH) at λmax 322 nm (Δε = -1.10), 274 nm (-1.29) and 204 nm (-3.23) while the **(*R*)-42a** showed opposite ECD data compared to **42** (CD, 4.3 x 10-4 M, MeOH, λmax (Δε) 323 nm (+1.39), 267 nm (+6.00) and 207 nm (+2.50) (Figure 2.5).

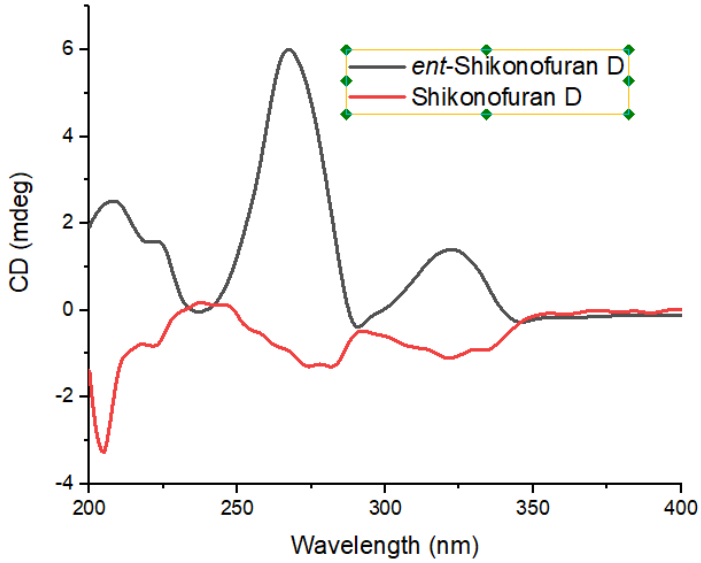
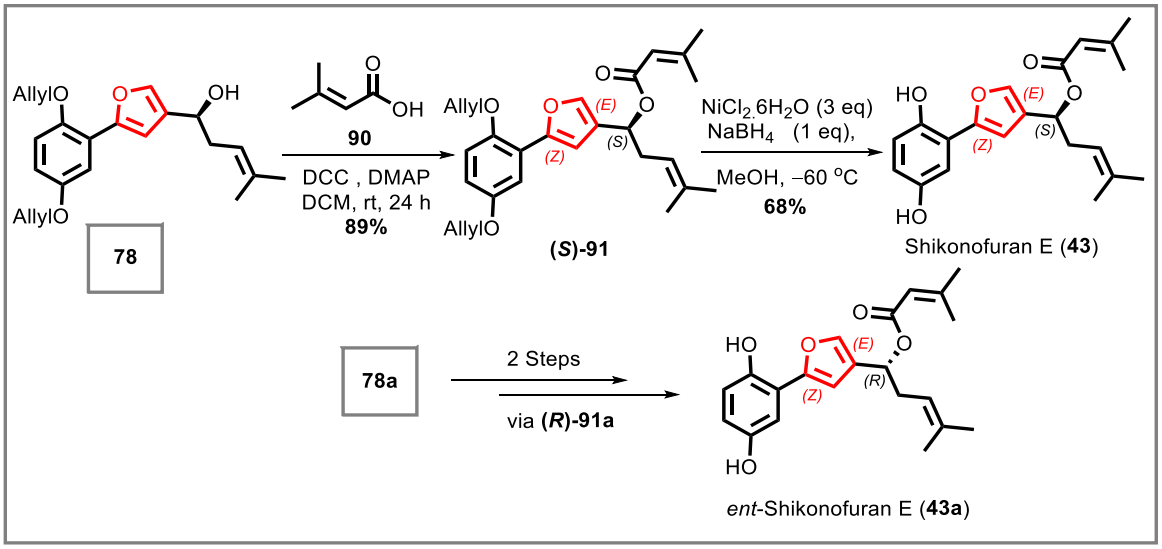


Figure 2.5. | ECD spectra of Shikonofuran D [**(*S*)-42**] and *ent*-Shikonofuran D [**(*R*)-42a**].

2.2.6.3. Synthesis and absolute configuration of shikonofuran E (43):

To synthesize the reported structure of shikonofuran E (**43**), the alcohol **78** was subjected to esterification using commercially available 3-methylbut-2-enoic acid (**90**) under DCC and DMAP conditions to get the corresponding ester **91**, which served as a common precursor for both the natural products shikonofuran E and C. Subsequent phenolic allyl deprotection using $NiCl_2.6H_2O$ and $NaBH_4$ in MeOH at –60 °C delivered shikonofuran E (**43**, reported structure) in 57% yield. Similarly, common intermediate **78a** (an enantiomer of **78**, that was used in the synthesis of ent-shikonofuran J) was converted into *ent*-shikonofuran E (**43a**) in two steps of esterification and allyl deprotection. (Scheme 2.22).



Scheme 2.22 | Enantioselective total synthesis of shikonofuran E (**43**), and its enantiomers (**43a**).

The optical rotation data of [**(*S*)-43**] [$[\alpha]_D^{30.49}$ = -62.40 (*c* = 0.1, $CHCl_3$)] was found to be very close to the reported data which is [$[\alpha]_D^{20}$ = -69 (c = 0.5, $CHCl_3$) (Scheme 2.2). To further verify the authenticity of the reported optical rotation data and absolute stereochemistry of shikonofuran E [**(*S*)-43**], we further carried out ECD analyses of [**(*S*)-43**] and **(*R*)-43a**, where (*S*)-(+)-shikonofuran E ([**(*S*)-43**], this work) showed a negative Cotton effect (CE; CD, 4.3 x 10-4 M, MeOH) at λmax 316 nm (Δε = -

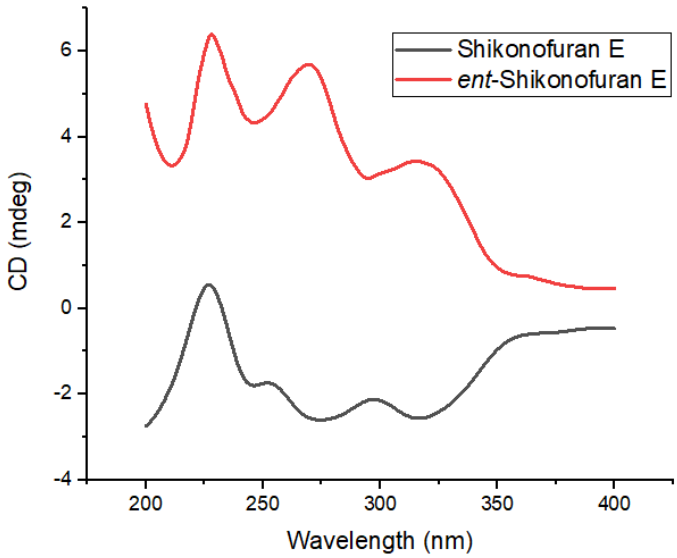
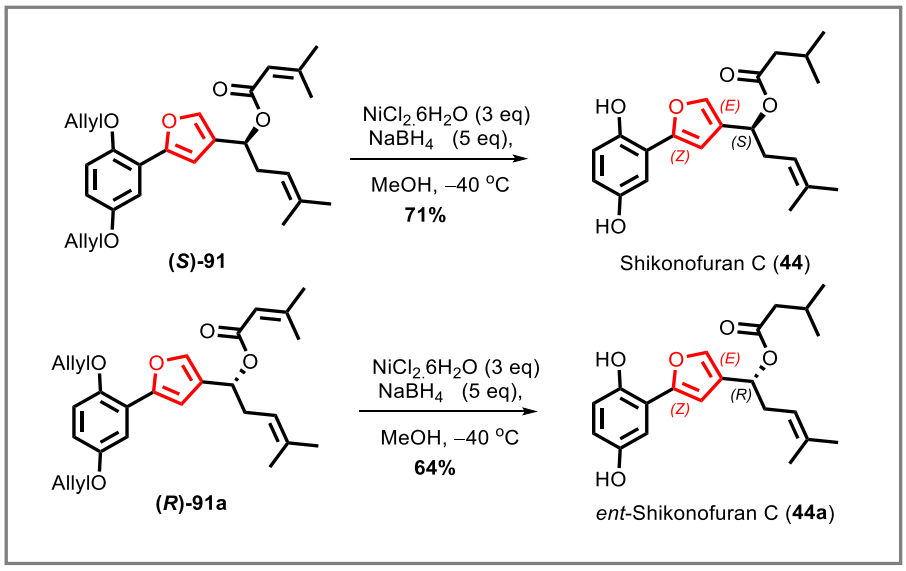


Figure 2.6. | ECD spectra of Shikonofuran E [**(*S*)-43**] and *ent*-Shikonofuran E [**(*R*)-43a**].

2.56), 274 nm (-2.59), 245 nm (-1.79) and a positive Cotton effect at 227 nm (+0.549) while the **(*R*)-43a** showed opposite ECD data compared to **43** (CD, 4.3 x 10-4 M, MeOH, λmax (Δε) 319 nm (+3.39), 270 nm (+5.69), 227 nm (+6.33) and 212 nm (+3.34) (Figure 2.6).

2.2.6.4. Synthesis and absolute configuration of shikonofuran C (44):

While optimizing the allyl deprotection of **91** at various temperatures using $NiCl_2$ and $NaBH_4$, we observed the reduction of the butenoic ester segment at –40 °C, which led to the formation of shikonofuran C (**44**). Utilizing a strategy similar to this, synthesized *ent*-shikonofuran C (**44a**) from **78a** (Scheme 2.23).



Scheme 2.23 | Enantioselective total synthesis of shikonofuran C (**44**), and their enantiomers (**44a**).

Surprisingly, the optical rotation data of **44a** [$[\alpha]_D^{27.96}$ = +57.56 (*c* = 1.1, $CHCl_3$)] was found to be very close to the reported data which is [$[\alpha]_D^{20}$ = +64 (*c* = 0.1, $CHCl_3$) (Scheme 2.23). To further verify the authenticity of the reported optical rota tion data and absolute stereochemistry of shikonofuran C [**(*S*)-44**], we further carried out ECD analyses of [**(*S*)-44**] and **(*R*)-44a**, where (*S*)-(+)-shikonofuran C ([**(*S*)-44**], this work) showed a negative Cotton effect (CE; CD, 4.3 x 10^{-4} M, MeOH) at λmax 321 nm (Δε = -1.76), 283 nm (-1.68), 260 nm (-1.19) and 224 nm (-3.02) while the **(*R*)-44a** showed opposite ECD data compared to **44** (CD, 4.3 x 10^{-4} M, MeOH, λmax (Δε) 321 nm (0.79), 277 nm (+2.82), 269 nm (+4.07) and 220 nm (+2.28) (Figure 2.7).

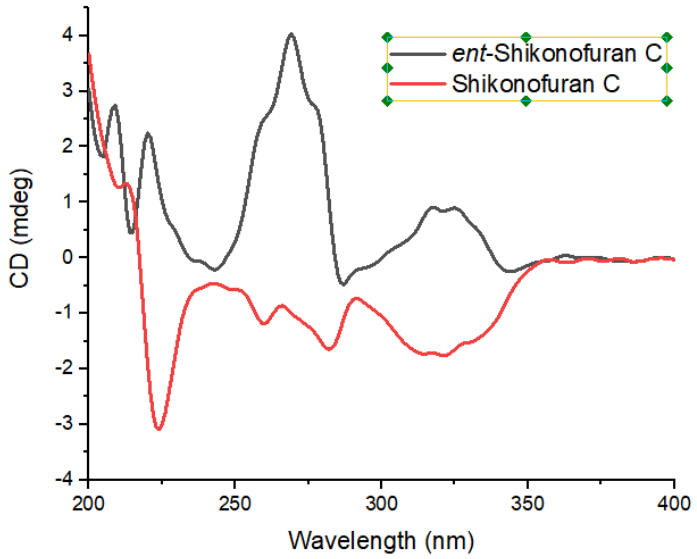


Figure 2.7. | ECD spectra of Shikonofuran C [**(*S*)-44**] and *ent*-Shikonofuran C [**(*R*)-44a**].

In addition to analytical studies like NMR (^{1}H and ^{13}C), MS, optical rotation, ECD, chiral-HPLC data also supported our conclusions on this work.

2.2.7. Conclusion

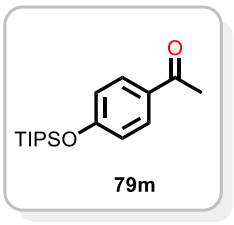
In conclusion, employing a novel methodology developed as part of this work, i.e, Bi(III)-catalyzed dehydrative cycloisomerization of α-hydroxy oxetane-tethered ketones to access hydroxy methyl-tethered furans, we have successfully completed the first enantioselective total synthesis of furyl-hydroquinone-derived antimicrobial natural products, shikonofurans J, D, E, and C in 7 linear steps with 38.24%, 21.4 %, 34.20%, 35.70% overall yield respectively. The absolute stereochemistry of all these natural products was established on the basis of comparison of optical rotation and ECD (electric circular dichroism) analyses. Biological activity investigations of all-natural products and their enantiomers are in progress.

2.2.8. Experimental procedures and data:

General Information: All reactions were performed under an argon atmosphere with an oven (80 °C) or flame-dried glassware with a septum seal. Tetrahydrofuran (THF) was distilled from sodium benzo-phenone under an argon atmosphere immediately prior to use. Anhydrous toluene and dichloromethane were purchased

from commercial sources. Reaction temperatures are reported as the temperature of the bath surrounding the reaction vessel. Analytical thin layer chromatography (TLC) was performed on TLC Silica gel 60 F254. Visualization was accomplished with short-wave UV light, anisaldehyde, or $KMnO_4$ staining solutions, followed by heating. chromatography was performed on silica gel (100-200 mesh) by standard techniques eluting with solvents as indicated. ^1H and ^{13}C NMR spectra were recorded on Bruker AV 200, 400, and 500 in solvents as indicated. Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δ H = 7.26 ppm, δ C = 77.16 ppm), the following abbreviations were used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublet; td, triplet of doublet; and br, broad. HRMS data were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump. . ECD spectra were recorded on a JACSO J-815 CD spectrometer. Chiral HPLC separations were achieved using an Agilent 1260 Infinity series normal phase HPLC unit and HP Chemstation software with Chiralpak Diacel columns (250 mm × 4.6 mm). Experimental procedures for all new compounds and known compounds without published experimental procedures are described below.

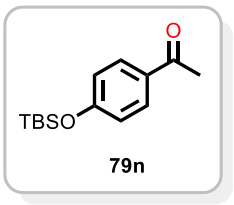
1-(4-((Triisopropylsilyl)oxy)phenyl)ethan-1-one (79m). To the 4'-hydroxy acetophenone (1 g, 7.34 mmol) in dry dichloromethane (10 mL) imidazole (1.24 g, 18.3 mmol) were added, and the reaction was stirred for 10 minutes. Then TIPSCl (1.88 g, 8.81 mmol) were added dropwise and the reaction was stirred up to starting material was completely consumed (5h). After completion of the reaction, it was quenched with water, the aqueous layer was extracted with DCM (10 mL x 3), dried over Na_2SO_4, filtered, and concentrated and the crude product was purified using silica gel column chromatography to afford the desired product **79m** (1.45 g, 68%) as a colourless liquid. (TLC: R_f = 0.8 (SiO_2, 10% EtOAc/ hexanes). IR (neat) 3891, 3777, 3665, 3441, 3359, 3175, 2961, 2883, 2388, 2336, 1823, 1678, 1600, 1524, 1469, 1373, 1274, 1174, 1077, 1008, 900, 833, 673 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91-7.81 (m, 2H), 6.95-6.85 (m, 2H), 2.54 (s, 3H), 1.35-1.21 (m, 3H), 1.11 (s, 9H), 1.05 - 1.10 (m, 9H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 197.0, 160.8, 130.7, 130.7, 119.8,



79m

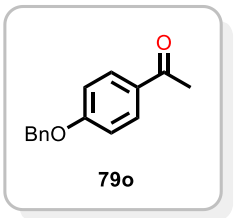
119.8, 26.5, 18.0, 17.8, 12.8; HRMS (ESI): *m/z* calcd for $C_{17}H_{29}O_2Si$ $[M+H]^+$ 293.1931, found 293.1933.

1-(4-((*Tert*-butyldimethylsilyl)oxy)phenyl)ethan-1-one (79n). To the 4'-hydroxy acetophenone (1 g, 7.34 mmol) in dry DMF (10 mL), imidazole (1.49 g, 22.0 mmol) was added, and the reaction was stirred for 10 minutes. Then TBSCl (1.90 g, 11.0 mmol) was added, and the reaction was stirred overnight at room temperature. The reaction progress was monitored by TLC. After completion of the reaction, it was quenched with water, the aqueous layer was extracted with DCM (10 mL x 3), dried over Na_2SO_4, filtered, and concentrated and the crude product was purified using silica gel column chromatography to afford the desired product **79n** (1.7 g, 93%) as white solid. (TLC: R_f = 0.8 (SiO_2, 10% EtOAc/ hexanes). IR (neat) 3682, 2949, 2862, 1673, 1596, 1513, 1472, 1363, 1266, 1112, 1015, 918, 672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93-7.84 (m, 2H), 6.91-6.82 (m, 2H), 2.55 (s, 3H), 0.98 (s, 10H), 0.23 (s, 6H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 197.0, 160.4, 131.0, 130.6, 120.0, 26.5, 25.7, 18.4, -4.2; HRMS (ESI): *m/z* calcd for $C_{14}H_{23}O_2Si$ $[M+H]^+$ 251.1462, found 251.1461.



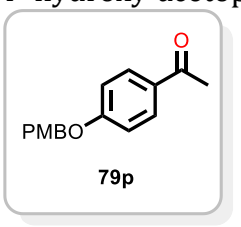
79n

1-(4-(Benzyloxy)phenyl)ethan-1-one (79o). To the 4'-hydroxy acetophenone (1 g, 7.34 mmol) in dry acetone (10 mL), K_2CO_3 (2.03 g, 14.6 mmol) and benzyl bromide (1.30 mL, 11.0 mmol) were added, and the reaction was refluxed for 24 h. After completion of the reaction, it was diluted with water, the aqueous layer was extracted with Et_2O (10 mL x 3), dried over Na_2SO_4, filtered, and concentrated, and the crude product was purified using silica gel column chromatography to afford the desired product **79o** (1.5 g, 90 %) as colorles liquid. (TLC: R_f = 0.8 (SiO_2, 10% EtOAc/ hexanes). IR (neat) 3683, 3332, 2878, 1960, 1888, 1673, 1597, 1510, 1423, 1365, 1312, 1261, 1174, 1118, 1078, 959, 922, 834, 771, 674 cm-1; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.88 Hz, 2H), 7.46-7.32 (m, 5H), 7.01 (d, *J* = 8.88 Hz, 2H), 5.12 (s, 2H), 2.55 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 196.8, 162.7, 136.2, 130.7, 130.6, 128.8, 128.3, 127.5, 114.6, 70.2, 26.4; HRMS (ESI): *m/z* calcd for $C_{15}H_{15}O_2$ $[M+H]^+$ 227.1067, found 227.1067.



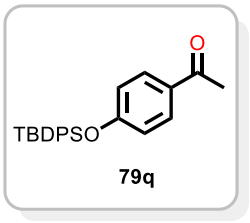
79o

1-(4-((4-Methoxybenzyl)oxy)phenyl)ethan-1-one (79p). To a stirred solution of 4'-hydroxy acetophenone (1 g, 7.34 mmol) in dry DMF (10 mL), K_2CO_3 (2.03 g, 14.6 mmol) and PMBCl (0.98 mL, 7.34 mmol) were added, and the reaction was stirred for 5 h at room temperature. After completion of the reaction it was quenched with ice water, the aqueous layer was extracted with ethyl acetate (10 mL x 3), then the combined organic layer was washed with brine (20 mL),), dried over Na_2SO_4, filtered, and concentrated and the crude product was purified using silica gel column chromatography to afford the desired product **79p** (1.68 g, 89%) as a colorless liquid. (TLC: R_f = 0.8 (SiO_2, 10% EtOAc/ hexanes). IR (neat) 3686, 2952, 2842, 1673, 1602, 1515, 1467, 1365, 1307, 1242, 1218, 1175, 1113, 1027, 927, 795, 746, 642 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.98-7.89 (m, 2H), 7.42-7.32 (m, 2H), 7.05-6.95 (m, 2H), 6.95-6.89 (m, 2H), 5.06 (s, 2H), 3.82 (s, 3H), 2.55 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 196.9, 162.9, 159.8, 130.7, 130.6, 129.4, 128.3, 114.7, 114.3, 70.1, 55.5, 26.5; HRMS (ESI): *m/z* calcd for $C_{16}H_{17}O_3$ $[M+H]^+$ 257.1172, found 257.1169.



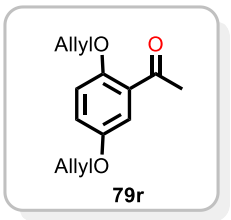
79p

1-(4-((*Tert*-butyldiphenylsilyl)oxy)phenyl)ethan-1-one (79q): To the 4'-hydroxy acetophenone (1 g, 7.34 mmol) in dry DMF (10 mL), imidazole (1.24 g, 18.3 mmol) were added, and the reaction was stirred for 10 minutes. Then TBDPSCl (3.02 mL, 11.0 mmol) were added, and reaction was stirred for 5h at room temperature. The reaction progress was monitored by TLC. After completion of the reaction it was quenched with water, the aqueous layer was extract-ed with DCM (10 mL x 3), dried over Na_2SO_4, filtered, and concentrated in vacuo and the crude product was purified using silica gel column chromatography to afford the desired product **79q** (2.1 g, 77%) as white solid. (TLC: R_f = 0.8 (SiO_2, 10% EtOAc/ hex-anes). IR (neat) cm^{-1} 3674, 3468, 2945, 2893, 2860, 1965, 1892, 1670, 1597, 1515, 1472, 1363, 1265, 1110, 1014, 919, 749, 673; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75-7.69 (m, 7H), 7.42-7.35 (m, 6H), 6.81- 6.77 (m, 2H), 2.48 (s, 3H), 1.11 (s, 9H); ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 197.1, 160.2, 135.5, 135.4, 134.9, 132.3, 130.8, 130.5, 130.3, 129.8, 128.1, 127.9, 119.8, 26.7, 26.5, 26.4, 19.6; HRMS (ESI): *m/z* calcd for $C_{24}H_{27}O_2Si$ $[M+H]^+$ 375.1775, found 375.1776.



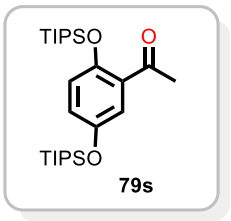
79q

1-(2,5-Bis(allyloxy)phenyl)ethan-1-one (79r): To the 4'-hydroxy acetophenone (5 g, 32.8 mmol) in dry acetone (50 mL), K_2CO_3 (18.17 g, 131.5 mmol) and allyl bromide (8.52 mL, 98.6 mmol) were added, and the reaction was stirred at room temperature for 24 h. After completion of the reaction, it was filtered through celite. The residue was washed with DCM. The filtrate was evaporated in vacuo and the crude product was purified using silica gel column chromatography to afford the desired product **79r** (7.3 g, 96%) as a white solid. TLC: R_f = 0.6 (SiO_2, 10% EtOAc/ hexanes). IR (neat) 3948, 3767, 3702, 3633, 3536, 3317, 3166, 3103, 2885, 2554, 2390, 2031, 1944, 1680, 1494, 1422, 1207, 1016, 927, 811, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 3.25 Hz, 1 H), 7.02 (dd, *J* = 3.25, 9.01 Hz, 1 H), 6.88 (d, *J* = 9.01 Hz, 1 H), 6.11-5.98 (m, 1 H), 5.44-5.41 (m, 1 H), 5.39-5.37 (m, 1 H), 5.31-5.25 (m, 2 H), 4.58 (td, *J* = 1.38, 5.38 Hz, 2 H), 4.51 (td, *J* = 1.38, 5.38 Hz, 2 H), 2.63 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 199.5, 152.7, 152.6, 133.3, 133.0, 128.9, 121.2, 118.2, 117.9, 115.0, 114.7, 70.2, 69.5, 32.1; HRMS (ESI): *m/z* calcd for $C_{14}H_{16}O_3Na$ $[M+Na]^+$ 255.0992 found 255.0991.



79r

1-(2,5-Bis((triisopropylsilyl)oxy)phenyl)ethan-1-one (79s). To the 4'-hydroxy acetophenone (1 g, 6.57 mmol) in dry DMF (10 mL), Et_3N (2.75 mL, 19.7 mmol) and DMAP (0.08 g, 0.65 mmol) were added at 0 °C and the reaction was stirred for 15 minutes then TIPSCl (4.11 mL, 16.4 mmol) was added dropwise to this. The reaction was stirred at room temperature for 5h. After completion of the reaction the mixture was filtered through celite, the filtrate was diluted with dichloromethane (30 mL) and washed consecutively with water (2 x 40 mL) and brine (50 mL) then dried over Na_2SO_4, the solvent was removed in vacuo and the crude product was purified using silica gel column chromatography to afford the desired product **79s** (2.46 g, 81%) as white solid. (TLC: R_f = 0.8 (SiO_2, 10% EtOAc/ hexanes). IR (neat) cm^{-1} 3429, 2953, 2867, 1674, 1480, 1413, 1272, 1067, 1002, 896; ^1H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, *J* = 3.13 Hz, 1H), 6.85 (dd, *J* = 3.25, 8.88 Hz, 1H), 6.72 (d, *J* = 8.76 Hz, 1H), 2.60 (s, 3H), 1.38-1.17 (m, 7H), 1.14-1.04 (m, 36H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 200.5, 149.8, 149.6, 131.2, 124.5, 120.4, 120.3, 31.4, 18.1, 18.1, 18.0, 13.4, 12.7; HRMS (ESI): *m/z* calcd for $C_{26}H_{49}O_3Si_2$ $[M+H]^+$ 465.3215, found 465.3230.

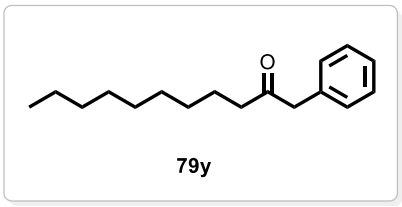


79s

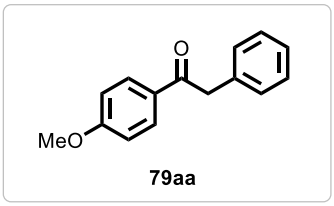
General procedure B for 1-(alkyl/aryl)-2-phenylethan-1-one (A)

To the 100 mL RBF, Mg turnings (1.2 equiv) were taken in dry THF (10 mL) was taken and BnBr (1 equiv) was added dropwise at 0 ℃. The reaction was stirred for 1 h at room temperature until the Grignard was generated. The freshly prepared Grignard reagent was added dropwise to a solution of Weinreb amide (1 equiv) in dry THF at 0 ℃. The reaction mixture was allowed to room temperature and stirred for 12 h. After completion of the reaction, it was quenched with a saturated aqueous solution of NH_4Cl. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (20 mL x 3), dried over Na_2SO_4, filtered, and concentrated in vacuo, and the crude product was purified using silica gel column chromatography to afford the desired product.

1-Phenylundecan-2-one (79y). The title compound was prepared following general procedure A, using N-methoxy-N-methyldecanamide (1 g, 4.64 mmol)), Mg (0.133 g, 5.57 mmol) and BnBr (0.55 mL, 4.64 mmol), THF (20 mL). Yield (0.97 g, 85 %) as colorless liquid. (TLC: R_f = 0.4 (SiO_2, 40% EtOAc/ hexanes). IR (neat) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (m, 2H), 7.23-7.15 (m, 3H), 3.68 (s, 2H), 2.43 (t, J = 7.38 Hz, 2H), 1.22 (s, 12H), 0.89-0.85 (m, 3H); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$) δ 208.9, 134.5, 129.5, 128.8, 128.6, 128.5, 127.1, 50.3, 42.2, 38.1, 32.0, 29.8, 29.5, 29.5, 29.4, 29.2, 23.9, 22.8, 14.3; HRMS (ESI): *m/z* calcd for $C_{17}H_{27}O$ $[M+H]^+$ 247.2056, found 247.2056.

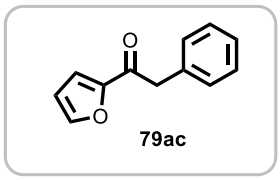


1-(4-Methoxyphenyl)-2-phenylethan-1-one (79aa). The title compound was prepared following general procedure A, using N-4-dimethoxy-N-methylbenzamide (1 g, 5.12 mmol)), Mg (0.147 g, 6.14 mmol) and BnBr (0.68 mL, 5.12 mmol), THF (20 mL). Yield (0.95 g, 83%) as a yellowish liquid. (TLC: R_f = 0.4 (SiO_2, 40% EtOAc/ hexanes). IR (neat) 2942, 2842, 2574, 2409, 1919, 1674, 1600, 1507, 1454, 1425, 1318, 1260, 1170, 1113, 1026, 927, 835, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.88 Hz, 2H), 7.38-7.22 (m, 5H), 6.93 (d, J = 9.01 Hz, 2H), 4.23 (s, 2H), 3.86 (s, 3H); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$) δ 196.4, 163.7, 135.1,



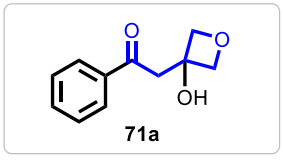
131.1, 129.8, 129.5, 128.8, 126.9, 113.9, 55.6, 45.4; HRMS (ESI): *m/z* calcd for $C_{15}H_{15}O_2$ $[M+H]^+$ 227.1067, found 227.1064.

1-(Furan-2-yl)-2-phenylethan-1-one (79ac). The title compound was prepared following general procedure A, using N-methoxy-N-methylfuran-2-carboxamide (1 g, 6.44 mmol)), Mg (0.185 g, 7.72 mmol) and BnBr (0.74 mL, 6.44 mmol), THF (20 mL).): Yield (0.96 g, 81%) as a colorless liquid. (TLC: R_f = 0.4 (SiO_2, 40% EtOAc/ hexanes). IR (neat) 3777, 3573, 3341, 2938, 1743, 1674, 1579, 1468, 1399, 1307, 1250, 1164, 1084, 1037, 910, 837, 717 cm-1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.53 (m, 1 H), 7.33-7.27 (m, 4 H), 7.25-7.19 (m, 1 H), 7.18 (d, *J* = 3.63 Hz, 1 H), 6.48 (dd, *J* = 1.63, 3.5 Hz, 1 H), 4.08 (s, 2 H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 186.7, 152.4, 146.7, 134.1, 129.6, 128.7, 127.1, 118.0, 112.5, 45.5; HRMS (ESI): *m/z* calcd for $C_{12}H_{11}O_2$ $[M+H]^+$ 187.0754, found 187.0754.



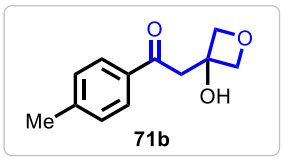
General Procedure B for the synthesis of α-hydroxy oxetane-tethered ketone: To a 100 mL two necked round bottom flask were added DIPA (1.2 equiv.) in anhydrous THF (mL) at 0 ℃ with stirring. To it, *n*-BuLi (1.2 equiv.) was added dropwise, and the reaction was stirred for 45 min at the same temperature. Then it was cooled to -78 ℃, to this freshly prepared LDA enolate solution of acetophenone derivatives (equiv.) in anhydrous THF was added dropwise. The mixture was stirred for 1 hour at -78 ℃ followed by slow addition of 3-oxetanone (1 equiv.). Then the reaction was slowly warmed to room temperature and stirred for additional four hours. Then, reaction progress was monitored by TLC. Then, the reaction was quenched with saturated NH_4Cl (50mL), and the aqueous layer was extracted with EtOAc (3 x 50 mL), dried over Na_2SO_4, filtered, and concentrated under vaccuo and the resulting crude product was purified by silica gel column chromatography (SiO_2, 20% EtOAc/hexane) to afford desired product in high to moderate yields.

2-(3-Hydroxyoxetan-3-yl)-1-phenylethan-1-one (71a). The titled compound was prepared following general procedure B, using acetophenone (**79a**) (3 g, 24.96 mmol), 3-oxetanone (**77**) (1.46 mL, 24.96 mmol), *n*-BuLi (2.5 M, 11.98 mL, 29.95 mmol) and DIPA (3.5 mL, 29.95 mmol) and anhydrous THF (50 mL): yield (4.3 g, 90%) as a white solid.



(TLC: Rf = 0.4 (SiO_2, 40% EtOAc/ hexanes). IR (neat) 3684, 3539, 2958, 2880, 1674, 1593, 1519, 1442, 1397, 1338, 1115, 1036, 970, 926, 676, 633 cm-1; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01-7.95 (m, 2H), 7.67-7.60 (m, 1H), 7.54-7.47 (m, 2H), 4.78 (d, *J* = 7.25 Hz, 2H), 4.49 (d, *J* = 7.38 Hz, 2H), 4.03 (s, 1 H), 3.64 (s, 2H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$): δ 200.3, 136.3, 134.3, 129.0, 128.3, 83.3, 72.4, 45.7; HRMS (ESI): *m/z* calcd for $C_{11}H_{13}O_3$ $[M+H]^+$ 193.0859, found 193.0860.

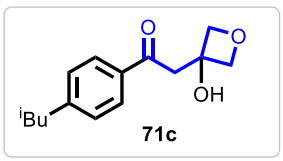
2-(3-Hydroxyoxetan-3-yl)-1-(*p*-tolyl)ethan-1-one (71b). The title compound was



71b

prepared following general procedure B, using acetophenone (**79b**) (3 g, 22.35 mmol), 3-oxetanone (**77**) (1.30 mL, 22.35 mmol), *n*-BuLi (2.5 M, 10.73 mL, 26.82 mmol) and DIPA (3.7 mL, 26.82 mmol) and anhydrous THF (50 mL): yield (3.74 g, 81.12%) as a white solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3755, 3636, 3421, 3365, 2970, 2690, 2393, 2303, 1680, 1617, 1419, 1342, 1226, 1119, 1034, 972, 812, 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ : 7.88 (d, *J* = 8.25 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 4.78 (d, *J* = 7.25 Hz, 2H), 4.47 (d, *J* = 7.25 Hz, 2H), 4.10 (s, 1H), 3.60 (s, 2H), 2.44 (s, 3H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ : 199.9, 145.4, 133.9, 129.7, 128.5, 83.4, 72.4, 45.5, 21.9; HRMS (ESI): *m/z* calcd for $C_{12}H_{15}O_3$ $[M+H]^+$ 207.1016, found 207.1015.

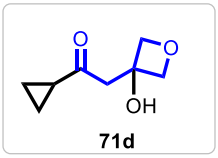
2-(3-Hydroxyoxetan-3-yl)-1-(4-isobutylphenyl)ethan-1-one (71c). The title



71c

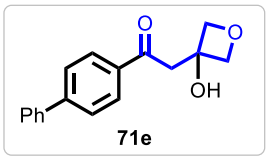
compound was prepared following general procedure B, using acetophenone (**79c**) (0.3 g, 1.70 mmol), 3-oxetanone (**77**) (0.09 mL, 1.70 mmol), *n*-BuLi (1.6 M, 1.27 mL, 2.04 mmol) and DIPA (0.28 mL, 2.04 mmol) and anhydrous THF (5 mL): yield (0.36 g, 87%) as a white solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3861, 3763, 3648, 3527, 3443, 3356, 2967, 2770, 2663, 2337, 1682, 1615, 1410, 1226, 1120, 973, 849, 755 cm-1; ^{1}H NMR (400 MHz, $CDCl_3$) δ : 7.89 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.76 Hz, 2H), 4.78 (d, *J* = 6.75 Hz, 2H), 4.47 (d, *J* = 6.75 Hz, 2H), 4.09 (s, 1 H), 3.61 (s, 2 H), 2.55 (d, *J* = 7.25 Hz, 2H), 1.91 (quind, *J* = 6.8, 13.5 Hz, 1 H), 0.92 (s, 3 H), 0.91 (s, 3 H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ : 200.0, 149.1, 134.2, 129.7, 128.4, 83.4, 77.5, 77.4, 76.8, 72.4, 45.6, 45.6, 30.3, 22.5; HRMS (ESI): *m/z* calcd for $C_{15}H_{21}O_3$ $[M+H]^+$ 249.1485, found 249.1486.

Cyclopropyl(3-hydroxyoxetan-3-yl)methanone (71d): The title compound was prepared following general procedure B, using acetophenone (**79d**) (0.5 g, 5.94 mmol), 3-oxetanone (**77**) (0.34 mL, 5.94 mmol), *n*-BuLi (1.6 M, 4.45 mL, 7.13 mmol) and DIPA (0.99 mL, 7.13 mmol) and anhydrous THF (5 mL): yield (0.839 g, 90%) as a yellowish liquid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3423, 3012, 2957, 2878, 2090, 1913, 1825, 1688, 1395, 1328, 1260, 1116, 1080, 1031, 967, 833 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.64 (d, *J* = 6.88 Hz, 2H), 4.37 (d, *J* = 7.00 Hz, 2H), 4.05 (s, 1H), 3.19 (s, 2H), 2.01-1.90 (m, 1H), 1.10-1.03 (m, 2H), 0.98-0.92 (m, 2H); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$) δ 211.4, 83.2, 72.0, 50.0, 21.5, 11.8; HRMS (ESI): *m/z* calcd for $C_8H_{13}O_2$ $[M+H]^+$ 157.0864, found 157.0855.



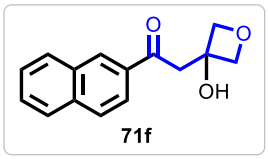
71d

1-([1,1'-Biphenyl]-4-yl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (71e). The title compound was prepared following general procedure B, using acetophenone (**79e**) (0.5 g, 2.54 mmol), 3-oxetanone (**77**) (0.14 mL, 2.54 mmol), *n*-BuLi (1.6 M, 1.6 mL, 3.05 mmol) and DIPA (0.43 mL, 3.05 mmol) and anhydrous THF (8 mL): yield (0.58 g, 85%) as a white solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3925, 3874, 3690, 3398, 3040, 2762, 2373, 1591, 1221, 745, 672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ : 8.09-8.03 (d, *J* = 8.38 Hz, 2H), 7.76-7.71 (d, *J* = 8.38 Hz, 2H), 7.67-7.61 (m, 2H), 7.53-7.40 (m, 3H), 4.81 (d, *J* = 7.0 Hz, 2H), 4.51 (d, *J* = 7.25 Hz, 2H), 4.09 (s, 1H), 3.67 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ : 199.9, 147.0, 139.6, 134.9, 129.2, 129.0, 128.7, 127.6, 127.4, 83.4, 72.4, 45.7; HRMS (ESI): *m/z* calcd for $C_{17}H_{17}O_3$ $[M+H]^+$ 269.1172 found 269.1171.



71e

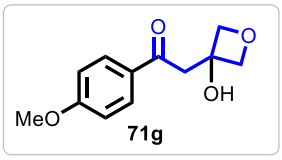
2-(3-Hydroxyoxetan-3-yl)-1-(naphthalen-2-yl)ethan-1-one (71f). The title compound was prepared following general procedure B, using acetophenone (**79f**) (3 g, 17.62 mmol), 3-oxetanone (**77**) (1.46 mL, 17.62 mmol), *n*-BuLi (2.5 M, 8.4 mL, 21.15 mmol) and DIPA (2.98 mL, 21.15 mmol) and anhydrous THF (50 mL): yield (3.85 g, 90%) as a white solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat): 3858, 3742, 2960, 2880, 2405, 2313, 1669, 1517, 1396, 1119, 966, 672, 623 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ : 8.52 (s, 1H), 8.05-7.97 (m, 2H), 7.96-7.88 (m, 2H), 7.68-7.57 (m, 2H), 4.82 (d, *J* = 7.25 Hz, 2H), 4.54 (d, *J* = 7.38 Hz, 2H), 4.10 (s, 1 H), 3.78 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz,



71f

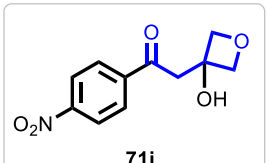
$CDCl_3$) δ : 200.3, 136.2, 133.7, 132.6, 130.6, 129.9, 129.3, 129.0, 128.0, 127.3, 123.4, 83.4, 72.5, 45.7; HRMS (ESI): *m/z* calcd for $C_{15}H_{15}O_3$ $[M+H]^+$ 243.1016, found 243.1016.

2-(3-Hydroxyoxetan-3-yl)-1-(4-methoxyphenyl)ethan-1-one (71g). The title compound was prepared following general procedure B, using acetophenone (**79g**) (3 g, 19.97 mmol), 3-oxetanone (**77**) (1.17 mL, 19.97 mmol), *n*-BuLi (2.5 M, 9.5 mL, 23.96 mmol) and DIPA (3.37 mL, 23.96 mmol) and anhydrous THF (50 mL): yield (3.82 g, 86%) as a white solid. (TLC: R_f = 0.4 (SiO_2, 40% EtOAc/ hexanes). IR (neat) 3860, 3517, 2957, 2880, 2312, 1664, 1601, 1514, 1414, 1342, 1259, 1172, 1114, 1028, 966, 835, 671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ : 7.95-7.90 (m, 2H), 6.96-6.91 (m, 2H), 4.74 (d, *J* = 6.88 Hz, 2H), 4.46 (d, *J* = 7.38 Hz, 2H), 4.24 (s, 1H), 3.86 (s, 3H), 3.54 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ : 198.5, 164.4, 130.6, 129.4, 114.1, 83.4, 72.4, 55.6, 45.1; HRMS (ESI): *m/z* calcd for $C_{12}H_{15}O_4$ $[M+H]^+$ 223.0965, found 223.0964.



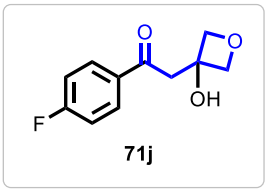
71g

2-(3-Hydroxyoxetan-3-yl)-1-(4-nitrophenyl)ethan-1-one (71i). The title compound was prepared following general procedure B, using acetophenone (**79i**) (3 g, 18.16 mmol), 3-oxetanone (**77**) (1.06 mL, 18.16 mmol), *n*-BuLi (2.5 M, 8.7 mL, 21.79 mmol) and DIPA (3.07 mL, 21.79 mmol) and anhydrous THF (50 mL): yield (3.10 g, 72%) as a yellow solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3686, 3560, 2960, 2880, 1686, 1600, 1528, 1415, 1346, 1114, 1011, 971, 927, 850, 673 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.75 Hz, 2H), 8.15-8.09 (m, 2H), 4.75 (d, *J* = 7.13 Hz, 2H), 4.52 (d, *J* = 7.63 Hz, 2H), 3.66 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ : 198.4, 151.0, 140.6, 129.4, 124.2, 83.2, 72.3, 46.4; HRMS (ESI): *m/z* calcd for $C_{11}H_{12}O_5N$ $[M+H]^+$ 238.0710, found 238.0710.



71i

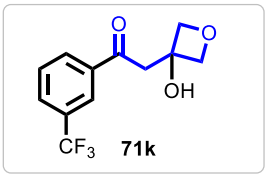
1-(4-Fluorophenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (71j). The title compound was prepared following general procedure B, using acetophenone (**79j**) (3 g, 21.71 mmol), 3-oxetanone (**77**) (1.27 mL, 21.71 mmol), *n*-BuLi (2.5 M, 10.40 mL, 26.06 mmol) and DIPA (3.67 mL, 26.06 mmol) and anhydrous THF (50 mL): yield (4.2 g, 92%) as a white solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat)



71j

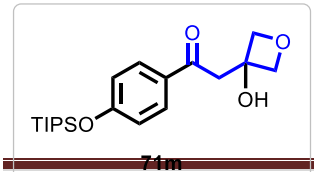
3858, 3669, 3455, 2957, 2880, 1676, 1598, 1509, 1407, 1342, 1157, 1114, 1043, 968, 924, 837, 669, 624 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ : 8.02-7.95 (m, 2H), 7.18-7.11 (m, 2 H), 4.74 (d, *J* = 7.13 Hz, 2H), 4.47 (d, *J* = 7.38 Hz, 2H), 4.05 (s, 1H), 3.58 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ : 198.3, 167.6, 165.1, 132.8, 131.1, 131.0, 116.2, 116.0, 83.3, 72.3, 45.6; HRMS (ESI): *m/z* calcd for $C_{11}H_{12}O_3F$ $[M+H]^+$ 211.0765, found 211.0764.

2-(3-Hydroxyoxetan-3-yl)-1-(3-(trifluoromethyl)phenyl)-ethan-1-one (71k).



The title compound was prepared following general procedure B, using acetophenone (**79k**) (0.3 g, 1.59 mmol), 3-oxetanone (**77**) (0.08 mL, 1.59 mmol), *n*-BuLi (1.6 M, 1.19 mL, 1.91 mmol) and DIPA (0.26 mL, 1.91 mmol) and anhydrous THF (5 mL): yield (0.34 g, 82%) as a white solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3832, 3785, 3674, 3510, 3350, 3284, 3192, 2975, 2898, 2762, 2347, 1833, 1695, 1619, 1330, 1178, 1126, 1078, 967, 811, 661 cm^{-1}; ^1H NMR (400 MHz ,$CDCl_3$) δ : 8.22 (s, 1H), 8.16 (d, *J* = 7.88 Hz, 1H), 7.89 (d, *J* = 7.75 Hz, 1H), 7.66 (t, *J* = 7.75 Hz, 1H), 4.78 (d, *J* = 7.38 Hz, 2H), 4.51 (d, *J* = 7.5 Hz, 2H), 3.84 (s, 1 H), 3.66 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ : 198.7, 136.8, 131.9, 131.6, 131.4, 130.6, 129.8, 125.2, 125.0, 83.2, 72.3, 46.0; HRMS (ESI): *m/z* calcd for $C_{12}H_{12}O_3F_3$ $[M+H]^+$ 261.0733 found 261.0733.

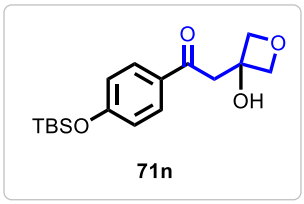
(*E*)-1-(3-Hydroxyoxetan-3-yl)-4-phenylbut-3-en-2-one (71l). The title compound was prepared following general procedure B, using acetophenone (**79l**) (0.3 g, 2.05 mmol), 3-oxetanone (**77**) (0.14 mL, 2.05 mmol), *n*-BuLi (1.6 M, 1.53 mL, 2.46 mmol) and DIPA (0.34 mL, 2.46 mmol) and anhydrous THF (5 mL): yield (0.21 g, 48%) as a white solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3918, 3829, 3690, 3578, 3462, 3397, 3338, 3279, 3093, 2938, 2881, 2601, 2349, 1833, 1728, 1454, 966, 758, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ : 7.69-7.52 (m, 3H), 7.49-7.38 (m, 3H), 6.76 (d, *J* = 16.26 Hz, 1H), 4.75 (d, *J* = 6.88 Hz, 2H), 4.45 (d, *J* = 7.0 Hz, 2H), 4.10 (s, 1H), 3.35 (s, 2H); $^{13}C\{1H\}$NMR (101 MHz, $CDCl_3$) δ : 200.3, 145.0, 134.0, 131.3, 129.2, 128.7, 126.0, 83.4, 72.4, 47.1; HRMS (ESI): *m/z* calcd for $C_{13}H_{15}O_3$ $[M+H]^+$ 219.1021found 219.1017.



2-(3-Hydroxyoxetan-3-yl)-1-(4-((triisopropylsilyl)oxy)phenyl)ethan-1-one (71m). The

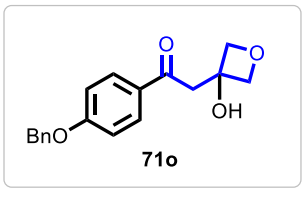
title compound was prepared following general procedure B, using acetophenone (**79m**) (1.45 g, 4.96 mmol), 3-oxetanone (**77**) (0.29 mL, 4.96 mmol), *n*-BuLi (1.6 M, 3.72 mL, 5.95 mmol) and DIPA (0.84 mL, 5.95 mmol) and anhydrous THF (30 mL): yield (1.61 g, 89%) as a colorless liquid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3541, 2954, 2873, 1660, 1597, 1515, 1473, 1420, 1280, 1113, 1009, 917, 632 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95-7.86 (m, 2H), 6.97-6.89 (m, 2H), 4.76 (d, *J* = 7.13 Hz, 2H), 4.47 (d, *J* = 7.25 Hz, 2H), 4.21 (s, 1H), 3.56 (s, 2H), 1.33 - 1.23 (m, 3H), 1.10 (d, *J* = 7.38 Hz, 18H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 198.8, 161.8, 130.7, 129.7, 120.1, 83.4, 72.4, 45.2, 18.0, 12.8; HRMS (ESI): *m/z* calcd for $C_{20}H_{33}O_4Si$ $[M+H]^+$ 365.2143, found 365.2141.

1-(4-((*Tert*-butyldimethylsilyl)oxy)phenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (71n). The title compound was prepared following general procedure B, using acetophenone (**79n**) (1.5 g, 5.99 mmol), 3-oxetanone (**77**) (0.43 mL, 5.99 mmol), *n*-BuLi (1.6 M, 4.5 mL, 7.18 mmol) and DIPA (1.01mL, 7.18 mmol) and anhydrous THF (20 mL): yield (1.79 g, 67.04%) as a white solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3685, 3385, 2947, 2867, 1665, 1599, 1512, 1473, 1422, 1355, 1265, 1173, 1109, 1015, 916, 839, 747, 672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.76 Hz, 2H), 6.91 (d, *J* = 8.75 Hz, 2H), 4.78 (d, *J* = 7.13 Hz, 2H), 4.48 (d, *J* = 7.25 Hz, 2H), 4.19 (s, 1H), 0.99 (s, 9H), 0.25 (s, 6H); ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 198.9, 161.5, 131.1, 130.7, 126.9, 120.5, 120.4, 115.4, 83.4, 72.5, 45.2, 25.7, 18.4, -4.2; HRMS (ESI): *m/z* calcd for $C_{17}H_{27}O_4Si$ $[M+H]^+$ 323.1673, found 323.1671.



71n

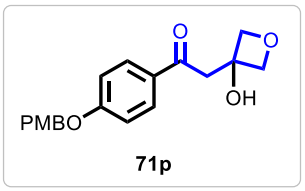
1-(4-(Benzyloxy)phenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (71o). The title compound was prepared following general procedure B, using acetophenone (**79o**) (1.2 g, 5.30 mmol), 3-oxetanone (**77**) (0.38 mL, 5.30 mmol), *n*-BuLi (1.6 M, 3.98 mL, 6.37 mmol) and DIPA (0.89 mL, 6.37 mmol) and anhydrous THF (15 mL): yield (1.19 g, 75%) as a white solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3606, 3541, 2956, 2880, 1661, 1600, 1508, 1420, 1316, 1174, 1116, 1011, 925, 672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.88 Hz, 2H), 7.49-7.34 (m, 5H), 7.04 (d, *J* = 8.88 Hz, 2H), 5.15 (s, 2H), 4.77 (d, *J* = 6.88 Hz, 2H), 4.47 (d, *J*



71o

= 7.00 Hz, 2H), 4.20 (s, 1H), 3.57 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 198.7, 163.6, 136.0, 130.7, 129.6, 128.9, 128.5, 127.6, 115.0, 83.4, 72.4, 70.4, 45.2; HRMS (ESI): *m/z* calcd for $C_{18}H_{19}O_4$ $[M+H]^+$ 299.1278, found 299.1277.

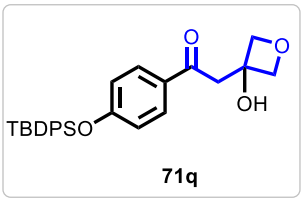
2-(3-Hydroxyoxetan-3-yl)-1-(4-((4-methoxybenzyl)oxy)phenyl)ethan-1-one



71p

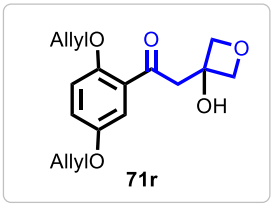
(71p). The title compound was prepared following general procedure B, using acetophenone (**79p**) (0.772 g, 3.01mmol), 3-oxetanone (**77**) (0.17 mL, 3.01 mmol), *n*-BuLi (1.6 M, 2.25 mL, 3.61 mmol) and DIPA (0.51mL, 3.61mmol) and anhydrous THF (10 mL): yield (0.856 g, 87%) as a white solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3686, 3399, 2929, 2858, 2360, 1626, 1515, 1471, 1367, 1102, 1025, 927, 739, 674, 630 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.88 Hz, 2H), 7.36 (d, *J* = 8.63 Hz, 2H), 7.03 (d, *J* = 8.88 Hz, 2H), 6.93 (d, *J* = 8.76 Hz, 2H), 5.08 (s, 2H), 4.77 (d, *J* = 7.13 Hz, 2H), 4.47 (d, *J* = 7.25 Hz, 2H), 4.18 (br. s., 1H), 3.82 (s, 3H), 3.57 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 198.7, 163.7, 159.9, 130.7, 129.5, 129.5, 128.0, 115.0, 114.3, 83.4, 72.5, 70.3, 55.5, 45.2; HRMS (ESI): *m/z* calcd for $C_{19}H_{21}O_5$ $[M+H]^+$ 329.1384, found 329.1380.

1-(4-((*Tert*-butyldiphenylsilyl)oxy)phenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (72q). The title compound was prepared following general procedure B, using acetophenone (**79q**) (2.1 g, 5.61 mmol), 3-oxetanone (**77**) (0.39 mL, 5.61 mmol), *n*-BuLi (1.6 M, 4.2 mL, 6.73 mmol) and DIPA (0.95 mL, 6.73 mmol) and anhydrous THF (30 mL): yield (2.41 g, 96%) as a white solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3905, 3853, 3781, 3641, 3568, 3445, 3366, 3088, 3047, 2957, 2879, 2691, 2624, 2558, 2389, 2336, 1019, 1954, 1801, 1628, 1516, 1267, 1177, 1144, 920, 838, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81-7.74 (m, 2H), 7.73-7.67 (m, 4H), 7.49-7.43 (m, 2H), 7.42-7.36 (m, 4H), 6.86-6.79 (m, 2H), 4.74 (d, *J* = 7.00 Hz, 2H), 4.43 (d, *J* = 7.13 Hz, 2H), 4.18 (s, 1H), 3.50 (s, 2H), 1.13 (s, 9H); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$) δ 198.7, 161.1, 135.5, 132.0, 130.4, 130.4, 129.7, 128.1, 120.1, 83.3, 77.5, 76.8, 72.4, 45.2, 26.5, 19.6; HRMS (ESI): *m/z* calcd for $C_{27}H_{31}O_4Si$ $[M+H]^+$ 447.1986, found 447.1987.



71q

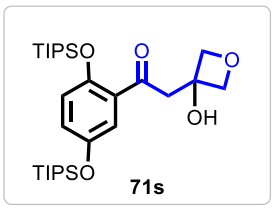
1-(2,5-Bis(allyloxy)phenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (71r). The



71r

title compound was prepared following general procedure B, using acetophenone (**79r**) (5 g, 21.5 mmol), 3-oxetanone (**77**) (1.55 mL, 21.5 mmol), *n*-BuLi (2.5 M, 10.33 mL, 25.8 mmol) and DIPA (3.68 mL, 25.8 mmol) and anhydrous THF (100 mL): yield (5.9 g, 90%) as a white solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3795, 3643, 3434, 3315, 3170, 2940, 2795, 2689, 1672, 1493, 1420, 1270, 1220, 1178, 1116, 1011, 956, 819, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 3.00 Hz, 1H), 7.13-7.06 (m, 1H), 6.92 (d, *J* = 9.01 Hz, 1H), 6.13-5.95 (m, 2H), 5.49-5.20 (m, 4H), 4.73 (d, *J* = 6.63 Hz, 2H), 4.63 (d, *J* = 5.50 Hz, 2H), 4.53-4.49 (m, 2H), 4.46 (d, *J* = 7.13 Hz, 2H), 4.04 (br. s., 1H), 3.68 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 201.1, 153.3, 152.7, 133.1, 132.6, 127.2, 122.6, 118.7, 118.0, 114.8, 114.7, 83.5, 72.6, 70.2, 69.5, 51.6; HRMS (ESI): *m/z* calcd for $C_{17}H_{21}O_5$ $[M+H]^+$ 305.1384, found 305.1380.

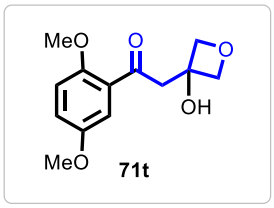
1-(2,5-Bis((triisopropylsilyl)oxy)phenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one



71s

(71s). The title compound was prepared following general procedure B, using acetophenone (**79s**) (2.6 g, 5.59 mmol), 3-oxetanone (**77**) (0.40 mL, 5.59 mmol), *n*-BuLi (1.6 M, 4.19 mL, 6.71 mmol) and DIPA (0.94 mL, 6.71 mmol) and anhydrous THF (8 mL): yield (1.9 g, 63%) as a white solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 2953, 2870, 1657, 1483, 1413, 1268, 1172, 1113, 1008, 896 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 3.25 Hz, 1H), 6.94 (dd, *J* = 3.13, 8.76 Hz, 1H), 6.76 (d, *J* = 8.88 Hz, 1H), 4.74 (d, *J* = 7.00 Hz, 2H), 4.43 (d, *J* = 7.13 Hz, 2H), 4.03 (s, 1H), 3.69 (s, 2H), 1.40-1.31 (m, 3H), 1.28-1.19 (m, 3H), 1.13 (d, *J* = 7.38 Hz, 18H), 1.08 (d, *J* = 7.13 Hz, 18H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 201.5, 150.7, 150.0, 128.8, 126.3, 120.8, 120.2, 83.4, 72.6, 51.0, 18.1, 18.0, 13.6, 12.7; HRMS (ESI): *m/z* calcd for $C_{29}H_{53}O_5Si_2$ $[M+H]^+$ 537.3426, found 537.3419.

1-(2,5-Dimethoxyphenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (71t). The title

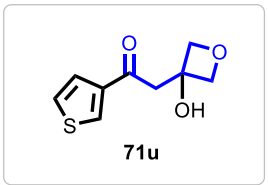


71t

compound was prepared following general procedure B, using acetophenone (**79t**) (0.70 g, 3.88 mmol), 3-oxetanone (**77**) (0.22 mL, 3.88 mmol), *n*-BuLi (1.6 M, 2.91 mL, 4.66 mmol) and DIPA (0.65 mL, 4.66 mmol) and anhydrous THF (8 mL): yield (0.82 g, 84%) as a white solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat)

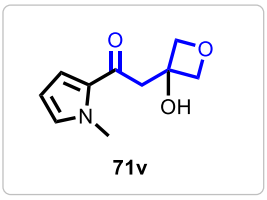
3605, 3444, 3018, 2950, 2840, 2404, 1759, 1603, 1502, 1456, 1275, 1172, 1040, 974, 936, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 3.38 Hz, 1H), 7.10 (dd, *J* = 3.25, 9.13 Hz, 1H), 6.95 (d, *J* = 9.13 Hz, 1H), 4.75 (d, *J* = 6.88 Hz, 2H), 4.48 (d, *J* = 7.25 Hz, 2H), 3.91 (s, 3H), 3.80 (s, 3H), 3.66 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 201.3, 154.2, 153.6, 126.8, 122.0, 113.6, 113.4, 83.5, 72.7, 56.1, 56.0, 51.4; HRMS (ESI): *m/z* calcd for $C_{13}H_{17}O_5$ $[M+H]^+$ 253.1071, found 253.1066.

2-(3-Hydroxyoxetan-3-yl)-1-(thiophen-3-yl)ethan-1-one (71u). The title compound was prepared following general procedure B, using acetophenone (**79u**) (3 g, 23.77 mmol), 3-oxetanone (**6**) (1.71 mL, 23.77 mmol), *n*-BuLi (2.5 M, 11.41 mL, 28.53 mmol) and DIPA (4.0 mL, 28.53 mmol) and anhydrous THF (50 mL): yield (2.91 g, 62%) as a white solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3806, 3740, 3684, 3600, 3337, 3116, 2975, 2898, 2758, 2353, 1666, 1412, 1338, 1238, 1104, 962, 881, 809, 683 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ : 8.15 (dd, *J* = 1.25, 2.88 Hz, 1H), 7.56 (dd, *J* = 1.13, 5.13 Hz, 1H), 7.37 (dd, *J* = 2.88, 5.13 Hz, 1H), 4.76 (d, *J* = 7.3 Hz, 2H), 4.47 (d, *J* = 7.3 Hz, 2H), 4.07 (s, 1H), 3.54 (s, 2H); $^{13}C\{1H\}$ NMR (101MHz, $CDCl_3$) δ : 194.3, 141.8, 133.6, 127.2, 126.7, 83.3, 72.4, 46.7; HRMS (ESI): *m/z* calcd for $C_9H_{11}O_3S$ $[M+H]^+$ 199.0423, found 199.0424.



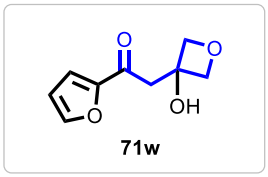
71u

2-(3-Hydroxyoxetan-3-yl)-1-(1-methyl-1H-pyrrol-2-yl)ethan-1-one (71v). The title compound was prepared following general procedure C, using acetophenone (**79v**) (3 g, 24.36 mmol), 3-oxetanone (**77**) (1.42 mL, 24.36 mmol), *n*-BuLi (2.5 M, 11.69 mL, 29.20 mmol) and DIPA (4.12 mL, 29.20 mmol) and anhydrous THF (50 mL): yield (4.64 g, 98%) as a white solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3687, 3456, 2958, 2879, 1630, 1521, 1475, 1410, 1107, 1060, 1026, 971, 927, 672, 624 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ : 7.07-7.02 (m, 1H), 6.86 (s, 1H), 6.16 (d, *J* = 2.38 Hz, 1H), 4.71 (d, *J* = 6.63 Hz, 2H), 4.57 (br. s., 1 H), 4.46 (d, *J* = 6.38 Hz, 2H), 3.90 (s, 3H), 3.39 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ : 189.8, 132.5, 130.3, 121.1, 108.8, 83.5, 72.7, 45.0, 37.8; HRMS (ESI): *m/z* calcd for $C_{10}H_{14}NO_3$ $[M+H]^+$ 196.0968 found 196.0968.



71v

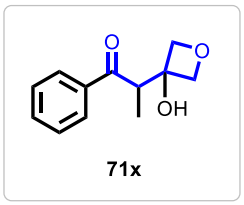
1-(Furan-2-yl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (71w). The title compound



71w

was prepared following general procedure B, using acetophenone (**79w**) (0.5 g, 4.54 mmol), 3-oxetanone (6) (0.25 mL, 4.54 mmol), *n*-BuLi (1.6 M, 3.40 mL, 5.44 mmol) and DIPA (0.75 mL, 5.44 mmol) and anhydrous THF (8 mL): yield (0.67 g, 91%) as a white solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3685, 3427, 2959, 2880, 2402, 1661, 1566, 1519, 1469, 1416, 1327, 1118, 1021, 969, 928, 891, 672, 624 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ : 7.64 (dd, *J* = 0.63, 1.63 Hz, 1H), 7.29 (dd, *J* = 0.75, 3.63 Hz, 1H), 6.59 (dd, *J* = 1.63, 3.63 Hz, 1H), 4.74 (s, 1H), 4.72 (s, 1H), 4.48 (d, *J* = 7.38 Hz, 2H), 4.04 (s, 1 H), 3.48 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ : 188.6, 152.3, 147.5, 118.7, 112.9, 83.3, 77.5, 76.8, 72.4, 45.2; HRMS (ESI): *m/z* calcd for $C_9H_{11}O_4$ $[M+H]^+$ 183.0652, found 183.0652.

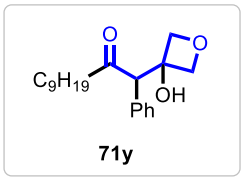
2-(3-Hydroxyoxetan-3-yl)-1-phenylpropan-1-one (71x). The title compound was



71x

prepared following general procedure B, using acetophenone (**79x**) (0.3 g, 2.23 mmol), 3-oxetanone (**77**) (0.12 mL, 2.23 mmol), *n*-BuLi (1.6 M, 1.67 mL, 2.68 mmol) and DIPA (0.37 mL, 2.68 mmol) and anhydrous THF (5 mL): yield (0.412 g, 89%) as a white solid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3905, 3785, 3421, 2961, 2889, 2374, 1676, 1600, 1459, 1395, 1342, 1287, 1221, 1074, 971, 893, 762, 700, 651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01-7.95 (m, 2H), 7.66-7.59 (m, 1H), 7.55-7.47 (m, 2H), 4.70 (dd, *J* = 6.8, 8.38 Hz, 2H), 4.56-4.50 (m, 1H), 4.32 (d, *J* = 6.75 Hz, 1H), 4.26 (d, *J* = 0.88 Hz, 1H), 4.12 (q, *J* = 7.25 Hz, 1H), 1.32 (d, *J* = 7.38 Hz, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 205.7, 135.4, 134.3, 129.1, 128.7, 83.8, 81.6, 75.3, 46.0, 12.7; HRMS (ESI): *m/z* calcd for $C_{12}H_{15}O_3$ $[M+H]^+$ 207.1016, found 207.1015.

1-(3-Hydroxyoxetan-3-yl)-1-phenylundecan-2-one (71y). The title compound

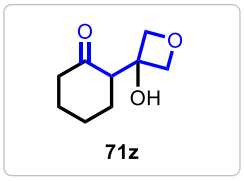


71y

was prepared following general procedure B, using acetophenone (**79y**) (0.5 g, 2.02 mmol), 3-oxetanone (**77**) (0.11 mL, 2.02 mmol), *n*-BuLi (1.6 M, 1.52 mL, 2.43 mmol) and DIPA (0.33 mL, 2.43 mmol) and anhydrous THF (8 mL): yield (0.427 g, 66 %) as a colorless liquid. TLC: *Rf* = 0.3 (SiO_2, 40% EtOAc/ hexanes). IR (neat) 3922, 3873, 3788, 3696, 3573, 3486, 3337, 3268, 2939, 2872, 2763, 1769, 1744, 1608, 1460, 1271, 991, 773, 705, 654 cm^{-1}; ^1H NMR (400 MHz ,$CDCl_3$) δ 8.01-7.95 (m, 2H),

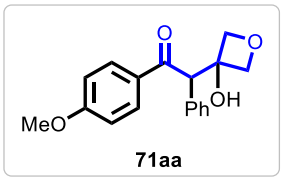
7.66-7.59 (m, 1H), 7.55-7.47 (m, 2H), 4.70 (dd, *J* = 6.8, 8.38 Hz, 2H), 4.56-4.50 (m, 1H), 4.32 (d, *J* = 6.75 Hz, 1H), 4.26 (d, *J* = 0.88 Hz, 1H), 4.12 (q, *J* = 7.25 Hz, 1H), 1.32 (d, *J* = 7.38 Hz, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 205.7, 135.4, 134.3, 129.1, 128.7, 83.8, 81.6, 75.3, 46.0, 12.7; HRMS (ESI): m/z calcd for $C_{20}H_{31}O_3$ $[M+H]^+$ 319.2268, found 319.2269.

2-(3-Hydroxyoxetan-3-yl)cyclohexan-1-one (71z). The title compound was prepared following general procedure B, using cyclohexanone (**79z**) (0.432 g, 2.13 mmol), 3-oxetanone (**77**) (0.12 mL, 2.13 mmol), *n*-BuLi (1.6 M, 1.6 mL, 2.56 mmol) and DIPA (0.35 mL, 2.56 mmol) and anhydrous THF (5 mL): yield (0.358 g, 61%) as a colorless liquid. TLC: R_f = 0.3 (SiO_2, 40% EtOAc/ hexanes). IR (neat) 3432, 3022, 2953, 2402, 2352, 2101, 1642, 1523, 1428, 1018, 926, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.67 (d, *J* = 7.13 Hz, 1H), 4.57 (d, *J* = 7.00 Hz, 1H), 4.42 (d, *J* = 7.13 Hz, 2H), 3.35 (s, 1H), 2.99-2.87 (m, 1H), 2.44-2.30 (m, 2H), 2.19-2.05 (m, 2H), 2.00-1.90 (m, 1H), 1.79-1.56 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.1, 83.5, 80.8, 74.1, 57.1, 42.6, 28.0, 27.8, 24.9; HRMS (ESI): *m/z* calcd for $C_9H_{15}O_3$ $[M+H]+$ 171.1021, found 171.1020.



71z

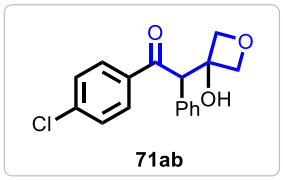
2-(3-Hydroxyoxetan-3-yl)-1-(4-methoxyphenyl)-2-phenylethan-1-one (71aa). The title compound was prepared following general procedure B, using acetophenone (**79aa**) (0.32 g, 1.41 mmol), 3-oxetanone (**77**) (0.08 mL, 1.41 mmol), *n*-BuLi (1.6 M, 1.06 mL, 1.69 mmol) and DIPA (0.23 mL, 1.69 mmol) and anhydrous THF (5 mL): yield (0.348 g, 83%) as a yellow liquid. TLC: R_f = 0.3 (SiO_2, 40% EtOAc/ hexanes). IR (neat) 3896, 3782, 3701, 3643, 3514, 3434, 3314, 2954, 2889, 2487, 2396, 2324, 2124, 1669, 1603, 1465, 1326, 1258, 1177, 973, 839, 715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95-7.89 (m, 2H), 7.37-7.27 (m, 5H), 6.88-6.82 (m, 2H), 5.16 (s, 1H), 4.80 (d, *J* = 6.63 Hz, 1H), 4.60 (d, *J* = 7.13 Hz, 1H), 4.46 (dd, *J* = 7.13, 10.76 Hz, 2H), 3.81 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 200.0, 164.3, 134.3, 131.7, 129.6, 129.1, 128.7, 128.0, 114.1, 84.2, 80.8, 75.7, 58.1, 55.6; HRMS (ESI): *m/z* calcd for $C_{18}H_{19}O_4$ $[M+H]^+$ 299.1278, found 299.1272.



71aa

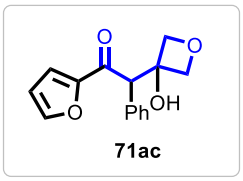
1-(4-Chlorophenyl)-2-(3-hydroxyoxetan-3-yl)-2-phenylethan-1-one (71ab). The title compound was prepared following general procedure B, using acetophenone

(**79ab**) (0.5 g, 2.16 mmol), 3-oxetanone (**77**) (0.12 mL, 2.16 mmol), *n*-BuLi (1.6 M, 1.62 mL, 2.60 mmol) and DIPA (0.36 mL, 2.60 mmol) and anhydrous THF (8 mL): yield (0.502 g, 77%) as a yellow liquid. TLC: R_f = 0.3 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3945, 3881, 3764, 3636, 3422, 3338, 2965, 2892, 2486, 2394, 1680, 1592, 1482, 1399, 1253, 1101, 973, 827, 717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91-7.79 (m, 2H), 7.40-7.27 (m, 7H), 5.13 (s, 1H), 4.81 (d, *J* = 6.75 Hz, 1H), 4.60 (d, *J* = 7.13 Hz, 1H), 4.48 (d, *J* = 7.25 Hz, 1H), 4.44 (d, *J* = 6.75 Hz, 1H), 4.39 (br. s., 1H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 200.2, 140.7, 134.0, 133.6, 130.6, 129.6, 129.3, 129.3, 128.4, 83.9, 80.7, 75.6, 58.9; HRMS (ESI): *m/z* calcd for $C_{17}H_{16}O_3Cl$ $[M+H]^+$ 303.0782, found 303.0777.



71ab

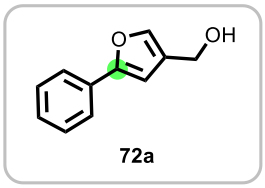
1-(Furan-2-yl)-2-(3-hydroxyoxetan-3-yl)-2-phenylethan-1-one (71ac). The title compound was prepared following general procedure B, using acetophenone (**79ac**) (0.594 g, 3.18 mmol), 3-oxetanone (**77**) (0.18 mL, 3.18 mmol), *n*-BuLi (1.6 M, 2.39 mL, 3.82 mmol) and DIPA (0.53 mL, 3.82 mmol) and anhydrous THF (8 mL): yield (0.685 g, 83%) as a colorless liquid. TLC: R_f = 0.3 (SiO_2, 40% EtOAc/ hexanes). IR (neat) 3686, 3433, 3023, 2959, 2402, 2351, 1676, 1603, 1522, 1473, 1423, 1023, 928, 672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57-5.55 (m, 1H), 7.42-7.37 (m, 2H), 7.37-7.29 (m, 3H), 7.20 (d, *J* = 3.63 Hz, 1H), 6.49 (dd, *J* = 1.63, 3.63 Hz, 1H), 5.01 (s, 1H), 4.78 (d, *J* = 6.75 Hz, 1H), 4.59-4.49 (m, 2H), 4.49-4.41 (m, 2H); $^{13}C\{H\}$NMR (101 MHz $CDCl_3$) δ 189.8, 151.8, 147.8, 133.6, 129.7, 129.0, 128.3, 120.2, 112.9, 84.0, 80.8, 75.6, 58.3; HRMS (ESI): *m/z* calcd for $C_{15}H_{15}O_4$ $[M+H]^+$ 259.0965, found 259.0974.



71ac

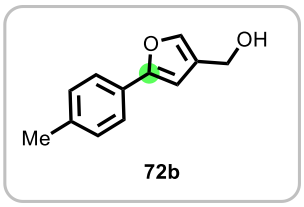
***General Procedure C* for the synthesis of 5-phenylfuran-3-yl)methanol:** To the α-hydroxy oxetane-tethered ketone **71a-71ac**(1 equiv) in anhydrous DCM, $Bi(OTf)_3$ (10 mol%) were added at room temperature and the reaction was stirred up to starting material was completely consumed (1 minute). After completion of the reaction, it was quenched with saturated aqueous solution of $NaHCO_3$ and the aqueous layer was extracted with DCM (3 x 10 mL), dried over Na_2SO_4, filtered, and concentrated in vaccuo, and the resulting crude product was purified by silica gel column chromatography (SiO_2, 20% EtOAc/hexane) to afford desired product in high to moderate yields.

(5-Phenylfuran-3-yl)methanol (72a): The title compound was prepared following general procedure C using 2-(3-hydroxyoxetan-3-yl)-1-phenylethan-1-one (**71a**, 0.05 g, 0.26 mmol), $Bi(OTf)_3$ (0.017 g, 0.026 mmol) and DCM (0.5 mL): yield (0.0448 g, 99%) as white solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3687, 3602, 1769, 1601, 1520, 1426, 1020, 927, 678, 624 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66-7.59 (m, 2H), 7.44-7.39 (m, 1H), 7.39-7.32 (m, 2H), 7.25-7.21 (m, 1H), 6.67 (s, 1H), 4.56 (d, *J* = 2.6 Hz, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 154.9, 139.4, 130.8, 128.8, 127.7, 127.3, 123.9, 105.2, 56.9; HRMS (ESI): *m/z* calcd for $C_{11}H_{11}O_2$ $[M+H]^+$ 175.0754, found 175.0753.



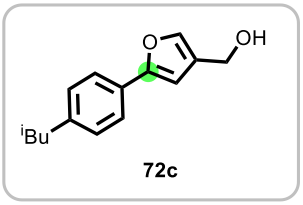
72a

(5-(*p*-Tolyl)furan-3-yl)methanol (72b): The title compound was prepared following general procedure C using 2-(3-hydroxyoxetan-3-yl)-1-(*p*-tolyl)ethan-1-one (**71b**, 0.05 g, 0.242 mmol), $Bi(OTf)_3$ (0.015 g, 0.024 mmol) and DCM (0.5 mL): yield (0.044 g, 98%) as white solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3685, 3610, 3451, 2931, 2880, 1901, 1757, 1600, 1498, 1423, 1021, 971, 923, 672, 624 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57-7.53 (m, 2H), 7.42 (d, *J* = 0.88 Hz, 1H), 7.21-7.17 (m, 2H), 6.64 (s, 1H), 4.59 (s, 2H), 2.36 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 155.2, 139.1, 137.6, 129.5, 128.1, 127.2, 123.9, 104.5, 57.0, 21.4; HRMS (ESI): *m/z* calcd for $C_{12}H_{13}O_2$ $[M+H]^+$ 189.0910, found 189.0909.



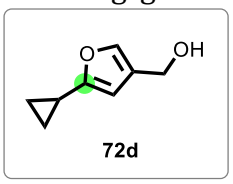
72b

(5-(4-Isobutylphenyl)furan-3-yl)methanol (72c): The title compound was prepared following general procedure C using 2-(3-hydroxyoxetan-3-yl)-1-(4-isobutylphenyl)ethan-1-one (**71c**, 0.05 g, 0.201 mmol), $Bi(OTf)_3$ (0.013 g, 0.020 mmol) and DCM (0.5 mL): yield (0.044 g, 96%) as white solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3625, 3363, 3008, 2945, 2832, 2513, 2040, 1638, 1456, 1112, 1026, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.13 Hz, 2H), 7.43 (s, 1H), 7.16 (d, *J* = 8.25 Hz, 2H), 6.65 (s, 1H), 4.59 (s, 2H), 2.48 (d, *J* = 7.13 Hz, 2H), 1.87 (quind, *J* = 6.63, 13.38 Hz, 1H), 0.92 (s, 3H), 0.90 (s, 3H); 13C NMR (101 MHz, $CDCl_3$) δ 155.2, 141.5, 139.1, 129.6, 128.4, 127.2, 123.8, 114.2, 104.5, 57.1, 45.3, 30.4, 22.5; HRMS (ESI): m/z calcd for $C_{15}H_{19}O_2$ [M+H]+ 231.1380, found 231.1380.



72c

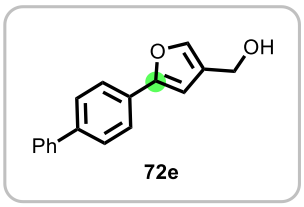
(5-Cyclopropylfuran-3-yl)methanol (72d). The title compound was prepared following general procedure C using cyclopropyl(3-hydroxyoxetan-3-yl)methanone



72d

(**71d**, 0.05 g, 0.201 mmol), $Bi(OTf)_3$ (0.013 g, 0.020 mmol) and DCM (0.5 mL): yield (0.045 g, 94%) as colorless liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3427, 3022, 2956, 2402, 1641, 1426, 1023, 932, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (s, 1H), 6.00 (s, 1H), 4.48 (s, 2H), 1.90-1.79 (m, 1H), 0.88-0.83 (m, 3H), 0.77-0.72 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 137.8, 125.9, 103.8, 57.0, 8.9, 6.7; HRMS (ESI): m/z calcd for $C_8H_{11}O_2$ [M+H]+ 139.0754, found 139.0755.

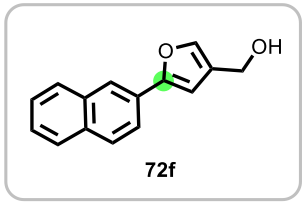
(5-([1,1'-Biphenyl]-4-yl)furan-3-yl)methanol (72e): The title com-pound was



72e

prepared following general procedure C using 1-([1,1'-biphenyl]-4-yl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (**71e,** 0.05 g, 0.186 mmol), $Bi(OTf)_3$ (0.012 g, 0.018 mmol) and DCM (0.5 mL): yield (0.0448 g, 97%) as white solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3023, 2927, 2402, 1727, 1604, 1414, 1044, 850, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76-7.70 (m, 2H), 7.65-7.60 (m, 4H), 7.49-7.42 (m, 3H), 7.38-7.33 (m, 1H), 6.75 (s, 1H), 4.62 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz , $CDCl_3$) δ 154.7, 140.4, 139.6, 129.8, 129.0, 127.6, 127.5, 127.1, 124.4, 105.3, 57.0; HRMS (ESI): *m/z* calcd for $C_{17}H_{15}O_2$ $[M+H]^+$ 251.1067, found 251.1066.

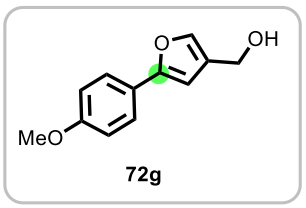
(5-(Naphthalen-2-yl)furan-3-yl)methanol (72f): The title compound was



72f

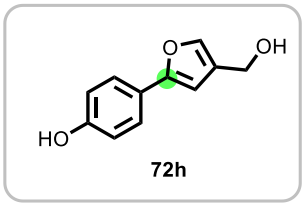
prepared following general procedure C using 2-(3-hydroxyoxetan-3-yl)-1-(naphthalen-2-yl)ethan-1-one (**71f**, 0.05 g, 0.206 mmol), $Bi(OTf)_3$ (0.013 g, 0.020 mmol) and DCM (0.5 mL): yield (0.0453 g, 98%) as white solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3021, 1518, 1216, 1022, 769, 671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.88-7.79 (m, 3H), 7.74 (dd, *J* = 1.75, 8.63 Hz, 1H), 7.53-7.42 (m, 3H), 6.82 (s, 1H), 4.62 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 155.0, 139.7, 133.6, 132.9, 128.6, 128.3, 128.1, 127.9, 127.5, 126.7, 126.2, 122.4, 122.4, 105.8, 57.0; HRMS (ESI): *m/z* calcd for $C_{15}H_{13}O_2$ $[M+H]^+$ 225.0910, found 225.0909.

(5-(4-Methoxyphenyl)furan-3-yl)methanol (72g): The title compound was prepared following general procedure C using 2-(3-hydroxyoxetan-3-yl)-1-(4-methoxyphenyl)ethan-1-one (**71g**, 0.05 g, 0.224 mmol), $Bi(OTf)_3$ (0.014 g, 0.0224 mmol) and DCM (0.5 mL): yield (0.043 g, 95%) as white solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3864, 3736, 3257, 2953, 2842, 2315, 2042, 1893, 1611, 1537, 1497, 1290, 1179, 1108, 1034, 914, 835, 670, 624 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61-7.56 (m, 2H), 7.40 (s, 1H), 6.94-6.90 (m, 2H), 6.56 (s, 1H), 4.58 (s, 2H), 3.83 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 159.3, 155.0, 138.8, 127.3, 125.4, 123.9, 114.3, 103.6, 57.1, 55.5; HRMS (ESI): *m/z* calcd for $C_{12}H_{13}O_3$ $[M+H]^+$ 205.0859, found 205.0859.



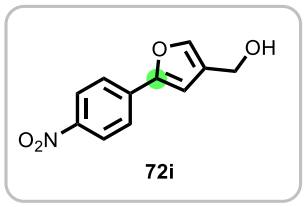
72g

4-(4-(Hydroxymethyl)furan-2-yl)phenol (72h): To a solution of (5-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-furan-3-yl)methanol (**72n**) (0.03 g, 0.098 mmol) in dry THF at 0 °C , TBAF (1 M in THF, 0.11 mL, 0.118 mmol) were added dropwise and the reaction mixture was stirred for 30 min. at the same temperature. The reaction was monitored by TLC and After completion of the reaction, it was quenched with H_2O. The organic layer was separated and aqueous layer was extracted with EtOAc (3x3 mL) and combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuum and crude product was purified by silica gel column chromatography (using 60% EtOAc in hexanes) to afford **72h** (15 mg, 83%) as white solid. TLC: R_f = 0.3 (SiO_2, 60% EtOAc/hexanes); FTIR: 3949, 3870, 3762, 3700, 3639, 3540, 3323, 3173, 2975, 2862, 2687, 2493, 2376, 2231, 2084, 1914, 1665, 1532, 1466, 1120, 1029, 977, 771, 683 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.53-7.45 (m, 2H), 7.42 (s, 1H), 6.83-6.74 (m, 2H), 6.57 (s, 1H), 4.48 (s, 2H); $^{13}C\{H\}$ NMR (101 MHz, CD_3OD) δ 158.4, 156.5, 139.7, 129.0, 126.4, 124.4, 116.6, 104.3, 56.9; HRMS (ESI): *m/z* calcd for $C_{11}H_{11}O_3$ $[M+H]^+$ 191.0703, found 191.0704.



72h

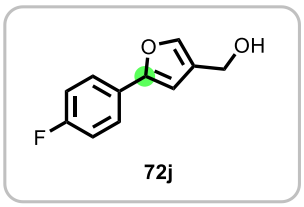
(5-(4-Nitrophenyl)furan-3-yl)methanol (72i): The title compound was prepared following general procedure C using 2-(3-hydroxyoxetan-3-yl)-1-(4-nitrophenyl)ethan-1-one (**71i**, 0.05 g, 0.210 mmol), $Bi(OTf)_3$ (0.013 g, 0.021 mmol) and DCM (0.5 mL): yield (0.042 g, 89%) as yellow solid. TLC: R_f = 0.4 (SiO_2, 20%



72i

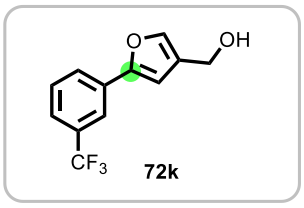
EtOAc/ hexanes). IR (neat) 3862, 3738, 3615, 2936, 2404, 2313, 1600, 1518, 1433, 1341, 1217, 1107, 1022, 924, 856, 672, 624 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.63 Hz, 2H), 7.76 (d, *J* = 8.63 Hz, 2H), 7.54 (s, 1H), 6.92 (s, 1H), 4.62 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 152.5, 146.7, 141.4, 136.4, 128.1, 124.5, 124.1, 109.1, 56.7; HRMS (ESI): *m/z* calcd for $C_{11}H_{10}O_4N$ $[M+H]^+$ 220.0604, found 220.0605.

(5-(4-Fluorophenyl)furan-3-yl)methanol (72j): The title compound was prepared following general procedure C using 1-(4-fluorophenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (**71j**, 0.05 g, 0.237 mmol), $Bi(OTf)_3$ (0.015 g, 0.023 mmol) and DCM (0.5 mL): yield (0.044 g, 98%) as white solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3686, 3601, 2926, 1708, 1612, 1518, 1424, 1310, 1047, 925, 672, 624 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65-7.58 (m, 2H), 7.43 (s, 1H), 7.07 (t, *J* = 8.63 Hz, 2H), 6.63 (s, 1H), 4.58 (s, 2H), 1.70 (br. s., 1H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 163.6, 161.2, 154.1, 139.4, 127.3, 127.2, 125.8, 125.7, 116.0, 115.8, 104.9, 56.9; HRMS (ESI): *m/z* calcd for $C_{11}H_{10}O_2F$ $[M+H]^+$ 193.0659, found 193.0659.



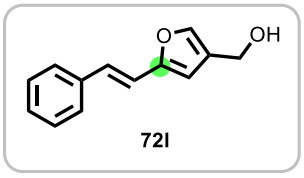
72j

(5-(3-(Trifluoromethyl)phenyl)furan-3-yl)methanol (72k): The title compound was prepared following general procedure C using 2-(3-hydroxyoxetan-3-yl)-1-(3-(trifluoromethyl)phenyl)ethan-1-one (**71k**, 0.05 g, 0.192 mmol), $Bi(OTf)_3$ (0.0126 g, 0.019 mmol) and DCM (0.5 mL): yield (0.0434 g, 94%) as white solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3627, 3378, 3016, 2946, 2835, 2407, 1768, 1708, 1623, 1440, 1332, 1173, 1132, 1078, 1024, 926, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.82 - 7.78 (m, 1H), 7.51 - 7.47 (m, 3H), 6.79 (s, 1H), 4.61 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz , $CDCl_3$) δ 153.4, 140.1, 131.5, 129.4, 127.6, 126.9, 124.2, 124.1, 120.7, 120.68, 106.5, 56.9; HRMS (ESI): *m/z* calcd for $C_{12}H_{10}O_2F_3$ $[M+H]^+$ 243.0627, found 243.0623.



72k

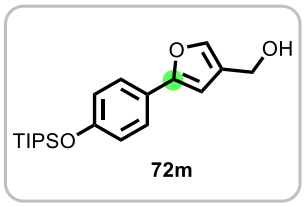
(*E*)-(5-Styrylfuran-3-yl)methanol (72l): The title compound was prepared following general procedure C using (*E*)-1-(3-hydroxyoxetan-3-yl)-4-phenylbut-3-en-2-one (**71l**, 0.05 g, 0.229 mmol), $Bi(OTf)_3$ (0.015 g, 0.022 mmol) and DCM (0.5 mL): yield (0.028 g, 62%) as off white solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat)



72l

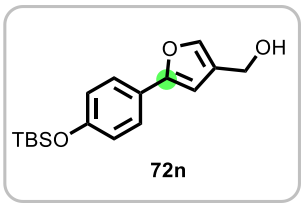
3627, 3375, 3013, 2946, 2883, 2407, 2037, 1632, 1415, 1110, 1025, 929, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.38 Hz, 2H), 7.39 (s, 1H), 7.34 (t, *J* = 7.13 Hz, 3H), 7.04 (d, *J* = 16.88 Hz, 1H), 6.86 (d, *J* = 16.38 Hz, 1H), 6.40 (s, 1H), 4.57 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 154.2, 139.5, 137.0, 128.9, 127.8, 127.4, 126.5, 116.5, 108.6, 57.0. HRMS (ESI): *m/z* calcd for

(5-(4-((Triisopropylsilyl)oxy)phenyl)furan-3-yl)methanol (72m): The title compound was prepared following general procedure C using 2-(3-hydroxyoxetan-3-yl)-1-(4-((triisopropylsilyl)oxy)-phnyl)ethan-1-one (**71m**, 0.05 g, 0.137 mmol), $Bi(OTf)_3$ (0.008 g, 0.013 mmol) and DCM (0.5 mL): yield (0.042 g, 89%) as yellow solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3899, 3767, 3643, 3426, 3320, 2956, 2885, 2694, 2633, 2379, 1919, 1609, 1503, 1272, 1176, 1009, 909, 837, 746, 682 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.63 Hz, 2H), 7.40 (s, 1H), 6.89 (d, *J* = 8.75 Hz, 3H), 6.56 (s, 1H), 4.58 (s, 2H), 1.29-1.24 (m, 3H), 1.12 (s, 9H), 1.10 (s, 9H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 156.0, 155.2, 138.7, 127.3, 125.3, 124.1, 120.3, 103.6, 57.1, 18.1, 12.8; HRMS (ESI): *m/z* calcd for $C_{20}H_{31}O_3Si$ $[M+H]^+$ 347.2037, found 347.2036.



72m

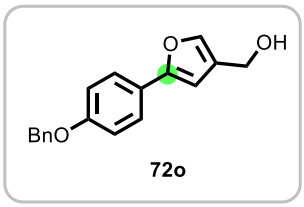
(5-(4-((*Tert*-butyldimethylsilyl)oxy)phenyl)furan-3-yl)methanol (72n): The title compound was prepared following general procedure C using 1-(4-((tert-butyldimethylsilyl)oxy)phenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (**71n**, 0.05 g, 0.155 mmol), $Bi(OTf)_3$ (0.010 g, 0.015 mmol) and DCM (0.5 mL): yield (0.043 g, 91%) as white solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3876, 3798, 3671, 3566, 3474, 3390, 2938, 2875, 2758, 2644, 2102, 1598, 1468, 1372, 1276, 913, 779, 661 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54-7.49 (m, 2H), 7.42-7.38 (m, 1H), 6.87-6.83 (m, 2H), 6.57-6.54 (m, 1H), 4.58 (s, 2H), 0.99 (s, 9H), 0.21 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6, 153.0, 138.8, 130.7, 127.3, 125.4, 125.3, 120.5, 120.3, 103.7, 57.1, 25.8, 18.1, -4.3; HRMS (ESI): m/z calcd for $C_{17}H_{25}O_3Si$ $[M+H]^+$ 305.1567, found 305.1567.



72n

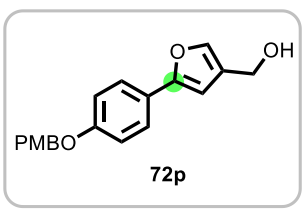
(5-(4-(Benzyloxy)phenyl)furan-3-yl)methanol (72o): The title com-pound was prepared following general procedure C using 1-(4-(benzyloxy)phenyl)-2-(3-

hydroxyoxetan-3-yl)ethan-1-one (**71o**, 0.05 g, 0.167 mmol), $Bi(OTf)_3$ (0.011 g, 0.016 mmol) and DCM (0.5 mL): yield (0.045 g, 97%) as white solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3931, 3878, 3806, 3769, 3680, 3603, 3398, 3333, 3272, 3203, 2764, 2349, 1603, 1501, 1383, 1308, 1256, 1180, 1112, 1041,819, 735, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62-7.55 (m, 2H), 7.46-7.36 (m, 5H), 7.03-6.95 (m, 2H), 6.57 (s, 1H), 5.09 (s, 2H), 4.58 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 158.5, 155.0, 138.8, 137.0, 128.8, 128.2, 127.6, 127.3, 125.4, 124.2, 115.2, 103.7, 70.2, 57.1; HRMS (ESI): *m/z* calcd for $C_{18}H_{17}O_3$ $[M+H]^+$ 281.1172, found 281.1167.



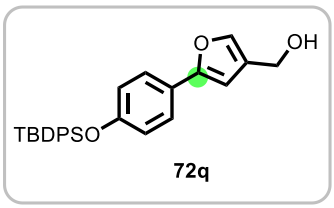
72o

(5-(4-((4-Methoxybenzyl)oxy)phenyl)furan-3-yl)metha-nol (72p): The title compound was prepared following general procedure C using 2-(3-hydroxyoxetan-3-yl)-1-(4-((4-methoxybenzyl)-oxy)phenyl)ethan-1-one (**71p**, 0.05 g, 0.152 mmol), $Bi(OTf)_3$ (0.009 g, 0.015 mmol) and DCM (0.5 mL): yield (0.034 g, 72%) as white solid TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3952, 3854, 3780, 3700, 3608, 3430, 3293, 3170, 3056, 2999, 2937, 2879, 2770, 2680, 2396, 2338, 1923, 1713, 1520, 1383, 1255, 1183, 1117, 1030, 912, 838, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.88 Hz, 2H), 7.41 (m, 1H), 7.36 (d, *J* = 8.75 Hz, 2H), 6.98 (d, *J* = 8.88 Hz, 2H), 6.92 (d, *J* = 8.63 Hz, 2H), 6.56 (s, 1H), 5.01 (s, 2H), 4.58 (s, 2H), 3.82 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 159.7, 158.6, 155.0, 138.8, 129.4, 129.0, 127.3, 125.4, 124.1, 115.3, 114.2, 103.7, 70.0, 57.1, 55.5; HRMS (ESI): *m/z* calcd for $C_{19}H_{19}O_4$ $[M+H]^+$ 311.1278, found 311.1275.



72p

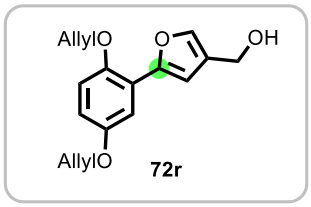
(5-(4-((*Tert*-butyldiphenylsilyl)oxy)phenyl)furan-3-yl)methanol (72q): The title compound was prepared following general procedure C using 1-(4-((*tert*-butyldiphenylsilyl)oxy)phenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (**71q**, 0.05 g, 0.111 mmol), $Bi(OTf)_3$ (0.007 g, 0.011 mmol) and DCM (0.5 mL): yield (0.037 g, 79%) as white solid TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3892, 3822, 3747, 3681, 3278, 3082, 2955, 2876, 2762, 2352, 1625, 1509, 1263, 1180, 1110, 920, 838, 751, 706 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75-7.68 (m, 4H), 7.47-7.33 (m, 9H), 6.77 (d, *J* = 8.75 Hz, 2H), 6.49 (s, 1H), 4.55 (s, 2H), 1.10 (s, 9H);



72q

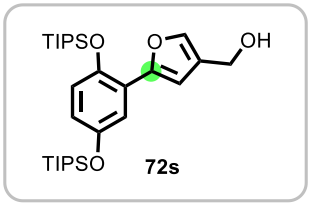
$^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$) δ 155.4, 155.1, 138.7, 135.6, 132.8, 130.1, 128.0, 127.2, 125.2, 124.1, 120.1, 103.6, 57.1, 26.6, 19.6; HRMS (ESI): *m/z* calcd for $C_{27}H_{29}O_3Si$ $[M+H]^+$ 429.1880, found 429.1881.

(5-(2,5-Bis(allyloxy)phenyl)furan-3-yl)methanol (72r): The title compound was

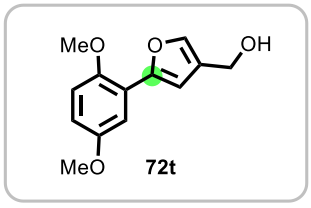


prepared following general procedure C using 1-(2,5-bis(allyloxy)phenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (**71r**, 0.05 g, 0.164 mmol), $Bi(OTf)_3$ (0.010 g, 0.016 mmol) and DCM (0.5 mL): yield (0.044 g, 95%) as white solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3923, 3800, 3545, 3438, 3095, 2936, 2881, 1767, 1653, 1610, 1503, 1431, 1284, 1218, 1013, 932, 809, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.42 (d, *J* = 3.00 Hz, 1H),, 7.04 (s, 1H), 6.87 (d, *J* = 8.88 Hz, 1H), 6.79 (dd, *J* = 3.00, 8.88 Hz, 1H), 6.21-5.99 (m, 2H), 5.43 (td, *J* = 1.50, 17.14 Hz, 2H), 5.36-5.25 (m, 2H), 4.64-4.59 (m, 4H), 4.55 (d, *J* = 5.38 Hz, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 153.0, 151.0, 149.0, 138.6, 133.6, 133.6, 127.4, 118.1, 117.7, 114.8, 114.0, 112.2, 110.5, 77.5, 77.4, 76.8, 70.1, 69.6, 57.2; HRMS (ESI): *m/z* calcd for $C_{17}H_{19}O_4$ $[M+H]^+$ 287.1278 found 287.1277.

(5-(2,5-Bis((triisopropylsilyl)oxy)phenyl)furan-3-yl)methanol (72s): The title



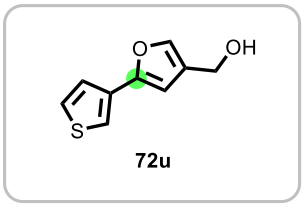
compound was prepared following general procedure C using 1-(2,5-bis((triisopropylsilyl)oxy)phenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (**71s**, 0.05 g, 0.0931 mmol), $Bi(OTf)_3$ (0.006 g, 0.0093 mmol) and DCM (0.5 mL): yield (0.03 g, 62%) as colorless liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3894, 3793, 3706, 3645, 3313, 3166, 2958, 2881, 1491, 1390, 1221, 1012, 899, 824, 766, 672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.27 (d, *J* = 1.63 Hz, 1H), 6.93 (s, 1H), 6.75 (d, *J* = 8.76 Hz, 1H), 6.67 (dd, *J* = 3.00, 8.75 Hz, 1H), 4.59 (s, 2H), 1.35-1.23 (m, 6H), 1.13-1.10 (m, 36H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 151.8, 149.9, 146.6, 138.5, 127.2, 122.2, 119.8, 119.5, 117.7, 109.5, 57.2, 18.1, 18.1, 13.5, 12.7; HRMS (ESI): *m/z* calcd for $C_{29}H_{51}O_4Si_2$ $[M+H]^+$ 519.3320 found 519.3326.



(5-(2,5-Dimethoxyphenyl)furan-3-yl)methanol (72t): The title com-pound was prepared following general procedure C using 1-(2,5-dimethoxyphenyl)-2-(3-

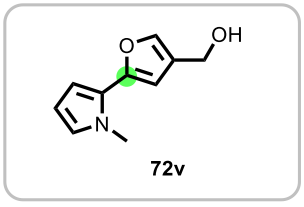
hydroxyoxetan-3-yl)ethan-1-one (**71t**, 0.05 g, 0.198 mmol), $Bi(OTf)_3$ (0.013 g, 0.019 mmol) and DCM (0.5 mL): yield (0.034 g, 74%) as yellow liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3021, 2943, 2403, 1765, 1601, 1503, 1456, 1042, 931, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.43 (m, 1H), 7.39 (d, *J* = 3.13 Hz, 1H), 7.02 (s, 1H), 6.88 (d, *J* = 9.01 Hz, 1H), 6.79 (dd, *J* = 3.13, 9.01 Hz, 1H), 4.60 (s, 2H), 3.89 (s, 3H), 3.82 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 153.8, 151.0, 150.0, 138.6, 127.4, 120.3, 113.8, 112.4, 111.1, 110.4, 57.2, 56.0, 56.0; HRMS (ESI): *m/z* calcd for $C_{13}H_{15}O_4$ $[M+H]^+$ 235.0965, found 235.0963.

(5-(Thiophen-3-yl)furan-3-yl)methanol (72u): The title compound was prepared following general procedure C using 2-(3-hydroxyoxetan-3-yl)-1-(thiophen-3-yl)ethan-1-one (**71u**, 0.05 g, 0.252 mmol), $Bi(OTf)_3$ (0.016 g, 0.025 mmol) and DCM (0.5 mL): yield (0.0432 g, 96%) as yellow solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3863, 3736, 3601, 3391, 3112, 2938, 2880, 1723, 1566, 1482, 1413, 1025, 975, 941, 856, 674 cm^{-1}; ^1H NMR (400 MHz ,$CDCl_3$) δ 7.46 (dd, *J* = 1.25, 2.88 Hz, 1H), 7.39-7.37 (m, 1H), 7.33 (dd, *J* = 2.88, 5.0 Hz, 1H), 7.29 (dd, *J* = 1.38, 5.13 Hz, 1H), 6.52 (s, 1H), 4.57 (s, 2H); $^{13}C\{1H\}$ NMR (101 MHz , $CDCl_3$) δ 151.9, 138.7, 132.5, 127.0, 126.4, 124.7, 119.4, 104.9, 56.9; HRMS (ESI): *m/z* calcd for $C_9H_9O_2S$ $[M+H]^+$ 181.0318, found 181.0319.



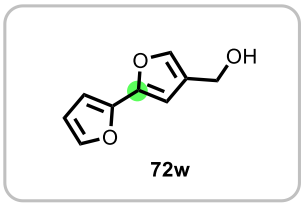
72u

(5-(1-Methyl-1*H*-pyrrol-2-yl)furan-3-yl)methanol (72v): The title compound was prepared following general procedure C using 2-(3-hydroxyoxetan-3-yl)-1-(1-methyl-1H-pyrrol-2-yl)ethan-1-one (**71v**, 0.05 g, 0.256 mmol), $Bi(OTf)_3$ (0.016 g, 0.025 mmol) and DCM (0.5 mL): yield (0.042 g, 94%) as yellow solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3884, 3830, 3787, 3670, 3543, 3334, 3131, 2969, 2754, 2499, 2383, 2346, 2125, 1630, 1469, 1317, 1266, 1175, 1030, 917, 794, 719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1H), 6.66 (s, 1H), 6.45-6.41 (m, 1H), 6.38 (s, 1H), 6.18-6.14 (m, 1H), 4.55 (s, 2H), 3.75 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 148.8, 138.3, 126.7, 124.8, 124.3, 108.9, 107.9, 105.3, 56.7, 35.8; HRMS (ESI): *m/z* calcd for $C_{10}H_{12}O_2N$ $[M+H]^+$ 178.0863, found 178.0862.



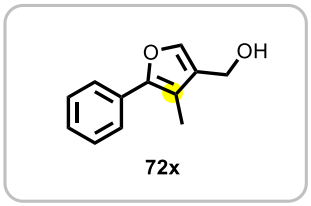
72v

[2,2'-Bifuran]-4-ylmethanol (72w): The title compound was prepared following general procedure C using 1-(furan-2-yl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (**71w**, 0.05 g, 0.274 mmol), $Bi(OTf)_3$ (0.018 g, 0.027 mmol) and DCM (0.5 mL): yield (0.044 g, 98%) as yellow solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3880, 3790, 3689, 3555, 3422, 3340, 3285, 2937, 2878, 2762, 2362, 2049, 1672, 1601, 1459, 1394, 1303, 1182, 1013, 883, 805, 785, 667 cm^{-1}; 1H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 0.75, 1.75 Hz, 1H), 7.38 (d, *J* = 0.88 Hz, 1H), 6.58 (s, 1H), 6.55 (d, *J* = 3.38 Hz, 1H), 6.45 (dd, *J* = 1.75, 3.38 Hz, 1H), 4.58-4.56 (m, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 147.5, 146.4, 142.1, 139.1, 127.1, 111.5, 105.6, 105.2, 56.8; HRMS (ESI): *m/z* calcd for $C_9H_9O_3$ $[M+H]^+$ 165.0546, found 165.0546.



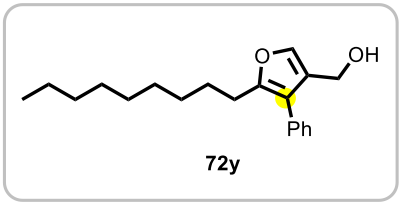
72w

(4-Methyl-5-phenylfuran-3-yl)methanol (72x): The title compound was prepared following general procedure C using 2-(3-hydroxyoxetan-3-yl)-1-phenylpropan-1-one (**71x**, 0.05 g, 0.242 mmol), $Bi(OTf)_3$ (0.015 g, 0.024 mmol) and DCM (0.5 mL): yield (0.041 g, 91%) as white solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3413, 3022, 2928, 2403, 1761, 1677, 1436, 1017, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 1.38, 8.5 Hz, 2H), 7.45-7.39 (m, 3H), 7.31-7.27 (m, 1H), 4.58 (s, 2H), 2.29 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 150.0, 139.2, 131.8, 128.7, 127.5, 127.1, 125.7, 115.8, 55.9, 9.7; HRMS (ESI): *m/z* calcd for $C_{12}H_{13}O_2$ $[M+H]^+$ 189.0910, found 189.0908.



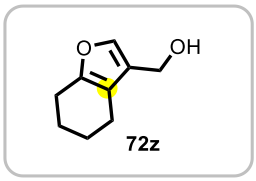
72x

(5-Nonyl-4-phenylfuran-3-yl)methanol (72y): The title compound was prepared following general procedure C using 1-(3-hydroxyoxetan-3-yl)-1-phenylundecan-2-one (**71y**, 0.05 g, 0.157 mmol), $Bi(OTf)_3$ (0.010 g, 0.015 mmol) and DCM (0.5 mL): yield (0.038 g, 81%) as white solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44-7.31 (m, 6H), 4.51 (s, 2H), 2.68-2.57 (m, 2H), 1.67-1.61 (m, 2H), 1.26-1.22 (m, 10H), 0.87 (t, *J* = 7.00 Hz, 3 H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 153.7, 138.9, 130.1, 129.5, 128.7, 127.0, 125.2, 120.8, 56.0, 32.0, 29.4, 29.4, 28.6, 26.6, 22.8, 14.3.



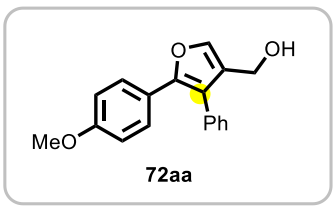
72y

(4,5,6,7-Tetrahydrobenzofuran-3-yl)methanol (72z): The title compound was prepared following general procedure C using 2-(3-hydroxyoxetan-3-yl)cyclohexan-1-one (**71z**, 0.05 g, 0.193 mmol), $Bi(OTf)_3$ (0.012 g, 0.019 mmol) and DCM (0.5 mL): yield (0.043 g, 93%) as colorless liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3432, 3024, 2348, 2097, 1642, 1428, 1018, 669 cm^{-1}; 1H NMR (400 MHz, $CDCl_3$) δ 7.24 (s, 1H), 4.48 (s, 2H), 2.56 (t, *J* = 6.00 Hz, 3H), 2.47-2.41 (m, 3H), 1.82 (dt, *J* = 3.75, 5.82 Hz, 2H), 1.77-1.70 (m, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 152.0, 138.0, 124.6, 116.6, 77.5, 76.8, 56.1, 23.3, 23.0, 22.9, 20.7; HRMS (ESI): *m/z* calcd for $C_9H_{13}O_2$ $[M+H]^+$ 153.0915, found 153.0905.



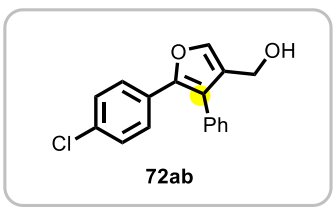
72z

(5-(4-Methoxyphenyl)-4-phenylfuran-3-yl)methanol (72aa): The title compound was prepared following general procedure C using 2-(3-hydroxyoxetan-3-yl)-1-(4-methoxyphenyl)-2-phenylethan-1-one (**71aa**, 0.05 g, 0.167 mmol), $Bi(OTf)_3$ (0.010 g, 0.016 mmol) and DCM (0.5 mL): yield (0.045 g, 98%) as white solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3870, 3782, 3665, 3550, 3465, 3334, 3273, 3081, 2938, 2876, 2760, 2548, 2400, 2053, 1754, 1608, 1454, 1258, 1183, 1031, 842, 780, 671 cm-1; 1H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.44-7.36 (m, 5H), 7.36-7.32 (m, 3H), 6.84-6.74 (m, 2H), 4.48 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 149.9, 139.2, 133.4, 130.0, 129.0, 127.6, 127.4, 127.2, 123.8, 120.5, 113.9, 55.8, 55.4; HRMS (ESI): m/z calcd for C18H17O3 [M+H]+ 281.1172, found 281.1167.



72aa

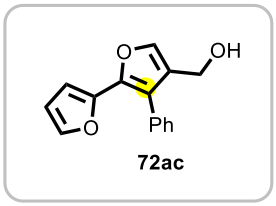
(5-(4-Chlorophenyl)-4-phenylfuran-3-yl)methanol (72ab): The title compound was prepared following general procedure C using 1-(4-chlorophenyl)-2-(3-hydroxyoxetan-3-yl)-2-phenylethan-1-one (**71ab**, 0.05 g, 0.165 mmol), $Bi(OTf)_3$ (0.010 g, 0.016 mmol) and DCM (0.5 mL): yield (0.041 g, 87%) as white solid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3900, 3799, 3753, 3635, 3434, 3304, 3063, 2942, 2881, 2703, 2546, 2421, 2335, 2136, 1961, 1766, 1601, 1488, 1265, 1093, 1018, 835, 769, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56-7.54 (m, 1H), 7.46-7.30 (m, 7H), 7.22-7.17 (m, 2H), 4.47 (d, *J* = 0.75 Hz, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 148.8, 140.0, 133.3, 132.9, 129.9, 129.5, 129.2, 128.7, 128.0,



72ab

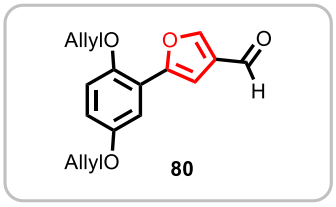
127.5, 127.0, 122.5, 55.7; HRMS (ESI): m/z calcd for C17H14O2Cl [M+H]+ 285.0677, found 285.0673.

(3-Phenyl-[2,2'-bifuran]-4-yl)methanol (72ac): The title compound was prepared following general procedure C using 1-(furan-2-yl)-2-(3-hydroxyoxetan-3-yl)-2-phenylethan-1-one (**71ac**, 0.05 g, 0.193 mmol), $Bi(OTf)_3$ (0.012 g, 0.019 mmol) and DCM (0.5 mL): yield (0.043 g, 93%) as colorless liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat)3426, 3022, 2402, 2350, 1641, 1523, 1426, 1022, 927, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.47-7.33 (m, 6H), 6.35 (dd, *J* = 1.75, 3.38 Hz, 1H), 6.30 (d, *J* = 3.00 Hz, 1H), 4.51 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 146.0, 142.7, 142.1, 140.0, 132.0, 129.9, 128.7, 127.9, 126.9, 121.7, 111.3, 107.0, 55.7; HRMS (ESI): *m/z* calcd for $C_{15}H_{13}O_3$ $[M+H]^+$ 241.0859, found 241.0863.



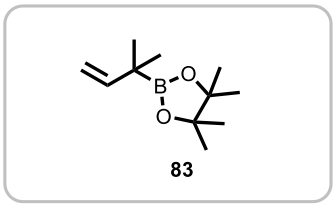
72ac

5-(2,5-Bis(allyloxy)phenyl)furan-3-carbaldehyde (80): To the furyl alcohol **72r** (2.1 g, 7.33 mmol) in dry DCM, Dess Martin Periodinane (DMP, 6.22 g, 14.6 mmol) were added at 0 ℃ and the reac-tion mixture was stirred for 1h at the same temperature. The reac-tion progress was monitored by TLC. After completion of the reaction it was quenched with 1:1 ratio of saturated aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$ and and the aqueous layer was extracted with DCM (3 x 50 mL), then the combined organic layer was washed with brine and dried over Na_2SO_4, filtered, and concentrated in vaccuo and the resulting crude product was purified by silica gel column chromatography to afford the desired product **80** (1.77g, 85%). TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). IR (neat) 3885, 3806, 3664, 3598, 3443, 3354, 2934, 2877, 2761, 2606, 2351, 2214, 2047, 1690, 1606, 1504, 1427, 1382, 1283, 1227, 1146, 1029, 933, 811, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1H), 8.07 (s, 1H), 7.42 (d, *J* = 3.00 Hz, 1H), 7.32 (s, 1H), 6.94-6.87 (m, 1H), 6.87-6.80 (m, 1H), 6.17-6.01 (m, 2H), 5.47-5.38 (m, 2H), 5.34-5.26 (m, 2H), 4.63 (d, *J* = 5.38 Hz, 2H), 4.54 (d, *J* = 5.38 Hz, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 184.9, 152.8, 149.9, 149.4, 133.5, 133.2, 130.6, 119.3, 118.4, 117.8, 115.7, 113.9, 112.6, 106.6, 77.5, 76.8, 70.0, 69.6; HRMS (ESI): *m/z* calcd for $C_{17}H_{17}O_4$ $[M+H]^+$ 285.1121, found 285.1120.



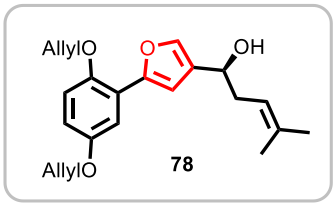
80

4,4,5,5-Tetramethyl-2-(2-methylbut-3-en-2-yl)-1,3,2-dioxaborolane (83): To a suspension of Mg turnings (1.03 g, 39.3 mmol) in THF, pinacol borane (**82**, 5 g, 43.2 mmol) and prenyl bromide (**81**, 9.09 mL, 78.7 mmol) were added dropwise and th reaction was stirred for 0.5 h at room temperature and then another equivalent of prenyl bromide were added to the reaction mixture. The reaction was stirred for additional 2h at room temperature then diluted with hexane and quenched with 0.1 N HCl solution at 0 °C. After that the organic layer was separated and aqueous layer was extracted with hexane. Then the combined organic layer was washed with brine and dried over Na_2SO_4, filtered, and concentrated in vaccuo and used for next step without purification. TLC: R_f = 0.9 (SiO_2, 10% EtOAc/ hexanes). IR (neat) 3891, 3782, 3632, 3431, 3293, 2955, 2387, 2321, 2133, 1469, 1389, 1264, 1023, 803, 686 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{11}H_{22}O_2B$ $[M+H]^+$ 197.1707, found 197.1707.



83

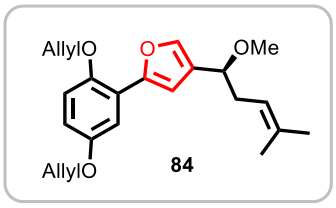
(*S*)-1-(5-(2,5-Bis(allyloxy)phenyl)furan-3-yl)-4-methylpent-3-en-1-ol (78): To an oven dried 100 ml RBF with a stirring bar (*S*)-TRIP (0.264 g, 5.27 mmol) and 4 Å MS were added in N_2 atmosphere. Then aldehyde **80** in dry toluene were added to this mixture drop-wise at room temperature. The reaction mixture was cooled to -60 °C and a solution of borane ester **83** (1.03 g, 5.77 mmol) in dry toluene were added dropwise over 20 minutes. The reaction mixture was stirred at the same temperature for 30 h. then After completion of the reaction, it was filtered through sintered funnel and solvent was evaporated under vacuum. The crude product was purified using silica gel column chromatography to afford the desired product prenyl alcohol **78** (1.01 g, 81%, 94% ee) as yellow liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). The enantiomeric purity was determined by HPLC (CHIRALPAK AD-H column, n-hexane: *i*PrOH = 90:10, flow rate = 1 mL/min, λ = 254 nm, t_{major} = 11.18 min, t_{minor} = 13.22 min), *ee* = 94%, $[\alpha]_D^{28.73}$= -12.81 (*c* = 2.1, $CHCl_3$). IR (neat) 3894, 3791, 3601, 3542, 3426, 3320, 2942, 2559, 2490, 2343, 1716, 1489, 1283, 1214, 1015, 927, 805, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 3.00 Hz, 1H), 7.40 (t, *J* = 0.88 Hz, 1H), 7.03-7.01 (m, 1H), 6.87 (d, *J* = 9.01 Hz, 1H), 6.78 (dd, *J* = 3.13, 9.01 Hz, 1H), 6.17-6.01 (m, 2H), 5.43 (qdd, *J* = 1.63, 4.88, 17.26 Hz, 2H), 5.29



78

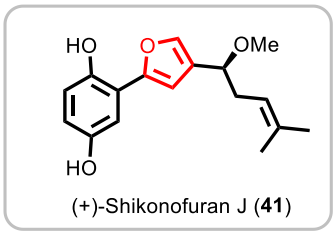
(qdd, *J* = 1.38, 9.13, 10.51 Hz, 2H), 5.23-5.17 (m, 1H), 4.69 (t, *J* = 6.50 Hz, 1H), 4.60 (td, *J* = 1.50, 5.38 Hz, 2H), 4.54 (td, *J* = 1.50, 5.38 Hz, 2H), 2.56-2.46 (m, 2H), 1.75-1.73 (m, 3H), 1.66 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 153.0, 150.6, 149.0, 137.7, 135.8, 133.7, 133.6, 131.0, 121.0, 119.7, 117.9, 117.7, 114.7, 114.1, 112.1, 109.4, 70.1, 69.6, 67.2, 36.9, 26.1, 18.2; HRMS (ESI): *m/z* calcd for $C_{22}H_{27}O_4$ $[M+H]^+$ 355.1904 found 355.1902.

(*S*)-2-(2,5-Bis(allyloxy)phenyl)-4-(1-methoxy-4-methylpent-3-en-1-yl)furan



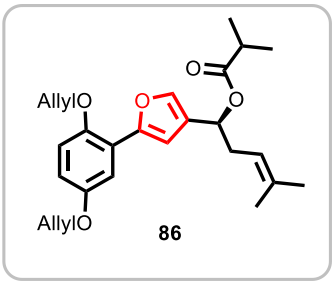
(84): To the suspension of NaH (0.006 g, 0.028 mmol) in dry THF (1 mL), alcohol **78** (0.1 g, 0.028 mmol) in dry THF (2 mL) were added dropwise at 0 ℃ and the reaction was stirred for 10 minutes at the same temperature. After that MeI (0.02 mL, 0.042 mmol) dissolved in THF (0.5 mL) were added to this dropwise and the reaction was stirred for overnight at room temperature. After completion of the reaction, it was quenched with water and the aqueous layer was extracted with EtOAc (3 x 10 mL), then the combined organic layer was washed with brine and dried over Na_2SO_4, fil-tered and concentrated in vaccuo and the resulting crude product was purified by silica gel column chromatography to afford the desired product **84** (0.097 g, 94%) as yellow liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). The enantiomeric purity was deter-mined by HPLC (CHIRALPAK AD-H column, *n*-hexane:*i*-PrOH = 95:5, flow rate = 1 mL/min, λ = 254 nm, t_{major} = 4.74 min, t_{minor} = 5.06 min), *ee* = 90%, $[\alpha]_D^{28.73}$= -+1.27 (*c* = 0.5, $CHCl_3$). IR (neat) 3929, 3789, 3670, 3600, 3555, 3460, 3392, 3332, 3216, 2938, 2760, 2363, 1775, 1502, 1441, 1379, 1286, 1225, 1106, 1016, 940, 816, 663 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 3.00 Hz, 1H), 7.37 (s, 1H), 7.02-6.98 (m, 1H), 6.87 (d, *J* = 9.01 Hz, 1H), 6.78 (dd, *J* = 3.13, 9.01 Hz, 1H), 6.09 (dtd, *J* = 2.13, 5.25, 10.51 Hz, 1H), 6.17-6.02 (m, 2H), 5.47-5.39 (m, 2H), 5.33-5.25 (m, 2H), 5.18-5.11 (m, 1H), 4.60 (td, *J* = 1.50, 5.38 Hz, 2H), 4.55 (td, *J* = 1.50, 5.38 Hz, 2H), 4.13 (t, *J* = 6.75 Hz, 1H), 3.29 (s, 3H), 2.61-2.51 (m, 1H), 2.47-2.37 (m, 1H), 1.71-1.68 (m, 3H), 1.59 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 153.0, 150.7, 149.0, 138.9, 133.8, 133.7, 133.6, 128.1, 121.0, 120.1, 117.9, 117.7, 114.6, 114.1, 112.1, 109.7, 76.2, 70.1, 69.6, 56.4, 35.2, 25.9, 18.1; HRMS (ESI): *m/z* calcd for $C_{23}H_{29}O_4$ $[M+H]^+$ 369.2060, found 369.2062.

Shikonofuran J (41): To the methoxy furan **84** (0.075 g, 0.20 mmol), in dry MeOH (2 mL) $Pd(PPh_3)_4$ (0.023 g, 0.020 mmol) were added at room temperature and the reaction was stirred for 5 minutes then activated K_2CO_3 (0.168 g, 1.21 mmol) were added to the reaction mixture and the reaction was refluxed for 15 minutes. After completion of reaction, MeOH was removed under vaccum and the residue was treated with 2 N HCl, and the aqueous layer was ex-tracted with EtOAc (3 x 10 mL), then the combined organic layer was washed with brine and dried over Na_2SO_4, filtered, and concentrated in vaccuo and the resulting crude product was purified by silica gel column chromatography to afford the desired product **41** (0.042 g, 72%) as yellow liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). The enantiomeric purity was determined by HPLC (CHIRALPAK AD-H column, n-hexane:i-PrOH = 90:10, flow rate = 1 mL/min, λ = 254 nm, t_{minor} = 21.09 min, t_{major} = 21.90 min), *ee* = 90%, $[\alpha]_D^{28.73}$= -+7.07 (*c* = 0.5, MeOH). ECD (4.3 x 10-4 M, MeOH) (Δε) λ_{max} at 283 (-0.180), 245 (−0.134) and 213 (+0.187); IR (neat) 3869, 3775, 3638, 3446, 3352, 3176, 2941, 2768, 2635, 2562, 2396, 2328, 1957, 1522, 1459, 1360, 1205, 1086, 806, 690 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.42 (s, 1H), 7.17 (d, *J* = 3.05 Hz, 1H), 6.95 (s, 1H), 6.71 (d, *J* = 8.54 Hz, 1H), 6.55 (dd, *J* = 3.05, 8.85 Hz, 1H), 5.16-5.12 (m, 1H), 4.16 (t, *J* = 6.71 Hz, 1H), 3.27 (s, 3H), 2.58-2.49 (m, 1H), 2.44-2.36 (m, 1H), 1.68 (s, 3H), 1.59 (s, 3H); $^{13}C\{1H\}$ NMR (126 MHz, CD_3OD) δ 153.0, 151.2, 148.2, 140.0, 134.7, 129.0, 121.4, 119.9, 117.7, 116.1, 112.7, 109.6, 77.7, 56.5, 36.1, 26.1, 18.2; HRMS (ESI): *m/z* calcd for $C_{17}H_{21}O_4$ $[M+H]^+$ 289.1434, found 289.1432.



(+)-Shikonofuran J (**41**)

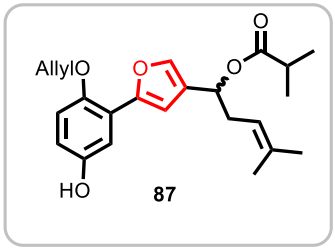
(*S*)-1-(5-(2,5-Bis(allyloxy)phenyl)furan-3-yl)-4-methylpent-3-en-1-yl isobutyrate (86): To the prenyl alcohol **78** (0.2 g, 0.56 mmol) in dry DCM (2 mL), DMAP (0.006 g, 0.0056 mmol) and then Et_3N (0.15 mL, 1.12 mmol) were added at 0 ℃. then isobutyryl chloride **85** (0.07 mL, 0.67 mmol) were added dropwise at the same temper-ature. The reaction mixture was stirred for 3h at room temperature. After completion of the reaction, water were added, and the aqueous layer was extracted with DCM (3 x 50 mL), then the combined organic layer was washed with aq. 2 M NaOH and dried over Na_2SO_4, filtered, and concentrated in vaccuo and the resulting crude product was purified by



86

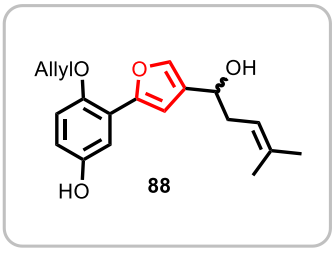
silica gel column chromatography to afford the desired product **86** (0.206 g, 86%) as yellow liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). The enantiomeric purity was determined by HPLC (CHIRALART Cellulose-SC column, n-hexane: *i*PrOH = 95:5, flow rate = 1 mL/min, λ = 254 nm, tmajor = 5.24 min, tminor = 6.36 min), *ee* = 92%, $[\alpha]_D^{26.65}$= -29.96 (*c* = 1.85, $CHCl_3$). IR (neat) 3904, 3795, 3696, 3435, 3315, 2935, 2882, 2646, 2492, 2330, 2132, 1738, 1503, 1211, 1023, 935, 809, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44-7.37 (m, 2H), 7.03-6.96 (m, 1H), 6.87 (d, *J* = 9.01 Hz, 1H), 6.78 (dd, *J* = 3.13, 8.88 Hz, 1H), 6.16-6.02 (m, 2H), 5.78 (t, *J* = 6.75 Hz, 1H), 5.43 (qdd, *J* = 1.63, 9.25, 17.26 Hz, 2H), 5.34-5.25 (m, 2H), 5.11 (tt, *J* = 1.38, 7.13 Hz, 1H), 4.59 (td, *J* = 1.50, 5.25 Hz, 2H), 4.54 (td, *J* = 1.50, 5.25 Hz, 2H), 2.66-2.47 (m, 3H), 1.71-1.67 (m, 3H), 1.63 (s, 3H), 1.17 (d, *J* = 7.13 Hz, 3H), 1.15 (d, *J* = 7.00 Hz, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 176.6, 153.0, 150.5, 149.0, 138.7, 134.8, 133.7, 133.6, 127.3, 120.9, 119.1, 117.9, 117.7, 114.7, 114.2, 112.1, 109.7, 70.2, 69.6, 68.5, 34.3, 33.8, 25.9, 19.1, 19.0, 18.1; HRMS (ESI): *m/z* calcd for $C_{26}H_{33}O_5$ $[M+H]^+$ 425.2323, found 425.2319.

1-(5-(2-(Allyloxy)-5-hydroxyphenyl)furan-3-yl)-4-methylpent-3-en-1-yl isobutyrate (87): yellow colored liquid. TLC: R_f = 0.4 (SiO_2, 30% EtOAc/ hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.07 (d, *J* = 3.00 Hz, 1H), 6.86 (d, *J* = 8.88 Hz, 1H), 6.79 (dd, *J* = 3.00, 8.88 Hz, 1H), 6.70 (s, 1H), 6.44 (br. s., 1H), 6.11-6.00 (m, 1H), 5.77 (t, *J* = 6.88 Hz, 1H), 5.41 (qd, *J* = 1.50, 17.26 Hz, 1H), 5.28 (dd, *J* = 1.38, 10.51 Hz, 1H), 5.09 (t, *J* = 7.00 Hz, 1H), 4.51 (td, *J* = 1.50, 5.38 Hz, 2H), 2.67-2.47 (m, 3H), 1.69 (s, 3H), 1.63 (s, 3H), 1.17 (d, *J* = 7.00 Hz, 3H), 1.15 (d, *J* = 7.00 Hz, 3H); HRMS (ESI): *m/z* calcd for $C_{23}H_{29}O_5$ $[M+H]^+$ 385.2010, found 385.2011.



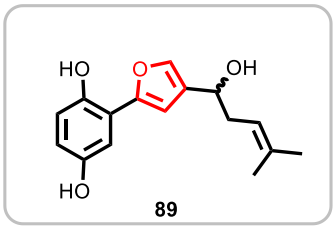
87

4-(Allyloxy)-3-(4-(1-hydroxy-4-methylpent-3-en-1-yl)furan-2-yl)phenol (88): yellow colored liquid. TLC: R_f = 0.3 (SiO_2, 30% EtOAc/ hexanes). ^1H NMR (500 MHz, CD_3OD) δ 7.41 (d, *J* = 2.93 Hz, 1H), 7.29-7.22 (m, 1H), 7.04-6.99 (m, 1H), 6.78 (d, *J* = 8.80 Hz, 1H), 6.72-6.63 (m, 1H), 6.19-6.02 (m, 1H), 5.47-5.37 (m, 1H), 5.30-5.22 (m, 1H), 5.22-5.16 (m, 1H), 4.63-4.57 (m, 2H), 4.50 (td, *J* = 1.49, 5.19 Hz, 1H), 2.53-2.40 (m, 2H), 1.70 (s, 3H), 1.63 (s, 3H); HRMS (ESI): *m/z* calcd for $C_{19}H_{23}O_4$ $[M+H]^+$ 315.1591, found 315.1585.



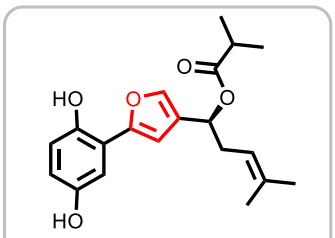
88

2-(4-(1-Hydroxy-4-methylpent-3-en-1-yl)furan-2-yl)benzene-1,4-diol (89): Red colored liquid. TLC: R_f = 0.2 (SiO_2, 30% EtOAc/ hexanes). IR (neat) 3022, 2929, 2402, 1721, 1517, 1432, 1021, 929, 670 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.39 (s, 1H), 7.16 (d, *J* = 3.00 Hz, 1H), 7.00 - 7.02 (m, 1H), 6.70 (d, *J* = 8.63 Hz, 1H), 6.55 (dd, *J* = 3.00, 8.63 Hz, 1H), 5.20 (tt, *J* = 1.36, 7.14 Hz, 1H), 4.59 (t, *J* = 6.69 Hz, 1H), 2.42-2.53 (m, 2H), 1.69-1.72 (m, 4H), 1.63 (s, 3H); HRMS (ESI): *m/z* calcd for $C_{16}H_{19}O_4$ $[M+H]^+$ 275.1278, found 275.1275.



89

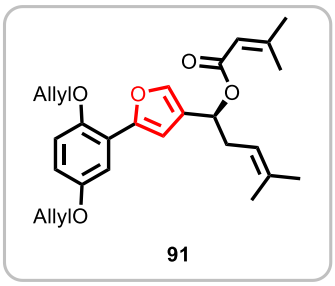
Shikonofuran D (42): To the isobutyryl ester **86** (0.073 g, 0.17 mmol) in dry MeOH (2 mL), $NiCl_2.6H_2O$ (0.122 g, 0.51 mmol) were added at 0 °C. Then $NaBH_4$ (0.032 g, 0.85 mmol) were added at the same temperature. The reaction was stirred for 10 minutes. After completion of the reaction, it was quenched with MeOH and stirred for another 20 minutes. Then it was filtered through celite and the filtrate was concentrated and the crude product was purified by silica gel column chromatography to afford the desired product **42** (0.026 g, 44%) as reddish liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). The enantiomeric purity was determined by HPLC (CHIRALART Cellulose-SC column, *n*-hexane:*i*PrOH = 95:5, flow rate = 1 mL/min, λ = 254 nm, t_{major} = 15.32 min, t_{minor} = 17.51 min), *ee* = 92%, $[\alpha]_D^{31.77}$ = -25.32 (*c* = 0.2, $CHCl_3$). ECD (4.3 x 10-4 M, MeOH) λ_{max} (Δε) at 322 nm (-1.10), 274 nm (-1.29) and 204 nm (-3.23); IR (neat) 3778, 3645 3528, 3269, 3167, 2936, 2872, 2701, 2387, 2129, 1752, 1468, 1267, 1184, 861, 809, 737, 625 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.01 (d, *J* = 3.00 Hz, 1H), 6.81 (d, *J* = 8.63 Hz 1H), 6.72-6.65 (m, 2H), 6.44 (br. s., 1H), 5.77 (t, *J* = 6.75 Hz, 1H), 5.14-5.03 (m, 1H), 4.89 (br. s., 1H), 2.71-2.45 (m, 3H), 1.71-1.67 (m, 3H), 1.62 (s, 3H), 1.19-1.17 (m, 3H), 1.15 (d, *J* = 7.00 Hz, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 176.8, 152.5, 149.3, 146.7, 138.9, 135.2, 127.3, 118.7, 118.2, 117.0, 116.6, 112.2, 106.8, 68.3, 34.3, 33.7, 25.9, 19.1, 19.0, 18.1; HRMS (ESI): *m/z* calcd for $C_{20}H_{25}O_5$ $[M+H]^+$ 345.1697, found 345.1692.



Shikonofuran D (**42**)

(*S*)-1-(5-(2,5-Bis(allyloxy)phenyl)furan-3-yl)-4-methylpent-3-en-1-yl-3-methylbut-2-enoate (91): To the stirred solution of prenyl alcohol **78** (0.2 g, 0.56 mmol) in dry DCM (4 mL) DCC (0.186 g, 0.090 mmol) and DMAP (0.006 g, 0.056

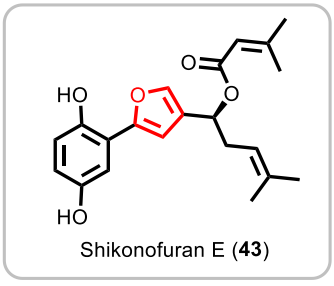
mmol) were added at 0 °C and the reaction mixture was stirred for 10 minutes. After



91

that 3-methylbut-2-enoic acid **90** (0.067 g, 0.067 mmol) were added to this. The reaction was stirred for 12 h at room temperature. After completion of the reaction it was quenched with water and the aqueous layer was extracted with DCM (3 x 10 mL) and dried over Na_2SO_4, filtered, and concentrated in vaccuo and the resulting crude product was purified by silica gel column chromatography to afford the desired product **91** (0.22 g, 89%) as yellow liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). The enantiomeric purity was determined by HPLC (CHIRALPAK AD-H column, *n*-hexane:*i*PrOH = 95:5, flow rate = 1 mL/min, λ = 254 nm, t_{minor} = 5.43 min, t_{major} = 5.95 min), *ee* =88%, $[\alpha]_D^{28.73}$= -14.35 (*c* = 0.5, $CHCl_3$). IR (neat) 3905, 3804, 3763, 3650, 3572, 3433, 3316, 2962, 2923, 2861, 1721, 1647, 1497, 1452, 1376, 1273, 1222, 1137, 1026, 804, 672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.40 (d, *J* = 3.00 Hz, 1H), 7.03-7.01 (m, 1H), 6.86 (d, *J* = 9.01 Hz, 1H), 6.77 (dd, *J* = 3.00, 8.88, 1H), 6.17-6.01 (m, 2H), 5.81 (t, *J* = 6.88 Hz, 1H), 5.72-5.69(m, 1H), 5.43 (qdd, *J* = 1.63, 9.76, 17.26 Hz, 2H), 5.29 (qt, *J* = 1.25, 10.26 Hz, 2H), 5.15-5.09 (m, 1H), 4.59 (td, *J* = 1.38, 5.25 Hz, 2H), 4.54 (td, *J* = 1.50, 5.25 Hz, 2H), 2.69-2.49 (m, 2H), 2.17 (d, *J* = 1.25 Hz, 3H), 1.89 (d, *J* = 1.25 Hz, 3H), 1.70-1.67 (m, 3H), 1.62 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.1, 156.8, 153.0, 150.4, 149.0, 138.9, 134.8, 133.6, 133.6, 127.3, 121.0, 119.1, 117.8, 117.7, 116.4, 114.6, 114.1, 112.1, 109.9, 70.1, 69.6, 67.8, 33.8, 27.6, 25.9, 20.4, 18.1; HRMS (ESI): *m/z* calcd for $C_{27}H_{33}O_5$ $[M+H]^+$ 437.2323, found 437.2317.

Shikonofuran E (43): To the ester **91** (0.15 g, 0.343 mmol) in dry MeOH (2 mL),

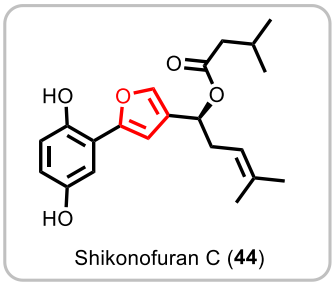


Shikonofuran E (**43**)

$NiCl_2.6H_2O$ (0.245 g, 1.03 mmol) were added at -60 °C. Then $NaBH_4$ (0.013 g, 0.343 mmol) were added at the same temperature. The reaction was stirred for 10 minutes. After completion of the reaction, it was quenched with MeOH and stirred for another 20 minutes. Then it was filtered through celite and the filtrate was concentrated and the crude product was purified by silica gel column chromatography to afford the desired product **43** (0.083 g, 68%) as reddish liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). The enantiomeric purity was determined by HPLC (CHIRALPAK AD-H column, n-hexane:*i*PrOH = 80:20, flow rate = 1 mL/min, λ = 254 nm, t_{minor} = 6.74 min,

t_{major} = 7.68 min), *ee* = 66%, %, $[\alpha]_D^{30.49}$ = -62.40 (*c* = 0.1, $CHCl_3$); ECD (4.3 x 10-4 M, MeOH) λ_{max} ($\Delta\varepsilon$) at 316 nm -2.56), 274 nm (-2.59), 245 nm (-1.79) and a positive Cotton effect at 227 nm (+0.549); IR (neat) 3894, 3841, 3784, 3652, 3544, 3422, 3379, 3327, 2986, 2937, 2777, 2706, 2632, 2551, 2334, 2053, 1952, 1845, 1697, 1457, 1230, 1161, 1085, 1022, 768, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 6.98 (d, *J* = 3.00 Hz, 1H), 6.80 (d, *J* = 8.63 Hz, 1H), 6.69 (s, 1H), 6.69-6.66 (m, 1H), 6.51 (s, 1H), 5.79 (t, *J* = 6.88 Hz, 1H), 5.73-5.69 (m, 1H), 5.12-5.07 (m, 1H), 2.67-2.48 (m, 2H),, 2.17 (d, *J* = 1.25 Hz, 3H), 1.90 (d, *J* = 1.25 Hz, 3H), 1.68 (s, 3H), 1.61 (s, 3H); $^{13}C\{1H\}$NMR (101 MHz, $CDCl_3$) δ 166.3, 157.7, 152.5, 149.3, 146.6, 139.0, 135.2, 127.4, 118.8, 118.2, 117.0, 116.6, 116.1, 112.2, 106.8, 67.7, 33.8, 27.6, 25.9, 20.5, 18.1; HRMS (ESI): *m/z* calcd for $C_{21}H_{25}O_5$ $[M+H]^+$ 357.1697, found 357.1691

Shikonofuran C (44): To the ester **91** (0.10 g, 0.229 mmol) in dry MeOH (2 mL),

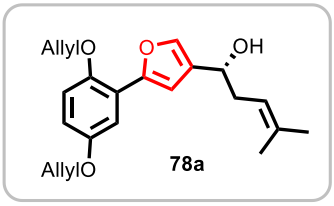


Shikonofuran C (**44**)

$NiCl_2.6H_2O$ (0.163 g, 0.687 mmol) were added at -40 °C. Then $NaBH_4$ (0.043 g, 1.14 mmol) were added at the same temperature. The reaction was stirred for 10 minutes. After completion of the reaction, it was quenched with MeOH and stirred for another 20 minutes. Then it was filtered through celite and the filtrate was concentrated and the crude product was purified by silica gel column chromatography to afford the desired product **44** (0.059 g, 71%) as reddish liquid. TLC: R_f= 0.4 (SiO_2, 20% EtOAc/ hexanes). The enantiomeric purity was determined by HPLC (CHIRALPAK AD-H column, n-hexane:^{i}PrOH = 80:20, flow rate = 1 mL/min, λ = 254 nm, tminor = 7.89 min, tmajor = 9.10 min), *ee* = 94%, $[\alpha]_D^{27.51}$= -58.05 (c = 0.5, $CHCl_3$); ECD (4.3 x 10-4 M, MeOH) λ_{max} ($\Delta\varepsilon$) at 321 nm (-1.76), 283 nm (-1.68), 260 nm (-1.19) and 224 nm (-3.02); IR (neat) 3863, 3780, 3710, 3611, 3548, 3442, 3352, 3274, 3198, 3136, 3094, 2978, 2936, 2884, 2764, 2628, 2552, 2505, 2431, 2373, 2326, 2209, 2109, 2049, 1998, 1891, 1717, 1509, 1452, 1360, 1291, 1202, 1110, 1038, 989, 875, 817, 753, 708, 671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ; 7.45 (s, 1H), 7.01 (d, *J* = 2.88 Hz, 1H), 6.81 (d, *J* = 8.63 Hz, 1H), 6.74-6.64 (m, 2H), 6.43 (s, 1H), 5.79 (t, *J* = 6.88 Hz, 1H), 5.09 (t, *J* = 7.13 Hz, 1H), 4.99 (br. s., 1H), 2.68-2.57 (m, 1H), 2.56-2.44 (m, 1H), 2.23-2.17 (m, 2H), 2.17-2.02 (m, 1H), 1.69 (s, 3H), 1.62 (s, 3H), 0.94 (dd, *J* = 1.13, 6.63 Hz, 6H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 172.9, 152.5, 149.4, 146.6, 139.1, 135.3, 127.2, 118.7, 118.2, 117.1, 116.6, 112.2,

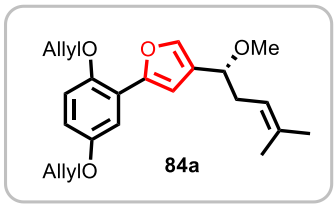
106.9, 68.3, 43.9, 33.7, 26.0, 25.9, 22.5, 18.1; HRMS (ESI): *m/z* calcd for $C_{21}H_{27}O_5$ $[M+H]^+$ 359.1853, found 359.1848.

(*R*)-1-(5-(2,5-Bis(allyloxy)phenyl)furan-3-yl)-4-methylpent-3-en-1-ol (78a): To



an oven dried 100 ml RBF with a stirring bar (*R*)-TRIP (0.264 g, 5.27 mmol) and 4 Å MS were added in N_2 atmosphere. Then aldehyde **80** (1 g, 3.51 mmol) in dry toluene were added to this mixture drop-wise at room temperature. The reaction mixture was cooled to -60 ℃ and a solution of borane ester **83** (1.03 g, 5.77 mmol) in dry toluene were added dropwise over 20 minutes. The reaction mixture was stirred at the same temperature for 30 h. then After completion of the reaction, it was filtered through sintered funnel and solvent was evaporated under vacuum. The crude product was purified using silica gel column chromatography to afford the desired product prenyl alcohol **78a** (0.97 g, 79%, 94% ee) as yellow liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). The enantiomeric purity was determined by HPLC (CHIRALPAK AD-H column, n-hexane: *i*PrOH = 90:10, flow rate = 1 mL/min, λ = 254 nm, t_{minor} = 11.32 min, t_{major} = 13.20 min), *ee* = 93%, $[\alpha]_D^{32.24}$= +13.38 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 3.13 Hz, 1H), 7.40 (s, 1H), 7.04-6.98 (m, 1H), 6.87 (d, *J* = 9.01 Hz, 1H), 6.78 (dd, *J* = 3.00, 8.88 Hz, 1H), 6.17-6.01 (m, 2H), 5.46-5.40 (m, 2H), 5.22-5.18 (m, 2H), 5.17 - 5.24 (m, 1H), 4.69 (t, *J* = 6.38 Hz, 1H), 4.60 (td, *J* = 1.50, 5.25 Hz, 2H), 4.54 (td, *J* = 1.50, 5.25 Hz, 2H), 2.57-2.45 (m, 2H), 1.77-1.72 (m, 3H), 1.66 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.0, 150.6, 149.0, 137.7, 135.8, 133.7, 133.6, 131.0, 121.0, 119.7, 117.9, 117.7, 114.7, 114.1, 112.1, 109.4, 70.1, 69.6, 67.2, 36.9, 26.1, 18.2;

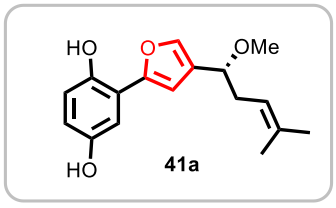
(*R*)-2-(2,5-Bis(allyloxy)phenyl)-4-(1-methoxy-4-methylpent-3-en-1-yl)furan



(84a): To the suspension of NaH (0.006 g, 0.028 mmol) in dry THF (1 mL), alcohol **78a** (0.1 g, 0.028 mmol) in dry THF (2 mL) were added dropwise at 0 ℃ and the reaction was stirred for 10 minutes at the same temperature. After that MeI (0.02 mL, 0.042 mmol) dissolved in THF (0.5 mL) were added to this dropwise and the reaction was stirred for overnight at room temperature. After completion of the reaction, it was quenched with water and the aqueous layer was extracted with EtOAc (3 x 10 mL), then the combined organic layer was washed with

brine and dried over Na_2SO_4, fil-tered and concentrated in vaccuo and the resulting crude product was purified by silica gel column chromatography to afford the desired product **84a** (0.097 g, 94%) as yellow liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). The enantiomeric purity was deter-mined by HPLC (CHIRALPAK AD-H column, n-hexane:*i*-PrOH = 95:5, flow rate = 1 mL/min, λ = 254 nm, t_{minor} = 4.70 min, t_{major} = 5.01 min), *ee* = 90%, $[\alpha]_D^{28.73}$= -1.94 (*c* = 1.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 3.00 Hz, 1H), 7.37 (s, 1H), 7.00 (s, 1H), 6.87 (d, *J* = 9.01 Hz, 1H), 6.78 (dd, *J* = 3.00, 8.88 Hz, 1H), 6.15-6.04 (m, 2H), 5.43 (td, *J* = 1.75, 17.26 Hz, 2H), 5.31-5.27 (m, 2H), 5.15 (t, *J* = 6.88 Hz, 1H), 4.60 (d, *J* = 5.25 Hz, 2H), 4.55 (d, *J* = 5.25 Hz, 2H), 4.13 (t, *J* = 6.75 Hz, 1H), 3.29 (s, 3H), 2.61-2.51 (m, 1H), 2.48-2.36 (m, 1H), 1.69 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.0, 150.7, 149.0, 138.9, 133.8, 133.7, 133.6, 128.1, 121.0, 120.2, 117.9, 117.7, 114.6, 114.1, 112.1, 109.7, 77.5, 76.8, 76.2, 70.1, 69.6, 56.4, 35.2, 25.9, 18.1

***ent*-Shikonofuran J (41a):** To the methoxy furan **84a** (0.026 g, 0.0705 mmol), in dry

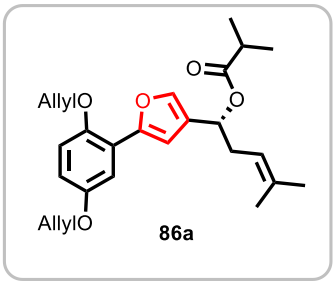


41a

MeOH (1 mL) $Pd(PPh_3)_4$ (0.008 g, 0.00705 mmol) were added at room temperature and the reaction was stirred for 5 minutes then activated K_2CO_3 (0.058 g, 0.423 mmol) were added to the reaction mixture and the reaction was refluxed for 15 minutes. After completion of the reaction, MeOH was removed under vaccum and the residue was treated with 2 N HCl, and the aqueous layer was ex-tracted with EtOAc (3 x 5 mL), then the combined organic layer was washed with brine and dried over Na_2SO_4, filtered, and concentrated in vaccuo and the resulting crude product was purified by silica gel column chromatography to afford the desired product **41a** (0.015 g, 75%) as yellow liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). The enantiomeric purity was determined by HPLC (CHIRALPAK AD-H column, n-hexane:*i*-PrOH = 90:10, flow rate = 1 mL/min, λ = 254 nm, t_{major} = 31.46 min, t_{minor} = 34.06 min), *ee* = 90%, $[\alpha]_D^{27.13}$= -7.63 (*c* = 0.5, MeOH); ECD (4.3 x 10-4 M, MeOH) λ_{max} (Δε) at 283 (−0.018), 245 (+0.026) and 213 (−0.312) nm); ^{1}H NMR (500 MHz, CD_3OD) δ 7.42 (s, 1H), 7.17 (d, *J* = 3.05 Hz, 1H), 6.95 (s, 1H), 6.71 (d, *J* = 8.54 Hz, 1H), 6.56 (dd, *J* = 3.05, 8.54 Hz, 1H), 5.17-5.11 (m, 1H), 4.15 (t, *J* = 6.71 Hz, 1H), 3.26 (s, 3H), 2.58-2.49 (m, 1H), 2.44-2.36 (m, 1H), 1.70-1.66 (m, 3H), 1.59 (s, 3H); ^{13}C NMR

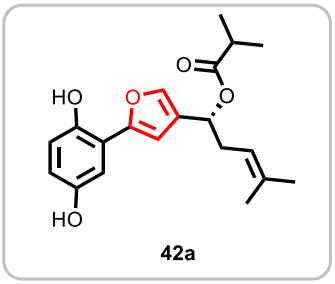
(126 MHz, CD_3OD) δ 153.0, 151.2, 148.2, 140.0, 134.7, 129.0, 121.4, 119.9, 117.7, 116.1, 112.7, 109.6, 77.6, 56.5, 36.1, 26.1, 18.2

(*R*)-1-(5-(2,5-Bis(allyloxy)phenyl)furan-3-yl)-4-methylpent-3-en-1-yl isobutyrate (86a): To the prenyl alcohol **78a** (0.2 g, 0.56 mmol) in dry DCM (2 mL), DMAP (0.006 g, 0.0056 mmol) and then Et_3N (0.15 mL, 1.12 mmol) were added at 0 °C. then isobutyryl chloride **85** (0.07 mL, 0.67 mmol) were added dropwise at the same temper-ature. The reaction mixture was stirred for 3h at room temperature. After completion of the reaction, water were added, and the aqueous layer was extracted with DCM (3 x 50 mL), then the combined organic layer was washed with aq. 2 M NaOH and dried over Na_2SO_4, filtered, and concentrated in vaccuo and the resulting crude product was purified by silica gel column chromatography to afford the desired product **86a** (0.198 g, 83%) as yellow liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). The enantiomeric purity was determined by HPLC (CHIRALART Cellulose-SC column, n-hexane: *i*PrOH = 95:5, flow rate = 1 mL/min, λ = 254 nm, t_{minor} = 5.27 min, t_{major} = 6.36 min), *ee* = 92%, $[\alpha]_D^{26.72}$ = +30.84 (*c* = 0.3, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.38 (m, 2H), 7.00 (s, 1H), 6.87 (d, *J* = 9.01 Hz, 1H), 6.78 (dd, *J* = 3.13, 9.01 Hz, 1H), 6.16-6.02 (m, 2H), 5.79 (t, *J* = 6.75 Hz, 1H), 5.43 (qdd, *J* = 1.63, 9.76, 17.26 Hz, 2H), 5.34-5.24 (m, 2H), 5.16-5.09 (m, 1H), 4.59 (td, *J* = 1.38, 6.75 Hz, 2H), 4.54 (td, *J* = 1.50, 6.75 Hz, 2H), 2.68-2.47 (m, 3H), 1.71-1.67 (m, 3H), 1.63 (s, 3H), 1.17 (d, *J* = 7.00 Hz, 3H), 1.15 (d, *J* = 7.00 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.5, 153.0, 150.5, 149.0, 138.7, 134.8, 133.6, 133.6, 127.2, 120.9, 119.0, 117.9, 117.7, 114.7, 114.1, 112.1, 109.7, 70.1, 69.6, 68.4, 34.3, 33.8, 25.9, 19.1, 19.0, 18.1



86a

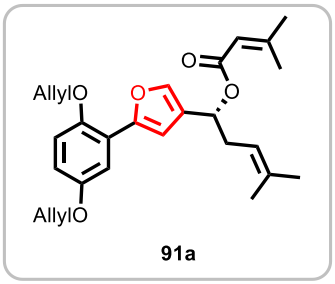
***ent*-Shikonofuran D (42a):** To the isobutyryl ester **86a** (0.062 g, 0.146 mmol) in dry MeOH (2 mL), $NiCl_2.6H_2O$ (0.104 g, 0.438 mmol) were added at 0 °C. Then $NaBH_4$ (0.027 g, 0.73 mmol) were added at the same temperature. The reaction was stirred for 10 minutes. After completion of the reaction, it was quenched with MeOH and stirred for another 20 minutes. Then it was filtered through celite and the filtrate was



42a

concentrated and the crude product was purified by silica gel column chromatography to afford the desired product **42a** (0.023 g, 46%) as reddish liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). The enantiomeric purity was determined by HPLC (CHIRALART Cellulose-SC column, *n*-hexane:*i*PrOH = 95:5, flow rate = 1 mL/min, λ = 254 nm, t_{minor} = 15.52 min, t_{major} = 17.30 min), *ee* = 92%, $[\alpha]_D^{26.54}$= +26.19 (*c* = 1.3, $CHCl_3$); ECD (4.3 x 10-4 M, MeOH) λ_{max} (Δε) at 323 nm (+1.39), 267 nm (+6.00) and 207 nm (+2.50); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.00 (d, *J* = 3.00 Hz, 1H), 6.82 (d, *J* = 8.75 Hz, 1H), 6.72-6.65 (m, 2H), 6.39 (s, 1H), 5.77 (t, *J* = 6.82 Hz, 1H), 5.12-5.06 (m, 1H), 4.53 (br. s., 1H), 2.67-2.47 (m, 3H), 1.69 (s, 3H), 1.63 (s, 4H), 1.18 (d, *J* = 7.00 Hz, 3H), 1.15 (d, *J* = 7.00 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.6, 152.5, 149.3, 146.7, 138.9, 135.2, 127.3, 118.7, 118.2, 117.0, 116.6, 112.2, 106.8, 68.1, 34.3, 33.7, 25.9, 19.1, 19.0, 18.1.

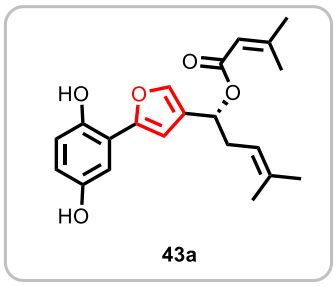
(*R*)-1-(5-(2,5-Bis(allyloxy)phenyl)furan-3-yl)-4-methylpent-3-en-1-yl-3-methylbut-2-enoate (91a): To the stirred solution of prenyl alcohol **78a** (0.287 g, 0.809 mmol) in dry DCM (4 mL) DCC (0.267 g, 1.29 mmol) and DMAP (0.009 g, 0.080 mmol) were added at 0 ℃ and the reaction mixture was stirred for 10 minutes. After that 3-methylbut-2-enoic acid **90** (0.067 g, 0.067 mmol) were added to this. The reaction was stirred for 12 h at room temperature. After completion of the reaction it was quenched with water and the aqueous layer was extracted with DCM (3 x 10 mL) and dried over Na_2SO_4, filtered, and concentrated in vaccuo and the resulting crude product was purified by silica gel column chromatography to afford the desired product **91a** (0.298 g, 84%) as yellow liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). The enantiomeric purity was determined by HPLC (CHIRALPAK AD-H column, n-hexane:^{i}PrOH = 95:5, flow rate = 1 mL/min, λ = 254 nm, t_{major} = 5.22 min, t_{minor} = 5.96 min), *ee* =92%, $[\alpha]_D^{31.57}$ = +53.23 (*c* = 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.36 (m, 2H), 7.01 (s, 1H), 6.86 (d, *J* = 8.88 Hz, 1H), 6.77 (dd, *J* = 3.00, 8.88 Hz, 1H), 6.16-6.02 (m, 2H), 5.80 (t, *J* = 6.75 Hz, 1H), 5.72-5.66 (m, 1H), 5.43 (qdd, *J* = 1.63, 9.38, 17.26 Hz, 2H), 5.34-5.24 (m, 2H), 5.17-5.09 (m, 1H), 4.59 (td, *J* = 1.50, 5.38 Hz, 2H), 4.54 (td, *J* = 1.50, 5.25 Hz, 2H), 2.67-2.48 (m, 2H), 2.17 (d, *J* = 1.13 Hz, 3H), 1.89 (d, *J* = 1.25 Hz, 3H), 1.72-1.66 (m, 3H), 1.62 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 156.8, 153.0, 150.4, 149.0,



91a

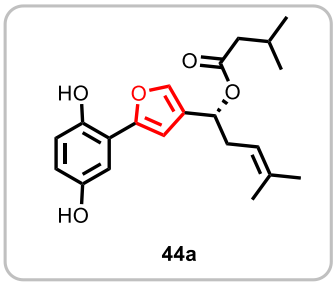
138.9, 134.8, 133.7, 133.6, 127.4, 119.2, 117.8, 117.7, 116.5, 114.7, 114.2, 112.1, 109.9, 70.2, 69.6, 67.9, 33.8, 27.6, 25.9, 20.4, 18.1

***ent*-Shikonofuran E (43a):** To the ester **91a** (0.251 g, 0.574 mmol) in dry MeOH (4 mL), $NiCl_2.6H_2O$ (0.409 g, 1.72 mmol) were added at -60 °C. Then $NaBH_4$ (0.022 g, 0.574 mmol) were added at the same temperature. The reaction was stirred for 10 minutes. After completion of the reaction, it was quenched with MeOH and stirred for another 20 minutes. Then it was filtered through celite and the filtrate was concentrated and the crude product was purified by silica gel column chromatography to afford the desired product **43a** (0.113 g, 55%) as reddish liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). The enantiomeric purity was determined by HPLC (CHIRALPAK AD-H column, n-hexane:*i*PrOH = 80:20, flow rate = 1 mL/min, λ = 254 nm, t_{major} = 6.82 min, t_{minor} = 7.70 min), *ee* = 92%, $[\alpha]_D^{30.40}$= +68.26 (c = 1.4, $CHCl_3$); ECD (4.3 x 10-4 M, MeOH) λ_{max} (Δε) at 319 nm (+3.39), 270 nm (+5.69), 227 nm (+6.33) and 212 nm (+3.34); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 6.99 (d, *J* = 2.88 Hz, 1H), 6.79 (d, *J* = 8.75 Hz, 1H), 6.70 (s, 1H), 6.67 (dd, *J* = 2.88, 8.63 Hz, 1H), 5.78 (t, *J* = 6.75 Hz, 1H), 5.72-5.68 (m, 1H), 5.13-5.05 (m, 1H), 2.67-2.57 (m, 1H), 2.57-2.48 (m, 1H), 2.19-2.15 (m, 3H), 1.92-1.87 (m, 3H), 1.68 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 157.7, 152.4, 149.3, 146.6, 139.0, 135.2, 127.4, 118.8, 118.2, 117.1, 116.6, 116.2, 112.2, 106.9, 67.7, 33.8, 27.6, 25.9, 20.5, 18.2



43a

***ent*-Shikonofuran C (44a):** To the ester **91a** (0.150 g, 0.343 mmol) in dry MeOH (4 mL), $NiCl_2.6H_2O$ (0.245 g, 1.03 mmol) were added at -40 °C. Then $NaBH_4$ (0.052 g, 1.37 mmol) were added at the same temperature. The reaction was stirred for 10 minutes. After completion of the reaction, it was quenched with MeOH and stirred for another 20 minutes. Then it was filtered through celite and the filtrate was concentrated and the crude product was purified by silica gel column chromatography to afford the desired product **44a** (0.078 g, 64%) as reddish liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/ hexanes). The enantiomeric purity was determined by HPLC (CHIRALPAK AD-H column, n-hexane:^{i}PrOH = 80:20, flow rate = 1 mL/min, λ = 254 nm, t_{major} = 7.92 min,



44a

t_{minor} = 9.14 min), *ee* = 92%, $[\alpha]_D^{27.96}$ = +57.56 (c = 1.1, $CHCl_3$); ECD (4.3 x 10-4 M, MeOH) λ_{max} ($\Delta\varepsilon$) at 321 nm (0.79), 277 nm (+2.82), 269 nm (+4.07) and 220 nm (+2.28); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.01 (d, *J* = 3.00 Hz, 1H), 6.81 (d, *J* = 8.76 Hz, 1H), 6.72-6.66 (m, 2H), 6.43 (br. s, 1H), 5.79 (t, *J* = 6.88 Hz, 1H), 5.14-5.05 (m, 1H), 2.66-2.59 (m, 1H), 2.54-2.47 (m, 1H), 2.22-2.17 (m, 2H), 2.15-2.05 (m, 1H), 1.69 (s, 3H), 1.62 (s, 3H), 0.95 (d, *J* = 1.38 Hz, 3H), 0.93 (d, *J* = 1.25 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 152.5, 149.3, 146.7, 139.0, 135.3, 127.2, 118.7, 118.2, 117.1, 116.6, 112.2, 106.9, 68.3, 43.8, 33.7, 26.0, 25.9, 22.5, 18.1

2.2.9. References

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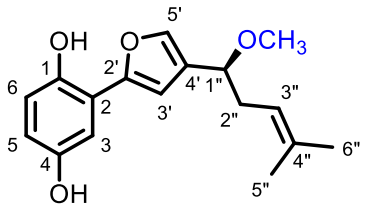
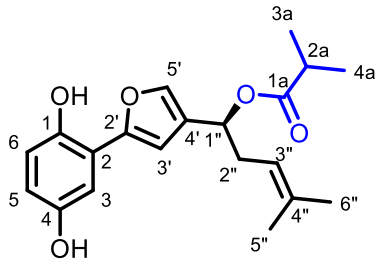
Table S1: Comparison of ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR data of natural and synthetic shikonofuran J (41).



Shikonofuran J (**1**)

Position	Synthetic (This work)		Natural	
	δ_H (mult, *J* in Hz) (500 MHz)	δ_C (126 MHz)	δ_H (mult, *J* in Hz) (400 MHz)	δ_C (100 MHz)
1	-	148.2	-	148.0
2	-	119.9	-	119.7
3	7.17, d (3.05), CH	112.7	7.17, d (2.7), CH	112.5
4	-	151.2	-	151.1
5	6.55, dd (8.85,3.05), CH	116.1	6.55 dd (8.6, 2.7), CH	115.9
6	6.71, d (8.54), CH	117.7	6.71, d (8.6), CH	117.6
2′	-	153.0	-	152.9
3′	6.95, s, CH	109.6	6.94, s, CH	109.5
4′	-	129.0	-	128.9
5′	7.42, s, CH	140.0	7.41, s, CH	139.8
1″	4.16, t (6.71), CH	77.7	4.15 dd (6.7, 6.7), CH	77.5
2″	2.53 m, 2.40 m, CH_2	36.1	2.53 m, 2.40 m, CH_2	35.9
3″	5.14, m, CH	121.4	5.13 dd (6.5, 6.5), CH	121.2
4″	-	134.7	-	134.5
5″	1.59, s, CH_3	18.2	1.59, s, CH_3	18.0
6″	1.68, s, CH_3	26.1	1.68, s, CH_3	25.9
OCH_3	3.27, s, OCH_3	56.5	3.26, s, OCH_3	56.4

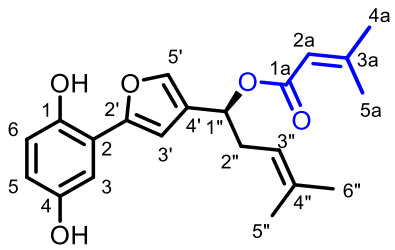
Table S2: Comparison of ^{1}H and ^{13}C NMR data of natural and synthetic shikonofuran D (42).



Shikonofuran D (**2**)

Position	Synthetic (This work)		Natural	
	δ_H (mult, *J* in Hz) (500 MHz)	δ_C (126 MHz)	δ_H (mult, *J* in Hz) (400 MHz)	δ_C (100 MHz)
1	-	149.3	-	149.3
2	-	117.0	-	117.0
3	7.01, d (3.00), CH	112.2	7.02, d (3.4), CH	112.1
4	-	146.7	-	146.6
5 & 3′	6.72-6.65, m, CH & CH	116.6 & 106.8	6.69–6.66, m, CH & CH	116.6, 106.7
6	6.81 d (8.6), CH	118.2	6.80, d (8.8), CH	118.1
2′	-	152.5	-	152.4
4′	-	127.3	-	128.9
5′	7.44, s, CH	138.9	7.43, s, CH	138.8
1″	5.77, t (6.7), CH	68.3	5.76, t (6.7), CH	68.2
2″ & 2a	2.71-2.45, m, CH_2, CH	33.7 & 34.3	2.62–2.48, m, CH_2, CH	33.6 & 34.3
3″	5.14-5.03, m, CH	118.7	5.08, t (7.14), CH	118.6
4″	-	135.2	-	135.2
5″	1.62, s, CH_3	18.1	1.61, s, CH_3	18.1
6″	1.71-1.67, m, CH_3	25.9	1.68, s, CH_3	25.8
1a	-	176.8	-	176.8
3a	1.18, d (7.0), CH_3	19.1	1.17, d (6.7), CH_3	19.0
4a	1.15, d (7.00), CH_3	19.0	1.15, d (6.7), CH_3	18.9

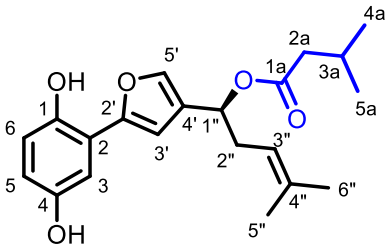
Table S3: Comparison of ^{1}H and ^{13}C NMR data of natural and synthetic shikonofuran E (43).



Shikonofuran E (**3**)

Position	Synthetic (This work)		Natural	
	δ_H (mult, *J* in Hz) (400 MHz)	δ_C (mult, *J* in Hz) (126 MHz)	δ_H (mult, *J* in Hz) (500 MHz)	δ_C (mult, *J* in Hz) (100 MHz)
1	-	149.3	-	149.3
2	-	117.0	-	117.0
3	6.98 d, (2.9), CH,	112.2	6.99, d (3), CH	112.1
4	-	146.6	-	146.5
5	6.69-6.66, m, CH,	116.6	6.68 dd (9, 3), CH	116.5
6	6.80 d, (8.6), CH	118.2	6.79 d, (9), CH	118.1
2′	-	152.5	-	152.4
3′	6.69, s, CH	106.8	6.70, s, CH	106.8
4′	-	127.4	-	127.3
5′	7.44, s, CH	139.0	7.44, s, CH	139.0
1″	5.79, t, (6.8), CH	67.7	5.79, t, (7), CH	67.7
2″	2.67-2.48 m, CH_2	33.8	2.60, t, (7), CH_2	33.7
3″	5.12-5.07, m, CH	118.8	5.09, br t, (7) CH	118.7
4″	-	135.2	-	135.2
5″	1.61, s, CH_3	18.1	1.61, s, CH_3	18.1
6″	1.68, s, CH_3	25.9	1.68, s, CH_3	25.9
1a	-	166.3	-	166.3
2a	5.73-5.69, m, CH	116.1	5.71, br., s, CH	116.1
3a	-	157.7	-	157.7
4a	1.90, d, (1.25) CH_3	27.6	1.90, s, CH_3	27.6
5a	2.17 d, (1.25), CH_3	20.5	2.17, s, CH_3	20.4

Table S7: Comparison of ^{1}H and ^{13}C NMR data of natural and synthetic shikonofuran C (44).

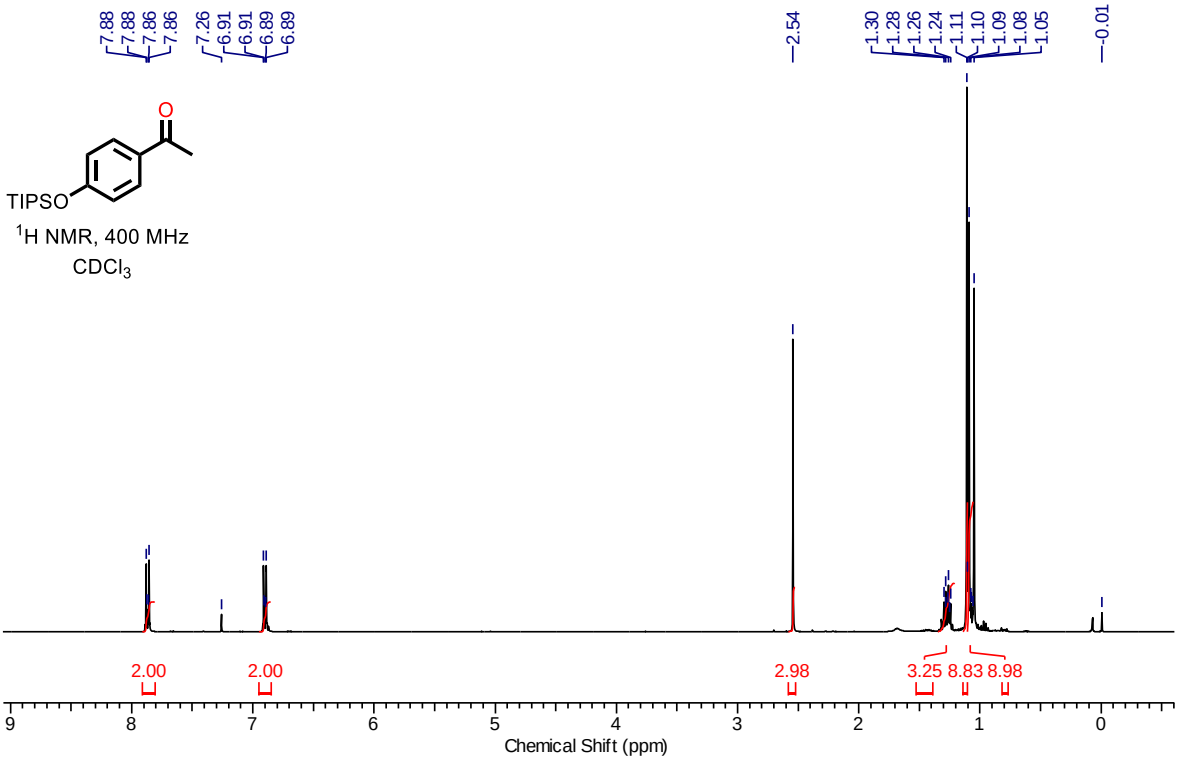


Shikonofuran C (**4**)

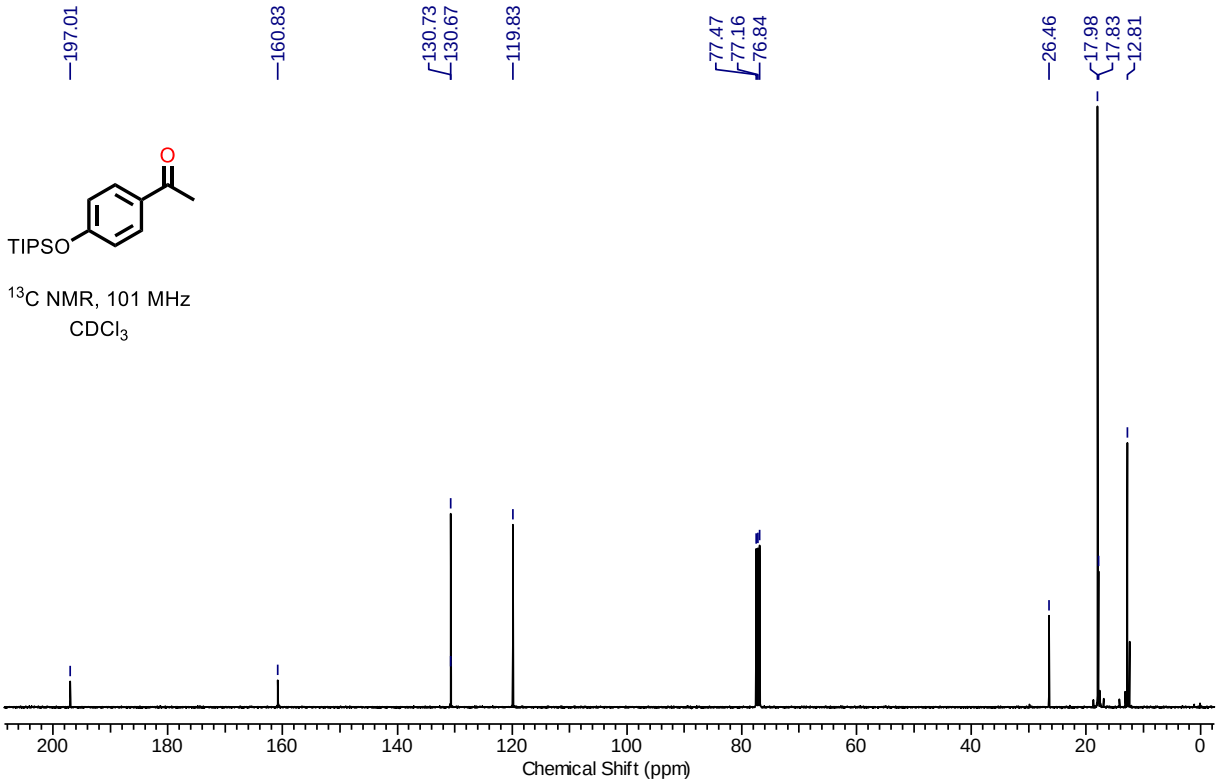
Position	Synthetic (This work)		Natural	
	δ_H (mult, *J* in Hz) (400 MHz)	δ_C (mult, *J* in Hz) (126 MHz)	δ_H (mult, *J* in Hz) (500 MHz)	δ_C (mult, *J* in Hz) (100 MHz)
1	-	149.3	-	149.2
2	-	117.1	-	106.7
3	7.01, d, (2.88), CH,	112.2	7.00, d (2.0), CH	111.2
4	-	146.6	-	146.6
3′ & 5	6.74-6.64, m, CH & CH	106.9 & 116.6	6.69, m, CH & CH	106.8 & 116.5
6	6.81, d, (8.63), CH	118.2	6.81, d, (8.4), CH	118.1
2′	-	152.5	-	152.4
4′	-	127.2	-	127.2
5′	7.45, s, CH	139.1	7.43, d, (3.2) CH	139.0
1″	5.79, t, (6.88), CH	68.3	5.76, t, (6.9), CH	68.2
2″	2.68-2.57, m, & 2.56-2.44, m, CH_2	33.7	2.61, m, & 2.51, m, CH_2	33.6
3″	5.09, t, (7.13), CH	118.7	5.08, m, CH	118.6
4″	-	135.3	-	135.2
5″	1.62, s, CH_3	18.1	1.62, s, CH_3	18.0
6″	1.69, s, CH_3	25.9	1.68, s, CH_3	25.8
1a	-	172.9	-	172.8
2a	2.23-2.17, m, CH_2	43.9	2.20, m, CH_2	43.8
3a	2.17-2.02, m, CH	26.0	2.09, m , CH	16.7
4a & 5a	0.94, dd, (1.13, 6.63), CH_3 & CH_3	22.5	0.94, dd, (1.6, 6.8), CH_3 & CH_3	22.4

^{1}H and ^{13}C NMR Spectra

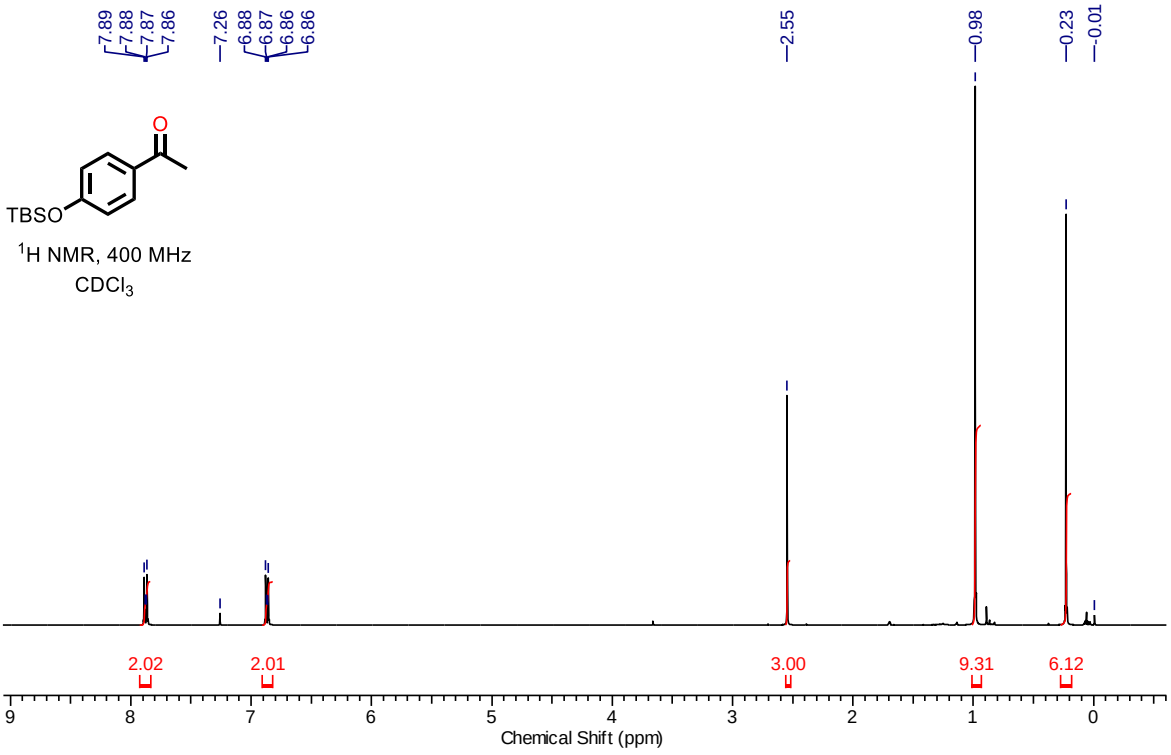
1-(4-((Triisopropylsilyl)oxy)phenyl)ethan-1-one (**79m**)



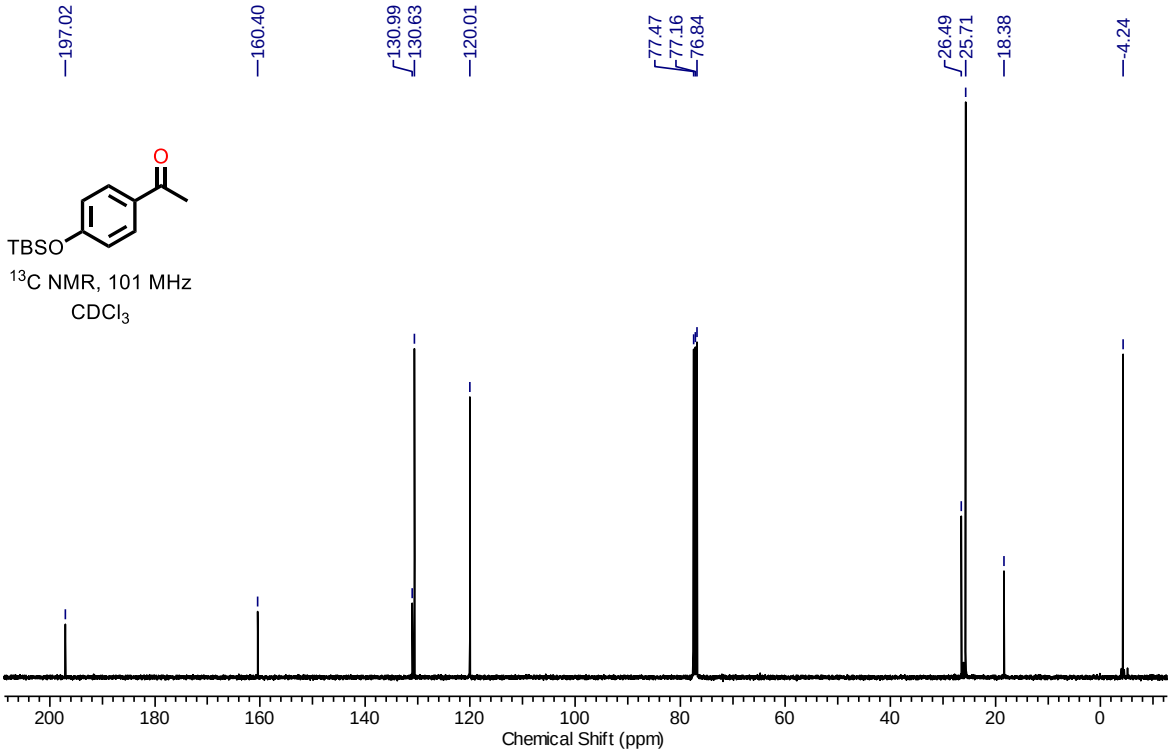
1-(4-((Triisopropylsilyl)oxy)phenyl)ethan-1-one (**79m**)



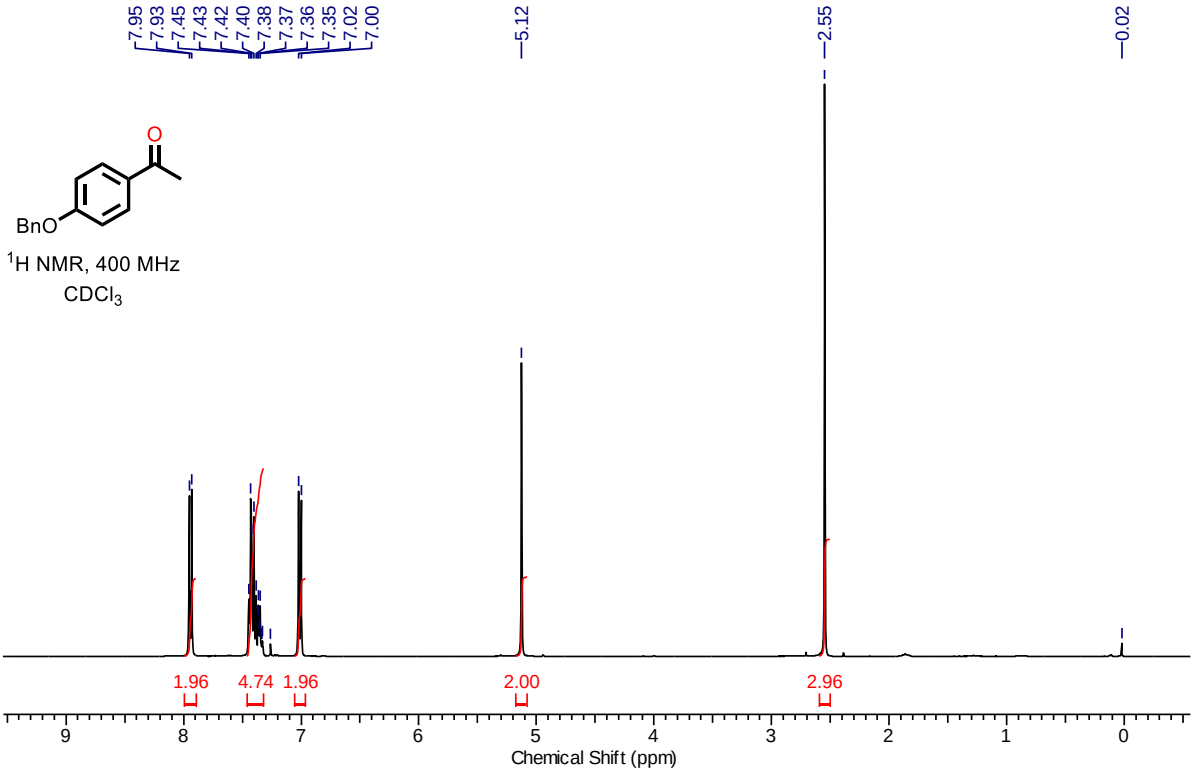
1-(4-((*Tert*-butyldimethylsilyl)oxy)phenyl)ethan-1-one (**79n**)



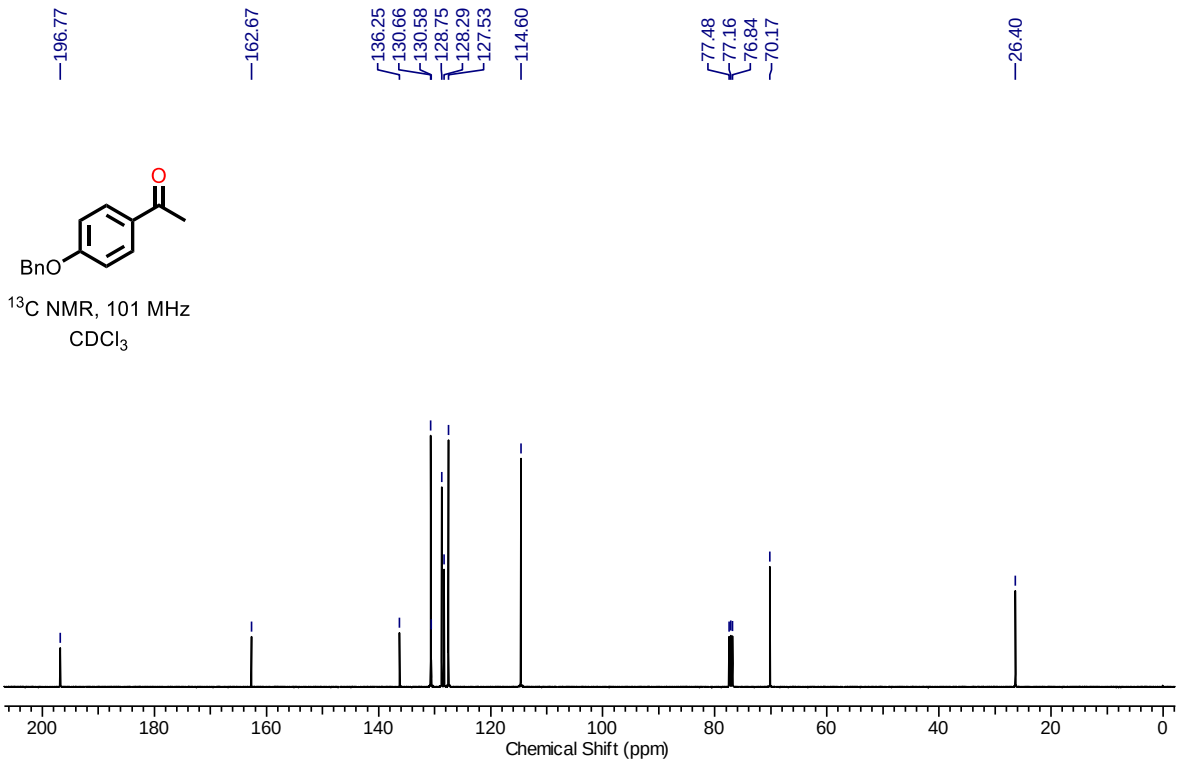
1-(4-((*Tert*-butyldimethylsilyl)oxy)phenyl)ethan-1-one (**79n**)



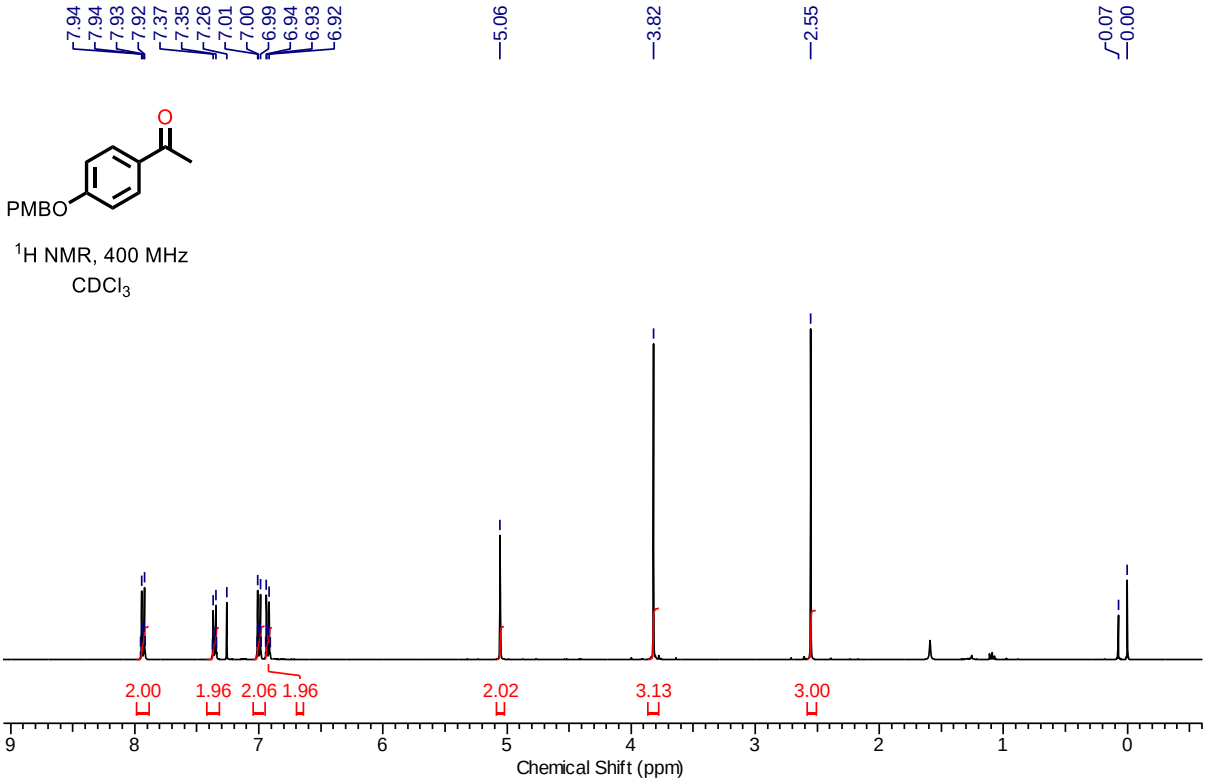
1-(4-(Benzyloxy)phenyl)ethan-1-one (**79o**):



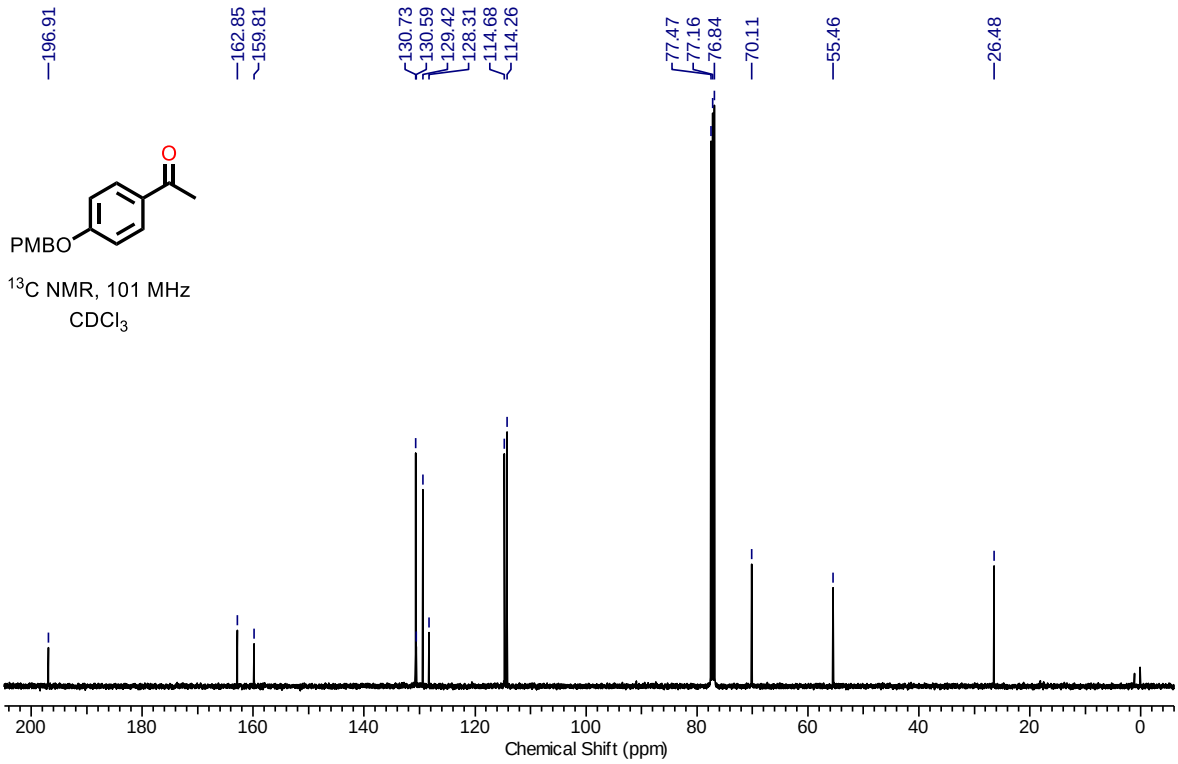
1-(4-(Benzyloxy)phenyl)ethan-1-one (**79o**):



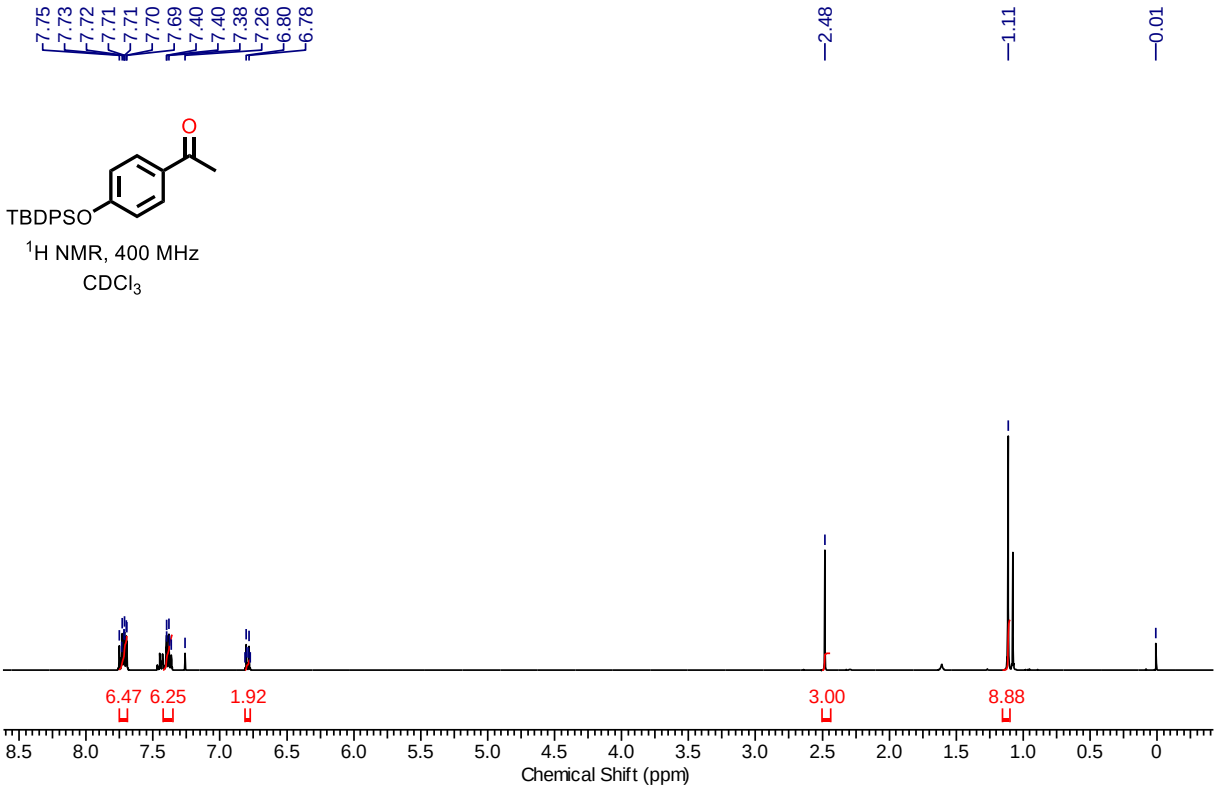
1-(4-((4-Methoxybenzyl)oxy)phenyl)ethan-1-one (**79p**):



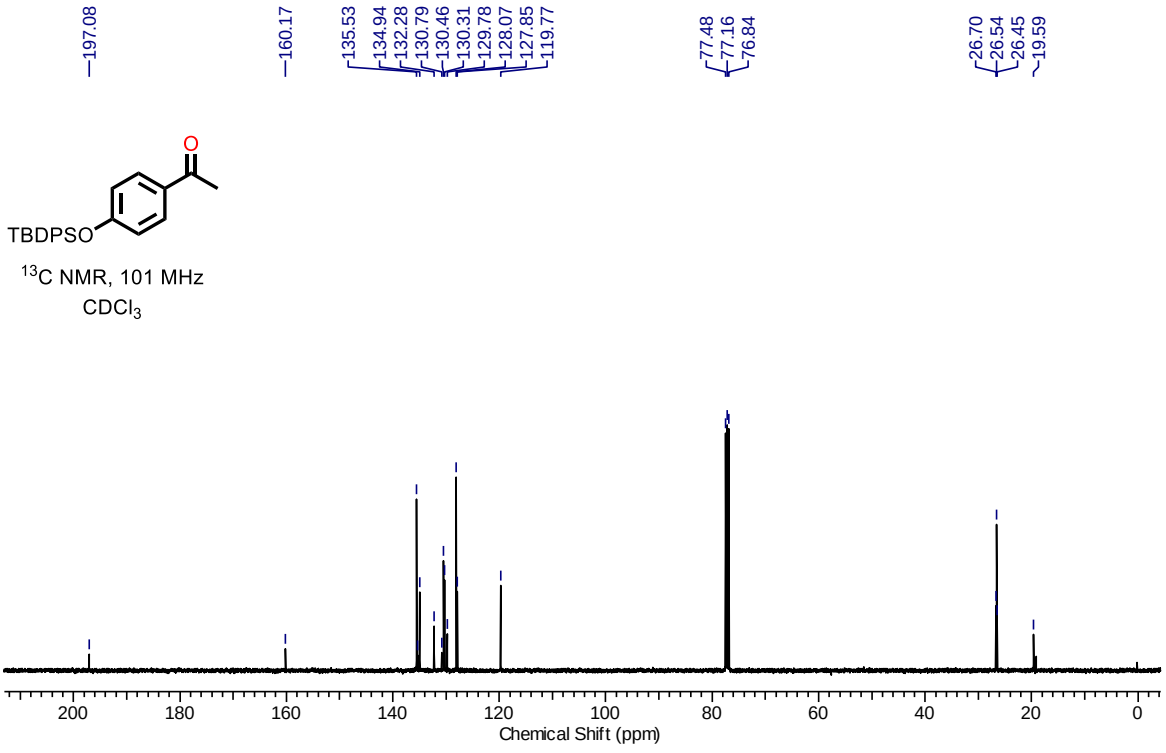
1-(4-((4-Methoxybenzyl)oxy)phenyl)ethan-1-one (**79p**):



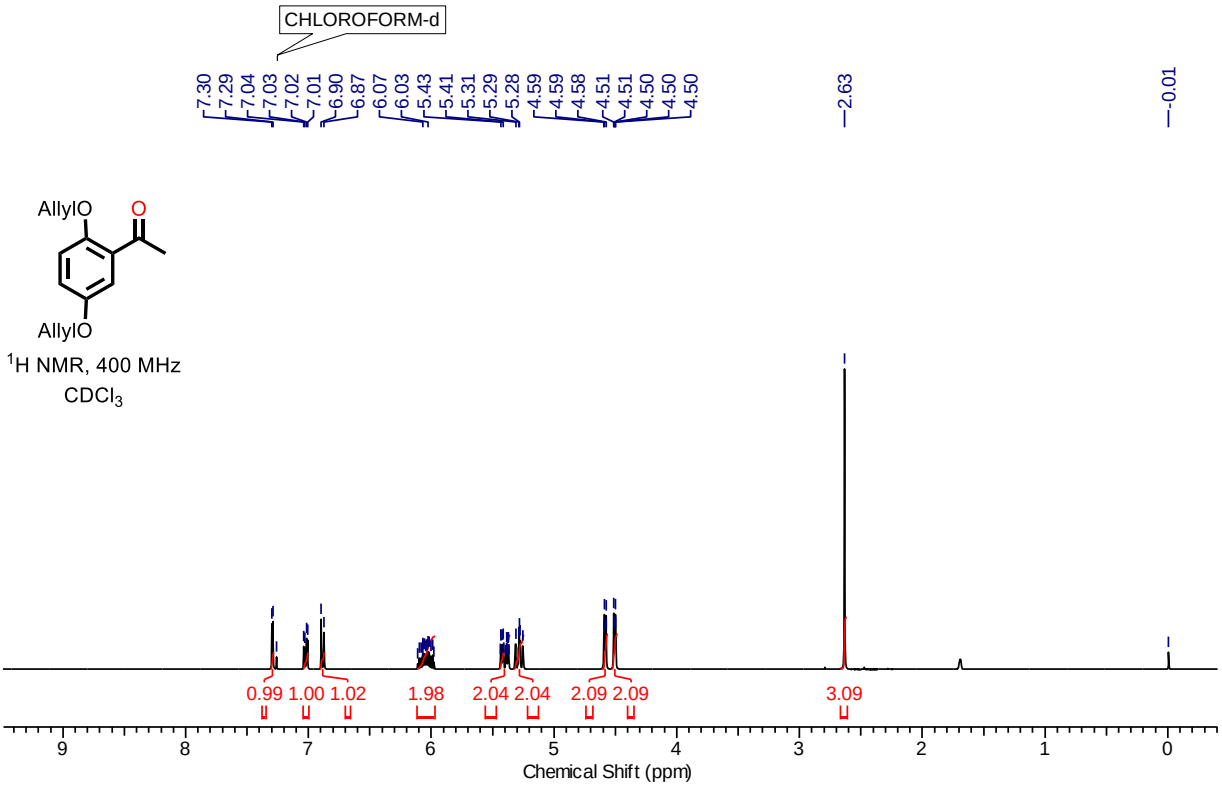
1-(4-((*Tert*-butyldiphenylsilyl)oxy)phenyl)ethan-1-one (**79q**):



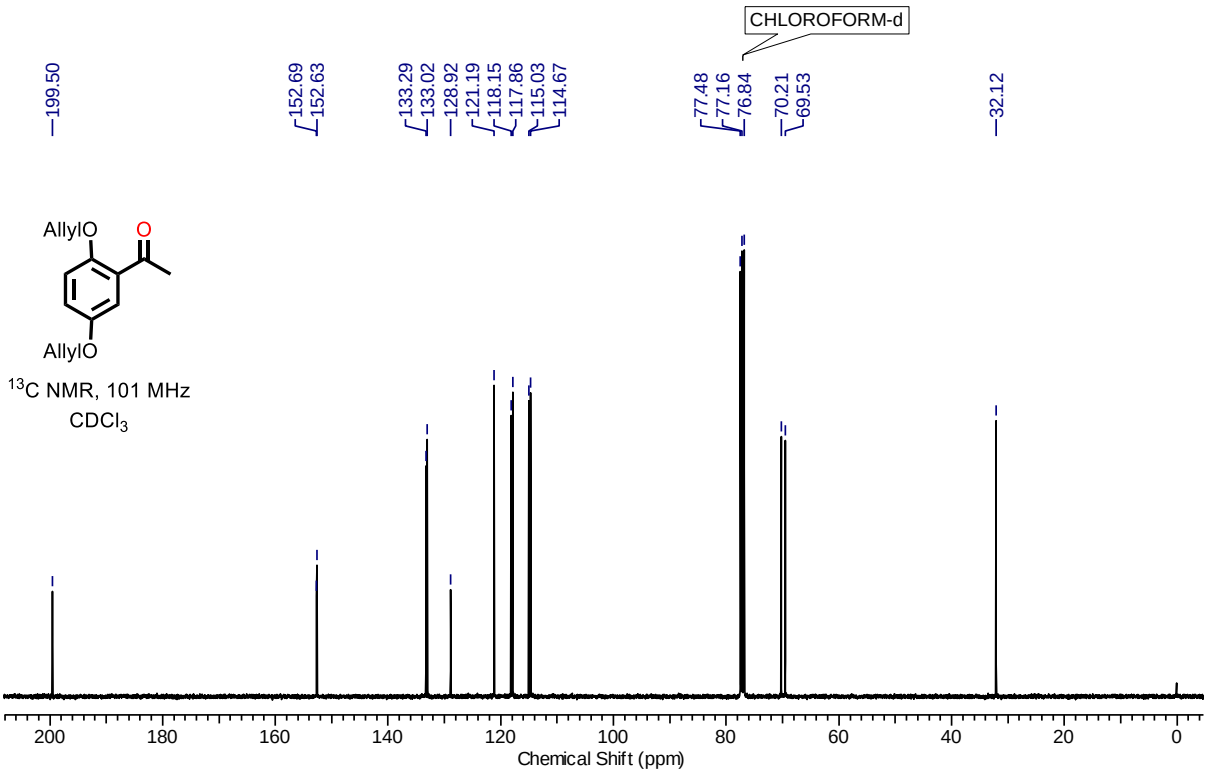
1-(4-((*Tert*-butyldiphenylsilyl)oxy)phenyl)ethan-1-one (**79q**):



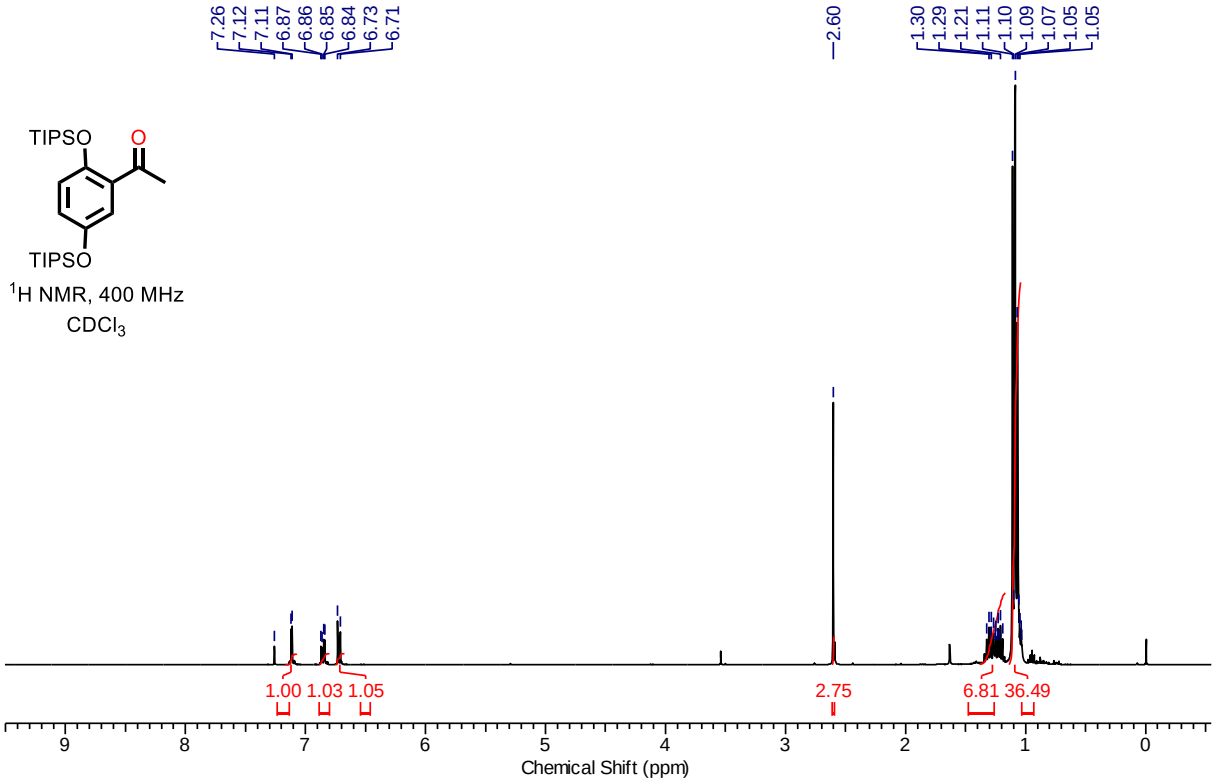
1-(2,5-Bis(allyloxy)phenyl)ethan-1-one (**79r**):



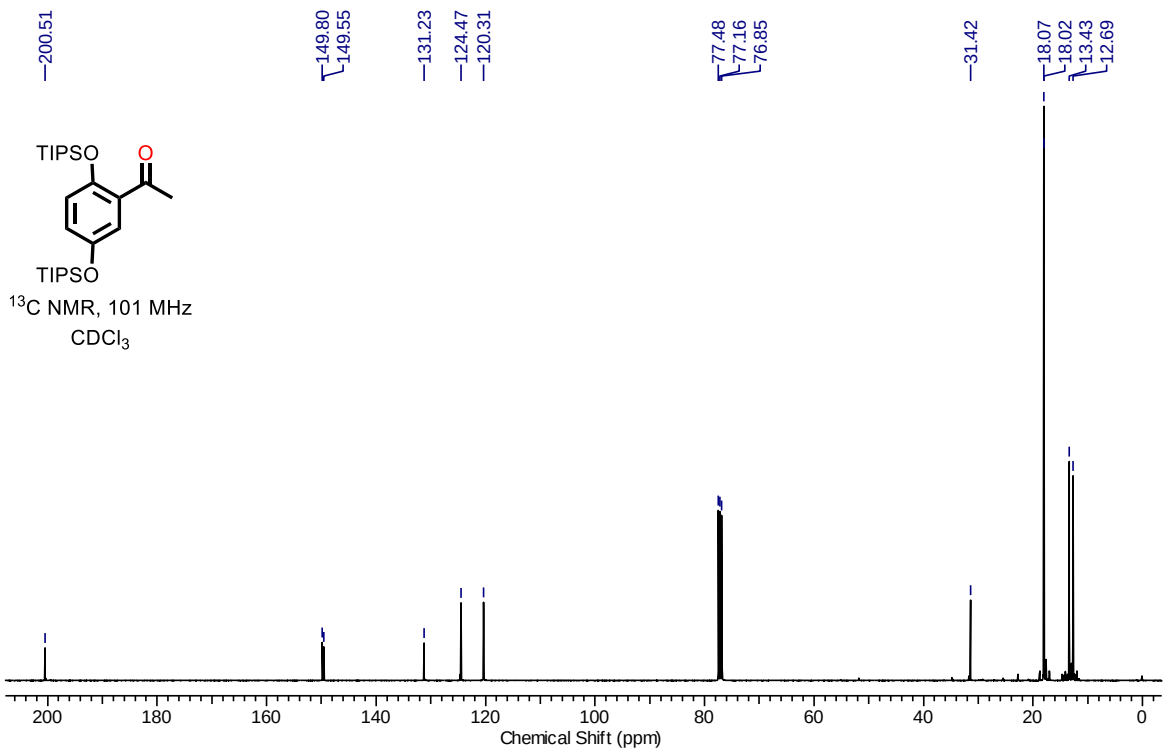
1-(2,5-Bis(allyloxy)phenyl)ethan-1-one (**79r**):



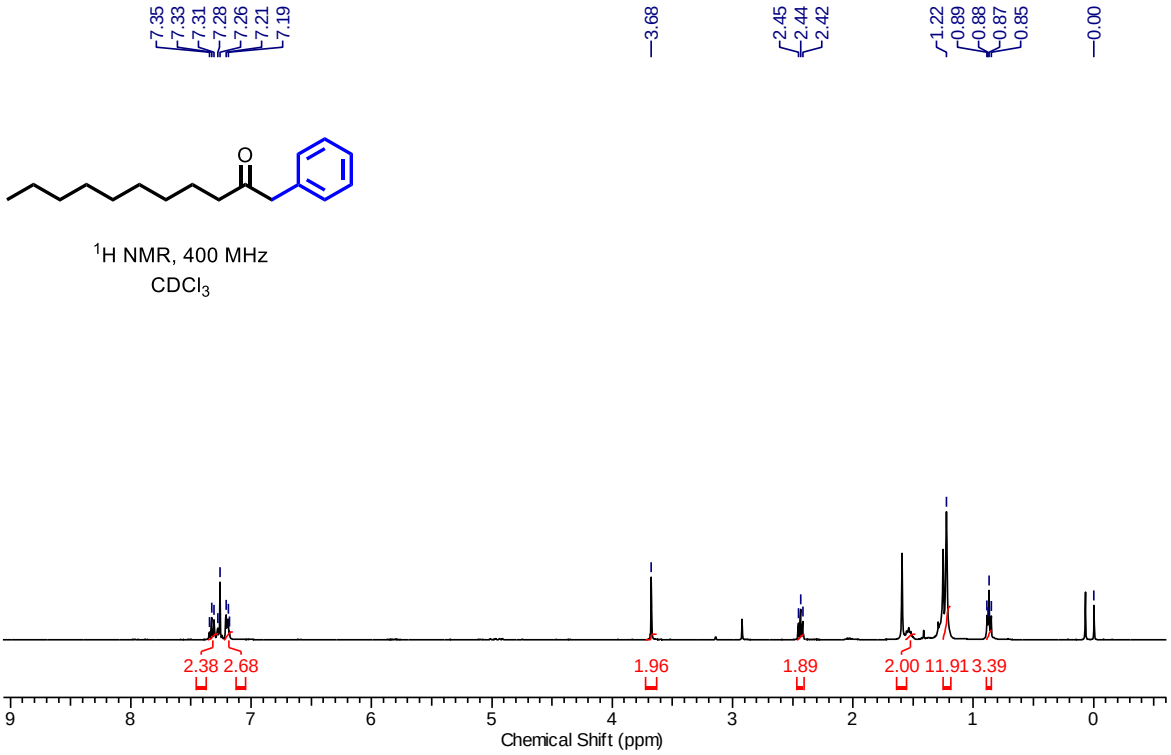
1-(2,5-Bis((triisopropylsilyl)oxy)phenyl)ethan-1-one (**79s**):



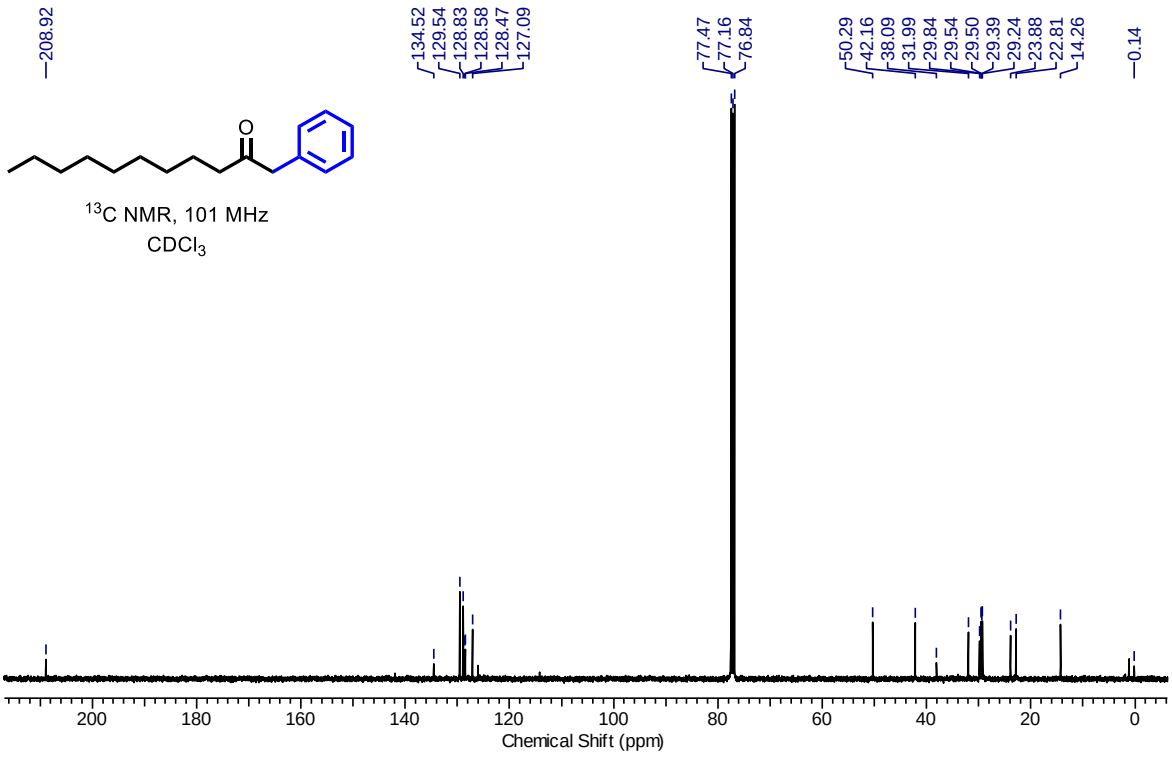
1-(2,5-Bis((triisopropylsilyl)oxy)phenyl)ethan-1-one (**79s**):



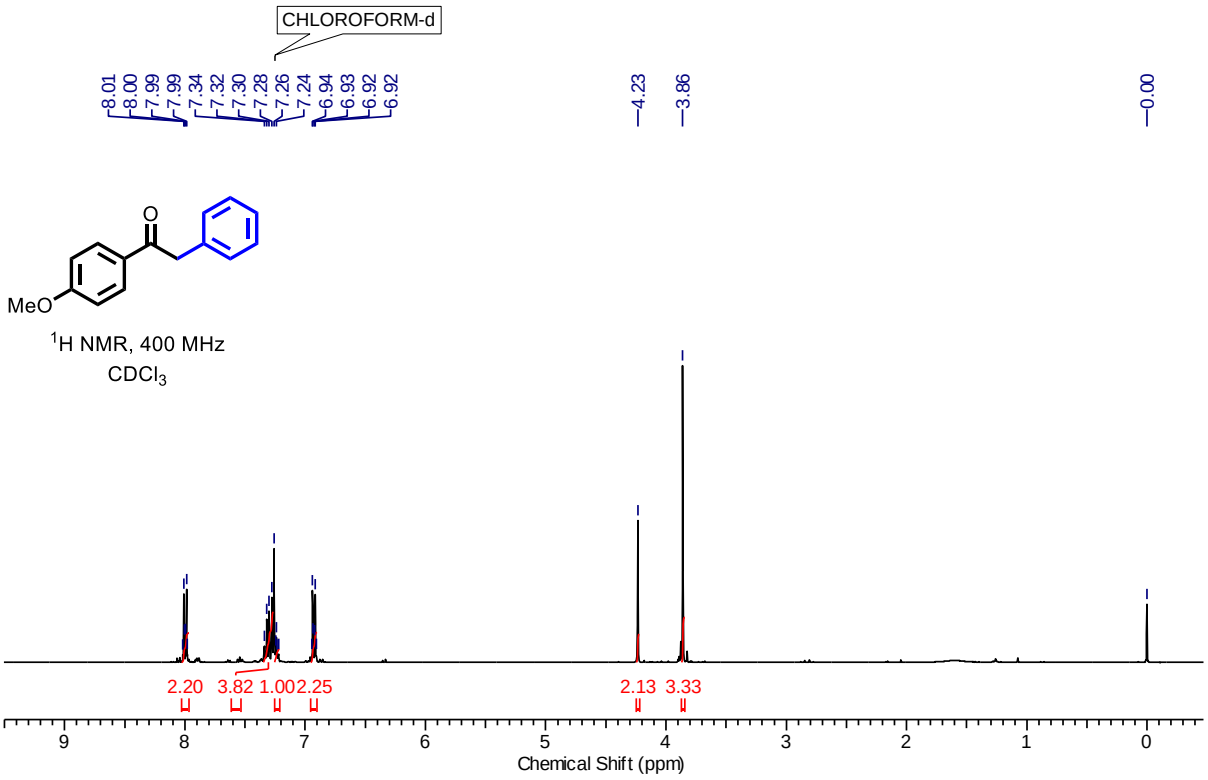
1-Phenylundecan-2-one (**79y**):



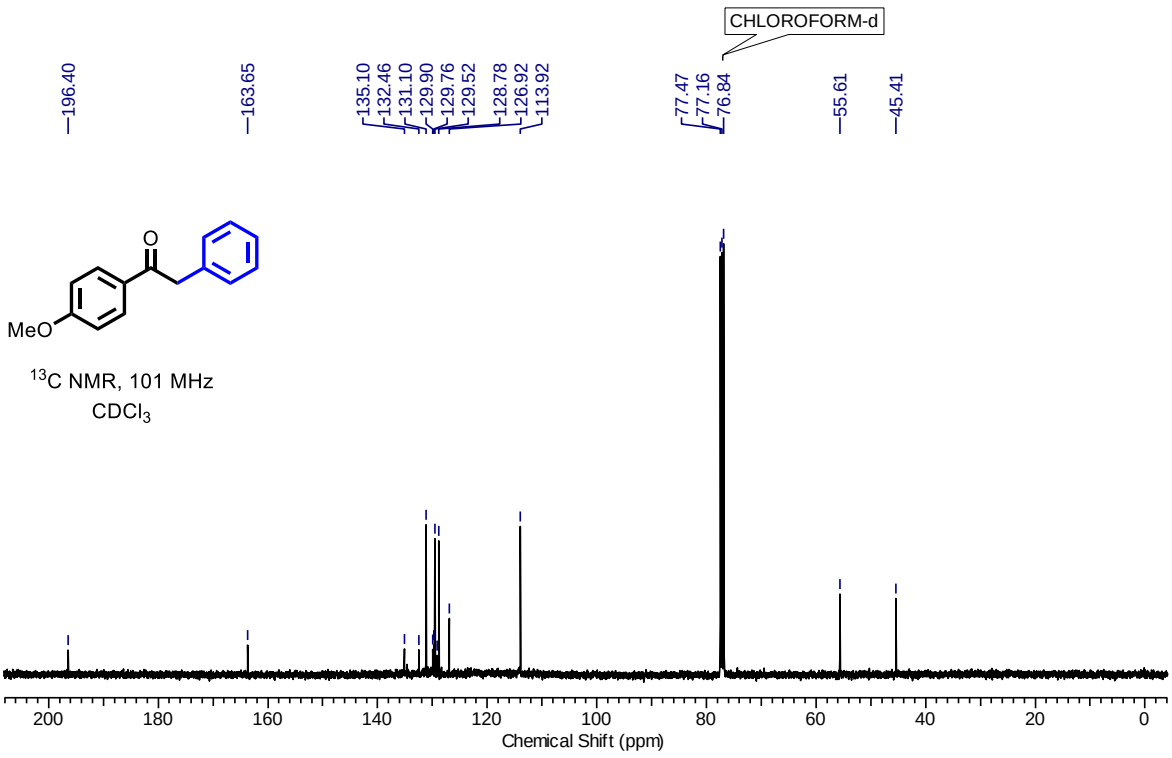
1-Phenylundecan-2-one (**79y**):



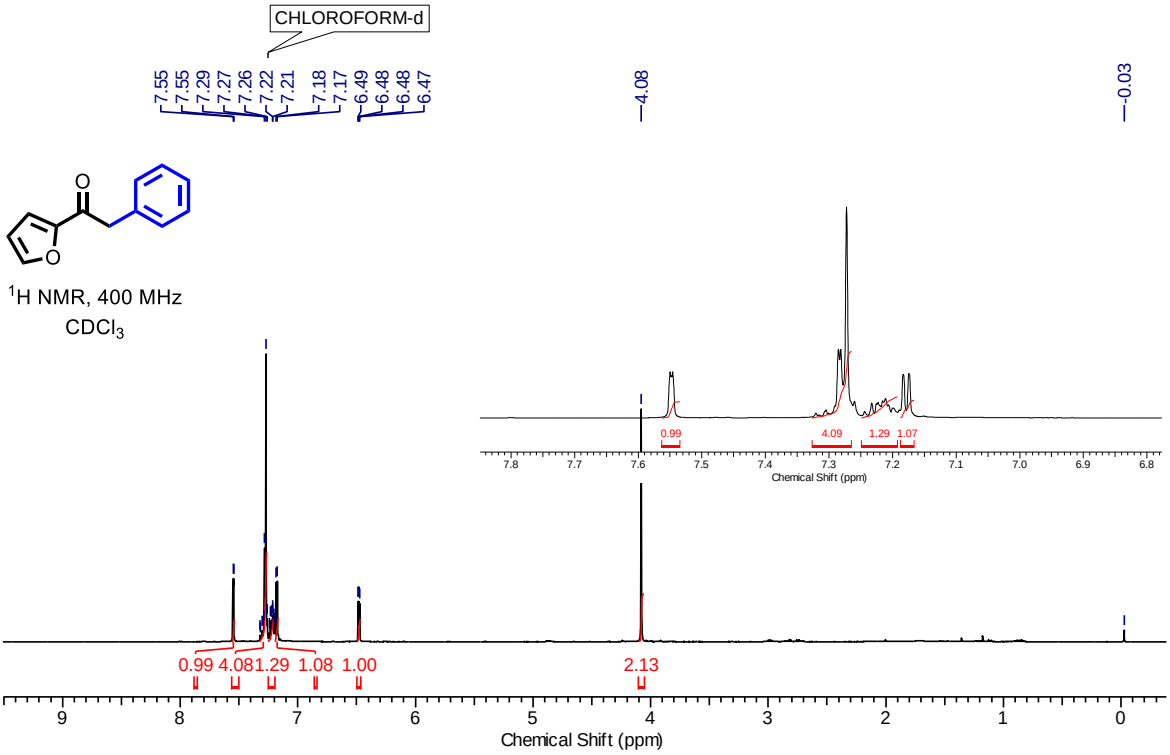
1-(4-Methoxyphenyl)-2-phenylethan-1-one (**79aa**):



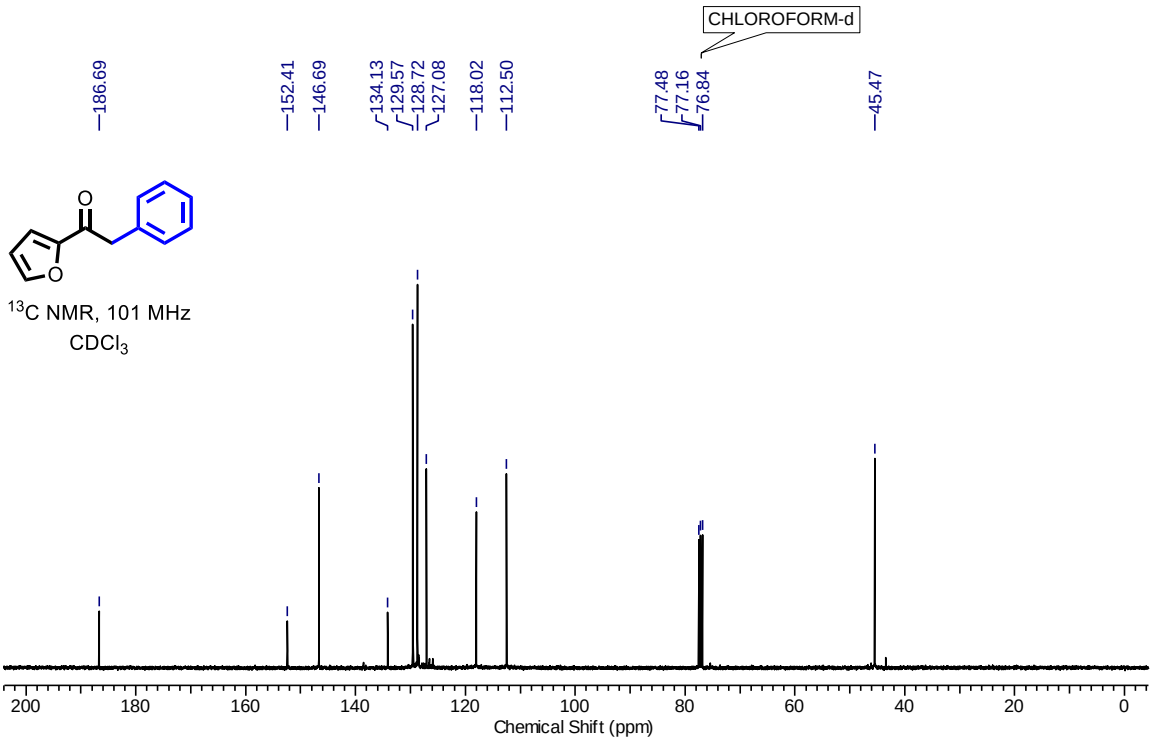
1-(4-Methoxyphenyl)-2-phenylethan-1-one (**79aa**):



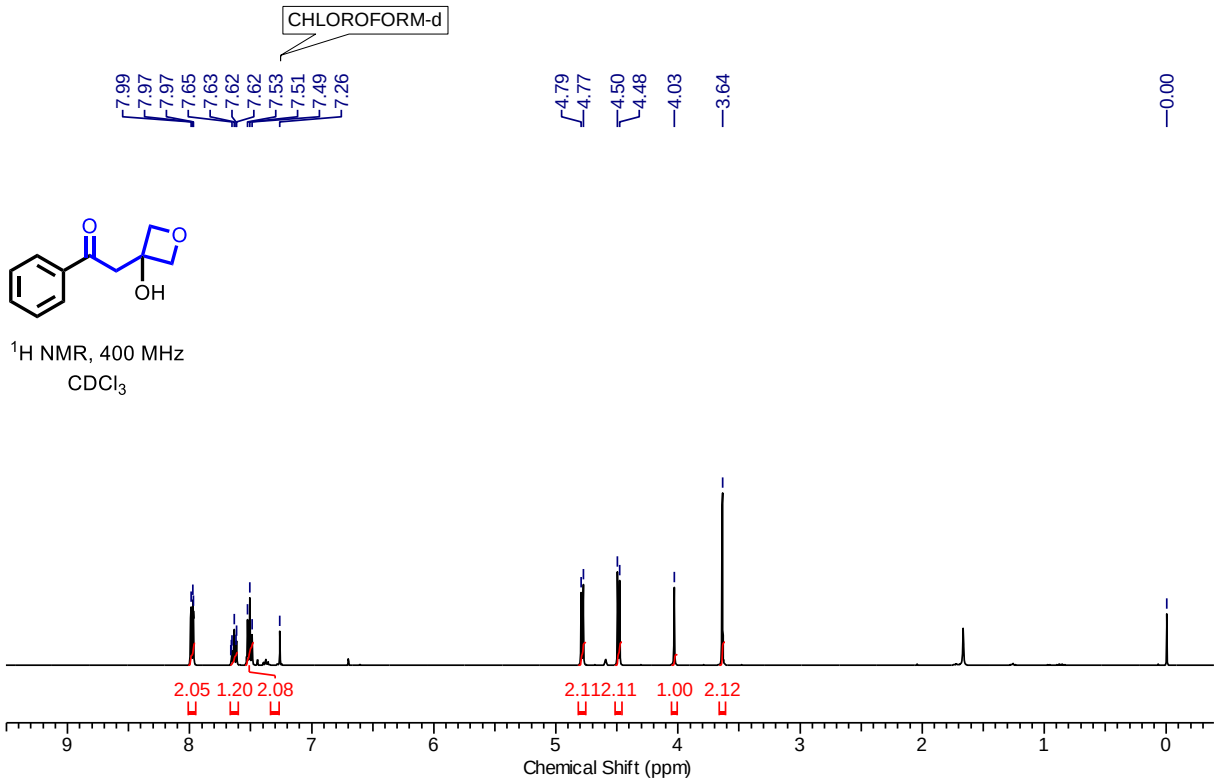
1-(Furan-2-yl)-2-phenylethan-1-one (**79ac**):



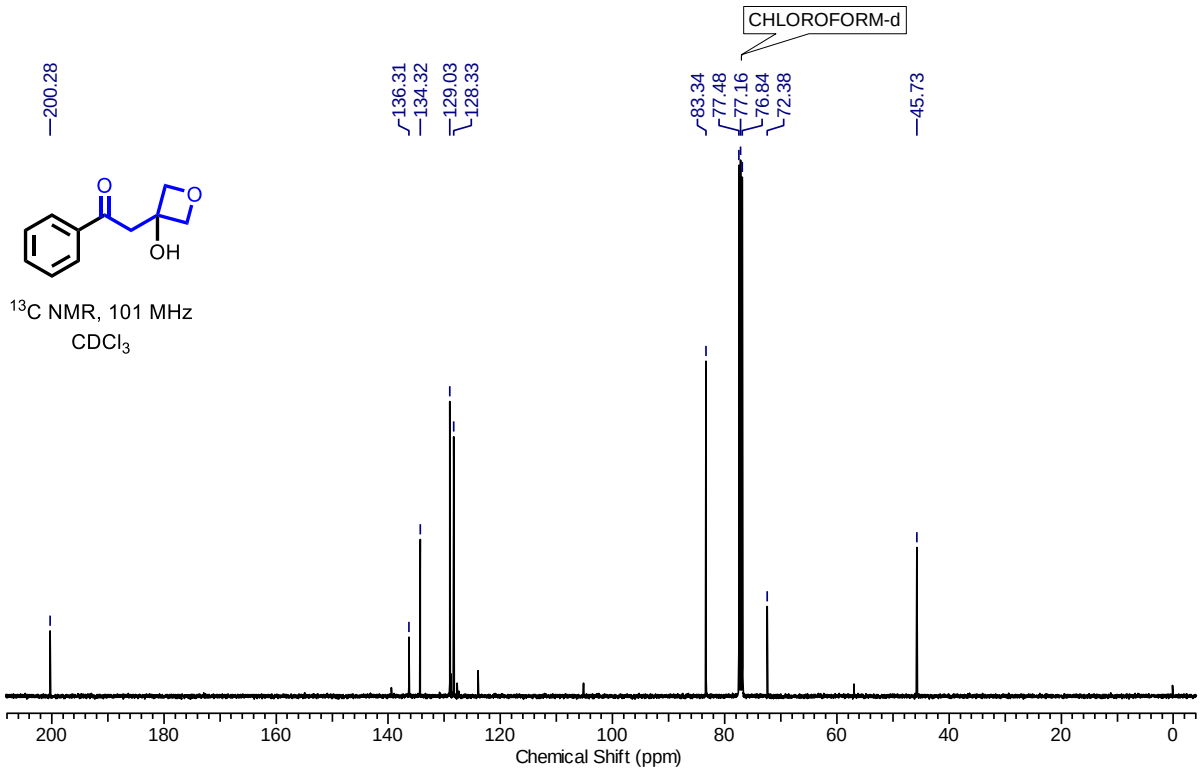
1-(Furan-2-yl)-2-phenylethan-1-one (**79ac**):



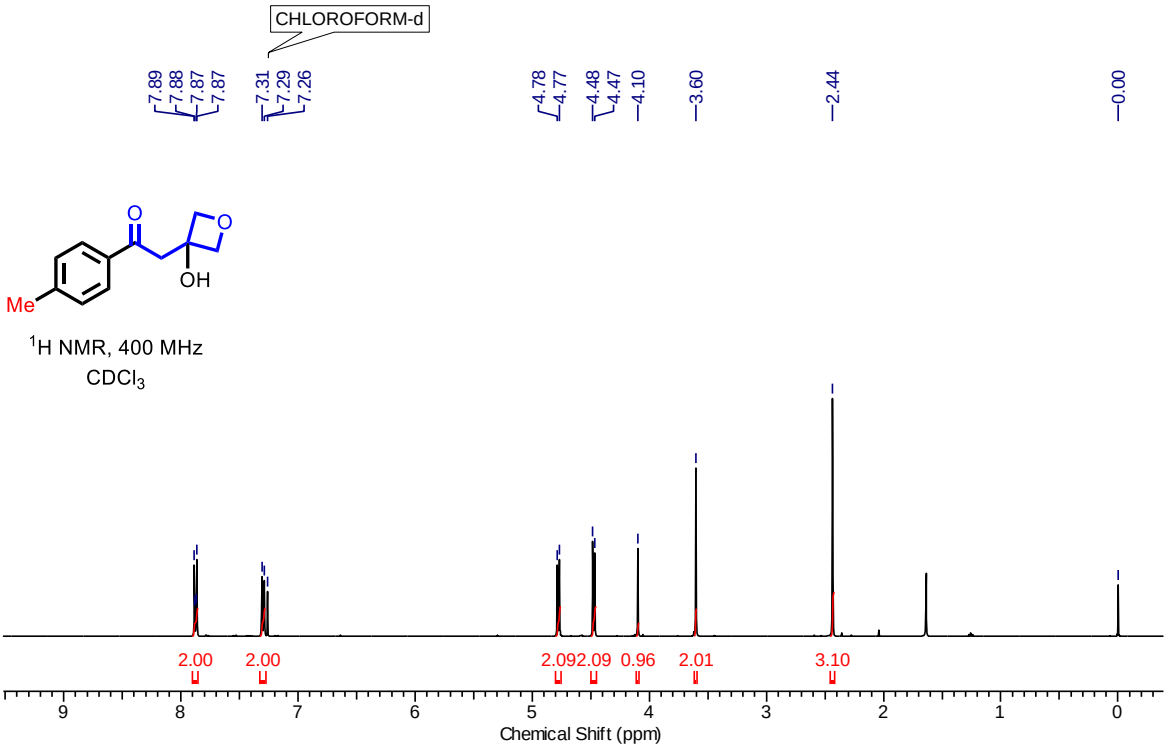
2-(3-Hydroxyoxetan-3-yl)-1-phenylethan-1-one (**71a**):



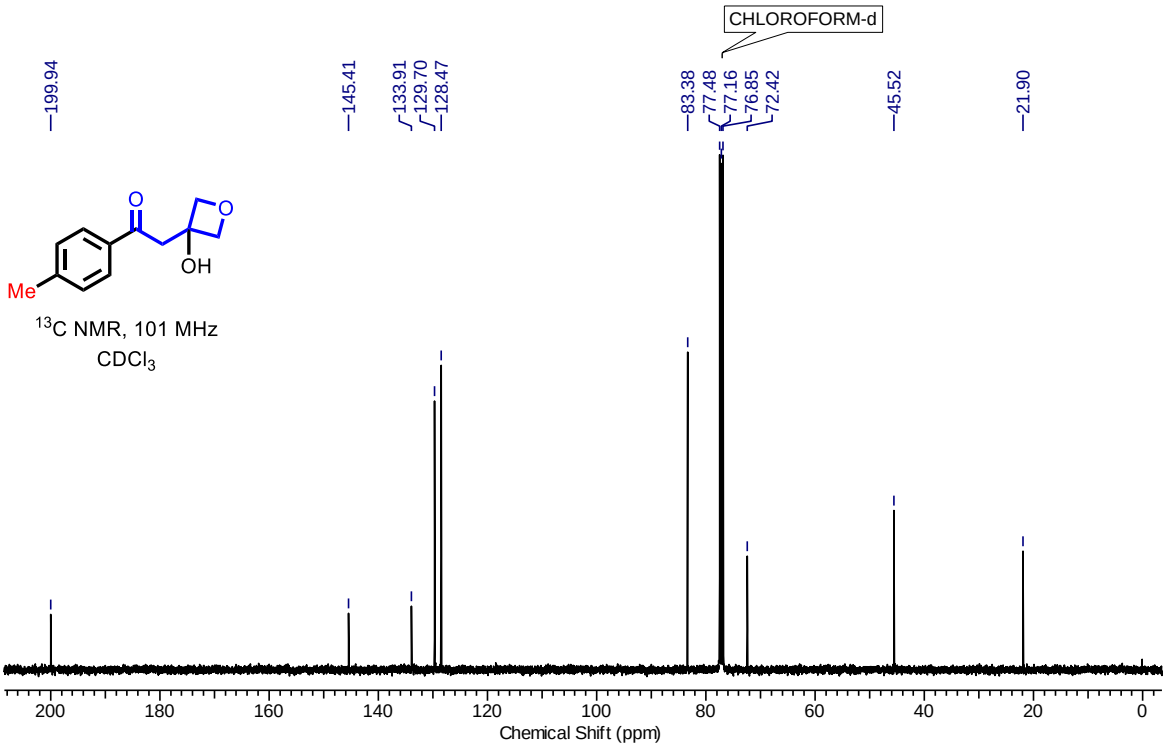
2-(3-Hydroxyoxetan-3-yl)-1-phenylethan-1-one (**71a**):



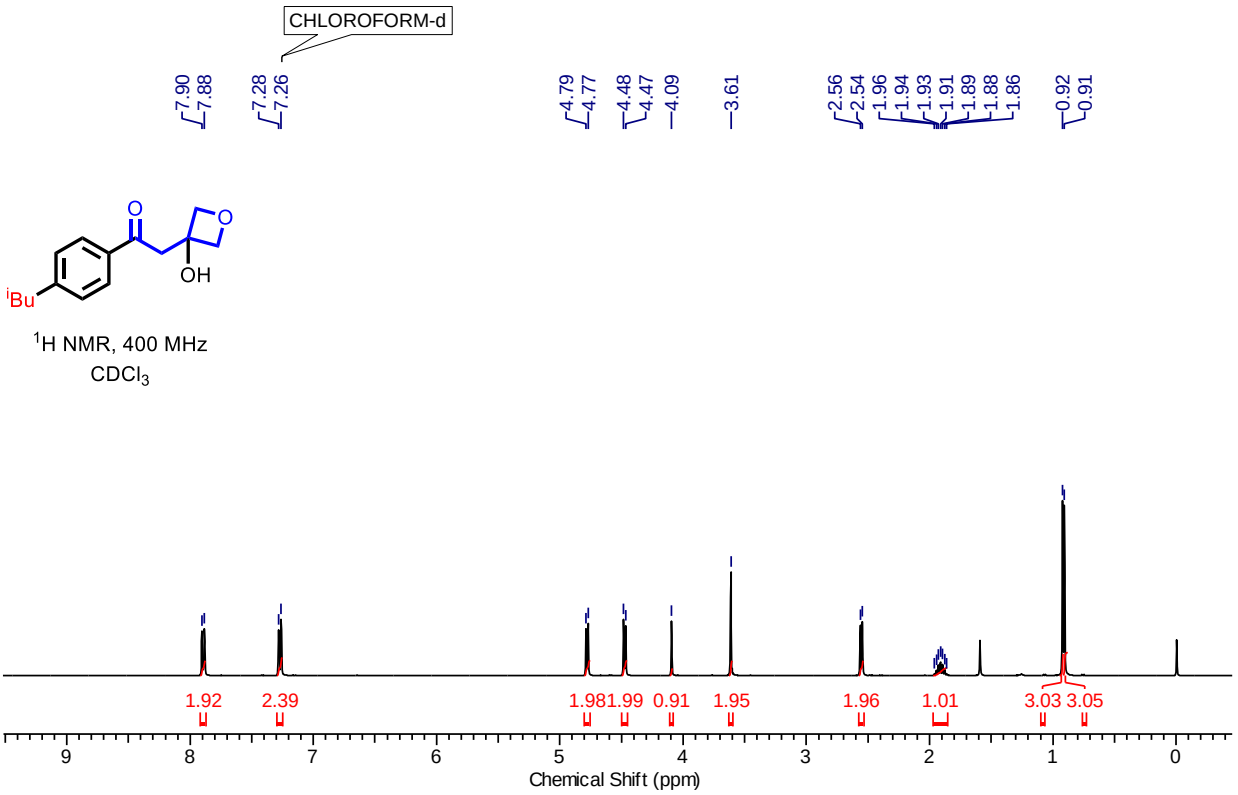
2-(3-Hydroxyoxetan-3-yl)-1-(*p*-tolyl)ethan-1-one (**71b**):



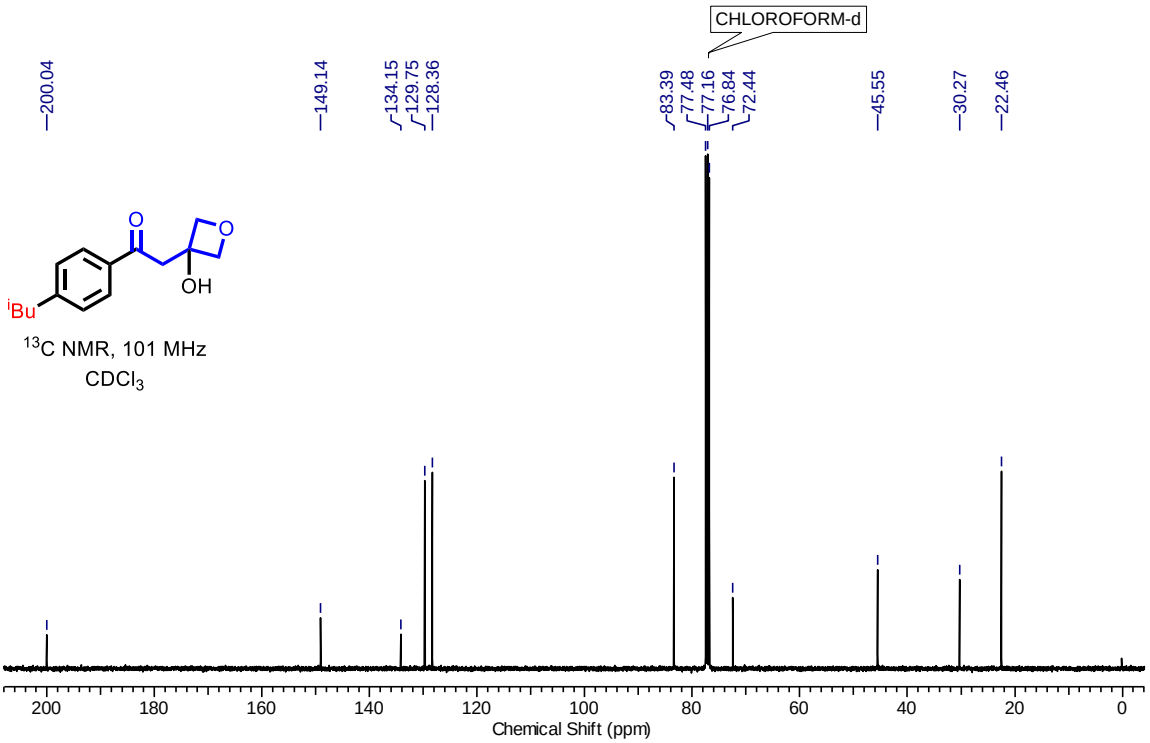
2-(3-Hydroxyoxetan-3-yl)-1-(*p*-tolyl)ethan-1-one (**71b**):



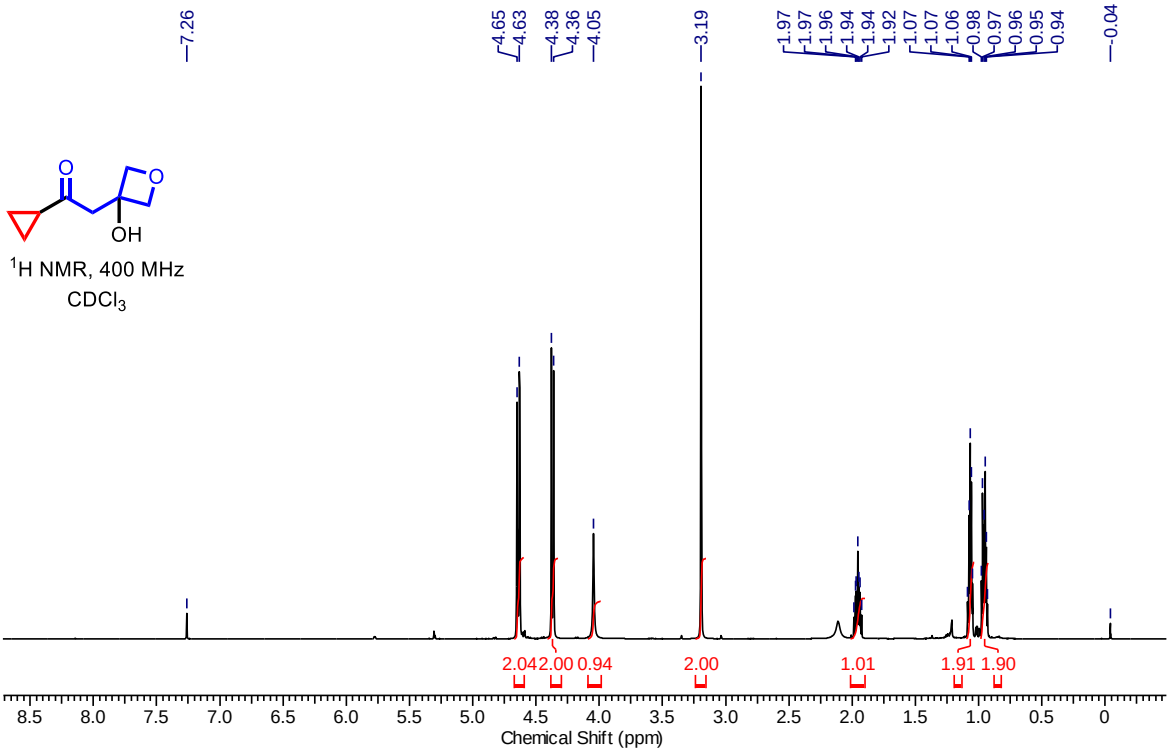
2-(3-Hydroxyoxetan-3-yl)-1-(4-isobutylphenyl)ethan-1-one (**71c**):



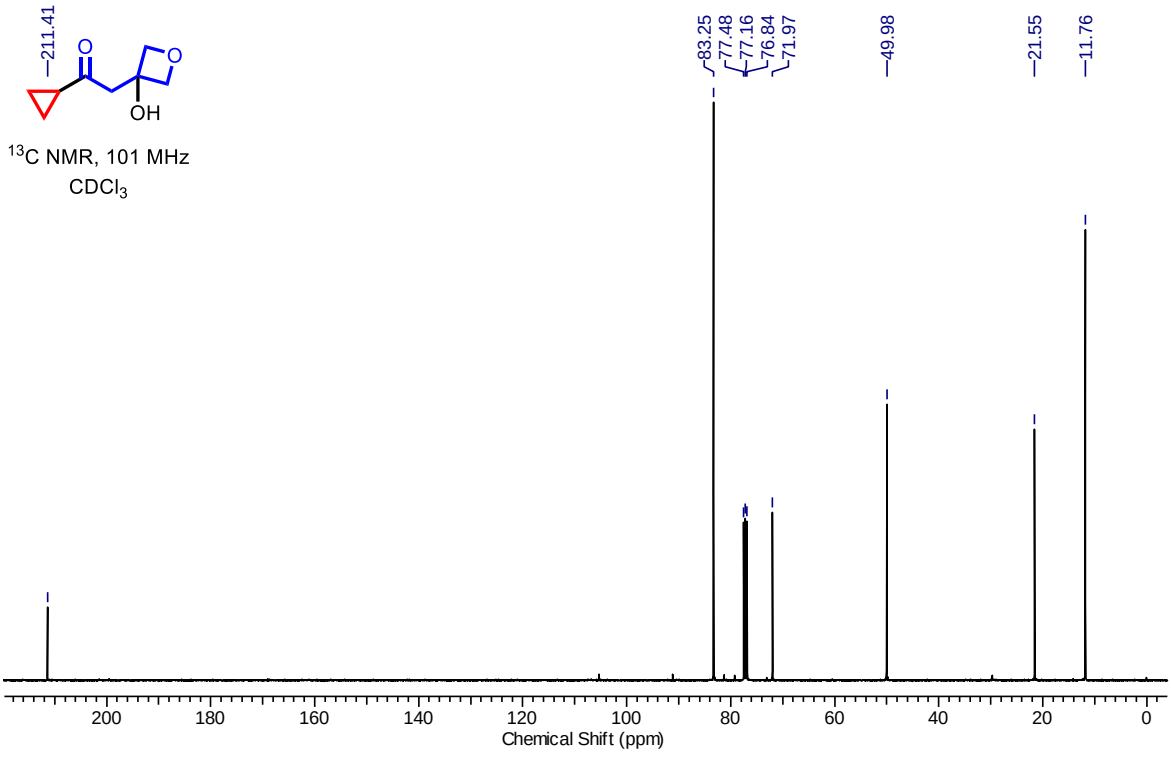
2-(3-Hydroxyoxetan-3-yl)-1-(4-isobutylphenyl)ethan-1-one (**71c**):



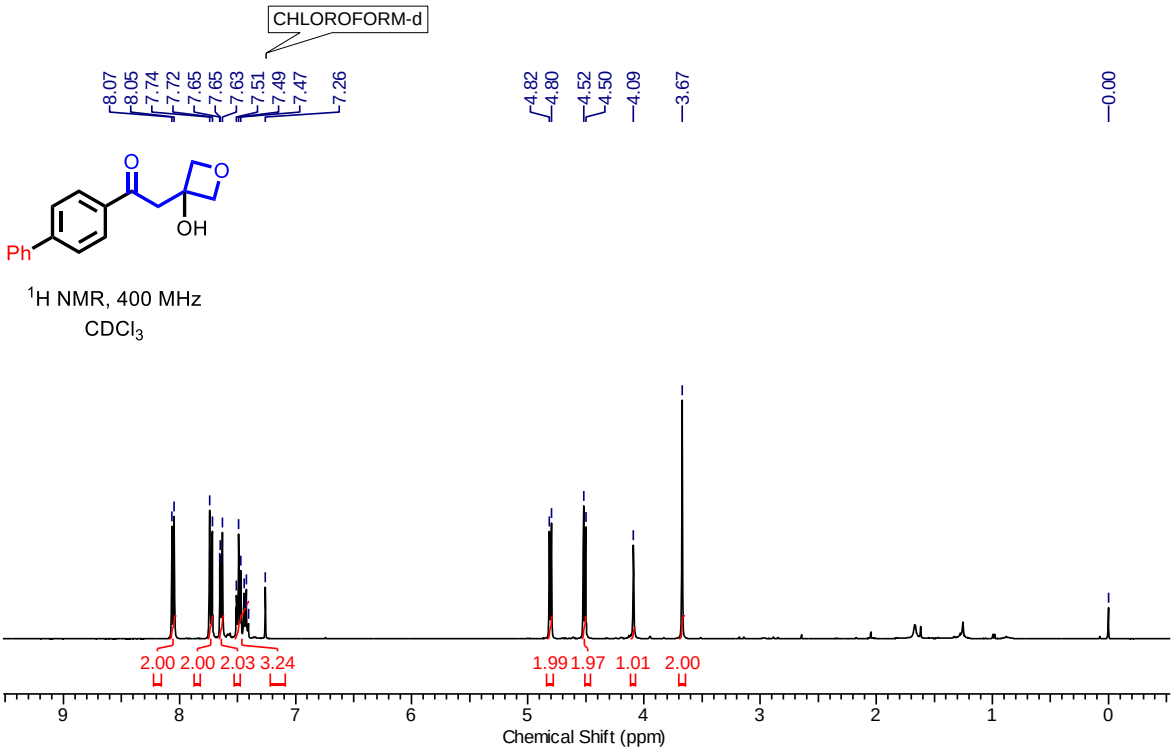
Cyclopropyl(3-hydroxyoxetan-3-yl)methanone (**71d**):



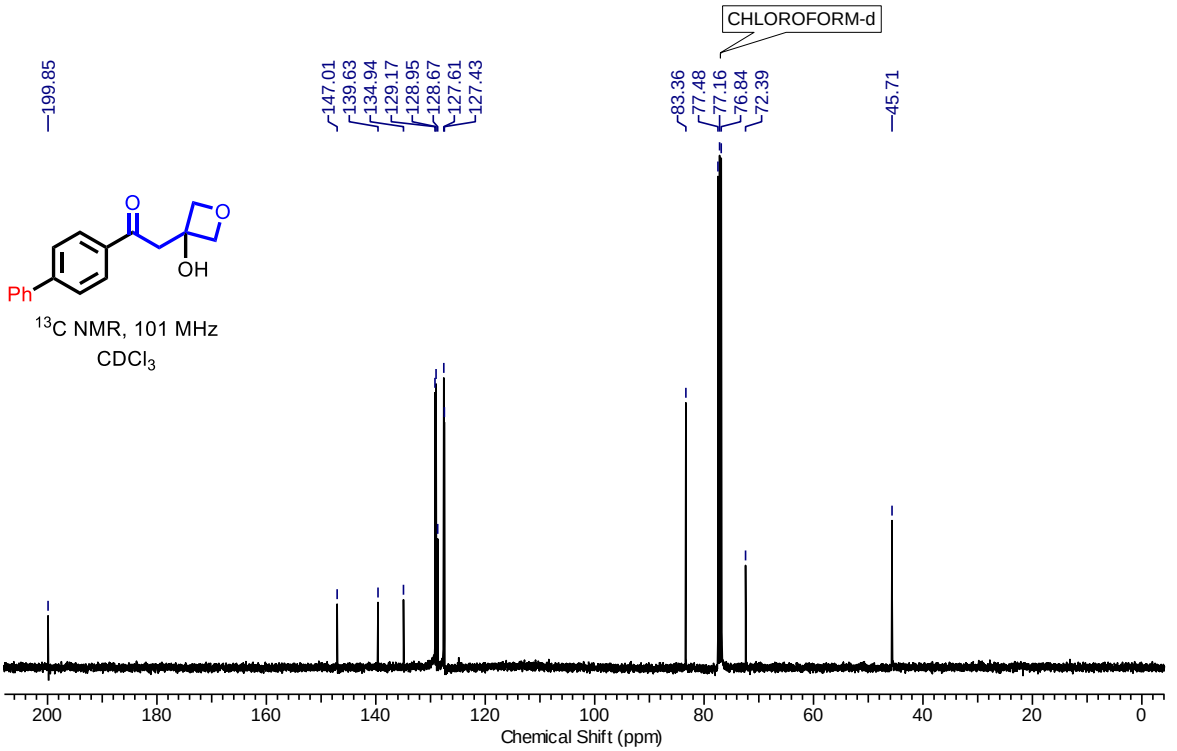
Cyclopropyl(3-hydroxyoxetan-3-yl)methanone (**71d**):



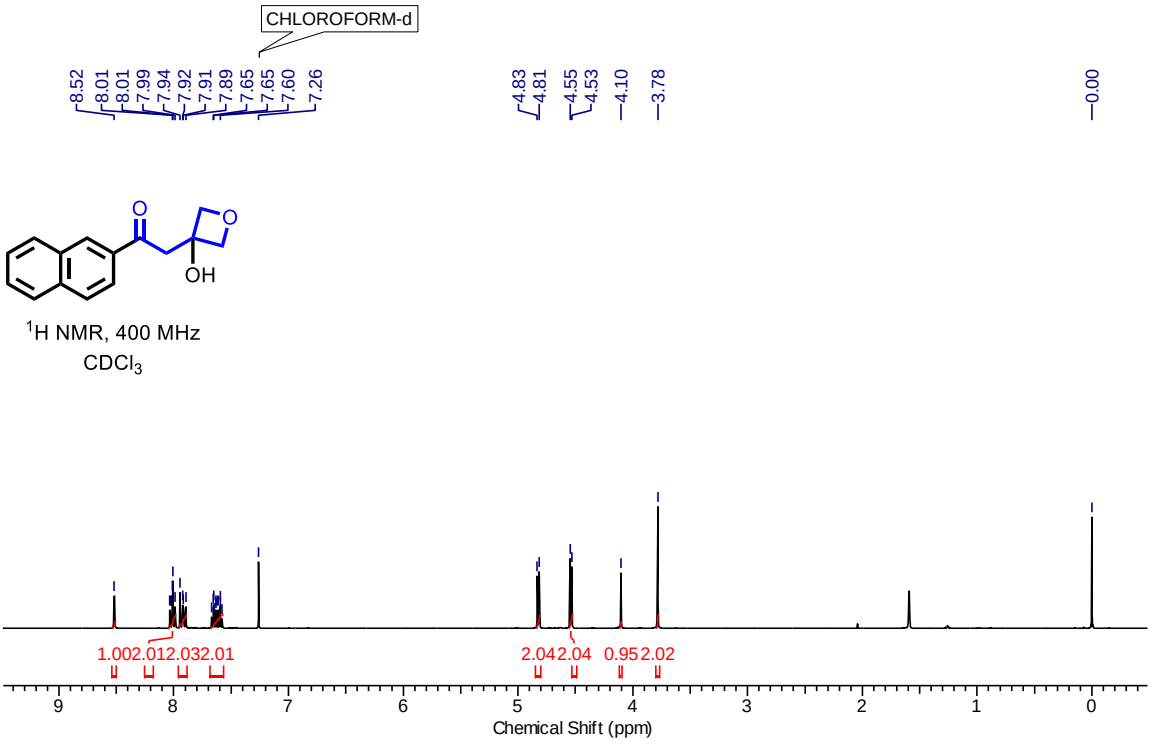
1-([1,1'-Biphenyl]-4-yl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (**71e**):



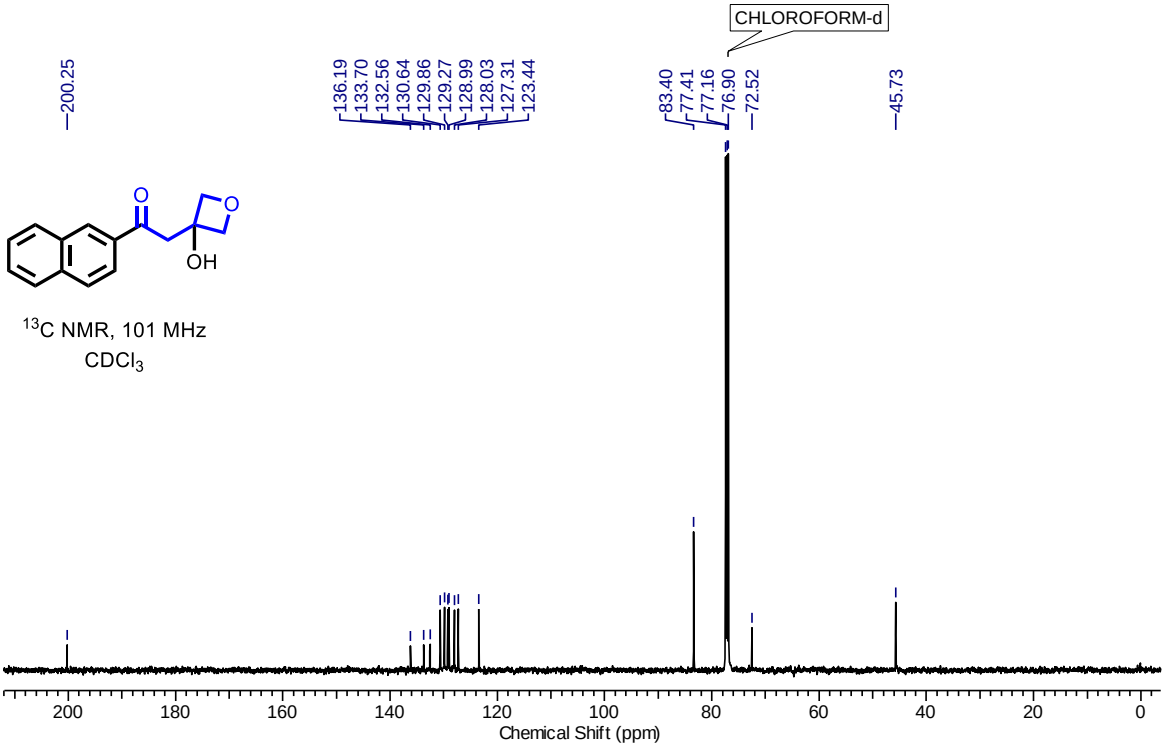
1-([1,1'-Biphenyl]-4-yl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (**71e**):



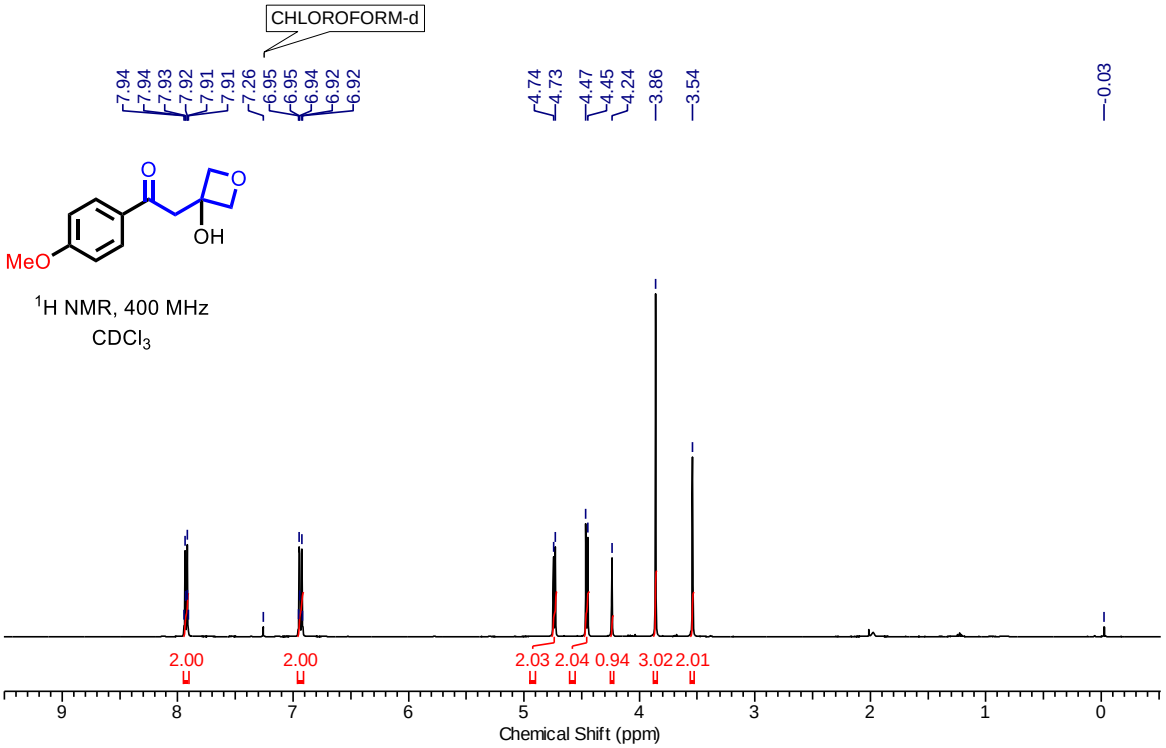
2-(3-Hydroxyoxetan-3-yl)-1-(naphthalen-2-yl)ethan-1-one (**71f**):



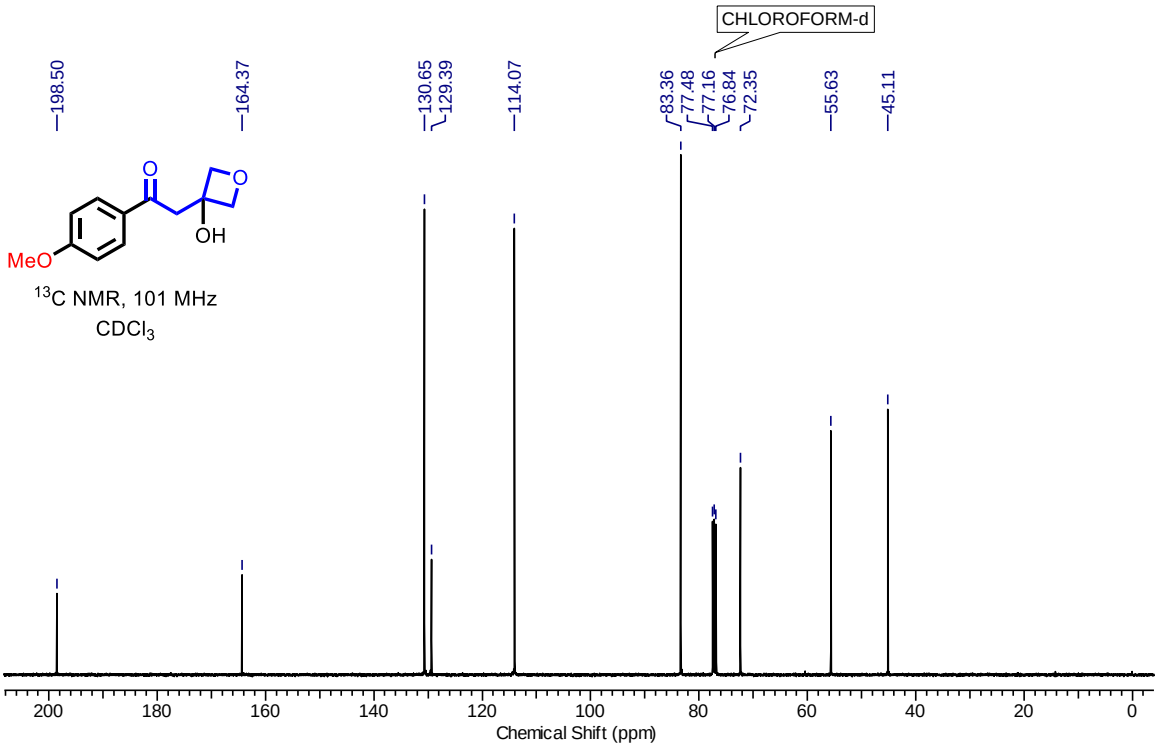
2-(3-Hydroxyoxetan-3-yl)-1-(naphthalen-2-yl)ethan-1-one (**71f**):



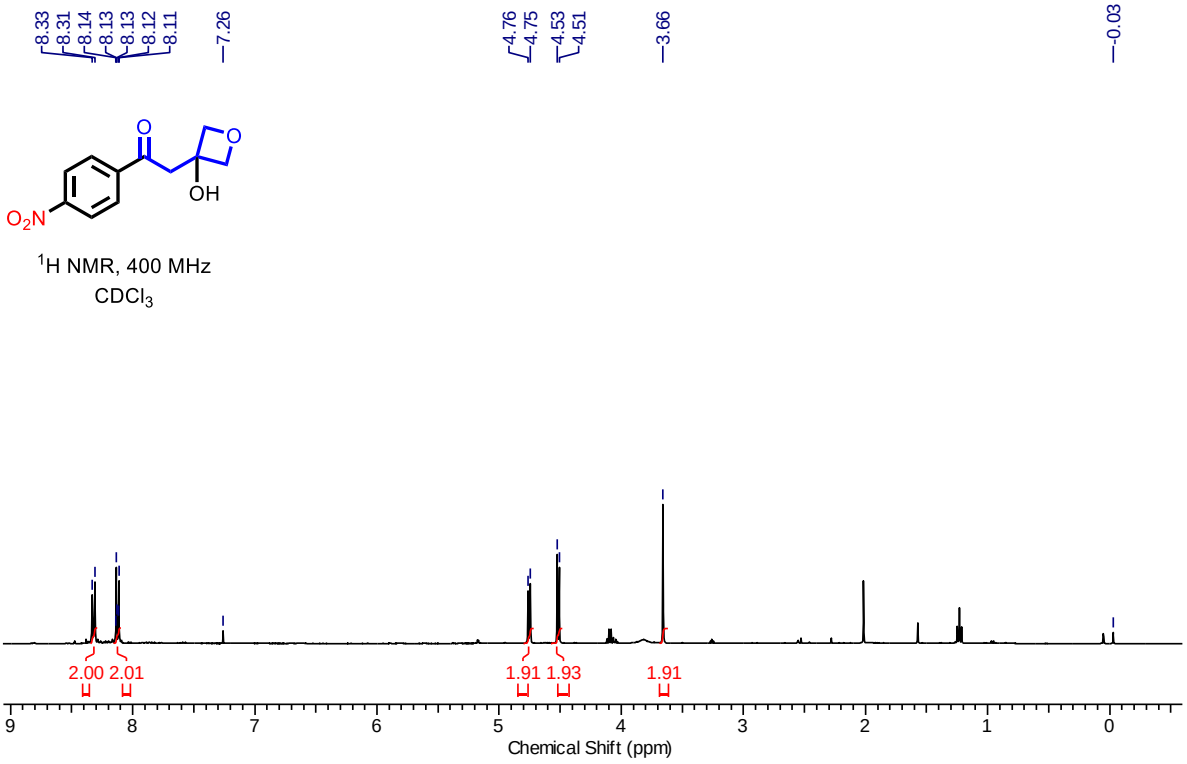
2-(3-Hydroxyoxetan-3-yl)-1-(4-methoxyphenyl)ethan-1-one (**71g**):



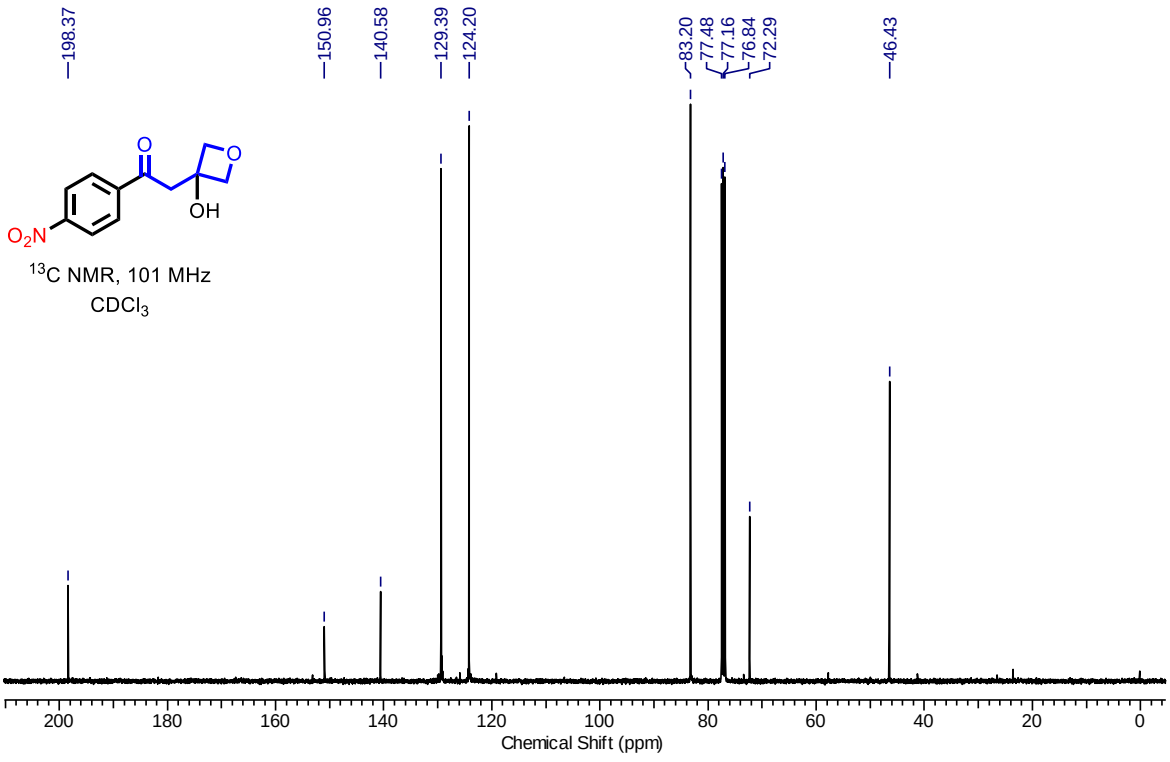
2-(3-Hydroxyoxetan-3-yl)-1-(4-methoxyphenyl)ethan-1-one (**71g**):



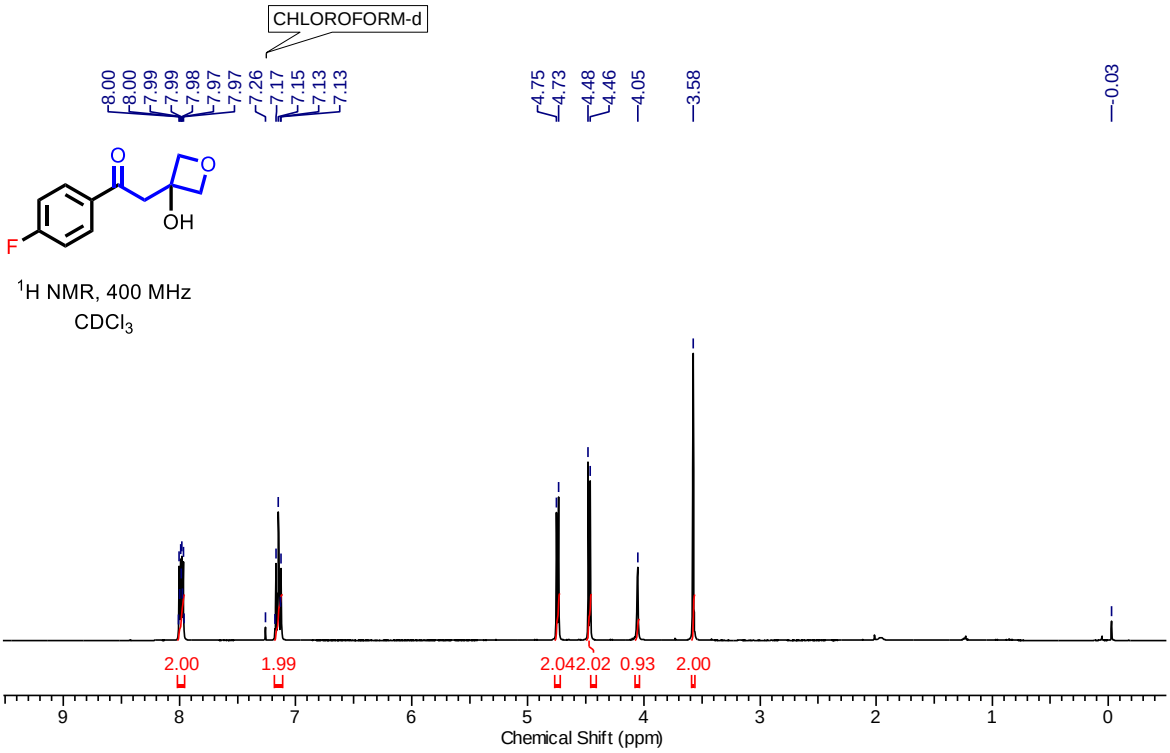
2-(3-Hydroxyoxetan-3-yl)-1-(4-nitrophenyl)ethan-1-one (**71i**):



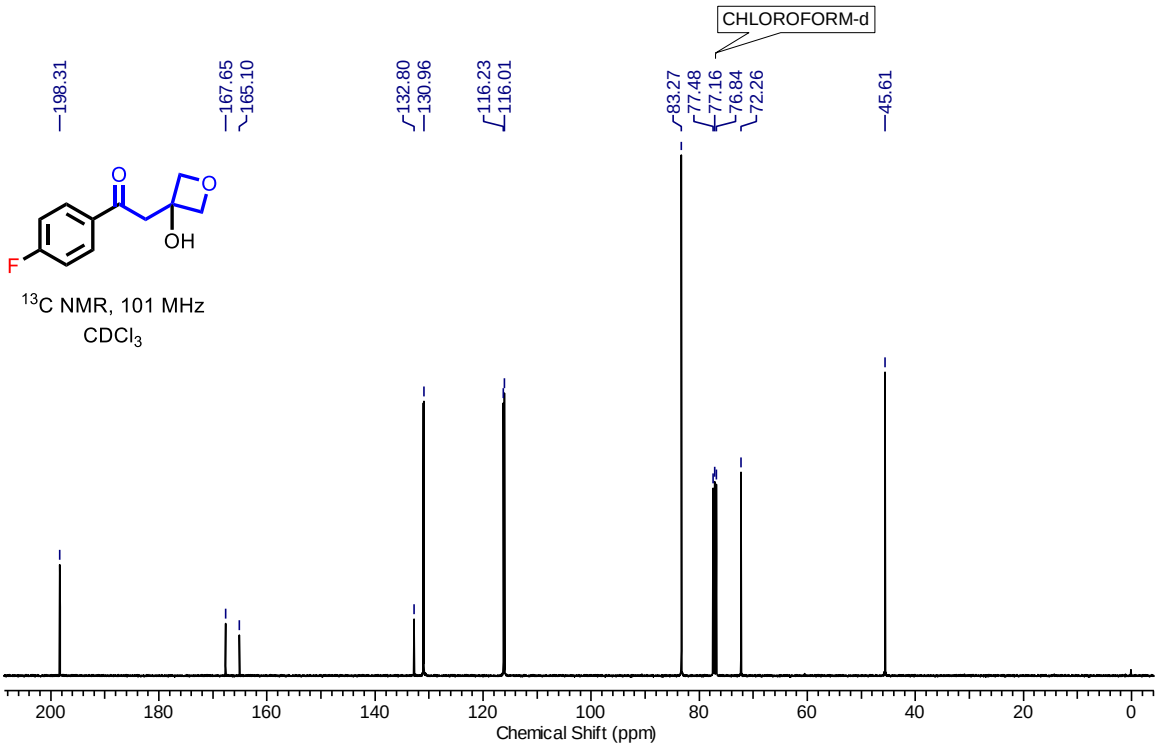
2-(3-Hydroxyoxetan-3-yl)-1-(4-nitrophenyl)ethan-1-one (**71i**):



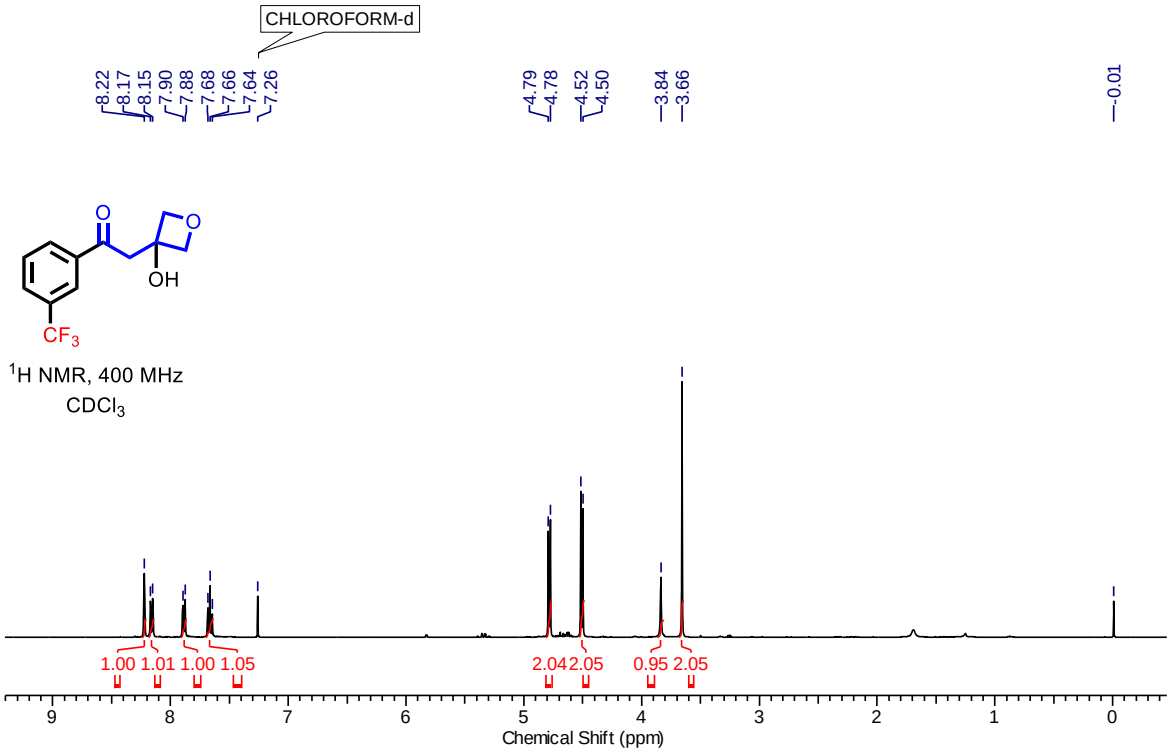
1-(4-Fluorophenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (**71j**):



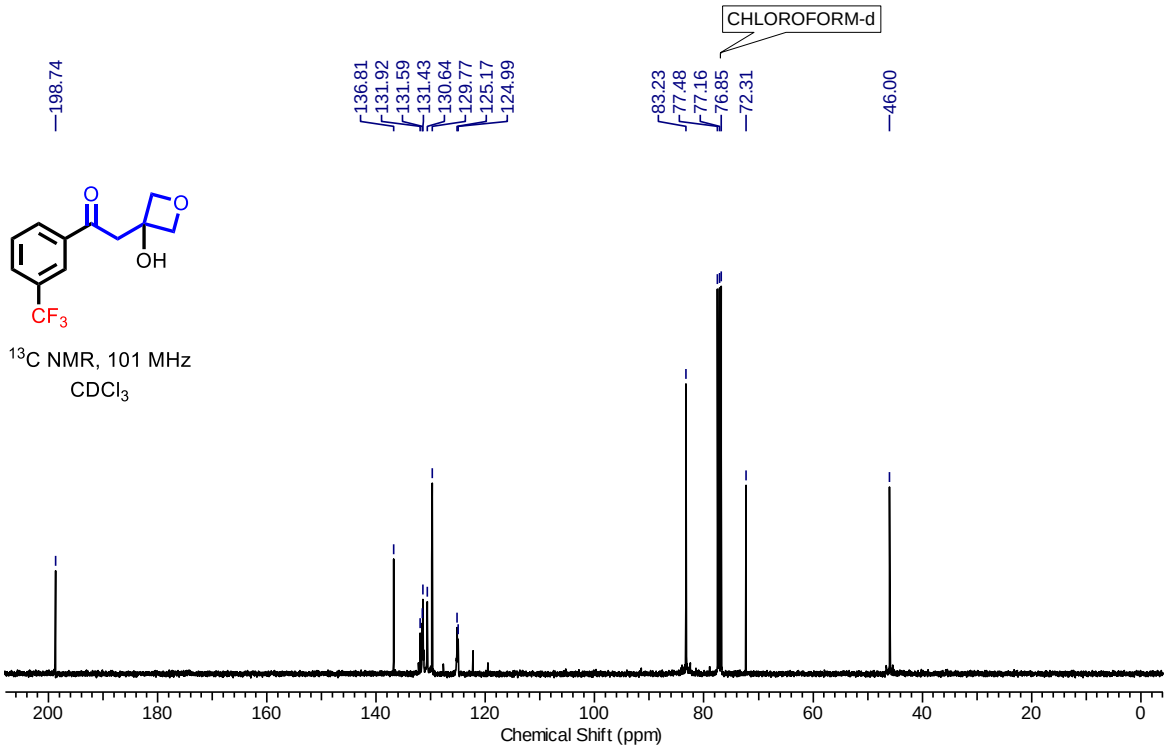
1-(4-Fluorophenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (**71j**):



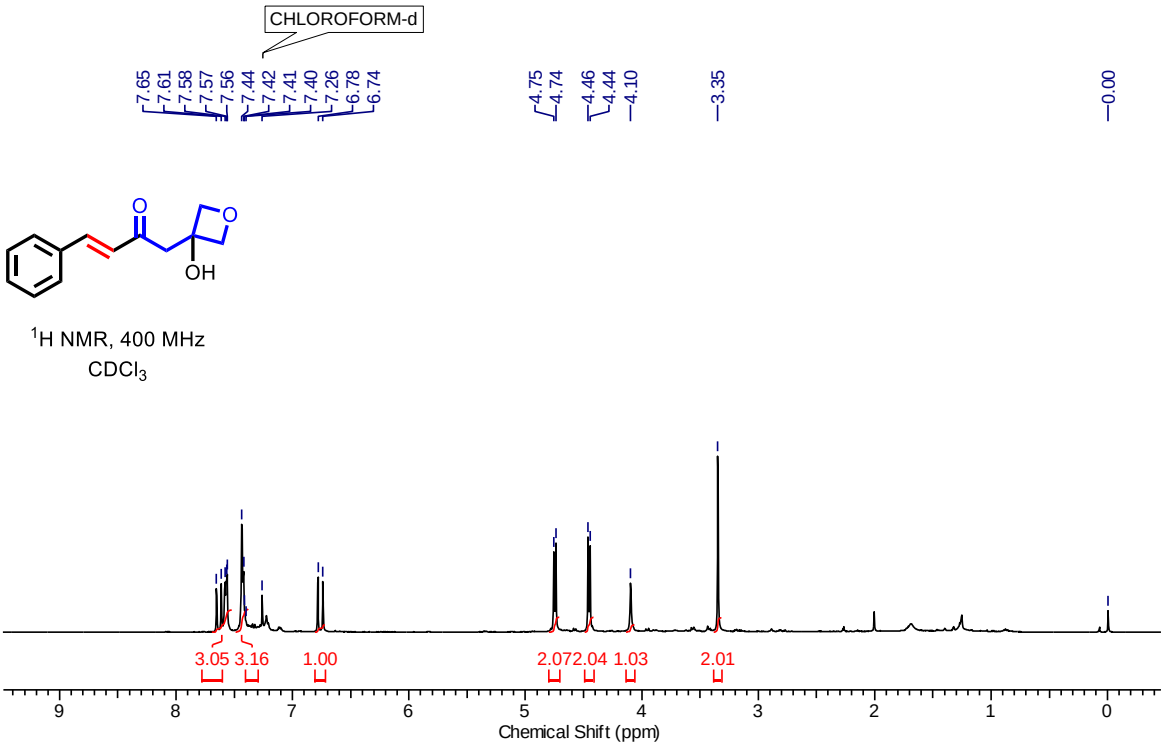
2-(3-Hydroxyoxetan-3-yl)-1-(3-(trifluoromethyl)phenyl)ethan-1-one (**71k**):



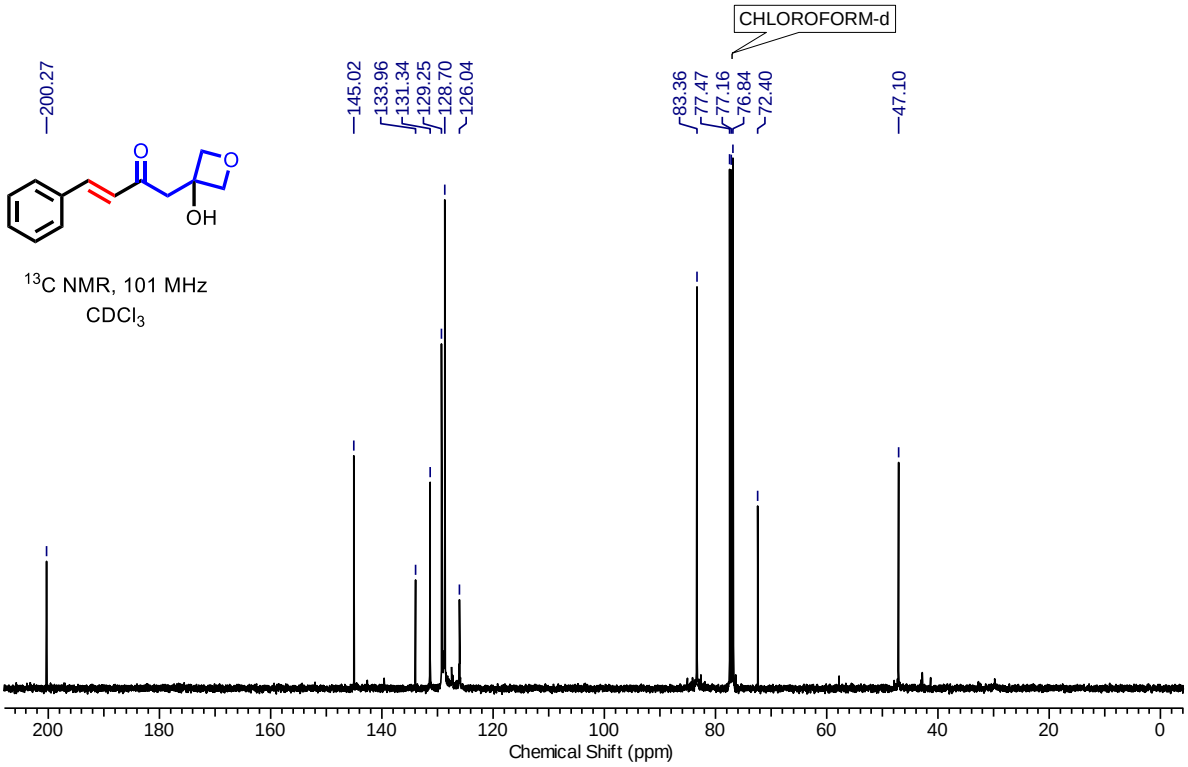
2-(3-Hydroxyoxetan-3-yl)-1-(3-(trifluoromethyl)phenyl)ethan-1-one (**71k**):



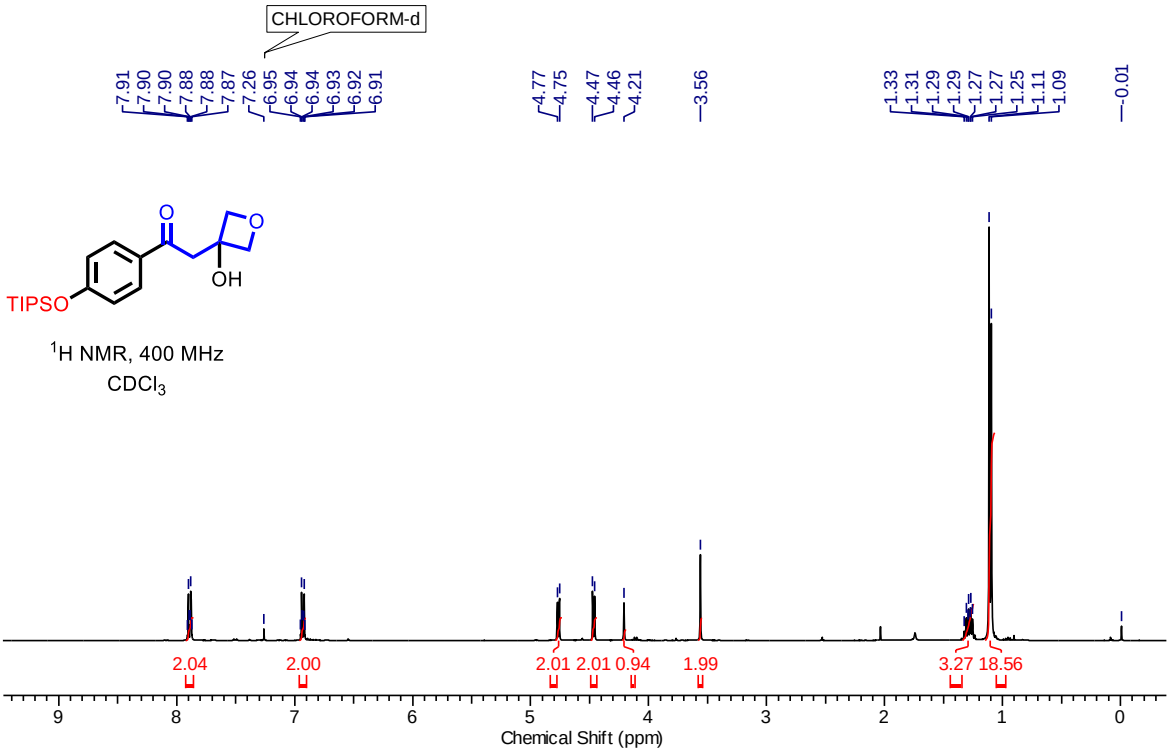
(*E*)-1-(3-Hydroxyoxetan-3-yl)-4-phenylbut-3-en-2-one (**71l**):



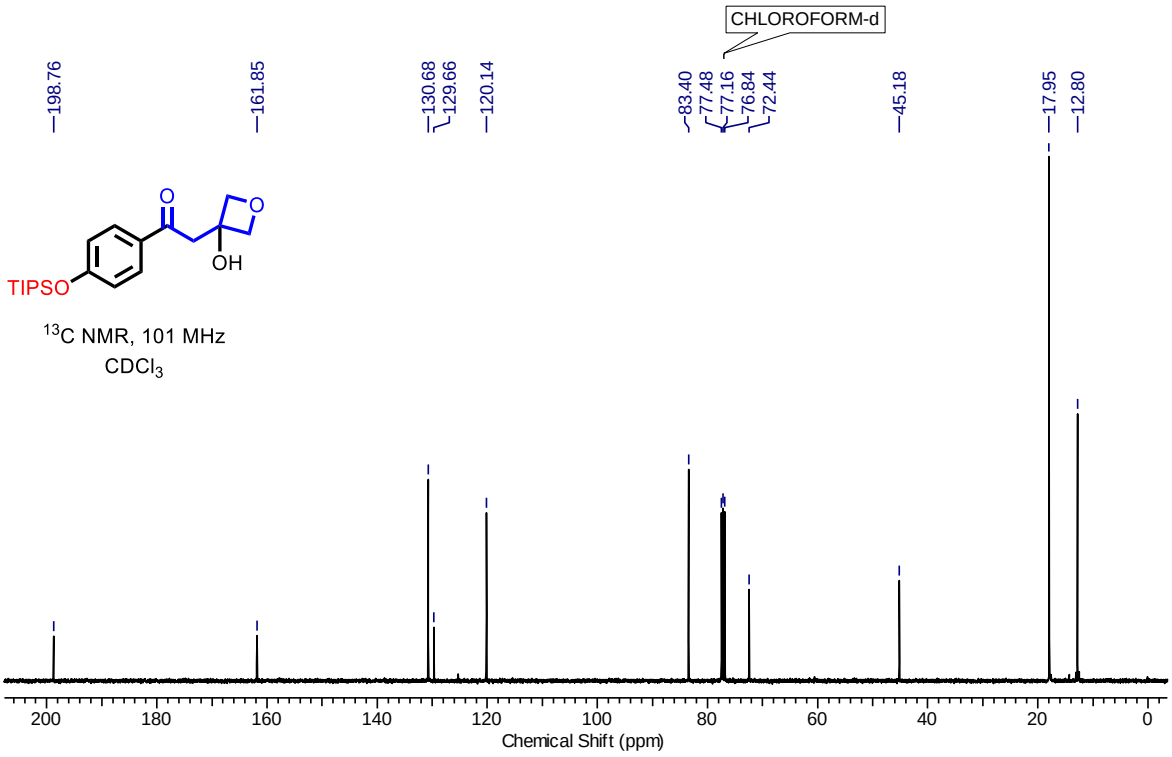
(*E*)-1-(3-Hydroxyoxetan-3-yl)-4-phenylbut-3-en-2-one (**71l**):



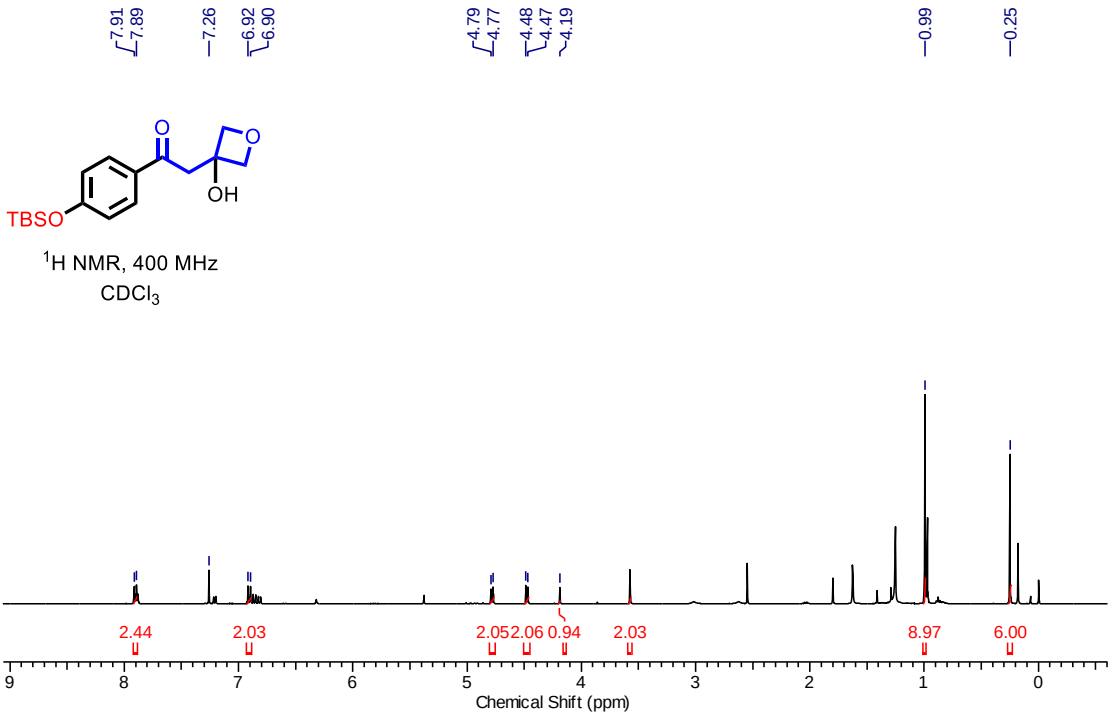
2-(3-Hydroxyoxetan-3-yl)-1-(4-((triisopropylsilyl)oxy)phenyl)ethan-1-one (**71m**):



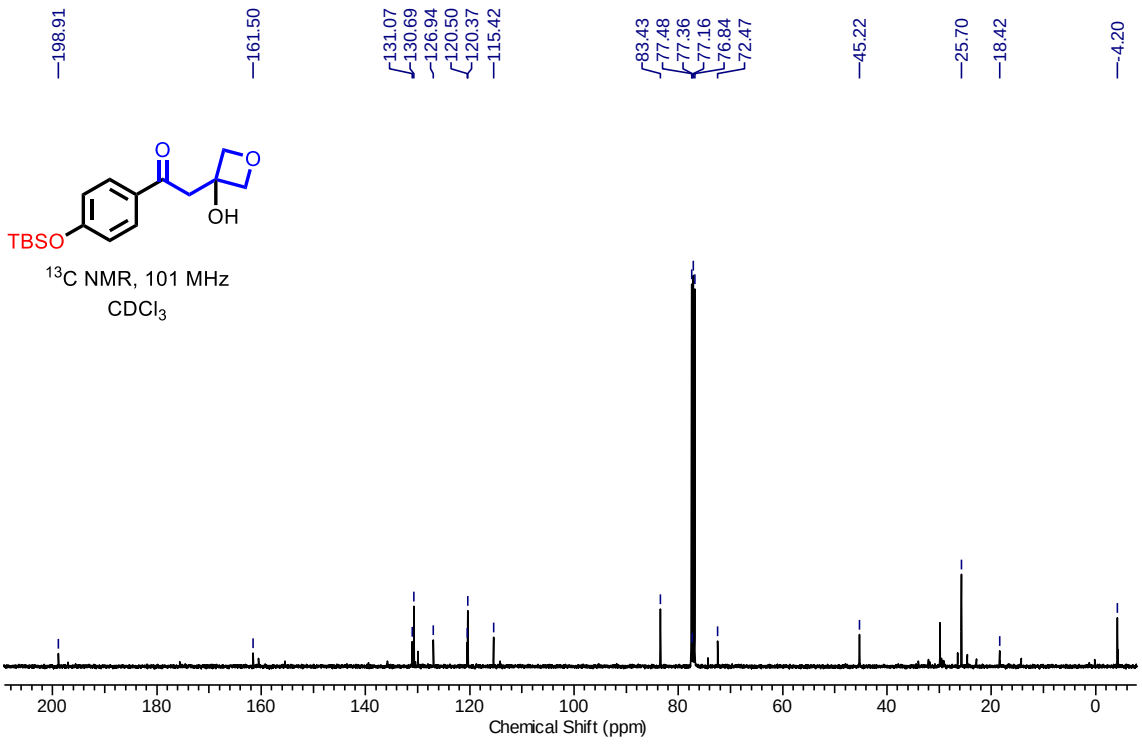
2-(3-Hydroxyoxetan-3-yl)-1-(4-((triisopropylsilyl)oxy)phenyl)ethan-1-one (**71m**):



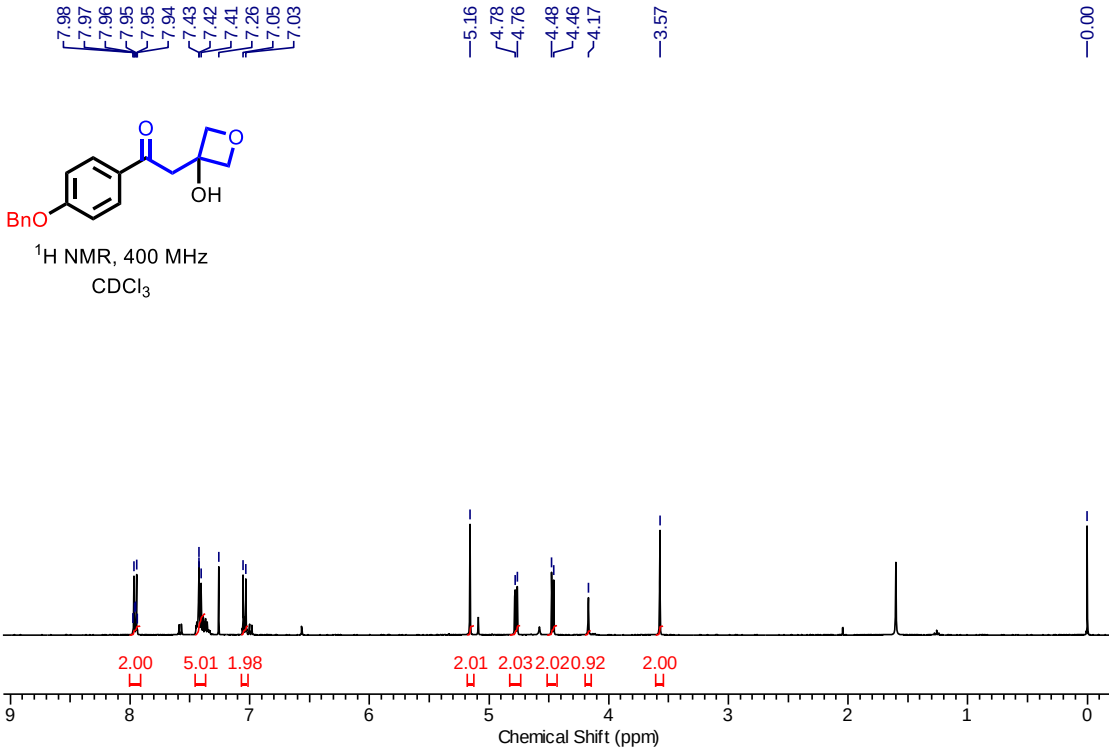
1-(4-((*Tert*-butyldimethylsilyl)oxy)phenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (**71n**):



1-(4-((*Tert*-butyldimethylsilyl)oxy)phenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (**71n**):

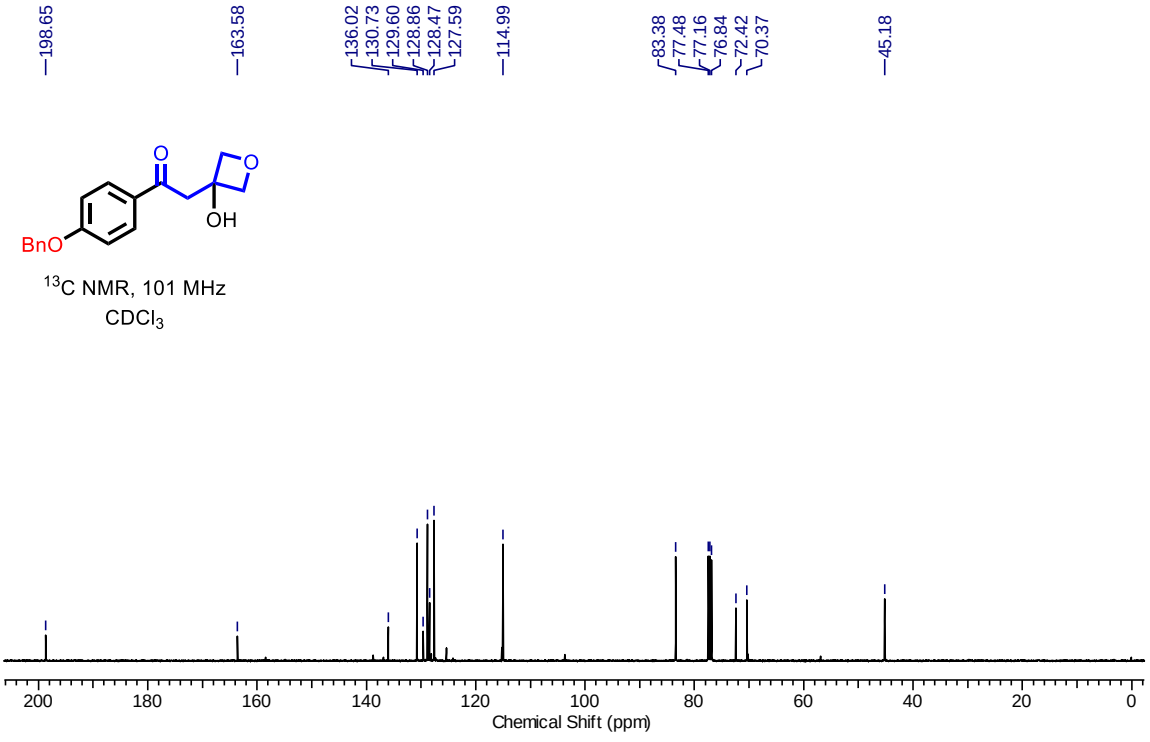


1-(4-(Benzyloxy)phenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (**71o**):



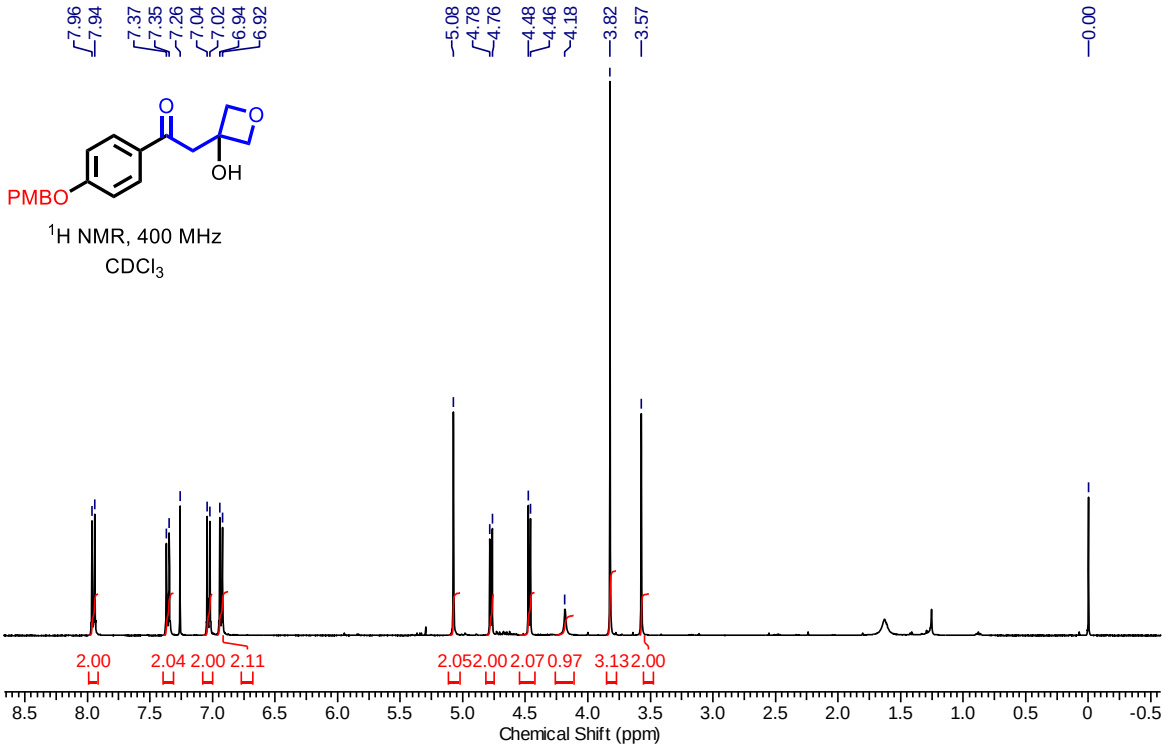
^{1}H NMR, 400 MHz
$CDCl_3$

1-(4-(Benzyloxy)phenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (**71o**):

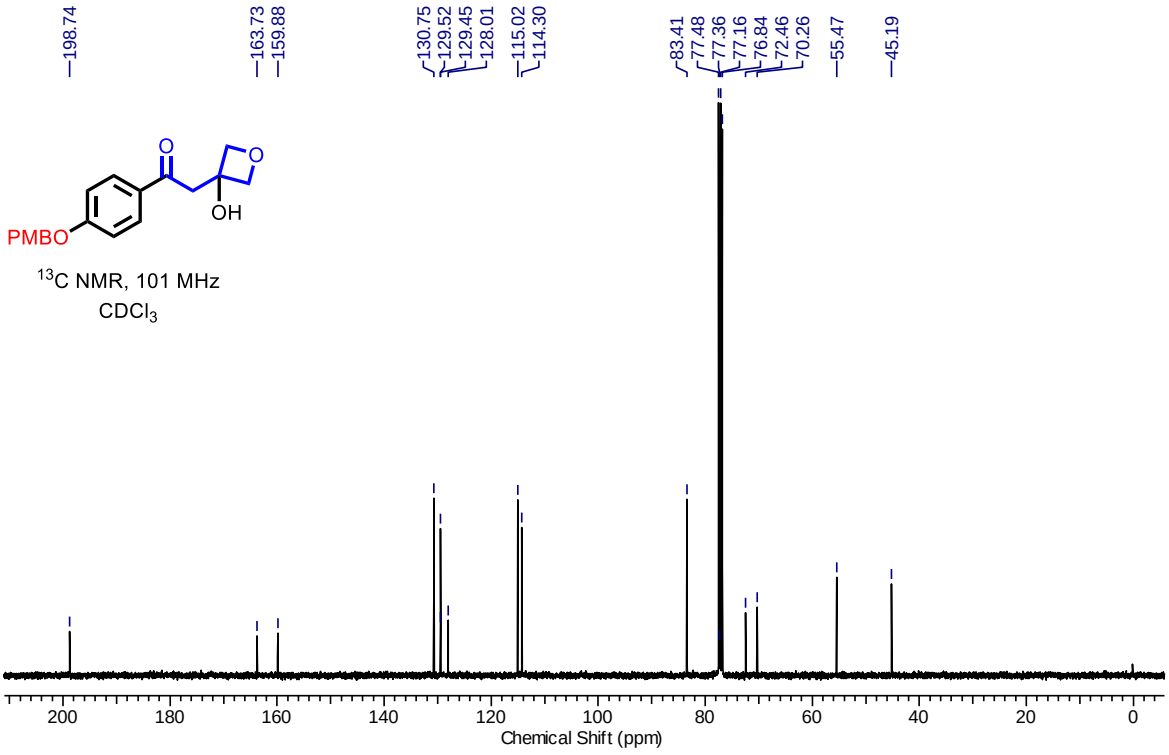


^{13}C NMR, 101 MHz
$CDCl_3$

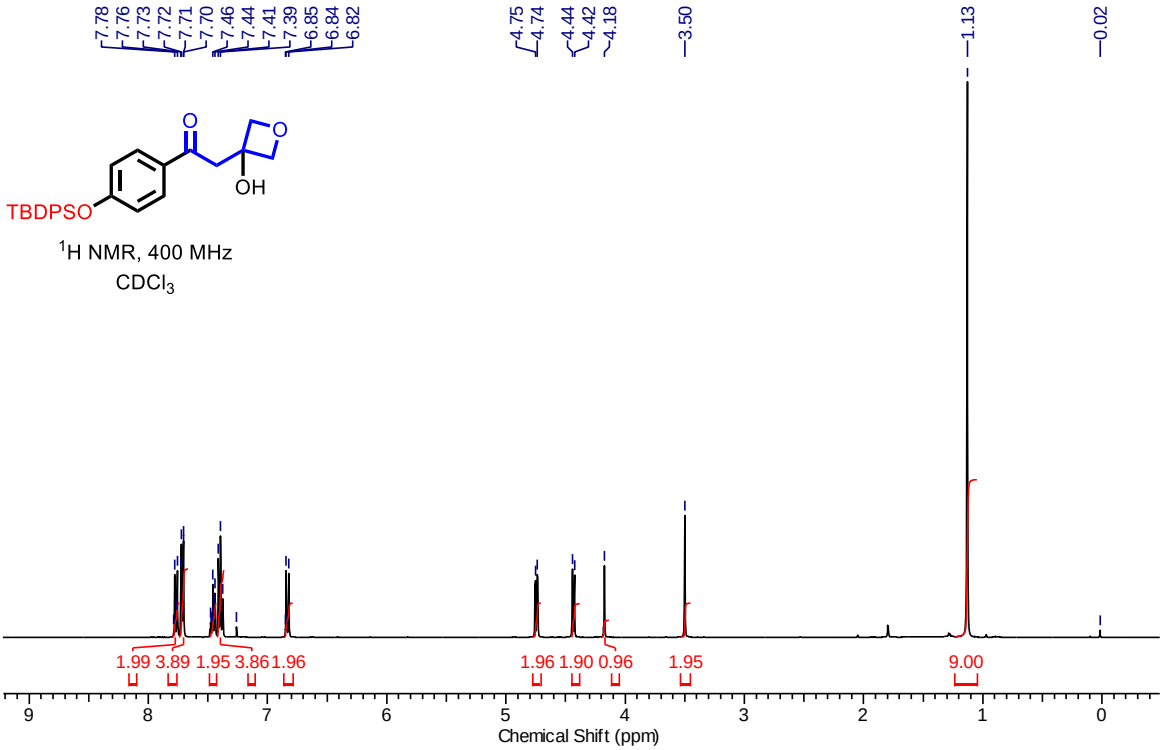
2-(3-Hydroxyoxetan-3-yl)-1-(4-((4-methoxybenzyl)oxy)phenyl)ethan-1-one (**71p**):



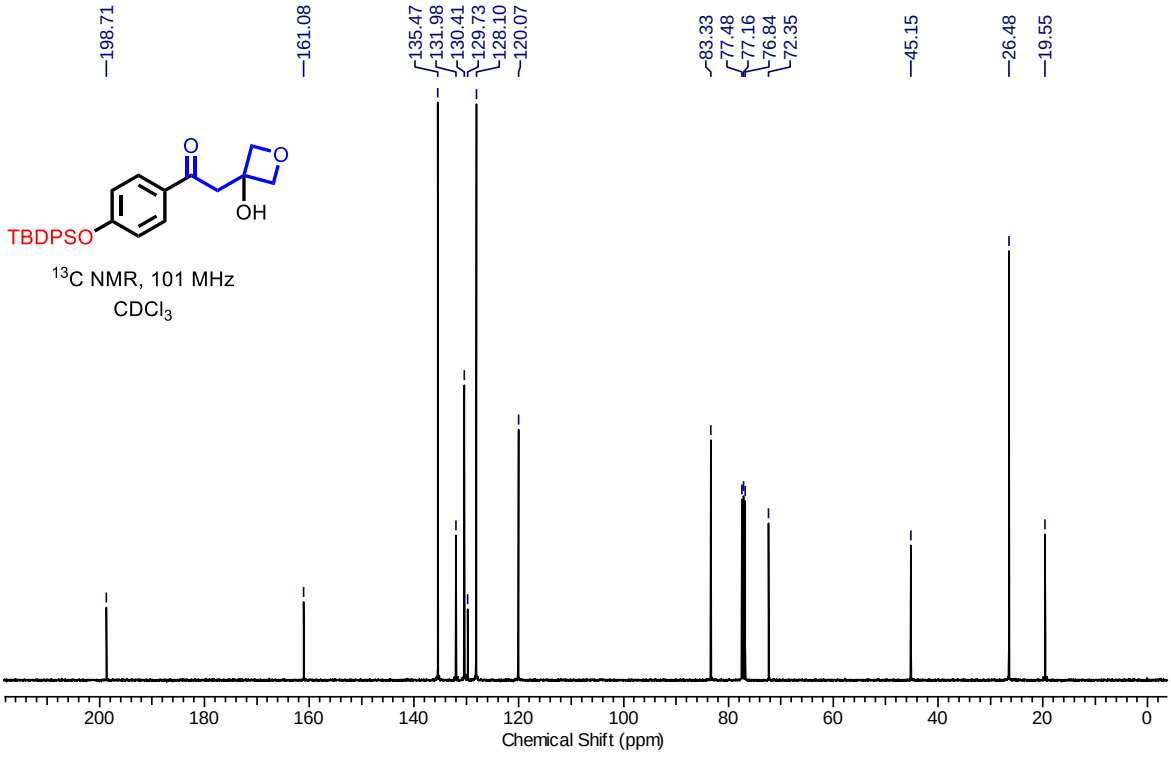
2-(3-Hydroxyoxetan-3-yl)-1-(4-((4-methoxybenzyl)oxy)phenyl)ethan-1-one (**71p**):



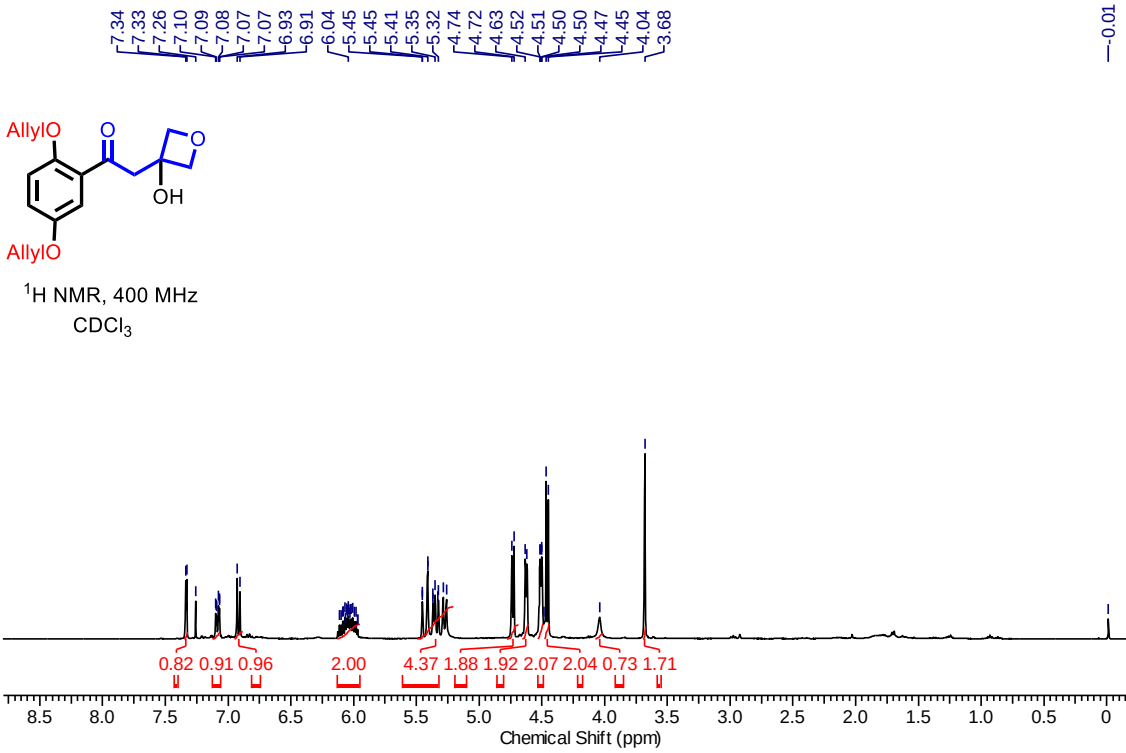
1-(4-((*Tert*-butyldiphenylsilyl)oxy)phenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (**71q**):



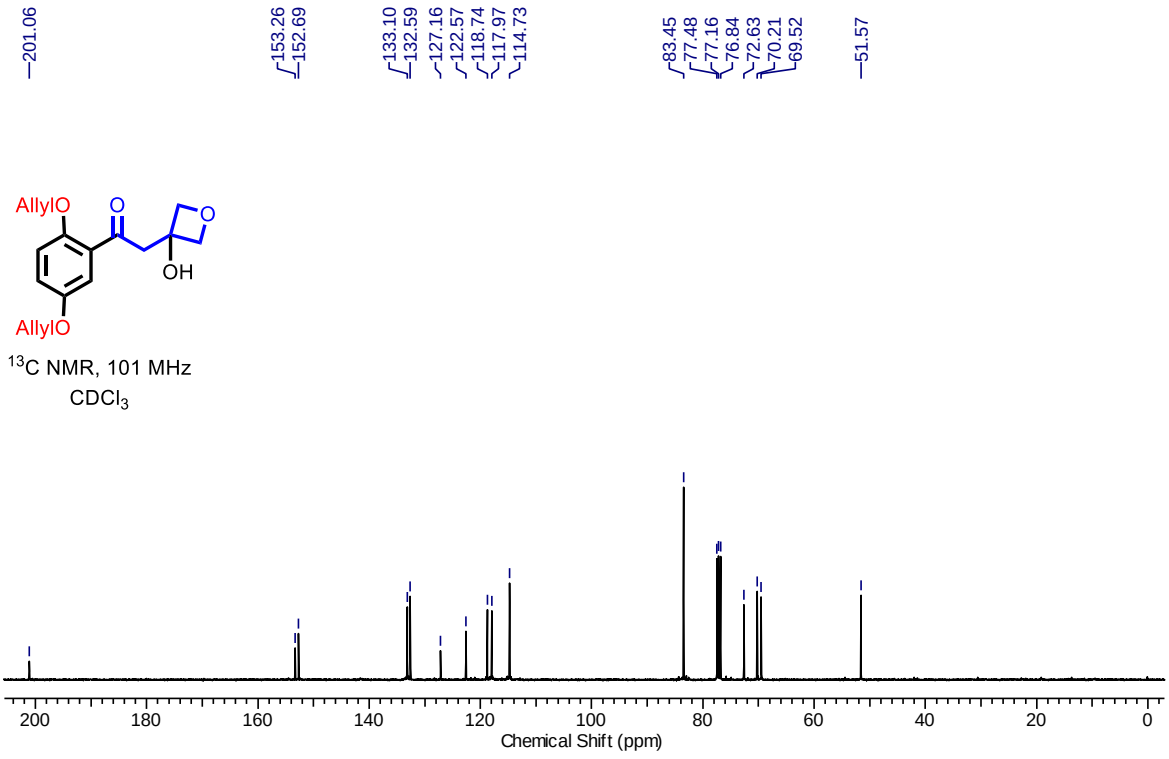
1-(4-((*Tert*-butyldiphenylsilyl)oxy)phenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (**71q**):



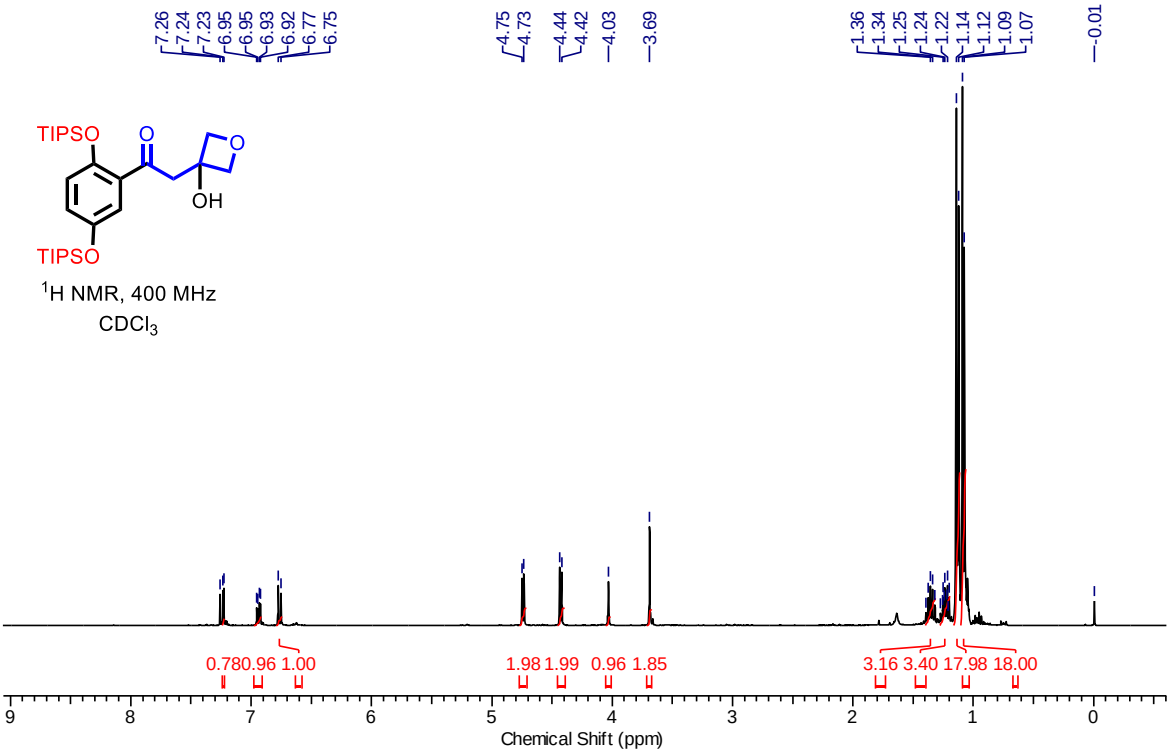
1-(2,5-Bis(allyloxy)phenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (**71r**):



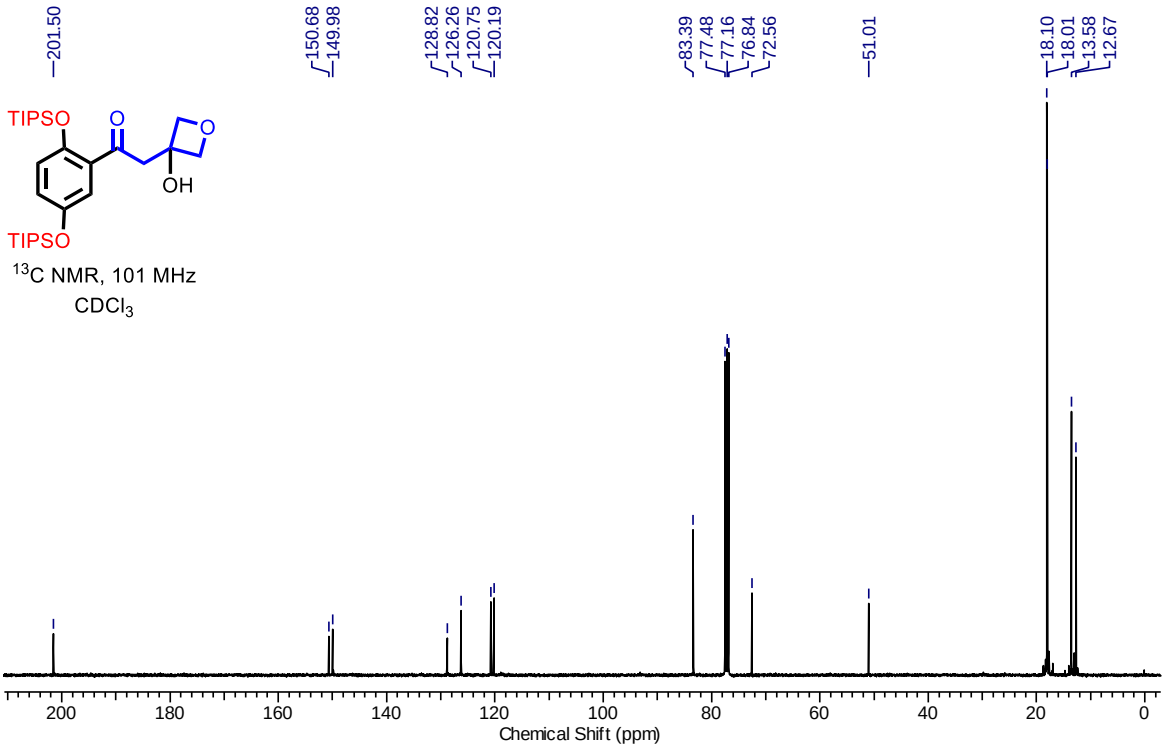
1-(2,5-Bis(allyloxy)phenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (**71r**):



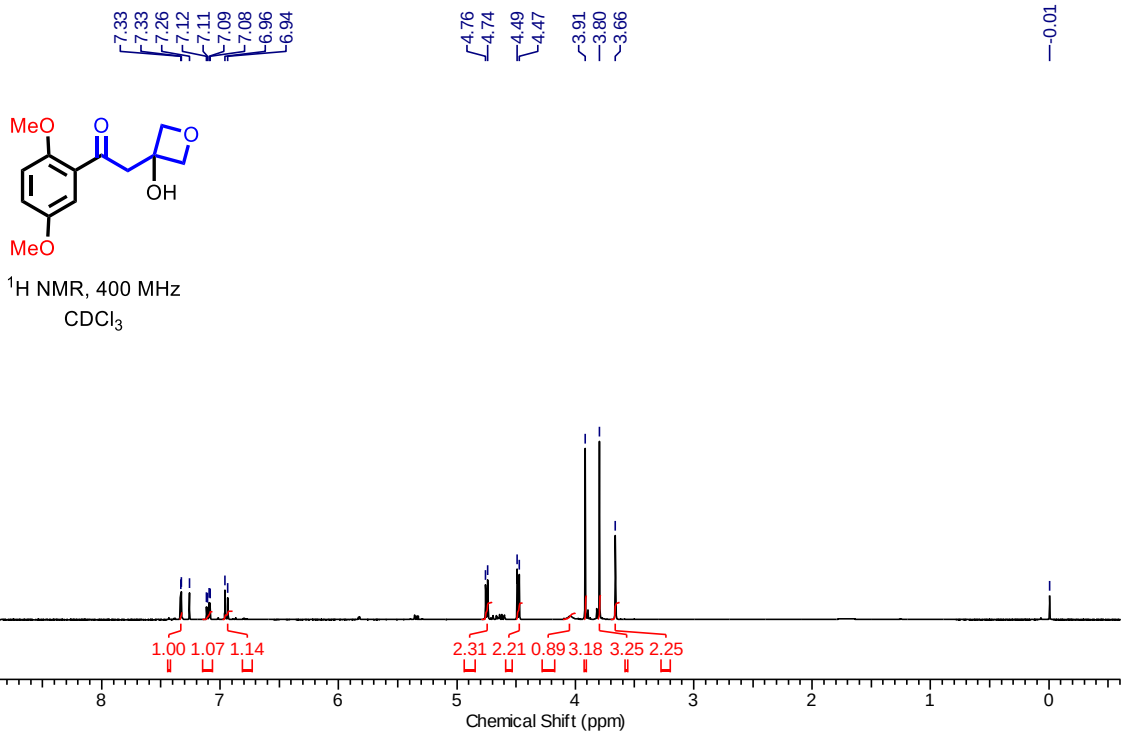
1-(2,5-Bis((triisopropylsilyl)oxy)phenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (**71s**):



1-(2,5-Bis((triisopropylsilyl)oxy)phenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (**71s**):

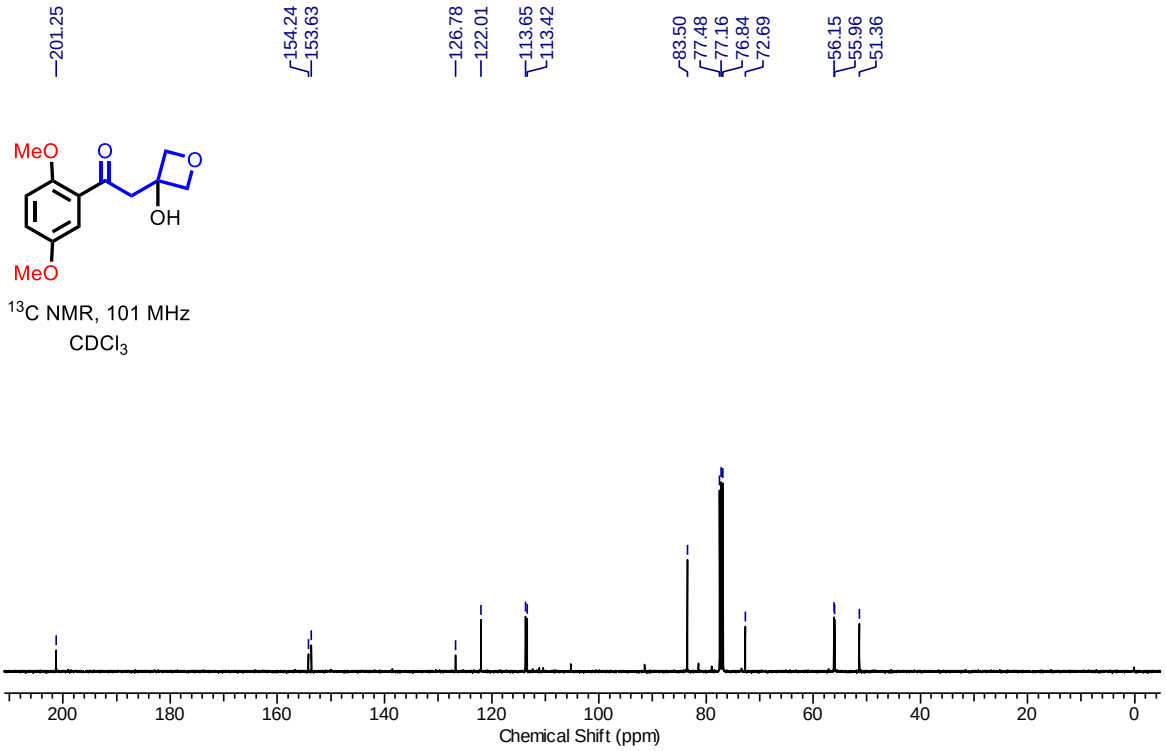


1-(2,5-Dimethoxyphenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (**71t**):



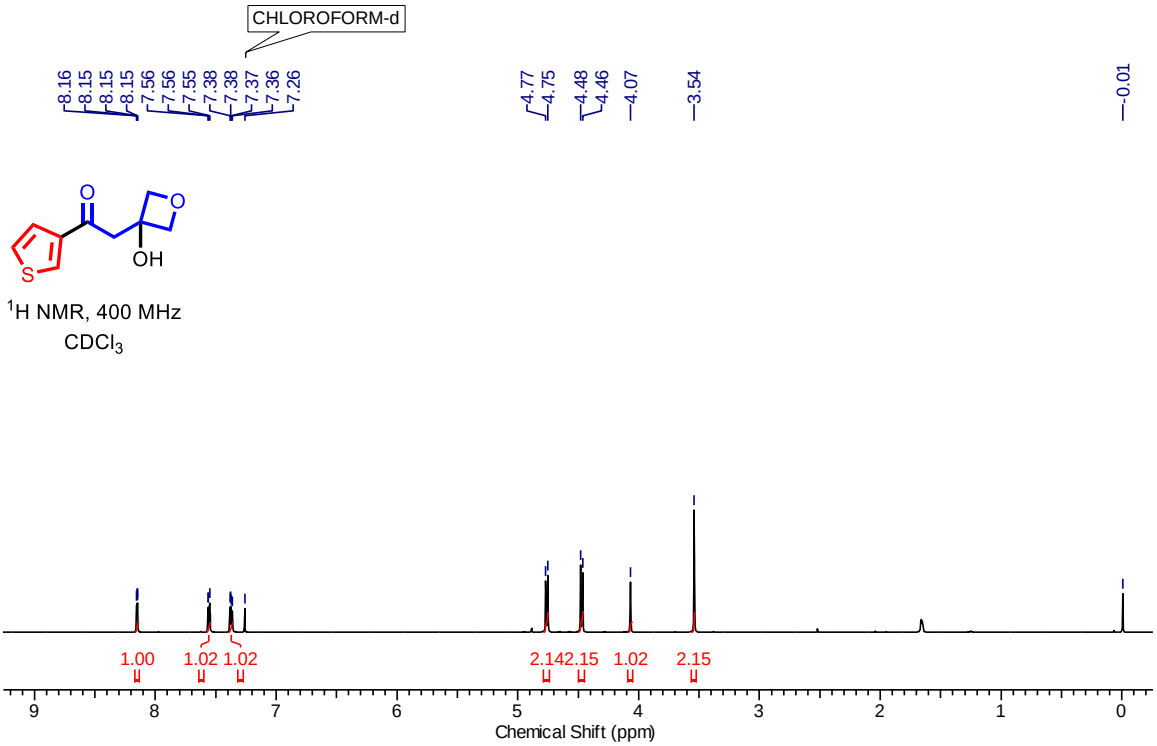
^{1}H NMR, 400 MHz
$CDCl_3$

1-(2,5-Dimethoxyphenyl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (**71t**):

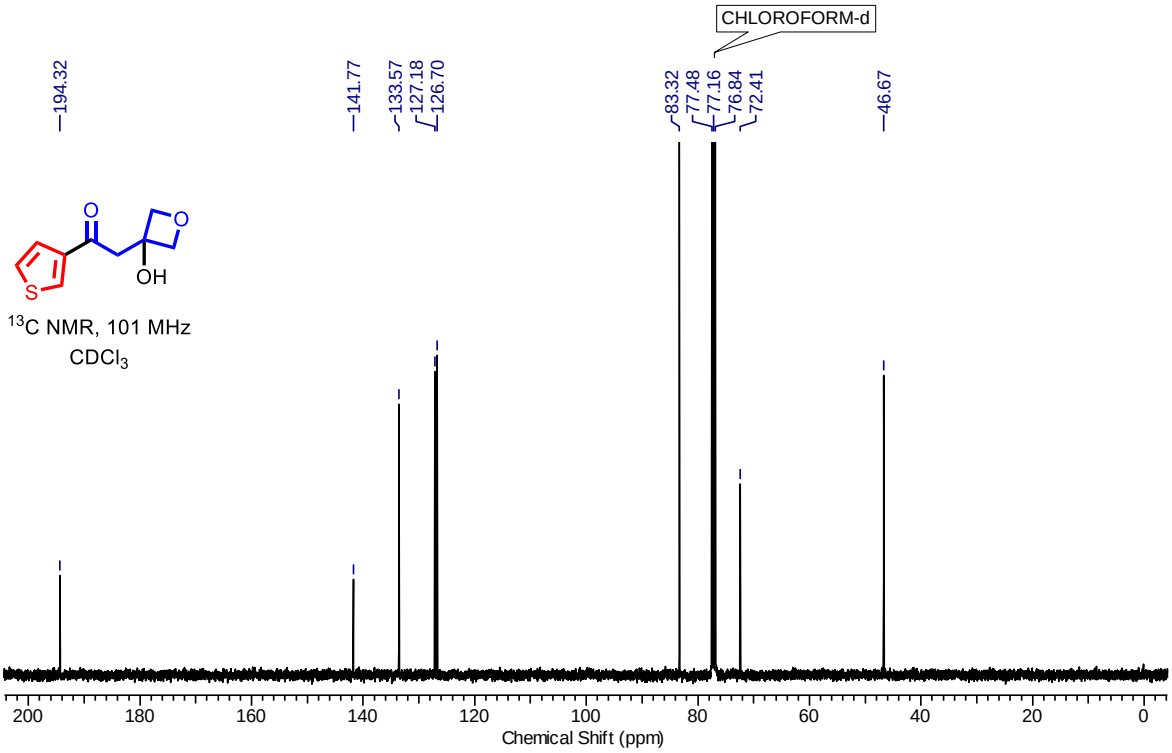


^{13}C NMR, 101 MHz
$CDCl_3$

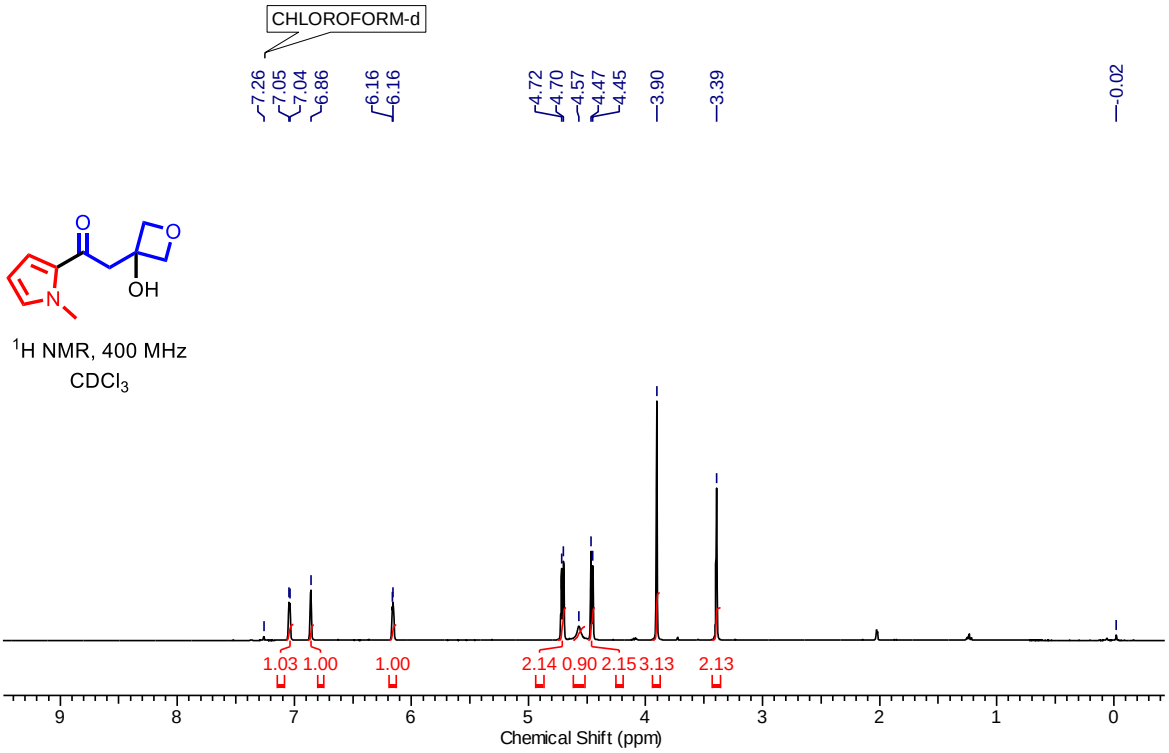
2-(3-Hydroxyoxetan-3-yl)-1-(thiophen-3-yl)ethan-1-one (**71u**):



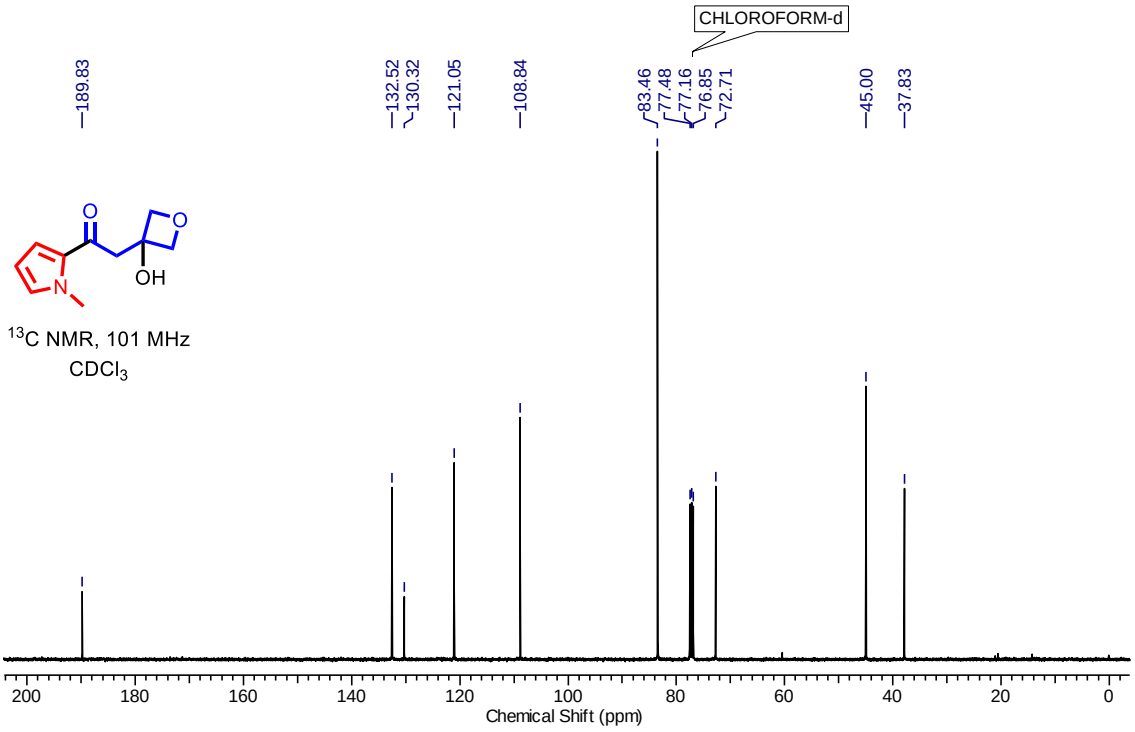
2-(3-Hydroxyoxetan-3-yl)-1-(thiophen-3-yl)ethan-1-one (**71u**):



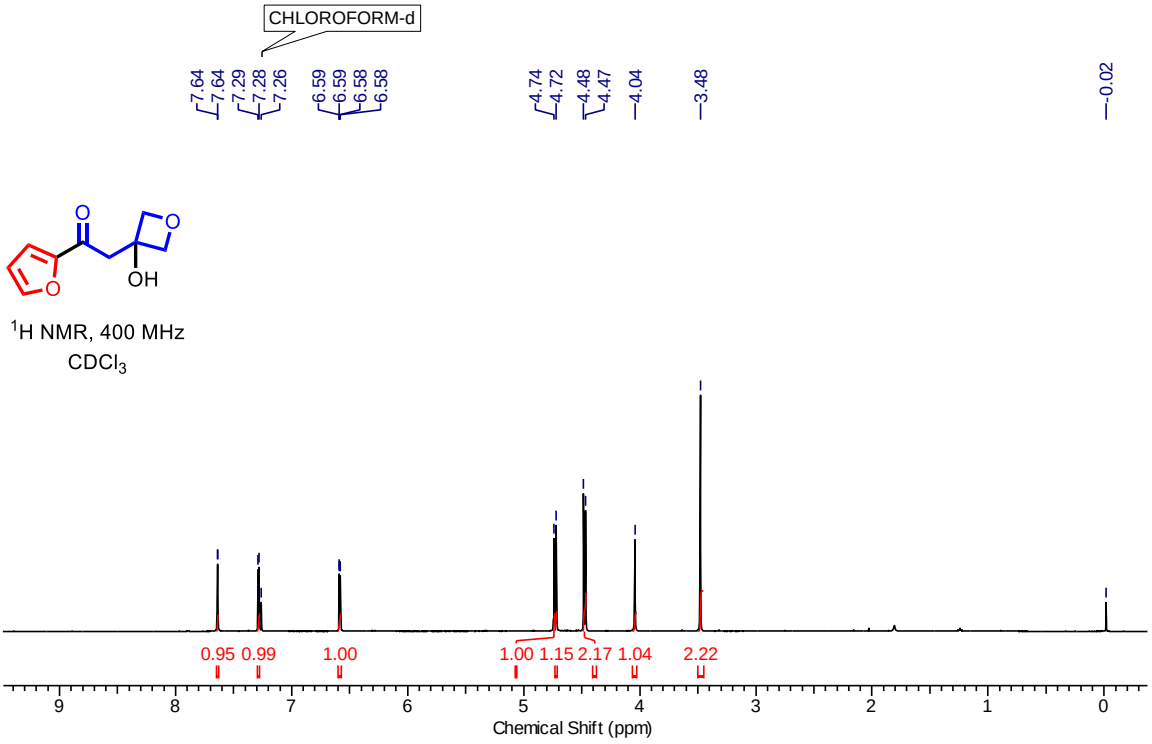
2-(3-Hydroxyoxetan-3-yl)-1-(1-methyl-1H-pyrrol-2-yl)ethan-1-one (**71v**):



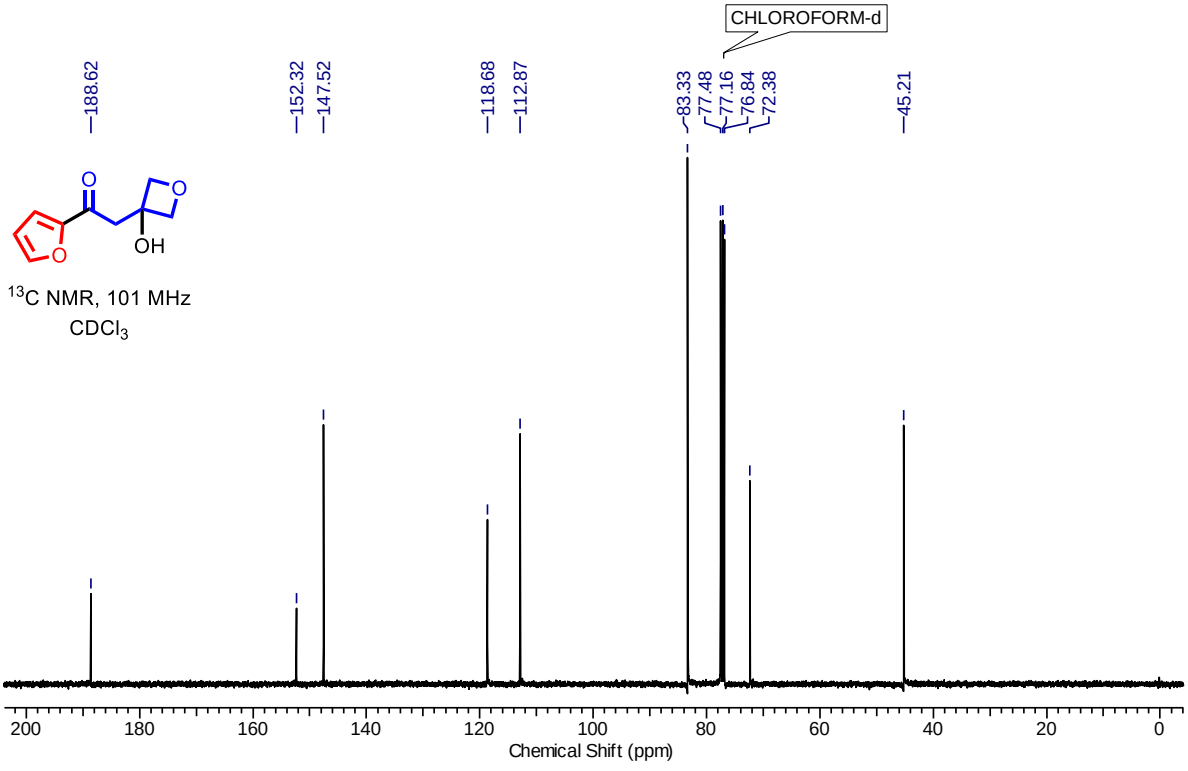
2-(3-Hydroxyoxetan-3-yl)-1-(1-methyl-1H-pyrrol-2-yl)ethan-1-one (**71v**):



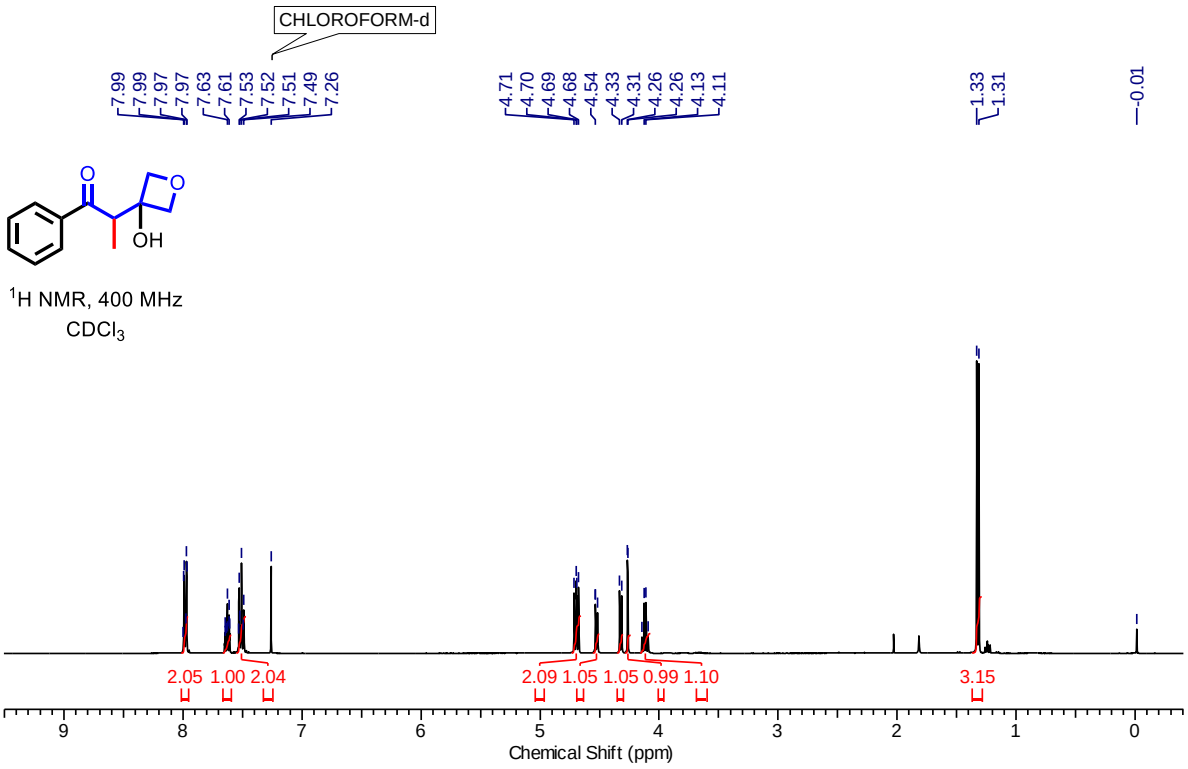
1-(Furan-2-yl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (**71w**):



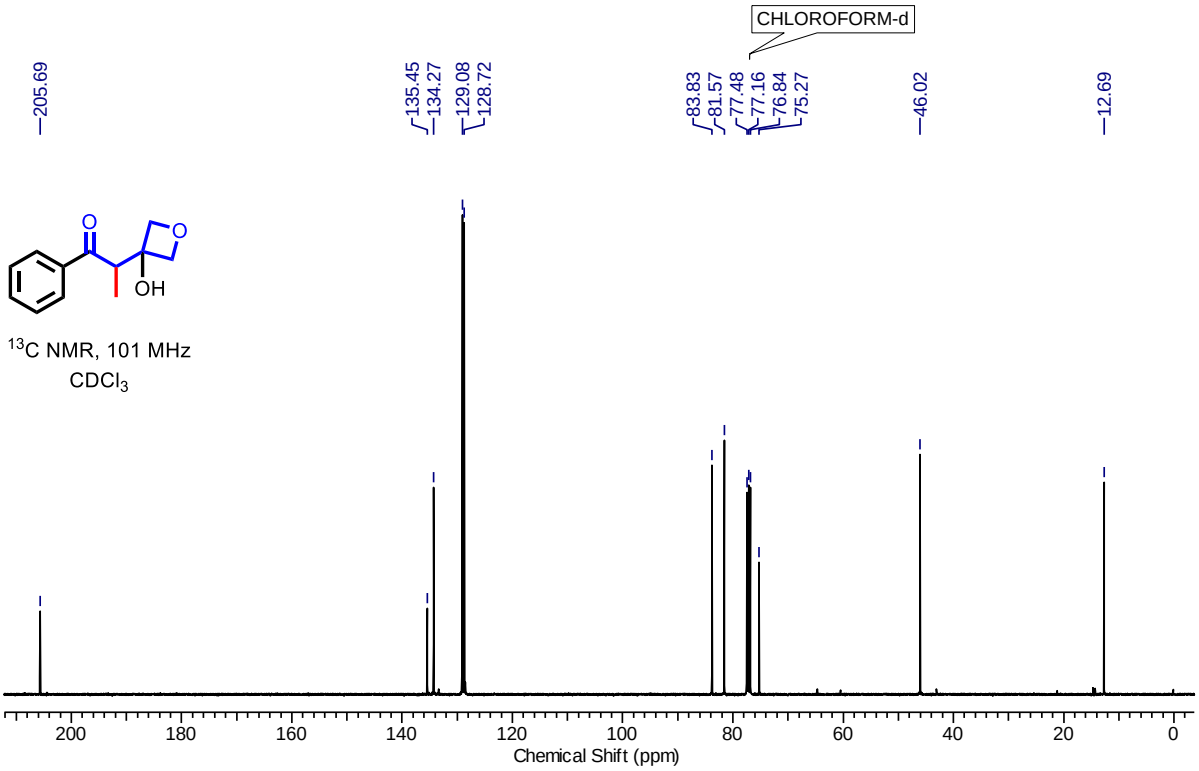
1-(Furan-2-yl)-2-(3-hydroxyoxetan-3-yl)ethan-1-one (**71w**):



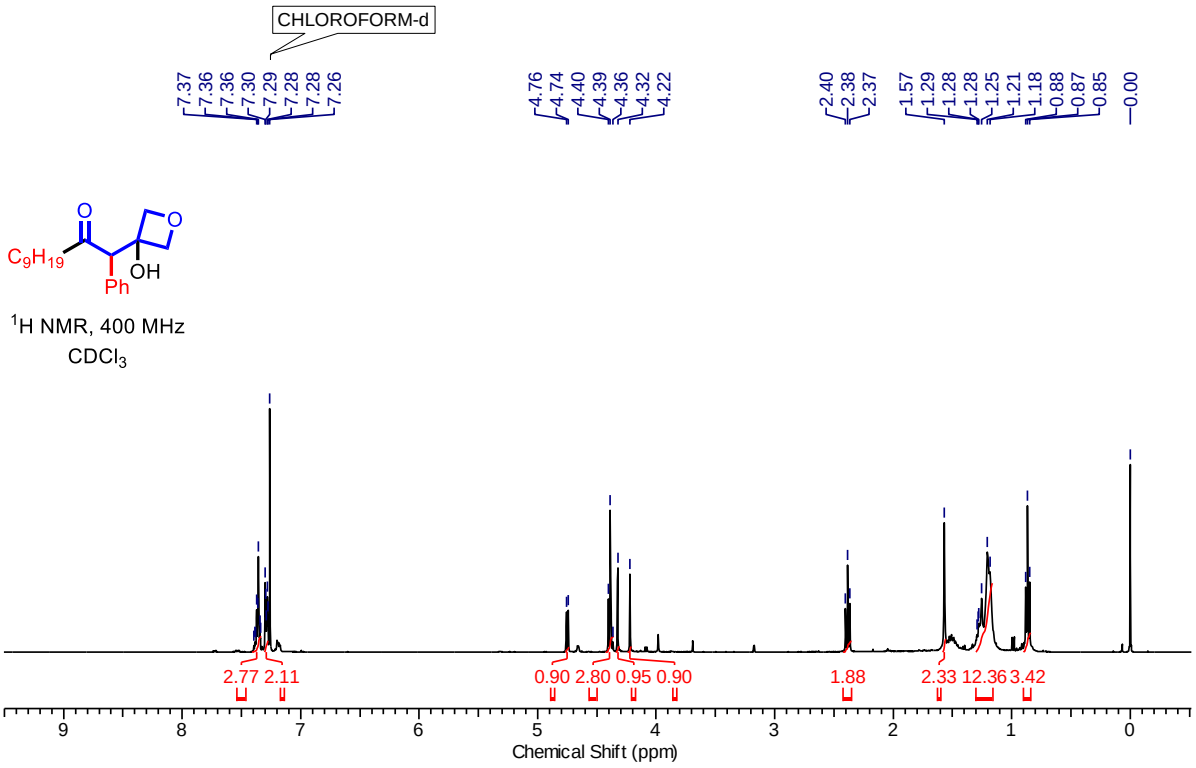
2-(3-Hydroxyoxetan-3-yl)-1-phenylpropan-1-one (**71x**):



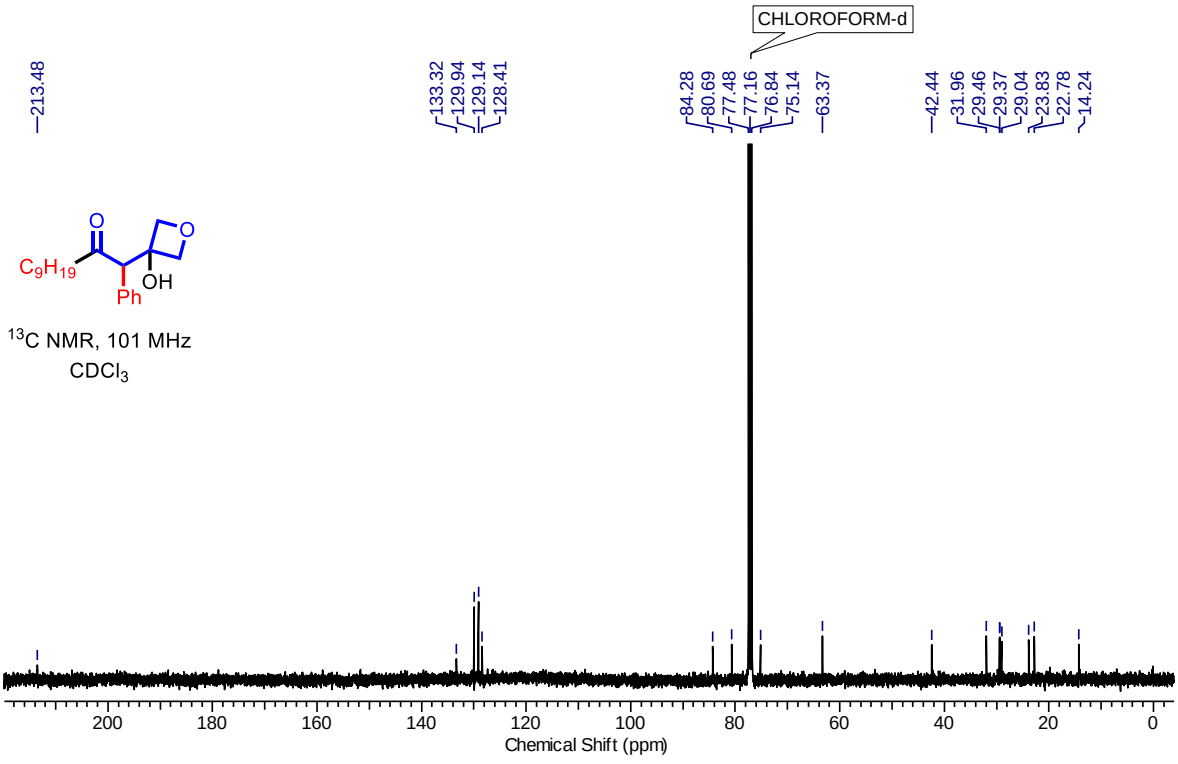
2-(3-Hydroxyoxetan-3-yl)-1-phenylpropan-1-one (**71x**):



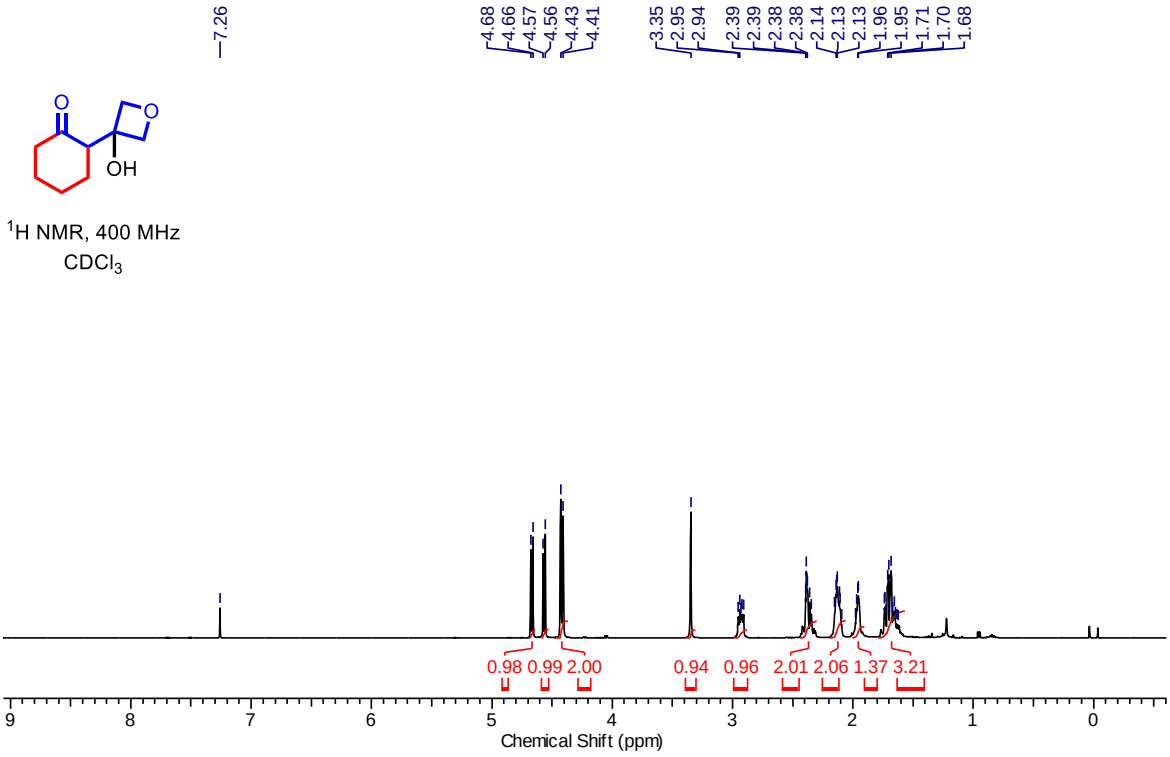
1-(3-Hydroxyoxetan-3-yl)-1-phenylundecan-2-one (**71y**):



1-(3-Hydroxyoxetan-3-yl)-1-phenylundecan-2-one (**71y**):

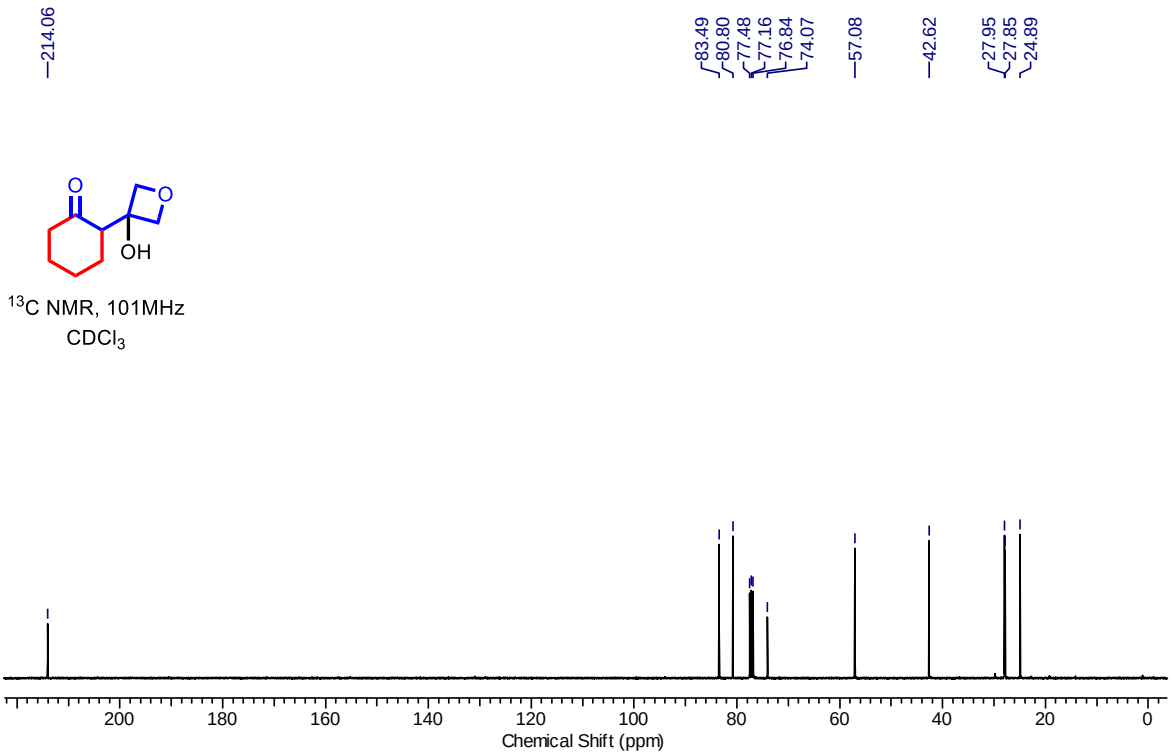


2-(3-Hydroxyoxetan-3-yl)cyclohexan-1-one (**71z**):



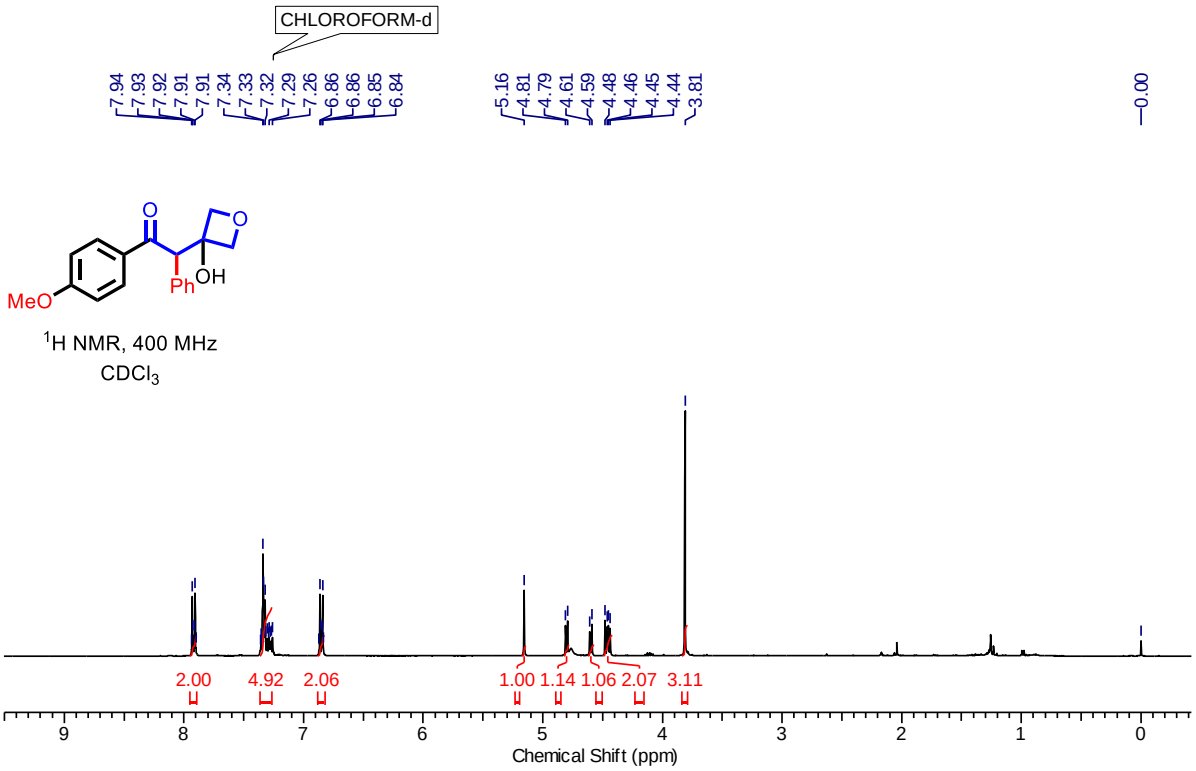
^{1}H NMR, 400 MHz
$CDCl_3$

2-(3-Hydroxyoxetan-3-yl)cyclohexan-1-one (**71z**):

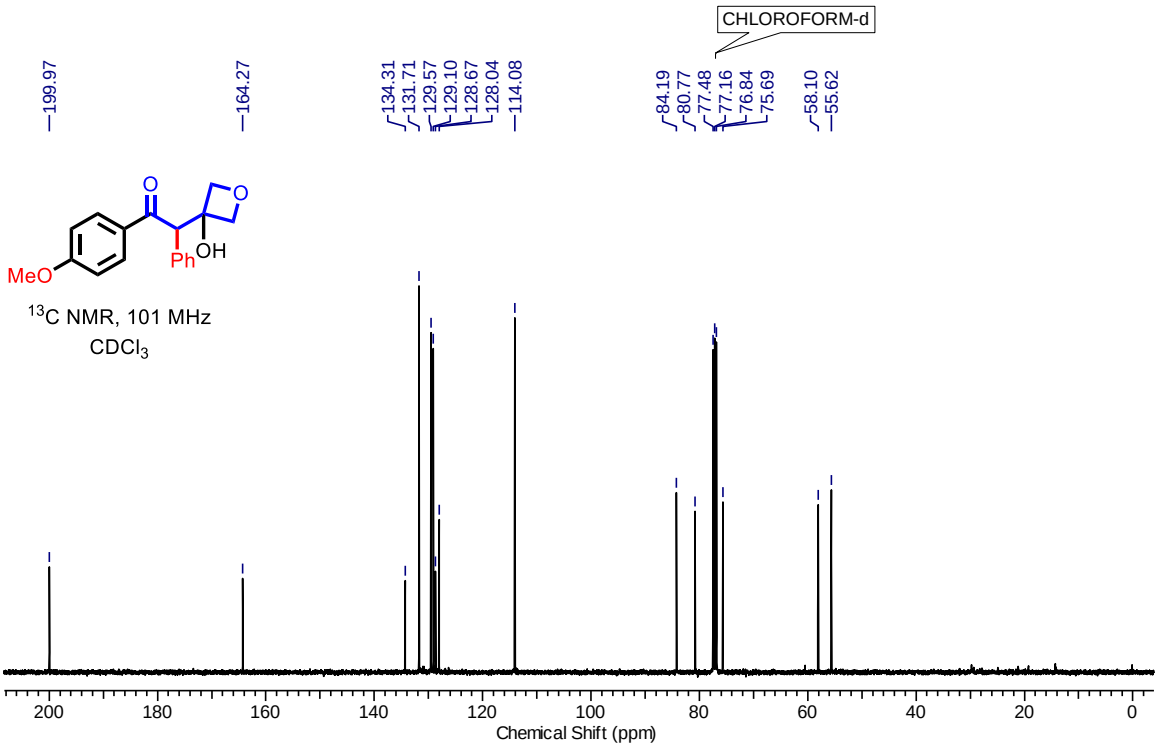


^{13}C NMR, 101MHz
$CDCl_3$

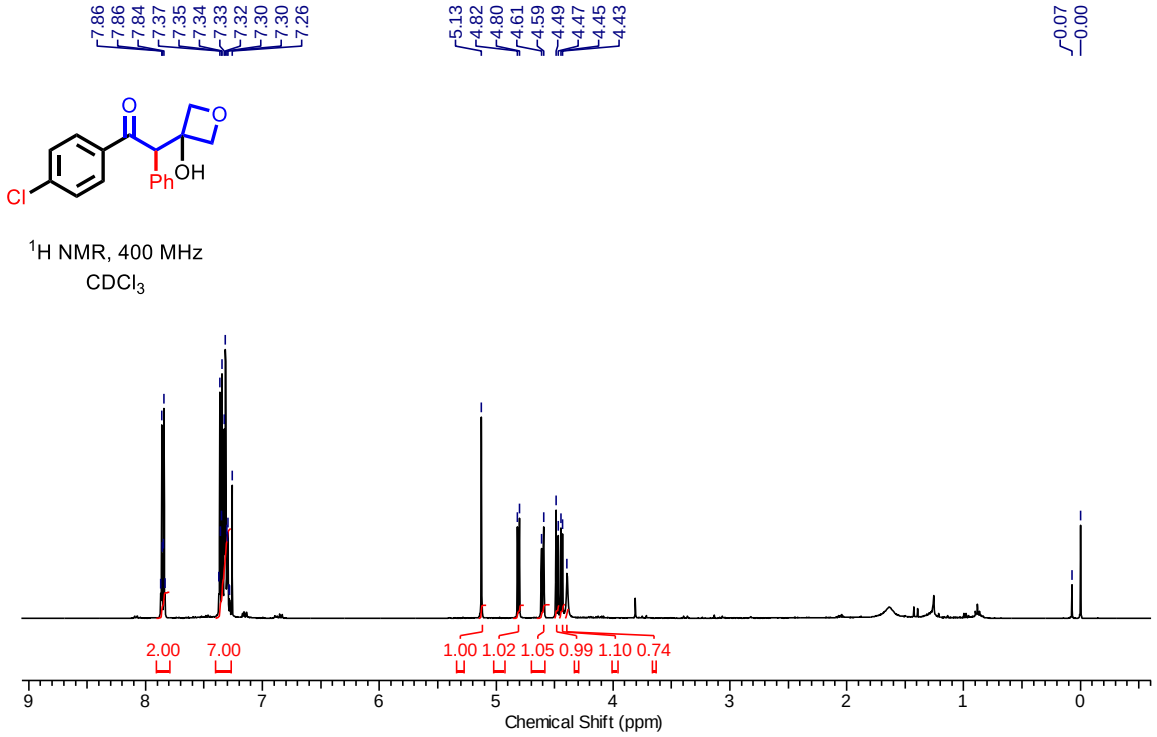
2-(3-Hydroxyoxetan-3-yl)-1-(4-methoxyphenyl)-2-phenylethan-1-one (**71aa**):



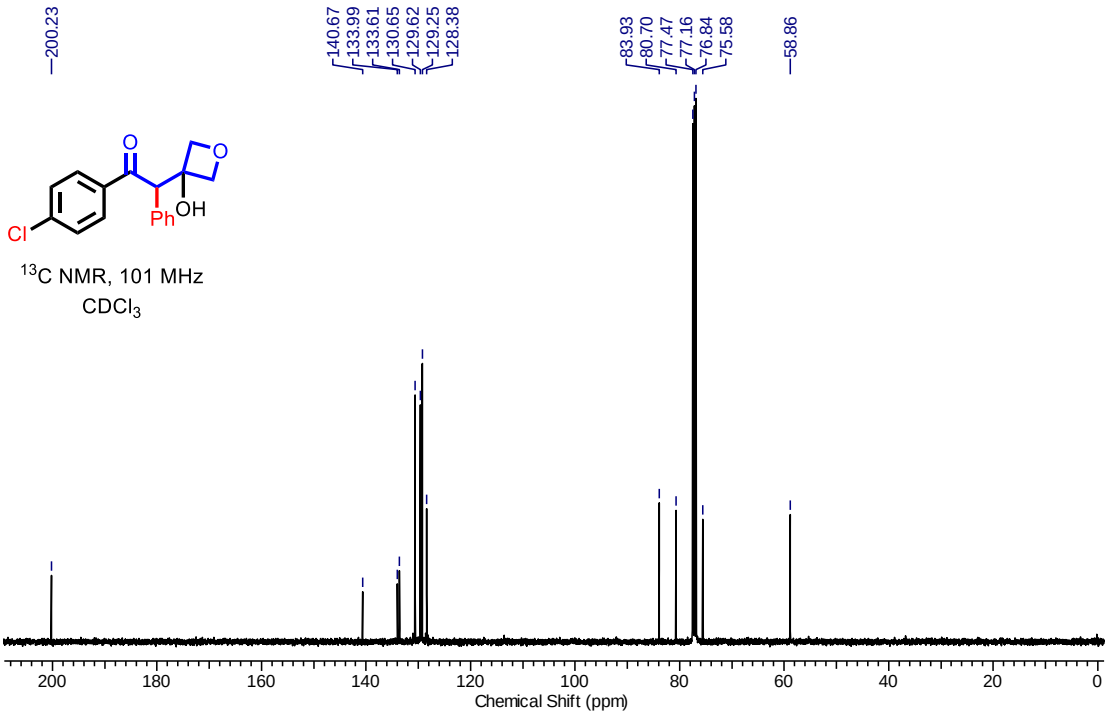
2-(3-Hydroxyoxetan-3-yl)-1-(4-methoxyphenyl)-2-phenylethan-1-one (**71aa**):



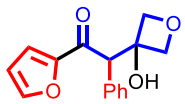
1-(4-Chlorophenyl)-2-(3-hydroxyoxetan-3-yl)-2-phenylethan-1-one (**71ab**):



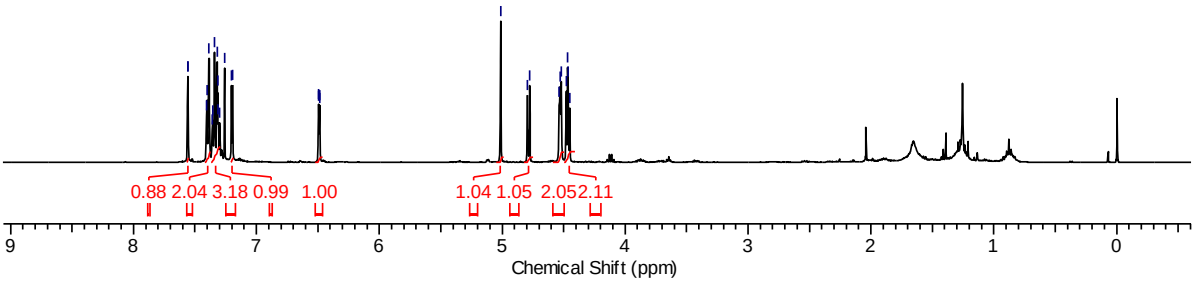
1-(4-Chlorophenyl)-2-(3-hydroxyoxetan-3-yl)-2-phenylethan-1-one (**71ab**):



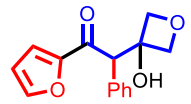
1-(Furan-2-yl)-2-(3-hydroxyoxetan-3-yl)-2-phenylethan-1-one (**71ac**):



^{1}H NMR, 400 MHz
$CDCl_3$

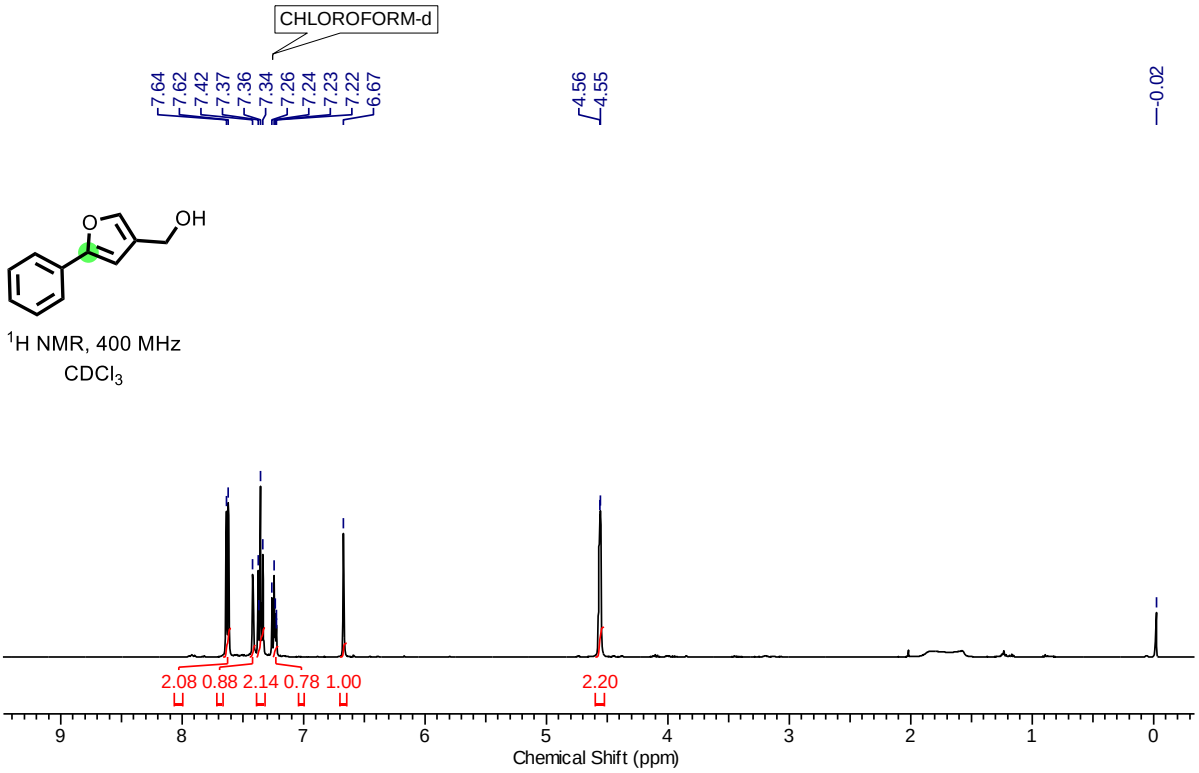


1-(Furan-2-yl)-2-(3-hydroxyoxetan-3-yl)-2-phenylethan-1-one (**71ac**):

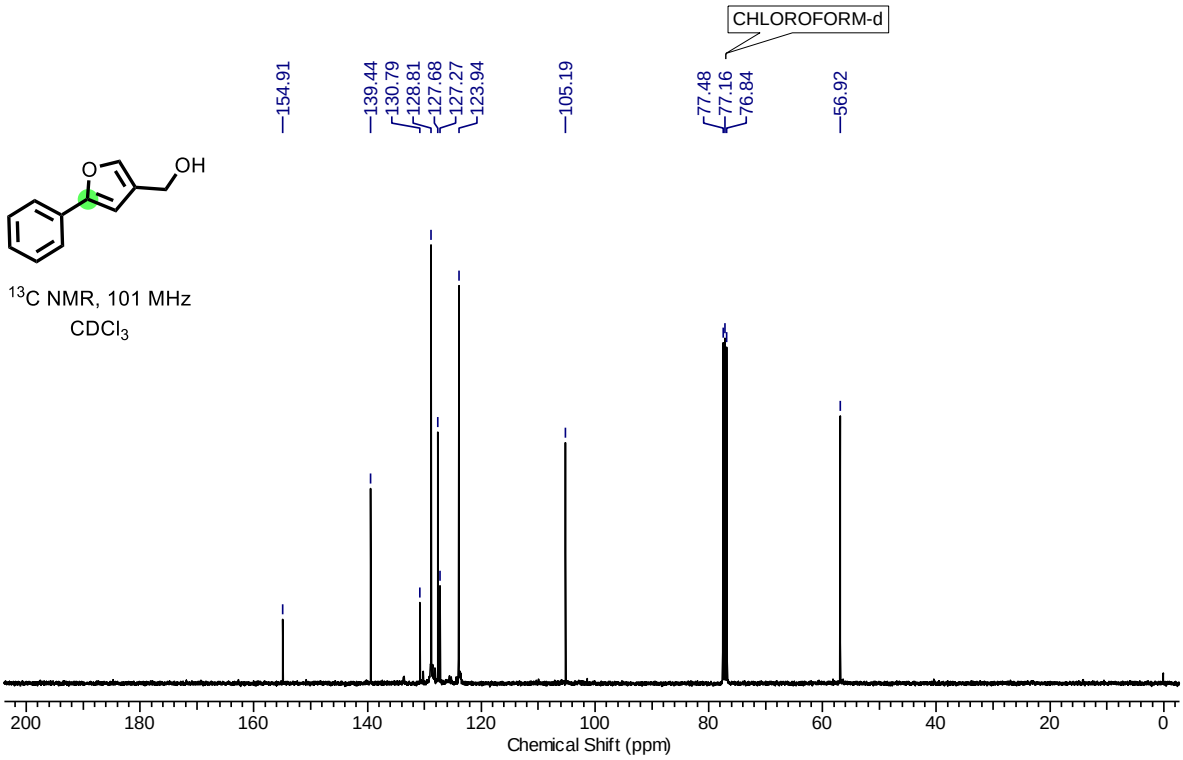


^{13}C NMR, 101 MHz
$CDCl_3$

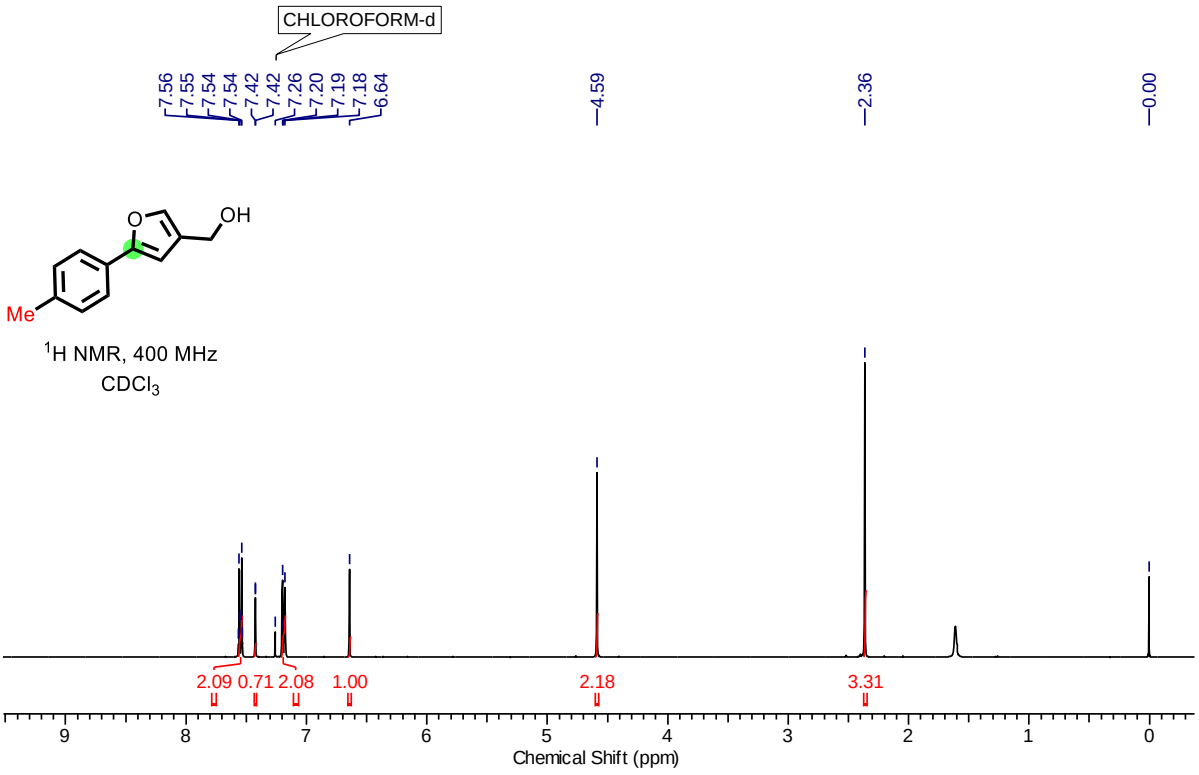
(5-Phenylfuran-3-yl)methanol (**72a**):



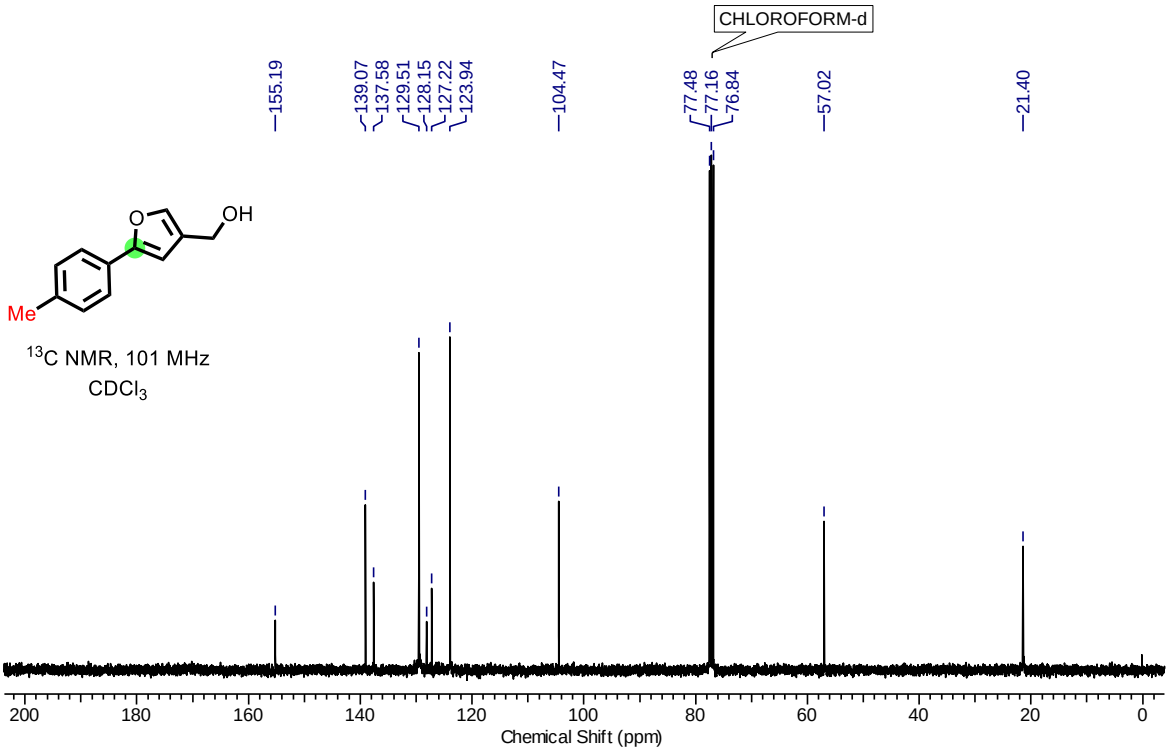
(5-Phenylfuran-3-yl)methanol (**72a**):



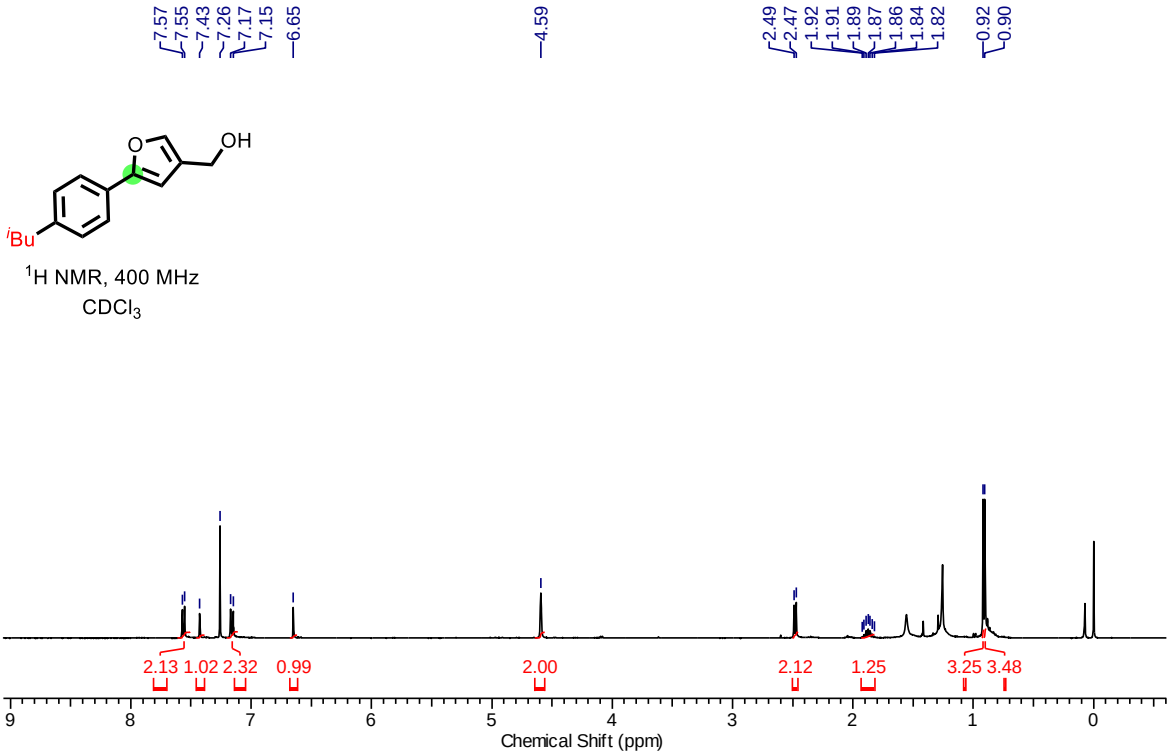
(5-(*p*-Tolyl)furan-3-yl)methanol (**72b**):



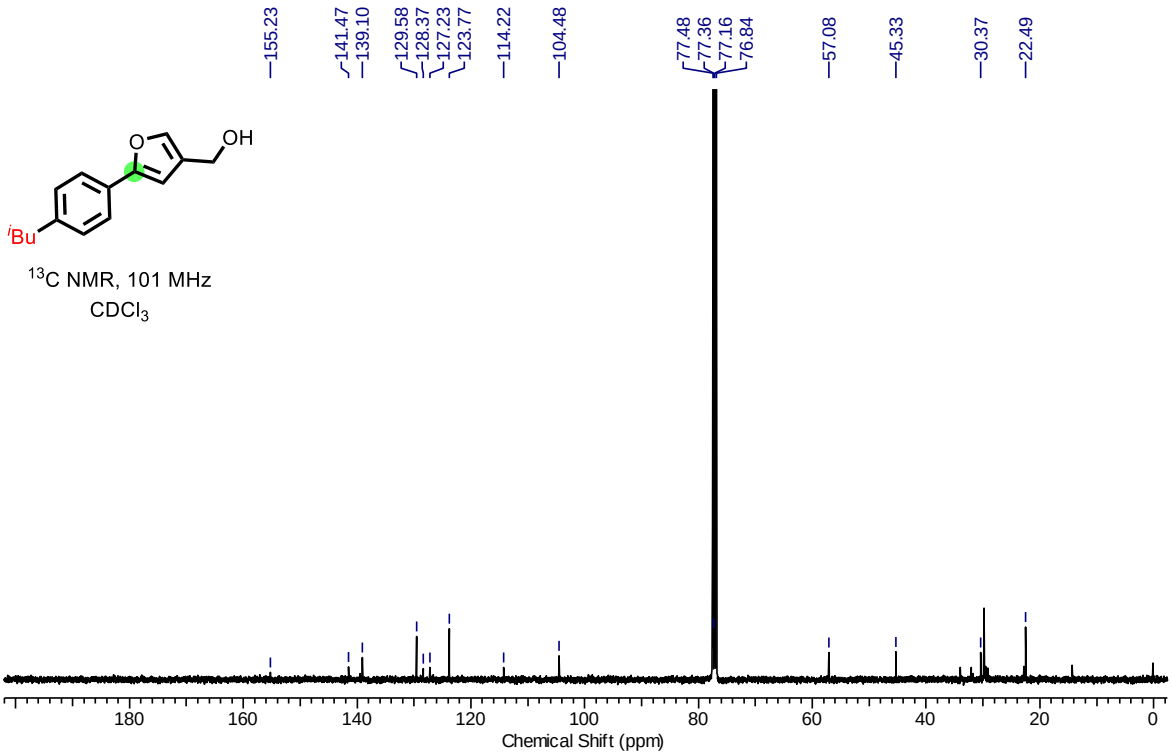
(5-(*p*-Tolyl)furan-3-yl)methanol (**72b**):



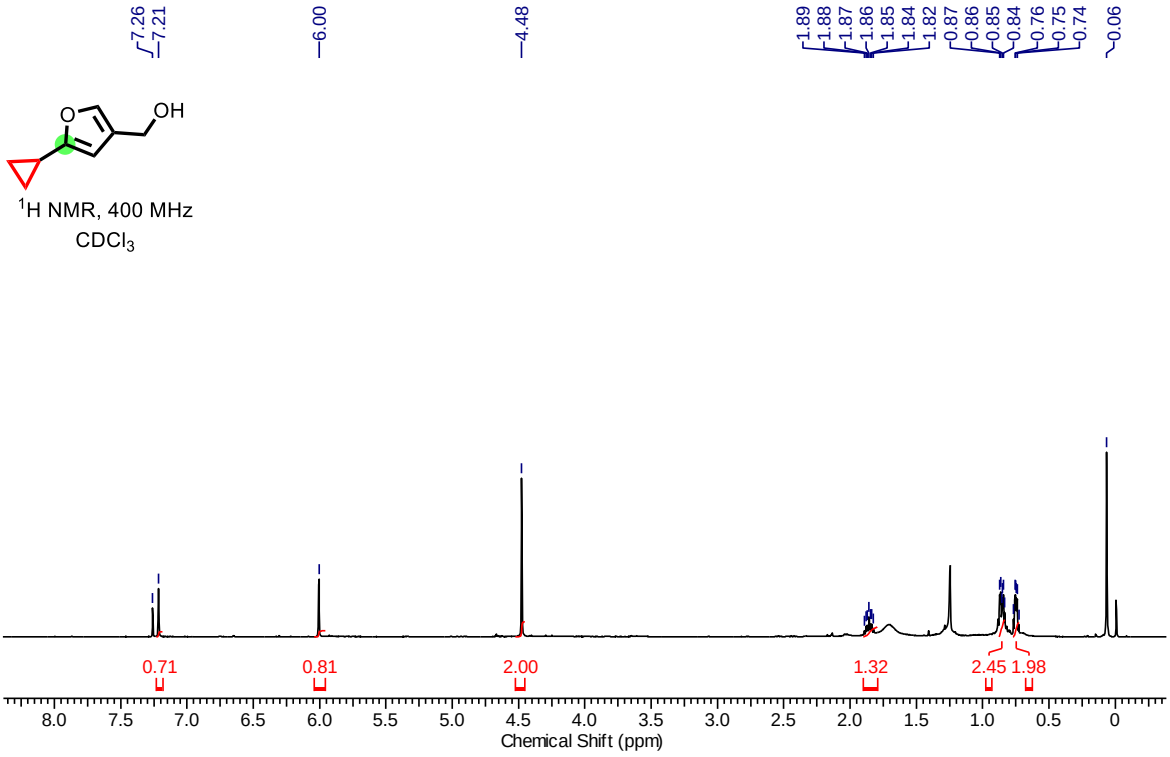
(5-(4-Isobutylphenyl)furan-3-yl)methanol (**72c**):



(5-(4-Isobutylphenyl)furan-3-yl)methanol (**72c**):

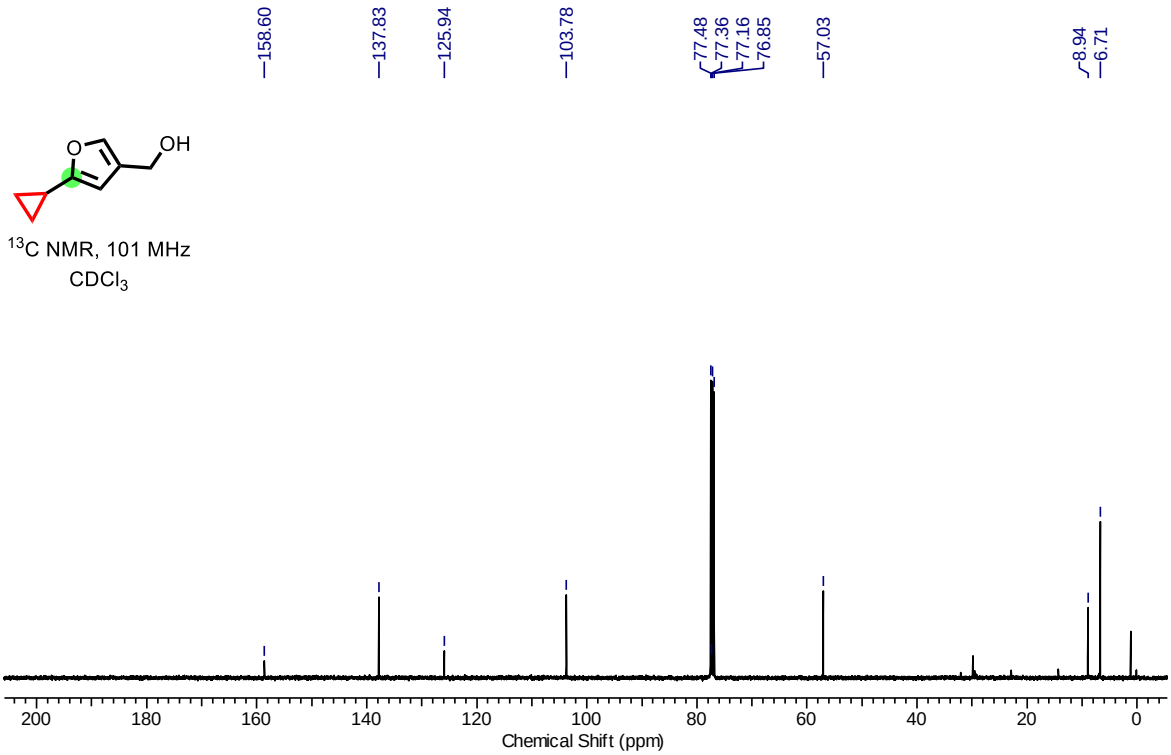


(5-Cyclopropylfuran-3-yl)methanol (**72d**):



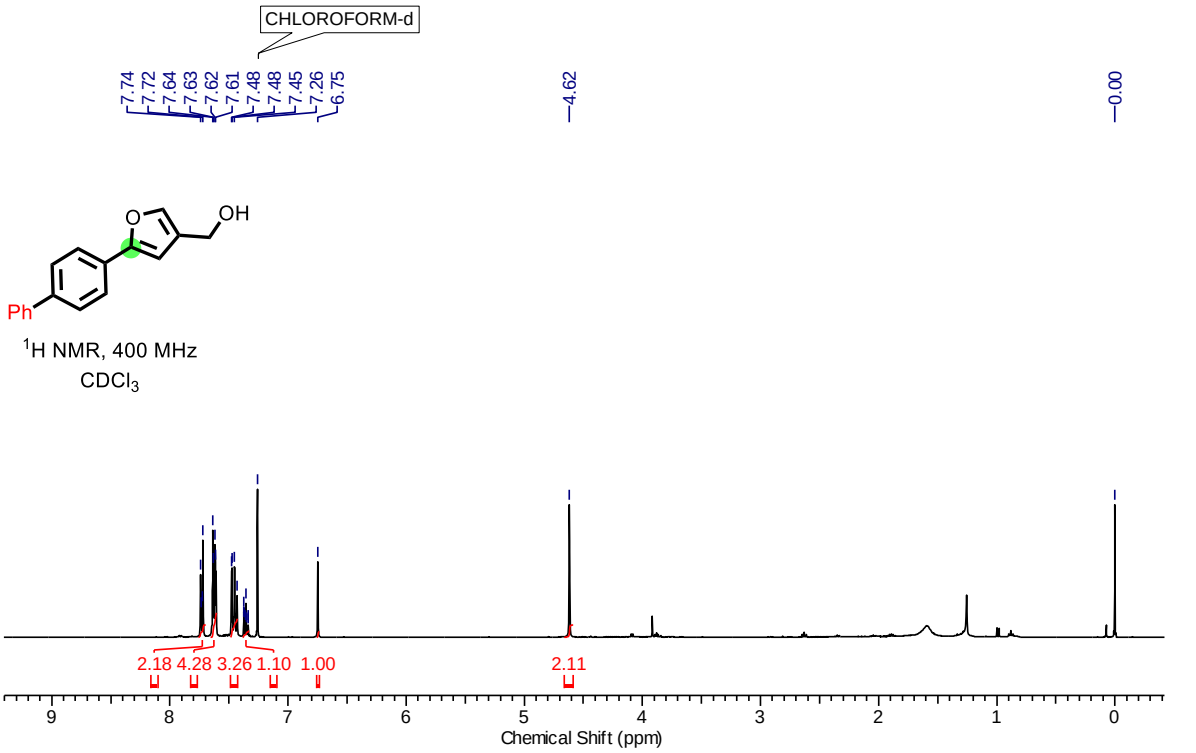
^{1}H NMR, 400 MHz
$CDCl_3$

(5-Cyclopropylfuran-3-yl)methanol (**72d**):

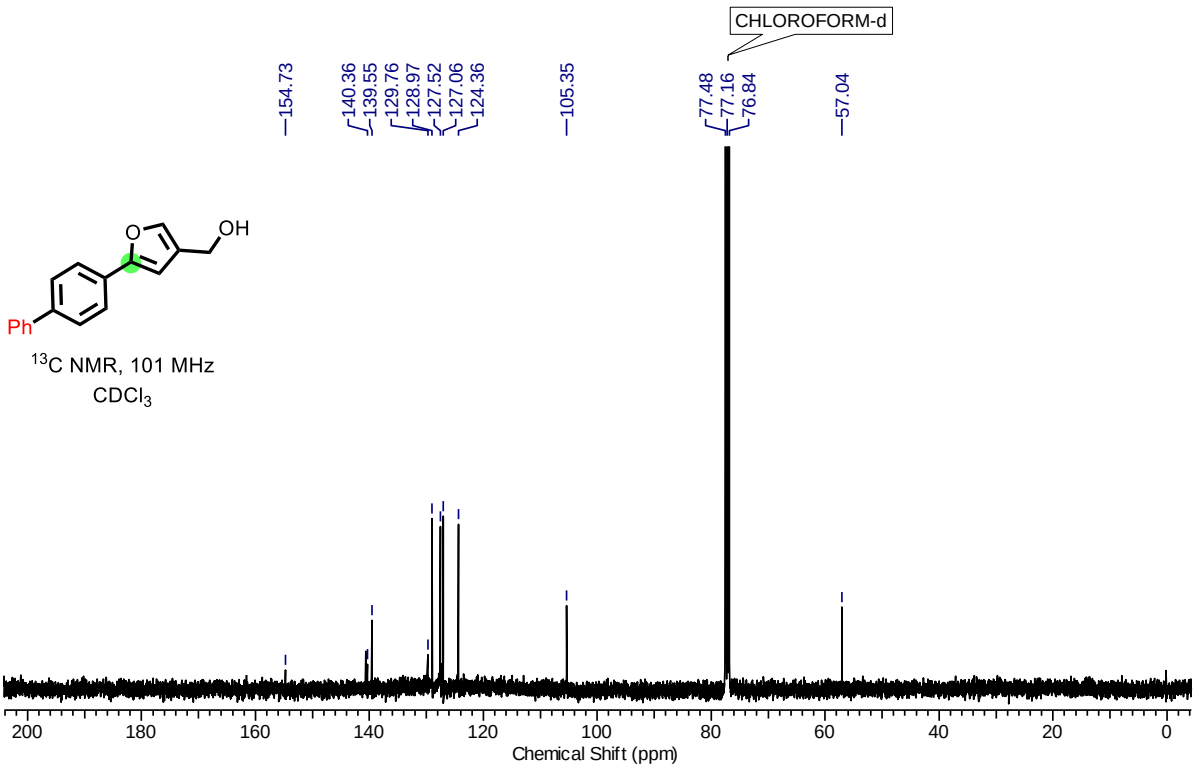


^{13}C NMR, 101 MHz
$CDCl_3$

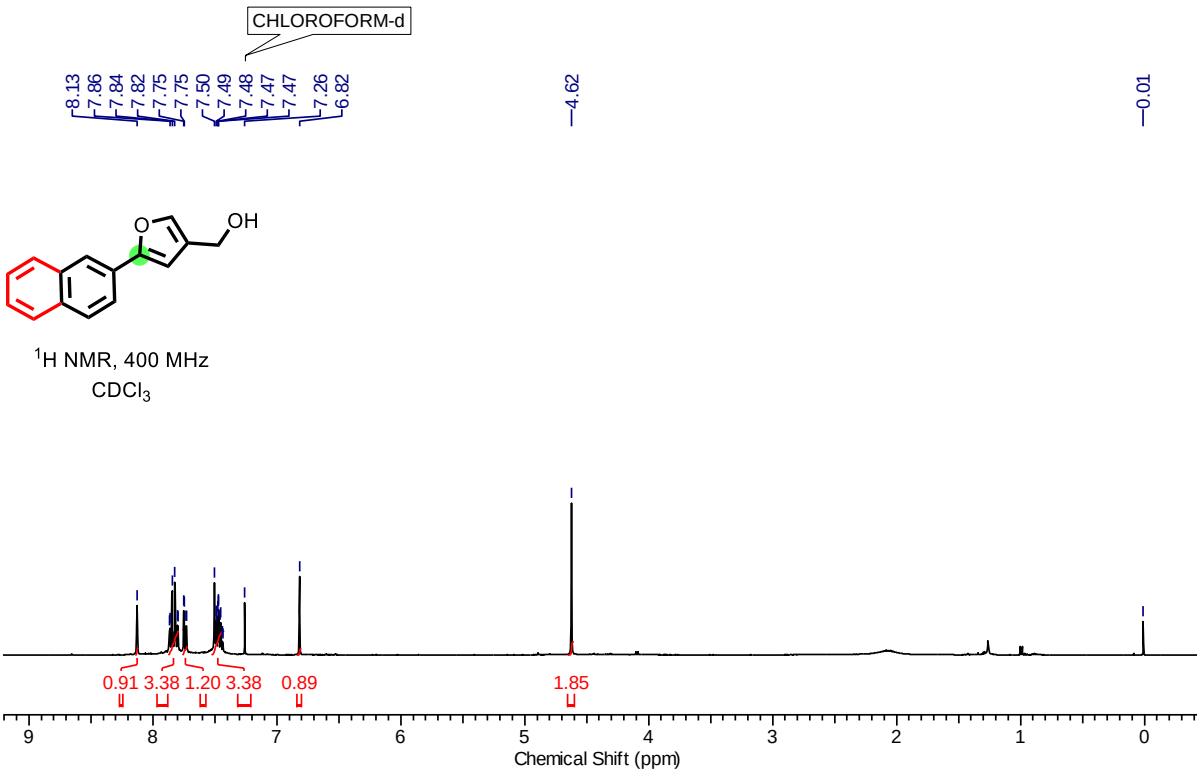
(5-([1,1'-Biphenyl]-4-yl)furan-3-yl)methanol (**72e**):



(5-([1,1'-Biphenyl]-4-yl)furan-3-yl)methanol (**72e**):

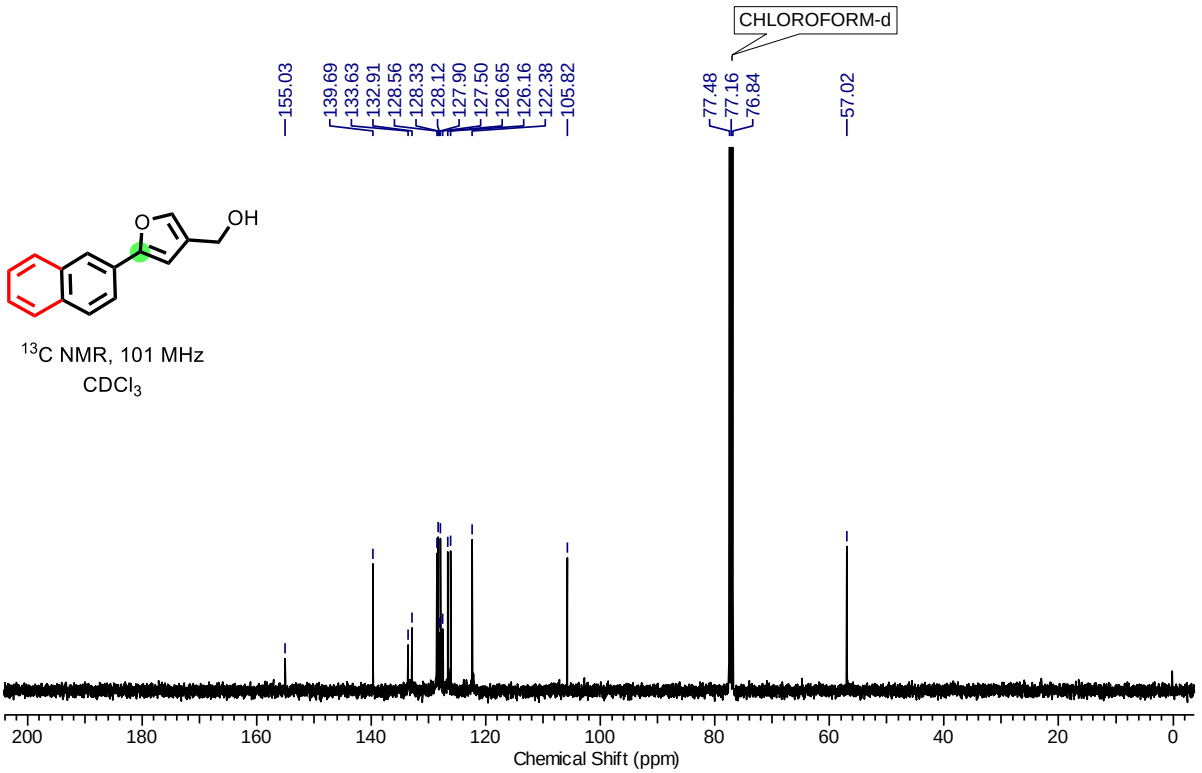


(5-(Naphthalen-2-yl)furan-3-yl)methanol (**72f**):



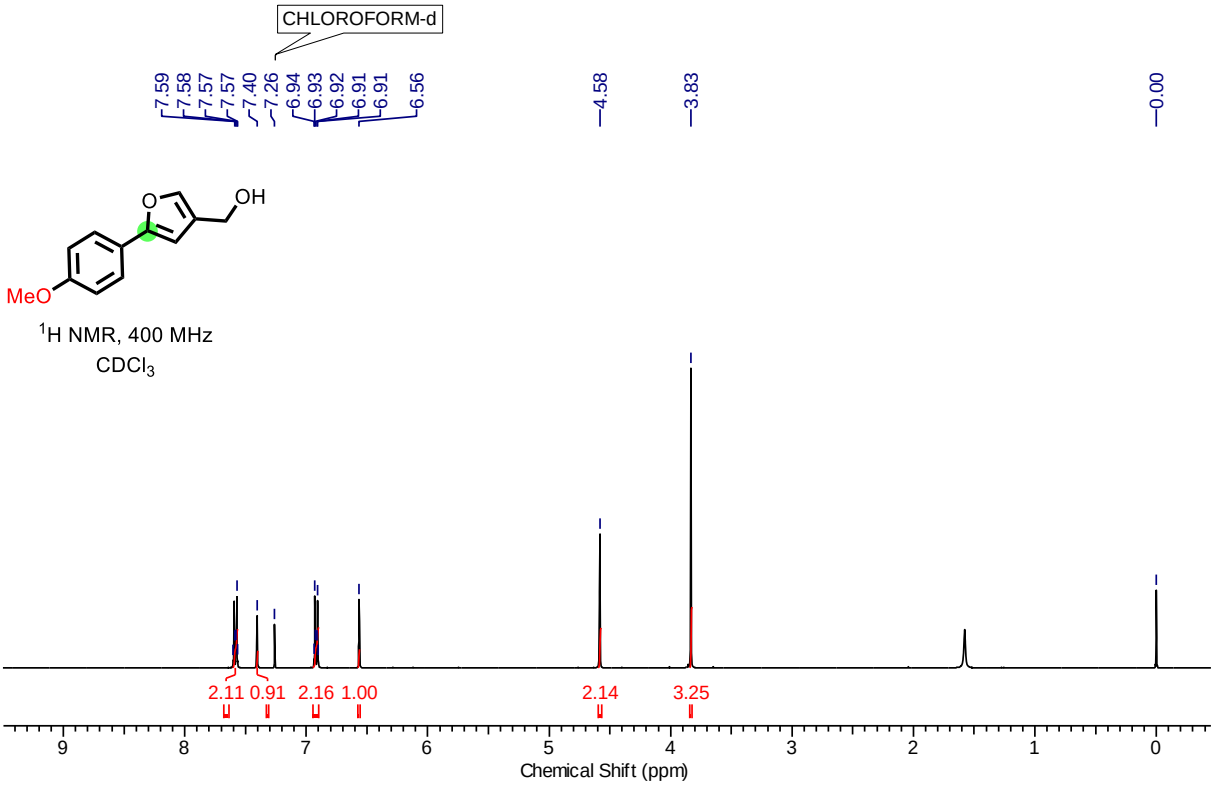
^{1}H NMR, 400 MHz
$CDCl_3$

(5-(Naphthalen-2-yl)furan-3-yl)methanol (**72f**):

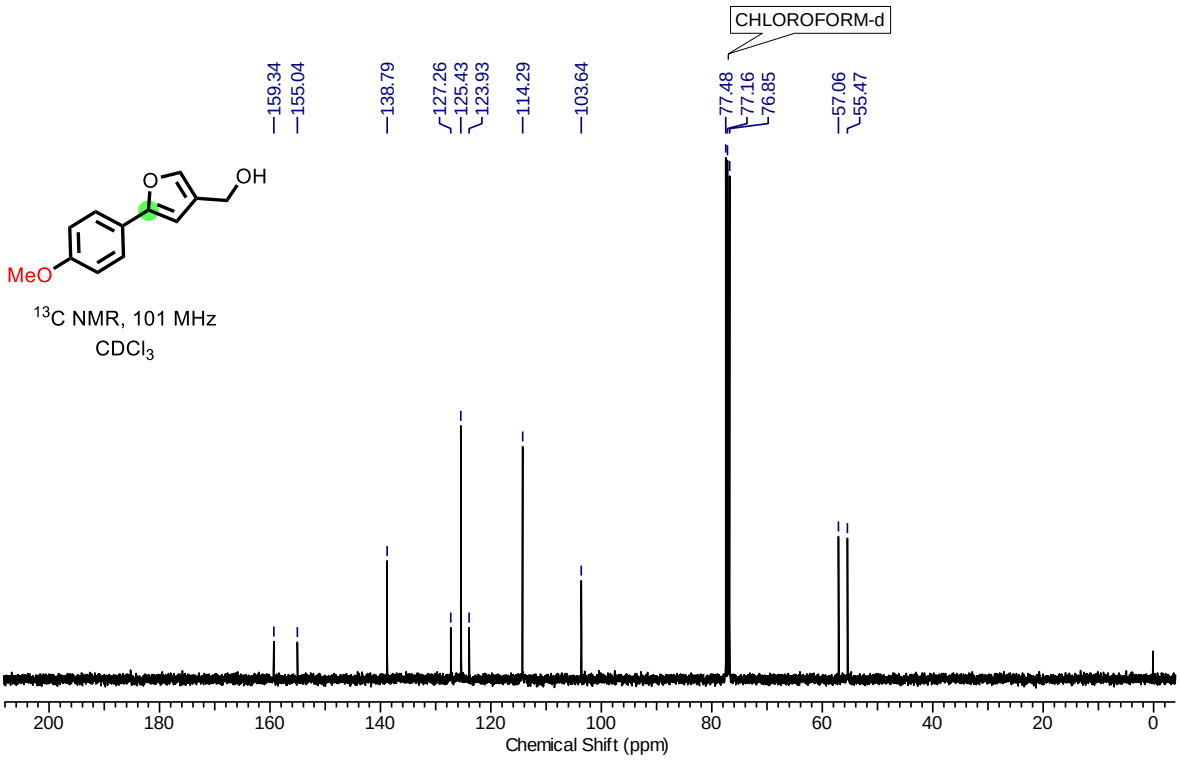


^{13}C NMR, 101 MHz
$CDCl_3$

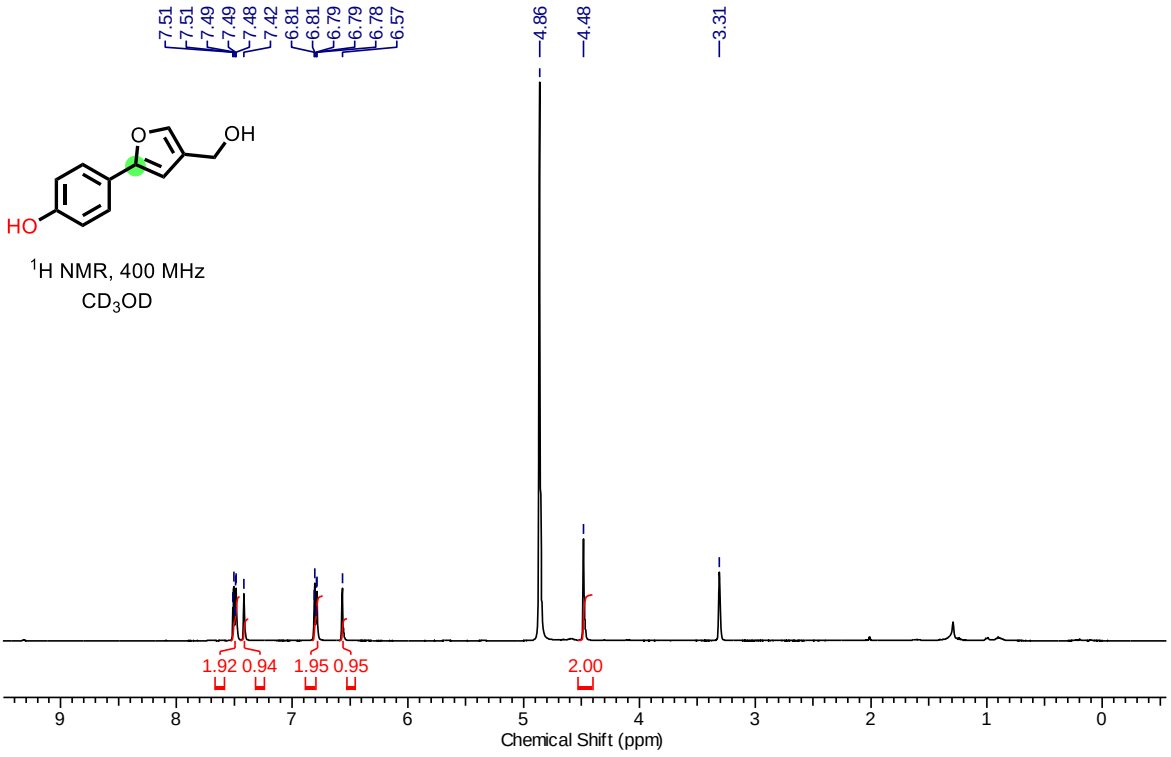
(5-(4-Methoxyphenyl)furan-3-yl)methanol (**72g**):



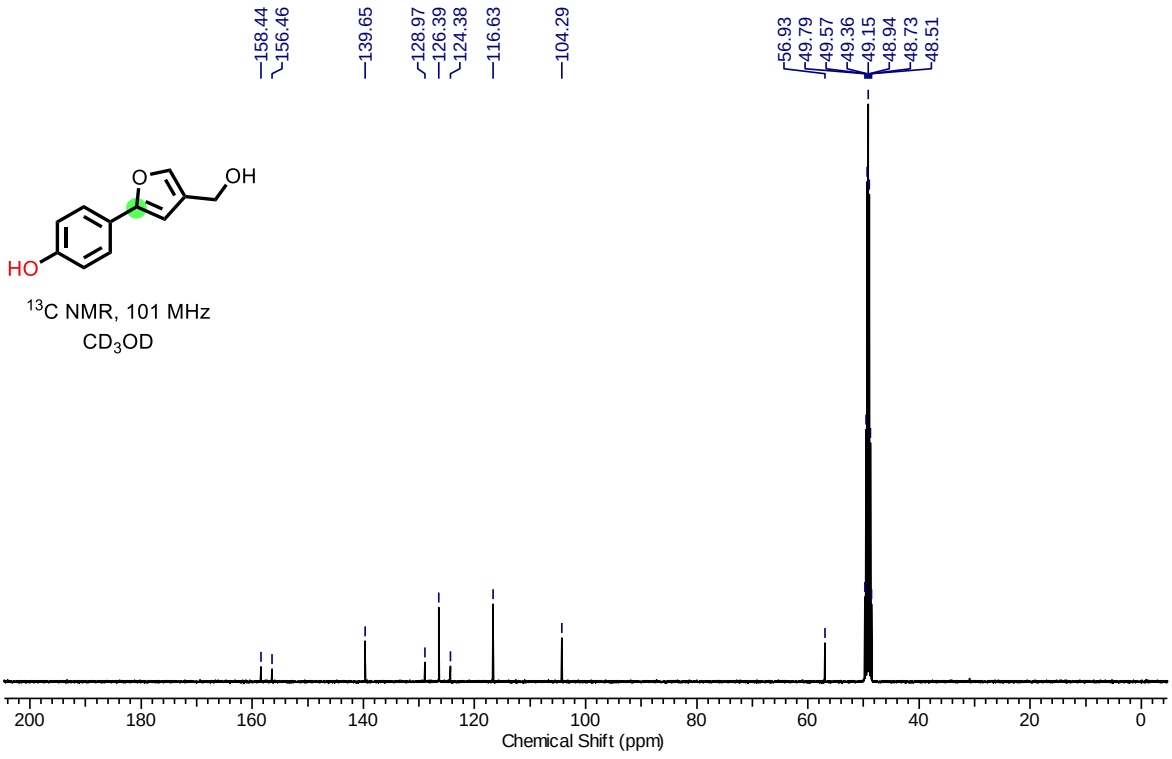
(5-(4-Methoxyphenyl)furan-3-yl)methanol (**72g**):



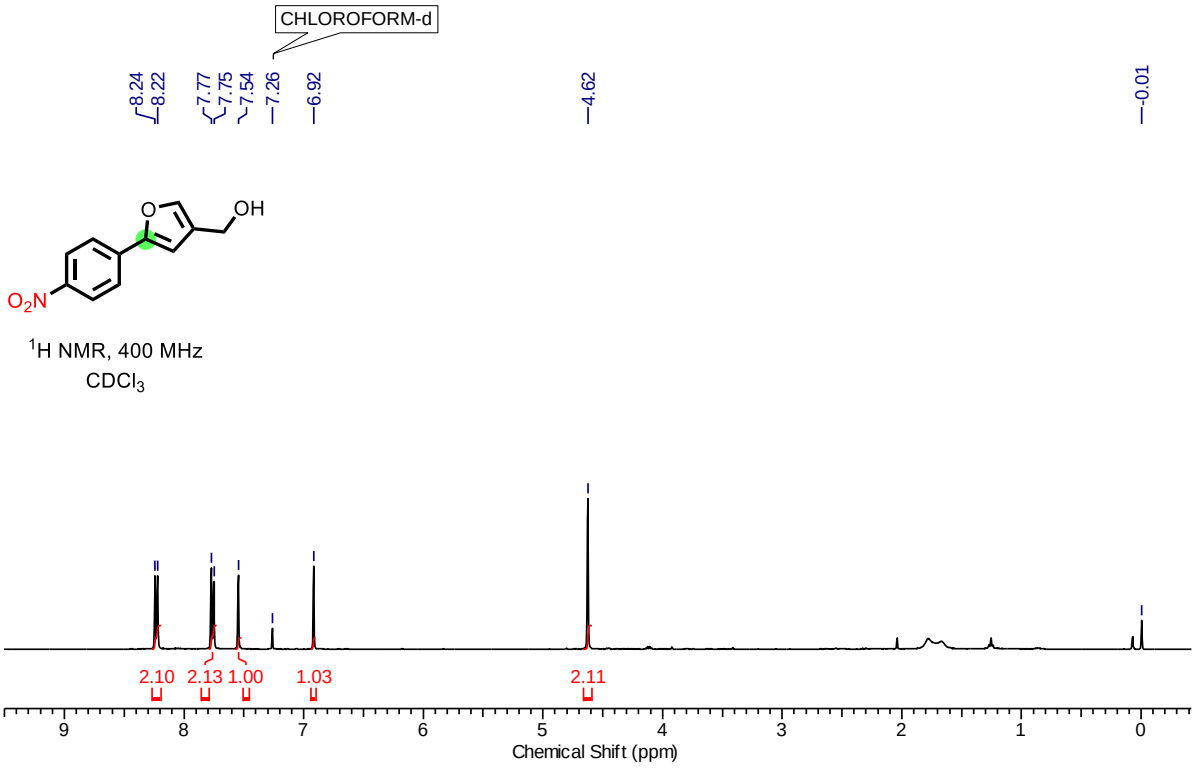
4-(4-(Hydroxymethyl)furan-2-yl)phenol (**72h**):



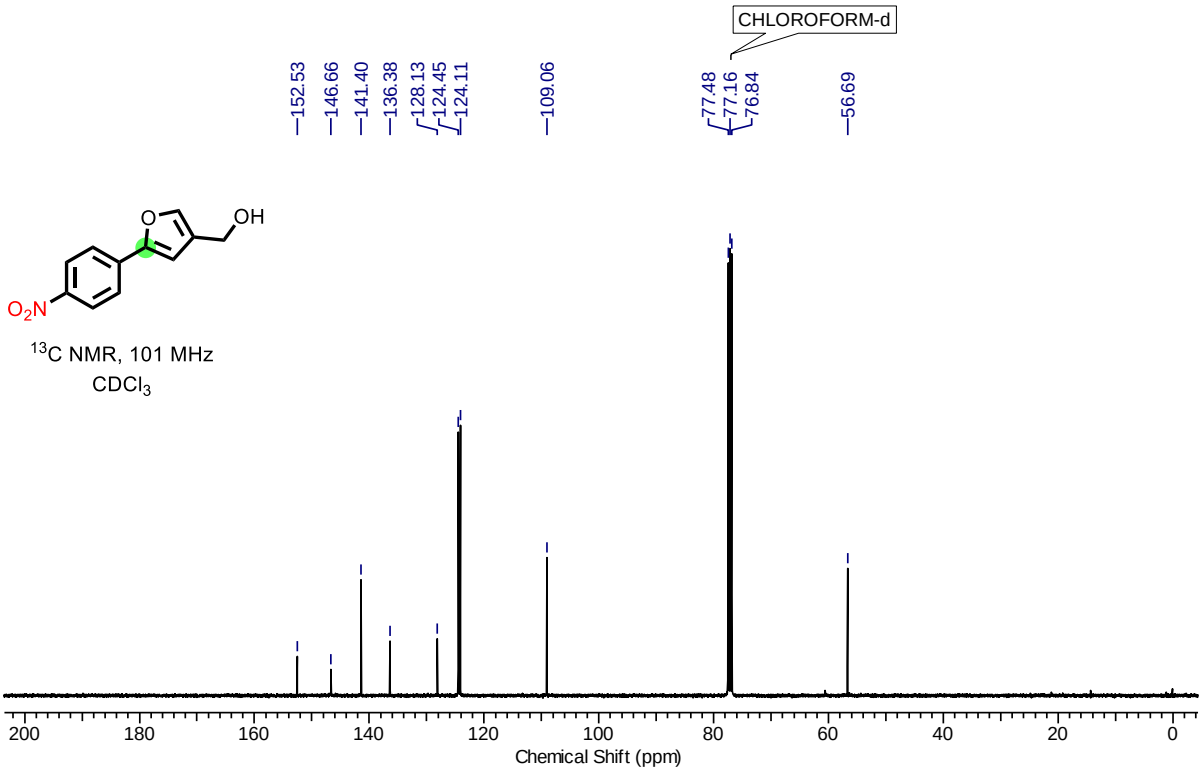
4-(4-(Hydroxymethyl)furan-2-yl)phenol (**72h**):



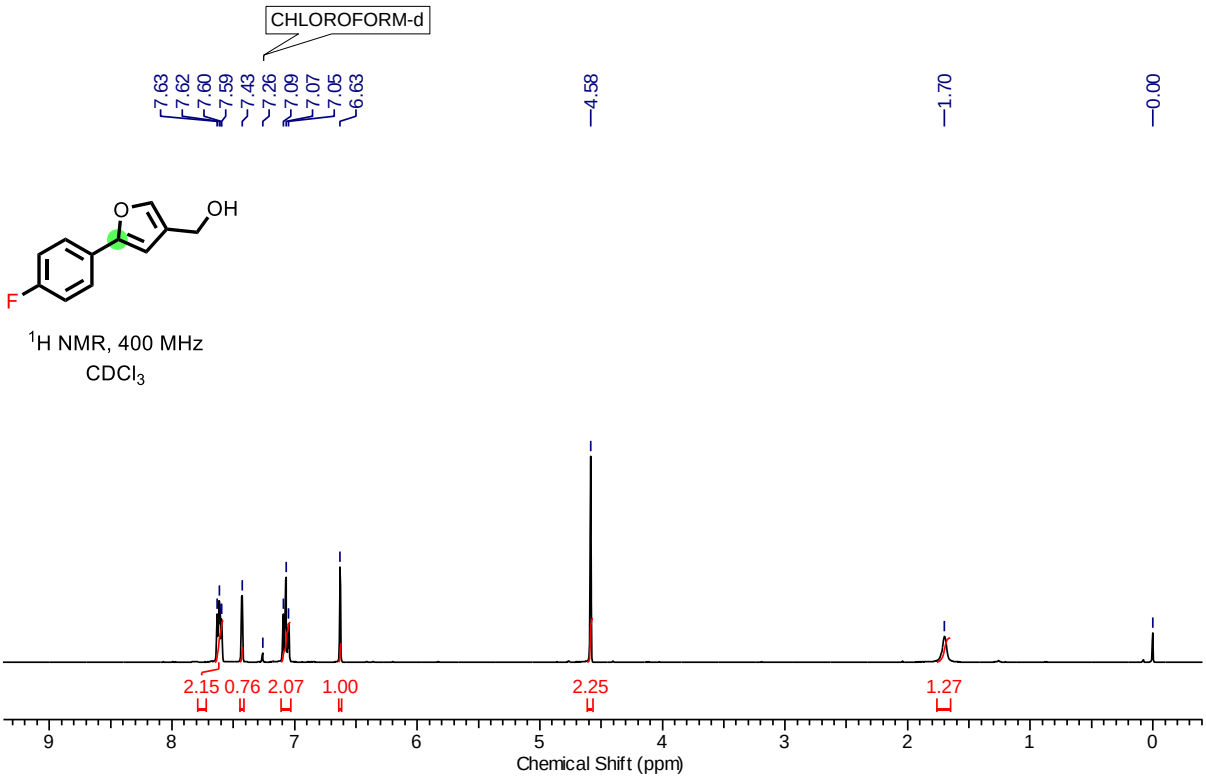
(5-(4-Nitrophenyl)furan-3-yl)methanol (**72i**):



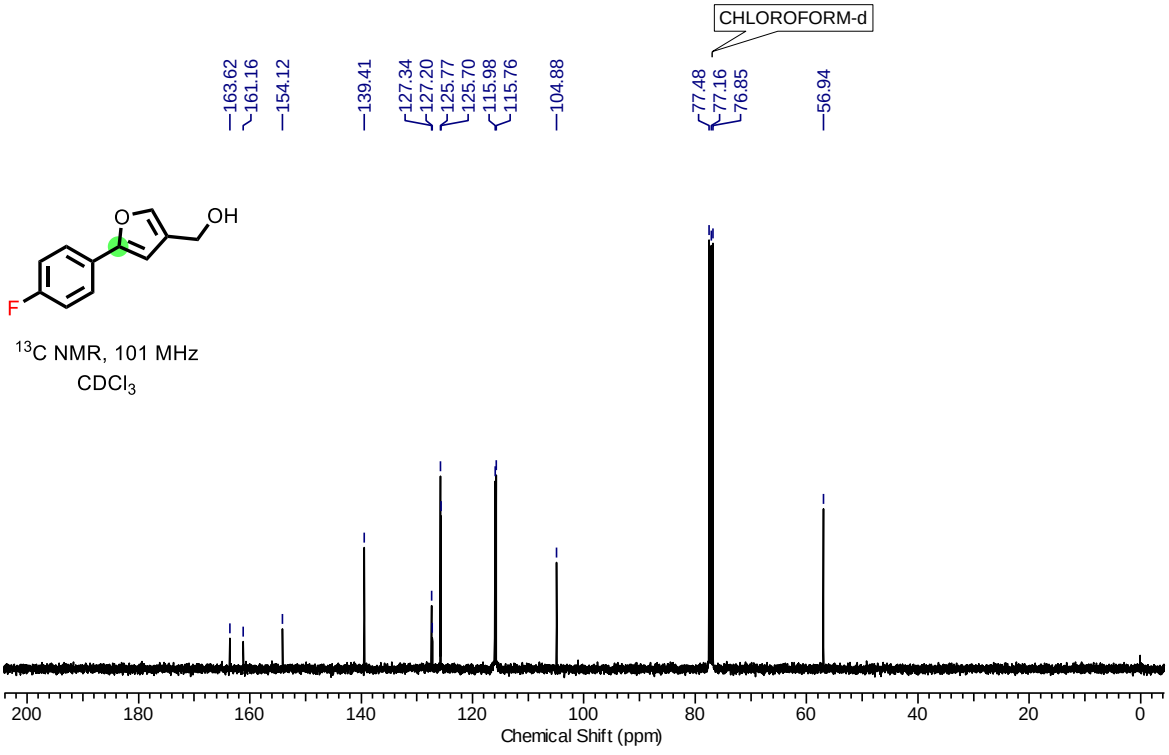
(5-(4-Nitrophenyl)furan-3-yl)methanol (**72i**):



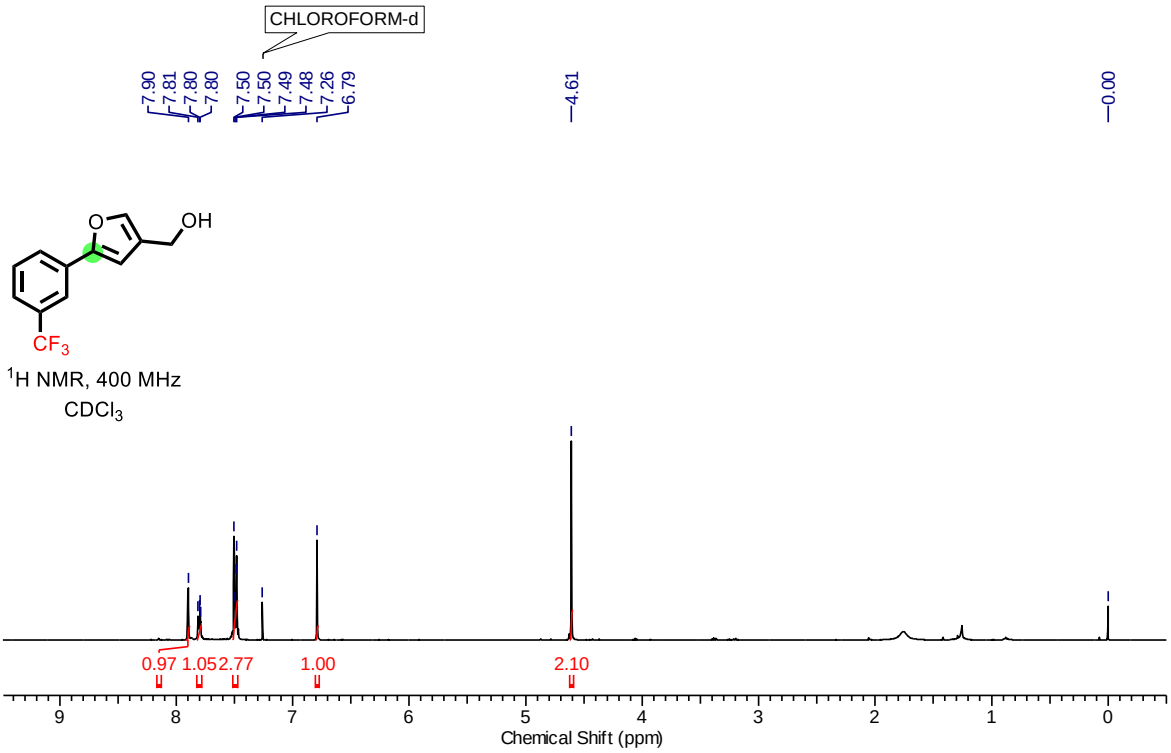
(5-(4-Fluorophenyl)furan-3-yl)methanol (**72j**):



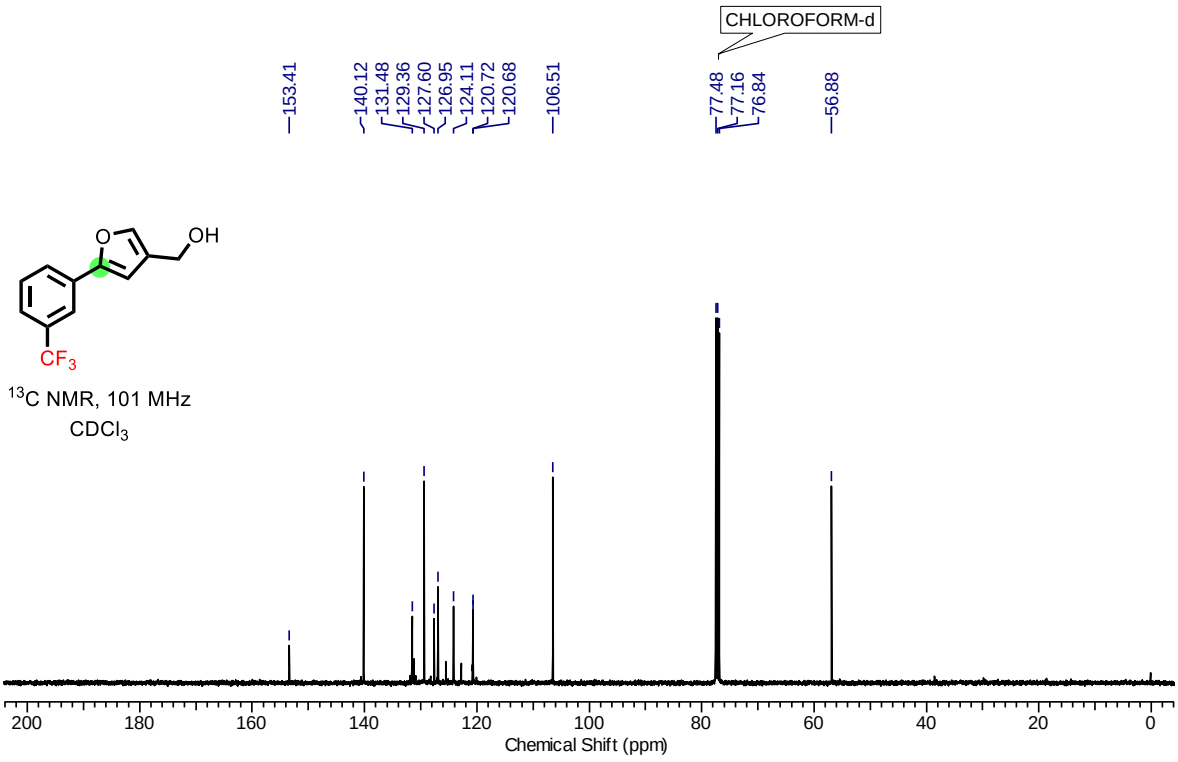
(5-(4-Fluorophenyl)furan-3-yl)methanol (**72j**):



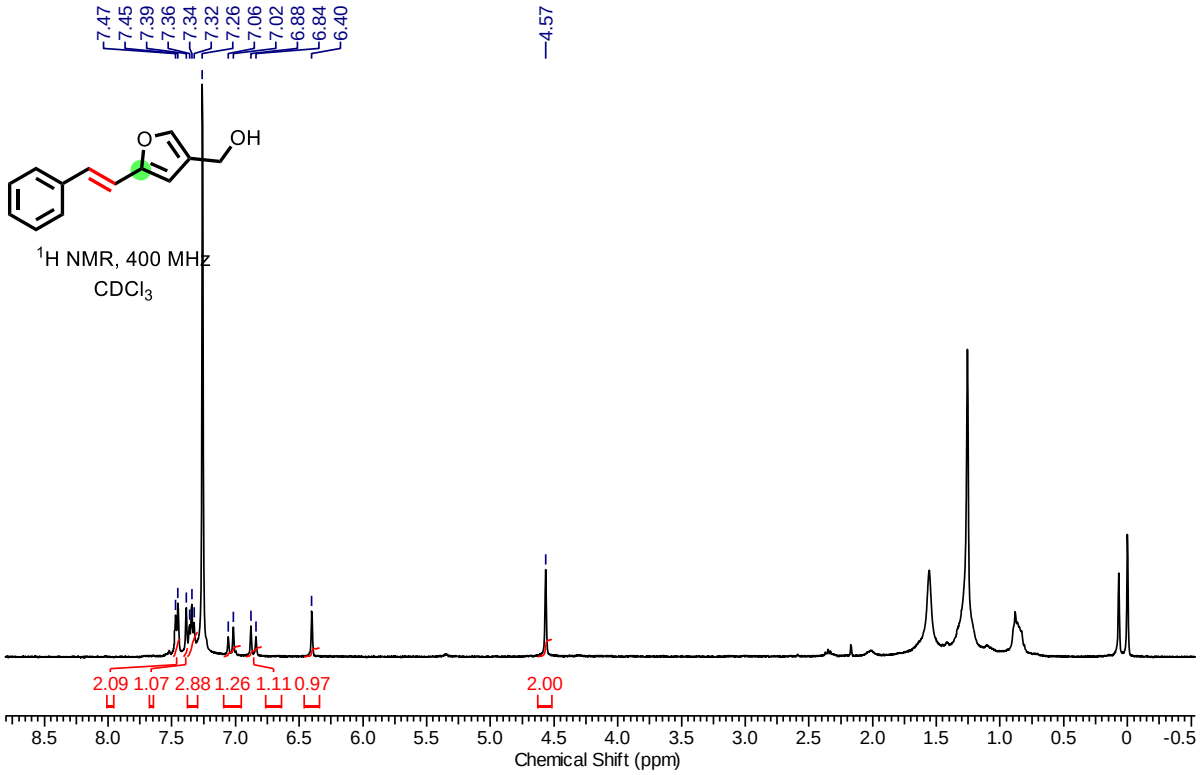
(5-(3-(Trifluoromethyl)phenyl)furan-3-yl)methanol (**72k**):



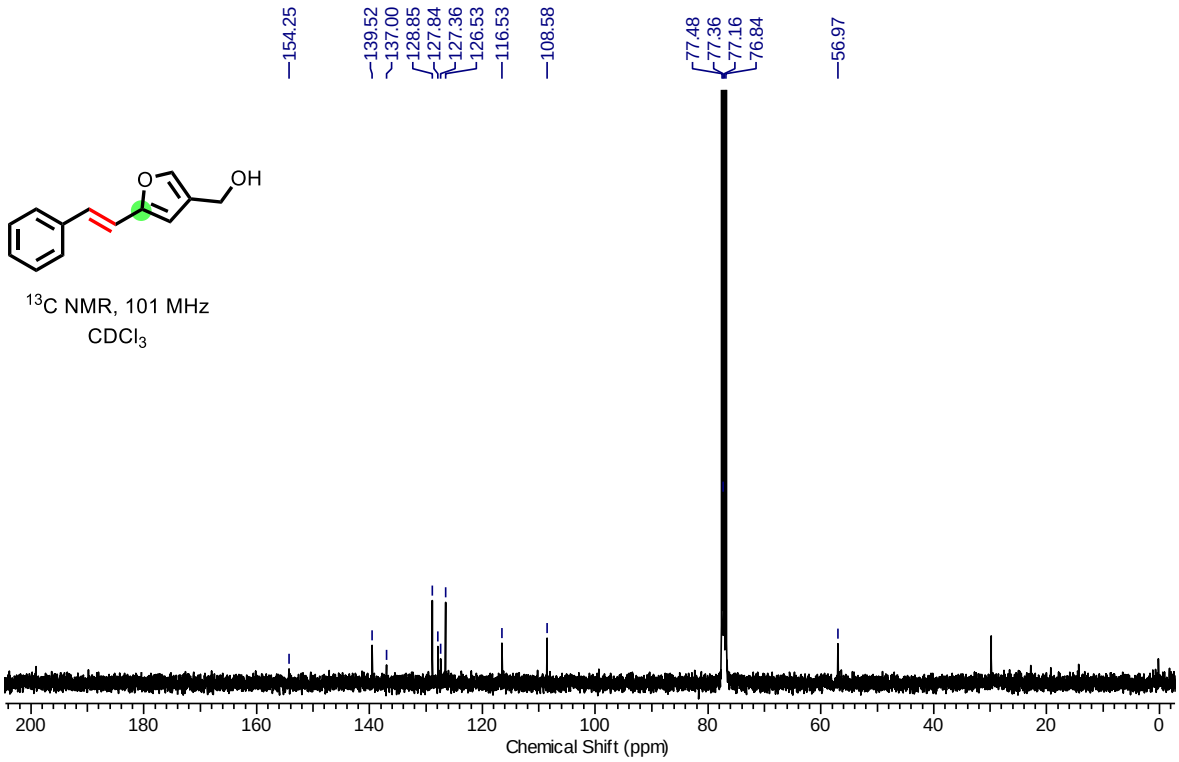
(5-(3-(Trifluoromethyl)phenyl)furan-3-yl)methanol (**72k**):



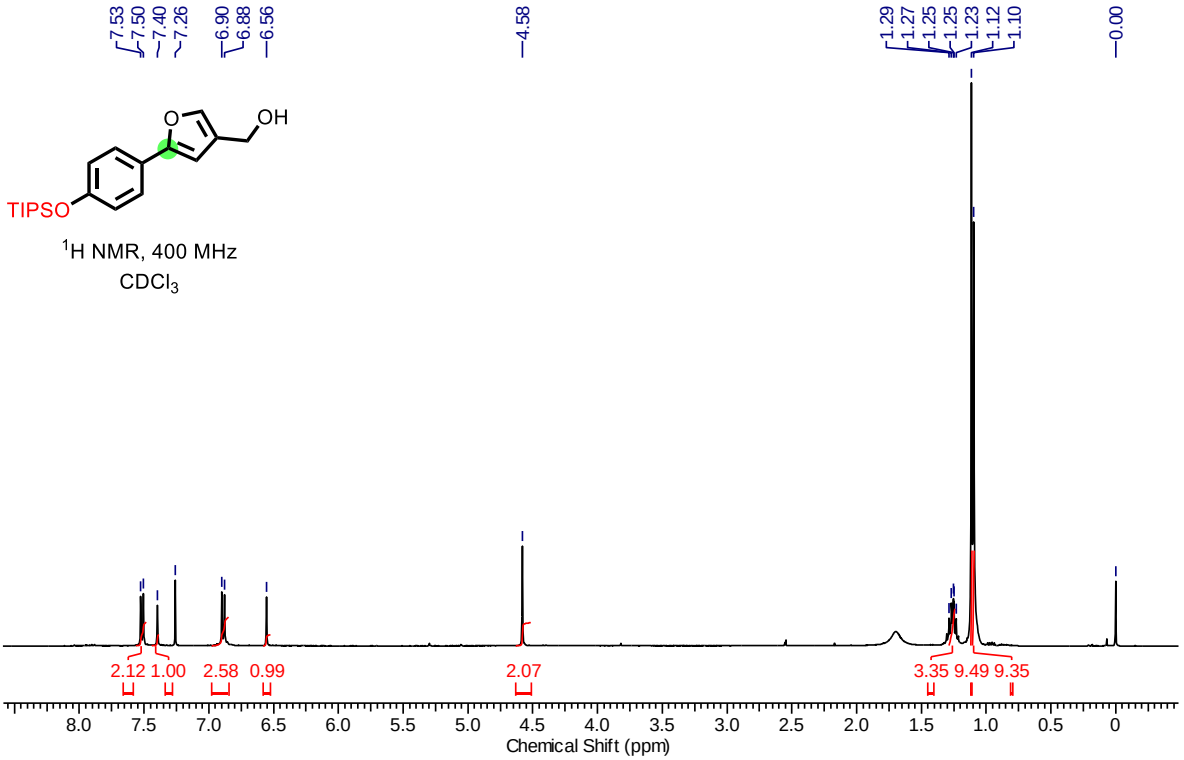
(*E*)-(5-styrylfuran-3-yl)methanol (**72l**):



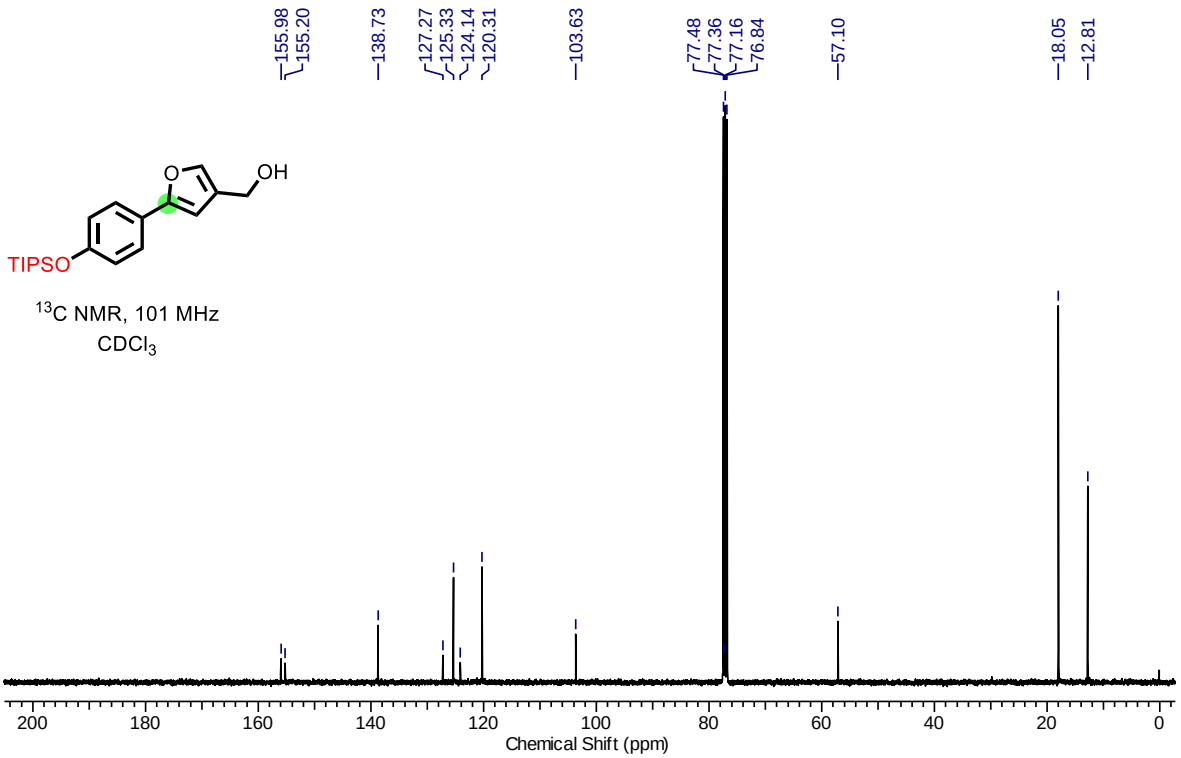
(*E*)-(5-styrylfuran-3-yl)methanol (**72l**):



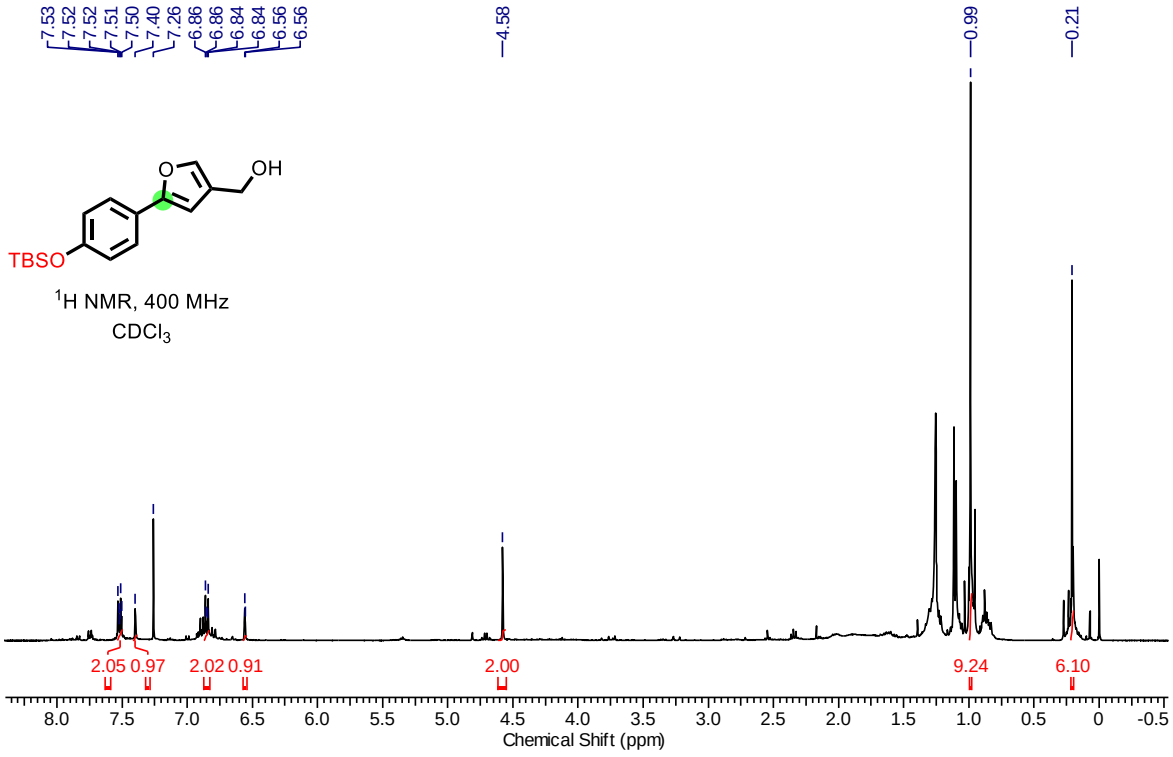
(5-(4-((Triisopropylsilyl)oxy)phenyl)furan-3-yl)methanol (**72m**):



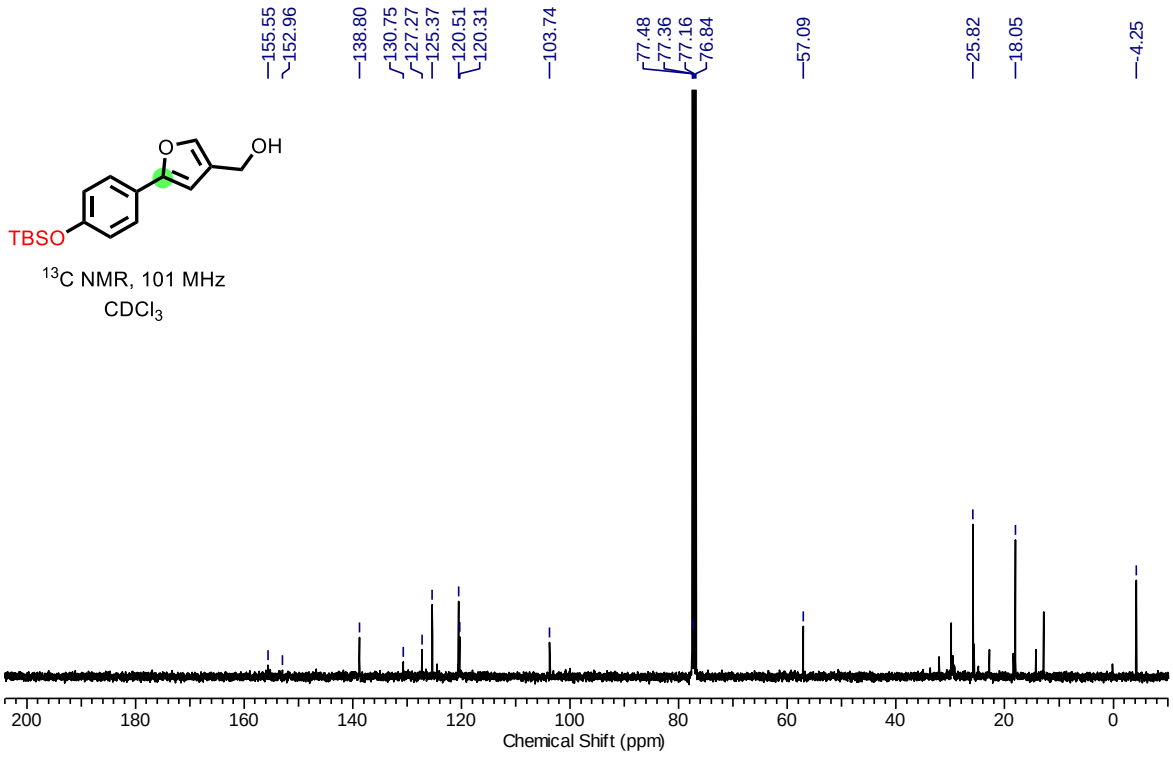
(5-(4-((Triisopropylsilyl)oxy)phenyl)furan-3-yl)methanol (**72m**):



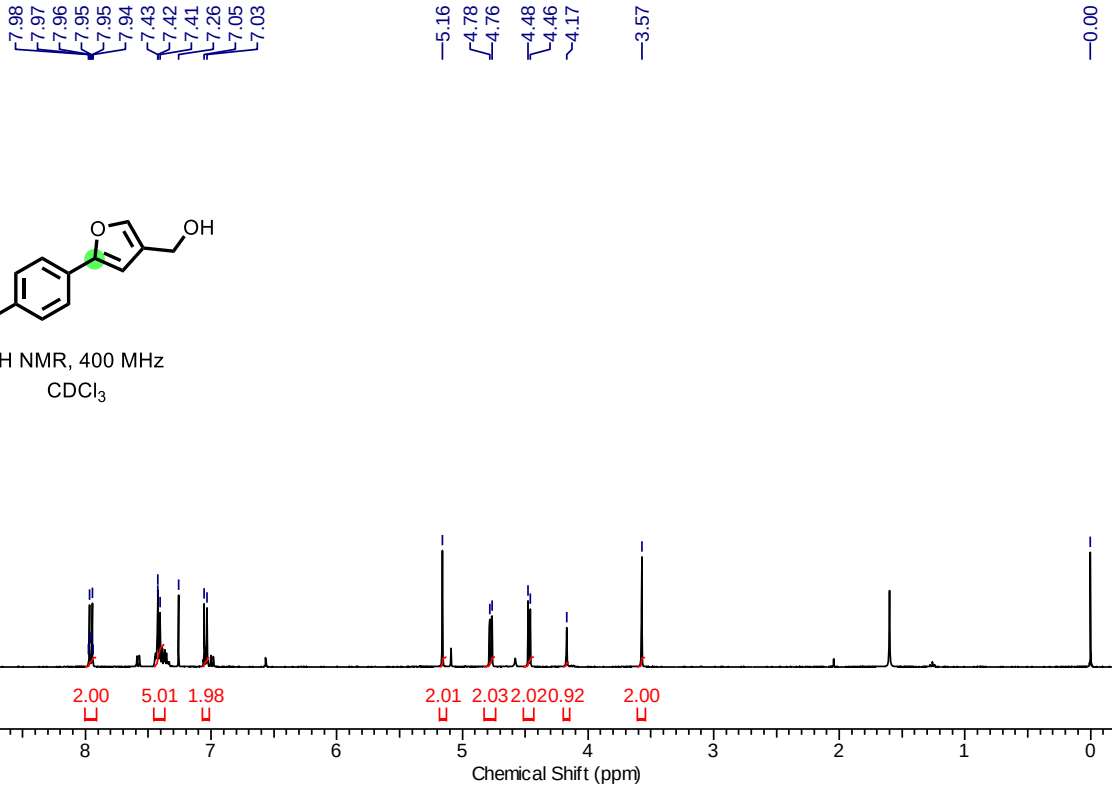
(5-(4-((*Tert*-butyldimethylsilyl)oxy)phenyl)furan-3-yl)methanol (**72n**):



(5-(4-((*Tert*-butyldimethylsilyl)oxy)phenyl)furan-3-yl)methanol (**72n**):

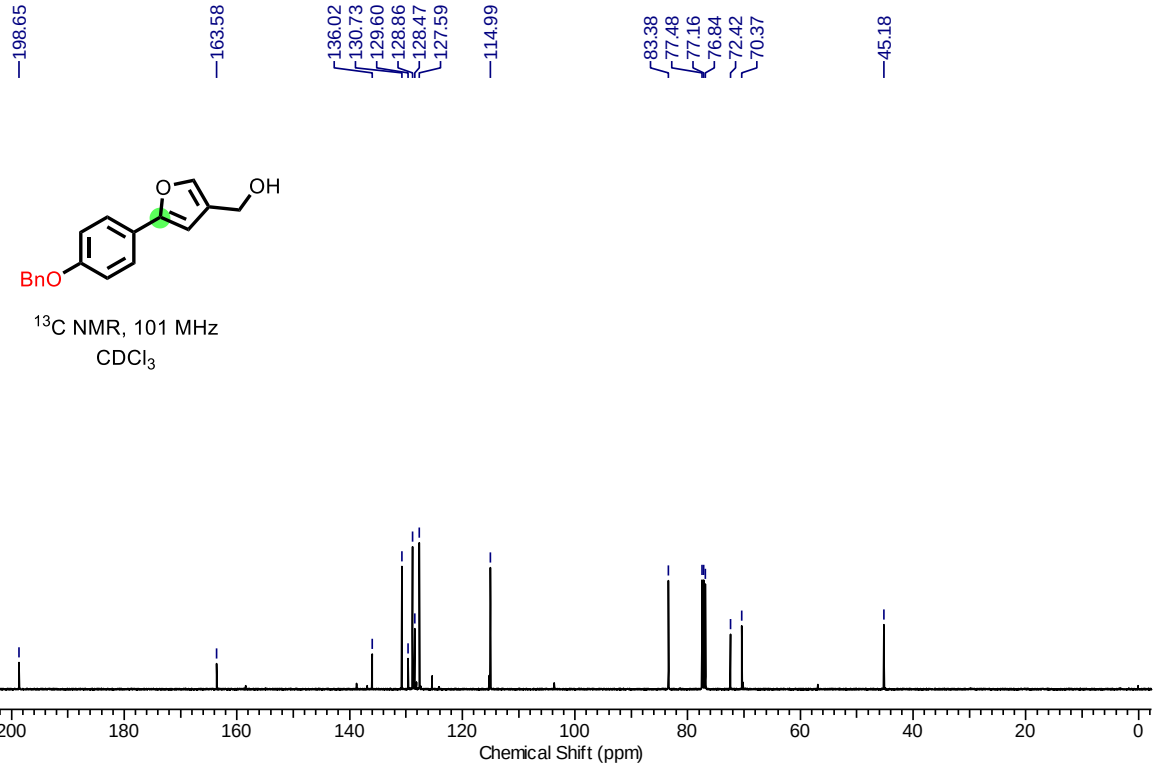


(5-(4-(Benzyloxy)phenyl)furan-3-yl)methanol (**72o**):



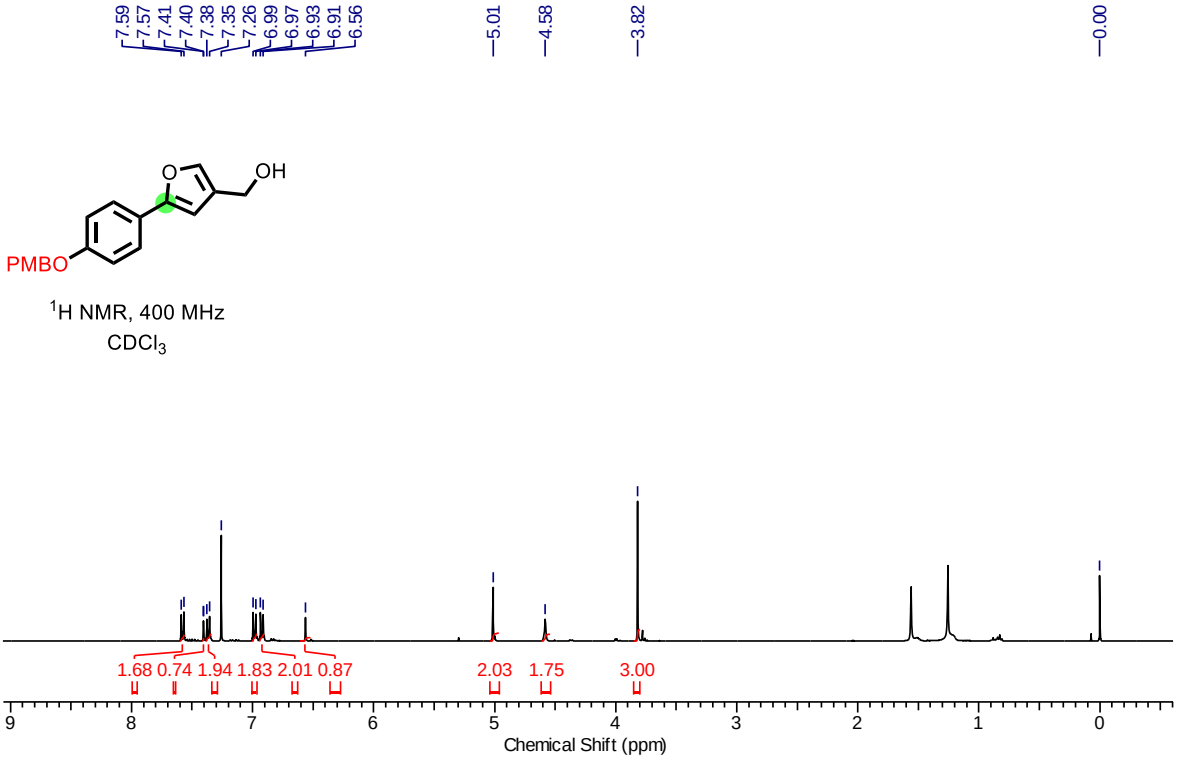
^{1}H NMR, 400 MHz
$CDCl_3$

(5-(4-(Benzyloxy)phenyl)furan-3-yl)methanol (**72o**):

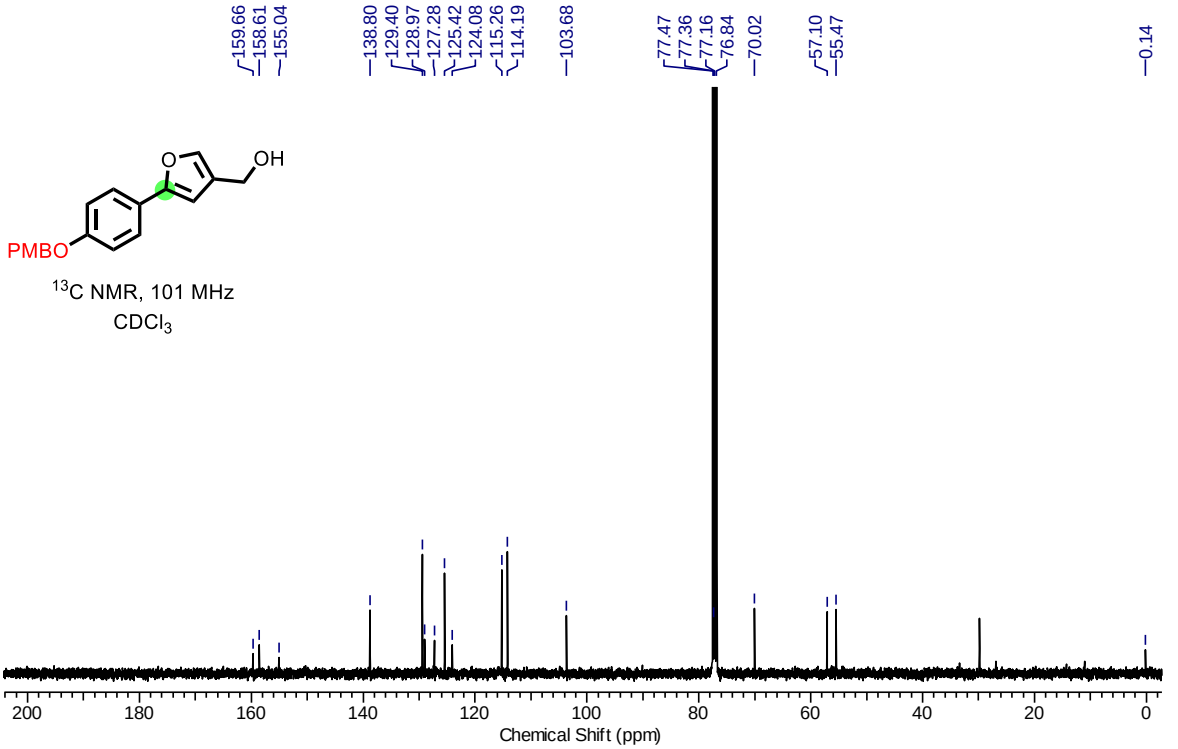


^{13}C NMR, 101 MHz
$CDCl_3$

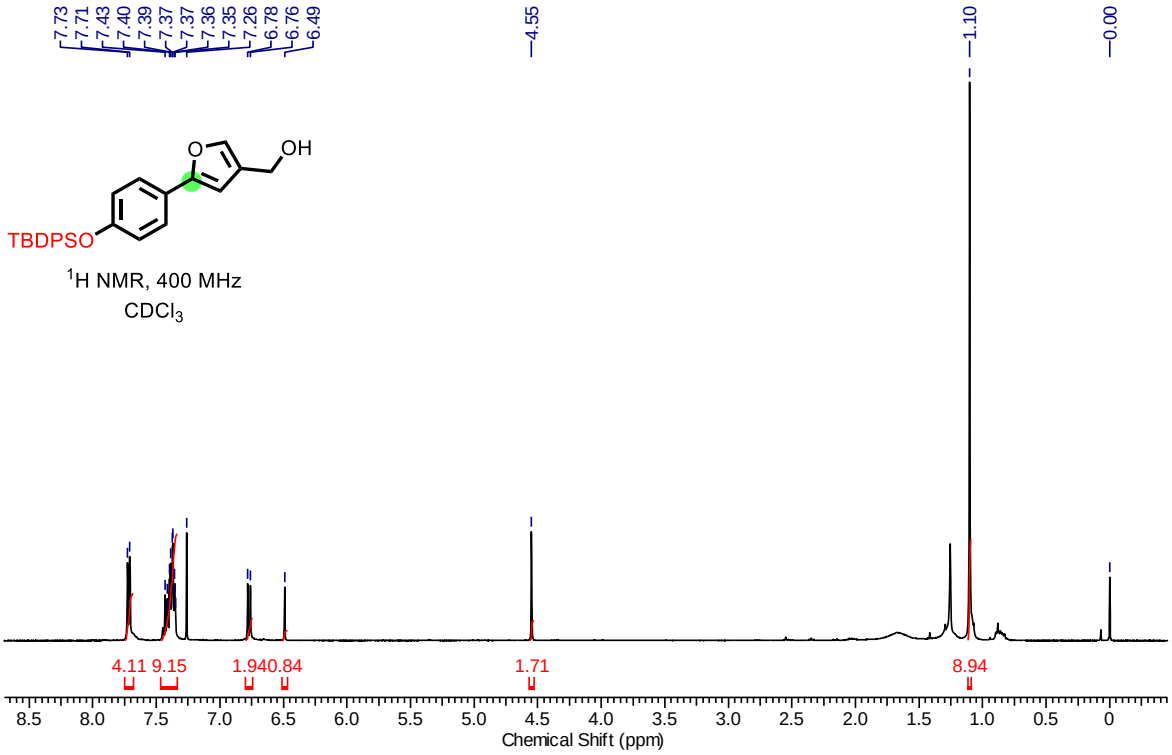
(5-(4-((4-Methoxybenzyl)oxy)phenyl)furan-3-yl)methanol (**72p**):



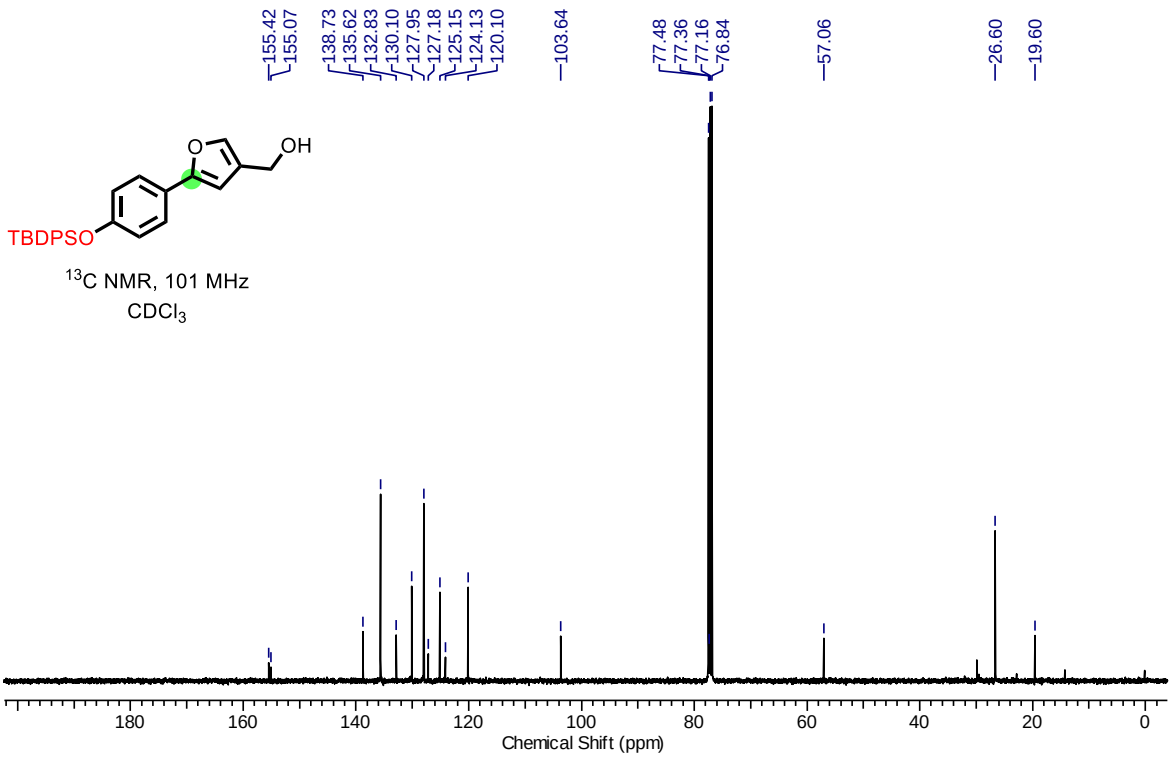
(5-(4-((4-Methoxybenzyl)oxy)phenyl)furan-3-yl)methanol (**72p**):



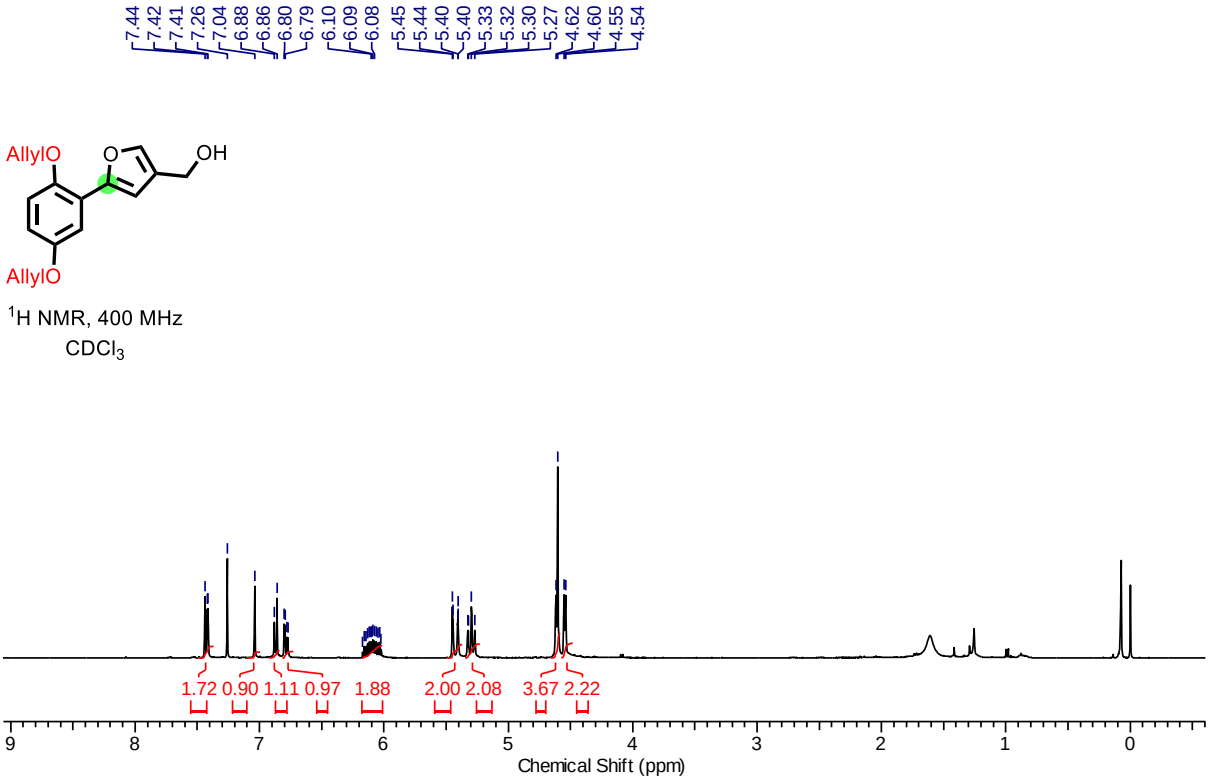
(5-(4-((*Tert*-butyldiphenylsilyl)oxy)phenyl)furan-3-yl)methanol (**72q**):



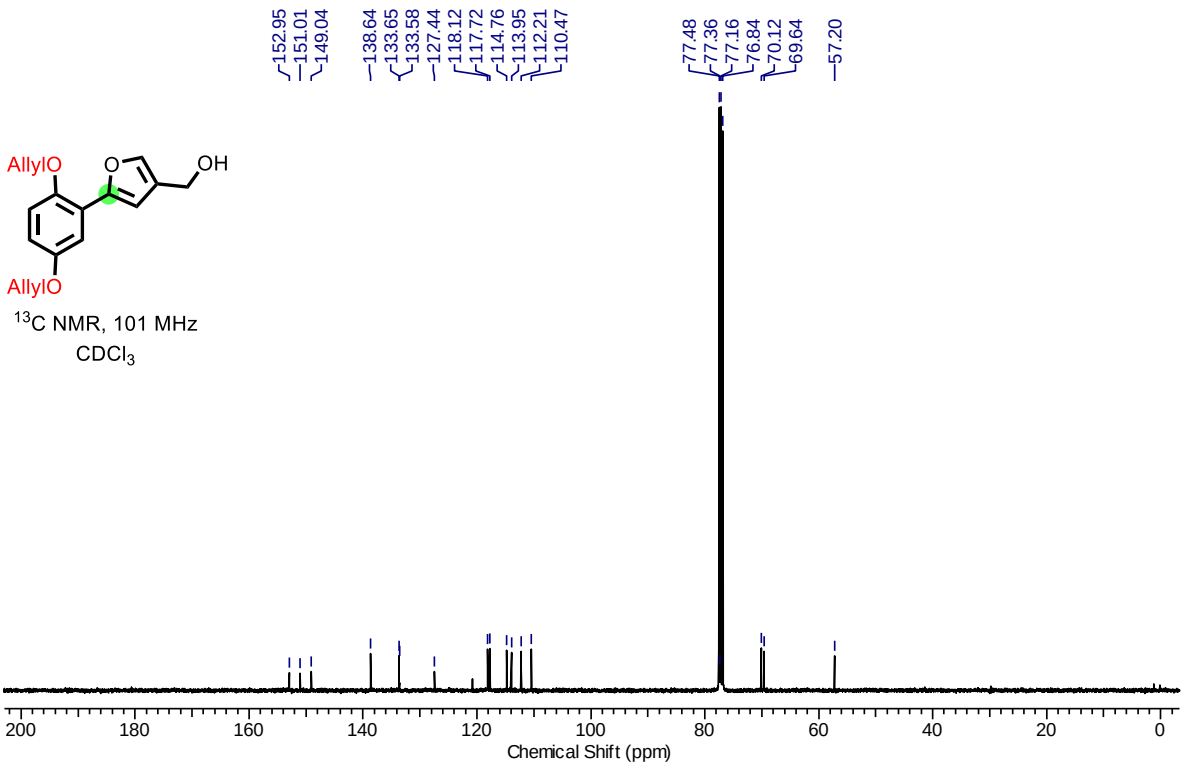
(5-(4-((*Tert*-butyldiphenylsilyl)oxy)phenyl)furan-3-yl)methanol (**72q**):



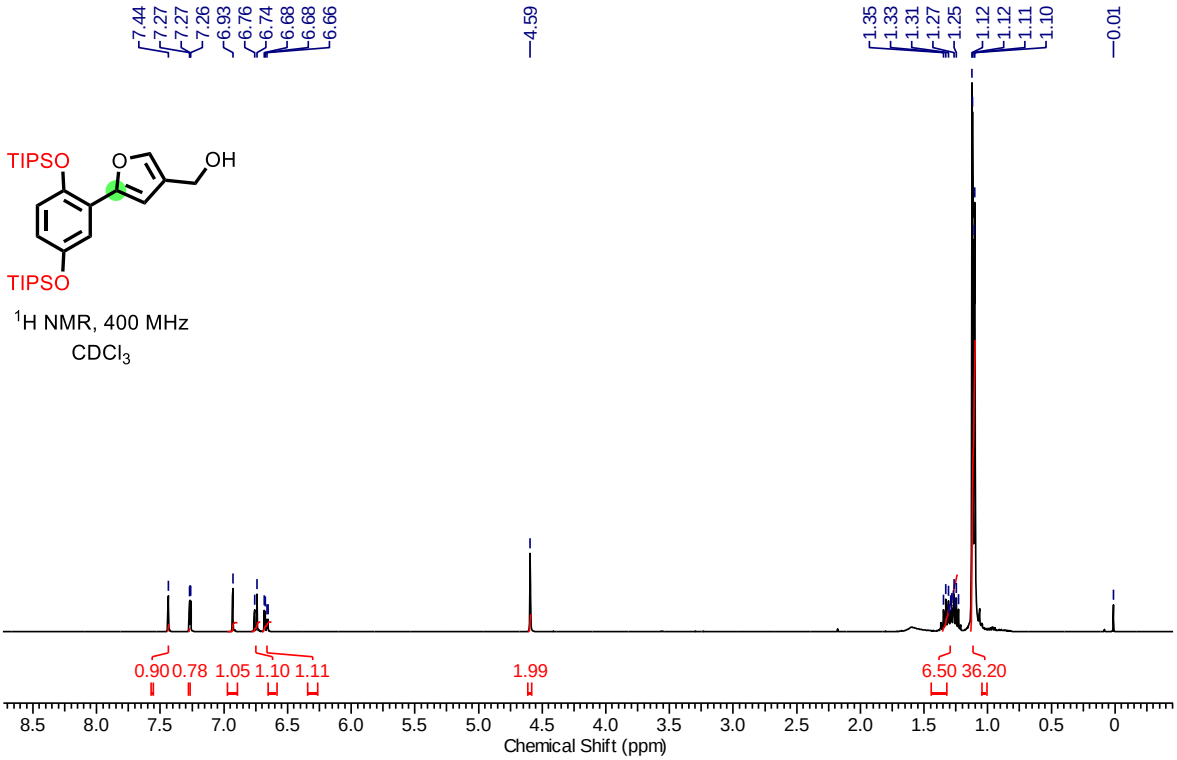
(5-(2,5-Bis(allyloxy)phenyl)furan-3-yl)methanol (**72r**):



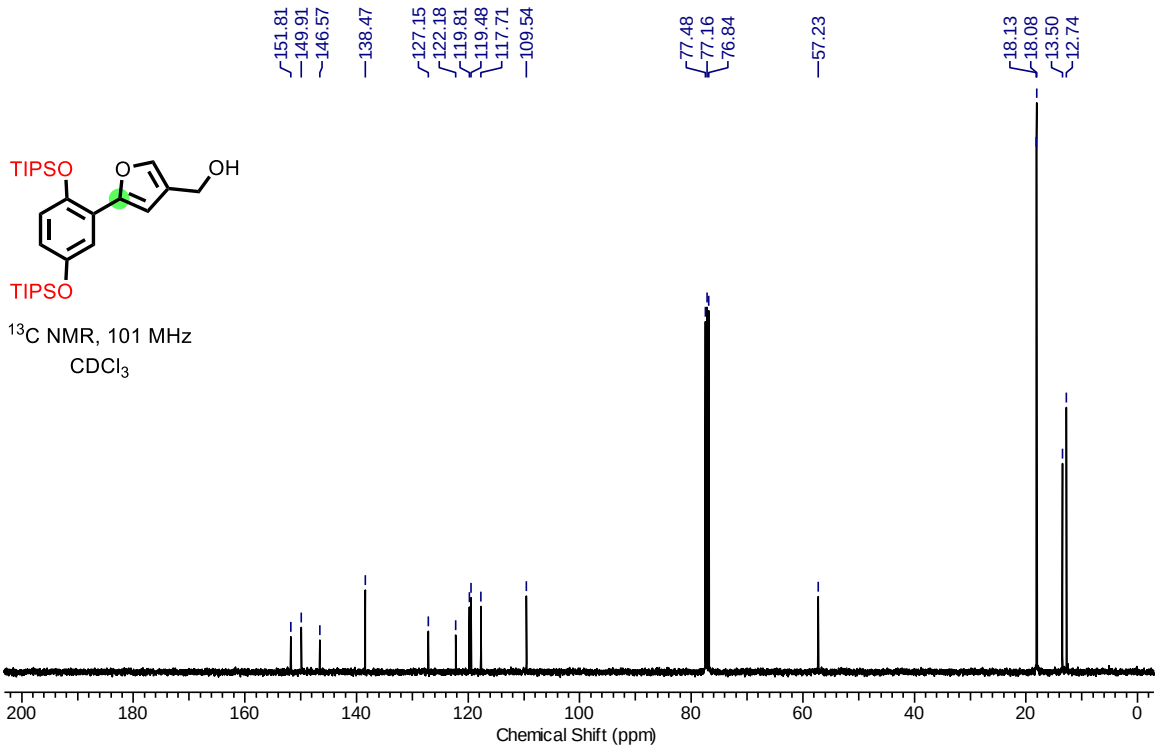
(5-(2,5-Bis(allyloxy)phenyl)furan-3-yl)methanol (**72r**):



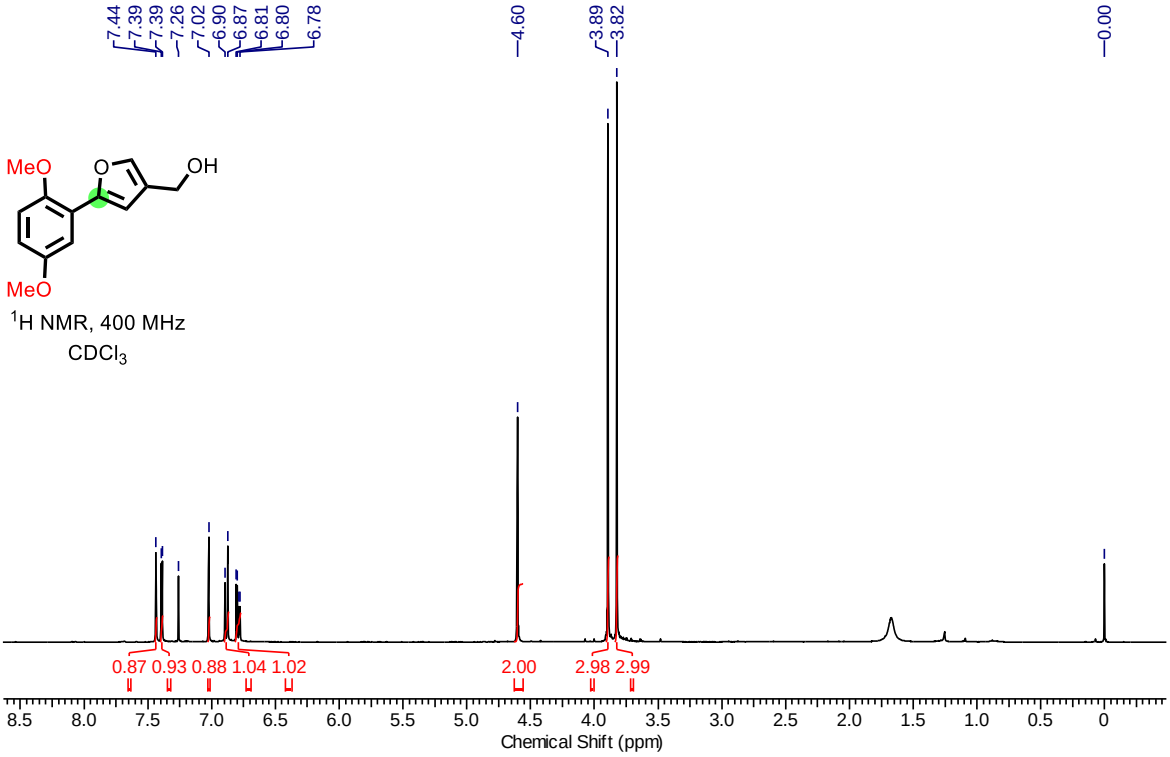
(5-(2,5-Bis((triisopropylsilyl)oxy)phenyl)furan-3-yl)methanol (**72s**):



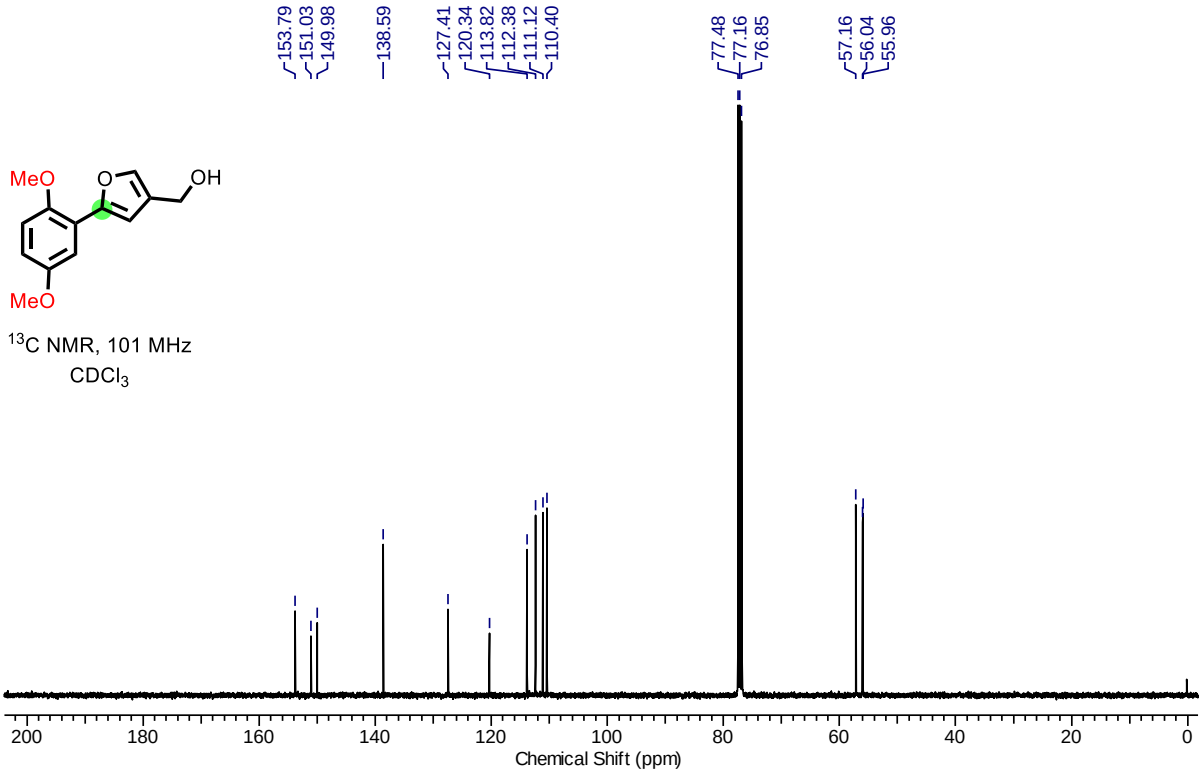
(5-(2,5-Bis((triisopropylsilyl)oxy)phenyl)furan-3-yl)methanol (**72s**):



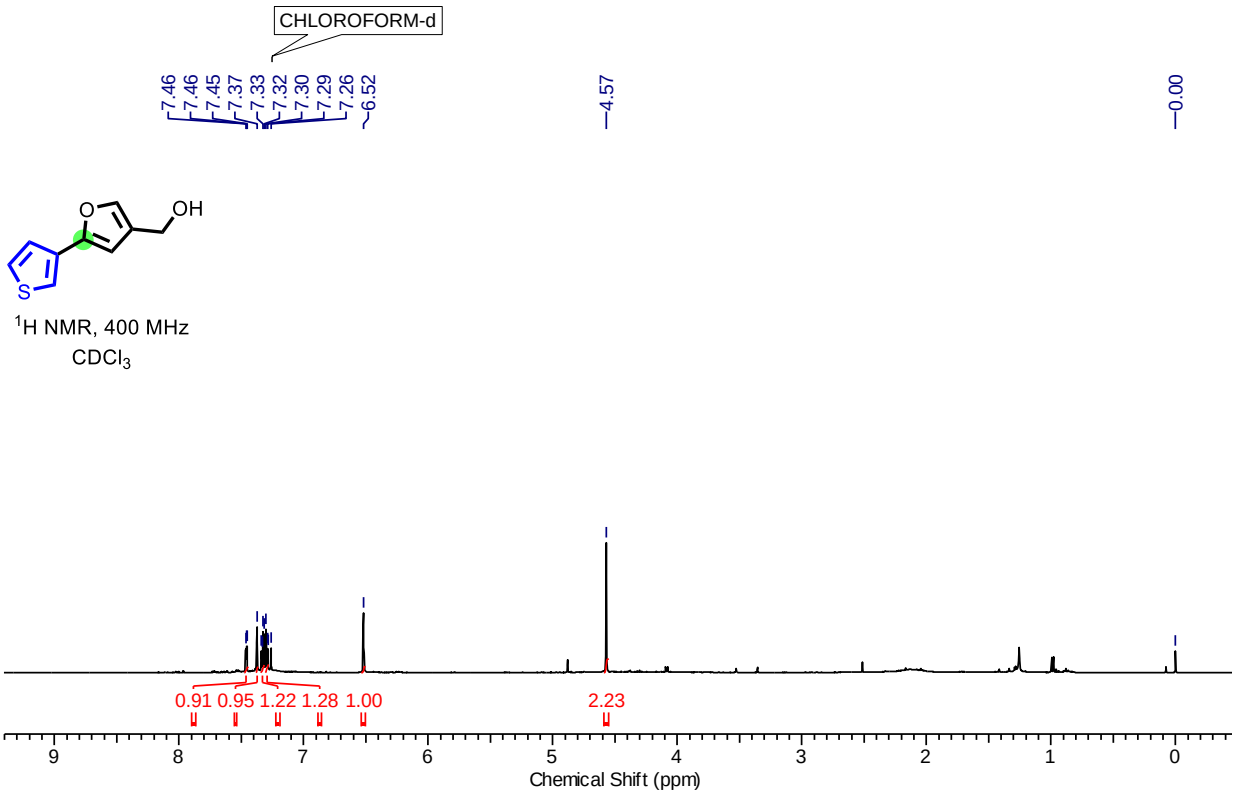
(5-(2,5-Dimethoxyphenyl)furan-3-yl)methanol (**72t**):



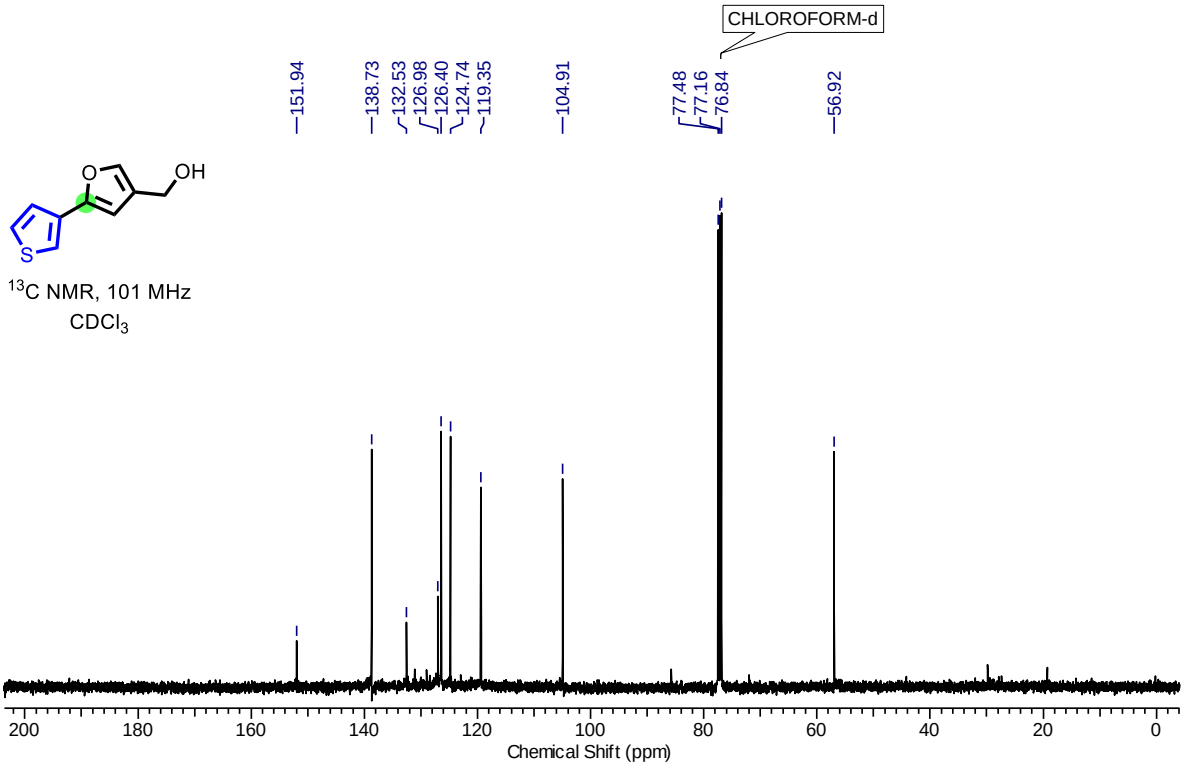
(5-(2,5-Dimethoxyphenyl)furan-3-yl)methanol (**72t**):



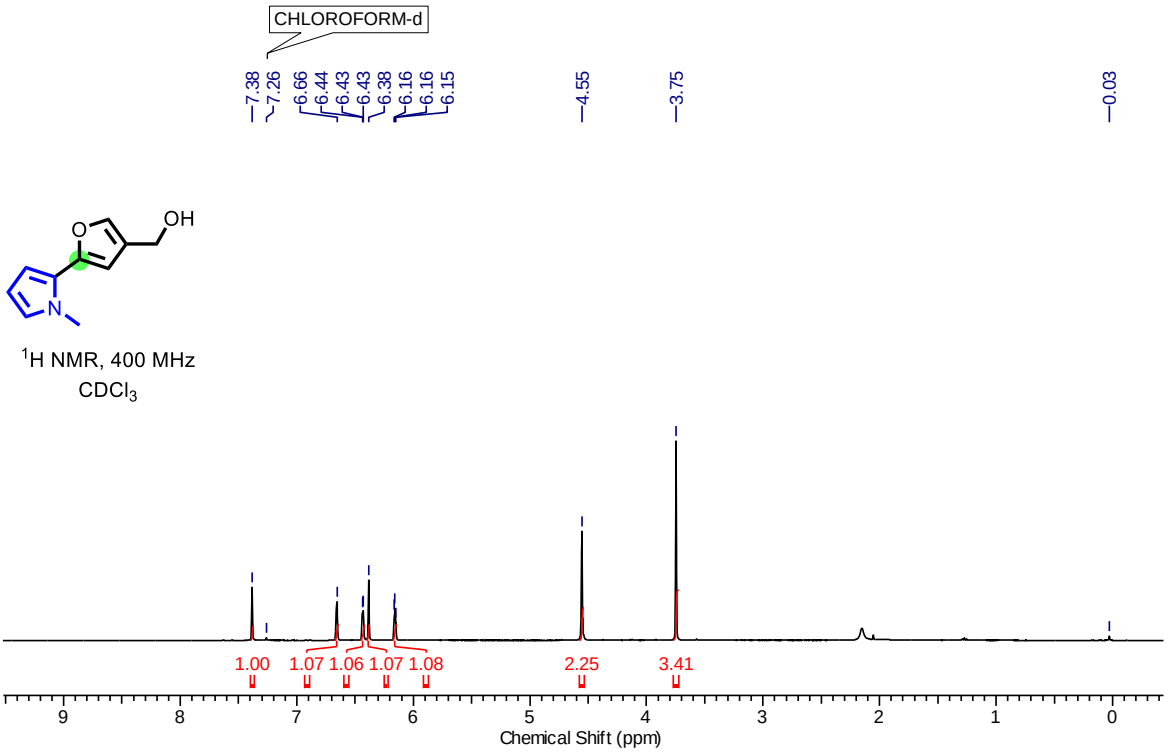
(5-(Thiophen-3-yl)furan-3-yl)methanol (**72u**):



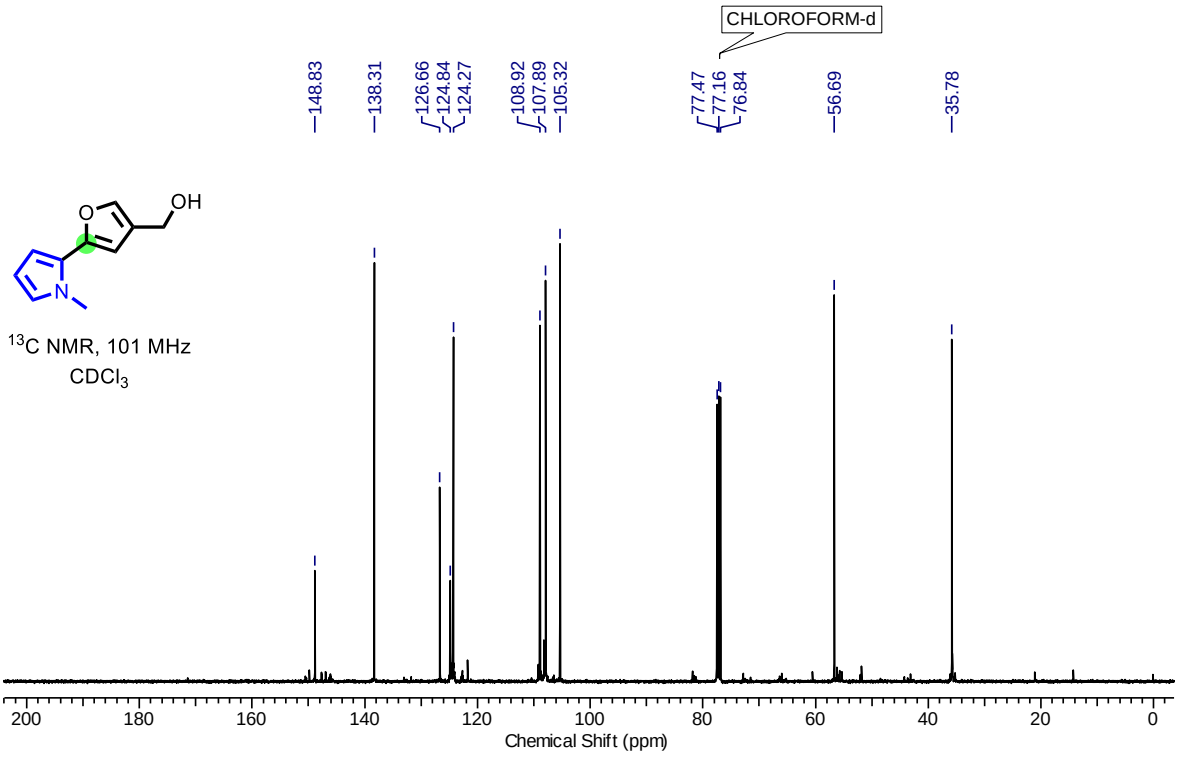
(5-(Thiophen-3-yl)furan-3-yl)methanol (**72u**):



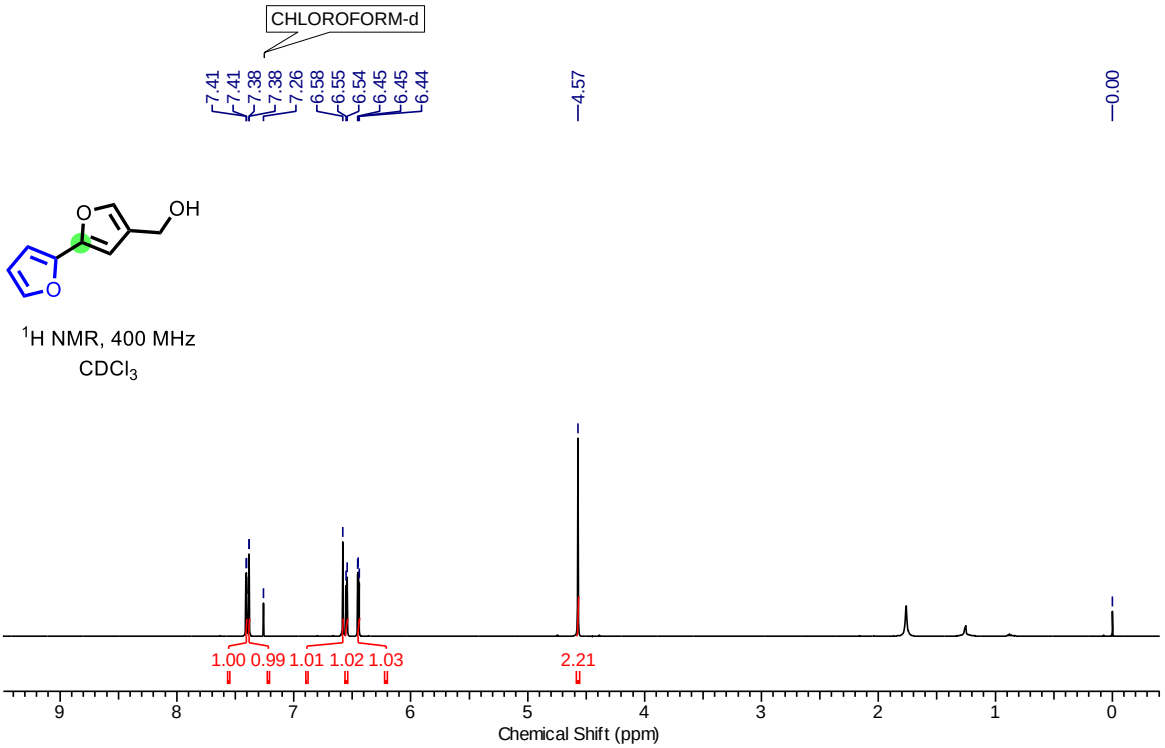
(5-(1-Methyl-1H-pyrrol-2-yl)furan-3-yl)methanol (**72v**):



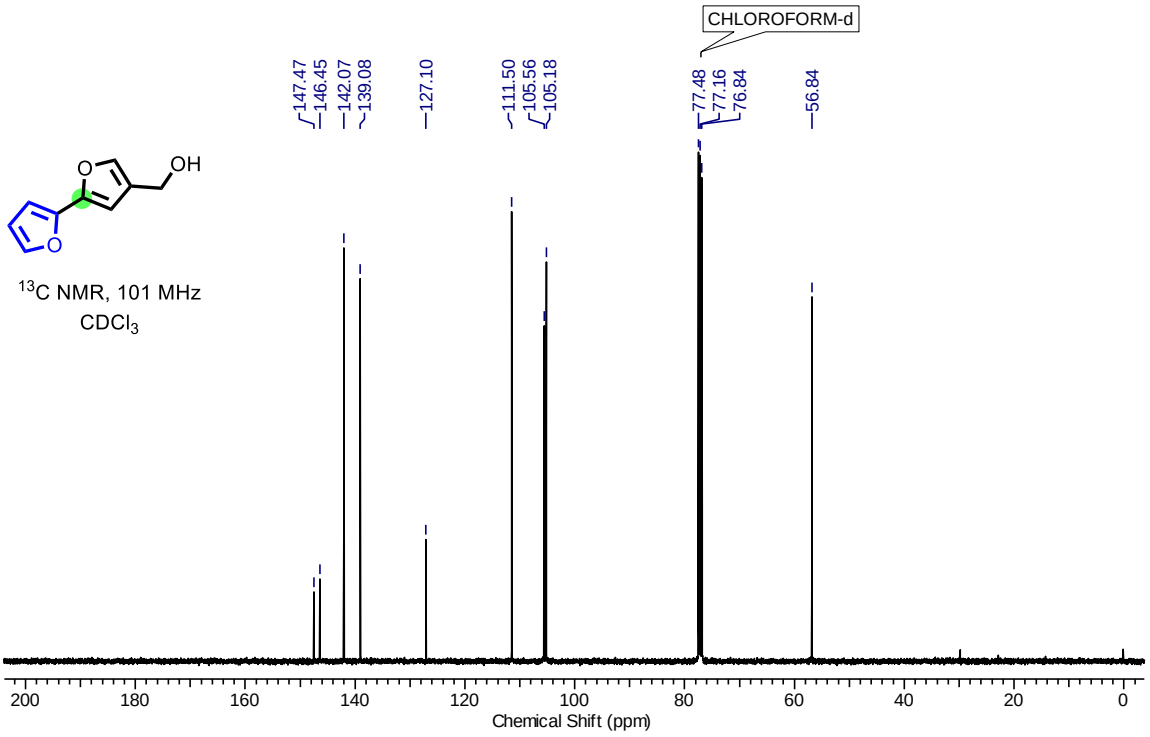
(5-(1-Methyl-1H-pyrrol-2-yl)furan-3-yl)methanol (**72v**):



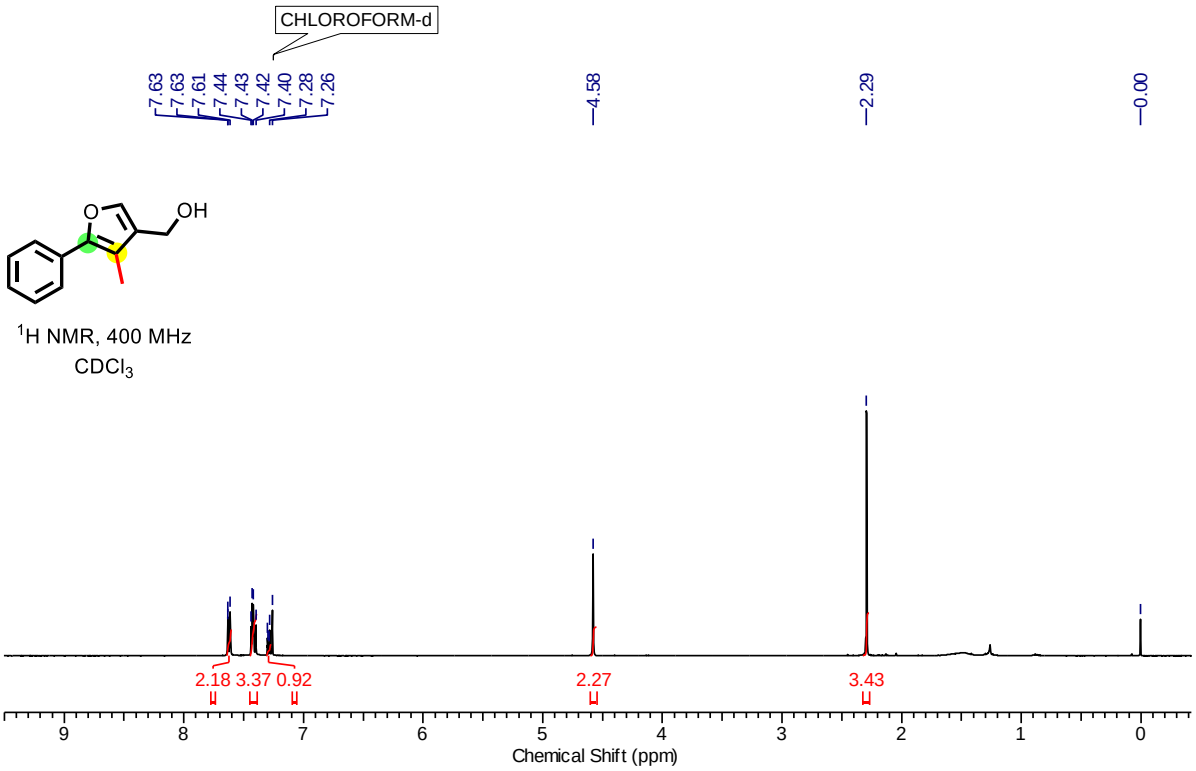
[2,2'-Bifuran]-4-ylmethanol (**72w**):



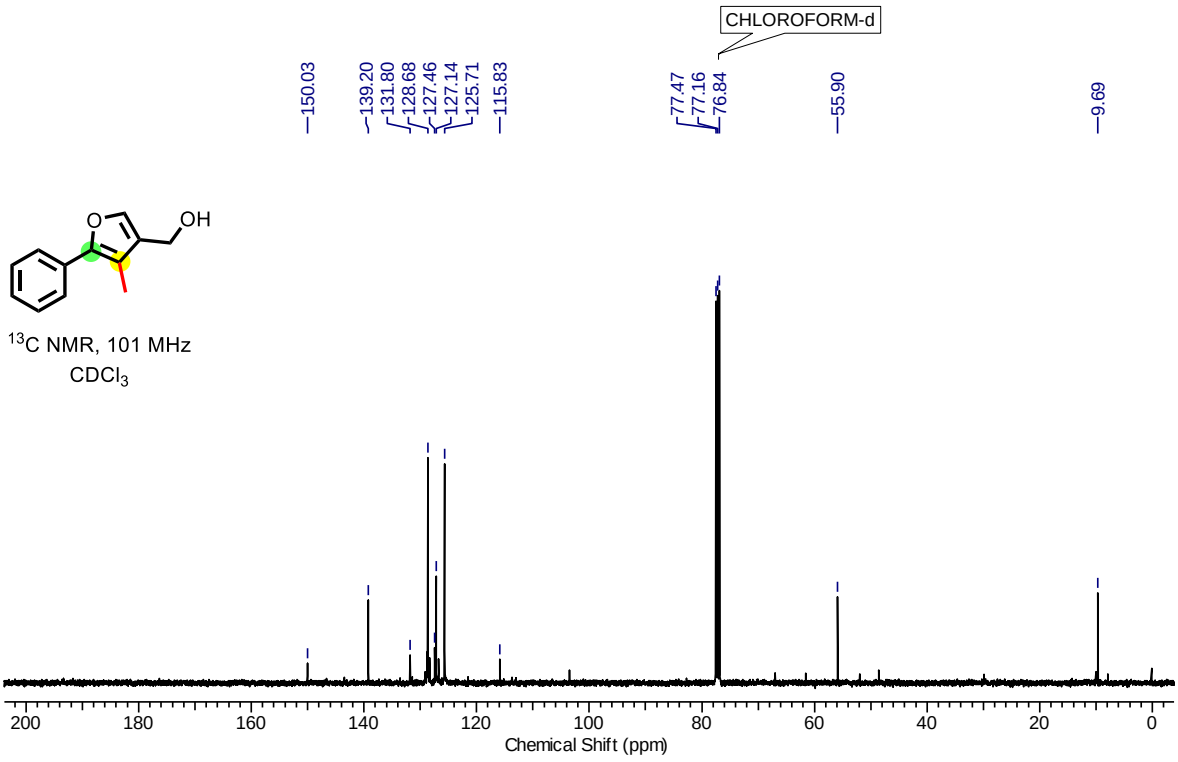
[2,2'-Bifuran]-4-ylmethanol (**72w**):



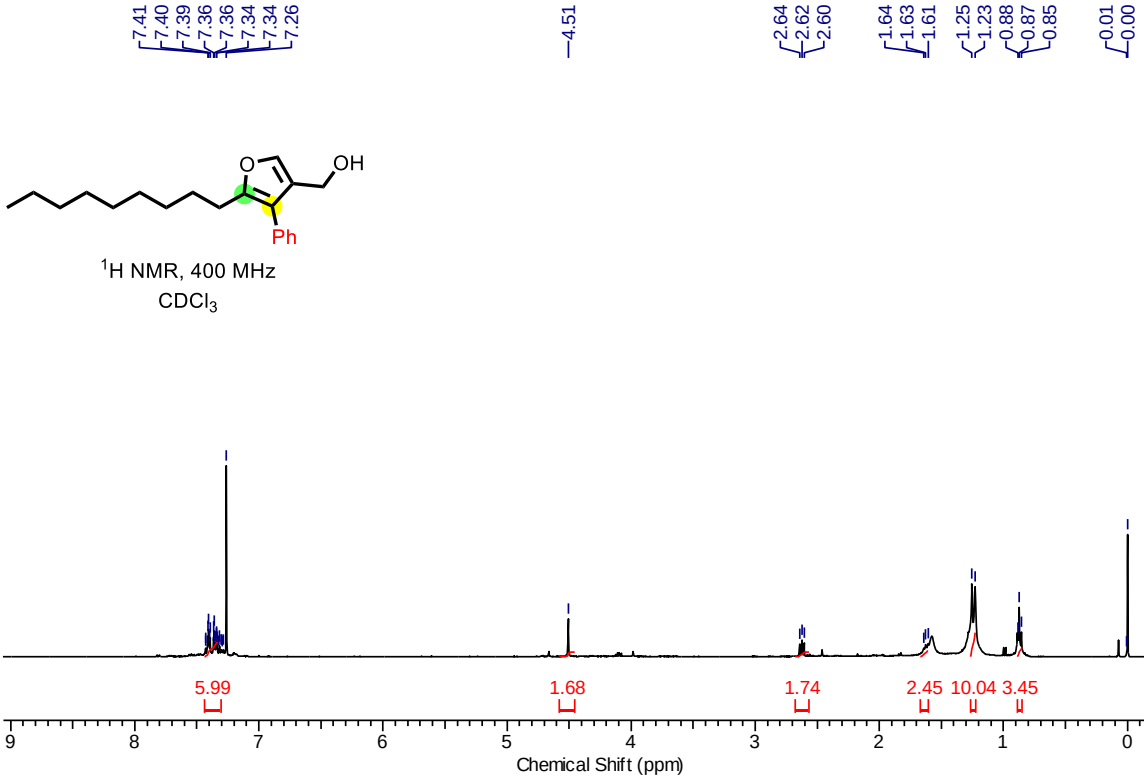
(4-Methyl-5-phenylfuran-3-yl)methanol (**72x**):



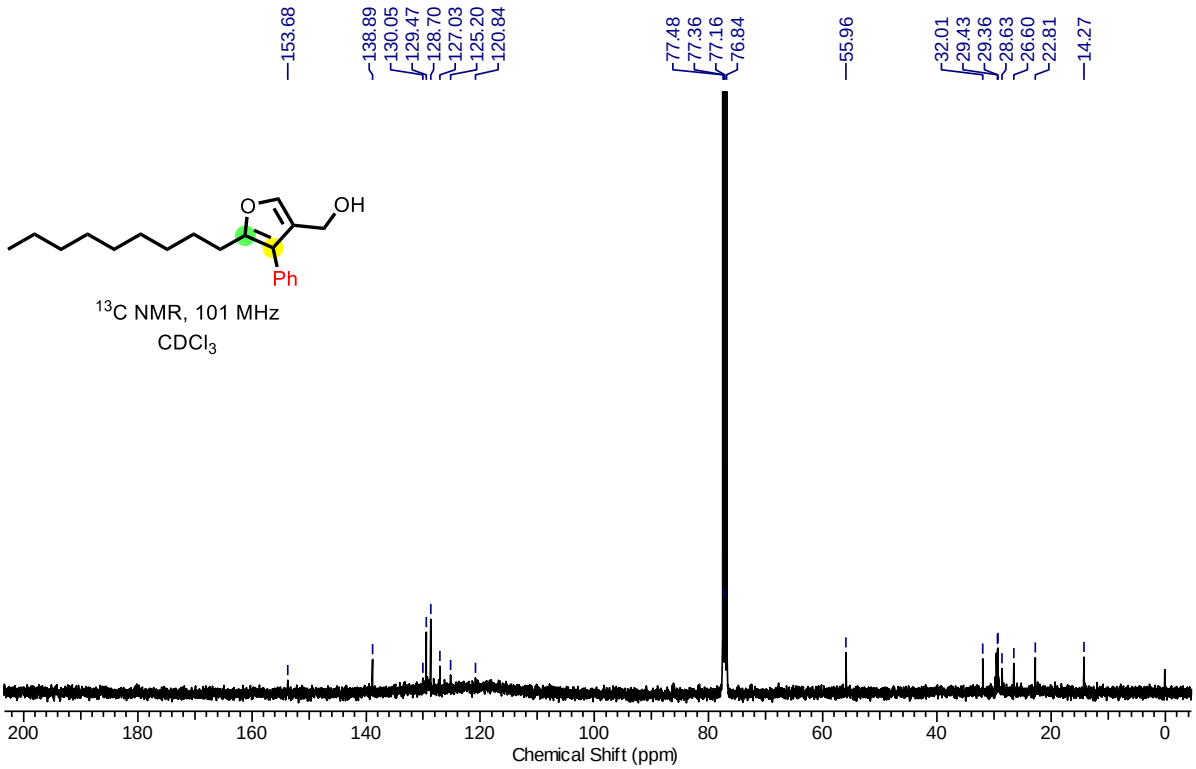
(4-Methyl-5-phenylfuran-3-yl)methanol (**72x**):



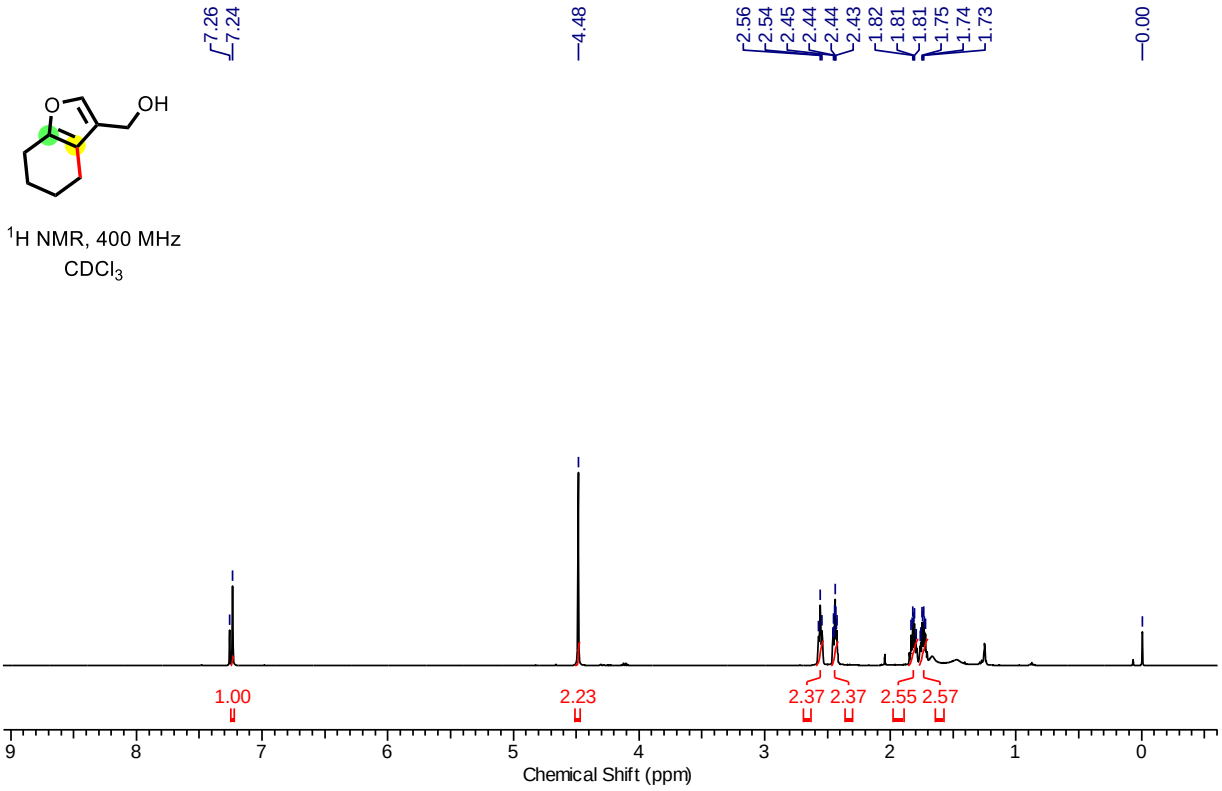
(5-Nonyl-4-phenylfuran-3-yl)methanol (**72y**):



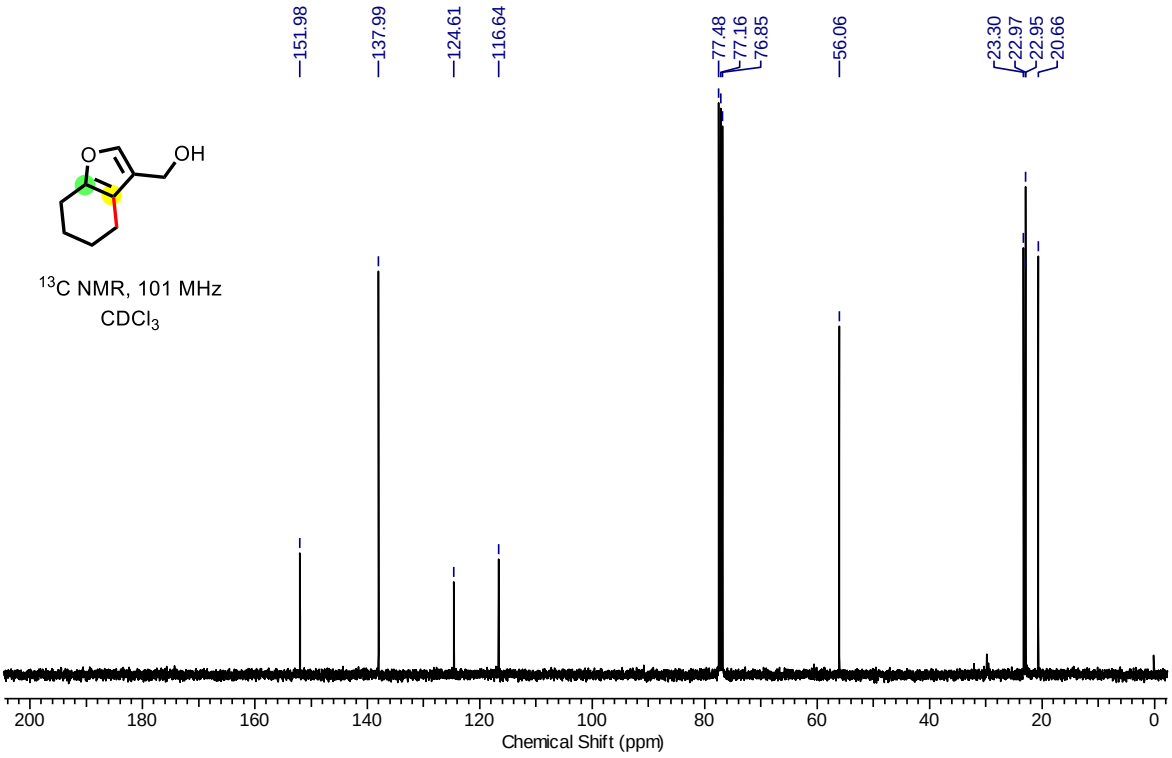
(5-Nonyl-4-phenylfuran-3-yl)methanol (**72y**):



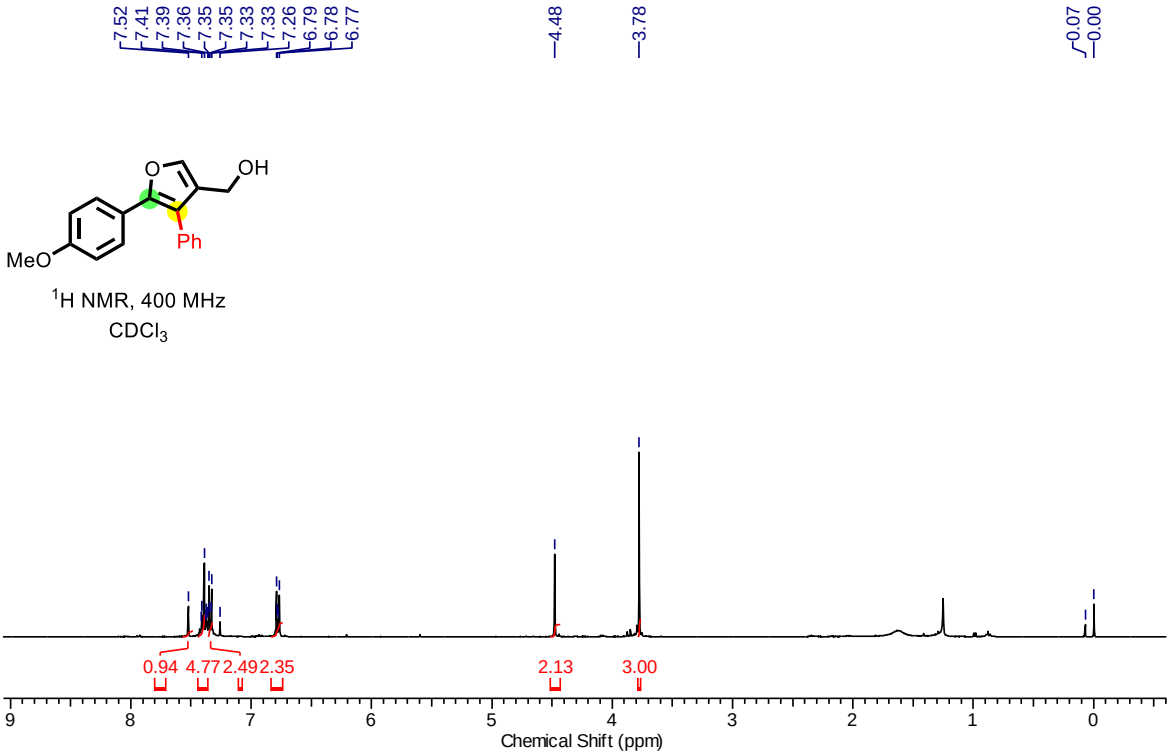
(4,5,6,7-Tetrahydrobenzofuran-3-yl)methanol (**72z**):



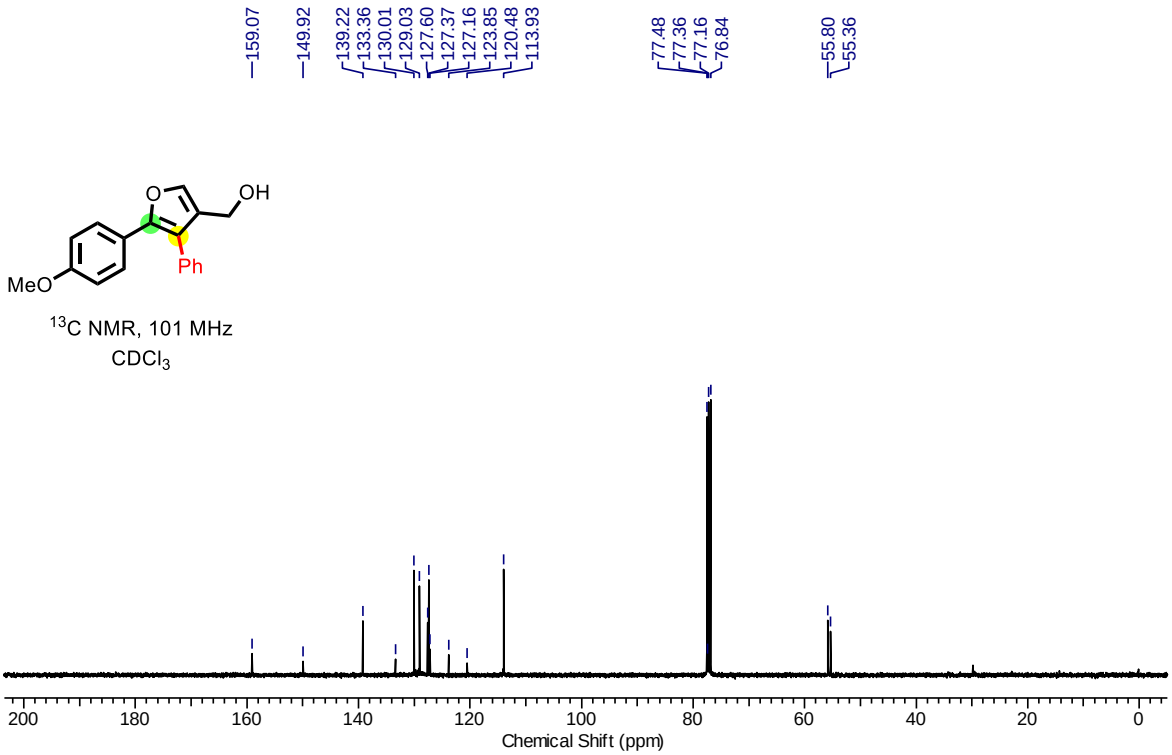
(4,5,6,7-Tetrahydrobenzofuran-3-yl)methanol (**72z**):



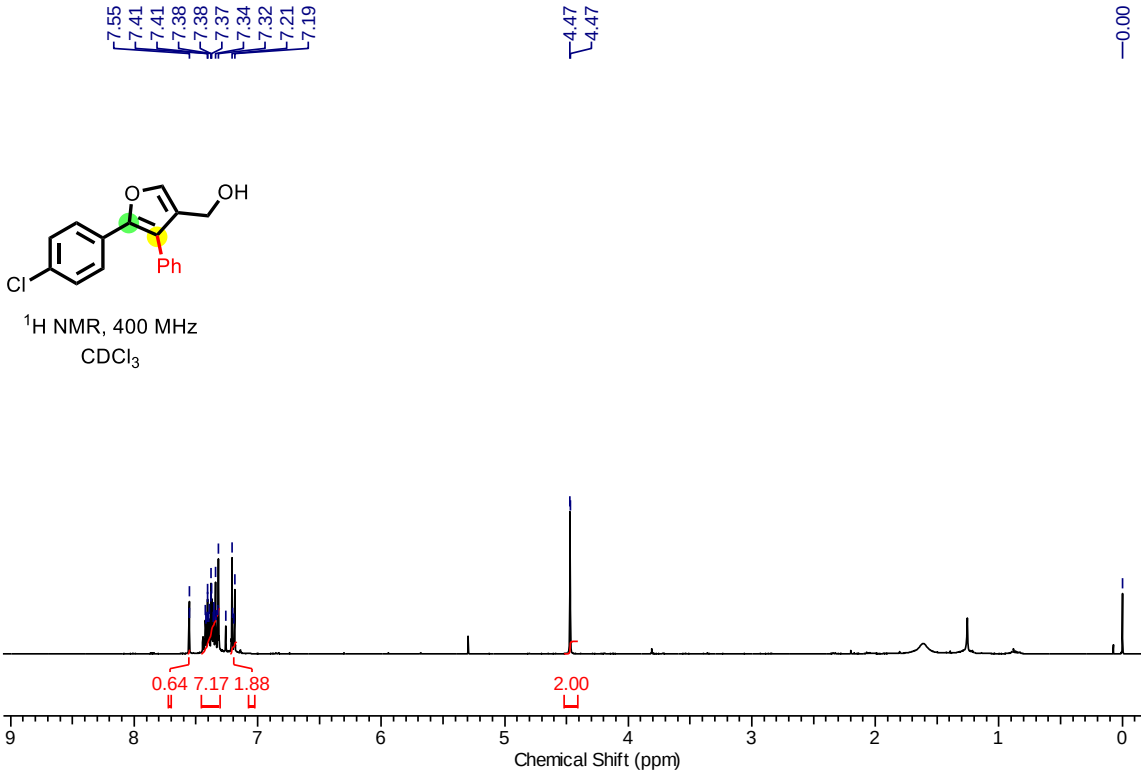
(5-(4-Methoxyphenyl)-4-phenylfuran-3-yl)methanol (**72aa**):



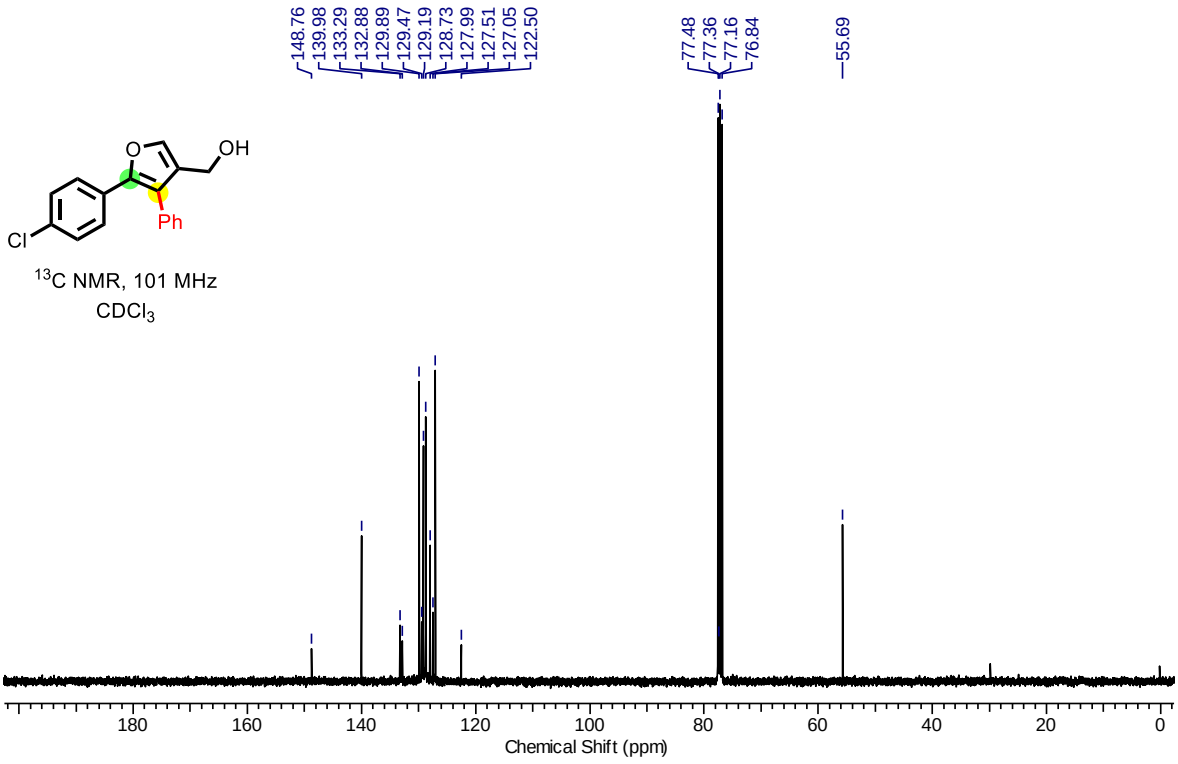
(5-(4-Methoxyphenyl)-4-phenylfuran-3-yl)methanol (**72aa**):



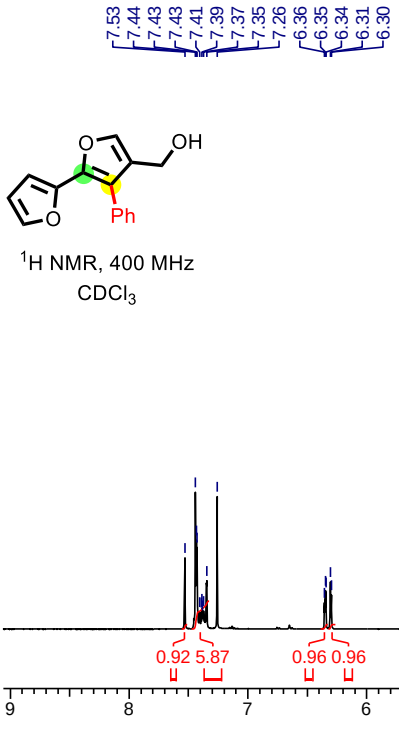
(5-(4-Chlorophenyl)-4-phenylfuran-3-yl)methanol (**72ab**):



(5-(4-Chlorophenyl)-4-phenylfuran-3-yl)methanol (**72ab**):

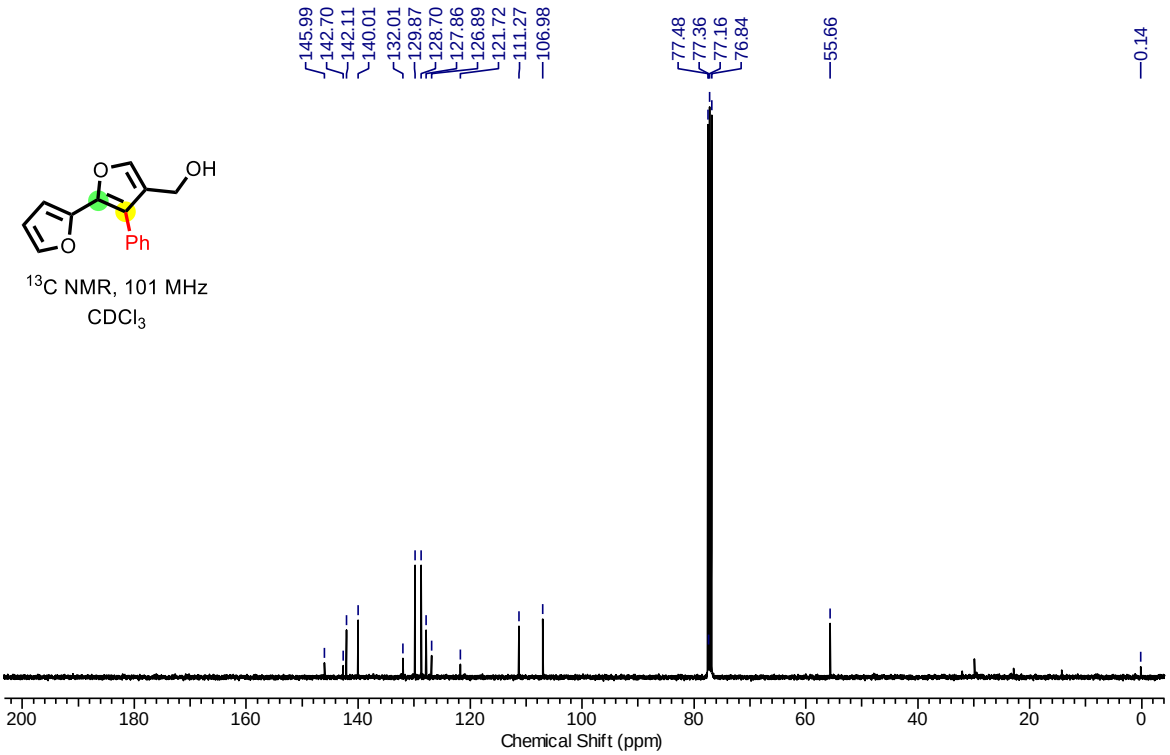


(3-Phenyl-[2,2'-bifuran]-4-yl)methanol (**72ac**):



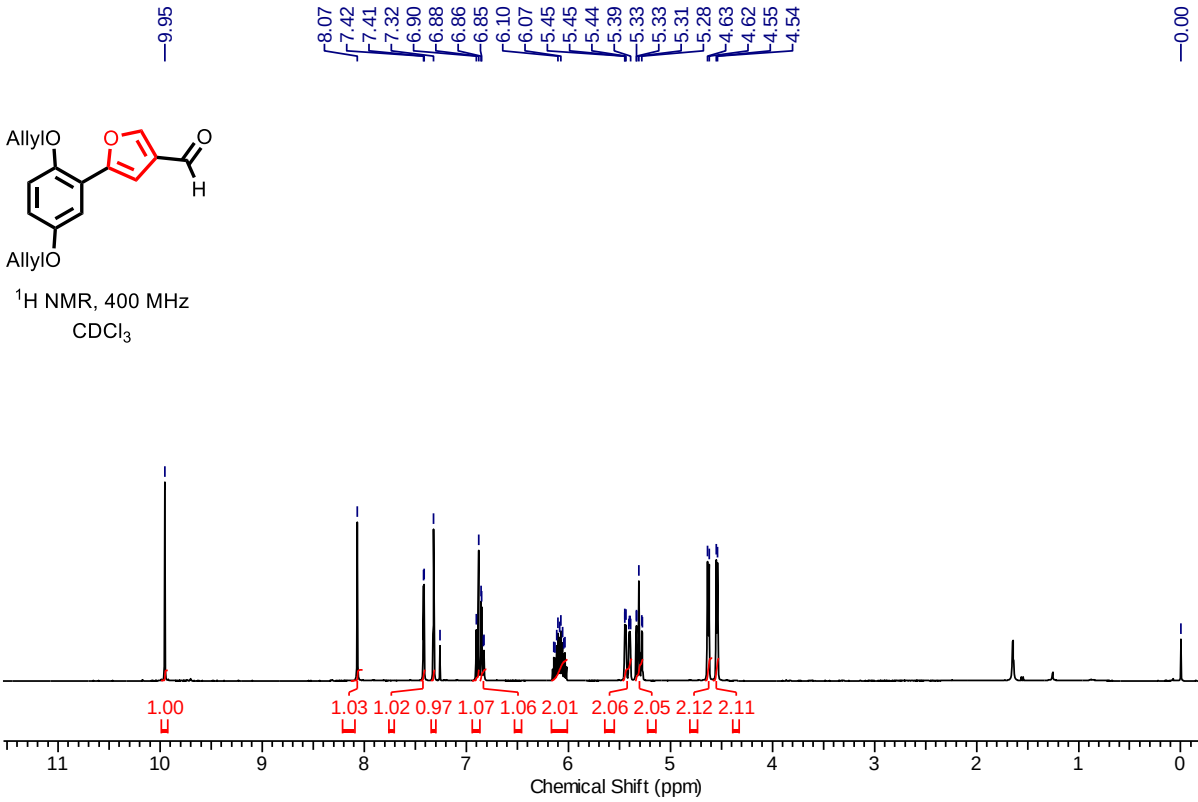
^{1}H NMR, 400 MHz
$CDCl_3$

(3-Phenyl-[2,2'-bifuran]-4-yl)methanol (**72ac**):



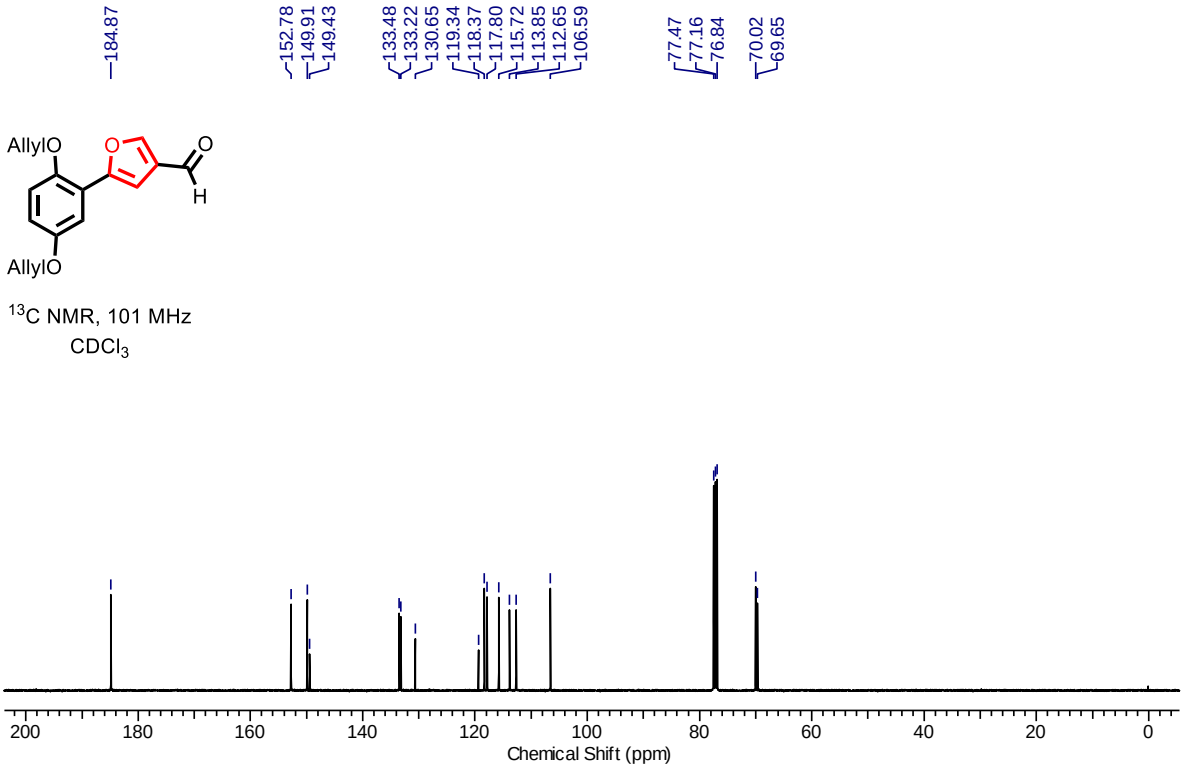
^{13}C NMR, 101 MHz
$CDCl_3$

5-(2,5-Bis(allyloxy)phenyl)furan-3-carbaldehyde (**80**):



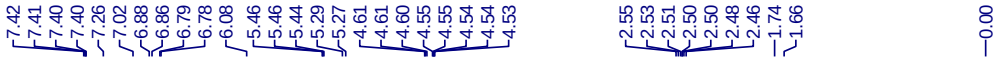
^{1}H NMR, 400 MHz
$CDCl_3$

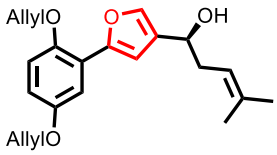
5-(2,5-Bis(allyloxy)phenyl)furan-3-carbaldehyde (**80**):



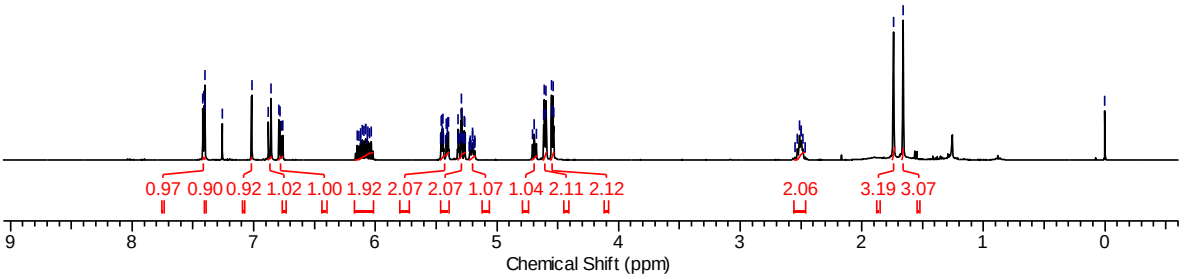
^{13}C NMR, 101 MHz
$CDCl_3$

(*S*)-1-(5-(2,5-Bis(allyloxy)phenyl)furan-3-yl)-4-methylpent-3-en-1-ol (**78**):

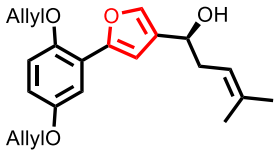




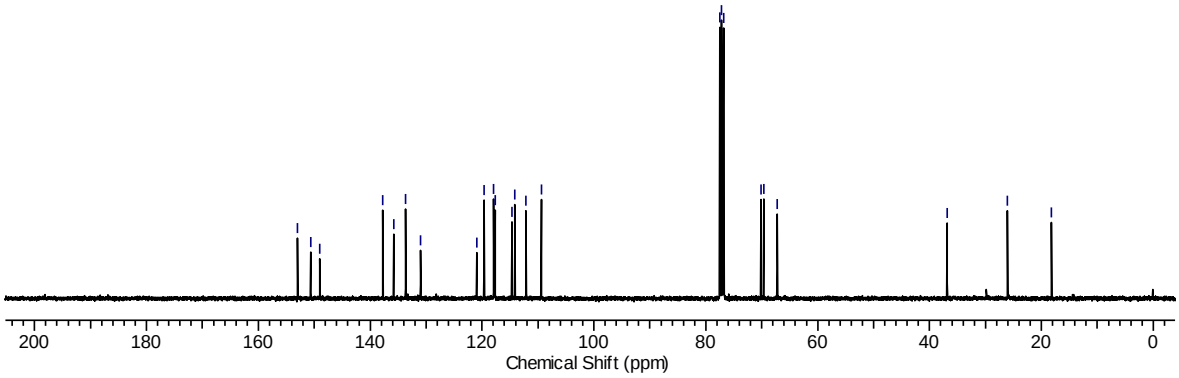
^{1}H NMR, 400 MHz
$CDCl_3$



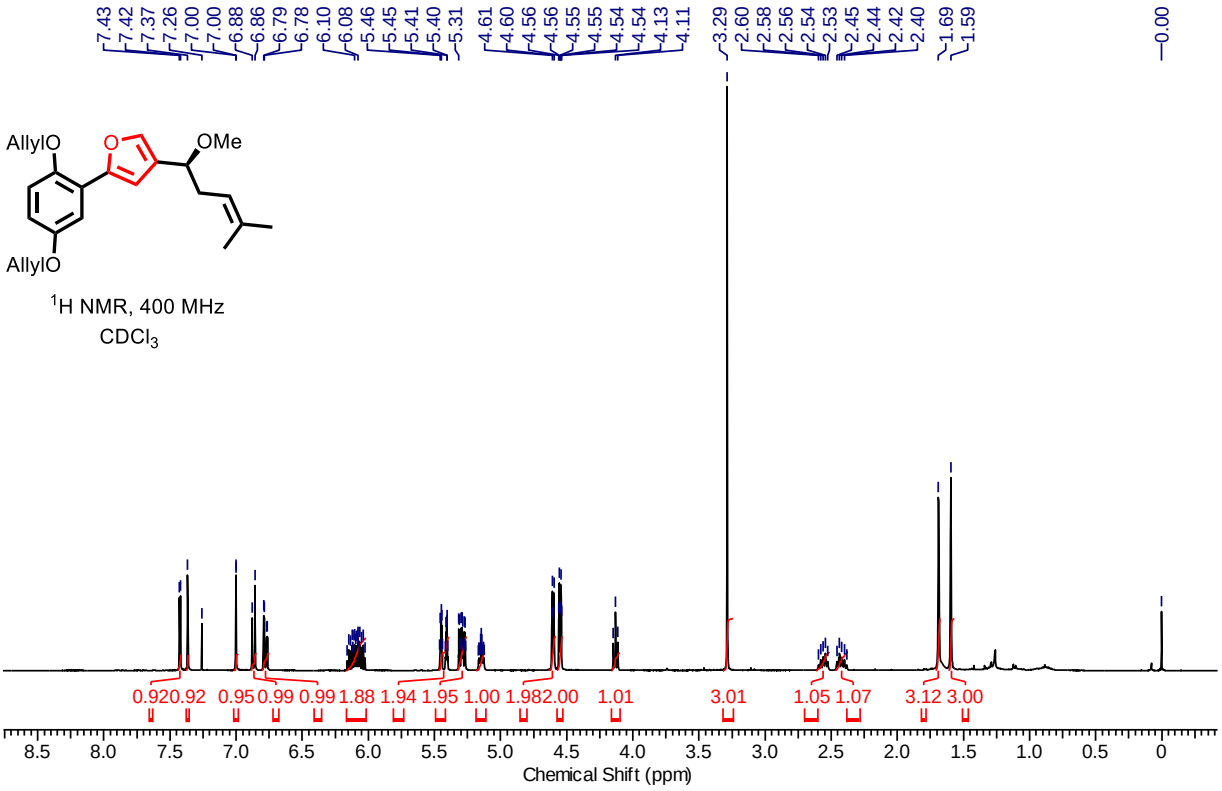
(*S*)-1-(5-(2,5-Bis(allyloxy)phenyl)furan-3-yl)-4-methylpent-3-en-1-ol (**78**):



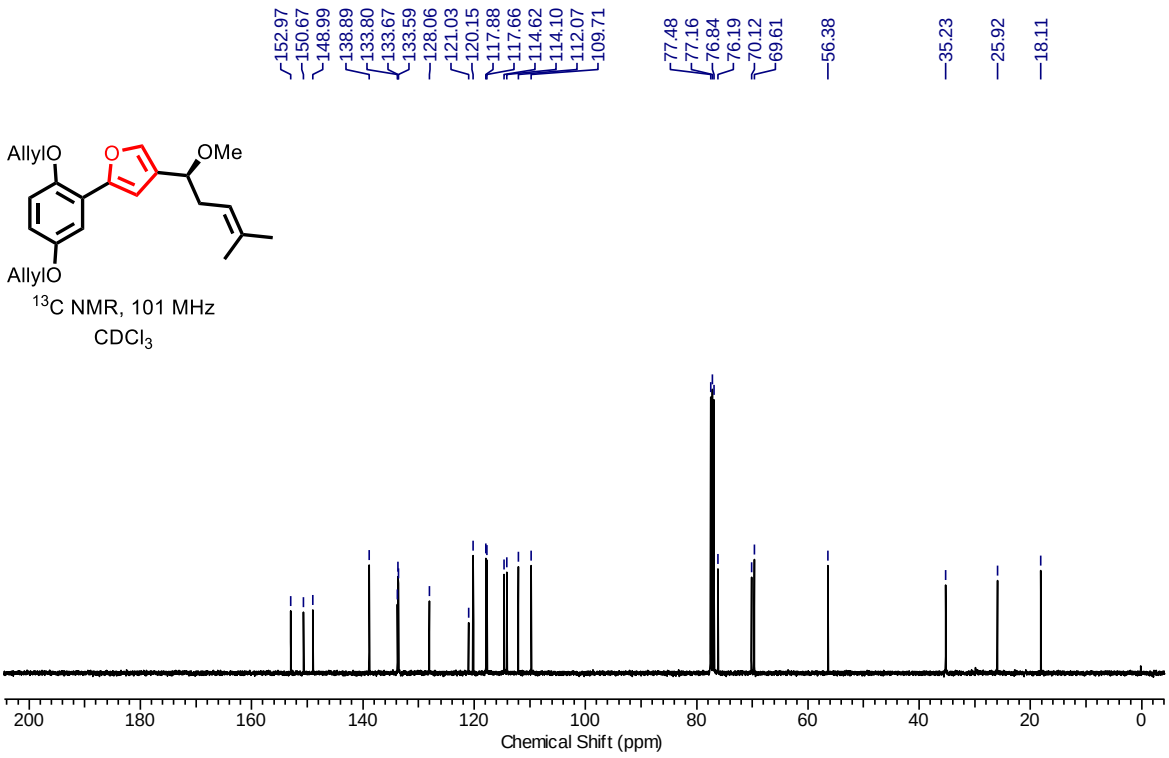
^{13}C NMR, 101 MHz
$CDCl_3$



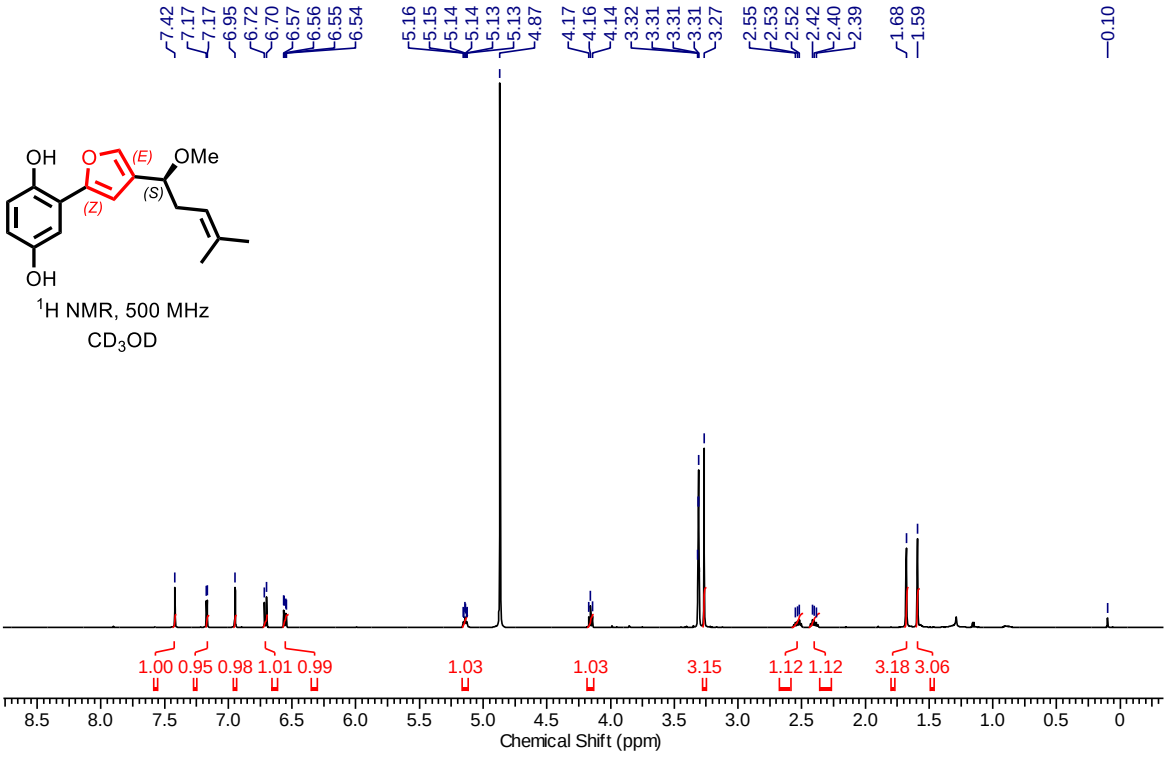
(*S*)-2-(2,5-Bis(allyloxy)phenyl)-4-(1-methoxy-4-methylpent-3-en-1-yl)furan (**84**):



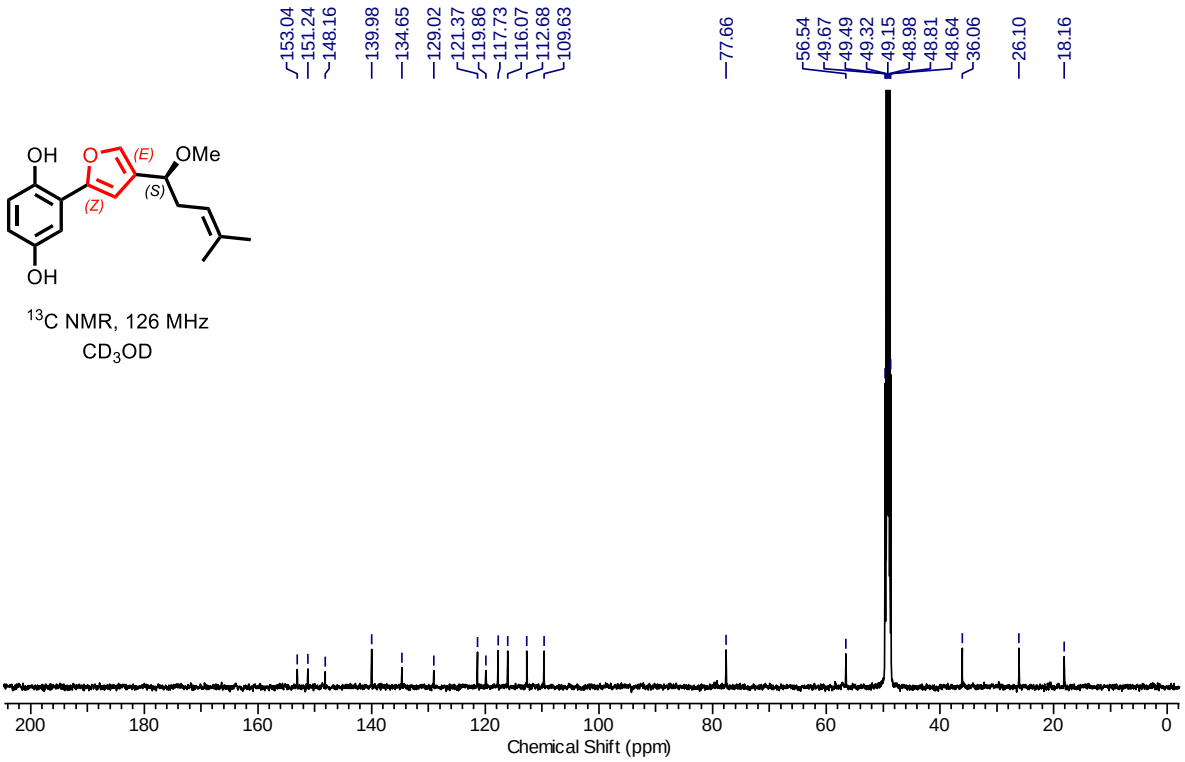
(*S*)-2-(2,5-Bis(allyloxy)phenyl)-4-(1-methoxy-4-methylpent-3-en-1-yl)furan (**84**):



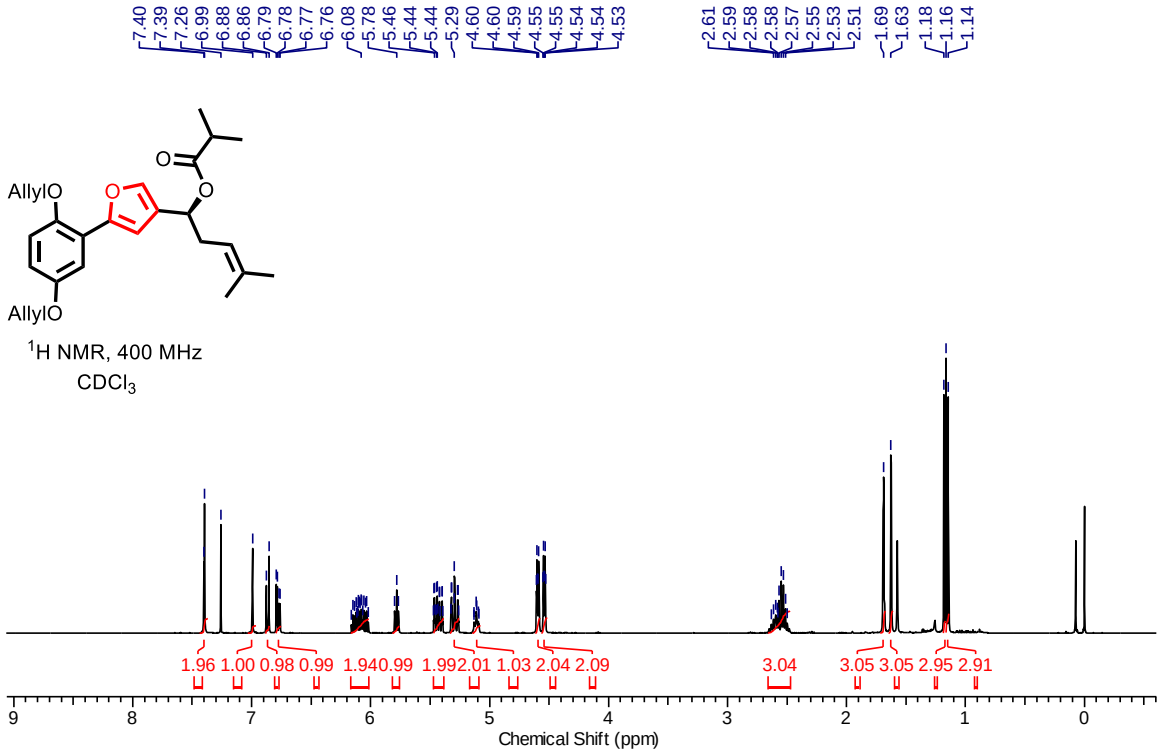
Shikonofuran J (**41**):



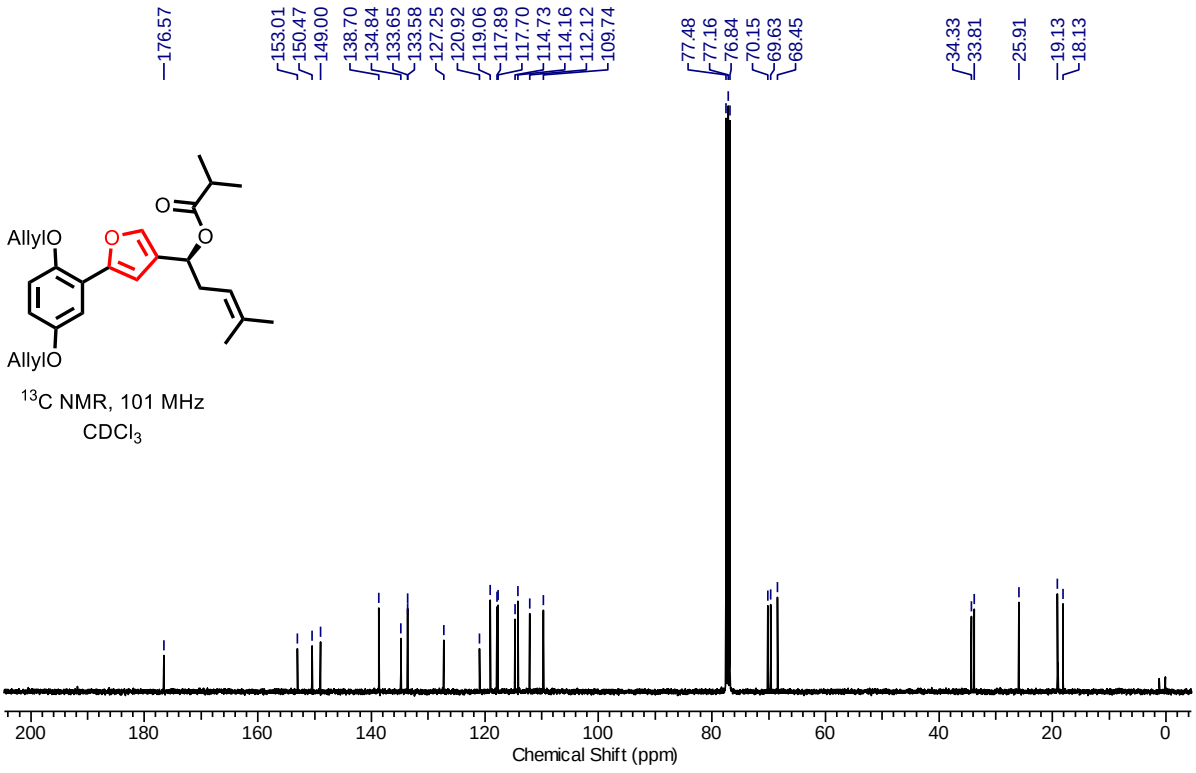
Shikonofuran J (**41**):



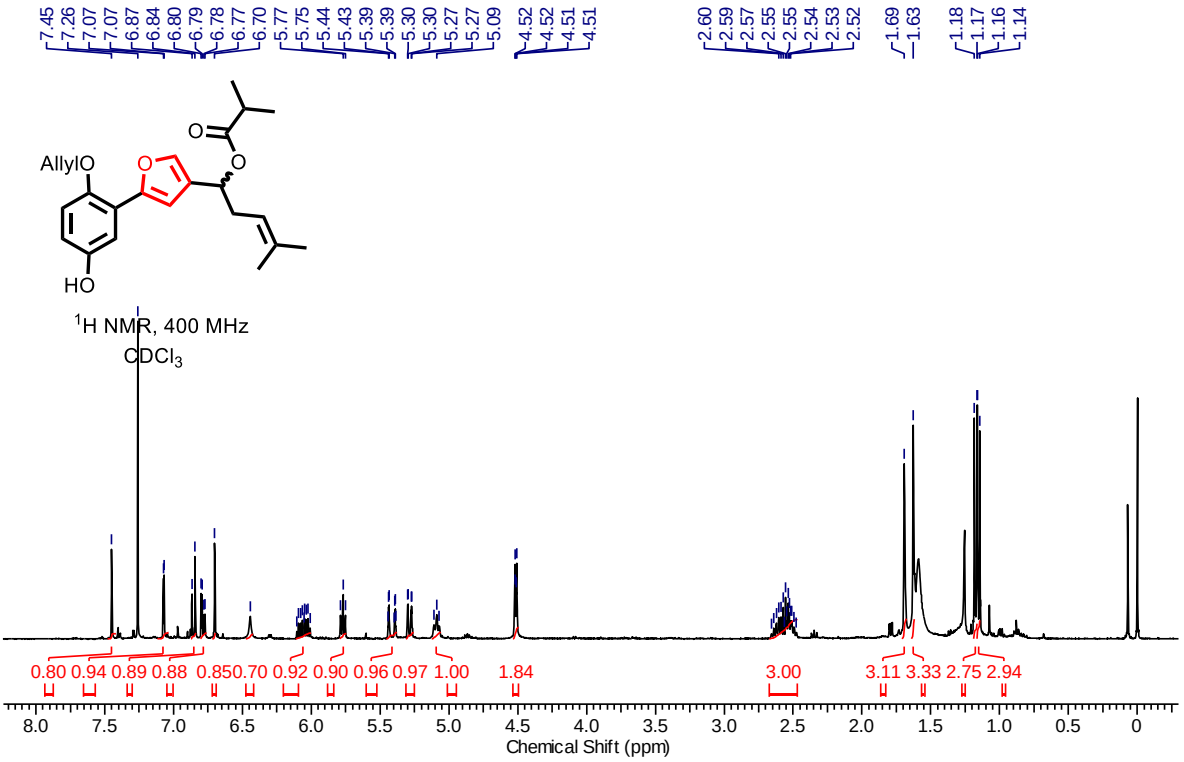
(*S*)-1-(5-(2,5-Bis(allyloxy)phenyl)furan-3-yl)-4-methylpent-3-en-1-yl isobutyrate (**86**):



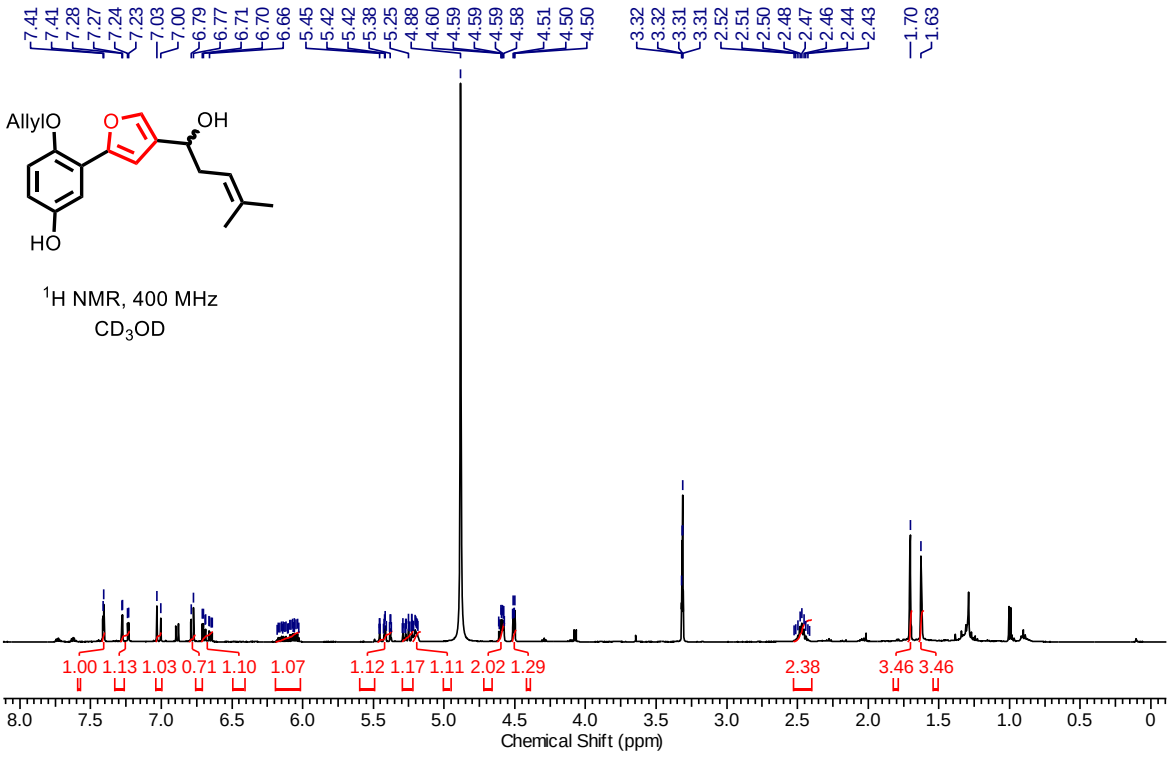
(*S*)-1-(5-(2,5-Bis(allyloxy)phenyl)furan-3-yl)-4-methylpent-3-en-1-yl isobutyrate (**86**):



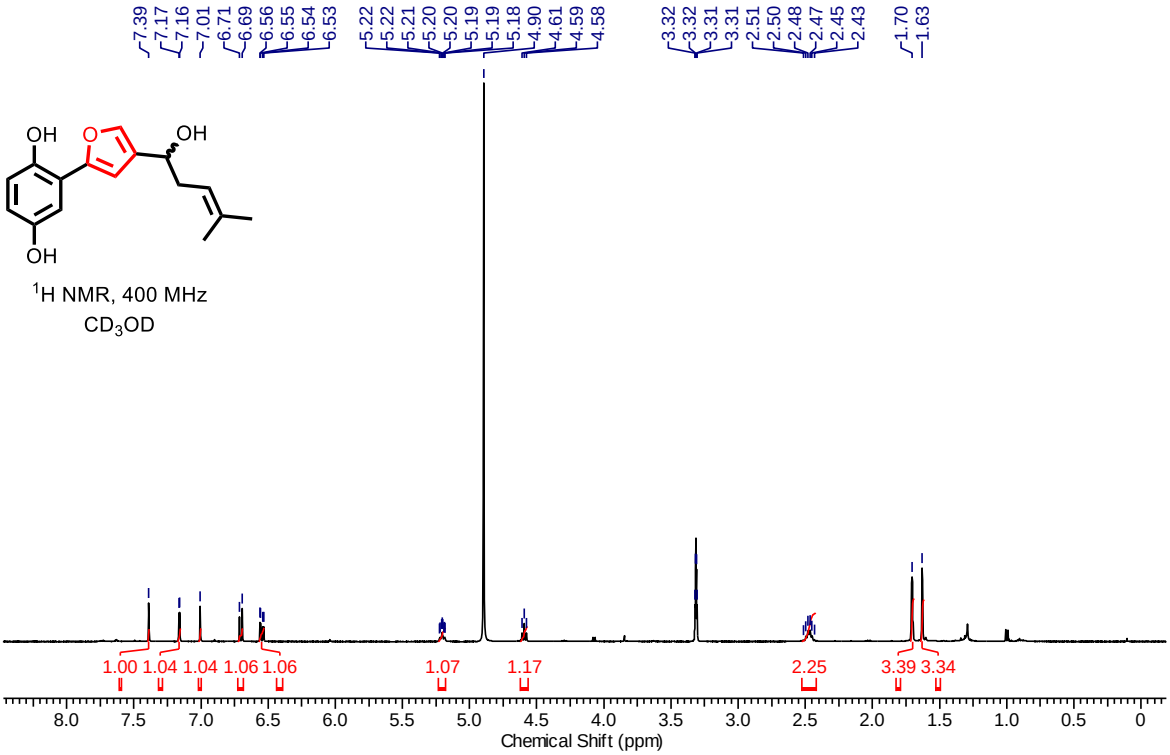
1-(5-(2-(Allyloxy)-5-hydroxyphenyl)furan-3-yl)-4-methylpent-3-en-1-yl isobutyrate (**87**):



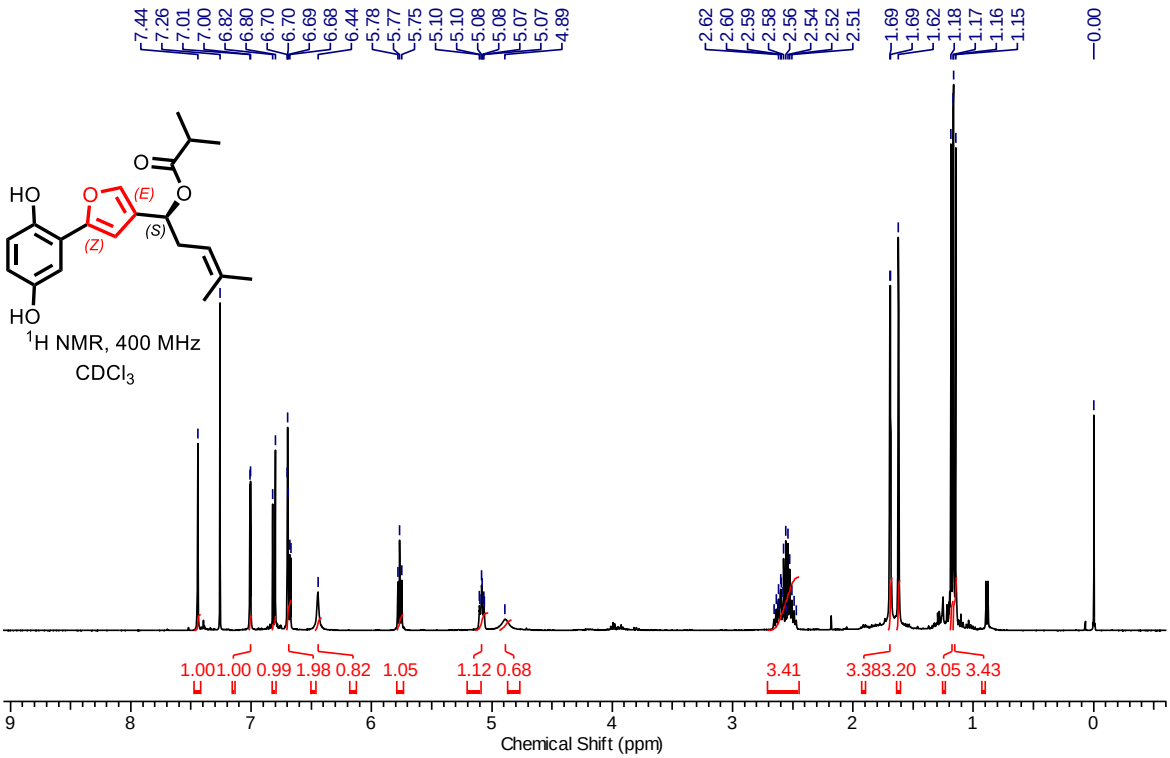
4-(Allyloxy)-3-(4-(1-hydroxy-4-methylpent-3-en-1-yl)furan-2-yl)phenol (**88**):



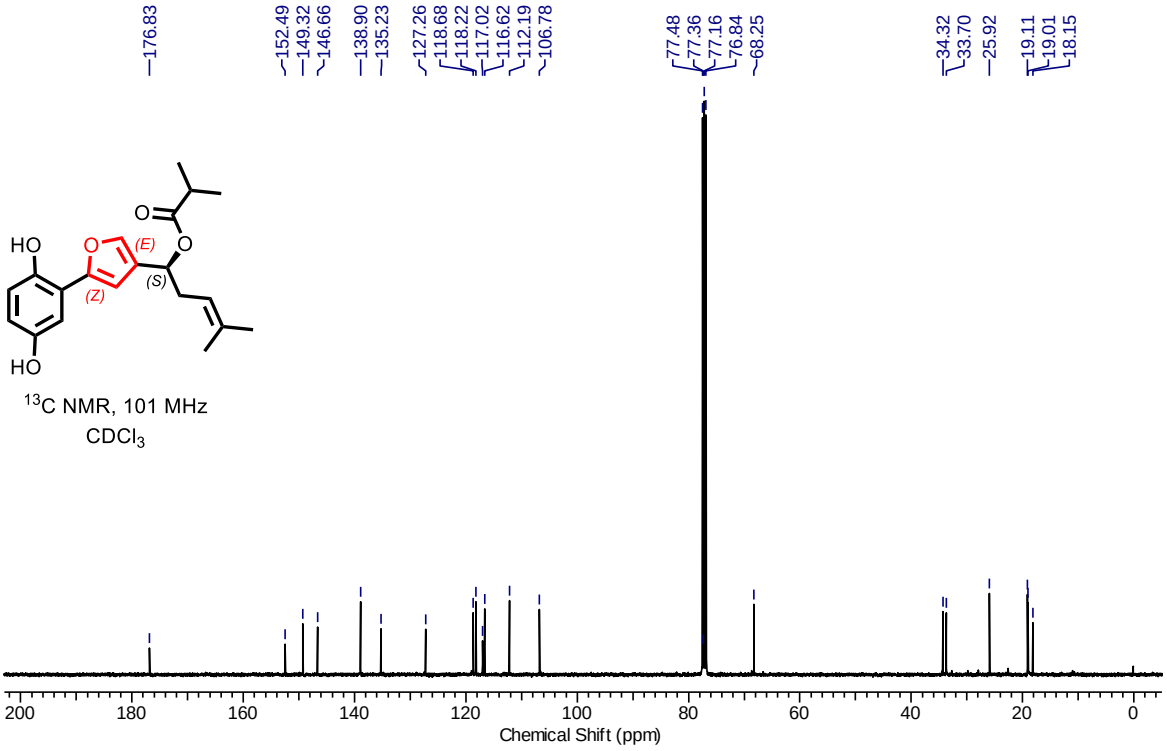
2-(4-(1-Hydroxy-4-methylpent-3-en-1-yl)furan-2-yl)benzene-1,4-diol (**89**):



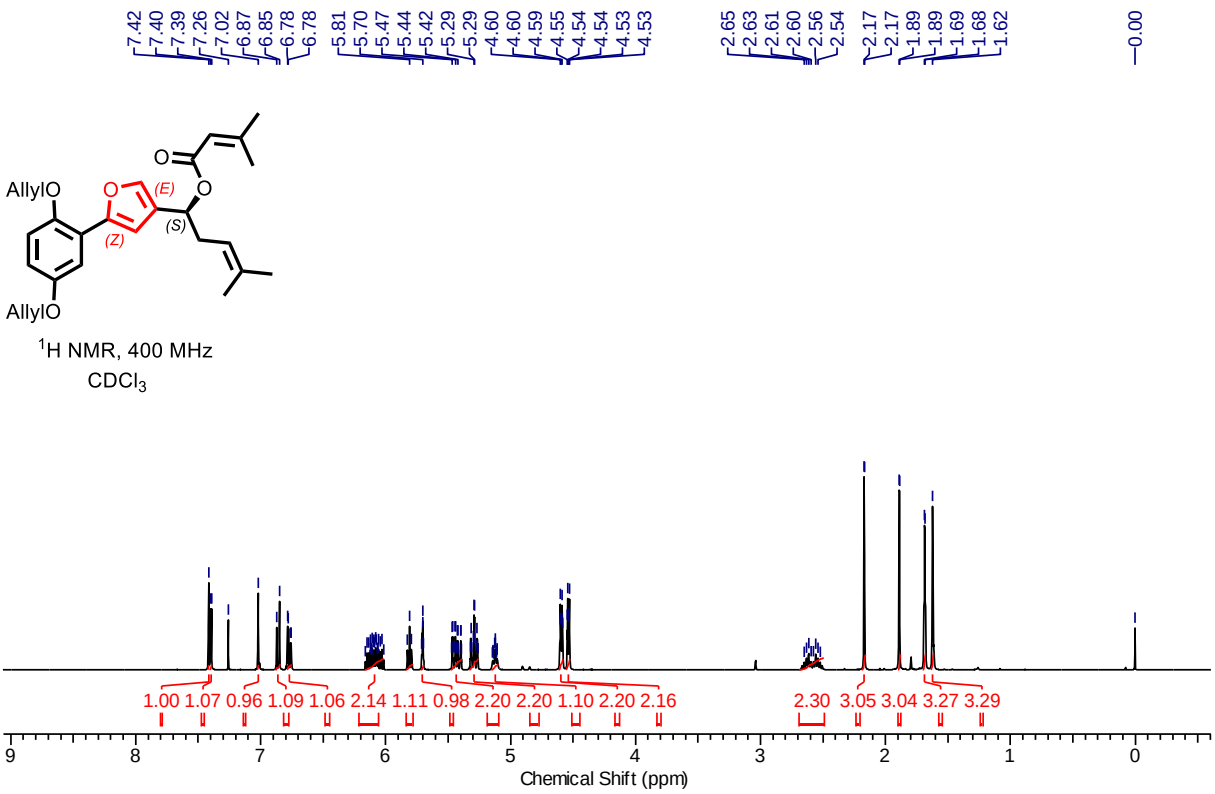
Shikonfuran D **(42):**



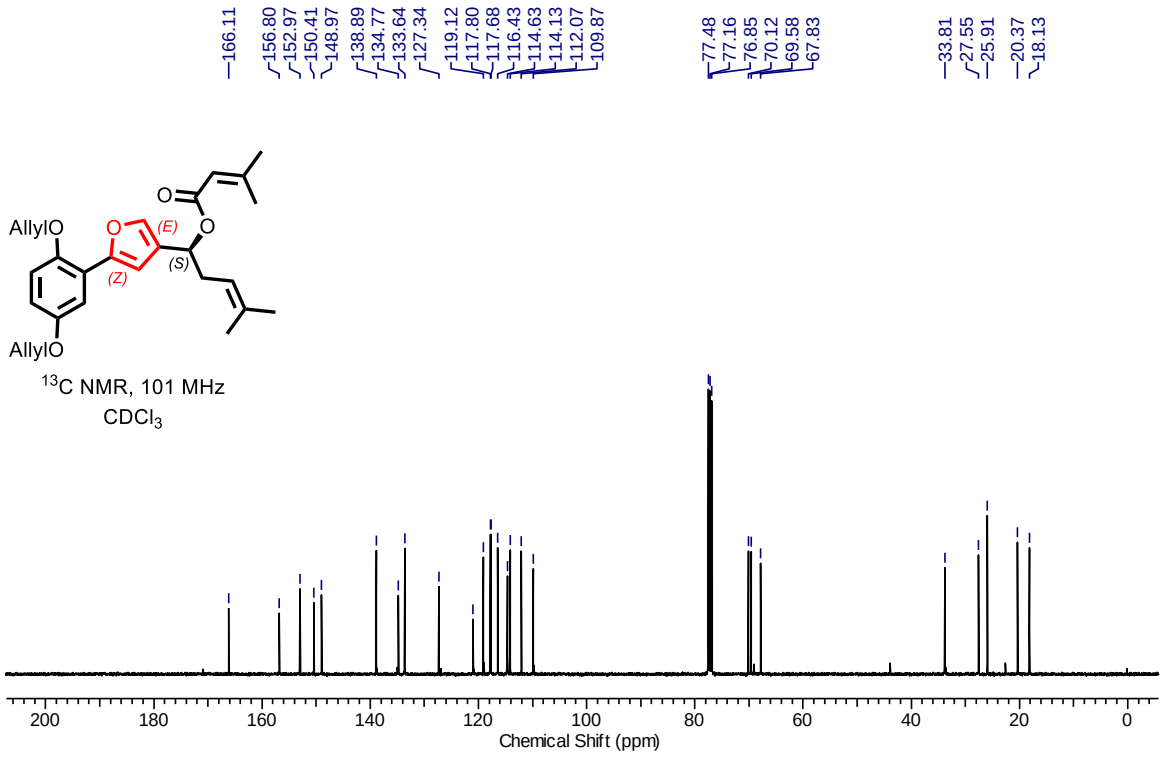
Shikonfuran D **(42):**



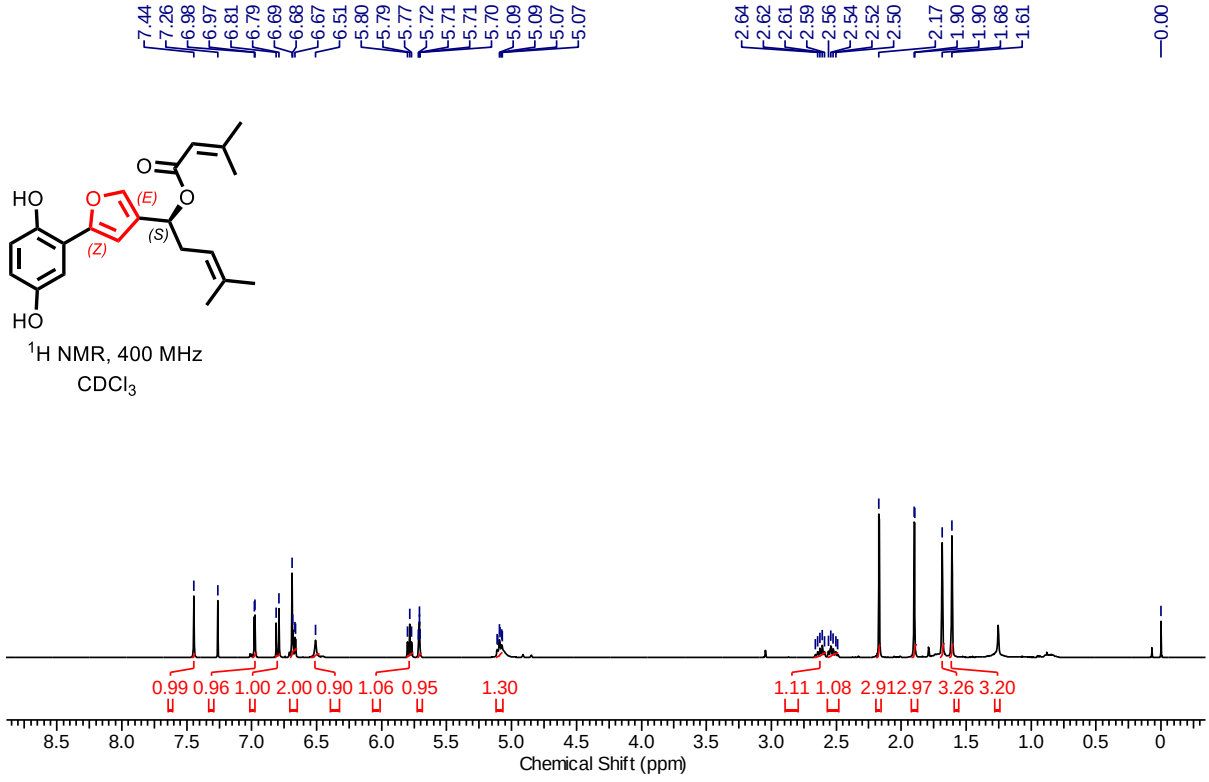
(*S*)-1-(5-(2,5-Bis(allyloxy)phenyl)furan-3-yl)-4-methylpent-3-en-1-yl 3-methylbut-2-enoate (**91**):



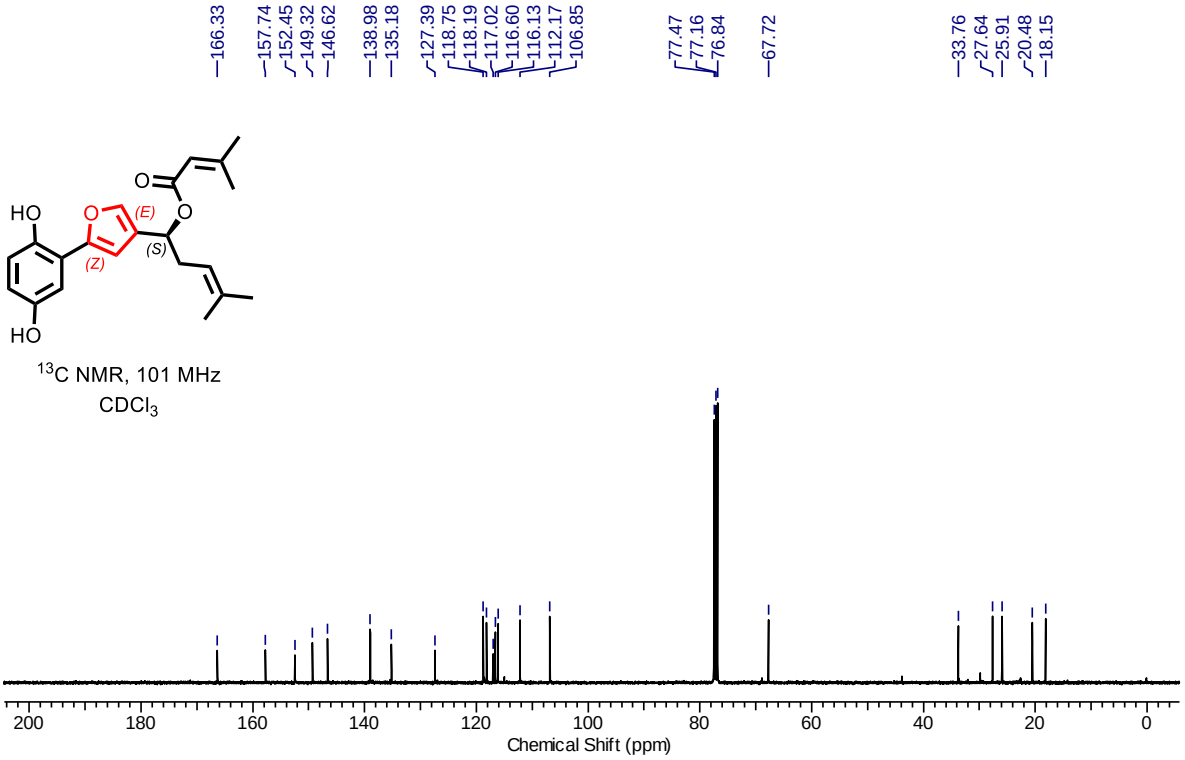
(*S*)-1-(5-(2,5-Bis(allyloxy)phenyl)furan-3-yl)-4-methylpent-3-en-1-yl 3-methylbut-2-enoate (**91**):



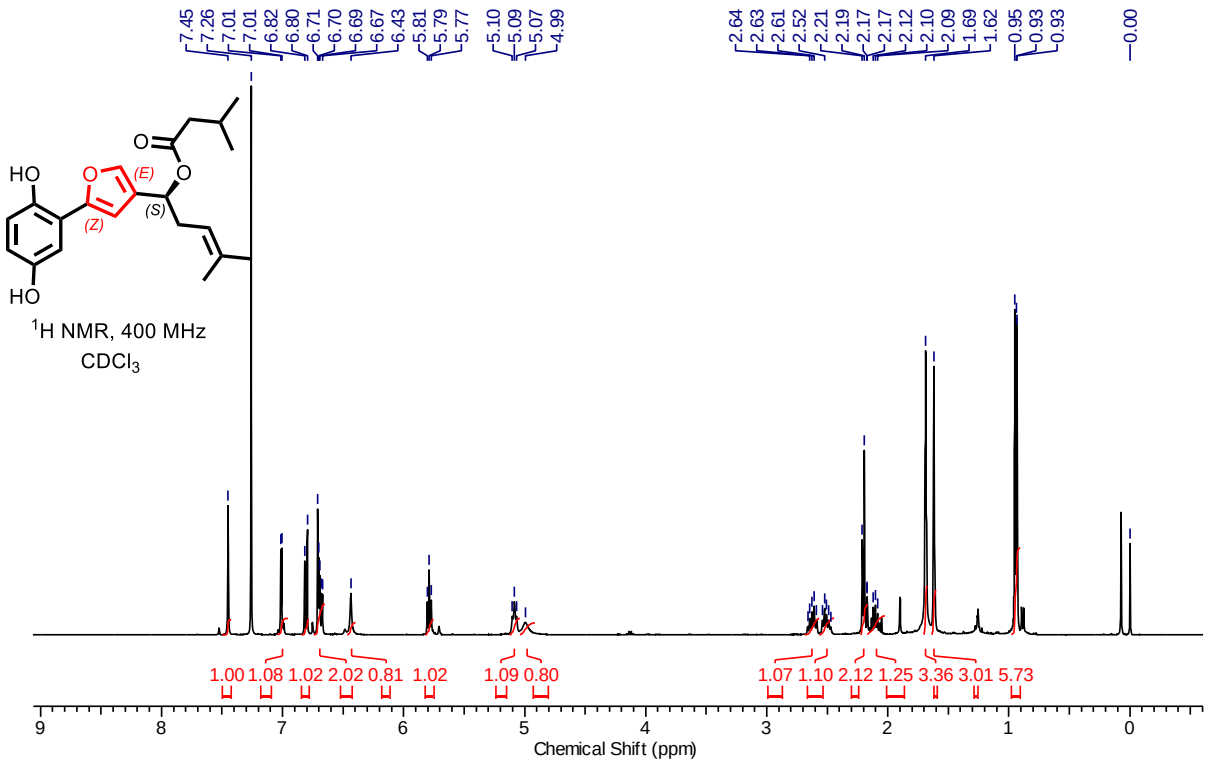
Shikonofuran E **(43):**



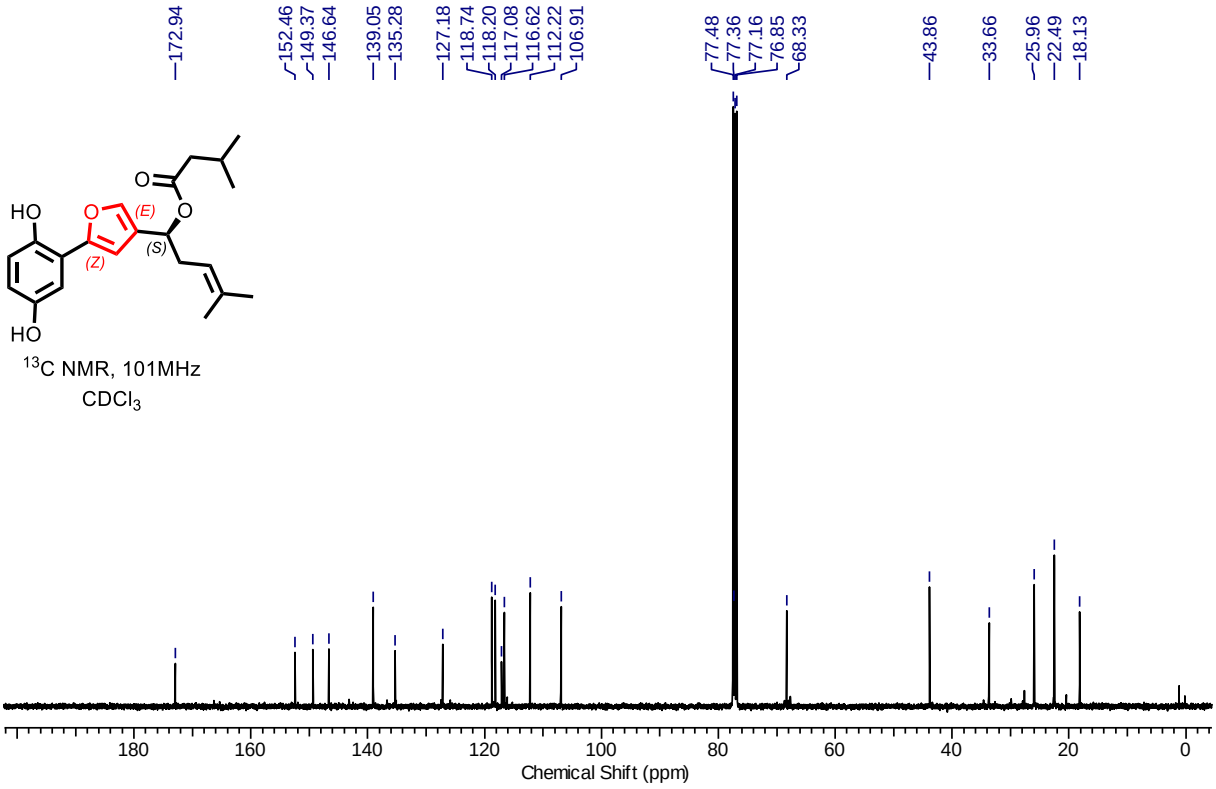
Shikonofuran E **(43):**



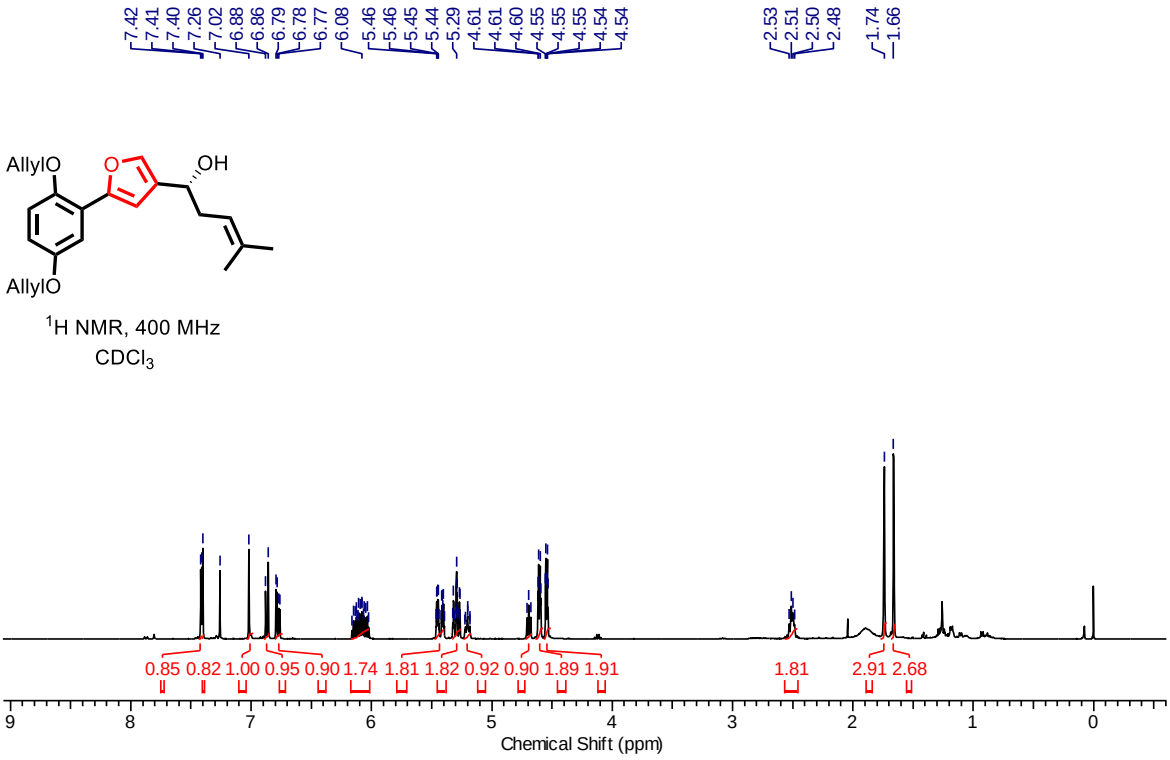
Shikonofuran C (**44**):



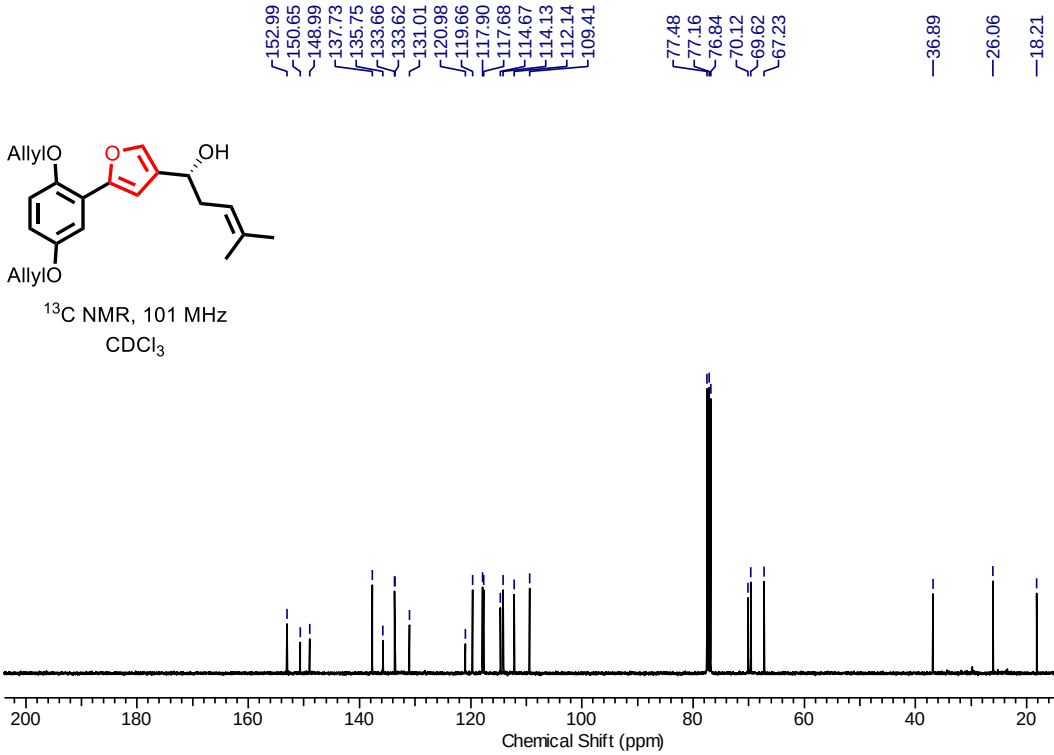
Shikonofuran C (**44**):



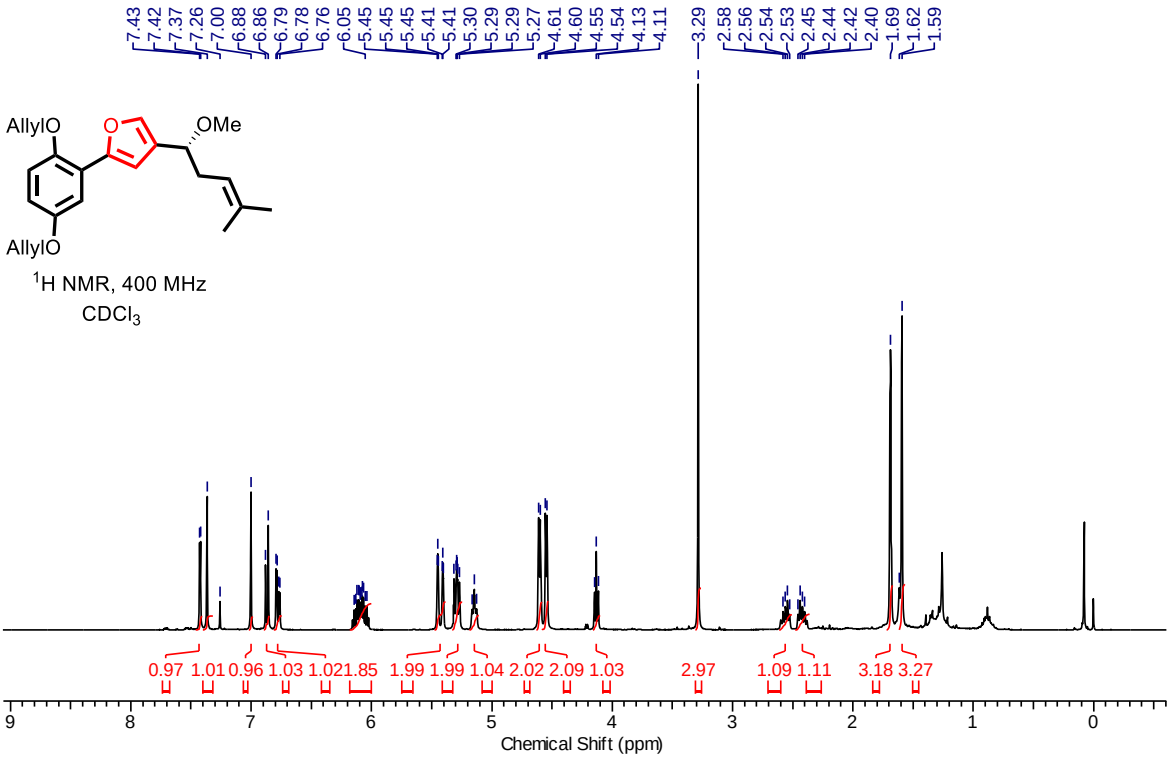
(*S*)-1-(5-(2,5-Bis(allyloxy)phenyl)furan-3-yl)-4-methylpent-3-en-1-ol (**78a**):



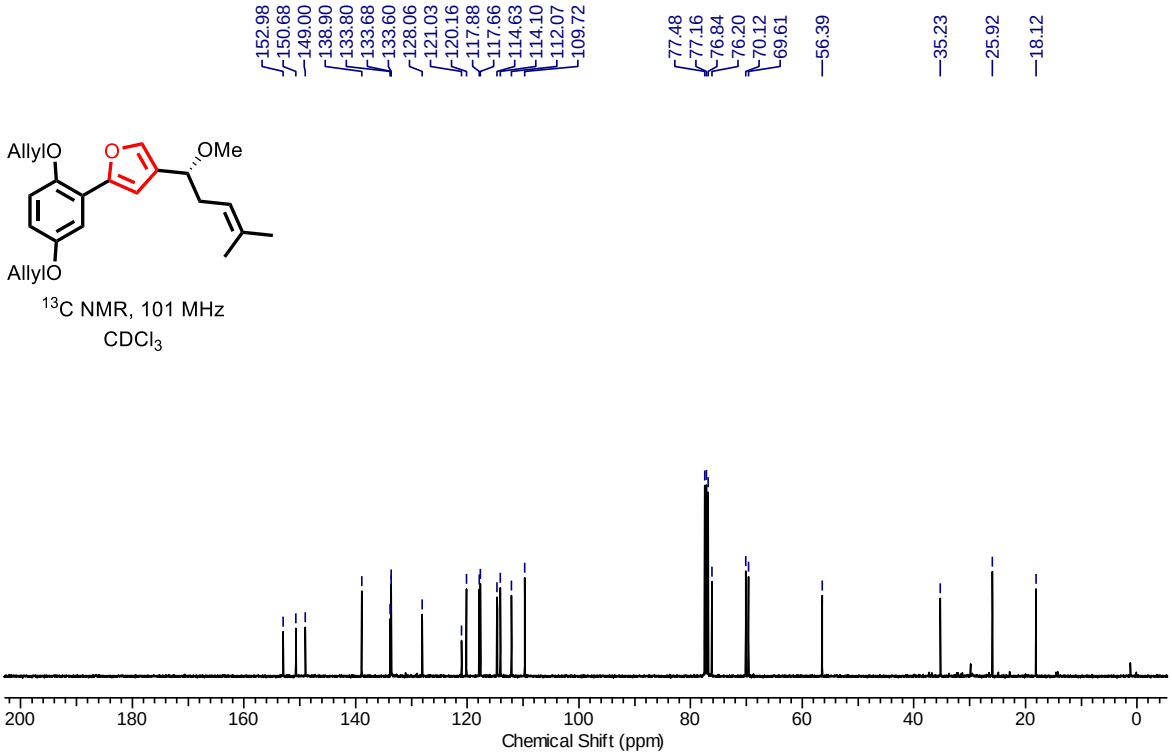
(*S*)-1-(5-(2,5-bis(allyloxy)phenyl)furan-3-yl)-4-methylpent-3-en-1-ol (**78a**):



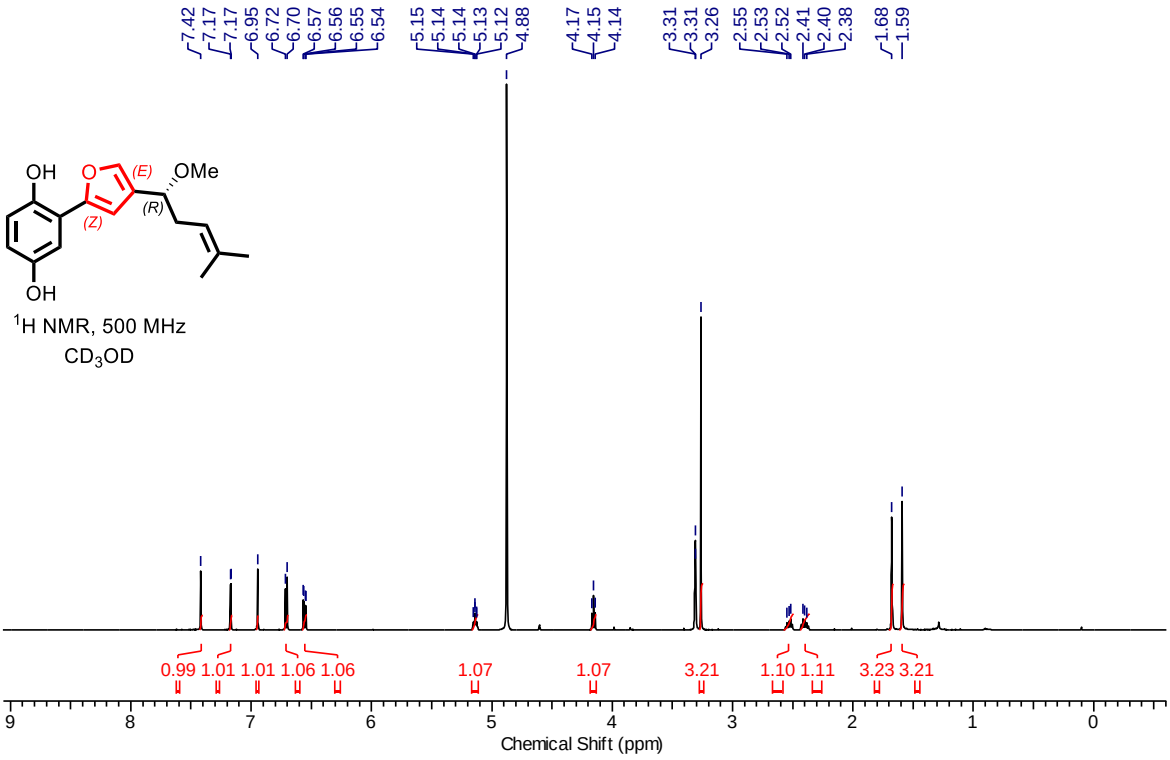
(*R*)-2-(2,5-bis(allyloxy)phenyl)-4-(1-methoxy-4-methylpent-3-en-1-yl)furan (**84a**):



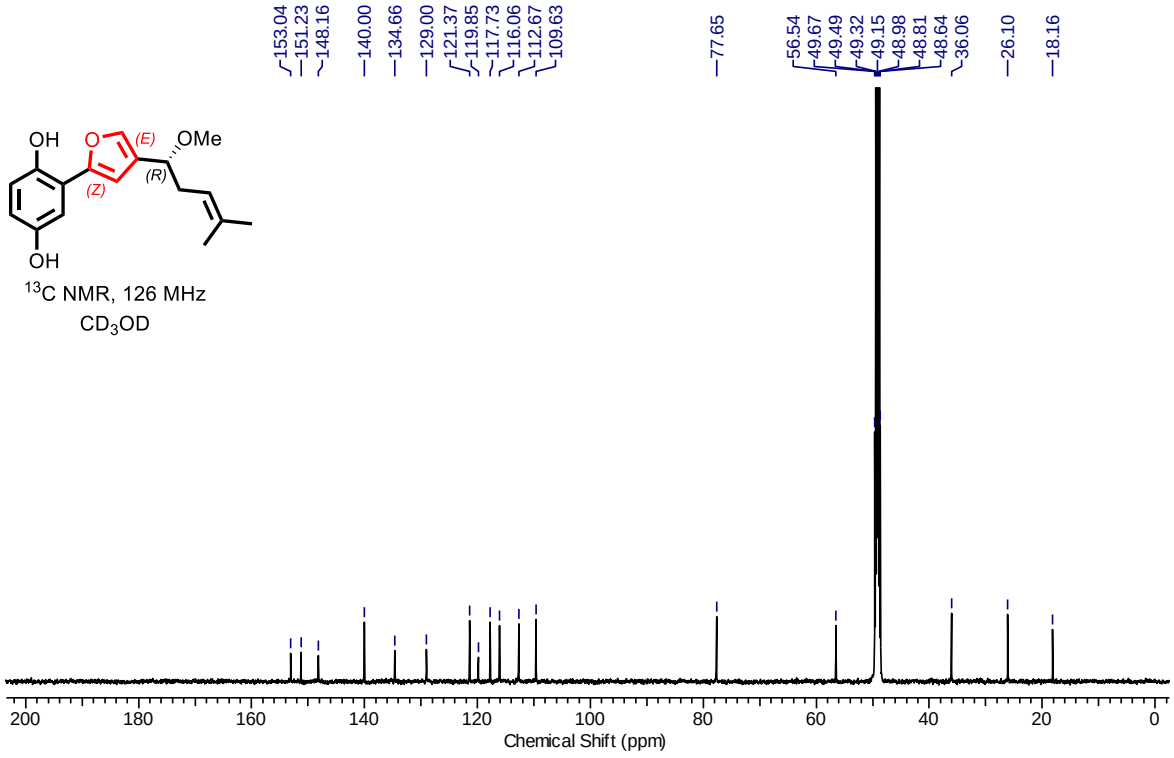
(*R*)-2-(2,5-Bis(allyloxy)phenyl)-4-(1-methoxy-4-methylpent-3-en-1-yl)furan (**84a**):



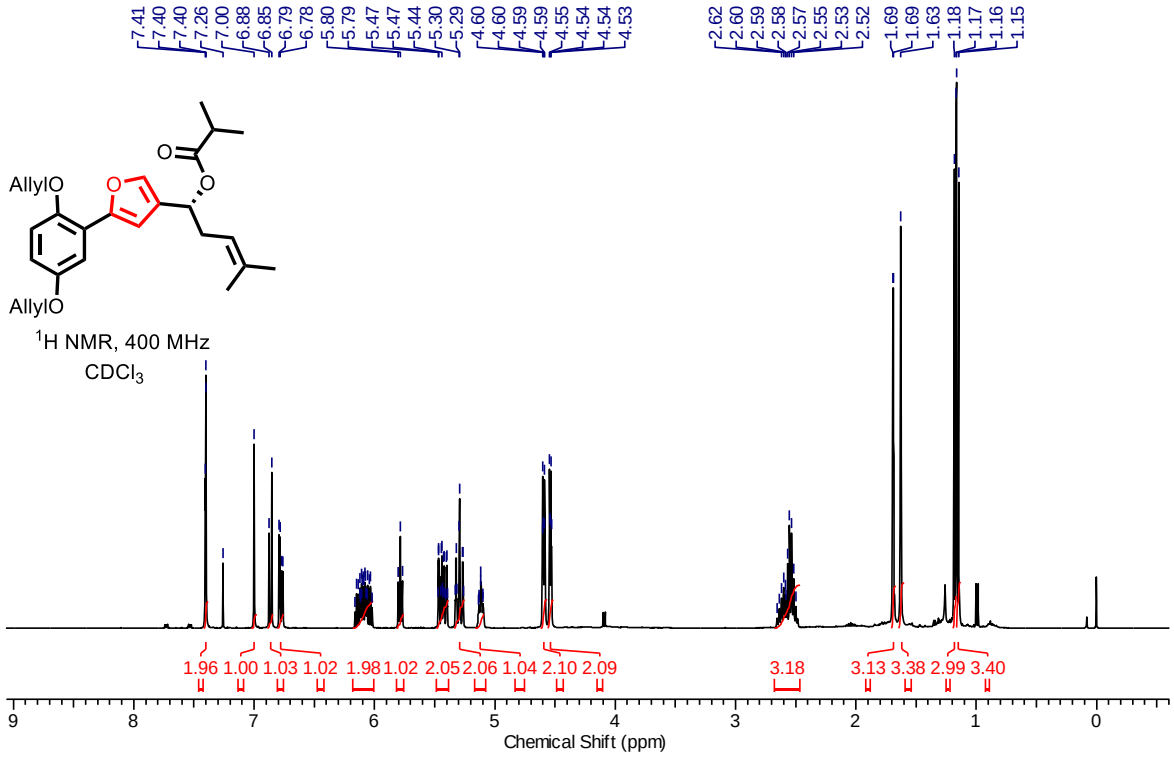
Shikonofuran J (**41a**):



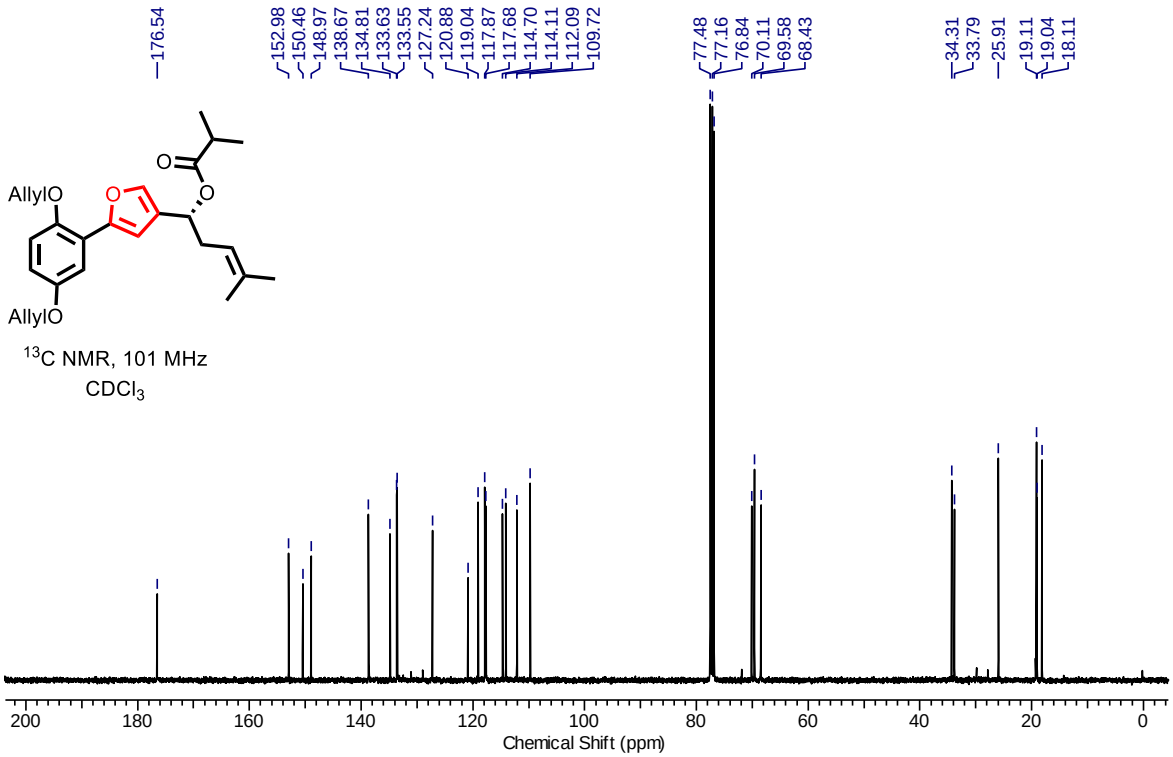
Shikonofuran J (**41a**):



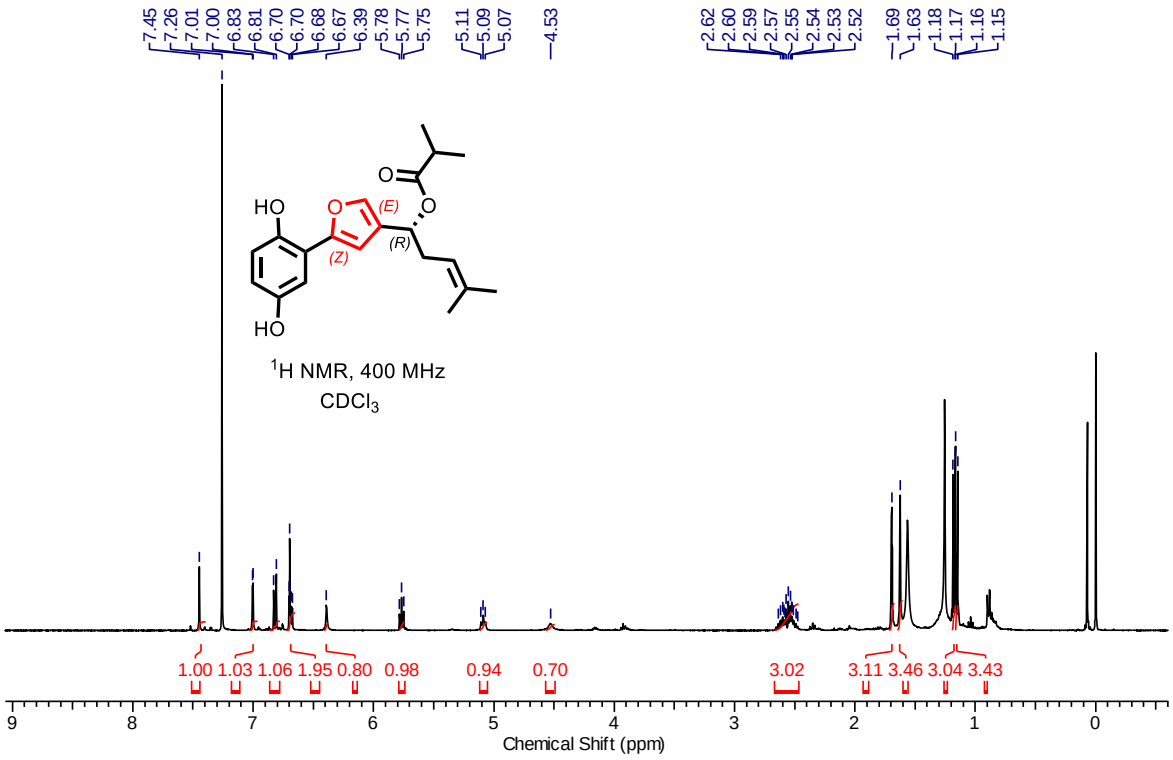
(*R*)-1-(5-(2,5-Bis(allyloxy)phenyl)furan-3-yl)-4-methylpent-3-en-1-yl isobutyrate (**86a**):



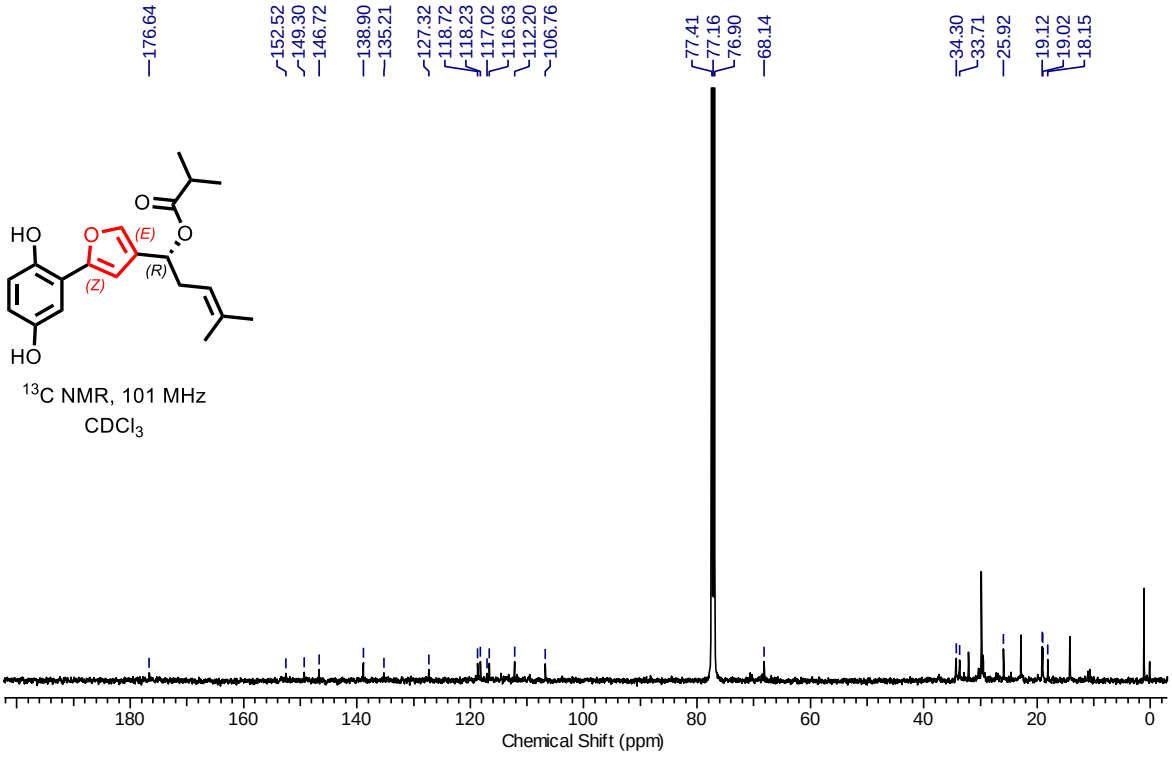
(*R*)-1-(5-(2,5-Bis(allyloxy)phenyl)furan-3-yl)-4-methylpent-3-en-1-yl isobutyrate (**86a**):



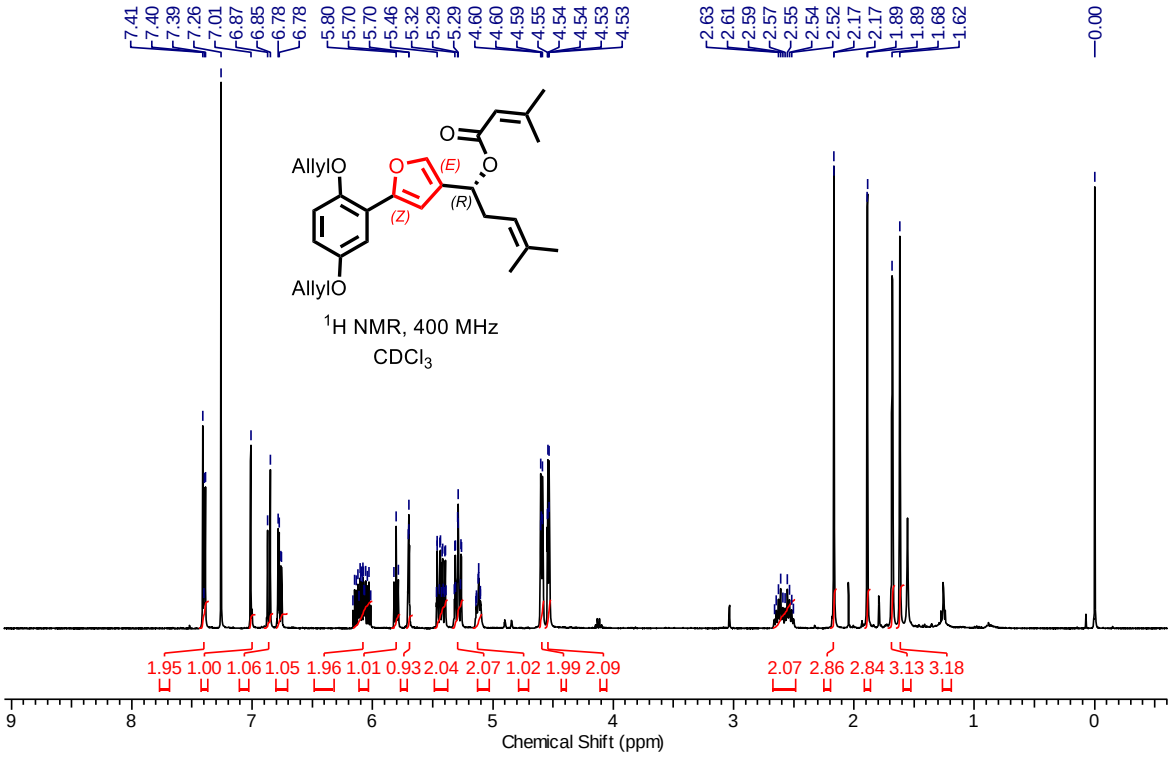
ent-Shikonfuran D **(42a):**



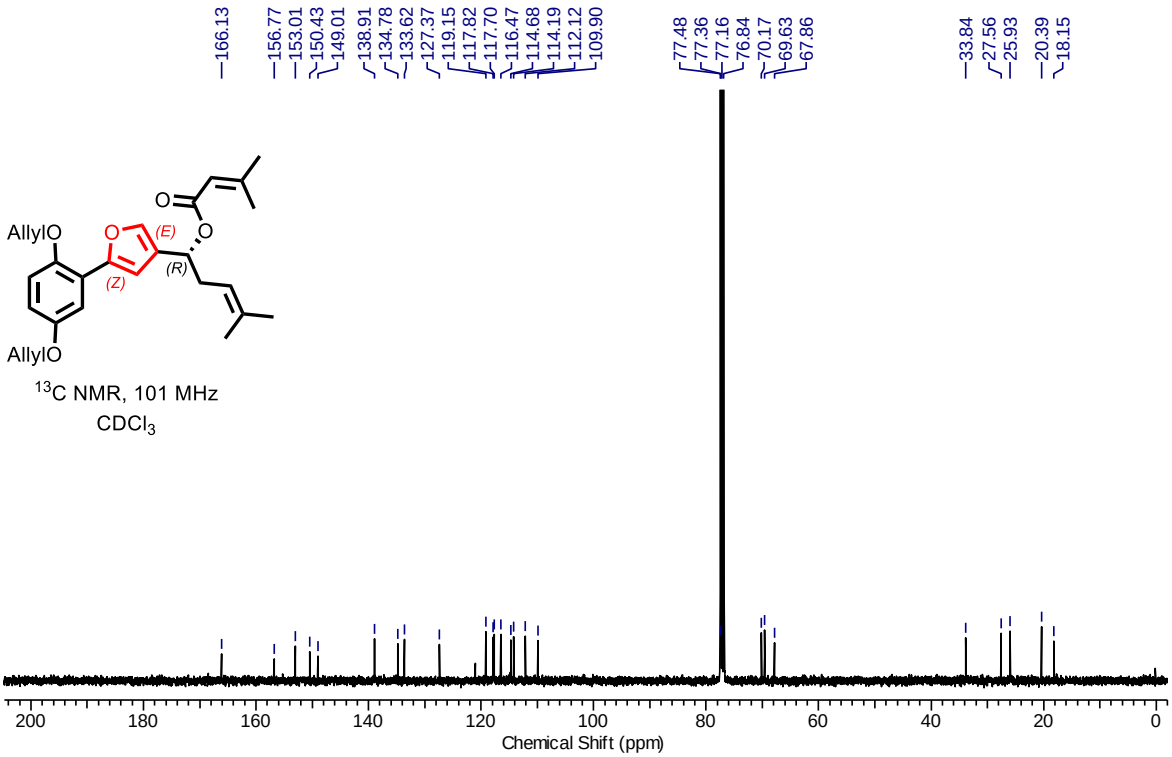
ent-Shikonfuran D **(42a):**



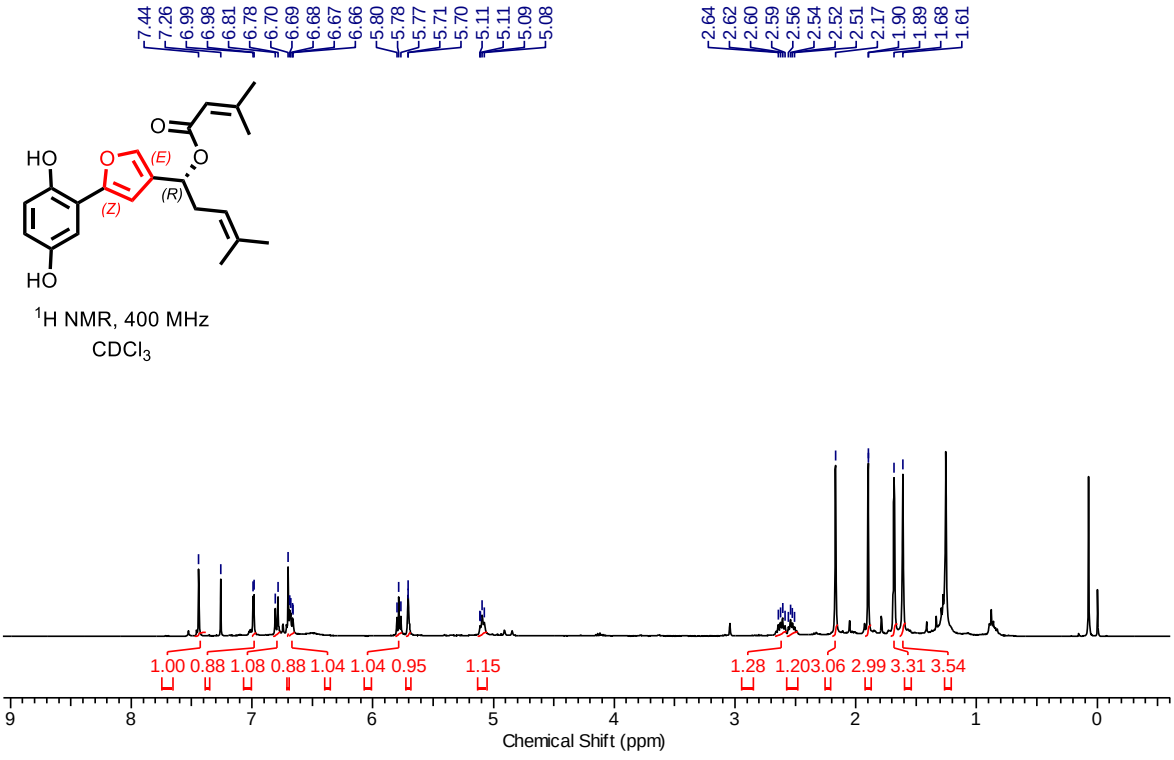
(*R*)-1-(5-(2,5-Bis(allyloxy)phenyl)furan-3-yl)-4-methylpent-3-en-1-yl 3-methylbut-2-enoate (**91a**):



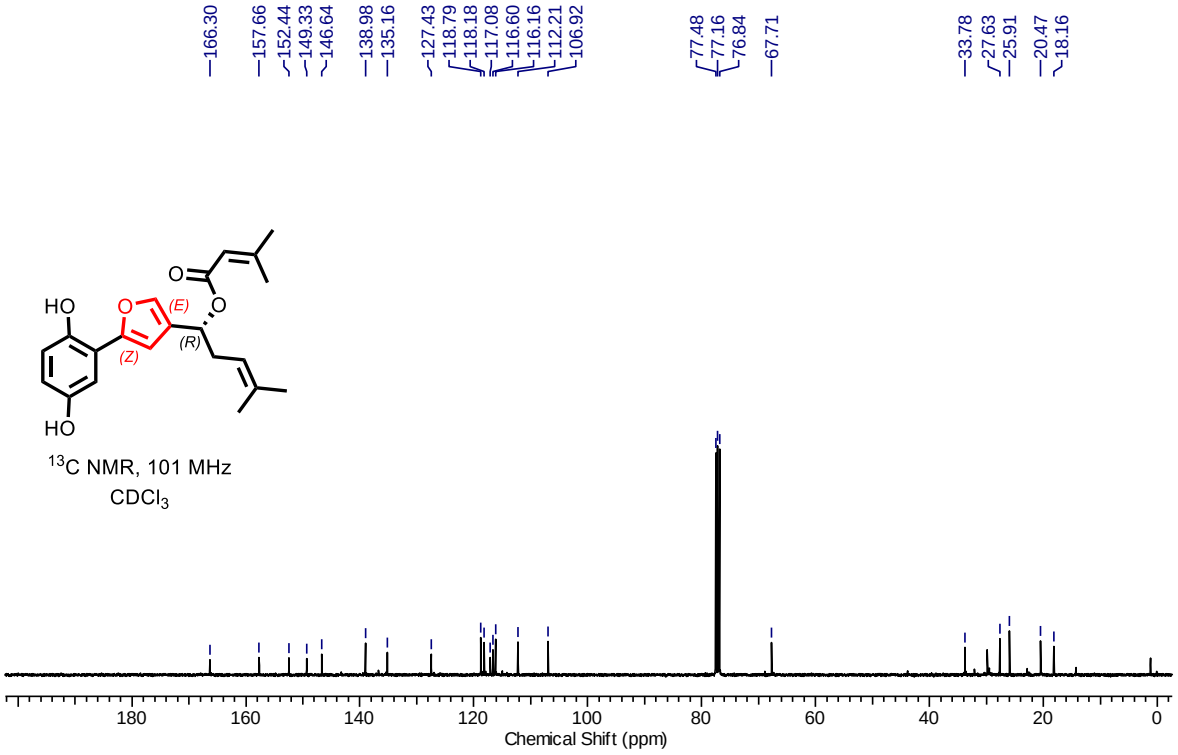
(*R*)-1-(5-(2,5-bis(allyloxy)phenyl)furan-3-yl)-4-methylpent-3-en-1-yl 3-methylbut-2-enoate (**91a**):



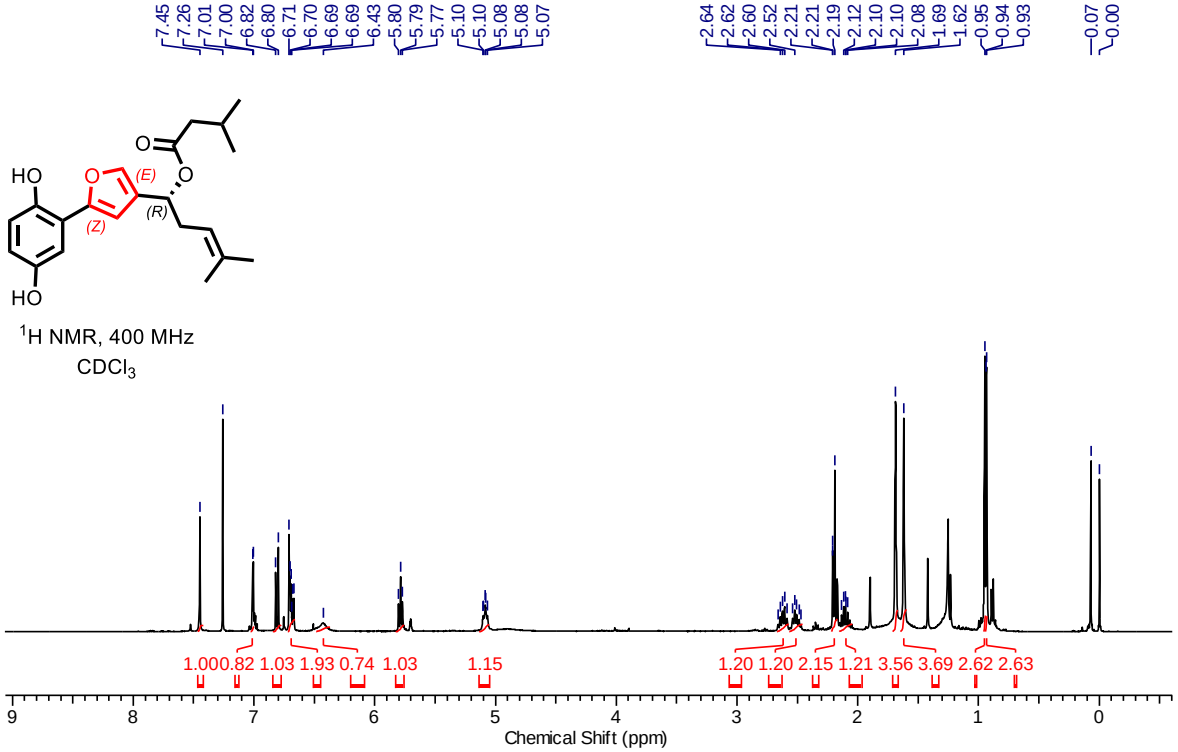
ent-Shikonfuran E **(43a):**



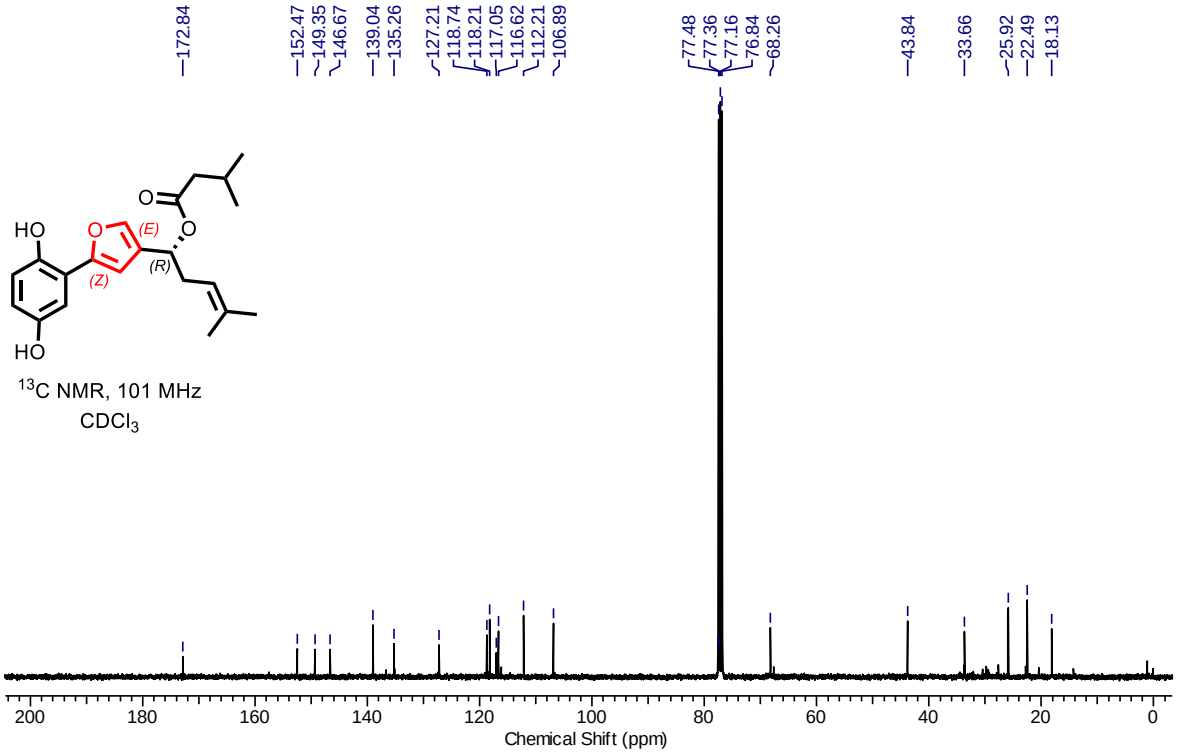
^{13}C NMR spectrum of compound *ent*-Shikonfuran E **(3a):**



ent-Shikonofuran C (**44a**):

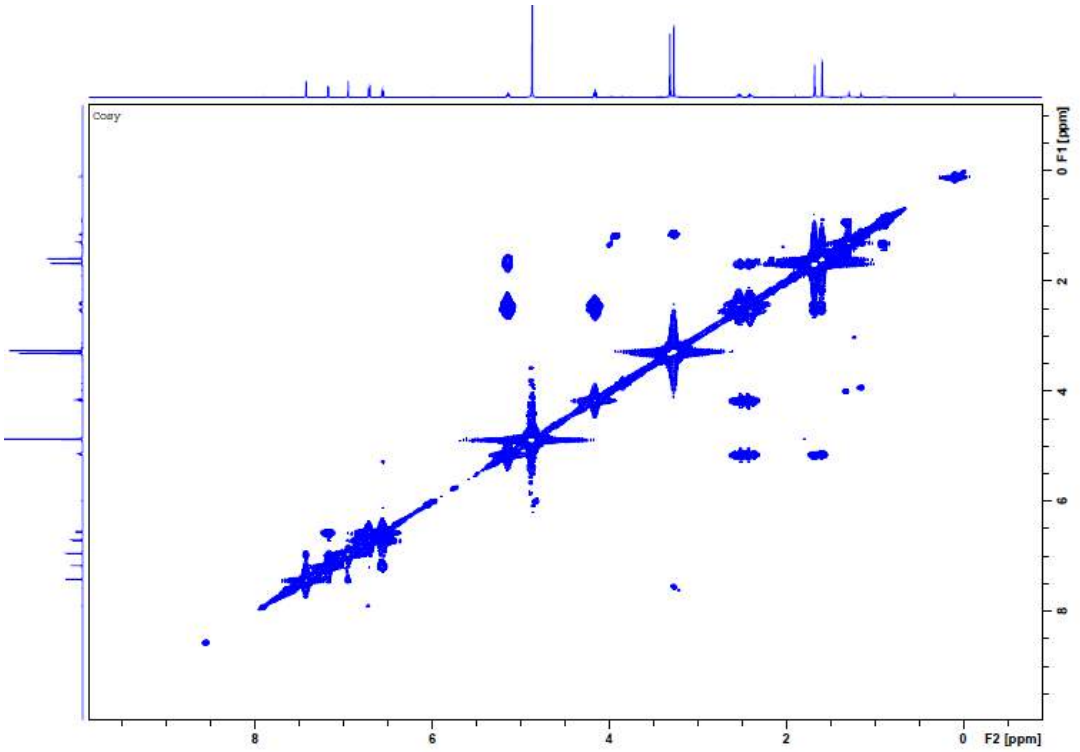


ent-Shikonofuran C (**44a**):

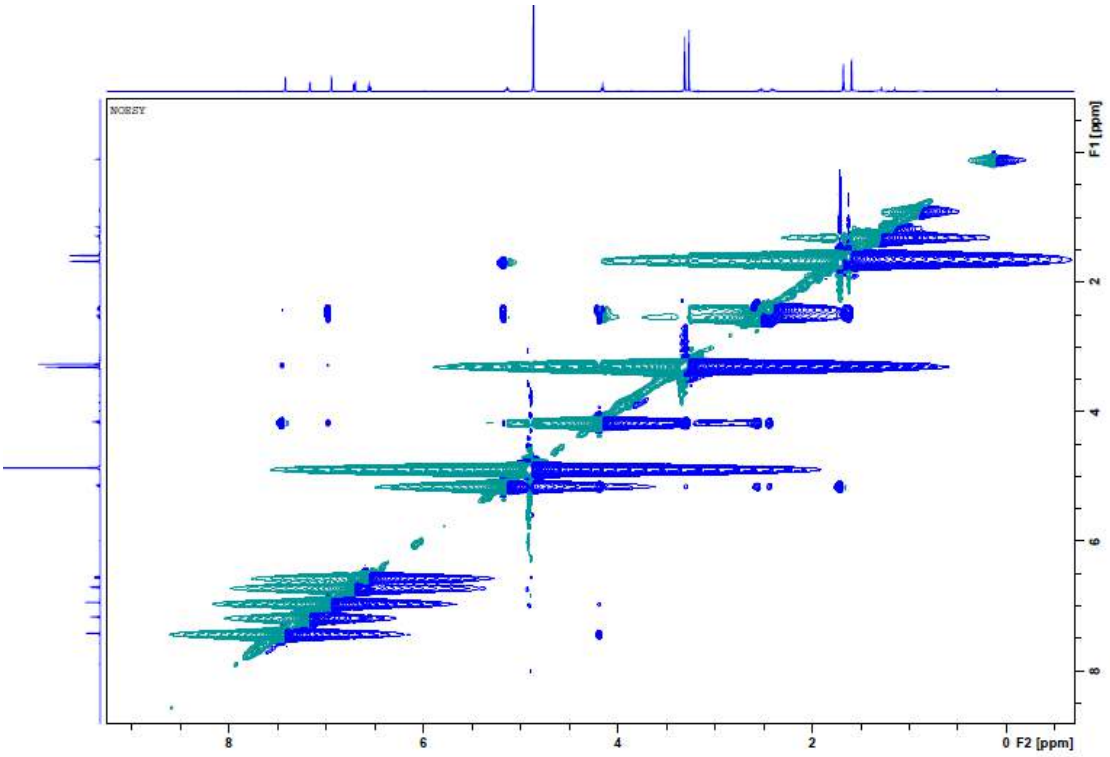


2D-NMR

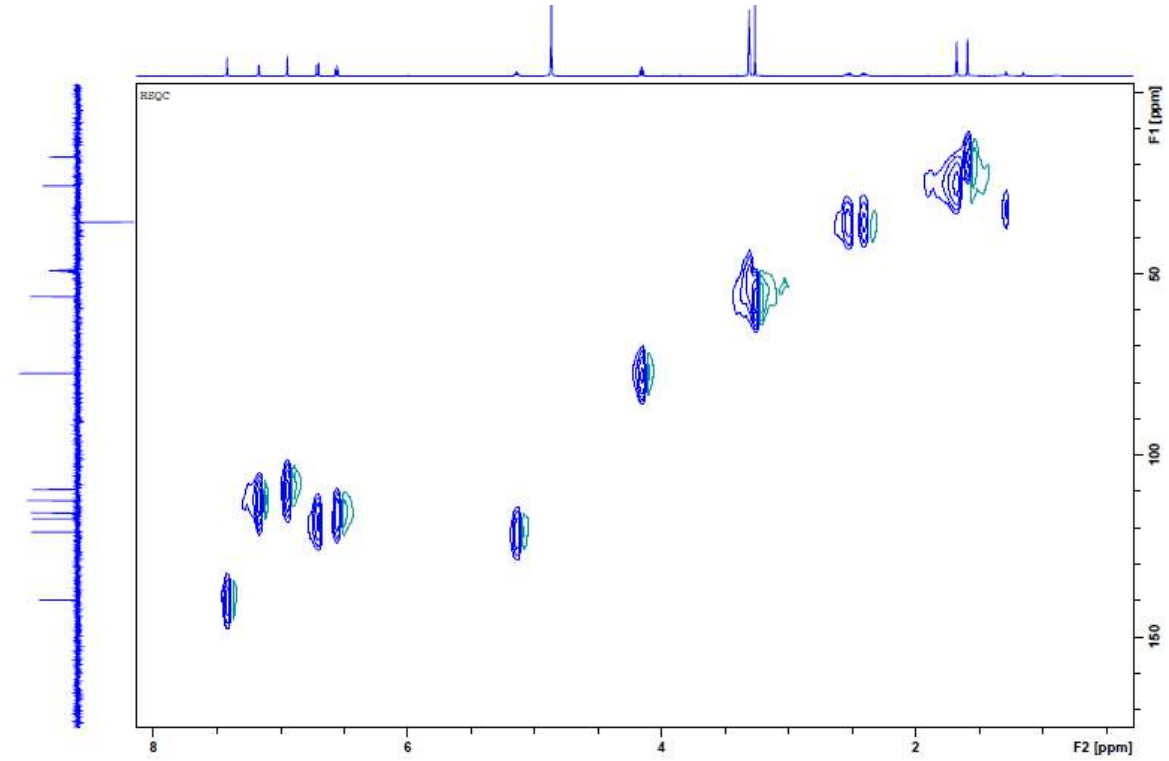
COSY spectrum of shikonofuran J (41)



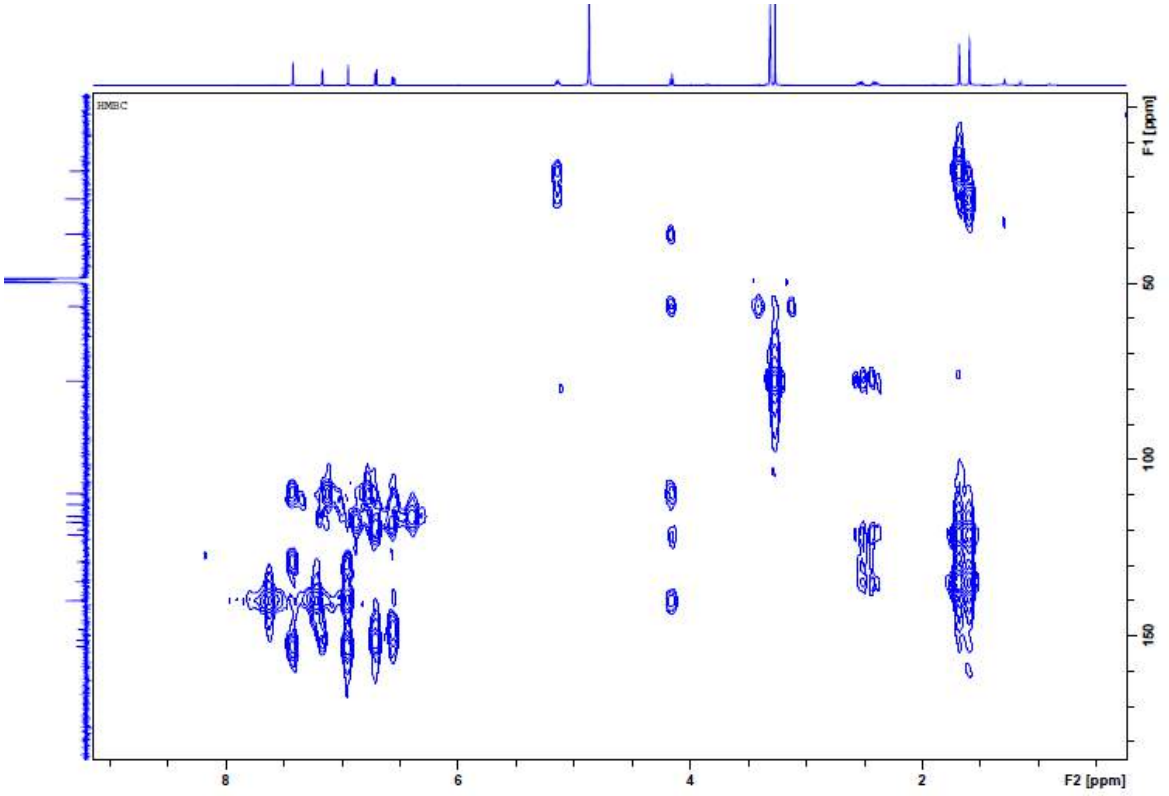
NOESY spectrum of shikonofuran J (41)



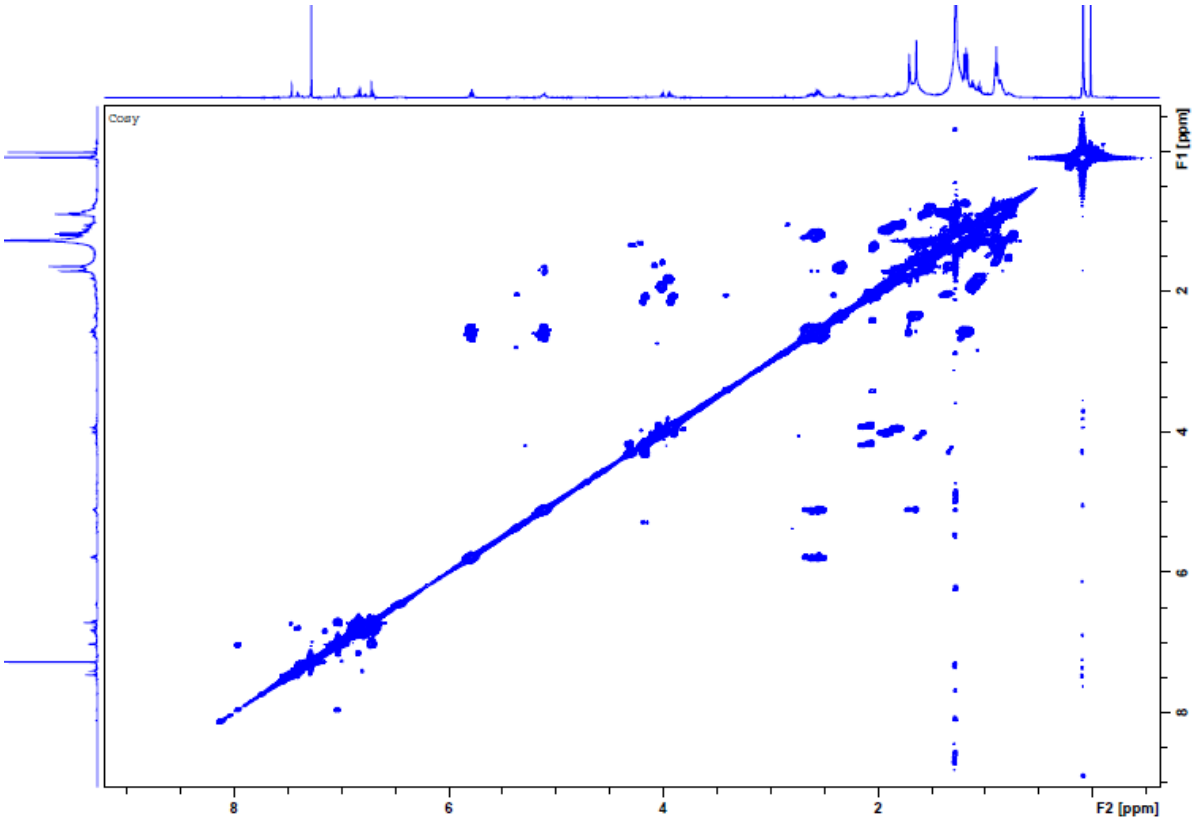
HSQC spectrum of shikonofuran J (41)



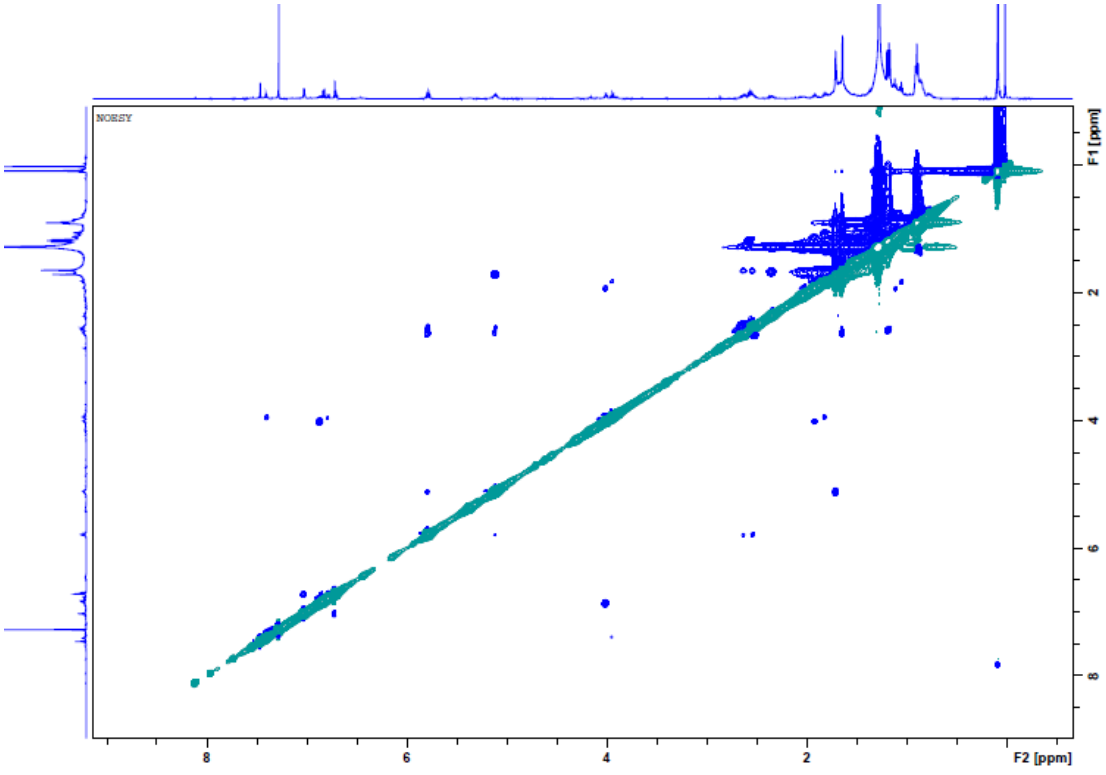
HMBC spectrum of shikonofuran J (41)



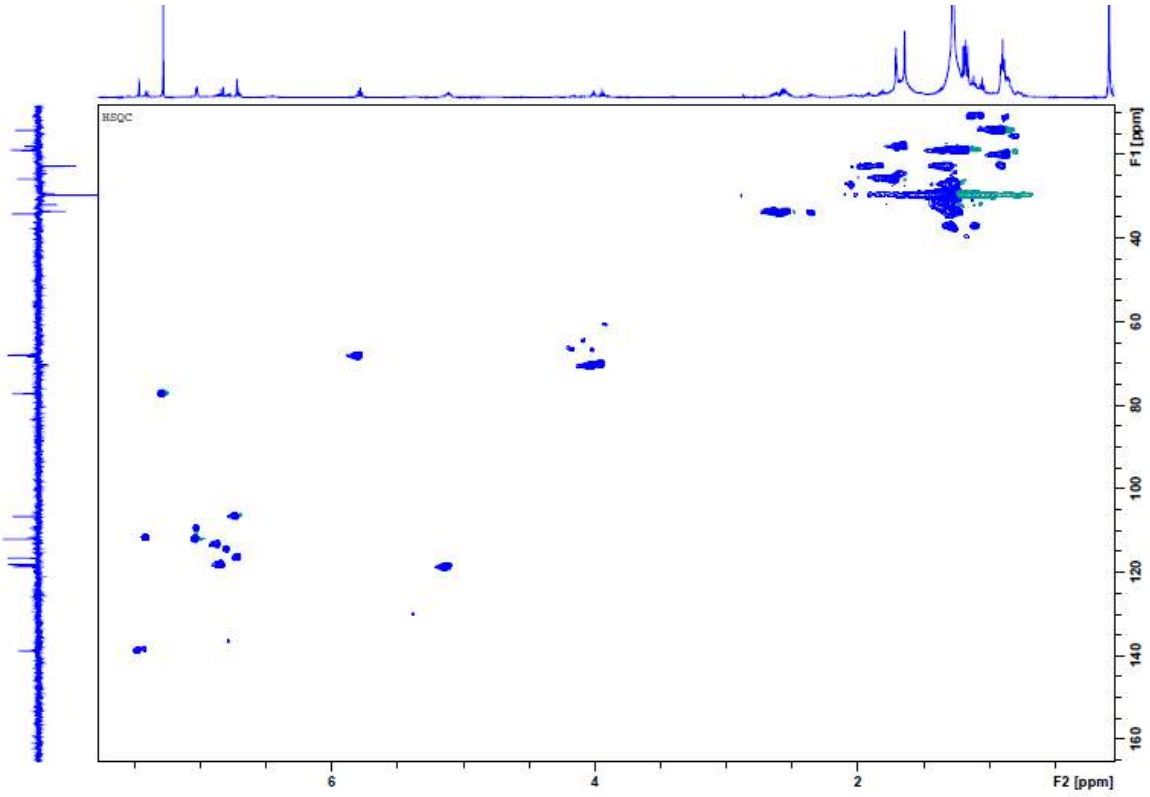
COSY spectrum of shikonofuran D (42):



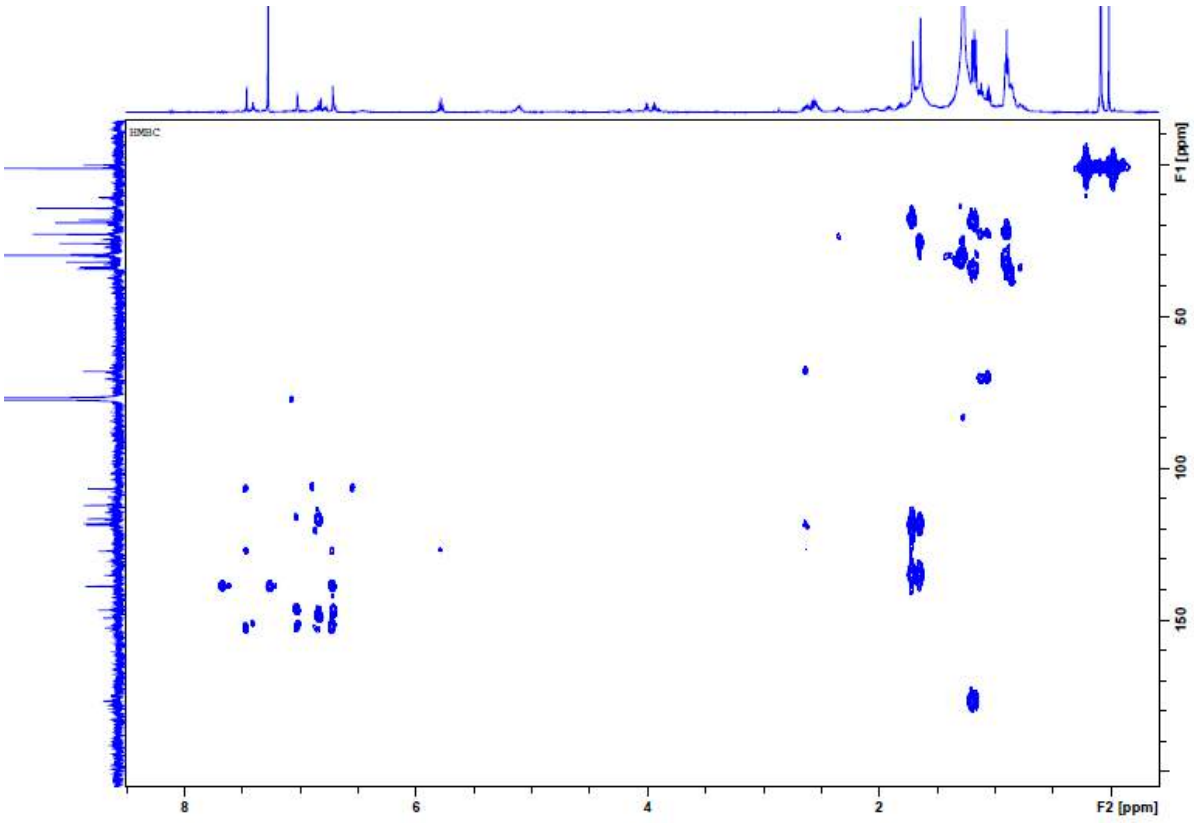
NOESY spectrum od shikonofuran D (42):



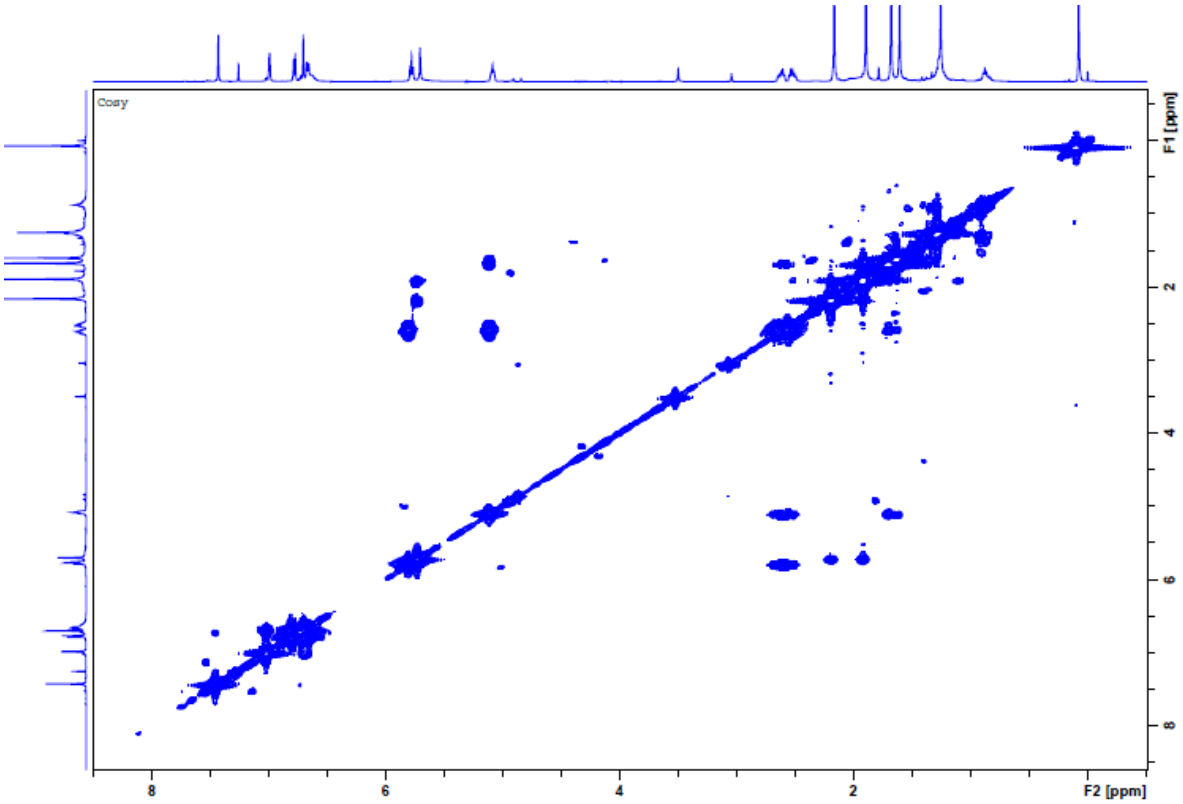
HSQC spectrum of shikonofuran D (42):



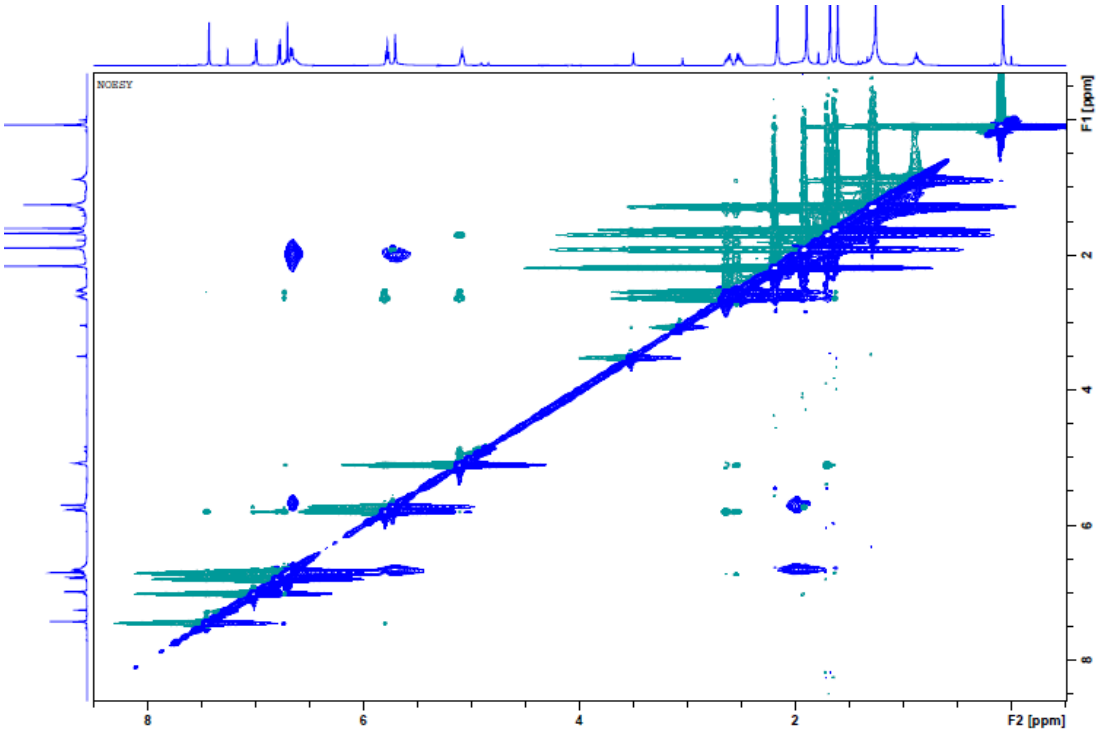
HMBC spectrum of Shikonofuran D (42):



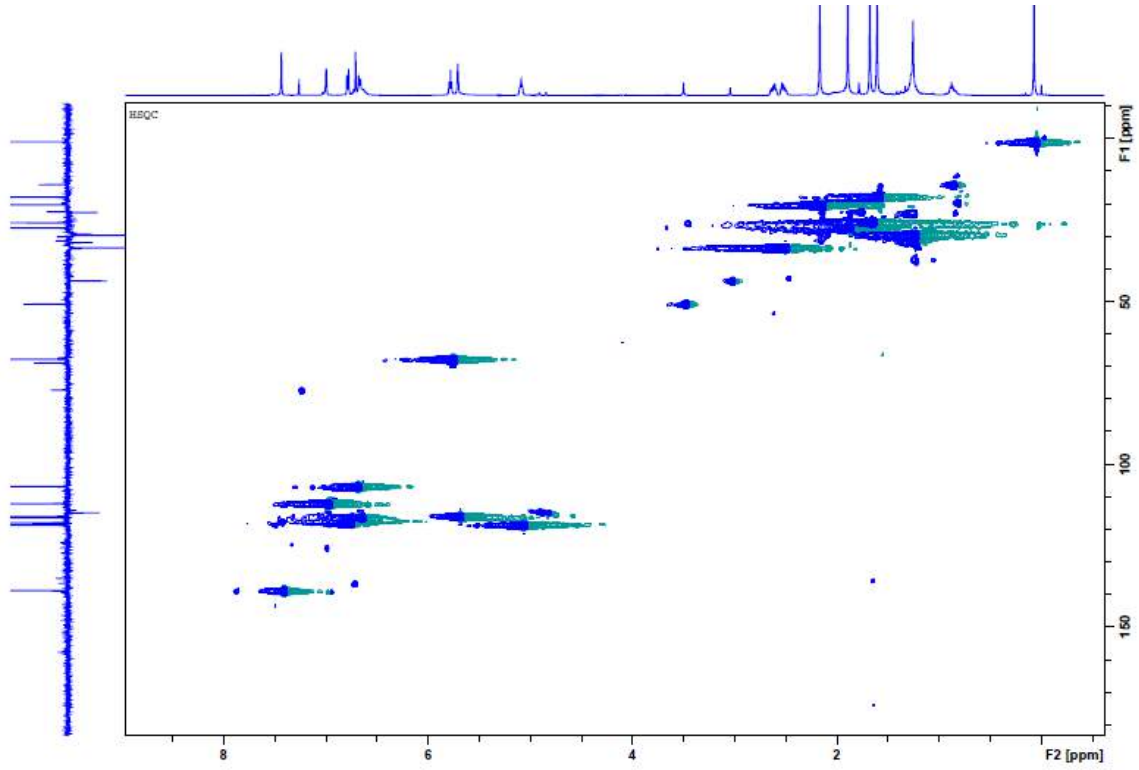
COSY spectrum of shikonofuran E (43):



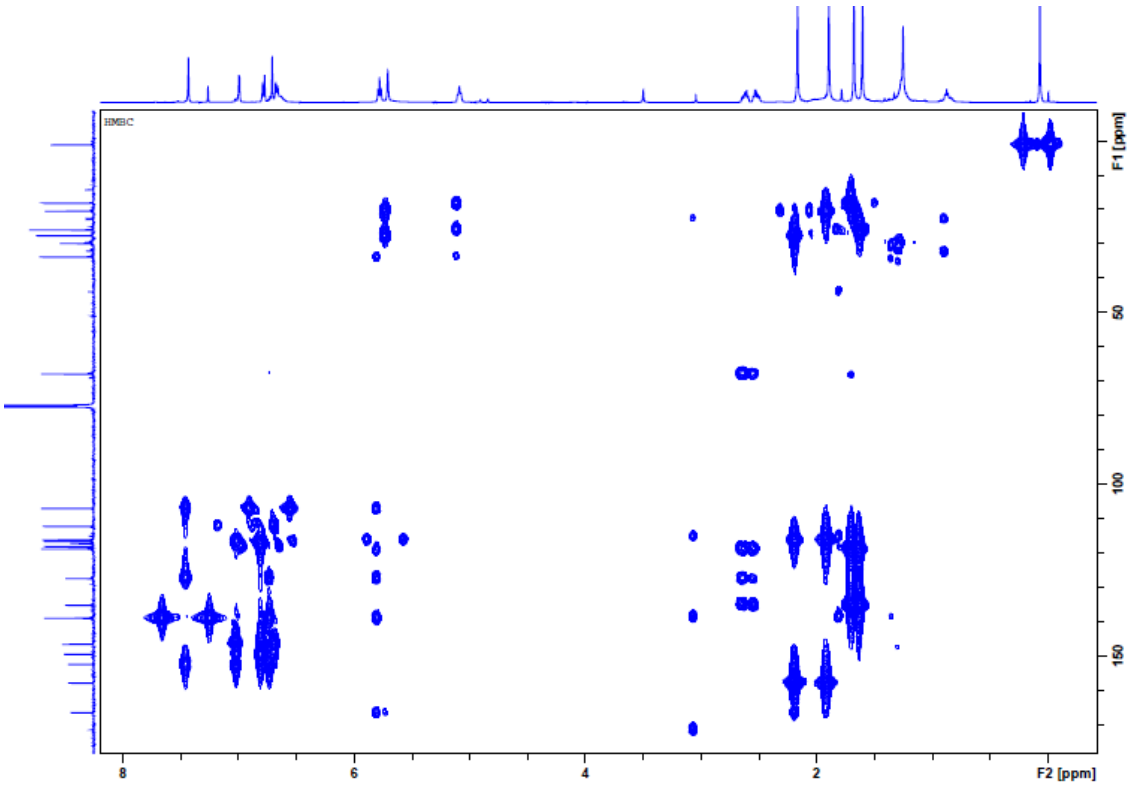
NOESY spectrum of shikonofuran E (43):



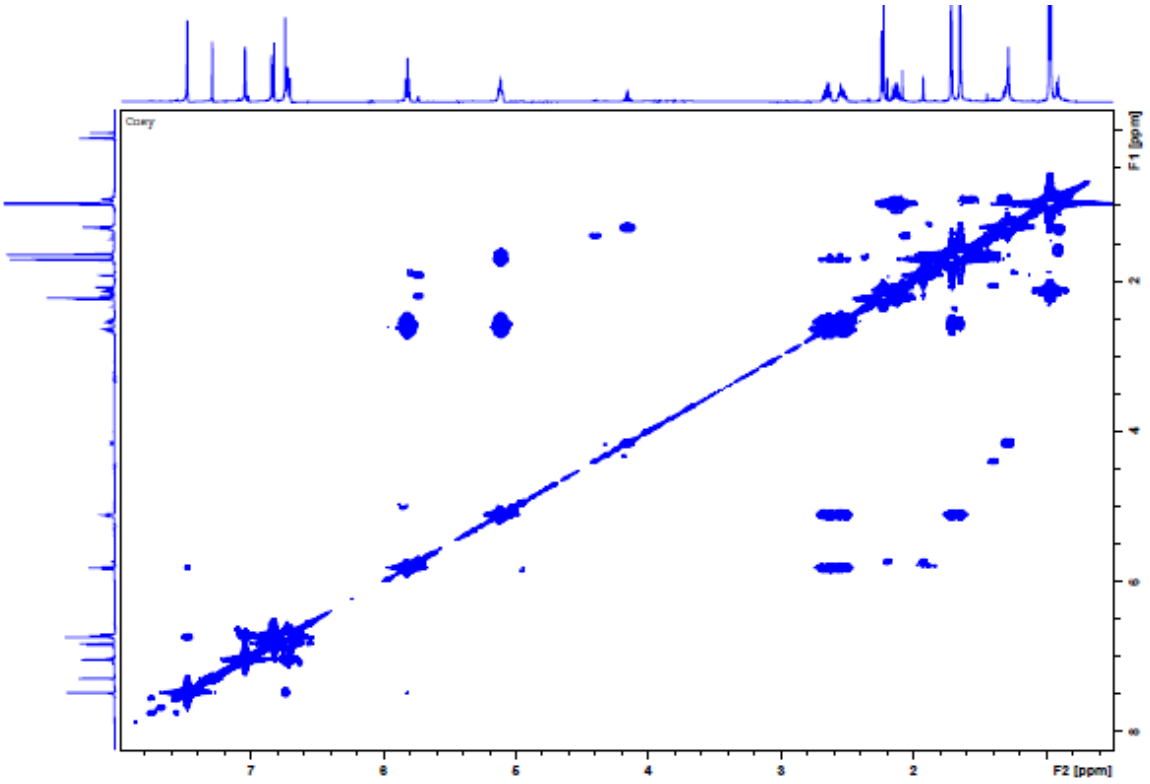
HSQC spectrum of shikonofuran E (43):



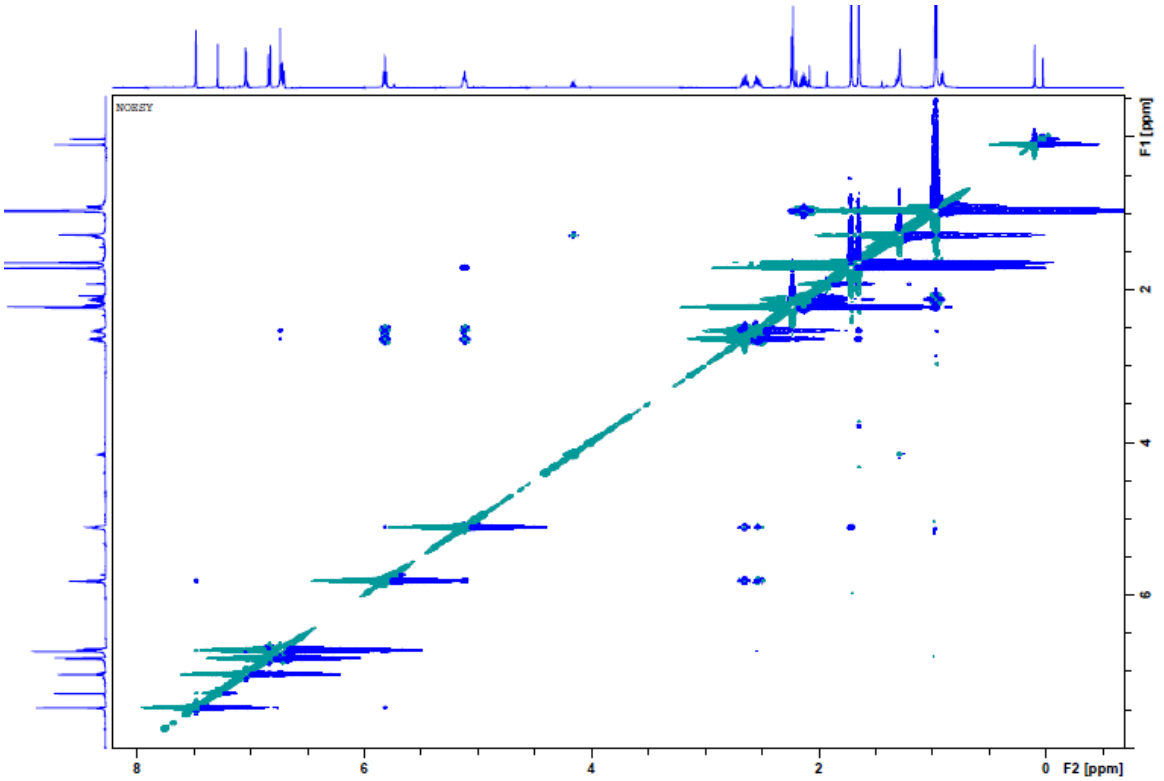
HMBC spectrum of shikonofuran E (43):



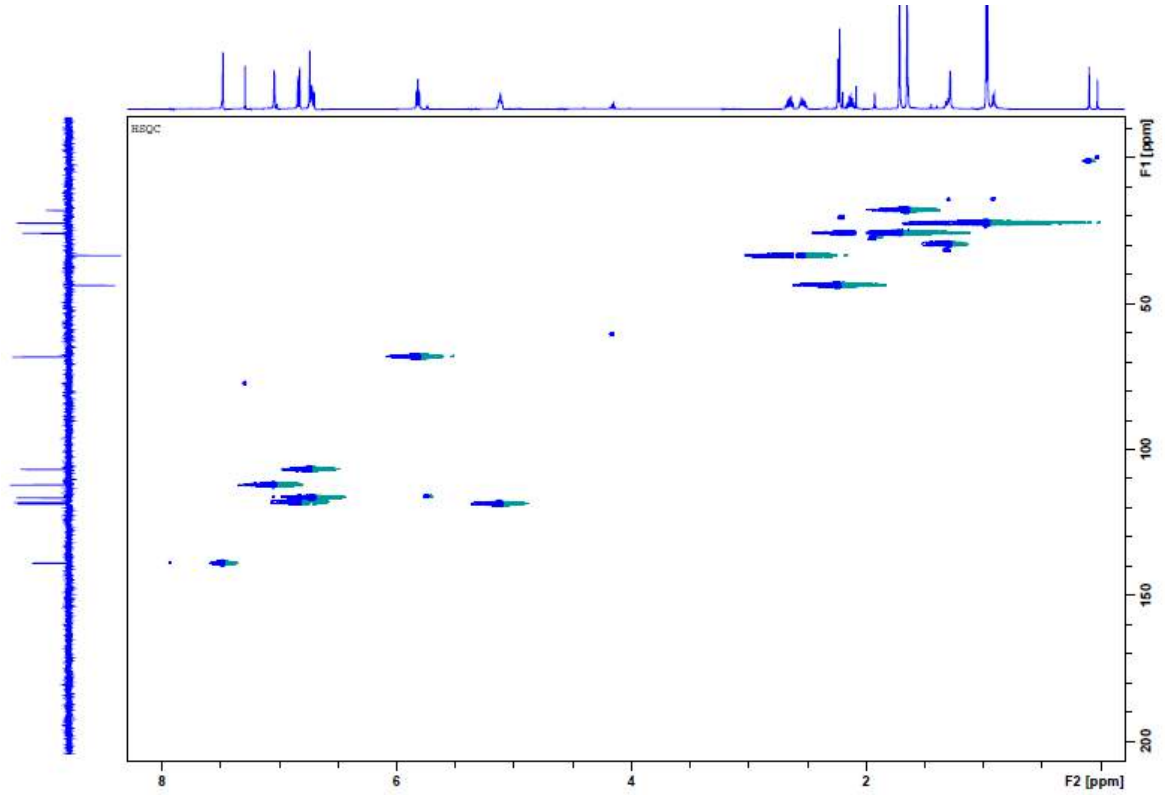
COSY spectrum of shikonofuran C (44):



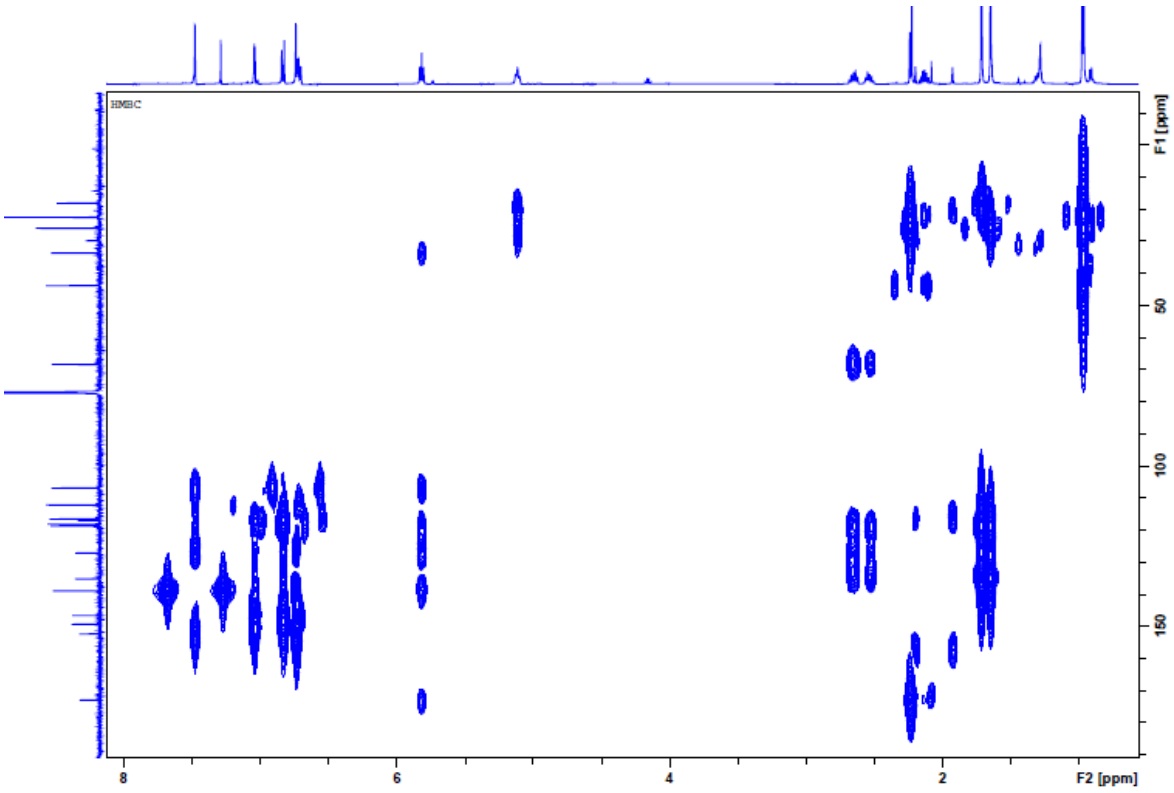
NOESY spectrum of shikonofuran C (44):



HSQC spectrum of shikonofuran C (44):

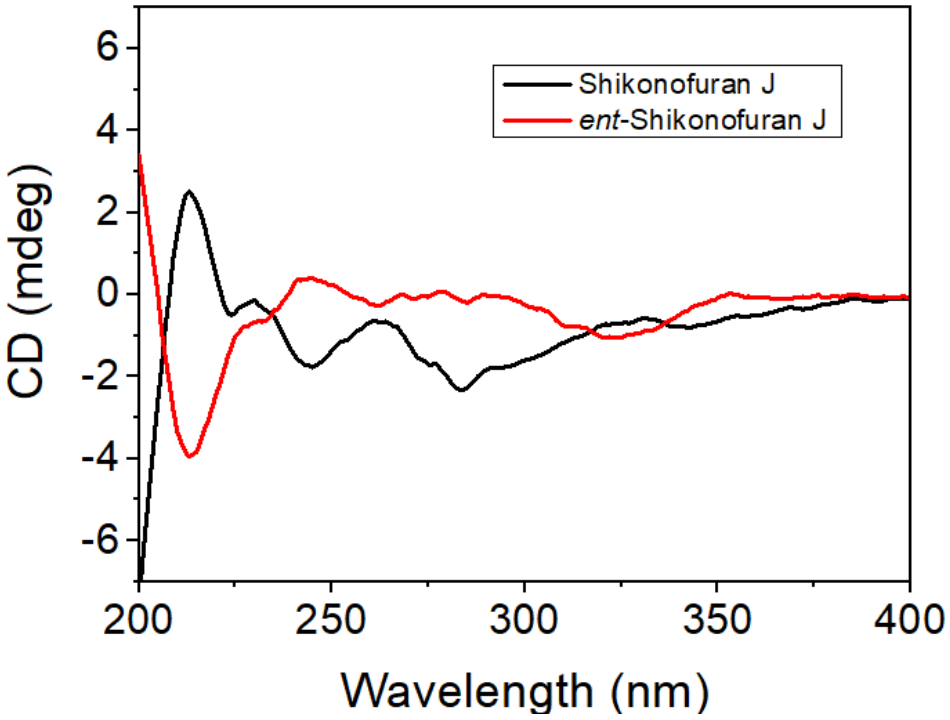


HMBC spectrum of shikonofuran C (44):

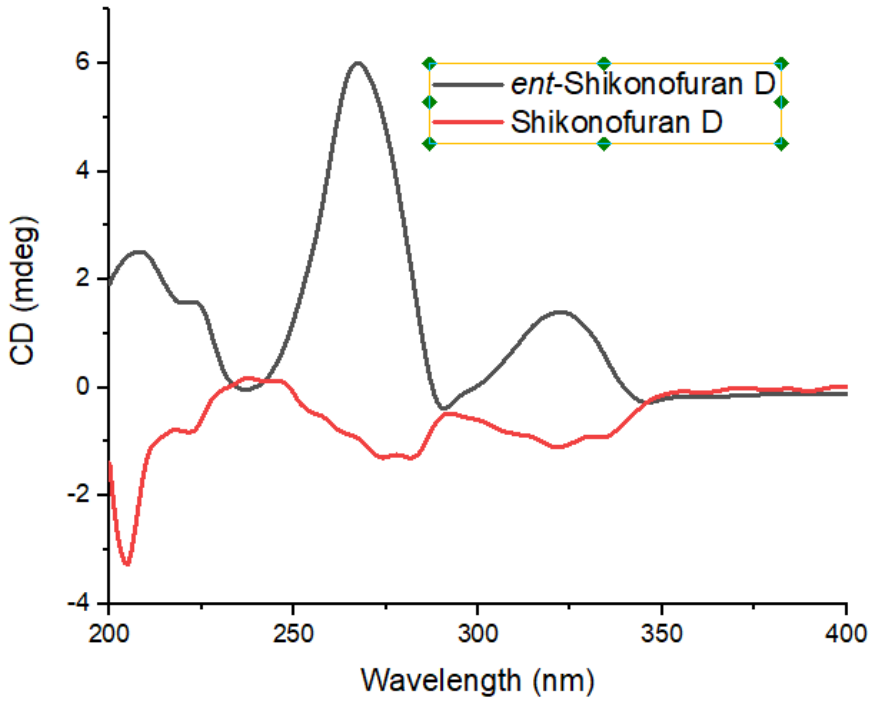


ECD Analysis

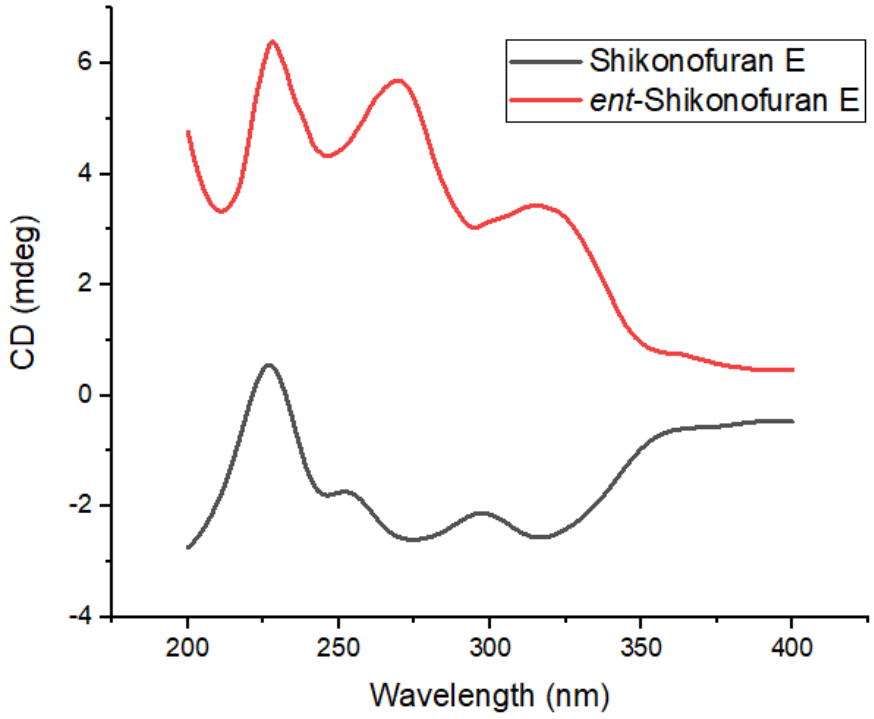
Shikonofuran J (41) and *ent*-shikonofuran J (41a)



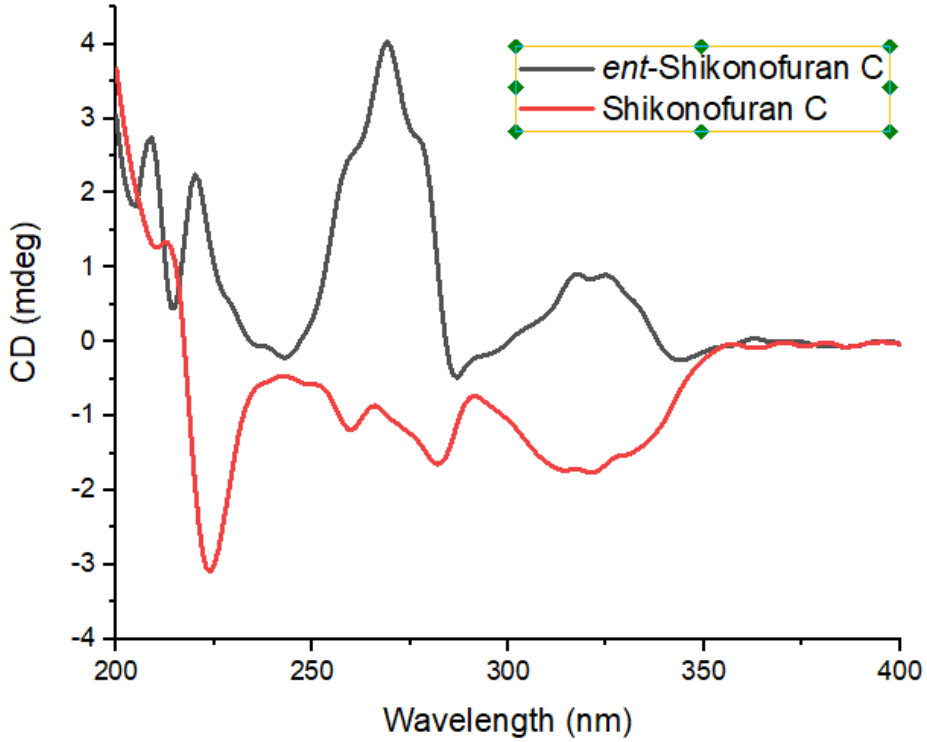
Shikonofuran D (42) and ent-shikonofuran D (42a):



Shikonofuran E (43) and *ent*-shikonofuran E (43a):

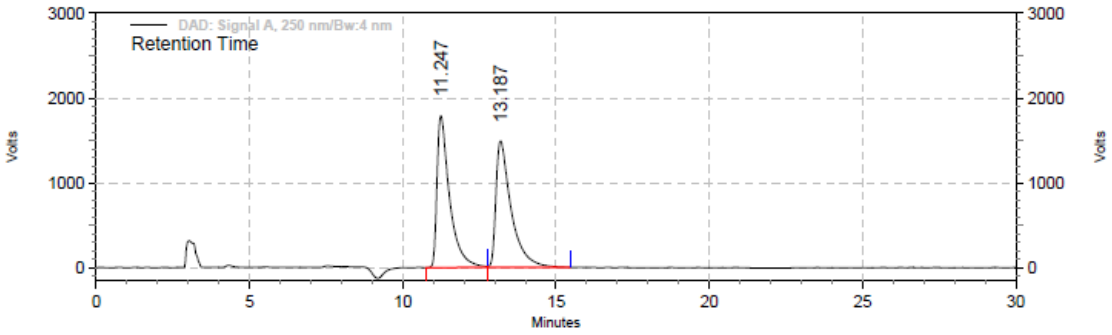


Shikonofuran C (44) and *ent*-shikonofuran C (44a):



HPLC Spectra

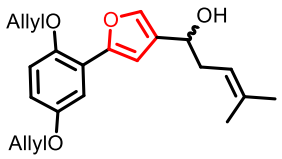
1-(5-(2,5-Bis(allyloxy)phenyl)furan-3-yl)-4-methylpent-3-en-1-ol **(±)-78**:



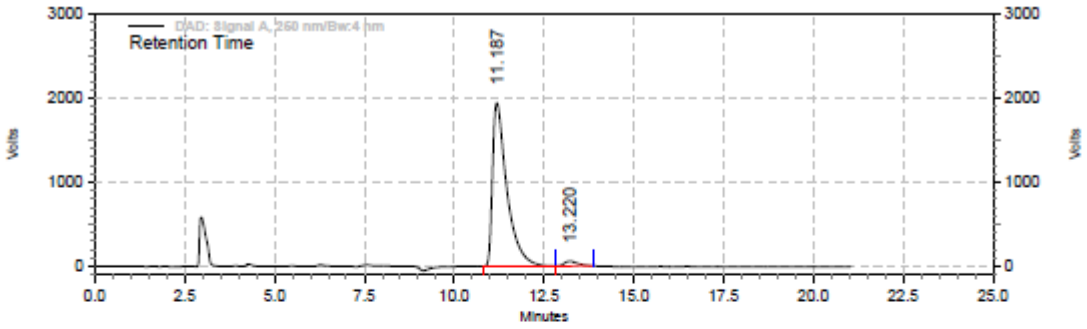
DAD: Signal A, 250 nm/Bw:4 nm
Results

Retention Time	Area	Area %
11.247	107034083	49.80
13.187	107894660	50.20
Totals	214928743	100.00

Column: CHIRALPAK AD-H
Eluent System: 90 : 10 (HEXANE:IPA)
Flow rate: 1.0 ml/min
Injection vol.: 10 ul
Wavelength: 254 nm
Sample Conc.: 1.5mg/ml



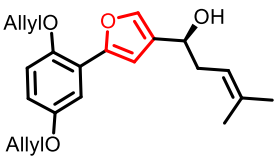
(*S*)-1-(5-(2,5-Bis(allyloxy)phenyl)furan-3-yl)-4-methylpent-3-en-1-ol **(78):**



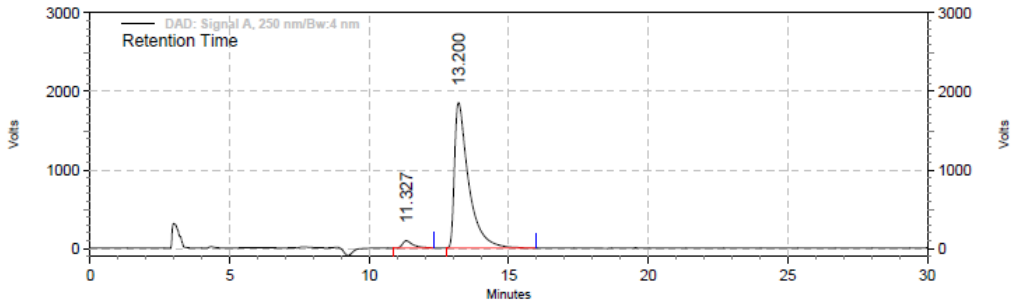
DAD: Signal A, 250 nm/Bw:4 nm
Results

Retention Time	Area	Area %
11.187	113655148	97.31
13.220	3146385	2.69
Totals	116801533	100.00

Column: CHIRALPAK AD-H
Eluent System: 90 : 10 (HEXANE:IPA)
Flow rate: 1.0 ml/min
Injection vol.: 10 ul
Wavelength: 254 nm
Sample Conc.: 1.5mg/ml



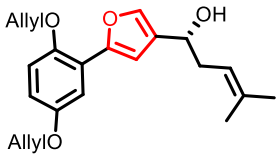
(*R*)-1-(5-(2,5-bis(allyloxy)phenyl)furan-3-yl)-4-methylpent-3-en-1-ol **(78a):**



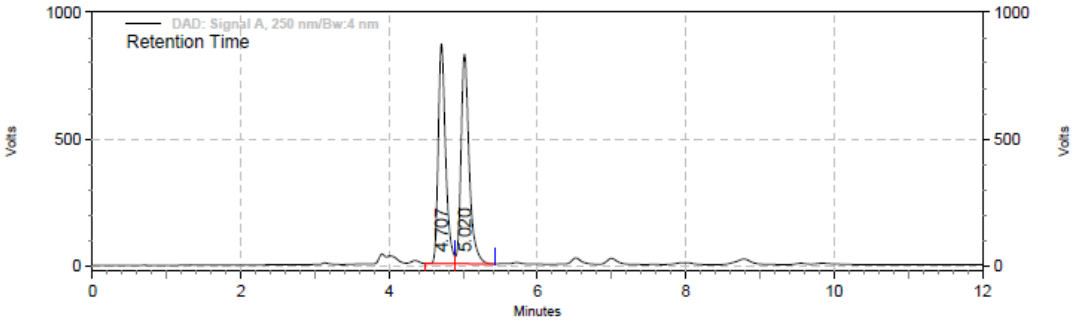
DAD: Signal A, 250 nm/Bw:4 nm
Results

Retention Time	Area	Area %
11.327	4919381	3.50
13.200	135793806	96.50
Totals		
	140713187	100.00

Column: CHIRALPAK AD-H
Eluent System: 90 : 10 (HEXANE:IPA)
Flow rate: 1.0 ml/min
Injection vol.: 10 ul
Wavelength: 254 nm
Sample Conc.: 1.5mg/ml



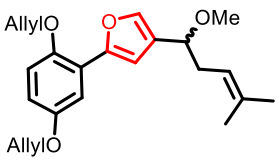
2-(2,5-bis(allyloxy)phenyl)-4-(1-methoxy-4-methylpent-3-en-1-yl)furan **(±)-(84):**



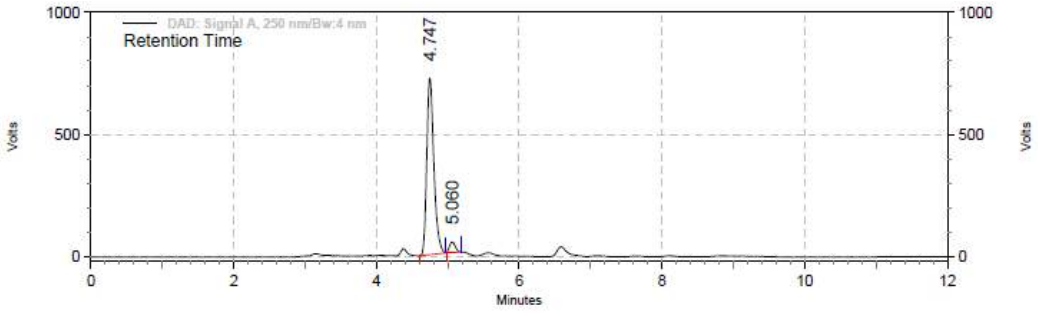
DAD: Signal A, 250 nm/Bw:4 nm
Results

Retention Time	Area	Area %
4.707	12538741	48.70
5.020	13207891	51.30
Totals		
	25746632	100.00

Column: CHIRALPAK AD-H
Eluent System: 90 : 10 (HEXANE:IPA)
Flow rate: 1.0 ml/min
Injection vol.: 10 ul
Wavelength: 254 nm
Sample Conc.: 1.5mg/ml



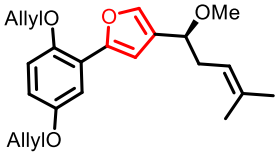
(*S*)-2-(2,5-Bis(allyloxy)phenyl)-4-(1-methoxy-4-methylpent-3-en-1-yl)furan **(84):**



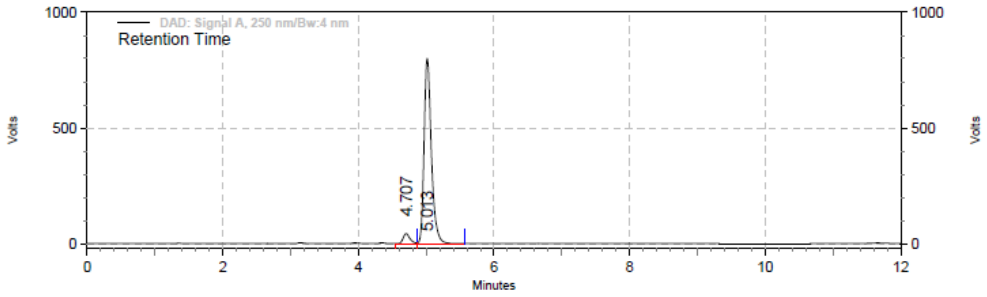
DAD: Signal A, 250 nm/Bw:4 nm
Results

Retention Time	Area	Area %
4.747	10440943	95.40
5.060	503709	4.60
Totals		
	10944652	100.00

Column: CHIRALPAK AD-H
Eluent System: 90 : 10 (HEXANE:IPA)
Flow rate: 1.0 ml/min
Injection vol.: 10 ul
Wavelength: 254 nm
Sample Conc.: 1.5mg/ml



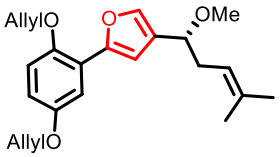
(*R*)-2-(2,5-Bis(allyloxy)phenyl)-4-(1-methoxy-4-methylpent-3-en-1-yl)furan **(84a):**



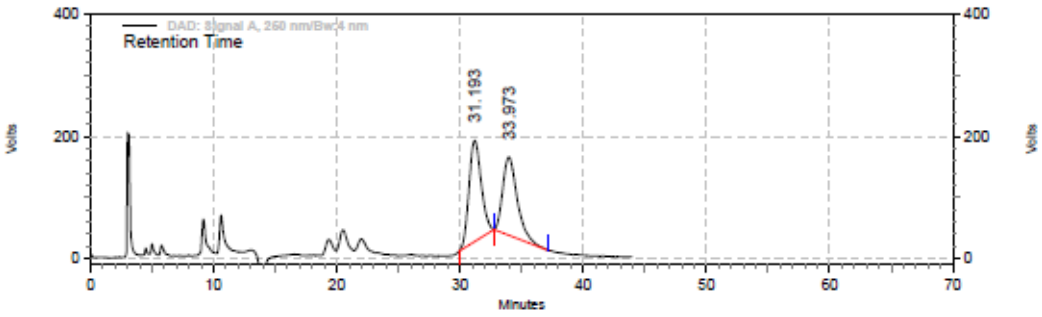
DAD: Signal A, 250 nm/Bw:4 nm
Results

Retention Time	Area	Area %
4.707	627530	4.80
5.013	12453976	95.20
Totals		
	13081506	100.00

Column: CHIRALPAK AD-H
Eluent System: 90 : 10 (HEXANE:IPA)
Flow rate: 1.0 ml/min
Injection vol.: 10 ul
Wavelength: 254 nm
Sample Conc.: 1.5mg/ml



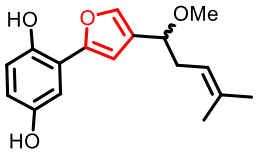
Shikonofuran J **(±)- (41):**



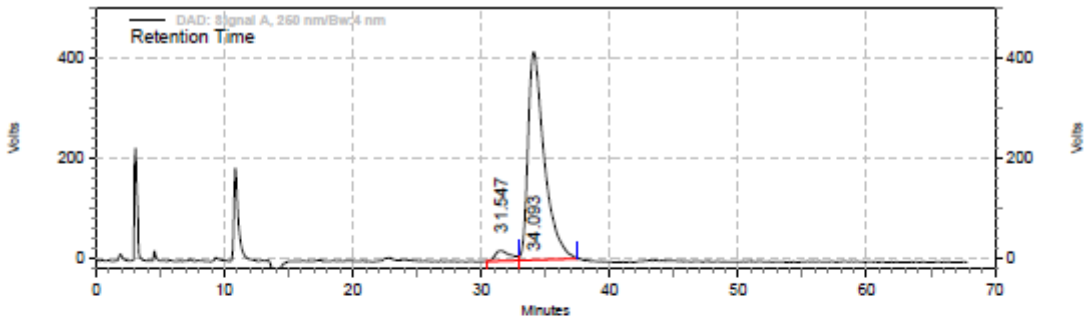
DAD: Signal A, 250 nm/Bw:4 nm
Results

Retention Time	Area	Area %
31.193	23898982	52.06
33.973	22005151	47.94
Totals	45904133	100.00

Column: CHIRALPAK AD-H
Eluent System: 95 : 5 (HEXANE:IPA)
Flow rate: 1.0 ml/min
Injection vol.: 10 ul
Wavelength: 254 nm
Sample Conc.: 1.5mg/ml



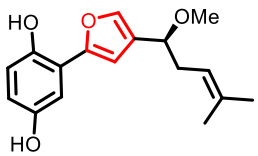
Shikonofuran J **(41):**



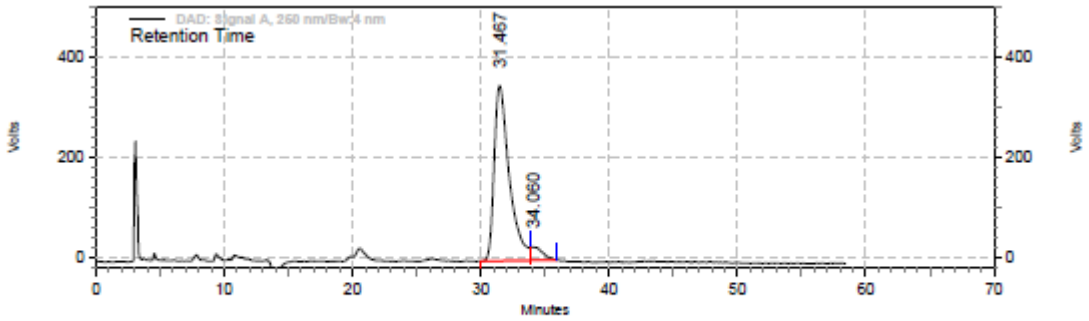
DAD: Signal A, 250 nm/Bw:4 nm
Results

Retention Time	Area	Area %
31.547	3624519	4.50
34.093	76920800	95.50
Totals	80545319	100.00

Column: CHIRALPAK AD-H
Eluent System: 93 : 7(HEXANE:IPA)
Flow rate: 1.0 ml/min
Injection vol.: 10 ul
Wavelength: 254 nm
Sample Conc.: 1.5mg/ml



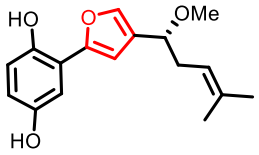
ent-Shikonofuran J **(41a):**



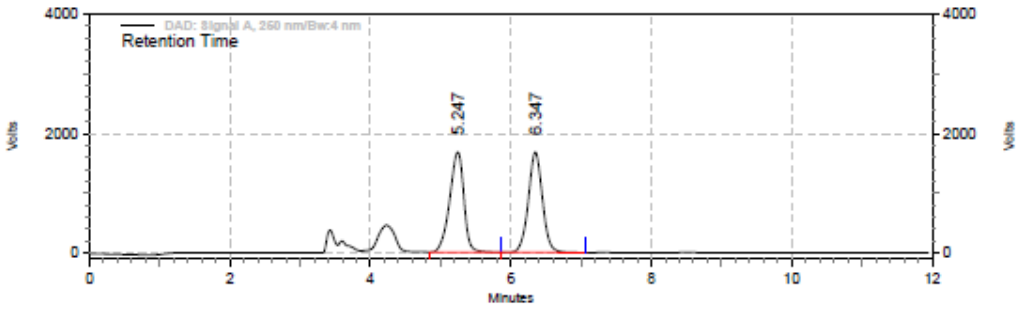
DAD: Signal A, 250 nm/Bw:4 nm
Results

Retention Time	Area	Area %
31.467	59815060	94.10
34.060	3751782	5.90
Totals	63566842	100.00

Column: CHIRALPAK AD-H
Eluent System: 93 : 7 (HEXANE:IPA)
Flow rate: 1.0 ml/min
Injection vol.: 10 ul
Wavelength: 254 nm
Sample Conc.: 1.5mg/ml



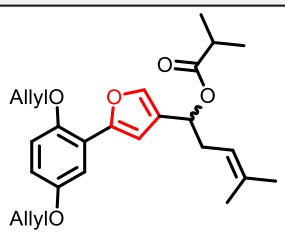
1-(5-(2,5-bis(allyloxy)phenyl)furan-3-yl)-4-methylpent-3-en-1-yl isobutyrate **(±)-86:**



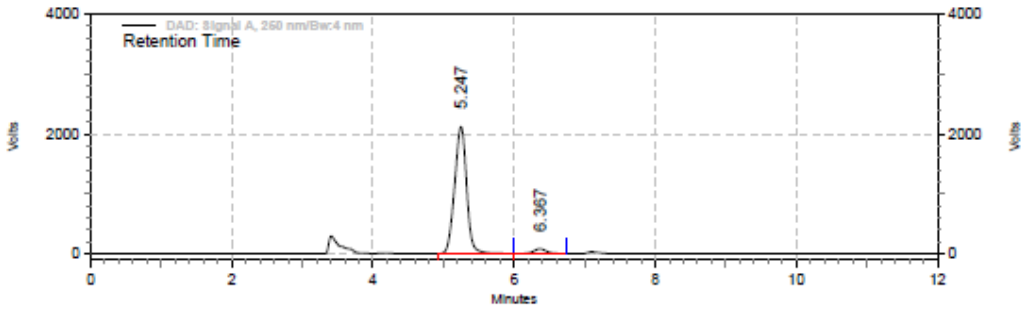
DAD: Signal A, 250 nm/Bw:4 nm
Results

Retention Time	Area	Area %
5.247	49549448	50.12
6.347	49305774	49.88
Totals	98855222	100.00

Column: CHIRALART Cellulose-SC
Eluent System: 95 : 5 (HEXANE:IPA)
Flow rate: 1.0 ml/min
Injection vol.: 10 ul
Wavelength: 254 nm
Sample Conc.: 1.5mg/ml



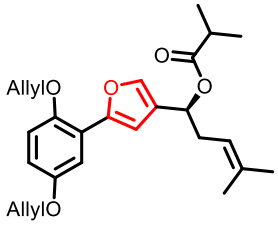
(*S*)-1-(5-(2,5-bis(allyloxy)phenyl)furan-3-yl)-4-methylpent-3-en-1-yl isobutyrate **(86):**



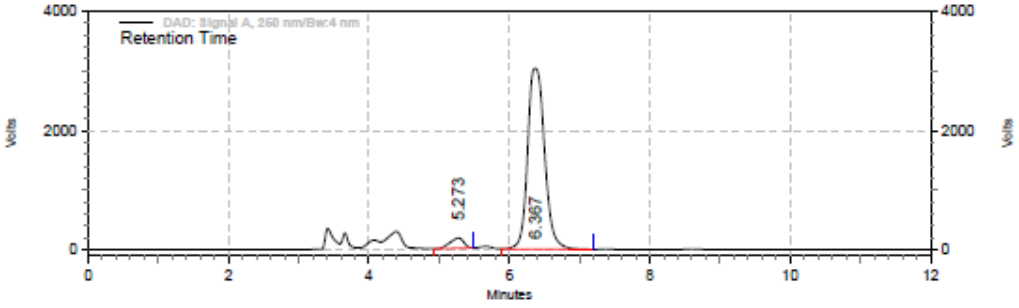
DAD: Signal A, 250 nm/Bw:4 nm
Results

Retention Time	Area	Area %
5.247	52208846	96.42
6.367	1936754	3.58
Totals	54145600	100.00

Column: CHIRALART Cellulose-SC
Eluent System: 95 : 5 (HEXANE:IPA)
Flow rate: 1.0 ml/min
Injection vol.: 10 ul
Wavelength: 254 nm
Sample Conc.: 1.5mg/ml



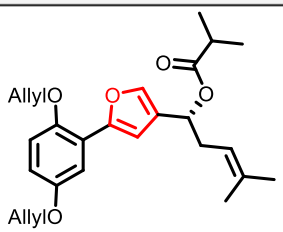
(*R*)-1-(5-(2,5-bis(allyloxy)phenyl)furan-3-yl)-4-methylpent-3-en-1-yl isobutyrate **(86a):**



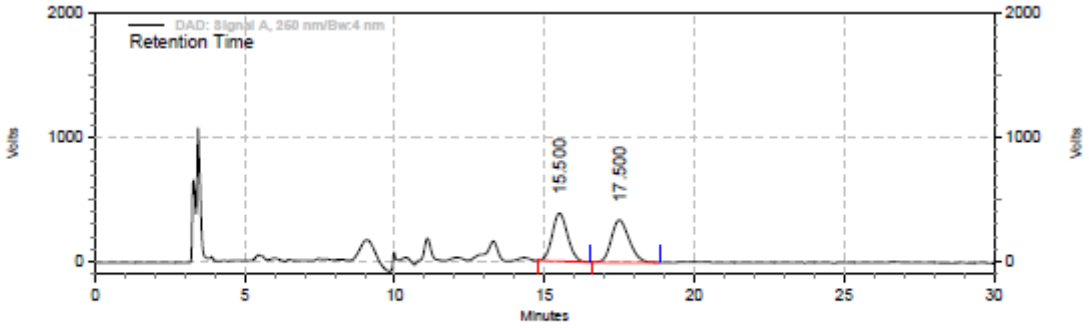
DAD: Signal A, 250 nm/Bw:4 nm
Results

Retention Time	Area	Area %
5.273	4934668	4.41
6.367	106842964	95.59
Totals	111777632	100.00

Column: CHIRALART Cellulose-SC
Eluent System: 99 : 1 (HEXANE:IPA)
Flow rate: 1.0 ml/min
Injection vol.: 10 ul
Wavelength: 254 nm
Sample Conc.: 1.5mg/ml



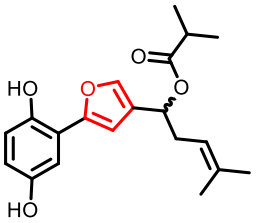
Shikonofuran D **(±)-(42) :**



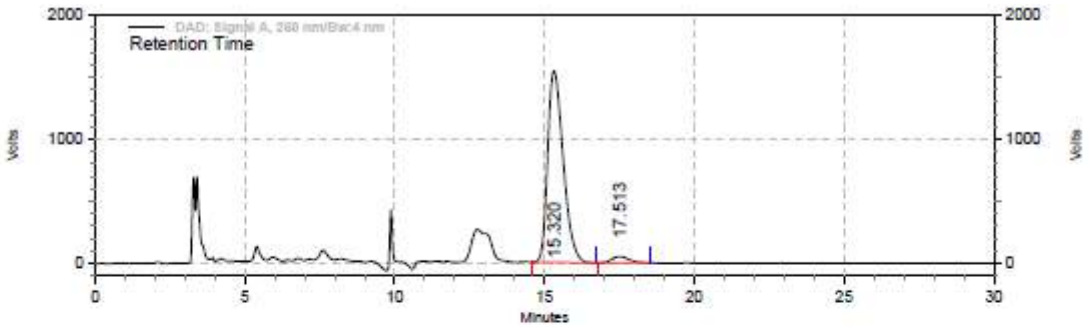
DAD: Signal A, 250 nm/Bw:4 nm
Results

Retention Time	Area	Area %
15.500	28789825	49.45
17.500	29425102	50.55
Totals		
	58214927	100.00

Column: CHIRALART Cellulose-SC
Eluent System: 95 : 5 (HEXANE:IPA)
Flow rate: 1.0 ml/min
Injection vol.: 10 ul
Wavelength: 254 nm
Sample Conc.: 1.5mg/ml



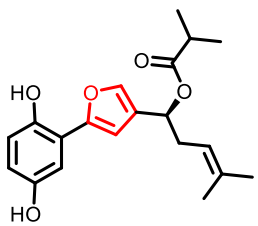
Shikonofuran D **(42):**



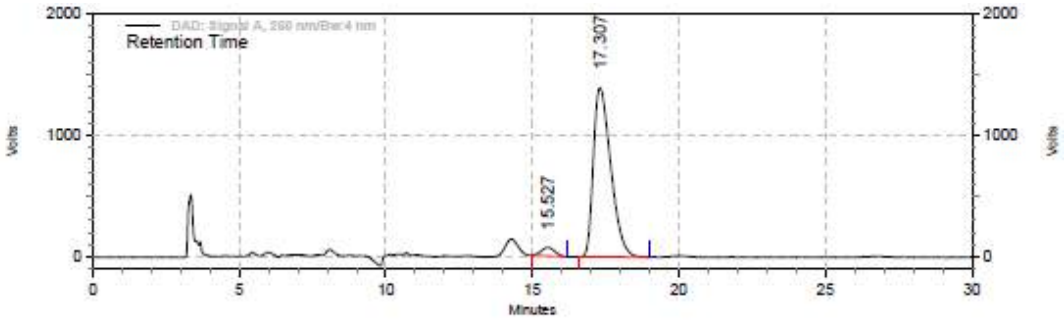
DAD: Signal A, 250 nm/Bw:4 nm
Results

Retention Time	Area	Area %
15.320	116653936	96.39
17.513	4363420	3.61
Totals		
	121017356	100.00

Column: CHIRALART Cellulose-SC
Eluent System: 95 : 5 (HEXANE:IPA)
Flow rate: 1.0 ml/min
Injection vol.: 10 ul
Wavelength: 254 nm
Sample Conc.: 1.5mg/ml



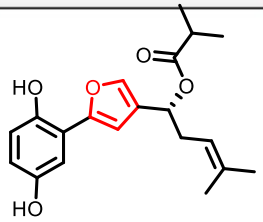
ent-Shikonofuran D **(42a):**



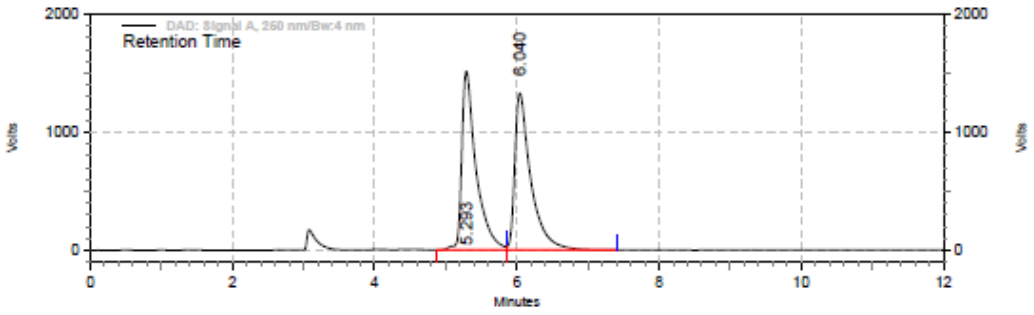
DAD: Signal A, 250 nm/Bw:4 nm
Results

Retention Time	Area	Area %
15.527	4639523	3.71
17.307	120459998	96.29
Totals	125099521	100.00

Column: CHIRALART Cellulose-SC
Eluent System: 95 : 5 (HEXANE:IPA)
Flow rate: 1.0 ml/min
Injection vol.: 10 ul
Wavelength: 254 nm
Sample Conc.: 1.5mg/ml



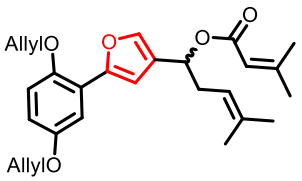
1-(5-(2,5-Bis(allyloxy)phenyl)furan-3-yl)-4-methylpent-3-en-1-yl-3-methylbut-2-enoate **(±)-(91):**



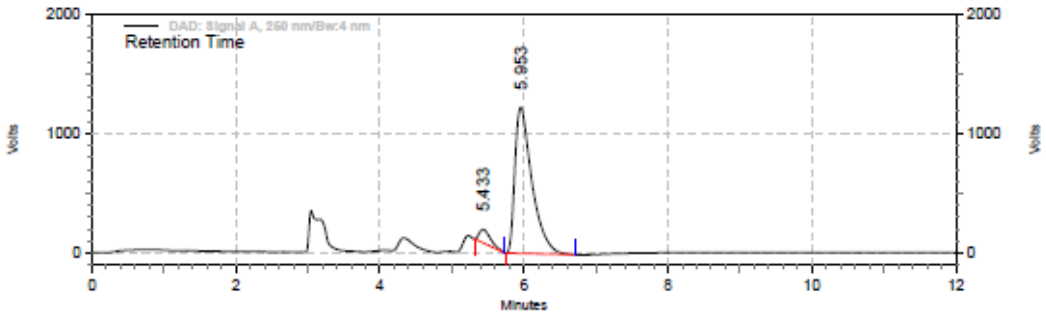
DAD: Signal A, 250 nm/Bw:4 nm
Results

Retention Time	Area	Area %
5.293	44240749	50.31
6.040	43702687	49.69
Totals	87943436	100.00

Column: CHIRALPAK AD-H
Eluent System: 95 : 5 (HEXANE:IPA)
Flow rate: 1.0 ml/min
Injection vol.: 10 ul
Wavelength: 254 nm
Sample Conc.: 1.5mg/ml



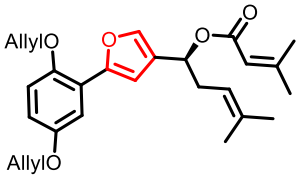
(*S*)-1-(5-(2,5-Bis(allyloxy)phenyl)furan-3-yl)-4-methylpent-3-en-1-yl-3-methylbut-2-enoate **(91):**



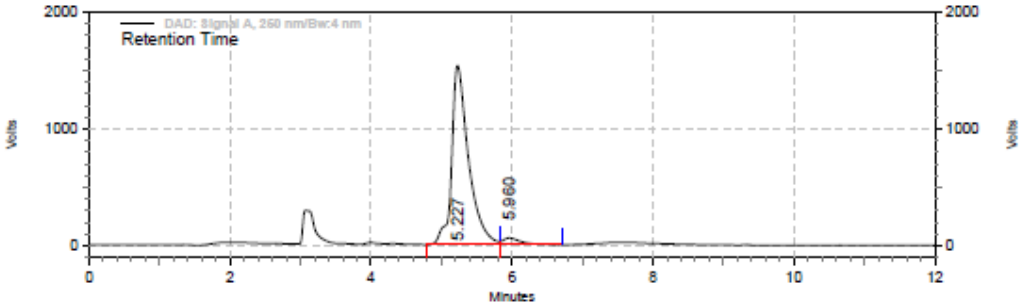
DAD: Signal A, 250 nm/Bw:4 nm
Results

Retention Time	Area	Area %
5.433	2573237	5.76
5.953	42092773	94.24
Totals	44666010	100.00

Column: CHIRALPAK AD-H
Eluent System: 95 : 5 (HEXANE:IPA)
Flow rate: 1.0 ml/min
Injection vol.: 10 ul
Wavelength: 254 nm
Sample Conc.: 1.5mg/ml



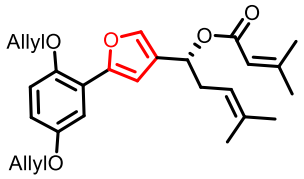
(*R*)-1-(5-(2,5-bis(allyloxy)phenyl)furan-3-yl)-4-methylpent-3-en-1-yl-3-methylbut-2-enoate **(91a):**



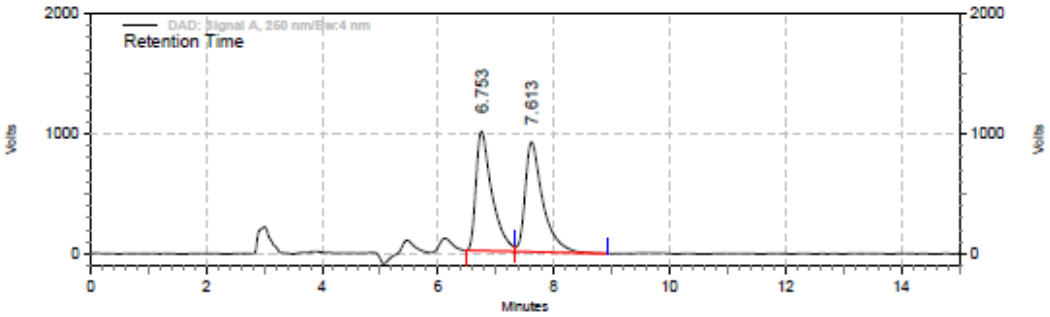
DAD: Signal A, 250 nm/Bw:4 nm
Results

Retention Time	Area	Area %
5.227	53405732	96.23
5.960	2093449	3.77
Totals	55499181	100.00

Column: CHIRALPAK AD-H
Eluent System: 95 : 5 (HEXANE:IPA)
Flow rate: 1.0 ml/min
Injection vol.: 10 ul
Wavelength: 254 nm
Sample Conc.: 1.5mg/ml



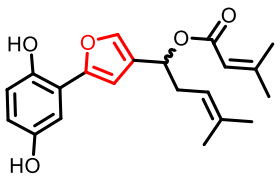
Shikonofuran E **(±)-(43):**



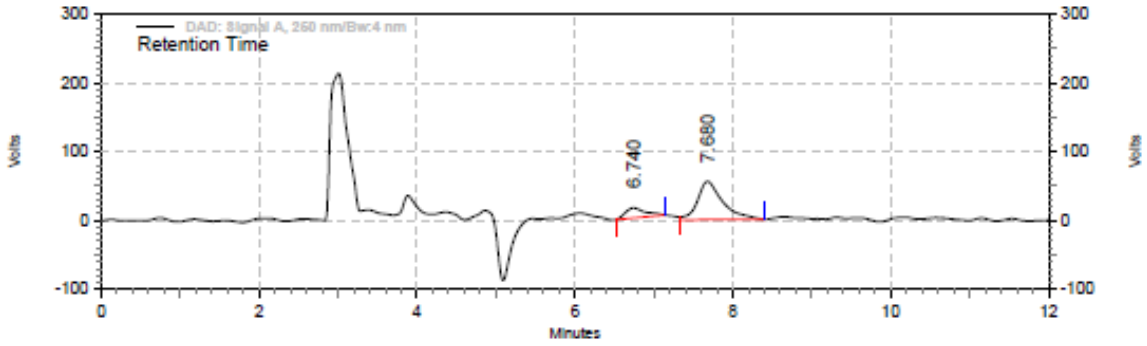
DAD: Signal A, 250 nm/Bw:4 nm
Results

Retention Time	Area	Area %
6.753	39859627	49.41
7.613	40813271	50.59
Totals	80672898	100.00

Column: CHIRALPAK AD-H
Eluent System: 80 : 20 (HEXANE:IPA)
Flow rate: 1.0 ml/min
Injection vol.: 10 ul
Wavelength: 254 nm
Sample Conc.: 1.5mg/ml



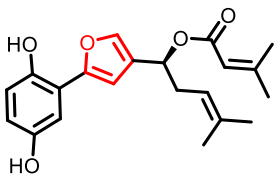
Shikonofuran E **(43):**



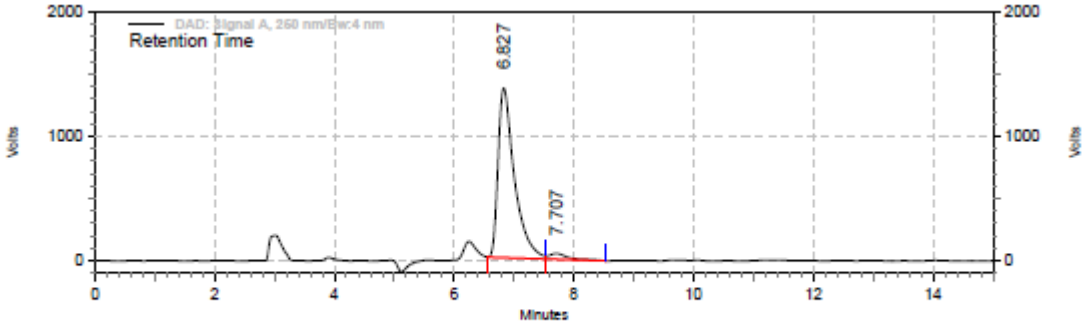
DAD: Signal A, 250 nm/Bw:4 nm
Results

Retention Time	Area	Area %
6.740	538331	17.17
7.680	2596370	82.83
Totals	3134701	100.00

Column: CHIRALPAK AD-H
Eluent System: 80 : 20 (HEXANE:IPA)
Flow rate: 1.0 ml/min
Injection vol.: 10 ul
Wavelength: 254 nm
Sample Conc.: 1.5mg/ml



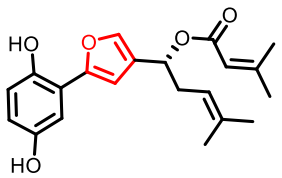
ent-Shikonofuran E **(43a):**



DAD: Signal A, 250 nm/Bw:4 nm
Results

Retention Time	Area	Area %
6.827	54250842	96.01
7.707	2254536	3.99
Totals		
	56505378	100.00

Column: CHIRALPAK AD-H
Eluent System: 80 : 20 (HEXANE:IPA)
Flow rate: 1.0 ml/min
Injection vol.: 10 ul
Wavelength: 254 nm
Sample Conc.: 1.5mg/ml



Shikonofuran C **(±)-(44) :**

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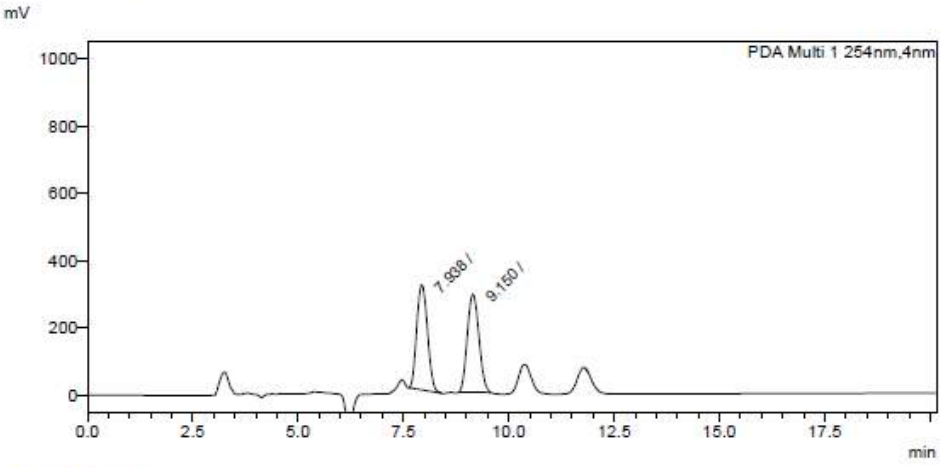

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PDA Ch1 254nm

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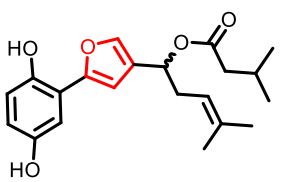

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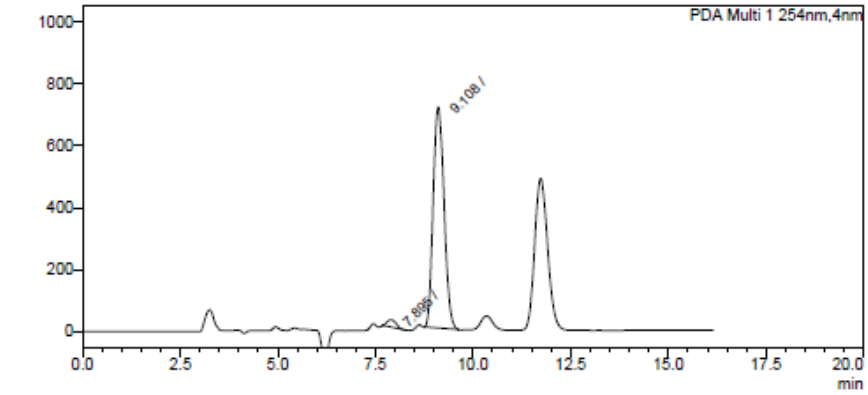

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PDA Ch1 254nm

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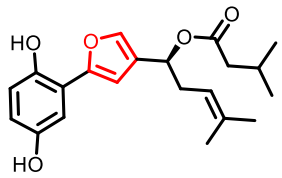

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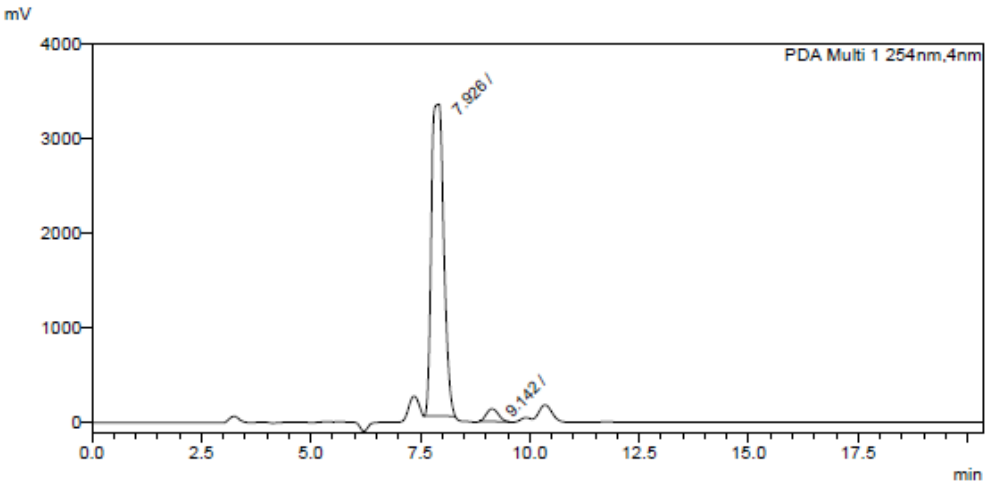

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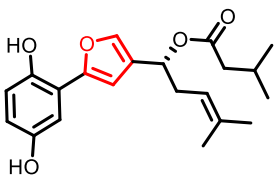


CHAPTER-3

Design, Synthesis and Biological Evaluation of Eugenol Derivatives as Potential Antidiabetic Agents

Chapter-3, Section-A: Introduction and previous approaches

3.1 Introduction

Diabetes mellitus is one of the world's fastest-growing health crises in the twenty-first century. It is a serious & chronic disorder that occurs when the human body is incapable of producing or ineffectively uses hormone insulin, resulting in elevation of blood glucose level (hyperglycemia). According to the International Diabetic Federation, in the year 2021 five hundred thirty seven million people on earth suffer from diabetes and it is probable to increase to six hundred fourty three million by 2030 and seven hundred eighty three million by 2045. According to diabetes predictions for 2021, the prevalence of diabetes is rising with age, and similar patterns are anticipated for 2045. Adults aged 20 to 24 have the lowest prevalence rates, with 2.2 % in 2021. For adults beyond age, the expected prevalence of diabetes is 24% in 2021 in those aged 75 to 79 and is predicted to increase to 24.7% by 2045. The world's population is getting older, which will result in a more significant percentage of people with diabetes now over the age of sixty (Figure 3.1).[1] In addition, preliminary studies suggest that people with diabetes have a high risk of developing severe complications while suffering from COVID-19 infection, such as SARS CoV 2 pneumonia, failure of respiratory organs, and acute respiratory distress syndrome (ARDS).[2] However, it has been demonstrated that SARS-CoV-2 infections might cause new cases of metabolic abnormalities and the worsening of existing ones. Diabetes patients are at an elevated risk for COVID-19's acute phase, but they also appear to be more frequently impacted by long-COVID and to suffer from longer-lasting effects than persons without diabetes.[3]

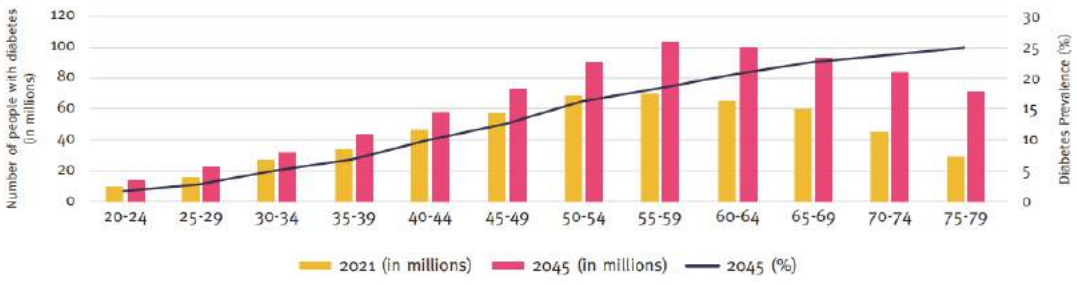


Figure 3.1. The number of people with diabetes in 2021 and estimated prevalence in 2045 by age group.

There are four types of diabetes based on etiology and diagnostic norms viz; T1DM, T2DM, Gestational diabetes, and other specific types. In case of, T1DM (5%) which is an autoimmune disease, and T2DM (95%), which is related to obesity, are the two most prevalent types of diabetes. Gestational diabetes develops during pregnancy, and other types of diabetes are exceedingly rare and caused by a single gene mutation.

Type 1 diabetes (T1DM): It is a chronic autoimmune disease that selectively destroys the pancreatic β-cells that produce insulin, resulting in a deficiency of insulin, causing accumulation of high glucose levels in the blood. The phenomenon is caused by type hypersensitivity reaction, also known as a cell-mediated immune response, where the individual's own T-cells attack the pancreatic β-cells. The body produces "self-tolerance" in response to the reaction. This self-tolerance among T lymphocytes that target specific beta cell antigens is lost in T1DM due to a genetic anomaly. As a result, T-cells are allowed to coordinate an attack against insulin-secreting beta cells with the help of other immune cells. This occurs when twin recipients who have chronic diabetes receive pancreatic transplants from identical twin donors without immune suppression and designated as insulin-dependent diabetes mellitus (IDDM) or juvenile-onset diabetes.

It is caused due to the inherent tendency of type 1 diabetes, specific viruses (e.g. German measles or mumps), environmental elements, etc. As mentioned above, In type 1 diabetes, the human body cannot produce insulin due to the loss of pancreatic β-cells. So they entirely depend upon the administered insulin, without this, they may not survive.

Type 2 diabetes (T2DM): T2DM, is the non-insulin dependent diabetes mellitus (NIDDM), which is also called as adult-onset diabetes. It is defined as the body's inability to react appropriately to insulin action or insulin secretion, which is produced by pancreatic β-cells. T2DM is shown to be the cause of almost 90% of diabetes patients. T2DM is most frequently carried by adults. Early stages of T2DM are characterized by decreased insulin sensitivity. Around the world, it has an influence on 5-7% of the population. The disease is generally under control with dietary changes, regular exercise, and hypoglycemic medication. This is the most

prevalent kind of diabetes mellitus, and family history of the disease, old age, obesity, and inactivity are all directly correlated to it.

Gestational diabetes (GDM): This disorder is often recognized in women with increased blood glucose during pregnancy due to the pregnancy hormones that interfere with insulin's actions and insulin receptors. Gestational diabetes is not present in pregnant women with diabetes mellitus (DM) that began before becoming pregnant; instead of GDM, they have DM.

Other types of diabetes mellitus include some exclusive reasons like (i) Genetic defects of beta cells of the pancreas (like chromosome 20, HNF4α, chromosome 7, glucokinase, etc.), (ii) Genetic defect in insulin production or insulin action (lipoatrophic diabetes, leprechaunism, etc.), (iii) Exocrine pancreas diseases (fibrocalculous, pancreatopathy, pancreatitis, cystic fibrosis, pancreatectomy, etc.), (iv) Endocrinopathies (v) Medication induced diabetes, (vi) Microbe-induced (congenital rubella, cytomegalovirus, etc.), (vii) DM caused by rare forms of immune-mediated syndromes, (viii) DM caused by genetic disorders.

Diabetes treatments: In Type-1 diabetes body is not produce insulin as we already discussed above, so the only treatment for T1DM patients is insulin given by outsourcing. Patients with Type-2 diabetes are usually treated with orally given anti-diabetic medications. These medications help in controlling hyperglycemia by increasing secretion of insulin and its sensitivity. It helps with absorption of glucose and decreases glucose production in hepatic cells. However, due to limited effects and unwanted side effects, the efficacies of these medications are debatable. Here we have discussed various oral drugs used for diabetes management.[5]

1. Biguanide: Metformin is a biguanide sold under the brand name Glucophage (Figure 3.2.1). It reduces hyperglycemia by preventing the liver to make an excess of glucose and aids in the uptake of glucose by cells.[5] It is the most commonly used medicine worldwide to treat type 2 diabetes. The side effects of this medicine include diarrhea, gas, indigestion, weakness, dizziness, nausea, vomiting, headache, and lactic acidosis (in patients with kidney problems; rare). The other biguanides are phenformin, Buformin etc.

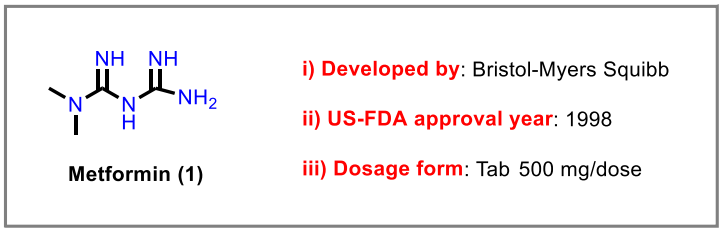


Figure 3.2.1

2. Sulfonylureas: It helps the body to stimulate the secretion of insulin by attaching to specific sulphonylurea receptors on pancreatic β-cells. Glimepiride, glyburide, chlorpropamide, glipizide, tolbutamide, and tolazamide are anti-hyperglycemic sulfonylurea agents used to treat type-2 DM.[5] The common side effects of sulfonylurea drugs are hypoglycemia, weight gain, dizziness, and headache (Figure 3.2.2).

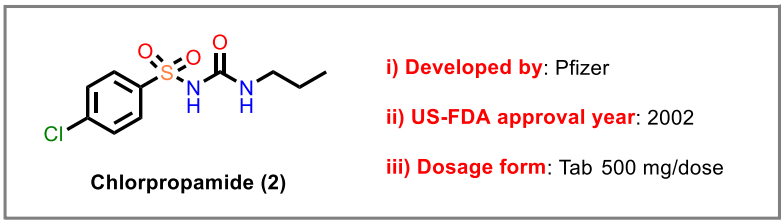


Figure 3.2.2

3. Meglitinides: These are also called non-sulfonylureas insulin secretagogues which act as antihyperglycemic agents by binding with non-sulfonylurea receptors present on pancreatic beta cells and increasing insulin secretion.[5] Repaglinide and nateglinide drugs are examples of meglitinides (Figure 3.2.3). The side effect of these drugs is hypoglycaemia.

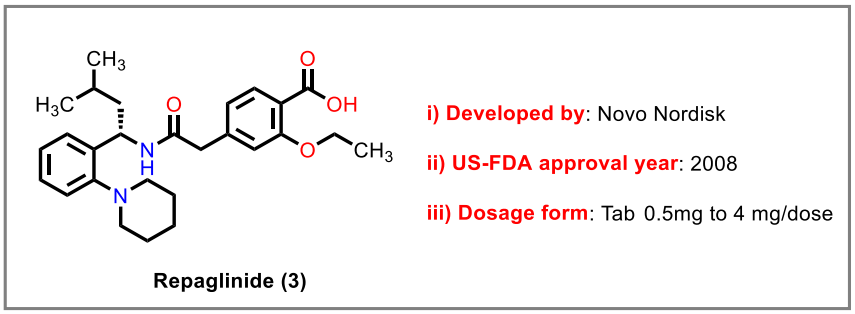


Figure 3.2.3

4. Thiazolidinediones (TZDs): They are heterocyclic compounds that act as antihyperglycemic agents by helping the body's cells utilize glucose. The examples of TZDs are pioglitazone and rosiglitazone (Figure 3.2.4).[5] The side effects of these drugs are fluid retention, weight gain, heart failure, low RBC count, infection in the upper respiratory path etc.

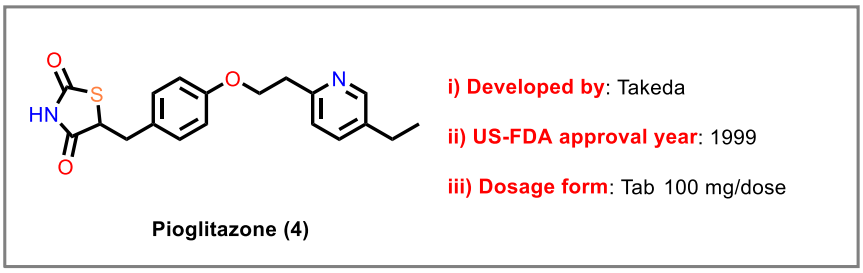


Figure 3.2.4

5. α-Glucosidase inhibitors: The inhibition of α-glucosidase is found beneficial in the treatment of diabetes. They control the levels of blood glucose by inhibition of higher sugar digestion into glucose.[5] Miglitol and acarbose are α-glucosidase inhibiting agents (Figure 3.2.5). Among these acarbose is a widely used α-glucosidase inhibitor agent worldwide to treat T2DM. They show stomach pain, diarrhea, gas, and liver problems as side effects.

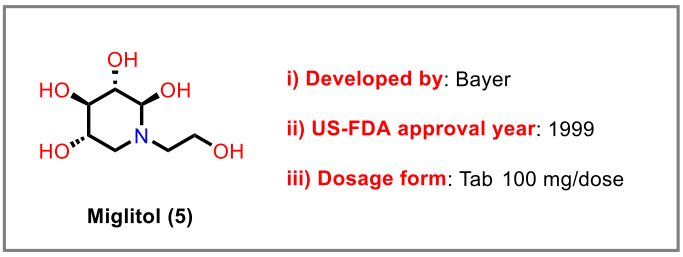
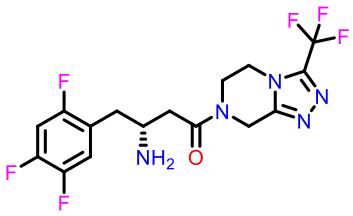


Figure 3.2.5

6. Dipeptidyl-peptidase-4 inhibitors (DPP-4 inhibitors): These inhibitors like Sitagliptin is sold under the brand name Januvia (Figure 3.2.6). It is also used with the combination of metformin which is sold as Janumet and Janumet XR. It was the 88th most frequently prescribed medication in the US in 2019.[5] It acts as an antihyperglycemic agent by increasing insulin secretion to treat T2DM. The others DPP-4 inhibitors include alogliptin, saxagliptin, and linagliptin. The common side effect of these agents is upper respiratory infection and headache.



Sitagliptin (6)

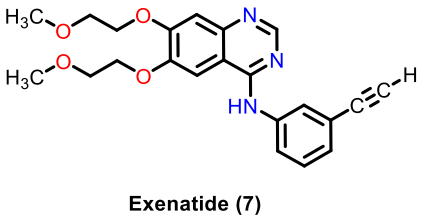
i) Developed by: Merck & Co.

ii) US-FDA approval year: 2006

iii) Dosage form: Tab 100 mg/dose

Figure 3.2.6

7. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs): These therapeutic agents protect pancreatic β-cells without generating hypoglycemia while enhancing glycemic control through controlling glucose-dependent insulin release.[5] Exenatide, albiglutide, dulaglutide, and liraglutide are the drugs included in this class of anti-hyperglycemic agents (Figure 3.2.7). These drugs have a lesser risk of hypoglycemia than the other class of drugs like sulfonylureas and meglitinides, which stimulate insulin secretion.



Exenatide (7)

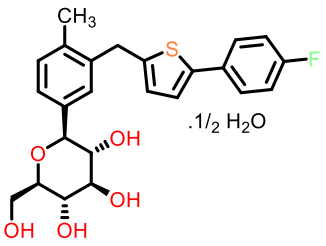
i) Developed by: Amylin Pharmaceutical Byetta

ii) US-FDA approval year: 2005

iii) Dosage form: Injectable solution of 5 mg/dose

Figure 3.2.7

8. Sodium-glucose co-transporter-2 inhibitors (SGLT-2 inhibitors): These inhibitors show hypoglycemic effects through increasing glycosuria. They prevent the resorption of glucose in the close convoluted path of the kidney to reduce the blood glucose level.[5] For example, invokamet, dapagliflozin, canagliflozin, and empagliflozin are SGLT-2 inhibitors (Figure 3.2.8) and the side effect of these drugs includes the infection in vagina by yeasts and UTIs.



Invokamet (8)

i) Developed by: Janssen Pharmaceuticals

ii) US-FDA approval year: 2014

iii) Dosage form: Tab combining Canagliflozin (50 mg) Metformin hydrochloride (300 mg) in single dose

Figure 3.2.8

Among various drugs with diverse pharmacological action described above, the therapeutic strategies like inhibition of α-glucosidase and advanced glycation end products (AGEs) helps in regulating diabetic complications and found to be beneficial in the treatment of diabetes. The inhibition of the α-glucosidase enzyme regulates the levels of blood glucose by retarding the digestion of higher sugars into glucose. A sequence of non-enzymatic reactions among reducing sugars and amino groups of the protein forms AGEs. AGEs bind to the receptor for AGEs (RAGE), reactive oxygen species, and downstream signaling elicits a pro-inflammatory response.

Conventional modern medication does not always work well to control DM, in all cases due to the emergence of insulin resistance and the production of insulin antagonists in the body. Insulin cannot always be considered to be a viable treatment, whereas oral anti-hyperglycemic drugs are found to have limited utility in many situations due to the significant side effects. Therefore search for improved treatment from natural sources is still in progress. Ayurvedic medications help diabetes patients maintain their metabolic stability and immune power, in addition to their hypoglycemic effects. According to the international ayurvedic medical journal, there are more than 400 conventional plant-based treatments available for diabetes management, but only a few of them are recognized scientifically and evaluated for medicinal use. There are many ayurvedic plants like *Allium cepa, Allium sativum, Azadirachta indica, Curcuma Longa, Syzygium cumini, Momordica charantia, Ocimum sanctum, Syzygium aromaticum*., etc which are reported in the literature for their anti-diabetic activities.[6]

Eugenol belongs to the phenylpropanoid class of natural products, which was isolated from various plant-like *Syzygium aromaticum, Ocimum basilicum, Cinnamomum tamala, Myristica fragrans*, etc. However, the major source of eugenol is

Syzygium aromaticum (clove oil) only in which 45-90% of eugenol is present as its component. It is a natural monoterpene molecule, isolated as pale yellow color oil, that is very cheap, readily available, and pharmacologically active. It has the IUPAC name of 4-allyl-2-methoxyphenol with a molecular weight of 164.2 and molecular formula $C_{10}H_{12}O_2$. It can also be synthesized at the industrial level via allylation of guaiacol using allyl chloride which is showing similar properties with respect to the isolated one (Figure 3.3)

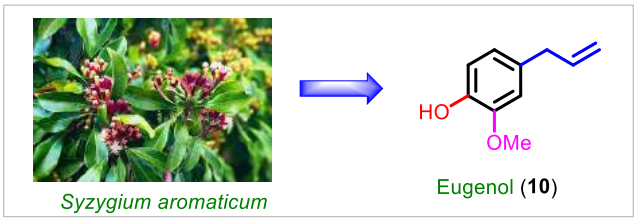


Figure 3.3. Structures of eugenol

It has attracted the attention of researchers in past years because of its chemical versatility and biological activity toward diabetes management. In addition to the extraordinary antioxidant[7], antidiabetic[8] and anti-inflammatory[9] properties, it also shows hypotensive[10], anticarcinogenic[11], antiparasitic[12], antifungal[13], antibacterial[14], antimicrobial[15], antiseptic[16], dental analgesic[17], antiviral[18] properties. However, molecules with antioxidant activity have been demonstrated to have a better potential for preventing and treating diabetes (Figure 3.4).

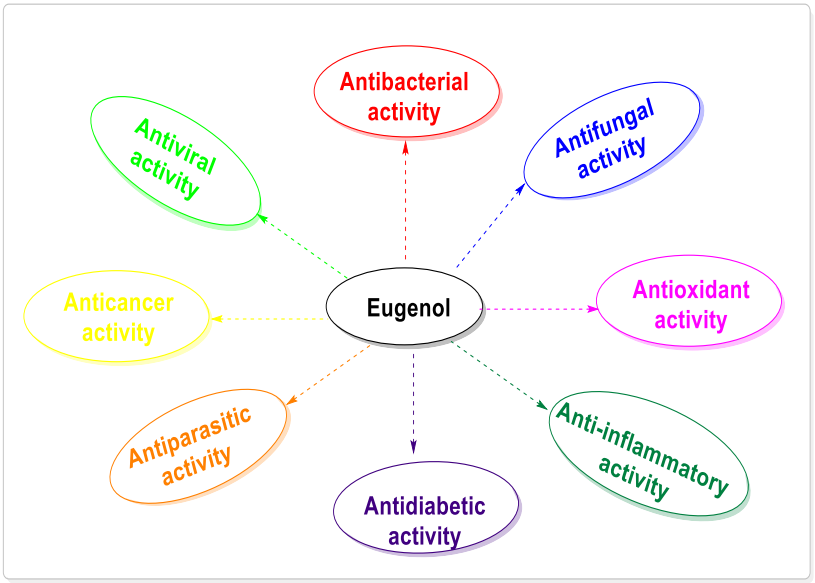


Figure 3.4. Therapeutic Properties of Eugenol

In 2016, Ashok Giri and co-workers reported the dual role of eugenol isolated from *Ocimum* species acts as an inhibitor of α-glucosidase as well as an AGEs. For that, they screened the leaf and inflorescent extracts of different *Ocimum* species (such as *O. gratissimum, O. tenuiflorum, and O. kilimandscharicum*) for the antiglycation activities by BSA-AGE assay. The major metabolites in these species include ocimene, camphor, eugenol methyl ether (EME), eugenol, eucalyptol, β–caryophyllene, terpinolene, farnesene, and α–pinene (Figure 3.5). Among all three species, the inflorescent leaf extract of *O. gratissimum* extract showed the highest inhibition of glycation by inhibiting AGEs formation with 74% and 72% respectively. These species have high eugenol content, and the leaf extract of *O. tenuiflorum* with high EME shows very less antiglycation activity with 10% inhibition.

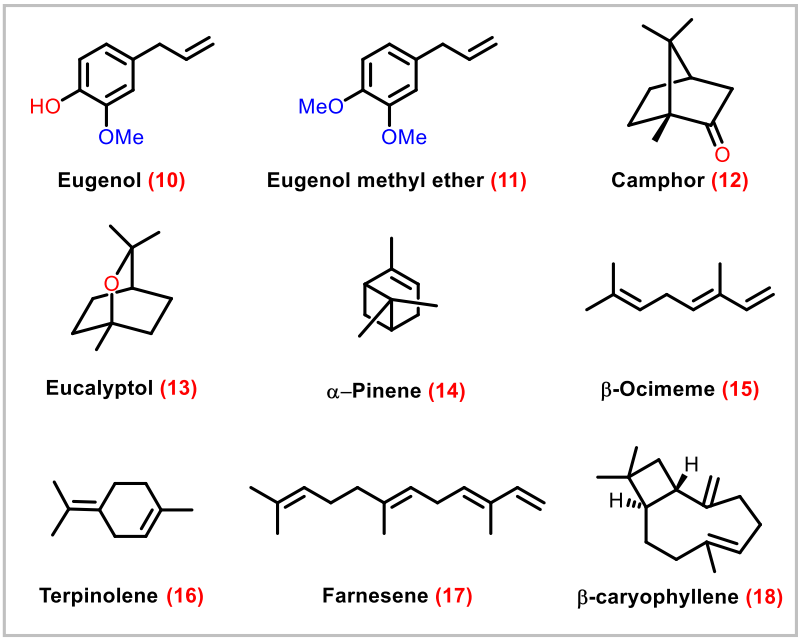


Figure 3.5. Structure of *Ocimum* species metabolites

The leaf and inflorescence of *O. kilimandscharicum* with major metabolites camphor and eucalyptol showed moderate AGE inhibition with 46% and 42%, respectively, and the other components like ocimene, β–caryophyllene, terpinolene, farnesene, and α–pinene, etc. were not showed AGE inhibition significantly. Among all these components eugenol shows very good antiglycation activity *in vitro*, hence they have chosen this metabolite for the *in vitro* and *in vivo* SAR (structure-activity relationship) studies.

According to the assay of BSA-AGE, 4-allyl-2-methoxyphenol (eugenol) has proved to be a effective AGE inhibitor as compared to eugenol methyl ether which is because of the existence of a hydroxy group in eugenol, which participates in protein-eugenol interaction. For more study about protein (serum albumin) and eugenol interaction, they performed docking study. The result shows stronger binding (which is approx 6 kcal/mol binding energy) of eugenol with surface exposed lysine (*Lys*-236 and *Lys*-375) that is more than aminoguanidine hydrochloride (4.3 kcal/mol). Thus to understand the role of eugenol-protein interaction, they also performed an assay related to intrinsic fluorescence and electronic circular dichroism (ECD). The intrinsic assay clearly revealed that the binding of eugenol with BSA is a concentrate-dependent pattern in which a steady drop in intrinsic fluorescence intensity was observed as eugenol concentration was raised, and the CD indicated the secondary structure of the protein was unaffected after binding with eugenol.

Further, the *in vivo* studies showed a significant lowering of blood glucose level in mice which was treated with eugenol as compared to those without treating eugenol mice. Hence less formation of the advanced glycation end product and the other reason for low blood glucose level due to α-glucosidase inhibition. The α-glucosidase is an enzyme that is present in the small intestine (at brush border epithelium), it converts the higher carbohydrates like maltose, sucrose, etc into glucose and increases the blood glucose level. Thus, eugenol act as an α-glucosidase inhibitor by inhibiting this conversion and lowering the blood glucose level (Figure 3.6) This proves that the eugenol which is isolated from the species *O. gratissimum* is a potent inhibitor by showing the dual mode of action as a inhibitor of α-glucosidase as well as AGE and can be used in diabetes management. [19]

Inspired by the dual activation of eugenol in diabetes management we focused on the studies related to the inhibition of α-amylase, α-glucosidase, glycation inhibition, and antioxidant properties of the eugenol molecule. These activities are further optimized by the derivatization of functional groups of eugenol because eugenol

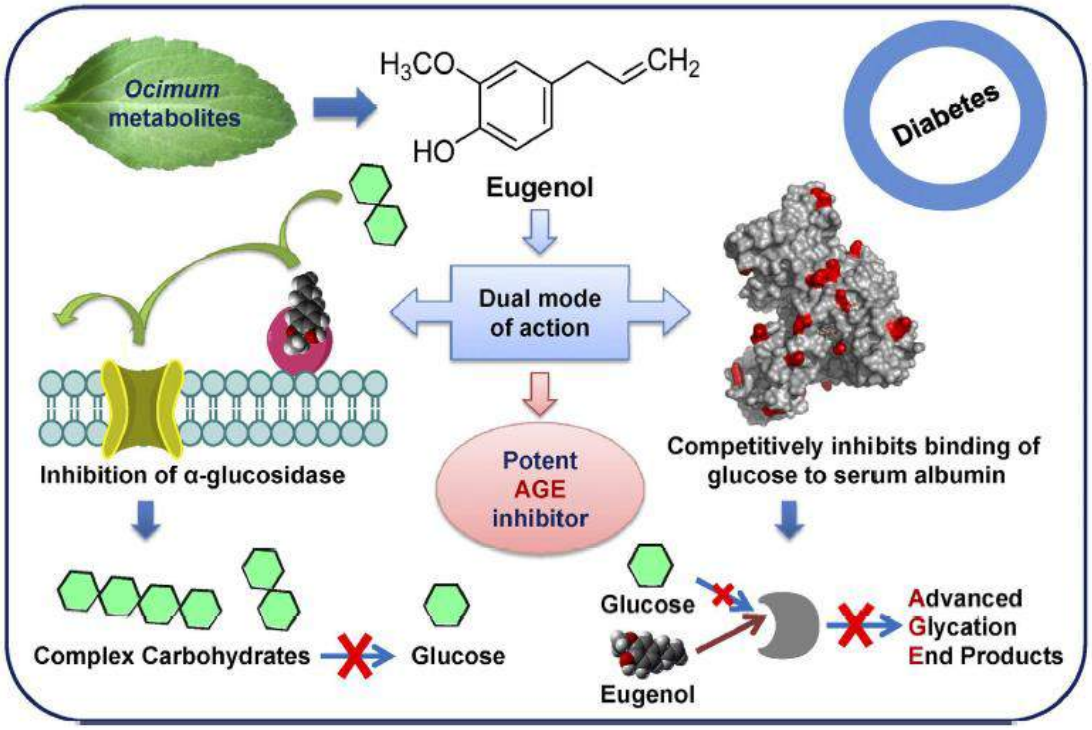


Figure 3.6. The dual action of eugenol in diabetes management

is an oily compound, and it is not water-soluble. It should be administered into the body by the intra-peritoneal route only, and we cannot use it orally. Thus, there was a desperate need for the synthesis of water-soluble derivatives which could be given orally to diabetic patients.

In this chapter, we have discussed the synthesis and biological studies of various eugenol derivatives of lipophilic esters, amino acid conjugates, and carbamates based on a pro-drug concept. Prodrugs are molecules whose pharmacological activity is either less or none which converted into an active parent drug, under *in vivo* conditions. This takes place with the help of enzymatic or chemical reactions, or both. Prodrugs have emerged from being developed by chance to being intentionally designed (Figure 3.6). Such advancement has aided in overcoming drug development challenges, which have limited the options of formulations or resulted in the poor biochemical performance. The prodrug concept improves the biochemical properties of active compounds by overcoming the barriers like solubility, orally absorption, and slow mechanism of action. More than 30 prodrugs, which accounts for more than 12% of all authorised small-molecule new chemical entities have been approved by the US Food and Drug Administration in last decade (Figure 3.7).[20]

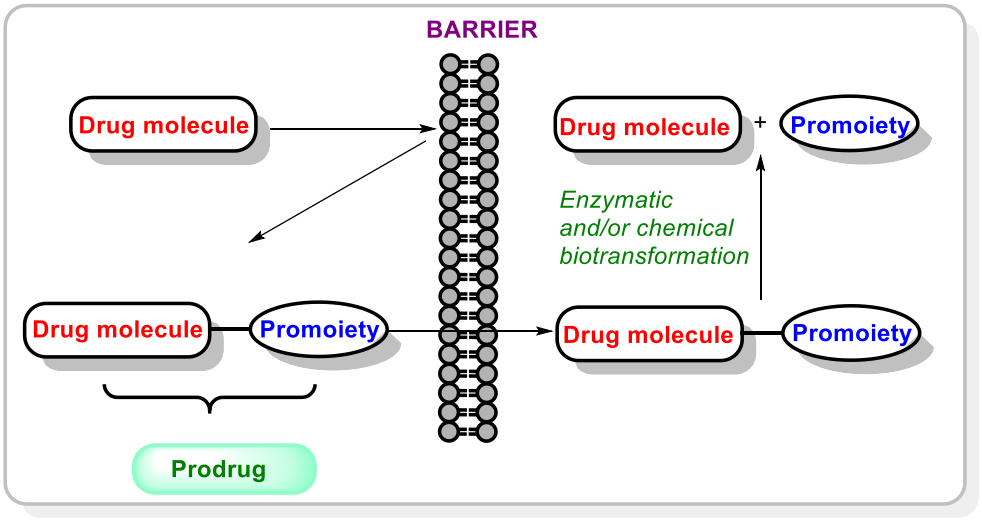


Figure 3.7. Prodrug concept

This approach opens the opportunity for a flexible & wide therapeutic window for the treatment of diabetes. These derivatives further show better solubility, bioavailability, permeability, adsorption, and anti-diabetic activity

Chapter-3, Section-B: Present work

3.2.1 Hypothesis

As we discussed in the introduction, eugenol showed anti-diabetic activity by inhibiting α-glucosidases and the formation of AGEs. Major concerns associated with this natural product are the lowest water solubility and bioavailability. Hence, designed a series of novel analogs of eugenol based on the prodrug concept, which undergoes in vivo non-enzymatic or enzymatic transformations (with the aid of acidic/basic environment or lipases/esterase/amidases) and releases active ingredient eugenol into extracellular and/or intracellular domains.

3.2.2 Result and discussion:

3.2.2.1: Synthesis of eugenol analogs:

Accordingly, the free hydroxyl group of eugenol is used as a functional handle to synthesize corresponding lipophilic esters (enhances the cell-membrane permeability and undergoes enzymatic hydrolysis with the aid of lipases), amino acid esters, amino acid ester-salts, and carbamates (soluble in highly polar solvents like water and DMSO (undergoes enzymatic hydrolysis with the aid of esterases), as shown in Figure 3.8.

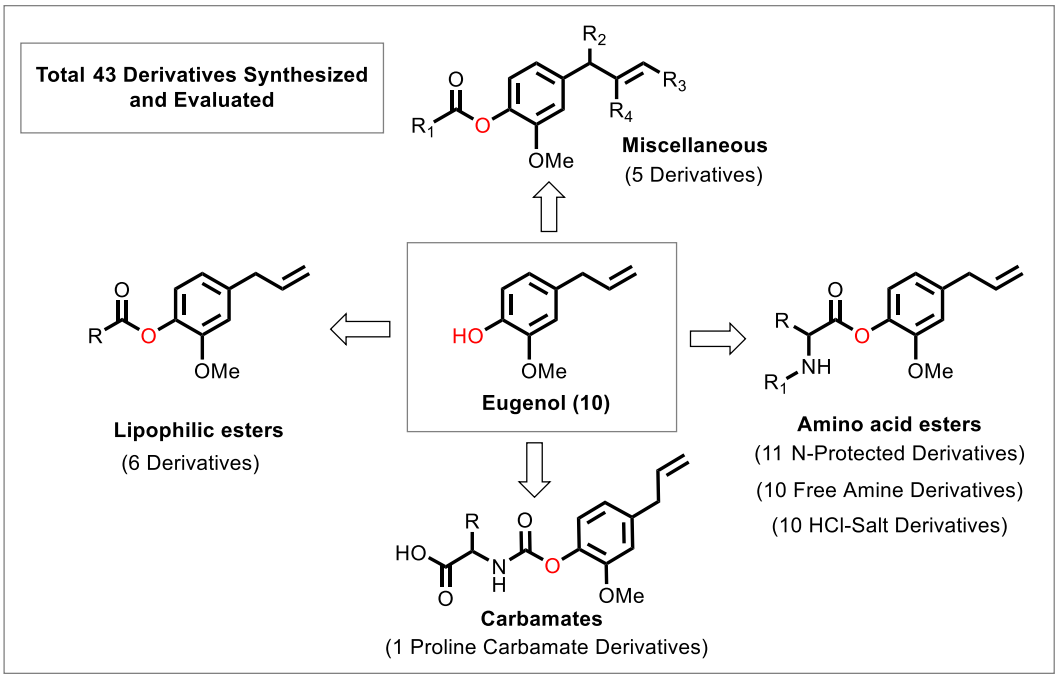
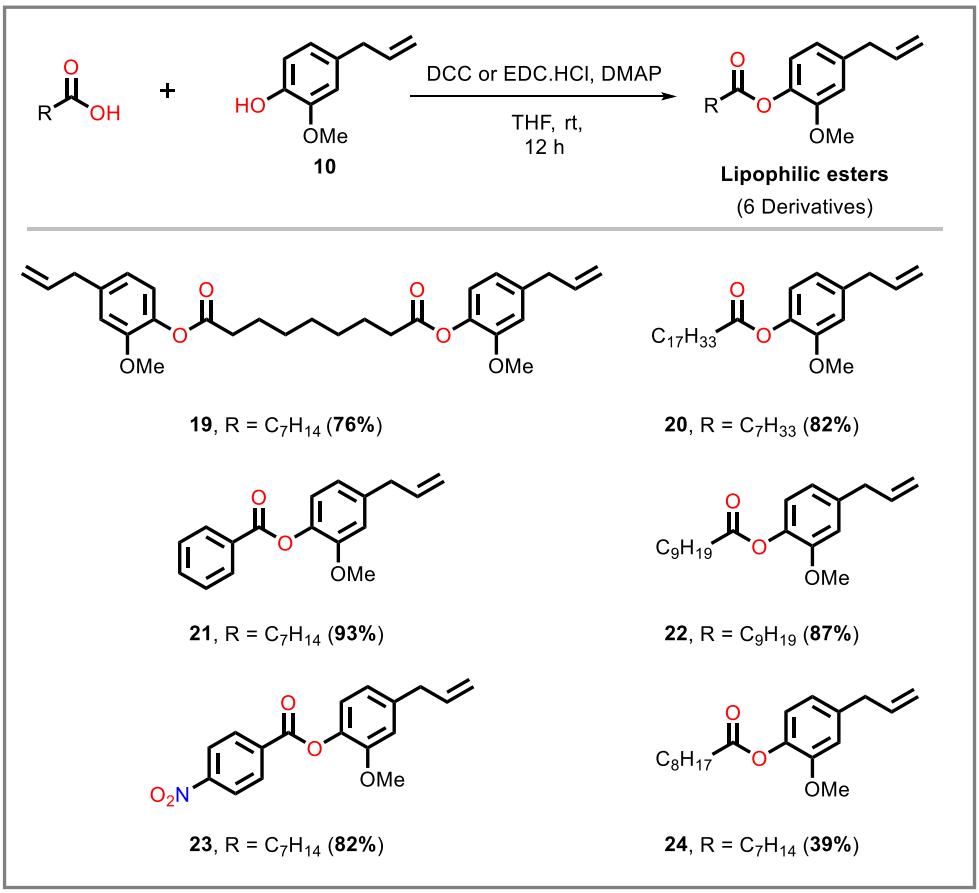


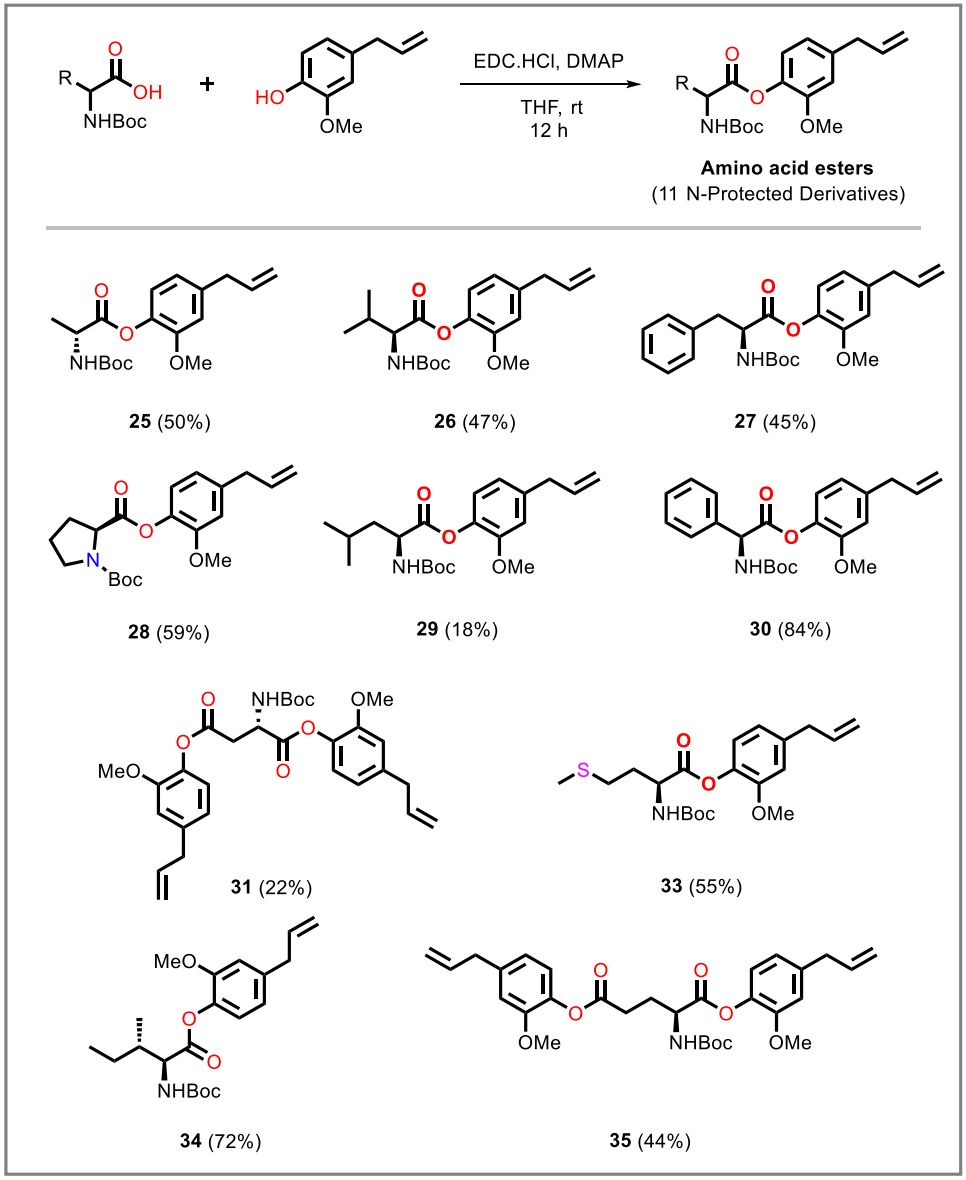
Figure 3.8. The general classification of eugenol derivatives.

1. Lipophilic ester derivatives of eugenol: Long-chain aliphatic and aromatic ester derivatives of eugenol were synthesized aiming at increasing the cell wall permeability of eugenol. The general procedure for the synthesis of lipophilic esters (**19-24**) is shown in Scheme 3.1. Using the appropriate acid and eugenol in the presence of the coupling reagent EDC.HCl or DCC[21], esters **29-24** were produced. The coupling reagent was chosen based on yield and purification ease. In general, EDC.HCl was utilized for aliphatic acids whereas DCC was used for aromatic acids.



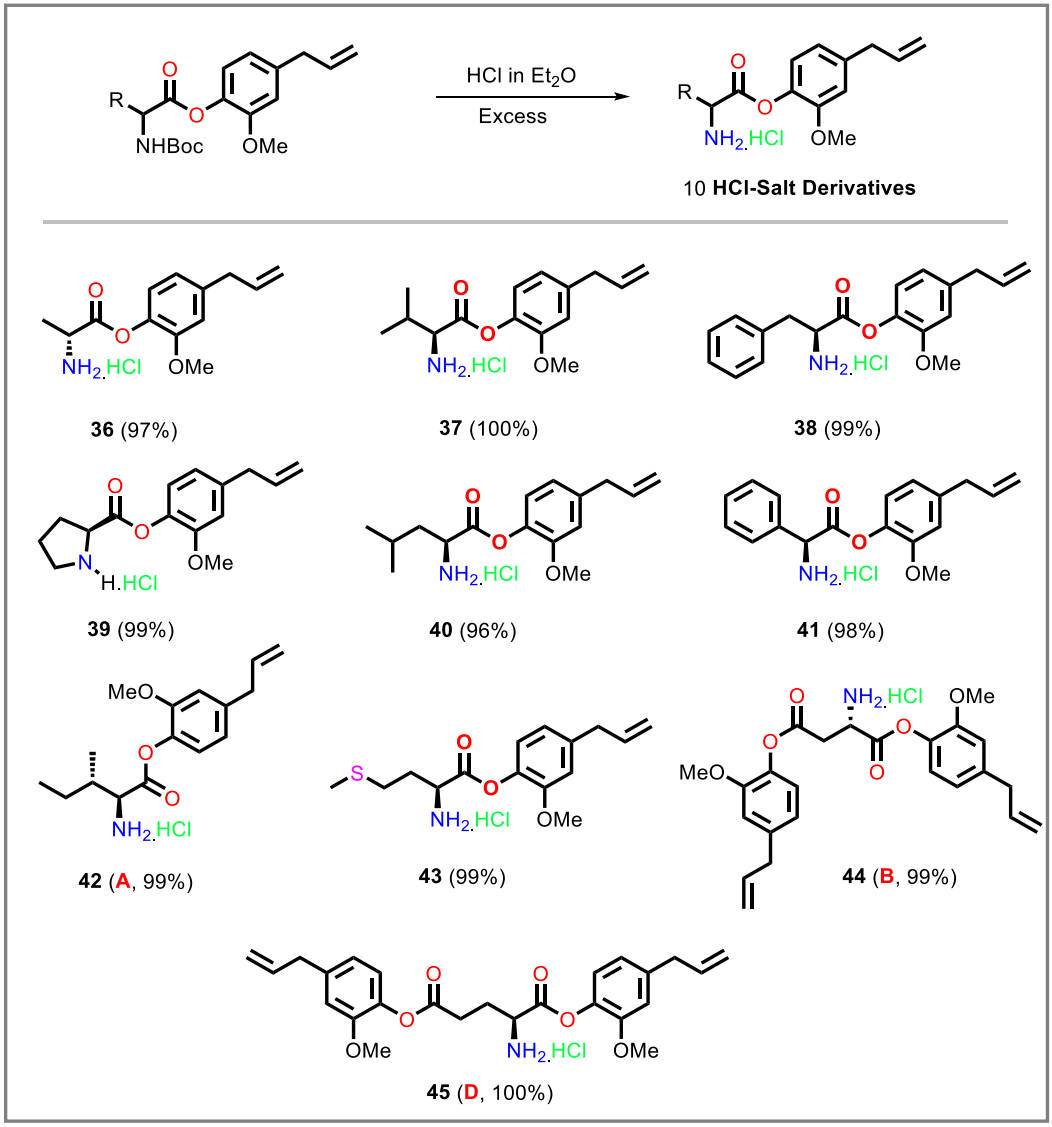
Scheme 3.1. Lipophilic ester derivatives of eugenol (**19-24**).

2. Amino acid-derived ester derivatives of eugenol: To increase the solubility and bioavailability of eugenol, connected polar amino acid (Boc-protected) to eugenol via ester linkage using EDC.HCl as a coupling reagent to access corresponding amino acid conjugates of eugenol **25-35** (Scheme 3.2).



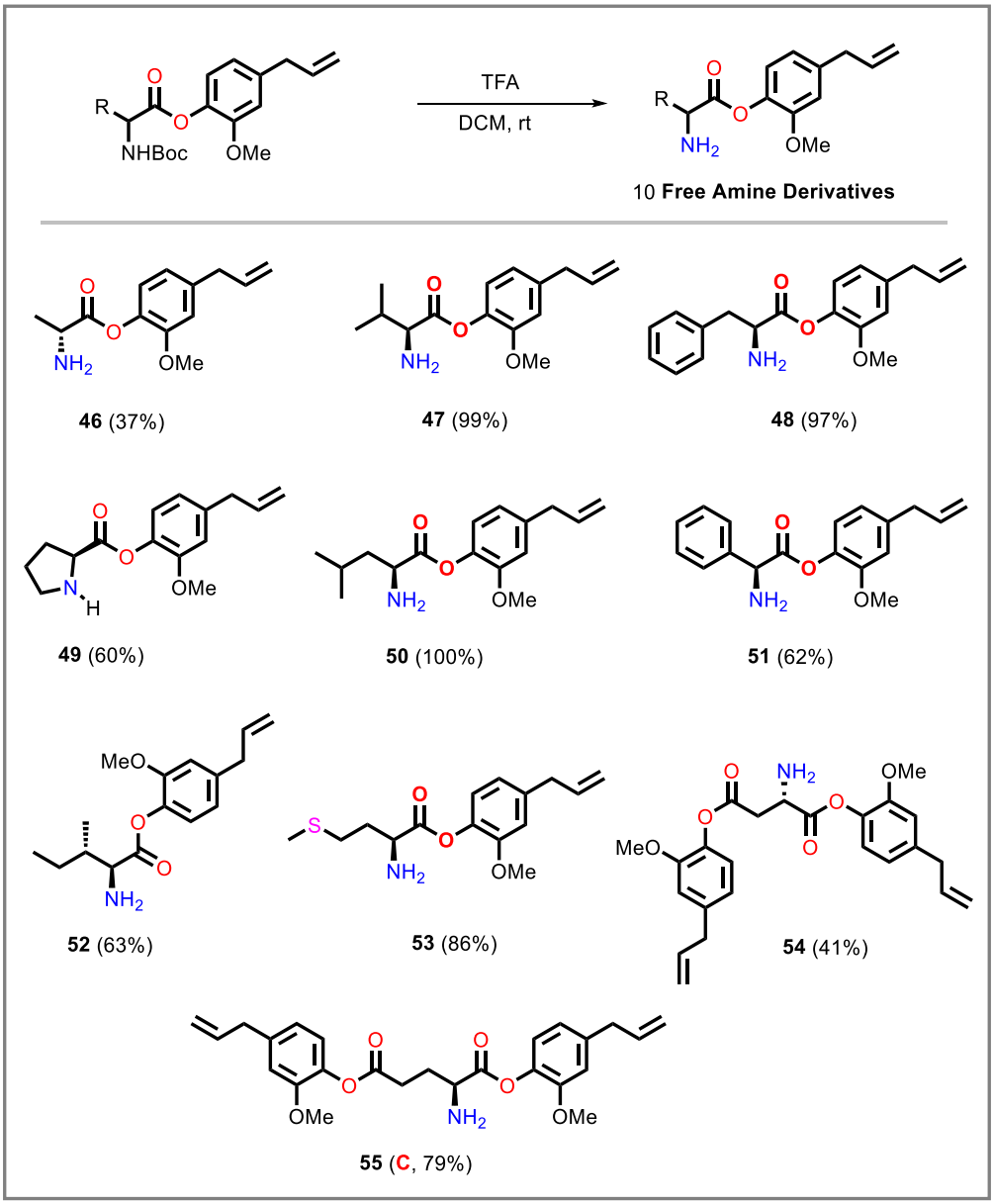
Scheme 3.2. Synthesis of Amino acid derivatives of Eugenol

Subsequently, the Boc group was removed using HCl in diethyl ether (etherial HCl), which concomitantly delivered corresponding HCl salts of amino acid-derived eugenol analogs **36-45** (Scheme 3.3).



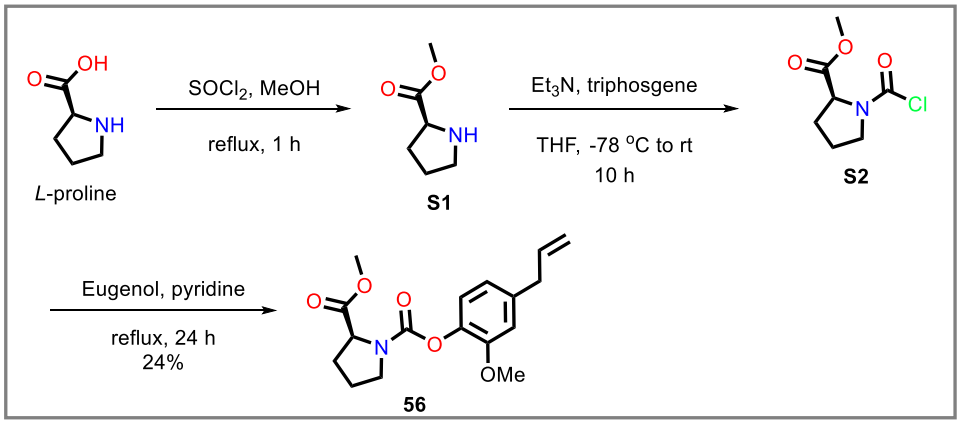
Scheme 3.3. Synthesis of HCl salt of amino acid derivatives of eugenol

Next, The boc-protected amino acid ester derivatives of eugenol were treated with TFA in DCM at room temperature,[22] to access corresponding free amine analogs of eugenol **46-55** (Scheme 3.4).



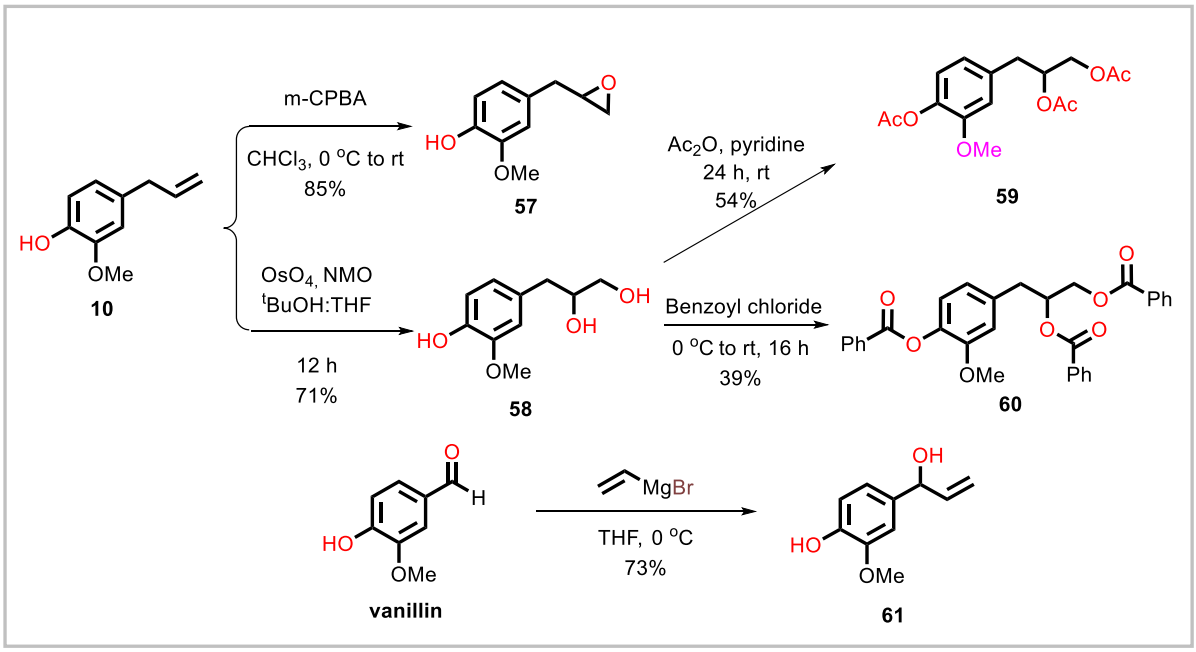
Scheme 3.4. Synthesis of TFA salt of amino acid derivatives of eugenol

3. Carbamate derivatives of eugenol: Another class of amino acid-based analog of eugenol was synthesized using L-proline. Accordingly, L-proline was converted into its methyl ester **S1** using $SOCl_2$-mediated acid chloride formation followed by in situ methanolysis.[23] Next, **S1** was converted into carbamoyl chloride **S2** using triphosgene and Et_3N, in THF.[24] Finally, carbamoyl chloride was coupled with eugenol in pyridine at reflux conditions to form carbamate derivative **56** (Scheme 3.5).[25]



Scheme 3.5. Synthesis of carbamate derivative of eugenol

4. Miscellaneous analogs of eugenol: Other eugenol derivatives (**57-61**) were synthesized through the modification of allyl and hydroxyl functionalities. Epoxidation of the double bond of eugenol using *m*-CPBA gave analog **57,**[26] and OsO_4-



Scheme 3.5. Synthesis of miscellaneous analogs of eugenol

mediated dihydroxylation delivered corresponding diol analog **58** in 71% yield.[27] This trihydroxy derivative of eugenol **58** was further transformed into triacetate **59** and tribenzoate **60** derivatives using known the reaction conditions.[28] The reactionof vinyl magnesium chloride with vanillin gave the hydroxyl vinyl derivative of eugenol **61** in a 73% isolated yield (Scheme 3.6).[29]

3.2.2.2: Biochemical Studies:

Docking Studies:

Docking is an effective and competent tool for in silico screening. In studying the various properties associated with protein-ligand interactions, docking is a powerful tool. The molecules in nature have a tendency to be found in their energy form. Understanding these properties is crucial in the rational design of potent inhibitors. It plays an important and ever-increasing role in rational drug design. Docking is a computational procedure for an appropriate ligand that fits both energetically the protein's binding site. In other words, it is a study of how two or more molecules e.g. ligand and protein, fit together. Docking has been proven very efficient tool for novel drug discovery for targeting protein. Among different types of docking, protein-ligand docking is of special interest, because of its application in the medical industry. Protein-ligand docking refers to searching for the accurate ligand conformations within a targeted protein when the structure of proteins is known. Docking procedures are basically a combination of search algorithms and scoring functions.

Experimental Procedures:

Ligand preparation: The ligand structures were retrieved from PubChem. All the molecules were checked for stereo-chemical properties and then converted to *.pdbqt format using Auto Dock Tools. This library was used for further docking studies.

Preparation of the target molecules: Crystal structures of Human α-amylase (HAA; PDB ID: 5E0F), human α-glucosidase (HAG; PDB ID: 5NN5), and human serum albumin (HAS; PDB ID: 4LA0) were downloaded from the RCSB Protein Data Bank. Water and other heteroatoms were deleted from these structures. The grid was set around active site residues with the dimension of 24 x 24 x 24 Å using the Auto Grid program of Auto Dock Tools. The protein is converted to *.pdbqt for further docking studies. These target molecules were then further used for virtual screening.

Virtual screening using Auto dock vina: Prepared receptor molecules and ligands were set for the virtual screening by Auto Dock Vina based Lamarckian Genetic

Algorithm (LGA) parameter for ligand tethering of the proteins using 10 runs criteria. The top hits of ligands were selected based on their docking score against targets. Two-dimensional ligand interaction images are made using Biovia Discovery Studio 4.5.

The results of the docking study revealed that the binding score comparison illustrated that all the derived molecules are binding with higher interaction energy. The eugenol, A, B, C, and D compounds have shown good binding scores with the energy of -5.6, -6.4, -6.1, -6.7, and -6.2 kcal/mol against α-amylase respectively, energy of -5.2, -5.4, -6.1, -5.9 and -6.2 kcal/mol against α-glucosidase respectively and -6.4, -7.6, -7.4, -7.4, -.6.5 against human serum albumin (HSA) respectively. These results indicate that A, B, C, and D derivatives are more potent as compared to parental molecules i. e. Eugenol.

All these prodrug-based analogs (Figure 3.9) can deliver eugenol (active molecule) into the biological system with the aid of naturally abundant enzymes such as lipases, esterases, amidases, etc. After preliminary investigations, we found that

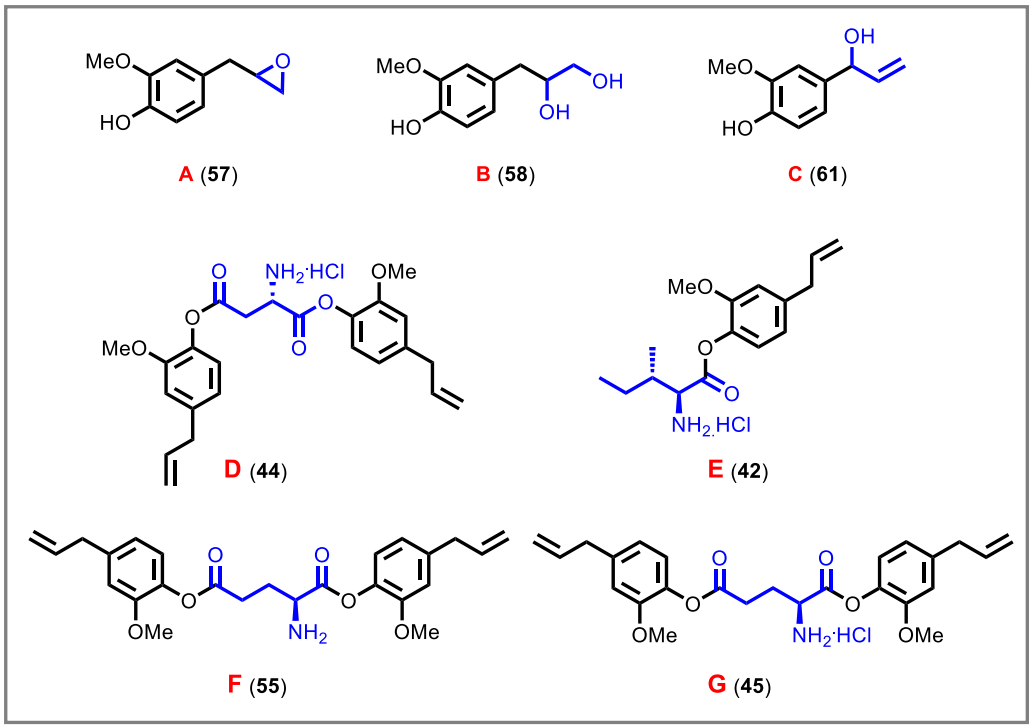


Figure 3.9. Active eugenol derivatives

analogs A, B, C, D, E, F, and G are relatively more aqueous soluble and are chosen for in vitro inhibitory activity analyses (α-amylase, α -glucosidase and glycation

inhibition, and the results were furnished below. Since *Oxidative Stress* is also a predisposing factor for the development of diabetes, we have investigated further the antioxidant activity of these selected molecules (A to G) using DPPH free radical scavenging studies (Figure 3.9).

DPPH Free Radical Scavenging Activity:

Free radicals, which are produced by the chemical the reaction of organic compounds, could damage the body's tissues and cells, and produces oxidative stress which leads to many human diseases like diabetes, cancer, cardiac damage etc. Oxidative stress is the main culprit of many diseases. Therefore, it is very important to find antioxidants for scavenging these free radicals. Various in-vitro and in-vivo methods have been developed for the assessment of antioxidative activities. From the standpoint of *in-vitro*, the standard method that has been proposed for evaluating the antioxidative activity is the 1,1-diphenyl-2-pierylhydrazyl (DPPH) method. DPPH method is one of the universal tools for estimating the antioxidative activities of different products. DPPH radical, a very stable nitrogen-centered radical, can be used to determine the free radical scavenging ability, which is related to their antioxidative activities. The method is based on the spectrophotometric measurement of DPPH• concentration changes resulting from the DPPH• the reaction with an antioxidant. If free radicals have been scavenged, DPPH will have generated its color to yellow. We have performed this assay to evaluate the antioxidant property of eugenol and its derivatives. The molecule which has antioxidant property those molecules can treat diabetes in a better way.

Procedure: The solutions of test compounds (Shown in Figure 3.10) were prepared in absolute ethanol at concentrations ranging from 25-1000 µg/µL. A DPPH blank was prepared without compound, and ethanol was used for the baseline correction. The well-known antioxidant, ascorbic acid was used for comparison or as a positive control. DPPH solution was freshly prepared daily and was kept in the dark at 4°C between the measurements. 1 mL of each compound solution having different concentrations were taken in different test tubes, and 1 mL of 0.1mM ethanol solution of DPPH was added, and shaken vigorously. The tubes were then incubated at 37°C for 30min. Changes in absorbance were measured at 517 nm using a UV/Vis

spectrophotometer and the remaining DPPH was calculated. The radical scavenging activity was expressed as percentage inhibition of DPPH and was calculated using the equation.

Inhibition Percentage = [Abs517 (control) - Abs517 Test compound] / Abs517 (control) x 100

Where, A0 is the absorbance of the control (blank, without compound) and A1 is the absorbance of the compounds.

Mean of DPPH assay values

Compound	Concentration (µg/µl)						
	25	**100**	**200**	**400**	**600**	**800**	**1000**
Ascorbic acid	76.6± 1.18	90.7± 3.55	91.6± 0.43	94.4± 1.19	95.7± 1.03	95.9± 0.63	95.1± 0.67
Eugenol	28.4± 1.24	30.1± 2.00	36.7± 1.12	40.3± 0.98	59.9± 0.63	65.6± 2.08	74.9± 1.13
A	39.6± 0.49	39.8± 2.06	45.4± 0.75	58.9± 0.70	61.8± 0.73	70.5± 1.19	76.5± 0.70
B	34.6± 0.49	38.5± 3.64	40.5± 1.22	59.6± 1.12	60.7± 0.98	61.2± 0.87	82.9± 0.89
C	36.5± 0.94	37.3± 3.51	39.7± 0.46	43.8± 0.60	51.6± 1.20	53.9± 0.66	78.6± 1.13
D	35.8± 1.18	37.2± 3.14	38.4± 0.68	43.1± 1.06	57.2± 1.20	77.9± 1.12	85.2± 0.92
E	31.4± 0.84	36.5± 3.36	39.4± 0.89	49.1± 0.84	66.3± 1.11	68.7± 1.21	79.5± 0.84
F	30.5± 0.66	33.5± 2.42	36.7± 0.55	50.2± 0.90	68.1± 1.12	70.9± 1.13	78.3± 1.17
G	31.3± 0.71	39.6± 1.83	47.2± 1.09	49.6± 1.21	71.3± 1.06	72.8± 1.12	76.4± 1.28

At varying concentrations, DPPH Free Radical Scavenging was done with the compounds, taking Ascorbic Acid as the standard. At the highest concentration (100µg/µl), the highest percentage of inhibition was observed. The values of A, B, C, D, E, F, and G are 76.5, 82.9, 78.6, 85.2, 79.5, 78.3, and 76.4, respectively. The Ascorbic acid and eugenol showed 95.1 and 74.9 % inhibition at the highest concentration. The percentage of inhibitions of A, B, C, D, E, F, and G compounds was better than eugenol but slightly less than ascorbic acid (Figure 3.10).

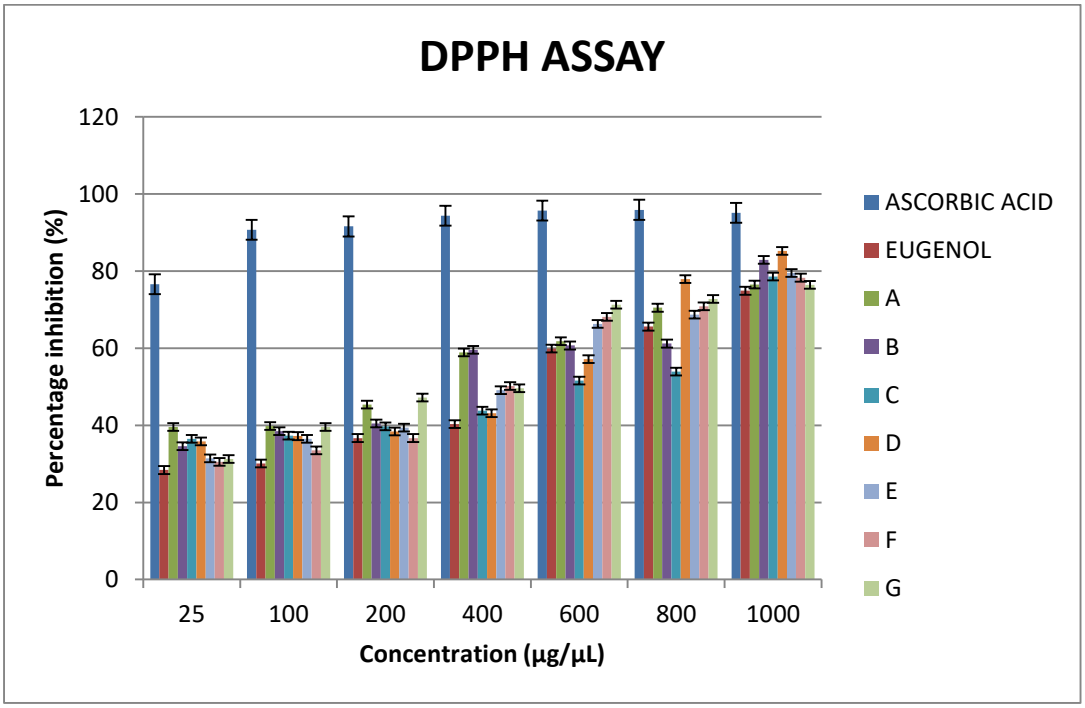


Figure 3.10. Graph represents DPPH free radical scavenging activity of the test compounds

α-Amylase inhibitory activity:

α-amylase is an enzyme that converts starch into glucose. Complex carbohydrates are broken into simpler substances, giving rise to high blood glucose levels. It causes hyper-glycemia i. e. Diabetes Mellitus. In the α-amylase inhibition assay, α-amylase acts on the substrate i.e. starch, releasing reducing sugar (glucose). The reducing groups released from starch are measured by the reduction of 3,5 di-nitrosalicylic acid. The primary role of the enzyme is starch digestion. The enzyme that we used was pancreatic porcine α-amylase. DNSA is an aromatic compound that reacts with the reducing sugars and αother reducing molecules to form 3-amino-5-nitrosalicylic acid, which absorbs light at 540 nm. On heating with reducing sugars, the 3-nitro group (NO_2) of DNSA is reduced to an amino group (NH_2). The color changes depending upon the concentration of reducing sugar present. The purpose of heating is dual inactivation of the enzyme as well as efficient binding of reducing sugar to DNS to give ANS, which shows maximum absorbance. The maximum inhibition of enzyme means maximum antidiabetic activity.

Procedure: The assay mixture containing 200µL of 0.02M sodium phosphate buffer pH 7.0, 20µl of α-amylase en-zyme and the test compounds (Given in figure 3.11) in con-centration range 20-100 µg/µL of distilled water (Eugenol in DMSO) were incubated for 15 minutes at room temperature followed by addition of 200µl of starch in all eppendorf tube. The reaction was terminated with the addition of 500µl DNSA (3,5-dinitro salicylic acid) reagent and placed in a boiling water bath for 5 minutes, cooled, and absorbance was measured at 540 nm. The control samples were prepared without test compounds. The percentage inhibition was calculated according to the formula

Inhibition Percentage = [Abs540 (control) - Abs540 Test compound] / Abs540 (control) x 100

As it can be inferred from the graphical representation, Acarbose was taken as the standard, while the compounds A, B, C, D, E, F, and G were put into experimentation with respect to it. The values fluctuated within the range of 60 to 90% inhibition, at the different concentrations taken, i.e., 20, 40, 60, 80, and 100 (µg/µL). The highest percentage of inhibition was observed at 100 µg/µL, with compound A showing the highest inhibition activity. The values obtained at the highest concentration are 89.1, 86.9, 88.4, 84.1, 85.1, 86.9, and 85.2, for compounds A, B, C, D, E, F, and G respectively. The standard compound acarbose and eugenol showed 93.3 and 83.4 percent of α-amylase inhibition at the same concentration. The percentage of inhibitions of A A, B, C, D, E, F, and G compounds was better than eugenol but slightly less than acarbose (Figure 3.11).

Mean of α-amylase assay values

Compound	**Concentration (µg/µl)**				
	20	**40**	**60**	**80**	**100**
Acarbose	77.2± 0.26	85.8 ± 0.58	89.1 ±0.57	90.7 ±0.52	93.3 ±0.75
Eugenol	69.5±0.35	70.3 ±0.63	75.9 ±0.63	78.7 ±0.11	83.4 ±0.61
A	70.4 ±1.32	78.3 ±0.99	85.7 ±0.66	86.5 ±0.44	89.1 ±0.52
B	75.9 ±0.56	79.6 ±0.61	80.5 ±0.88	81.4 ±0.61	86.9 ±0.45
C	78 ±0.63	82.4 ±0.61	84.7 ±0.57	87.1 ±0.49	88.4 ±0.31

D	72.2 ±0.95	79.6 ±0.99	81.6 ±1.00	86.7 ±0.28	84.1 ±0.17
E	74.3 ±0.52	77.5 ±0.49	79.2 ±0.46	84.7±0.46	85.1 ±0.40
F	73.9± 0.33	75.4 ±0.54	80.1 ±0.57	84.5±0.57	86.9 ±0.63
G	72.5±0.37	77.4 ± 0.46	81.6±0.55	83.5± 0.63	85.2±1.21

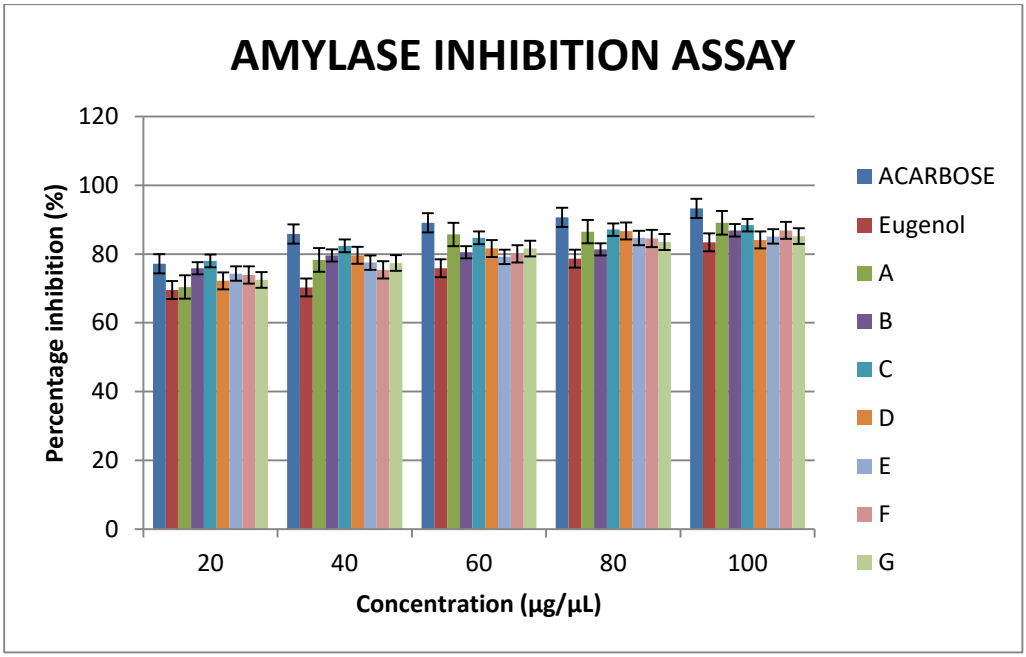


Figure 3.11. Graph represents α-amylase inhibitory activity of the test compounds.

α-Glucosidase inhibitory activity:

α-Glucosidase enzymes catalyze the hydrolysis of starch to simple sugars. In humans, these enzymes aid digestion of dietary carbohydrates and starches to produce glucose for intestinal absorption, which in turn, leads to an increase in blood glucose levels. α-glucosidase is an enzyme that converts complex polysaccharides into simple monosaccharides, resulting in increased blood glucose levels. It causes hyperglycemia i.e. Diabetes Mellitus. In the α-glucosidase inhibition assay, In contrast to glucoamylases, α-glucosidases favor oligosaccharides as substrates.

Procedure: 50µL of the test compounds (given in figure 3.12) in a concentration range 20-100 µg/µL of distilled water (Eugenol in DMSO) with 100 µL of the α-glucosidase enzyme was incubated for 10min in 96 well microplates after the incubation 50 µL of the substrate (5 mM, *p*-nitrophenyl α-D-glucopyranoside in 100mM phosphate buffer pH, 6.9) was added. The reaction mixtures were incubated

for 5 min at 25 ℃. Release of *p*-nitrophenyl is measured at 405 nm by 96 well microplate reader (BioTek synergy4 multimode microplate reader). The control samples were prepared without test compounds. The percentage inhibition was measured by using the following formulae given below.

Inhibition Percentage = [Abs405 (control) -Abs405 Test compound] / Abs405 (control) x 100

α-Glucosidase inhibitory potential of A, B, C, D, E, F, and G at the highest concentration (100 µg/µL) was 83.3, 78.9, 85.37, 86.58, 79.58, 88.26, and 87.63 respectively. The standard compound acarbose and eugenol showed 90.2 and 77.1 percent of α-glucosidase inhibition at the same concentration. The percentage of inhibitions of A, B, C, D, E, F, and G compounds was better than eugenol but slightly less than acarbose (Figure 3.12).

Mean of α-glucosidase assay values

Compound	**Concentration (µg/µl)**				
	20	**40**	**60**	**80**	**100**
Acarbose	62.5± 0.72	78.5± 0.73	83.4±0.29	90.1±0.52	90.2±0.46
Eugenol	20.1±0.57	48.6±0.49	68.3±0.43	70.2±0.46	77.1±0.63
A	21.6±0.43	46.4±0.74	75.4±0.35	77.8±0.55	83.3±0.52
B	23.7±0.56	57.6±0.40	67.1±0.14	69.7±0.18	78.9±0.66
C	24.8 ±0.51	54.1±0.41	71.6±0.42	74.5±0.30	85.3±0.56
D	23.3±0.64	60.2±0.45	69.4±0.39	72.3±0.35	86.5±0.66
E	21.3±0.34	59.1±0.54	64.2±0.90	72.6±0.51	79.5±0.30
F	20.1±0.033	61.3±0.61	70.1±0.46	78.2±0.49	88.2±0.057
G	23.1±0.033	64.2± 0.69	77.3±0.46	78.2± 0.66	87.6±0.61

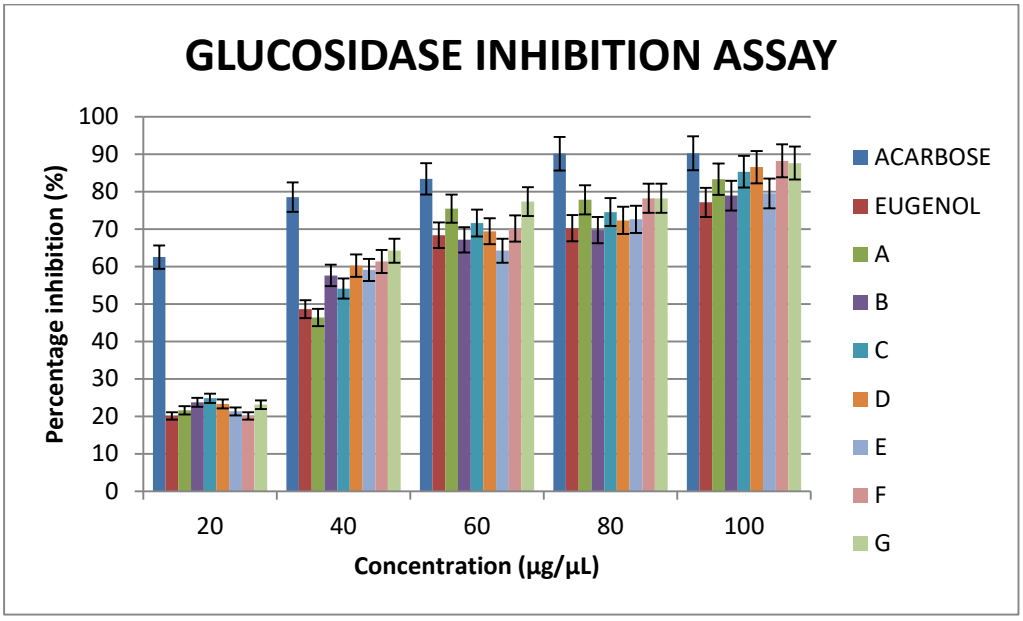


Figure 3.12. Graph represents α-glucosidase inhibitory activity of the test compounds.

BSA-AGE Glycation Inhibition Assay: The glycation the reaction involves a series of non-enzymatic the reactions between the carbonyl group on reducing sugars, and the amino group on proteins to form advanced glycation end product (AGE's), which are involved in the pathogenesis of diabetes mellitus and aging-related complications. In the case of postprandial hyperglycemia, there is a high blood glucose level that leads to an increase in glycation the reaction, which can alter protein conformation and impair function by altering enzyme activity, altering immunogenicity, modifying protein half-life, and causing crosslinking of structural proteins. Due to the good α-amylase and α-glucosidase inhibition potential of the compounds A, B, C, D, E, F, G and eugenol, it was further tested for glycation inhibition potential. Bovine Serum Albumin (BSA) is a filler or a carrier protein found in cow's milk, identical to Human Serum Albumin (HSA). In fact, Human Serum Albumin (HSA) and Bovine Serum Albumin (BSA) are the two most abundant multifunctional proteins in human and bovine blood. Digging deeper into human albumin, it belongs to the family of globular proteins made by the liver. Albumin keeps the fluid in the bloodstream avoiding its leakage into the other tissues. It is primarily a carrier protein for steroids, fatty acids, and thyroid hormones, playing an eminent role in stabilizing extracellular fluid volume. BSA is used in AGE inhibition assay due to several reasons. One of them is

that it prevents low-level binding of aliquot growth factor to the storage container and prevents inactivation, while under frozen conditions. It also prevents precipitation of the pure protein in water solution, as well as sticking to the carrier vessel by hydrophobic interactions. BSA is a protein that binds with dextrose, a form of glucose, undergoing glycation. Glucose can be bonded and transported by BSA, mainly involving hydrogen bonds and Vander Waal interactions (ΔH= -86.13 KJ/mol). In the BSA-AGE inhibition assay, protein BSA binds with the substrate dextrose monohydrate, producing AGEs. The buffer supports the pH of the reaction, and the temperature is kept at 37 ℃. The bacteriostat, Sodium Azide is used to avoid microbial growth and contamination in the reaction.

Procedure: BSA glycation the reaction was carried out by incubating 1mL of 50mg/mL BSA in 0.1 mM phosphate buffer (pH 7.4) and 0.5M dextrose monohydrate containing 5 mM sodium azide as bacteriostat at 37°C for 7 days with 50µl of the test compounds (given in Figure 3.13). The concentrations of test compounds were 2.5-15 µg/µL. The BSA glycation was monitored for excitation at 330nm and emission at 440nm by using a spectrofluorometer (Thermo, Varioskan Flash Multimode Reader). The control samples were prepared without test compounds. Percentage inhibition of glycation was calculated by using the following formulae.

$$(C-T) / C \times 100$$

Where C is the relative fluorescence intensity of glycated BSA in the absence of an inhibitor and T is the relative fluorescence intensity of glycated BSA in the presence of an inhibitor.

At varying concentrations, glycation inhibition activity was done with the compounds, taking amino-guanidine hydrochloride as the standard. At the highest concentration (15 µg/µL), the highest percentage of inhibition was observed. The values of A, B, C, D, E, F, and G are 90, 89, 85, 91, 88, 92, and 91, respectively. The aminoguanidine hydrochloride and eugenol showed 96% and 77% inhibition respectively at the highest concentration. The percentage of inhibitions of A, B, C, D, E, F, and G compounds was better than eugenol but slightly less than aminoguanidine hydrochloride (Figure 3.13).

Mean of glycation inhibition assay values:

Compound	Concentration (µg/µl)				
	2.5	5	7.5	10	15
Aminoguanidine	88.3± 0.29	90.1± 0.40	92.7±0.38	95.2±0.34	96.4±0.35
Eugenol	71.6±0.36	72.4±0.1	72.5±0.057	74.3±0.21	76.8±0.057
A	75.3±0.57	80.6±0.11	82.1±0.088	85.7±0.46	90.4±0.80
B	77.3±0.42	82.5±0.72	86.2±0.52	85.1±0.11	89.7±0.37
C	72.4±0.15	78.6±0.26	79.1±0.11	82.4±0.91	85.5±0.81
D	79.6±0.55	81.2±0.14	83.8±0.58	89.3±0.40	91.1±0.45
E	71.7±0.61	79.9±0.17	82.6±0.84	86.2±0.26	88.5±0.52
F	79.3± 0.11	81.2±0.057	84.2±0.057	87.4±0.11	92.7±0.28
G	77.5±0.37	79.4± 0.31	84.3±0.21	89.8± 0.35	91.7±0.93

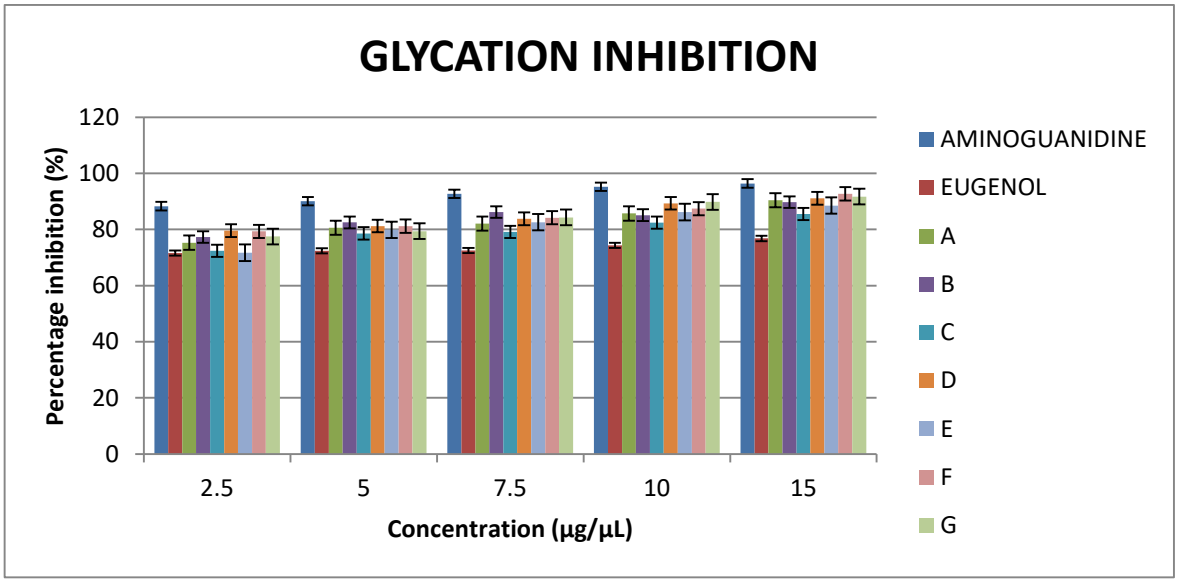


Figure 3.13. Graph represents α-glucosidase inhibitory activity of the test compounds.

Animals Study (In-Vivo Experiment):

Postprandial non-insulin dependent anti-hyperglycemic activity of compounds A, B, C, D, E, F, G, Eugenol, and Acarbose was determined by standard method i.e. postprandial glycemic test (Tiwari et.al 2008, Tiwari et.al 2011, Tiwari et.al 2013, Rao et.al 2011, Agawane et.al 2019, Misra et.al 2011 and Raju et.al 2009). The animal

experiment was carried out at the NCL-IISER animal house facility (NIAU), Pune (Registration No. CPCSEA Reg No. 1496/GO/ReBi/S/11/CPCSEA) upon approval by the Institutional Animal Ethics Committee of IISER, Pune. Healthy CD-1 mice were obtained from an in-house source. Mice were quarantined for 7 days. Animals were maintained under standard laboratory conditions. Animal welfare guidelines were observed during the maintenance and experimentation period. All animals were fed with standard rodent pelleted feed. All animals were given good-quality drinking water.

For this study, 48 male CD-1 mice were divided into 8 different groups each containing 6 male CD-1 mice. All the animals were kept for overnight fasting. The next day morning, blood was collected from the retroorbital plexus, and blood glucose level ('0' hr) was estimated. All the groups of animals DC, A, B, C, D, E, F, G, Eugenol, and Acarbose except the NC group were given soluble Potato Starch 2 g/kg b.w. to induce diabetes mellitus. Group NC mice served as Normal Controls and received a normal diet and water. Group DC mice served as Diabetes Control and received only distilled water followed by Potato Starch. Mice of groups A, B, C, D, E, F, G Eugenol and Acarbose served as Treatment Groups and received the specific treatments orally as mentioned in Table 1 @ 100 mg/kg b.w. 15min before starch feeding. Blood was collected, and glucose levels were measured at the intervals of 0th, 30th, 60th, 90th, 120th, and 180th minutes. All the data related to the animal study were analyzed by standard statistical methods. Determination of the degree of significance $p < 0.05$ between the groups of animals was done by the Two Way ANOVA test.

Table 1: (Treatments)

Group name	**Specification (n=6)**
NC	Normal Control didn't receive any treatment
DC	Disease Control received Potato Starch 2 gm/kg b.w.
A	Potato Starch 2gm/kg b.w. + 2-methoxy-4-(oxiran-2-ylmethyl) phenol 100mg/kg b.w.
B	Potato Starch 2gm/kg b.w. + 3-(4-hydroxy-3-methoxyphenyl) propane-1,2-diol 100mg/kg b.w..

C	Potato Starch 2gm/kg b.w. + bis(4-allyl-2-methoxyphenyl) L-aspartate hydrochloride 100mg/kg b.w.
D	Potato Starch 2gm/kg b.w. + 4-(1-hydroxyaIIyI)-2-methoxyphenoI 100mg/kg b.w.
E	Potato Starch 2gm/kg b.w. + 4-allyl-2-methoxyphenyl L-isoleucinate hydrochloride 100mg/kg b.w.
F	Potato Starch 2gm/kg b.w. + bis(4-allyl-2-methoxyphenyl) L-glutamate 100mg/kg b.w.
G	Potato Starch 2gm/kg b.w. + bis(4-allyl-2-methoxyphenyl) L-glutamate hydrochloride 100mg/kg b.w.
Eugenol	Potato Starch 2gm/kg b.w. + Eugenol 100mg/kg b.w.
Acarbose	Potato Starch 2gm/kg b.w. + Acarbose 100mg/kg b.w.

Table 2:- Mean of Blood Glucose estimations (mg/dl)

Treatments	On 0th	On 30th	On 60th	On 90th	On 120th	On 180th
Normal Control	83.98± 2.08	85.90 ± 3.31	87.08 ±4.29	83.78 ±6.33	79.70 ±5.01	80.95 ±2.56
Diabetic Control	85.91± 4.20	184.5 ±8.86	214.1 ±4.98	234.65 ±6.01	258.56 ±9.19	288.63 ±11.30
Compound A	84.7± 0.68	190.45± 2.53	112.3± 3.32	102.56± 2.15	92.98± 2.75	85.25± 0.51
Compound B	83.65± 1.80	186.43± 2.41	112.05± 1.87	102.51± 3.71	92.61± 1.82	86.25± 1.48
Compound C	85.43± 0.99	189.43± 2.68	113.3± 2.54	101.46± 2.45	96.8± 1.04	89.43± 0.95
Compound D	86.51 ±5.74	188.78 ±7.92	111.5 ±7.24*	96.11 ±5.61*	89.53 ±6.65*	84.13 ±2.45*
Compound E	83.13 ±3.36	184.8 ±7.71	108.2 ±8.65*	98.00 ±5.61*	92.21 ±4.79*	86.10 ±3.53*
Compound F	85.28 ±4.98	189.6 ±7.52	108.28 ±5.18*	99.86 ±2.62*	97.46 ±3.07*	87.16 ±5.33*
Compound G	84.20 ±3.81	189.46 ±6.42	111.21 ±6.48*	95.70 ±3.21*	92.51 ±4.83*	84.73 ±4.12*
Eugenol	83.43 ±2.30	187.41 ±6.05	138.95 ±5.31*	123.98±5.24*	96.55 ±2.57*	93.58 ±4.25*
Acarbose	84.8 ± 5.50	187.66 ±8.61	109.36 ±7.82*	98 .00±6.00*	87.81 ±6.07*	83.76 ±4.43*

Each of the values is expressed as mean ± S.E.M , n = 6.

*Significantly different from control, $p < 0.05$.

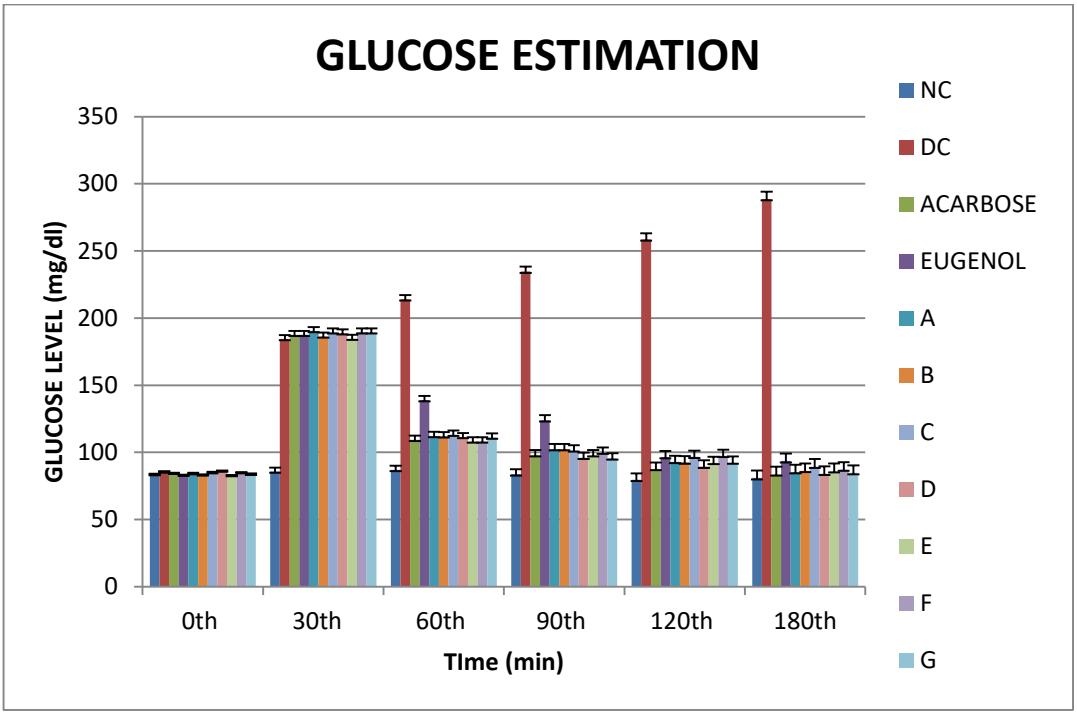


Figure 3.14. Blood Glucose Estimation in Mice.

Anti-hyperglycemic activity of Compounds A, B, C, D, E, F, and G in mice revealed the reduction of blood glucose levels at different time points 0th, 30th, 60th, 90th, 120th, and 180th minutes (Figure 3.14). Two ways ANOVA analysis was applied to find the difference between the groups of animals at $p < 0.05$ when compared to the control. Compounds A, B, C, D, E, F, and G significantly reduced the blood glucose levels when compared to the diabetic control and had equally potent antidiabetic potential when compared with acarbose. The animal study proved the antidiabetic activity of Compounds A, B, C, D, E, F and G is better than Eugenol. It is due to its better absorption, pharmacokinetics, retention, time and bioavailability than Eugenol.

Discussion:

The antioxidant activity of eugenol derivatives (Compounds A, B, C, D, E, F and G) and eugenol is due to the presence of phenylpropanoid i.e. phenol. The phenols are very important constituents of eugenol and its derivatives. They showed a high scavenging ability of free radicals due to their hydroxyl group. The high correlation between the content of phenolic compounds leads to antioxidant activity has been well studied (Borneo et al., 2008). Antioxidants play an important role in neutralizing

free radicals and protecting important biological molecules from being damaged by free radicals. Antioxidants significantly prevent the oxidation of cell content like proteins, lipids, carbohydrates, and DNA (Borneo et al., 2008). There are many therapeutic approaches, which may prove to be beneficial for the treatment of type II diabetes mellitus (postprandial hyperglycemia). This can be done by reducing the absorption of glucose through the inhibition of two key enzymes linked to type II diabetes mellitus (PPHG) in the digestive tract. It has been studied that the inhibition of carbohydrate hydrolyzing enzymes, like α-amylase and α-glucosidase are better therapeutic approaches to treat type 2 diabetes mellitus (Shobana et al., 2009). In-vitro and in-vivo evaluation of eugenol derivatives (A, B, C, D, E, F, and G) and eugenol have very good antidiabetic activity.

Inhibitors of α-amylase and α-glucosidase enzymes delay carbohydrate digestion in the body and overall carbohydrate digestion time causing a significant decrease in the rate of glucose absorption by blunting the postprandial plasma glucose level. In Type2 Diabetes Mellitus (Post Prandial Hyperglycemia), inhibition of α-amylase and α-glucosidase therapy is beneficial to delay the absorption of glucose after a meal. These enzymes play a role in the conversion of carbohydrates into glucose. By inhibiting α-amylase and α-glucosidase, glucose levels in the blood can be returned within normal limits (Elya et al., 2011). The glycation the reaction involves a series of non-enzymatic the reactions between the carbonyl group on reducing sugars and the amino group on proteins to form advanced glycation end products (AGEs), which are involved in the pathogenesis of diabetes mellitus and aging-related complications.

In the case of postprandial hyperglycemia, there is a high blood glucose level that leads to an increase in glycation the reaction, which can alter protein conformation and impair function by altering enzyme activity, altering immunogenicity, modifying protein half-life and causing cross-linking of structural proteins. A decrease in blood glucose level subsequently results in the reduction of AGE formation. The glycation inhibition potential of eugenol derivatives (A, B, C, D, E, F, and G) and eugenol is due to the higher content of phenylpropanoid i.e. phenols. It has been already been studied that phenols block the formation of AGEs and other glycated proteins. Eugenol and its derivatives competitively inhibit the binding of sugar to serum albumin by binding to the amine group of surface-exposed lysine

residues via its reactive 4′-OH group. Anti-hyperglycemic activity of (A, B, C, D, E, F, and G) and eugenol in mice revealed the reduction of blood glucose levels at different time points 0th, 30th, 60th, 90th, 120th, and 180th minutes. The (A, B, C, D, E, F, and G) and eugenol significantly reduced the blood glucose levels when compared to the diabetic control and had equally potent antidiabetic potential when compared with acarbose. Animal studies proved that the antidiabetic activity of compounds A, B, C, D, E, F, and G is better than Eugenol. It may be due to its better absorption, pharmacokinetics, retention time, and bioavailability than Eugenol.

3.2.3 Conclusion

In conclusion, we designed and synthesized 43 derivatives of eugenol comprising ester, carbamate, and hydroxyl functionalities based on the prodrug approach, which were found to be more soluble and bioavailable than eugenol. These novel compounds showed very good α-glucosidase and α-amylase inhibition (mimicking the effect of combination therapy). Besides, these analogs displayed very good antioxidant activity, which plays a critical role in many illnesses including diabetes. Molecular docking investigations strongly supported our findings of in-vitro and in-vivo studies. The antidiabetic activity of compounds A, B, C, D, E, F, and G was found to be better than the parent molecule eugenol.

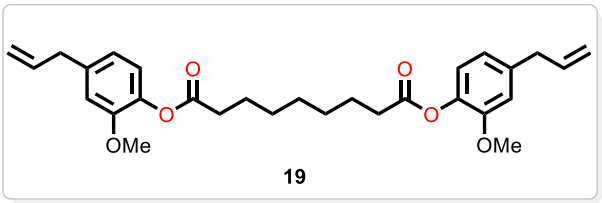
3.2.4 Experimental Procedures and Data:

Experimental section: All the reactions were performed under an argon atmosphere with an oven (80 °C) or flame-dried glassware with a septum seal. Tetrahydrofuran (THF) was distilled from sodium benzophenone under an argon atmosphere immediately before use. Anhydrous dichloromethane was purchased from commercial sources. The reaction temperatures are reported as the temperature of the bath surrounding the reactionvessel. Analytical thin-layer chromatography (TLC) was performed on TLC Silica gel 60 F254. Visualization was accomplished short-wave wave UV light, anisaldehyde, or $KMnO_4$ staining solutions, followed by heating. Chromatography was performed on silica gel (100–200 mesh) by standard techniques eluting with solvents as indicated. 1H and 13C NMR spectra were recorded on Bruker AV 200, 400, and 500 MHz in solvents as indicated. Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references, and

the chemical shifts were converted to the TMS scale ($CDCl_3$: δ H = 7.26 ppm, δ C = 77.16 ppm, and CD_3OD: δ ^1H = 3.31 ppm, δ C = 49.15 ppm for ^{13}C NMR). The following abbreviations were used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublet; td, triplet of doublet; and br, broad. HRMS data were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump. Experimental procedures for all new compounds and known compounds without published experimental procedures are described below.

General procedure for preparation of lipophilic ester derivatives of Eugenol: To the acid (aliphatic 1eq) in anhydrous THF, DCC, or EDC.HCl (1.4 eq) was added, and the suspension was stirred at 0 ^oC, After 10 min., DMAP (0.1 eq) was added, and the reaction mixture was stirred for 20 min at 0 ^oC, then eugenol (1 eq)was added to the reaction mixture and stirred for 24 h at rt. After the completion of the reaction(checked by TLC), the solvent was evaporated in vacuo. The crude was partitioned between ethyl acetate (3-10 mL) and sodium bicarbonate. The aqueous layer was extracted with ethyl acetate thrice, and the combined organic layer was washed with water followed by brine and dried over Na_2SO_4, filtered and concentrated in vacuo, and the crude was purified by silica gel column chromatography.

Bis(4-allyl-2-methoxyphenyl) nonanediote (19): Azelaic acid (1 g, 5.31 mmol),

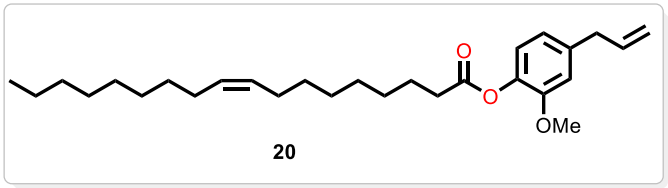


19

Eugenol (1.62 mL, 10.62 mmol), EDC.HCl (4.0 g, 21.25 mmol), DMAP (0.285 g, 2.33 mmol); TLC: R_f = 0.8 (SiO_2, 10% EtOAc/hexanes), the solvent system for column chromatography (2% EtOAc in hexanes); Yield (1.76 g, 70%); ^1H NMR (400 MHz, $CDCl_3$) δ : 6.94 (d, *J* = 8.00 Hz, 2H), 6.81-6.72 (m, 4H), 6.03-5.89 (m, 2H), 5.15-5.05 (m, 4H), 3.81 (s, 6H), 3.38 (d, *J* = 6.75 Hz, 4H), 2.62-2.53 (m, 4H), 1.86-1.72 (m, 4H), 1.52-1.41 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 151.0, 139.0, 138.2, 137.2, 122.6, 120.8, 116.2, 112.8, 55.9, 40.2, 34.1, 29.0, 29.0, 25.1; ; HRMS (ESI): *m/z* calcd for $C_{29}H_{37}O_6$ $[M+H]^+$ 481.2585, found 481.2581.

4-Allyl-2-methoxyphenyl oleate (20): Oleic acid (1 g, 5.31 mmol), Eugenol (1.62 mL, 10.62 mmol), EDC.HCl (4.0 g, 21.25 mmol), DMAP (0.285 g, 2.33 mmol); TLC: R_f =

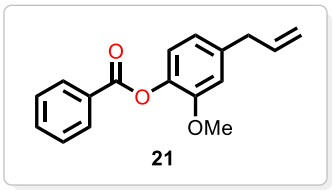
0.8 (SiO_2, 10% EtOAc/hexanes), ^1H NMR (200 MHz, $CDCl_3$) δ : 7.02-6.87 (m, 1H), 6.87-



20

6.68 (m, 2H), 6.19-5.72 (m, 1H), 5.51-5.25 (m, 2H), 5.22-4.99 (m, 2H), 3.88-3.71 (m, 3H), 3.50-3.25 (m, 2H), 2.68-2.49 (m, 2H), 2.26-1.88 (m, 4H), 1.88-1.61 (m, 2H), 1.49-1.15 (m, 20H), 1.00-0.79 (m, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 172.1, 151.0, 138.9, 138.2, 137.2, 130.1, 129.9, 122.7, 120.8, 116.2, 112.8, 55.9, 40.2, 34.2, 32.0, 29.9, 29.8, 29.7, 29.7, 29.4, 29.3, 29.3, 29.2, 27.3, 27.3, 27.3, 25.2, 22.8, 14.2; HRMS (ESI): *m/z* calcd for C28H44O3Na $[M+Na]^+$ 451.3183, found 451.3394.

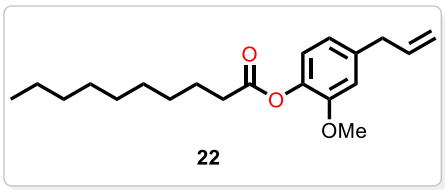
4-Allyl-2-methoxyphenyl benzoate (21): Eugenol (1 g, 6.09 mmol), DMAP (0.14 g,



21

1.22 mmol), DCC (9.13 mmol), benzoic acid (1.15 g, 9.13 mmol), TLC: R_f = 0.6 (SiO_2, 10% EtOAc/hexanes), the solvent system for column chromatography (4% EtOAc in hexanes); Yield (1.52 g, 93%); FTIR (cm-1): 3545.15, 3020.95, 2924.94, 1739.30, 1593.53, 1215.32; ^1H NMR (200 MHz, $CDCl_3$) δ 8.22 (d, *J* = 7.32 Hz, 2H), 7.63 (t, *J* = 7.32 Hz, 1H), 7.51 (t, *J* = 7.93 Hz, 2H), 7.07 (d, *J* = 7.93 Hz, 1H), 6.90-6.79 (m, 2H), 6.08-5.91 (m, 1H), 5.19-5.05 (m, 2H), 3.81 (s, 3H), 3.41 (d, *J* = 6.71 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.0, 151.2, 139.2, 138.3, 137.2, 133.5, 130.4, 129.7, 128.6, 122.8, 120.9, 116.3, 113.0, 56.0, 40.3; HRMS (ESI): *m/z* calcd for $C_{17}H_{16}O_3Na$ $[M+Na]^+$ 291.0992, found 291.0987.

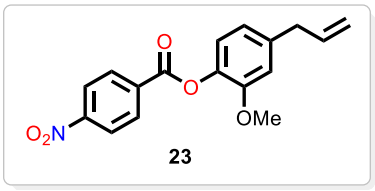
4-Allyl-2-methoxyphenyl decanoate (22): decanoic acid (1 g, 5.31 mmol), Eugenol



22

(1.62 mL, 10.62 mmol), EDC.HCl (4.0 g, 21.25 mmol), DMAP (0.285 g, 2.33 mmol); TLC: R_f = 0.8 (SiO_2, 10% EtOAc/hexanes), FTIR (cm^{-1}): 3019.52, 2927.92, 1755.45, 1604.25, 1439.81, 1215.68; ^1H NMR ($CDCl_3$, 200 MHz) δ : 6.96 (d, *J* = 7.71 Hz, 1H), 6.86-6.68 (m, 2H), 6.14-5.83 (m, 1H), 5.25-5.01 (m, 2H), 3.90-3.72 (m, 3H), 3.39 (d, *J* = 6.69 Hz, 2H), 2.59 (t, *J* = 7.33 Hz, 2H), 1.93-1.69 (m, 2H), 1.50-1.20 (br. s., 12H), 0.99-0.84 (t, *J* = 6.06 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ : 172.0, 151.0, 138.8, 138.1, 137.1, 122.5, 120.6, 116.1, 112.7, 55.7, 40.1, 34.1, 31.9, 29.5, 29.3, 29.1, 25.1, 22.7, 14.1 HRMS (ESI): *m/z* calcd for $C_{20}H_{30}O_3Na$ $[M+Na]^+$ 341.2087, found 341.2082.

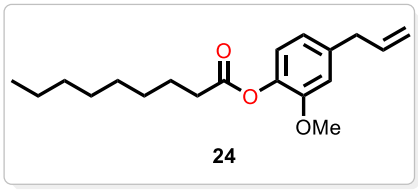
4-Allyl-2-methoxyphenyl 4-nitrobenzoate (23): Eugenol (1 g, 6.09 mmol), DMAP



23

(0.14 g, 1.22 mmol), DCC (9.13 mmol), nitrobenzoic acid (1.52 g, 9.13 mmol), TLC: R_f = 0.6 (SiO_2, 10% EtOAc/hexanes), the solvent system for column chromatography (4% EtOAc in hexanes); Yield (1.56 g, 82%); FTIR (cm-1): 3687.24, 3022.34, 1744.25, 1602.53, 1215.46; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.47-8.26 (m, 4H), 7.16-7.02 (m, 1H), 6.90-6.78 (m, 2H), 6.15-5.86 (m, 1H), 5.27-5.04 (m, 2H), 3.81 (s, 3H), 3.42 (d, J = 6.69 Hz, 2H); ^{13}C NMR (50 MHz, CDCl3) δ : 163.1, 150.9, 139.8, 137.8, 137.0, 135.1, 131.5, 123.7, 122.4, 120.9, 116.4, 113.0, 56.0, 40.2; HRMS (ESI): *m/z* calcd for $C_{17}H_{15}NO_5Na$ $[M+Na]^+$ 336.0842, found 336.0838.

4-Allyl-2-methoxyphenyl nonanoate (24): nonanoic acid (1 g, 5.31 mmol), Eugenol

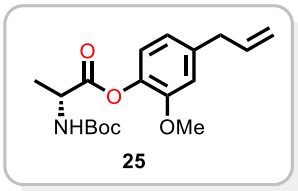


24

(1.62 mL, 10.62 mmol), EDC.HCl (4.0 g, 21.25 mmol), DMAP (0.285 g, 2.33 mmol); TLC: R_f = 0.8 (SiO_2, 10% EtOAc/hexanes), FTIR (cm^{-1}): 3020.34, 2929.47, 1754.23, 1604.00, 1453.97, 1216.06; ^{1}H NMR (200 MHz, $CDCl_3$) δ : 7.05-6.88 (m, 1H), 6.88-6.65 (m, 2H), 6.16-5.80 (m, 1H), 5.25-4.97 (m, 2H), 3.87-3.76 (m, 3H), 3.38 (d, *J* = 6.57 Hz, 2H), 2.66-2.47 (m, 2H), 1.91-1.69 (m, 2H), 1.30 (br. s., 11H), 1.02-0.78 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ : 172.1, 151.1, 138.9, 138.2, 137.2, 122.7, 120.8, 116.2, 112.9, 55.9, 40.2, 34.2, 31.9, 29.4, 29.3, 29.2, 25.2, 22.8, 14.2; HRMS (ESI): *m/z* calcd for $C_{19}H_{28}O_3Na$ $[M+Na]^+$ 327.1931, found 327.1927.

General procedure for preparation of amino acid derivatives of Eugenol: To the acid (amino acid 1eq) in anhydrous THF, EDC.HCl (1.4 eq) was added, and the suspension was stirred at 0 ^{o}C, After 10 min., DMAP (0.1 eq) was added, and the reaction mixture was stirred for 20 min at 0 ^{o}C, then eugenol (1 eq) was added to the reaction mixture and stirred for 24 h at rt. After the completion of the reaction (checked by TLC), the solvent was evaporated in vacuo. The crude was partitioned between ethyl acetate (3-10 mL) and sodium bicarbonate. The aqueous layer was extracted with ethyl acetate thrice and the combined organic layer was washed with water followed by brine and dried over Na_2SO_4, filtered and concentrated in vacuo and the crude was purified by silica gel column chromatography.

4-Allyl-2-methoxyphenyl (*tert*-butoxycarbonyl)-D-alaninate (25): Amino acid

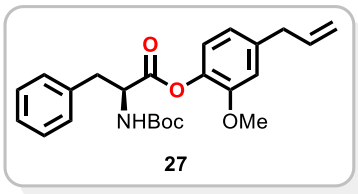


25

(0.5 g, 0.00264 mmol), Amount of Eugenol (0.477 g, 0.00291 mmol), EDC.HCl (0.728 g, 0.00380 mmol), DMAP (0.035 g, 0.00029 mmol). The solvent system for column chromatography: 20% ethyl acetate in hexane. Yield: 50.05%; IR (cm^{-1}): 3437.01, 3022.94, 1644.75, 1216.15; ^1H NMR (400 MHz, $CDCl_3$): δ 6.97 (d, *J* = 7.9 Hz, 1 H), 6.71 - 6.82 (m, 2 H), 5.88 - 6.04 (m, 1 H), 5.04 - 5.17 (m, 2 H), 4.54 - 4.66 (m, 1 H), 3.80 (s, 3 H), 3.38 (d, *J* = 6.7 Hz, 2 H), 1.57 (d, *J* = 7.3 Hz, 4 H), 1.47 ppm (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.8, 155.1, 150.7, 139.2, 137.8, 137.0, 122.3, 120.7, 116.2, 112.8, 79.9, 77.4, 77.0, 76.7, 55.8, 49.3, 40.1, 28.3, 18.9 ppm; HRMS (ESI): *m/z* calcd for $C_{18}H_{26}NO_5$ $[M+H]^+$ 336.1805, found 336.1800.

4-Allyl-2-methoxyphenyl (*tert*-butoxycarbonyl)-L-valinate (26): Amino acid (2 g, 9.20 mmol), Amount of Eugenol (1.41 mL, 9.20 mmol), EDC.HCl (2.53g, 13.2 mmol), DMAP (0.123 g, 0.101 mmol). The solvent system for column chromatography: 20% ethyl acetate in hexane. Yield: 46.96%., IR (cm^{-1}): 3436.73, 3024.21, 1644.37, 1216.17; ^1H NMR (400MHz, CDCl3): δ 6.98-6.91 (m, 1H), 6.81-6.74 (m, 2H), 6.02-5.90 (m, 1H), 5.13-5.06 (m, 2H), 4.55-4.50 (dd, *J* = 4.58, 9.16 Hz, 1H), 3.79 (s, 3H), 3.38 (d, *J* = 6.10 Hz, 2H), 2.44-2.33 (m, 1H), 1.47 (s, 9H), 1.09 (d, *J* = 6.87 Hz, 3H), 1.04 (d, *J* = 6.87 Hz, 3H); ^{13}C NMR (101 MHz, CDCl3): δ 170.7, 155.8, 150.8, 139.3, 137.7, 137.1, 122.6, 122.5, 120.8, 116.3, 112.8, 79.9, 58.6, 55.9, 55.7, 40.1, 31.5, 28.4, 19.2, 17.3; HRMS (ESI): m/z calcd for C20H29O5NNa [M+Na]+ 386.1938, found 386.1932.

4-Allyl-2-methoxyphenyl (*tert*-butoxycarbonyl)-L-phenylalaninate (27): Amino

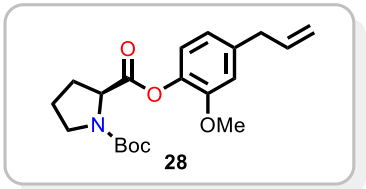


27

acid (2g, 7.53 mmol), Amount of Eugenol (1.15 mL, 7.53 mmol), EDC.HCl (2.07g, 10.8 mmol), DMAP (0.101 g, 0.828 mmol). The solvent system for column chromatography: 20% ethyl acetate in hexane. Yield: 44.86%., IR (cm-1): 3435.90, 3023.52, 2402.04, 1645.00, 1216.31. ^1H NMR (400MHz, $CDCl_3$): δ 7.34-7.22 (m, 5H), 6.88 (d, *J* = 7.63 Hz, 1H), 6.79-6.72 (m, 2H), 5.99-5.88 (m, 1H), 5.13-5.05 (m, 2H), 5.02 (d, *J* = 8.39 Hz, 1H), 4.89-4.80 (m, 1H), 3.79 (s, 3H), 3.36 (d, *J* = 6.87 Hz, 2H), 3.34-3.27 (m, 1H), 3.20 (dd, *J* = 6.10, 13.73 Hz, 1H), 1.40 (s, 9H);

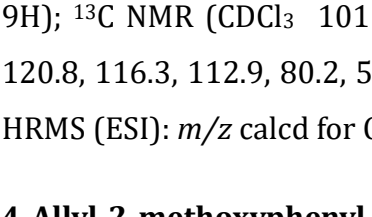
^{13}C NMR (101 MHz, $CDCl_3$): δ 170.4, 155.2, 150.8, 139.4, 137.7, 137.1, 136.2, 129.8, 128.6, 127.1, 122.5, 120.8, 116.4, 112.9, 80.1, 55.8, 54.5, 40.2, 38.4, 28.4; HRMS (ESI): *m/z* calcd for $C_{24}H_{29}O_5NNa$ $[M+Na]^+$ 434.1938, found 434.1934.

2-(4-Allyl-2-methoxyphenyl) 1-(*tert*-butyl) (*S*)-pyrrolidine-1,2-dicarboxylate (28): Amino acid (0.726 g, 0.00337 mmol), Amount of Eugenol (0.5 g, 0.00304 mmol), EDC.HCl (0.841 g, 0.00438 mmol), DMAP (0.04g, 0.000337 mmol). The solvent system for column chromatography: 20% ethyl acetate in hexane. Yield: 57.4%. IR (cm^{-1}): 3436.09, 3023.57, 1645.09, 1215.57; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.91 (d, *J* = 7.63 Hz, 1H), 6.79-6.75 (m, 2H), 6.01-5.88 (m, 1H), 5.14-5.05 (m, 2H), 4.48 (dd, *J* = 3.81, 8.39 Hz, 1H), 3.79 (s, 3H), 3.66-3.59 (m, 1H), 3.53-3.45 (m, 1H), 3.39-3.34 (m, 3H), 2.39-2.23 (m, 3H), 2.13-1.87 (m, 3H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$ 101 MHz): δ 171.4, 154.0, 150.9, 139.2, 137.9, 137.1, 122.3, 120.8, 116.3, 112.9, 80.2, 59.2, 59.0, 55.9, 55.8, 46.5, 40.2, 31.2, 28.6, 28.5, 23.6 ppm; HRMS (ESI): *m/z* calcd for $C_{20}H_{28}O_5N$ $[M+H]^+$ 362.1962, found 362.1957.



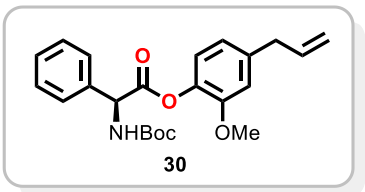
28

4-Allyl-2-methoxyphenyl (*tert*-butoxycarbonyl)-L-leucinate (29): Amino acid (1g, 4.32 mmol), Amount of Eugenol (0.66 mL, 4.32 mmol), EDC.HCl (1.192g, 6.22 mmol), DMAP (0.058 g, 0.47 mmol). The solvent system for column chromatography: 20% ethyl acetate in hexane. Yield: 18.34%., IR (cm^{-1}): 3440.53, 3022.79, 2402.64, 1644.75, 1216.19; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, J = 7.63 Hz, 2H), 7.42-7.33 (m, 4H), 6.88 (d, *J* = 8.39 Hz, 1H), 6.74-6.70 (m, 2H), 5.98-5.87 (m, 1H), 5.62 (br. s., 1H), 5.11-5.07 (m, 1H), 5.06 (s, 1H), 3.63 (s, 3H), 3.34 (d, *J* = 6.87 Hz, 2H), 1.45 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.6, 154.9, 150.8, 139.4, 137.9, 137.1, 136.9, 128.9, 128.6, 127.7, 122.3, 120.8, 116.3, 113.0, 80.3, 57.8, 55.7, 40.1, 28.4; HRMS (ESI): *m/z* calcd for $C_{21}H_{31}O_5NNa$ $[M+Na]^+$ 400.2094, found 400.2091.



29

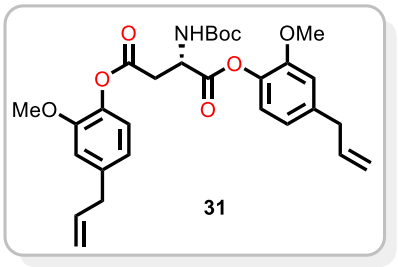
4-Allyl-2-methoxyphenyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-2-phenylacetate (30): Amino acid (2g, 7.95 mmol), Amount of Eugenol (1.22 mL, 7.95 mmol), EDC.HCl (2.194g, 11.4 mmol), DMAP (0.106 g, 0.87 mmol). The solvent system for



30

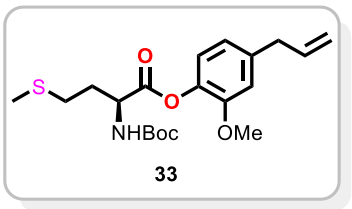
column chromatography: 20% ethyl acetate in hexane. Yield: 83.79%., IR (cm-1): 3437.92, 3023.09, 1645.29, 1216.28; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, *J* = 7.63 Hz, 2H), 7.43-7.34 (m, 4H), 6.89 (d, *J* = 8.39 Hz, 1H), 6.75-6.71 (m, 2H), 5.99-5.88 (m, 1H), 5.63 (br. s., 1H), 5.12-5.08 (m, 1H), 5.07 (s, 1H), 3.64 (s, 3H), 3.35 (d, *J* = 6.87 Hz, 2H), 1.46 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.6, 154.9, 150.8, 139.4, 137.8, 137.0, 136.9, 128.8, 128.6, 127.6, 122.2, 120.7, 116.3, 113.0, 80.3, 57.8, 55.7, 40.1, 28.4; HRMS (ESI): *m/z* calcd for $C_{23}H_{27}O_5NNa$ $[M+Na]^+$ 420.1781, found 420.1775.

Bis(4-allyl-2-methoxyphenyl)(*tert*-butoxycarbonyl)-L-aspartate (31): Amino acid (0.5 g, 2.14 mmol), Amount of Eugenol (0.65 mL, 4.28 mmol), EDC.HCl (1.23 g, 6.42 mmol), DMAP (0.057 g, 0.47 mmol). The solvent system for column chromatography: 20% ethyl acetate in hexane. Yield: 21.96%., IR (cm^{-1}): 3437.57, 3023.00, 1763.42, and 1216.22. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.14-6.88 (m, 2H), 6.88-6.52 (m, 4H), 6.09-5.79 (m, 2H), 5.18-4.96 (m, 4H), 3.88-3.78 (m, 3H), 3.77-3.68 (m, 3H), 3.47-3.29 (m, 4H), 3.29-3.13 (m, 1H), 1.53-1.41 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.4, 168.8, 155.5, 150.9, 150.7, 139.4, 137.9, 137.7, 137.1, 122.6, 120.8, 116.3, 112.9, 112.8, 80.3, 77.8, 76.5, 55.9, 50.3, 40.2, 37.2, 28.5; HRMS (ESI): *m/z* calcd for $C_{29}H_{35}O_8NNa$ $[M+Na]^+$ 548.2255, found 548.2248.



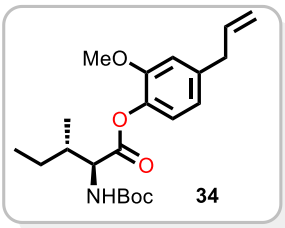
31

4-Allyl-2-methoxyphenyl (*tert*-butoxycarbonyl)-L-methioninate (33): Amino acid (1.553 g, 6.23 mmol), Amount of Eugenol (0.95 mL, 6.23 mmol), EDC.HCl (1.719 g, 8.96 mmol), DMAP (0.083 g, 0.68 mmol). The solvent system for column chromatography: 20% ethyl acetate in hexane. Yield: 55.28%. IR (cm^{-1}): 3463.13, 3022.86, 1644.44, 1216.45; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96 (d, *J* = 7.63 Hz, 1H), 6.81-6.71 (m, 2H), 6.01-5.89 (m, 1H), 5.24 (d, *J* = 8.39 Hz, 1H), 5.13-5.05 (m, 2H), 4.76-4.63 (m, 1H), 3.79 (s, 3H), 3.37 (d, *J* = 6.10 Hz, 2H), 2.67 (t, *J* = 8.39 Hz, 2H),2.37-2.23 (m, 1H), 2.18-2.13 (m, 3H), 2.13-2.03 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.8, 155.4, 150.7, 139.5, 137.7, 137.1, 122.4, 120.9, 116.4, 112.8, 80.2, 55.8, 53.1, 40.2, 32.6, 29.8, 28.4, 15.6; HRMS (ESI): *m/z* calcd for $C_{20}H_{29}O_5NNaS$ $[M+Na]^+$ 418.1659, found 418.1659.



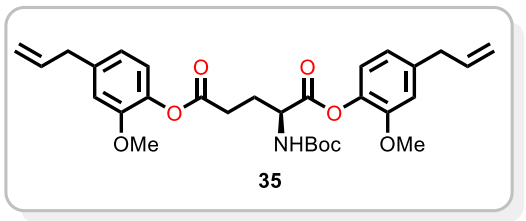
33

4-Allyl-2-methoxyphenyl (*tert*-butoxycarbonyl)-L-isoleucinate (34): Amino acid (1.56 g, 6.76 mmol), Amount of Eugenol (0.93 mL, 6.09 mmol), EDC.HCl (1.685 g, 8.79 mmol), DMAP (0.081 g, 0.66 mmol). The solvent system for column chromatography: 20% ethyl acetate in hexane. Yield: 71.65%. IR (cm^{-1}): 3440.90, 3022.89, 1644.97, 1216.28; ^1H NMR (200 MHz, $CDCl_3$) δ 6.95 (d, *J* = 7.71 Hz, 1H), 6.83-6.70 (m, 2H), 6.08-5.80 (m, 1H), 5.15-5.04 (m, 2H), 3.78 (s, 3H), 3.37 (d, *J* = 6.57 Hz, 2H), 2.08 (br. s., 1H), 1.74-1.56 (m, 1H), 1.46 (s, 9H), 1.06 (d, *J* = 6.82 Hz, 3H), 0.99 (t, *J* = 7.33 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 155.7, 150.8, 139.4, 138.0, 137.7, 137.1, 122.6, 121.3, 120.8, 116.3, 115.7, 114.4, 112.8, 111.2, 79.9, 58.2, 56.0, 55.7, 40.2, 40.0, 38.4, 28.5, 24.8, 15.6, 12.0; HRMS (ESI): *m/z* calcd for $C_{21}H_{31}O_5NNa$ $[M+Na]^+$ 400.2094, found 400.2090.



34

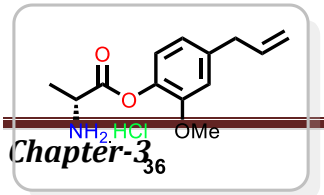
Bis(4-allyl-2-methoxyphenyl) (*tert*-butoxycarbonyl)-L-glutamate (35): Amino acid (1.7 g, 6.87 mmol), Amount of Eugenol (2.11 mL, 13.7 mmol), EDC.HCl (1.896 g, 9.89 mmol), DMAP (0.092 g, 0.755 mmol). The solvent system for column chromatography: 20% ethyl acetate in hexane. Yield: 44.24%., IR (cm^{-1}): 3435.37, 3023.13, 1644.85, and 1216.45. 1H NMR (400 MHz, $CDCl_3$): δ 7.02-6.93 (m, 2H), 6.82-6.74 (m, 4H), 6.04-5.88 (m, 2H), 5.38 (d, *J* = 7.93 Hz, 1H), 5.16-5.02 (m, 4H), 4.77-4.67 (m, 1H), 3.81 (s, 6H), 3.38 (d, *J* = 6.71 Hz, 4H), 2.92-2.75 (m, 2H), 2.57-2.26 (m, 2H), 1.47 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.2, 170.7, 155.4, 150.8, 150.6, 139.4, 139.1, 137.9, 137.7, 137.1, 137.0, 122.6, 122.4, 120.8, 120.7, 116.3, 116.2, 112.7, 80.2, 55.8, 55.7, 53.1, 40.1, 30.1, 28.4, 28.0; HRMS (ESI): *m/z* calcd for $C_{30}H_{37}O_8NNa$ $[M+Na]^+$ 562.2411, found 562.2409.



35

General procedure for preparation of HCl salt of amino acid derivatives of Eugenol: To the amino acid ester, HCl in ether 2M (in excess) was added at 0°C and stirred for 30 minutes. The reaction mixture was then evaporated in vacuo and then kept for high vacuum for 1 hr to get the desired salt without purification.

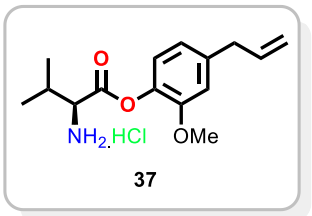
4-Allyl-2-methoxyphenyl D-alaninate hydrochloride (36): Ester of the amino acid (0.357 g, 0.59 mmol), HCl etherate (in excess). Yield: 97%. IR



36

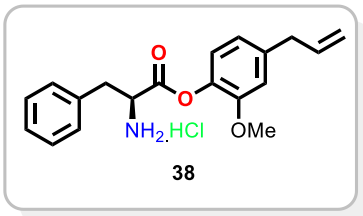
(cm^{-1}): 3436.10, 3023.32, 2102.08, 1643.50, 1215.86. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76 (br. s., 2H), 6.97 (d, *J* = 7.63 Hz, 1H), 6.74-6.65 (m, 2H), 5.96-5.82 (m, 1H), 5.09-5.02 (m, 2H), 4.35-4.25 (m, 1H), 3.75 (s, 3H), 3.32 (d, *J* = 6.87 Hz, 2H), 2.48 (br. s., 2H), 1.72 (d, *J* = 6.87 Hz, 3H) ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.8, 150.6, 139.7, 137.5, 137.0, 122.5, 120.7, 116.4, 112.8, 56.1, 49.4, 40.2, 16.3; HRMS (ESI): *m/z* calcd for $C_{13}H_{18}O_3N$ $[M+H]^+$ 236.1281, found 236.1278.

4-Allyl-2-methoxyphenyl L-valinate hydrochloride (37): Ester of the amino acid (0.5 g, 1.37 mmol), HCl etherate (in excess); Yield: 100%. IR (cm^{-1}): 3440.72, 3022.53, 2103.08, 1643.38, 1271.71. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.98-6.87 (m, 1H), 6.83-6.69 (m, 2H), 6.11-5.80 (m, 1H), 5.17-5.02 (m, 2H), 3.84-3.75 (m, 3H), 3.63-3.50 (m, 1H), 3.37 (d, *J* = 6.62 Hz, 3H), 2.35-2.20 (m, 1H), 2.05 (br. s., 2H), 1.03 (d, *J* = 6.84 Hz, 3H), 1.10 (d, *J* = 6.84 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 207.1, 170.7, 155.8, 150.8, 139.3, 137.7, 137.1, 122.5, 120.8, 116.3, 112.8, 79.9, 58.6, 55.9, 55.7, 40.1, 31.5, 31.0, 28.4, 19.1, 17.2; HRMS (ESI): *m/z* calcd for $C_{15}H_{22}O_3N$ $[M+H]^+$ 264.1594 found 264.1592.



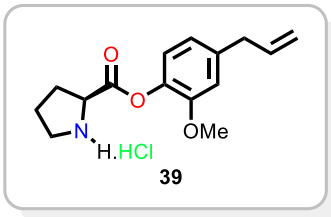
37

4-Allyl-2-methoxyphenyl L-phenylalaninate hydrochloride (38): Ester of the amino acid (0.5 g, 1.21 mmol), HCl etherate (in excess); Yield: 99%. IR (cm^{-1}): 3432.56, 3022.91, 1643.60, 1216.37; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 (br. s., 2H), 7.40-7.19 (m, 5H), 6.95-6.86 (m, 1H), 6.83-6.62 (m, 2H), 6.05-5.79 (m, 1H), 5.17-5.00 (m, 2H), 4.56 (br. s., 1H), 3.82 (s, 1H), 3.75 (s, 2H), 3.56 - 3.47 (m, 1H), 3.39 (d, *J* = 6.87 Hz, 1H), 3.35 - 3.19 (m, 2H), 2.45 (br. s., 1H), 1.43 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.4, 167.3, 155.2, 150.8, 150.5, 139.7, 139.4, 137.7, 137.2, 137.1, 136.9, 136.1, 133.9, 130.0, 129.7, 128.9, 128.6, 127.7, 127.1, 122.5, 120.8, 120.8, 116.3, 112.8, 80.0, 56.0, 55.8, 54.4, 40.2, 40.1, 38.3, 36.2, 28.4; HRMS (ESI): *m/z* calcd for $C_{19}H_{22}O_3N$ $[M+H]^+$ 312.1594 found 312.1591.



38

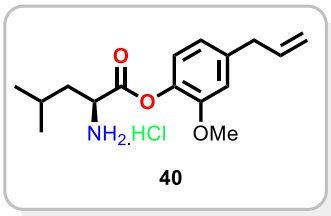
4-Allyl-2-methoxyphenyl L-prolinate hydrochloride (39): Ester of the amino acid (0.5 g, 0.00138 mmol), HCl etherate (in excess); Yield: 99%. IR (cm^{-1}): 3438.71, 3025.4, 2102.56, 1644.30, 1215.75; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96-6.84 (m, 1H),



39

6.78-6.68 (m, 2H), 6.08-5.78 (m, 1H), 5.15-4.98 (m, 2H), 4.62 (t, *J* = 7.61 Hz, 1H), 3.75 (s, 3H), 3.50-3.26 (m, 4H), 2.57-2.23 (m, 2H), 2.16-1.90 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.6, 150.4, 139.9, 137.2, 136.9, 122.4, 120.8, 116.4, 112.6, 77.5, 77.2, 76.8, 59.2, 56.0, 46.1, 40.1, 29.2, 28.4, 23.5 ppm; HRMS (ESI): *m/z* calcd for $C_{15}H_{20}O_3N$ $[M+H]^+$ 262.1438 found 262.1436.

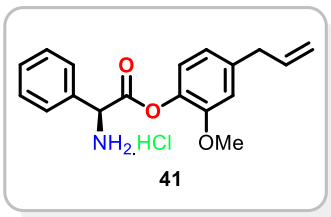
4-Allyl-2-methoxyphenyl L-leucinate hydrochloride (40): Ester of the amino acid



40

(0.3 g, 0.75 mmol), HCl etherate (in excess). Yield: 96%. IR (cm-1): 3433.98, 3022.88, 2402.92, 1643.01, 1216.22; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.92 (br. s., 1H), 7.05 (d, *J* = 7.63 Hz, 1H), 6.81-6.67 (m, 2H), 6.02-5.85 (m, 1H), 5.15-5.02 (m, 2H), 4.19 (t, *J* = 6.87 Hz, 1H), 3.84-3.73 (m, 3H), 3.38 (d, *J* = 6.87 Hz, 1H), 3.33 (d, *J* = 6.10 Hz, 1H), 2.31 (s, 1H), 2.18 (s, 2H), 2.10-1.92 (m, 2H), 1.46 (s, 2H), 1.01 (d, *J* = 6.10 Hz, 1H), 0.97-0.73 (m, 4H) ppm (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.3, 150.6, 139.6, 139.1, 138.0, 137.9, 137.4, 137.1, 137.0, 122.6, 121.2, 120.8, 116.3, 115.6, 112.8, 112.8, 111.2, 56.0, 55.9, 51.9, 42.0, 40.2, 40.1, 40.0, 39.7, 31.0, 28.4, 24.4, 23.0, 22.3, 22.1, 20.8; HRMS (ESI): *m/z* calcd for $C_{16}H_{24}O_3N[M+H]^+$ 278.1751 found 278.1749.

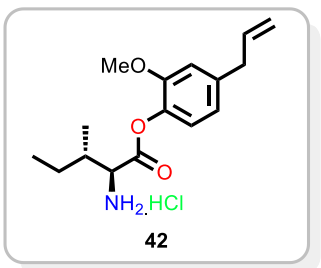
4-Allyl-2-methoxyphenyl (*S*)-2-amino-2-phenylacetate hydrochloride (41):



41

Ester of the amino acid (0.5 g, 1.25 mmol), HCl etherate (in excess); Yield: 100%. IR (cm^{-1}): 3443.32, 3023.22, 2403.17, 1645.58, 1216.67; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.57-7.30 (m, 5H), 6.99-6.81 (d, *J* = 8.60 Hz, 1H), 6.81-6.55 (m, 2H), 6.07-5.79 (m, 1H), 5.62 (br. s., 1H), 5.15-5.00 (m, 2H), 3.64 (s, 3H), 3.49 (s, 1H), 3.35 (d, *J* = 6.39 Hz, 2H); HRMS (ESI): *m/z* calcd for $C_{18}H_{20}O_3N[M+H]^+$ 298.1438 found 298.1434.

4-Allyl-2-methoxyphenyl L-isoleucinate hydrochloride (42): Ester of the amino

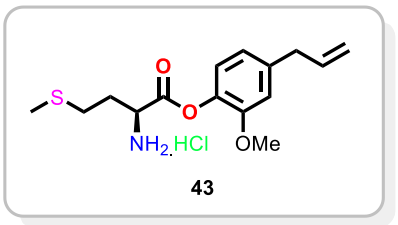


42

acid (0.5 g, 1.32 mmol), HCl etherate (in excess). Yield: 99%. IR (cm^{-1}): 3438.57, 3023.09, 2402.74, 1644.61, 1216.15. : ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (br. s., 2H), 7.06 (d, *J* = 7.63 Hz, 1H), 6.75-6.65 (m, 2H), 6.01-5.81 (m, 1H), 5.11-5.00 (m, 2H), 4.19 (d, *J* = 3.81 Hz, 1H), 3.75 (s, 3H),

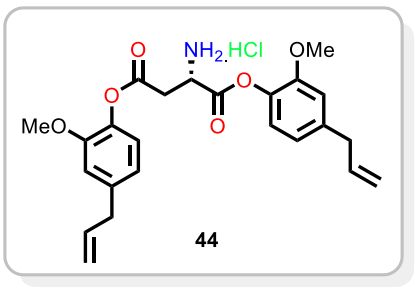
3.39-3.27 (m, 3H), 3.32-2.16 (m, 1H), 1.68-1.55 (m, 1H), 1.52-1.37 (m, 2H), 1.12 (d, *J* = 6.87 Hz, 3H), 0.89 (t, *J* = 7.25 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 150.6, 139.6, 137.3, 137.1, 122.8, 120.8, 116.3, 112.7, 57.6, 55.8, 40.2, 36.8, 25.4, 14.8, 11.8; HRMS (ESI): *m/z* calcd for $C_{21}H_{31}O_5NNa$ $[M+Na]^+$ 400.2094, found 400.2086.

4-Allyl-2-methoxyphenyl L-methioninate hydrochloride (43): Ester of the amino acid (0.5 g, 1.26 mmol), HCl etherate (in excess). Yield: 99%. IR (cm^{-1}): 3436.19, 3023.54, 2096.85, 1642.35, 1216.11. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04 (d, *J* = 8.39 Hz, 1H), 6.75-6.65 (m, 2H), 5.99-5.81 (m, 1H), 5.10-5.00 (m, 2H), 4.42 (t, *J* = 6.10 Hz, 1H), 3.76 (s, 4H), 3.32 (d, *J* = 6.87 Hz, 2H), 2.82-2.74 (m, 1H), 2.71-2.64 (m, 1H), 2.39 (q, *J* = 6.87 Hz, 2H), 2.06 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.1, 150.4, 139.8, 137.2, 137.0, 122.6, 120.9, 116.4, 112.7, 56.0, 52.4, 40.2, 29.8, 29.0, 28.4, 15.1; HRMS (ESI): *m/z* calcd for $C_{15}H_{22}O_3NS[M+H]^+$ 296.1315 found 296.1313.



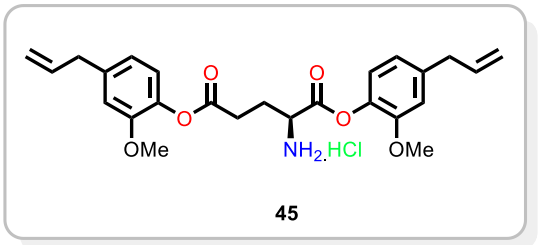
43

Bis(4-allyl-2-methoxyphenyl) L-aspartate hydrochloride (44): Ester of the amino acid (0.5 g, 1.17 mmol), HCl etherate (in excess). Yield: 99%. IR (cm^{-1}): 3438.41, 3023.78, 2110.60, 1644.57, 1216.59; ^{1}H NMR (200 MHz, $CDCl_3$) : δ 9.07 (br. s., 2H), 7.10-6.96 (m, 2H), 6.77-6.64 (m, 4H), 6.04-5.77 (m, 2H), 5.15-4.96 (m, 4H), 4.85 (br. s., 1H), 3.70 (s, 3H), 3.72 (s, 3H), 3.61-3.45 (m, 1H), 3.32 (d, *J* = 5.40 Hz, 4H), 2.63 (br. s., 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.2, 150.6, 139.7, 137.0, 133.9, 130.1, 129.0, 127.7, 122.5, 120.8, 116.4, 112.9, 56.0, 54.4, 40.2, 40.2, 36.3; HRMS (ESI): *m/z* calcd for $C_{24}H_{28}O_6N$ $[M+H]^+$ 426.1911, found 426.1908.



44

Bis(4-allyl-2-methoxyphenyl) L-glutamate hydrochloride (45): Ester of the amino acid (0.5 g, 9.26 mmol), HCl etherate (in excess). Yield: 100%. IR (cm^{-1}): 3436.17, 3023.57, 1642.85, 1216.28; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.66 (br. s., 1H), 8.46 (br. s., 1H), 7.03 (t, *J* = 8.16 Hz, 1H), 6.94-6.83 (m, 1H), 6.78-6.55 (m, 4H), 6.07-5.76 (m, 2H), 5.61 (br. s., 4H), 5.19-4.94 (m, 4H), 4.47 (br.

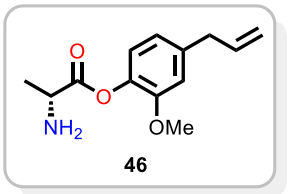


45

s., 1H), 3.88 (s, 2H), 3.73 (t, *J* = 5.95 Hz, 4H), 3.09-2.88 (m, 1H), 2.77- 2.32 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.5, 170.5, 150.6, 146.6, 144.0, 139.6, 137.9, 137.5, 137.0, 132.0, 122.2, 121.2, 120.8, 116.4, 115.6, 114.4, 112.8, 111.3, 77.5, 76.8, 56.0, 55.9, 55.5, 40.1, 40.0, 29.8, 29.3, 25.1 HRMS (ESI): *m/z* calcd for $C_{25}H_{30}O_6N[M+H]^+$ 440.2068 found 440.2054.

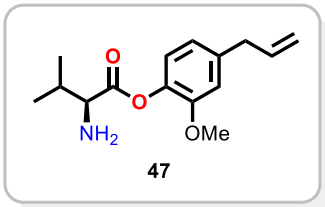
General procedure for preparation of TFA salt of amino acid derivatives of Eugenol: To the ester (1 eq) in dry DCM, TFA (5 eq) was added, and the reactionwas run at room temperature by checking TLC constantly. After complete consumption of the starting material, the reaction mixture was evaporated under reduced pressure and $NaHCO_3$ was added, and the aqueous layer was extracted with DCM thrice and the combined organic layer was washed brine and dried over Na_2SO_4, filtered and concentrated in vacuo and the crude was purified by silica gel column chromatography.

4-Allyl-2-methoxyphenyl D-alaninate (46): Ester of the amino acid (0.1 g, 0.001902 mmol), TFA (0.091 mL, 0.00095 mmol). Yield: 40.7%. IR (cm^{-1}): 3435.91, 3023.74, 2106.04, 1645.15, 1216.13; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.98-6.81 (m, 1H), 6.81-6.64 (m, 2H), 6.11-5.81 (m, 1H), 5.17-5.01 (m, 2H), 3.88-3.77 (m, 3H), 3.35 (dd, *J* = 6.62, 12.13 Hz, 2H), 2.70 (br. s., 1H), 1.52 (d, *J* = 7.06 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): 175.2, 150.8, 146.7, 144.1, 139.2, 138.0, 137.9, 137.1, 131.9, 122.4, 121.2, 120.8, 116.3, 115.6, 114.5, 112.8, 111.3, 77.5, 76.8, 55.9, 50.1, 40.2, 40.0, 20.7; HRMS (ESI): *m/z* calcd for $C_{13}H_{18}O_3N[M+H]^+$ 236.1281 found 236.1280.



46

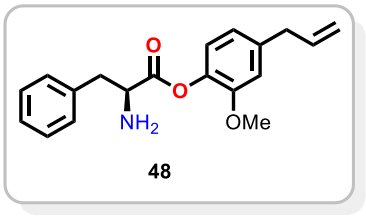
4-Allyl-2-methoxyphenyl L-valinate (47): Ester of the amino acid (0.5 g, 1.37 mmol), TFA (0.52 mL, 6.87 mmol); Yield: 99.6%. IR (cm^{-1}): 3435.49, 3024.05, 2107.66, 1646.22, 1216.08. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.97-6.89 (m, 1H), 6.79-6.72 (m, 2H), 6.05-5.88 (m, 1H), 5.13-5.01 (m, 2H), 3.78 (s, 3H), 3.64-3.52 (m, 1H), 3.37 (d, *J* = 6.87 Hz, 2H), 2.32-2.22 (m, 1H), 2.13 (br. s., 1H), 2.05 (br. s., 1H), 1.10 (d, *J* = 6.87 Hz, 3H), 1.03 (d, *J* = 6.87 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.0, 150.9, 139.1, 137.9, 137.9, 137.1, 122.5, 120.7, 116.2, 112.7, 59.9, 55.7, 40.1,



47

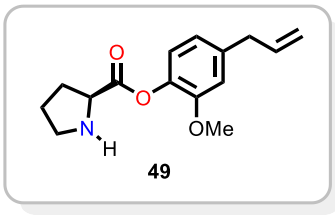
32.1, 19.4, 16.9; HRMS (ESI): *m/z* calcd for $C_{15}H_{22}O_3N$ $[M+H]^+$ 264.1594, found 264.1594.

4-Allyl-2-methoxyphenyl L-phenylalaninate (48): Ester of the amino acid (0.5 g, 1.21 mmol), TFA (0.46 mL, 6.07 mmol); Yield: 100%. IR (cm^{-1}): 3435.23, 3023.61, 2401.98, 1649.02, 1215.91; ^1H NMR (400 MHz, $CDCl_3$): δ 7.42-7.18 (m, 5H), 6.88-6.84 (m, 1H), 6.78-6.67 (m, 3H), 6.04-5.86 (m, 1H), 5.43 (br. s., 3H), 5.14-5.05 (m, 3H), 4.29-4.23 (m, 1H), 3.77 (s, 3H), 3.34 (dd, *J* = 6.10, 11.44 Hz, 4H), 3.28-3.17 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.4, 150.8, 150.6, 139.7, 139.4, 137.1, 136.2, 134.0, 130.1, 129.8, 129.0, 128.6, 127.7, 122.5, 120.8, 120.8, 116.4, 112.9, 80.1, 77.5, 76.8, 55.8, 54.4, 40.2, 40.2, 36.3, 28.4; HRMS (ESI): *m/z* calcd for $C_{19}H_{22}O_3N$ $[M+H]^+$ 312.1594, found 312.1590.



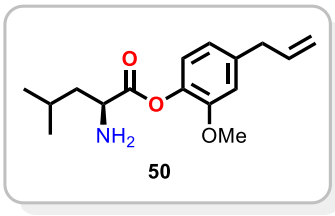
48

4-Allyl-2-methoxyphenyl L-prolinate (49): Ester of the amino acid (0.3 g, 0.83 mmol), TFA (0.31 mL, 4.15 mmol); Yield: 59.55%. IR (cm^{-1}): 3435.81, 3023.08, 2108.99, 1649.79, 1214.30; ^1H NMR (200 MHz, $CDCl_3$): δ 6.98-6.84 (m, 1H), 6.81-6.62 (m, 2H), 6.08-5.76 (m, 1H), 5.16-4.98 (m, 2H), 4.62 (t, *J* = 6.73 Hz, 1H), 3.75 (s, 3H), 3.52-3.27 (m, 4H), 2.62-2.28 (m, 2H), 2.20-1.94 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 166.4, 146.7, 144.1, 137.9, 131.8, 121.1, 115.5, 114.5, 111.3, 60.5, 55.8, 45.2, 39.9, 27.7, 23.3; HRMS (ESI): *m/z* calcd for $C_{15}H_{20}O_3N$ $[M+H]^+$ 262.1438, found 262.1435.



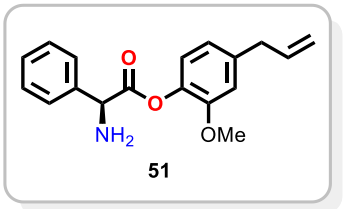
49

4-Allyl-2-methoxyphenyl L-leucinate (50): Ester of the amino acid (0.328 g, 0.86 mmol), TFA (0.33 mL, 4.34 mmol). Yield: 100%. ^1H NMR (200 MHz, $CDCl_3$): δ 7.06-6.86 (m, 1H), 6.78-6.67 (m, 2H), 6.05-5.82 (m, 1H), 5.15-5.03 (m, 2H), 4.10 (br. s., 1H), 3.75 (s, 3H), 3.35 (d, *J* = 6.17 Hz, 3H), 1.87 (br. s., 3H), 0.89 (br. s., 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.9, 150.5, 146.6, 144.0, 139.9, 137.9, 137.2, 136.9, 132.1, 122.2, 121.3, 120.9, 116.4, 115.6, 114.4, 112.8, 111.3, 56.0, 55.8, 51.7, 40.2, 40.1, 40.0, 39.8, 24.3, 22.0, 21.9; HRMS (ESI): *m/z* calcd for $C_{16}H_{24}O_3N$ $[M+H]^+$ 278.1751, found 278.1751.



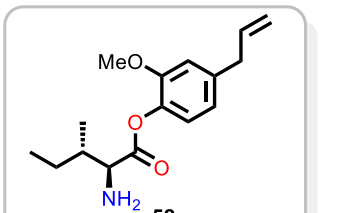
50

4-Allyl-2-methoxyphenyl (*S*)-2-amino-2-phenylacetate (51): Ester of the amino acid (0.5 g, 1.25 mmol), TFA (0.484 mL, 6.28 mmol). Yield: 62.22%. IR (cm^{-1}): 3441.55, 3023.13, 2402.26, 1647.72, 1215.83; ^1H NMR (400 MHz, $CDCl_3$): 7.52 (d, *J* = 6.87 Hz, 2H), 7.44-7.31 (m, 3H), 6.87-6.83 (m, 1H), 6.75-6.70 (m, 2H), 6.03-5.89 (m, 1H), 5.12-5.06 (m, 2H), 4.91 (s, 1H), 3.67 (s, 3H), 3.36 (d, *J* = 6.87 Hz, 2H), 3.23 (br. s., 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.4, 150.8, 146.7, 144.1, 139.6, 139.2, 137.9, 137.0, 131.8, 128.7, 128.2, 127.2, 122.2, 121.1, 120.6, 116.2, 115.5, 114.6, 112.8, 111.3, 58.7, 55.8, 55.6, 40.0, 39.9; HRMS (ESI): *m/z* calcd for $C_{18}H_{20}O_3N$ $[M+H]^+$ 298.1438, found 298.1434.



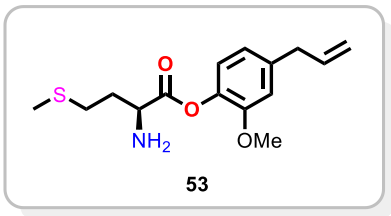
51

4-Allyl-2-methoxyphenyl L-isoleucinate (52): Ester of the amino acid (0.5 g, 1.27 mmol), TFA (0.49 mL, 6.38 mmol). Yield: 63.27%. IR (cm^{-1}): 3435.23, 3022.44, 2402.60, 1646.31, 1270.18; ^1H NMR (400 MHz, $CDCl_3$): δ 8.97-8.67 (m, 2H), 7.07 (d, *J* = 8.00 Hz, 1H), 6.78-6.65 (m, 3H), 6.00-5.83 (m, 1H), 5.11-5.00 (m, 2H), 4.19 (d, *J* = 3.00 Hz, 1H), 3.75 (s, 3H), 3.38-3.26 (m, 3H), 2.30-2.14 (m, 1H), 1.70-1.55 (m, 1H), 1.51-1.37 (m, 1H), 1.11 (d, *J* = 6.88 Hz, 3H), 0.89 (t, *J* = 7.25 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.1, 150.6, 139.6, 137.3, 137.0, 122.8, 120.8, 116.3, 112.7, 57.6, 55.8, 40.1, 40.0, 36.7, 25.4, 14.7, 11.8; HRMS (ESI): *m/z* calcd for $C_{21}H_{31}O_5NNa$ $[M+Na]^+$ 400.2094, found 400.2094.



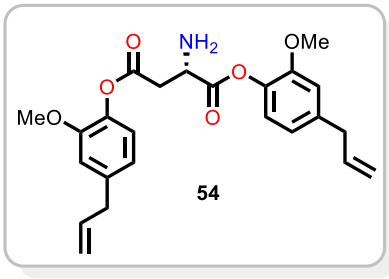
52

4-Allyl-2-methoxyphenyl L-methioninate (53): Ester of the amino acid (0.5 g, 1.26 mmol), TFA (0.48 mL, 6.32 mmol). Yield: 85.75%. IR (cm^{-1}): 3438.66, 3024.21, 2108.13, 1646.91, 1215.81; ^1H NMR (400 MHz, DMSO-d_6): δ 8.72 (br. s., 1H), 6.79-6.64 (m, 2H), 6.55 (dd, *J* = 1.63, 7.88 Hz, 1H), 6.00-5.83 (m, 1H), 5.12-4.94 (m, 2H), 4.01-3.90 (m, 1H), 3.73 (s, 4H), 3.24 (d, J = 6.63 Hz, 3H), 2.64-2.51 (m, 2H), 2.13-1.99 (m, 3H), 1.97-1.83 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 167.8, 147.5, 144.7, 138.2, 130.5, 120.5, 115.4, 115.3, 112.6, 55.5, 54.9, 53.0, 32.4, 28.8, 14.4; HRMS (ESI): *m/z* calcd for $C_{19}H_{22}O_3N$ $[M+H]^+$ 312.1594, found 312.1590.

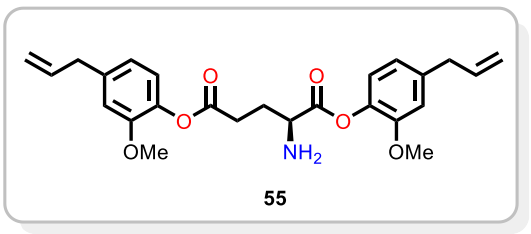


53

Bis(4-allyl-2-methoxyphenyl) L-aspartate (54): Ester of the amino acid (0.1 g, 1.92 mmol), TFA (0.091 mL, 0.95 mmol). Yield: 40.07%. IR (cm-1): 3436.48, 3022.91, 2402.44, 1645.93, 1215.94; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.08-6.89 (m, 2H), 6.84-6.59 (m, 4H), 6.16-5.68 (m, 2H), 5.19-4.97 (m, 4H), 4.26 (br. s., 1H), 3.86-3.73 (m, 6H), 3.38 (d, *J* = 6.28 Hz, 4H), 3.33-3.04 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.5, 169.5, 150.8, 139.3, 137.9, 137.9, 137.8, 137.1, 122.6, 122.5, 121.3, 120.8, 116.3, 115.6, 114.4, 112.8, 111.2, 56.0, 55.9, 51.6, 40.2, 40.0, 39.3; HRMS (ESI): *m/z* calcd for $C_{24}H_{28}O_6N$ $[M+H]^+$ 426.1911, found 426.1900.

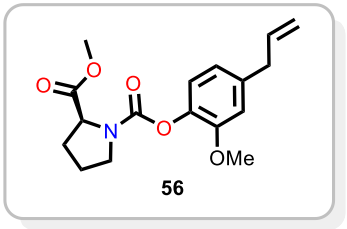


Bis(4-allyl-2-methoxyphenyl) L-glutamate (55): Ester of the amino acid (0.224 g, 0.415 mmol), TFA (0.15 mL, 2.07 mmol); Yield: 78.57%. IR (cm^{-1}): 3443.16, 3023.76, 2402.16, 1642.78, 1216.32; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.94 (d, *J* = 7.63 Hz, 1H), 6.86-6.82 (m, 1H), 6.80-6.75 (m, 2H), 6.70-6.66 (m, 2H), 6.01-5.89 (m, 2H), 5.14-5.02 (m, 4H), 4.50 (dd, *J* = 3.81, 8.39 Hz, 1H), 3.86 (s, 3H), 3.79 (s, 3H), 3.38 (d, *J* = 6.87 Hz, 2H), 3.32 (d, *J* = 6.10 Hz, 2H), 2.64-2.53 (m, 1H), 2.53-2.37 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 178.3, 170.6, 150.6, 146.6, 144.0, 139.6, 137.9, 137.5, 137.0, 131.9, 122.2, 121.2, 120.8, 116.4, 115.6, 114.4, 112.8, 111.3, 55.9, 55.9, 55.4, 40.1, 39.9, 29.8, 29.2, 25.1; HRMS (ESI): *m/z* calcd for $C_{25}H_{30}O_6N$ $[M+H]^+$ 440.2068, found 440.2049.



2.4. Carbamate derivatives of eugenol:

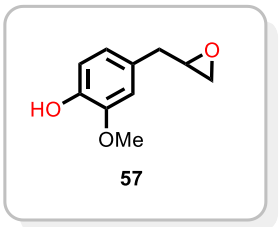
1-(4-Allyl-2-methoxyphenyl) 2-methyl (*S*)-pyrrolidine-1,2-dicarboxylate (56): Eugenol (0.01 mL, 0.07 mmol) was added to carbamoyl chloride (0.072 g, 0.37 mmol) obtained, and then dissolved in pyridine (5 mL). The mixture was stirred at reflux conditions for 24 hrs. After completion of the reaction, pyridine was evaporated, and the residue was purified via column chromatography. Yield 24 % 1H NMR (200 MHz, $CDCl_3$) δ 6.98 (dd, *J* = 8.05, 15.99 Hz, 1H), 6.78-6.68 (m, 2H), 6.07-5.78 (m, 1H), 5.16-4.97 (m, 2H),



4.65-4.38 (m, 1H), 3.92-3.83 (m, 1H), 3.80 (d, *J* = 3.31 Hz, 3H), 3.73 (d, *J* = 4.63 Hz, 3H), 3.69-3.51 (m, 1H), 3.34 (d, *J* = 6.62 Hz, 2H), 2.39-2.20 (m, 1H), 2.17-1.91 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.3, 173.0, 153.3, 152.7, 151.6, 151.5, 138.6, 138.6, 138.5, 137.4, 123.2, 120.8, 120.7, 116.1, 116.1, 113.0, 113.0, 77.4, 76.9, 59.5, 59.4, 56.2, 56.1, 52.4, 47.2, 47.1, 40.2, 31.2, 30.1, 24.6, 23.7, HRMS (ESI): *m/z* calcd for $C_{17}H_{22}O_5N[M+H]^+$ 320.1492 found 320.1486.

Other eugenol derivatives:

2-Methoxy-4-(oxiran-2-ylmethyl)phenol (57): A solution of 10 mmol of *m*-chloroperoxy-benzoic acid (*m*-CPBA) was added dropwise over the period of 15 minutes to a solution of 5 mmol of Eugenol in chloroform under stirring at 0°C to room temperature. The mixture was stirred under nitrogen, and the progress of the reaction was monitored by thin-layered chromatography (TLC). After completion of the reaction mixture was washed with a saturated aqueous solution of $NaHCO_3$ (sodium bicarbonate) and distilled water. The organic layers were separated out and dried over anhydrous Na_2SO_4. Concentrate that compound by using a rotary evaporator and the crude was purified by silica gel column chromatography. TLC: R_f = 0.8 (SiO_2, 10% EtOAc/hexanes), FTIR (cm^{-1}): 3545.15, 3020.09, 1515, 1432.15, 1215.83; 1H NMR (400 MHz, $CDCl_3$) δ 6.85 (d, *J* = 7.63 Hz, 1H), 6.78-6.71 (m, 2H), 5.72 (br. s., 1H), 3.87 (s, 3H), 3.17-3.09 (m, 1H), 2.81-2.78 (m, 3H), 2.54 (dd, *J* = 2.78, 5.05 Hz, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ : 146.6, 144.5, 129.1, 121.7, 114.5, 111.7, 56.0, 52.8, 46.9, 38.4; HRMS (ESI): *m/z* calcd for $C_{17}H_{16}O_3$ $[M+H]^+$ 291.0992, found 291.0987.



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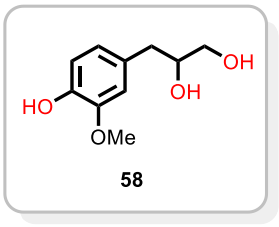
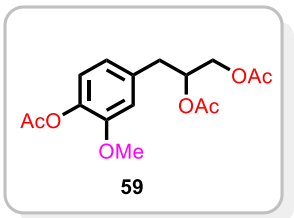
3-(4-Hydroxy-3-methoxyphenyl)propane-1,2-diol (58): Eugenol (1 mmol) in tertiary butanol (*t*-BuOH) 15 mL and tetrahydrofuran (THF) 5 mL were added to the solution of N-methylmorpholine N-oxide (NMO, 1.20 mmol) in water and osmium tetraoxide (OsO_4 2%mol) stirred at room temperature for 12 hours and progress of the reaction being monitored by thin layered chromatography (TLC). After completion of the reaction, it was cooled at 0 °C, and the mixture was washed with a saturated aqueous solution of $NaHSO_3$ (sodium bisulphate). The mixture was warmed



58

and stirred for 45 minutes and add ethyl acetate to it. The organic layers were separated out and dried over anhydrous Na_2SO_4. Concentrate that compound by using a rotary evaporator and the crude was purified by silica gel column chromatography. TLC: R_f = 0.8 (SiO_2, 10% EtOAc/hexanes), ^1H NMR (400 MHz, CD_3OD) δ 6.84 (s, 1H), 6.74 (d, *J* = 8.00 Hz, 1H), 6.68 (d, *J* = 8.13 Hz, 1H), 3.85 (s, 3H), 3.83-3.76 (m, 1H), 3.52 (dd, *J* = 4.38, 11.13 Hz, 1H), 3.46 (dd, *J* = 6.25, 11.13 Hz, 1H), 2.75 (dd, *J* = 5.75, 13.88 Hz, 1H), 2.62 (dd, *J* = 7.38, 13.88 Hz, 1H); ^{13}C NMR (101 MHz, CD_3OD) 148.8, 145.9, 131.6, 123.0, 116.1, 114.2, 74.8, 66.6, 56.5, 40.6; HRMS (ESI): *m/z* calcd for $C_{10}H_{14}O_4$ $[M+Na]^+$ 221.0784, found 221.0781.

3-(4-Acetoxy-3-methoxyphenyl)propane-1,2-diyl diacetate (59): A mixture of 3-(4-hydroxy-3-methoxyphenyl)propane-1,2-diol (0.24 g, 1.21 mmol), acetic anhydride (1.14 mL, 12.10 mmol) and anhydrous pyridine (3 mL) was stirred at room temperature for 24 hours and progress of the reaction being monitored by thin layered chromatography (TLC). After completion of the reaction mixture was washed with ethyl acetate (20 mL) and partitioned between 20% aqueous solution of $CuSO_4.5H_2O$ (copper sulphate 5 x 10mL). The organic layers were separated out and dried over anhydrous Na_2SO_4. Concentrate that compound by using rotary evaporator. After that purify that compound by silica gel column chromatography using (2% EtOAc in hexanes) to afford 3-(4-acetoxy-3-methoxyphenyl)propane-1,2-diyl diacetate **(59)** (0.212 g, 54%); TLC: R_f = 0.8 (SiO_2, 10% EtOAc/hexanes); FTIR (cm^{-1}): 3020.93, 1739.11, 1600.24, 1512.08, 1216.67; ^1H NMR (200 MHz, $CDCl_3$) δ : 6.98-6.87 (m, 1H), 6.84-6.68 (m, 2H), 5.38-5.13 (m, 1H), 4.29-4.16 (m, 1H), 4.13-3.94 (m, 1H), 3.79 (s, 3H), 2.86 (dd, *J* = 4.17, 6.95 Hz, 2H), 2.27 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (50 MHz, CDCl3) δ 170.7, 170.4, 169.1, 151.0, 138.6, 135.3, 122.8, 121.5, 113.3, 71.9, 64.2, 55.9, 36.9, 21.0, 20.8, 20.6; HRMS (ESI): *m/z* calcd for $C_{16}H_{20}O_7Na$ $[M+Na]^+$ 347.1101, found 347.1092.



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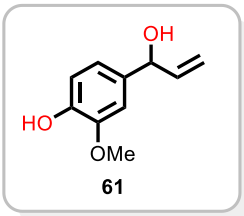
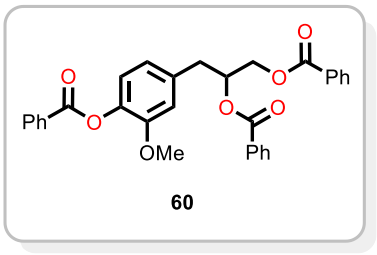


61

3-(4-(Benzoyloxy)-3-methoxyphenyl)propane-1,2-diyl dibenzoate (60): A 3-(4-hydroxy-3-methoxyphenyl)propane-1,2-diol (0.2 g, 1.01 mmol) was added dropwise in pyridine (5 mL) to benzoyl chloride (0.36 mL, 3.02 mmol) stirred at 0°C. The reactionmixture warmed to room temperature and stirred for 24

hours and progress of the reaction being monitored by thin layered chromatography



60

(TLC). After completion of the reaction mixture added to ethyl acetate (20 mL) and cold water (20 mL). After that separate organic layer and washed with saturated aqueous solution of $NaHCO_3$ (sodium bicarbonate) and brine solution. The organic layer were separate out and dried over anhydrous Na_2SO_4, concentrate that compound by silica gel column chromatography on using (2% EtOAc in hexanes) to afford 3-(4-(benzoyloxy)-3-methoxyphenyl)propane-1,2-diyl dibenzoate (**60**) (0.19 g, 39%); TLC: R_f = 0.8 (SiO_2, 10% EtOAc/hexanes); FTIR (cm^{-1}): 3020.49, 1721.10, 1215.32; ^1H NMR (200 MHz, $CDCl_3$) δ : 8.35-8.16 (m, 2H), 8.12-7.95 (m, 4H), 7.71-7.36 (m, 9H), 7.18-7.02 (m, 1H), 7.02-6.82 (m, 2H), 5.85-5.60 (m, 1H), 4.72-4.41 (m, 2H), 3.83-3.71 (m, 3H), 3.31-3.03 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ : 166.3, 166.0, 164.8, 151.4, 139.0, 135.3, 133.5, 133.3, 130.4, 130.1, 129.8, 129.5, 128.6, 123.1, 121.8, 113.7, 72.8, 64.8, 55.9, 37.3; HRMS (ESI): *m/z* calcd for $C_{31}H_{26}O_7Na$ $[M+Na]^+$ 533.1571, found 533.1585.

4-(1-Hydroxylallyl-2-methoxyphenol (61): To the vanillin (1 g, 6.57 mmol) in dry THF (10 mL), vinyl magnesium bromide (1 M in THF)(7.88 mL, 7.88 mmol) was added at 0 °C, and the reaction was stirred at the same temperature for 1 h, After completion of the reaction it was quenched with sat. aqueous NH_4Cl solution and extracted with EtOAc thrice, dried over Na_2SO_4, filtered, and concentrated in vacuo, and the crude product was purified by silica gel column chromatography using EtOAc in hexanes. (0.862 g, 73%); TLC: R_f = 0.4 (SiO_2, 30% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ : 6.92-6.88 (m, 1H), 6.88-6.81 (m, 2H), 6.09-5.98 (m, 1H), 5.75-5.69 (m, 1H), 5.33 (td, *J* = 1.38, 17.01 Hz, 1H), 5.18 (td, *J* = 1.38, 10.38 Hz, 1H), 5.12 (d, *J* = 5.75 Hz, 1H), 3.88 (s, 3H), 2.15 (br. s., 1H)); 13C NMR (101 MHz, $CDCl_3$) δ 146.8, 145.3, 140.4, 134.8, 119.6, 115.0, 114.4, 109.0, 75.3, 56.0; HRMS (ESI): *m/z* calcd for $C_{10}H_{13}O_3$ $[M+H]^+$ 181.0859, found 181.0859.

3.2.5 References

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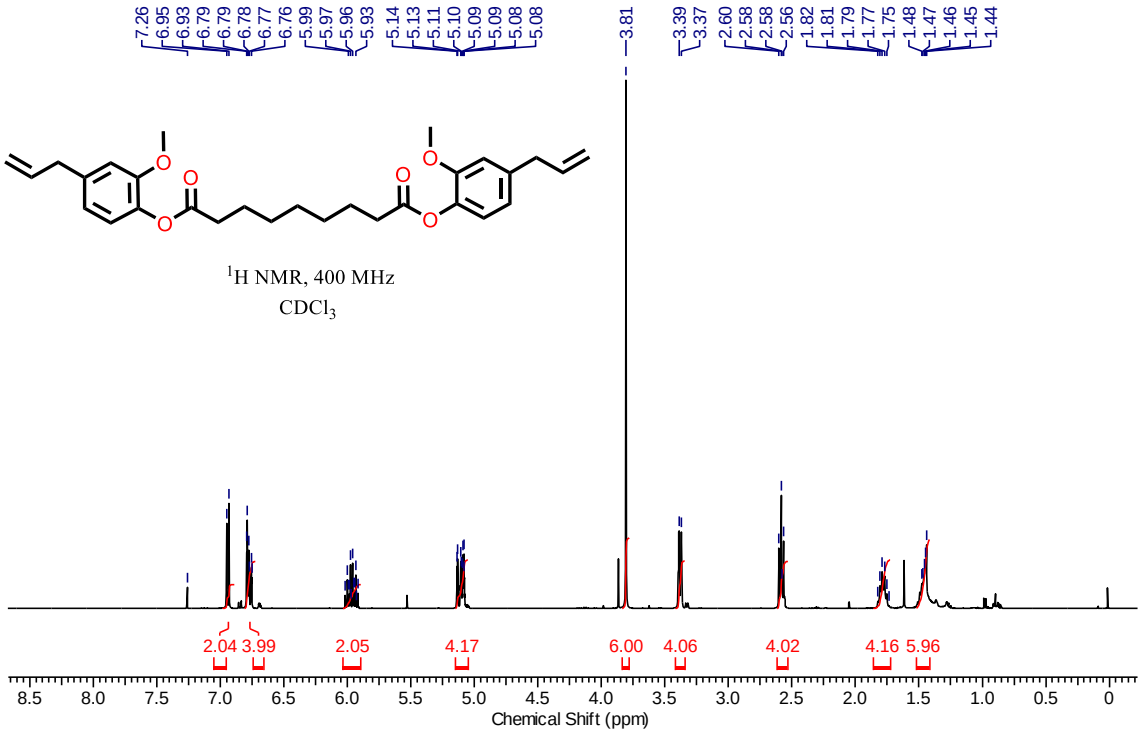
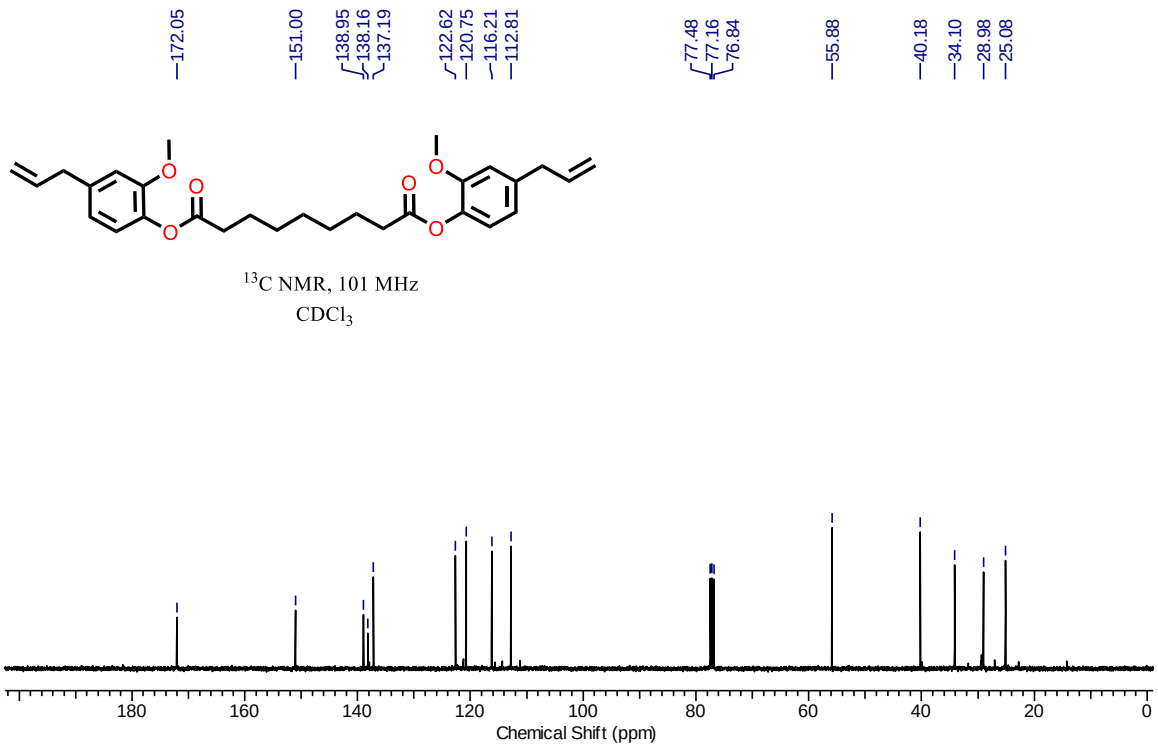
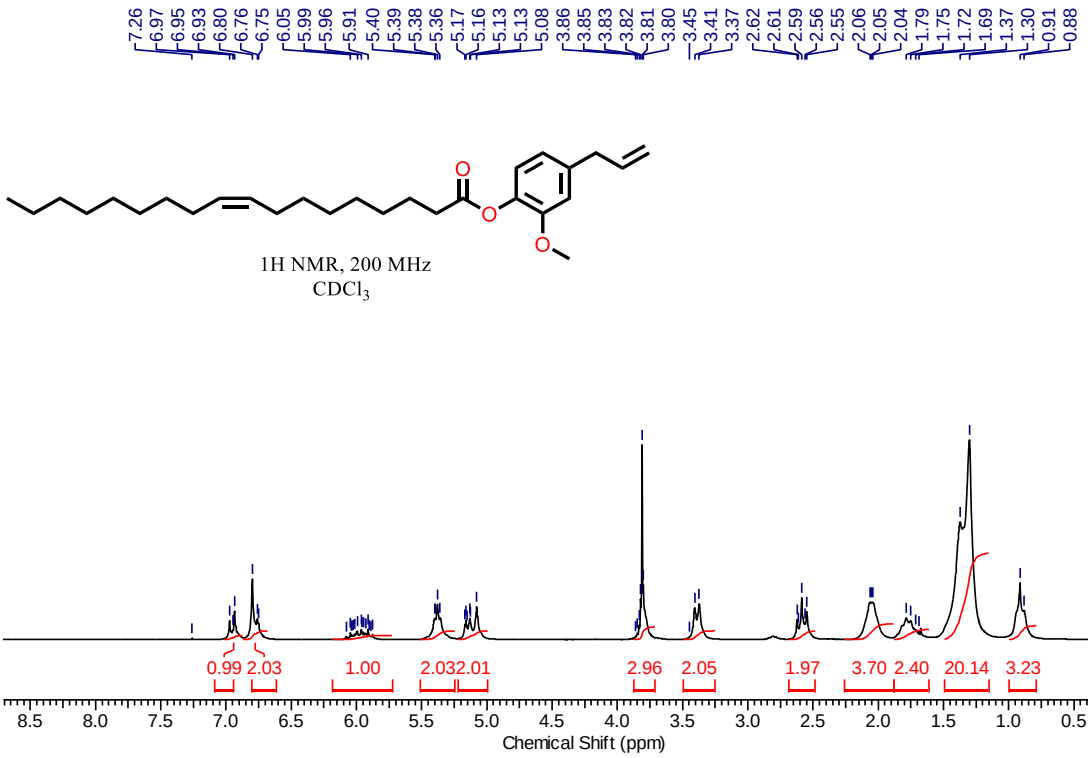
Bis(4-allyl-2-methoxyphenyl) nonanediote **(19):**



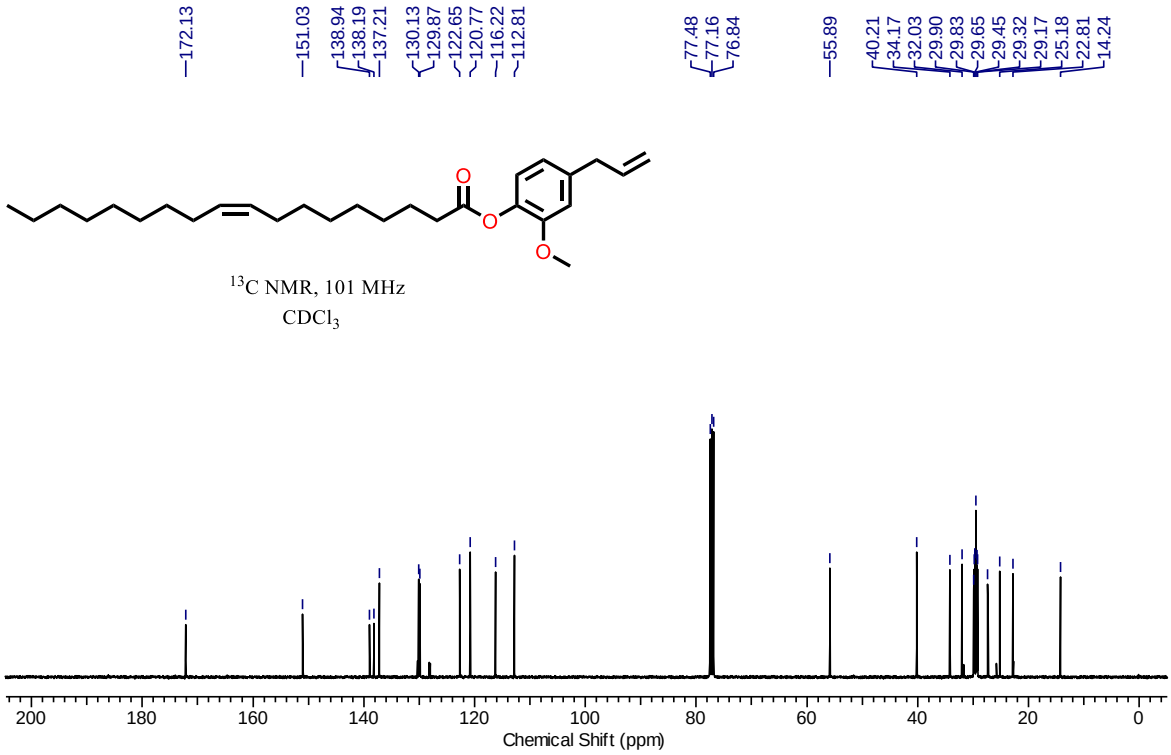
Bis(4-allyl-2-methoxyphenyl) nonanediote **(19):**



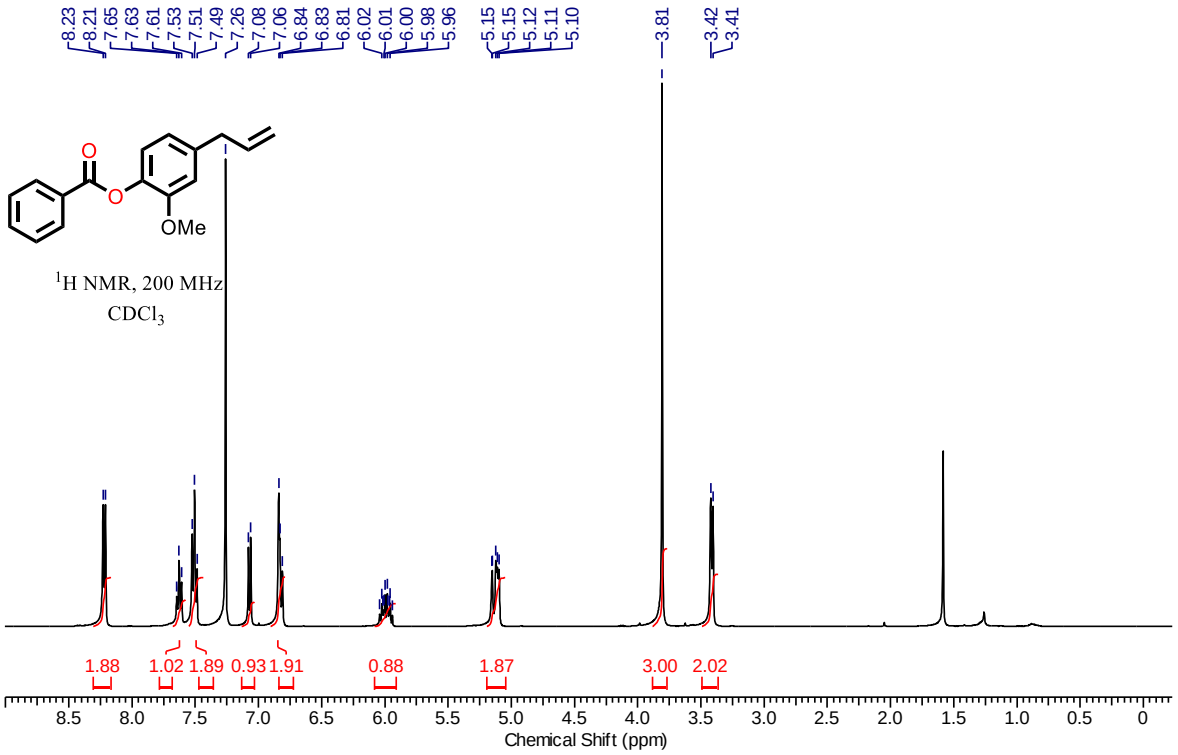
4-Allyl-2-methoxyphenyl oleate **(20):**



4-Allyl-2-methoxyphenyl oleate **(20):**



4-Allyl-2-methoxyphenyl benzoate **(21):**



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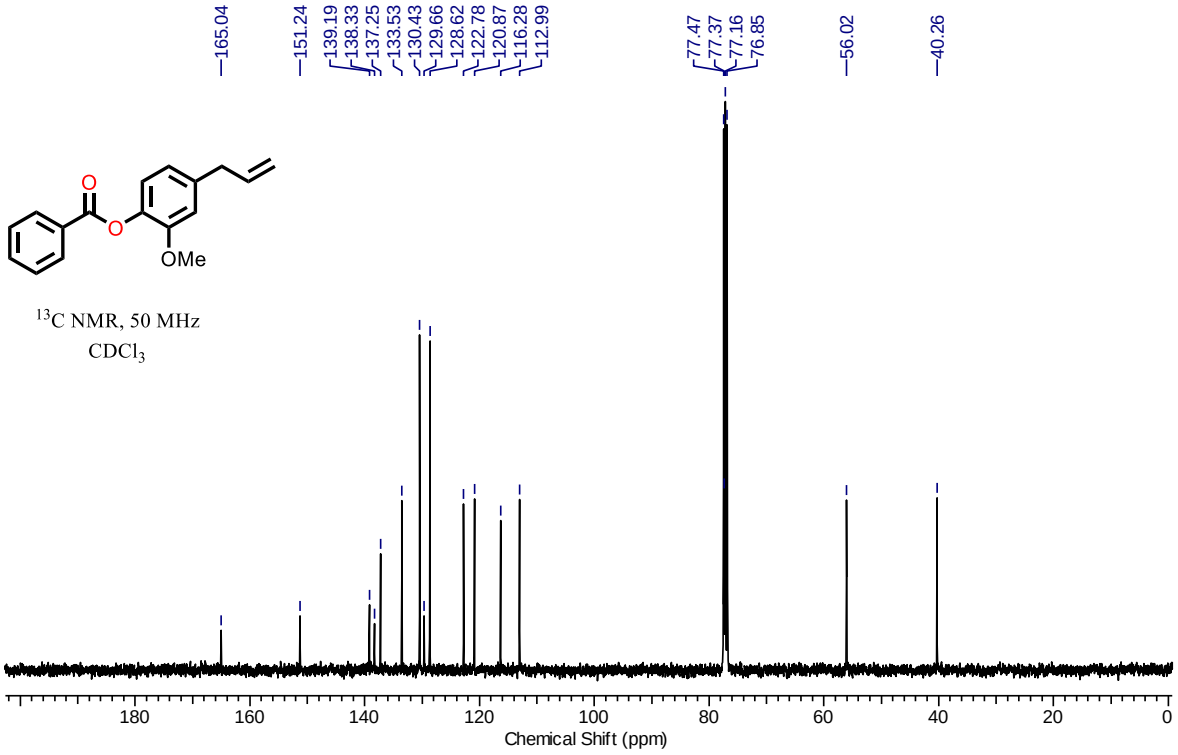

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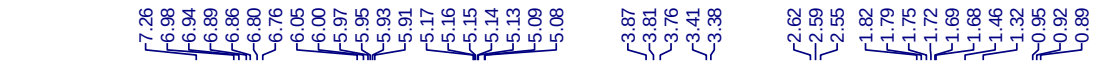
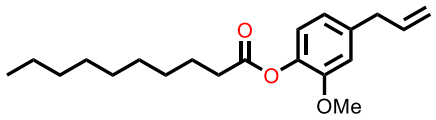
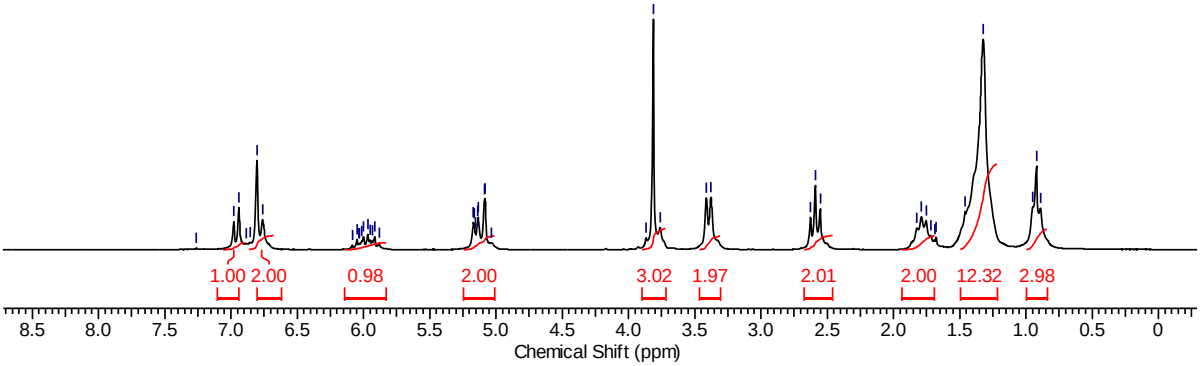
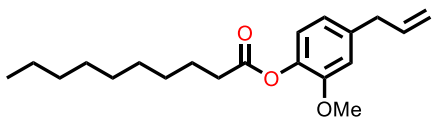




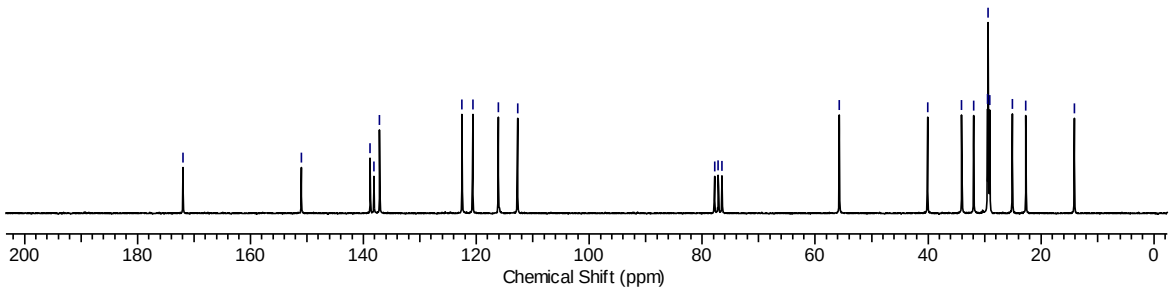
^{1}H NMR, 200 MHz
$CDCl_3$



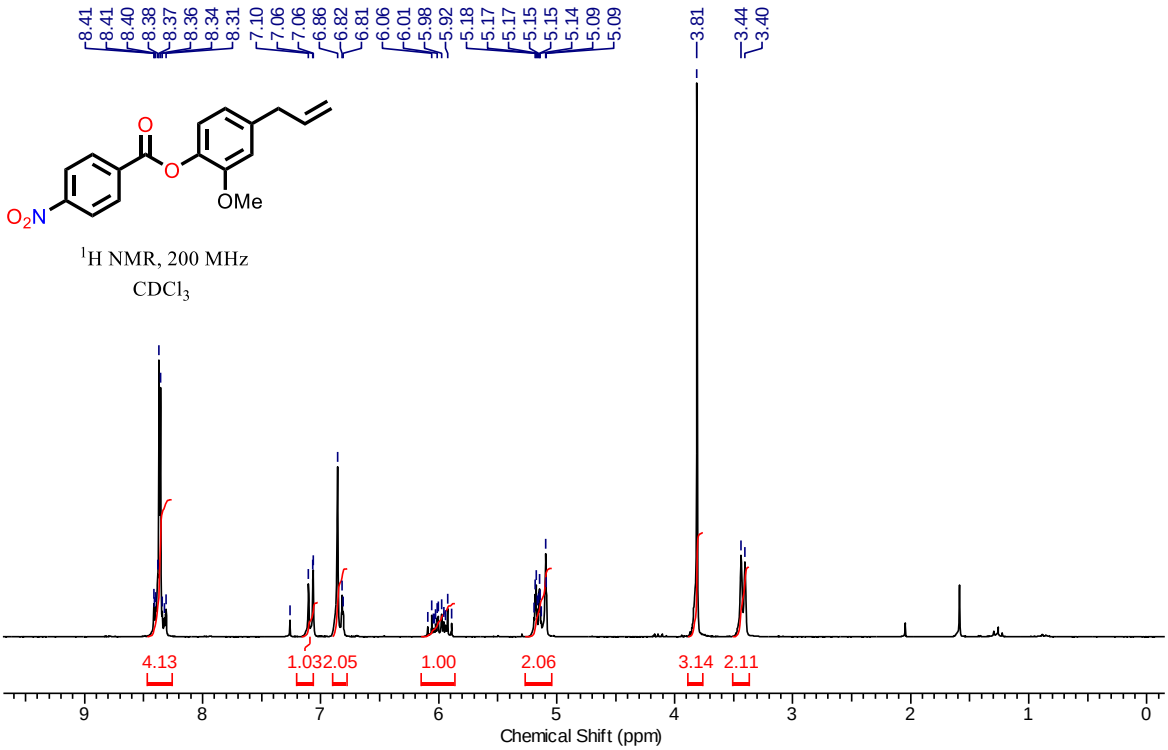
4-Allyl-2-methoxyphenyl decanoate **(22):**



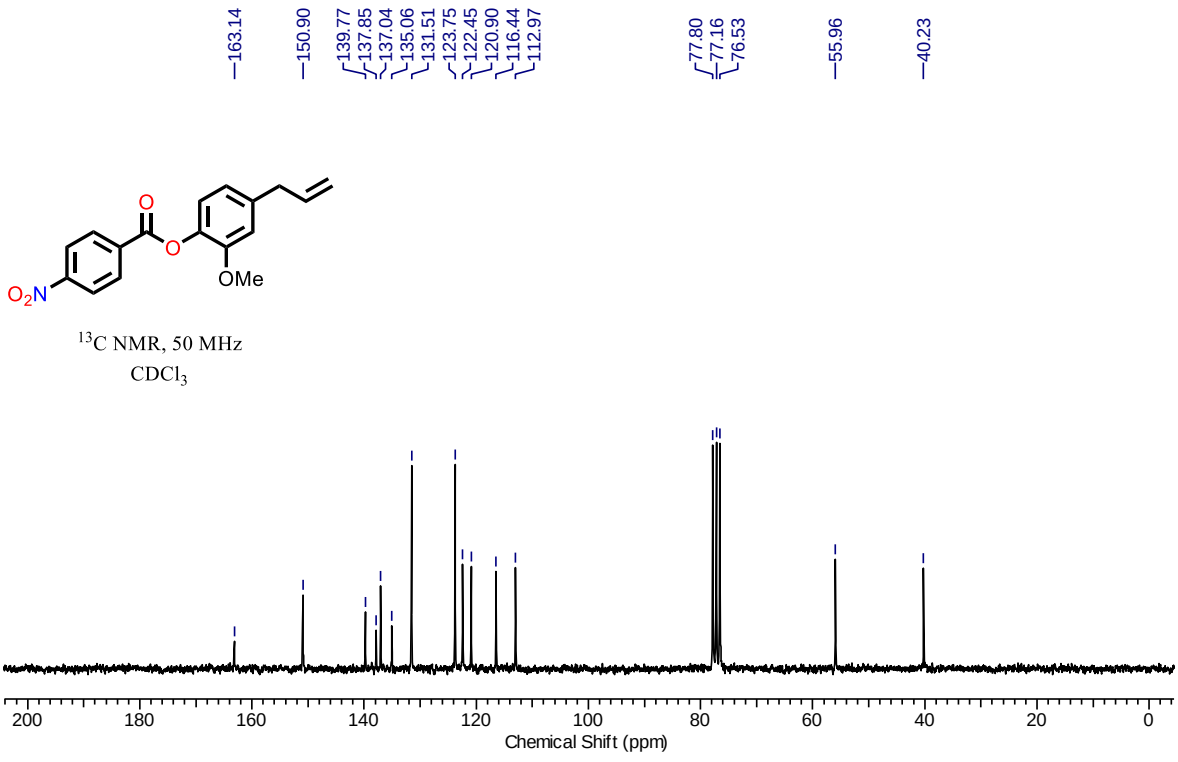
^{13}C NMR, 50 MHz
$CDCl_3$



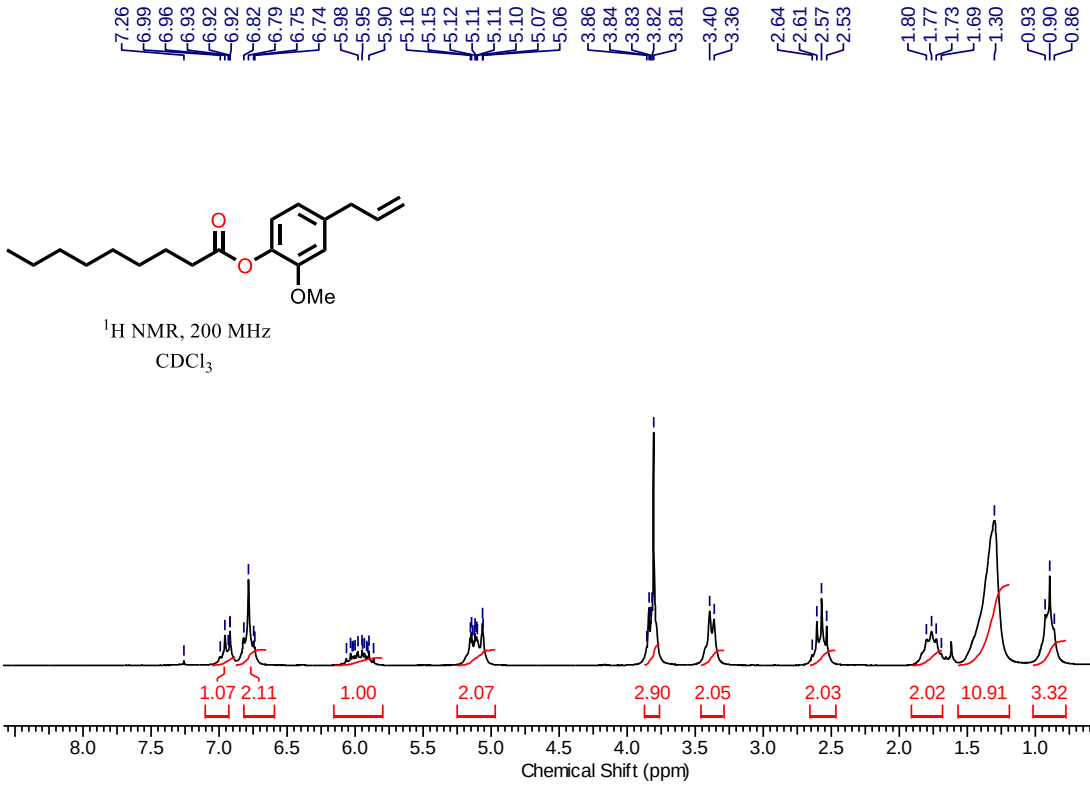
4-Allyl-2-methoxyphenyl 4-nitrobenzoate **(23):**



4-allyl-2-methoxyphenyl 4-nitrobenzoate **(23):**

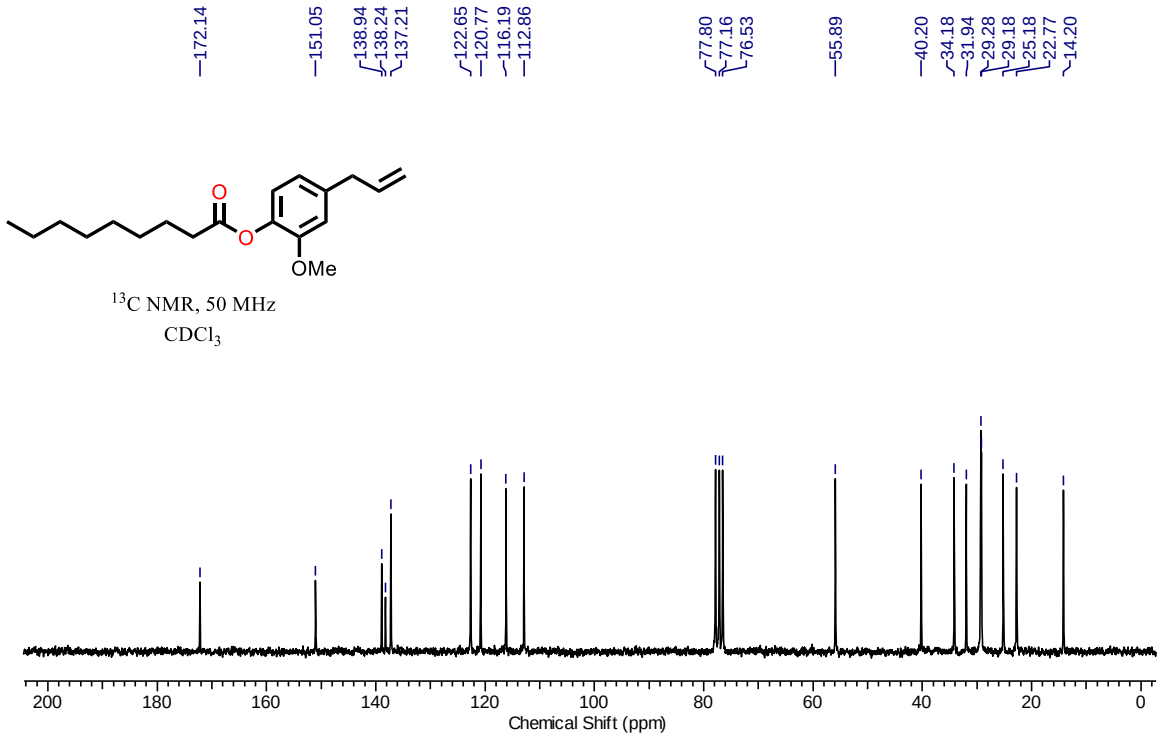


4-Allyl-2-methoxyphenyl nonanoate **(24):**



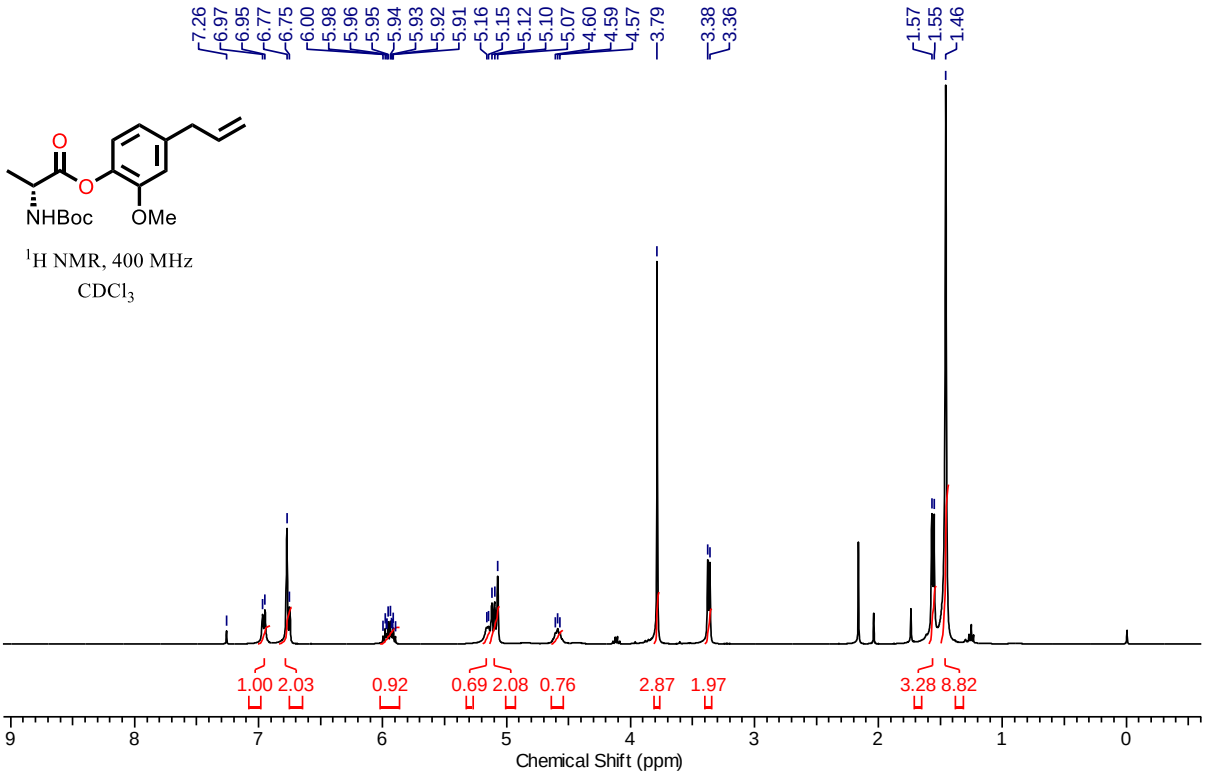
^{1}H NMR, 200 MHz
$CDCl_3$

4-Allyl-2-methoxyphenyl nonanoate **(24):**

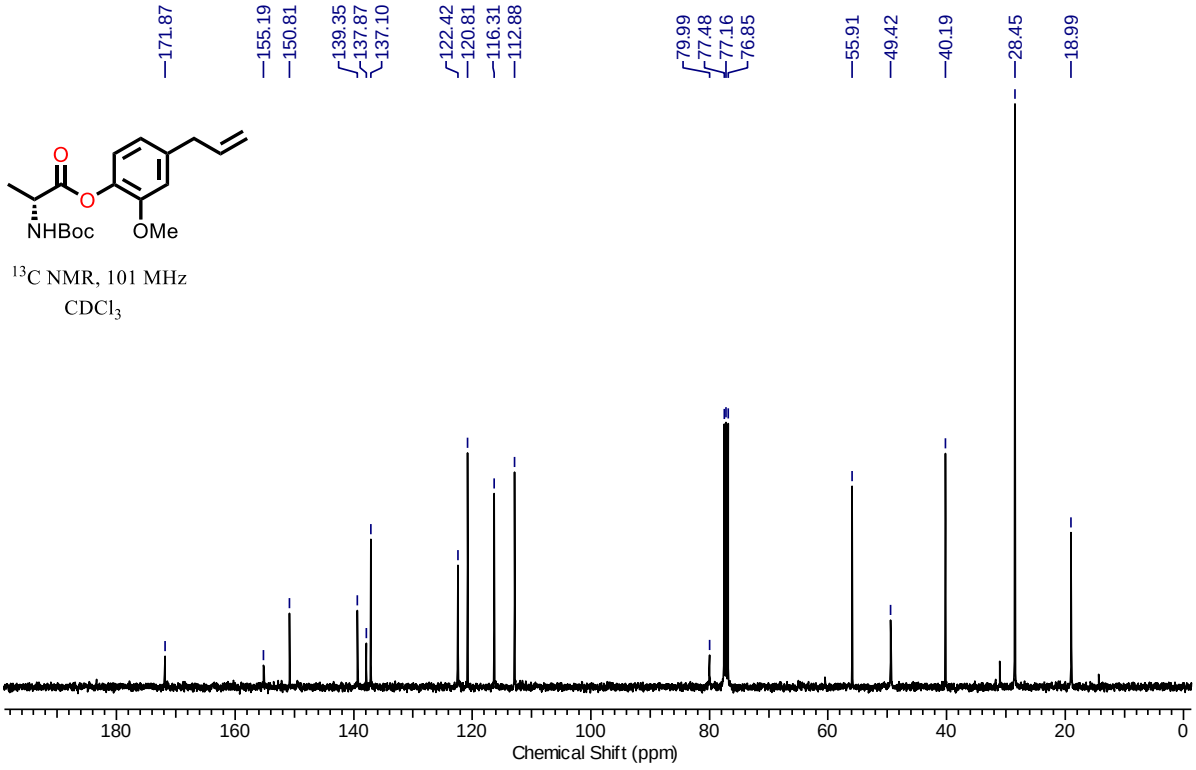


^{13}C NMR, 50 MHz
$CDCl_3$

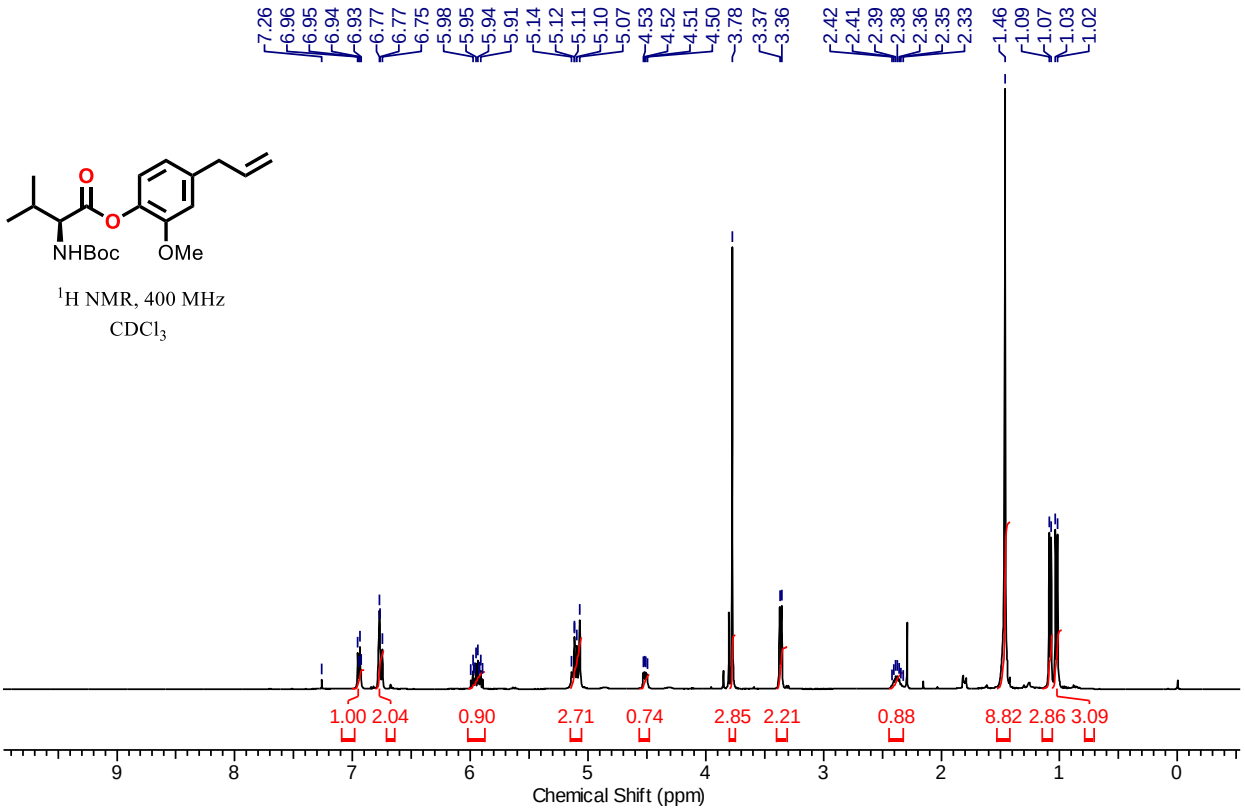
4-Allyl-2-methoxyphenyl (*tert*-butoxycarbonyl)-D-alaninate **(25):**



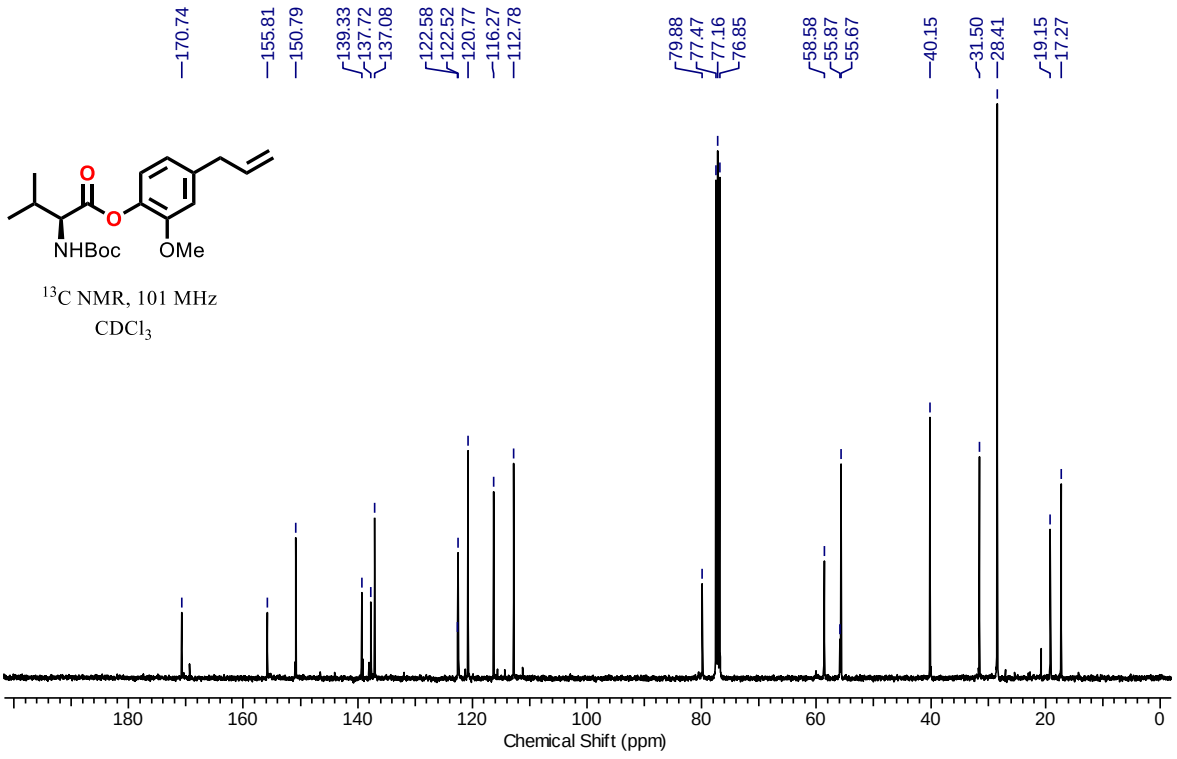
4-Allyl-2-methoxyphenyl (*tert*-butoxycarbonyl)-D-alaninate **(25):**



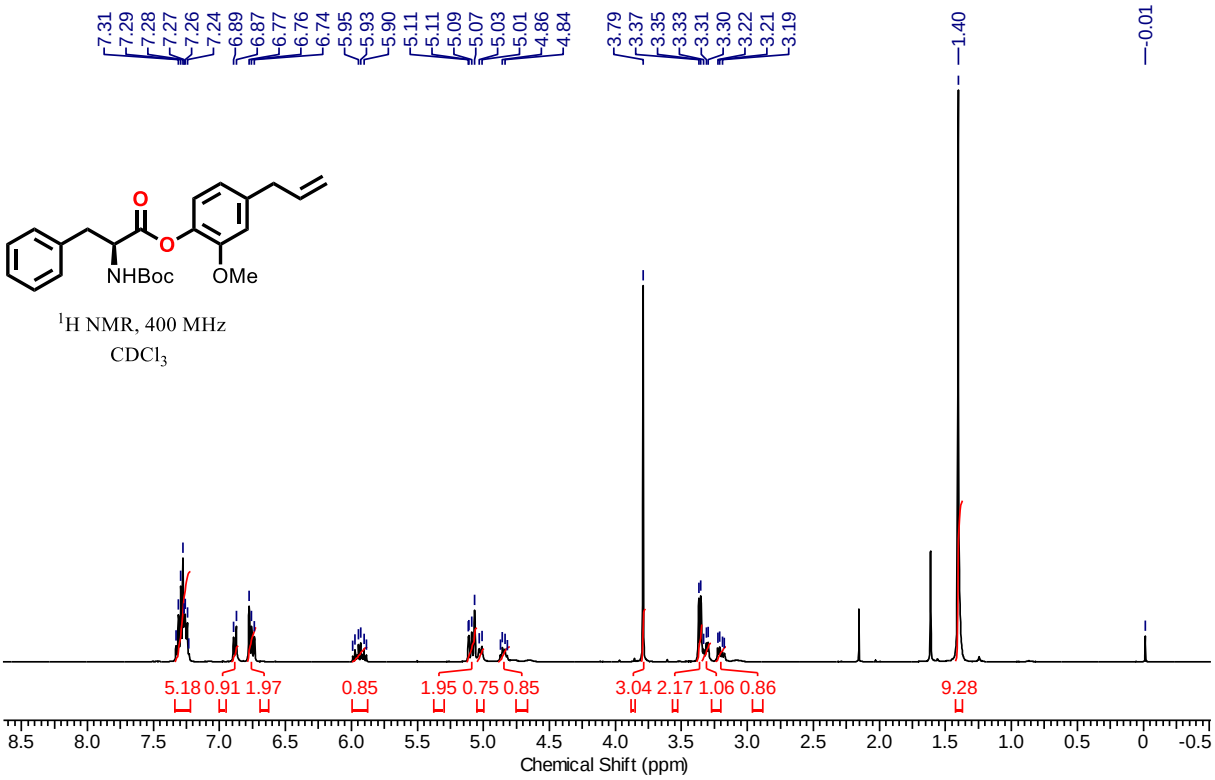
4-Allyl-2-methoxyphenyl (*tert*-butoxycarbonyl)-L-valinate **(26):**



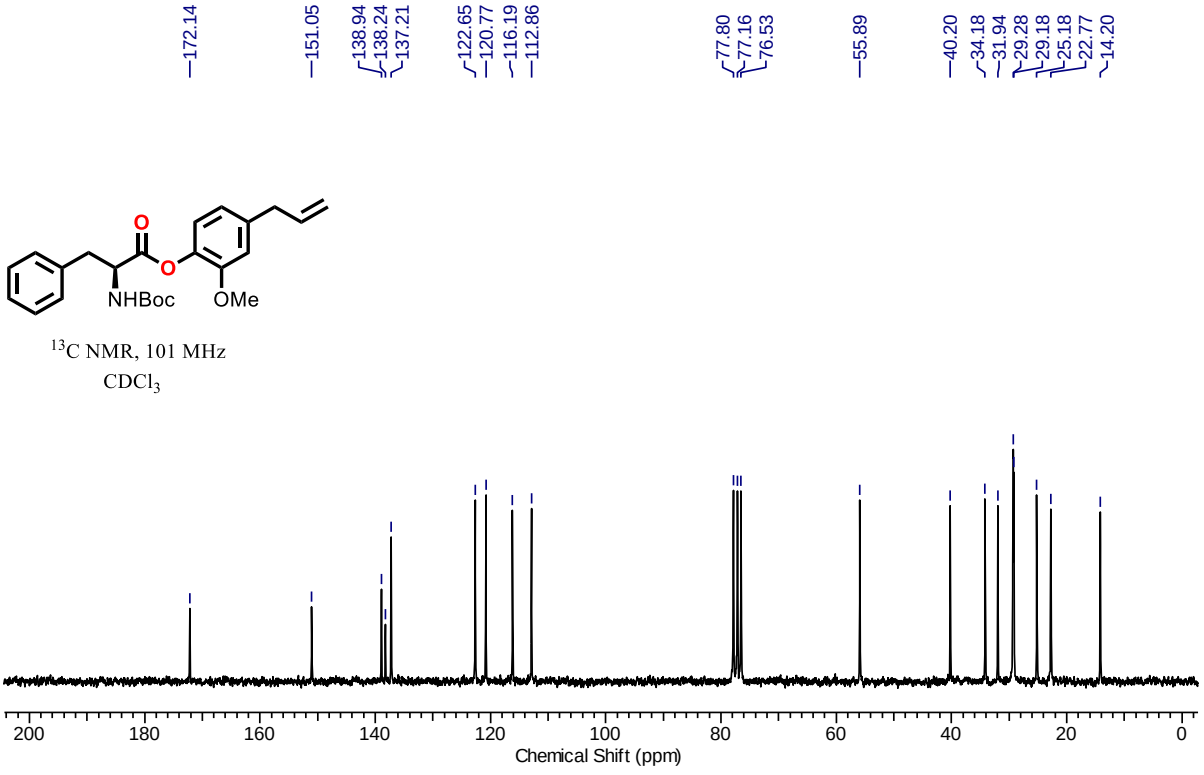
4-Allyl-2-methoxyphenyl (*tert*-butoxycarbonyl)-L-valinate **(26):**



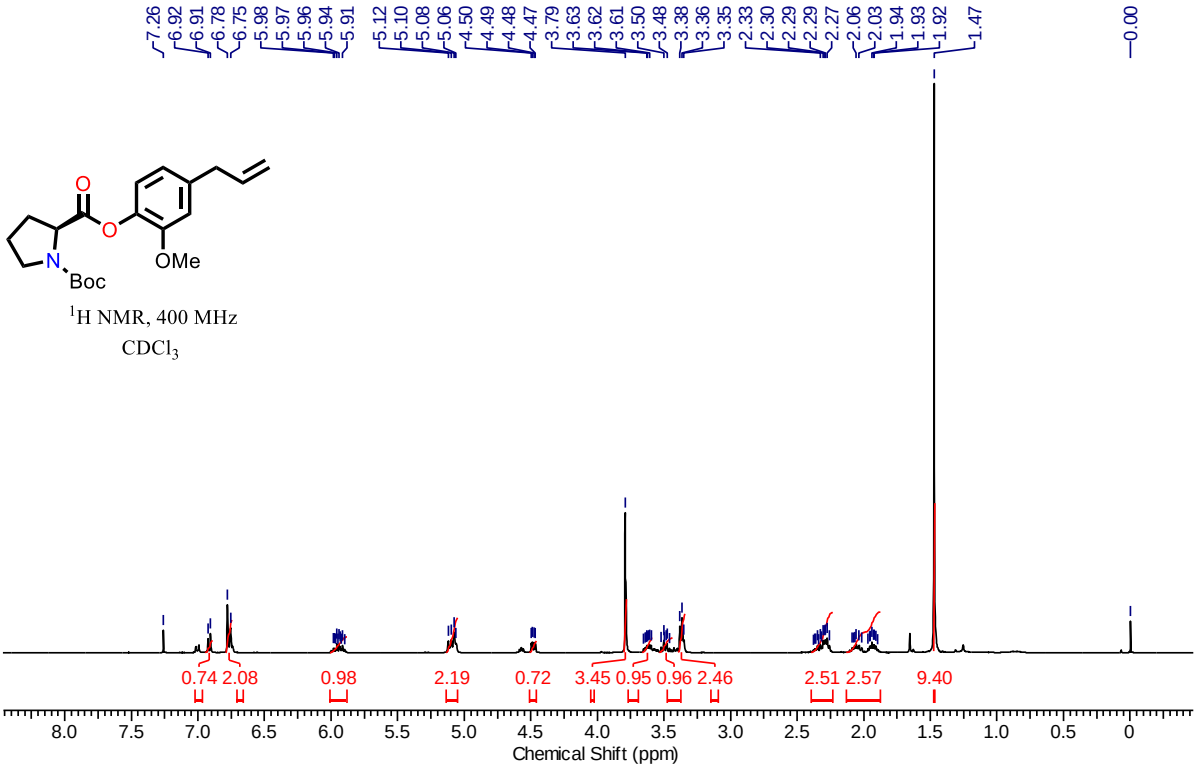
4-Allyl-2-methoxyphenyl (*tert*-butoxycarbonyl)-L-phenylalaninate **(27):**



4-Allyl-2-methoxyphenyl (*tert*-butoxycarbonyl)-L-phenylalaninate **(27):**

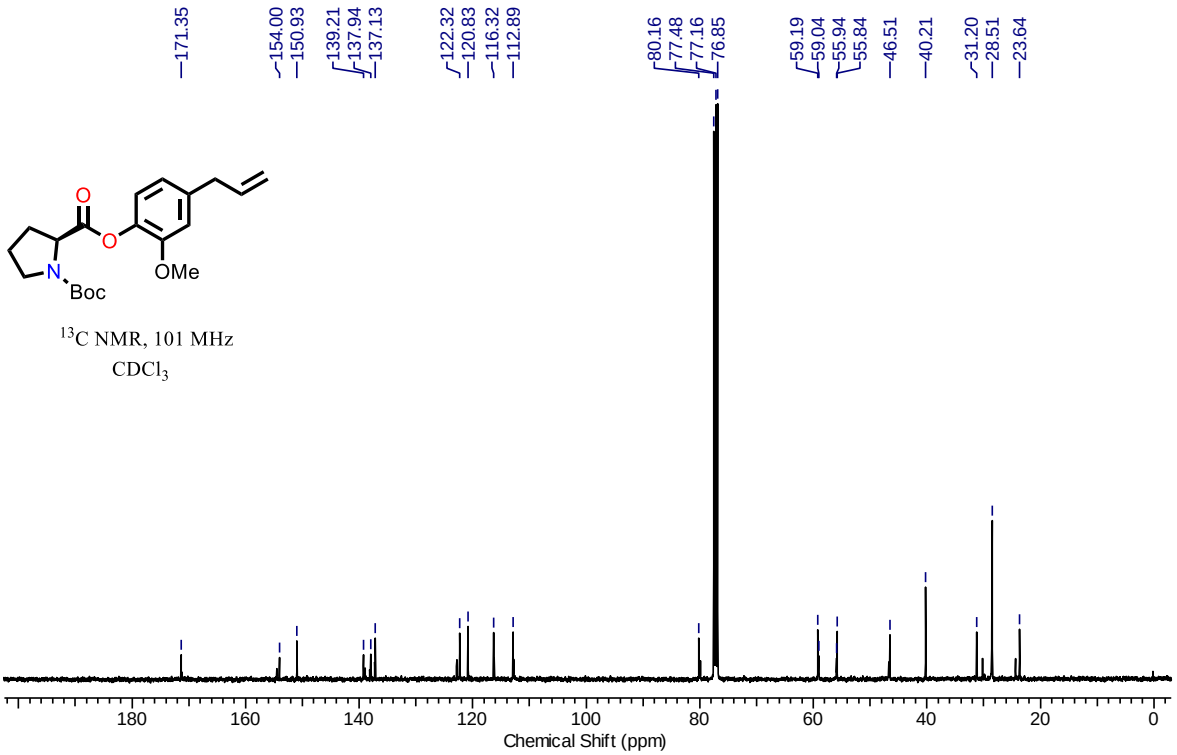


2-(4-Allyl-2-methoxyphenyl) 1-(*tert*-butyl) (*S*)-pyrrolidine-1,2-dicarboxylate **(28):**



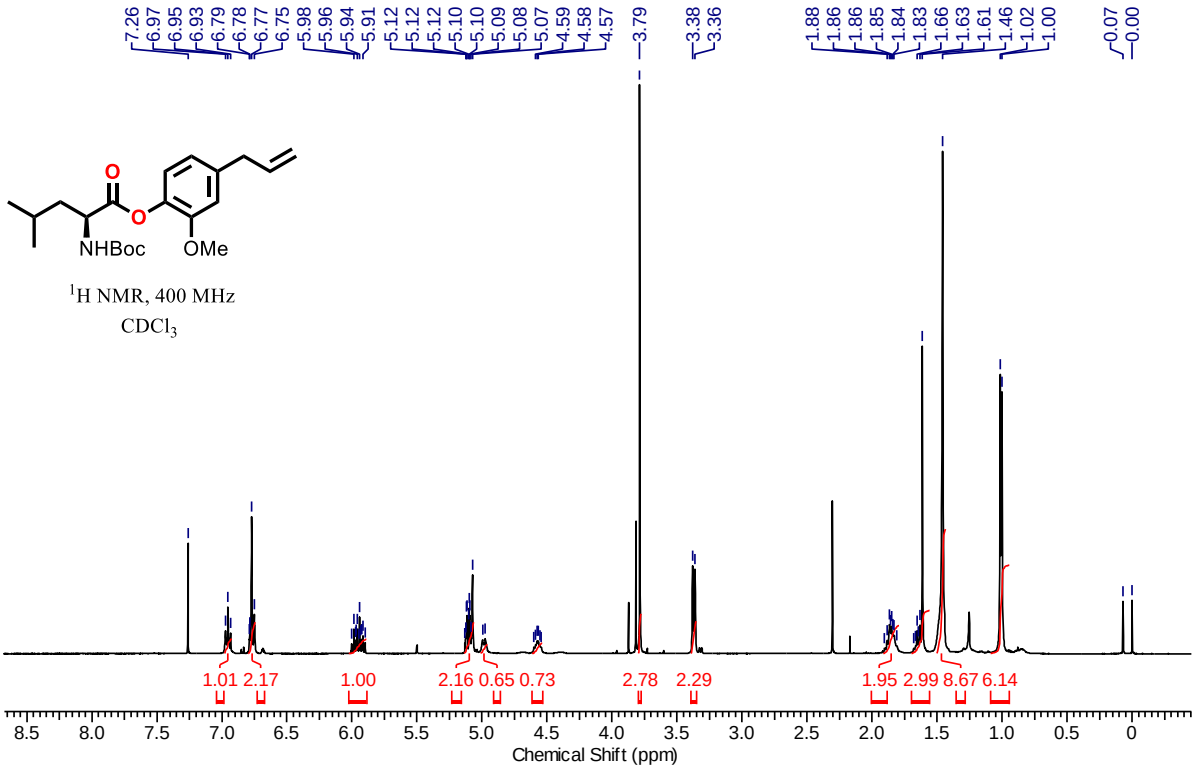
^{1}H NMR, 400 MHz
$CDCl_3$

2-(4-Allyl-2-methoxyphenyl) 1-(*tert*-butyl) (*S*)-pyrrolidine-1,2-dicarboxylate **(28):**

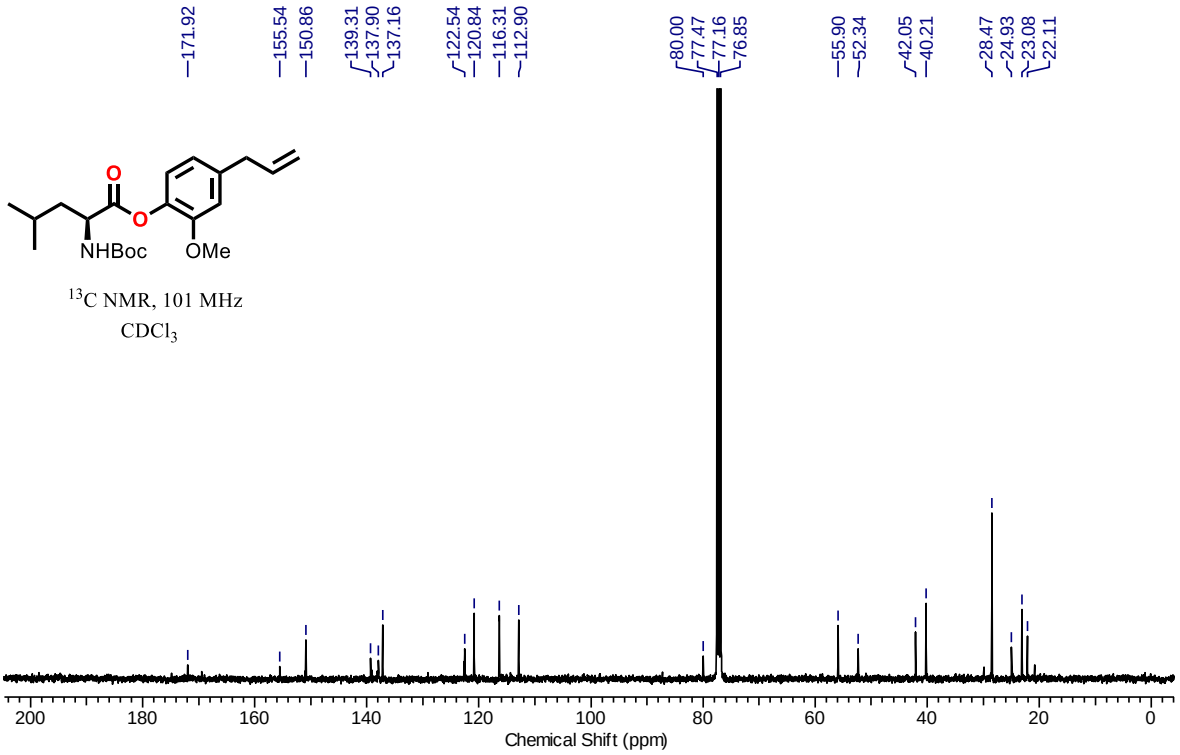


^{13}C NMR, 101 MHz
$CDCl_3$

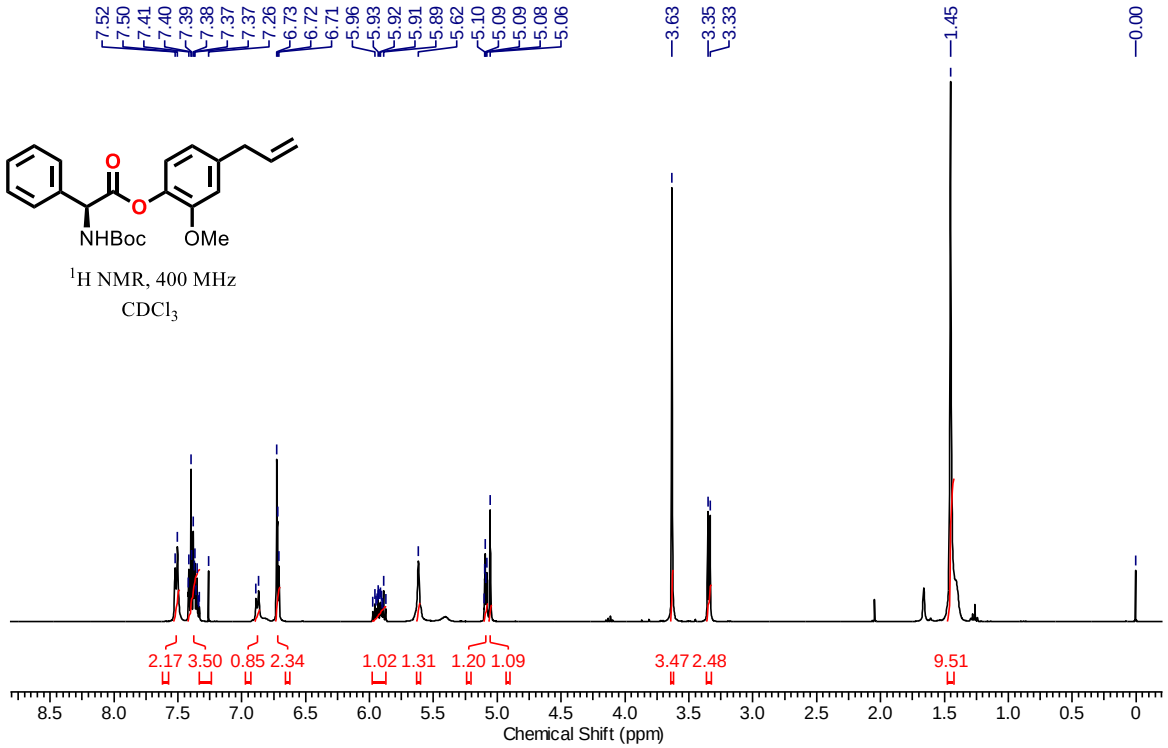
4-Allyl-2-methoxyphenyl (*tert*-butoxycarbonyl)-L-leucinate **(29):**



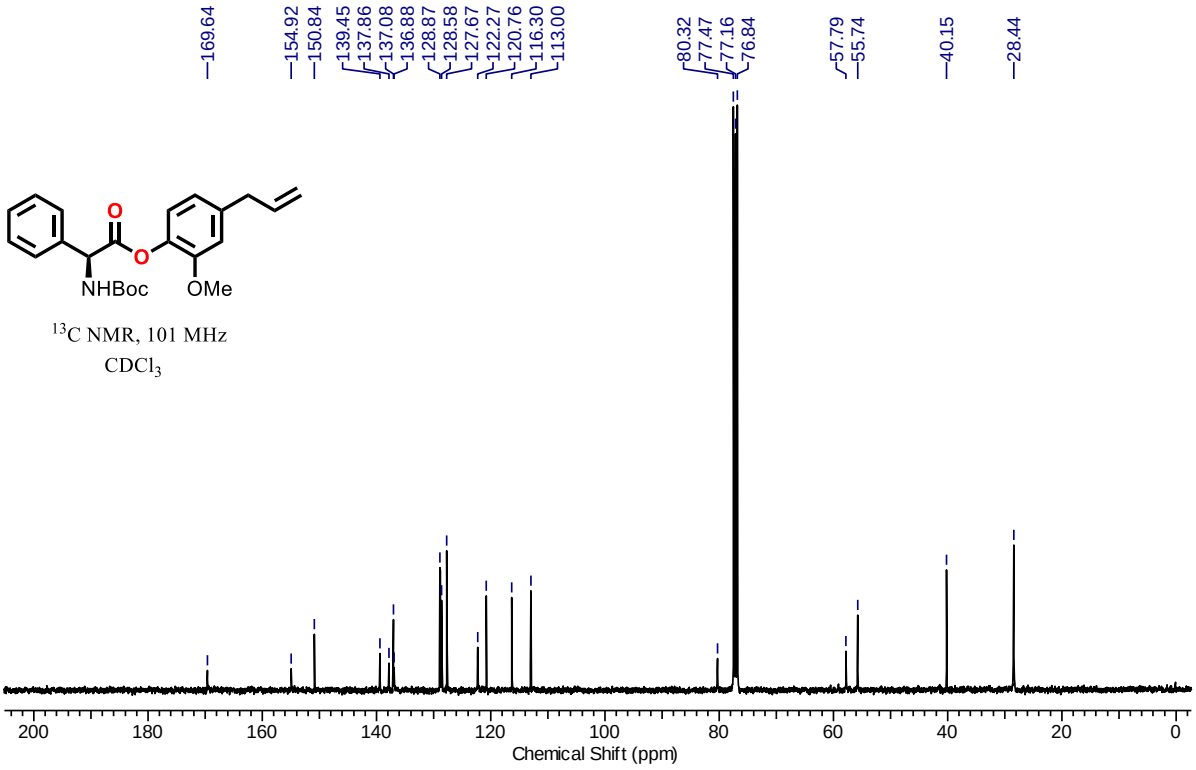
4-Allyl-2-methoxyphenyl (*tert*-butoxycarbonyl)-L-leucinate **(29):**



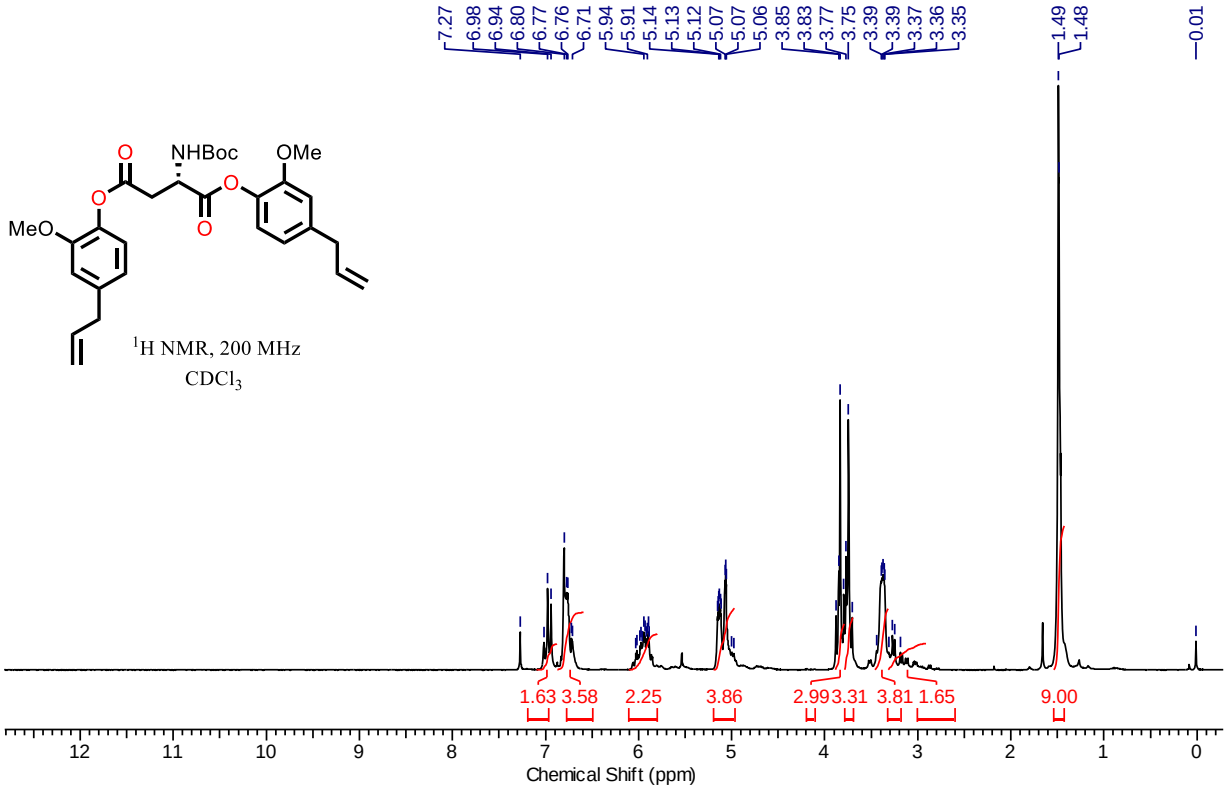
4-Allyl-2-methoxyphenyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-2-phenylacetate **(30):**



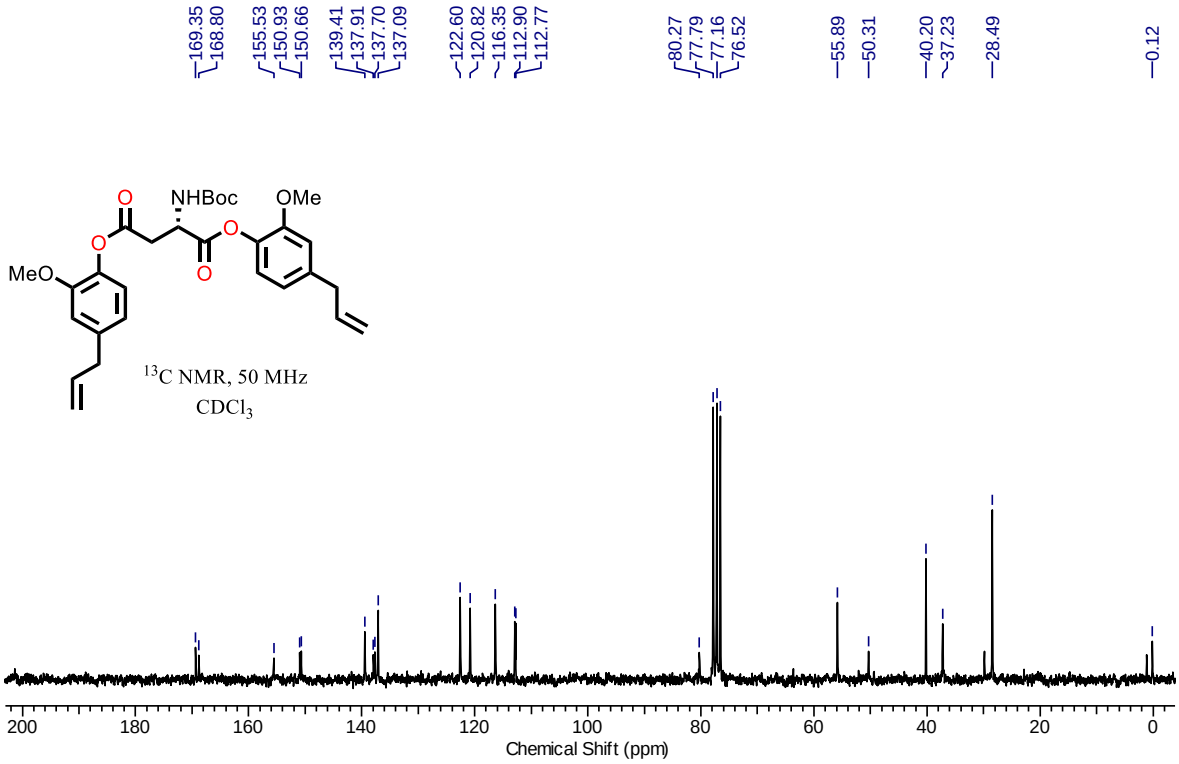
4-Allyl-2-methoxyphenyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-2-phenylacetate (30):



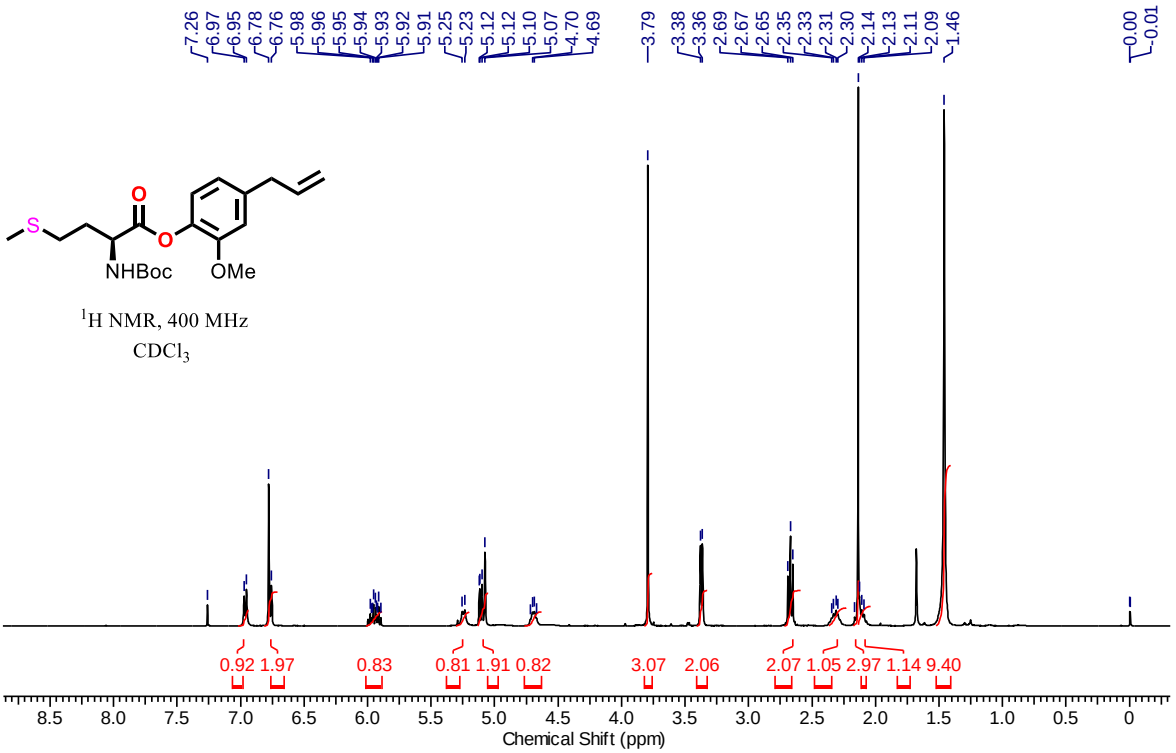
Bis(4-allyl-2-methoxyphenyl) (*tert*-butoxycarbonyl)-L-aspartate **(31):**



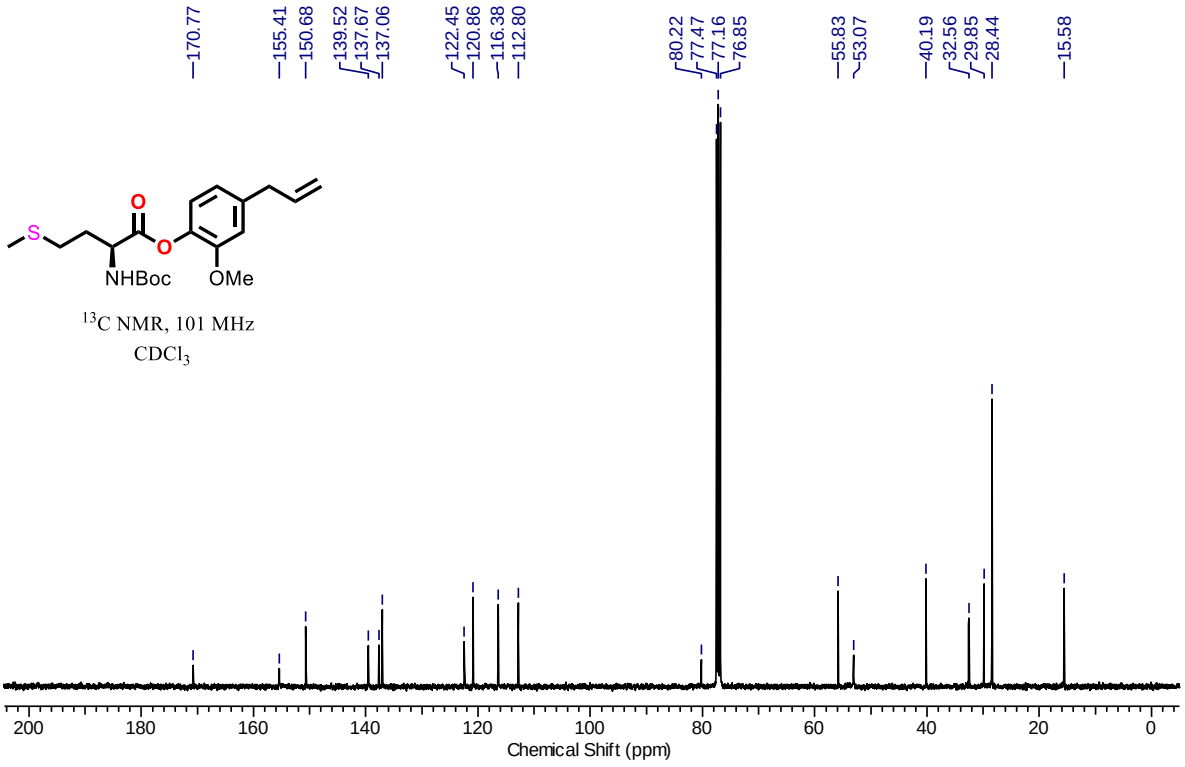
Bis(4-allyl-2-methoxyphenyl) (*tert*-butoxycarbonyl)-L-aspartate **(31):**



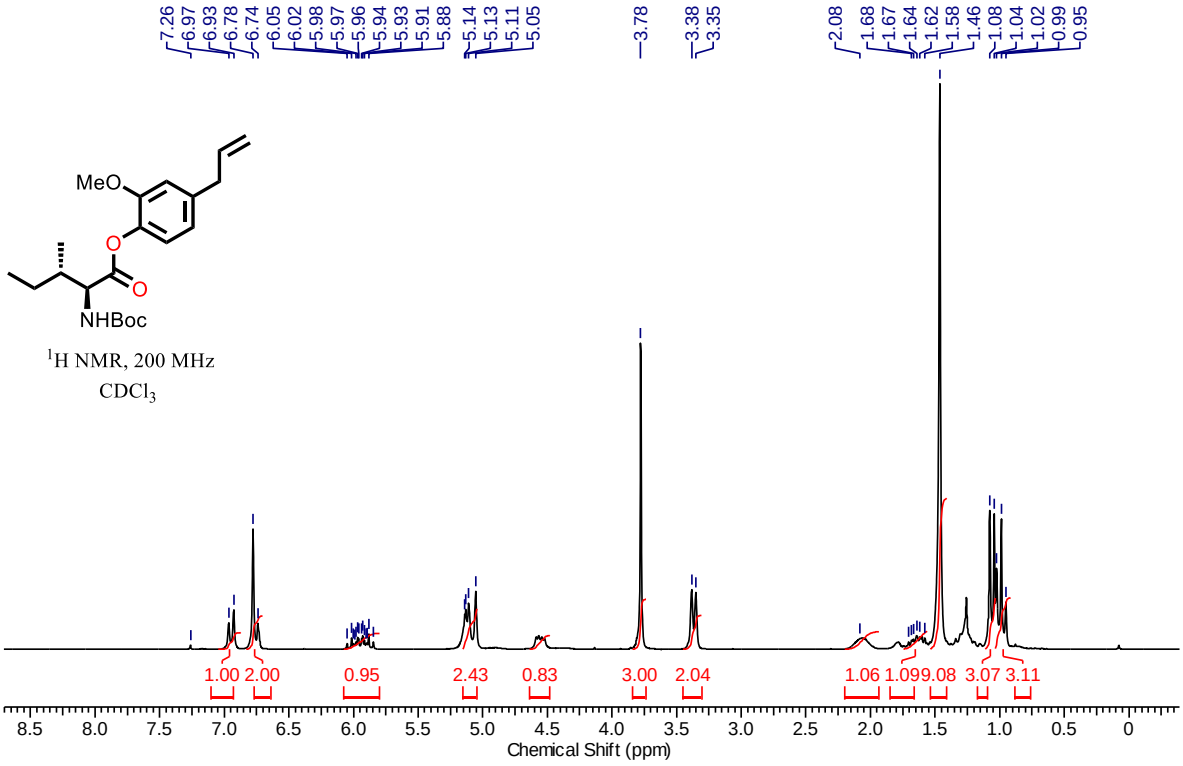
4-Allyl-2-methoxyphenyl (*tert*-butoxycarbonyl)-L-methioninate **(33)**:



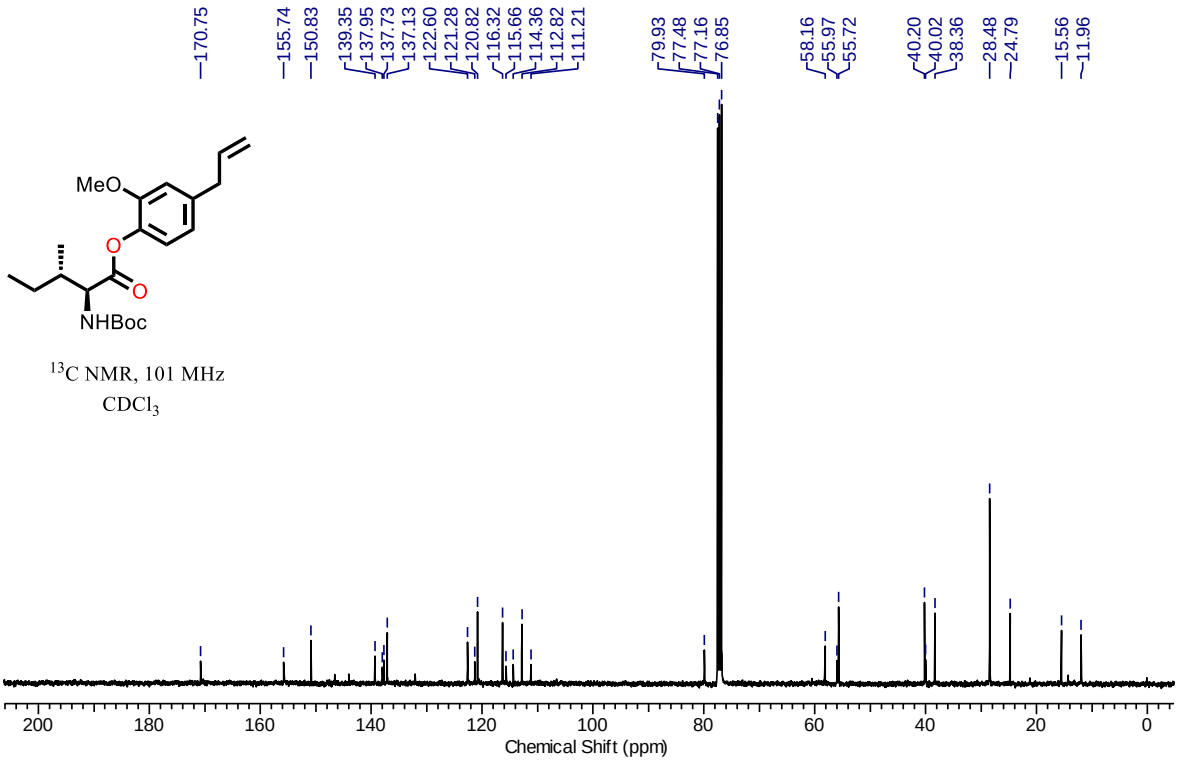
4-Allyl-2-methoxyphenyl (*tert*-butoxycarbonyl)-L-methioninate **(33):**



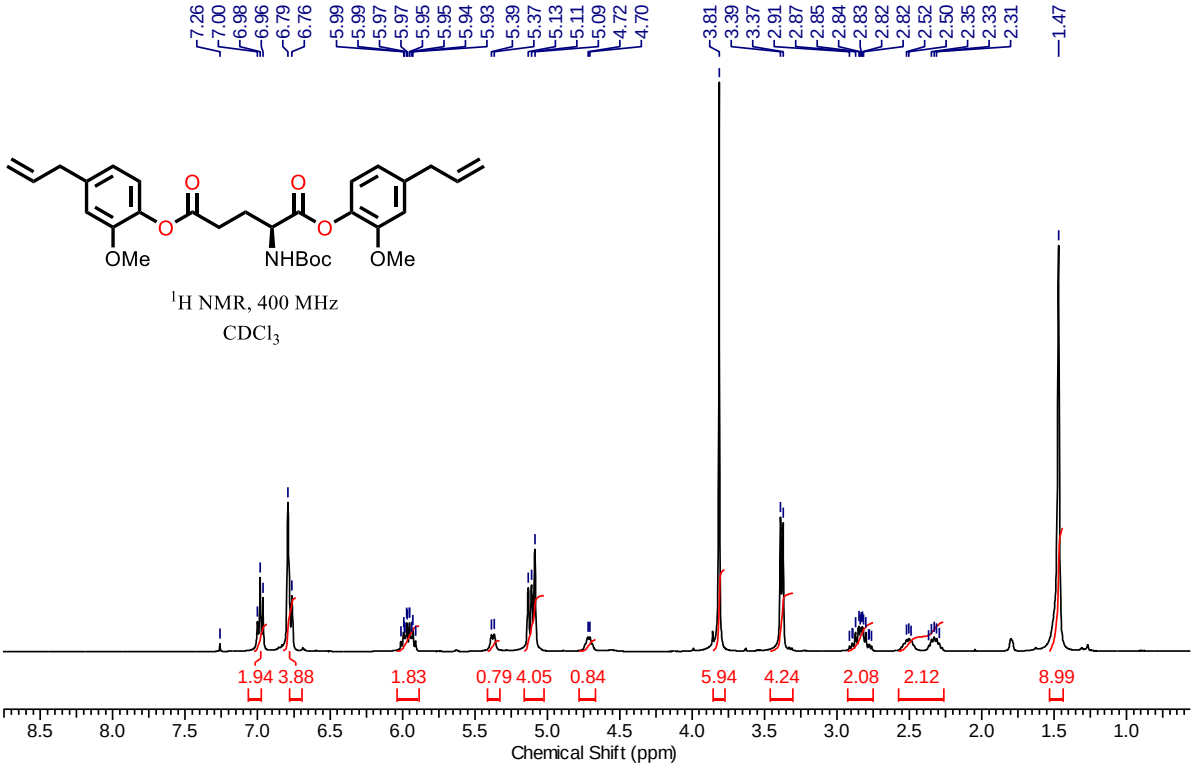
4-Allyl-2-methoxyphenyl (*tert*-butoxycarbonyl)-L-isoleucinate **(34):**



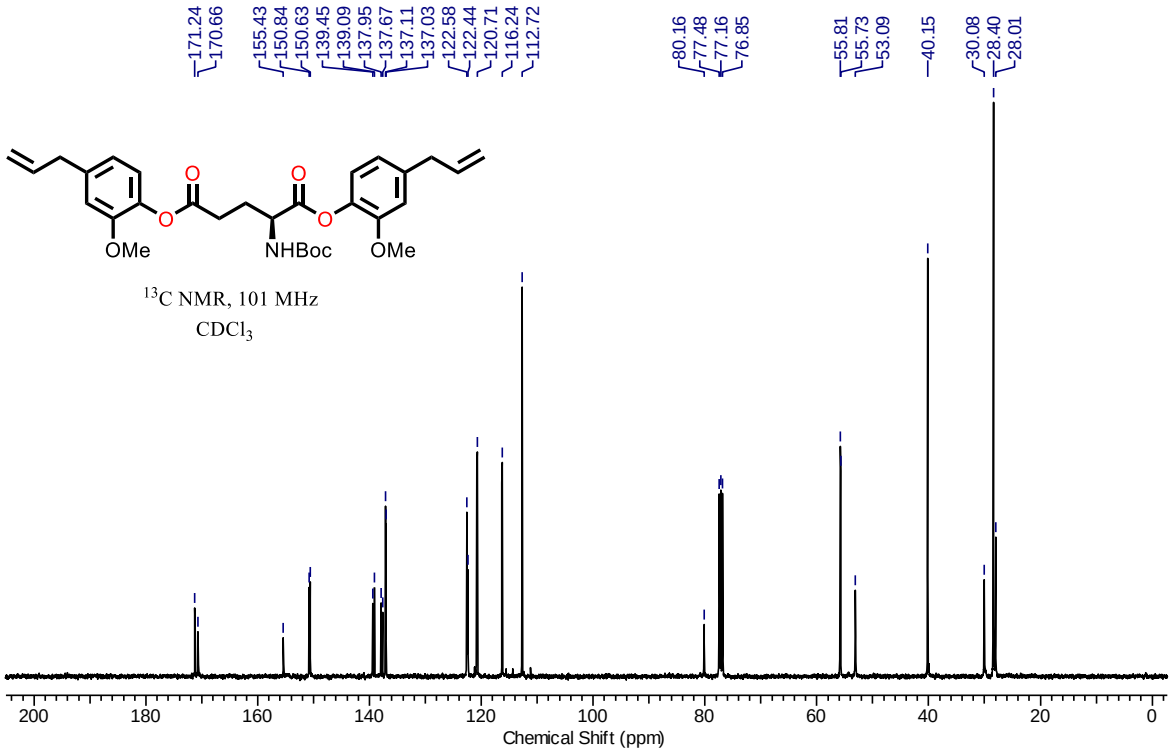
4-Allyl-2-methoxyphenyl (*tert*-butoxycarbonyl)-L-isoleucinate **(34):**



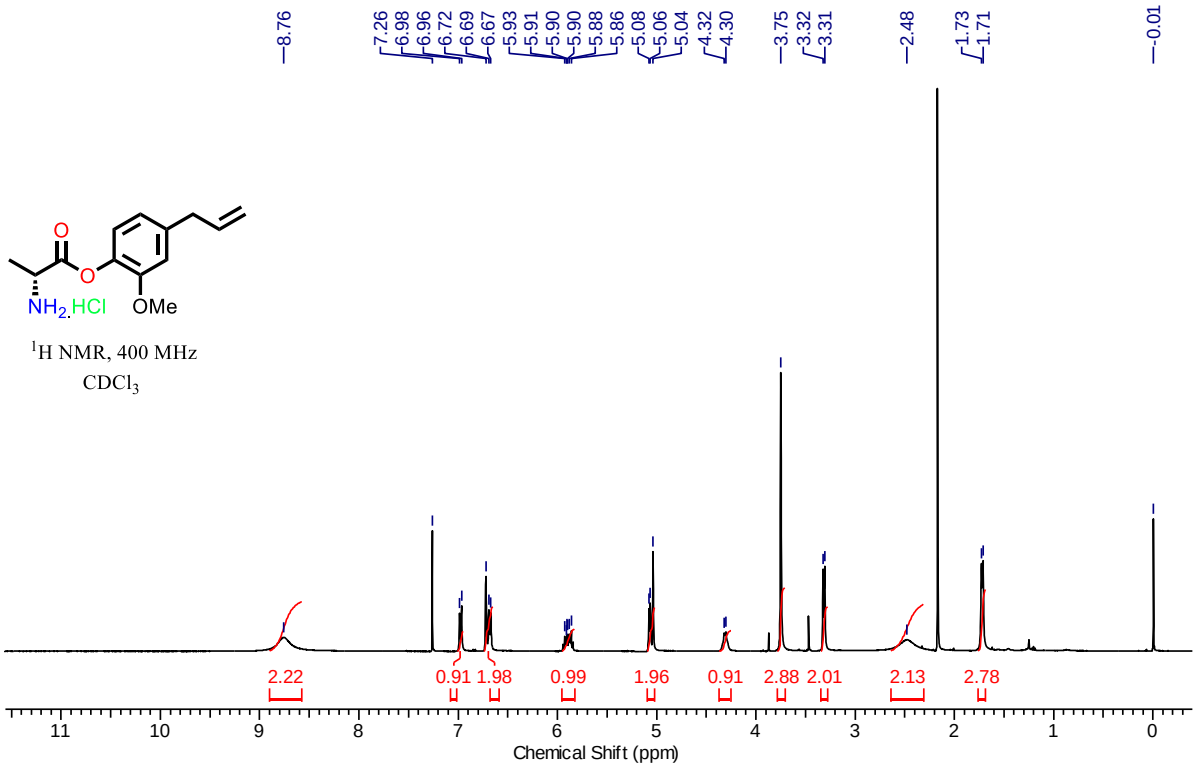
Bis(4-allyl-2-methoxyphenyl) (*tert*-butoxycarbonyl)-L-glutamate **(35):**



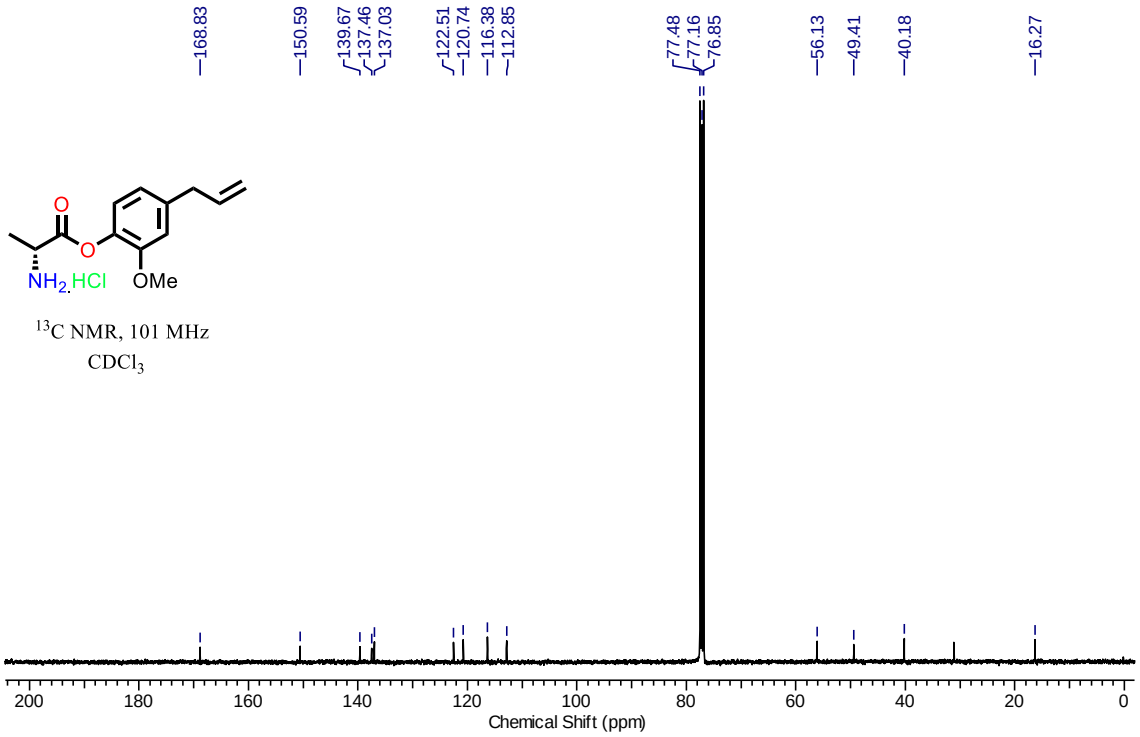
Bis(4-allyl-2-methoxyphenyl) (*tert*-butoxycarbonyl)-L-glutamate **(35):**



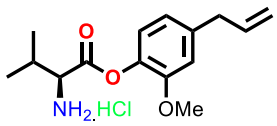
4-Allyl-2-methoxyphenyl D-alaninate hydrochloride **(36):**



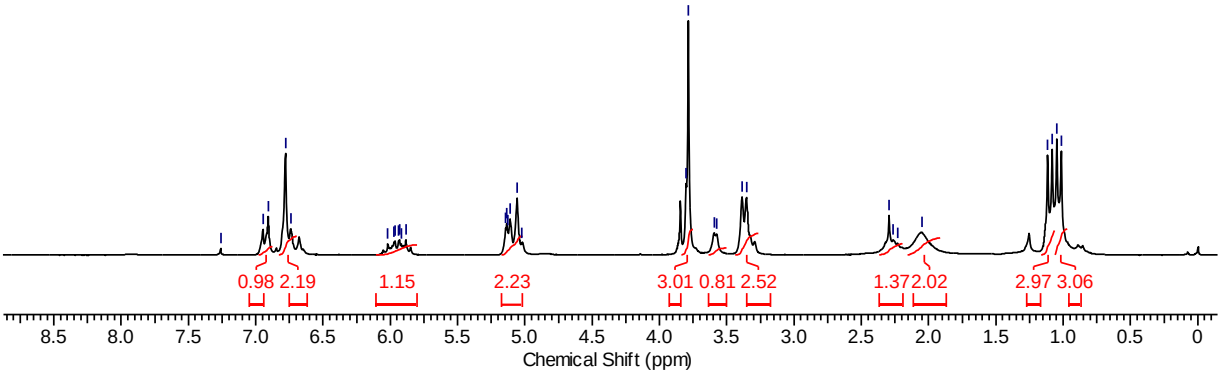
4-Allyl-2-methoxyphenyl D-alaninate hydrochloride **(36):**



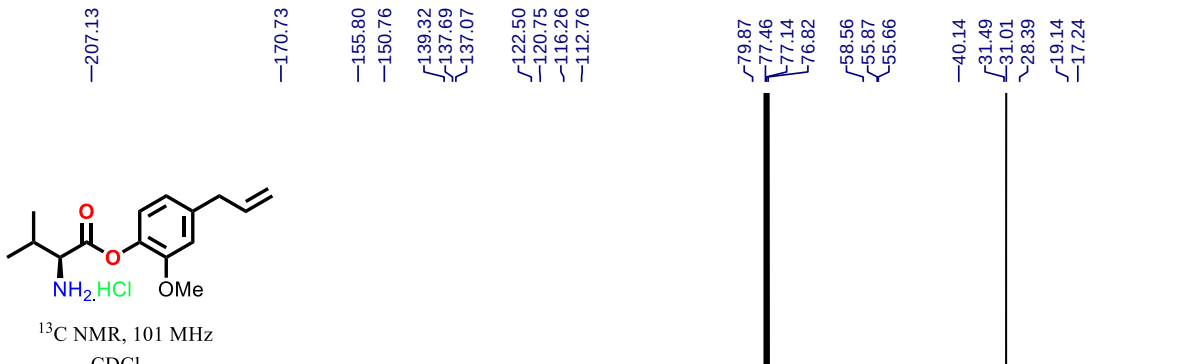
4-Allyl-2-methoxyphenyl L-valinate hydrochloride **(37):**



^{1}H NMR, 200 MHz
$CDCl_3$

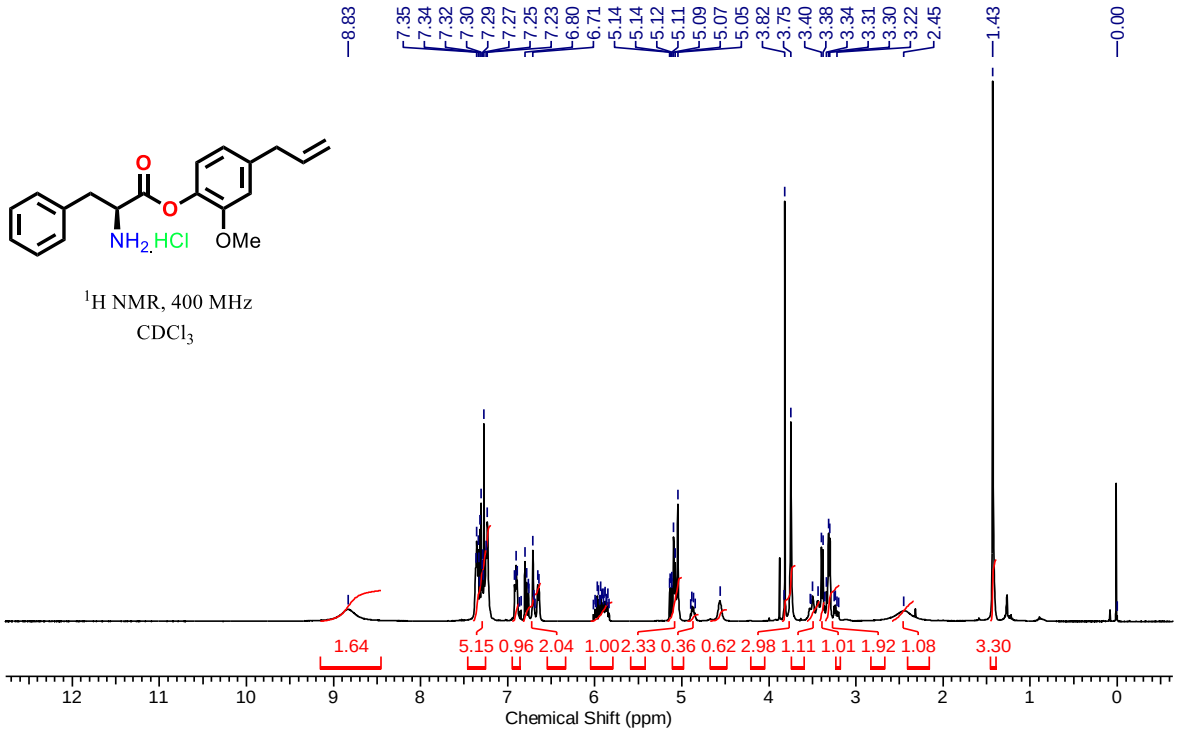


4-Allyl-2-methoxyphenyl L-valinate hydrochloride **(37):**

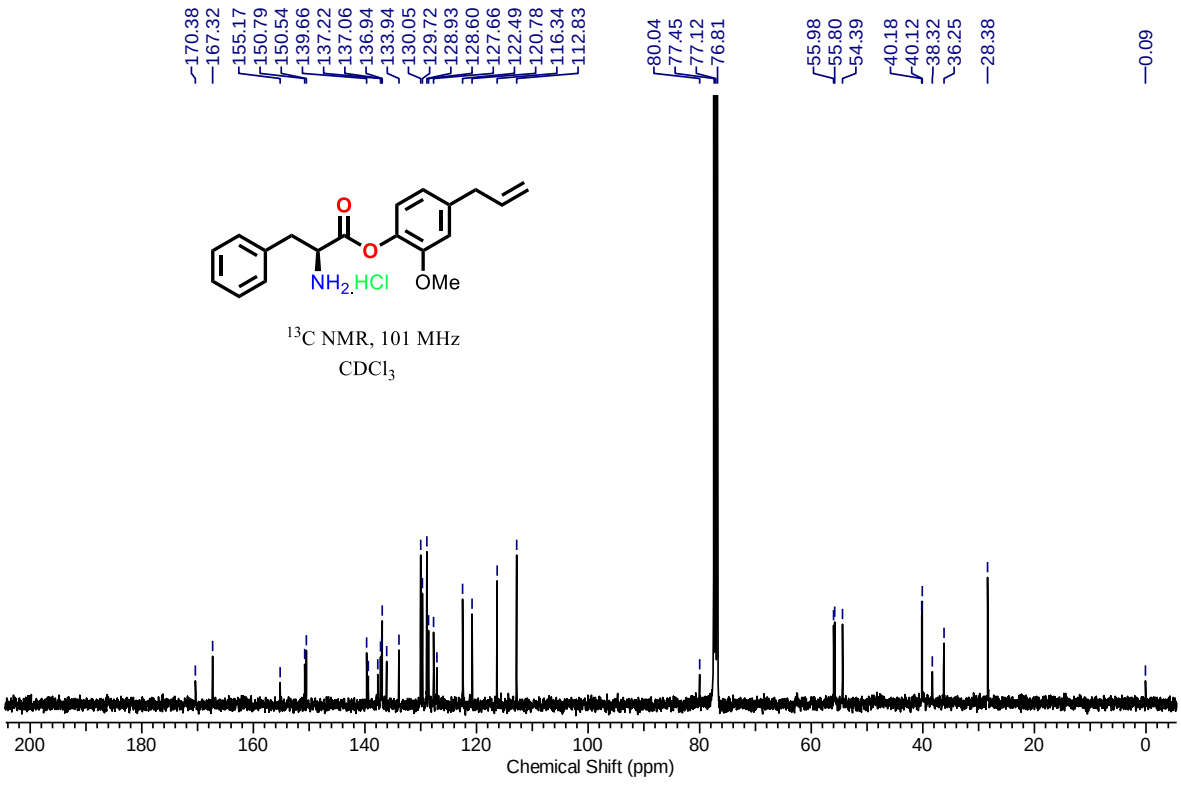


^{13}C NMR, 101 MHz
$CDCl_3$

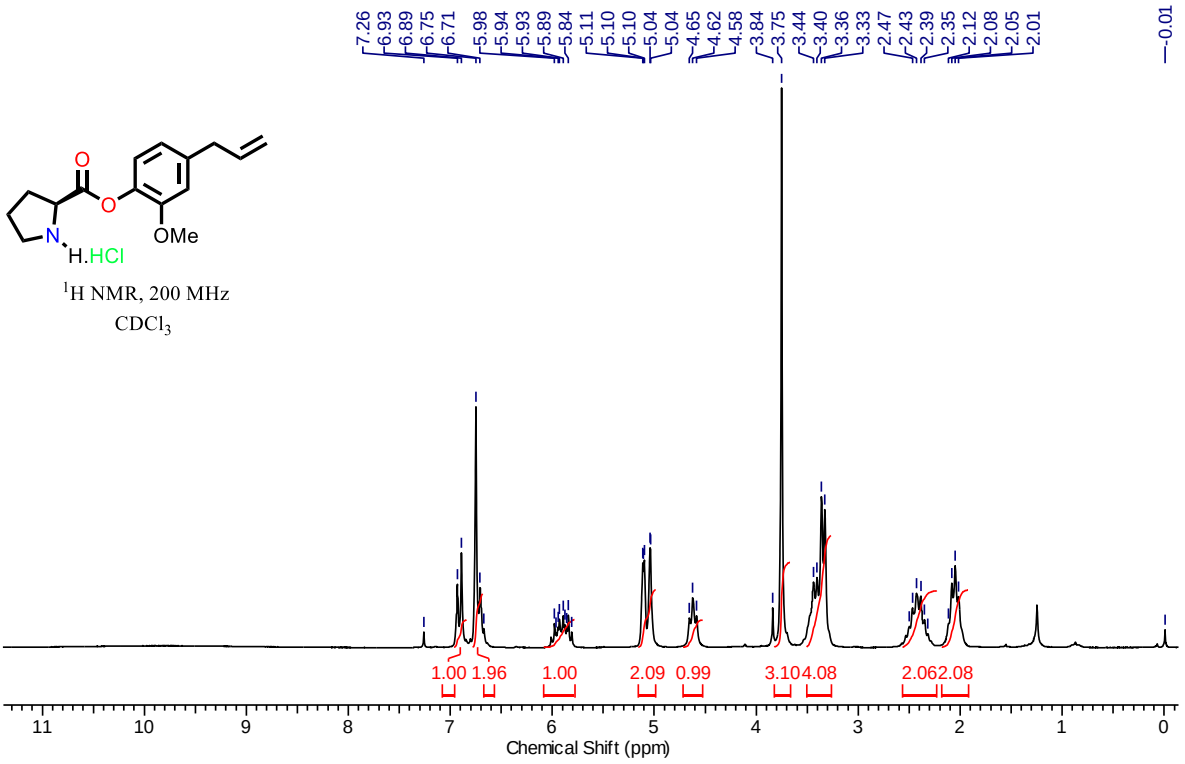
4-Allyl-2-methoxyphenyl L-phenylalaninate hydrochloride **(38):**



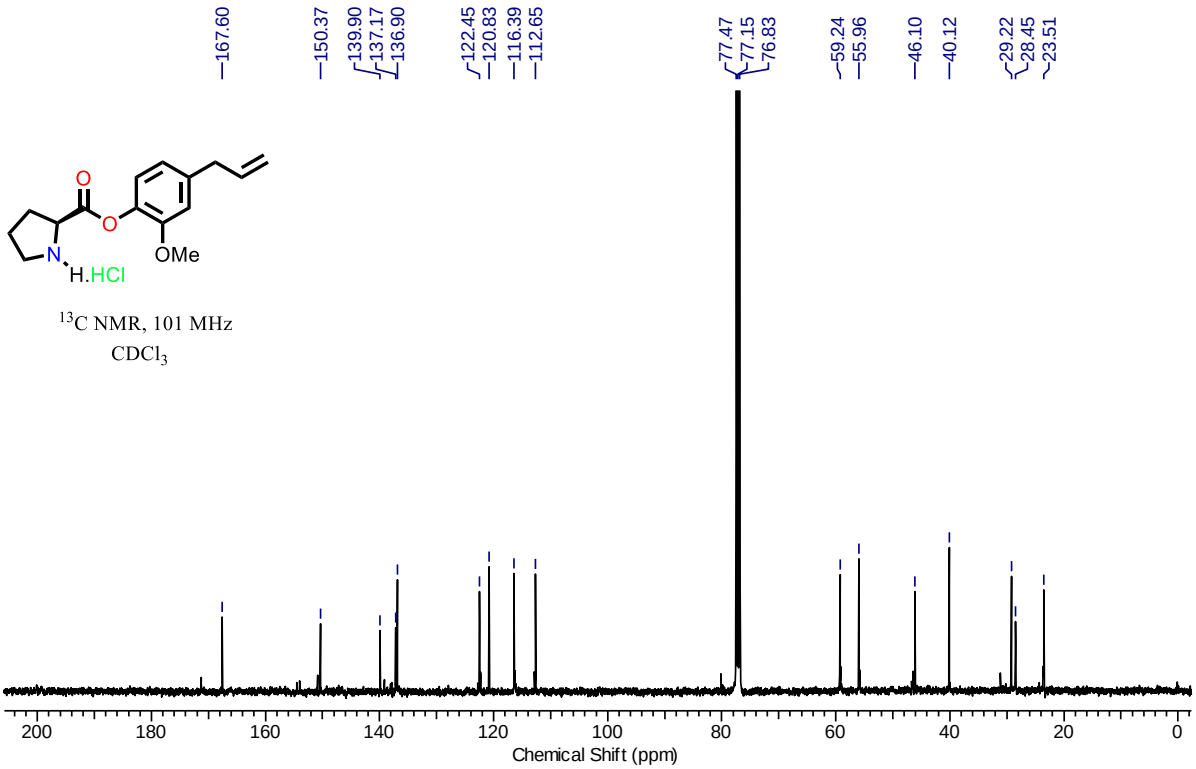
4-Allyl-2-methoxyphenyl L-phenylalaninate hydrochloride **(38):**



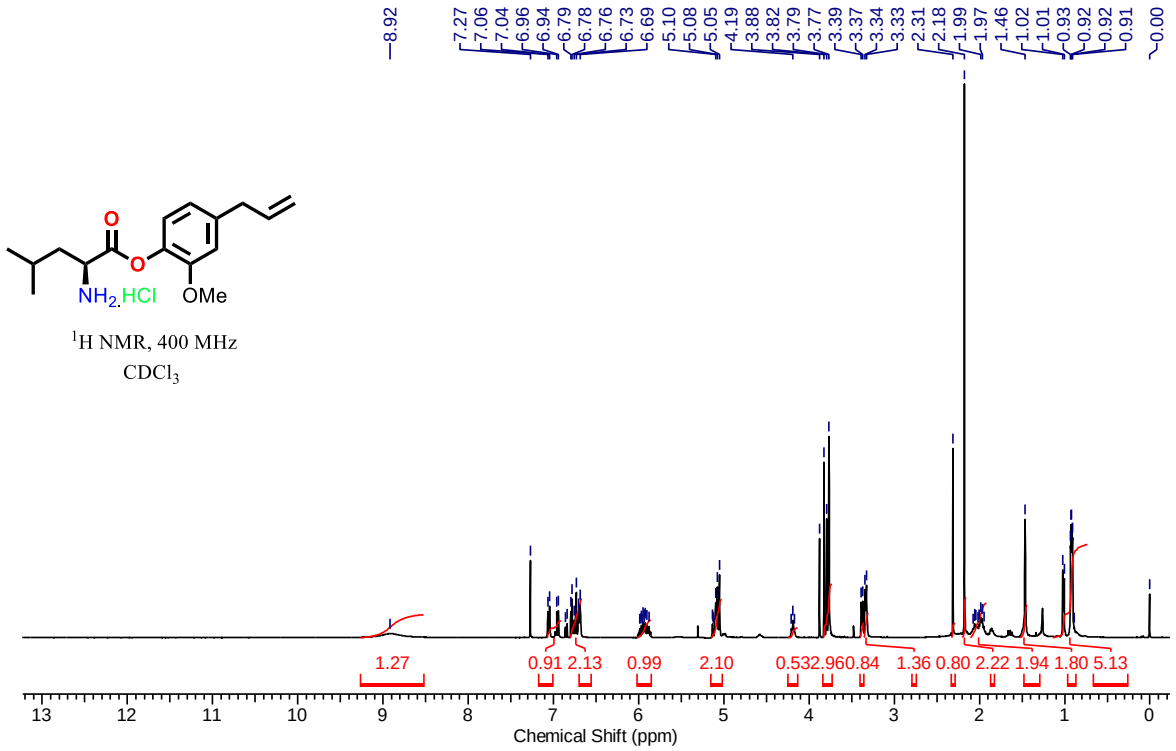
4-Allyl-2-methoxyphenyl L-prolinate hydrochloride **(39):**



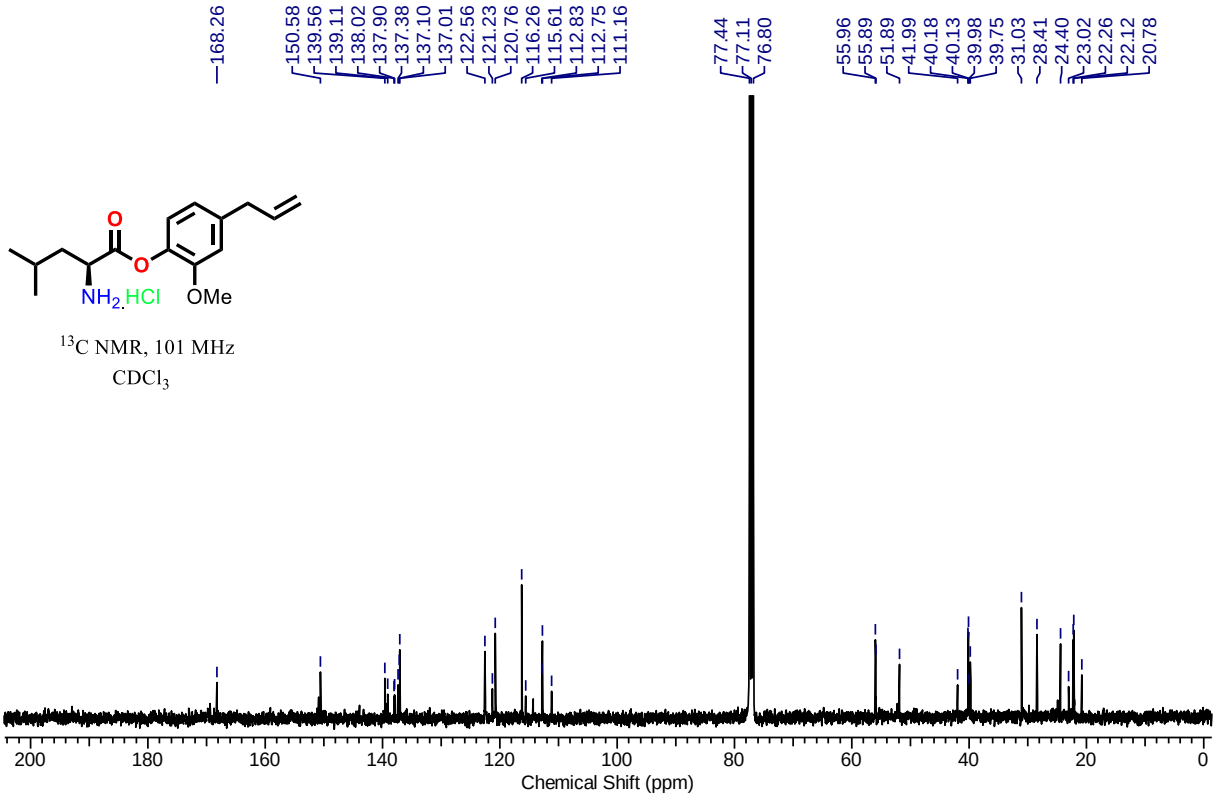
4-Allyl-2-methoxyphenyl L-prolinate hydrochloride **(39):**



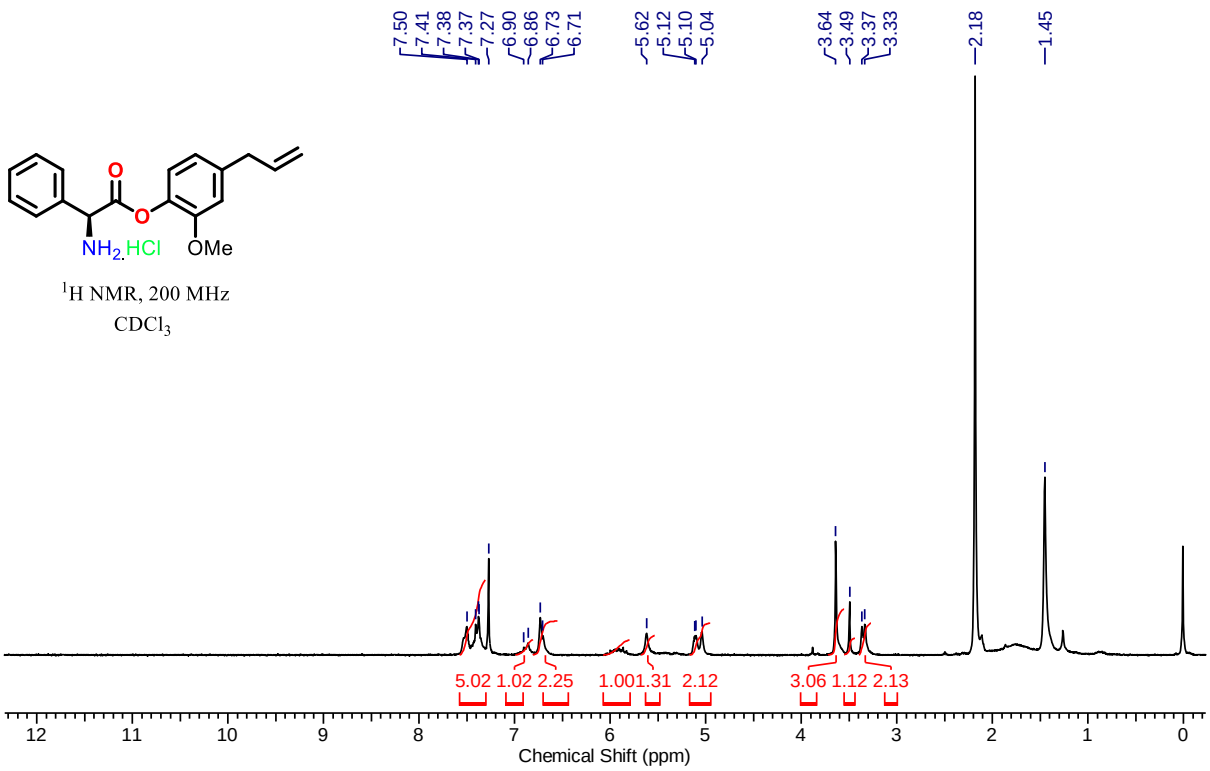
4-Allyl-2-methoxyphenyl L-leucinate hydrochloride **(40):**



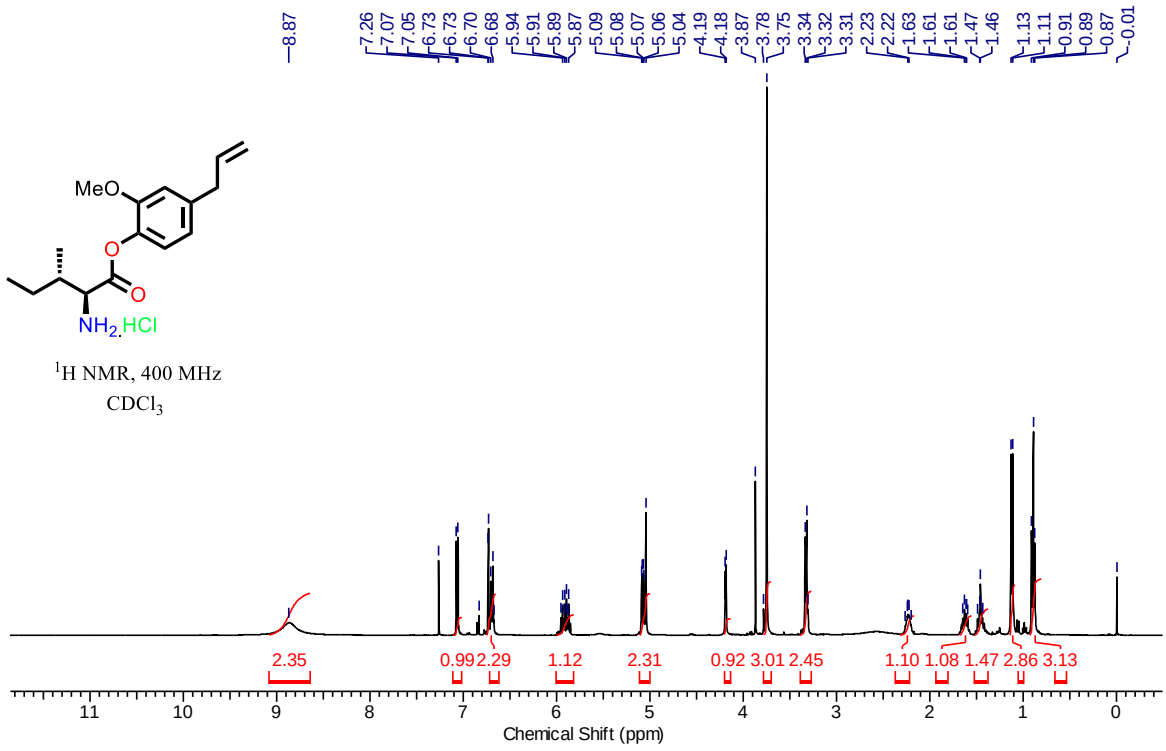
4-Allyl-2-methoxyphenyl L-leucinate hydrochloride **(40):**



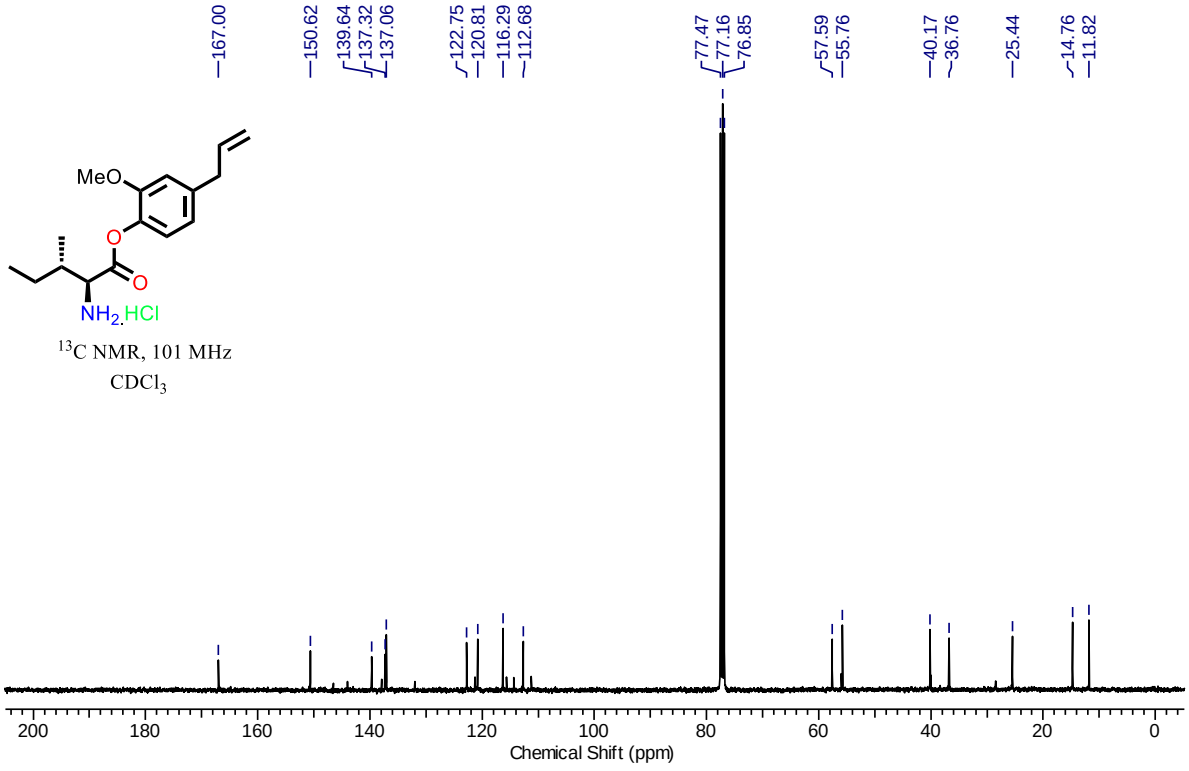
4-Allyl-2-methoxyphenyl (*S*)-2-amino-2-phenylacetate hydrochloride **(41):**



4-Allyl-2-methoxyphenyl L-isoleucinate hydrochloride **(42):**

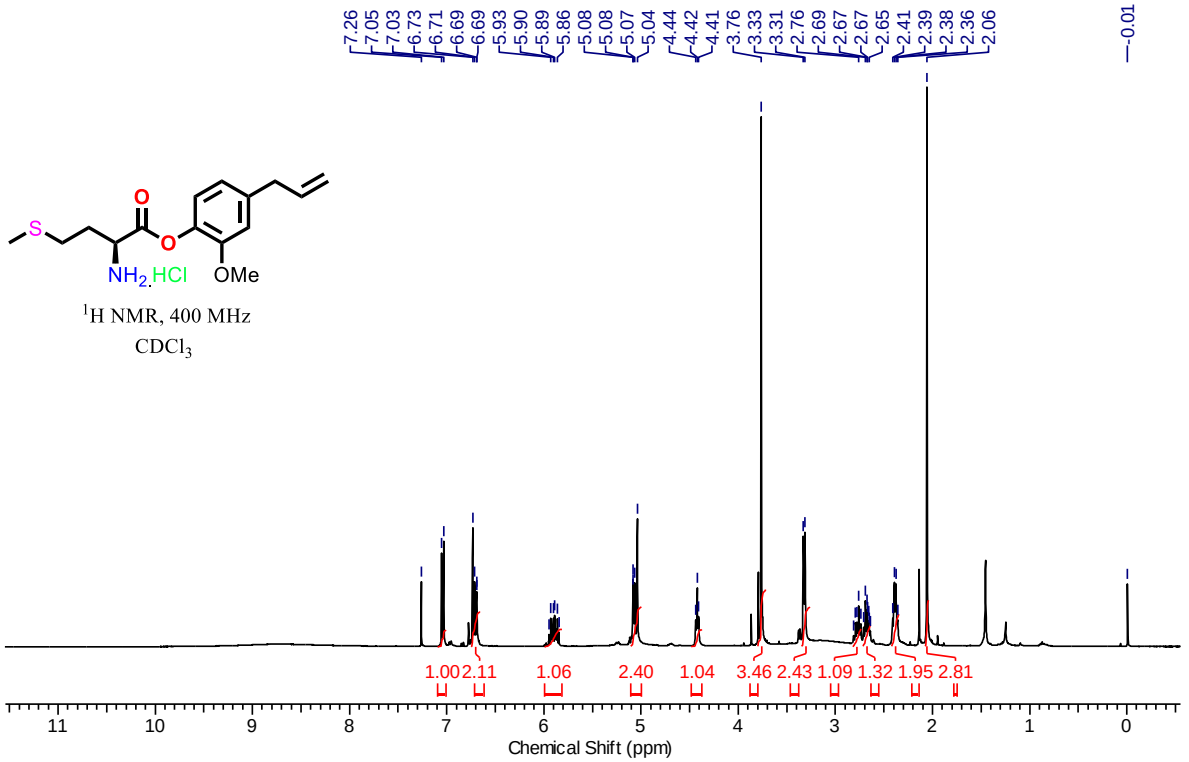


4-Allyl-2-methoxyphenyl L-isoleucinate hydrochloride **(42):**



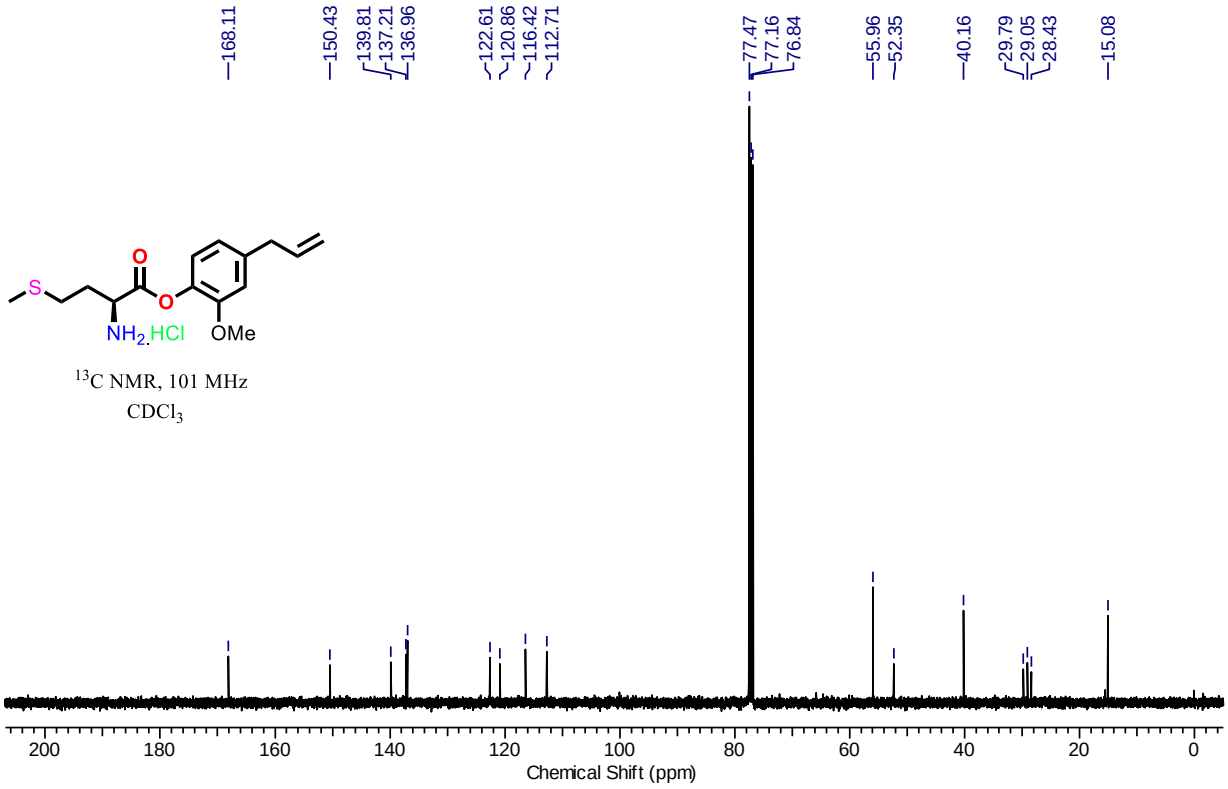
^{13}C NMR, 101 MHz
$CDCl_3$

4-Allyl-2-methoxyphenyl L-methioninate hydrochloride **(43):**

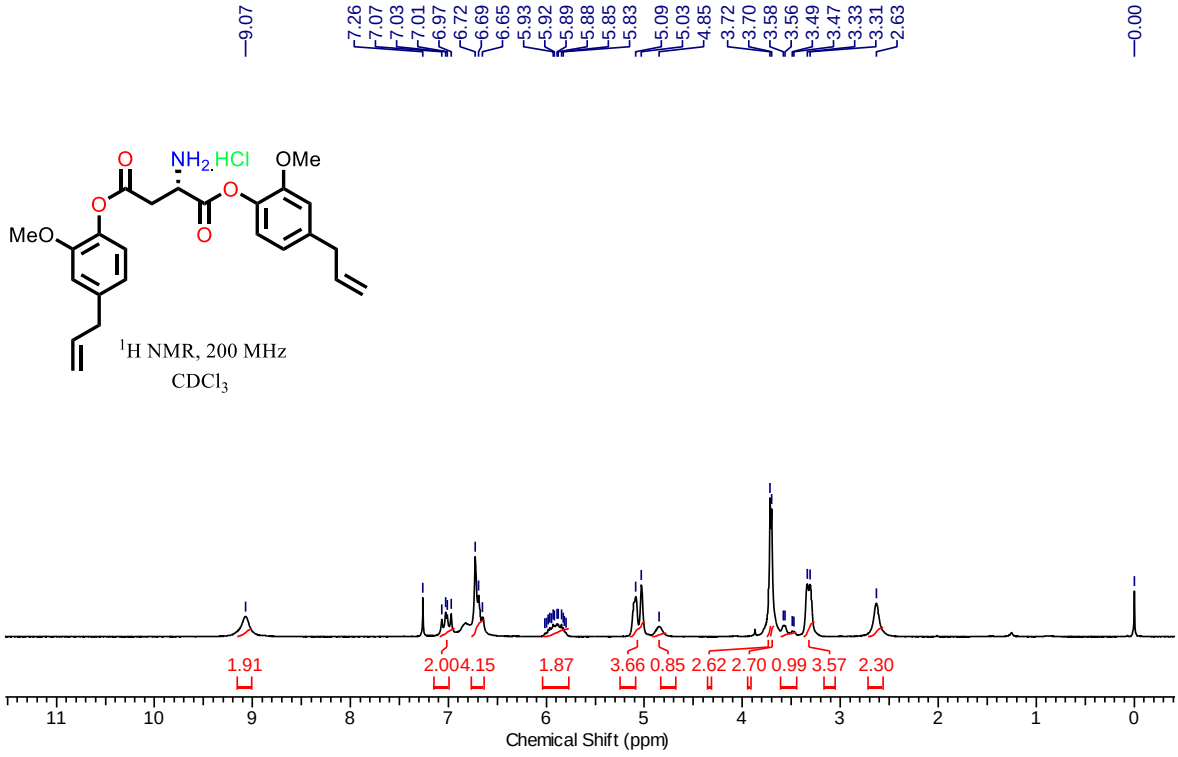


^{1}H NMR, 400 MHz
$CDCl_3$

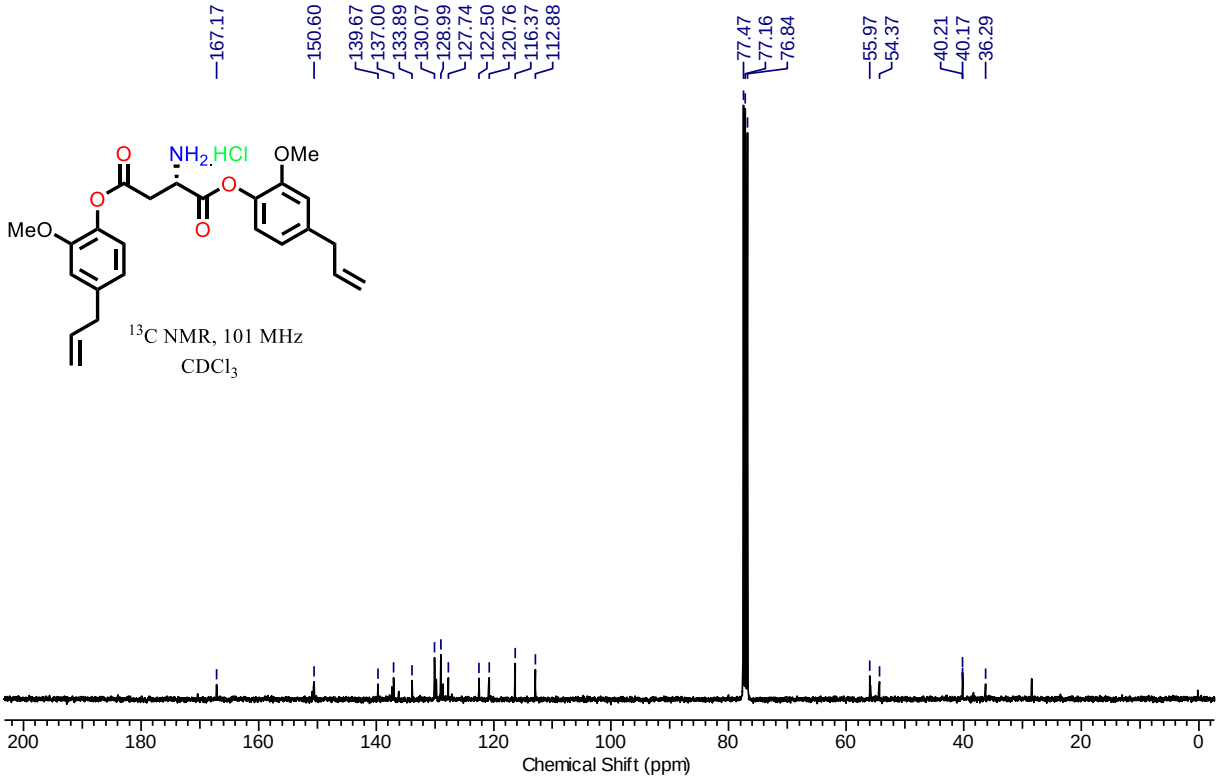
4-Allyl-2-methoxyphenyl L-methioninate hydrochloride **(43):**



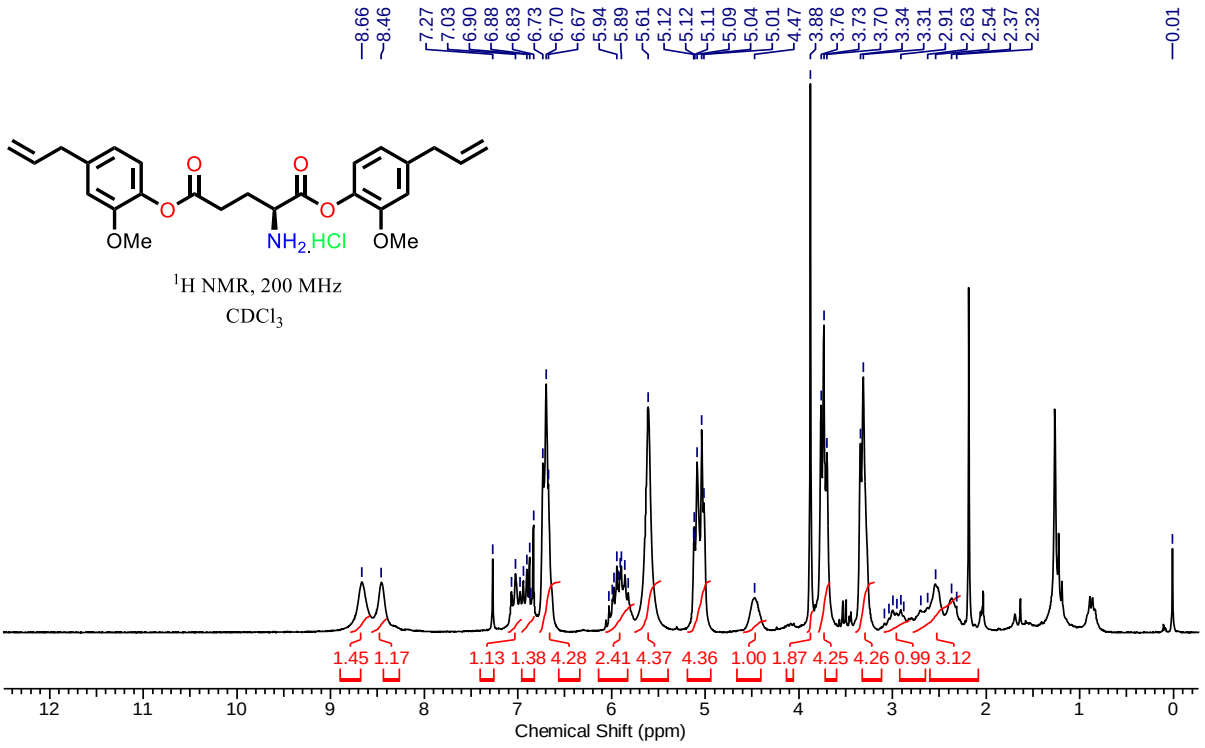
Bis(4-allyl-2-methoxyphenyl) L-aspartate hydrochloride **(44):**



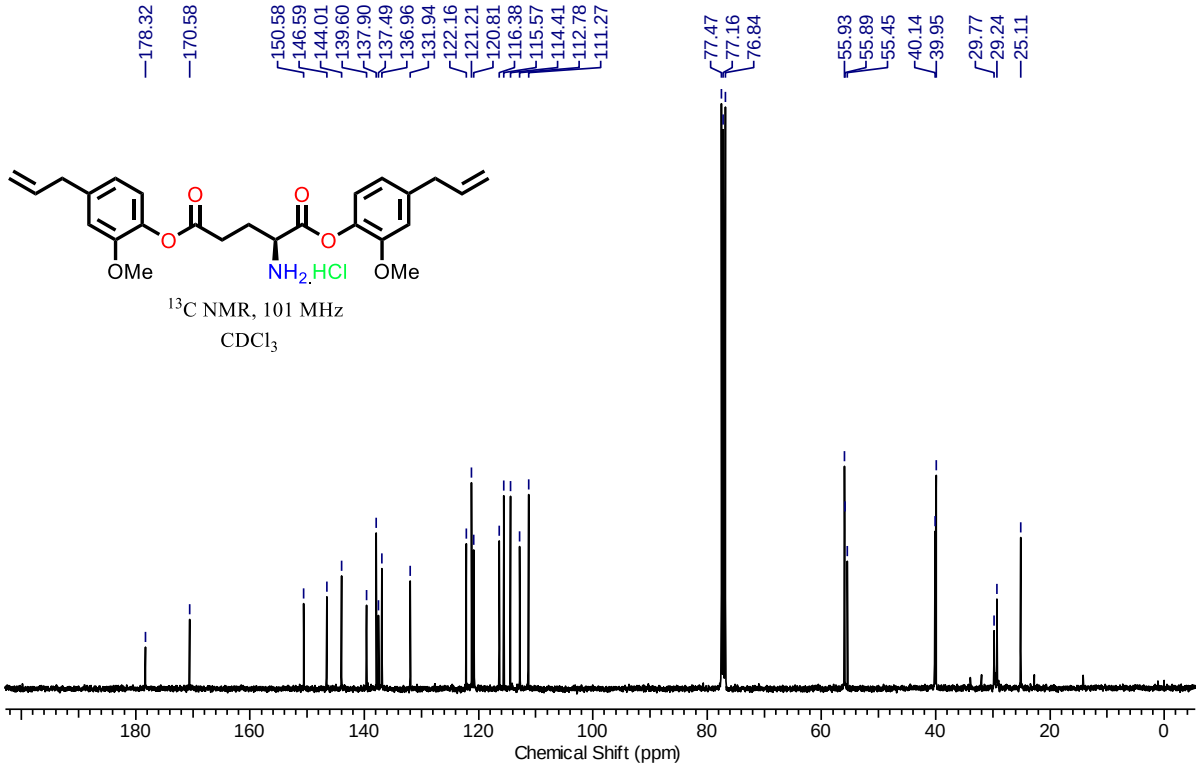
Bis(4-allyl-2-methoxyphenyl) L-aspartate hydrochloride **(44):**



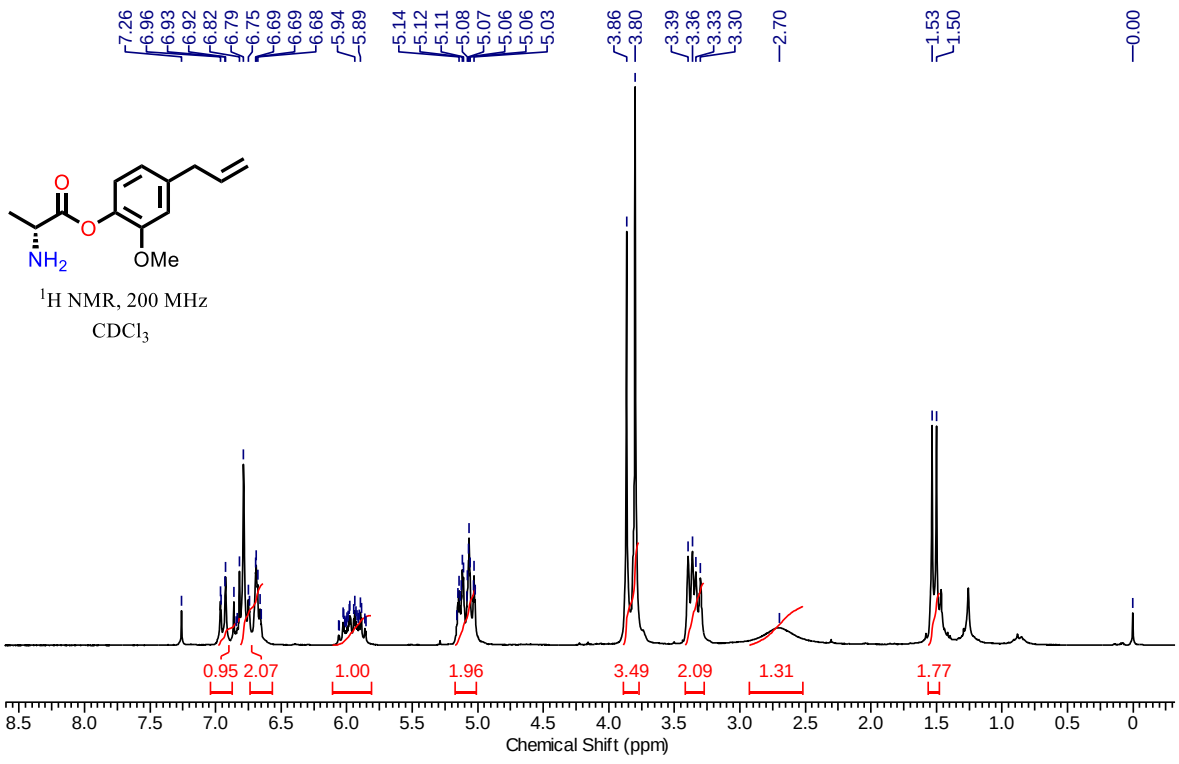
Bis(4-allyl-2-methoxyphenyl) L-glutamate hydrochloride **(45):**



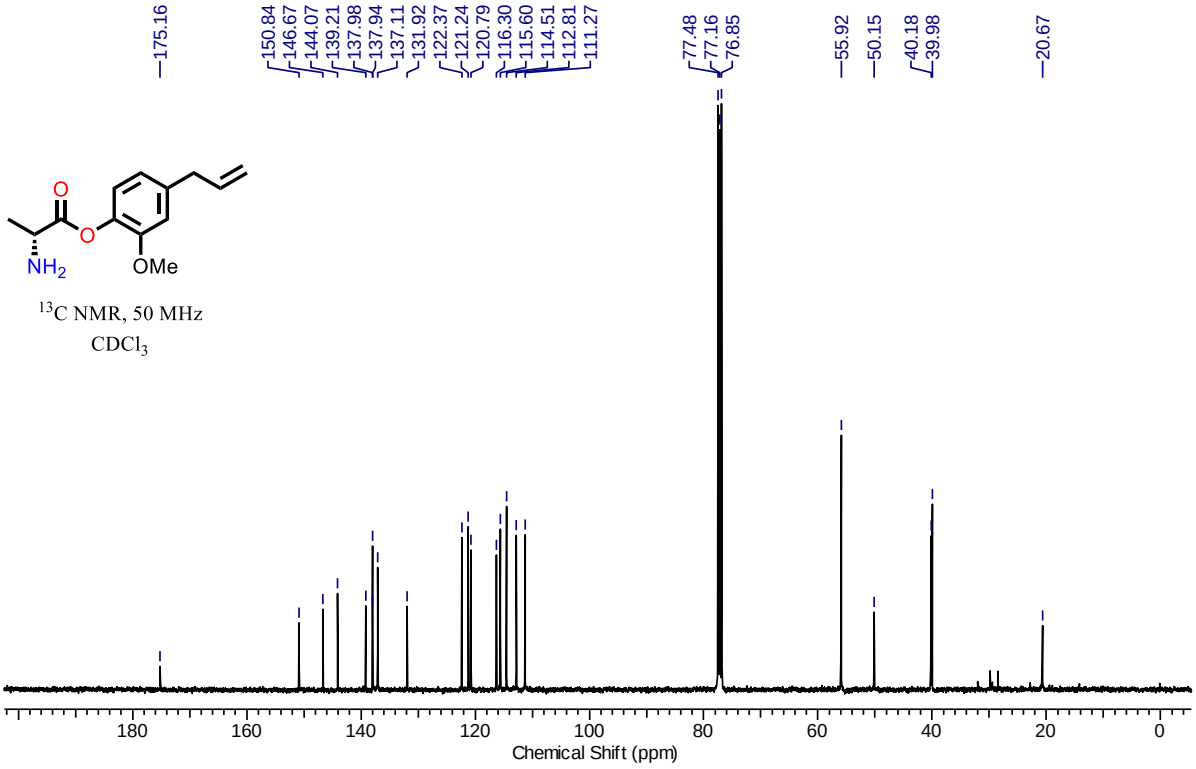
Bis(4-allyl-2-methoxyphenyl) L-glutamate hydrochloride **(45):**



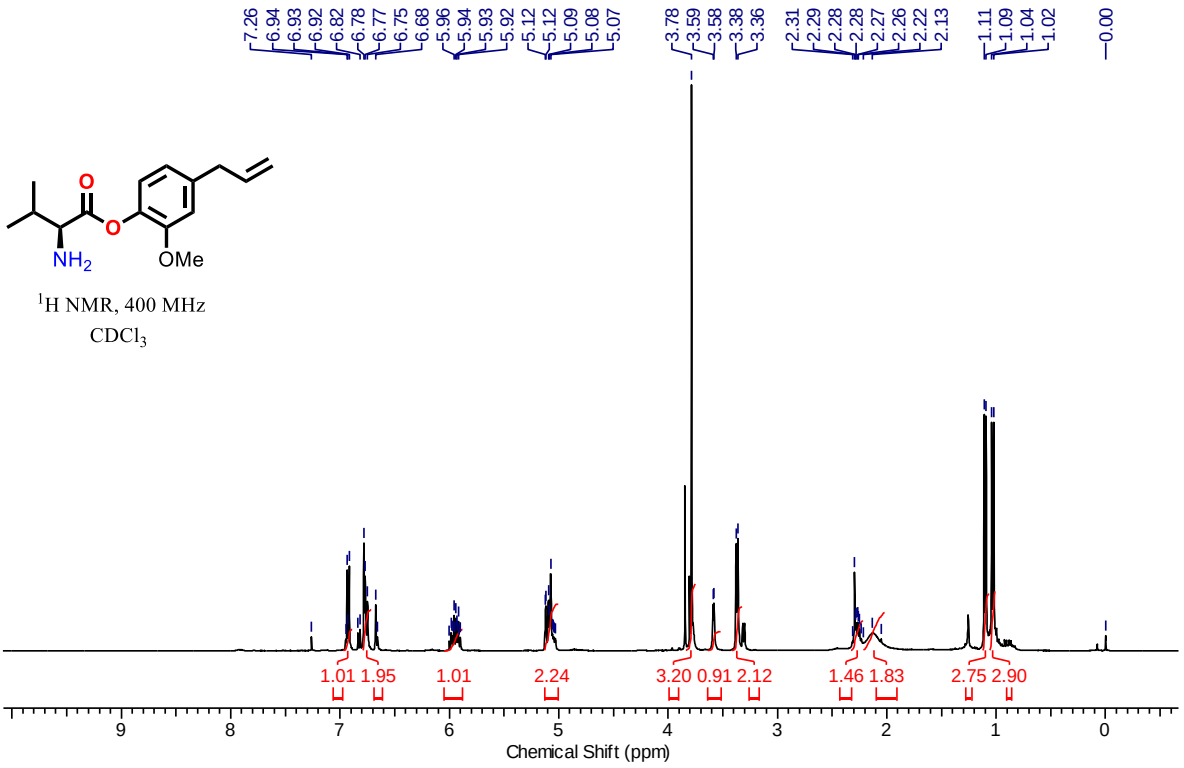
4-Allyl-2-methoxyphenyl D-alaninate **(46):**



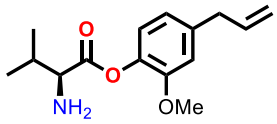
4-Allyl-2-methoxyphenyl D-alaninate **(46):**



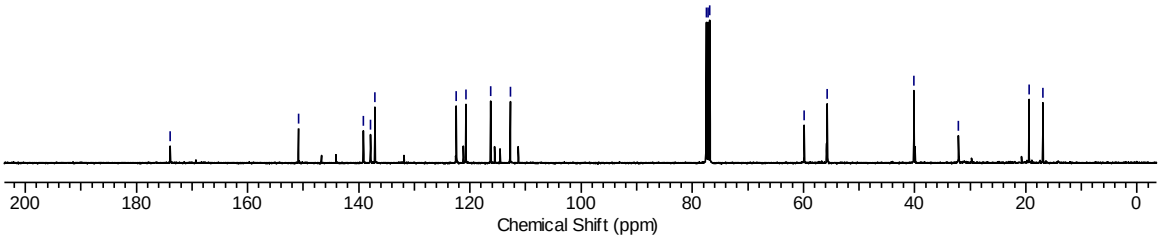
4-Allyl-2-methoxyphenyl L-valinate **(47):**



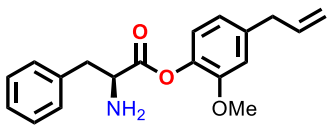
4-Allyl-2-methoxyphenyl L-valinate **(47):**



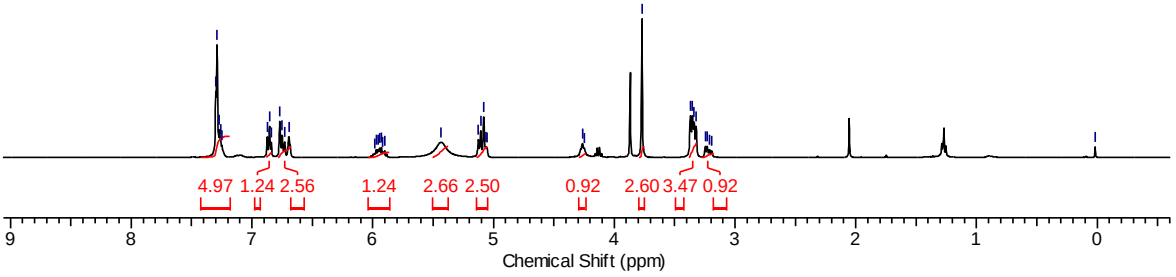
^{13}C NMR, 101 MHz
$CDCl_3$



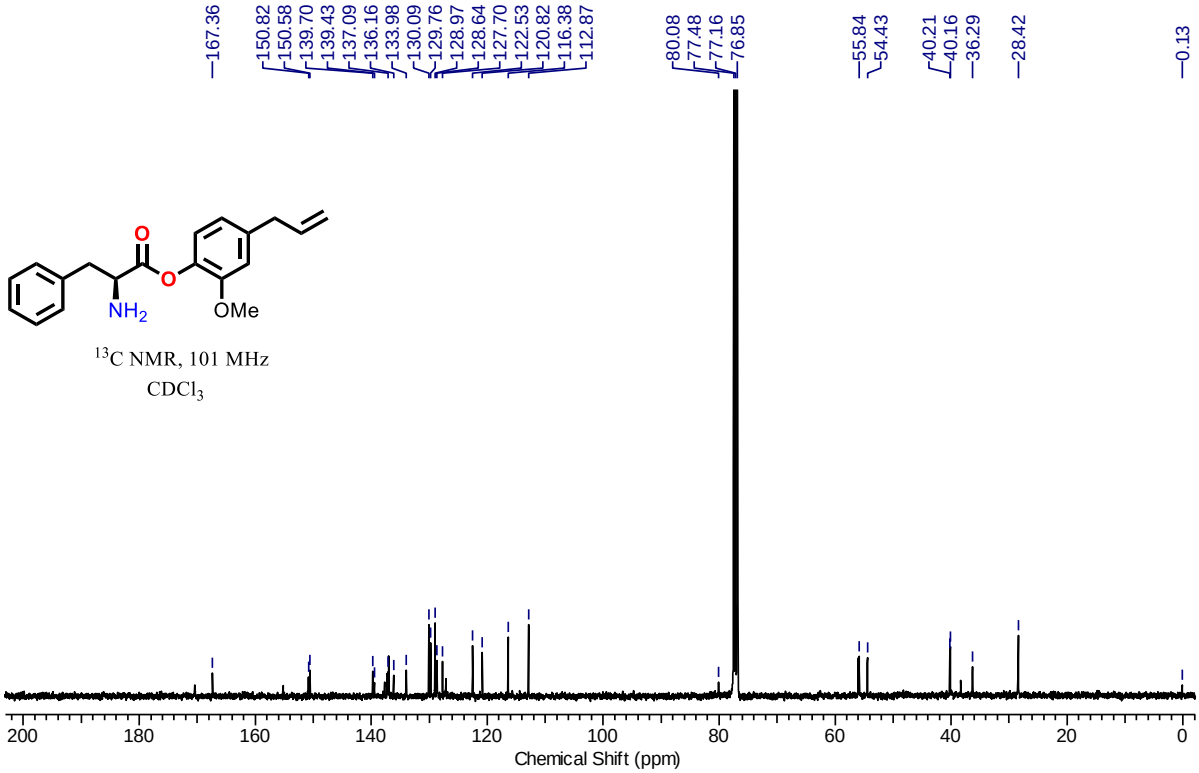
4-Allyl-2-methoxyphenyl L-phenylalaninate **(48):**



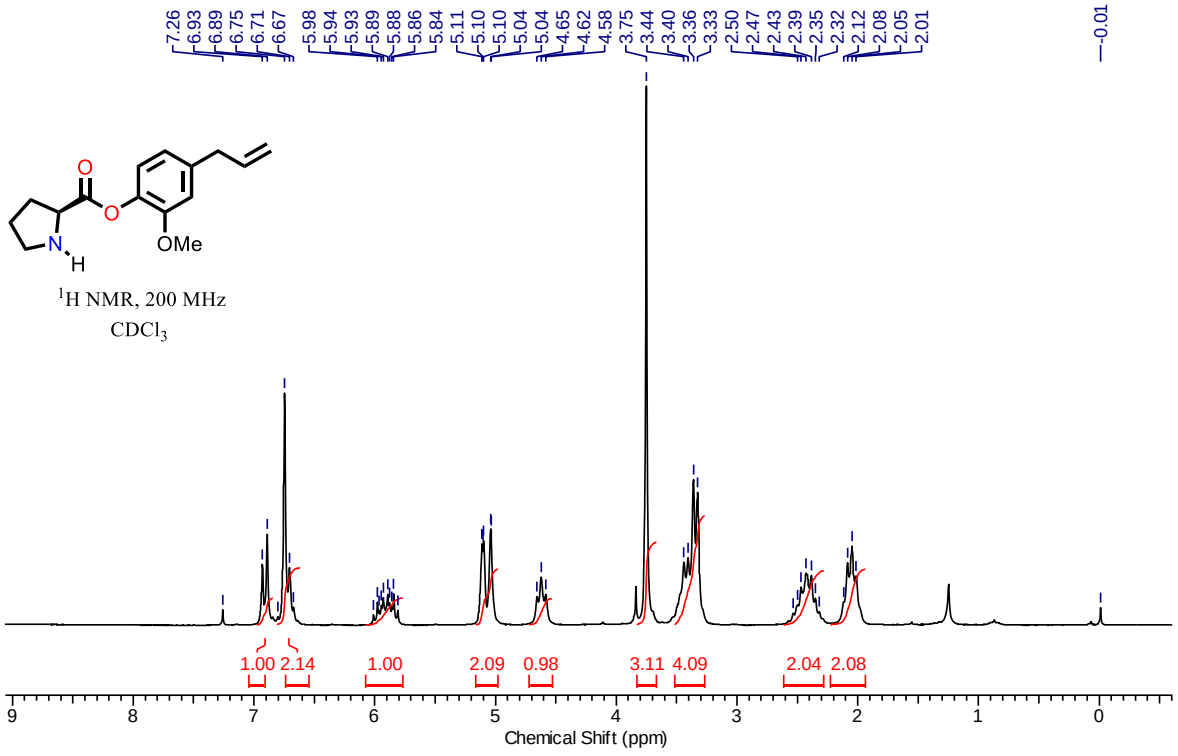
^{1}H NMR, 400 MHz
$CDCl_3$



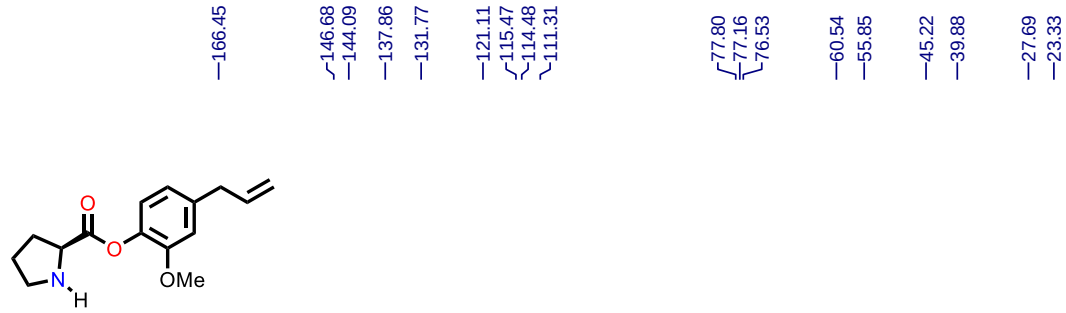
4-Allyl-2-methoxyphenyl L-phenylalaninate **(48):**



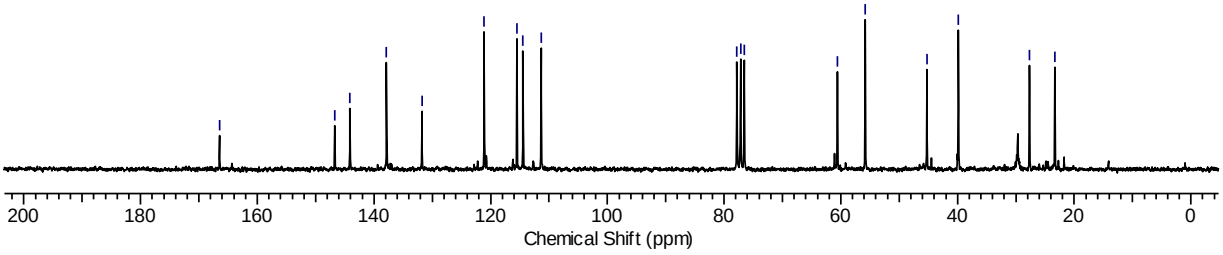
4-Allyl-2-methoxyphenyl L-prolinate **(49):**



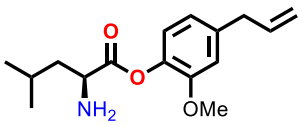
4-Allyl-2-methoxyphenyl L-prolinate **(49):**



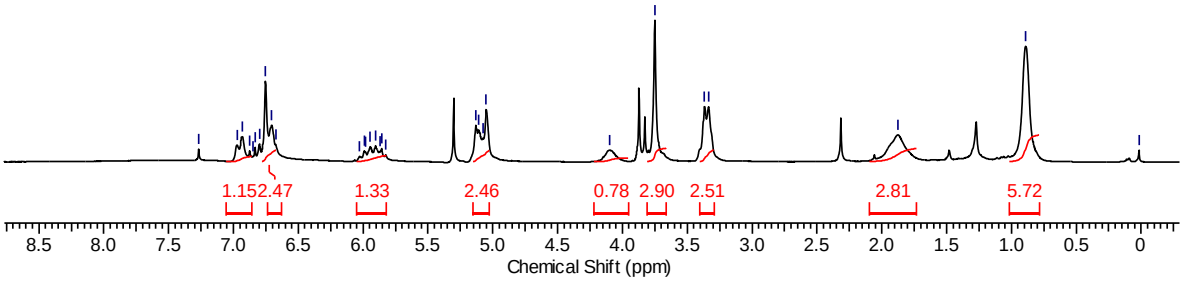
^{13}C NMR, 50 MHz
$CDCl_3$



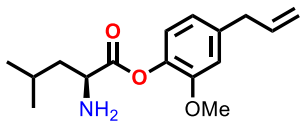
4-Allyl-2-methoxyphenyl L-leucinate **(50):**



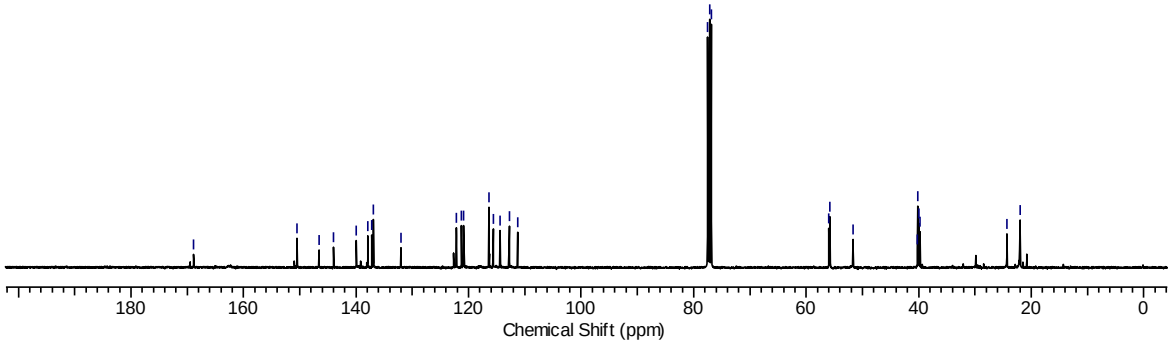
^{1}H NMR, 200 MHz
$CDCl_3$



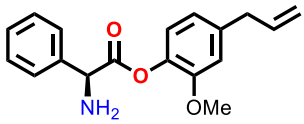
4-Allyl-2-methoxyphenyl L-leucinate **(50):**



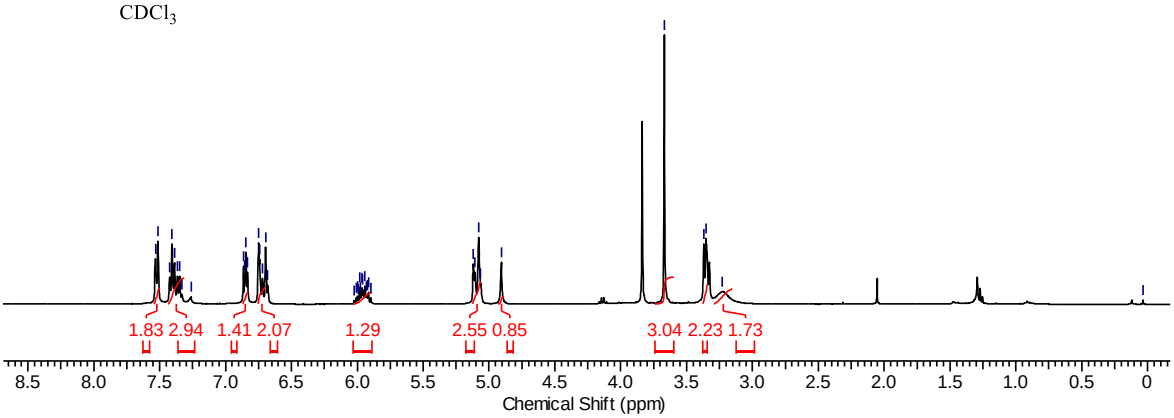
^{13}C NMR, 101 MHz
$CDCl_3$



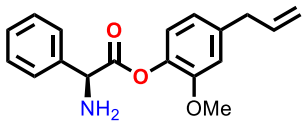
4-Allyl-2-methoxyphenyl (*S*)-2-amino-2-phenylacetate **(51):**



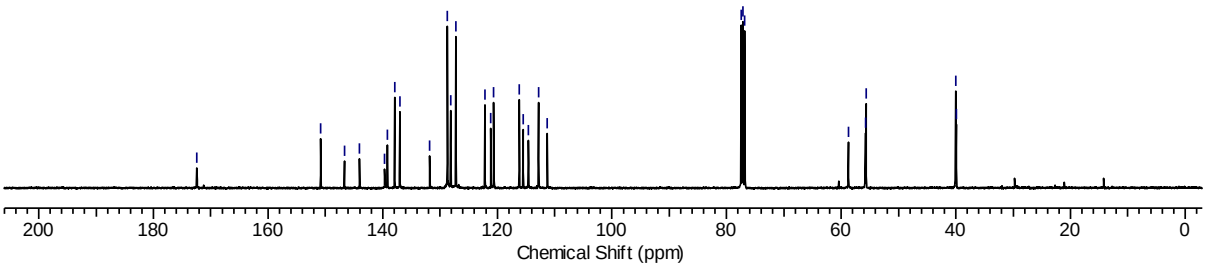
^{1}H NMR, 400 MHz
$CDCl_3$



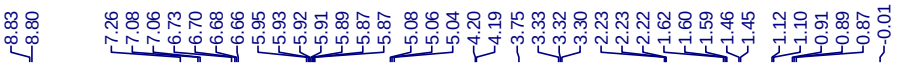
4-Allyl-2-methoxyphenyl (*S*)-2-amino-2-phenylacetate **(51):**

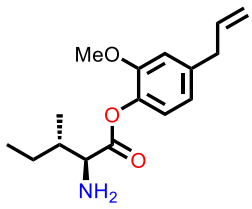


^{13}C NMR, 101 MHz
$CDCl_3$

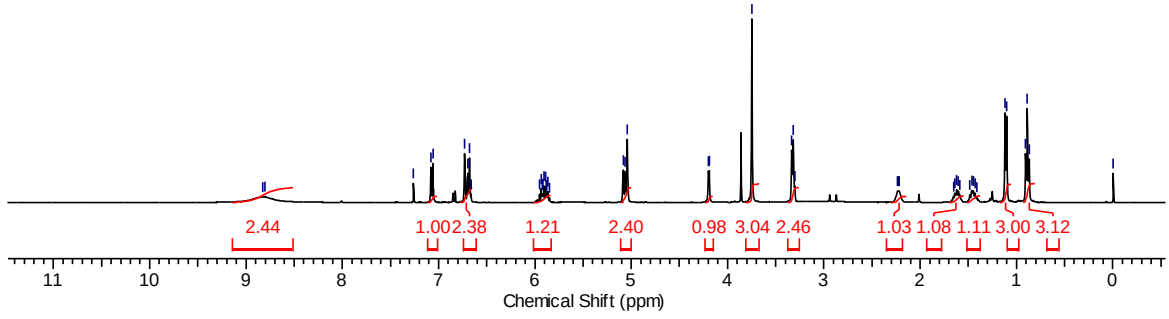


4-Allyl-2-methoxyphenyl L-isoleucinate **(52):**

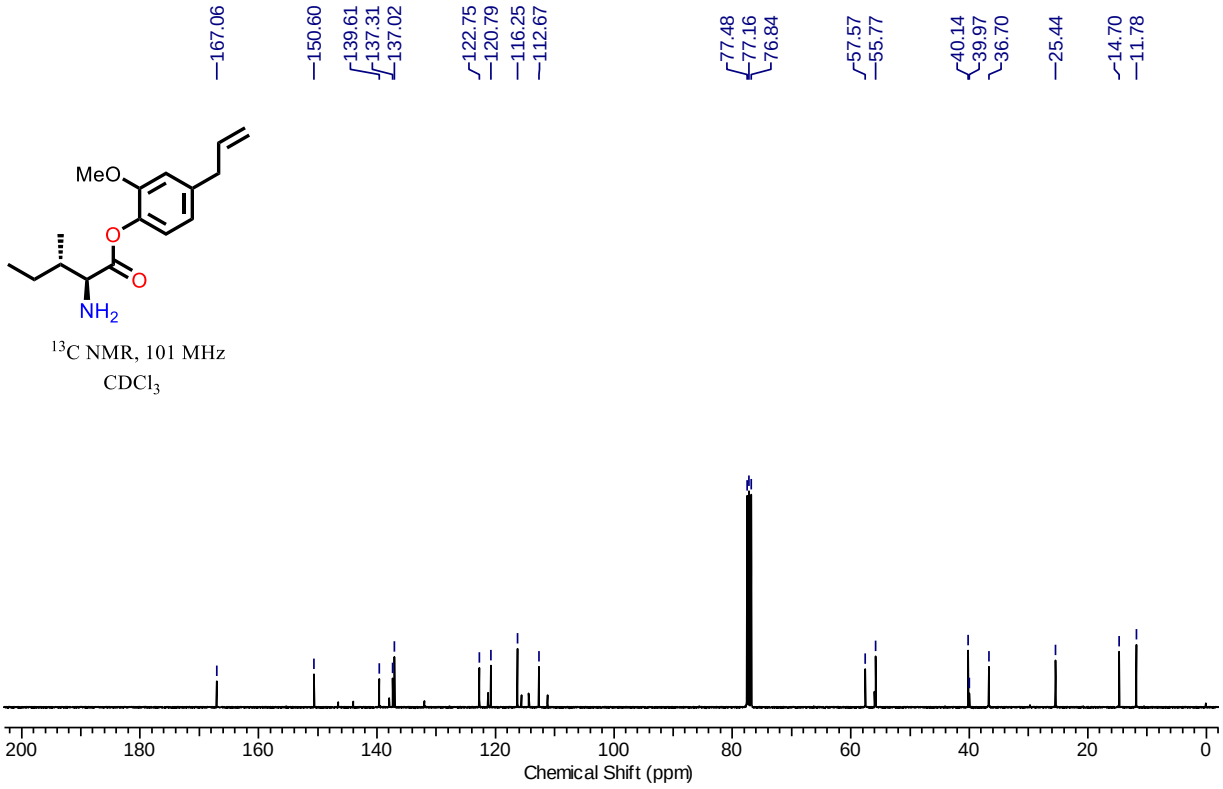




^{1}H NMR, 400 MHz
$CDCl_3$

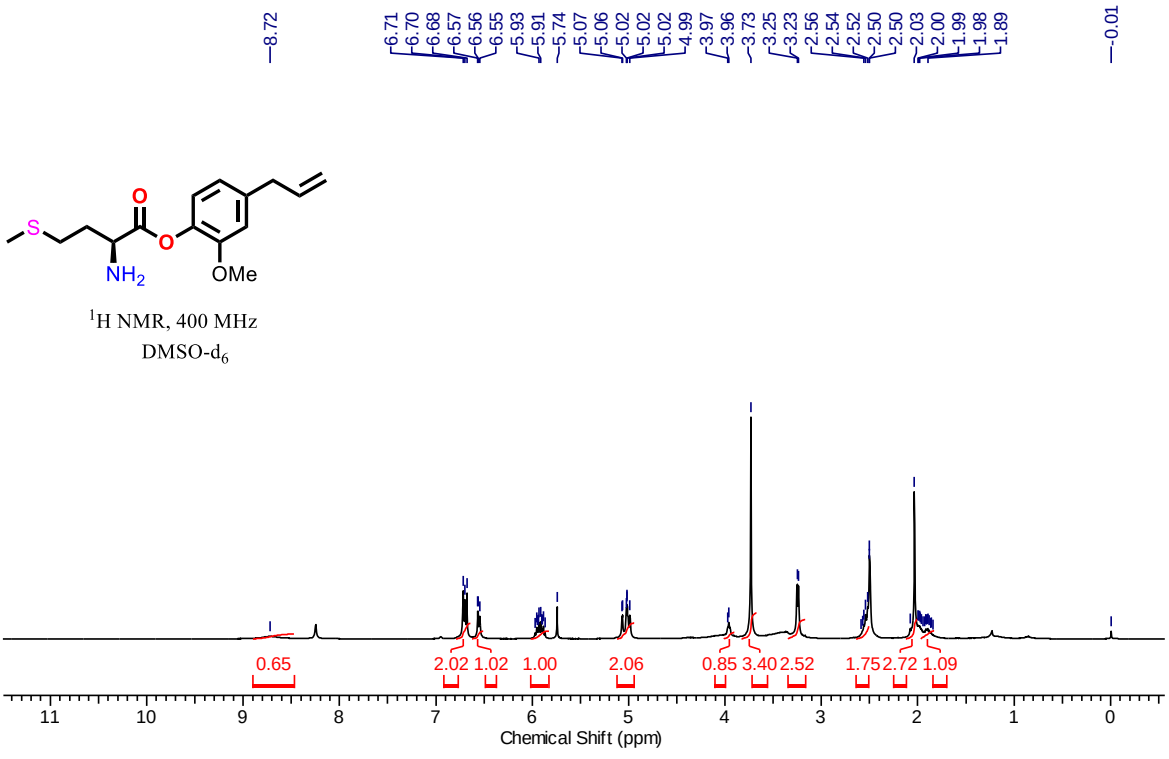


4-Allyl-2-methoxyphenyl L-isoleucinate **(52):**



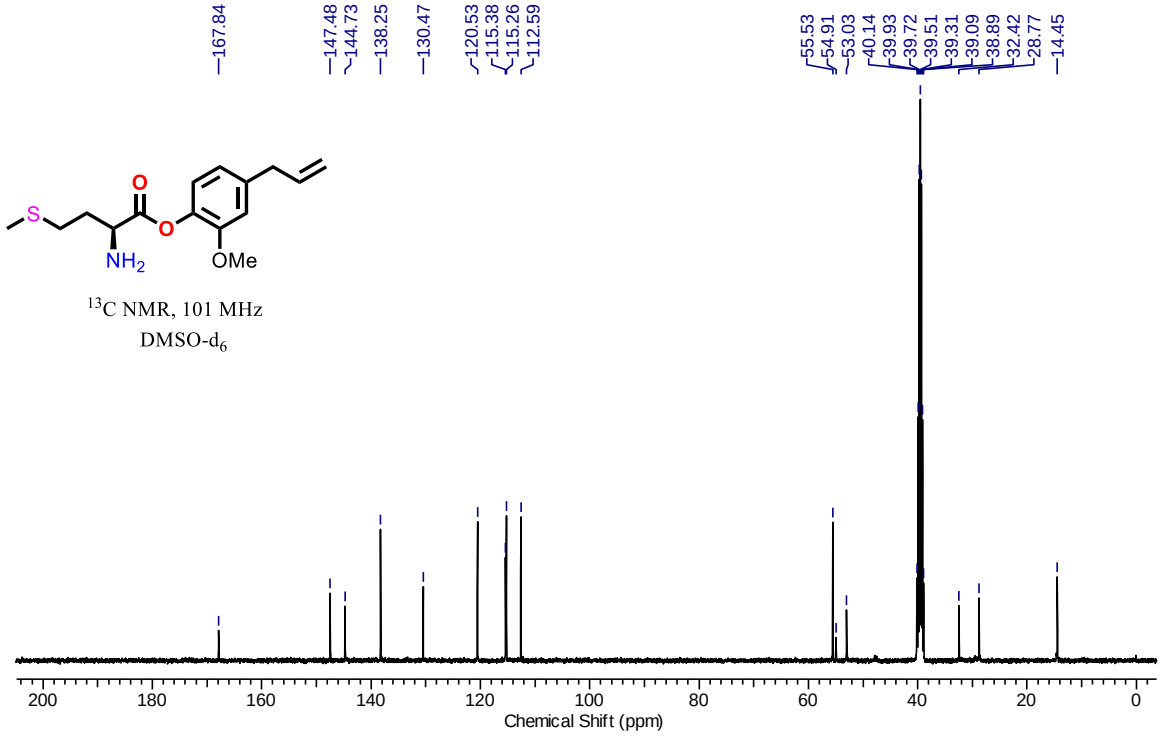
^{13}C NMR, 101 MHz
$CDCl_3$

4-Allyl-2-methoxyphenyl L-methioninate **(53):**

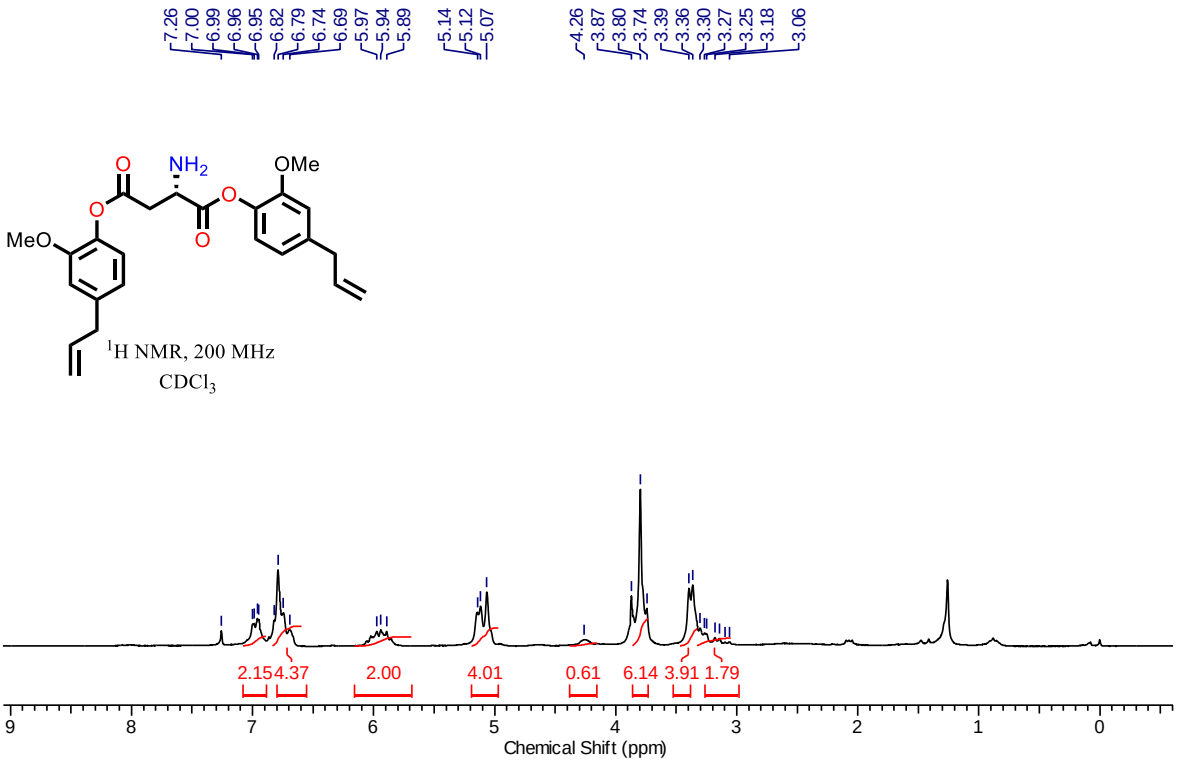


^{1}H NMR, 400 MHz
DMSO-d_6

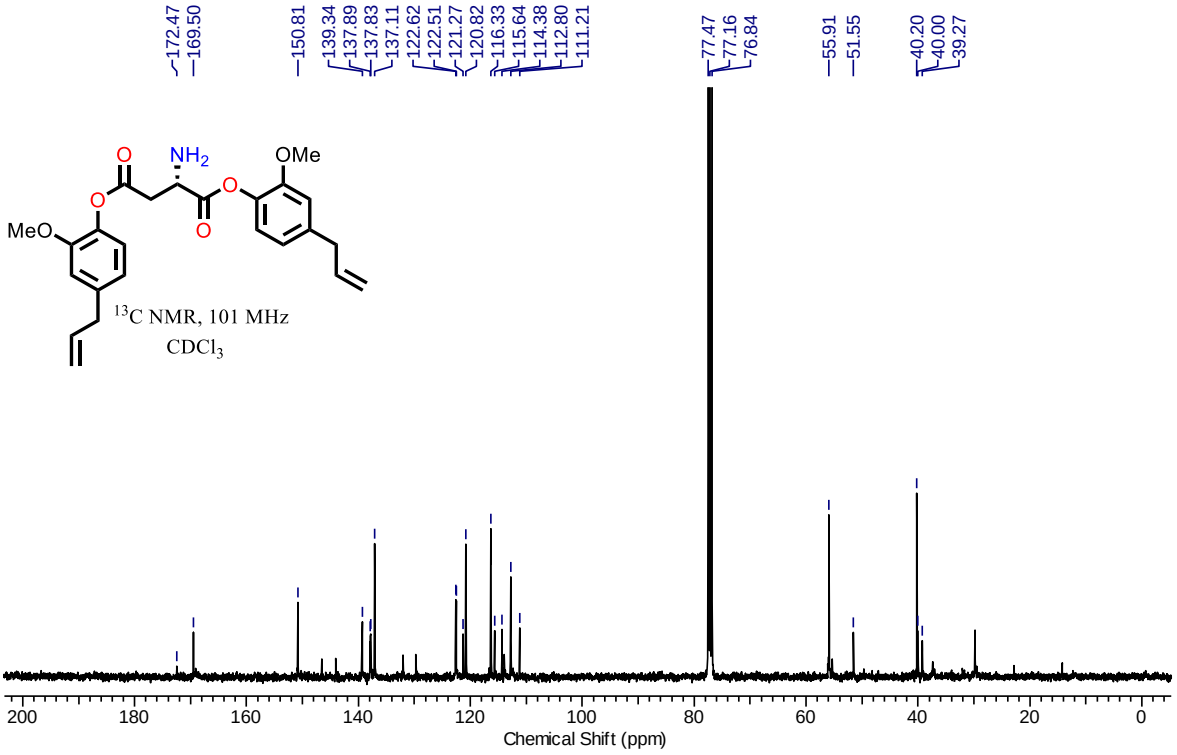
4-Allyl-2-methoxyphenyl L-methioninate **(53):**



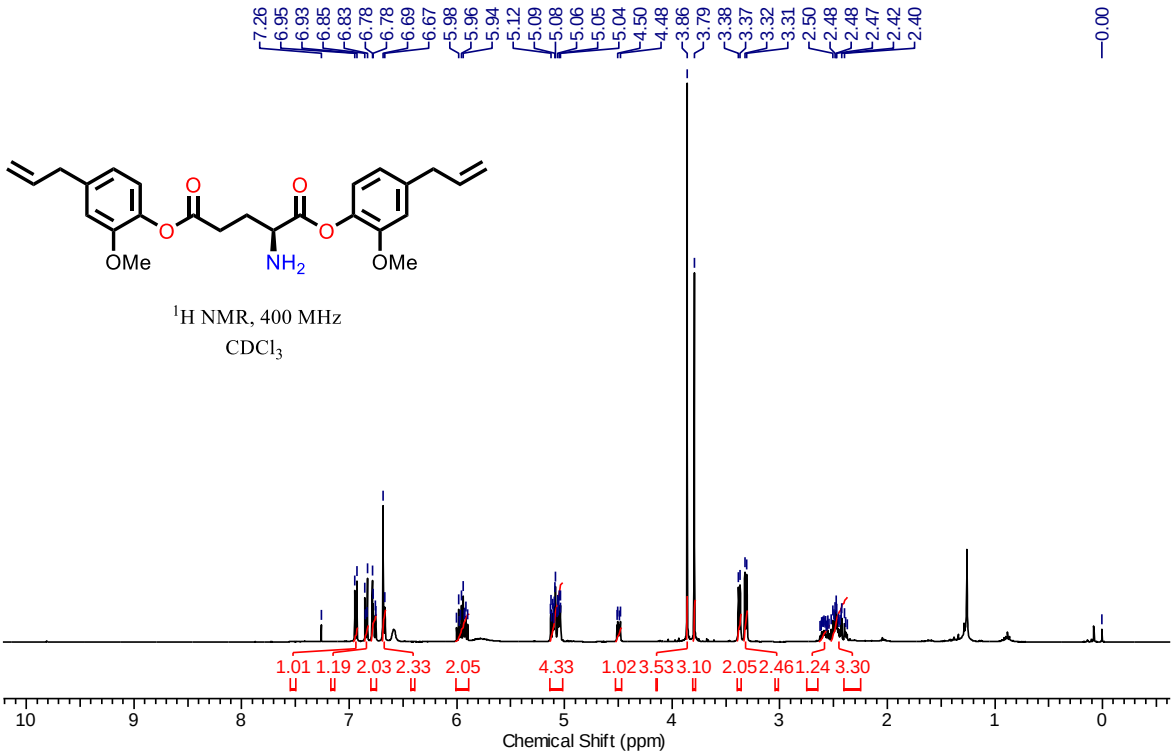
Bis(4-allyl-2-methoxyphenyl) L-aspartate **(54):**



Bis(4-allyl-2-methoxyphenyl) L-aspartate **(54):**

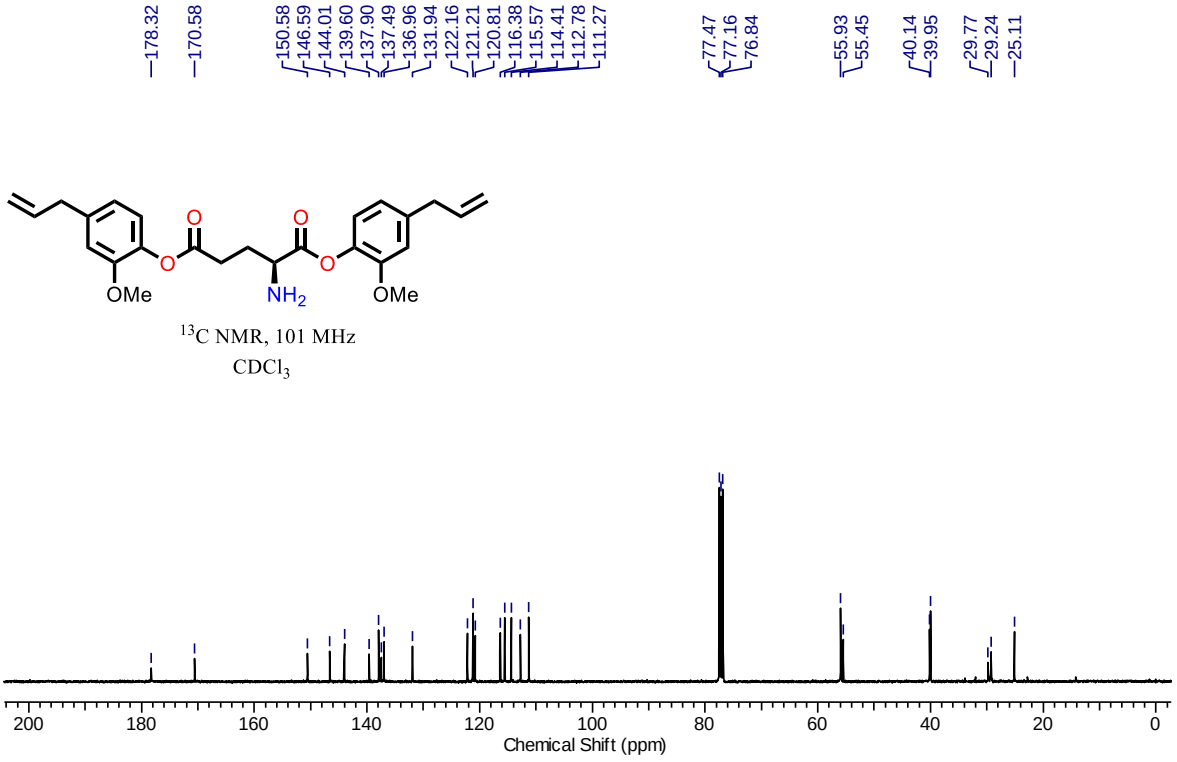


Bis(4-allyl-2-methoxyphenyl) L-glutamate **(55):**



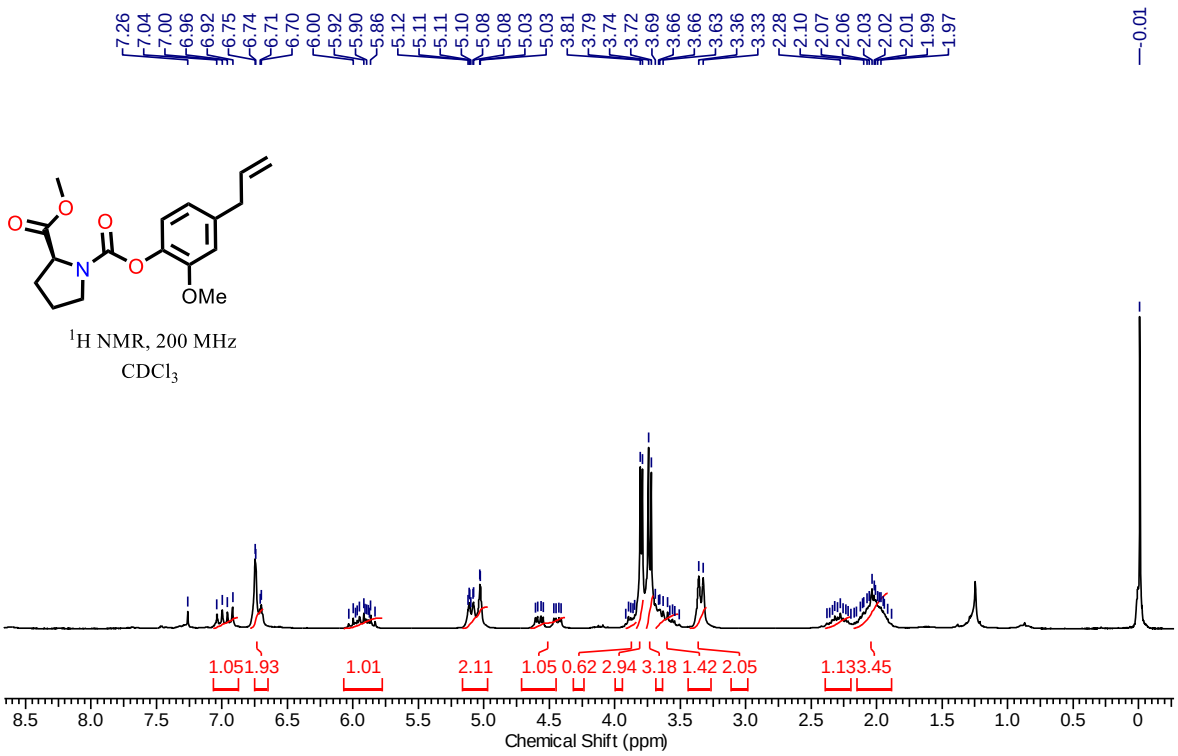
^{1}H NMR, 400 MHz
$CDCl_3$

Bis(4-allyl-2-methoxyphenyl) L-glutamate **(55):**

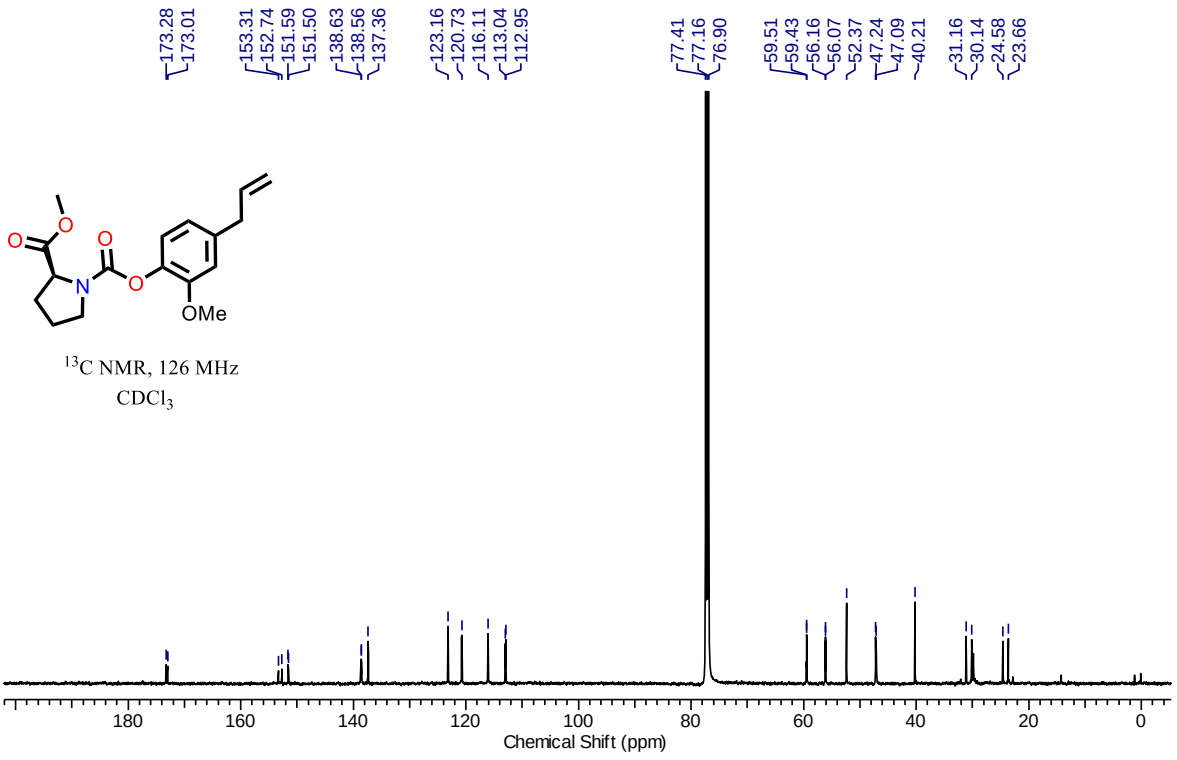


^{13}C NMR, 101 MHz
$CDCl_3$

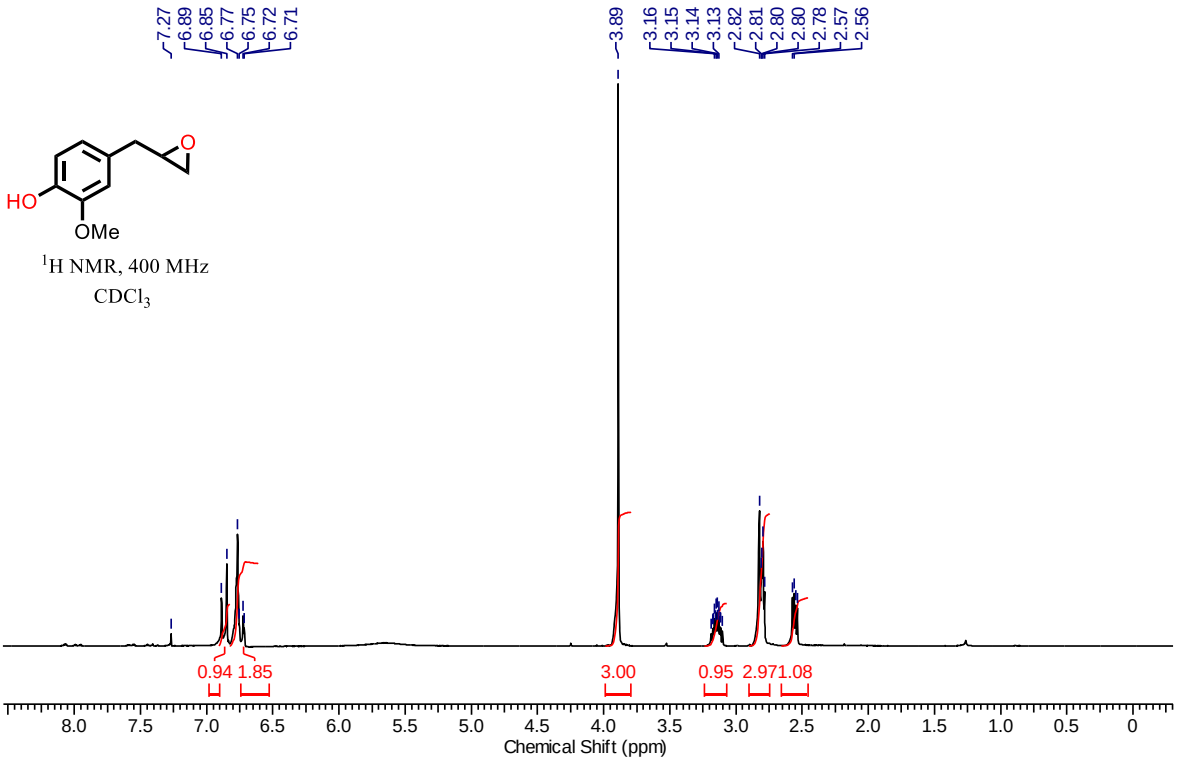
1-(4-Allyl-2-methoxyphenyl) 2-methyl (*S*)-pyrrolidine-1,2-dicarboxylate **(56):**



1-(4-Allyl-2-methoxyphenyl) 2-methyl (*S*)-pyrrolidine-1,2-dicarboxylat**e (56):**

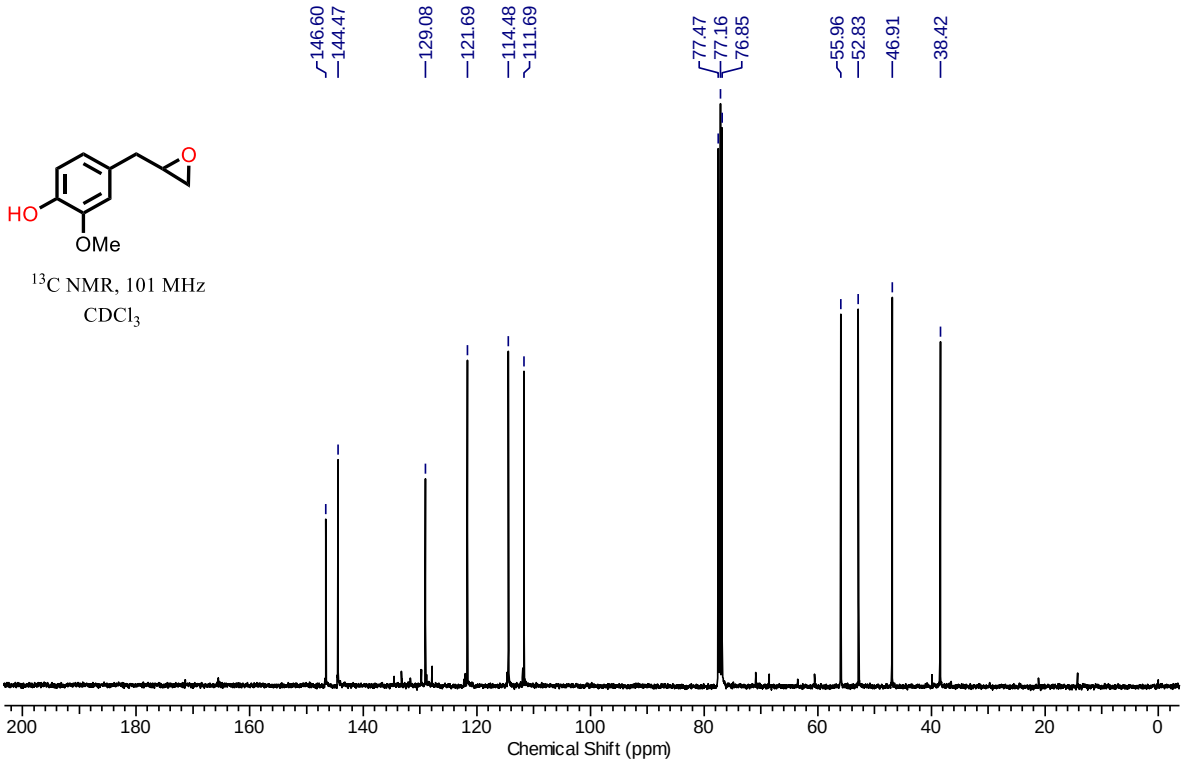


2-Methoxy-4-(oxiran-2-ylmethyl)phenol **(57):**



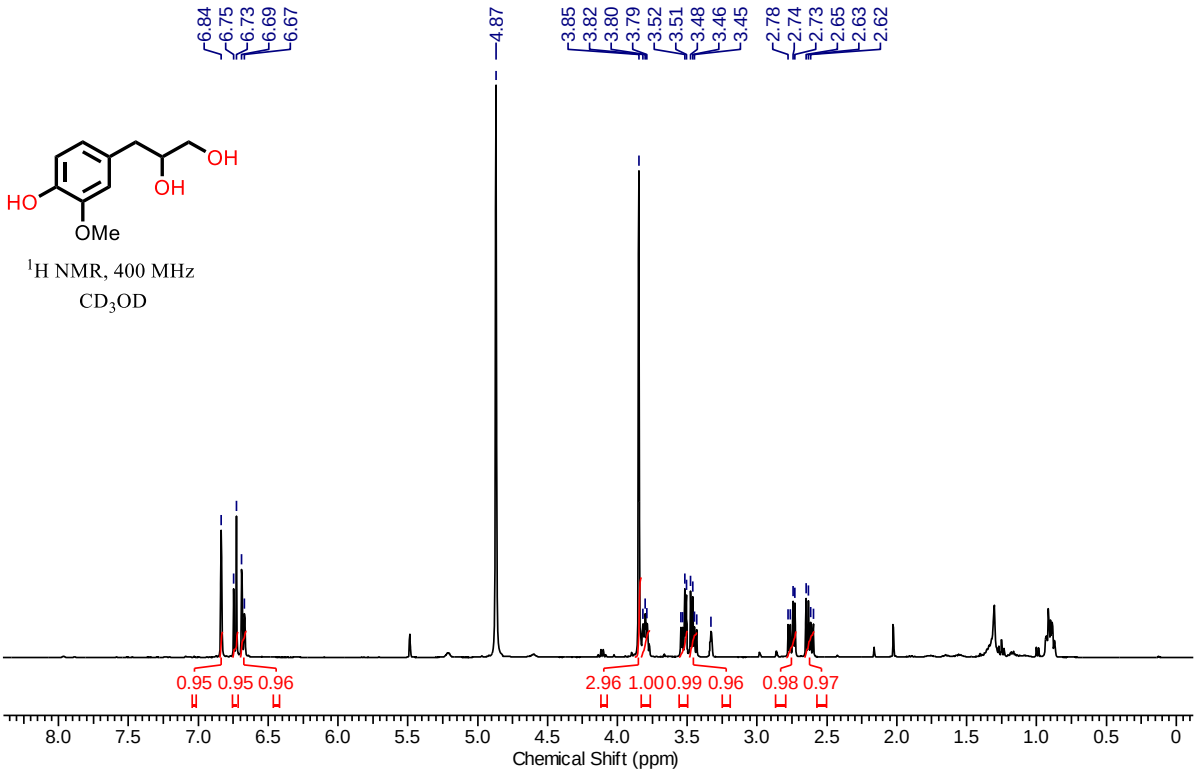
^{1}H NMR, 400 MHz
$CDCl_3$

2-Methoxy-4-(oxiran-2-ylmethyl)phenol **(57):**

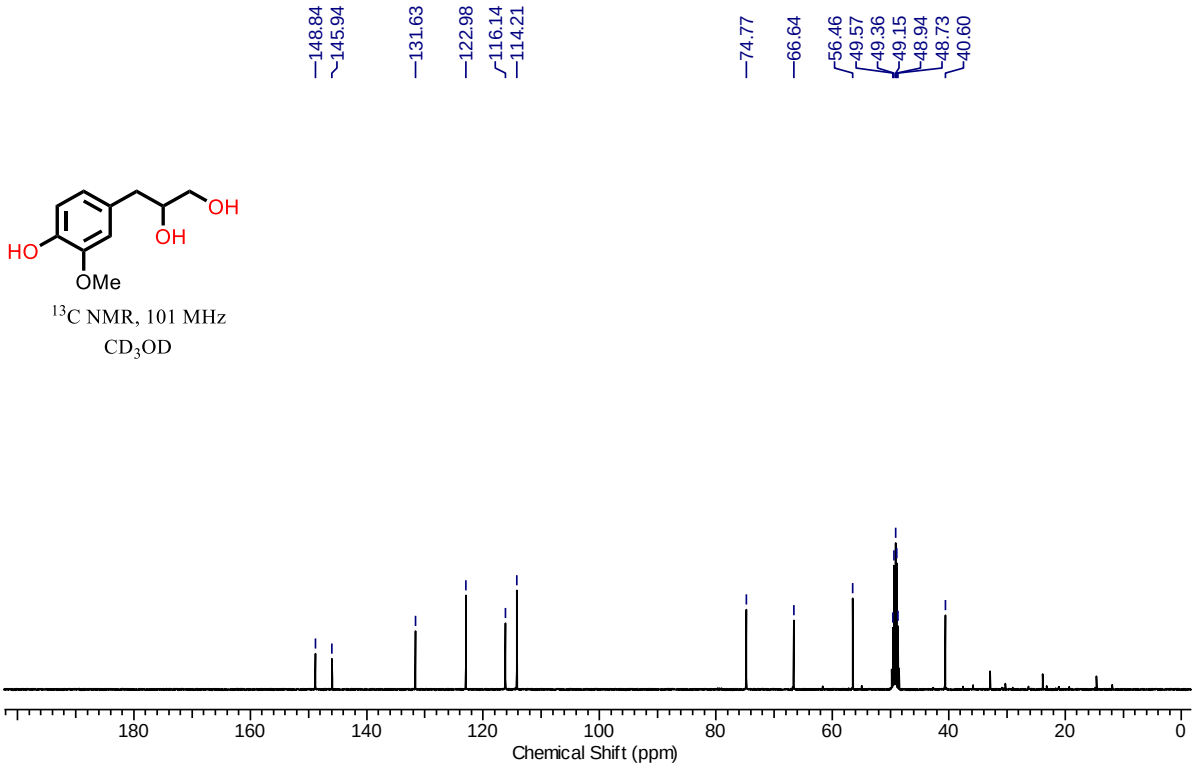


^{13}C NMR, 101 MHz
$CDCl_3$

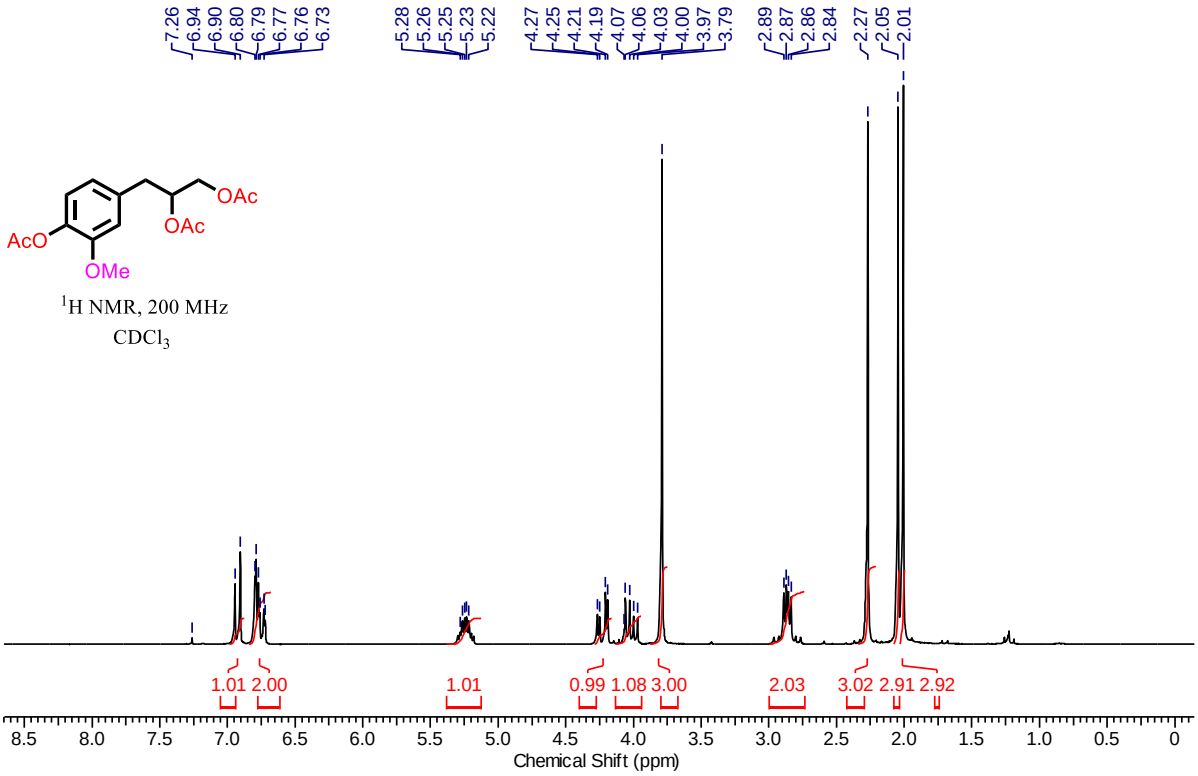
3-(4-Hydroxy-3-methoxyphenyl)propane-1,2-diol **(58):**



3-(4-Hydroxy-3-methoxyphenyl)propane-1,2-diol **(58):**

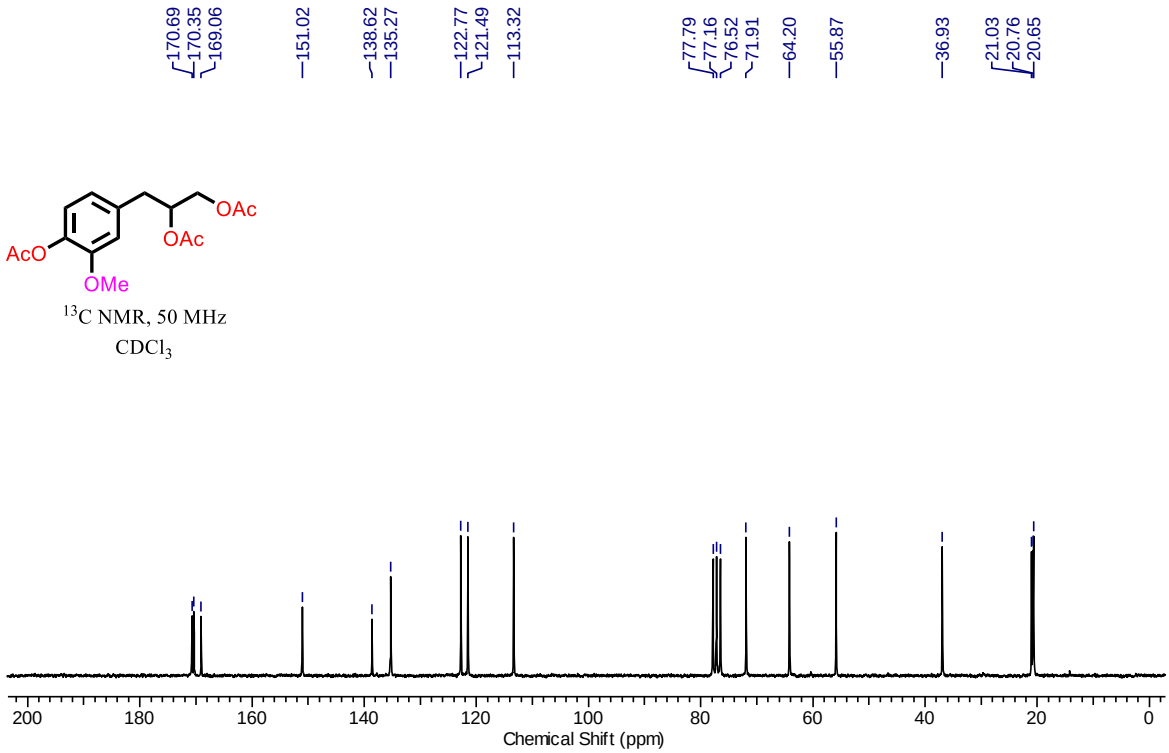


3-(4-Acetoxy-3-methoxyphenyl)propane-1,2-diyl diacetate **(59):**



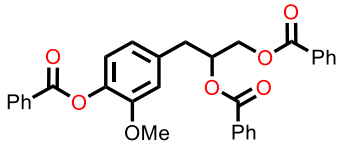
^{1}H NMR, 200 MHz
$CDCl_3$

3-(4-Acetoxy-3-methoxyphenyl)propane-1,2-diyl diacetate **(59):**

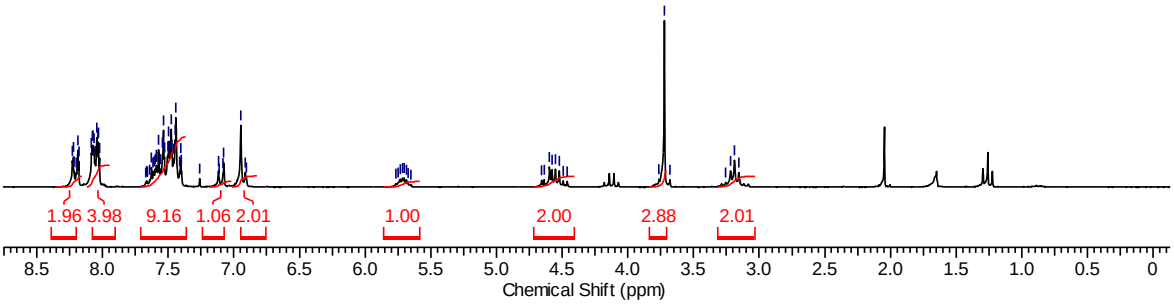


^{13}C NMR, 50 MHz
$CDCl_3$

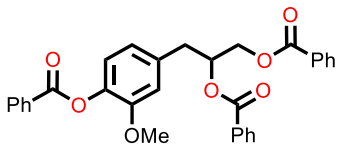
3-(4-(Benzoyloxy)-3-methoxyphenyl)propane-1,2-diyl dibenzoate **(60):**



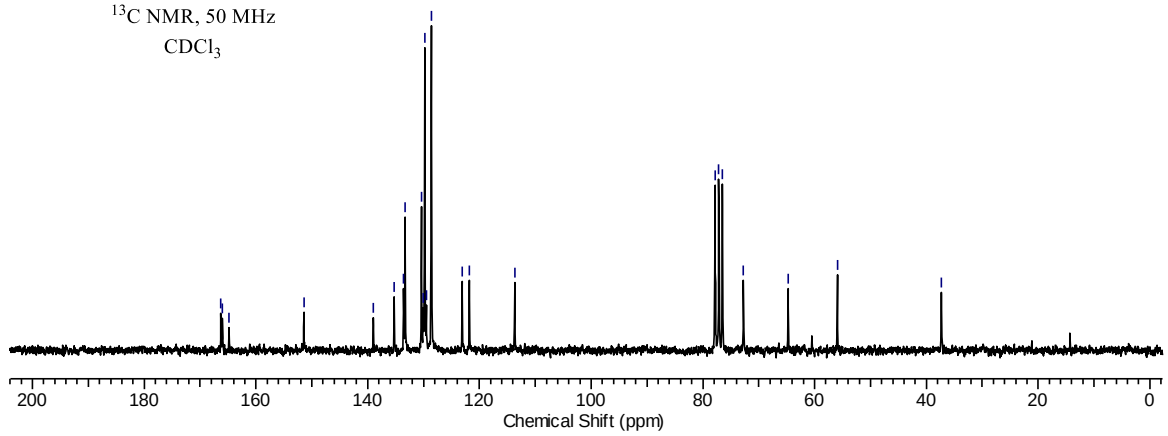
^{1}H NMR, 200 MHz
$CDCl_3$



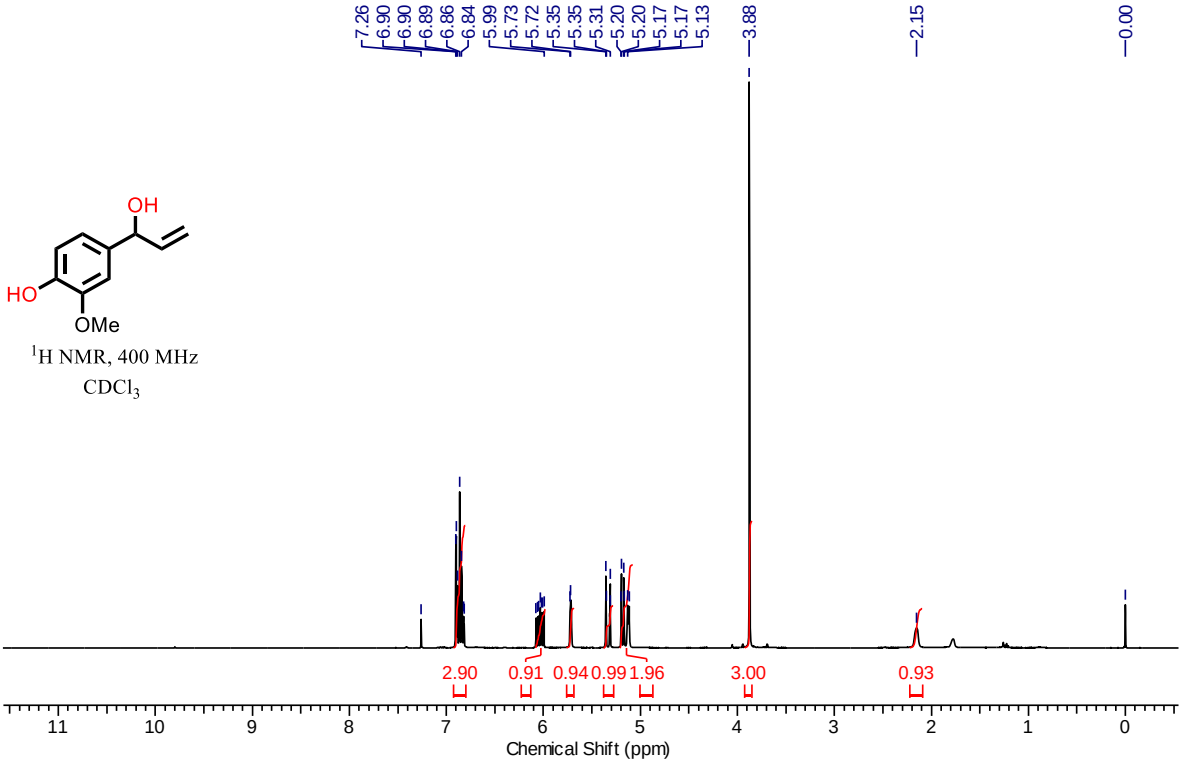
3-(4-(Benzoyloxy)-3-methoxyphenyl)propane-1,2-diyl dibenzoate **(60):**



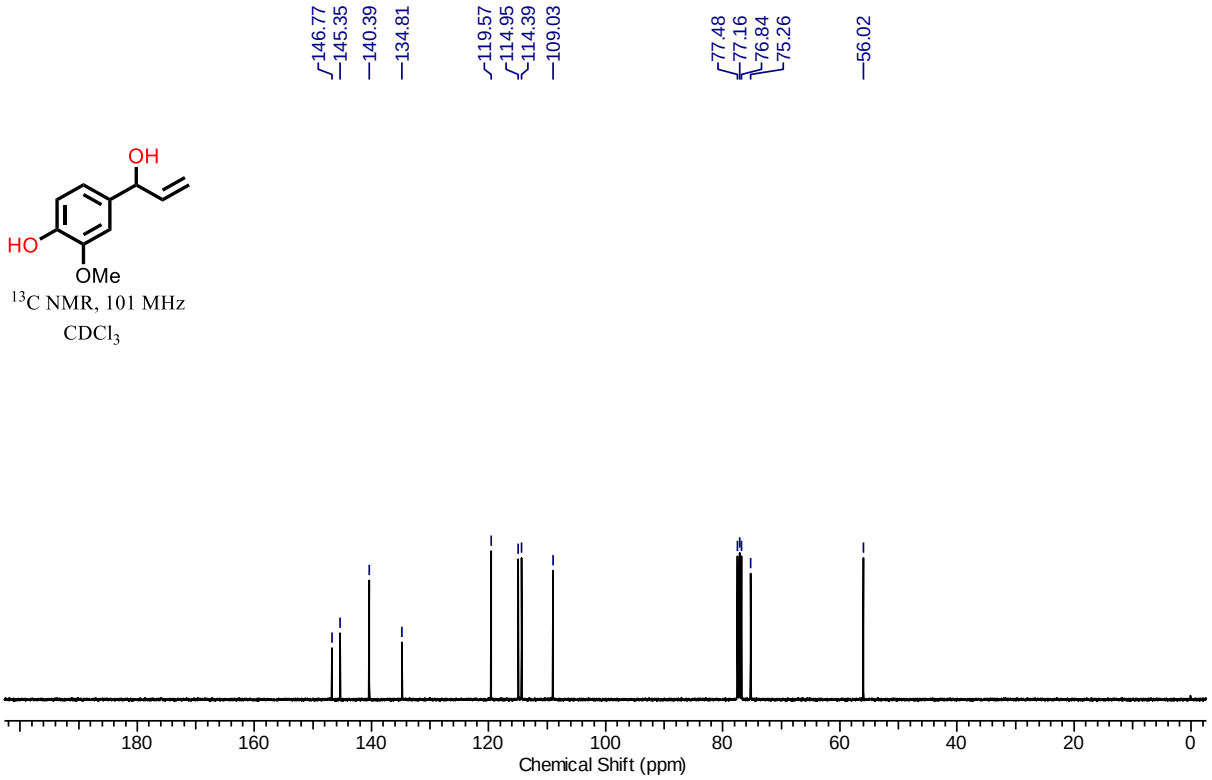
^{13}C NMR, 50 MHz
$CDCl_3$



4-(1-Hydroxylallyl-2-methoxyphenol **(61):**



4-(1-Hydroxylallyl-2-methoxyphenol **(61):**


146.77
145.35
140.39
134.81
119.57
114.95
114.39
109.03
77.48
77.16
76.84
75.26
56.02
OH
HO
OMe
^{13}C NMR, 101 MHz
$CDCl_3$
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

ABSTRACT

Name of the Student: Ms. Priyanka Kataria **Registration No.:** 10CC16J26018

Faculty of Study: Chemical Science **Year of Submission:** 2022

AcSIR academic centre/CSIR Lab: CSIR-National Chemical Laboratory, Pune **Name of the Supervisor:** Dr. Ravindar Kontham

Title of the thesis: "Studies on the Enantioselective Total Synthesis of Diarylheptanoid and Furylhydroquinone-Derived Natural Products, and Eugenol Derivatives as Potential Antidiabetic Agents"

Natural products are a diverse group of chemical substances produced by nature (living organism like animal plant and microorganism) However, these molecules are often produced in minimal quantities, which creates supply issues and hamper systematic chemical and biochemical investigations and utilization. Hence, the development of efficient, facile, and sustainable synthetic methodologies and their application in devising concise and practical synthetic routes for biologically potent natural and unnatural molecules is one of the pivotal objectives for synthetic organic chemists worldwide. In this context, in ***chapter 1***, we have developed concise and enantioselective synthetic routes for diarylheptanoid-derived natural product *des*-hydroxy hedycoropyran B, and in ***chapter 2*** we established the absolute configuration for anti-inflammatory and antibacterial natural products shikonofurans J, D, E, C and their enantiomers possessing furylhydroquinone scaffold as a key structural unit, using an unprecedented $Bi(OTf)_3$-catalyzed furan construction from acyl-hydroxy oxetanes, followed by chiral-phosphoric acid (TRIP)-mediated asymmetric prenylation reactions as key steps. In addition, in ***chapter 3***, we synthesised the derivatives of eugenol and in vitro antidiabetic activity evaluation of natural product eugenol and its derivatives having improved bioavailability.

List of Publications Emanating from the Thesis Work

1. **Kataria, P.**; Nomula, R. and Kontham R.; Studies directed toward the synthesis of hedycoropyrans: total synthesis of *des*-hydroxyl (−)-hedycoropyran B (*ent*-rhoiptelol B). *Org. Biomol. Chem*., **2022,** *20*, 444–463.
2. **Kataria, P.**; Sahoo S. S.; Kontham, R.; Development of a facile synthetic strategy for substituted furans from keto-oxetanes using Bi(III) catalysis: application to unified total synthesis of furylhydroquinone-derived natural products shikonofuran J, D, E, and C. *Manuscript under preparation.*
3. **Kataria, P.**; Kontham, R.; Kulkarni M. J.; Giri A. P.; Agawane S. B.; Design, synthesis and biological evaluation of eugenol derivatives as potential antidiabetic agents. *Manuscript under preparation.*
4. **Kataria. P.**; Kontham, R. Kulkarni M. J.; Giri A. P.; Agawane S. B.; Eugenol derivatives with improved anti-diabetic and related activitives, NCLI-INV-2019-031 (*Patent submitted*)

List of Publications Non-Emanating from the Thesis Work

5. Thorat, S. S.; **Kataria. P.**; Kontham, R.Synthesis of Furo[2,3-b]pyran-2-ones through Ag(I)- or Ag(I)−Au(I)-catalyzed cascade annulation of alkynols and α-ketoesters *Org. Lett*. **2018**, *20*, 872-875.
6. Nakate, A. K.; **Kataria P.**; Gamidi, R. K.; Kontham, R.; $Bi(OTf)_3$-catalyzed cascade annulations of alkynols and sulfonyl imine: remote α,β-unsaturated imine C=C activation for inverse-electron-demand aza-Diels-Alder reaction. *Manuscript under preparation.*

List of Posters Presented with Details

1. Oral presentation in Annual Student's Conference 2022, organised by NCL Research Foundation & CSIR-National Chemical Laboratory, Pune (November 29-30, **2022**).

   Title: Synthesis of Substituted Furans from Keto-Oxetanes using Bi(III) Catalysis: Application to Unified Total Synthesis of Shikonofuran J, D, E and C.

   Abstract: A mild, efficient, and facile methodology for the synthesis of hydroxy methyl-derived polysubstituted furans employing an unprecedented Bi(III)-catalyzed dehydrative cycloisomerization of α-hydroxy oxetane-tethered ketones is developed. Following this simple and facile protocol, a broad range of products was prepared in good to excellent yields and we successfully applied this protocol in the first enantioselective total synthesis of furyl-hydroquinone-derived antibacterial and anti-inflammatory natural products shikonofurans J, D, E, and C in 7 linear steps from simple and readily accessible building blocks of 2,5-dihydroxy acetophenone, 3-oxetanone and prenyl bromide employing chiral-phosphoric acid (TRIP)-catalyzed asymmetric prenylation, and also synthesized their enantiomers to establish the absolute stereochemistry

2. Oral presentation (YouTube) at Indian National Young Academy of Sciences (INYAS)-Saransh – Thesis Competition for PhD students 2022 (October 25, **2022**).
3. Received Dr. D. S. Bhakuni Award for the oral presentation in the 58th Annual Convention of Chemists, 2021 & International Conference on "Recent Trends in Chemical Sciences (RTCS-2021)" organized by the Indian Chemical Society, Kolkata (December 21– 24, **2021**).

   Title: Studies directed toward the synthesis of hedycoropyrans: total synthesis of des-hydroxy (-)-hedycoropyran B (ent-rhoiptelol B).

4. Oral presentation in Annual Student's Conference 2021, organised by NCL Research Foundation & CSIR-National Chemical Laboratory, Pune (November 29, **2021**).

   Title: Studies directed toward the synthesis of hedycoropyrans: total synthesis of *des*-hydroxy (-)-hedycoropyran B (*ent*-rhoiptelol B).

Abstract: A full account of our efforts directed towards the synthesis of diarylheptanoid-derived natural products hedycoropyrans that led to the total synthesis of *ent*-rhoiptelol B is described. In this endeavor, we have attempted two distinct synthetic strategies to access hedycoropyrans A and B, which led us to establish a facile synthetic route for *des*-hydroxy (-)-hedycoropyran B (*ent*-rhoiptelol B) from simple and readily accessible building blocks of 4-allylanisole and vanillin employing Sharpless asymmetric epoxidation, CBS-reduction, and intramolecular AgOTf-catalyzed oxa-Michael reaction of suitably functionalized hydroxy-ynone as key transformations. Investigations disclosed herein would provide insights in designing novel synthetic routes for THP-DAH-derived natural products.

5. National Science Day Poster presentation at CSIR-National Chemical Laboratory, Pune (February 25-27, **2021**):

   Title: Stereoselective Total Synthesis of *ent*-Rhioptelol B.

   Abstract: Diarylheptanoids constitute an important class of natural products due to their interesting biological and pharmacological properties (anti-inflammatory, antioxidant, anticancer, inhibition of NO production, DPPH-radical scavenging activity, etc) Rhoiptelol B, a diarylheptanoid containing a tetrahydropyran ring, was first isolated in 1996 from the fruits of Rhoiptelea chiliantha, having inhibitory activity against LPS-induced NF-kB activation, NO and TNF-α production and HIF-1 in AGS cells. During our efforts towards the total synthesis of hedycoropyran B, a simple and efficient total synthesis of *ent*-rhoiptelol B (antipode of Rhioptelol B) is achieved using Sharpless asymmetric epoxidation, CBS-reduction, aldol reaction and AgOTf-catalyzed oxa-Michael reaction of hydroxy-ynone as key transformations.

6. National Science Day Poster presentation at CSIR-National Chemical Laboratory, Pune (February 25-27, **2018**):

   Title: Synthesis of Furo[2,3-b]pyran-2-ones through Ag(I)- or Ag(I)−Au(I)-Catalyzed Cascade Annulation of Alkynols and α-Ketoesters

   Abstract: Ag(I)- or Ag(I)−Au(I)-catalyzed cascade annulation of alkynols (5-hexyn-1-ol systems) with α-ketoesters involving a dual activation process (π and σ) has been

developed for the first time. This reaction proceeds through cycloisomerization of alkynol to give the 6-endo-enol ether followed by annulation with an α-ketoester to furnish furo[2,3- b]pyran-2-ones in good yields. Chemical structures of all products were rigorously confirmed by single crystal X-ray analysis and analogy.

List of Conference Attended with Details

International Conference on Nature Inspired Initiatives in Chemical Trends Organic synthesis (**2016**).

Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

PAPER

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Cite this: DOI: 10.1039/d1ob01972d

Studies directed toward the synthesis of hedycoropyrans: total synthesis of des-hydroxy (–)-hedycoropyran B (*ent*-rhoiptelol B)†

Priyanka Kataria, [a,b] Rajesh Nomula [a] and Ravindar Kontham *[a,b]

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Accepted 1st December 2021

DOI: 10.1039/d1ob01972d

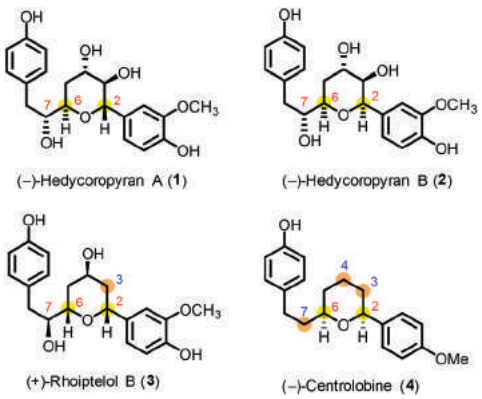
rsc.li/obc

A full account of our efforts directed towards the synthesis of the diarylheptanoid-derived natural products hedycoropyrans that led to the total synthesis of *ent*-rhoiptelol B is described. In this endeavor, we have attempted two distinct synthetic strategies to access hedycoropyrans A and B, which led us to establish a facile synthetic route for des-hydroxy (–)-hedycoropyran B (*ent*-rhoiptelol B) from simple and readily accessible building blocks of 4-allylanisole and vanillin, employing Sharpless asymmetric epoxidation, CBS reduction, and an intramolecular AgOTf-catalyzed oxa-Michael reaction of suitably functionalized hydroxy-ynone as key transformations. The investigations disclosed herein will provide insights into designing novel synthetic routes for THP-DAH-derived natural products.

Introduction

Diarylheptanoids (DAHs) belong to one of the emerging structural classes of natural products known to display interesting biological profiles of anti-inflammatory, antioxidation, anticancer, inhibition of NO production, DPPH-radical scavenging activity, and others.[1] These DAHs are structurally either acyclic or cyclic (containing a tetrahydropyran/tetrahydrofuran ring), and two aryl rings are connected at the C1 and C7 positions of the heptanoid skeleton.[2] Interesting biological profiles of tetrahydropyran-containing diarylheptanoids (THP-DAHs), particularly centrolobines, calyxins, diospongins, rhoiptelol B, and others, have led to a substantial interest in medicinal and synthetic organic chemistry that has produced elegant synthetic strategies involving Prins cyclization, reductive etherification, oxa-Michael reactions, Diels–Alder reactions, palladium-mediated cyclization, $FeCl_3$-mediated cyclization, radical cyclization, Maitland–Japp reactions (Knoevenagel/Michael addition cascades), olefin metathesis and intramolecular Barbier-type reactions as key transformations for the construction of the THP ring system.[3]

In 2015, Lee and co-workers isolated two new DAHs, hedycoropyrans A (**1**) and B (**2**), from the *n*-BuOH soluble fraction of the rhizome of *Hedychium coronarium*, which possesses 2,6-*trans* and 2,6-*cis* configured THP-DAHs, respectively, along with other hedycorofurans and several cytotoxic labdane-type diterpenoids. The chemical structures of hedycoropyrans A and B were established using density functional theory (DFT) and 2D NMR analyses, and the absolute configurations were assigned through quantum chemical calculations of the ECD spectra.[4] Hedycoropyrans A and B possessed extra hydroxyl groups at C3 and C4 of the THP ring and at C7 compared with centrolobines (**4**), and only at C3 compared with rhoiptelol B (**3**). Recently in 2017, Li/Tong disclosed an elegant first asymmetric total synthesis of (–)-hedycoropyrans A and B in 18 and 19 steps, respectively, using their in-house-developed Achmatowicz rearrangement, Zn-mediated reductive deoxygenation, and Heck–Matsuda coupling reactions to construct an unusual and thermodynamically disfavored *trans*-2-aryl-6-alkyl THP core (Scheme 1).[5]



Scheme 1 Chemical structures of representative diarylheptanoid-derived natural products.

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[b]*Academy of Scientific and Innovative Research (AcSIR), Ghaziabad-201002, India*

†Electronic supplementary information (ESI) available. See DOI: 10.1039/d1ob01972d

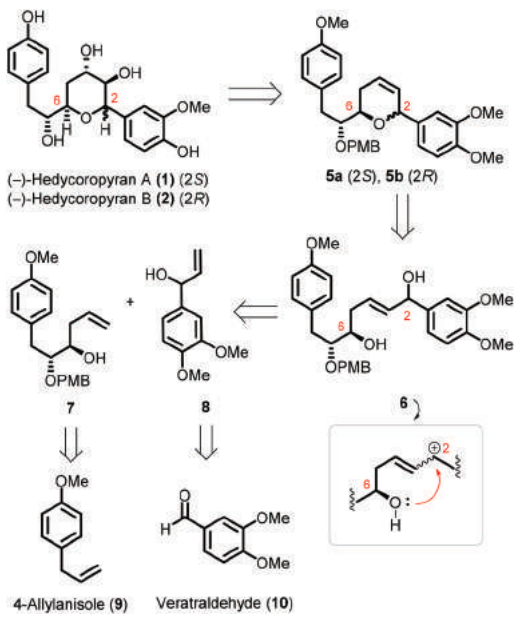
In continuation of our interest in the stereoselective total synthesis of THP-containing biologically potent natural products,[6] we herein report our studies directed toward the total synthesis of hedycoropyrans that led us to showcase very interesting synthetic transformations and establish a facile synthetic route for des-hydroxy (−)-hedycoropyran B, which is *ent*-rhoiptelol B, from the readily accessible building blocks of 4-allylanisole and vanillin using Sharpless asymmetric epoxidation, Corey–Bakshi–Shibata reduction and an AgOTf-catalyzed oxa-Michael reaction of hydroxyl alkyl tethered ynone as key steps.

Results and discussion

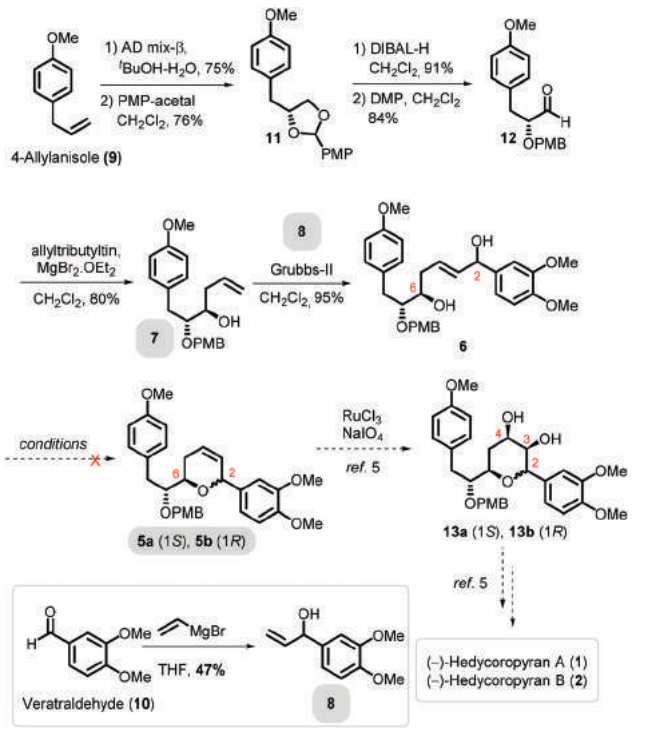
In the initial retrosynthetic analysis, as described in Scheme 2, we envisioned a unified approach for the synthesis of hedycoropyrans A (**1**) and B (**2**) from a suitably functionalized dihydroxy alkene intermediate **6** (containing allylic and homoallylic alcohol functionalities) *via* allylic carbocation-mediated ring-closure that would deliver advanced 2,6-*trans*/2,6-*cis* dihydropyran intermediate **5a**/**5b**. This key intermediate **6** could be obtained through a cross-metathesis reaction of homoallylic alcohol **7** and allylic alcohol **8**. Alkenols **7** and **8** would be synthesized from the commercially available and cost-effective building blocks 4-allylanisole (estragole, **9**) and veratraldehyde (**10**), employing interesting synthetic manipulations (Scheme 2).

Hence, our efforts began to access the key DAH-derived dihydroxy alkene intermediate **6** starting from building blocks **9** and **10**. 4-Allylanisole (estragole, **9**) was subjected to Sharpless asymmetric dihydroxylation[7] using AD mix-β/$MeSO_2NH_2$ to obtain the corresponding 1,2-diol, which was subsequently protected as its *p*-methoxy benzylidene acetal **11**.[8] The regioselective reductive opening[9] of the 1,2-acetal **11** using DIBAL-H followed by Dess–Martin periodinane oxidation[10] delivered aldehyde **12**. The substrate-controlled addition of allyltributyltin onto aldehyde **12** in the presence of $MgBr_2{\cdot}OEt_2$ delivered the requisite homoallylic alcohol **7** as only a diastereomer.[11] Then, cross-metathesis reaction[12] of **7** and **8** (prepared from the vinylation of veratraldehyde **10**)[13] using the Grubbs 2nd-generation catalyst furnished the desired DAH-derived dihydroxy alkene intermediate **6** (exclusively *trans*-olefin) in an excellent yield of 95%. Next, the crucial allylic carbocation-induced ring-closure reaction of alkene-diol **6** was attempted using well-established reaction conditions of $BF_3{\cdot}OEt_2/CH_2Cl_2$,[12] $PdCl_2(PPh_3)_2/CH_2Cl_2$ [12] and $Pd(CH_3CN)_2Cl_2/CH_2Cl_2$ [12] at low to ambient (−78 °C to rt) temperatures, which proved to be unsuccessful, and starting material **6** was decomposed in all cases. If this proposed transformation to access **5a**/**5b** from **6** had worked well, our next sequence of reactions (as reported by Li and Tong)[5] as described *via* diols **13a**/**13b** would have led to the total synthesis of hedycoropyrans A (**1**) and B (**2**) (Scheme 3).

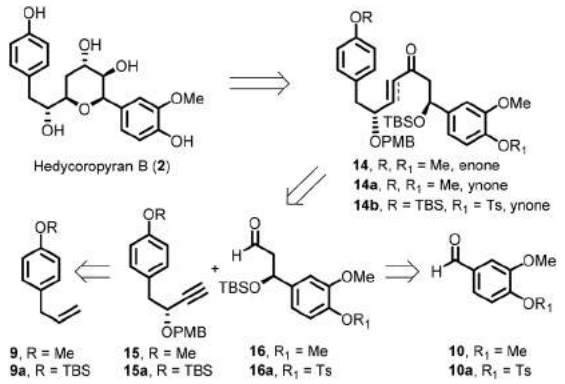
Since this initially designed strategy was unsuccessful, we were required to seek a distinct approach to access natural products **1** and/or **2**, and we considered a new retrosynthetic analysis based on the intramolecular oxa-Michael reaction that provides access to the THP ring system with desired stereochemistry as depicted in Scheme 4. Thus, we envisioned the construction of hedycoropyran B (**2**) *via* intramolecular oxa-



Scheme 2 Initial retrosynthetic analysis of hedycoropyrans A (**1**) and B (**2**).



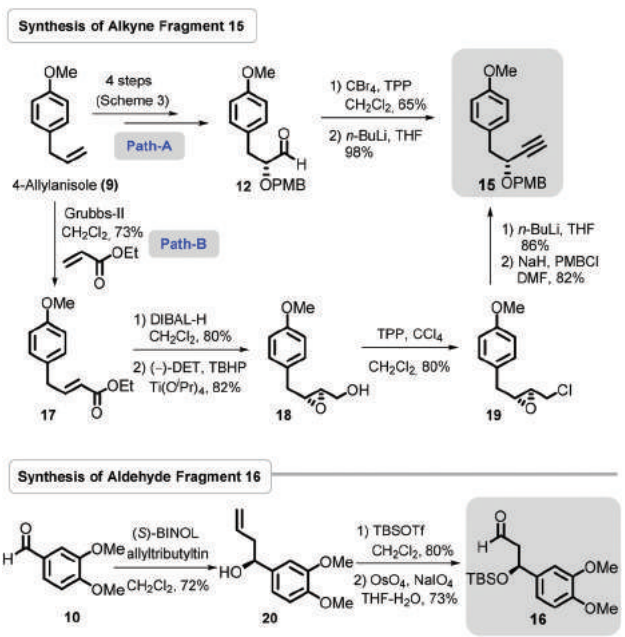
Scheme 3 Efforts toward the synthesis of hedycoropyrans A (**1**) and B (**2**) *via* allylic carbocation-mediated ring closure.



Scheme 4 New retrosynthetic analysis of hedycoropyran B (**2**) based on the oxa-Michael reaction of hydroxy-enone or hydroxy-ynone.

Michael-induced ring closure of suitably constructed enone **14** or ynone **14a**/**14b** intermediates with varying O-substituents. In this context, we anticipated a convergent approach comprising Li-acetylide (generated from **15**/**15a**) addition onto the chiral-aldehydes **16**/**16a** followed by oxidation to access the enone/ynone intermediates (**14**/**14a**, **14b**). Intermediates **15**/**15a** and **16**/**16a** could be obtained from commercially available 4-allylanisole (**9**) and veratraldehyde (**10**) or their congeners (**9a** and vanillin) respectively (Scheme 4).

Hence, this alternate route began with the synthesis of alkyne intermediate **15** from 4-allylanisole (**9**) in two distinct pathways. In the first route, aldehyde **12** (prepared from **9** in Scheme 3) was subjected to Corey–Fuchs olefination[14] and subsequently treated with *n*-BuLi[14] to afford the desired alkyne fragment **15** (path A, Scheme 5). Furthermore, an alternate route for **15** was also evaluated *via* epoxy alcohol **18**. Thus, allylanisole **9** was converted into α,β-unsaturated ester **17** employing a cross-metathesis reaction,[12] and was then reduced using DIBAL-H to afford allylic alcohol and subsequently converted into chiral epoxy alcohol **18** under Sharpless conditions.[15] Next, epoxy alcohol **18** was transformed into chloride **19** using TPP and CCl_4.[16] It was subjected to a base-mediated (*n*-BuLi) rearrangement reaction to obtain propargylic alcohol, which was subsequently protected as its PMB ether to get the desired alkyne fragment **15** (path B, Scheme 5).[17] After establishing a reliable synthetic route for **15**, we synthesized an aldehyde coupling partner **16** from veratraldehyde **10**. Asymmetric Keck allylation of **10** (using (*S*)-BINOL, $Ti(O^iPr)_4$, and allyltributyltin) to give allyl alcohol **20**,[18] followed by TBS protection[19] and dihydroxylative cleavage (OsO_4, 2,6-lutidine, and $NaIO_4$)[20] steps, cleanly delivered aldehyde **16** (Scheme 5).

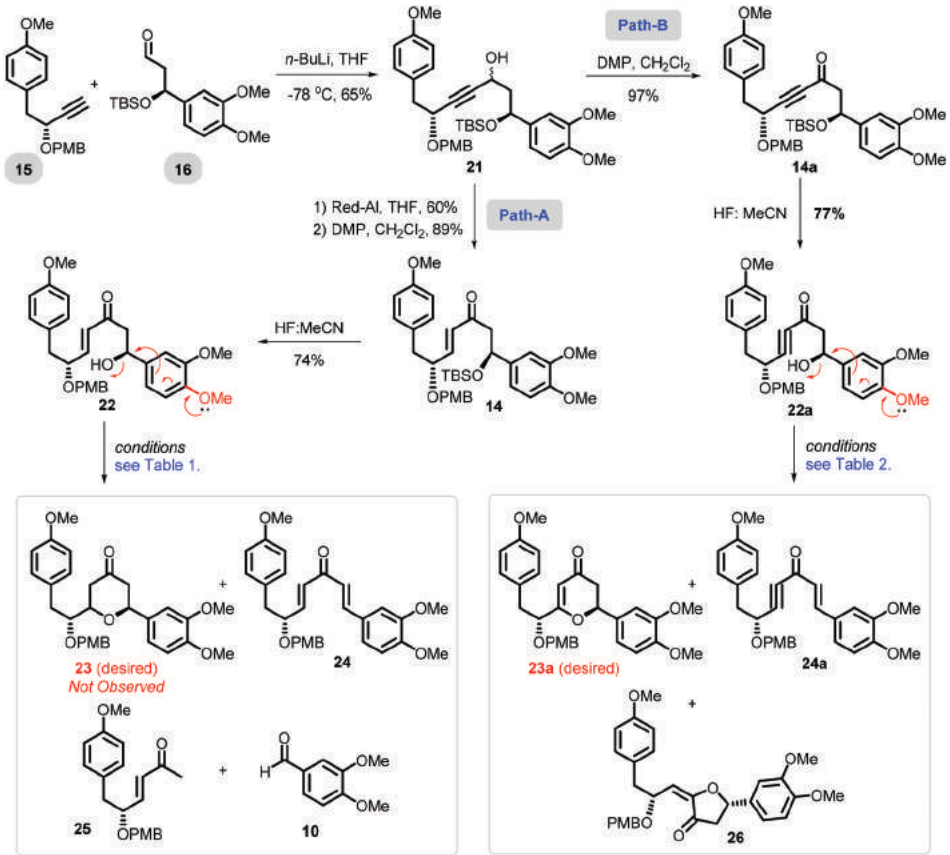


Scheme 5 Synthesis of alkyne fragment **15** and aldehyde fragment **16**.

Having synthesized alkyne **15** and aldehyde **16** fragments on a gram scale, the stage was set for the coupling and to verify our hypothesis of an intramolecular oxa-Michael reaction. Initially, we wanted to evaluate the oxa-Michael reaction using enone **14** as a substrate (path A, Scheme 6). Thus, alkyne **15** and aldehyde **16** were coupled using *n*-BuLi in THF to obtain propargylic alcohol **21**.[21] Next, partial reduction of alkyne **21** using Red-Al[22] followed by Dess–Martin periodinane oxidation[10] cleanly delivered enone **14** in a good yield. TBS deprotection[23] of **14** using HF in CH_3CN gave hydroxy-alkyl tethered enone **22** in 74% yield. Next, the crucial oxa-Michael reaction of the hydroxy-enone **22** to give pyranone **23** proved to be insurmountable, under base (KO^tBu,[24a] NaH,[24b,c] DBU[24d]), acid (Amberlyst-15)[24e,f] and Pd(II) catalyzed[24g,h] reaction conditions, leading to either the corresponding dehydrated product **24** or retro-aldol products **10** and **25** (path A, Scheme 6; Table 1).

Hence, we slightly altered the strategy by replacing enone **22** with the corresponding ynone **22a** as an oxa-Michael addition precursor to verify the reactivity patterns, as shown in path B of Scheme 6. Therefore, ynone **22a** was prepared from **21** through Dess–Martin periodinane oxidation,[10] and HF-CH_3CN-mediated TBS deprotection[23] steps, and was evaluated for the intramolecular oxa-Michael reaction using well-reported procedures (Table 2). Initial conditions of using Pd$(CH_3CN)_2Cl_2$-mediated cyclization[25a] led to the decomposition of the starting material. Cyclization using NaH[25b] and/or mild Lewis acid (AgOTf, catalytic)[25c] resulted in the undesired dehydrated product **24a**, whereas AuCl-catalyzed cyclization[26] was found to be non-selective towards this oxa-Michael reaction by providing an inseparable mixture (1 : 1 ratio) of desired pyranone **23a** (through the 6-*exo*-dig mode of cyclization) and furanone **26** (through the 5-*endo*-dig mode of cyclization) (path-B, Scheme 6). These unfruitful results (except for the AuCl reaction of entry 4, Table 2) reveal the sensitivity of the benzylic hydroxyl group (of **22** and **22a**) toward basic or acidic conditions, which could be due to the stabilization of the benzylic carbocation through the mesomeric effect of the *p*-OMe group of the phenyl ring (path A and path B, Scheme 6).

Suspecting the role of the *p*-OMe group (of **22** and **22a**, Scheme 6) in the failure of the above intramolecular oxa-



Scheme 6 Efforts toward the synthesis of hedycoropyran B (**2**) *via* an oxa-Michael reaction of hydroxy-enone/hydroxy-ynone.

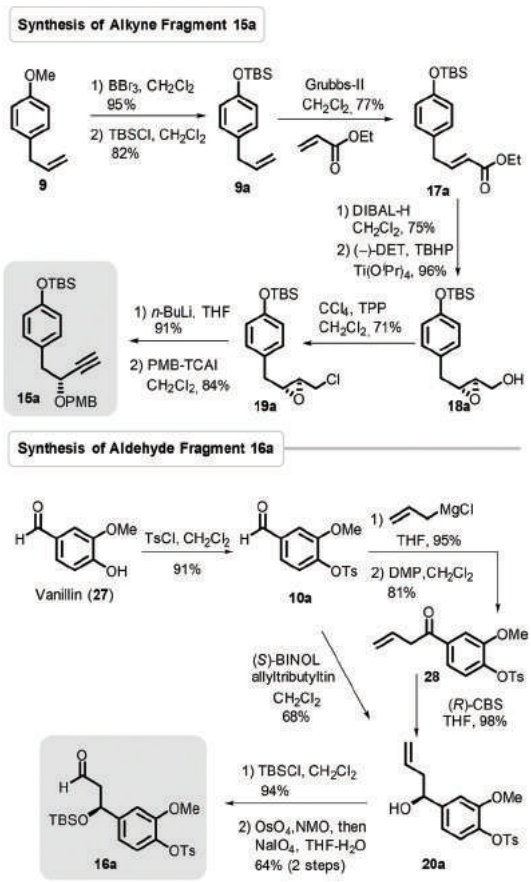
Table 1 Efforts toward the synthesis of pyranone **23**

Entry	Conditions	Result
1	KO^{t}Bu (0.1 equiv.) EtOH, 0 °C to rt	**24**, 13%; **25**, 60% and **10**, 26%
2	NaH (2.2 equiv.) −78 °C, THF	**24**, 8%; **25**, 49% and **10**, 32%
3	DBU (4 equiv.) DCM, 0 °C	**24**, 68%
4	Amberlyst-15 (2 equiv.) CH_2Cl_2, rt	**24**, 74%
5	$Pd(MeCN)_2Cl_2$ (0.1 equiv.) CH_2Cl_2, rt	**22**, recovered

Table 2 Efforts toward the synthesis of dihydropyranone **23a**

Entry	Conditions	Result
1	$Pd(CH_3CN)_2Cl_2$ (0.1 equiv.), Cu $(OAc)_2{\cdot}H_2O$ (0.1 equiv.), PPh_3, DME, 65 °C, 24 h	**22a**, decomposed
2	NaH (1 equiv.), THF, 0 °C, 1 h	**24a**, 78%
3	AgOTf (0.1 equiv.), CH_2Cl_2, rt, 18 h	**24a**, 72%
4	AuCl (0.02 equiv.), $NaHCO_3$, MS 4 Å, 5 h	**23a** and **26** (1 : 1), 90%, inseparable

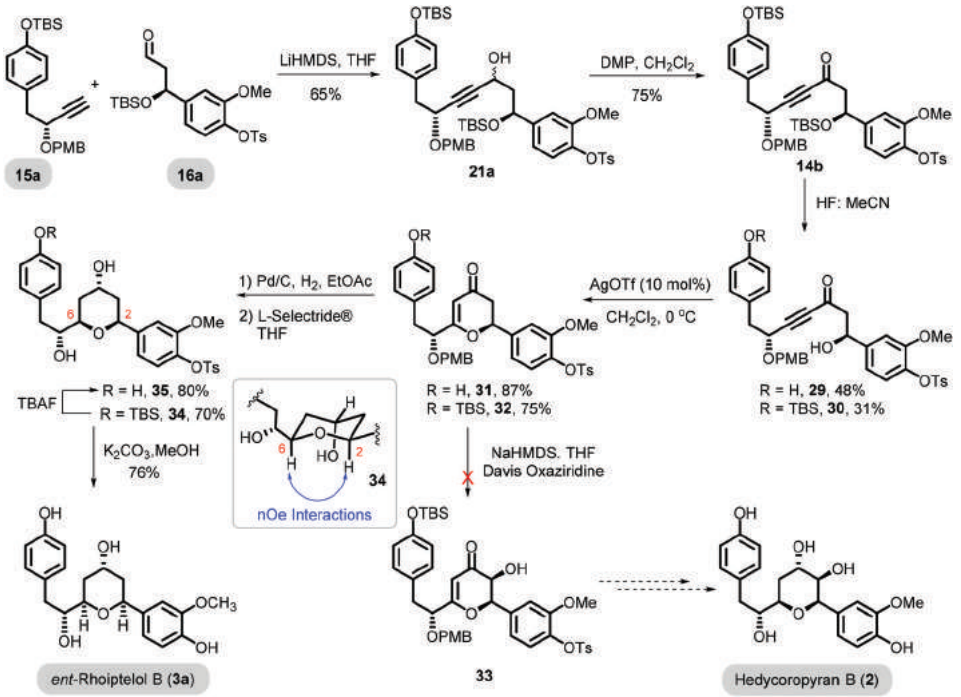
Michael reactions and the literature precedence of a successful survival of similar benzylic hydroxyl groups in the presence of *p*-OAc and *p*-OTs substituents,[3] we intended to verify the fate of our endeavor by replacing the *p*-OMe group with *p*-OTs (replacing alkyne **15** and aldehyde **16** fragments with **15a** (having *p*-OTBS) and **16a** (having *p*-OTs) respectively), as described in Scheme 7. Demethylation[27] of 4-allylanisole (**9**) using BBr_3 followed by TBS protection gave allylbenzene **9a**. Next, the cross-metathesis reaction[12] of **9a** with ethyl acrylate delivered α,β-unsaturated ester **17a**. The DIBAL-H reduction of **17a** followed by Sharpless epoxidation using (−)-DET, TBHP, and $Ti(O^iPr)_4$ resulted in epoxy alcohol **18a**. We then used a similar reaction sequence employed for preparation of **15** (Scheme 5) to obtain alkyne fragment **15a** from **18a**. Next, the aldehyde coupling partner **16a** containing the *p*-OTs group was obtained from vanillin (**27**). A four-step sequence comprising tosylation, Keck asymmetric allylation, and TBS protection followed by dihydroxylative cleavage of olefin (OsO_4, NMO, then $NaIO_4$) delivered the desired fragment **16a** (**27** → **10a** → **20a** → **16a**). In an alternative route, allylic alcohol **20a** was obtained from a common tosylate intermediate **10a**, in which **10a** was subjected to allylation, and Dess–Martin periodinane oxidation steps to obtain ketone **28**. Subsequent Corey–Bakshi–Shibata reduction[28] (using (*R*)-CBS catalyst) of **28** gave the common precursor **20a** (**27** → **10a** → **28** → **20a**; Scheme 7).



Scheme 7 Synthesis of alkyne fragment **15a** and aldehyde fragment **16a**.

Now, the stage was set to verify our envisioned ultimate strategy to access hedycoropyrans using *p*-OTs substituted intermediates. Accordingly, lithiated alkyne **15a** was coupled with aldehyde **16a** to obtain propargylic alcohol **21a** as a mixture of diastereomers in a good yield of 65%, which was then subjected to DMP oxidation to furnish the desired ynone **14b**. As expected, HF-CH_3CN-mediated TBS deprecation led to the fully and partially deprotected alcohols **29** and **30**. Then we tested the subsequent intramolecular oxa-Michael reaction of **29**/**30** using 10 mol% of AgOTf at 0 °C. To our delight, pyranones **31**/**32** were obtained in good yields without anticipated retro-aldol by-products. At this stage, the TBS-protected dihydro-pyranone **32** was subjected to α-hydroxylation using diverse conditions of NaHMDS, Davis oxaziridine,[29] and PIDA,[30] which failed to provide the desired product **33** and hampered the possibility to access hedycoropyran B (**2**) (Scheme 8).

As we had a sufficient quantity of intermediates **31** and **32** in hand, we embarked on accessing the structurally close diarylheptanoid *ent*-rhoiptelol B (des-hydroxy hedycoropyran B, **3a**). Rhoiptelol B (**3**) was isolated from the fruits of *Rhoiptelea chiliantha* and also from the bark of *Alnus hirsuta* in 1996 and 2007 and is known to display inhibitory activities against LPS-induced NF-KB activation, NO and TNF-α production, and HIF-1 in AGS cells.[3] Thus, dihydropyranones **31** and **32** were subjected to hydrogenation (Pd/C, H_2) of the olefin followed by L-selectride reduction of the carbonyl group, which cleanly delivered the respective pyrans **35** and **34** (**34** was subjected to TBS deprotection to get **35**; NOE analyses confirmed 2,6-*cis* stereochemistry of THP **34**). Finally, K_2CO_3 in MeOH-mediated



Scheme 8 Completion of the total synthesis of des-hydroxy hedycoropyran B (*ent*-rhoiptelol B).

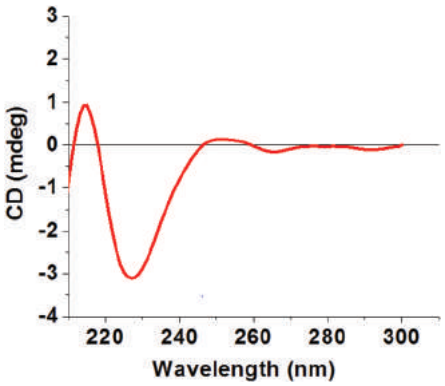


Fig. 1 ECD spectrum of *ent*-rhoiptelol (**3a**).

detosylation of **35** delivered des-hydroxy hedycoropyran B (*ent*-rhoiptelol B, **3a**) (Scheme 8).

ent-Rhoiptelol B (**3a**) was confirmed by comparing ^{1}H, ^{13}C NMR, and ESI-MS (HRMS) data with the reported data. As expected, the optical rotation value of **3a** ($[\alpha]_D^{26.6}$ = −81.04 (*c* = 0.1, MeOH), this work) was found to be opposite to the reported value of natural product (+)-rhoiptelol B (4) ($[\alpha]_D^{12}$ = +97 (*c* = 0.3, MeOH), literature data). The assigned absolute configuration of **3a** was further supported by electronic circular dichroism (ECD) analyses; the ECD spectrum of **3a** showed a negative Cotton effect (CE) at 227.10 nm (CD, 0.4 × 10^{-3} M, EtOH), λ_{max} ($\Delta\varepsilon$) 214.44 (+0.91), 227.10 (−3.09) (nm), which was similar to the data reported for structurally and stereochemically (particularly 2,6-*cis* THP) closer hedycoropyran B (**2**) (which showed ECD (MeCN, *c* 2.66 × 10^{-5} M) $[\theta]_{231}$ −3226, $[\theta]_{285}$ +1556) (Fig. 1).[4]

Conclusions

In conclusion, we have attempted a couple of synthetic strategies for the total synthesis of the diarylheptanoid natural products hedycoropyrans, which were unfruitful, but led us to showcase some efficient synthetic organic chemistry and the development of a total synthetic route for des-hydroxy hedycoropyran B (*ent*-rhoiptelol B) in 19 steps using the commercially available and affordable building blocks 4-allylanisole (estragole), veratraldehyde and vanillin. Cross-metathesis, Sharpless asymmetric epoxidation, CBS-reduction/Keck asymmetric allylation, and AgOTf-mediated intramolecular oxa-Michael addition of hydroxy-ynone were used as key steps in this work. Our investigations disclosed in this paper would provide insights into designing novel synthetic routes for THP-DAH-derived natural products. Further study of the structure–activity relationships of rhoiptelol B and its congeners is in progress and will be published in due course.

Experimental

General information

All reactions were performed under an argon atmosphere with oven (90 °C) or flame dried glassware with a septum seal. Anhydrous dichloromethane, tetrahydrofuran, *N*,*N*-dimethylformamide, benzene, and methanol solvents were purchased from commercial sources and used under an argon atmosphere. The temperature of 26 °C corresponded to the room temperature (rt) of the laboratory when the experiments were carried out. The reaction temperatures are reported as the temperatures of the bath surrounding the reaction vessel. Analytical thin-layer chromatography (TLC) was performed on TLC Silica gel 60 F254. Visualization was accomplished with short-wave UV light, anisaldehyde, or $KMnO_4$ staining solutions followed by heating. Chromatography was performed on silica gel (100–200 mesh) by standard techniques eluting with solvents as indicated. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AV 200, 400, and 500 spectrometers in solvents as indicated. Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references and the chemical shifts were converted to the TMS scale ($CDCl_3$: δ H = 7.26 ppm, δ C = 77.16 ppm); the following abbreviations were used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; AB q, AB quartet; dd, doublet of doublets; td, triplet of doublets; and br, broad. HRMS data were recorded on a Q Exactive Hybrid™ Quadrupole-Orbitrap™ mass spectrometer (Thermo Scientific™, Accela 1250 pump). ECD spectra were recorded on a JASCO J-815 CD spectrometer. Experimental procedures for all new compounds and known compounds without published experimental procedures are described below.

(*R*)-3-(4-Methoxyphenyl)propane-1,2-diol (S1)

To a stirred solution of *t*-BuOH : H_2O (1 : 1, 20 mL) were added AD mix-β (6.74 g, 13.4 mmol) and $CH_3SO_2NH_2$ (1.28 g, 13.4 mmol) at room temperature. The mixture was vigorously stirred at room temperature until both the phases were clear, and was then cooled to 0 °C. A solution of *p*-allylanisole **9** (2 g, 13.4 mmol) in *t*-BuOH was added at 0 °C. The reaction was stirred at the same temperature for about 48 h. The reaction was quenched at 0 °C by the addition of solid sodium sulphite, warmed to rt and further stirred for 1 h at rt. The reaction mixture was extracted with EtOAc and the combined layers were washed with 2N KOH solution, water and brine. The organic layer was dried over Na_2SO_4, filtered, concentrated and subjected to column chromatography (using 40% EtOAc in hexanes) to afford **S1** (1.84 g, 75%) as a white solid. R_f = 0.6 (SiO_2, 100% EtOAc in hexanes); reported $[\alpha]_D^{25}$ = +12.90 (*c* = 2, $CHCl_3$), observed $[\alpha]_D^{26.30}$ = +5.495 (*c* = 1.8, $CHCl_3$); FTIR (cm^{-1}): 3682, 3614, 3444, 2402, 1612, 1515, 1427, 1036, 927; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.13 (d, *J* = 7.9 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 3.95–3.85 (m, 1H), 3.79 (s, 3H), 3.71–3.64 (m, 1H), 3.53–3.47 (m, 1H), 2.80–2.63 (m, 2H), 2.19 (br. s, 2H); $^{13}C\{H\}$ NMR ($CDCl_3$, 101 MHz): δ 158.5, 130.4, 129.7, 114.2, 73.3, 66.2, 55.4, 39.0; HRMS (ESI): *m*/*z* calcd for $C_{10}H_{14}O_3Na$ $[M + Na]^+$ 205.0835, found 205.0835.

(4*R*)-4-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-1,3-dioxolane (11)

To a solution of **S1** (1.96 g, 10.75 mmol) in CH_2Cl_2 were added 1-(dimethoxymethyl)-4-methoxybenzene (2.93 g, 16.13 mmol) and PPTS (270 mg, 1.07 mmol) at rt. The resulting mixture was

stirred at rt for 5 h, and then the reaction was quenched with aq. NH_4Cl and extracted with EtOAc (3 × 10 mL). The organic layer was dried over Na_2SO_4, filtered, concentrated under reduced pressure and subjected to silica gel column chromatography (using 12% EtOAc in hexanes) to afford **11** (2.6 g, 76%) as a white solid (mixture of diastereomers). TLC: R_f = 0.6 (SiO_2, 30% EtOAc/hexanes); FTIR (cm^{-1}): 3425, 2973, 2402, 1622, 1516, 1430, 1299, 1078, 1037, 927; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.49–7.34 (m, 2H), 7.20–7.13 (m, 2H), 6.95–6.82 (m, 4H), 5.84 (m, 1H), 4.48–4.36 (m, 1H), 4.20–3.96 (m, 1H), 3.85–3.79 (m, 6H), 3.79–3.64 (m, 1H), 3.11–3.01 (m, 1H), 2.89–2.73 (m, 1H); $^{13}C\{H\}$ NMR ($CDCl_3$, 50 MHz): δ 160.4, 158.5, 130.6, 130.3, 129.3, 128.2, 127.9, 114.1, 113.9, 104.3, 103.5, 70.3, 69.6, 55.4, 39.2, 38.7; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{20}O_4Na$ $[M + Na]^+$ 323.1254, found 323.1251.

(*R*)-2-((4-Methoxybenzyl)oxy)-3-(4-methoxy-phenyl)propan-1-ol (S2)

To a solution of (4*R*)-4-(4-methoxybenzyl)-2-(4-methoxyphenyl)-1,3-dioxolane (**11**) (2.6 g, 8.27 mmol) in CH_2Cl_2 and stirred at −78 °C, DIBAL-H (13.72 mL, 13.70 mmol) was added dropwise and the mixture was stirred for about 2 h. The reaction was monitored by TLC. After completion of the reaction, it was quenched with sodium potassium tartrate (Na^+–K^+ tartrate) and the reaction mass was extracted with EtOAc (3 × 20 mL) and filtered through Celite. The filtrate containing organic compound was filtered through Na_2SO_4 and concentrated, and the crude product was subjected to silica gel column chromatography (using 30% EtOAc in hexanes) to afford **S2** (2.28 g, 91%) as a yellow liquid. TLC: R_f = 0.4 (SiO_2, 40% EtOAc/hexanes); $[\alpha]_D^{26.30}$ = +2.93 (*c* = 1.3, $CHCl_3$); FTIR (cm^{-1}): 3417, 1638, 1381, 1249, 1072, 805, 743; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.21 (d, *J* = 8.46 Hz, 2H), 7.13 (d, *J* = 8.59 Hz, 2H), 6.91–6.80 (m, 4H), 4.55–4.38 (m, 2H), 3.85–3.77 (m, 6H), 3.71–3.58 (m, 2H), 3.54–3.41 (m, 1H), 2.94–2.80 (m, 1H), 2.80–2.66 (m, 1H), 2.10 (br. s, 1H); $^{13}C\{H\}$ NMR ($CDCl_3$, 50 MHz): δ 159.3, 158.2, 130.4, 130.3, 129.5, 113.9, 80.7, 71.6, 63.7, 55.3, 36.6; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{22}O_4Na$ $[M + Na]^+$ 325.1410, found 325.140.

(*R*)-2-((4-Methoxybenzyl)oxy)-3-(4-methoxy-phenyl)propanal (12)

To a solution of (*R*)-2-((4-methoxybenzyl)oxy)-3-(4-methoxyphenyl)propan-1-ol (**S2**) (846 mg, 2.81 mmol) in CH_2Cl_2 was added Dess–Martin Periodinane (DMP) (1.79 g, 4.22 mmol) at 0 °C under an inert atmosphere. The reaction progress was monitored by TLC. After completion of the reaction, aqueous $NaHCO_3$ and sodium thiosulphate (1 : 1) were added. Then, extracted with DCM using a separating funnel. The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated, and the crude product was subjected to silica gel column chromatography (using 15% EtOAc in hexanes) to afford **12** (712 mg, 84%) as a colorless oil. TLC: R_f = 0.6 (SiO_2, 30% EtOAc/hexanes); $[\alpha]_D^{26.23}$ = +4.36 (*c* = 1.2, $CHCl_3$); FTIR (cm^{-1}): 3686, 3618, 3455, 2975, 2402, 1721, 1603, 1518, 1426, 1039, 927; ^1H NMR (200 MHz, $CDCl_3$): δ 9.64 (d, *J* = 1.98 Hz, 1H), 7.14 (d, *J* = 7.72 Hz, 4H), 6.92–6.72 (m, 4H), 4.58–4.35 (m, 2H), 4.00–3.85 (m, 1H), 3.80 (s, 6H), 3.07–2.70 (m, 2H); $^{13}C\{H\}$ NMR (50 MHz, $CDCl_3$): δ 203.6, 191.1, 142.1, 133.6, 132.2, 130.6, 129.8, 128.2, 114.5, 114.0, 84.2, 72.7, 55.7, 55.4, 36.0; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{20}O_4Na$ $[M + Na]^+$ 323.1254, found 323.1249.

(2*R*,3*R*)-2-((4-Methoxybenzyl)oxy)-1-(4-methoxyphenyl)hex-5-ene-3-ol (7)

To a solution of aldehyde **12** (500 mg, 1.66 mmol) in Et_2O in a 100 mL round-bottom flask at 0 °C, $MgBr_2{\cdot}OEt_2$ (687 mg, 2.66 mmol) was added in one portion. After 10 min, allyltributyltin (0.87 mL, 2.82 mmol) was added dropwise over 10 min. After completion of the addition, the reaction mixture was stirred for 3 h at 0 °C and the reaction progress was monitored by TLC. After completion of the reaction it was quenched by aq. sat. $NaHCO_3$, the layers were separated, the aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, filtered and concentrated in a vacuum. The residue was purified by silica gel column chromatography (using 15% EtOAc in hexanes) to afford **7** (456 mg, 80%) as a colorless liquid. TLC: R_f = 0.5 (SiO_2, 30% EtOAc/hexanes); $[\alpha]_D^{25.23}$ = +4.49 (*c* = 1.9, $CHCl_3$); FTIR (cm^{-1}): 3680, 3620, 2975, 2399, 1611, 1512, 1476, 1423, 1300, 1035, 928, 877, 849; ^1H NMR (200 MHz, $CDCl_3$): δ 7.23–7.08 (m, 4H), 6.94–6.76 (m, 5H), 5.95–5.67 (m, 1H), 5.18–4.98 (m, 2H), 4.52–4.23 (m, 2H), 3.82–3.78 (m, 6H), 3.57–3.40 (m, 2H), 2.97–2.74 (m, 2H), 2.36–2.15 (m, 3H); $^{13}C\{H\}$ NMR (126 MHz, $CDCl_3$): δ 159.4, 158.2, 135.0, 130.6, 130.3, 129.7, 129.7, 117.3, 113.9, 113.9, 82.0, 72.6, 71.5, 55.3, 38.5, 36.2; HRMS (ESI): *m*/*z* calcd for $C_{21}H_{26}O_4Na$ $[M + Na]^+$ 365.1723, found 365.1728.

1-(3,4-Dimethoxyphenyl)prop-2-en-1-ol (8)

To a solution of aldehyde **10** (2 g, 12.0 mmol) in dry THF, vinyl magnesium bromide (1 M in THF, 14.44 mL, 14.4 mmol) was added at −78 °C and the reaction mixture was stirred for 1 h at the same temperature. After completion of the reaction, the reaction was quenched with sat. aq. solution of NH_4Cl. The layers were separated, the aqueous layer was extracted with ethyl acetate (3 × 15 mL), the combined organic layer was washed with brine and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* and the crude product was purified by silica gel column chromatography (using 30% EtOAc in hexanes) to afford **8** (1.05 g, 47%) as a colorless liquid. TLC: R_f = 0.4 (SiO_2, 40% EtOAc/hexanes); FTIR (cm^{-1}): 3673, 3490, 2841, 2598, 2410, 2054, 1847, 1729, 1648, 1598, 1512, 1457, 1423, 1374, 1146, 1036, 928, 858; ^1H NMR (200 MHz, $CDCl_3$): δ 6.97–6.75 (m, 3H), 6.15–5.90 (m, 1H), 5.31 (d, *J* = 17.05 Hz, 1H), 5.23–5.03 (m, 2H), 3.95–3.75 (m, 6H), 2.28 (br. s., 1H); $^{13}C\{H\}$ NMR (50 MHz, $CDCl_3$): δ 149.3, 148.8, 140.4, 135.4, 118.8, 115.1, 111.2, 109.6, 75.2, 56.1, 56.0; HRMS (ESI): *m*/*z* calcd for $C_{11}H_{14}O_3Na$ $[M + Na]^+$ 217.0835, found 217.0835.

(5*R*,6*R*,*E*)-1-(3,4-Dimethoxyphenyl)-6-((4-methoxybenzyl)oxy)-7-(4-methoxyphenyl)hept-2-ene-1,5-diol (6)

To a solution of **7** (450 mg, 2.33 mmol) and **8** (100 mg, 0.292 mmol) in CH_2Cl_2 (1 mL) was added the G-II generation

catalyst (20 mg, 0.05 mmol) and the mixture was stirred at rt for 1 h. The solvent was evaporated in a vacuum and the residue was purified by silica gel column chromatography (using 40% EtOAc in hexanes) to afford **6** (637 mg, 95%) as a yellow liquid. TLC: R_f = 0.8 (SiO_2, 50% EtOAc/hexanes); FTIR (cm^{-1}): 3685, 3618, 2974, 2403, 1674, 1596, 1516, 1426, 1149, 1034, 927; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.20–7.12 (m, 3H), 7.09 (d, J = 3.16 Hz, 1H), 6.91 (s, 1H), 6.88–6.78 (m, 6H), 5.77–5.62 (m, 2H), 5.10 (d, J = 4.04 Hz, 1H), 4.47–4.20 (m, 2H), 3.98–3.92 (m, 1H), 3.89 (br. s., 1H), 3.87 (s, 6H), 3.79 (s, 6H), 3.57–3.37 (m, 2H), 2.84 (dd, J = 2.78, 5.81 Hz, 2H), 2.34–2.24 (m, 2H); ^{13}C{H} NMR (101 MHz, $CDCl_3$): δ 159.5, 158.4, 149.3, 148.6, 135.4, 130.6, 130.3, 129.9, 118.5, 114.0, 111.2, 109.5, 82.1, 74.9, 72.6, 56.0, 55.4, 36.3; HRMS (ESI): m/z calcd for $C_{30}H_{36}O_7Na$ $[M + Na]^+$ 531.2353, found 531.2367.

(*R*)-1-(((4,4-Dibromo-1-(4-methoxyphenyl)but-3-en-2-yl)oxy) methyl)-4-methoxybenzene (S3)

To a solution of CBr_4 (4.86 g, 14.6 mmol) in CH_2Cl_2 at −40 °C, TPP ((7.70 g, 29.3 mmol) dissolved in a minimum amount of CH_2Cl_2) under an inert atmosphere was added. After stirring for 20 min, a cold solution of **12** (1.47 g, 4.89 mmol) containing Et_3N (0.68 mL, 4.89 mmol) was added dropwise to the reaction mixture. The reaction was monitored by TLC. After completion of the reaction, Et_3N and MeOH were added successively at the same temperature, then the solvent was evaporated and diethyl ether was added, and then the reaction mass was filtered through a sintered funnel containing Celite. The filtrate was collected, concentrated and subjected to column chromatography (using 7% EtOAc in hexanes) to afford **S3** (1.45 g, 65% yield) as a white solid. TLC: R_f = 0.6 (SiO_2, 20% EtOAc/hexanes); FTIR (cm^{-1}): 3685, 3619, 3453, 2975, 2402, 1608, 1518, 1427, 1049, 927; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.23–7.05 (m, 4H), 6.91–6.76 (m, 4H), 6.43 (d, J = 8.34 Hz, 1H), 4.51 (d, J = 11.49 Hz, 1H), 4.30 (d, J = 11.49 Hz, 1H), 4.26–4.13 (m, 1H), 3.84–3.78 (m, 6H), 2.99–2.67 (m, 2H); ^{13}C{H} NMR ($CDCl_3$, 126 MHz): δ 159.3, 158.4, 139.6, 130.8, 130.2, 129.4, 129.3, 113.8, 113.8, 91.4, 80.1, 70.9, 55.4, 40.0; HRMS (ESI): m/z calcd for $C_{19}H_{20}O_3Br_2Na$ $[M + Na]^+$ 478.9651, found 478.9646.

(*R*)-1-Methoxy-4-(2-((4-methoxybenzyl)oxy)but-3-yn-1-yl) benzene (15)

To a solution of (*R*)-1-(((4,4-dibromo-1-(4-methoxyphenyl)but-3-en-2-yl)oxy)methyl)-4-methoxybenzene (**S3**) (1.45 g, 3.17 mmol) in anhydrous tetrahydrofuran at −78 °C was added *n*-BuLi (1.6 M, 4.3 mL, 6.99 mmol) dropwise at the same temperature. The reaction was monitored with TLC for about an hour. After the completion of the reaction, saturated aqueous NH_4Cl was added to quench the reaction mass and this was extracted with EtOAc (3 × 20 mL). The combined organic layer was dried over Na_2SO_4, concentrated under reduced pressure and subjected to silica gel column chromatography (using 10% EtOAc in hexanes) to afford **15** (800 mg, 98% yield) as a colorless oil. TLC: R_f = 0.5 (SiO_2, 20% EtOAc/hexanes); $[\alpha]_D^{26.20}$ = +20.0 (c = 1.4, $CHCl_3$); FTIR (cm^{-1}): 3685, 3415, 2927, 2402, 1610, 1516, 1428, 1036, 927; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.25–7.14 (m, 4H), 6.90–6.79 (m, 4H), 4.75 (d, J = 11.49 Hz, 1H), 4.45 (d, J = 11.49 Hz, 1H), 4.21 (dt, J = 2.02, 6.82 Hz, 1H), 3.83–3.77 (m, 6H), 3.11–2.87 (m, 2H), 2.49 (d, J = 2.02 Hz, 1H); ^{13}C{H} NMR ($CDCl_3$, 126 MHz): δ 159.3, 158.5, 130.8, 129.9, 129.6, 129.3, 113.9, 113.7, 82.7, 74.7, 70.4, 69.5, 55.4, 55.3, 41.3; HRMS (ESI): m/z calcd for $C_{19}H_{20}O_3Na$ $[M + Na]^+$ 319.1305, found 319.1302.

Ethyl(*E*)-4-(4-methoxyphenyl)but-2-enoate (17)

To a solution of Grubb's 2nd generation catalyst (21 mg, 0.03 mmol) *p*-allylanisole **9** (500 mg, 3.37 mmol) and ethyl acrylate (0.71 mL, 6.74 mmol) were added simultaneously *via* a syringe. The resulting mixture was heated at 40 °C until consumption of the starting material occurred as determined by TLC analysis. The reaction was cooled to rt, and concentrated and the residue was purified by column chromatography (using 10% EtOAc in hexanes) to afford **17** (540 mg, 73%) as a colorless liquid. TLC: R_f = 0.6 (SiO_2, 20% EtOAc/hexanes); FTIR (cm^{-1}): 3681, 3427, 2842, 2403, 1711, 1651, 1611, 1513, 1432, 1376, 1037, 984, 926; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.18–6.96 (m, 3H), 6.91–6.77 (m, 2H), 5.78 (td, J = 1.64, 15.54 Hz, 1H), 4.17 (q, J = 7.20 Hz, 2H), 3.79 (s, 3H), 3.46 (dd, J = 1.39, 6.69 Hz, 2H), 1.27 (t, J = 7.07 Hz, 3H); ^{13}C{H}NMR (101 MHz, $CDCl_3$): δ 166.2, 158.2, 147.6, 132.1, 132.0, 131.4, 131.3, 129.6, 129.4, 128.4, 128.3, 127.2, 121.8, 113.9, 113.7, 60.0, 54.9, 37.3, 14.1; HRMS (ESI): m/z calcd for $C_{13}H_{16}O_3Na$ $[M + Na]^+$ 243.0992, found 243.0990.

(*E*)-4-(4-Methoxyphenyl)but-2-en-1-ol (S4)

To a solution of the corresponding ester **17** (1.08 g, 4.9 mmol) in DCM (10 mL) at −78 °C was added DIBAL-H (1 M in toluene, 10.30 mL, 10.3 mmol) dropwise. The solution was stirred at this temperature until consumption of the starting material was observed by TLC, at which point the reaction was quenched by the careful addition of methanol. The reaction was allowed to warm to rt whereupon sat. aq. Na^+–K^+ tartrate and EtOAc were added and the mixture was stirred vigorously for 1 h. The phases were then separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The organic phases were combined, washed with sat. aq. Na^+–K^+ tartrate, water and brine, dried over Na_2SO_4, filtered and concentrated and the crude product was purified by silica gel column chromatography (using 20% EtOAc in hexanes) to afford **S4** (703 mg, 80%) as a colorless liquid. TLC: R_f = 0.3 (SiO_2, 30% EtOAc/hexanes) FTIR (cm^{-1}): 3686, 3619, 3444, 2973, 2402, 1766, 1600, 1521, 1426, 1041, 927; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (d, J = 8.54 Hz, 2H), 6.84 (d, J = 8.54 Hz, 2H), 5.88–5.77 (m, 1H), 5.74–5.62 (m, 1H), 4.10 (d, J = 5.49 Hz, 2H), 3.79 (s, 3H), 3.32 (d, J = 6.10 Hz, 2H), 1.79 (br. s, 1H); ^{13}C{H} NMR (101 MHz, $CDCl_3$): δ 158.1, 132.2, 132.0, 130.1, 129.6, 114.0, 63.5, 55.4, 37.8; HRMS (ESI): m/z calcd for $C_{11}H_{14}O_2Na$ $[M + Na]^+$ 201.0886, found 201.0886.

((2*R*,3*R*)-3-(4-Methoxybenzyl)oxiran-2-yl)methanol (18)

To a stirred suspension of M.S. (4 Å, 2.0 g) in anhydrous DCM (5 mL) was added (−)-DET (0.09 mL, 0.561 mmol) and the

resulting mixture was cooled to −25 °C. To this $Ti(O^iPr)_4$ (0.24 mL, 0.084 mmol) and TBHP (2.46 mL, 1.23 mmol) were added and the mixture was stirred at −25 °C for 30 min. A solution of allylic alcohol **S4** (1 g, 5.61 mmol) in dry DCM was added to the above mixture and it was kept in a freezer at about −25 °C for 18 h. Water was added to the reaction mixture and this was stirred at 0 °C for 30 min. A solution of 10% aq. NaOH was then added and the mixture was warmed to rt for 1 h. The product was extracted with DCM (3 × 10 mL), dried over Na_2SO_4, filtered and concentrated in a vacuum and purified by silica gel column chromatography (using 25% EtOAc in hexanes) to afford **18** (980 mg, 82%) as a colorless liquid. TLC: R_f = 0.4 (SiO_2, 40% EtOAc/hexanes); $[\alpha]_D^{25.27}$ = +15.71 (c = 2.9, $CHCl_3$); FTIR (cm^{-1}): 3415, 2404, 1615, 1515, 1432, 1035, 927; ^1H NMR (500 MHz, $CDCl_3$): 7.15 (d, J = 8.39 Hz, 2H), 6.85 (d, J = 8.77 Hz, 2H), 3.93–3.85 (m, 1H), 3.79 (s, 3H), 3.66–3.59 (m, 1H), 3.17 (dt, J = 2.29, 5.34 Hz, 1H), 3.02–2.94 (m, 1H), 2.92–2.78 (m, 2H), 1.81 (t, J = 6.10 Hz, 1H); $^{13}C\{H\}$NMR (126 MHz, $CDCl_3$): δ 158.6, 130.1, 129.0, 114.1, 61.6, 58.3, 56.2, 55.4, 37.0; HRMS (ESI): m/z calcd for $C_{11}H_{14}O_3Na$ $[M + Na]^+$ 217.0835, found 217.083.

(2*S*,3*R*)-2-(Chloromethyl)-3-(4-methoxybenzyl)oxirane (19)

To a solution of epoxy alcohol **18** (1.68 g, 8.64 mmol) in DCM, CCl_4 (1.67 mL, 17.2 mmol) and triphenylphosphine (3.01 g, 14.9 mmol) were added at 0 °C and the mixture was refluxed for 6 h. After completion of the reaction, the mixture was diluted with hexane and filtered through Celite. The filtrate was concentrated to give a residue which was purified by silica gel column chromatography (using 5% EtOAc in hexanes) to afford **19** (1.48 g, 80%) as a yellowish liquid. TLC: R_f = 0.8 (SiO_2, 20% EtOAc/hexanes); $[\alpha]_D^{25.30}$ = +9.46 (c = 1.9, $CHCl_3$); FTIR (cm^{-1}): 3415, 2402, 1611, 1516, 1432, 1038, 928; ^1H NMR (400 MHz, $CDCl_3$): δ 7.20–7.13 (m, 2H), 6.91–6.81 (m, 2H), 3.80 (s, 3H), 3.60–3.49 (m, 2H), 3.12–3.01 (m, 2H), 2.95–2.79 (m, 2H); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$): δ 158.6, 130.1, 128.6, 114.1, 59.2, 57.0, 55.4, 44.6, 36.9; HRMS (ESI): m/z calcd for $C_{11}H_{14}O_2Cl$ $[M + H]^+$ 213.0677, found 213.0679.

(*R*)-1-(4-Methoxyphenyl)but-3-yn-2-ol (S5)

To a solution of chloride **19** (1.48 g, 6.97 mmol) in dry THF (20 mL), *n*-BuLi (15.25 mL, 24.3 mmol) was added dropwise at −78 °C. The reaction mixture was stirred at the same temperature for 30 min. After completion of the reaction, the reaction was quenched with aq. sat. NH_4Cl at 0 °C. The organic phase was separated and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in a vacuum, and the crude product was purified by silica gel column chromatography (using 12% EtOAc in hexanes) to afford **S5** (1.05 g, 86%) as a yellow liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/hexanes); $[\alpha]_D^{25.32}$ = +3.50 (c = 2.9, $CHCl_3$); FTIR (cm^{-1}): 3683, 3303, 2926, 2850, 2403, 1728, 1609, 1511, 1455, 1298, 1036, 925; ^1H NMR (400 MHz, $CDCl_3$): δ 7.24–7.17 (m, 2H), 6.91–6.81 (m, 2H), 4.53 (br. s, 1H), 3.79 (s, 3H), 3.03–2.88 (m, 2H), 2.49 (d, J = 1.83 Hz, 1H), 2.13 (br. s, 1H); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$): δ 158.7, 130.9, 128.3, 114.0, 84.4, 73.9, 63.2, 55.3, 43.0; HRMS (ESI): m/z calcd for $C_{11}H_{12}O_2Na$ $[M + Na]^+$ 199.0730, found 199.0727.

(*R*)-1-Methoxy-4-(2-((4-methoxybenzyl)oxy)but-3-yn-1-yl) benzene (15)

To a suspension of NaH (0.1 g, 4.19 mmol) in DMF (2 mL) at 0 °C was added a solution of alcohol **S5** (369 mg, 2.09 mmol) in DMF (3 mL). After that the reaction mixture was stirred for 1 h at 0 °C and then PMBCl (0.313 mL, 2.29 mmol) and TBAI (43 mg, 0.209 mmol) were added at 0 °C. The reaction mixture was stirred for 40 min at rt. After completion of the reaction saturated aqueous $NaHCO_3$ was added at 0 °C. The mixture was extracted with diethyl ether (3 × 5 mL) and the organic layer was dried over Na_2SO_4, and filtered and the solvent was evaporated; then the crude product was purified by silica gel column chromatography (using 10% EtOAc in hexanes) to afford **15** (510 mg, 82%) as a yellow oil. TLC: R_f = 0.5 (SiO_2, 20% EtOAc/hexanes); $[\alpha]_D^{26.19}$ = +22.10 (c = 1.4, $CHCl_3$); FTIR (cm^{-1}): 3684, 3619, 3454, 3304, 2964, 2403, 1612, 1514, 1456, 1298, 1039, 928; ^1H NMR (500 MHz, $CDCl_3$): δ 7.18 (d, J = 8.39 Hz, 2H), 7.21 (d, J = 8.39 Hz, 2H), 6.85 (t, J = 8.39 Hz, 4H), 4.75 (d, J = 11.44 Hz, 1H), 4.44 (d, J = 11.44 Hz, 1H), 4.20 (dt, J = 1.91, 6.87 Hz, 1H), 3.86–3.76 (m, 6H), 3.08–2.92 (m, 2H), 2.48 (d, J = 1.91 Hz, 1H); $^{13}C\{H\}$ NMR (50 MHz, $CDCl_3$): δ 159.3, 158.5, 130.8, 129.9, 129.6, 129.3, 113.9, 113.7, 82.7, 74.7, 70.4, 69.5, 55.4, 55.3, 41.3.

(*S*)-1-(3,4-Dimethoxyphenyl)but-3-en-1-ol (20)

To a 50 mL round-bottom flask, a mixture of (*S*)-BINOL (861 mg, 3.00 mmol), 1.0 M $Ti(O^iPr)_4$ (3 mL, 3.00 mmol) in DCM and freshly activated 4 Å MS powder in DCM was refluxed for 1 h. The red-brown mixture was cooled to rt and then aldehyde **10** (5 g, 30.08 mmol) was added. After being stirred for 10 min the contents were cooled to −78 °C and allyltributyltin (10.95 mL, 33.08 mmol) was added. The reaction mixture was stirred for 10 min and then placed in a −20 °C freezer. After 70 h, saturated $NaHCO_3$, 1.5 mL, was then added and the contents were stirred for 1 h, dried with anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (using 20% EtOAc in hexanes) to afford **20** (4.52 g, 72%) as a white solid. TLC: R_f = 0.5 (SiO_2, 40% EtOAc/hexanes); $[\alpha]_D^{26.07}$ = −4.13 (c = 0.3, $CHCl_3$); FTIR (cm^{-1}): 3686, 3616, 2974, 2402, 1599, 1517, 1426, 1146, 1036, 926, 860; ^1H NMR (200 MHz, $CDCl_3$): δ 6.93 (s, 1H), 6.91–6.82 (m, 2H), 5.96–5.67 (m, 1H), 5.19 (d, J = 7.96 Hz, 1H), 5.12 (s, 1H), 4.69 (dt, J = 2.78, 6.69 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 2.51 (t, J = 6.95 Hz, 2H), 1.99 (d, J = 2.91 Hz, 1H); $^{13}C\{H\}$ NMR (50 MHz, $CDCl_3$): δ 149.2, 148.6, 136.7, 134.7, 118.5, 118.2, 111.1, 109.1, 73.3, 56.1, 56.0, 44.0; HRMS (ESI): m/z calcd for $C_{12}H_{16}O_3Na$ $[M + Na]^+$ 231.0992, found 231.0991.

(*S*)-*tert*-Butyl((1-(3,4-dimethoxyphenyl)but-3-en-1-yl)oxy) dimethylsilane (S6)

2,6-Lutidine (2.97 mL, 25.58 mmol) was added to a solution of alcohol **20** (3.6 g, 17.28 mmol) in dry DCM (30 mL) at −78 °C.

After 10 min TBSOTf (3.97 mL, 17.28 mmol) was added and the reaction mixture was stirred for 20 min at this temperature. The reaction mixture was diluted with DCM and the organic layers were washed with water and saturated aqueous NH_4Cl. The combined organic layer was dried over Na_2SO_4, filtered and concentrated in a vacuum. The crude product was purified by silica gel column chromatography (using 5% EtOAc in hexanes) to afford **S6** (4.5 g, 80%) as a yellow liquid. TLC: R_f = 0.5 (SiO_2, 30% EtOAc/hexanes); $[\alpha]_D^{26.11}$ = −34.53 (c = 2.8, $CHCl_3$); FTIR (cm^{-1}): 3775, 3685, 3619, 3456, 2966, 2402, 2358, 1600, 1516, 1466, 1425, 1148, 1079, 1037, 925; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.90 (s, 1H), 6.83–6.72 (m, 2H), 5.91–5.63 (m, 1H), 5.04 (d, J = 3.79 Hz, 1H), 4.98 (s, 1H), 4.62 (dd, J = 5.43, 7.07 Hz, 1H), 3.87 (m, 6H), 2.54–2.25 (m, 2H), 0.92–0.83 (m, 9H), 0.02 (s, 3H), −0.09–0.16 (m, 3H); ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 148.8, 148.0, 138.1, 135.5, 118.1, 116.9, 110.6, 109.2, 74.9, 56.0, 55.9, 45.8, 26.0, 18.4, −4.5, −4.8; HRMS (ESI): m/z calcd for $C_{18}H_{30}O_3NaSi$ $[M + Na]^+$ 345.1856, found 345.1855.

(*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-3-(3,4-dimethoxyphenyl)-propanal (16)

To a solution of olefin **S6** (1.29 g, 4.00 mmol) in THF : H_2O (3 : 1, 7.5 mL: 2.5 mL) were added 2,6-lutidine (1.86 mL, 16.02 mmol), OsO_4 (0.02 g, 0.08 mmol) and $NaIO_4$ (1.70 g, 8.00 mmol). The reaction mixture was stirred for 2 h at rt. After completion of the reaction, the reaction was quenched with solid Na_2SO_3 and then filtered through Celite using EtOAc. The filtrate was concentrated in a vacuum and the crude product was purified by silica gel column chromatography (using 10% EtOAc in hexanes) to afford the desired product **16** (938 mg, 73%) as a yellowish liquid. TLC: R_f = 0.6 (SiO_2, 20% EtOAc/hexanes); $[\alpha]_D^{26.13}$ = −32.98 (c = 0.2, $CHCl_3$); FTIR (cm^{-1}): 3683, 3615, 3433, 2976, 2402, 2357, 1637, 1520, 1426, 1041, 927; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.76 (dd, J = 2.13, 2.75 Hz, 1H), 6.90 (d, J = 1.75 Hz, 1H), 6.86–6.76 (m, 2H), 5.15 (dd, J = 4.13, 8.25 Hz, 1H), 3.85 (s, 3H), 3.86 (s, 3H), 2.82 (ddd, J = 2.88, 8.25, 15.76 Hz, 1H), 2.60 (ddd, J = 2.00, 4.13, 15.76 Hz, 1H), 0.85 (s, 9H), 0.03 (s, 3H), −0.14 (s, 3H); ^{13}C{H} NMR (101 MHz, $CDCl_3$): δ 201.5, 149.1, 148.4, 136.6, 117.8, 110.9, 108.8, 70.6, 56.0, 55.9, 54.2, 25.8, 18.2, −4.5, −5.1; HRMS (ESI): m/z calcd for $C_{17}H_{28}O_4NaSi$ $[M + Na]^+$ 347.1649, found 347.1645.

(1*S*,6*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-1-(3,4-dimethoxyphenyl)-6-((4-methoxybenzyl)-oxy)-7-(4-methoxyphenyl)hept-4-yn-3-ol (21)

To the alkyne **15** (482 mg, 1.62 mmol) in dry THF (5 mL), n-BuLi (1.1 g, 1.78 mmol) was added at −78 °C and stirred for 1 h at the same temperature. After that aldehyde **16** (263 mg, 0.81 mmol) was added in one shot and the reaction mixture was stirred for 2 h. After completion of the reaction, the reaction was quenched with sat. aq. NH_4Cl and extracted with EtOAc (3 × 10 mL), dried over Na_2SO_4, filtered and concentrated and subjected to silica gel column chromatography to afford the desired product **21** (650 mg, 65%) as a yellowish liquid. TLC: R_f = 0.5 (SiO_2, 30% EtOAc/hexanes; $[\alpha]_D^{26.11}$ = +4.85 (c = 3.7, $CHCl_3$); FTIR (cm^{-1}): 3685, 3618, 2972, 2402, 1604, 1517, 1426, 1216, 1040, 927; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24–7.12 (m, 4H), 6.93–6.72 (m, 7H), 5.02 (ddd, J = 3.05, 7.93, 15.87 Hz, 1H), 4.76–4.66 (m, 1H), 4.59 (br. s., 1H), 4.41 (d, J = 11.60 Hz, 1H), 4.24 (t, J = 6.10 Hz, 1H), 3.88 (s, 6H), 3.84–3.74 (m, 6H), 3.08–2.88 (m, 2H), 2.27–2.04 (m, 1H), 2.04–1.86 (m, 1H), 0.94–0.87 (m, 9H), 0.10–0.01 (m, 3H), −0.15 to −0.23 (m, 3H); ^{13}C{H} NMR (101 MHz, $CDCl_3$): δ 159.3, 158.5, 149.0, 148.4, 136.8, 130.8, 130.0, 129.5, 118.3, 118.1, 113.8, 113.6, 110.8, 109.1, 87.5, 83.5, 72.9, 70.4, 69.7, 60.2, 56.0, 55.9, 55.4, 55.3, 48.6, 47.1, 46.9, 41.5, 25.9, 18.2, −4.3, −4.4, −4.9; HRMS (ESI): m/z calcd for $C_{36}H_{48}O_7NaSi$ $[M + Na]^+$ 643.3062, found 643.3053.

(1*S*,6*R*,*E*)-1-((*tert*-Butyldimethylsilyl)oxy)-1-(3,4-dimethoxyphenyl)-6-((4-methoxybenzyl)-oxy)-7-(4-methoxyphenyl)hept-4-en-3-ol (S7)

To a stirred solution of alcohol **21** (50 mg, 0.048 mmol) in dry THF, Red-Al (0.031 mL, 0.161 mmol) was added at 0 °C under argon. The reaction mixture was stirred at the same temperature for 40 minutes. After completion of the reaction, it was quenched with sat. aq. Rochelle salt and the whole reaction mixture was stirred at rt for 30 min and extracted with EtOAc (3 × 5 mL). The combined organic layer was washed with water and brine, dried over Na_2SO_4, filtered and concentrated and the crude product was purified by silica gel column chromatography using (10% EtOAc in hexanes) to afford **S7** (30 mg, 60%) as a yellow liquid. TLC: R_f = 0.5 (SiO_2, 20% EtOAc/hexanes). $[\alpha]_D^{29.77}$ = −10.48 (c = 0.1, $CHCl_3$); FTIR (cm^{-1}): 3685, 3619, 3461, 2971, 2402, 1728, 1604, 1515, 1426, 1040, 925; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, J = 8.39 Hz, 1H), 7.12–7.05 (m, 3H), 6.91–6.87 (m, 1H), 6.82–6.75 (m, 6H), 5.69–5.52 (m, 2H), 4.90–4.77 (m, 1H), 4.61 (s, 1H), 4.52–4.43 (m, 1H), 4.37–4.29 (m, 1H), 4.25–4.19 (m, 1H), 3.89–3.87 (m, 6H), 3.81–3.76 (m, 6H), 2.89–2.81 (m, 1H), 2.74–2.66 (m, 1H), 2.01–1.74 (m, 2H), 1.69–1.63 (m, 1H), 0.93–0.89 (m, 9H), 0.09–0.05 (m, 3H), −0.10–0.14 (m, 1H), −0.22 (s, 2H); ^{13}C{H} NMR (101 MHz, $CDCl_3$): δ 159.0, 158.1, 149.1, 148.4, 137.4, 135.5, 130.8, 130.7, 130.3, 129.2, 129.2, 128.8, 118.2, 114.0, 113.7, 113.5, 110.8, 110.7, 109.0, 80.4, 80.4, 76.1, 71.6, 70.0, 65.1, 56.0, 55.9, 55.4, 55.3, 55.3, 47.7, 41.7, 31.1, 25.9, 18.1, −4.2, −4.5, −4.9; HRMS (ESI): m/z calcd for $C_{36}H_{50}O_7NaSi$ $[M + Na]^+$ 645.3218 found 645.3210.

(1*S*,6*R*,*E*)-1-((*tert*-Butyldimethylsilyl)oxy)-1-(3,4-dimethoxyphenyl)-6-((4-mehoxybenzyl)-oxy)-7-(4-methoxyphenyl)hept-4-en-3-one (14)

To a stirred solution of alcohol **S7** (104 mg, 0.167 mmol) in dry DCM, DMP (212 mg, 0.501 mmol) was added at 0 °C and the reaction mixture was stirred for 1 h at the same temperature. After completion of the reaction, the reaction mixture was quenched with hypo solution (sat. aq. solution of $NaHCO_3$ and sat. aq. solution of $Na_2S_2O_3$ (1 : 1)) and the aqueous layer was extracted with DCM (3 × 10 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concen-

trated and the crude product was purified by silica gel column chromatography (using 10% EtOAc in hexanes) to afford **14** (92 mg, 89%) as a yellow liquid. TLC: R_f = 0.6 (SiO_2, 20% EtOAc/hexanes); $[\alpha]_D^{28.93}$ = −12.33 (c = 1.6, $CHCl_3$); FTIR (cm^{-1}): 3425, 2967, 2403, 1614, 1513, 1464, 1426, 1079, 1036, 927; ^1H NMR (400 MHz, $CDCl_3$): δ 7.13–7.05 (m, 4H), 6.96–6.90 (m, 1H), 6.89–6.78 (m, 6H), 6.75–6.62 (m, 1H), 6.28–6.16 (m, 1H), 5.17 (ddd, J = 1.75, 3.88, 8.38 Hz, 1H), 4.49–4.38 (m, 1H), 4.26–4.19 (m, 1H), 4.13–4.04 (m, 1H), 3.82–3.91 (m, 6H), 3.82–3.76 (m, 6H), 3.06 (dd, J = 8.76, 14.88 Hz, 1H), 2.92–2.81 (m, 1H), 2.79–2.70 (m, 1H), 2.62 (dd, J = 4.13, 14.76 Hz, 1H), 0.91–0.76 (m, 9H), 0.0 to −0.02 (m, 3H), −0.11 to −0.18 (m, 3H); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$): δ 198.6, 159.3, 158.4, 149.0, 148.3, 146.6, 137.5, 131.2, 130.6, 130.1, 129.6, 129.4, 118.0, 113.9, 113.8, 110.8, 109.0, 79.3, 72.0, 71.1, 71.1, 56.0, 55.4, 55.4, 51.5, 41.0, 25.9, 18.3, −4.5, −5.0; HRMS (ESI): m/z calcd for $C_{36}H_{48}O_7NaSi$ $[M + Na]^+$ 643.3062, found 643.3051.

(1*S*,6*R*,*E*)-1-(3,4-Dimethoxyphenyl)-1-hydroxy-6-((4-methoxybenzyl)oxy)-7-(4-methoxyphenyl)-hept-4-en-3-one (22)

To the TBS-alcohol **14** (77 mg, 0.12 mmol), HF : MeCN (5 : 95, 4 mL) was added at 0 °C. The reaction mixture was stirred at the same temperature for 24 h. After completion of the reaction, the reaction mixture was quenched with sat. aq. $NaHCO_3$. Both aqueous and organic layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated and the crude product was purified by silica gel chromatography (using 25% EtOAc in hexanes) to afford **22** (46 mg, 74%) as a yellow viscous liquid. TLC: R_f = 0.2 (SiO_2, 30% EtOAc/hexanes). $[\alpha]_D^{28.56}$ = +4.35 (c = 1.5, $CHCl_3$).; FTIR (cm^{-1}): 3687, 3402, 1600, 1518, 1426, 1026, 922; ^1H NMR (400 MHz, $CDCl_3$): δ 7.13–7.02 (m, 4H), 6.95 (d, J = 1.75 Hz, 1H), 6.91–6.79 (m, 6H), 6.72 (ddd, J = 1.75, 6.00, 16.01 Hz, 1H), 6.20 (ddd, J = 1.13, 3.13, 16.01 Hz, 1H), 5.13 (dd, J = 2.75, 8.50 Hz, 1H), 4.45 (dd, J = 1.88, 11.51 Hz, 1H), 4.29 (d, J = 11.38 Hz, 1H), 4.17–4.06 (m, 1H), 3.94–3.86 (m, 6H), 3.84–3.75 (m, 6H), 3.41 (br. s, 1H), 3.01–2.85 (m, 3H), 2.76 (dd, J = 6.00, 13.88 Hz, 1H); $^{13}C\{H\}$ NMR (126 MHz, $CDCl_3$): δ 200.2, 159.4, 158.5, 149.3, 148.7, 147.5, 135.7, 130.6, 130.2, 130.0, 129.4, 129.3, 118.0, 113.9, 113.9, 111.2, 109.1, 79.3, 79.2, 71.3, 70.0, 56.1, 56.0, 55.4, 55.4, 48.9, 48.8, 40.8; HRMS (ESI): m/z calcd for $C_{30}H_{34}O_7Na$ $[M + Na]^+$ 529.2197, found 529.2197.

(*R*,1*E*,4*E*)-1-(3,4-Dimethoxyphenyl)-6-((4-methoxybenzyl)oxy)-7-(4-methoxyphenyl)hepta-1,4-dien-3-one (24): (*R*,*E*)-5-((4-methoxybenzyl)oxy)-6-(4-methoxyphenyl)hex-3-en-2-one (25) and 3,4-dimethoxybenzaldehyde (10)

To the alcohol **22** (46 mg, 0.090 mmol) in EtOH at 0 °C, KO^{t}Bu (1.0 mg, 0.013 mmol) in EtOH (2 mL) was added and the reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated in a vacuum, then sat. aq. solution of NH_4Cl was added and the aqueous layer was extracted with EtOAc (3 × 5 mL), dried over Na_2SO_4, filtered and concentrated and the crude product was purified by silica gel column chromatography to afford **24** as a yellow liquid (6 mg, 13%). TLC: R_f = 0.5 (SiO_2, 50% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, J = 16.01 Hz, 1H), 7.20–7.06 (m, 5H), 6.93–6.76 (m, 7H), 6.54 (d, J = 15.76 Hz, 1H), 4.53 (d, J = 11.38 Hz, 1H), 4.33 (d, J = 11.51 Hz, 1H), 4.13–4.14 (m, 1H), 3.97–3.86 (m, 6H), 3.79 (s, 3H), 3.80 (s, 3H), 2.94 (dd, J = 7.25, 13.88 Hz, 1H), 2.83 (dd, J = 5.88, 13.76 Hz, 1H); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$): δ 189.1, 159.4, 158.4, 151.6, 149.4, 145.9, 144.0, 130.8, 130.2, 129.7, 129.4, 129.1, 127.8, 123.4, 123.3, 113.9, 113.8, 111.2, 109.9, 79.7, 71.2, 56.2, 56.1, 55.4, 55.4, 41.1; HRMS (ESI): m/z calcd for $C_{30}H_{33}O_6$ $[M + H]^+$ 489.2272, found 489.2273.

(*R*,*E*)-5-((4-Methoxybenzyl)oxy)-6-(4-methoxyphenyl)hex-3-en-2-one (25)

Colorless oil (18 mg, 60%); TLC R_f = 0.7 (SiO_2, 50% EtOAc/hexanes); $[\alpha]_D^{29.80}$ = +8.76 (c = 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): 7.15–7.04 (m, 4H), 6.88–6.79 (m, 4H), 6.65 (dd, J = 6.38, 16.13 Hz, 1H), 6.15 (dd, J = 1.13, 16.13 Hz, 1H), 4.47 (d, J = 11.51 Hz, 1H), 4.29 (d, J = 11.51 Hz, 1H), 4.10 (q, J = 7.00 Hz, 1H), 3.80 (s, 6H), 2.92 (dd, J = 7.25, 13.88 Hz, 1H), 2.78 (dd, J = 5.88, 13.88 Hz, 1H), 2.24 (s, 3H); ^{13}C {H} NMR (101 MHz, $CDCl_3$): δ 198.5, 159.4, 158.5, 146.7, 131.3, 130.7, 130.1, 129.4, 129.4, 113.9, 113.9, 79.3, 71.2, 55.4, 55.4, 41.0, 27.4; HRMS (ESI): m/z calcd for $C_{21}H_{24}O_4Na$ $[M + Na]^+$ 363.1567, found 363.1573.

3,4-Dimethoxybenzaldehyde (10)

Off white solid (4 mg, 26%); TLC R_f = 0.6 (SiO_2, 50% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$): δ 9.85–9.82 (m, 1H), 7.47–7.42 (m, 1H), 7.41–7.37 (m, 1H), 7.00–6.93 (m, 1H), 3.97–3.94 (m, 3H), 3.93–3.90 (m, 3H); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$): δ 191.0, 154.6, 149.7, 130.2, 127.0, 110.5, 109.0, 56.3, 56.1; HRMS (ESI): m/z calcd for $C_9H_{11}O_3$ $[M + H]^+$ 167.0703, found 167.0703.

(1*S*,6*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-1-(3,4-dimethoxyphenyl)-6-((4-methoxybenzyl)-oxy)-7-(4-methoxyphenyl)hept-4-yn-3-one (14a)

To the alcohol **21** (395 mg, 0.63 mmol) in dry DCM (5 mL), Dess–Martin periodinane (DMP) (405 mg, 0.95 mmol) was added at 0 °C and stirred for 1 h. After completion of the reaction, the reaction was quenched with hypo solution 1 : 1 (aq. $NaHCO_3$: aq. $Na_2S_2O_3$), extracted with DCM (3 × 5 mL), dried over Na_2SO_4, filtered, and concentrated, and the crude product was purified by silica gel column chromatography (using 12% EtOAc in hexanes) to afford **14a** (395 mg, 97%) as a yellow liquid. TLC: R_f = 0.6 (SiO_2, 30% EtOAc/hexanes; $[\alpha]_D^{26.12}$ = +16.41 (c = 0.7, $CHCl_3$); FTIR (cm^{-1}): 3424, 2974, 2402, 1622, 1517, 1428, 1039, 927; ^1H NMR (500 MHz, $CDCl_3$): δ 7.20–7.13 (m, 4H), 6.90 (s, 1H), 6.86–6.78 (m, 6H), 5.17 (ddd, J = 3.81, 9.16, 17.93 Hz, 1H), 4.71 (dd, J = 7.63, 11.44 Hz, 1H), 4.41 (dd, J = 5.34, 11.44 Hz, 1H), 4.33 (dt, J = 1.53, 6.87 Hz, 1H), 3.87 (s, 3H), 3.88 (s, 3H), 3.80 (m, 3H), 3.78 (s, 3H), 3.09–2.94 (m, 3H), 2.69 (ddd, J = 3.81, 7.25, 14.88 Hz, 1H), 0.85–0.83 (m, 9H), 0.02 (d, J = 10.68 Hz, 3H), −0.16 (d, J = 9.16 Hz, 3H)); $^{13}C\{H\}$ NMR

(126 MHz, $CDCl_3$): 185.2, 159.5, 158.7, 149.1, 148.5, 136.7, 130.8, 129.7, 129.3, 128.6, 118.1, 114.0, 113.9, 110.9, 109.0, 91.0, 86.0, 71.4, 71.0, 69.7, 69.5, 56.8, 56.0, 56.0, 55.4, 55.4, 40.7, 31.7, 25.9, −4.5, −5.0; HRMS (ESI): *m*/*z* calcd for $C_{36}H_{46}O_7NaSi$ $[M + Na]^+$ 641.2905, found 641.2895.

(1*S*,6*R*)-1-(3,4-Dimethoxyphenyl)-1-hydroxy-6-((4-methoxybenzyl)oxy)-7-(4-methoxyphenyl)hept-4-yn-3-one (22a)

To the TBS-alcohol **14a** (50 mg, 0.08 mmol), HF : MeCN (5 : 95, 2 mL) was added and stirred at 0 °C until the starting material was completely consumed (24 h). After completion of the reaction, the reaction was quenched with sat. aq. $NaHCO_3$, extracted with EtOAc (3 × 5 mL), dried over Na_2SO_4, filtered, concentrated and subjected to column chromatography (using 30% EtOAc in hexanes) to afford **22a** (31 mg, 77%) as a yellow liquid. TLC: R_f = 0.4 (SiO_2, 40% EtOAc/hexanes; $[\alpha]_D^{26.13}$ = +16.97 (*c* = 1.6, $CHCl_3$). FTIR (cm^{-1}): 3686, 3618, 3444, 2974, 2403, 1605, 1518, 1427, 1039, 927; ^1H NMR (500 MHz, $CDCl_3$): δ 7.18 (d, *J* = 8.77 Hz, 2H), 7.16–7.12 (m, 2H), 6.93–6.89 (m, 1H), 6.87–6.79 (m, 6H), 5.13 (d, *J* = 8.01 Hz, 1H), 4.69 (d, *J* = 11.83 Hz, 1H), 4.43 (d, *J* = 11.44 Hz, 1H), 4.35 (t, *J* = 6.49 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.79 (s, 3H), 3.77–3.74 (m, 3H), 3.09–2.94 (m, 3H), 2.91–2.84 (m, 1H), 2.76 (br. s., 1H); $^{13}C\{H\}$ NMR (126 MHz, $CDCl_3$): δ 186.2, 159.5, 158.8, 149.3, 148.8, 135.1, 130.8, 129.7, 129.2, 128.4, 118.0, 114.0, 113.8, 111.2, 109.0, 92.1, 85.3, 71.2, 69.7, 69.5, 56.1, 56.0, 55.4, 55.3, 54.3, 40.6; HRMS (ESI): *m*/*z* calcd for $C_{30}H_{32}O_7Na$ $[M + Na]^+$ 527.2040, found 527.2045.

(*S*)-2-(3,4-Dimethoxyphenyl)-6-((*R*)-1-((4-methoxybenzyl)oxy)-2-(4-methoxyphenyl)ethyl)-2,3-dihydro-4*H*-pyran-4-one (23a), and (*S*,*E*)-5-(3,4-dimethoxyphenyl)-2-((*R*)-2-((4-methoxybenzyl)oxy)-3-(4-methoxyphenyl)propylidene)dihydrofuran-3(2*H*)-one (26)

AuCl (1.0 mg) was taken in DCM in a 10 mL round-bottom flask, then activated molecular sieves were added to this and the mixture was stirred for 15 min. Then hydroxy-ynone **22a** (11 mg, 0.021 mmol) in DCM was added to the AuCl mixture dropwise, $NaHCO_3$ was added to the reaction mixture and the mixture was stirred for 1 h at rt. After completion of the reaction, the mixture was filtered through Celite, the filtrate was concentrated, and the crude product was purified by silica gel column chromatography (using 30% EtOAc in hexanes) to afford the inseparable mixture of **23a** and **26** (10 mg, 90%) as a yellow oil. TLC: R_f = 0.5 (SiO_2, 40% EtOAc/hexanes); $[\alpha]_D^{26.12}$ = −2.31 (*c* = 0.6, $CHCl_3$); FTIR (cm^{-1}): 3686, 3620, 3455, 2975, 2403, 1600, 1521, 1427, 1041, 927; ^1H NMR (400 MHz, $CDCl_3$): δ 7.15–7.07 (m, 4H), 6.89 (s, 2H), 6.86–6.78 (m, 5H), 5.66 (d, *J* = 15.57 Hz, 1H), 5.33 (dd, *J* = 3.66, 13.28 Hz, 1H), 5.11 (dd, *J* = 2.75, 14.20 Hz, 1H), 4.51 (dd, *J* = 11.45, 16.49 Hz, 1H), 4.39–4.23 (m, 1H), 4.09–4.00 (m, 1H), 3.93–3.86 (m, 7H), 3.81–3.76 (m, 6H), 3.02–2.88 (m, 2H), 2.87–2.74 (m, 1H), 2.65–2.54 (m, 1H); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$): δ 192.9, 192.7, 176.4, 175.4, 159.4, 158.5, 149.6, 149.3, 130.6, 130.5, 130.2, 129.5, 129.1, 119.1, 119.1, 113.9, 113.8, 111.2, 109.8, 109.6, 104.1, 104.0, 81.1, 79.8, 79.7, 71.9, 71.8, 56.1, 55.4, 55.3, 42.8, 42.6, 39.9, 39.5; HRMS (ESI): *m*/*z* calcd for $C_{30}H_{33}O_7$ $[M + H]^+$ 505.2221, found 505.2217.

(*R*,*E*)-1-(3,4-Dimethoxyphenyl)-6-((4-methoxybenzyl)oxy)-7-(4-methoxyphenyl)hept-1-en-4-yn-3-one (24a)

To the solution of alcohol **22a** (40 mg, 0.079 mmol), NaH (1 mg, 0.079 mmol, 55–60% in mineral oil) was added in one portion at 0 °C. The reaction was stirred for 15 min. After completion of the reaction, it was quenched with water and extracted with EtOAc (3 × 5 mL), dried over Na_2SO_4, filtered, concentrated and subjected to column chromatography (using 15% EtOAc in hexanes) to afford **24a** (30.4 mg, 78%) as a yellow viscous liquid. TLC: R_f = 0.4 (SiO_2, 30% EtOAc in hexanes); FTIR (cm^{-1}): 3433, 2974, 2402, 2361, 2104, 1630, 1518, 1427, 1340, 1040, 927; ^1H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, *J* = 16.01 Hz, 1H), 7.25–7.19 (m, 4H), 7.05 (dd, *J* = 1.88, 8.25 Hz, 1H), 6.99 (d, *J* = 1.75 Hz, 1H), 6.91–6.81 (m, 5H), 6.64 (d, *J* = 16.01 Hz, 1H), 4.80 (d, *J* = 11.51 Hz, 1H), 4.52 (d, *J* = 11.51 Hz, 1H), 4.46 (t, *J* = 6.88 Hz, 1H), 3.95–3.93 (m, 3H), 3.92 (s, 3H), 3.80 (s, 3H), 3.73 (s, 3H), 3.12 (dd, *J* = 6.63, 13.76 Hz, 1H), 3.06 (dd, *J* = 7.00, 13.63 Hz, 1H); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$): δ 177.9, 159.5, 158.7, 152.2, 149.5, 149.2, 130.9, 129.8, 129.4, 128.6, 127.1, 126.6, 123.9, 114.0, 113.9, 111.2, 110.1, 90.9, 84.2, 71.1, 69.8, 56.2, 56.1, 55.4, 55.3, 40.8; HRMS (ESI): *m*/*z* calcd for $C_{30}H_{31}O_6$ $[M + H]^+$ 487.2115, found 487.2132.

4-Allylphenol (S8)

Allyl anisole (5 g, 33.7 mmol) was dissolved in DCM (50 mL) and BBr_3 (3.52 mL, 37.1 mmol) was added at 0 °C. Then the reaction mixture was stirred for 1 h at the same temperature. After completion of the reaction, it was quenched with water and extracted with DCM (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (using 8% EtOAc in hexanes) to afford 4-allylphenol (**S8**) (4.3 g, 95%) as a colorless liquid. TLC: R_f = 0.2 (SiO_2, 10% EtOAc/hexanes); FTIR (cm^{-1}): 3944, 3687, 3583, 2986, 2685, 2521, 2410, 2304, 1605, 1546, 1512, 1428, 1171, 995, 898; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.11–7.03 (m, 2H), 6.86–6.72 (m, 2H), 6.07–5.89 (m, 1H), 5.42 (br. s., 1H), 5.16–5.03 (m, 2H), 3.34 (d, *J* = 6.63 Hz, 2H); $^{13}C\{H\}$NMR ($CDCl_3$, 101 MHz): δ 153.8, 138.0, 132.4, 129.8, 115.6, 115.4, 39.4; HRMS (ESI): *m*/*z* calcd for $C_9H_{11}O$ $[M + H]^+$ 135.0804, found 135.0809.

(4-Allylphenoxy)(*tert*-butyl)dimethylsilane (9a)

To the allyphenol **S8** (4.3 g, 32.0 mmol) in dry DCM, (*tert*-butyl)dimethylsilylchloride (5.79 g, 38 mmol) and imidazole (4.35 g, 64 mmol) were added at 0 °C and the reaction mixture was stirred overnight. After completion of the reaction, the reaction was quenched with sat. NH_4Cl and the aqueous layer was extracted with DCM (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (using 3% EtOAc in hexanes) to afford **9a** (6.5 g, 82%) as a colorless liquid. TLC: R_f = 0.8 (SiO_2,

20% EtOAc/hexanes); FTIR (cm^{-1}): 3685, 3620, 2940, 2894, 2861, 2403, 1887, 1609, 1511, 1446, 1426, 1258, 1101, 1043, 915, 834; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.08–7.01 (m, 2H), 6.83–6.73 (m, 2H), 6.03–5.89 (m, 1H), 5.12–5.01 (m, 2H), 3.33 (d, J = 6.63 Hz, 2H), 0.99 (s, 9H), 0.20 (s, 6H); ^{13}C{H}NMR ($CDCl_3$, 101 MHz): δ 154.0, 138.1, 132.8, 129.6, 120.1, 115.5, 39.6, 25.9, 25.8, 18.3, −4.3; HRMS (ESI): m/z calcd for $C_{15}H_{25}OSi$ $[M + H]^+$ 249.1669, found 249.1670.

Ethyl-(*E*)-4-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)but-2-enoate (17a)

To a solution of Grubb's 2nd generation catalyst (123 mg, 0.1 mmol) (4-allylphenoxy)(*tert*-butyl)dimethylsilane (**9a**) (4.89 g, 19.7 mmol) and ethyl acrylate (4.33 mL, 39.4 mmol) were added simultaneously *via* a syringe. The resulting mixture was heated at 40 °C until consumption of the starting material occurred as determined by TLC analysis. The reaction was cooled to rt, and concentrated and the residue was purified by column chromatography (using 10% EtOAc in hexanes) to afford **17a** (4.88 g, 77%) as a yellowish liquid. TLC: R_f = 0.6 (SiO_2, 20% EtOAc/hexanes); FTIR (cm^{-1}): 3531, 2985, 2481, 2254, 2090, 2015, 1887, 1742, 1561, 1449, 1374, 1232, 1165, 1099, 1046, 914, 847; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.07 (d, J = 15.51 Hz, 1H), 7.04–6.99 (m, 2H), 6.83–6.73 (m, 2H), 5.78 (td, J = 1.75, 15.63 Hz, 1H), 4.18 (q, J = 7.13 Hz, 2H), 3.44 (dd, J = 1.50, 6.88 Hz, 2H), 1.27 (t, J = 7.13 Hz, 4H), 0.98 (s, 9H), 0.19 (s, 6H); ^{13}C{H}NMR ($CDCl_3$, 101 MHz): δ 166.8, 154.5, 147.9, 130.4, 129.9, 122.2, 120.4, 60.4, 37.9, 25.8, 18.3, 14.4, −4.3; HRMS (ESI): m/z calcd for $C_{18}H_{28}O_3NaSi$ $[M + Na]^+$ 343.1700, found 343.1709.

(*E*)-4-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)but-2-en-1-ol (S4a)

To a solution of the corresponding ester **17a** (4.88 g, 15.2 mmol) in DCM at −78 °C was added DIBAL-H (1 M in toluene, 12.99 mL, 22.8 mmol) dropwise. The solution was stirred at this temperature until consumption of the starting material was observed by TLC, at which point the reaction was quenched by the careful addition of methanol. The reaction mixture was allowed to warm to rt, whereupon sat. aq. Na^+–K^+ tartrate and EtOAc were added and the mixture was stirred vigorously for 1 h. The phases were then separated and the aqueous phase was extracted with EtOAc (3 × 20 mL). The organic phases were combined, washed with sat. aq. Na^+–K^+ tartrate, water and brine, dried over Na_2SO_4, filtered and concentrated and the crude product was purified by silica gel column chromatography (using 20% EtOAc in hexanes) to afford **S4a** (3.2 g, 75%) as a yellow liquid. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/hexanes); FTIR (cm^{-1}): 3944, 3424, 3056, 2987, 2685, 2522, 2410, 2304, 1764, 1640, 1552, 1427, 1263, 1159, 1055, 901; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.08–6.98 (m, 2H), 6.81–6.71 (m, 2H), 5.90–5.78 (m, 1H), 5.75–5.61 (m, 1H), 4.17–4.09 (m, 2H), 3.31 (d, J = 6.50 Hz, 2H), 0.98 (s, 9H), 0.18 (s, 6H); ^{13}C{H} NMR ($CDCl_3$, 101 MHz): δ 154.1, 132.7, 132.2, 130.1, 129.6, 120.1, 63.7, 38.0, 25.8, 18.3, −4.3; HRMS (ESI): m/z calcd for $C_{16}H_{27}O_2Si$ $[M + H]^+$ 279.1775, found 279.1773.

((2*R*,3*R*)-3-(4-((*tert*-Butyldimethylsilyl)oxy)benzyl)oxiran-2-yl) methanol (18a)

To a stirred suspension of M.S. (4 Å, 10 g) in anhydrous DCM (20 mL) was added (−)-DET (0.27 mL, 1.59 mmol), then the suspension was cooled to −25 °C. To this $Ti(O^iPr)_4$ (0.70 mL, 2.39 mmol) and TBHP (5 M in DCM, 7.02 mL, 35.1 mmol) were added and the mixture was stirred at −25 °C for 30 min. A solution of allylic alcohol **S4a** (4.45 g, 15.97 mmol) in dry DCM was added to the above mixture and it was kept in a freezer at about −25 °C for 18 h. Water was added to the reaction mixture, and the mixture was stirred at 0 °C for 30 min. A solution of 10% aq. NaOH was then added and the mixture was warmed to rt for 1 h. The product was extracted with DCM (3 × 20 mL), dried over Na_2SO_4, filtered and concentrated in a vacuum and purified by silica gel column chromatography using (20% EtOAc in hexanes) to afford **18a** (4.53 g, 96%) as a yellow liquid. TLC: R_f = 0.5 (SiO_2, 40% EtOAc/hexanes); $[\alpha]_D^{26.49}$ = +15.31 (c = 2.1, $CHCl_3$); FTIR (cm^{-1}): 3434, 2964, 2865, 2403, 2361, 2086, 1763, 1614, 1513, 1471, 1425, 1257, 1216, 1043, 917, 838; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.12–7.03 (m, 2H), 6.84–6.71 (m, 2H), 3.96–3.84 (m, 1H), 3.68–3.57 (m, 1H), 3.17 (dt, J = 2.25, 5.50 Hz, 1H), 3.00–2.94 (m, 1H), 2.91–2.75 (m, 2H), 1.69 (t, J = 6.25 Hz, 1H), 0.98 (s, 9H), 0.19 (s, 6H); ^{13}C{H} NMR ($CDCl_3$, 101 MHz): δ 154.6, 130.0, 129.7, 120.3, 61.6, 58.3, 56.2, 37.2, 25.8, 18.3, −4.3; HRMS (ESI): m/z calcd for $C_{16}H_{27}O_3Si$ $[M + H]^+$ 295.1724, found 295.1716.

***tert*-Butyl(4-(((2*R*,3*S*)-3-(chloromethyl)oxiran-2-yl)methyl) phenoxy)dimethylsilane (19a)**

To a solution of epoxy alcohol **18a** (5 g, 17.9 mmol) in DCM (50 mL), CCl_4 (3.47 mL, 35.9 mmol) and triphenylphosphine (6.57 g, 25.06 mmol) were added at 0 °C and the mixture was then refluxed for 6 h. After completion of the reaction, the mixture was diluted with hexane and filtered through Celite. The filtrate was concentrated to give a residue which was purified by silica gel column chromatography (using 3% EtOAc in hexanes) to afford **19a** (4.01 g, 71%) as a yellow liquid. TLC: R_f = 0.6 (SiO_2, 20% EtOAc/hexanes; $[\alpha]_D^{26.51}$ = +22.24 (c = 1.4, $CHCl_3$); FTIR (cm^{-1}): 3679, 3426, 2971, 2402, 2361, 2096, 1764, 1640, 1516, 1478, 1426, 1043, 921; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.11–7.06 (m, 2H), 6.80–6.76 (m, 2H), 3.62–3.49 (m, 2H), 3.13–3.02 (m, 2H), 2.96–2.74 (m, 2H), 0.98 (s, 9H), 0.19 (s, 6H); ^{13}C{H} NMR ($CDCl_3$, 101 MHz): δ 154.7, 130.3, 130.1, 129.3, 120.5, 120.3, 59.3, 57.1, 44.7, 37.1, 25.8, 25.8, 18.3, −4.3; HRMS (ESI): m/z calcd for $C_{16}H_{26}O_2ClSi$ $[M + H]^+$ 313.1385, found 313.1385.

(*R*)-1-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)but-3-yn-2-ol (S5a)

To a solution of chloride **19a** (4 g, 12.7 mmol) in dry THF, *n*-BuLi (2.5 M in hexane, 17.78 mL, 44.7 mmol) was added dropwise at −78 °C. The reaction mixture was stirred at the same temperature for 30 min after completion of the reaction; the reaction was quenched with aq. sat. NH_4Cl at 0 °C. The organic phase was separated and the aqueous phase was

extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in a vacuum and the crude product was purified by silica gel column chromatography (using 5% EtOAc in hexanes) to afford **S5a** (3.2 g, 91%) as a yellow liquid. TLC: R_f = 0.6 (SiO_2, 20% EtOAc/hexanes); $[\alpha]_D^{26.20}$ = +1.87 (c = 1.2, $CHCl_3$); FTIR (cm^{-1}): 3685, 3615, 3305, 2965, 2893, 2402, 1606, 1513, 1473, 1426, 1257, 1216, 1041, 919; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.06–7.12 (m, 2H), 6.81–6.77 (m, 2H), 4.54 (dq, J = 1.91, 6.10 Hz, 1H), 3.00–2.90 (m, 2H), 2.48 (d, J = 1.91 Hz, 1H), 1.92 (d, J = 5.72 Hz, 1H), 0.98 (s, 9H), 0.19 (s, 6H); $^{13}C\{H\}$ NMR ($CDCl_3$, 125 MHz): δ 154.9, 130.9, 128.9, 120.2, 84.4, 73.8, 63.2, 43.2, 25.8, 18.3, −4.3; HRMS (ESI): m/z calcd for $C_{16}H_{25}O_2Si$ $[M + H]^+$ 277.1618, found 277.1618.

(*R*)-*tert*-Butyl(4-(2-((4-methoxybenzyl)oxy)but-3-yn-1-yl) phenoxy)dimethylsilane (15a)

PMB-TCAI in CH_2Cl_2 (20 mL) was added *via* a cannula to a solution of (*R*)-1-(4-((*tert*-butyldimethyl-silyl)oxy)phenyl)but-3-yn-2-ol **S5a** (3.421 g, 10.87 mmol) in anhydrous CH_2Cl_2 (200 mL) under N_2 at room temperature. PPTS (856 mg, 3.372 mmol) was then added and the resultant mixture was stirred for 17 h. After the addition of a saturated solution of $NaHCO_3$ (50 mL), the phases were separated and the organic layer was washed with brine (50 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (using 5% EtOAc in hexanes) to afford **15a** (3.0 g, 84%) as a yellow liquid. TLC: R_f = 0.7 (SiO_2, 20% EtOAc/hexanes); $[\alpha]_D^{26.51}$ = +17.0 (c = 2.6, $CHCl_3$); FTIR (cm^{-1}): 3425, 2976, 2402, 1640, 1519, 1427, 1041, 927; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.18 (d, J = 8.39 Hz, 2H), 7.10 (d, J = 8.39 Hz, 2H), 6.84 (d, J = 9.16 Hz, 2H), 6.77 (d, J = 8.39 Hz, 2H), 4.74 (d, J = 11.44 Hz, 1H), 4.44 (d, J = 11.44 Hz, 1H), 4.19 (dt, J = 1.53, 6.87 Hz, 1H), 3.80 (s, 3H), 3.05–2.91 (m, 2H), 2.47 (d, J = 2.29 Hz, 1H), 0.99 (s, 9H), 0.20 (s, 6H); $^{13}C\{H\}$ NMR ($CDCl_3$, 101 MHz): δ 159.3, 154.5, 130.7, 130.0, 129.9, 129.6, 119.8, 113.8, 82.7, 74.6, 70.4, 69.4, 55.4, 41.5, 25.8, 18.3, −4.3; HRMS (ESI): m/z calcd for $C_{24}H_{33}O_3Si$ $[M + H]^+$ 397.2193, found 397.2193.

4-Formyl-2-methoxyphenyl-4-methylbenzenesulfonate (10a)

To a stirred solution of vanillin (5 g, 32.86 mmol) in DCM at 0 °C was added Et_3N (4.5 mL, 32.86 mmol) followed by *p*-toluene sulphonylchloride (6.26 g, 32.86 mmol); then the reaction temperature was raised to 25 °C and the mixture was stirred for 2 h. The reaction mixture was diluted with 1N HCl and the layers were separated. The organic layer was further washed with 1N HCl followed by sat. aq. $NaHCO_3$ and brine. The combined organic layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (using 8% EtOAc in hexanes) to afford **10a** (9.2 g, 91%) as a white solid. TLC: R_f = 0.7 SiO_2, 20% EtOAc/hexanes; FTIR (cm^{-1}): 3859, 3425, 2926, 2856, 1694, 1502, 1379, 1276, 1214, 1103, 1035, 855; ^1H NMR (500 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.74 (d, J = 8.01 Hz, 2H), 7.40 (s, 1H), 7.36–7.33 (m, 2H), 7.30 (m, 2H), 3.62 (s, 3H), 2.44 (s, 3H); $^{13}C\{H\}$ NMR (126 MHz, $CDCl_3$): δ 190.9, 152.7, 145.6, 143.1, 135.9, 133.0, 129.6, 128.7, 124.6, 124.4, 111.2, 55.9, 21.8; HRMS (ESI): m/z calcd for $C_{15}H_{15}O_5S$ $[M + H]^+$ 307.0635, found 307.0634.

4-(1-Hydroxybut-3-en-1-yl)-2-methoxyphenyl-4-methylbenzenesulphonate (S9)

To a solution of aldehyde **10a** (9.2 g, 30.2 mmol) in dry THF (100 mL), allyl magnesium chloride (2 M in THF, 22.71 mL, 45.4 mmol) was added at −78 °C and the reaction mixture was stirred for 1 h at the same temperature. After completion of the reaction, the reaction was quenched with a sat. aq. solution of NH_4Cl. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, filtered and concentrated in a vacuum and the crude product was purified by silica gel column chromatography (using 15% EtOAc in hexanes) to afford **S9** (10 g, 95%) as a colorless oil. TLC: R_f = 0.4 (SiO_2, 30% EtOAc/hexanes, FTIR (cm^{-1}): 3434, 2971, 2927, 2860, 2403, 2068, 1640, 1606, 1507, 1460, 1372, 1273, 1104, 1039, 927, 854; ^1H NMR (400 MHz, $CDCl_3$): δ 7.78–7.73 (m, 2H), 7.32–7.27 (m, 2H), 7.10 (d, J = 8.26 Hz, 1H), 6.89 (d, J = 1.88 Hz, 1H), 6.86–6.81 (m, 1H), 5.85–5.73 (m, 1H), 5.20–5.13 (m, 2H), 4.69 (dd, J = 4.75, 8.00 Hz, 1H), 3.57 (s, 3H), 2.54–2.46 (m, 1H), 2.44 (s, 3H), 2.43–2.35 (m, 1H), 2.12–2.06 (br. s, 1H); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$): δ 151.9, 145.1, 144.2, 137.6, 134.2, 133.4, 129.5, 128.7, 123.9, 119.0, 117.9, 110.1, 72.8, 55.7, 44.1, 21.8.

4-(But-3-enoyl)-2-methoxyphenyl-4-methylbenzenesulfonate (28)

To the allyl alcohol **S9** (10 g, 28.7 mmol) in dry DCM (100 mL) at 0 °C, DMP (18.26 g, 43.0 mmol) was added and the reaction mixture was stirred up until the starting material was completely consumed (1 h). After completion of the reaction, the reaction was quenched with hypo solution (1 : 1 ratio of sat. $NaHCO_3$ and sat. $Na_2S_2O_3$) and the aqueous layer was extracted with DCM (3 × 50 mL). The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4, filtered and concentrated and the crude product was purified by silica gel column (using 15% EtOAc in hexanes) chromatography to afford **28** (8.1 g, 81%) as a yellow liquid. TLC: R_f = 0.5 (SiO_2, 30% EtOAc/hexanes), FTIR (cm^{-1}): 3680, 3517, 2970, 2928, 2858, 2625, 2405, 1917, 1674, 1596, 1502, 1455, 1409, 1374, 1281, 1167, 1119, 1032, 962, 914, 847; ^1H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 8.00 Hz, 2H), 7.50 (dd, J = 1.75, 8.25 Hz, 1H), 7.47–7.40 (m, 1H), 7.30 (d, J = 8.13 Hz, 2H), 7.26 (d, J = 8.26 Hz, 1H), 6.14–5.92 (m, 1H), 5.26–5.16 (m, 2H), 3.71 (d, J = 6.75 Hz, 2H), 3.60 (s, 3H), 2.44 (s, 3H); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$): δ 196.9, 152.2, 145.5, 142.2, 136.2, 133.1, 130.8, 129.6, 128.7, 124.1, 121.5, 119.1, 112.0, 55.8, 43.5, 21.8; HRMS (ESI): m/z calcd for $C_{18}H_{19}O_5S$ $[M + H]^+$ 347.0948, found 347.0948.

(*S*)-4-(1-Hydroxybut-3-en-1-yl)-2-methoxyphenyl-4-methylbenzenesulphonate (20a)

(*R*)-CBS (23.40 mL, 23.4 mmol) reagent was added to a solution of BH_3-Me_2S (2.21 mL, 23.4 mmol) in dry THF (10 mL), stirred

for 15 min at rt, and then cooled to −20 °C. After that a solution of 4-(but-3-enoyl)-2-methoxyphenyl-4-methylbenzenesulfonate **28** (8.1 g, 23.4 mmol) in dry THF (60 mL) was added to this dropwise. Then the reaction mixture was stirred for 2 h at the same temperature, quenched with MeOH and warmed to rt for 1 h. Then the solvent was removed in a vacuum and the crude product was purified by silica gel column chromatography (using 15% EtOAc in hexanes) to afford **20a** (8 g, 98%) as a colorless oil. TLC: R_f = 0.4 (SiO_2, 30% EtOAc/hexanes); reported $[\alpha]_D^{25}$ = +17.0 (*c* = 1.0, $CHCl_3$) for (***R***)-**20a**, observed $[\alpha]_D^{26.27}$ = −11.038 (*c* = 2.3, $CHCl_3$); FTIR (cm^{-1}): 3433, 2976, 2402, 2361, 2100, 1640, 1515, 1423, 1376, 1084, 1041, 926, 850; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.76–7.69 (m, 2H), 7.29–7.26 (m, 2H), 7.07 (d, *J* = 8.25 Hz, 1H), 6.87 (d, *J* = 1.88 Hz, 1H), 6.86–6.77 (m, 1H), 5.82–5.70 (m, 1H), 5.18–5.08 (m, 2H), 4.67 (dd, *J* = 4.75, 7.88 Hz, 1H), 3.54 (s, 3H), 2.52–2.44 (m, 1H), 2.43 (s, 3H), 2.42–2.36 (m, 1H), 2.13 (br. s, 1H); ^{13}C {H} NMR (101 MHz, $CDCl_3$): *δ* 151.9, 145.1, 144.2, 137.6, 134.2, 133.4, 129.5, 128.7, 123.9, 119.0, 117.9, 110.1, 72.8, 55.7, 44.1, 21.8; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{21}O_5S$ $[M + H]^+$ 349.1104, found 349.1320.

(*S*)-4-(1-Hydroxybut-3-en-1-yl)-2-methoxyphenyl-4-methylbenzenesulphonate (20a)

To a stirred solution of oven-dried MS 4 Å in DCM under a N_2 atmosphere was added *S*-BINOL (953 mg, 3.32 mmol), a 1.0 M solution of $Ti(O^iPr)_4$ (1.66 mL, 1.66 mmol) in DCM and a freshly prepared 1 M solution of TFA (0.09 mL, 0.099 mmol) in DCM. The reaction mixture was heated under reflux for a period of 3 h and then cooled to rt, and a solution of tosyl aldehyde **10a** (5.1 g, 16.64 mmol) in DCM was added to the reaction mixture, which was stirred for 0.5 h at rt and then cooled to −78 °C. Allyltributyltin (7.16 mL, 21.64 mmol) was slowly added and the reaction mixture was stirred for an additional 10 min at −78 °C and then kept in a −20 °C freezer. After 4 d, the reaction mixture was filtered through a pad of Celite into a 500 mL flask, then it was treated with sat. aq. $NaHCO_3$ solution, the resulting mixture was stirred for 1 h and then the layers were separated. The aq. layer was extracted with DCM. The combined layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. The crude product was purified by silica gel column chromatography to afford **20a** (3.97 g, 68%) as a colorless oil. TLC: R_f = 0.4 (SiO_2, 30% EtOAc/hexanes); $[\alpha]_D^{25.89}$ = −13.50 (*c* = 2.2, $CHCl_3$); FTIR (cm^{-1}): 3607, 3434, 3019, 2403, 2360, 2067, 1638, 1608, 1508, 1461, 1419, 1376, 1123, 1085, 1041, 938, 853; ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 7.73 (d, *J* = 8.39 Hz, 2H), 7.28 (d, *J* = 8.01 Hz, 2H), 7.09 (d, *J* = 8.01 Hz, 1H), 6.88 (s, 1H), 6.86–6.80 (m, 1H), 5.82–5.72 (m, 1H), 5.18–5.11 (m, 2H), 4.68 (dd, *J* = 4.96, 7.63 Hz, 1H), 3.56 (s, 3H), 2.51–2.45 (m, 1H), 2.43 (s, 3H), 2.42–2.37 (m, 1H), 2.18 (br. s, 1H); ^{13}C{H} NMR (126 MHz, $CDCl_3$): *δ* 151.9, 145.1, 144.2, 137.6, 134.2, 133.4, 129.4, 128.7, 123.9, 118.9, 117.9, 110.2, 72.8, 55.7, 44.0, 21.8; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{20}O_5NaS$ $[M + Na]^+$ 371.0924, found 371.0923.

(*S*)-4-(1-((*tert*-Butyldimethylsilyl)oxy)but-3-en-1-yl)-2-methoxyphenyl-4-methylbenzene sulphonate (S6a)

To a solution of (*S*)-4-(1-hydroxybut-3-en-1-yl)-2-methoxyphenyl-4-methyl-benzenesulphonate **20a** (8 g, 22.96 mmol) in dry DCM (50 mL), imidazole (2.34 g, 34.44 mmol) and DMAP (280 mg, 2.29 mmol) were added at 0 °C and the reaction mixture was stirred for 10 min. After that TBSCl (3.97 g, 26.4 mmol) was added to this reaction mixture and it was stirred for 24 h. After completion of the reaction it was quenched with sat. aq. NH_4Cl and the aqueous layer was extracted with DCM (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in a vacuum and the crude product was purified with silica gel column chromatography to afford **S6a** (10 g, 94%) as a colorless oil. TLC: R_f = 0.8 (SiO_2, 20% EtOAc/hexanes; $[\alpha]_D^{26.26}$ = −25.92 (*c* = 2.6, $CHCl_3$); FTIR (cm^{-1}): 3426, 2937, 2860, 2403, 1640, 1604, 1504, 1462, 1418, 1370, 1088, 1039, 925, 845; ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 7.68 (d, *J* = 8.39 Hz, 2H), 7.24 (d, *J* = 8.39 Hz, 2H), 7.10 (d, *J* = 8.01 Hz, 1H), 6.81 (d, *J* = 1.91 Hz, 1H), 6.76 (dd, *J* = 1.53, 8.01 Hz, 1H), 5.76–5.67 (m, 1H), 5.02–4.95 (m, 2H), 4.62 (dd, *J* = 5.34, 7.25 Hz, 1H), 3.49 (s, 3H), 2.41 (s, 3H), 2.40–2.29 (m, 2H), 0.86 (s, 9H), 0.01 (s, 3H), −0.15 (s, 3H); ^{13}C {H} NMR (126 MHz, $CDCl_3$): *δ* 151.5, 145.6, 145.0, 137.2, 134.8, 133.1, 129.2, 128.8, 123.5, 117.9, 117.3, 110.1, 74.5, 55.5, 45.4, 25.9, 21.7, 18.3, −4.6, −4.8; HRMS (ESI): *m*/*z* calcd for $C_{24}H_{34}O_5NaSSi$ $[M + Na]^+$ 485.1788, found 485.2017.

(*S*)-4-(1-((*tert*-Butyldimethylsilyl)oxy)-3-oxopropyl)-2-methoxyphenyl-4-methylbenzene sulfonate (16a)

To a solution of (*S*)-4-(1-((*tert*-butyldimethylsilyl)oxy)but-3-en-1-yl)-2-methoxyphenyl-4-methylbenzene sulphonate **S6a** (10 g, 21.6 mmol) in 30 mL of acetone : water (3 : 1, 45 mL : 5 mL) were added OsO_4 (54 mg, 2.16 mmol) and NMO (5.52 g (50% solution), 25.9 mmol) at rt and the mixture was stirred for 5 h. After that the solvent was evaporated and the residue was extracted with EtOAc (3 × 50 mL). The organic layers were washed with brine, dried over Na_2SO_4, and concentrated in a vacuum. To a solution of the above crude diol in 20 mL of THF : water (4 : 1), $NaIO_4$ (9.21 g, 43.2 mmol) was added and the reaction mixture was stirred 1 h at rt; then the solid was removed by filtration, and the filtrate was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in a vacuum. The crude aldehyde was purified by silica gel column chromatography to afford **16a** (6.4 g, 64%) as a colorless oil. TLC: R_f = 0.6 (SiO_2, 20% EtOAc/hexanes); $[\alpha]_D^{26.27}$ = −39.398 (*c* = 3.7, $CHCl_3$); FTIR (cm^{-1}): 3425, 2942, 2859, 2403, 1719, 1672, 1605, 1505, 1462, 1417, 1372, 1263, 1096, 1037, 933, 847; ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 9.74 (dd, *J* = 1.88, 2.50 Hz, 1H), 7.70 (d, *J* = 8.25 Hz, 2H), 7.28–7.25 (m, 2H), 7.11 (d, *J* = 8.13 Hz, 1H), 6.85 (d, *J* = 1.88 Hz, 1H), 6.83–6.80 (m, 1H), 5.15 (dd, *J* = 4.13, 8.25 Hz, 1H), 3.52 (s, 3H), 2.80 (ddd, *J* = 2.63, 8.13, 15.88 Hz, 1H), 2.60 (ddd, *J* = 1.75, 4.00, 16.01 Hz, 1H), 2.42 (s, 3H), 0.84 (s, 9H), 0.03 (s, 3H), −0.15 (s, 3H); ^{13}C{H}NMR (126 MHz, $CDCl_3$): *δ* 200.8, 151.9, 145.1, 144.3, 137.6, 133.1, 129.4, 128.8, 124.1, 117.7, 110.0, 70.2, 55.6, 54.0,

25.8, 21.8, 18.1, −4.6, −5.0; HRMS (ESI): *m*/*z* calcd for $C_{23}H_{33}O_6SSi$ $[M + H]^+$ 465.1762, found 465.3765.

4-((1*S*,6*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-7-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-3-hydroxy-6-((4-methoxybenzyl)oxy)hept-4-yn-1-yl)-2-methoxyphenyl-4-methylbenzenesulfonate (21a)

To the alkyne **15a** (2.76 g, 6.95 mmol) in dry THF (20 mL), LiHMDS (1.0 M in THF, 9.75 mL, 9.7 mmol) was added at −78 °C and the mixture was stirred for 1 h at the same temperature. After that aldehyde **16a** (3.23 g, 6.97 mmol) was added in one shot and the reaction mixture was stirred for 2 h. After completion of the reaction, the reaction was quenched with sat. aq. NH_4Cl and extracted with EtOAc (3 × 30 mL), dried over Na_2SO_4, filtered and concentrated and subjected to silica gel column chromatography (using 15% EtOAc in hexanes) to afford **21a** (3.9 g, 65%) as a yellow liquid. TLC: R_f = 0.5 (SiO_2, 30% EtOAc/hexanes); $[\alpha]_D^{26.26}$ = −4.74 (*c* = 2.6, $CHCl_3$); FTIR (cm^{-1}): 3684, 3615, 2968, 2403, 1730, 1599, 1413, 1468, 1424, 1374, 1085, 1040, 922; ^1H NMR (500 MHz, $CDCl_3$): δ 7.74–7.69 (m, 2H), 7.32–7.27 (m, 2H), 7.17–7.10 (m, 3H), 7.09–7.05 (m, 2H), 6.93–6.88 (m, 1H), 6.84–6.80 (m, 3H), 6.78–6.72 (m, 2H), 4.98 (dd, *J* = 3.15, 8.83 Hz, 0.5H), 4.78 (dd, *J* = 4.10, 9.46, 0.5H), 4.69 (dd, *J* = 5.67, 11.66 Hz, 1H), 4.63 (s, 1H), 4.54 (m, 1H), 4.40 (dd, *J* = 2.21, 11.66 Hz, 1H), 4.26–4.19 (m, 1H), 3.81–3.79 (m, 3H), 3.52–3.48 (m, 3H), 3.02–2.95 (m, 1H), 2.94–2.87 (m, 1H), 2.43 (s, 3H), 0.97 (s, 9H), 0.88 (s, 9H), 0.17 (s, 4H), 0.05 (d, *J* = 16.71 Hz, 3H), 0.00 (s, 3H), −0.19–0.25 (m, 3H); $^{13}C\{H\}$ NMR (126 MHz, $CDCl_3$): δ 163.4, 159.3, 154.5, 151.9, 145.1, 144.9, 144.8, 137.7, 137.6, 133.3, 130.7, 130.2, 130.1, 130.0, 129.5, 129.4, 128.9, 124.0, 119.9, 118.1, 118.0, 114.1, 113.9, 110.2, 91.9, 87.2, 87.0, 84.4, 83.9, 73.4, 72.3, 70.5, 69.7, 65.3, 61.1, 59.8, 55.6, 55.4, 48.5, 47.2, 41.7, 25.9, 25.9, 21.8, 18.4, 18.2, −4.3, −4.4, −4.9; HRMS (ESI): *m*/*z* calcd for $C_{47}H_{65}O_9SSi_2$ $[M + H]^+$ 861.3882, found 861.3925.

4-((1*S*,6*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-7-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-6-((4-methoxybenzyl)oxy)-3-oxohept-4-yn-1-yl)-2-methoxyphenyl-4-methylbenzenesulfonate (14b)

To the alcohol **21a** (1.6 g, 1.8 mmol) in dry DCM (15 mL), DMP (1.18 g, 2.7 mmol) was added at 0 °C and the mixture was stirred for 1 h. After completion of the reaction, the reaction was quenched with hypo solution 1 : 1 (saturated aq. $NaHCO_3$: saturated aq. $Na_2S_2O_3$), extracted with DCM (3 × 15 mL), dried over Na_2SO_4, filtered, and concentrated and the crude product was purified by silica gel column chromatography (using 10% EtOAc in hexanes) to afford the desired product **14b** (1.2 g, 75%) as a yellow viscous liquid. TLC: R_f = 0.6 (SiO_2, 30% EtOAc/hexanes); $[\alpha]_D^{26.26}$ = +1.69 (*c* = 2.5, $CHCl_3$); FTIR (cm^{-1}): 3681, 3613, 3409, 2973, 2402, 2360, 1729, 1612, 1516, 1425, 1042, 926; ^1H NMR (400 MHz, $CDCl_3$): δ 7.75–7.68 (m, 2H), 7.28–7.25 (m, 2H), 7.17–7.05 (m, 5H), 6.87–6.71 (m, 6H), 5.18 (dd, *J* = 3.88, 9.13 Hz, 1H), 4.73–4.65 (m, 1H), 4.43–4.37 (m, 1H), 4.35–4.30 (m, 1H), 3.81–3.77 (m, 3H), 3.54–3.50 (m, 3H), 3.07–2.91 (m, 3H), 2.72–2.64 (m, 1H), 2.43 (s, 3H), 0.98 (s, 9H), 0.84 (s, 9H), 0.18 (s, 6H), 0.05–0.01 (m, 3H), −0.15 to −0.20 (m, 3H); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$): δ 184.6, 159.5, 154.8, 151.9, 145.1, 144.3, 137.7, 133.2, 130.7, 129.6, 129.4, 129.2, 129.2, 128.8, 124.0, 120.0, 117.9, 113.9, 110.1, 91.4, 85.7, 71.1, 71.0, 69.5, 56.4, 55.6, 55.4, 40.8, 25.8, 21.8, 18.3, 18.2, −4.3, −4.5, −5.0; HRMS (ESI): *m*/*z* calcd for $C_{47}H_{62}O_9NaSSi_2$ $[M + Na]^+$ 881.3545, found 881.3540.

4-((1*S*,6*R*)-1-Hydroxy-7-(4-hydroxyphenyl)-6-((4-methoxybenzyl)oxy)-3-oxohept-4-yn-1-yl)-2-methoxyphenyl 4-methylbenzenesulfonate (29) and 4-((1*S*,6*R*)-7-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-1-hydroxy-6-((4-methoxybenzyl)-oxy)-3-oxohept-4-yn-1-yl)-2-methoxyphenyl 4-methylbenzenesulfonate (30)

To the TBS-keto intermediate **14b** (248 mg, 0.28 mmol), HF : MeCN (5 : 95, 6 mL) was added and the mixture was stirred at 0 °C up until the starting material was completely consumed. After completion of the reaction, the reaction was quenched with sat. aq. $NaHCO_3$, extracted with EtOAc (3 × 5 mL), dried over Na_2SO_4, filtered, concentrated and subjected to column chromatography to afford **29** and **30**.

29: yellow liquid (88 mg, 48%); TLC: R_f = 0.2 (SiO_2, 40% EtOAc/hexanes); $[\alpha]_D^{26.22}$ = +24.531 (*c* = 0.2, $CHCl_3$); FTIR (cm^{-1}): 3685, 3617, 3444, 2975, 2928, 2402, 1603, 1519, 1426, 1041, 927; ^1H NMR (400 MHz, $CDCl_3$): δ 7.84–7.74 (m, 2H), 7.35–7.30 (m, *J* = 8.00 Hz, 2H), 7.23–7.17 (m, 2H), 7.13–7.04 (m, 3H), 6.90 (d, *J* = 1.75 Hz, 1H), 6.88–6.83 (m, 2H), 6.79 (dd, *J* = 1.81, 8.32 Hz, 1H), 6.7–6.65 (m, 2H), 5.17 (s, 1H), 5.10 (d, *J* = 7.88 Hz, 1H), 4.69 (d, *J* = 11.51 Hz, 1H), 4.43 (d, *J* = 11.51 Hz, 1H), 4.39–4.33 (m, 1H), 3.79 (s, 3H), 3.61 (s, 3H), 3.08–3.00 (m, 1H), 2.98–2.89 (m, 2H), 2.87–2.80 (m, 2H), 2.45 (s, 3H); $^{13}C\{H\}$ NMR ((101 MHz, $CDCl_3$): δ 186.0, 159.6, 155.0, 152.2, 145.3, 142.7, 137.8, 133.4, 131.0, 129.7, 129.6, 129.1, 128.7, 128.2, 124.1, 117.7, 115.3, 114.0, 110.2, 93.1, 85.3, 71.3, 69.6, 69.3, 55.8, 55.4, 54.5, 40.6, 21.8; HRMS (ESI): *m*/*z* calcd for $C_{35}H_{34}O_9NaS$ $[M + Na]^+$ 653.1816, found 653.1830.

30: yellow liquid (68 mg, 31%); TLC: R_f = 0.5 (SiO_2, 40% EtOAc/hexanes); $[\alpha]_D^{26.25}$ = +5.11 (*c* = 0.5, $CHCl_3$); FTIR (cm^{-1}): 3425, 2976, 2402, 2359, 1640, 1520, 1426, 1041, 927; ^1H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.38 Hz, 2H), 7.30 (d, *J* = 7.88 Hz, 2H), 7.18–7.14 (m, 2H), 7.12–7.09 (m, 2H), 7.08–7.04 (m, 3H), 6.90 (d, *J* = 1.88 Hz, 1H), 6.85–6.82 (m, 2H), 6.77–6.74 (m, 2H), 5.18–5.11 (m, 1H), 4.68 (d, *J* = 11.51 Hz, 1H), 4.42 (d, *J* = 11.51 Hz, 1H), 4.34 (t, *J* = 6.63 Hz, 1H), 3.79 (s, 3H), 3.07–3.00 (m, 1H), 2.99–2.96 (m, 1H), 2.92–2.88 (m, 2H), 2.44 (s, 3H), 0.97 (s, 9H), 0.17 (s, 6H); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$): δ 186.0, 159.6, 154.8, 152.1, 145.1, 142.5, 137.9, 133.5, 131.1, 130.7, 129.7, 129.6, 129.5, 129.2, 129.0, 128.7, 124.1, 120.1, 117.7, 115.0, 114.0, 113.9, 110.2, 92.6, 71.3, 69.5, 69.3, 55.8, 55.4, 54.2, 40.8, 25.8, 21.8, 18.3, −4.3; HRMS (ESI): *m*/*z* calcd for $C_{41}H_{49}O_9SSi$ $[M + H]^+$ 745.2861, found 745.2863.

4-((*S*)-6-((*R*)-2-(4-Hydroxyphenyl)-1-((4-methoxybenzyl)oxy)ethyl)-4-oxo-3,4-dihydro-2*H*-pyran-2-yl)-2-methoxyphenyl 4-methylbenzenesulfonate (31)

To the hydroxy-ynone **29** (25 mg g, 0.03 mmol) in dry DCM (2 mL), AgOTf (1.0 mg, 0.003 mmol) was added at 0 °C and the

mixture was stirred at the same temperature for 24 h. After completion of the reaction, the reaction was quenched with brine, extracted with DCM (3 × 5 mL), dried over Na_2SO_4, filtered, and concentrated in a vacuum and the crude product was purified by silica gel column chromatography (using 30% EtOAc in hexanes) to afford **31** (21 mg, 87%) as a yellow liquid. TLC: R_f = 0.4 (SiO_2, 60% EtOAc/hexanes); $[\alpha]_D^{26.20}$ = +8.20 (c = 2.7, $CHCl_3$); FTIR (cm^{-1}): 3414, 2988, 2307, 1641, 1430, 1266, 1219, 1024, 897; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82–7.77 (m, 2H), 7.36–7.30 (m, 2H), 7.16–7.10 (m, 3H), 7.05–6.98 (m, 2H), 6.86–6.80 (m, 3H), 6.80–6.77 (m, 1H), 6.75–6.68 (m, 2H), 5.68–5.63 (m, 1H), 5.30 (dd, J = 4.13, 13.01 Hz, 1H), 5.11–5.01 (m, 1H), 4.49 (d, J = 11.38 Hz, 1H), 4.30 (d, J = 11.51 Hz, 1H), 4.02 (t, J = 6.50 Hz, 1H), 3.80 (s, 3H), 3.63–3.58 (m, 3H), 3.00–2.87 (m, 2H), 2.76–2.55 (m, 2H), 2.50–2.43 (m, 3H); ^{13}C{H} NMR ((101 MHz, $CDCl_3$): δ 192.1, 175.3, 159.5, 154.7, 152.3, 145.4, 138.7, 138.1, 133.5, 130.8, 129.6, 129.6, 129.4, 128.9, 128.7, 124.4, 118.4, 115.3, 114.0, 110.7, 104.3, 80.4, 79.7, 72.0, 55.9, 55.5, 42.8, 39.7, 21.9; HRMS (ESI): m/z calcd for $C_{35}H_{35}O_9S$ $[M + H]^+$ 631.1996, found 631.1995.

4-((*S*)-6-((*R*)-2-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)-1-((4-methoxybenzyl)oxy)ethyl)-4-oxo-3,4-dihydro-2*H*-pyran-2-yl)-2-methoxyphenyl-4-methylbenzenesulfonate (32)

To the hydroxyl-ynone **30** (116 mg, 0.155 mmol) in dry DCM (4 mL), AgOTf (3 mg, 0.0015 mmol) was added at 0 °C and the mixture was stirred for 24 h at the same temperature. After completion of the reaction, brine was added to the reaction mixture and the reaction mixture was extracted with DCM (3 × 5 mL), dried over Na_2SO_4, filtered, and concentrated in a vacuum and the crude product was purified by silica gel column chromatography (using 20% EtOAc in hexanes) to afford **32** (87 mg, 75%) as a yellow liquid. TLC: R_f = 0.4 (SiO_2, 40% EtOAc/hexanes); $[\alpha]_D^{26.22}$ = +7.15 (c = 0.9, $CHCl_3$); FTIR (cm^{-1}): 3686, 3619, 3457, 2972, 2928, 2402, 1721, 1602, 1519, 1426, 1041, 927; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82–7.75 (m, 2H), 7.37–7.29 (m, 2H), 7.19–7.07 (m, 3H), 7.06–7.00 (m, 2H), 6.87–6.78 (m, 4H), 6.78–6.70 (m, 2H), 5.67–5.61 (m, 1H), 5.31 (dd, J = 4.10, 13.24 Hz, 1H), 4.47 (d, J = 11.35 Hz, 1H), 4.28 (d, J = 11.35 Hz, 1H), 4.06–3.99 (m, 1H), 3.79 (s, 3H), 3.60 (s, 3H), 3.03–2.89 (m, 2H), 2.76–2.64 (m, 1H), 2.64–2.54 (m, 1H), 2.51–2.43 (m, 3H), 0.98 (s, 9H), 0.18 (s, 6H); ^{13}C{H}NMR (126 MHz, $CDCl_3$): δ 191.9, 175.1, 159.5, 154.7, 152.3, 145.3, 138.8, 138.2, 133.6, 130.6, 129.6, 129.5, 128.7, 124.4, 120.1, 118.4, 114.0, 110.6, 104.5, 80.5, 79.8, 72.0, 55.9, 55.4, 43.0, 39.7, 25.8, 21.9, 18.4, −4.3; HRMS (ESI): m/z calcd for $C_{41}H_{48}O_9NaSSi$ $[M + Na]^+$ 767.2681, found 767.2701.

4-((2*S*,6*R*)-6-((*R*)-1-Hydroxy-2-(4-hydroxyphenyl)ethyl)-4-oxotetrahydro-2*H*-pyran-2-yl)-2-methoxyphenyl 4-methylbenzenesulfonate (S10)

To the dihydropyranone **31** (89 mg, 0.14 mmol) in dry ethyl acetate (4 mL), Pd/C (40 mg, 10% wet weight) was added and the reaction mixture was stirred overnight under a hydrogen atmosphere. After completion of the reaction, the mixture was filtered through Celite and the resulting filtrate was concentrated in a vacuum. The crude product was purified by silica gel column chromatography (using 50% ethyl acetate in hexane) to afford **S10** (50 mg, 69%) as an amorphous solid. TLC: R_f = 0.3 (SiO_2, 60% EtOAc/hexanes); $[\alpha]_D^{24.29}$ = −17.64 (c = 0.8, $CHCl_3$); FTIR (cm^{-1}): 3687, 3599, 2927, 2402, 1600, 1519, 1426, 1022, 927; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J = 8.38 Hz, 2H), 7.33 (d, J = 8.13 Hz, 2H), 7.13 (d, J = 8.25 Hz, 1H), 7.07 (d, J = 8.51 Hz, 2H), 6.89–6.84 (m, 2H), 6.75 (d, J = 8.38 Hz, 2H), 4.95 (br. s., 1H), 4.58 (dd, J = 2.75, 11.51 Hz, 1H), 3.82–3.75 (m, 2H), 3.73–3.66 (m, 1H), 3.62 (s, 3H), 2.89 (dd, J = 5.88, 14.01 Hz, 1H), 2.87–2.80 (m, 1H), 2.79–2.66 (m, 2H), 2.64–2.59 (m, 1H), 2.56–2.50 (m, 1H), 2.46 (s, 3H); ^{13}C{H} NMR (101 MHz, $CDCl_3$): δ 206.0, 154.6, 152.2, 145.3, 140.6, 138.2, 133.5, 130.6, 129.7, 129.6, 129.5, 128.7, 124.3, 117.8, 115.6, 110.2, 78.4, 78.2, 74.5, 55.9, 49.4, 43.9, 38.8, 21.9; HRMS (ESI): m/z calcd for $C_{27}H_{28}O_8NaS$ $[M + Na]^+$ 535.1397, found 535.1392.

4-((2*S*,6*R*)-6-((*R*)-2-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)-1-hydroxyethyl)-4-oxotetrahydro-2*H*-pyran-2-yl)-2-methoxyphenyl 4-methylbenzenesulfonate (S11)

To the dihydropyranone **32** (18 mg, 0.0241 mmol) in dry ethyl acetate, Pd/C (10 mg) was added and the reaction mixture was stirred overnight under a hydrogen atmosphere. After completion of the reaction, the mixture was filtered through Celite and the resulting filtrate was concentrated in a vacuum. The crude product was purified by silica gel column chromatography using 50% ethyl acetate in hexanes to afford **S11** (11 mg, 73%) as an amorphous solid. TLC: R_f = 0.3 (SiO_2, 40% EtOAc/hexanes); $[\alpha]_D^{26.32}$ = −24.18 (c = 0.7, $CHCl_3$); FTIR (cm^{-1}): 3411, 3157, 2858, 2256, 1802, 1603, 1468, 1381, 1266, 1166, 1097, 908; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 8.39 Hz, 2H), 7.32 (d, J = 8.39 Hz, 2H), 7.13 (d, J = 8.39 Hz, 1H), 7.06 (d, J = 8.39 Hz, 2H), 6.91–6.86 (m, 2H), 6.80–6.75 (m, 2H), 4.59 (dd, J = 3.05, 11.44 Hz, 1H), 3.78 (br. s, 1H), 3.71–3.66 (m, 1H), 3.62 (s, 3H), 3.61–3.54 (m, 1H), 2.91–2.80 (m, 2H), 2.78–2.66 (m, 2H), 2.66–2.58 (m, 1H), 2.57–2.51 (m, 1H), 2.47–2.45 (m, 3H), 2.43–2.37 (m, 1H), 2.22 (br. s, 1H), 0.97 (s, 9H), 0.18 (s, 6H); ^{13}C{H} NMR ((101 MHz, $CDCl_3$): δ 206.1, 154.6, 152.2, 145.2, 140.6, 138.2, 133.5, 130.4, 130.0, 129.6, 128.7, 124.3, 120.3, 117.8, 110.1, 78.2, 78.2, 74.6, 58.7, 55.9, 49.3, 43.9, 38.9, 25.8, 21.9, 18.6, 18.3, 1.2, 0.1, −4.3; HRMS (ESI): m/z calcd for $C_{33}H_{42}O_8NaSSi$ $[M + Na]^+$ 649.2262, found 649.2269.

4-((2*S*,4*R*,6*R*)-6-((*R*)-2-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)-1-hydroxyethyl)-4-hydroxytetrahydro-2*H*-pyran-2-yl)-2-methoxyphenyl 4-methylbenzenesulfonate (34)

To a stirred solution of tetra-hydro-pyranone **S11** (12 mg, 0.019 mmol) in THF at −78 °C was added LS-selectride (0.02 mL, 0.021 mmol). The reaction mixture was stirred for 1 h at the same temperature. After completion of the reaction it was quenched with saturated aq. NH_4Cl and warmed to rt. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 3 mL); the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in a vacuum and the crude product was purified by

silica gel column chromatography (using 70% EtOAc in hexanes) to afford **34** (8.5 mg, 70%) as a thick liquid. TLC: R_f = 0.3 (SiO_2, 70% EtOAc/hexanes); $[\alpha]_D^{23.96}$ = −22.12 (c = 0.8, $CHCl_3$); FTIR (cm^{-1}): 3687, 2928, 2402, 2358, 2255, 1599, 1518, 1426, 1024, 911; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (d, J = 8.39 Hz, 2H), 7.30 (d, J = 8.01 Hz, 2H), 7.08 (d, J = 8.77 Hz, 3H), 6.88–6.84 (m, 2H), 6.76 (d, J = 8.77 Hz, 2H), 4.83 (d, J = 1.53, 11.83 Hz, 1H), 4.40–4.35 (m, 1H), 3.88 (ddd, J = 1.91, 4.96, 11.83 Hz, 1H), 3.72 (q, J = 6.87 Hz, 2H), 3.58 (s, 3H), 2.84 (dd, J = 5.34, 13.73 Hz, 1H), 2.75 (dd, J = 8.01, 14.11 Hz, 1H), 2.45 (s, 3H), 1.93–1.87 (m, 1H), 1.85–1.77 (m, 2H), 1.70–1.65 (m, 2H), 0.97 (s, 9H), 0.18 (s, 6H); ^{13}C{H} NMR (126 MHz, $CDCl_3$): δ 154.3, 151.9, 145.1, 143.0, 137.6, 133.6, 130.4, 129.5, 128.8, 123.9, 120.1, 117.9, 110.4, 75.2, 73.9, 73.3, 64.7, 55.8, 40.7, 38.8, 34.5, 25.8, 21.8, 18.6, 1.2, −4.3; HRMS (ESI): m/z calcd for $C_{33}H_{44}O_8NaSSi$ $[M + Na]^+$ 651.2418, found 651.2418.

4-((2*S*,4*R*,6*R*)-4-Hydroxy-6-((*R*)-1-hydroxy-2-(4-hydroxyphenyl)ethyl)tetrahydro-2*H*-pyran-2-yl)-2-methoxyphenyl 4-methylbenzenesulfonate (35)

To a stirred solution of tetrahydro-pyranone **S10** (15 mg, 0.02 mmol) in THF at −78 °C, LS-selectride (0.03 mL, 0.03 mmol) was added dropwise. Then the reaction was stirred for 1 h at the same temperature. After completion of the reaction it was quenched with saturated aq. NH_4Cl and warmed to rt. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 3 mL); the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in a vacuum and the crude product was purified by silica gel column chromatography (using 70% EtOAc in hexanes) to afford **35** (12 mg, 80%) as a colorless thick liquid. TLC: R_f = 0.2 (SiO_2, 60% EtOAc/hexanes); $[\alpha]_D^{25.22}$ = −15.45 (c = 0.3, $CHCl_3$); FTIR (cm^{-1}): 3687, 2402, 1600, 1519, 1426, 1022, 927; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82–7.72 (m, 2H), 7.31 (d, J = 8.00 Hz, 2H), 7.12–7.04 (m, 3H), 6.86–6.81 (m, 2H), 6.76–6.70 (m, 2H), 4.82 (dd, J = 1.88, 11.76 Hz, 1H), 4.38 (t, J = 2.75 Hz, 1H), 3.88 (ddd, J = 2.25, 4.88, 11.88 Hz, 1H), 3.74–3.69 (m, 1H), 3.59–3.55 (m, 3H), 2.85 (dd, J = 5.38, 13.88 Hz, 1H), 2.74 (dd, J = 7.75, 13.88 Hz, 1H), 2.45 (s, 3H), 1.92–1.86 (m, 1H), 1.84–1.78 (m, 1H), 1.71–1.64 (m, 2H); ^{13}C{H} NMR (101 MHz, $CDCl_3$): δ 154.4, 151.9, 145.1, 142.9, 137.6, 133.5, 130.6, 130.2, 129.5, 128.7, 123.9, 117.9, 115.5, 110.4, 75.2, 73.9, 73.3, 64.7, 55.8, 40.6, 38.7, 34.5, 21.8; HRMS (ESI): m/z calcd for $C_{27}H_{30}O_8NaS$ $[M + Na]^+$ 537.1554, found 537.1563.

4-((2*S*,4*R*,6*R*)-4-Hydroxy-6-((*R*)-1-hydroxy-2-(4-hydroxyphenyl)ethyl)tetrahydro-2*H*-pyran-2-yl)-2-methoxyphenyl 4-methylbenzenesulfonate (35)

To a solution of benzenesulfonate **34** (15 mg, 0.023 mmol) in dry THF at 0 °C, TBAF (0.02 mL, 0.028 mmol) was added dropwise and the reaction mixture was stirred for 30 min at the same temperature. The reaction was monitored by TLC and after completion of the reaction, it was quenched with H_2O. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 3 mL); the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in a vacuum and the crude product was purified by silica gel column chromatography (using 70% EtOAc in hexanes) to afford **35** (7 mg, 87%) as a colorless thick liquid. TLC: R_f = 0.2 (SiO_2, 60% EtOAc/hexanes); FTIR (cm^{-1}): 3686, 3425, 2402, 1611, 1519, 1426, 1023, 927, 672; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, J = 8.38 Hz, 2H), 7.31 (d, J = 8.13 Hz, 2H), 7.12–7.06 (m, 3H), 6.87–6.83 (m, 2H), 6.77–6.72 (m, 2H), 4.82 (dd, J = 1.88, 11.26 Hz, 1H), 4.41–4.35 (m, 1H), 4.14–4.09 (m, 1H), 3.88–3.83 (m, 1H), 3.60–3.57 (m, 3H), 2.90–2.82 (m, 1H), 2.78–2.70 (m, 1H), 2.45 (s, 3H), 1.94–1.86 (m, 1H), 1.85–1.78 (m, 1H), 1.72–1.65 (m, 2H).

ent-Rhoiptelol B (3a)

To a solution of **35** (9 mg, 0.017 mmol) in MeOH (2 mL) was added K_2CO_3 (12 mg, 0.08 mmol) and the mixture was heated under reflux for 2 h. After completion of the reaction, the reaction mixture was cooled to 0 °C and acidified with 1 N HCl until the pH of the solution reached 2. The combined aqueous/MeOH solution was extracted with ethyl acetate (3 × 3 mL). The organic layers were washed with brine, dried with Na_2SO_4, filtered and concentrated in a vacuum. The crude product was purified by silica gel column chromatography (using 70% EtOAc in hexanes) to obtain *ent*-rhoiptelol (3a) as an amorphous solid (4.6 mg, 76%). TLC: R_f = 0.3 (SiO_2, 70% EtOAc/hexanes); $[\alpha]_D^{26.63}$ = −81.04 (c = 0.1, MeOH); FTIR (cm^{-1}): 3687, 2968, 2402, 1722, 1520, 1427, 1025, 927, 672; ^{1}H NMR (400 MHz, CD_3OD): δ 7.05 (s, 2H), 7.03 (s, 1H), 6.84 (dd, J = 1.88, 8.38 Hz, 1H), 6.77 (d, J = 8.13 Hz, 1H), 6.71–6.68 (m, 2H), 4.69 (dd, 1H), 4.28 (m, 1H), 3.88 (s, 3H), 3.85–3.82 (m, 1H), 3.82–3.79 (m, 1H), 3.60–3.57 (m, 1H), 2.89 (dd, J = 7.00, 13.66 Hz, 1H), 2.71 (dd, J = 7.25, 13.26 Hz, 1H), 1.92–1.89 (m, 1H), 1.84–1.80 (m, 1H), 1.76 (d, J = 2.88 Hz, 1H), 1.57–1.54 (m, 1H); ^{13}C NMR (101 MHz, CD_3OD): δ 156.6, 148.8, 146.7, 136.2, 131.4, 131.2, 129.9, 119.9, 116.0, 115.8, 111.1, 76.4, 75.2, 74.3, 65.7, 56.4, 49.8, 49.6, 49.4, 49.2, 48.8, 48.6, 48.4, 41.3, 39.7, 34.9; HRMS (ESI): m/z calcd for $C_{20}H_{24}O_6Na$ $[M + Na]^+$ 383.1465, found 383.1462.

Author contributions

R. K. conceived the project and directed the research work. P. K. and R. N. carried out the synthetic experiments, analyzed data, and prepared the ESI.† All authors commented on the manuscript and the ESI.†

Conflicts of interest

There are no conflicts to declare.

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Erratum