Design and Tactics Towards Synthesis of 10 & 14-Membered Macrocyclic Lactones and Lewis Acid Mediated Regioselective C-C Bond Formation

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For the Award of the Degree of

DOCTOR OF PHILOSOPHY

In

CHEMICAL SCIENCES

By

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Under the guidance of
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December 2017

This dissertation is dedicated to all those people who have always given me the love, trust, and support to come to this stage of my life

-To My Mother-

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CERTIFICATE

This is to certify that the work incorporated in this Ph.D. thesis entitled **"Design and Tactics Towards Synthesis of 10 & 14-Membered Macrocyclic Lactones and Lewis Acid Mediated Regioselective C–C Bond Formation**" submitted by **Mr. Brijesh M. Sharma** to Academy of Scientific and Innovative Research (**AcSIR**) in fulfillment of the requirements for the award of the Degree of Doctor of Philosophy, embodies original research work under my supervision. I 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 obtained from other sources has been duly acknowledged in the thesis. Any text, illustration, table etc., used in the thesis from other sources, have been duly cited and acknowledged.

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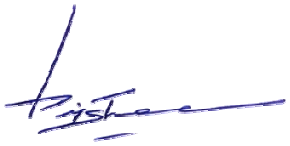
DECLARATION BY THE CANDIDATE

I hereby declare that the original research work embodied in this thesis entitled, **"Design and Tactics Towards Synthesis of 10 & 14-Membered Macrocyclic Lactones and Lewis Acid Mediated Regioselective C-C Bond Formation''** submitted to Academy of Scientific and Innovative Research for the award of degree of Doctor of Philosophy (Ph.D.) is the outcome of experimental investigations carried out by me under the supervision of **Dr. Pradeep Kumar**, Sci-G, Former Head, Division of Organic Chemistry, CSIR-National Chemical Laboratory, Pune. I affirm that the work incorporated is original and has not been submitted to any other academy, university or institute for the award of any degree or diploma.



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PhD is like a long journey; an experience that takes you through the untraversed path, the green lush meadows and the island of Cyclopes to conquer the final goal fixed in mind. Once you achieve the target and turn back, you realize that all your efforts and the pain was worth going through. The small successes & the serendipitous discoveries, the frustrating failures & unexpected crystallisations, the imparted chemical wisdom & the laboratory camaraderie; they are all important parts of this beautiful voyage. But you can't succeed in this journey without the guidance and support of many.

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— Brijesh M. Sharma

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Abbreviations

Units

°C	Degree centigrade
mg	Milligram
hr	Hour
Hz	Hertz
µg	Microgram
mL	Millilitre
min	Minutes
MHz	Megahertz
mmol	Millimole
nm	nanometre
ppm	Parts per million

Chemical Notations

Ac	Acetyl
AcOH	Acetic Acid
Ar	Aryl
MeCN	Acetonitrile
n-BuLi	*n*-Butyl Lithium
^{s}BuLi	*s*-Butyl Lithium
^{t}BuLi	*t*-Butyl Lithium
^{t}BuOH	*tert*-Butyl alcohol
BINAP	(2,2'-bis(Diphenylphosphino)-1,1'-binaphthyl)
MOMCl	Chloromethyl Methyl Ether
CBS	Corey-Bakshi-Shibata catalyst
CCl_4	Carbon tetrachloride
$CDCl_3$	Deuterated Chloroform
CD_3OD	Deuterated Methanol
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	Diisobutylaluminiumhydride
2,2-DMP	2,2-Dimethoxypropane
DMF	*N, N'*-Dimethylformamide

DMAP	*N,N'*-Dimethylaminopyridine
DIPEA	*N*, *N*-Diisopropylethylamine
Et_2O	Diethyl Ether
$(DHQ)_2PHAL$	1,4-bis(Dihydroquinin-9-*O*-yl)phthalazine
$(DHQD)_2PHAL$	1,4-bis(Dihydroquinindin-9-*O*-yl)phthalazine
DIAD	Diisopropyl azodicarboxylate
DCE	1,2-Dichloroethane
BIAB	(Diacetoxyiodo)benzene
DET	Diethyl Tartrate
DIPT	Diisopropyl Tartrate
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DCC	*N*,*N*'-Dicyclohexylcarbodiimide
EtOH	Ethanol
Et	Ethyl
EtOAc	Ethyl Acetate
HG-II	Hoveyda-Grubb's 2nd Generation Catalyst
IBX	Iodoxybenzoic Acid
Imid	Imidazole
LiHMDS	Lithium Hexamethyl Disilazide
LAH	Lithium Aluminum Hydride
m-CPBA	*m*-Chloroperbenzoic Acid
MeOH	Methanol
NMO	*N*-Methyl Morpholine Oxide
Me	Methyl
MeI	Methyl Iodide
PNBA	*p*-Nitrobenzoic Acid
Ph	Phenyl
PMB	*para*-Methoxy Benzyl
p-TSA	*par*a-Toluenesulfonic Acid
TsCl	*p*-Toluenesulphonyl Chloride
$NaBH_4$	Sodiumborohydride
NaH	Sodium Hydride
THF	Tetrahydrofuran

TBAI	Tetra-*n*-Butylammonium Iodide
TBAF	Tetra-*n*-Butylammonium Fluoride
TBDMS	*tert*-Butyldimethyl Silyl
TBSCl	*tert*-Butyldimethyl Silyl Chloride
TIPSOTf	Triisopropylsilyl Trifluoromethanesulfonate
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy
Ts	Toluenesulfonyl
TMS	Trimethylsilyl

Other Notations

calcd	Calculated
δ	Chemical shift
J	Coupling constant in NMR
CD	Circular Dichroism
CM	Cross Metathesis
DEPT	Distortionless Enhancement by Polarization Transfer
dr	Diastereomeric excess
ee	Enantiomeric excess
equiv.	Equivalents
ESI	Electrospray ionization Mass spectrometry
HPLC	High Pressure Liquid Chromatography
HMBC	Heteronuclear Multiple Bond Correlation
COSY	Homonuclear Correlation Spectroscopy
HRMS	High Resolution Mass Spectrometry
IR	Infra Red
m/*z*	Mass-to-charge ratio
M.S	Molecular sieves
mp	Melting Point
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
ORTEP	Oak Ridge Thermal Ellipsoid Plot
rt	Room temperature
TOCSY	Total Correlated Spectroscopy

General remarks

- Deuterated solvents for NMR spectroscopic analyses were used as received. All ^{1}H NMR and ^{13}C NMR and 2D NMR analysis were obtained using a Bruker or JEOL 200 MHz, 400 MHz or 500 or 700 MHz spectrometers. Coupling constants were measured in Hertz. All chemical shifts are quoted in ppm, relative to TMS, using the residual solvent peak as a reference standard. The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br =broad.
- HRMS spectra were recorded at UHPLC-MS (Q-exactive-Orbitrap Mass Spectrometer) using electron spray ionization [(ESI^{+}, +/– 5kV), solvent medium: water, acetonitrile, methanol and ammonium acetate] technique and mass values are expressed as *m*/*z*. GC-HRMS (EI) was recorded in Agilent 7200 Accurate-mass-Q-TOF.
- Infrared spectra were scanned on Bruker ALPHA spectrometers with sodium chloride optics and are measured in cm^{-1}.
- Optical rotations were measured with a JASCO P-2000 digital polarimeter.
- Melting points were recorded on Buchi M-535, M-560 melting point apparatus and are uncorrected and the temperatures are in centigrade scale.
- All reactions are monitored by Thin layer chromatography (TLC) with 0.25 mm pre-coated silica gel plates (60 F254). Visualization was accomplished with either UV light, Iodine adsorbed on silica gel or by immersion in ethanolic solution of phosphomolybdic acid (PMA), *p*-anisaldehyde or $KMnO_4$ followed by heating with a heat gun for ~15 sec.
- All solvents and reagents were purified and dried by according to procedures given in Vogel's Text Book of Practical Organic Chemistry. All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- Column chromatography was performed on silica gel (100-200 or 230-400 mesh size).
- Chemical nomenclature (IUPAC) and structures were generated using ChemDraw Professional 15.1.

- Reactions were carried out in oven-dried glassware under a positive pressure of argon unless otherwise mentioned with magnetic stirring. Air sensitive reagents and solutions were transferred *via* syringe or cannula and were introduced to the apparatus *via* rubber septa.
- The compounds, scheme and reference numbers given in each section of chapter refers to that particular section of the chapter only.
- All reagents, starting materials, and solvents were obtained from commercial suppliers and used as such without further purification.

Synopsis

AcSIR	**Synopsis of the Thesis to be submitted to the Academy of Scientific and Innovative Research for Award of the Degree of Doctor of Philosophy in Chemistry**
Name of the Candidate	**Brijesh M. Sharma**
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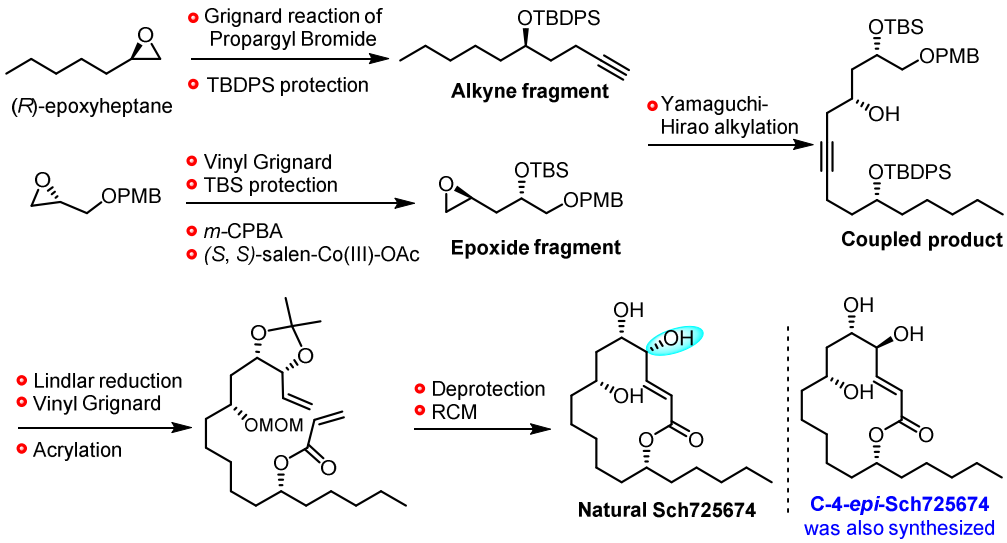
Research Supervisor	**Dr. Pradeep Kumar**

Keywords: *Natural products, Asymmetric synthesis, Macrocycles, Lewis acids, Synthetic methods.*

Biologically active natural products offer challenging structural features & have thus provided an impetus towards the development of methodologies to access them in economic and scalable synthetic routes. The thesis hereby presents a unique perspective for retrosynthetic design and state-of-the-art strategies towards enantioselective synthesis of 10 and 14-membered macrolactones, along with development of Lewis acid mediated scalable methods for C–C bond formation. The work embodied in this thesis has been divided into three chapters as described below.

Chapter I: **Enantioselective Modular Total Synthesis of Macrolides Sch725674 and C-4-*epi*-Sch725674**.

The 14-membered macrolide, Sch725674 was isolated by Yang *et al.*[1] from an Aspergillus *sp*. The intriguing structure of the Sch725674 and its significant biological properties have attracted lot of interest among chemists, and the groups of Curran, Prasad, Kaliappan, and Reddy *et al*. have achieved the synthesis of Sch725674. In terms of scalability and for the synthesis of a library of compounds involving both functional and stereochemical diversity, a modular synthesis was envisioned comprising of an assembly of five modules through sequential Jacobsen HKR, Yamaguchi–Hirao alkynylation, and RCM steps to construct the core skeleton of the macrolide Sch725674 in 15 steps. The same strategy was extended to the synthesis of its C-4 epimer.[2]



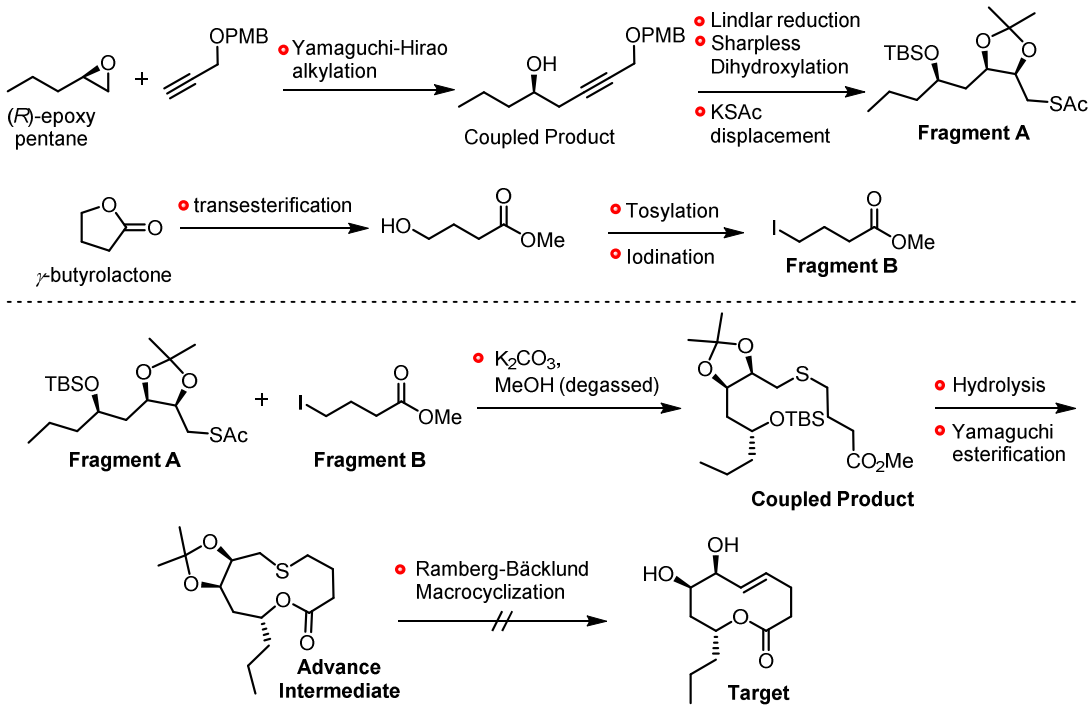
In addition, the influence of protecting groups on the efficiency of the ring-closing metathesis (RCM) macrocyclization has been studied to maximize its yields.[3]

Chapter II: **Studies Towards Total Synthesis of Nonenolide (6*S*,7*R*,9*R*)-6,7-dihydroxy-9-propylnon-4-eno-9-lactone**.

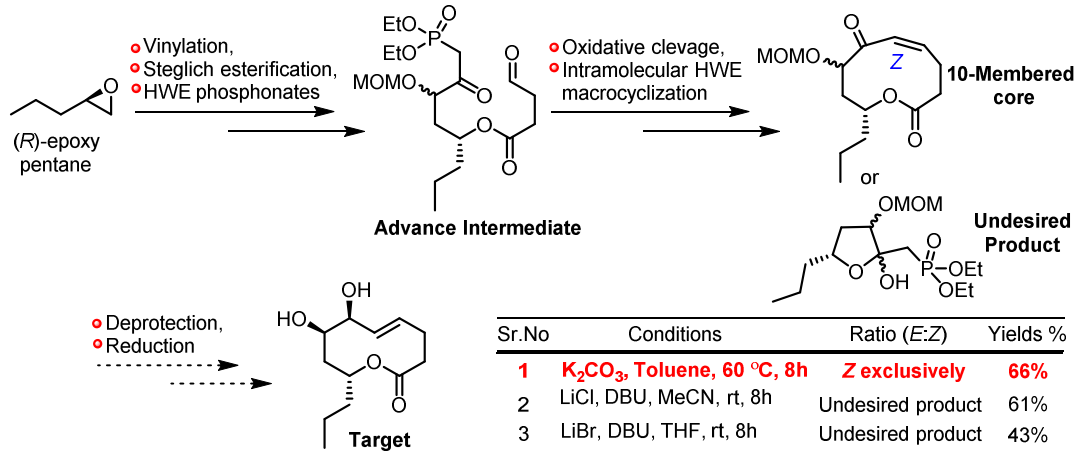
<u>Section A</u>: **Attempted synthesis of 10-Membered Lactone using intraannular Ramberg-Bäcklund reaction as a key step**.

A new 10-membered nonenolide, (6*S*,7*R*,9*R*)-6,7-dihydroxy-9-propylnon-4-eno-9-lactone was isolated by Daijie Chen *et al.*[4] from endophytic fungus *Phomopsis* strain HCCB03520 and found to exhibit good phytotoxic activity.

As documented in literature, unsuccessful attempts to construct *E*-isomer of nonenolide family using RCM or macrolactonization as a key step resulted either in formation of *Z*-isomer or dimerized product.[5] So the quest to accomplish the synthesis of desired natural product requires altogether new strategy. Our first approach using Ramberg-Bäcklund ring contraction strategy to construct *E*-double bond at C4–C5 of macrolactone was unsuccessful under the conditions screened and ended in decomposed or complex reaction mixture and there was a need to revise our synthetic approach.



Section B: **Intramolecular Horner–Wadsworth-Emmons approach towards the total synthesis of 10-Membered Lactone**

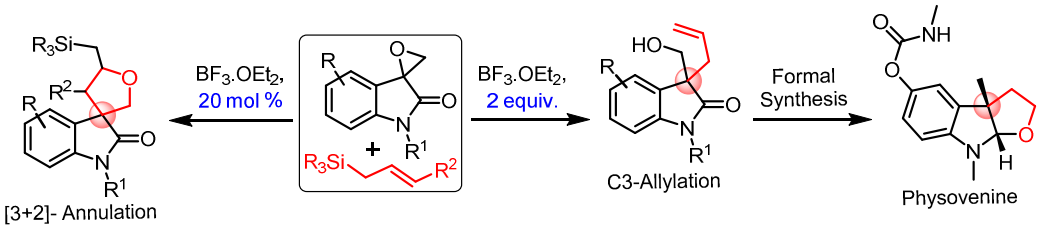


Sr.No	Conditions	Ratio (*E*:*Z*)	Yields %
1	K_2CO_3, Toluene, 60 °C, 8h	*Z* exclusively	66%
2	LiCl, DBU, MeCN, rt, 8h	Undesired product	61%
3	LiBr, DBU, THF, rt, 8h	Undesired product	43%
4	LiHMDS, THF, rt, 15h	Undesired product	72%

In continuation with the previous approaches, a revised strategy using intramolecular HWE reaction as a key step was insinuated to address the problem of getting *E*-selectivity, which worked efficiently to yield a macrocyclic *α,β*-unsaturated compound. Despite our efforts, we were unsuccessful in achieving the desired selectivity & ended getting exclusively the unnatural *Z*-diastereomer of the macrolactone core. Endeavour towards completion of the target moleucle is currently under progress.

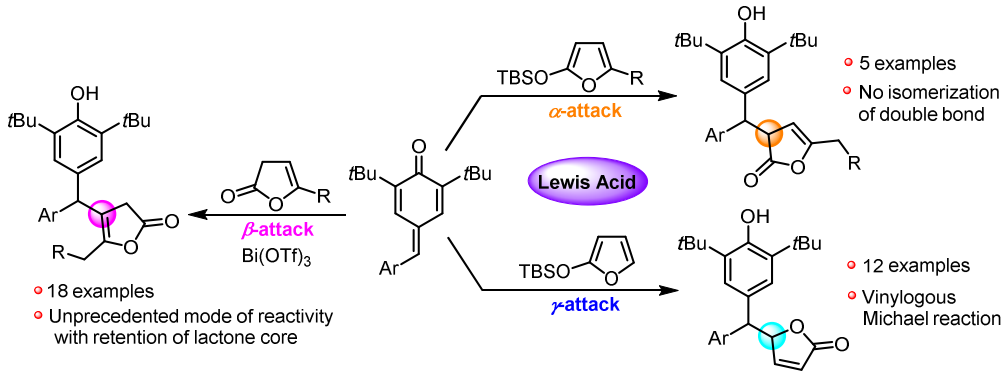
Chapter 3: Lewis Acid Mediated Regioselective C–C Bond Formation

Section A: Unified Approach for Fused and Spirocyclic Oxindoles *via* Lewis Acid Promoted Opening of Spiro-epoxyoxindoles with Allylsilanes



A protocol for the construction of oxindoles containing all-carbon quaternary centres in a highly regioselective manner has been developed. The reaction involves opening of spiroepoxyoxindoles with allylsilanes to give Hosomi–Sakurai type products as well as new silicon-containing spirocyclic oxindoles. A formal synthesis of (±)-physovenine was accomplished in five steps using this protocol.[6]

Section B: Unraveling the Nucleophilicity of Butenolides for 1,6-Conjugate Addition to para-Quinone Methides - A Direct Access to Diversely Substituted Butenolide-derived Diarylmethanes



Lewis acid catalyzed regioselective C–C bond formation through 1,6-conjugate additon of *para*-quinone methides with rarely exploited *β*-addition of deconjugated butenolides along with vinylogous Michael reaction of silyloxy furans[7] through *α* and *γ* positions have been developed. The reaction is mild with broad substrate scope, thus allowing easy access to *β*-bis-arylated *α*, *β*, *γ*-substituted butenolides. This method enables rapid access toward synthetically versatile butyrolactone substituted diarylmethane unit present in the core structure of biologically active natural products and synthetic intermediates.

Noteworthy Findings:

- Accomplished the total synthesis of Sch725674 and C-4-*epi*mer using modular approch towards identifying a potent antifungal molecule.
- Developed the first approach to construct 10-membered lactone skeleton using HWE reaction in an attempt to obtain *E*-isomer.
- Lewis acid catalyzed highly diversified and efficient protocol has been developed for C–C bond formation,
  - Product control *via* catalyst control gives either Hosomi-Sakurai or [3+2] annulations reaction containing all-carbon quaternary centres with high regioselectivity for the construction of oxindoles.
  - Vinylogous Michael reaction for regioselectively accessing all the carbon (α, β, γ) of butyrolactone.

References:

(1) Yang, S.-W.; Chan, T.-M.; Terracciano, J.; Loebenberg, D.; Patel, M.; Chu, M. *J. Antibiot.* **2005**, *58*, 535.

(2) Sharma, B. M.; Gontala, A.; Kumar, P. *Eur. J. Org. Chem.* **2016**, 1215.

(3) a) Si, D.; Sekar, N. M.; Kaliappan, K. P. *Org. Biomol. Chem.* **2011**, *9*, 6988; b) Grubbs, R. H.; O'Leary, D. J. *Handbook of metathesis: Applications in organic synthesis*; John Wiley & Sons, **2015**; c) Monfette, S.; Fogg, D. E. *Chem. Rev.* **2009**, *109*, 3783; d) Lin, Y. A.; Chalker, J. M.; Davis, B. G. *ChemBioChem* **2009**, *10*, 959; e) Lin, Y. A.; Davis, B. G. *Beilstein J. Org. Chem.* **2010**, *6*, 1219.

(4) Yang, Z.; Ge, M.; Yin, Y.; Chen, Y.; Luo, M.; Chen, D. *Chem. Biodiversity* **2012**, *9*, 403.

(5) a) Krishna, P. R.; Prabhakar, S.; Krishna, K. V. R. *RSC Adv.* **2013**, *3*, 23343; b) Reddy, C. R.; Das, B. *Tetrahedron Lett.* **2014**, *55*, 67; c) Vadhadiya, P. M.; Rout, J. K.; Ramana, C. *Tetrahedron* **2015**, *71*, 9088

(6) Sharma, B. M.; Yadav, M.; Gonnade, R. G.; Kumar, P. *Eur. J. Org. Chem.* **2017**, 2603.

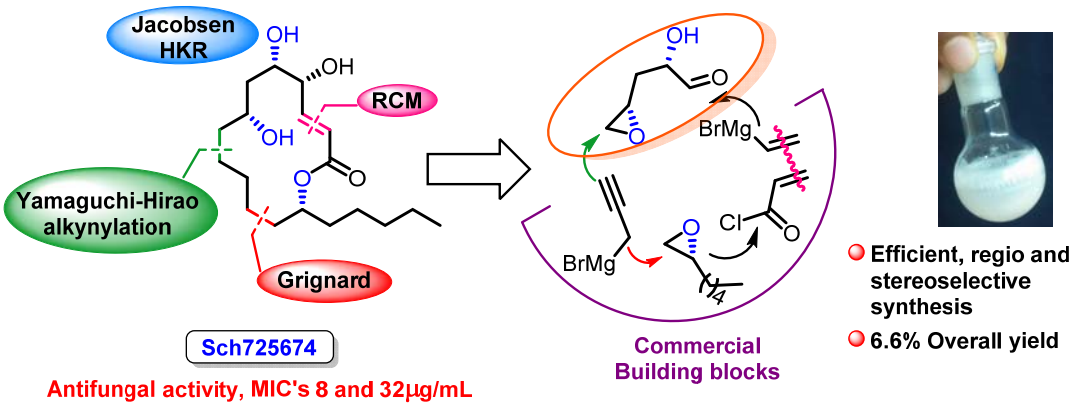
(7) a) Mao, B.; Fañanás-Mastral, M.; Feringa, B. L. *Chem. Rev.* **2017**, *117*, 10502; b) Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev.* **2011**, *111*, 3076.

"Where nature finishes producing its own species, man begins, using natural things and in harmony with this very nature, to create an infinity of species"

—Leonardo da Vinci (1452-1519)

Chapter I

Enantioselective Modular Total Synthesis of Macrolides Sch725674 and C-4-*epi*-Sch725674



1.1. Introduction

1.1.1. 14-Membered Macrocyclic Lactones

14-Membered macrolides have been promising research targets because of their exceptionally potent biological activities ranging from antibiotic to immunosuppressive, anti-inflammatory and anti-neoplastic acitivity. [1] For more than five decades, macrocycles have been subjected to chemical modifications for determination of structure-activity relationship which has resulted in improvement in their new therapeutic characteristic.[2] The mode of the antibacterial activity of the macrolides is expressed by inhibition of protein synthesis through their antagonistic interactions with bacterial 50S ribosomal subunits.[3] The uniqueness of 14-membered macrocycle lies in the compact ring architecture as compared to its 15- and 16-membered analogues, which leads to varying degrees of structurally pre-organized "folded-in" conformations.[4] These conformations allow key functional groups, present in the molecule, to interact with the binding sites in proteins selectively without much entropic loss on the binding.[5] Few examples [6] of such natural products with 14-membered macrolide are shown in Figure 1.1.

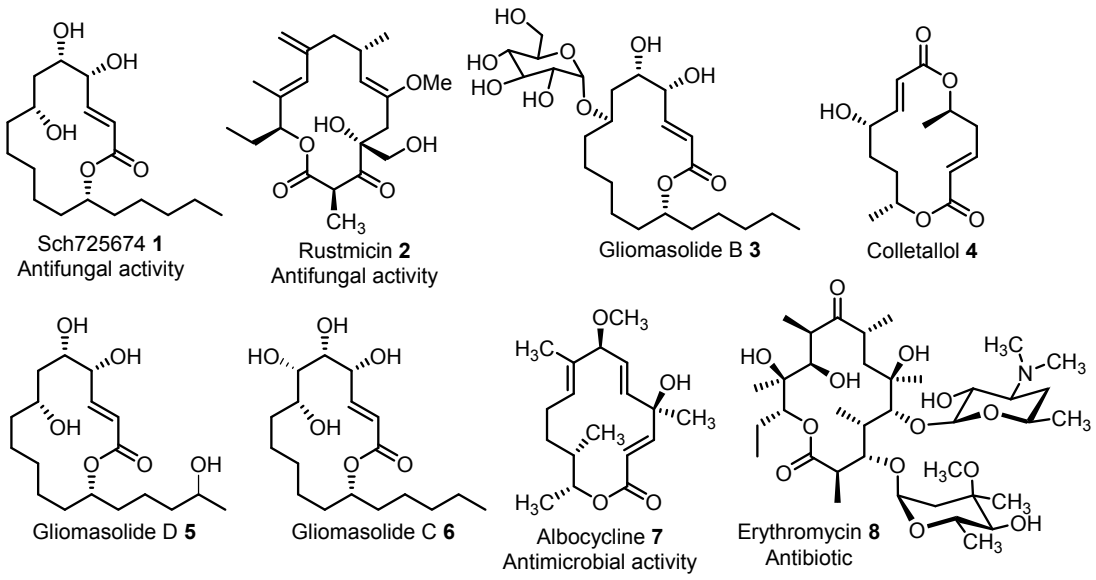


Figure 1.1. Structures of some representative 14-membered macrolides

Unlike small molecules[7] which are in preferential agreement with the 'Lipinski rule of 5', macrocycles can also demonstrate drug like physicochemical and pharmacokinetic properties such as good solubility, metabolic stability, lipophilicity, and bioavailability,

despite having high molecular masses. Natural-product macrocycles often have high-binding affinity for their targets, which illustrates its usage as therapeutics with minimal structural modification. Among the list of commercially available small-molecule drugs, approximately half are derived from synthetic precursors and are not based on any naturally occurring compound (albeit many have been motivated by nature).[8] By contrast, current macrocyclic drugs are almost exclusively derived from natural sources (or bioengineered microorganisms) and are either identical to or in close resemblance with naturally occurring macrocycles.[9] The discovery of erythromycin A, isolated from the actinomycete *Streptomyces erythreus* (*Saccharopolyspora erythraea*) is the best known 14-membered macrolide drug of the 20th century which is still in human use.[10] Apart from its activity, erythromycin A, is also one of the most celebrated molecule among synthetic chemists like Woodward,[11] Corey,[12] Masamune,[13] Stork,[14] Paterson,[15] Danishefsky,[16] Mulzar,[17] Hoffmann,[18] Evans,[19] Carreira[20] *etc*, who have elegantly achieved either its total synthesis or synthesized its derivatives/analogs. There is an extensive and growing literature around macrocycle synthesis,[21] and a developing consensus on the utilization of favored cyclization strategies includings ring-closing olefin metathesis,[22] multi-component reactions,[23] metal templated chelation[24] or ring-closing-contraction sequences[25] such as the Staudinger ligation.[26]

Macrocyclic compounds have been rather poorly exploited for drug discovery and design despite their proven therapeutic potential. The reluctance to investigate natural products can be attributed to their structural complexity and the allied difficulties in analog synthesis therein. Towards this goal, and based on our ongoing research interest in macrolides[27] and search for better pharmaceutical lead, recently, our group has accomplished the total synthesis of (–)-(6*R*,11*R*,14*S*)-isomer of colletallol **4**,[28] to study the detailed structure activity relashionships for this family of molecules[29] where its natural product (6*R*,11*R*,14*R*) isolated from the plant pathogen *Collectotrichum capsici*. was found to be inactive. The most distinguished application of macrolides is in their antimicrobial, antifungal and antibacterial activity. However, their active use has resulted in macrolide resistance in many organisms which fuels the quest for newer potentially active macrolides.

1.2. SCH725674

1.2.1. Isolation, Biological activity and Characterization

A novel 14-membered macrolide Sch725674 **1**, isolated by Yang *et al*.[30] in 2005 from an *Aspergillus sp*., culture (SPRI-0836) has been shown to exhibit good antifungal activity against *S. cereviceae* and *C. albicans* with minimum inhibitory concentrations (MICs) of 8 and 32 μg mL^{-1} respectively. The structure of Sch725674 **1** was elucidated by 1D and 2D NMR analyses. The coupling constant from ^{1}H NMR analysis (J = 15.8 Hz) between H-2 and H-3 established the *trans* configuration of the double bond (Δ2, 3). The HSQC-TOCSY data from ^{1}H–^{13}C correlation revealed the positions of double bond (Δ2, 3), four oxygen atoms attached on C-4, C-5, C-7, and C-13. These assignments were further supported by additional HMBC data analysis, where H-2 (δ 6.07, dd, J = 15.8, 1.6 Hz) showed a simple coupling pattern in ^{1}H NMR indicating that C-2 was adjacent to the carbonyl carbon C-1. Finally, the long-range correlation between H-13 (δ 4.94) and C-1 established the ester linkage, thus confirming the structure.

1.3. Literature Review

The intriguing structural features of Sch725674 **1**, is characterized by presence of polyhydroxylated 14-membered ring containing four stereogenic centers, an (*E*)-α,*β*-unsaturated ester, and an unusual *n*-pentyl carbon chain. The 14-membered mono-lactone skeleton without additional methyl group substitution on the ring (erythromycin-like) is very rare and unique in nature, thus making it an attractive target among synthetic organic chemists. The first total synthesis of Sch725674 **1** along with its 16 stereoisomeric analogs was reported by Curran *et al*.[31] using a fluorous-tagging strategy to generate the library of stereoisomers and thus consolidating its absolute stereochemistry as (4*R*, 5*S*, 7*R*, 13*R*). Later, a few more syntheses of the same macrolactone were reported from Prasad's group,[32] Kaliappan's group[33] and Reddy's group.[34] Very recently, Hanson's,[35] Aggarwal's[36] and Sabitha's group[37] have also elegantly accomplished the total synthesis of Sch725674 **1**. Till date, 8 syntheses for Sch725674 have been documented in the literature including our group[38] thus showcasing the importance of this synthetic target. Most of these approaches to access the 1,3-diol system are based on either asymmetric methods such as 1,3-asymmetric

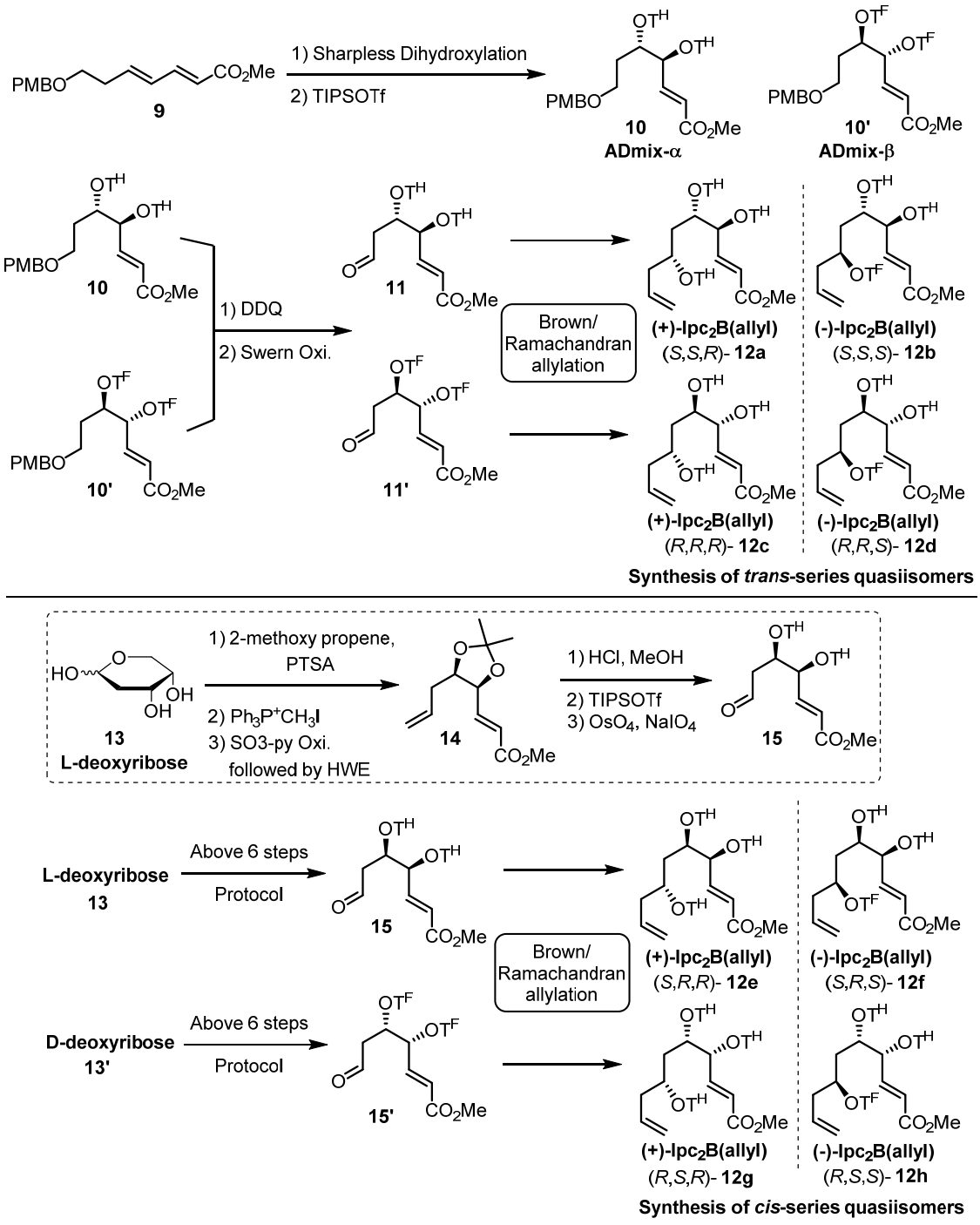
reduction, chiral allylboration and Sharpless asymmetric dihydroxylation or chiral pool approach. A detailed report of these syntheses is described below.

1.3.1. Curran's Approach [31]

Fluorous Tagging Technique:[39] In a Fluorous tagging or fluorous mixing synthesis (FMS) a series of substrates were tagged with various fluorous tags with increasing fluorine content and mixed in equimolar ratios to give fluorous mixture called quasiisomers. Multiple synthetic operations on these quasiisomers result in different analogues which then separated (demixing) by fluorous chromatography eluting in the order of increasing fluorine content. The separated products were detagged to give the individual final products.

Tagging: The synthesis of *trans*-series quasiisomers **M-12a-b** commenced from a diene ester **9** which on Sharpless asymmetric dihydroxylation with AD-mix-α followed by fluorous tagging using TIPSOTf ($Si(iPr)_3$ group is denoted as T^H) gave compound **10**. The PMB deprotection, followed by Swern oxidation resulted in aldehyde **11**, which on treatment with (+)-Ipc_2B(allyl) reagent followed by silylation with TIPSOTf (T^H) gave ester **12a**. On the other hand, aldehyde **11** on treatment with (–)-Ipc_2B(allyl) reagent followed by silylation with TIPSOTf ($Si(iPr)_2CH_2CH_2C_2F_5$, denoted as T^F) gave ester **12b**. Following similar reaction sequence, esters **12c** and **12d** were prepared from the aldehyde **11'** which was synthesized using Sharpless asymmetric dihydroxylation with AD-mix-β and was tagged using TIPSOTf (T^F) fluorous tag.

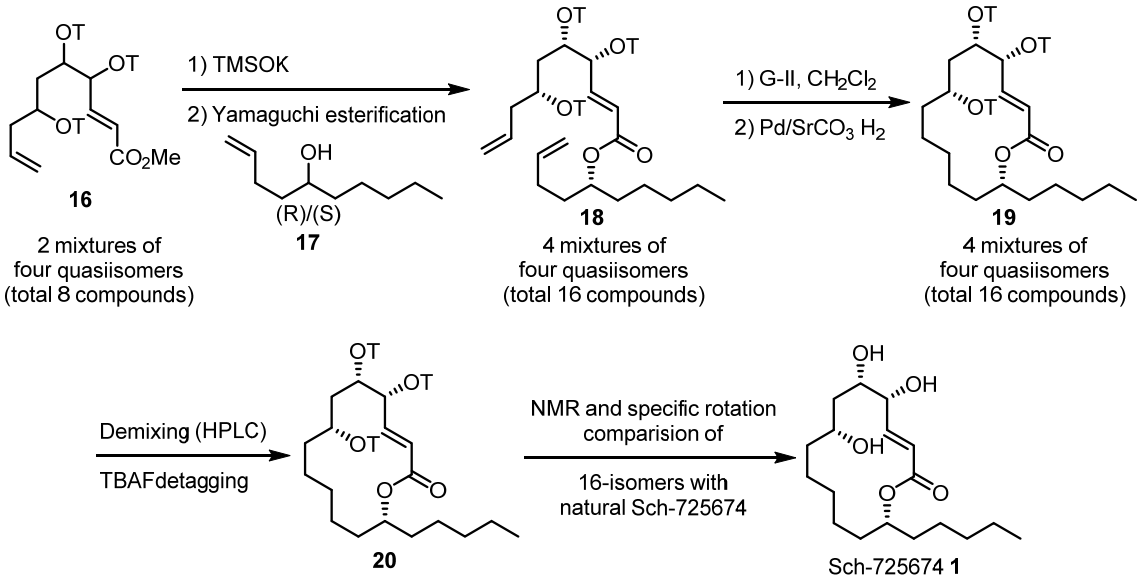
The synthesis of *cis*-series quasiisomers **M-12e-h** started from 2-deoxy-D-ribose **13**, which on acetonide protection followed by 1C-Wittig olefination, oxidation with SO_3-py followed by Horner–Wadsworth–Emmons (HWE) reaction afforded ester **14**. The acetonide deprotection followed by silylation with fluorous tag TIPSOTf (T^F) and its oxidative cleavage using $OsO_4/NaIO_4$ gave aldehyde **15**. Further, the aldehyde **15** on Brown/Ramachandran allylation with (+)-Ipc_2B(allyl) and its subsequent flurous tagging with TIPS (T^H) gave ester **12e**. The similar sets of reaction with of (−)Ipc_2B(allyl) followed by silylation with (T^F) gave compound **12f**. Esters **12g** and **12h** were synthesized from 2-deoxy-L-ribose **13'** using similar reaction sequence (Scheme 1.1).



Scheme 1.1. Synthesis of quasiisomers

Mixing: All the 4,5-*trans*-series-esters **12a-d** were mixed in equimolar ratio to give a mixture of four quasiisomers **M-12a-d**, in a similar way 4,5-*cis*-series esters **12e-h** were mixed in equimolar ratio to give a mixture of four quasiisomers **M-12e-h**.

Synthetic Steps: The two mixtures (**M-12a-d** and **M-12e-h**) of four quasiisomers were hydrolyzed with potassium trimethylsilanoate (TMSOK) followed by Yamaguchi esterification with both the enantiomers of compound **17** separately to give four mixtures of four quasiisomers. The diene **18** on ring closing metathesis with Grubbs' 2nd catalyst (G-II) followed by reduction of the isolated olefin using Pd-catalyst poisoned with $SrCO_3$, afforded the macrocycle **19** (which contains four mixtures of four quasiisomers). Demixing and detagging four mixtures of **19** gave 16-stereo isomers of Sch-725674 **1** (Scheme 1.2).



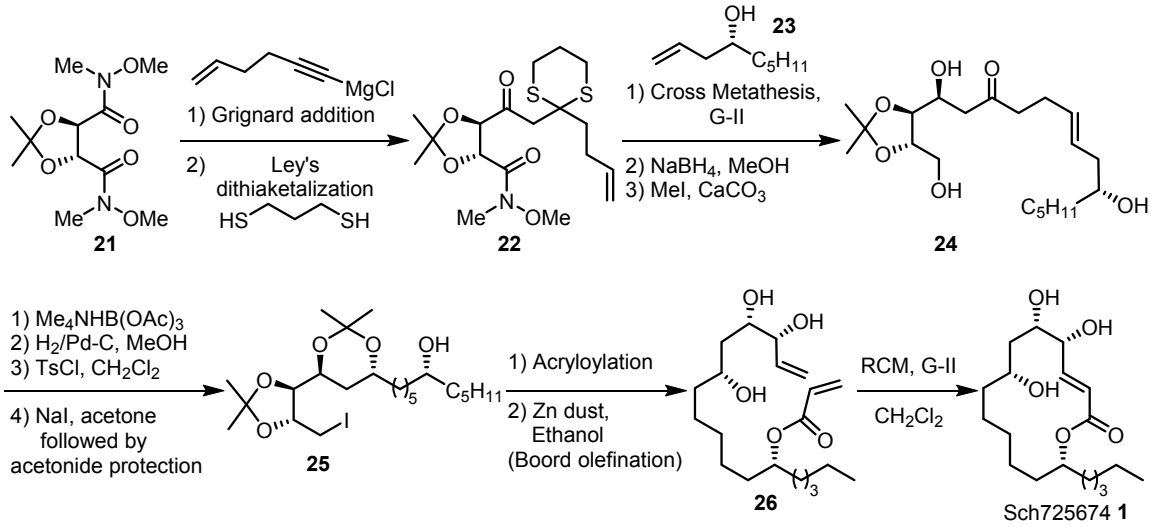
Scheme 1.2. Curran's fluorous tagging strategy for the synthesis of library of Sch725674

1.3.2. Prasad's Approach [32]

Prasad and co-workers in 2014 reported the synthesis of Sch725674 **1** in 12 steps with 2.6% overall yield using desymmetrization of bis-Weinreb amide, Ley dithiaketalization, and RCM reaction as the key steps.

Accordingly, the synthesis started with desymmetrization of bis-Weinreb amide **21** with hex-5-en-1-ynylmagnesium chloride, followed by Ley's dithianylation to afford the 1,3-dithianyl ketone **22**. Cross-metathesis of **22** with homoallylic alcohol **23** with G-II, $NaBH_4$ reduction and subsequent deprotection of dithiane with MeI/$CaCO_3$ resulted in formation of *β*-hydroxy ketone **24**. The ketone **24** was reduced in 1,3-*anti* fashion with $Me_4NHB(OAc)_3$, hydrogenation of double bond with 10% Pd/C, tosylation of primary amine, iodination of tosylate followed by 1,3-acetonide protection of the corresponding

1,3-diol furnished compound **25**. Acryloylation of **25** followed by Boord olefination in presence of zinc dust in refluxing ethanol gave the key precursor **26**. Ring-closing metathesis of diene **26** with G-II catalyst furnished the desired natural product Sch725674 **1** as shown in Scheme 1.3.

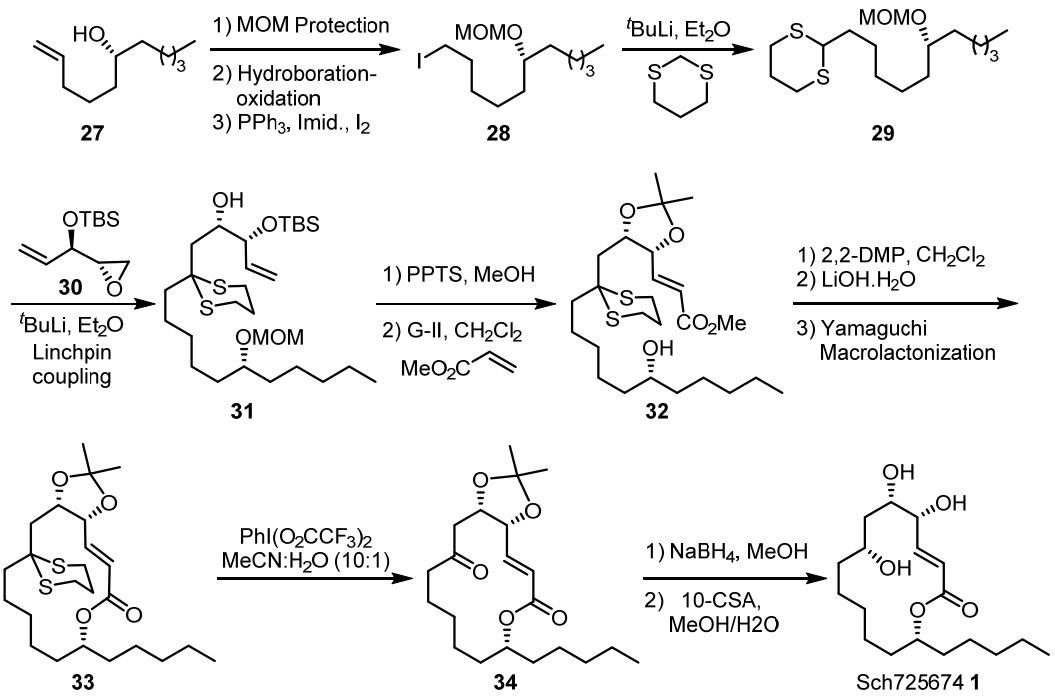


Scheme 1.3. Prasad's desymmetrization approach for the total synthesis of Sch725674

1.3.3. Kaliappan's Approach [33]

Kaliappan and co-workers in 2015 reported the synthesis of Sch725674 **1** in 13 steps using Linchpin coupling, cross metathesis, Yamaguchi macrolactonization and a substrate controlled stereoselective reduction of the keto group as key steps.

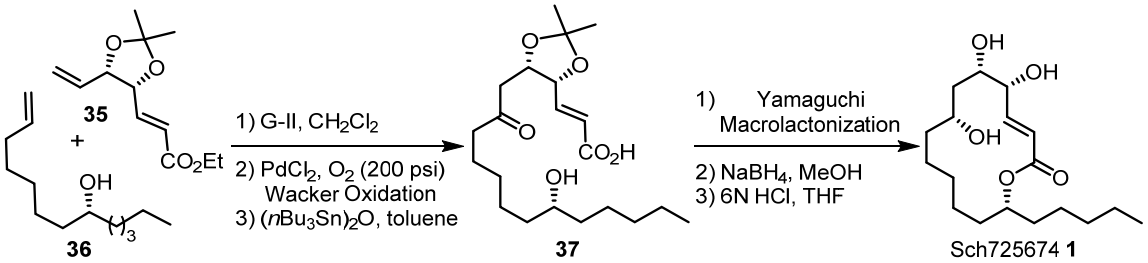
The synthesis commenced from known alcohol **27**, which on MOM ether protection, hydroboration followed by iodination resulted in formation of iodo compound **28**. The linchpin coupling of iodo fragment **28** with 1,3-dithiane resulted in formation of alkylated dithiane compound **29**. The second linchpin coupling of dithiane **29** with epoxide **30** afforded dithiane dialkylated product **31**. Desilylation and MOM deprotection using PPTS followed by cross-metathesis with methyl acrylate furnished the seco-ester **32**. The 1,2-diol acetonide protection, hydrolysis of methyl ester using $LiOH.H_2O$ resulted in formation of seco-acid which smoothly underwent key Yamaguchi macrolactonization delivering macrolactone **33**. The Stork's reagent mediated deprotection of dithiane afforded ketoester **34**. The substrate controlled stereoselective reduction using $NaBH_4$, followed by acetonide deprotection furnished the natural product Sch725674 **1** as shown in Scheme 1.4.



Scheme 1.4. Kaliappan's 1,3-dithianes approach for the total synthesis of Sch725674

1.3.4. Reddy's Approach [34]

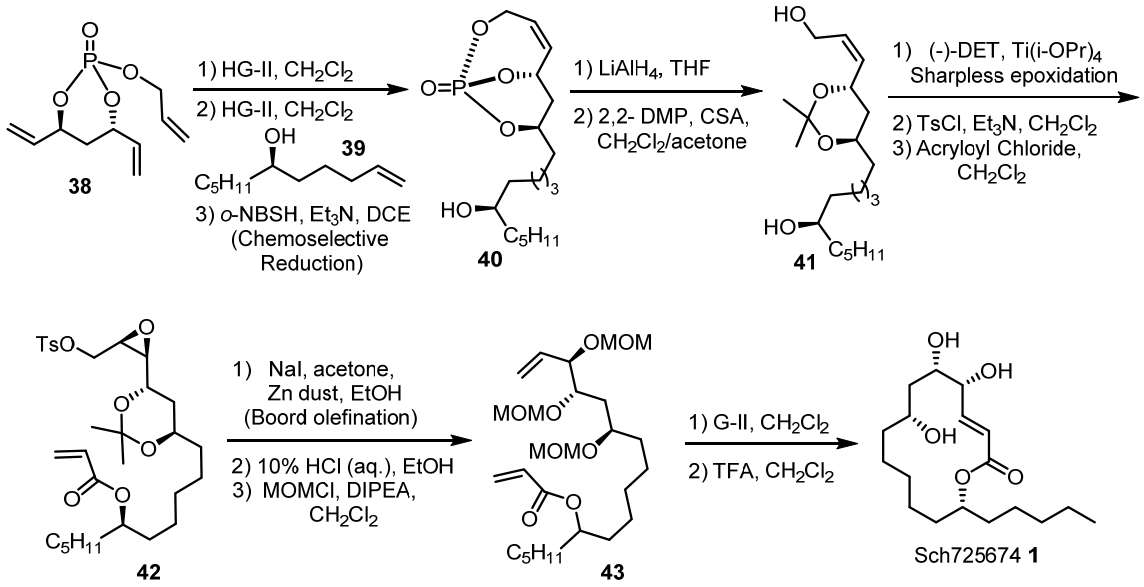
Reddy and co-workers in 2016 reported the formal synthesis of Sch725674 **1** using cross-metathesis and regioselective Wacker oxidation of internal olefin as key steps. The synthesis commenced with cross-metathesis of known building blocks **35** and **36**, followed by regioselective incorporation of ketone group under Wacker oxidation, which on treatment with bis(tributyltin)oxide yielded the desired seco-acid **37**. The Yamaguchi macrolactonization of seco-acid **37**, followed by stereoselective reduction using $NaBH_4$ and its subsequent acetonide deprotection using 6N HCl furnished the natural product Sch725674 **1** as shown in Scheme 1.5.



Scheme 1.5. Reddy's chiral pool approach for the formal synthesis of Sch725674

1.3.5. Hanson's Approach [35]

Hanson and co-workers in 2016 reported the synthesis of Sch725674 **1** in 14.6% overall yield using phosphate tether-mediated one-pot, sequential RCM/CM/chemoselective hydrogenation protocol as key steps.

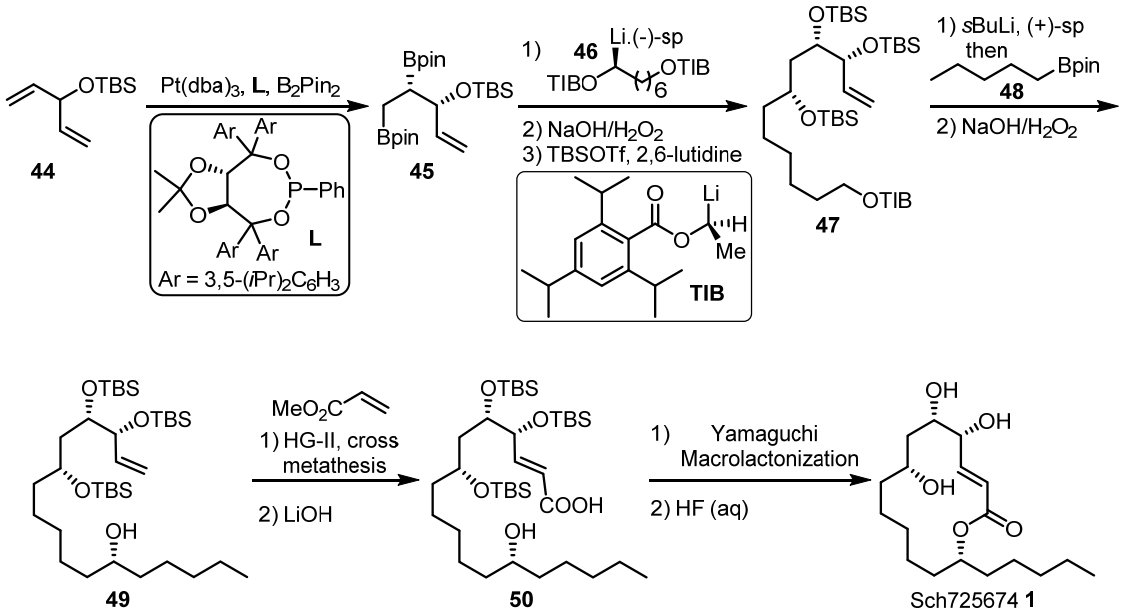


Scheme 1.6. Hanson's phosphate tether approach for the total synthesis of Sch725674

The synthetic journey started with, one-pot sequential ring closing metathesis of **38** followed by cross-metathesis with **39**, which on chemoselective diimide reduction of the resulting external olefin using *o*-nitrobenzenesulfonylhydrazine (*o*-NBSH) afforded bicyclic phosphate **40**. The compound **40** on LAH reduction followed by 1,3-diols acetonide protection gave compound **41**. The Sharpless epoxidation of allylic alcohol **41**, followed by tosylation and its concomitant acryloylation furnished the compound **42**. A sequential, one-pot Finkelstein substitution, Boord olefination (Zn, EtOH) and acetonide deprotection, followed by MOM protection resulted in formation of key diene intermediate **43**. The key precursor **43** on ring closing metathesis using G-II catalyst followed by global MOM deprotection using trifluoroacetic acid, delivered the natural product Sch725674 **1** as shown in Scheme 1.6.

1.3.6. Aggarwal's Approach [36]

Aggarwal and co-workers in 2016 reported the synthesis of Sch725674 **1** in 9 steps with 27% overall yield using novel desymmetrizing enantioselective diboration, late-stage cross-metathesis and Yamaguchi macrolactonization as key steps.

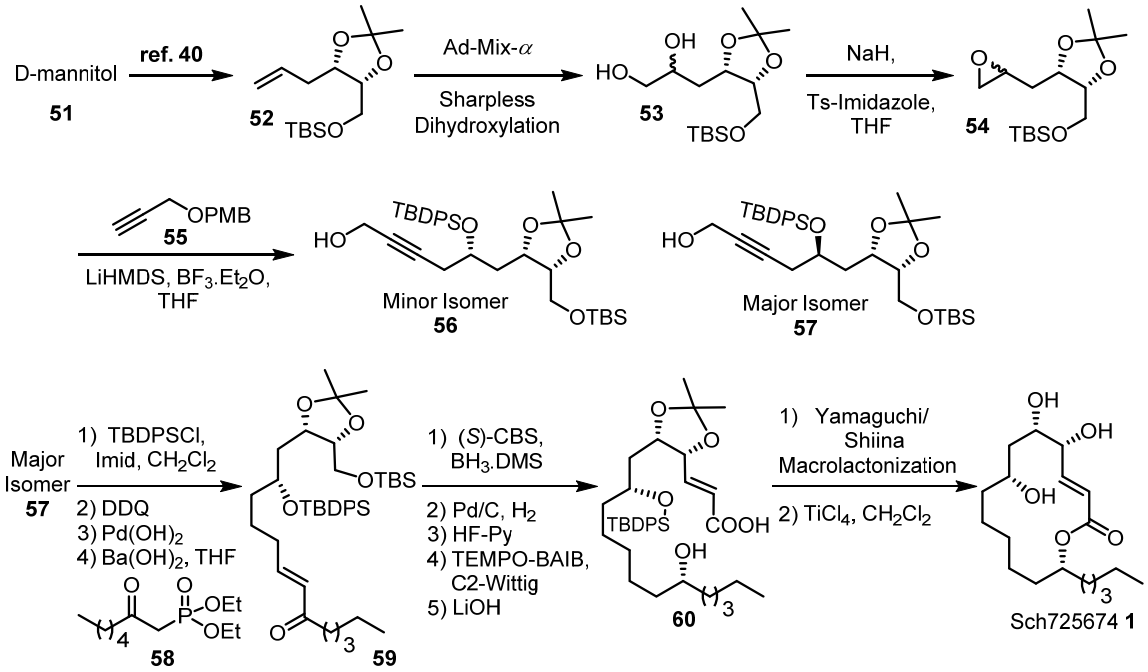


Scheme 1.7. Hanson's lithiation–borylation–oxidation approach for the total synthesis of Sch725674

Accordingly, *O*-silyl derivative **44** under desymmetrizing Morken/Nishiyama asymmetric diboration gave *anti* 1,2-bis(boronic ester) **45**. The compound **45** was converted to **47** by treatment with, sparteine-ligated lithiated carbamate **46**, followed by oxidation and its TBS protection. The compound **47** on further reaction with pentyl boronic ester **48** following lithiation-borylation-oxidation sequence gave tris(*tert*-butylsilyl)-protected tetrol **49**. The terminal alkene on cross-metathesis with methyl acrylate using HG-II, followed by methyl ester hydrolysis using LiOH delivered the seco-acid **50**. The Yamaguchi macrolactonization of seco-acid **50** accomplished the macrocyclic core, which on desilylation using HF (aq) gave the target natural product Sch725674 **1** as shown in Scheme 1.7.

1.3.7. Sabitha's Approach [37]

Sabitha and co-workers in 2016 reported the synthesis of Sch725674 **1** in 13 steps with 9.9% overall yield using Sharpless asymmetric dihydroxylation, HWE olefination, Yamaguchi or Shiina macrolactonization as key steps.



Scheme 1.8. Sabitha's chiral pool approach for the total synthesis of Sch725674

The synthesis commenced with commercially available D-mannitol **51** which was converted to known compound **52** using literature protocol. [40] The terminal olefin **52** under Sharpless dihydroxylation condition using AD-mix-α resulted in formation of 1,2-diol with desired stereochemistry as a major diastereomer **53**. The diol **53** was further converted to epoxide **54** in presence of tosylimidazole/NaH. Next the epoxide **54** and propargyl ether **55** were coupled to yield mixture of diastereomers **56** and **57**. The major diastereomer **57** was subjected to TBDPS ether protection, PMB deprotection followed by *E*-selective enone formation to give **59**. This includes $Pd(OH)_2$ catalyzed transformation of primary propargylic alcohol into an aldehyde and subsequent treatment with β-ketophosphonate **58** in the presence of $Ba(OH)_2$. The (*S*)-CBS mediated reduction of enone **59**, followed by H_2-Pd/C hydrogenation, selective TBS deprotection, TEMPO-BIAB oxidation/C2-Wittig olefination and its subsequent hydrolysis furnished the seco-

acid **60**. Finally Yamaguchi/Shiina macrolactonization, followed by global deprotection using $TiCl_4$ delivered the target Sch725674 **1** as shown in Scheme 1.8.

1.4. Present Work

1.4.1. Objective

The total synthesis of Sch725674 can lead to a plethora of opportunities in terms of achieving a function-oriented synthesis of new macrolides.[41] At the onset of this research project, only three syntheses were published. Therefore, there remained a need for a more efficient synthesis of Sch725674 and analogues thereof. The aim of this research was to develop an efficient and convergent synthesis of that would be amenable to the preparation of a variety of interesting analogues. More so, as this molecule can be readily converted into products that contain the structural scaffolds of pyran and furan rings[42] by using a simple intramolecular transannular oxy-Michael reaction to afford compounds that resemble those with established antineoplastic activity. Such transformations would help to tune the biological activity of a lead structure by incorporating activity-determining structural features as shown in Figure 1.2.

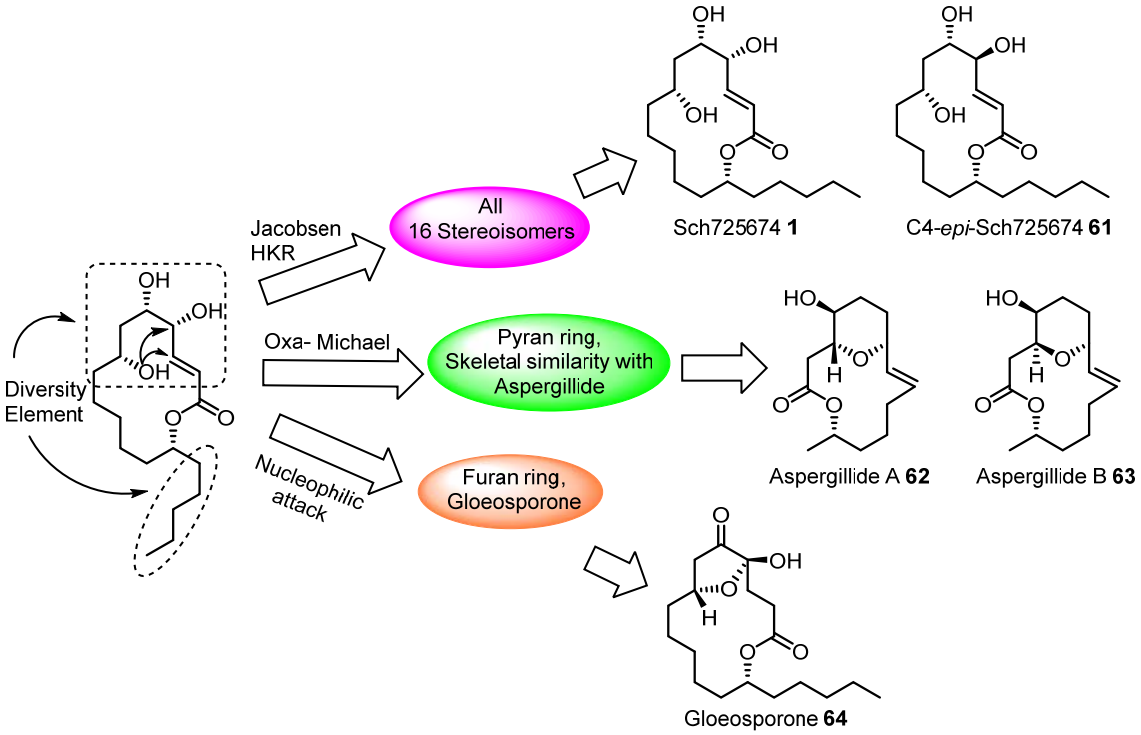
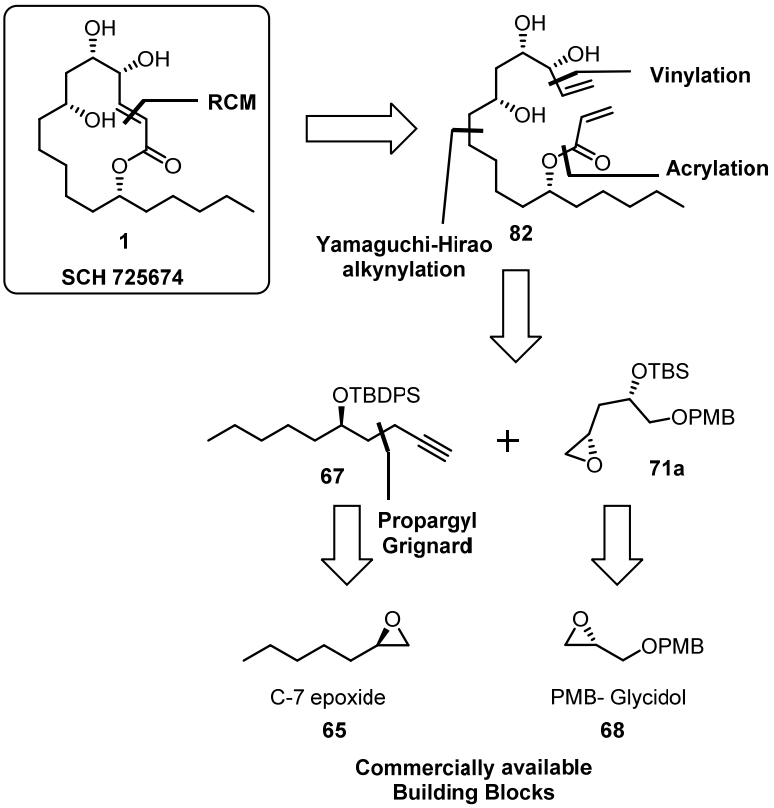


Figure 1.2. Function-Oriented synthetic approach to various analogues of Sch725674

The interesting structural features of Sch725674 **1**, scarcity of natural resources coupled with its biological activity prompted us to embark on its total synthesis. As a part of our research program, aimed towards development of natural products containing stereochemically diverse 1,3-polyols and library of its analogues,[43] we became interested to devise a new synthetic route for the total synthesis of Sch725674.

In order to allow maximum flexibility, we have designed a unified, efficient and convergent strategy for the easy synthesis of Sch725674 and C-4-*epi*-Sch725674, which comprised assembling of five modules through sequential Jacobsen HKR,[44] Yamaguchi–Hirao alkynylation,[45] and ring-closing metathesis (RCM) steps to construct the core skeleton of the macrolide. The details of findings are presented below.

1.4.1.1. Retrosynthetic Analysis



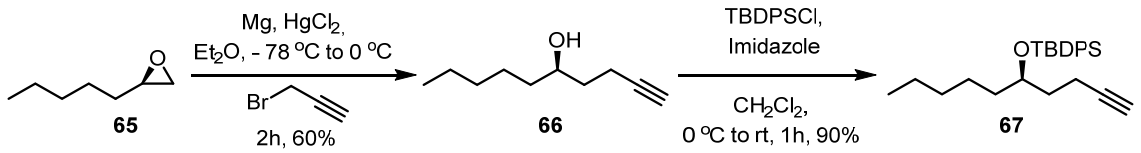
Scheme 1.9. Retrosynthetic Analysis

Our retrosynthetic analysis, involved disconnecting Sch725674 into five modules as outlined in Scheme 1.9. The assembly of 14-membered lactone was envisioned from diene **82** *via* ring- closing metathesis. The fragment **82** could be obtained by Yamaguchi-Hirao alkynylation reaction between epoxide **71a** and alkyne fragment **67**. The alkyne **67**

can be obtained using Grignard reaction from commercially available chiral starting material (*R*)-epoxyheptane **65**. The fragment **71a** could be accessed by Jacobsen HKR, which in turn could be prepared from commercially available (*S*)-PMB glycidol **68 (**Scheme 1.9).

1.4.1.2. Results and Discussion

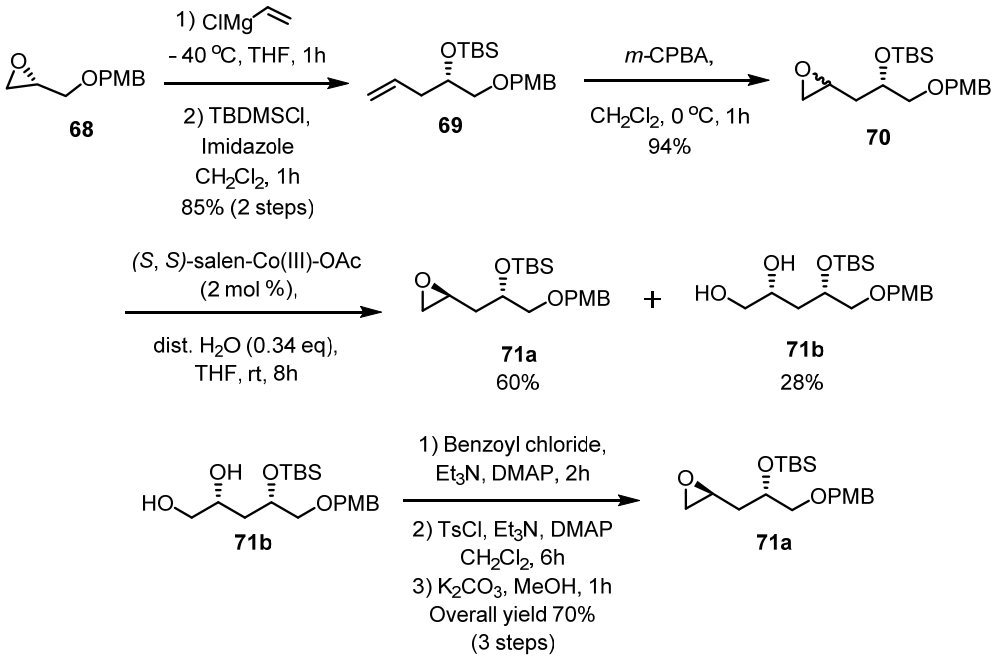
Our endeavor to synthesize the target molecule **1**, began with the synthesis of desired key coupling fragments **67** and **71a**. To access alkyne fragment **67**, the readily available (*R*)-epoxyheptane **65** was subjected to Grignard reaction. Regioselective epoxide ring opening with propargyl magnesium bromide in presence of catalytic $HgCl_2$ gave alkyne **66** in 60% yield. In the absence of $HgCl_2$, formation of allene was observed as a side product. The IR spectrum of **66** gave broad hydroxyl absorption at 3526 cm^{-1} and –C≡C–H stretch at 3020 cm^{-1}. Also, in ^1H NMR spectrum the signals at δ 3.77 - 3.71 (m, 1 H) and δ 1.97 (t, J = 2.7 Hz, 1 H)) correspond to proton attached to hydroxy group and acetylenic proton. The hydroxyl group was protected as TBDPS ether using TBDPSCl and imidazole to afford the required alkyne fragment **67** in 90% yield as shown in Scheme 1.10. The HRMS (ESI^+) peak at 393.2608 corresponding to formula $C_{26}H_{36}OSi$ $[M + H]^+$ (calculated value 393.2601) confirms the formation of alkyne fragment **67**.



Scheme 1.10. Synthesis of alkyne fragment **67**

As illustrated in Scheme 1.11, the synthesis of epoxy component **71a** started from (*S*)-PMB glycidol **68** which on vinyl Grignard reaction, followed by TBS ether protection of the hydroxy group gave the homoallylic alcohol **69**. [46] The formation of **69** was indicated by ^1H NMR signals at δ 5.92 - 5.72 (m, 1 H), 5.09 - 5.00 (m, 2 H) corresponding to the olefinic proton. Compound **69** was oxidized with *m*-CPBA to give the epoxide **70** in 94% yield as an inseparable diastereomeric mixture of 2:1 (*anti*:*syn*). The ^1H NMR spectrum of **70** clearly showed the signal for diastereomeric epoxide protons at δ 3.10 - 3.05 (m, 1 H), 2.82 - 2.76 (m, 1 H), 2.52 - 2.48 (m, 1 H). Epoxide **70** was subjected to Jacobsen hydrolytic kinetic resolution using (*S,S*)-salen-Co(III)-OAc catalyst to give the

diastereomerically pure epoxide **71a** (^{1}H NMR analysis) in 60% yield along with diol **71b** in 28% yield. The enantiopure diol **71b** (*dr* ~ 9:1) was converted into the desired epoxide **71a** following a sequence of reactions, as depicted in Scheme 1.11. Accordingly, the chemoselective benzoylation of diol **71b** followed by tosylation of the secondary hydroxyl and treatment of the crude tosylate product with K_2CO_3 in methanol led to deprotection of the benzoyl ester. Concomitant ring closure *via* intramolecular S_N2 displacement of the tosylate furnished the epoxide **71a** in 70% overall yield.



Scheme 1.11. Synthesis of epoxide fragment **71a**

After having successfully synthesized both fragments in substantial amounts, our next task was to couple them under Yamaguchi-Hirao protocol (Scheme 1.12). [45] Accordingly sequential treatment of alkyne **67** with *n*-BuLi, $BF_3.Et_2O$ followed by addition of epoxide **71a** in THF at –78 °C resulted in the formation of *β*-hydroxy alkyne **72** in 86% yield. The IR spectrum of **72** showed hydroxyl group absorption at 3417 cm^{-1}. The ^{1}H NMR spectrum of compound **72** showed signals for the corresponding 3 secondary hydroxy protons at δ 4.12 (quin, *J* = 5.6 Hz, 1 H), 3.93 - 3.87 (m, 1 H), 3.81 - 3.77 (m, 4 H) and ^{13}C NMR signals appeared at δ 82.5, 76.2 corresponding to the acetylenic carbon. The HRMS (ESI$^+$) peak at 767.4497 corresponds to formula $C_{45}H_{68}O_5Si_2$ $[M + Na]^+$ (calculated value 767.4490) further confirms the structure of coupled product **72**. The triple bond in **72** was completely reduced in presence of Raney Ni/H_2 at 1 atmospheric

pressure to give **73** in 95% yield. The formation of compound **73** was further confirmed by the disappearance of –C≡C– bond signals at δ 82.5 and 76.2 ppm in ^{13}C NMR. The relative stereochemistry at C5 and C7 centre of *anti*-1,3-diol **73** was determined by using Rychnovsky's acetonide method.[47] Towards this end, compound **73** was subjected to TBS deprotection to furnish the diol, which without further purification was treated with 2,2-DMP to give the acetonide **73b**. The stereochemistry of *anti*-acetonide **73b** was confirmed by the appearance of the methyl carbons resonance at δ 24.7 and 24.8 ppm and the acetal carbon at δ 100.3 ppm as shown in Figure 1.3.

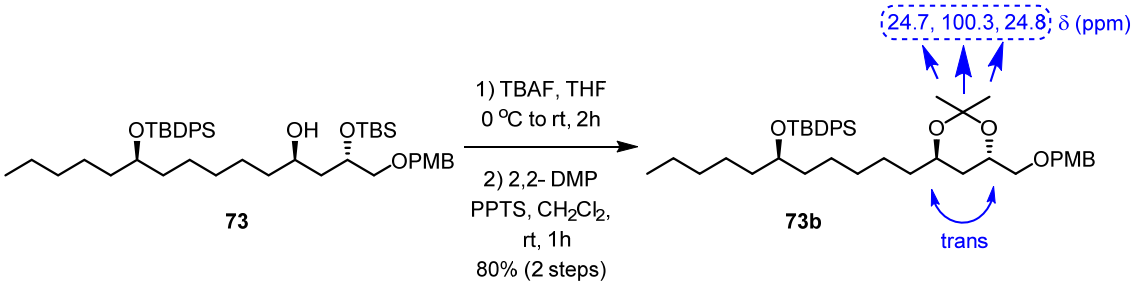
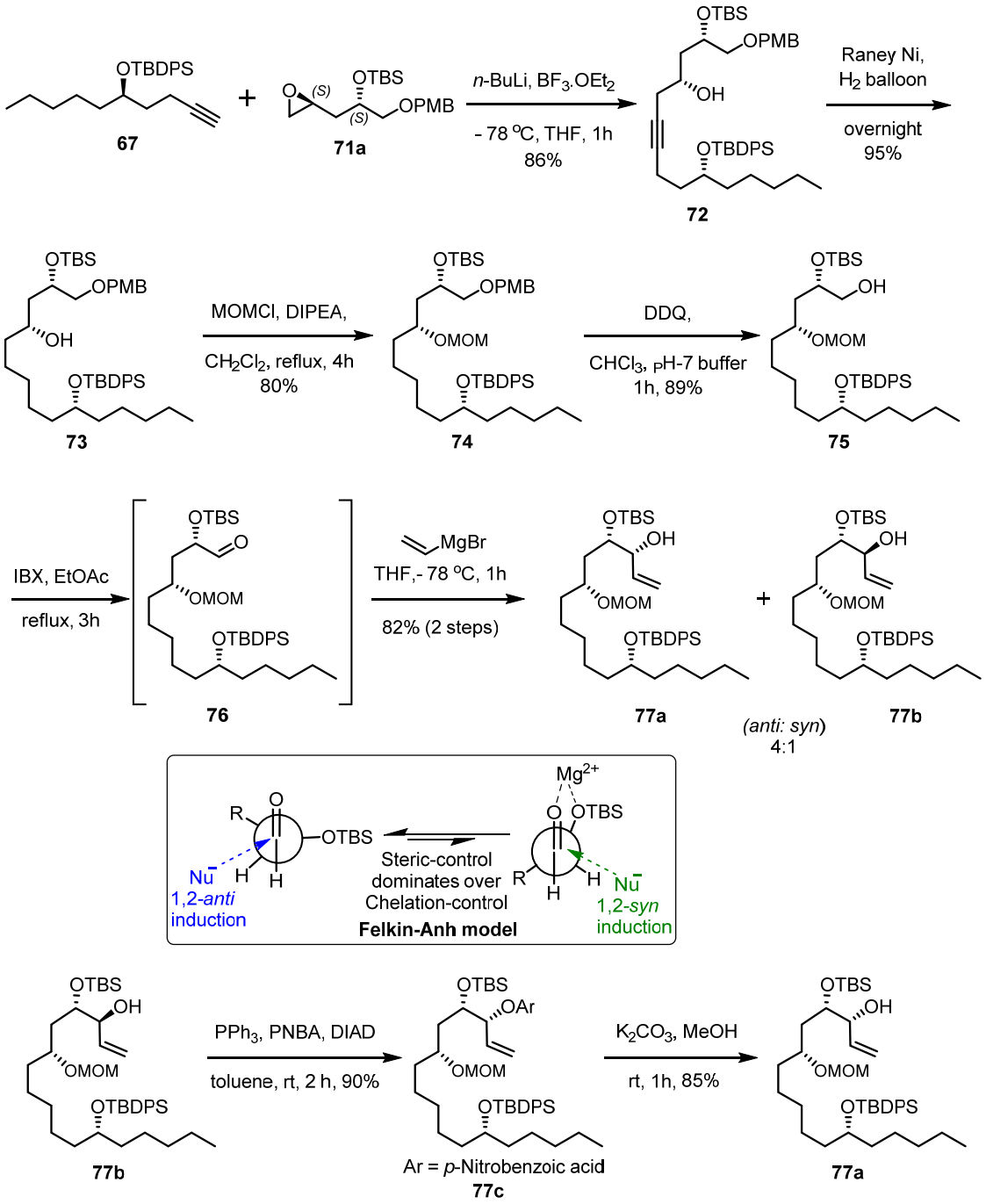


Figure 1.3. Determination of relative configuration by ^{13}C NMR measurement of 1,3-diol **73b**

After having confirmed the stereochemistry of 1,3-diol unambiguously, the free hydroxy group was then protected as its MOM ether using MOMCl and DIPEA under reflux to give **74** in 80% yield. The ^{1}H NMR spectrum of **74** showed methoxy protons at δ 3.83 (s, 3 H) and methyleneoxy protons at δ 4.51 - 4.44 (m, 2 H). In ^{13}C NMR, the presence of methyleneoxy carbon was confirmed by its distinct signal at δ 95.8. The deprotection of PMB using DDQ in (20:1) mixture of $CHCl_3$: pH 7 phosphate buffer resulted in primary alcohol **75** in 89% yield. The band at 3377 cm^{-1} in IR spectrum confirmed the presence of hydroxyl group. The ^{1}H NMR spectrum showed disappearance of aromatic and methoxy peaks of PMB group. Oxidation of alcohol **75** with 2-iodoxybenzoic acid (IBX) furnished the corresponding aldehyde which was subsequently treated with vinylmagnesium bromide at –78 °C to afford compound **77a** and **77b** as a diastereomeric mixture, *anti:syn* (4:1) in 82% yield over two steps.[48] The IR spectrum of major isomer **77a** showed absorption of resultant hydroxyl group at 3393 cm^{-1}. In ^{1}H NMR spectrum of **77a**, the vinyl protons appeared at δ 5.85 (ddd, J = 5.9, 10.8, 17.1 Hz, 1 H), 5.34 (dt, J = 1.5, 17.1 Hz, 1 H), 5.23 (dt, J = 1.5, 10.5 Hz, 1 H) and corresponding newly generated allylic proton signal appeared at δ 4.17 - 4.14 (m, 1 H). The HRMS (ESI^{+}) peak at

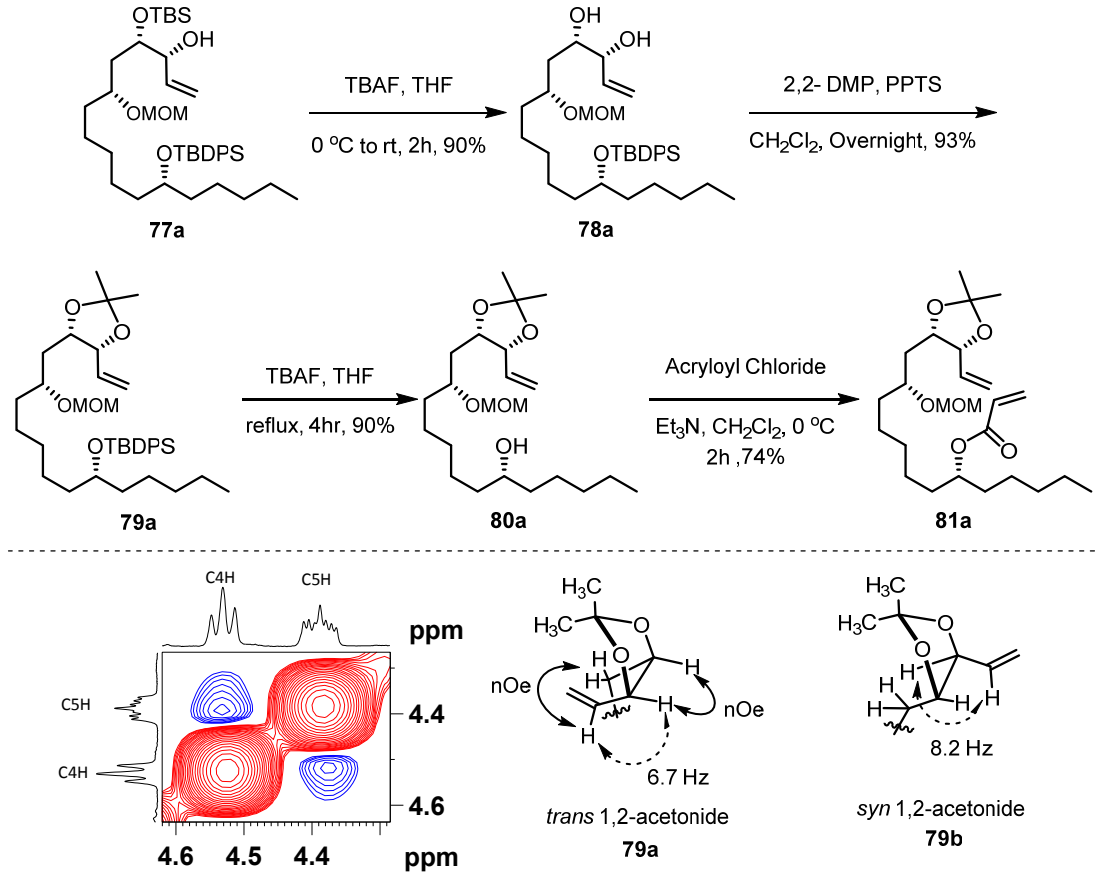
721.4654 corresponds to formula $C_{41}H_{70}O_5Si_2$ $[M + Na]^+$ (calculated value 721.4651). Similarly in ^1H NMR spectrum, the minor isomer **77b** showed signals at δ 5.97 - 5.87 (ddd, J = 5.1, 10.5, 17.0 Hz, 1 H), 5.33 (d, J = 17.1 Hz, 1 H), 5.21 (d, J = 10.5 Hz, 1 H) and 4.05 (t like, 1 H) for corresponding vinylic and allylic proton.



Scheme 1.12. Coupling of fragments **67** and **71a**

The diastereofacial selectivity on aldehyde **76** can be rationalized according to the Felkin model shown in Scheme 1.12, with the large –OTBS group placed opposite to the

approach of vinylmagnesium Grignard reagent. The diastereomers were separated by flash chromatography and minor *syn* isomer **77b** was taken forward to synthesize the *C4-epimer*. The stereochemistry of *anti* isomer **77a** achieved by Grignard attack was the desired natural stereoisomer. The *syn* isomer **77b** can however be smoothly converted to major *anti* isomer **77a** *via* Mitsunobu reaction. The compound **77b** was treated with p-nitrobenzoic acid and DIAD to give intermediate **77c**, which on subsequent hydrolysis gave the desired isomer **77a** explicitly. The IR spectrum of **77c** showed ester carbonyl peak at 1725 cm^{-1}. In ^{1}H NMR spectrum the aromatic protons of PNBA group appeared at δ 8.30 (d, J = 8.9 Hz, 2 H), 8.23 (d, J = 8.9 Hz, 2 H). The ^{13}C NMR signal at δ 164.0 corresponds to ($–CO_2–$). Both the diastereomers **77a** and **77b** in subsequent steps were converted to 1,2-acetonide **79a** and **79b** so as to confirm explicitly the configuration of newly generated stereocenters as shown in Scheme 1.13.

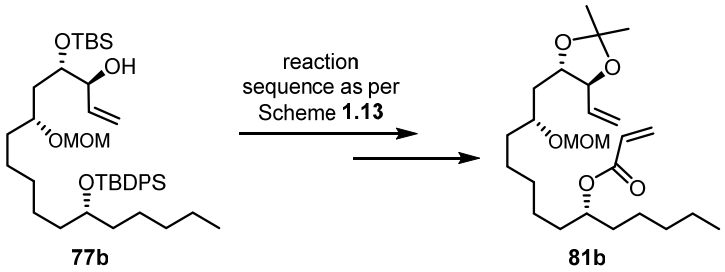


Scheme **1.13**. Key precursor for target molecule **1**

Having synthesized compound **77a** in substantial amount, it was subjected to desilyation using TBAF to give compound **78a** in 90% yield. The absorption band at 3423 cm^{-1}

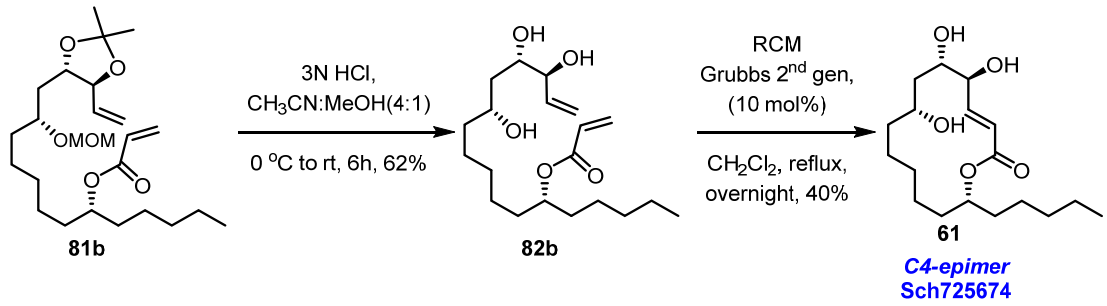
corresponds to free hydroxyl group. The acetonide protection of 1,2-diol using 2,2-dimethoxy propane in presence of catalytic PPTS gave compound **79a** in 93% yield. The relative configuration of more deshielded chiral protons of the *trans* **79a** and *syn* **79b** 1,2-acetonides was established by comparing the coupling constants of characteristic protons **79a** δ 4.52 (t, J = 6.7 Hz, 1 H) and **79b** δ 3.96 (t, J = 8.2 Hz, 1 H) which is in well accordance with the literature report.[49] The NOESY correlations between C^4H–C^5H and C^3H–C^6H further confirms the stereochemistry of desired diastereomer **79a** as shown in Scheme 1.13. The TBDPS ether deprotection of **79a** using TBAF followed by esterification of **80a** with acryloyl chloride gave compound **81a** in 74% yield as shown in Scheme 1.13. The IR spectrum of **81a** gave ester carbonyl absorption at 1722 cm^{-1}. The ^1H NMR signal at δ 6.39 (dd, J = 1.5, 17.4 Hz, 1 H), 6.12 (dd, J = 10.5, 17.4 Hz, 1 H) and ^{13}C NMR values at δ 166.0 validate the formation of *α,β*-unsaturated diene ester **81a**.

Starting from **77b**, similar sequence of reactions was executed for the synthesis of key precursor **81b** for the unnatural *C4-epimer* **61** as shown in Scheme 1.14. All the intermediate from steps (**77b** → **81b**) were well characterized using ^1H NMR, ^{13}C NMR and HRMS data analysis.



Scheme 1.14. Key precursor for unnatural *C4-epimer*

The global deprotection of **81b** by treatment with aqueous 3N HCl afforded compound **82b** in 62% yield. The ring closing metathesis employing Grubbs' 2nd generation catalyst eventually furnished the un-natural molecule, *C4-epimer* Sch725674 albeit in 40% yield only as shown in Scheme 1.15. The ^1H NMR spectrum gave signals at δ 7.04 (dd, J = 5.3, 15.9 Hz, 1 H), 6.11 (dd, J = 1.5, 15.9 Hz, 1 H) corresponding to *α,β*-unsaturated ester **61**. The HRMS (ESI^+) peak at 351.21420 corresponds to formula $C_{18}H_{32}O_5$ $[M + Na]^+$ (calculated value 351.21347) validates the formation of product **61**.



Scheme 1.15. Synthesis of unnatural Sch725674

In an effort to increase the overall yield of the total synthesis, we set out to optimize and improve the yield of the last step for the natural isomer **1**. Influences of protecting groups on highly functionalized dienes are known to play an important role in the failure as the reaction led to only a mixture of unidentifiable products, even after employing a variety of Grubbs' catalysts and different reaction conditions as depicted in Scheme 1.16. Failure could probably be attributed to steric hindrance of the protecting groups and as per the literature precedence, presence of acetonide in the vicinity of the RCM site might hinder the progress of the reaction thus disfavouring the RCM reaction[50] On removal of all the protecting groups (**82a** → **1**), the yield of RCM was comparable to that of the *C4-epi* isomer **61** already synthesized.

Poor yields of RCM reaction could be tentatively ascribed due to unproductive Ru coordination/chelation by the free hydroxyl group present on the substrate.[51] Therefore the substrate bearing free allylic and homoallylic hydroxyl groups along with one extra hydroxyl group protected was sought as documented in the literature.[52] The feasibility of RCM (with one free allylic hydroxyl group) could be explained by anticipating a co-operative O–H…Cl–Ru hydrogen bonding, thus enhancing the rate and the selectivity of the reaction[53] (Scheme 1.16, **IM**). The better yield on protecting C7-hydroxyl group by MOM may be reasoned due to hydrogen bonding of free (unprotected) hydoxyl with the carbonyl oxygen of acrylate as a most stable conformation **I**, as illustrated in the following figure 1.4. The MOM protection could lead to a conformation **II** as a most favoured conformation, a conformation where olefinic moiety of acrylate directly faces the metal center and thus could easily lead to the formation of the desired product.

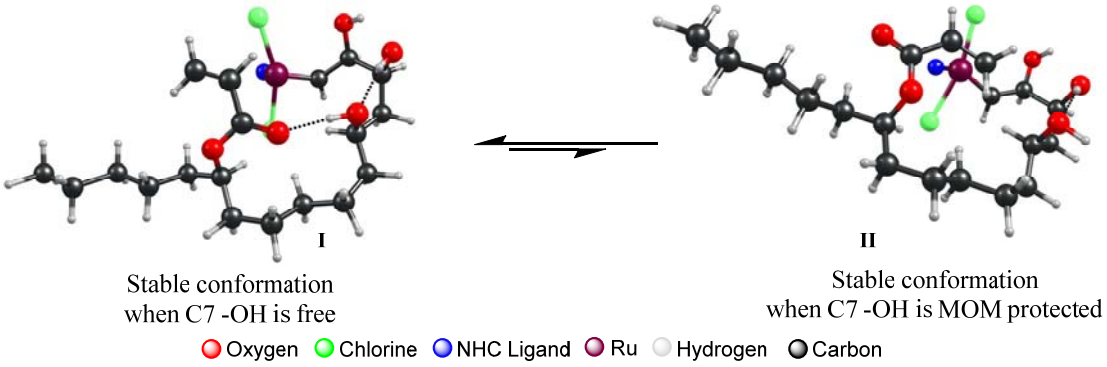
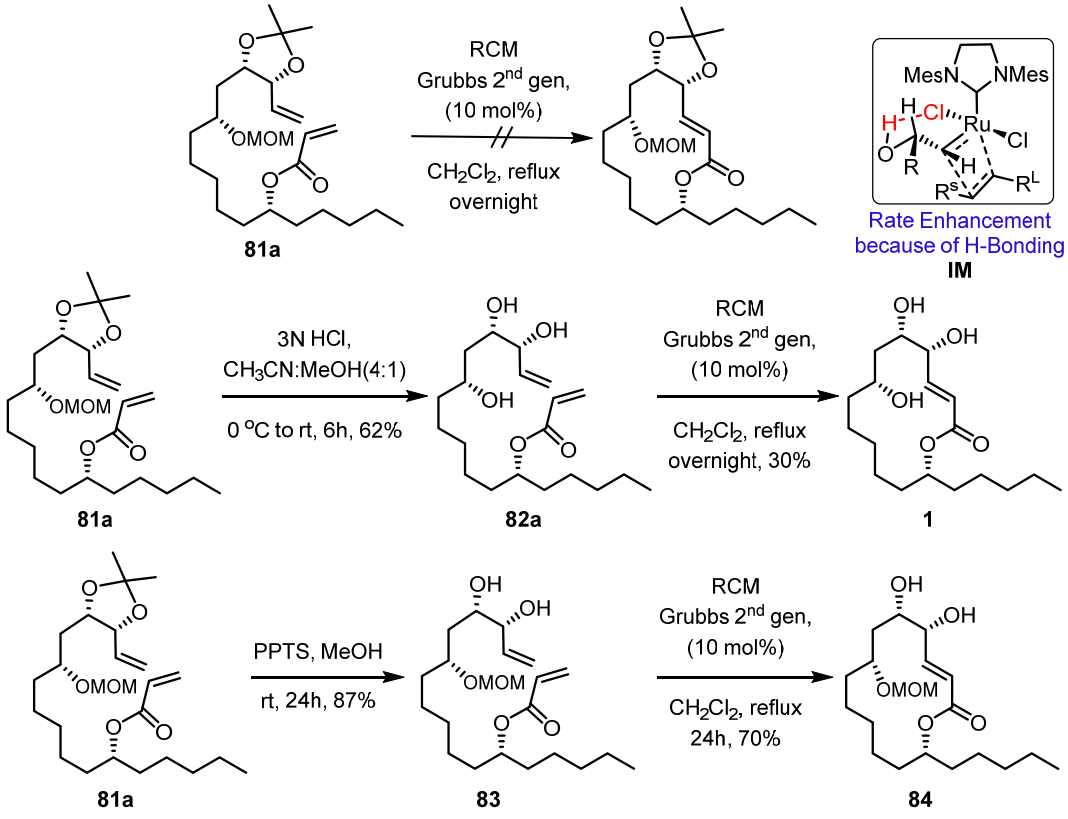


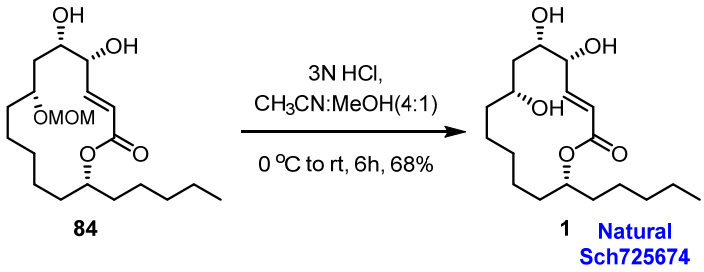
Figure 1.4. Plausible reason: H-bonding constraint for RCM reaction

In yet another attempt we considered examining the RCM with olefin containing the adjacent free hydroxy groups. Towards this end we initially carried out the selective deprotection of acetonide group of **81a** using PPTS to get the diol **83**. In ^{1}H NMR spectrum the signals at δ 1.48 (s, 3 H), 1.37 (s, 3 H) of corresponding methyl protons of acetonide disappeared indicating the formation of **83**. Subsequent ring closing metathesis on substrate **83** was found to be quite efficient and to our delight we observed a significant increase in the yield (70%) of the required compound **84** (Scheme 1.16).



Scheme 1.16. Attempts for ring closing metathesis: "Effects of protecting groups"

The success of RCM reaction was confirmed using ^{1}H NMR, which showed signals at δ 6.83 (dd, J = 5.3, 15.7 Hz, 1 H), 6.18 (dd, J = 1.4, 15.7 Hz, 1 H) corresponding to *α,β*-unsaturated ester **84**. The deprotection of MOM ether from **84** using aq. HCl (3N) gave the target macrolide Sch725674 **1** in 68% yield as shown in Scheme 1.17.



Scheme 1.17. End game for the total synthesis of "Natural Sch725674"

All the spectral data (^{1}H, ^{13}C NMR) of synthesized Sch725674 **1** were identical with those of the isolated natural product as shown in Table 1.1. The HRMS (ESI^{+}) peak of **1** at 351.21420 corresponding to formula $C_{18}H_{32}O_5$ $[M + Na]^{+}$ (calculated value 351.21417) validates the formation of product **61**. Optical rotation of synthetic Sch725674 **1** was measured at $[\alpha]_D$ = + 4.8 (c 0.3, CH_3OH), and the reported value was at $[\alpha]_D$ = + 5.15 (c 0.27, CH_3OH).

Table 1.1. Comparison of ^{1}H and ^{13}C NMR data of both natural and synthetic Sch725674

	Synthetic Sch725674 (500MHz, CD_3OD)		**Natural Sch725674 (500MHz, CD_3OD)**	
C/H	**1H (δ)**	**13C (δ)**	**1H (δ)**	**13C (δ)**
1		168.4		168.4
2	6.08, dd, J = 1.2, 15.6 Hz	123.1	6.07, dd, J = 15.8, 1.6 Hz	123.1
3	6.87, dd, J = 6.1, 15.6 Hz	149.3	6.86, J = dd, 15.8, 6.0 Hz	149.3
4	4.50 - 4.47, m	76.0	4.48, ddd, J = 6.0, 3.0, 1.6 Hz	76.0
5	3.87 - 3.83, m	72.9	3.84, ddd, J = 6.0, 4.7, 3.0 Hz	72.9
6	1.83, dt, J = 6.1, 14.7 Hz	38.3	1.82, ddd, J = 14.7, 6.5, 6.0 Hz 1.65, m	38.3

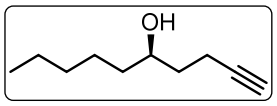
7	3.99, quin, J = 6.1 Hz	69.5	3.98, q, J = 6.5 Hz	69.5
8	1.70 - 1.52, m, 5 H	36.8	1.36, m	36.8
9		25.8	1.19, m; 1.37, m	25.8
10		29.5	1.15, m; 1.40, m	29.5
11		27.0	1.19, m; 1.45, m	27.0
12		34.1	1.54, m; 1.70, m	34.1
14	1.39 - 1.25, m, 11 H	36.5	1.57, m; 1.61, m	36.5
15		26.4	1.32, m	26.4
16		33.0	1.30, m	32.9
17		23.8	1.31, m	23.8
13	4.98 - 4.94, m	77.6	4.94, dddd, J = 9.8, 7.5, 5.0, 2.2 Hz	77.6
18	0.90, t, J = 6.8 Hz	14.5	0.89, t, J = 6.8 Hz	14.5

1.5. Conclusion and Prospect

The total synthesis of Sch725674 and *C4-epi*-Sch725674 was accomplished in 15 steps from the commercially available (*S*)-PMB glycidol and (*R*)-epoxyheptane. Though the number of steps is more than the one reported, each of the steps employed was accomplished with very high yields and as a result, the overall yield of the synthesis was 6.6% against previous reports of 2.6% (Prasad *et al*.)[32] and 2.04% (Kaliappan *et al.*)[33]. This strongly demonstrates the merit of our modular synthetic approach to this natural product. The synthetic pathway also led to the formation of the *C4-epimer*. Hence this strategy might enable practical parallel synthesis of a library of Sch725674 stereoisomers. Efforts to extend the synthetic strategy to the synthesis of gloeosporone and other related analogues are also underway and will be disclosed in due course of time.

1.6. Experimental Section

(*R*)-Dec-1-yn-5-ol (66):



Magnesium turnings (13.84 g, 569.27 mmol, 13 equiv.) were flame-dried under a vacuum, flushed with argon, and suspended in Et_2O (50 mL). A crystal of I_2 was added, and the solution was stirred until the color disappeared. $HgCl_2$ (713.4 mg, 2.63 mmol, 0.06 equiv.) was added, and after 10 min, the solution was cooled to 0 °C. Propargyl bromide (23.4 mL, 262.72 mmol, 6 equiv.) was slowly added at 0 °C, and the mixture was stirred at the same temperature for an additional 1 h. The dark grey solution was then decanted to give the propargylmagnesium bromide solution, which was added to a solution of epoxide **65** (5 g, 43.79 mmol, 1 equiv.) in Et_2O (170 mL) at –30 °C. After 2 h, the reaction was poured into a saturated aqueous solution of NH_4Cl (200 mL), and the aqueous layer was extracted with Et_2O (3 x 150 mL). The combined organic layers were dried with Na_2SO_4 and concentrated in *vacuo* to give a residue, which was purified by flash column chromatography (petroleum ether/EtOAc, 39:1) to afford **66** as a colorless liquid.

Yield = 4 g, 60%;

R_f = 0.3 (petroleum ether/EtOAc, 19:1);

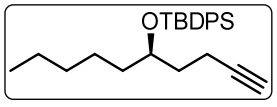
$[\alpha]^{25}_D$ = – 9.5 (*c* 1.01, $CHCl_3$);

IR ($CHCl_3$) ν_{max} = 3526, 3020, 2986, 1737, 1451, 1375, 1247, 1100, 1047, 931, 846, 762 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.77 - 3.71 (m, 1 H), 2.34 (td, *J* = 2.7, 7.1 Hz, 2 H), 1.97 (t, *J* = 2.7 Hz, 1 H), 1.74 - 1.60 (m, 2 H), 1.40 - 1.48 (m, 3 H), 1.35 - 1.26 (m, 5 H), 0.89 (t, *J* = 6.7 Hz, 3 H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 84.3, 77.3, 77.0, 76.7, 70.8, 68.6, 37.3, 35.6, 31.8, 25.2, 22.6, 15.0, 14.0.

(*R*)-*tert*-Butyl(dec-1-yn-5-yloxy)diphenylsilane (67):



To a stirred solution of alcohol **66** (3.8 g, 24.67 mmol, 1 equiv.) in CH_2Cl_2 (60 mL) was added imidazole (3.3 g, 49.34 mmol, 2 equiv.). To this solution was added *tert*-butyl(chloro)diphenylsilane (7 mL, 27.14 mmol, 1.1 equiv.) at 0 °C, and the resulting mixture was stirred at room temperature for 1 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl, and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated in *vacuo*. Flash column chromatography of the crude product provided **67** as a colorless liquid.

Yield = 9.1 g, 90%;

R_f = 0.6 (petroleum ether/EtOAc, 19:1);

$[\alpha]^{25}_{D}$ = – 4.7 (*c* 3.19, $CHCl_3$);

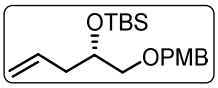
IR ($CHCl_3$) ν_{max} = 3305, 3132, 3062, 3014, 2951, 2863, 1463, 1433, 1376, 1218, 1104, 1064, 998, 934, 822, 760, 703 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz) δ = 7.72 - 7.67 (m, 4 H), 7.44 - 7.33 (m, 6 H), 3.83 (quin, *J* = 5.6 Hz, 1 H), 2.24 (td, td, *J* = 2.6, 7.3, 2 H), 1.87 (t, *J* = 2.6 Hz, 1 H), 1.70 (td, *J* = 5.6, 7.3 Hz, 2 H), 1.46 - 1.07 (m, 17 H), 0.81 (t, *J* = 6.5, 3 H);

^{13}C NMR ($CDCl_3$, 50 MHz) δ = 135.9, 134.6, 134.3, 129.5, 129.4, 127.5, 127.4, 84.6, 72.1, 68.0, 36.1, 35.1, 31.7, 27.1, 24.5, 22.5, 19.4, 14.3, 14.0;

HRMS (ESI^+) *m/z* = calcd for $C_{26}H_{36}OSi$ $[M + H]^+$ 393.2601; found, 393.2608.

(*S*)-*tert*-Butyl((1-((4-methoxybenzyl)oxy)pent-4-en-2-yl)oxy)dimethylsilane (69):



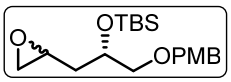
A round-bottomed flask was charged with copper(I) iodide (490 mg, 2.57 mmol, 0.05 equiv.), and the system was gently heated under vacuum and then slowly cooled under the flow of argon. Dry THF (120 mL) was added. The resulting suspension was cooled to –40 °C and vigorously stirred, and the vinylmagnesium chloride solution (1.6 M in THF, 64 mL, 102.97 mmol, 2 equiv.) was then added. A solution of (*S*)-PMB-protected glycidol **68** (10 g, 51.48 mmol, 1 equiv.) in THF (50 mL) was slowly added to the above mixture. The reaction was stirred at –40 °C for 1 h and then quenched by the addition of a saturated solution of NH_4Cl. The organic and aqueous layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed

with brine, dried with Na_2SO_4, and concentrated to dryness to afford crude product **68a** as a yellow liquid.

To a mixture of crude alcohol **68a** in CH_2Cl_2 (40 mL) was added imidazole (5.2 g, 76.48 mmol, 2 equiv.) followed by *tert*-butyl(chloro)dimethylsilane (6.3 g, 42.06 mmol, 1.1 equiv.) at 0 °C, and the resulting mixture was stirred at room temperature for 1 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl, and the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combine organic layers were washed with brine, dried with Na_2SO_4, and concentrated in *vacuo*. Flash column chromatography of the crude product (petroleum ether/EtOAc, 19:1) provided **69** as a colorless liquid.

Yield = 12.3 g, 85% (2 steps);
R_f = 0.5 (petroleum ether/EtOAc, 49:1);
$[\alpha]^{25}_{D}$ = – 0.6 (*c* 2.36, $CHCl_3$);
IR ($CHCl_3$) ν_{max} = 3019, 2943, 2860, 1612, 1515, 1464, 1372, 1299, 1217, 1091, 1040, 836, 768, 671 cm^{-1};
^{1}H NMR ($CDCl_3$, 200 MHz) δ = 7.25 (d, *J* = 8.2 Hz, 2 H), 6.87 (d, *J* = 8.2 Hz, 2 H), 5.92 - 5.72 (m, 1 H), 5.09 - 5.00 (m, 2 H), 4.44 (s, 2 H), 3.92 - 3.83 (m, 1 H), 3.80 (s, 3 H), 3.36 (d, *J* = 5.4 Hz, 2 H), 2.41 - 2.13 (m, 2 H), 0.88 (s, 9 H), 0.05 (s, 6 H);
^{13}C NMR ($CDCl_3$, 50 MHz) δ = 159.1, 135.0, 130.5, 129.2, 116.9, 113.7, 73.9, 72.9, 71.2, 55.2, 39.4, 25.8, 18.2, -4.5, -4.7;
HRMS (ESI^+) *m/z* =calcd for $C_{19}H_{32}O_3Si$ $[M + Na]^+$ 359.2014; found, 359.2013.

***tert*-Butyl(((2*S*)-1-((4-methoxybenzyl)oxy)-3-(oxiran-2-yl)propan-2-yl)oxy)dimethylsilane (70)**:



To a stirred solution of olefin **69** (12 g, 35.71 mmol, 1 equiv.) in CH_2Cl_2 (100 mL) at 0 °C was added *m*-CPBA (50 %, 2.9 g, 60.71 mmol, 1.7 equiv.). The reaction mixture was stirred at 0 °C for 1 h and then quenched by the addition of a saturated $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2, and the organic layer was washed with saturated $NaHCO_3$ and brine, dried with Na_2SO_4, and concentrated in *vacuo*. The crude residue was purified by flash column chromatography (petroleum ether/EtOAc, 24:1) to yield epoxide **70** (*anti*/*syn*, 2:1) as a colorless liquid.

Yield = 11.8 g, 94%;

R_f = 0.4 (petroleum ether/EtOAc, 19:1);

$[\alpha]^{25}_D$ = – 12.3 (*c* 1.1, $CHCl_3$);

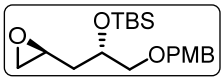
IR ($CHCl_3$) ν_{max} = 3020, 2936, 2403, 1603, 1517, 1217, 1104, 1040, 767, 671 cm^{-1};

^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.30 - 7.26 (m, 2 H), 6.90 (d, *J* = 8.5 Hz, 2 H), 4.51 - 4.45 (m, 2 H), 4.09 - 4.02 (m, 1 H), 3.83 (s, 3 H), 3.51 - 3.39 (m, 2 H), 3.10 - 3.05 (m, 1 H), 2.82 - 2.76 (m, 1 H), 2.52 - 2.48 (m, 1 H), 1.79 - 1.70 (m, 2 H), 0.92 (s, 9 H), 0.11 - 0.09 (m, 6 H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 159.1, 130.4, 130.3, 129.2, 113.7, 74.3, 74.0, 73.0, 72.9, 69.7, 69.2, 55.2, 49.6, 49.4, 47.8, 46.8, 38.0, 37.9, 25.8, 18.1, -4.4, -4.5, -4.9, -5.0;

HRMS (ESI^+) *m/z* =calcd for $C_{19}H_{32}O_4Si$ $[M + Na]^+$ 375.1957; found, 375.1962.

***tert*-Butyl(((*S*)-1-((4-methoxybenzyl)oxy)-3-((*S*)-oxiran-2-yl)propan-2-yl)oxy)dimethylsilane (71a)**:



A solution of epoxide **70** (10 g, 28.41 mmol, 1 equiv.) and (*S*,*S*)-(salen)CoIII-OAc (343 mg, 0.568 mmol, 0.02 equiv.) in THF (2 mL) was stirred at 0 °C for 5 min, and then distilled water (0.17 mL, 9.64 mmol, 0.34 equiv.) was added. After stirring for 8 h, the mixture was concentrated, and the residue was purified by flash column chromatography (petroleum ether/EtOAc, 24:1) to afford **71a** as a yellow liquid. Continued chromatography (petroleum ether/EtOAc, 2:3) provided diol **71b** (*dr* ~ 9:1) as a brown liquid. The diastereoselectivity of epoxide **70** was determined by ^{1}H and ^{13}C NMR spectroscopic and chiral HPLC analyses.

Yield = 6.0 g, 60%;

R_f = 0.4 (petroleum ether/EtOAc, 19:1);

$[\alpha]^{25}_D$ = – 15.6 (*c* 1.2, $CHCl_3$);

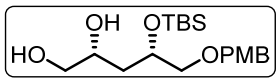
IR ($CHCl_3$) ν_{max} = 3017, 2955, 2930, 2857, 1613, 1513, 1464, 1363, 1250, 1217, 1100, 1037, 836, 771 cm^{-1};

^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.30 - 7.27 (m, 2 H), 6.91 (d, *J* = 8.5 Hz, 2 H), 4.51 - 4.46 (m, 2 H), 4.10 - 4.05 (m, 1 H), 3.84 (s, 3 H), 3.42 (ddd, *J* = 5.5, 9.8, 15.2 Hz , 2 H), 3.09 - 3.06 (m, 1 H), 2.83 - 2.81 (m, 1 H), 2.53 - 2.51 (m, 1 H), 1.76 - 1.69 (m, 2 H), 0.92 (s, 9 H), 0.09 (s, 3 H), 0.07 (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 159.1, 130.3, 129.2, 113.7, 74.3, 72.9, 69.2, 55.2, 49.6, 47.8, 38.0, 25.8, 18.1, -4.4, -5.0;

HRMS (ESI^+) *m/z* = calcd for $C_{19}H_{32}O_4Si$ $[M + Na]^+$ 375.19574; found, 375.19621.

(2*R*,4*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-5-((4-methoxybenzyl)oxy)pentane-1,2-diol (71b):



Yield = 2.8 g, 28%;

***R*$_f$** = 0.4 (petroleum ether/EtOAc, 3:1);

[α]$^{25}_D$ = + 35.6 (*c* 2.58, $CHCl_3$);

IR ($CHCl_3$) ν_{max} = 3436, 3017, 2943, 2864, 1613, 1514, 1463, 1300, 1250, 1218, 1095, 1039, 835, 768, 670 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.28 - 7.25 (m, 2 H), 6.90 (d, *J* = 8.6 Hz, 2 H), 4.48 - 4.46 (m, 2 H), 4.17 - 4.05 (m, 1 H), 3.94 (br. s., 1 H), 3.82 (s, 3 H), 3.65 - 3.60 (m, 1 H), 3.51 - 3.45 (m, 3 H), 3.42 - 3.38 (m, 1 H), 2.29 (br. s., 1 H), 1.74 - 1.65 (m, 2 H), 0.90 (s, 9 H), 0.09 (s, 3 H), 0.07 (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 159.2, 129.8, 129.4, 113.8, 74.2, 73.1, 73.0, 70.8, 70.0, 69.8, 68.9, 67.1, 66.9, 55.2, 38.0, 36.7, 25.8, 18.0, -4.3, -4.6, -4.9, -5.1.

Experimental Procedure for the Conversion of compound 71b into 71a:

Diol **71b** (2.8 g, 7.55 mmol, 1 equiv.) was dissolved in dry CH_2Cl_2 (15 mL) under argon, and the solution was treated with benzoyl chloride (1.23 mL, 10.58 mmol, 1.4 equiv.), Et_3N (2.63 mL, 18.88 mmol, 2.5 equiv.), and a catalytic amount of DMAP. The mixture was stirred at room temperature for 2 h followed by the workup procedure (i.e., extraction with CH_2Cl_2). The removal of volatiles under reduced pressure and purification by flash column chromatography (petroleum ether/EtOAc, 85:15) gave monobenzoate **71c** as a colorless liquid.

Yield = 3.1 g, 88%;

***R*$_f$** = 0.38 (petroleum ether/EtOAc, 9:1);

[α]$^{25}_D$ = – 4.8 (*c* 1.66, $CHCl_3$);

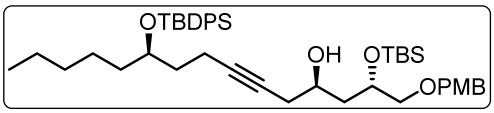
IR ($CHCl_3$) ν_{max} = 3455, 3020, 2946, 1716, 1606, 1516, 1457, 1260, 1217, 1107, 1037, 768, 671 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.10 - 8.07 (m, 2 H), 7.62 - 7.57 (m, 1 H), 7.48 - 7.44 (m, 2 H), 7.29 - 7.25 (m, 2 H), 6.90 - 6.87 (m, 2 H), 4.50 - 4.48 (m, 2 H), 4.36 - 4.29 (m, 2 H), 4.27 - 4.19 (m, 1 H), 4.17 - 4.10 (m, 1 H), 3.82 - 3.81 (m, 3 H), 3.53 - 3.41 (ddd, *J* = 5.9, 9.5, 15.6 Hz , 2 H), 1.97 - 1.76 (m, 2 H), 0.91 (s, 9 H), 0.12 (s, 3 H), 0.10 (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 166.6, 159.2, 133.4, 133.0, 130.1, 130.0, 129.9, 129.8, 129.7, 129.4, 129.2, 128.4, 128.3, 113.8, 113.7, 74.1, 73.1, 73.0, 72.9, 70.5, 69.7, 69.0, 68.7, 67.7, 66.8, 55.2, 38.4, 37.2, 25.9, 25.8, 18.0, -4.3, -4.6, -4.9, -5.1.

Compound **71c** (3.1 g, 6.53 mmol, 1 equiv.) was then dissolved in dry CH_2Cl_2 (15 mL) under argon, and the solution was treated with TsCl (1.5 g, 7.84 mmol, 1.2 equiv.), Et_3N (2.3 mL, 16.32 mmol, 2.5 equiv.), and catalytic amount of DMAP. The reaction mixture was stirred at room temperature for 6 h and then quenched with water. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated to give a residue. The crude product was dissolved in CH_3OH (20 mL), and the solution was treated with K_2CO_3 (1.0 g, 6.53 mmol). The reaction mixture was stirred at room temperature for 1 h and then filtered through celite. Concentration of the filtrate under reduced pressure and flash column chromatography on silica gel (petroleum ether/EtOAc, 19:1) gave epoxide **71a** (1.5 g, overall yield 70 %, 3 steps) as a yellow liquid.

(5*S*,7*R*,13*R*)-5-(((4-Methoxybenzyl)oxy)methyl)-2,2,3,3,16,16-hexamethyl-13-pentyl-15,15-diphenyl-4,14-dioxa-3,15-disilaheptadec-9-yn-7-ol (72):

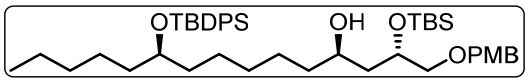


n-Butyllithium (1.6 M solution in hexanes, 7.8 mL, 12.5 mmol, 2.0 equiv.) was added dropwise to a stirred solution of alkyne **67** (4.9 g, 12.5 mmol, 2.0 equiv.) in dry THF (30 mL) under nitrogen at –78 °C. The resulting solution was stirred for 30 min and then treated dropwise with $BF_3{\cdot}Et_2O$ complex (1.5 mL, 12.5 mmol, 2.0 equiv.). After stirring at –78 °C for 15 min, epoxide **71a** (2.2 g, 6.25 mmol, 1 equiv.) in dry THF (12 mL) was added, and the mixture was stirred at –78 °C for approximately 1 h. The reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride (40

mL), and the organic layer was separated. The aqueous layer was then extracted with diethyl ether (5 × 30 mL), and the combined organic solutions were washed with brine and dried with Na_2SO_4. The solvents were evaporated to give the crude material, which was purified by flash column chromatography (petroleum ether/EtOAc, 7:1) to afford the coupled product **72** as a yellowliquid.

Yield = 4 g, 86%;
R_f = 0.3 (petroleum ether/EtOAc, 19:1);
$[\alpha]^{25}_D$ = – 1.02 (*c* 0.7, $CHCl_3$);
IR ($CHCl_3$) ν_{max} = 3417, 3021, 2970, 2403, 1600, 1427, 1216, 1043, 768, 671 cm^{-1};
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.70 - 7.67 (m, 4 H), 7.43 - 7.35 (m, 6 H), 7.25 (d, *J* = 8.6 Hz, 2 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 4.50 - 4.43 (m, 2 H), 4.12 (quin, *J* = 5.6 Hz, 1 H), 3.93 - 3.87 (m, 1 H), 3.81 - 3.77 (m, 4 H), 3.45 (ddd, *J* = 5.6, 9.5, 15.2 Hz, 2 H), 3.33 (br. s., 1 H), 2.29 - 2.26 (m, 2 H), 2.22 - 2.17 (m, 2 H), 1.81 (ddd, *J* = 2.2, 5.6, 7.6 Hz , 1 H), 1.71 - 1.63 (m, 3 H), 1.40 - 1.33 (m, 3 H), 1.17 - 1.12 (m, 5 H), 1.05 (s, 9 H), 0.88 (s, 9 H), 0.79 (t, *J* = 7.2 Hz, 3 H), 0.08 (s, 3 H), 0.06 (s, 3H);
^{13}C NMR ($CDCl_3$, 100 MHz) δ = 159.2, 135.9, 134.6, 134.3, 130.1, 129.5, 129.4, 129.3, 127.4, 127.4, 113.7, 82.5, 76.2, 73.5, 73.0, 72.3, 70.1, 67.4, 55.2, 40.1, 36.2, 35.6, 31.7, 28.0, 27.1, 25.8, 24.4, 22.5, 19.4, 18.0, 14.7, 14.0, -4.6, -5.0;
HRMS (ESI^+) *m/z* = calcd for $C_{45}H_{68}O_5Si_2$ $[M + Na]^+$ 767.4490; found, 767.4497.

(5*S*,7*R*,13*R*)-5-(((4-Methoxybenzyl)oxy)methyl)-2,2,3,3,16,16-hexamethyl-13-pentyl-15,15-diphenyl-4,14-dioxa-3,15-disilaheptadecan-7-ol (73):



Compound **72** (3 g, 4.02 mmol) in EtOH (10 mL) was hydrogenated under 1 atm with Raney-Ni catalyst. After the reaction stirring for overnight, the mixture was filtered through a short bed of celite. The filtrate was concentrated, and the residue was purified by flash column chromatography (petroleum ether/EtOAc, 34:1) to afford the completely hydrogenated product **73** as a pale yellow liquid.

Yield = 2.86 g, 95%;
R_f = 0.26 (petroleum ether/EtOAc, 19:1);
$[\alpha]^{25}_D$ = – 1.49 (*c* 0.8, $CHCl_3$);

IR ($CHCl_3$) ν_{max} = 3455, 3015, 2934, 2860, 1718, 1614, 1514, 1463, 1373, 1250, 1217, 1102, 1042, 830, 764, 671 cm^{-1};

^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.68 (dt, *J* = 1.2, 7.9 Hz, 4 H), 7.41 - 7.34 (m, 6 H), 7.25 (d, *J* = 8.6 Hz, 2 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 4.50 - 4.42 (m, 2 H), 4.14 - 4.10 (m, 1 H), 3.81 (s, 3 H), 3.80 - 3.78 (m, 1 H), 3.70 (quin, *J* = 5.8 Hz, 1 H), 3.46 (ddd, *J* = 5.8, 9.5, 15.2 Hz, 2 H), 1.72 - 1.70 (ddd, *J* = 2.0, 4.6, 14.6 Hz, 1 H), 1.62 (dd, *J* = 4.6, 10.1 Hz, 1 H), 1.43 - 1.37 (m, 5 H), 1.31 - 1.30 (m, 1 H), 1.24 - 1.08 (m, 12 H), 1.05 (s, 9 H), 0.89 (s, 9 H), 0.83 (t, *J* = 7.1 Hz, 3 H), 0.09 (s, 3H), 0.07 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ = 159.2, 135.9, 134.8, 130.1, 129.4, 129.3, 127.3, 113.8, 73.2, 73.1, 73.0, 70.5, 68.5, 55.2, 40.5, 38.0, 36.3, 36.2, 31.9, 29.8, 27.1, 25.8, 25.6, 24.9, 24.5, 22.6, 19.4, 18.0, 14.0, -4.6, -5.1;

HRMS (ESI^+) *m/z* = calcd for $C_{45}H_{72}O_5Si_2$ $[M + Na]^+$ 771.48059; found, 771.48105.

***tert*-Butyl(((*R*)-1-((4*R*,6*S*)-6-(((4-methoxybenzyl)oxy)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)undecan-6-yl)oxy)diphenylsilane (73b)**:

To a stirred solution of **73** (50 mg, 0.067 mmol, 1 equiv.) in THF (0.2 mL) was added TBAF (1.0 M in THF, 0.1 mL, 0.1 mmol, 1.5 equiv.) at 0 °C. After the mixture was stirred at room temperature for 2 h, the reaction was quenched by the addition of H_2O (1 mL). The aqueous layer was extracted with EtOAc (5 x 3 mL), and the combined organic layers were washed with brine (5 mL), dried with Na_2SO_4, and concentrated under reduced pressure to obtain the crude 1,3-diol.

To a solution of the crude 1,3-diol in CH_2Cl_2 (0.2 mL) were added 2,2-DMP (0.082 mL, 0.67 mmol, 10 equiv.) and a catalytic amount of PPTS (8 mg, 0.0335 mmol, 0.5 equiv.). The reaction mixture was stirred at room temperature for 1 h. When TLC analysis showed the completion of reaction, the mixture was quenched by the addition of dry Et_3N, and the solvent was evaporated in *vacuo* at room temperature. The crude product was purified by flash column chromatography (petroleum ether/EtOAc, 39:1) to give the acetonide **73b** as a colorless liquid.

Yield = 36 mg, 80%;

***R*$_f$** = 0.3 (petroleum ether/EtOAc, 9:1);

$[\alpha]^{25}_D$ = – 2.25 (*c* 2.4, $CHCl_3$);

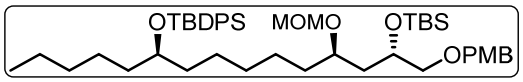
IR ($CHCl_3$) ν_{max} = 3407, 3013, 2933, 2861, 1775, 1716, 1599, 1517, 1426, 1218, 1104, 1040, 759 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.66 (d, *J* = 6.6 Hz, 4 H), 7.42 - 7.32 (m, 6 H), 7.25 (d, *J* = 8.6 Hz, 2 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 4.56 - 4.46 (m, 2 H), 4.04 - 3.98 (m, 1 H), 3.80 (s, 3 H), 3.74 - 3.65 (m, 2 H), 3.48 - 3.37 (m, 2 H), 1.65 - 1.57 (m, 2 H), 1.49 - 1.42 (m, 4 H), 1.37 (s, 3 H), 1.35 (s, 3 H), 1.21 - 1.08 (m, 14 H), 1.03 (s, 9 H), 0.81 (t, *J* = 6.9 Hz, 3 H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 159.1, 135.9, 134.8, 134.7, 130.3, 129.34, 129.3, 127.3, 113.7, 100.3, 73.2, 72.9, 72.4, 66.5, 66.2, 55.2, 36.2, 35.8, 34.9, 31.9, 29.6, 27.1, 25.3, 24.8, 24.77, 24.74, 24.5, 24.1, 22.5, 19.4, 14.0;

HRMS (ESI^+) *m/z* = calcd for $C_{42}H_{62}O_5Si$ $[M + Na]^+$ 697.42511; found, 697.42587.

5*S*,7*R*,13*R*)-5-(((4-Methoxybenzyl)oxy)methyl)-7-(methoxymethoxy)-2,2,3,3,16,16-hexamethyl-13-pentyl-15,15-diphenyl-4,14-dioxa-3,15-disilaheptadecane (74):



A mixture of compound **73** (2.6 g, 3.47 mmol, 1 equiv.), *N*,*N*-diisopropylethylamine (3 mL, 17.35 mmol, 5 equiv.), and methoxymethyl chloride (0.8 mL, 10.41 mL, 3 equiv.) in CH_2Cl_2 (6 mL) was heated at 40 °C for 4 h. The reaction mixture was cooled to room temperature, and the reaction was quenched by the addition of water. The aqueous phase was extracted with CH_2Cl_2, and the organic layer was washed with water and brine, dried with Na_2SO_4, and concentrated. Flash column chromatography of the crude product (petroleum ether/EtOAc, 33:1) gave alcohol **74** as a colorless liquid.

Yield = 2.2 g, 80%;

***R*$_f$** = 0.5 (petroleum ether/EtOAc, 19:1);

$[\alpha]^{25}_D$ = – 2.9 (*c* 3.3, $CHCl_3$);

IR ($CHCl_3$) ν_{max} = 3416, 3019, 2937, 2861, 1608, 1515, 1463, 1217, 1103, 1040, 831, 767, 671 cm^{-1};

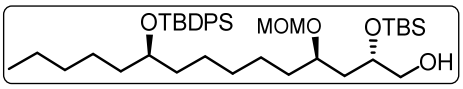
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.70 (d like, 4 H), 7.44 - 7.36 (m, 6 H), 7.80 (d, *J* = 8.6 Hz, 2 H), 6.90 (d, *J* = 8.6 Hz, 2 H), 4.66 (s, 2 H), 4.51 - 4.44 (m, 2 H), 4.02 - 3.97 (m, 1 H), 3.83 (s, 3 H), 3.74 - 3.65 (m, 2 H), 3.39 - 3.36 (m, 5 H), 1.73 - 1.67 (m, 1 H), 1.59 -

1.51 (m, 2 H), 1.46 - 1.40 (m, 5 H), 1.25 - 1.11 (m, 12 H), 1.07 (s, 9 H), 0.90 (s, 9 H), 0.84 (t, J = 7.1 Hz, 3 H), 0.07 (s, 3 H), 0.05 (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 159.0, 135.9, 134.8, 130.5, 129.3, 129.2, 127.3, 113.7, 95.8, 75.5, 75.0, 73.2, 72.8, 69.1, 55.5, 55.2, 40.4, 36.3, 36.2, 35.4, 31.9, 29.9, 27.1, 25.9, 25.0, 24.9, 24.5, 22.6, 19.4, 18.2, 14.0, -4.0, -4.8;

HRMS (ESI^+) *m/z* = calcd for $C_{47}H_{76}O_6Si_2$ $[M + Na]^+$ 815.50702; found, 815.50726.

(2*S*,4*R*,10*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-10-((*tert*-butyldiphenylsilyl)oxy)-4-(methoxymethoxy)pentadecan-1-ol (75):



To a solution of compound **74** (2.1 g, 2.65 mmol, 1 equiv.) in a mixture of $CHCl_3$/pH = 7 phosphate buffer (20:1) (20 mL), was added DDQ (1.8 g, 7.94 mmol, 3 equiv.), and the resulting mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$. The organic layer was separated, washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (petroleum ether/EtOAc, 19:1) to afford **75** as a pale yellow liquid.

Yield = 1.58 g, 89%;

R_f = 0.5 (petroleum ether/EtOAc, 9:1);

$[\alpha]^{25}_D$ = – 2.4 (*c* 0.6, $CHCl_3$);

IR ($CHCl_3$) ν_{max} = 3377, 3022, 2932, 2403, 1595, 1525, 1426, 1216, 1040, 927, 768, 671 cm^{-1};

^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.68 (d, J = 7.3 Hz, 4 H), 7.43 - 7.35 (m, 6 H), 4.66 - 4.63 (m, 2 H), 3.90 - 3.85 (m, 1 H), 3.72 - 3.67 (m, 1 H), 3.63 - 3.56 (m, 2 H), 3.50 - 3.45 (m, 1 H), 3.37 (s, 3 H), 1.52 - 1.37 (m, 7 H), 1.24 - 1.08 (m, 13 H), 1.05 (s, 9 H), 0.91 (s, 9 H), 0.82 (t, J = 7.3 Hz, 3 H), 0.11 (s, 6 H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ = 135.9, 134.8, 129.3, 127.3, 95.6, 75.6, 73.2, 70.7, 67.1, 55.6, 39.6, 36.3, 35.0, 31.9, 29.9, 29.7, 27.1, 25.8, 24.9, 24.8, 24.5, 22.6, 19.4, 18.1, 14.0, -4.4, -4.6;

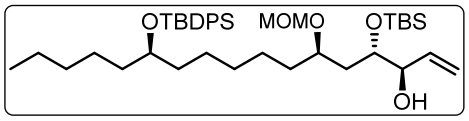
HRMS (ESI^+) *m/z* = calcd for $C_{39}H_{68}O_5Si_2$ $[M + Na]^+$ 695.44891; found, 695.44975.

(4*S*,6*R*,12*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-12-((*tert*-butyldiphenylsilyl)oxy)-6-(methoxymethoxy)heptadec-1-en-3-ol (77):

A stirred solution of **75** (1.4 g, 2.08 mmol, 1 equiv.) in EtOAc (30 mL) was treated with IBX (1.7 g, 6.24 mmol, 3 equiv.) in a portion wise manner, and the resulting mixture was heated at 80 °C for 3 h. The reaction was quenched by the addition of a saturated $NaHCO_3$ solution. The mixture was then filtered through celite, and the filter cake was washed with EtOAc. The organic layer was isolated, washed with water and brine, and then dried with Na_2SO_4. Evaporation of the solvent gave crude aldehyde **76** as a yellow liquid, which was used in subsequent experiments without any further purification.

To a precooled (–78 °C) solution of **76** in anhydrous THF (5.0 mL) was added vinylmagnesium bromide (1 M THF, 2.3 mL, 2.29 mmol, 1.1 equiv.) under argon. The mixture was stirred at –78 °C for 1 h, and the reaction was then cautiously quenched by the addition of a saturated solution of NH_4Cl (10 mL). The mixture was poured into H_2O (10 mL), and the resulting mixture was extracted with Et_2O (3 x 30 mL). The combined extracts were washed with brine (2 x 10 mL) and dried with Na_2SO_4. Removal of solvent under reduced pressure gave the crude residue as a diastereomeric mixture (*anti*/*syn*, 4:1). The diastereomers were separated by flash column chromatography (petroleum ether/EtOAc, 39:1) to afford alcohol **77a** and **77b** as a pale yellow liquid.

(3*R*,4*S*,6*R*,12*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-12-((*tert*-butyldiphenylsilyl)oxy)-6-(methoxymethoxy)heptadec-1-en-3-ol (77a):



Yield = 952 mg, 65.6%;

R_f = 0.34 (petroleum ether/EtOAc, 9:1);

$[\alpha]^{25}_{D}$ = – 1.5 (*c* 1.0, $CHCl_3$);

IR ($CHCl_3$) ν_{max} = 3393, 3021, 2934, 2861, 1596, 1528, 1426, 1217, 1040, 766, 671 cm^{-1};

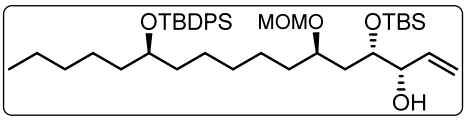
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.68 (d like, 4 H), 7.44 - 7.34 (m, 6 H), 5.85 (ddd, *J* = 5.9, 10.8, 17.1 Hz, 1 H), 5.34 (dt, *J* = 1.5, 17.1 Hz, 1 H), 5.23 (dt, *J* = 1.5, 10.5 Hz, 1 H), 4.65 - 4.61 (m, 2 H), 4.17 - 4.14 (m, 1 H), 3.89 (m, 1 H), 3.73 - 3.67 (m, 1 H), 3.62 - 3.56

(m, 1 H), 3.36 (s, 3 H), 1.62 - 1.56 (m, 3 H), 1.44 - 1.37 (m, 5 H), 1.27 - 1.08 (m, 12 H), 1.05 (s, 9 H), 0.92 (s, 9 H), 0.83 (t, J = 7.3 Hz, 3 H), 0.13 (s, 3 H), 0.11 (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 136.2, 135.9, 134.8, 129.3, 127.3, 116.6, 95.7, 76.2, 75.8, 73.2, 72.9, 55.6, 37.1, 36.3, 35.2, 31.9, 29.9, 27.1, 25.9, 25.0, 24.9, 24.5, 22.5, 19.4, 18.1, 14.0, -4.3, -4.5;

HRMS (ESI^+) *m/z* = calcd for $C_{41}H_{70}O_5Si_2$ $[M + Na]^+$ 721.4651; found, 721.4654.

(3*S*,4*S*,6*R*,12*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-12-((*tert*-butyldiphenylsilyl)oxy)-6-(methoxymethoxy)heptadec-1-en-3-ol (77b):



Yield = 238 mg, 16.4%,

R_f = 0.17 (petroleum ether/EtOAc, 9:1);

$[\alpha]^{25}_D$ = – 6.6 (*c* 0.5, $CHCl_3$);

IR ($CHCl_3$) ν_{max} = 3375, 3021, 2972, 1599, 1524, 1428, 1217, 1042, 927, 768, 671 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.68 (d, J = 6.8 Hz, 4 H), 7.42 - 7.35 (m, 6 H), 5.97 - 5.87 (ddd, J = 5.1, 10.5, 17.0 Hz, 1 H), 5.33 (d, J = 17.1 Hz, 1 H), 5.21 (d, J = 10.5 Hz, 1 H), 4.67 - 4.63 (m, 2 H), 4.05 (t like, 1 H), 3.82 - 3.78 (m, 1 H), 3.71 (quin, J = 5.4 Hz, 1 H), 3.66 - 3.60 (m, 1 H), 3.38 (s, 3 H), 1.56 - 1.46 (m, 2 H), 1.43 - 1.38 (m, 4 H), 1.25 - 1.18 (m, 10 H), 1.13 - 1.10 (m, 4 H), 1.06 (s, 9 H), 0.90 (s, 9 H), 0.83 (t, J = 7.3 Hz, 3 H), 0.10 (s, 3 H), 0.09 (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 138.4, 135.9, 134.8, 129.3, 127.3, 115.7, 95.3, 75.4, 74.9, 73.2, 72.8, 55.7, 39.0, 36.3, 34.9, 31.9, 29.9, 27.1, 25.9, 25.8, 24.9, 24.8, 24.5, 22.5, 19.4, 18.1, 14.0, -4.2, -4.3;

HRMS (ESI^+) *m/z* = calcd for $C_{41}H_{70}O_5Si_2$ $[M + Na]^+$ 721.4652; found, 721.4654.

Experimental Procedure for the Conversion of compound 77b into 77a:

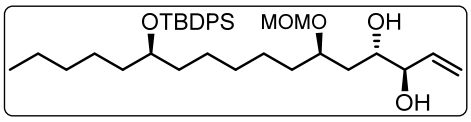
To a stirred solution of alcohol **77b** (200 mg, 0.286 mmol, 1 equiv.) in dry toluene (1 mL) were added PPh_3 (225 mg, 0.858 mmol, 3 equiv.), *p*-nitrobenzoic acid (144 mg, 0.858 mmol, 3 equiv.), and diisopropyl azodicarboxylate (DIAD) (0.17 mL, 0.858 mmol, 3 equiv.) at 0 °C, and the mixture was stirred at room temperature for 2 h. The toluene was evaporated, and the resulting mixture was directly transferred onto a silica gel

column and purified by flash column chromatography (petroleum ether/EtOAc, 24:1) to furnish **77c** as a pale yellow liquid.

Yield = 219 mg, 90%;
R_f = 0.5 (petroleum ether/EtOAc, 9:1);
$[\alpha]^{25}_{D}$ = + 4.03 (*c* 0.8, $CHCl_3$);
IR ($CHCl_3$) ν_{max} = 3425, 3020, 2935, 2860, 1725, 1604, 1530, 1463, 1428, 1359, 1270, 1218, 1107, 1041, 931, 835, 765, 671 cm^{-1};
^{1}H NMR ($CDCl_3$, 500 MHz) δ = 8.30 (d, *J* = 8.9 Hz, 2 H), 8.23 (d, *J* = 8.9 Hz, 2 H), 7.68 (d, *J* = 7.3 Hz, 4 H), 7.43 - 7.39 (m, 6 H), 6.01 (ddd, *J* = 7.0, 10.4, 17.4 Hz, 1 H), 5.53 (dt, *J* = 0.9, 7.0 Hz, 1 H), 5.42 - 5.37 (m, 2 H), 4.67 - 4.64 (m, 2 H), 4.15 - 4.13 (m, 1 H), 3.74 - 3.70 (m, 1 H), 3.68 - 3.63 (m, 1 H), 3.37 (s, 3 H), 1.81 - 1.74 (ddd, *J* = 4.3, 8.5, 12.8 Hz, 1 H), 1.62 (ddd, *J* = 3.4, 7.6, 11.0 Hz, 1 H), 1.54 - 1.39 (m, 7 H), 1.24 - 1.15 (m, 9 H), 1.13 - 1.08 (m, 2 H), 1.05 (s, 9 H), 0.88 (s, 9 H), 0.82 (t, *J* = 7.3 Hz, 3 H), 0.06 (s, 3 H), 0.05 (s, 3H);
^{13}C NMR ($CDCl_3$, 125 MHz) δ = 164.0, 150.6, 135.9, 134.9, 134.8, 131.9, 130.7, 129.3, 127.3, 123.6, 119.8, 95.8, 80.3, 75.5, 73.3, 71.1, 55.6, 39.0, 36.3, 35.2, 31.9, 29.9, 29.7, 27.1, 25.8, 25.0, 24.9, 24.6, 22.5, 19.4, 18.1, 14.0, -4.3, -4.5;
HRMS (ESI^+) *m/z* = calcd for $C_{48}H_{73}O_8NSi_2$ $[M + Na]^+$ 870.47662; found, 870.47669.

To a stirred solution of the *p*-nitrobenzoate ester **77c** (200 mg, 0.235 mmol, 1 equiv.) in CH_3OH (1 mL) was added K_2CO_3 (65.2 mg, 0.472 mmol, 2 equiv.), and the resulting mixture was stirred at room temp. for 1 h. Upon the complete consumption of the starting material (monitored by TLC analysis), the reaction was quenched by the addition of water, and the resulting mixture was extracted with EtOAc (5 x 3 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated in *vacuo*. The crude product was purified by flash column chromatography (petroleum ether/EtOAc, 39:1) to give **77a** (140.2 mg, 85 %) as colorless oil.

(3*R*,4*S*,6*R*,12*R*)-12-((*tert*-Butyldiphenylsilyl)oxy)-6-(methoxymethoxy)heptadec-1-ene-3,4-diol (78a):



A solution of TBAF (1 M in THF, 2.2 mL, 2.15 mmol, 1.5 equiv.) was added to a stirred solution of compound **77a** (1 g, 1.431 mmol, 1 equiv.) in THF (4 mL) at 0 °C. The resulting mixture was stirred at room temperature for 2 h and then diluted with water. The mixture was extracted with EtOAc, and the organic layer was washed with water, dried with Na_2SO_4, and concentrated. The crude product was purified by flash column chromatography (petroleum ether/EtOAc, 85:15) to provide compound **78a** as a pale yellow liquid.

Yield = 754 mg, 90%;

R_f= 0.45 (petroleum ether/EtOAc, 1.5:1);

$[\alpha]^{25}_{D}$ = – 3.5 (*c* 1.4, $CHCl_3$);

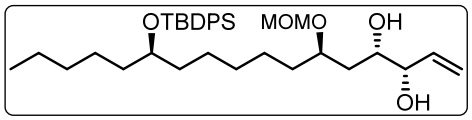
IR ($CHCl_3$) ν_{max} = 3423, 3018, 2936, 2861, 1639, 1462, 1428, 1376, 1217, 1104, 1037, 768, 671 cm^{-1};

^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.68 (dd, *J* = 1.4, 8.1 Hz, 4 H), 7.43 - 7.35 (m, 6 H), 5.91 (ddd, *J* = 6.1, 10.7, 17.1 Hz, 1 H), 5.35 (dt, *J* = 1.5, 17.1 Hz, 1 H), 5.26 (dt, *J* = 1.5, 10.7 Hz, 1 H), 4.66 (s, 2 H), 4.18 - 4.17 (m, 1 H), 3.96 (dt, *J* = 2.8, 10.7 Hz, 1 H), 3.80 - 3.76 (m, 1 H), 3.71 (quin, *J* = 5.5 Hz, 1 H), 3.41 (s, 3 H), 1.68 (ddd, *J* = 3.4, 10.7, 14.3 Hz, 1 H), 1.53 (ddd, *J* = 2.4, 10.4, 14.6 Hz, 2 H), 1.42 - 1.38 (m, 4 H), 1.25 - 1.09 (m, 13 H), 1.05 (s, 9 H), 0.83 (t, *J* = 7.2 Hz, 3 H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ = 136.4, 135.9, 134.8, 134.7, 129.3, 127.3, 116.9, 96.3, 76.1, 75.7, 73.2, 70.4, 55.8, 36.3, 36.2, 35.2, 34.7, 31.9, 29.8, 27.1, 25.4, 24.8, 24.6, 22.5, 19.4, 14.0;

HRMS (ESI^+) *m/z* = calcd for $C_{35}H_{56}O_5Si$ $[M + Na]^+$ 607.37842; found, 607.37892.

(3*S*,4*S*,6*R*,12*R*)-12-((*tert*-Butyldiphenylsilyl)oxy)-6-(methoxymethoxy)heptadec-1-ene-3,4-diol (78b):



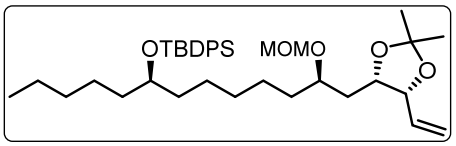
Compound **77b** (200 mg, 0.286 mmol, 1 equiv.) was treated with TBAF (1 M in THF, 0.43 mL, 0.43 mmol, 1.5 equiv.) in THF (0.5 mL) under the same conditions as described for the synthesis of **78a** to give compound **78b** as a pale yellow liquid.

Yield = 150 mg, 90%;

$[\alpha]^{25}_{D}$ = – 8.4 (*c* 3.6, $CHCl_3$);

IR ($CHCl_3$) ν_{max} = 3386, 3020, 2933, 1596, 1431, 1217, 1040, 767, 670 cm^{-1};
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.69 - 7.67 (m, 4 H), 7.42 - 7.35 (m, 6 H), 5.87 (ddd, *J* = 6.6, 10.5, 17.1 Hz, 1 H), 5.38 (d, *J* = 17.1 Hz, 1 H), 5.25 (d, *J* = 10.5 Hz, 1 H), 4.68 - 4.64 (m, 2 H), 3.93 (t, *J* = 6.2 Hz, 1 H), 3.81 - 3.75 (m, 2 H), 3.71 (quin, *J* = 5.6 Hz, 1 H), 3.51 (br. s., 1 H), 3.41 (s, 3 H), 2.72 (br. s., 1 H), 1.65 - 1.58 (m, 1 H), 1.56 - 1.49 (m, 1 H), 1.43 - 1.38 (m, 5 H), 1.24 - 1.08 (m, 13 H), 1.05 (s, 9 H), 0.83 (t, *J* = 7.2 Hz, 3 H);
^{13}C NMR ($CDCl_3$, 100 MHz) δ = 137.3, 135.9, 134.8, 134.7, 129.3, 127.3, 117.5, 96.5, 76.4, 76.1, 73.2, 70.7, 55.9, 37.2, 36.3, 36.2, 34.9, 31.9, 29.8, 27.1, 25.3, 24.8, 24.5, 22.5, 19.4, 14.0;
HRMS (ESI^+) *m/z* = calcd for $C_{35}H_{56}O_5Si$ $[M + Na]^+$ 607.37810; found, 607.37892.

(5*R*,11*R*)-5-(((4*S*,5*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)methyl)-14,14-dimethyl-11-pentyl-13,13-diphenyl-2,4,12-trioxa-13-silapentadecane (79a):



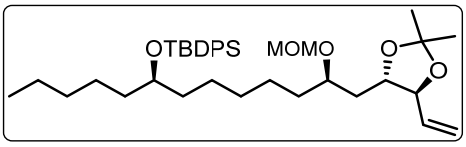
Diol **78a** (700 mg, 1.197 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (2 mL), and 2,2-DMP (1.5 mL, 11.97 mmol, 10 equiv.) and a catalytic amount of PPTS (150 mg, 0.598 mmol, 0.5 equiv.) were added to it. The reaction mixture was stirred at room temperature overnight. When TLC analysis showed that the reaction had reached completion, it was quenched by the addition of dry Et_3N, and the solvent was evaporated in *vacuo* at room temperature to give the crude product, which was purified by column chromatography (petroleum ether/EtOAc, 24:1) to afford compound **79a** as a yellow liquid.

Yield = 696 mg, 93%;
R_f = 0.46 (petroleum ether/EtOAc, 19:1);
$[\alpha]^{25}_D$ = – 3.7 (*c* 3.0, $CHCl_3$);
IR ($CHCl_3$) ν_{max} = 3620, 3400, 2938, 1592, 1350, 1218, 1021, 760, 670 cm^{-1};
^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.68 (d, *J* = 6.7 Hz, 4 H), 7.43 - 7.35 (m, 6 H), 5.81 (ddd, *J* = 7.6, 10.4, 17.2 Hz, 1 H), 5.31 (d, *J* = 17.2 Hz, 1 H), 5.24 (d, *J* = 10.4 Hz, 1 H), 4.69 - 4.66 (m, 2 H), 4.52 (t, *J* = 6.7 Hz, 1 H), 4.38 (ddd, *J* = 2.9, 6.7, 9.8 Hz, 1 H), 3.75 - 3.69 (m, 2 H), 3.39 (s, 3 H), 1.59 - 1.54 (m, 1 H), 1.49 (s, 3 H), 1.45 - 1.40 (m, 6 H), 1.38 (s, 3 H), 1.25 - 1.08 (m, 13 H), 1.06 (s, 9 H), 0.83 (t, *J* = 7.3 Hz, 3 H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ = 135.9, 134.8, 134.7, 134.6, 129.3, 127.3, 118.1, 108.1, 95.9, 79.7, 74.9, 74.7, 73.2, 55.6, 36.3, 35.8, 35.2, 31.9, 29.9, 28.3, 27.1, 25.7, 24.9, 24.5, 22.5, 19.4, 14.0;

HRMS (ESI^+) *m/z* = calcd for $C_{38}H_{60}O_5Si$ $[M + Na]^+$ 647.40926; found, 647.41022.

(5*R*,11*R*)-5-(((4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)methyl)-14,14-dimethyl-11-pentyl-13,13-diphenyl-2,4,12-trioxa-13-silapentadecane (79b):



Compound **78b** (140 mg, 0.239 mmol, 1 equiv.) was treated with 2,2-DMP (0.31 mL, 2.39 mmol, 10 equiv.) and PPTS (30 mg, 0.119 mmol, 0.5 equiv.) in CH_2Cl_2 (1 mL) under the same conditions as described for the synthesis of **79a** to give compound **79b** as a yellow liquid.

Yield = 139 mg, 92%;

$[\alpha]^{25}_D$ = – 1.8 (*c* 1.6, $CHCl_3$);

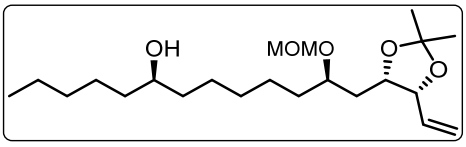
IR ($CHCl_3$) ν_{max} = 3412, 3020, 2935, 2862, 1594, 1428, 1378, 1217, 1104, 1041, 928, 767, 671 cm^{-1};

^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.69 - 7.67 (m, 4 H), 7.43 - 7.35 (m, 6 H), 5.81 (ddd, *J* = 7.3, 10.4, 17.2 Hz, 1 H), 5.37 (d, *J* = 17.2 Hz, 1 H), 5.26 (d, *J* = 10.4 Hz, 1 H), 4.68 - 4.65 (m, 2 H), 3.96 (t, *J* = 8.2 Hz, 1 H), 3.87 (td, *J* = 2.4, 8.2 Hz, 1 H), 3.77 - 3.69 (m, 2 H), 3.38 (s, 3 H), 1.69 - 1.59 (m, 2 H), 1.54 - 1.46 (m, 1 H), 1.43 (s, 3 H), 1.41 - 1.39 (m, 7 H), 1.28 - 1.09 (m, 13 H), 1.06 (s, 9 H), 0.83 (t, *J* = 7.3 Hz, 3 H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ = 135.9, 135.1, 134.9, 134.8, 129.3, 127.4, 118.9, 108.6, 95.8, 83.0, 77.2, 74.7, 73.3, 55.5, 37.1, 36.3, 35.2, 31.9, 29.9, 27.4, 27.1, 26.9, 24.9, 24.6, 22.6, 19.4, 14.0;

HRMS (ESI^+) *m/z* = calcd for $C_{38}H_{60}O_5Si$ $[M + Na]^+$ 647.40910; found, 647.41020.

(6*R*,12*R*)-13-((4*S*,5*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-12-(methoxymethoxy)tridecan-6-ol (80a):



A solution of TBAF (1 M in THF, 3 mL, 2.88 mmol, 3 equiv.) was added to a stirred solution of TBDPS ether **79a** (600 mg, 0.96 mmol, 1 equiv.) in THF. The mixture was heated at 70 °C for 4 h and then diluted with water. The resulting mixture was extracted with EtOAc. The organic layer was washed with water, dried with Na_2SO_4, and concentrated. The crude product was purified by flash column chromatography (petroleum ether/EtOAc, 88:12) to provide compound **80a** as a pale yellow liquid.

Yield = 334 mg, 90%;

R_f = 0.3 (petroleum ether/EtOAc, 85:15);

$[\alpha]^{25}_{D}$ = – 8.7 (*c* 1.5, $CHCl_3$);

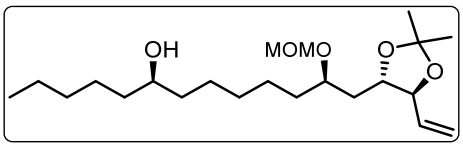
IR ($CHCl_3$) ν_{max} = 3423, 3018, 2936, 2861, 1693, 1462, 1428, 1376, 1217, 1104, 1037, 768, 671 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 5.80 (ddd, *J* = 7.6, 10.5, 17.2 Hz, 1 H), 5.30 (d, *J* = 17.2 Hz, 1 H), 5.24 (d, *J* = 10.5 Hz, 1 H), 4.71 - 4.67 (m, 2 H), 4.51 (t, *J* = 6.6 Hz, 1 H), 4.37 (ddd, *J* = 3.2, 6.6, 9.8 Hz, 1 H), 3.78 - 3.72 (m, 1 H), 3.62 - 3.57 (m, 1 H), 3.40 (s, 3 H), 1.61 - 1.52 (m, 7 H), 1.48 (s, 3 H), 1.46 - 1.42 (m, 4 H), 1.37 (s, 3 H), 1.35 - 1.29 (m, 9 H), 0.90 (t, *J* = 6.7 Hz, 3 H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 134.5, 118.1, 108.1, 96.0, 79.7, 74.9, 74.7, 71.9, 55.6, 37.5, 37.4, 35.8, 35.2, 31.9, 30.9, 29.8, 29.7, 28.3, 25.7, 25.6, 25.3, 24.9, 22.6, 14.0;

HRMS (ESI^+) *m/z* = calcd for $C_{22}H_{42}O_5$ $[M + Na]^+$ 409.29181; found, 409.29245.

6*R*,12*R*)-13-((4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-12-(methoxymethoxy)tridecan-6-ol (80b):



Compound **79b** (130 mg, 0.208 mmol, 1 equiv.) was treated with TBAF (1 M in THF, 0.6 mL, 0.624 mmol, 3 equiv.) in THF (2 mL) under the same conditions as described for the synthesis of **80a** to give compound **80b** as a pale yellow liquid.

Yield = 80 mg, 90%;

$[\alpha]^{25}_{D}$ = – 2.3 (*c* 1.6, $CHCl_3$);

IR ($CHCl_3$) ν_{max} = 3424, 3019, 2930, 2857, 1640, 1427, 1218, 1041, 771, 670 cm^{-1};

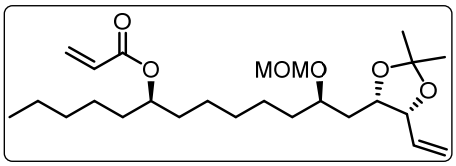
^{1}H NMR ($CDCl_3$, 500 MHz) δ = 5.81 (ddd, *J* = 7.3, 10.1, 17.1 Hz, 1 H), 5.36 (d, *J* = 17.1 Hz, 1 H), 5.25 (d, *J* = 10.1 Hz, 1 H), 4.69 - 4.66 (m, 2 H), 3.97 - 3.94 (t, *J* = 8.2 Hz, 1 H),

3.86 (dt, *J* = 2.8, 8.2 Hz, 1 H), 3.80 - 3.75 (m, 1 H), 3.57 - 3.57 (m, 1 H), 3.39 (s, 3 H), 1.71 - 1.66 (m, 1 H), 1.64 - 1.60 (m, 2 H), 1.58 - 1.54 (m, 1 H), 1.47 - 1.43 (m, 4 H), 1.42 - 1.4 (m, 8 H), 1.36 - 1.28 (m, 10 H), 0.90 (t, *J* = 6.9 Hz, 3 H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ = 135.1, 118.9, 108.6, 95.8, 83.0, 77.2, 74.7, 71.9, 55.6, 37.5, 37.4, 37.1, 35.1, 31.9, 29.8, 27.4, 26.9, 25.6, 25.3, 24.8, 22.6, 14.0;

HRMS (ESI^+) *m/z* = calcd for $C_{22}H_{42}O_5$ $[M + Na]^+$ 409.29144; found, 409.29245.

(6*R*,12*R*)-13-((4*S*,5*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-12-(methoxymethoxy)tridecan-6-yl acrylate (81a):



Acryloyl chloride (0.095 mL, 1.16 mmol, 1.5 equiv.) was added dropwise under N_2 to a solution of compound **80a** (300 mg, 0.776 mmol, 1 equiv.), Et_3N (0.33 mL, 2.33 mmol, 3 equiv.), and a catalytic amount of DMAP in anhydrous CH_2Cl_2 (2 mL) at 0 °C, and the mixture was stirred at 0 °C for 2 h. Upon completion of the reaction, the mixture was poured into brine (2 mL), and the resulting mixture was extracted with CH_2Cl_2 (3 x 4 mL). The combined organic phases were washed with brine (2 x 2 mL), dried with Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by flash column chromatography (petroleum ether/EtOAc, 19:1) to give **81**a as a pale yellow liquid.

Yield = 253 g, 74%;

R_f = 0.42 (petroleum ether/EtOAc, 85:15);

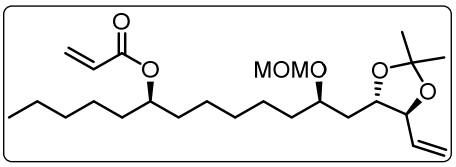
$[\alpha]^{25}_D$ = – 3.1 (*c* 3.8, $CHCl_3$);

IR ($CHCl_3$) ν_{max} = 3452, 3063, 2935, 2861, 1722, 1593, 1461, 1437, 1375, 1220, 1104, 1042, 926, 870, 824, 758, 704 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.39 (dd, *J* = 1.5, 17.4 Hz, 1 H), 6.12 (dd, *J* = 10.5, 17.4 Hz, 1 H), 5.84 - 5.76 (m, 2 H), 5.30 (d, *J* = 17.1 Hz, 1 H), 5.24 (d, *J* = 10.5 Hz, 1 H), 4.95 (quin, *J* = 6.4 Hz, 1 H), 4.68 (s, 2 H), 4.51 (t, *J* = 6.9 Hz, 1 H), 4.37 (ddd, *J* = 3.2, 6.9, 9.8 Hz, 1 H), 3.77 - 3.72 (m, 1 H), 3.39 (s, 3 H), 1.57 - 1.54 (m, 7 H), 1.48 (s, 3 H), 1.37 (s, 3 H), 1.35 - 1.25 (m, 13 H), 0.88 (t, *J* = 6.9 Hz, 3 H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ = 166.0, 134.5, 130.1, 129.0, 118.0, 108.1, 96.0, 79.7, 74.9, 74.7, 74.5, 55.6, 35.8, 35.2, 34.1, 31.7, 29.7, 28.2, 25.6, 25.2, 24.9, 24.8, 22.5, 13.9; **HRMS** (ESI^+) *m/z* = calcd for $C_{25}H_{44}O_6$ $[M + Na]^+$ 463.30240; found, 463.30301.

(6*R*,12*R*)-13-((4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-12-(methoxymethoxy)tridecan-6-yl acrylate (81b):



Compound **80b** (70 mg, 0.181 mmol, 1 equiv.) was treated with acryloyl chloride (22 µL, 0.272 mmol, 1.5 equiv.), Et_3N (76 µL, 0.543 mmol, 3 equiv.), and a catalytic amount of DMAP in CH_2Cl_2 (1 mL) under the same conditions as described for the synthesis of **81a** to give compound **81b** as a pale yellow liquid.

Yield = 59 mg, 74%;

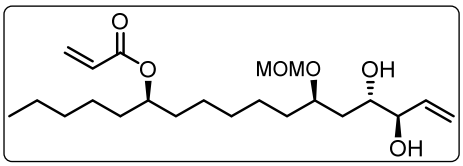
$[\alpha]^{25}_D$ = – 4.4 (*c* 1.2, $CHCl_3$);

IR ($CHCl_3$) ν_{max} = 3395, 3021, 2935, 1711, 1601, 1526, 1416, 1216, 1041, 927, 766, 671 cm^{-1};

^{1}H NMR ($CDCl_3$, 500 MHz) δ = 6.39 (dd, *J* = 1.2, 17.4 Hz, 1 H), 6.12 (dd, *J* = 10.4, 17.4 Hz, 1 H), 5.84 - 5.77 (m, 2 H), 5.36 (d, *J* = 17.1 Hz, 1 H), 5.25 (d, *J* = 10.4 Hz, 1 H), 4.95 (quin, *J* = 5.8 Hz, 1 H), 4.67 (s, 2 H), 3.95 (t, *J* = 8.2 Hz, 1 H), 3.86 (dt, *J* = 2.4, 8.5 Hz, 1 H), 3.78 - 3.74 (m, 1 H), 3.38 (s, 3 H), 1.71 - 1.66 (m, 1 H), 1.63 - 1.50 (m, 8 H), 1.42 (s, 3 H), 1.40 (s, 3 H), 1.34 - 1.27 (m, 11 H), 0.88 (t, *J* = 6.7 Hz, 3 H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ = 166.1, 135.1, 130.1, 129.0, 118.9, 108.6, 95.8, 83.0, 77.2, 74.8, 74.5, 55.6, 37.1, 35.1, 34.1, 31.7, 29.7, 27.4, 26.9, 25.3, 24.9, 24.8, 22.5, 14.0; **HRMS** (ESI^+) *m/z* = calcd for $C_{25}H_{44}O_6$ $[M + Na]^+$ 463.30145; found, 463.30301.

(6*R*,12*R*,14*S*,15*R*)-14,15-Dihydroxy-12-(methoxymethoxy)heptadec-16-en-6-yl acrylate (83):



A mixture of isopropylidene ketal **81a** (200 mg, 0.4545 mmol, 1 equiv.) and a catalytic amount of PPTS (12 mg, 0.0455, 0.1 equiv.) in CH_3OH (2 mL) was stirred at room temperature for 24 h. Upon completion of the reaction (as indicated by TLC analysis), methanol was evaporated, and the oily residue was diluted with water. The crude product was extracted by using EtOAc (5 x 5 mL). The combine EtOAc layers were dried with anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (petroleum ether/EtOAc, 1.5:1) to give **83** as a colorless liquid.

Yield = 157.5 mg, 87%

R_f = 0.26 (petroleum ether/EtOAc, 1.5:1);

$[\alpha]^{25}_{D}$ = – 10.2 (*c* 2.5, $CHCl_3$);

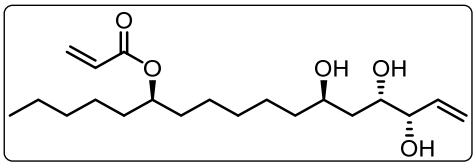
IR ($CHCl_3$) ν_{max} = 3455, 3013, 2937, 2863, 1721, 1629, 1456, 1408, 1375, 1208, 1143, 1098, 1040, 924, 758, 668 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.38 (dd, *J* = 1.2, 17.1 Hz, 1 H), 6.11 (dd, *J* = 10.3, 17.1 Hz, 1 H), 5.89 (ddd, *J* = 6.1, 10.5, 17.1 Hz, 1 H), 5.80 (dd, *J* = 1.2, 10.3 Hz, 1 H), 5.33 (d, *J* = 17.1 Hz, 1 H), 5.24 (d, *J* = 10.5 Hz, 1 H), 4.94 (quin, *J* = 6.2 Hz, 1 H), 4.66 (s, 2 H), 4.17 - 4.13 (m, 1 H), 3.94 (d like, 1 H), 3.82 - 3.77 (m, 1 H), 3.40 (s, 3 H), 3.32 (br. s., 1 H), 2.44 (br. s., 1 H), 1.70 - 1.49 (m, 8 H), 1.31 - 1.27 (m, 12 H), 0.87 (t, *J* = 6.9 Hz, 3 H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 166.1, 136.4, 130.2, 128.9, 116.9, 96.3, 76.0, 75.7, 74.5, 70.4, 55.8, 35.3, 34.7, 34.1, 34.0, 31.7, 29.5, 25.3, 25.2, 24.9, 22.5, 14.0;

HRMS (ESI^+) *m/z* = calcd for $C_{22}H_{40}O_6$ $[M + Na]^+$ 423.27185; found, 423.27171.

(6*R*,12*R*,14*S*,15*S*)-12,14,15-Trihydroxyheptadec-16-en-6-yl acrylate (82b):



To acetonide **81b** (50 mg, 0.113 mmol, 1 equiv.) in CH_3CN/CH_3OH (4:1, 0.2 mL) was added HCl (3 N solution, 19 μL) at 0 °C, and the resulting mixture was stirred at room temperature for 6 h. Upon completion of the reaction (as indicated by TLC analysis), the reaction mixture was quenched with a saturated $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc, and the organic layer was dried with Na_2SO_4 and

concentrated. The crude residue was purified by flash column chromatography (petroleum ether/EtOAc, 7:3) to afford **82b** as a colorless liquid.

Yield = 25 mg, 62%;

R_f = 0.26 (petroleum ether/EtOAc, 1.5:1);

$[\alpha]^{25}_D$ = – 4.4 (*c* 0.6, $CHCl_3$);

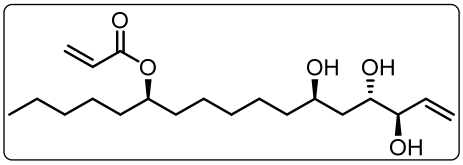
IR ($CHCl_3$) ν_{max} = 3375, 3020, 2929, 1710, 1600, 1420, 1216, 1044, 928, 763, 670 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.39 (dd, *J* = 1.0, 17.4 Hz, 1 H), 6.12 (dd, *J* = 10.5, 17.4 Hz, 1 H), 5.90 - 5.80 (m, 2 H), 5.37 (d, *J* = 17.4 Hz, 1 H), 5.26 (d, *J* = 10.5 Hz, 1 H), 4.95 (quin, *J* = 6.8 Hz, 1 H), 4.02 (t, *J* = 6.4 Hz, 1 H), 3.95 - 3.93 (m, 1 H), 3.81 (br. s., 1 H), 3.10 (br. s., 1 H), 2.52 (br. s., 1 H), 2.41 (br. s., 1 H), 1.74 - 1.69 (m, 1 H), 1.64 - 1.60 (m, 1 H), 1.60 - 1.55 (m, 4 H), 1.47 - 1.42 (m, 2 H), 1.30 - 1.28 (m, 11 H), 0.88 (t, *J* = 6.9 Hz, 3 H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 166.2, 137.2, 130.3, 128.9, 117.8, 76.2, 74.5, 71.8, 69.2, 38.4, 37.3, 34.1, 34.0, 31.7, 29.2, 25.5, 25.2, 24.9, 22.5, 14.0;

HRMS (ESI^+) *m/z* = calcd for $C_{20}H_{36}O_5$ $[M + Na]^+$ 379.24521; found, 379.24550.

(6*R*,12*R*,14*S*,15*R*)-12,14,15-Trihydroxyheptadec-16-en-6-yl acrylate (82a):



Compound **81a** (40 mg, 0.090 mmol) was treated with with HCl (3 N solution, 15 µL) in CH_3CN/CH_3OH (4:1, 0.15 mL) under the same conditions as described for the synthesis of **82b** to give compound **82a** as a colorless liquid.

Yield = 20.1 mg, 62%;

$[\alpha]^{25}_D$ = –1.8 (*c* 0.9, $CHCl_3$);

IR ($CHCl_3$) ν_{max} = 3416, 3018, 2934, 2865, 1711, 1626, 1521, 1412, 1289, 1215, 1110, 1048, 989, 767, 670 cm^{-1};

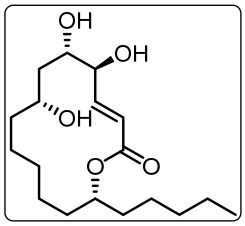
^{1}H NMR ($CDCl_3$, 500 MHz) δ = 6.39 (dd, *J* = 1.2, 17.4 Hz, 1 H), 6.12 (dd, *J* = 10.4, 17.4 Hz, 1 H), 5.91 (ddd, *J* = 6.4, 10.4, 17.1 Hz, 1 H), 5.81 (dd, *J* = 1.5, 10.4 Hz, 1 H), 5.35 (dt, *J* = 1.3, 17.1 Hz, 1 H), 5.27 (dt, *J* = 1.3, 10.4 Hz, 1 H), 4.98 - 4.93 (m, 1 H), 4.15 - 4.13 (m, 1 H), 4.00 - 3.91 (m, 2 H), 2.94 (br. s., 1 H), 2.47 - 2.40 (br. s., 2 H), 1.71 - 1.67

(m, 1 H), 1.58 - 1.50 (m, 6 H), 1.49 - 1.46 (m, 2 H), 1.33 - 1.28 (m, 11 H), 0.88 (t, *J* = 6.7 Hz, 3 H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ = 166.2, 136.4, 130.3, 128.9, 117.5, 76.1, 74.5, 71.2, 69.2, 37.5, 37.2, 34.1, 34.0, 31.7, 29.2, 25.6, 25.1, 24.9, 22.5, 14.0;

HRMS (ESI^+) *m/z* = calcd for $C_{20}H_{36}O_5$ $[M + Na]^+$ 379.24530; found, 379.24550.

(5*R*,6*S*,8*R*,14*R*,*E*)-5,6,8-Trihydroxy-14-pentyloxacyclotetradec-3-en-2-one (61):



To a solution of **82b** (20 mg, 0.0561 mmol, 1 equiv.) in freshly distilled and degassed anhydrous CH_2Cl_2 (60 mL) was added Grubbs second generation catalyst (5 mg, 0.00561 mmol, 0.1 equiv.), and the resulting mixture was heated at reflux for 8 h under argon until the starting material was completely consumed (monitored by TLC analysis). The solvent was evaporated to give a brown residue, which was purified by flash column chromatography (petroleum ether/EtOAc, 1:1) to afford **61** as a white amorphous solid.

Yield = 7.36 mg, 40%;

R_f = 0.42 (petroleum ether/EtOAc, 1.5:1);

$[\alpha]^{25}_D$ = – 8.8 (*c* 0.7, CH_3OH);

IR (CH_3OH) ν_{max} = 3413, 2955, 2845, 2120, 1649, 1459, 1403, 1272, 1109, 1018, 769 cm^{-1};

^{1}H NMR (CD_3OD, 500 MHz) δ = 7.04 (dd, *J* = 5.3, 15.9 Hz, 1 H), 6.11 (dd, *J* = 1.5, 15.9 Hz, 1 H), 4.95 (dddd, *J* = 12.5, 7.6, 5.2, 2.4 Hz, 1 H), 4.26 (ddd, *J* = 7.0, 5.3, 1.5 Hz, 1 H), 3.94 - 3.89 (m, 1 H), 3.77 (dt, *J* = 7.3, 4.3 Hz, 1 H), 1.70 (t like, 2 H), 1.62 - 1.57 (m, 4 H), 1.43 (br. s., 4 H), 1.34 - 1.31 (m, 7 H), 1.18 (br. s., 3 H), 0.90 (t, *J* = 6.7 Hz, 3 H);

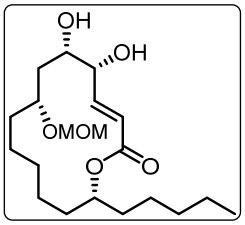
^{13}C NMR (CD_3OD, 125 MHz) δ = 168.0, 148.7, 123.5, 77.6, 75.8, 74.4, 69.2, 37.9, 36.8, 36.3, 34.1, 33.0, 29.7, 26.6, 26.4, 25.3, 23.8, 14.5;

HRMS (ESI^+) *m/z* = calcd for $C_{18}H_{32}O_5$ $[M + Na]^+$ 351.21347; found, 351.21420.

(5*R*,6*S*,8*R*,14*R*,*E*)-5,6,8-Trihydroxy-14-pentyloxacyclotetradec-3-en-2-one (1):

Compound **82a** (15 mg, 0.0421 mmol) was treated with Grubbs second generation catalyst (3.6 mg, 0.00421 mmol, 0.1 equiv.) in CH_2Cl_2 (45 mL) under the same conditions as described for the synthesis of **61** to give compound **1** (4.1 mg, 30 %) as a white amorphous solid.

(5*R*,6*S*,8*R*,14*R*,*E*)-5,6-Dihydroxy-8-(methoxymethoxy)-14-pentyloxacyclotetradec-3-en-2-one (84):



To a solution of **83** (50 mg, 0.125 mmol, 1 equiv.) in freshly distilled and degassed anhydrous CH_2Cl_2 (150 mL) was added Grubbs second generation catalyst (11 mg, 0.0125 mmol, 0.1 equiv.), and the resulting mixture was heated at reflux for 24 h under argon until the starting materials were completely consumed (monitored by TLC analysis). The solvent was evaporated to give a brown residue, which was purified by column chromatography (petroleum ether/EtOAc, 1:1) to afford **84** as a white solid.

Yield = 32.6 mg, 70%;

R_f = 0.24 (petroleum ether/EtOAc, 1:1);

$[\alpha]^{25}_{D}$ = – 5.8 (*c* 0.7, $CHCl_3$);

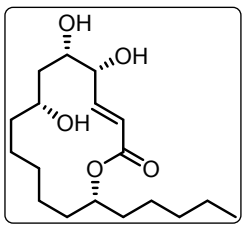
IR ($CHCl_3$) ν_{max} = 3427, 3021, 2933, 2863, 1712, 1524, 1431, 1216, 1036, 767, 671 cm^{-1};

^{1}H NMR ($CDCl_3$, 500 MHz) δ = 6.83 (dd, *J* = 5.3, 15.7 Hz, 1 H), 6.18 (dd, *J* = 1.4, 15.7 Hz, 1 H), 5.03 - 4.98 (m, 2 H), 4.72 - 4.68 (m, 2 H), 4.65 - 4.63 (m, 1 H), 4.02 - 3.98 (m, 1 H), 3.93 (q, *J* = 3.7 Hz, 1 H), 3.40 (s, 4 H), 1.81 (t, *J* = 4.0 Hz, 2 H), 1.71 - 1.66 (m, 2 H), 1.61 - 1.56 (m, 2 H), 1.54 - 1.46 (m, 4 H), 1.39 - 1.30 (m, 8 H), 1.11 - 1.03 (m, 2 H), 0.88 (t, *J* = 6.5 Hz, 3 H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ = 166.3, 145.5, 122.6, 96.1, 77.4, 76.2, 73.5, 71.4, 55.8, 35.2, 33.9, 33.7, 32.5, 31.7, 28.7, 26.6, 25.2, 25.0, 22.5, 14.0;

HRMS (ESI^+) *m/z* = calcd for $C_{20}H_{36}O_6$ $[M + Na]^+$ 395.24033; found, 395.24041.

(5*R*,6*S*,8*R*,14*R*,*E*)-5,6,8-Trihydroxy-14-pentyloxacyclotetradec-3-en-2-one (1):



To acetonide **84** (20 mg, 0.0537 mmol, 1 equiv.) in CH_3CN/CH_3OH (4:1, 90 μL) was added HCl (3 N solution, 9 μL) at 0 °C, and the resulting mixture was stirred at room temperature for 6 h. Upon the completion of the reaction (as indicated by TLC analysis), it was quenched by the additon of a saturated $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc, and the organic layer was dried with Na_2SO_4 and concentrated. The crude residue was purified by flash column chromatography (petroleum ether/EtOAc, 1:1) to afford **1** as a white amorphous solid.

Yield = 12 mg, 68%;

R_f = 0.35 (petroleum ether/EtOAc, 1.5:1);

$[\alpha]^{25}_D$ = + 4.8 (*c* 0.3, CH_3OH);

IR (CH_3OH) ν_{max} = 3557, 2934, 2837, 1716, 1659, 1456, 1418, 1113, 1029, 881 cm^{-1};

^{1}H NMR (CD_3OD, 400 MHz) δ = 6.87 (dd, *J* = 6.1, 15.6 Hz, 1 H), 6.08 (dd, *J* = 1.2, 15.6 Hz, 1 H), 4.98 - 4.94 (m, 1 H), 4.50 - 4.47 (m, 1 H), 3.99 (quin, *J* = 6.1 Hz, 1 H), 3.87 - 3.83 (m, 1 H), 1.83 (dt, *J* = 6.1, 14.7 Hz, 1 H), 1.70 - 1.52 (m, 5 H), 1.39 - 1.25 (m, 11 H), 1.20 - 1.16 (m, 3 H), 0.90 (t, *J* = 6.8 Hz, 3 H);

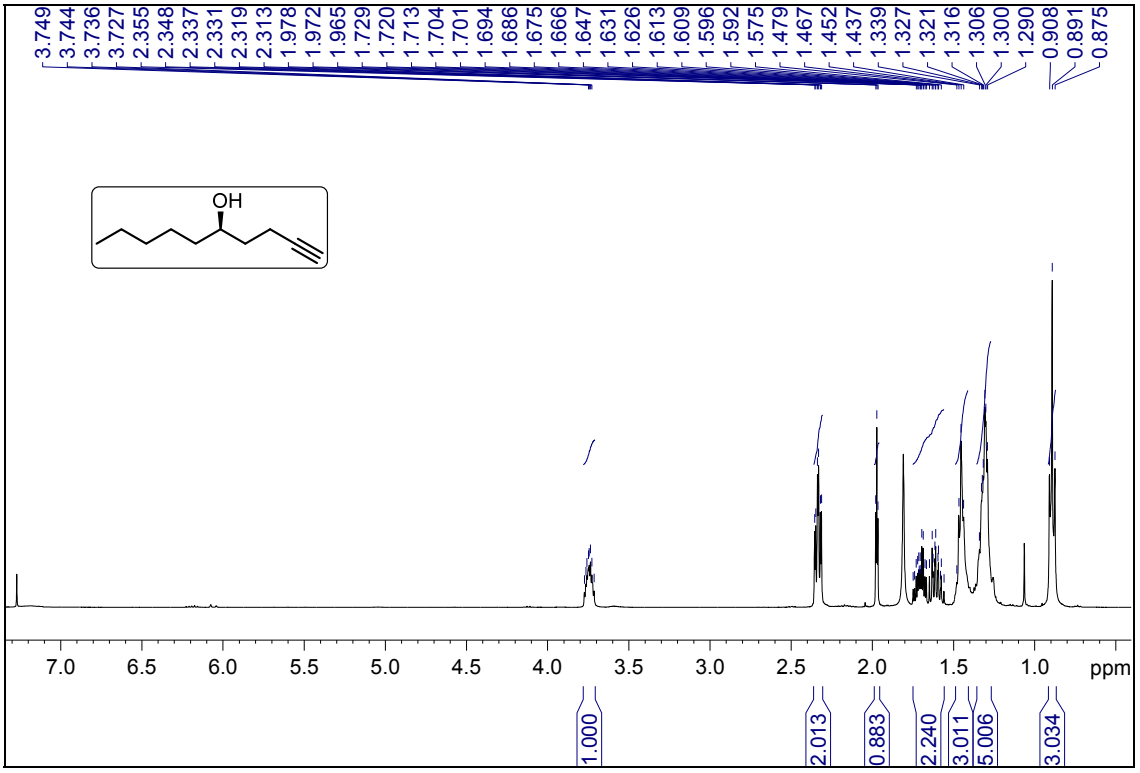
^{13}C NMR (CD_3OD, 100 MHz) δ = 168.4, 149.3, 123.1, 77.6, 76.0, 72.9, 69.5, 38.3, 36.8, 36.5, 34.1, 33.0, 29.5, 27.0, 26.4, 25.8, 23.8, 14.5;

HRMS (ESI^+) *m/z* = calcd for $C_{18}H_{32}O_5$ $[M + Na]^+$ 351.21417; found, 351.21420.

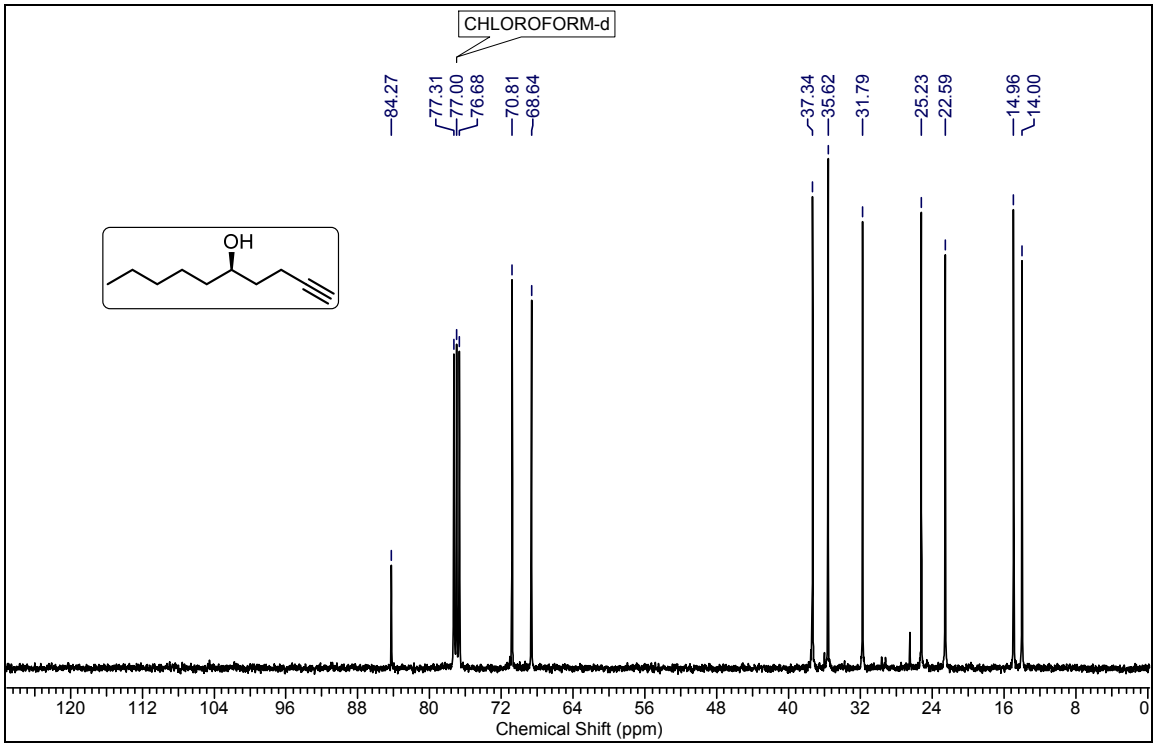
1.7. Spectral Data

Spectra

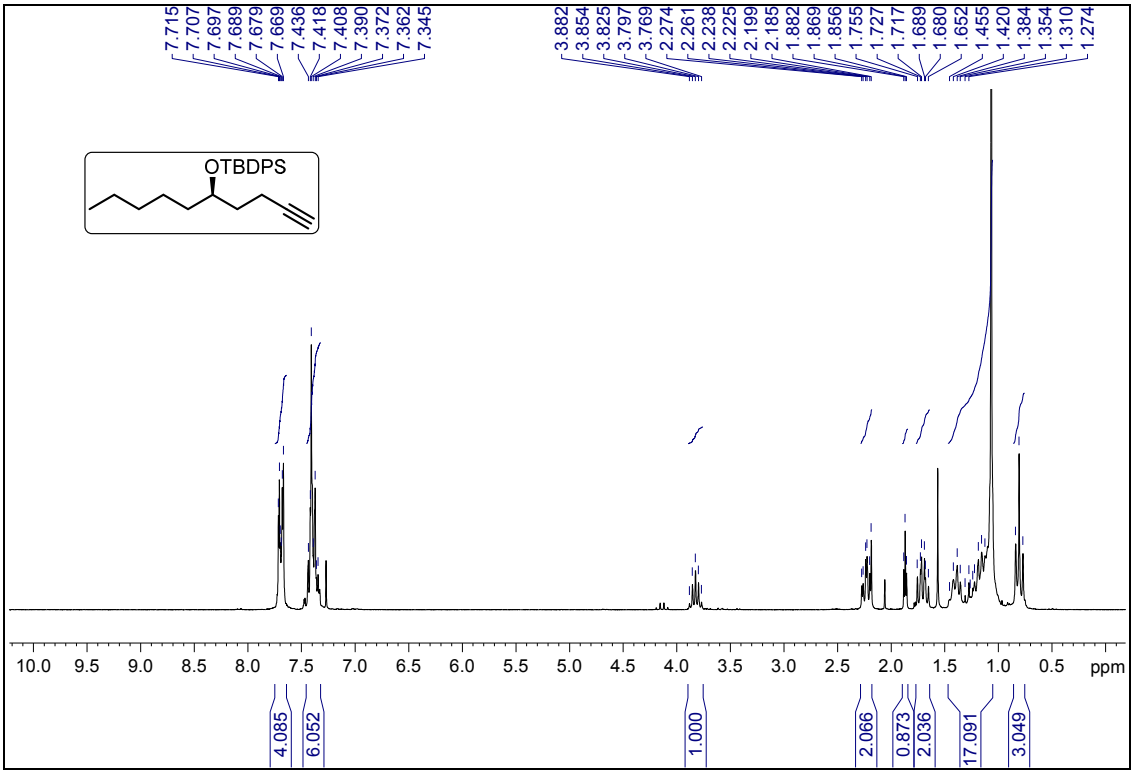
^{1}H NMR spectrum of compound **66** ($CDCl_3$, 400 MHz):



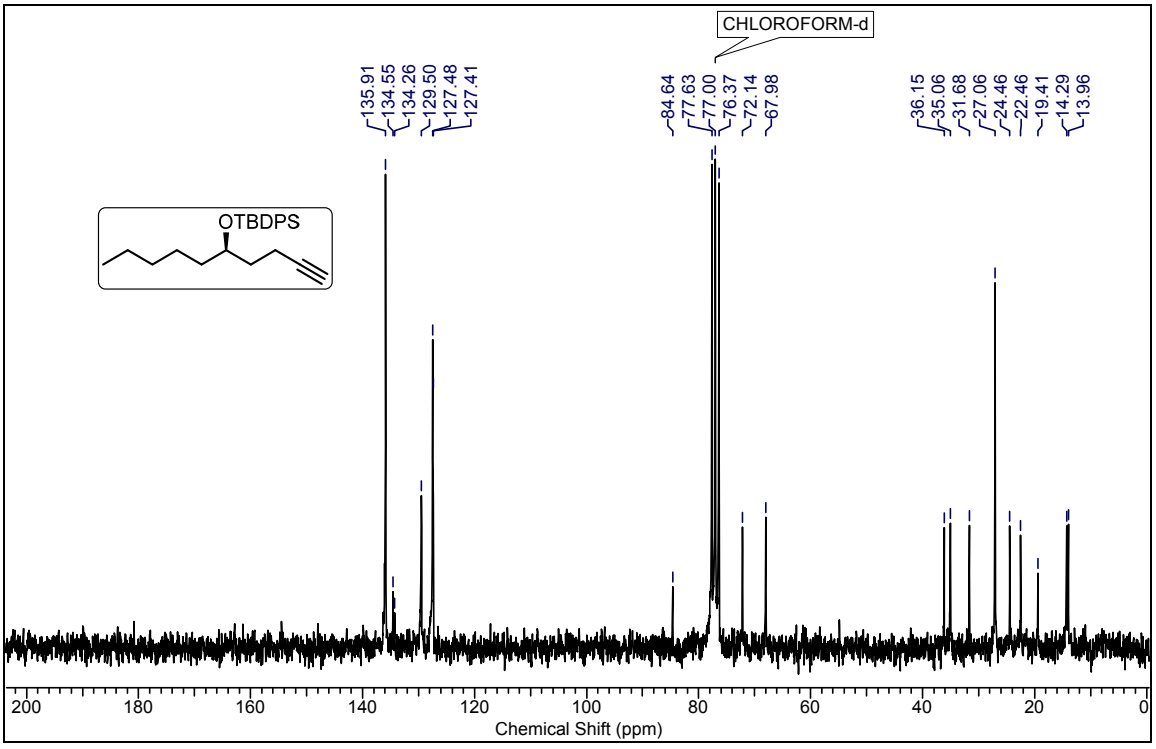
^{13}C NMR spectrum of compound **66** ($CDCl_3$, 100 MHz):



^{1}H NMR spectrum of compound **67** ($CDCl_3$, 200 MHz):

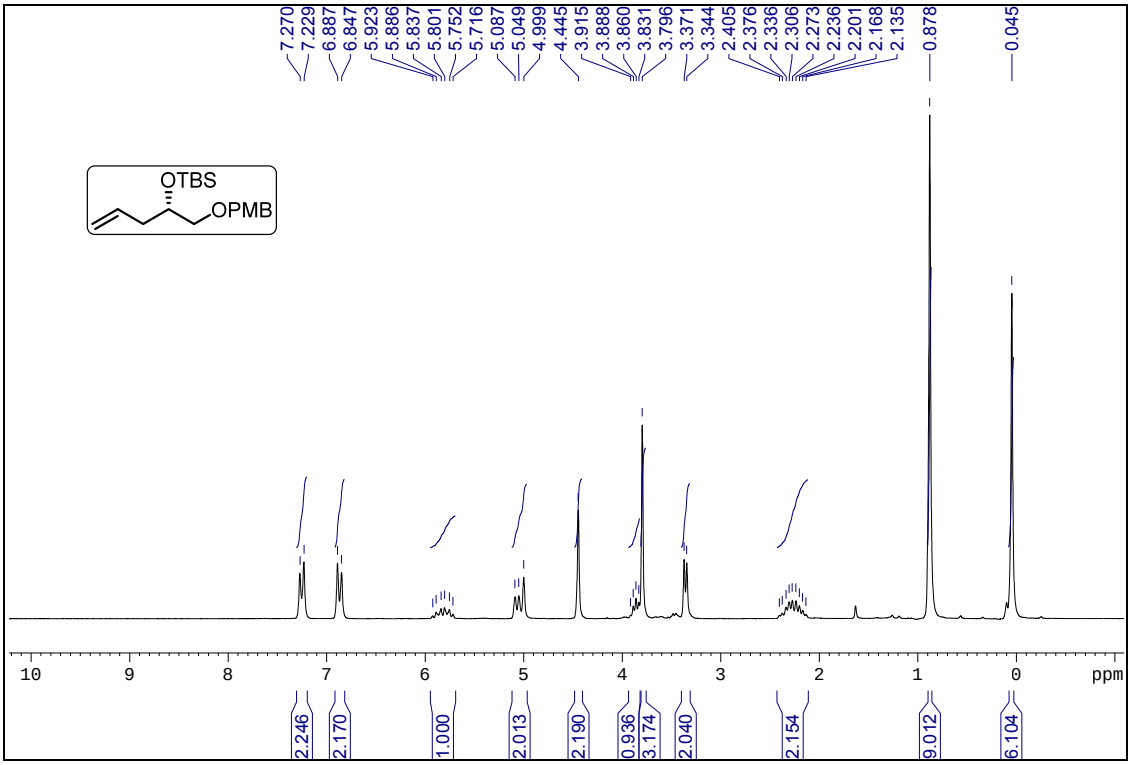


^{13}C NMR spectrum of compound **67** ($CDCl_3$, 50 MHz):

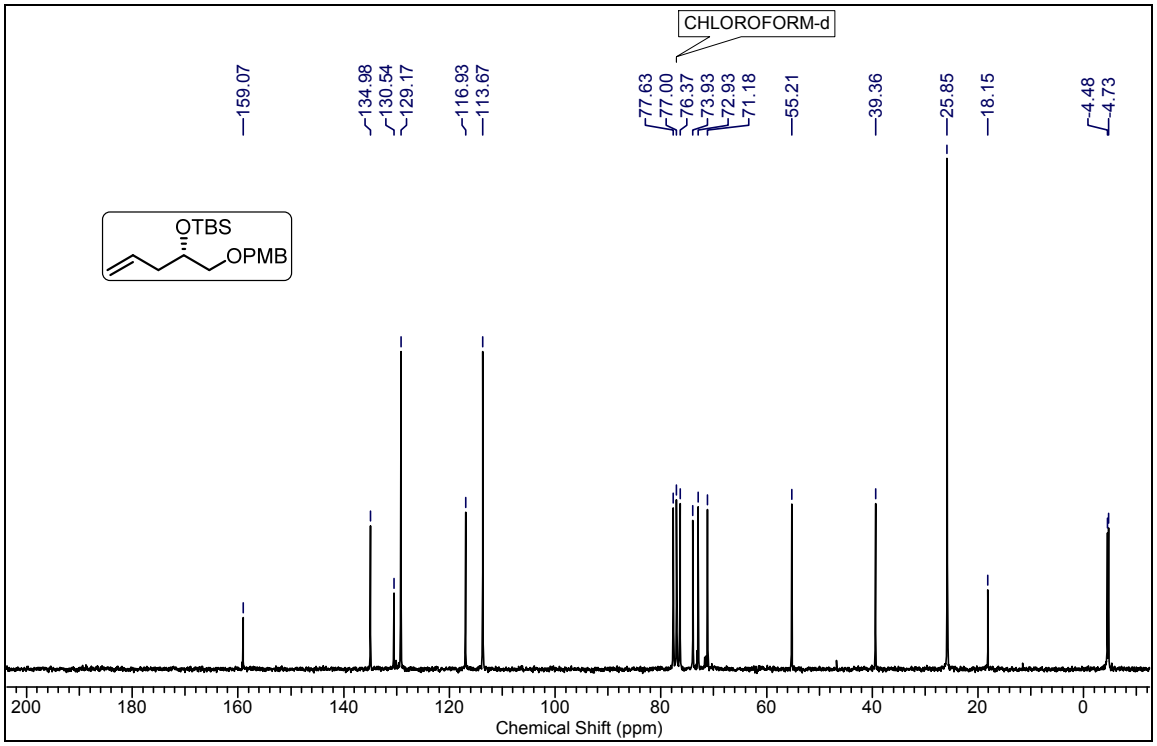


Spectra

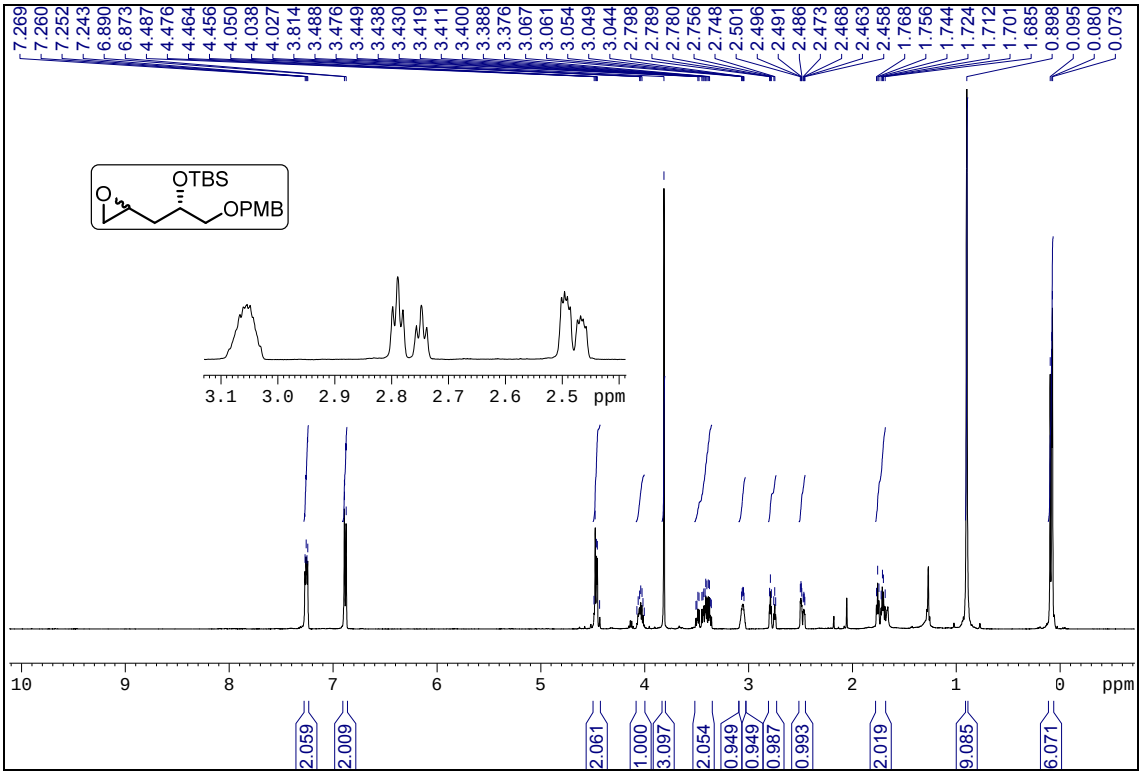
^{1}H NMR spectrum of compound **69** ($CDCl_3$, 200 MHz):



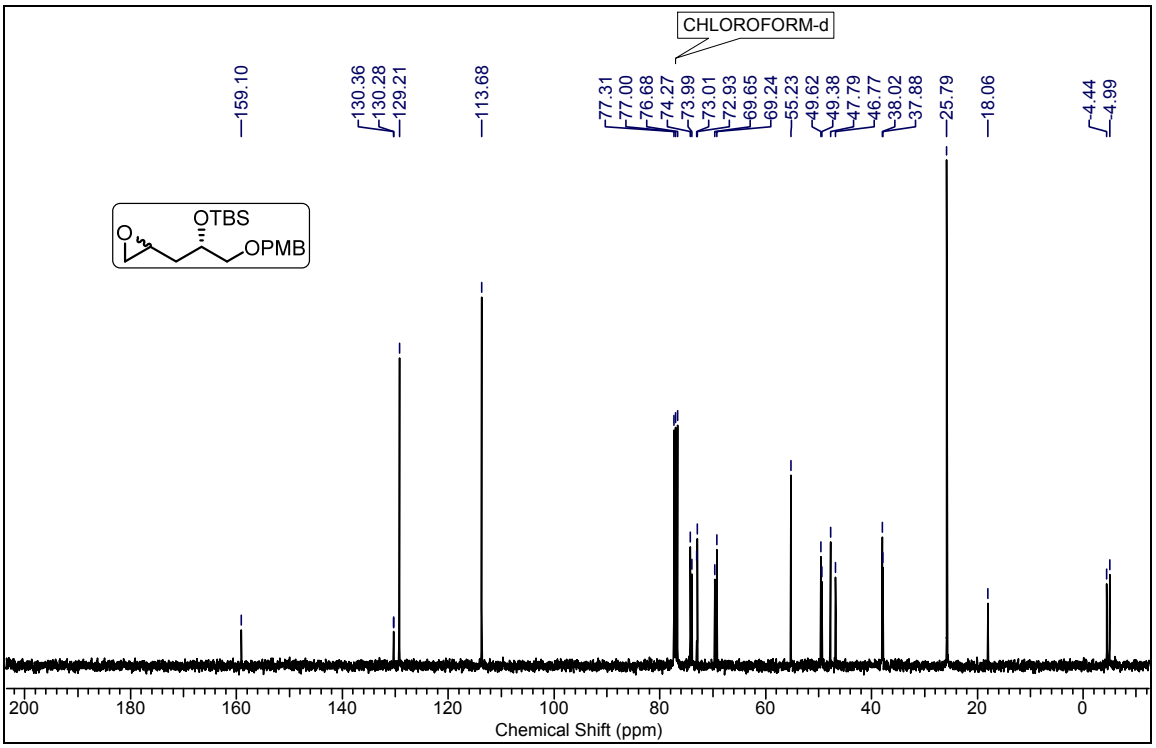
^{13}C NMR spectrum of compound **69** ($CDCl_3$, 50 MHz):



^{1}H NMR spectrum of compound **70** ($CDCl_3$, 500 MHz):

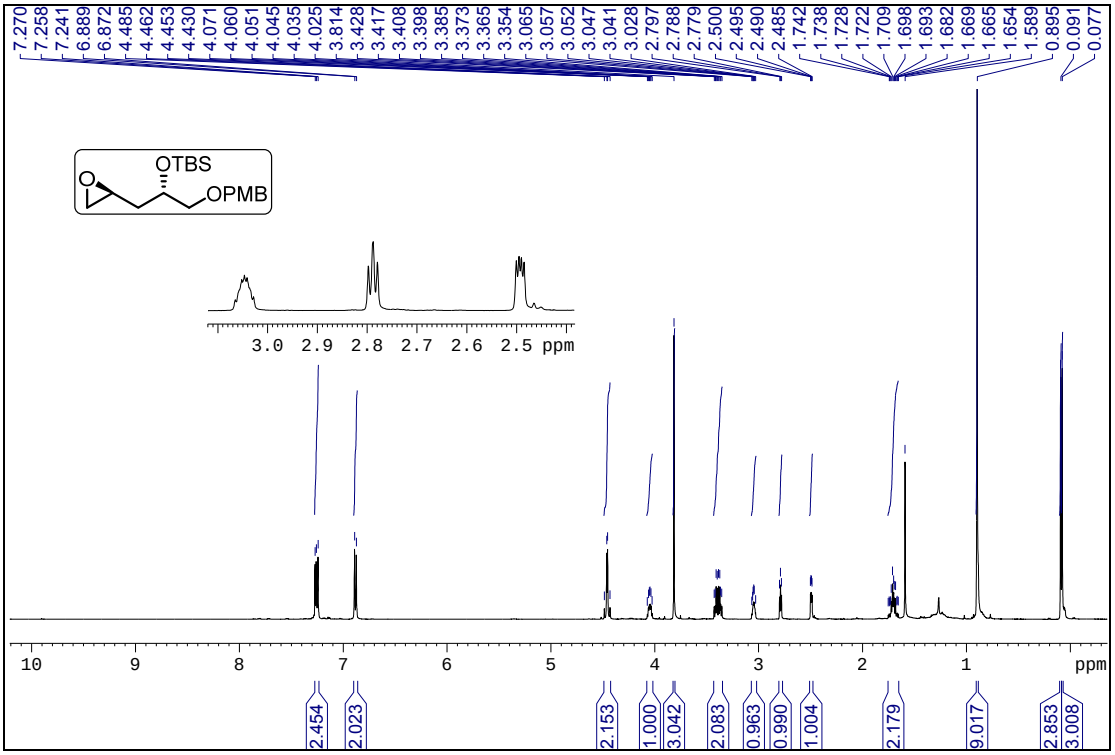


^{13}C NMR spectrum of compound **70** ($CDCl_3$, 100 MHz):

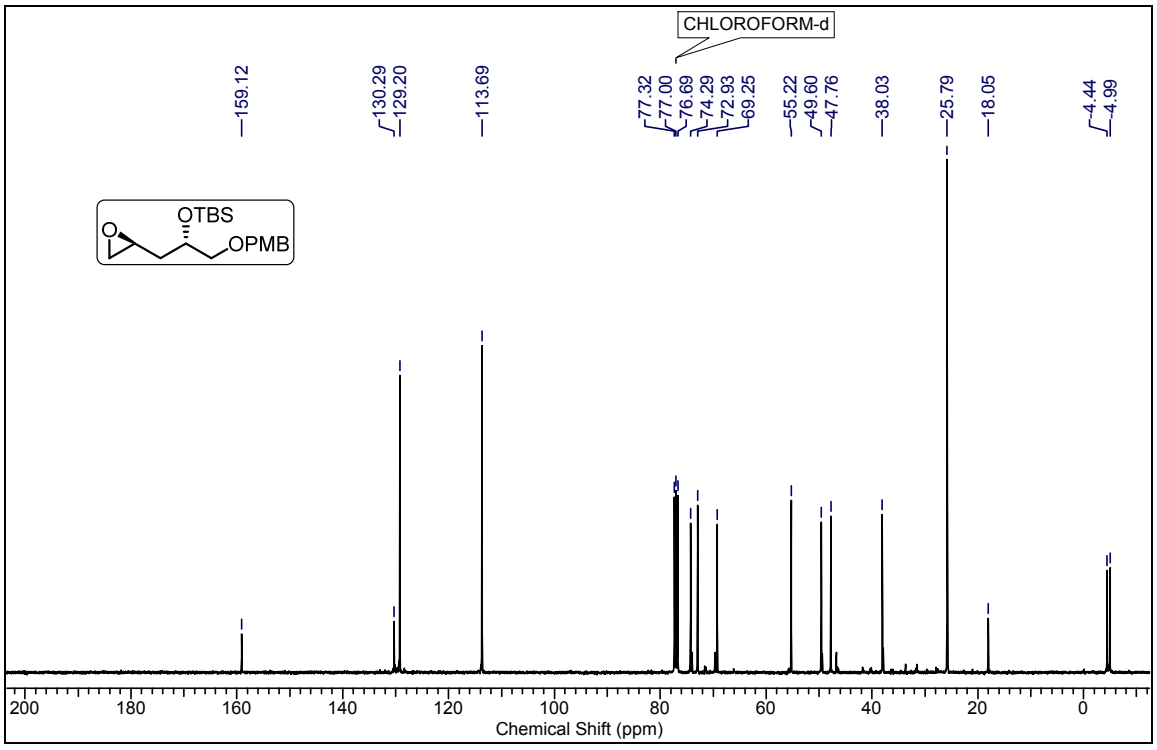


Spectra

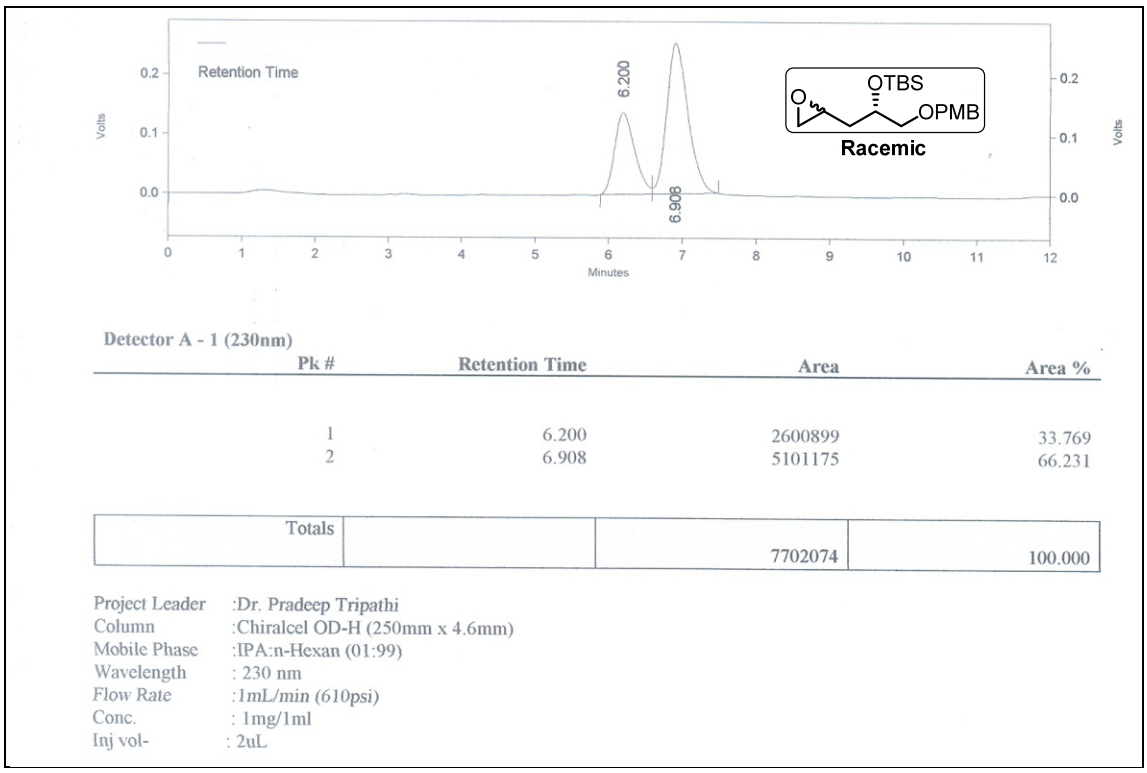
^{1}H NMR spectrum of compound **71a** ($CDCl_3$, 500 MHz):



^{13}C NMR spectrum of compound **71a** ($CDCl_3$, 100 MHz):



HPLC (*dr*) of the compound **70**:

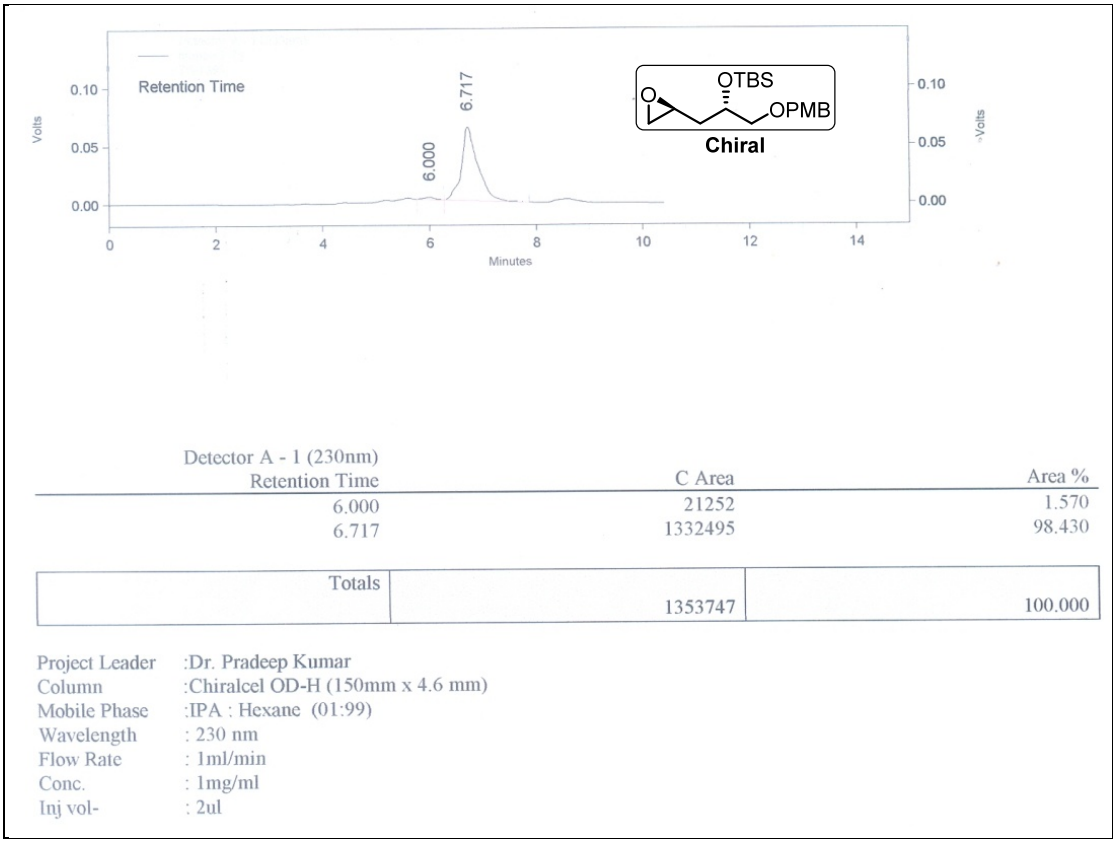


Detector A - 1 (230nm)

Pk #	Retention Time	Area	Area %
1	6.200	2600899	33.769
2	6.908	5101175	66.231
Totals		7702074	100.000

Project Leader :Dr. Pradeep Tripathi
Column :Chiralcel OD-H (250mm x 4.6mm)
Mobile Phase :IPA:n-Hexan (01:99)
Wavelength : 230 nm
Flow Rate :1mL/min (610psi)
Conc. : 1mg/1ml
Inj vol- : 2uL

HPLC (*dr*) of the compound **71a**:



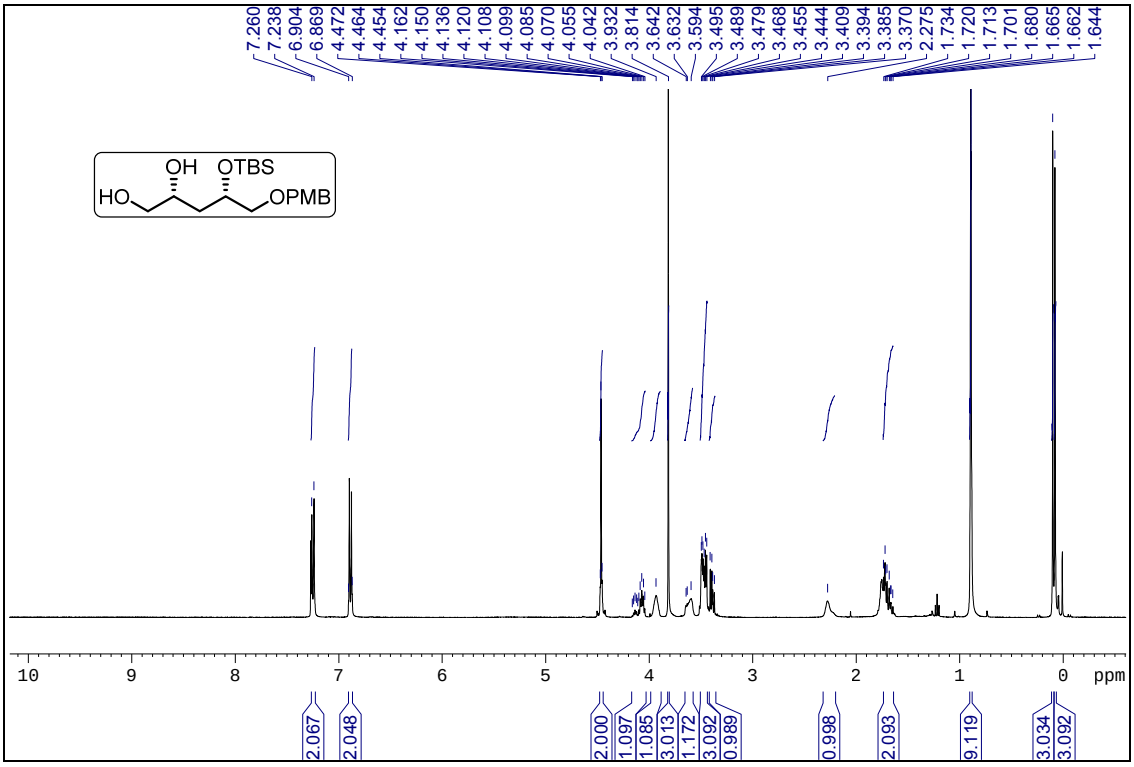
Detector A - 1 (230nm)

Retention Time	C Area	Area %
6.000	21252	1.570
6.717	1332495	98.430
Totals	1353747	100.000

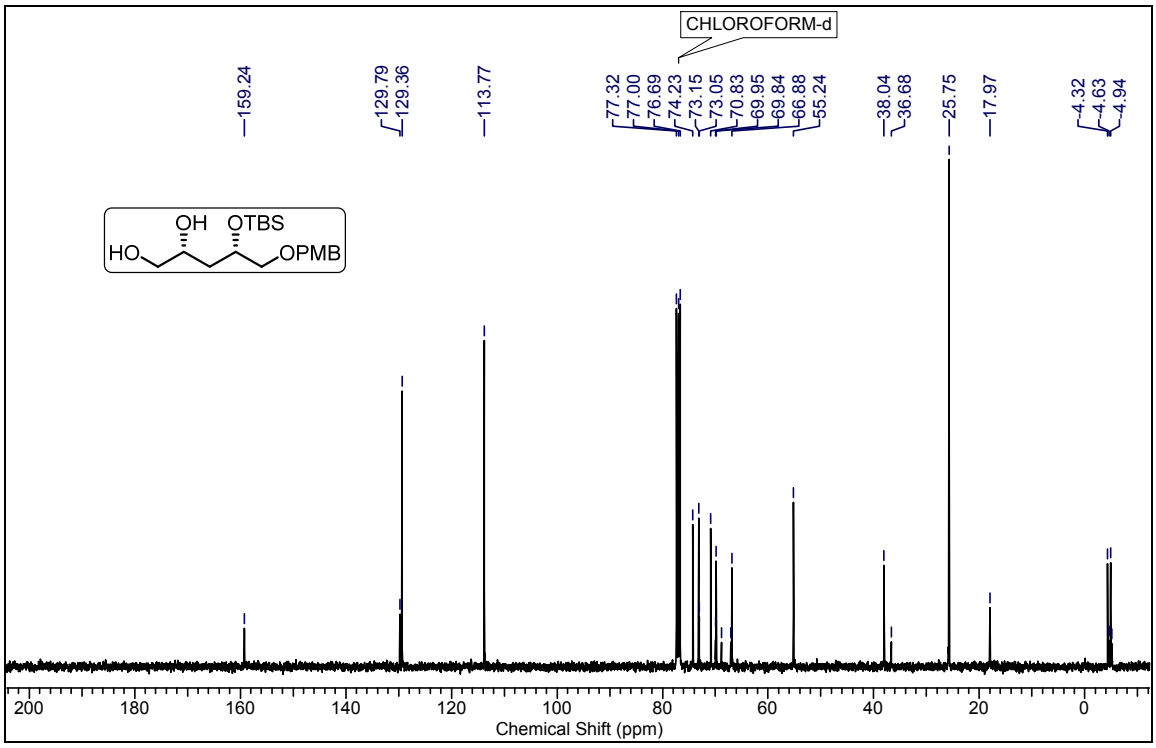
Project Leader :Dr. Pradeep Kumar
Column :Chiralcel OD-H (150mm x 4.6 mm)
Mobile Phase :IPA : Hexane (01:99)
Wavelength : 230 nm
Flow Rate : 1ml/min
Conc. : 1mg/ml
Inj vol- : 2ul

Spectra

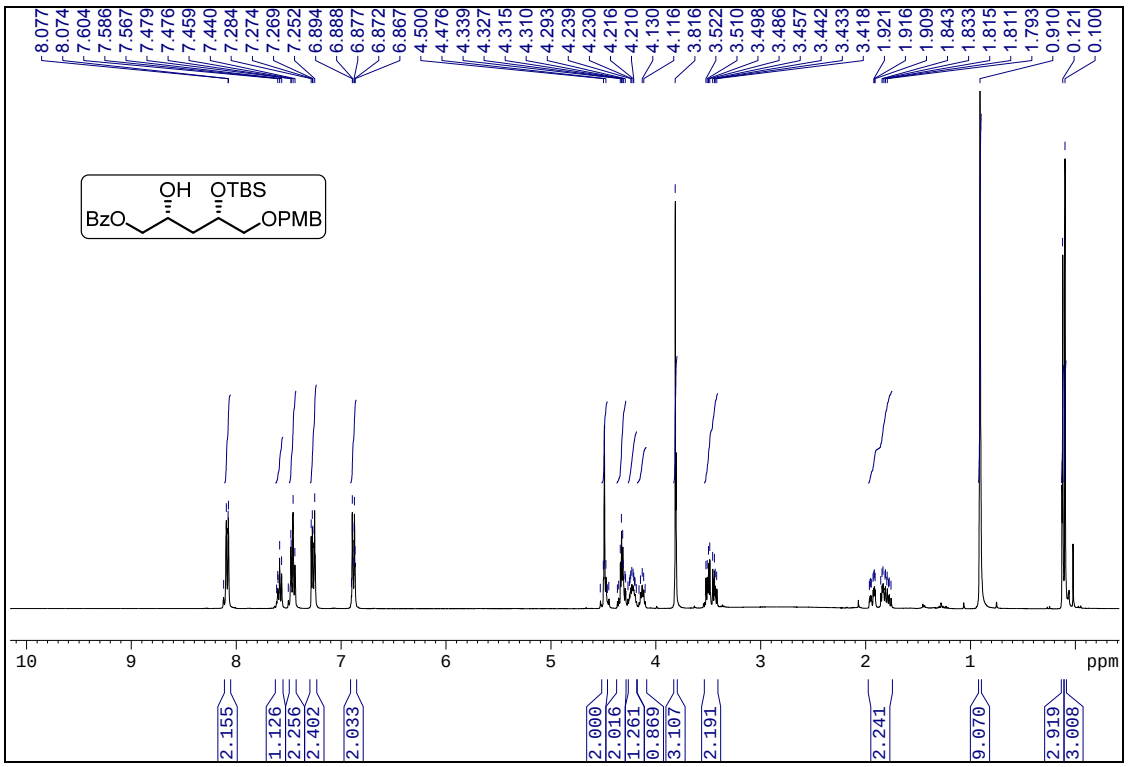
^{1}H NMR spectrum of compound **71b** ($CDCl_3$, 400 MHz):



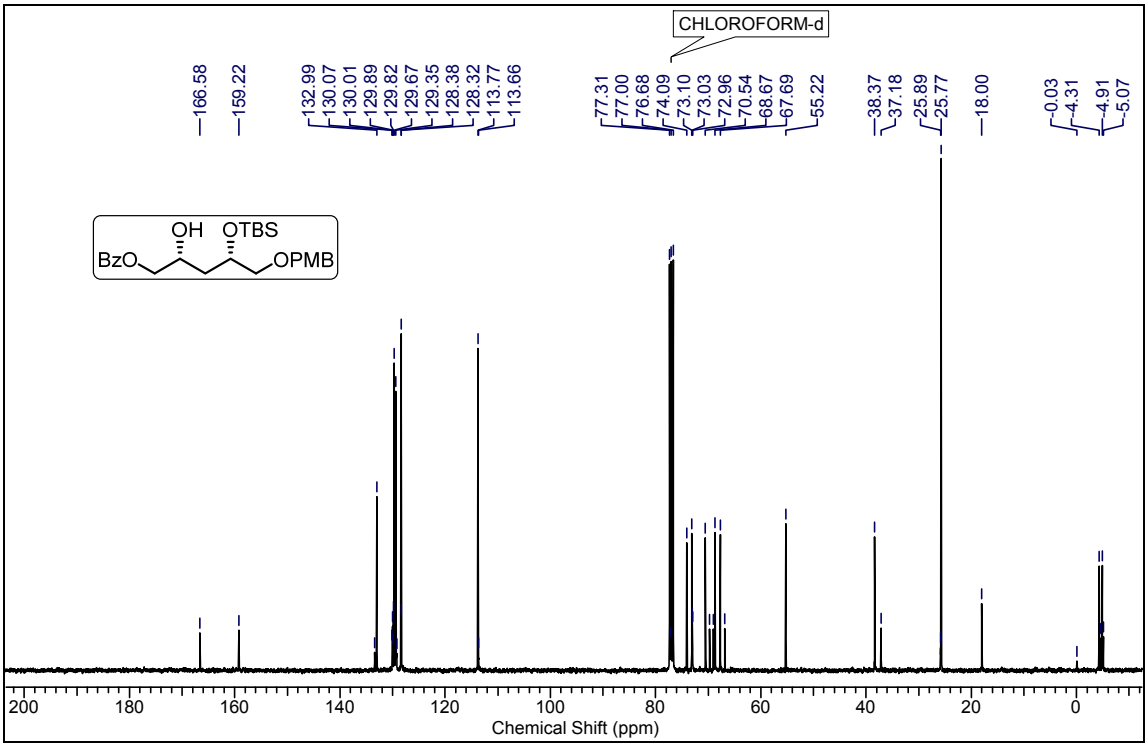
^{13}C NMR spectrum of compound **71b** ($CDCl_3$, 100 MHz):



^{1}H NMR spectrum of compound **71c** ($CDCl_3$, 400 MHz):

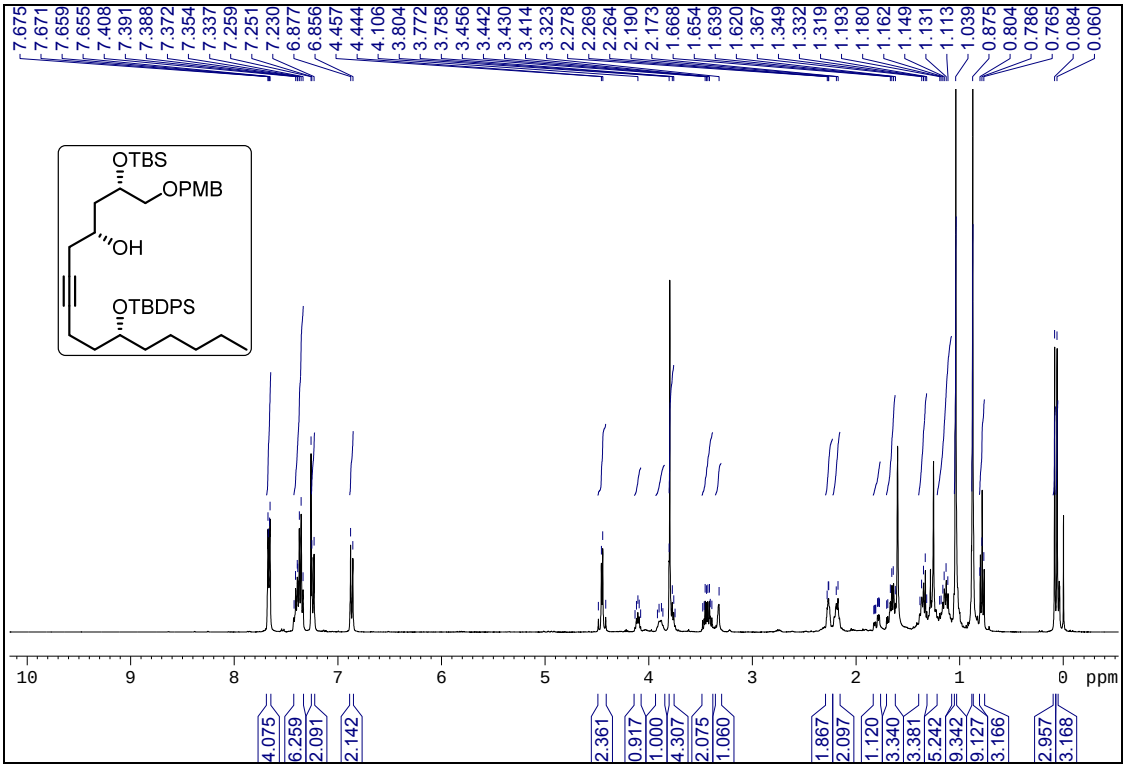


^{13}C NMR spectrum of compound **71c** ($CDCl_3$, 100 MHz):

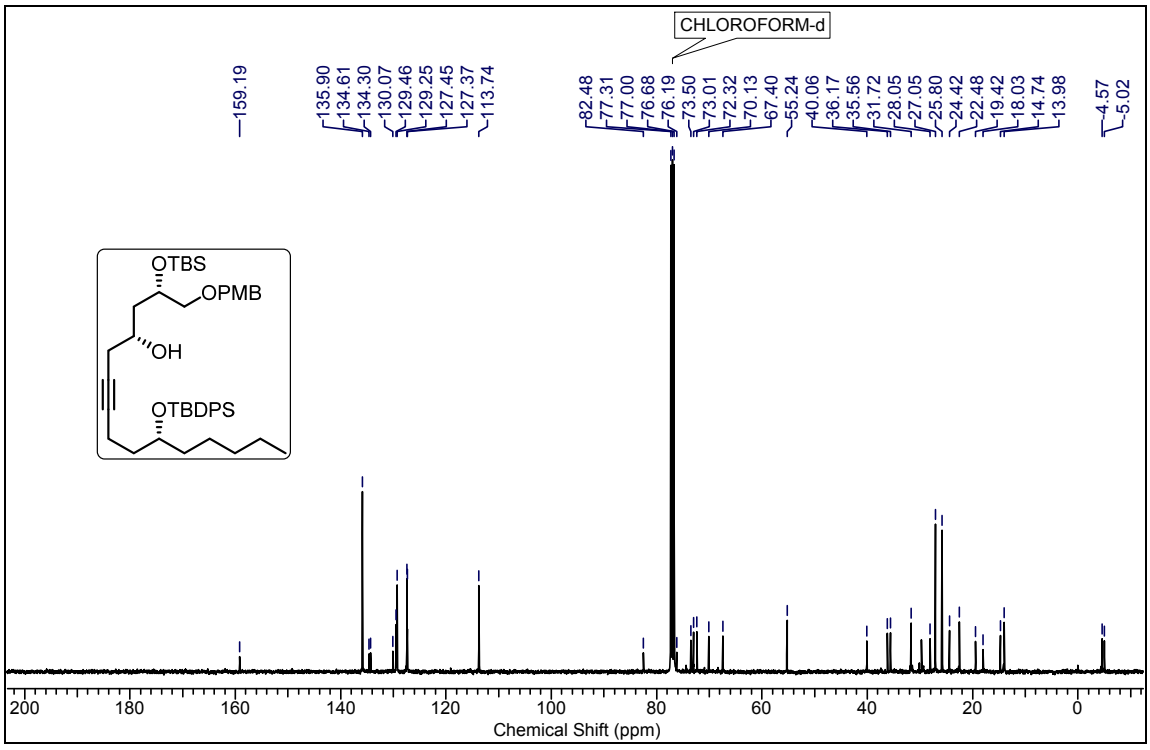


Spectra

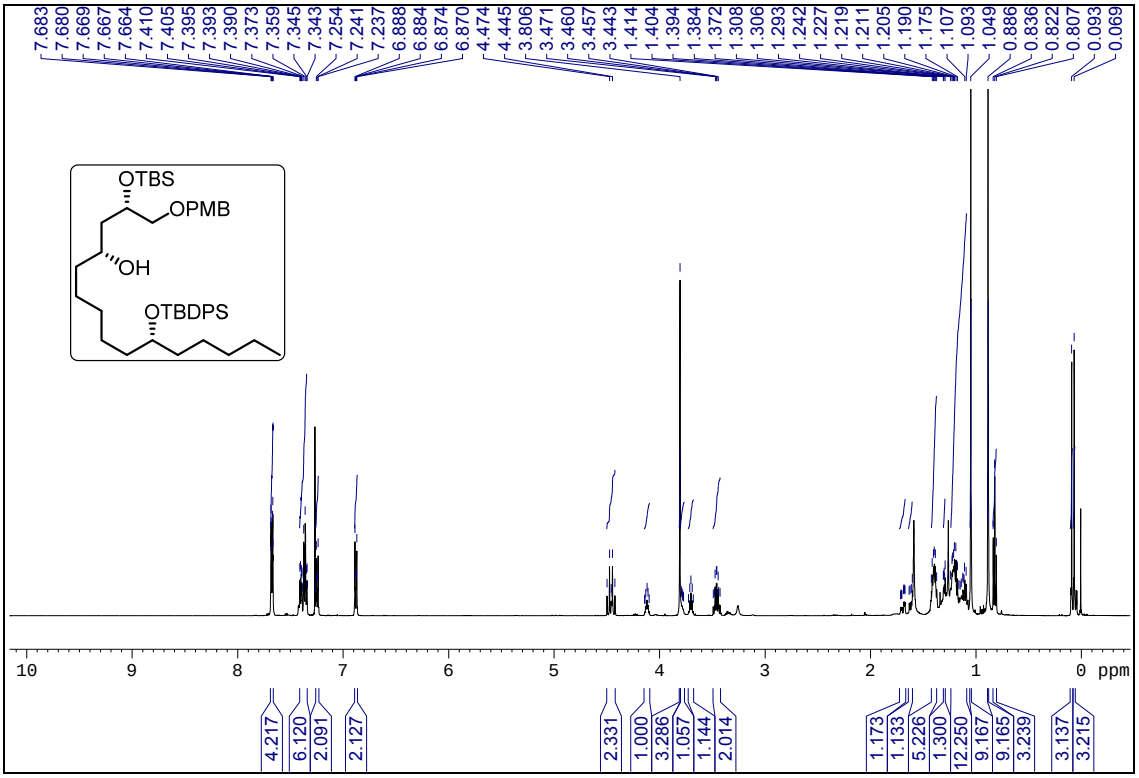
^{1}H NMR spectrum of compound **72** ($CDCl_3$, 400 MHz):



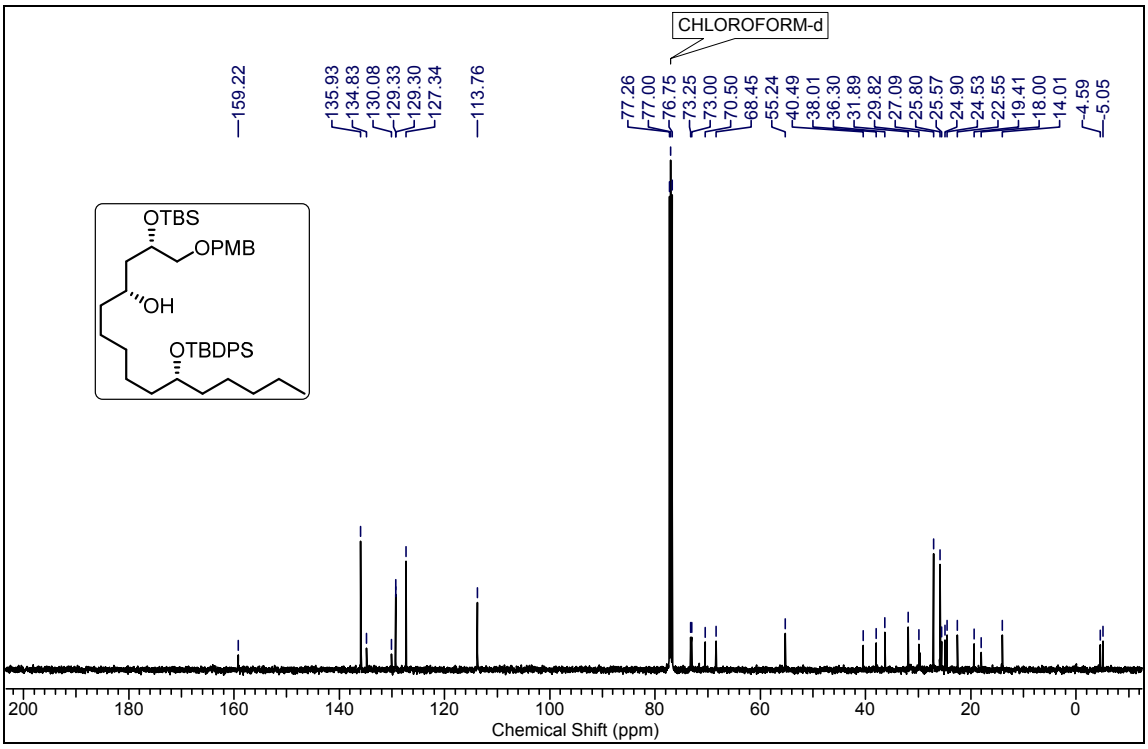
^{13}C NMR spectrum of compound **72** ($CDCl_3$, 100 MHz):



^{1}H NMR spectrum of compound **73** ($CDCl_3$, 500 MHz):

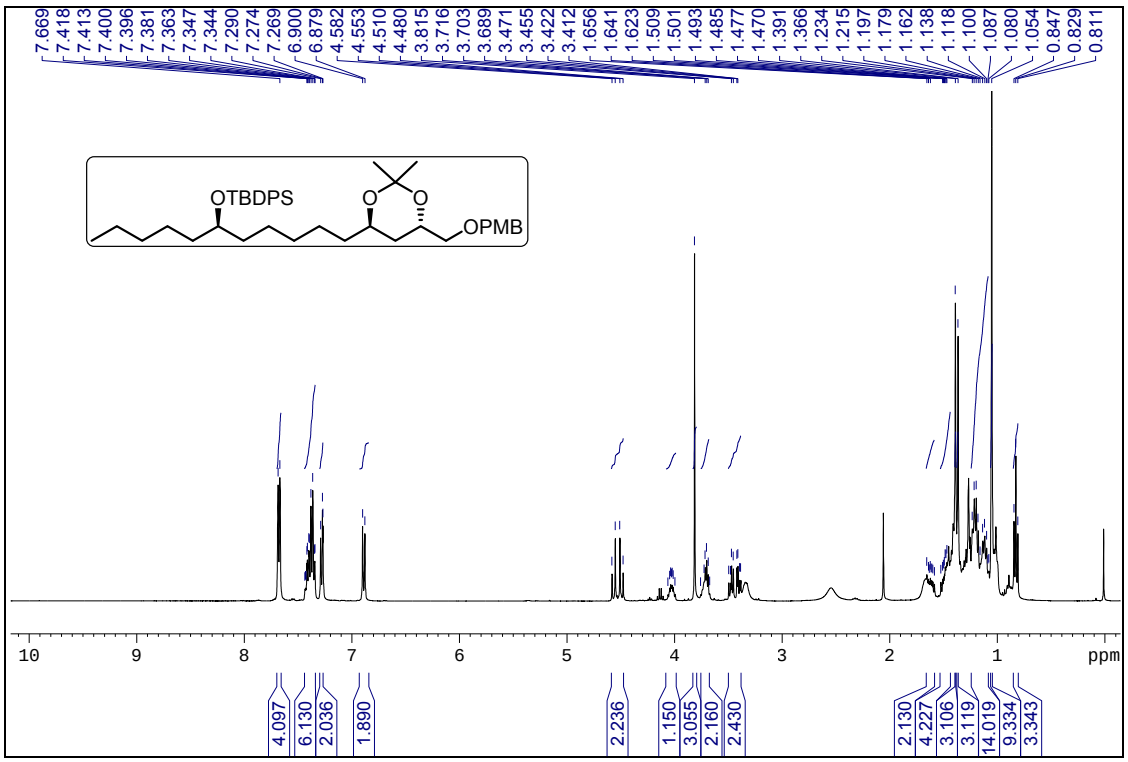


^{13}C NMR spectrum of compound **73** ($CDCl_3$, 125 MHz):

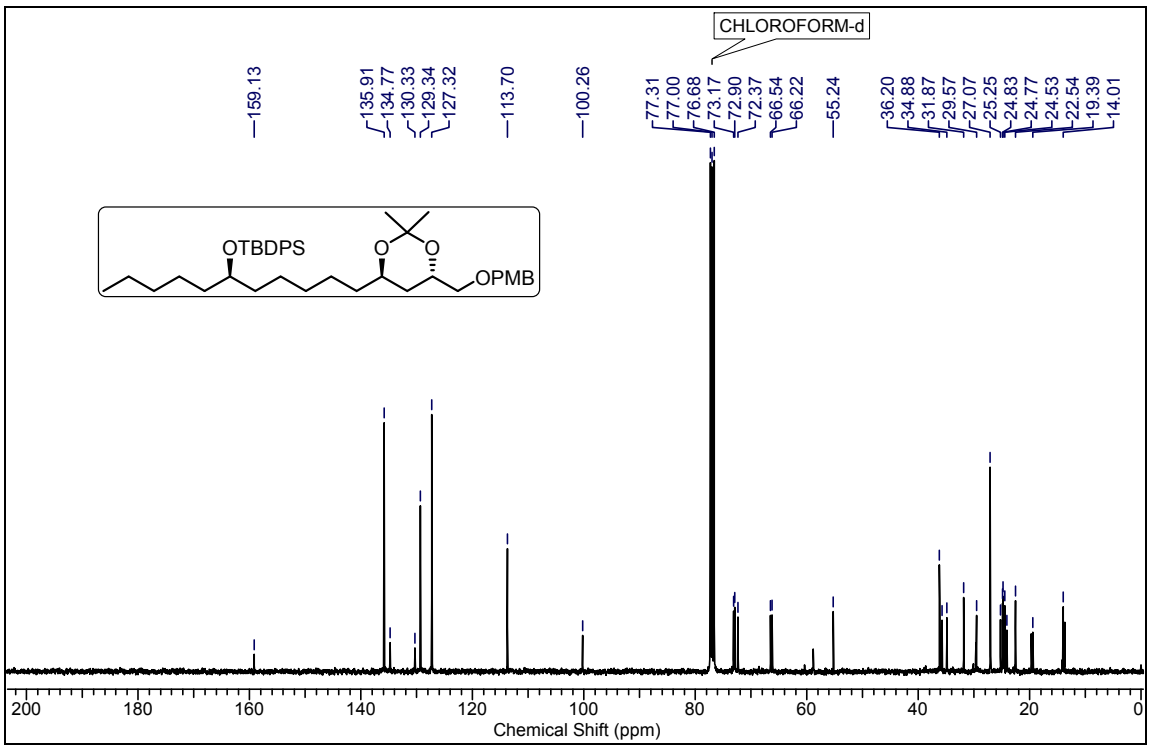


Spectra

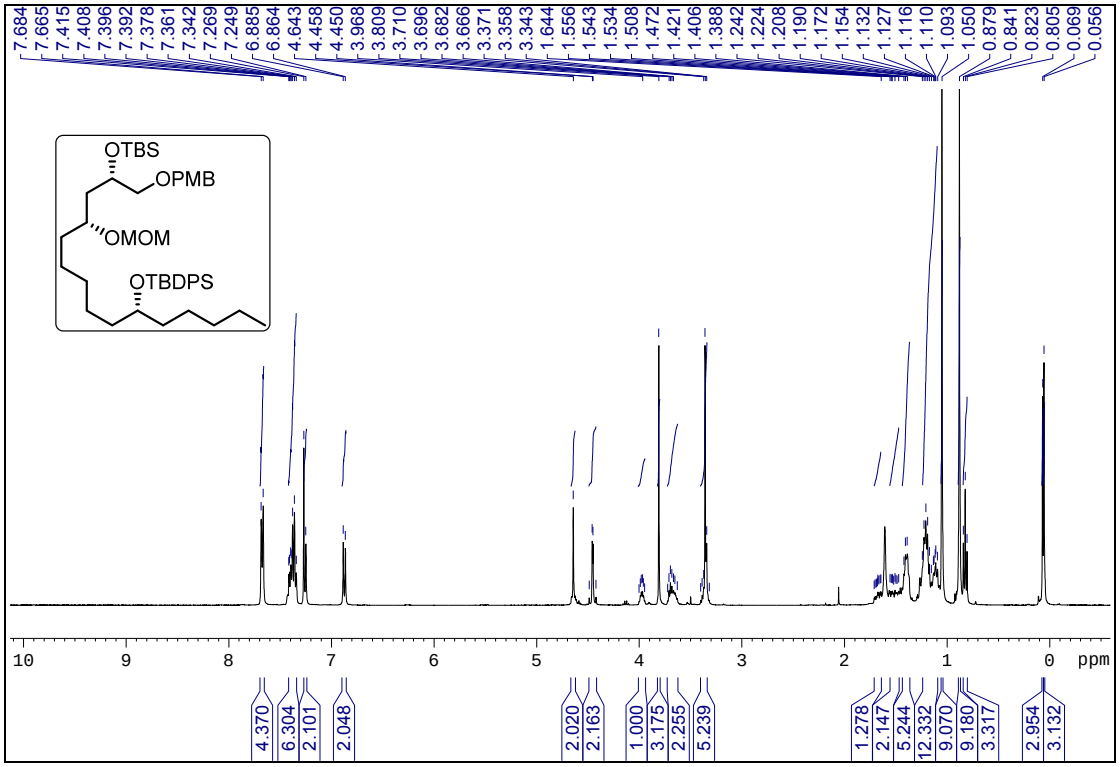
^{1}H NMR spectrum of compound **73b** ($CDCl_3$, 400 MHz):



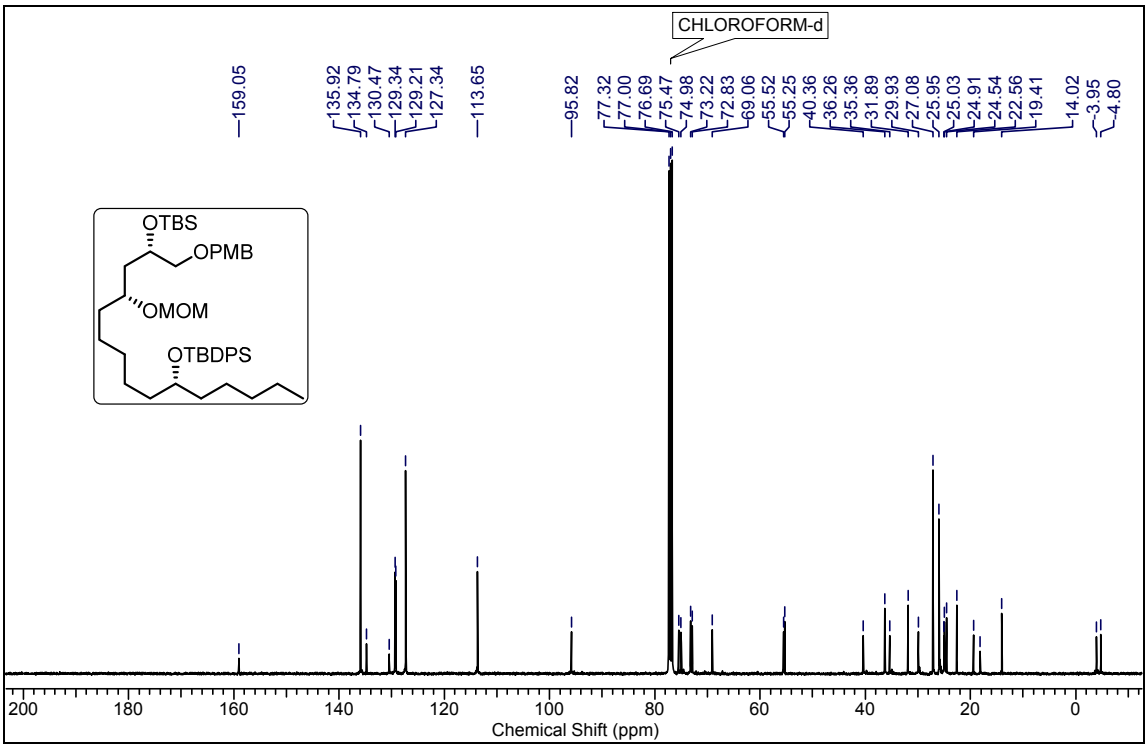
^{13}C NMR spectrum of compound **73b** ($CDCl_3$, 100 MHz):



^{1}H NMR spectrum of compound **74** ($CDCl_3$, 400 MHz):

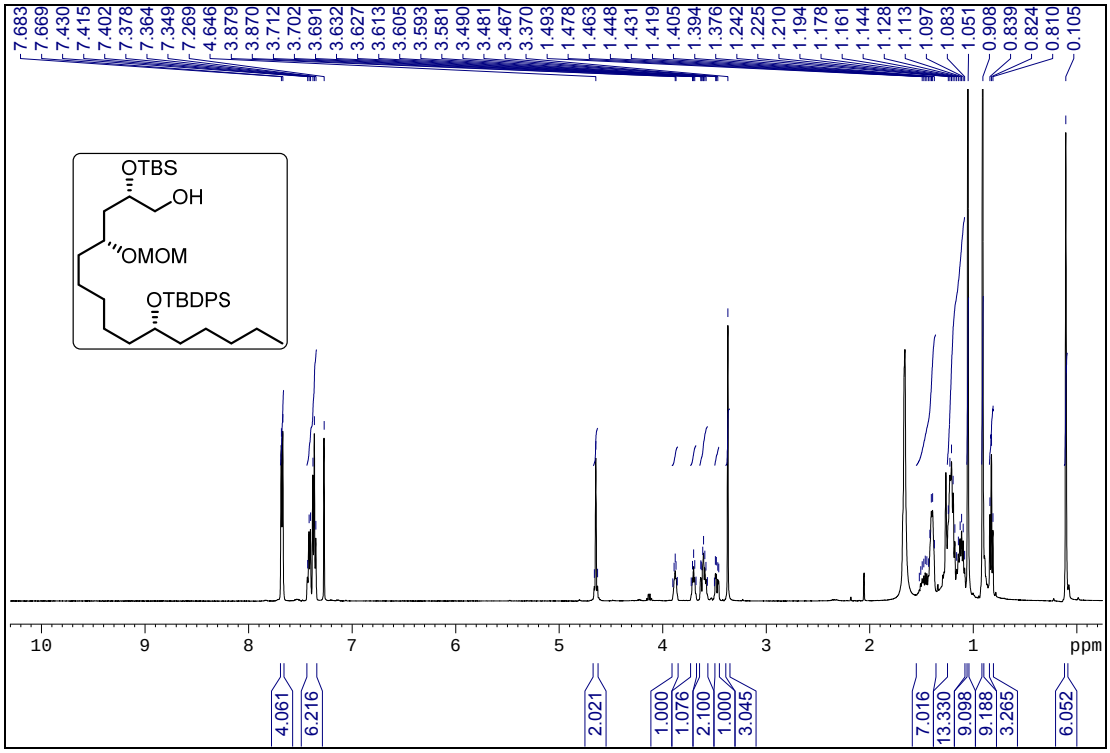


^{13}C NMR spectrum of compound **74** ($CDCl_3$, 100 MHz):

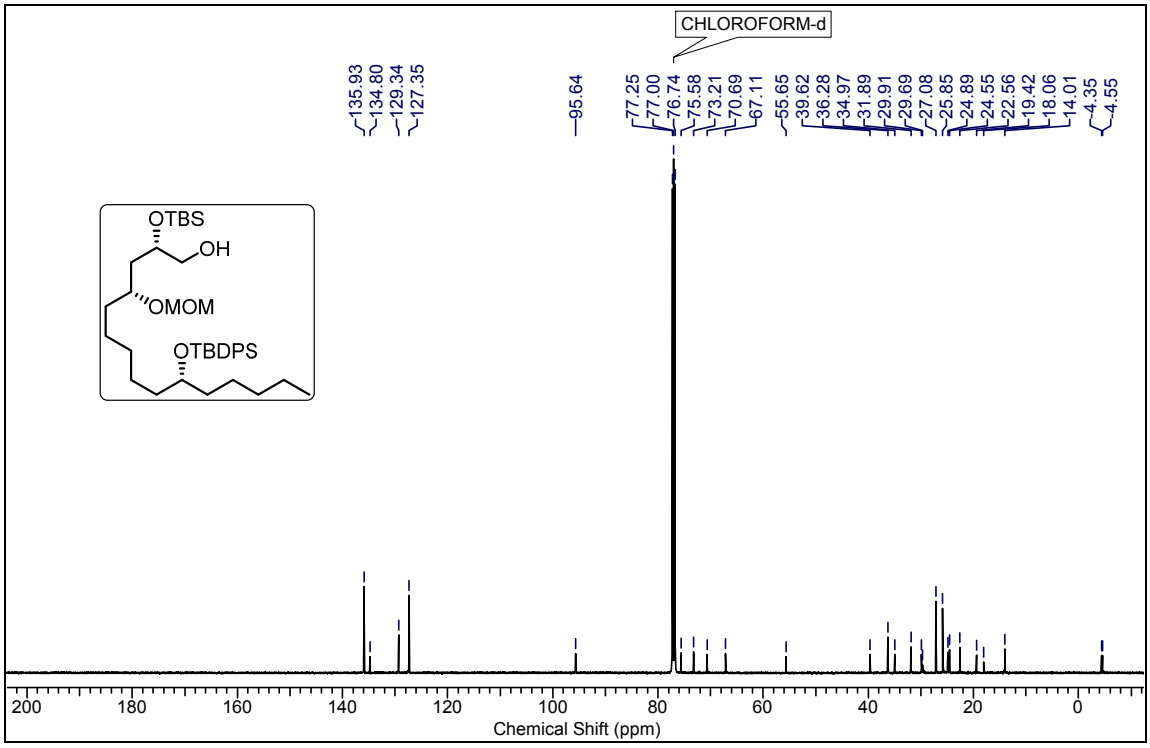


Spectra

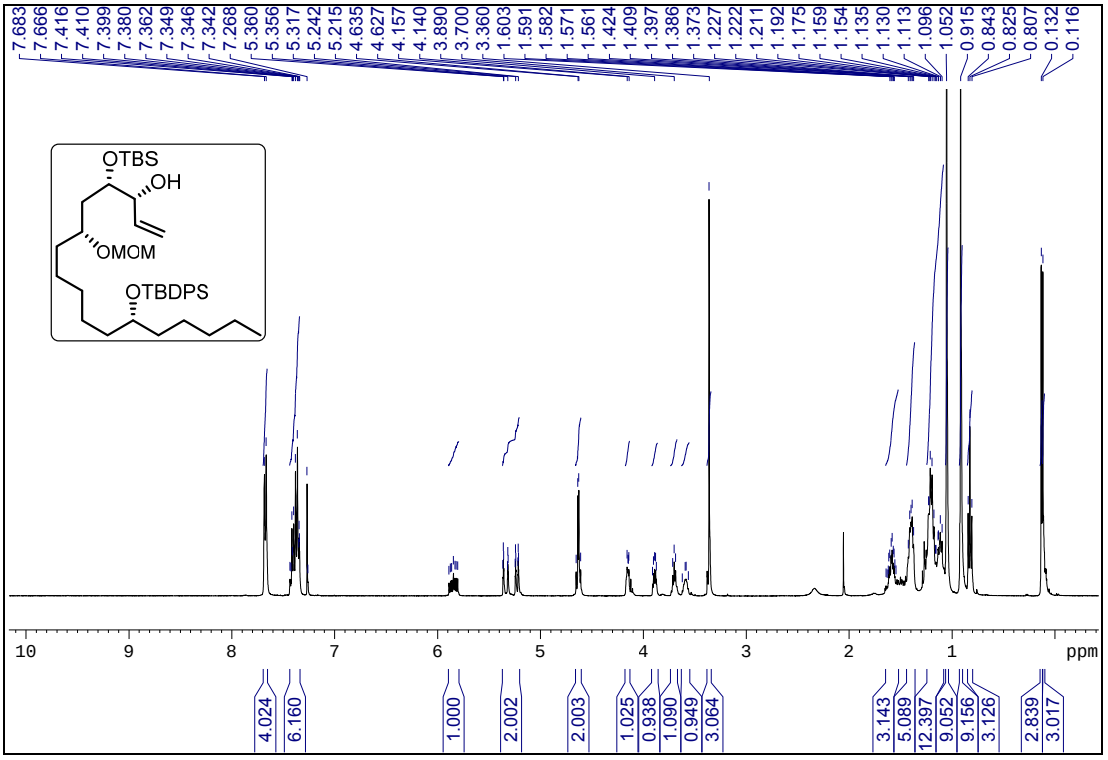
^{1}H NMR spectrum of compound **75** ($CDCl_3$, 500 MHz):



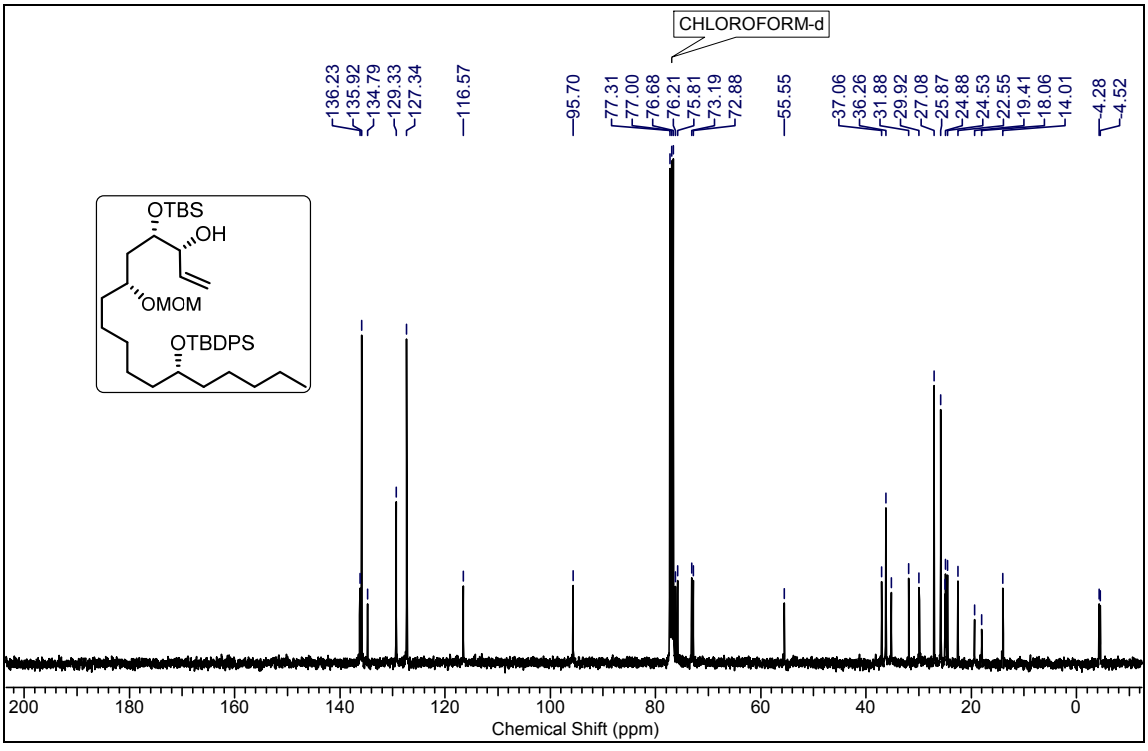
^{13}C NMR spectrum of compound **75** ($CDCl_3$, 125 MHz):



^{1}H NMR spectrum of compound **77a** ($CDCl_3$, 400 MHz):

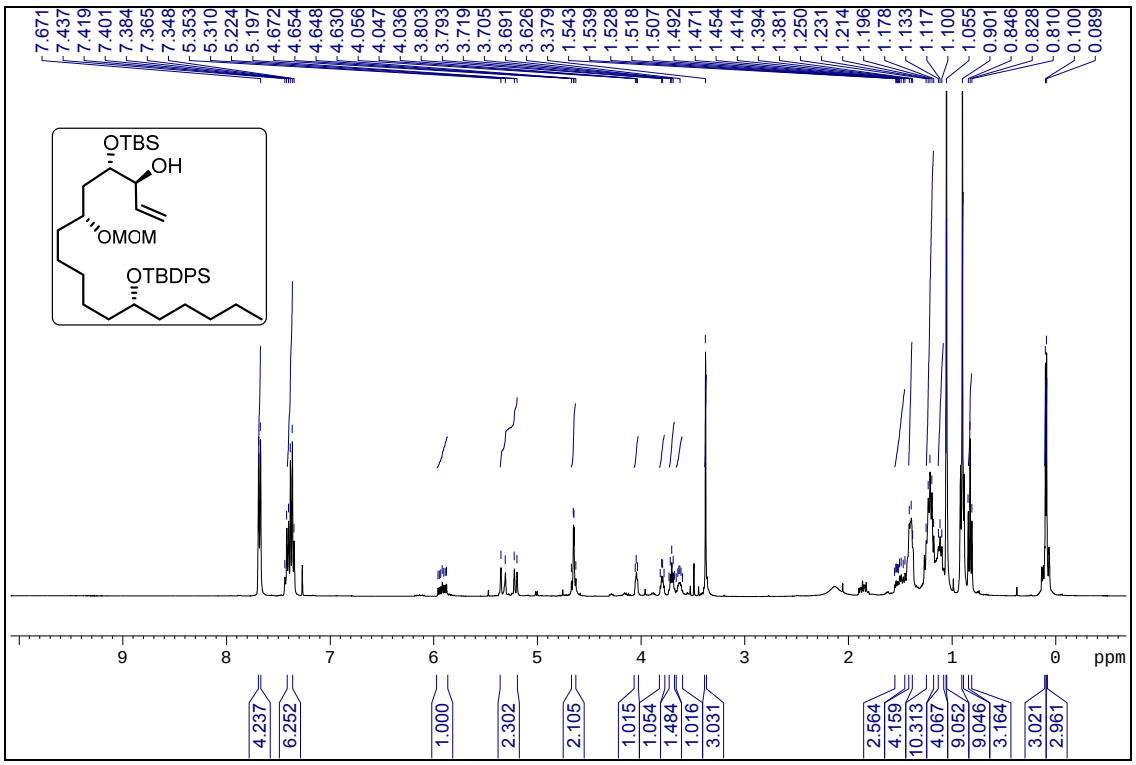


^{13}C NMR spectrum of compound **77a** ($CDCl_3$, 100 MHz):

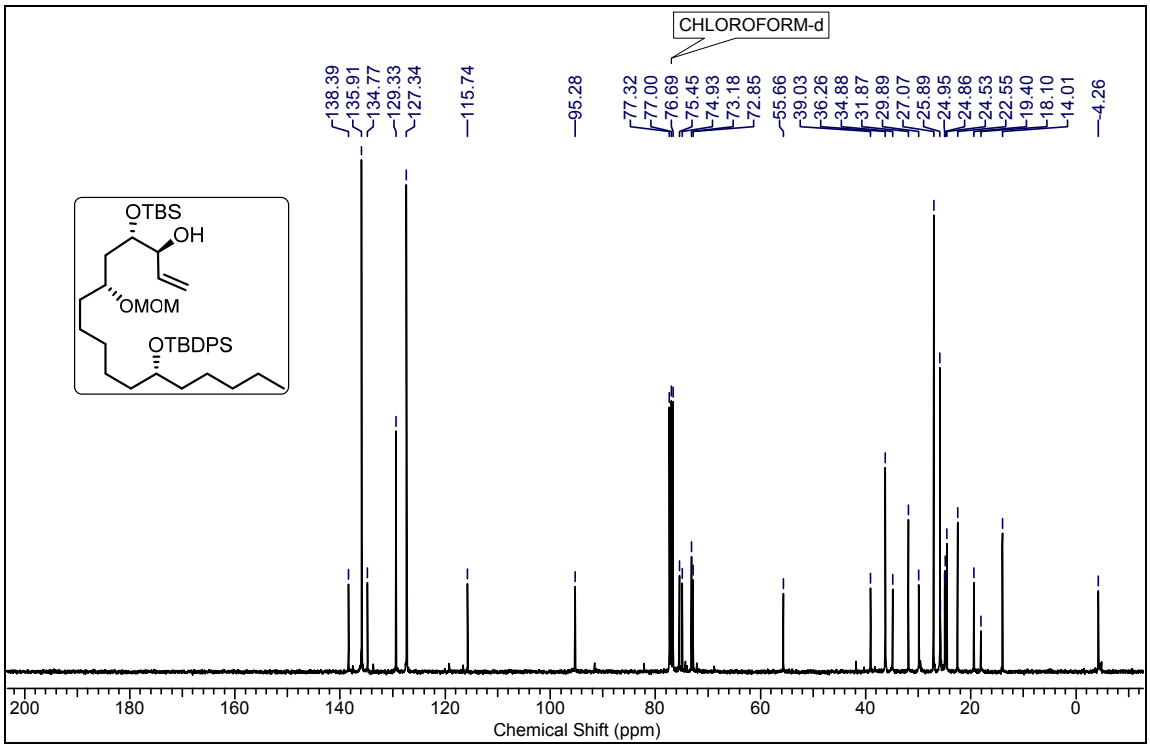


Spectra

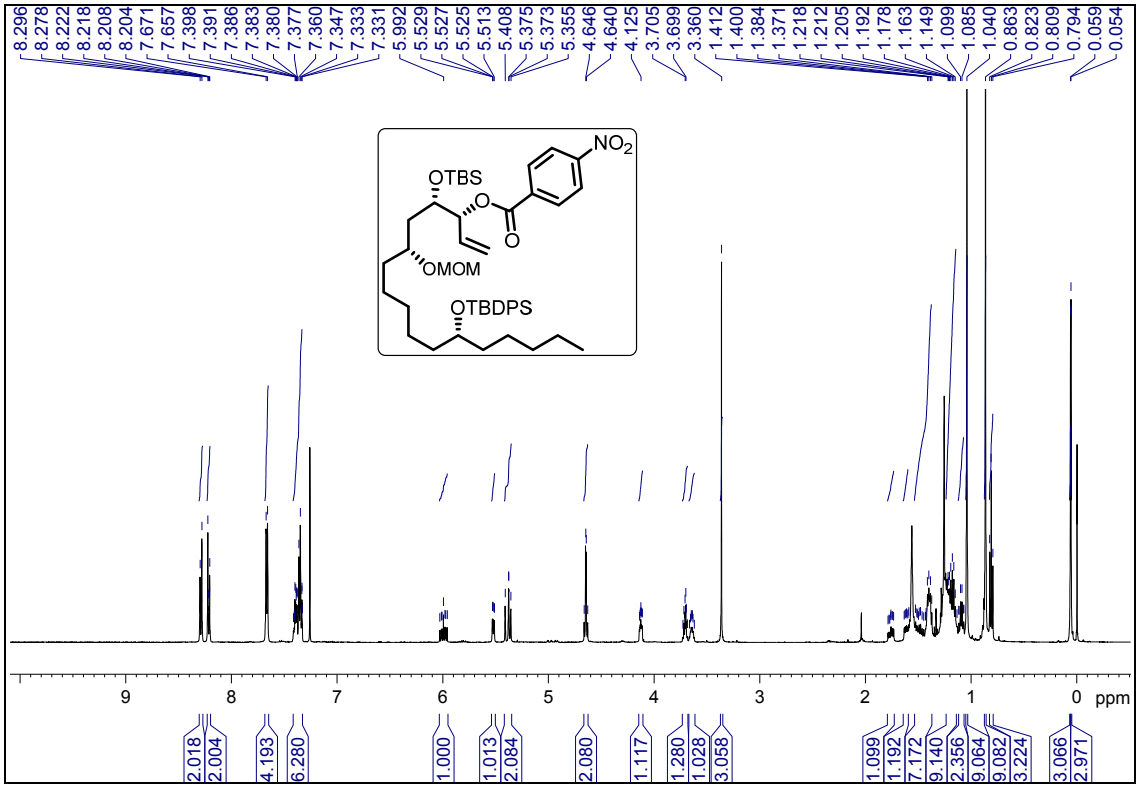
^{1}H NMR spectrum of compound **77b** ($CDCl_3$, 400 MHz):



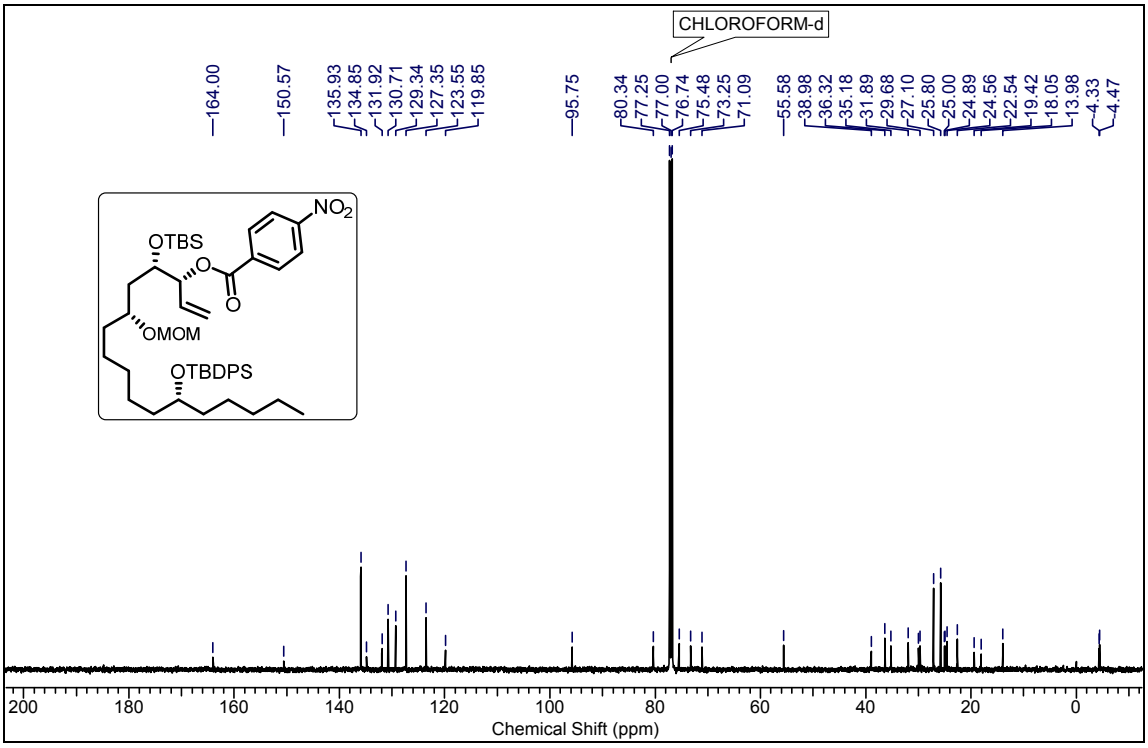
^{13}C NMR spectrum of compound **77b** ($CDCl_3$, 100 MHz):



^{1}H NMR spectrum of compound **77c** ($CDCl_3$, 500 MHz):

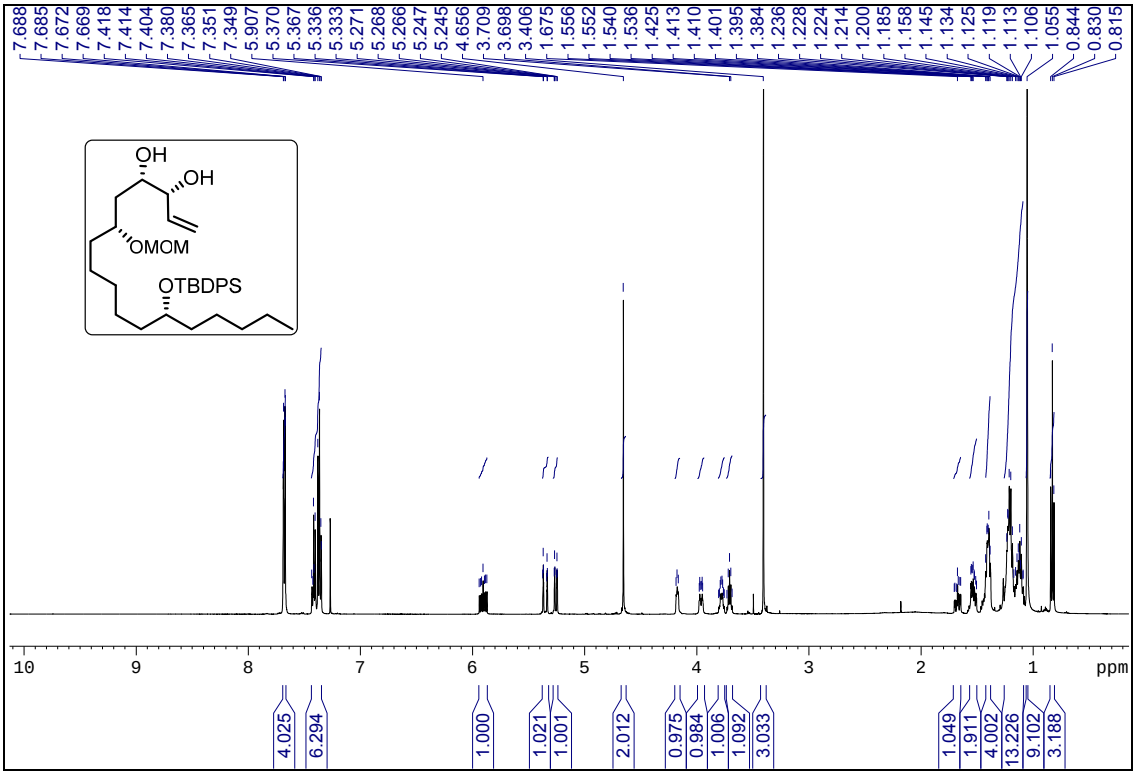


^{13}C NMR spectrum of compound **77c** ($CDCl_3$, 125 MHz):

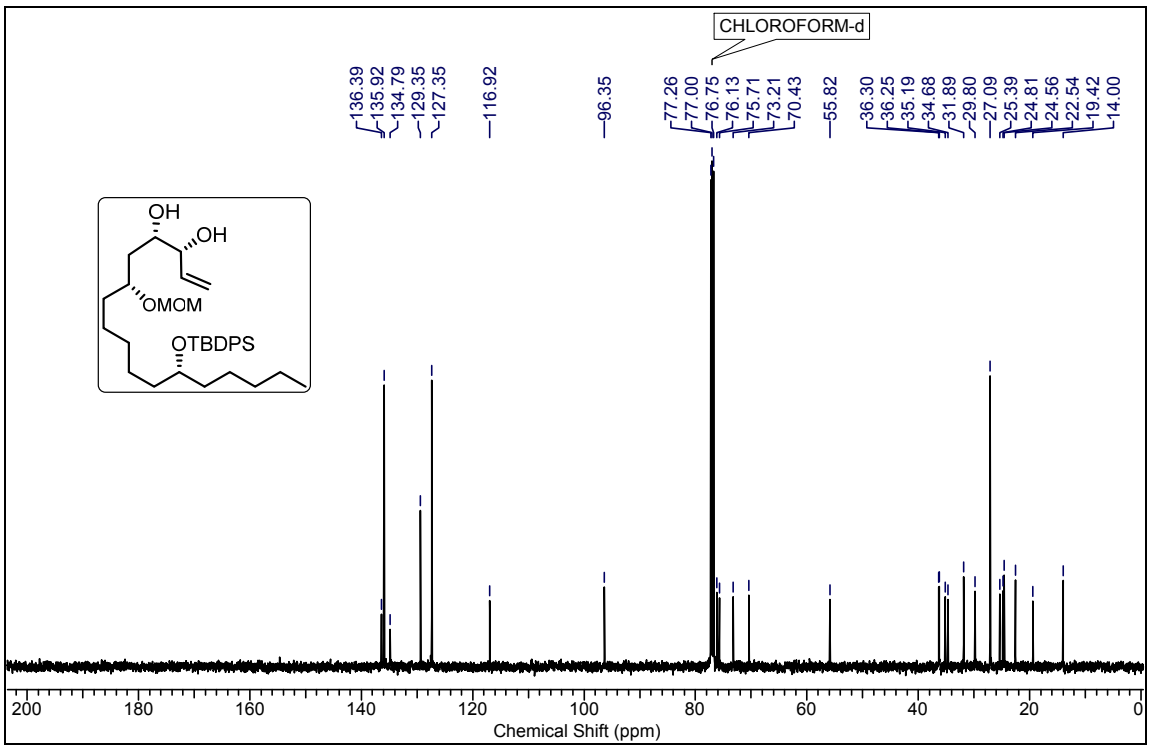


Spectra

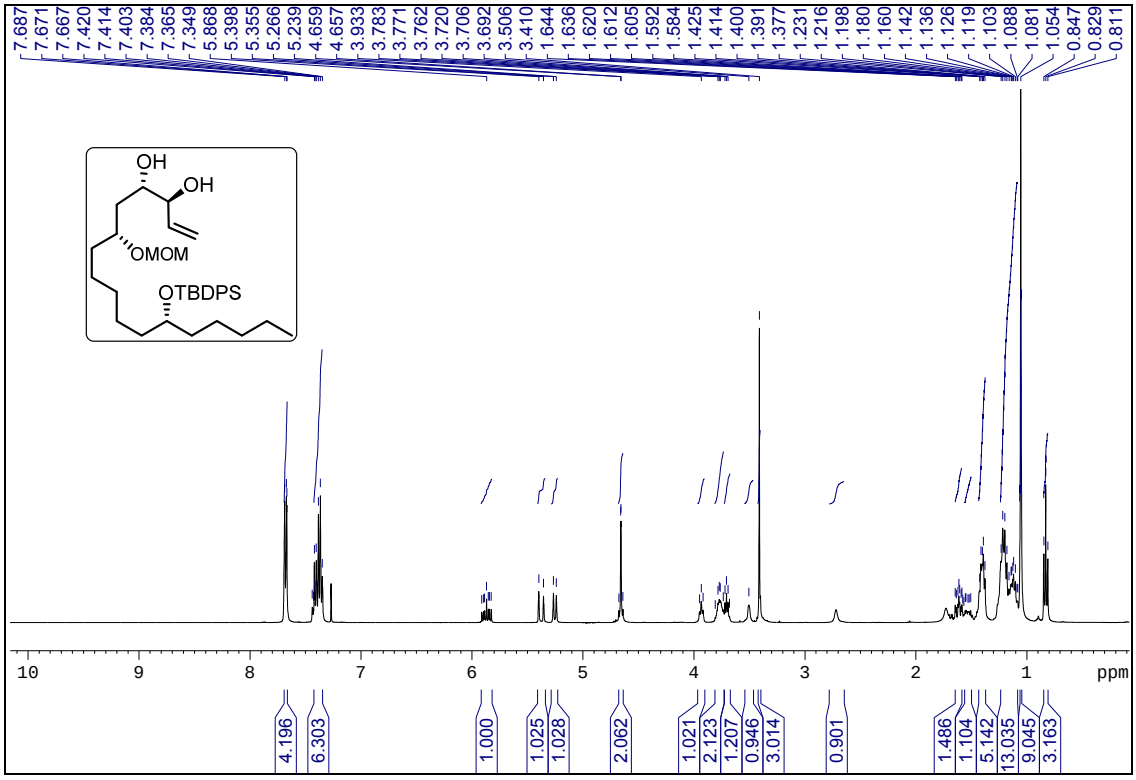
^{1}H NMR spectrum of compound **78a** ($CDCl_3$, 500 MHz):



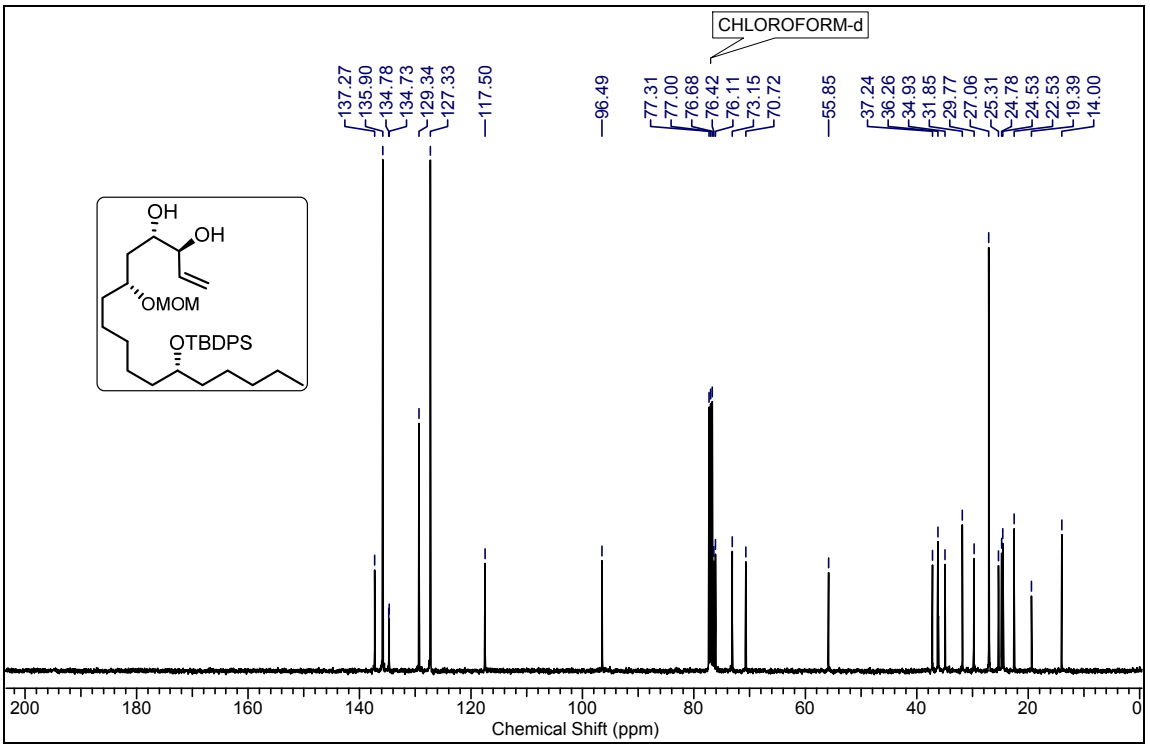
^{13}C NMR spectrum of compound **78a** ($CDCl_3$, 125 MHz):



^{1}H NMR spectrum of compound **78b** ($CDCl_3$, 400 MHz):

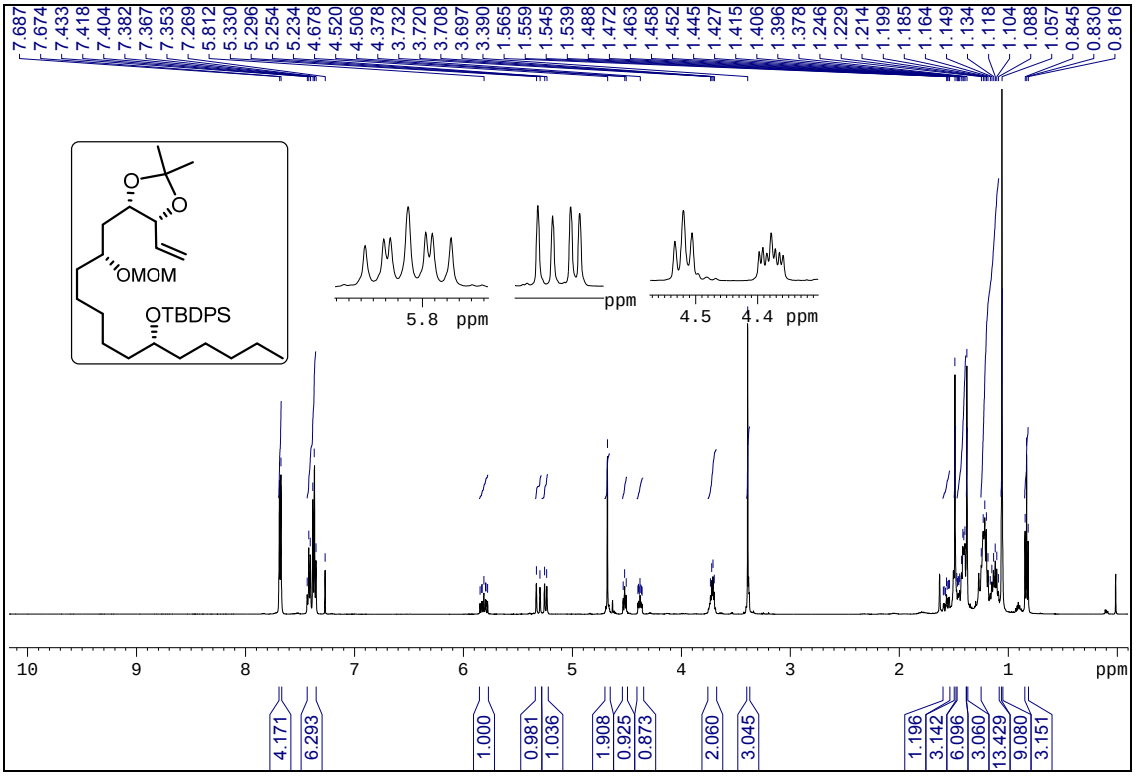


^{13}C NMR spectrum of compound **78b** ($CDCl_3$, 100 MHz):

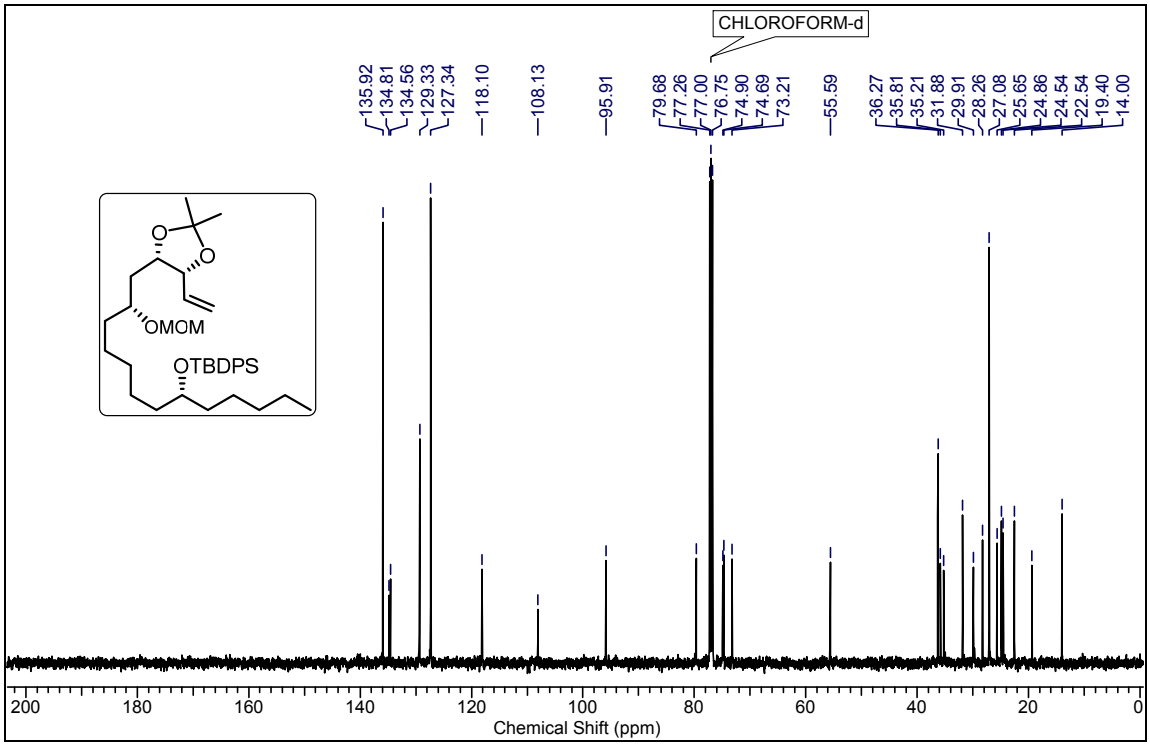


Spectra

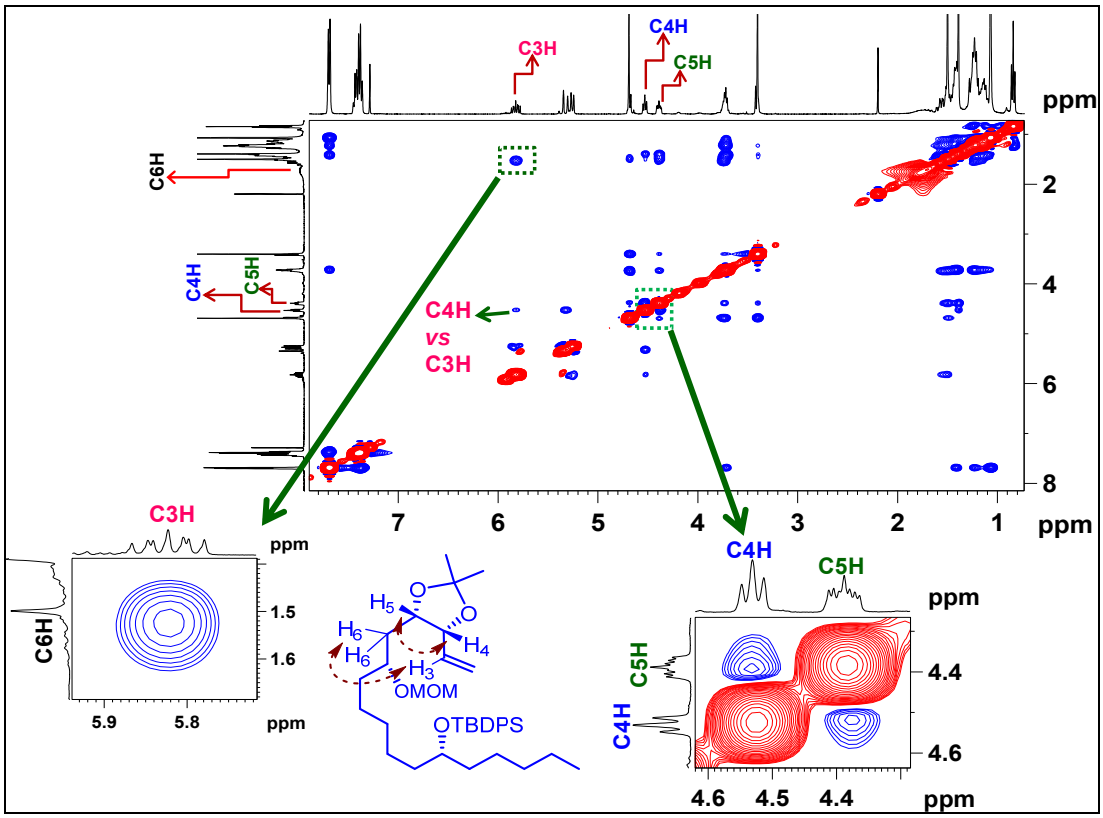
^{1}H NMR spectrum of compound **79a** ($CDCl_3$, 500 MHz):



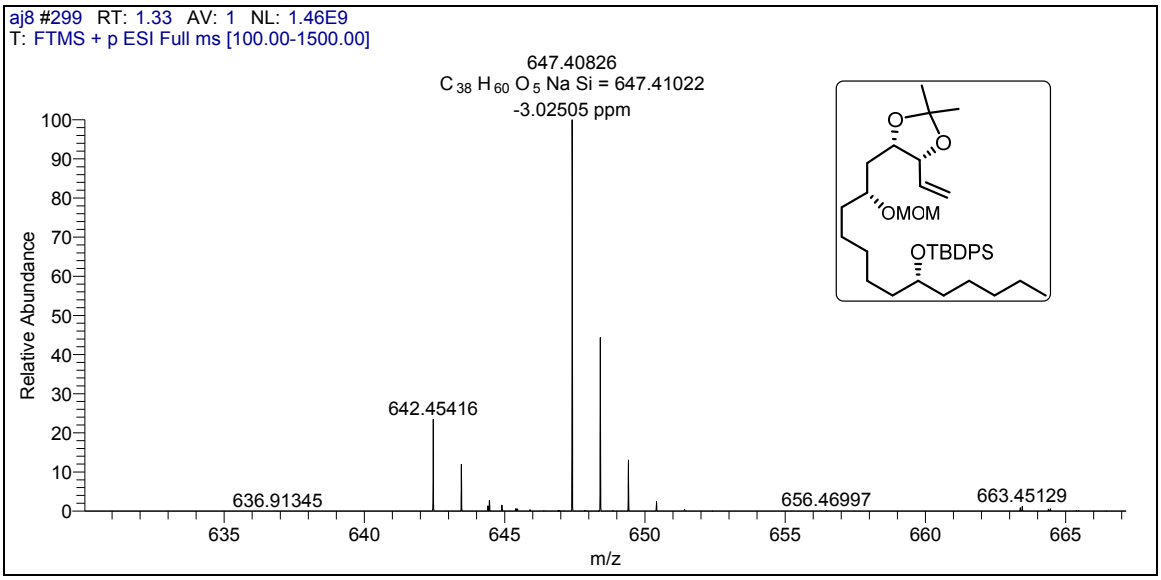
^{13}C NMR spectrum of compound **79a** ($CDCl_3$, 125 MHz):



2D NOESY full spectrum of compound **79a** and excerpt showing the *syn* geometry of C^4H and C^5H:

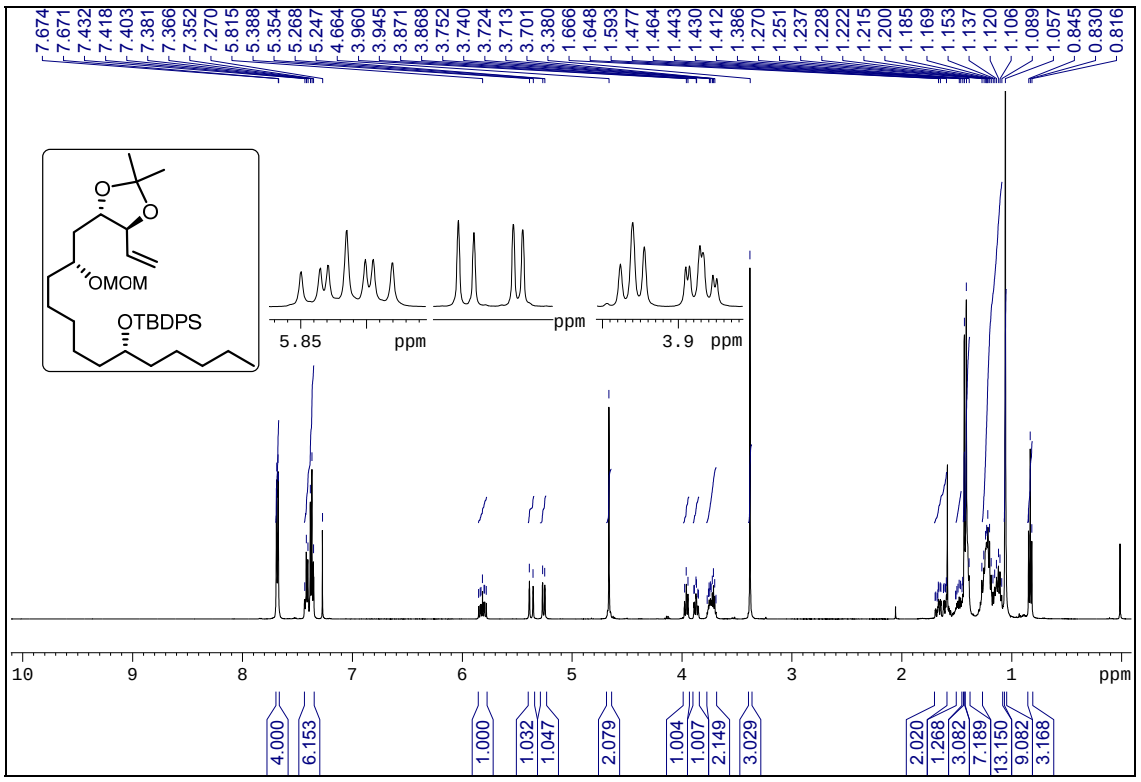


HR-ESI(+)-MS spectrum of compound **79a**:

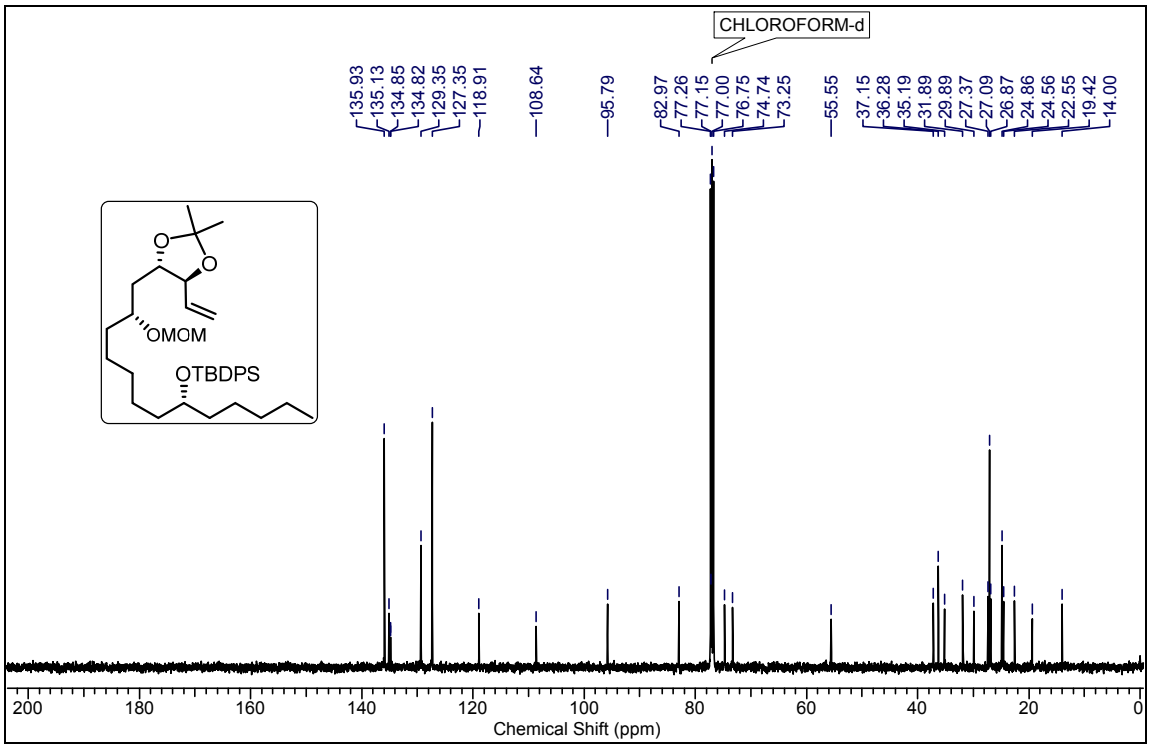


Spectra

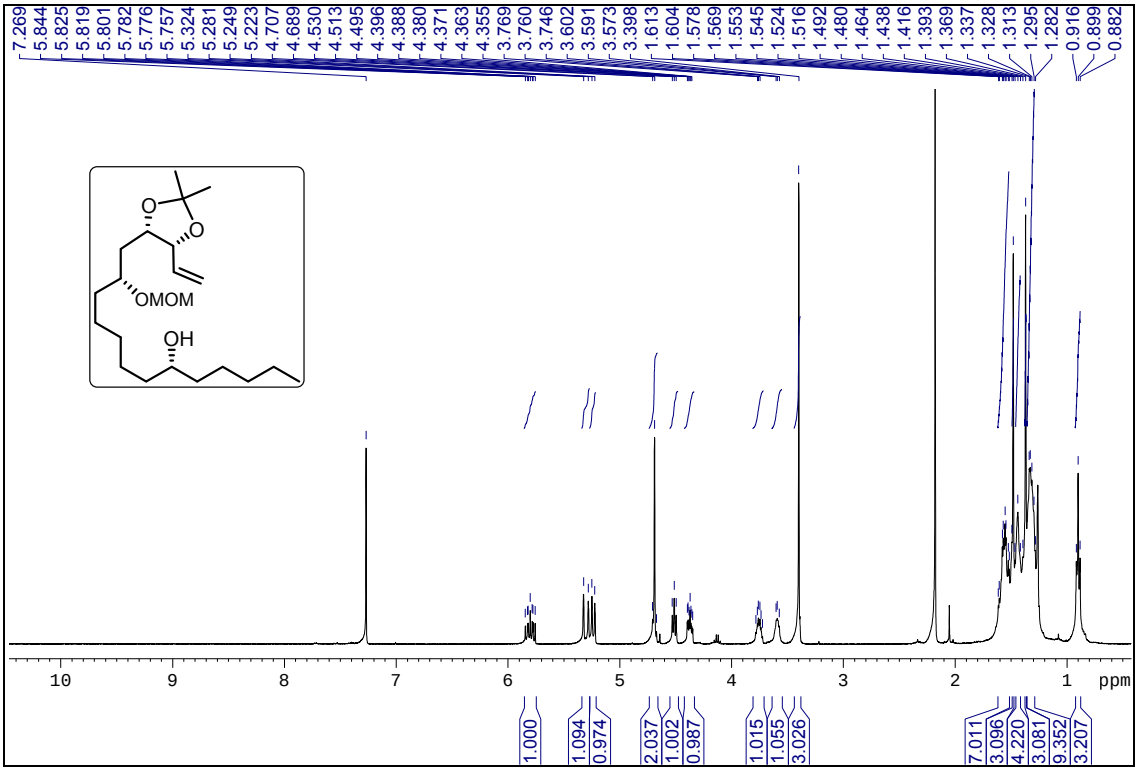
^{1}H NMR spectrum of compound **79b** ($CDCl_3$, 500 MHz):



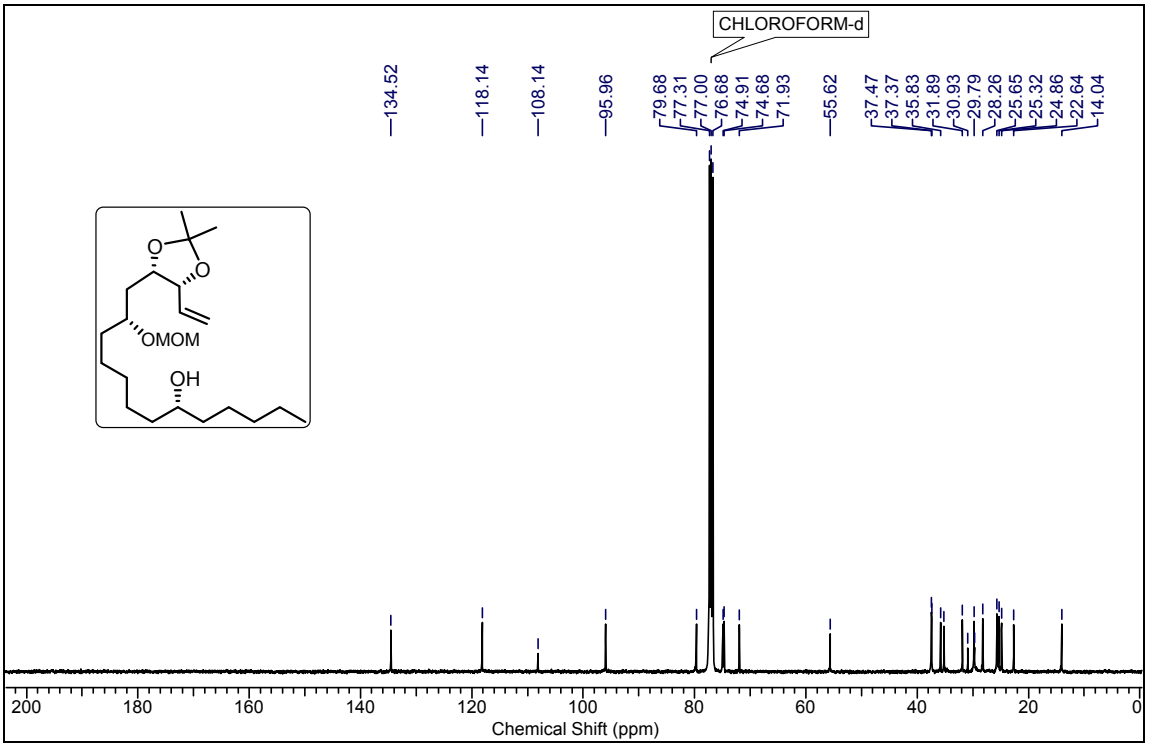
^{13}C NMR spectrum of compound **79b** ($CDCl_3$, 125 MHz):



^{1}H NMR spectrum of compound **80a** ($CDCl_3$, 400 MHz):

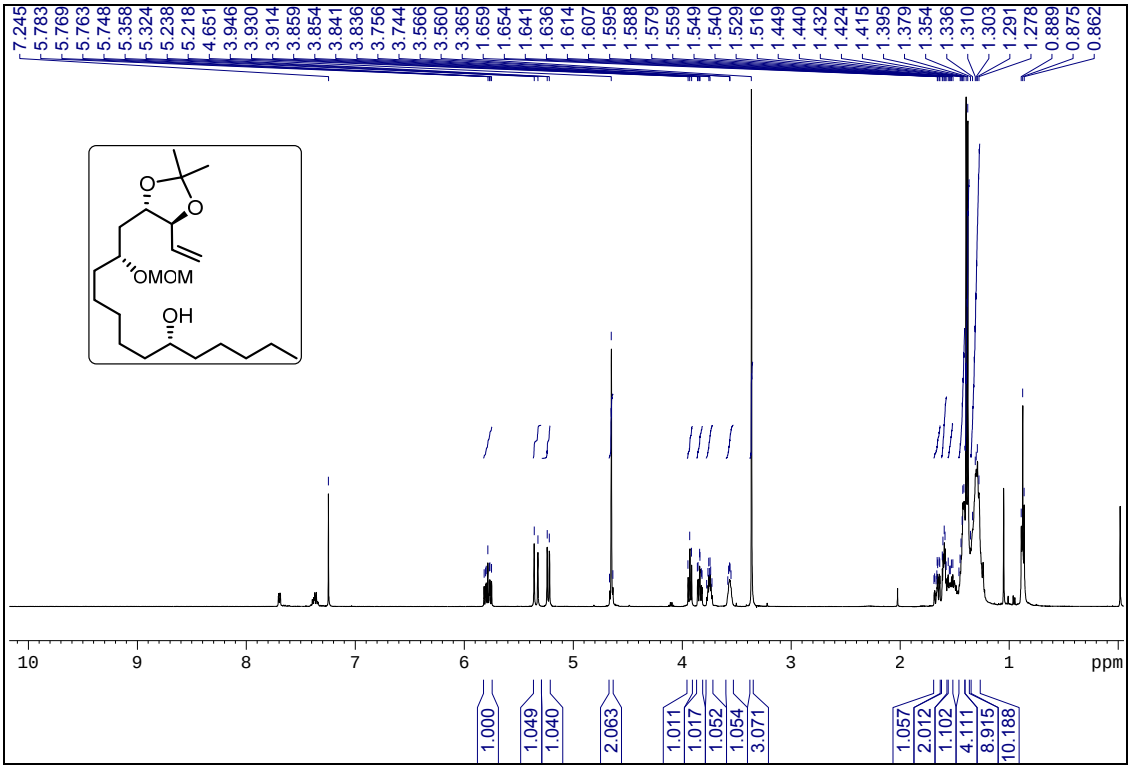


^{13}C NMR spectrum of compound **80a** ($CDCl_3$, 100 MHz):

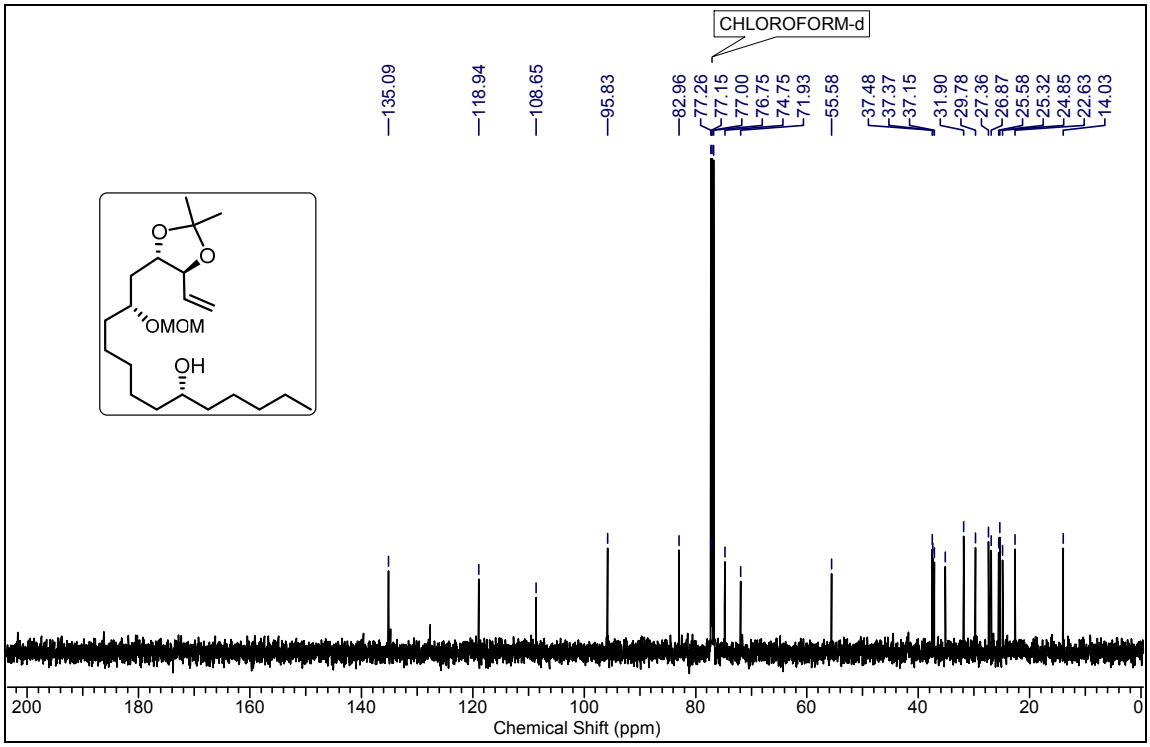


Spectra

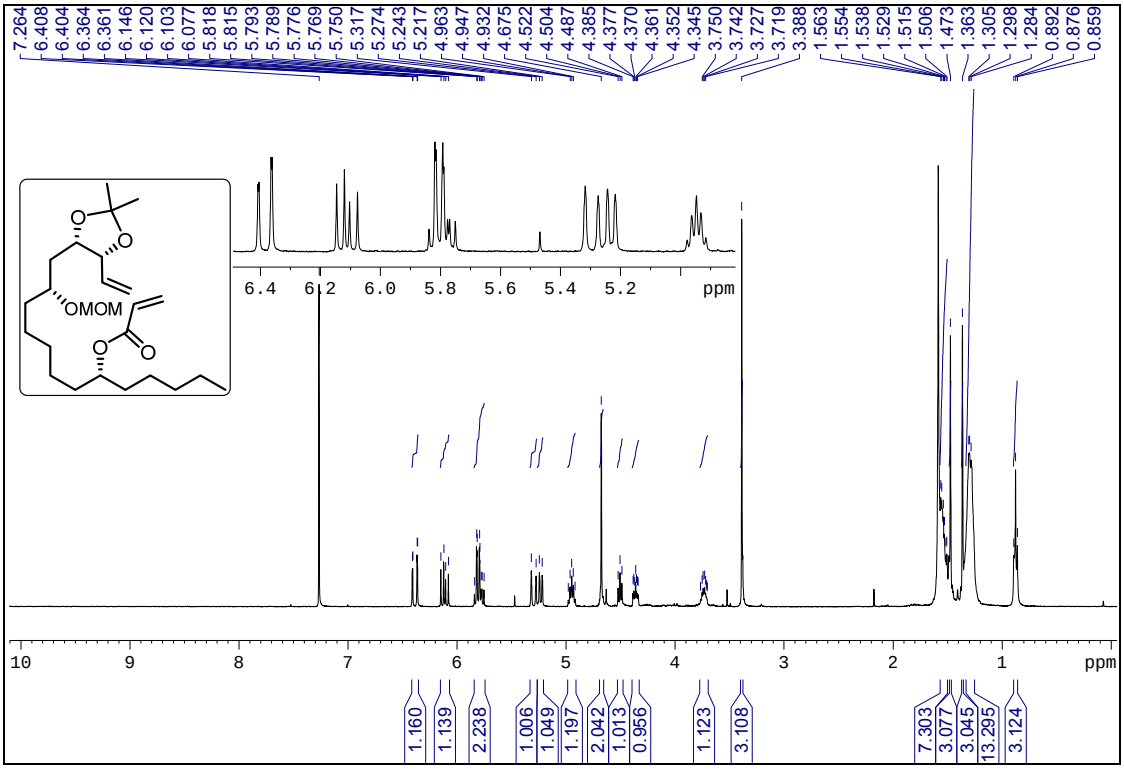
^{1}H NMR spectrum of compound **80b** ($CDCl_3$, 500 MHz):



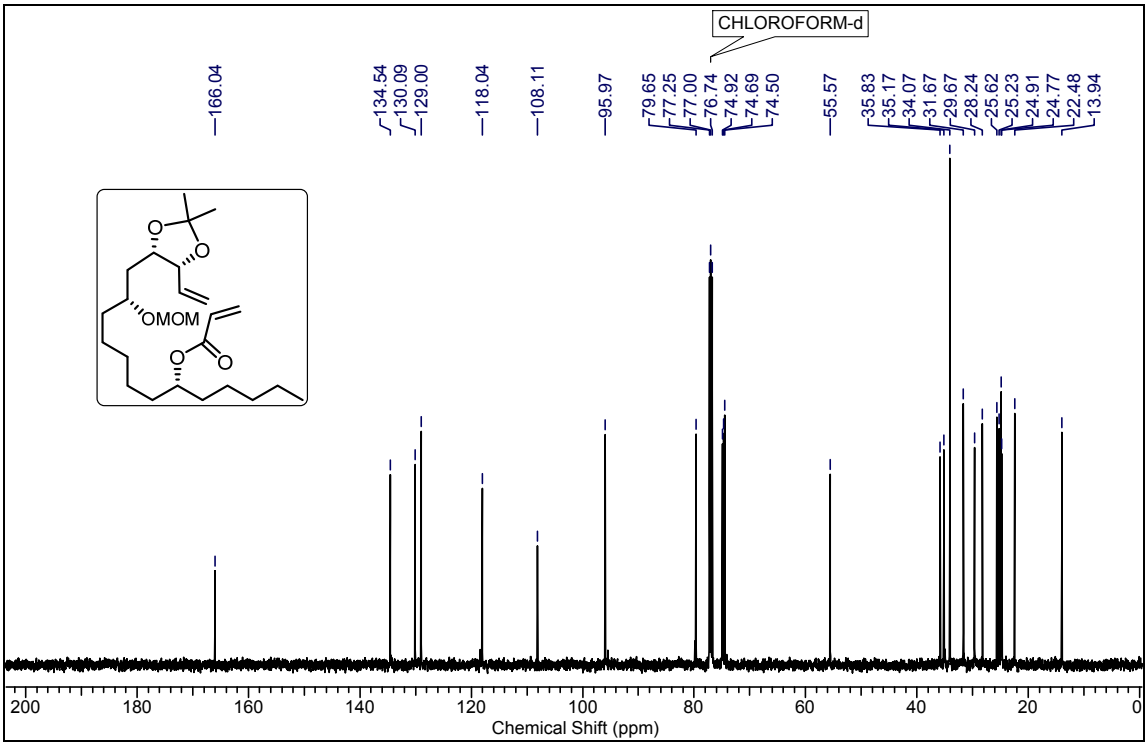
^{13}C NMR spectrum of compound **80b** ($CDCl_3$, 125 MHz):



^{1}H NMR spectrum of compound **81a** ($CDCl_3$, 400 MHz):

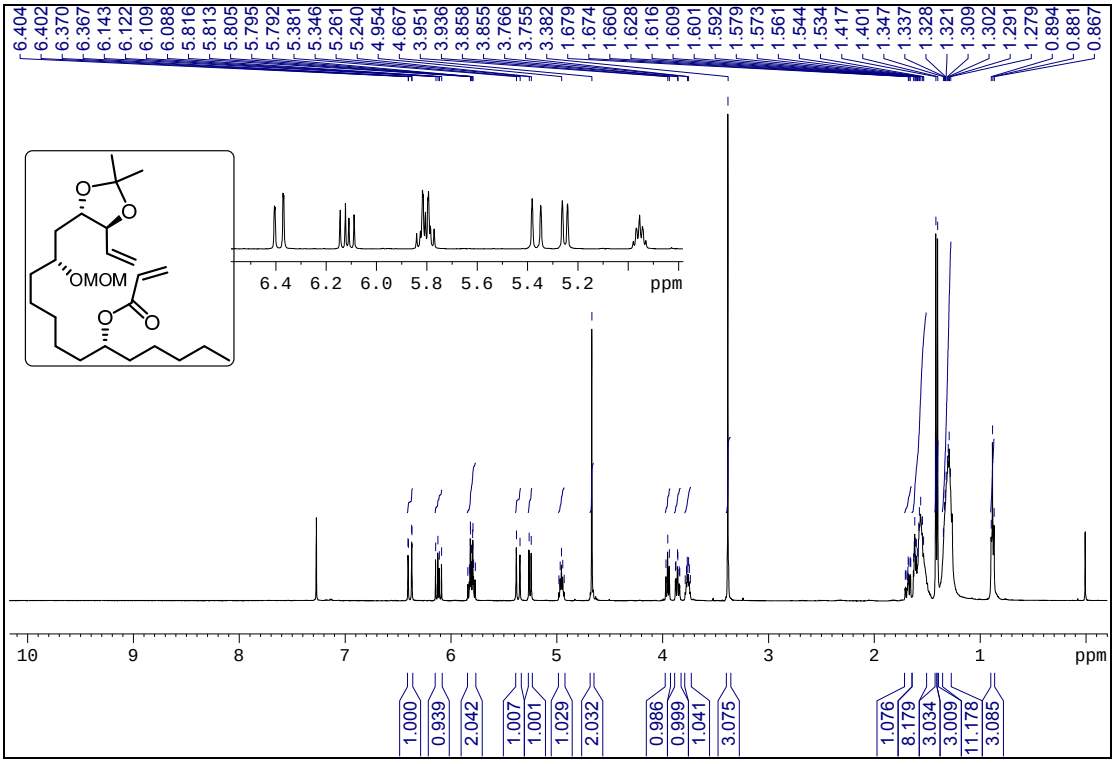


^{13}C NMR spectrum of compound **81a** ($CDCl_3$, 125 MHz):

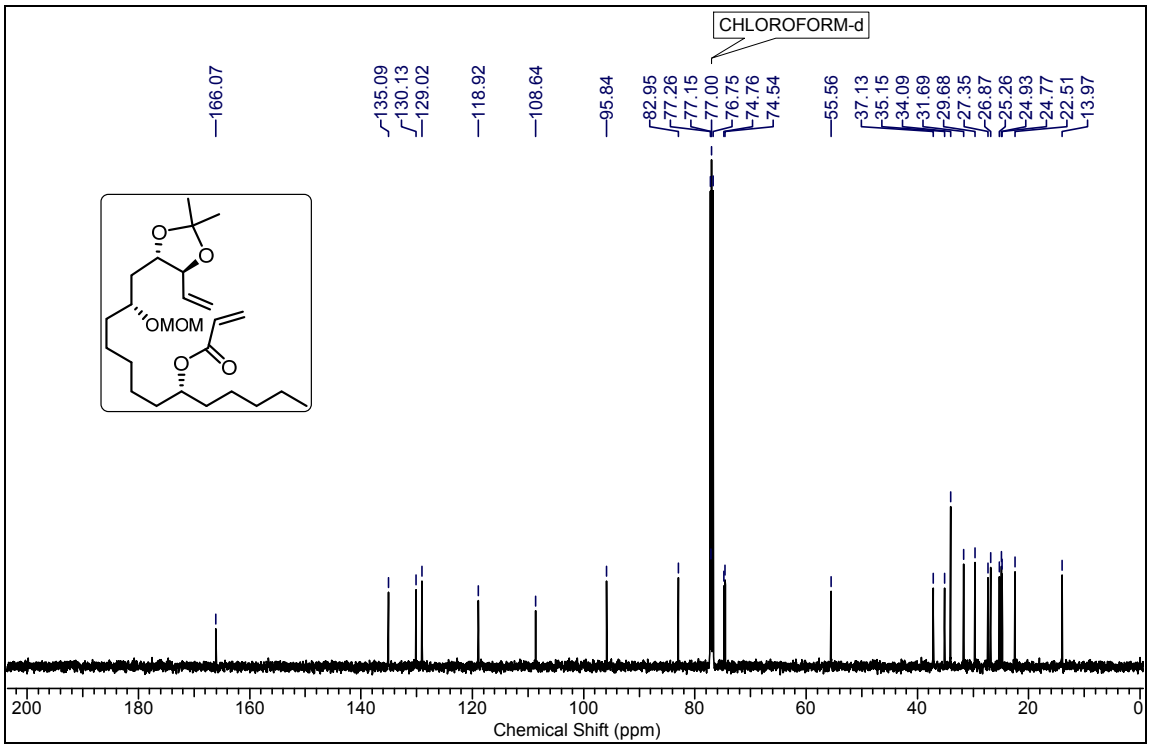


Spectra

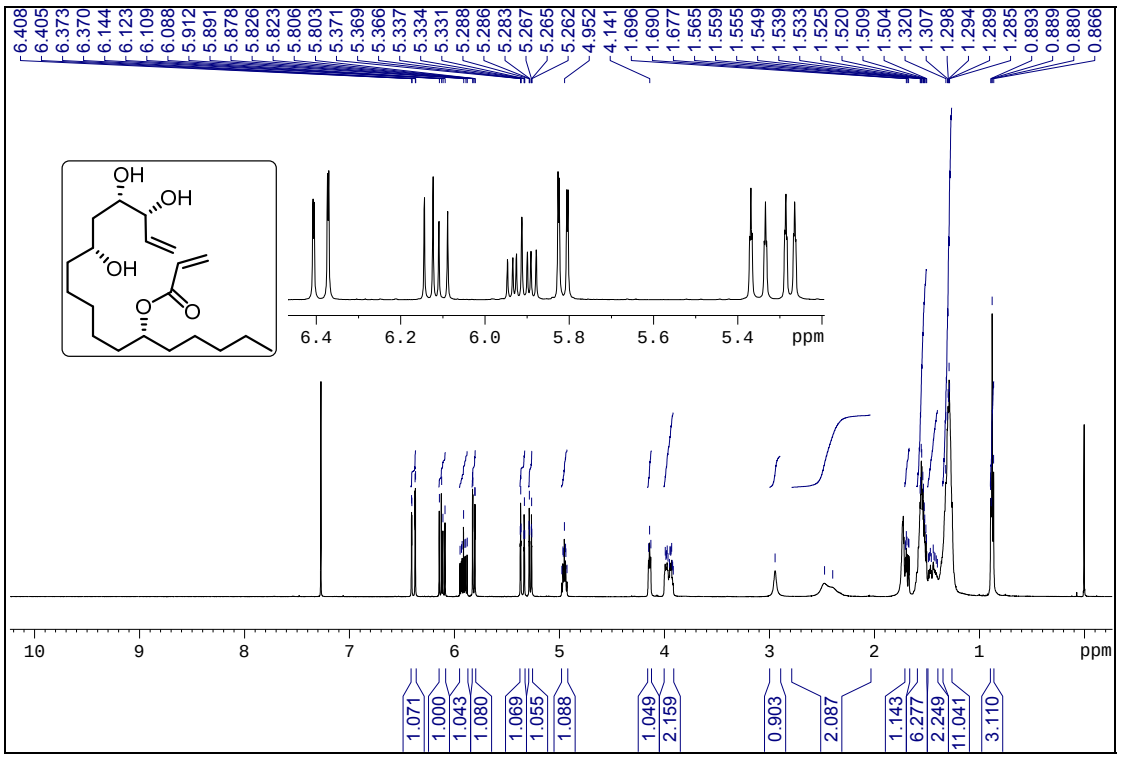
^{1}H NMR spectrum of compound **81b** ($CDCl_3$, 500 MHz):



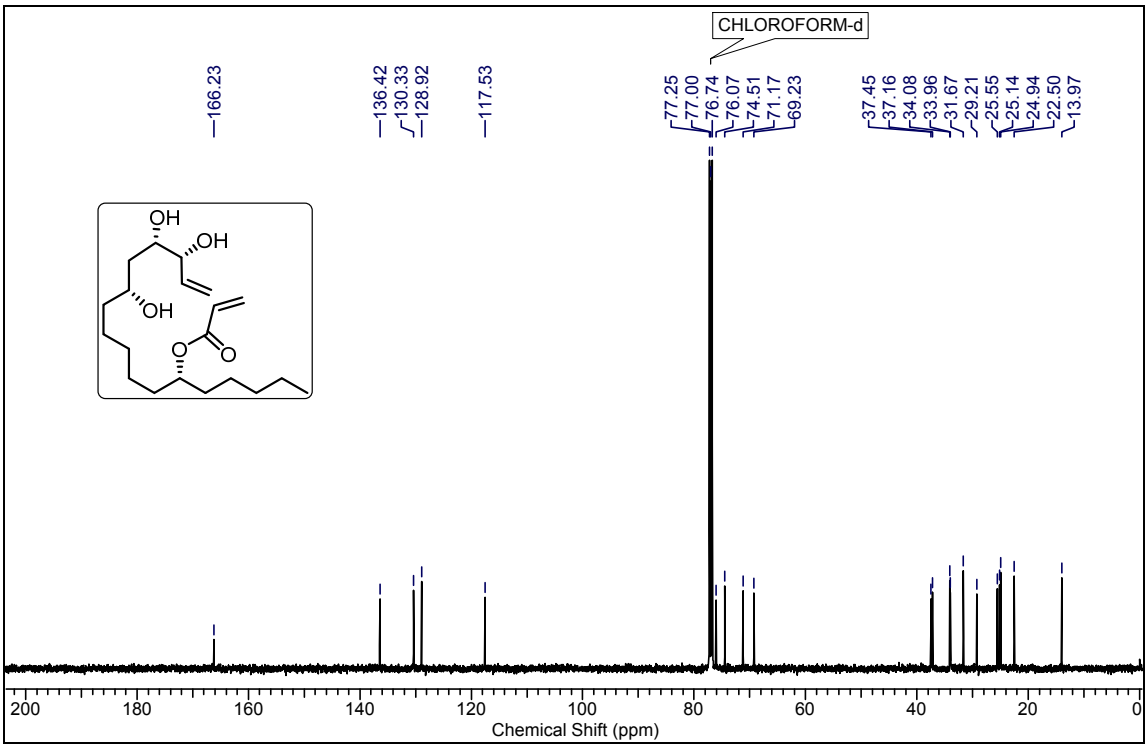
^{13}C NMR spectrum of compound **81b** ($CDCl_3$, 125 MHz):



^{1}H NMR spectrum of compound **82a** ($CDCl_3$, 500 MHz):

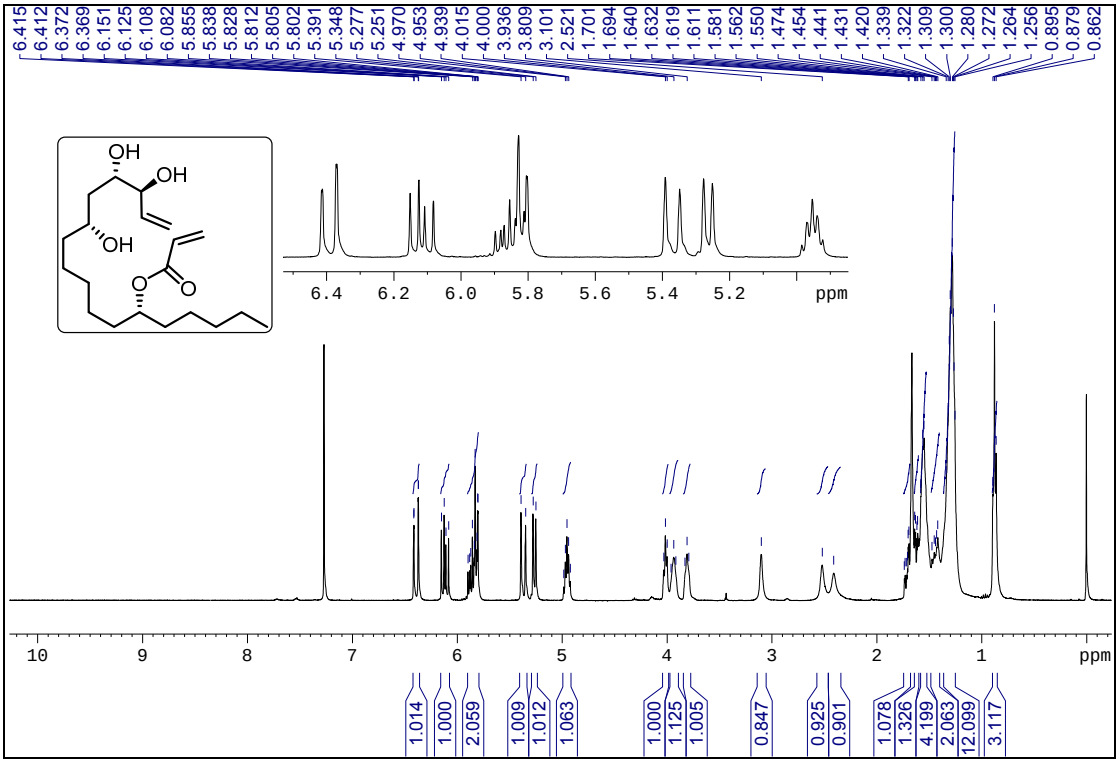


^{13}C NMR spectrum of compound **82a** ($CDCl_3$, 125 MHz):

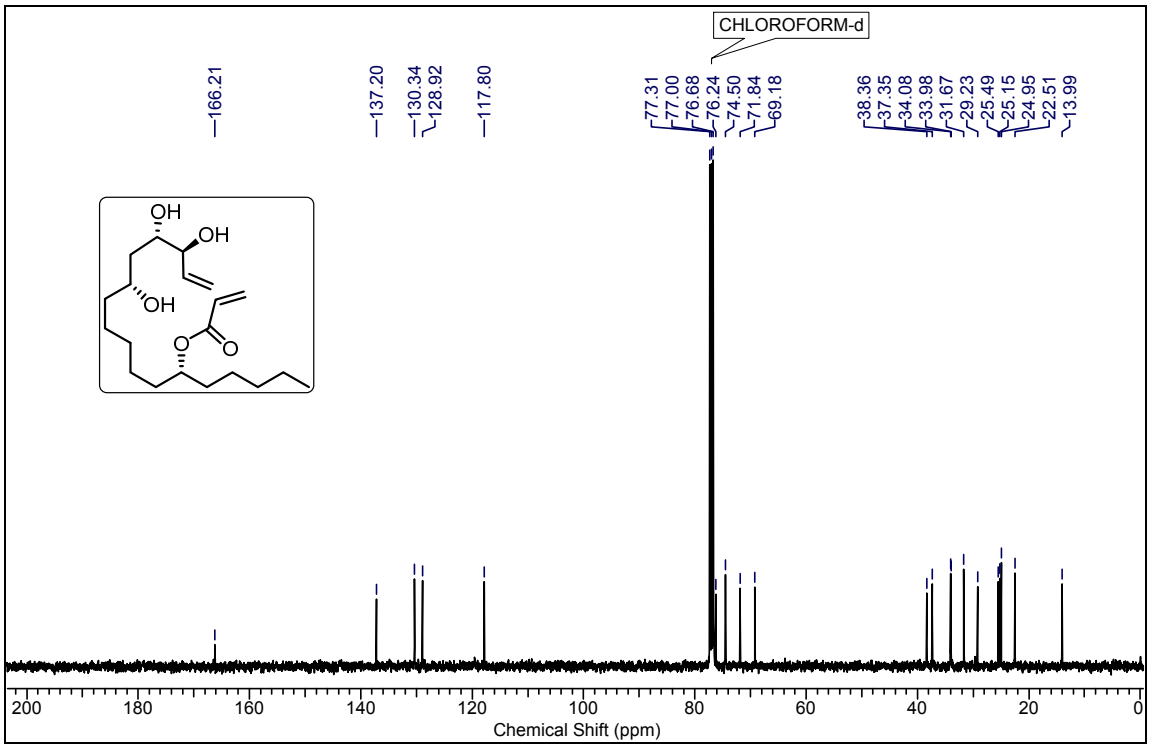


Spectra

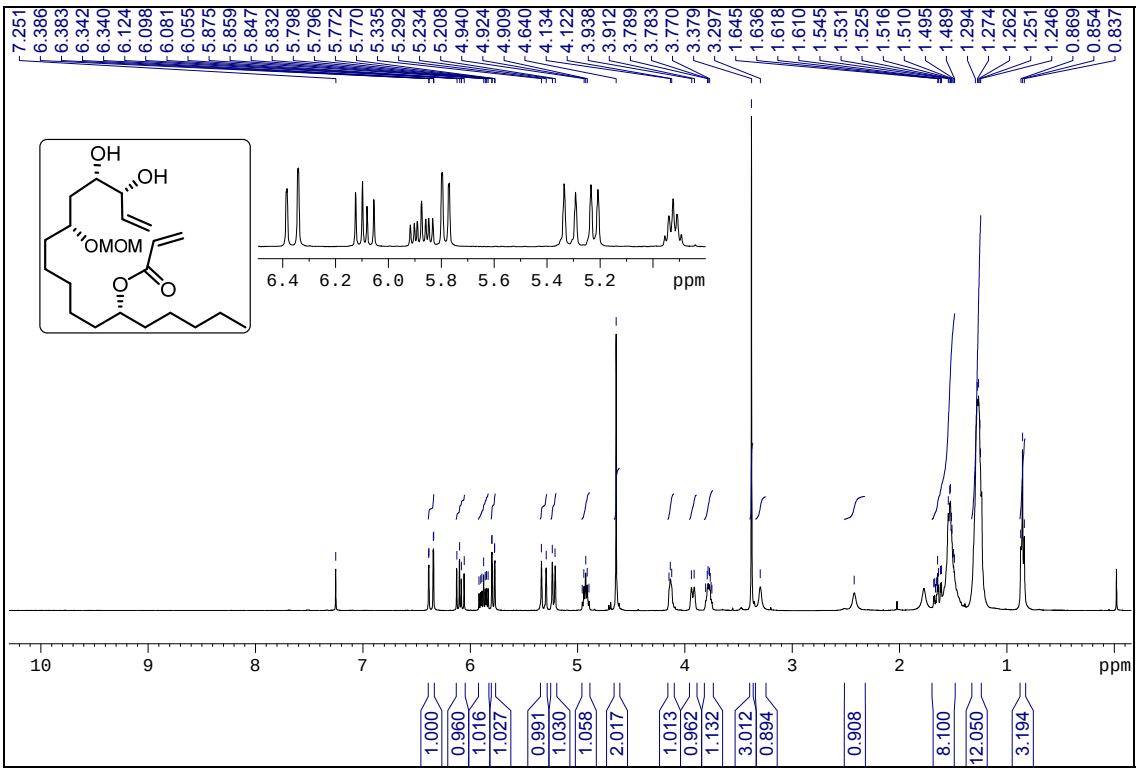
^{1}H NMR spectrum of compound **82b** ($CDCl_3$, 400 MHz):



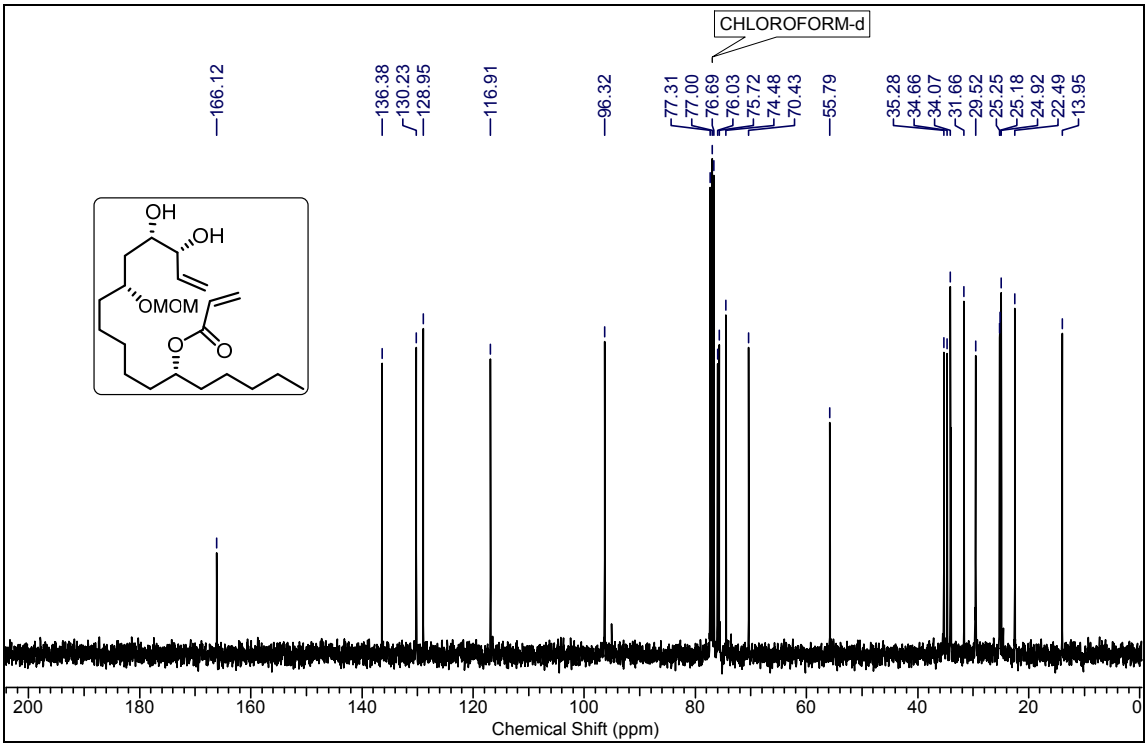
^{13}C NMR spectrum of compound **82b** ($CDCl_3$, 100 MHz):



^{1}H NMR spectrum of compound **83** ($CDCl_3$, 400 MHz):

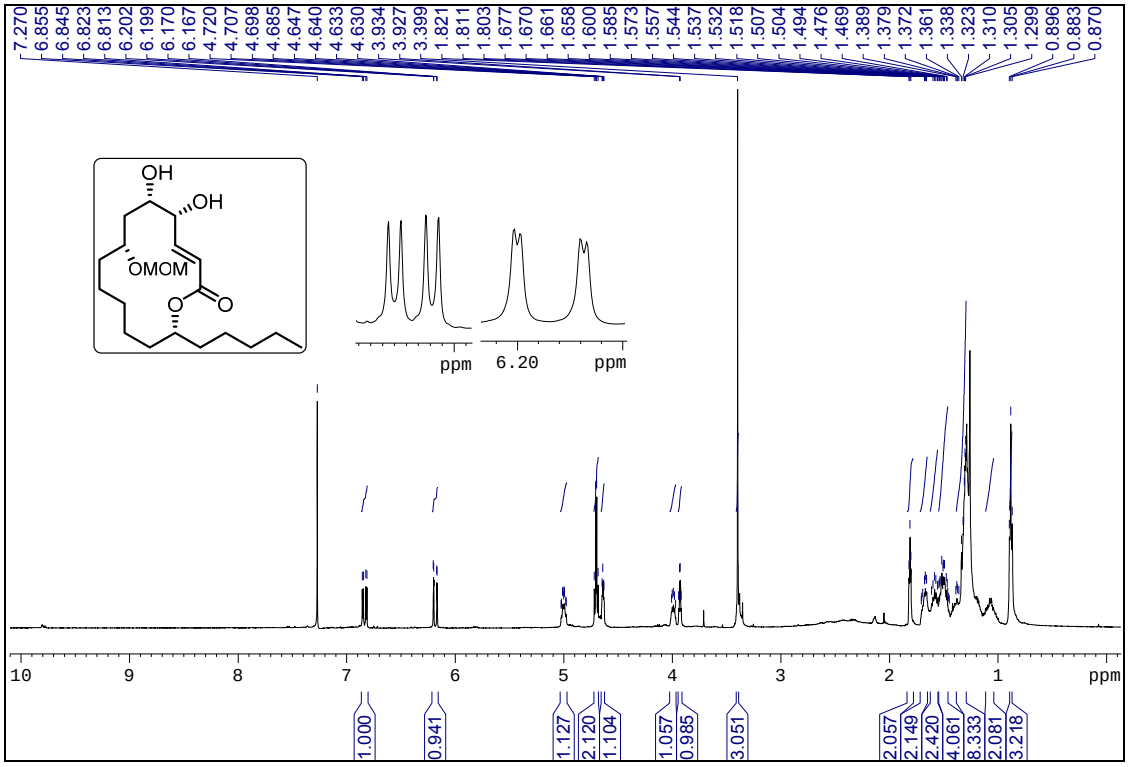


^{13}C NMR spectrum of compound **83** ($CDCl_3$, 100 MHz):

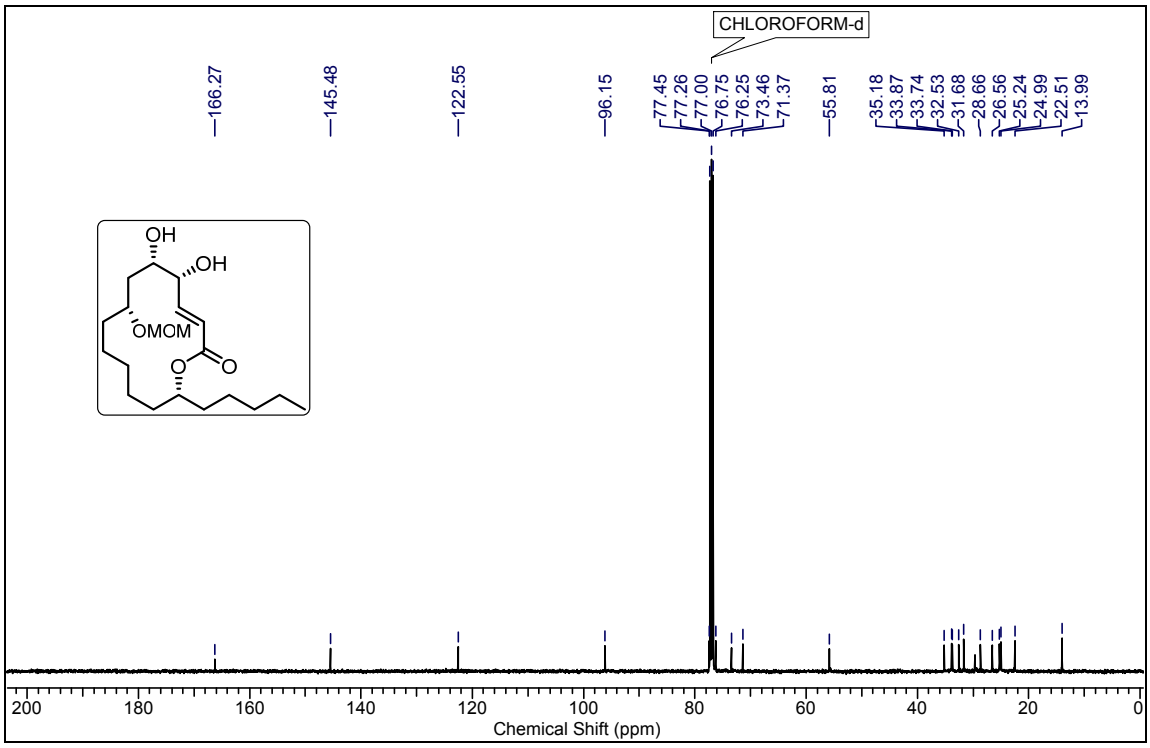


Spectra

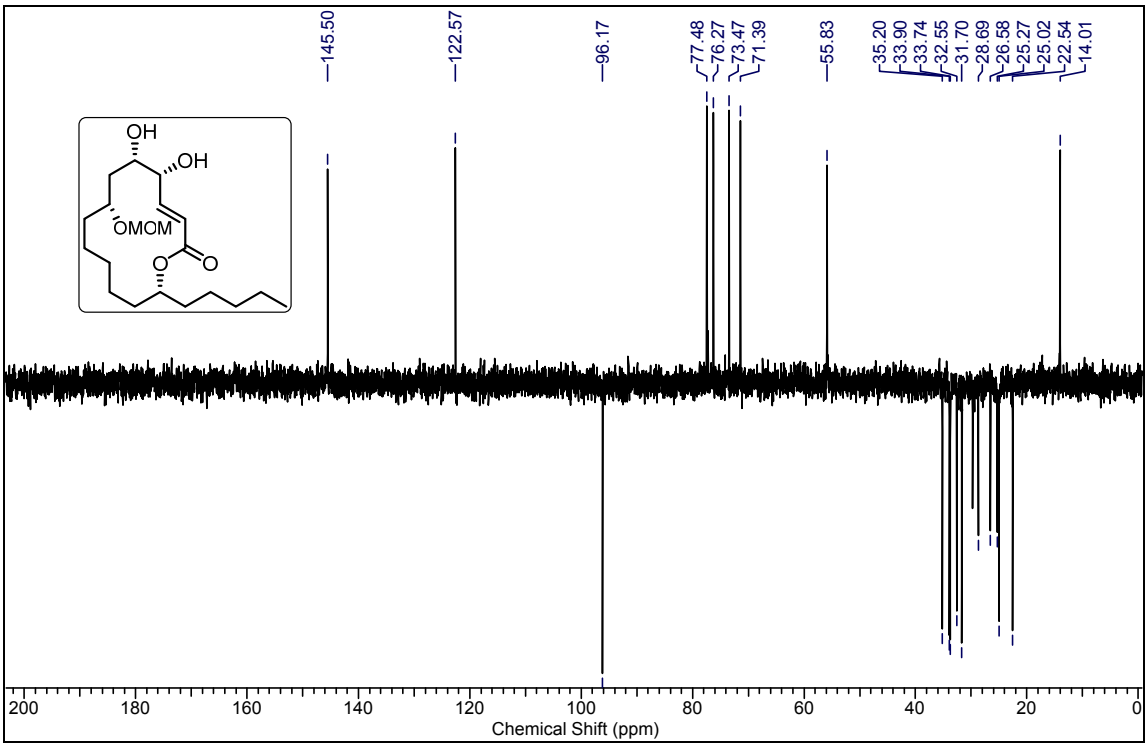
^{1}H NMR spectrum of compound **84** ($CDCl_3$, 500 MHz):



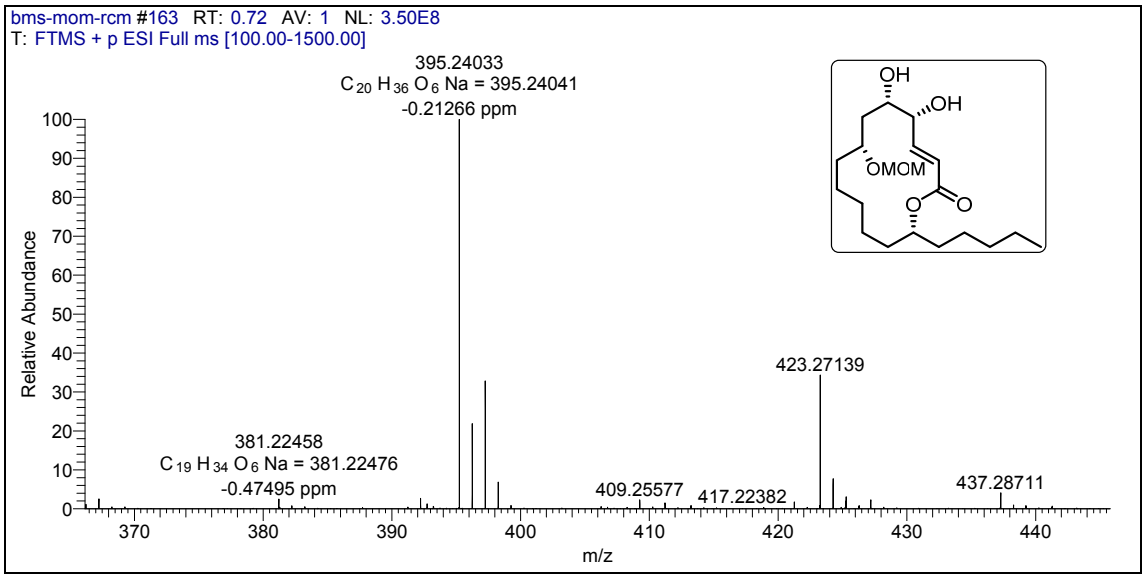
^{13}C NMR spectrum of compound **84** ($CDCl_3$, 125 MHz):



DEPT-135 NMR spectrum of compound **84** ($CDCl_3$, 100 MHz):

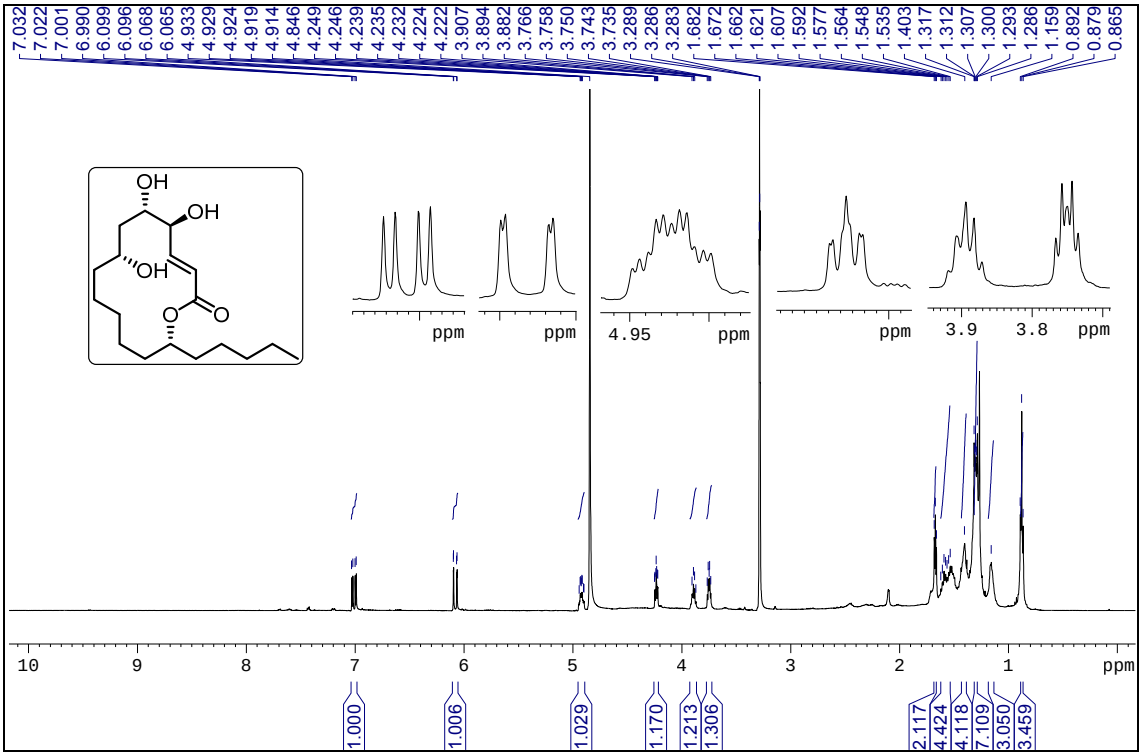


HR-ESI(+)-MS spectrum of compound **84**:

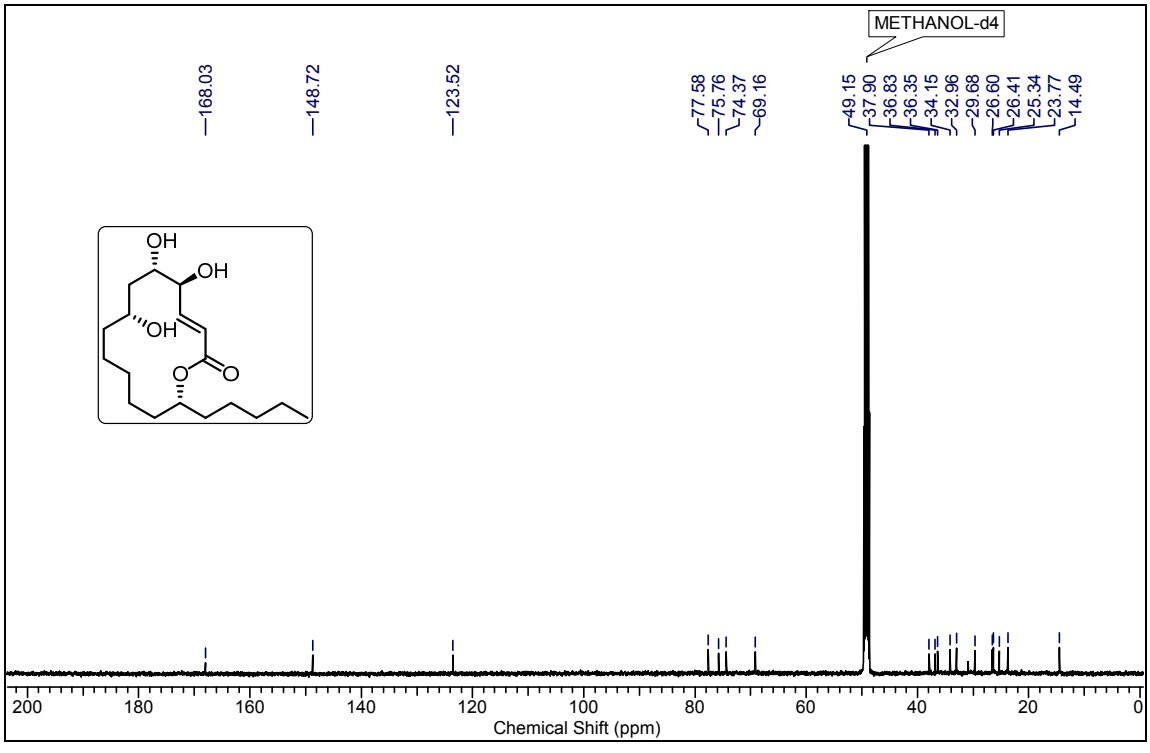


Spectra

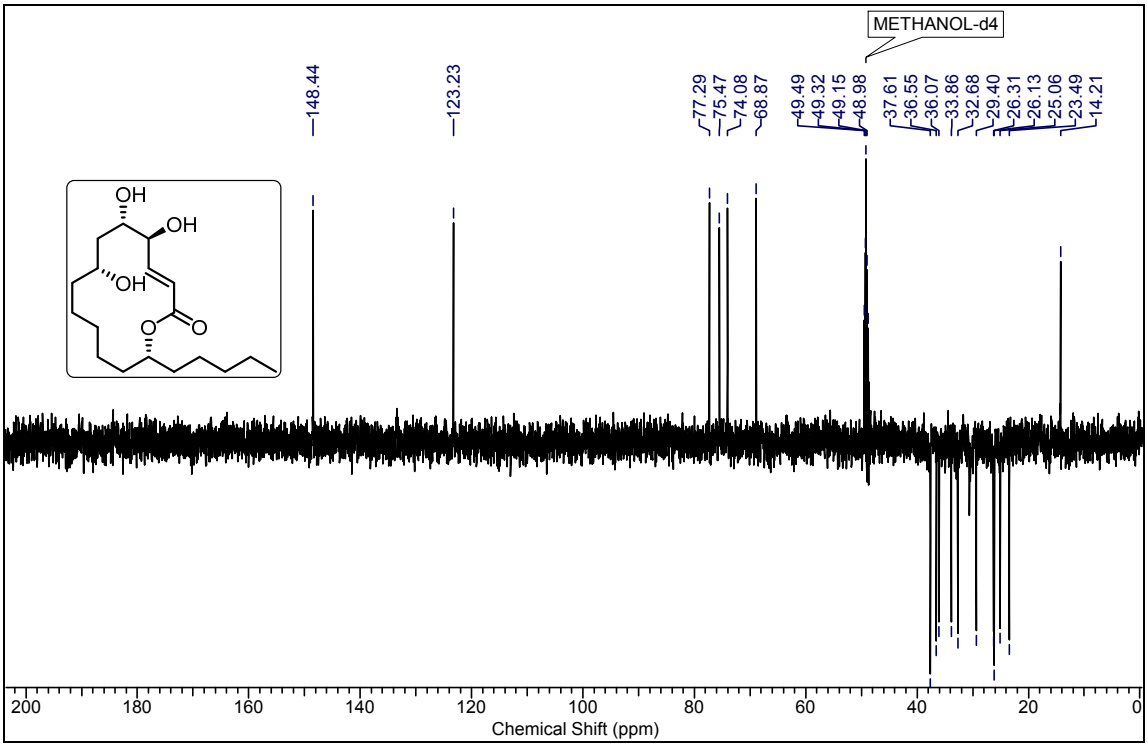
^{1}H NMR spectrum of C4-*epi*-Sch725674 **61** (CD3OD, 500 MHz):



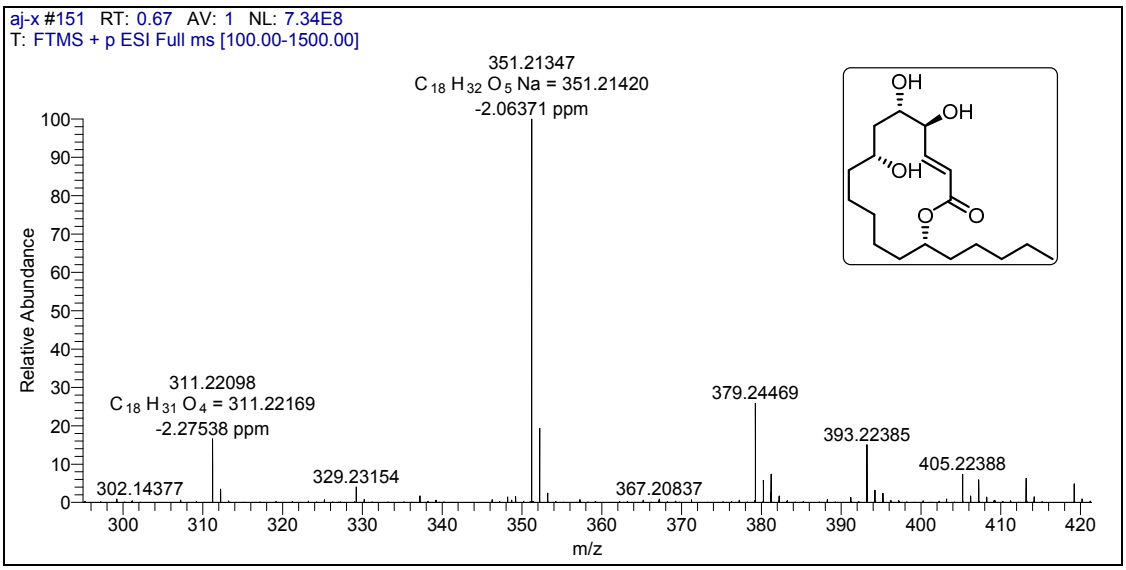
^{13}C NMR spectrum of C4-*epi*-Sch725674 **61** (CD_3OD, 125 MHz):



DEPT-135 NMR spectrum of C4-*epi*-Sch725674 **61** (CD_3OD, 125 MHz):

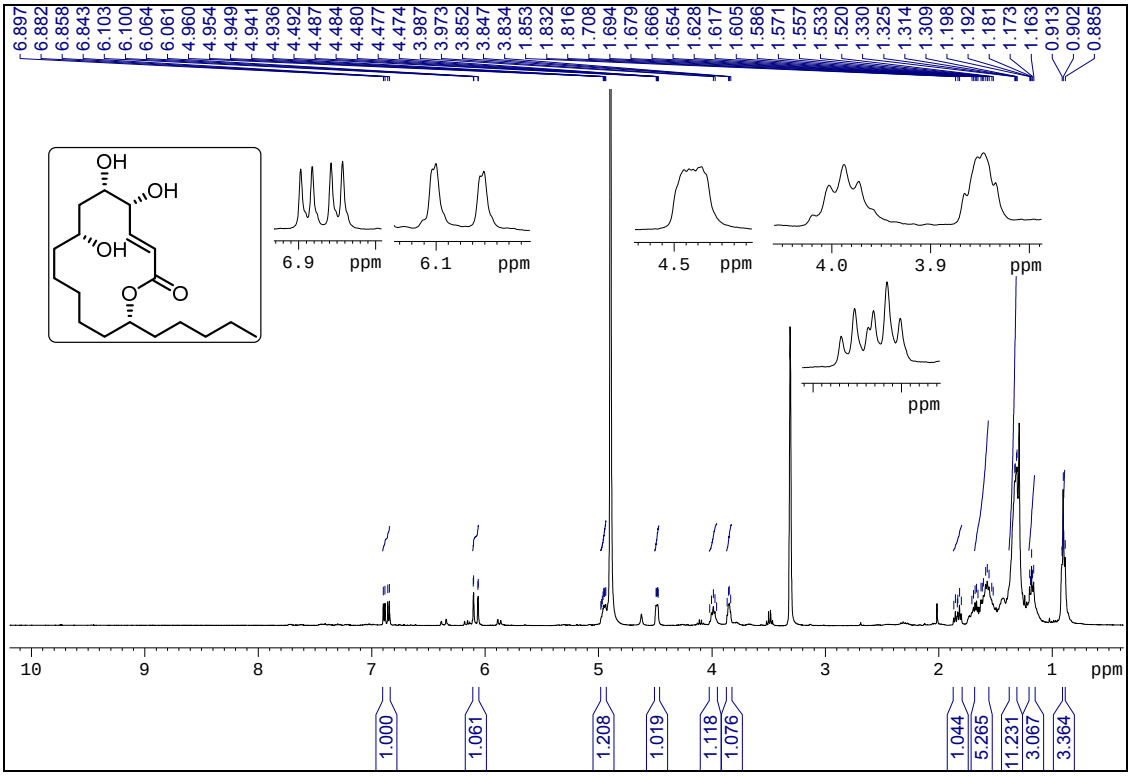


HR-ESI(+)-MS spectrum of C4-*epi*-Sch725674 **61**:

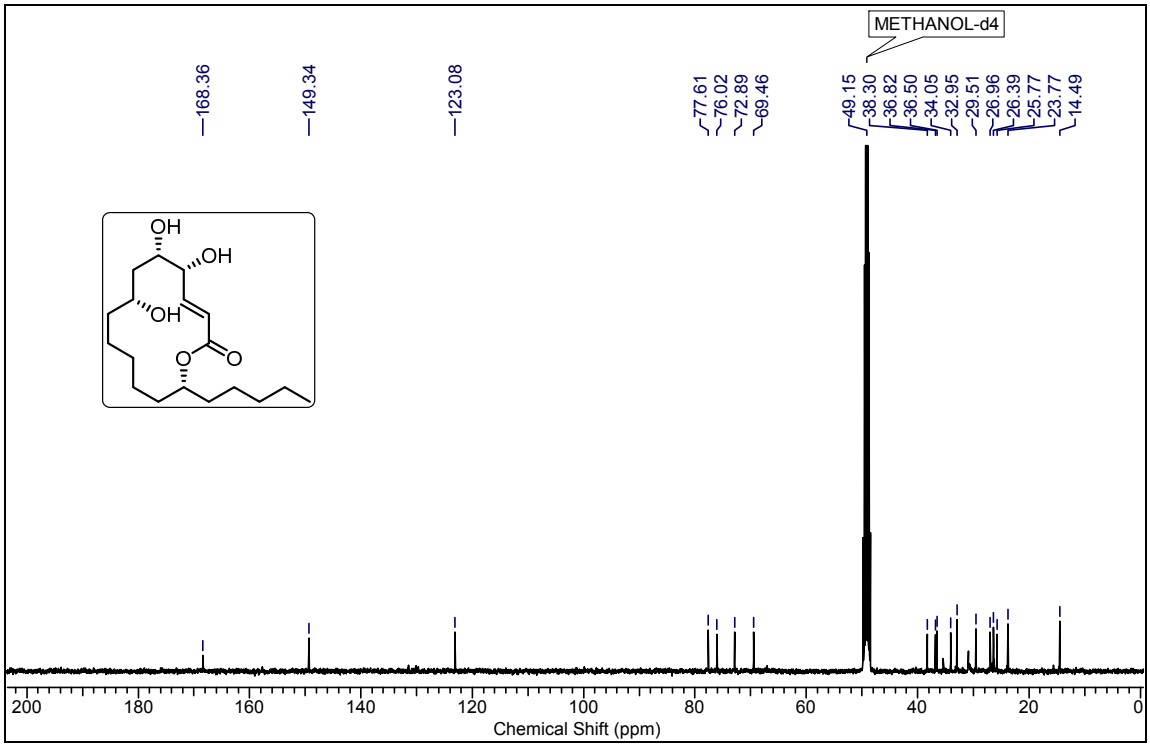


Spectra

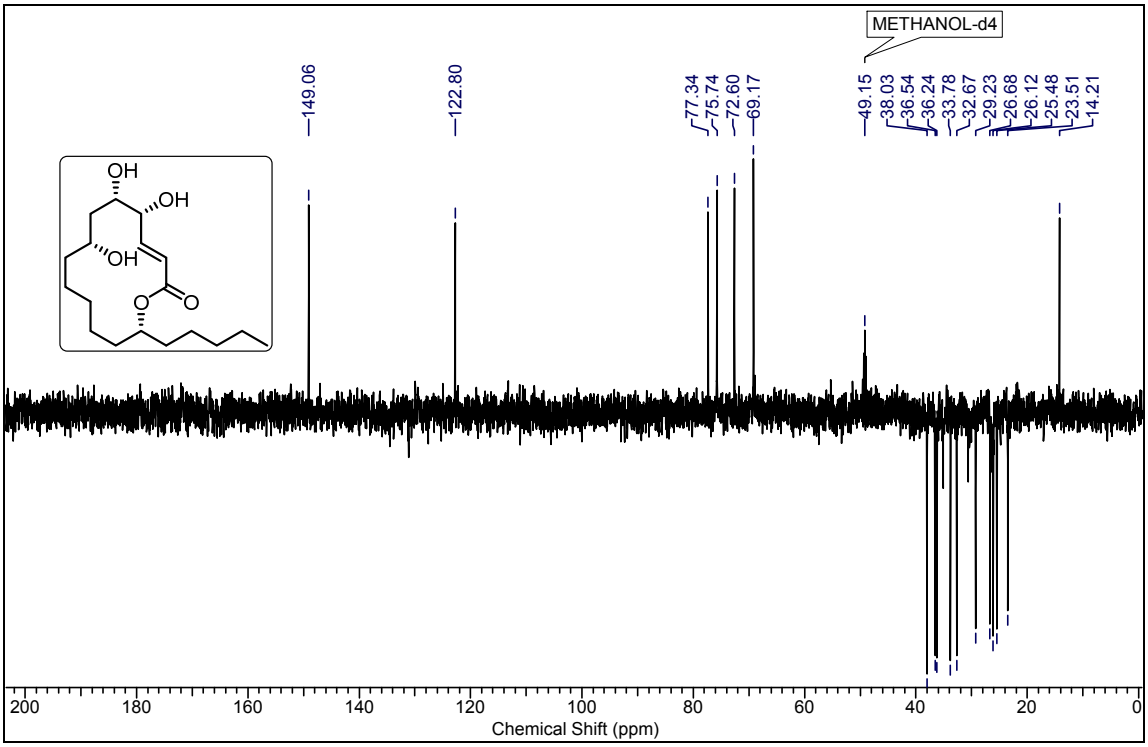
^{1}H NMR spectrum of Sch725674**1** (CD_3OD, 400 MHz):



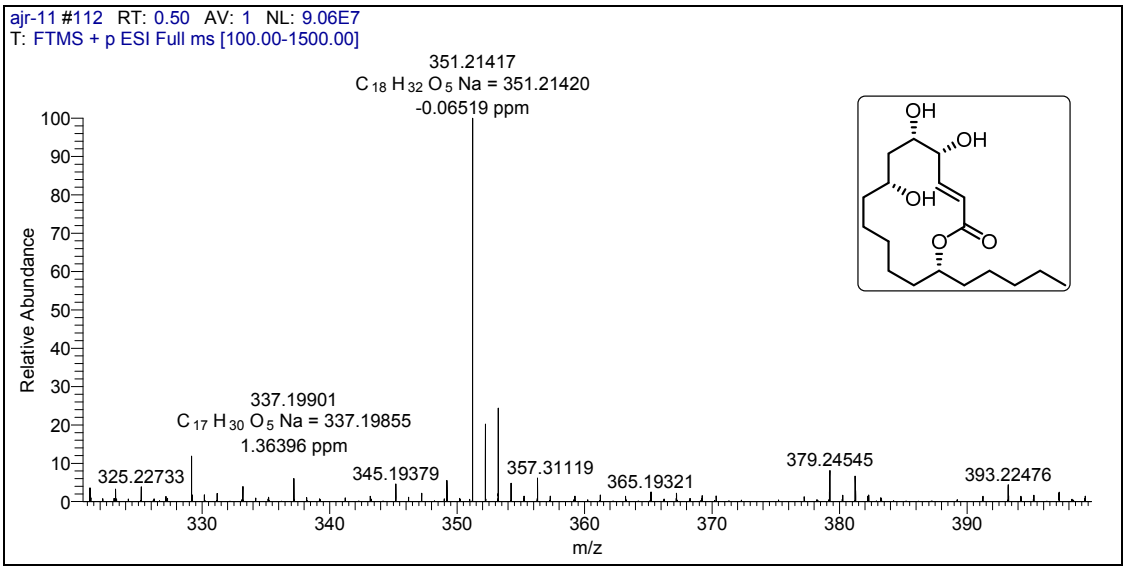
^{13}C NMR spectrum of compound **1** (CD_3OD, 100 MHz):



DEPT-135 NMR spectrum of compound **1** (CD_3OD, 100 MHz):



HR-ESI(+)-MS spectrum of Sch725674 **1**:



1.8. References

(1) a) Labro, M. *J. Antimicrob. Chemother.* **1998**, *41*, 37; b) Čulić, O.; Eraković, V.; Parnham, M. J. *Eur. J. Pharmacol.* **2001**, *429*, 209.

(2) a) Omura, S. *Macrolide antibiotics: chemistry, biology, and practice*; Academic press, **2002**; b) Mallinson, J.; Collins, I. .Chem .Future Med **2012**, *4*, 1409; c) K Oyelere, A. *Curr. Top. Med. Chem.* **2010**, *10*, 1359; d) Yu, X.; Sun, D. *Molecules* **2013**, *18*, 6230; e) Martí-Centelles, V.; Pandey, M. D.; Burguete, M. I.; Luis, S. V. *Chem. Rev.* **2015**, *115*, 8736.

(3) Jelić, D.; Antolović, R. *Antibiotics* **2016**, *5*, 29.

(4) Muchmore, S. W.; *Protein Crystallograpy in Drug Discovery* Edited by Robert E. Babine and Sherin S. Abdel-Meguid. Wiley-VCH Velag GmbH & Co., Weinheim, Germany. **2004**, 6654.

(5) Driggers, E. M.; Hale, S. P.; Lee, J.; Terrett, N. K. *Nat. Rev. Drug Discov.* **2008**, *7*, 608.

(6) a) Zhang, J.; Lin, X.-P.; Li, L.-C.; Zhong, B.-L.; Liao, X.-J.; Liu, Y.-H.; Xu, S.-H. *RSC Adv*. **2015**, *5*, 54645; b) Gurusiddaiah, S.; Ronald, R. *Antimicrob. Agents Chemother.* **1981**, *19*, 153; c) Mandala, S. M.; Harris, G. H. *Methods Enzymol.* **2000**, *311*, 335; d) Koyama, N.; Yotsumoto, M.; Onaka, H.; Tomoda, H. *J. Antibiot.* **2013**, *66*, 303; e) McGuire, J. M.; Bunch, R. L.; Anderson, R. C.; Boaz, H. E.; Flynn, E. H.; Powell, H. M.; Smith, J. W. *Antibiot. Chemother*. **1952**, *2*, 281.

(7) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Deliv. Rev.* **1997**, *23*, 3.

(8) a) Wessjohann, L. A.; Ruijter, E.; Garcia-Rivera, D.; Brandt, W. *Mol. Diversity.* **2005**, *9*, 171; b) Newman, D. J.; Cragg, G. M.; Snader, K. M. *J. Nat. Prod.* **2003**, *66*, 1022.

(9) O'Neil, M. J. *The Merck index: an encyclopedia of chemicals, drugs, and biologicals*; RSC Publishing, **2013**.

(10) Schönfeld, W.; Kirst, H. A. *Macrolide antibiotics*; Springer Science & Business Media, **2002**.

(11) Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B. W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H. *J. Am. Chem. Soc.* **1981**, *103*, 3210.

(12) Corey, E.; Trybulski, E. J.; Melvin Jr, L. S.; Nicolaou, K.; Secrist, J. A.; Lett, R.; Sheldrake, P. W.; Falck, J.; Brunelle, D. J. *J. Am. Chem. Soc.* **1978**, *100*, 4618.

(13) Masamune, S.; Hirama, M.; Mori, S.; Ali, S. A.; Garvey, D. S. *J. Am. Chem. Soc.* **1981**, *103*, 1568.

(14) Stork, G.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1987**, *109*, 1565.

(15) a) Paterson, I.; Laffan, D. D.; Rawson, D. J. *Tetrahedron Lett.* **1988**, *29*, 1461; b) Paterson, I.; Rawson, D. J. *Tetrahedron Lett.* **1989**, *30*, 7463.

(16) Myles, D. C.; Danishefsky, S. J.; Schulte, G. *J. Org. Chem.* **1990**, *55*, 1636.

(17) Mulzer, J.; Kirstein, H. M.; Buschmann, J.; Lehmann, C.; Luger, P. *J. Am. Chem. Soc.* **1991**, *113*, 910.

(18) Stürmer, R.; Ritter, K.; Hoffmann, R. W. *Angew. Chem. Int. Ed.* **1993**, *32*, 101.

(19) Evans, D. A.; Kim, A. S. *Tetrahedron Lett.* **1997**, *38*, 53.

(20) Muri, D.; Lohse-Fraefel, N.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4036.

(21) Wessjohann, L. A.; Ruijter, E. *Top. Curr. Chem*. **2005**, 243, 137.

(22) Gradillas, A.; Pérez-Castells, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6086.

(23) Wessjohann, L. A.; Ruijter, E. *Mol. Diversity.* **2005**, *9*, 159.

(24) Gerbeleu, N. V.; Arion, V. B. in Complex Formation and Stereochemistry of Coordination Compounds (ed. Buslaev, Y.). **1996**, 133 (Nova Science Publishers, New York, NY, USA).

(25) Meutermans, W. D.; Bourne, G. T.; Golding, S. W.; Horton, D. A.; Campitelli, M. R.; Craik, D.; Scanlon, M.; Smythe, M. L. *Org. Lett.* **2003**, *5*, 2711.

(26) David, O.; Meester, W. J.; Bieräugel, H.; Schoemaker, H. E.; Hiemstra, H.; van Maarseveen, J. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4373.

(27) Pandey, S. K.; Kumar, P. *Tetrahedron Lett.* **2005**, *46*, 6625.

(28) Kauloorkar, S. V.; Kumar, P. *RSC Adv.* **2016**, *6*, 63607.

(29) Amigoni, S. J.; Toupet, L. J.; Le Floc'h, Y. J. *J. Org. Chem.* **1997**, *62*, 6374.

(30) Yang, S.-W.; Chan, T.-M.; Terracciano, J.; Loebenberg, D.; Patel, M.; Chu, M. *J. Antibiot.* **2005**, *58*, 535.

(31) Moretti, J. D.; Wang, X.; Curran, D. P. *J. Am. Chem. Soc.* **2012**, *134*, 7963.

(32) a) Bali, A. K.; Sunnam, S. K.; Prasad, K. R. *Org. Lett.* **2014**, *16*, 4001; b) Sunnam, S. K.; Prasad, K. R. *Tetrahedron* **2014**, *70*, 2096.

(33) Ramakrishna, K.; Kaliappan, K. P. *Org. Biomol. Chem.* **2015**, *13*, 234.

(34) Seetharamsingh, B.; Khairnar, P. V.; Reddy, D. S. *J. Org. Chem.* **2016**, *81*, 290.

(35) Bodugam, M.; Javed, S.; Ganguly, A.; Torres, J.; Hanson, P. R. *Org. Lett.* **2016**, *18*, 516.

(36) Fawcett, A.; Nitsch, D.; Ali, M.; Bateman, J. M.; Myers, E. L.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2016**, *55*, 14663.

(37) Reddy, Y.; Sabitha, G. *ChemistrySelect* **2016**, *1*, 2156.

(38) Sharma, B. M.; Gontala, A.; Kumar, P. *Eur. J. Org. Chem.* **2016**, 1215.

(39) Luo, Z.; Zhang, Q.; Oderaotoshi, Y.; Curran, D. P. *Science* **2001**, *291*, 1766.

(40) Mohapatra, D. K.; Reddy, D. S.; Mallampudi, N. A.; Yadav, J. S. *Eur. J. Org. Chem.* **2014**, *2014*, 5023.

(41) a) Wender, P. A.; Baryza, J. L.; Brenner, S. E.; DeChristopher, B. A.; Loy, B. A.; Schrier, A. J.; Verma, V. A. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 6721; b) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2007**, *41*, 40.

(42) a) Kito, K.; Ookura, R.; Yoshida, S.; Namikoshi, M.; Ooi, T.; Kusumi, T. *Org. Lett.* **2008**, *10*, 225; b) Kanematsu, M.; Yoshida, M.; Shishido, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 2618; c)Mortimore, M.; Cockerill, G. S.; Kocieński, P.; Treadgold, R. *Tetrahedron Lett.* **1987**, *28*, 3747; d) Seebach, D.; Adam, G.; Zibuck, R.; Simona, W.; Rouilly, M.; Meyer, W. L.; Hinton, J. F.; Privett, T. A.; Templeton, G. E.; Heiny, D. K.; Gisi, U.; Binder, H. *Liebigs Ann. Chem.* **1989**, *1989*, 1233.

(43) a) Kumar, P.; Tripathi, D.; Sharma, B. M.; Dwivedi, N. *Org. Biomol. Chem.* **2017**, *15*, 733; b) Kumar, P.; Gupta, P. *Synlett* **2009**, 1367; c) Kumar, P.; Naidu, V.; Gupta, P. *Tetrahedron* **2007**, *63*, 2745; d) Kumar, P.; Dwivedi, N. *Acc. Chem. Res.* **2012**, *46*, 289.

(44) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307.

(45) Yamaguchi, M.; Hirao, I. C. *Tetrahedron Lett.* **1983**, *24*, 391.

(46) Bonini, C.; Chiummiento, L.; Videtta, V.; Solladié, G. *Synlett* **2006**, *15*, 2427.

(47) a) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099; b) Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I. *Acc. Chem. Res.* **1998**, *31*, 9; c) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945.

(48) a) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191; b) Evans, D. A.; Siska, S. J.; Cee, V. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 1761.

(49) Ryu, G.; Choi, B. W.; Lee, B. H. *Bull. Korean Chem. Soc.* **2002**, *23*, 1429.

(50) a) Giri, A. G.; Mondal, M. A.; Puranik, V. G.; Ramana, C. V. *Org. Biomol. Chem.* **2010**, *8*, 398; b) Si, D.; Sekar, N. M.; Kaliappan, K. P. *Org. Biomol. Chem.* **2011**, *9*, 6988.

(51) a) Grubbs, R. H.; O'Leary, D. J. *Handbook of metathesis: Applications in organic synthesis*; John Wiley & Sons, **2015**; b) Monfette, S.; Fogg, D. E. *Chem. Rev.* **2009**, *109*, 3783; c) Lin, Y. A.; Chalker, J. M.; Davis, B. G. *ChemBioChem* **2009**, *10*, 959.

(52) Lin, Y. A.; Davis, B. G. *Beilstein J. Org. Chem.* **2010**, *6*, 1219.

(53) a) Fürstner, A. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 3012; b) Feng, L.; Liu, Y.; Hou, B.; Yuan, Z.; Yu, F.-C.; Yan, T.; Qin, Q.; Ji, R.; Li, Y.-M.; Shen, Y. *Org. Biomol. Chem.* **2016**, *14*, 10705; c) Engelhardt, F. C.; Schmitt, M. J.; Taylor, R. E. *Org. Lett.* **2001**, *3*, 2209.

"A number of times along the way, I thought the journey was complete. However, the reactions keep fooling me. It will be interesting to see where it leads next"

—Robert H. Grubbs

Chapter II

Studies Towards Total Synthesis of Nonenolide (6*S*,7*R*,9*R*)-6,7-dihydroxy-9-propylnon-4-eno-9-lactone

2. Introduction

2.1. 10-Membered Macrocyclic Lactones

Naturally occurring macrocyclic lactones are privileged motifs. Macrocyclic lactones from 10 to greater than 20-membered rings have been synthetically explored extensively as they form the core of diverse bioactive natural products and have thus become a prominent means of discovery of new pharmaceutical leads.[1] The subset of this class of molecules encompassing the 10-membered macrolactones[2] and especially the nonenolide family of natural products has garnered much attention in recent years, with respect to development of various synthetic methods to access its skeletal core.[3] The well-defined geometry of the double bond and the presence of stereochemically diverse hydroxyl and epoxy groups have presented considerable synthetic challenges. Nonenolides form a large family of secondary metabolites featuring a 10-membered macrolactone core, embedded with an *E*-configured olefin moiety, decorated with hydroxyl groups and distinctive and unique structural features for this class of molecules characterized by the presence of hydrophobic appendage at the C9 position (Figure 1).[4] They exhibit a broad spectrum of bioactivities like antifungal, antibacterial, anticancer and antimalarial activities.

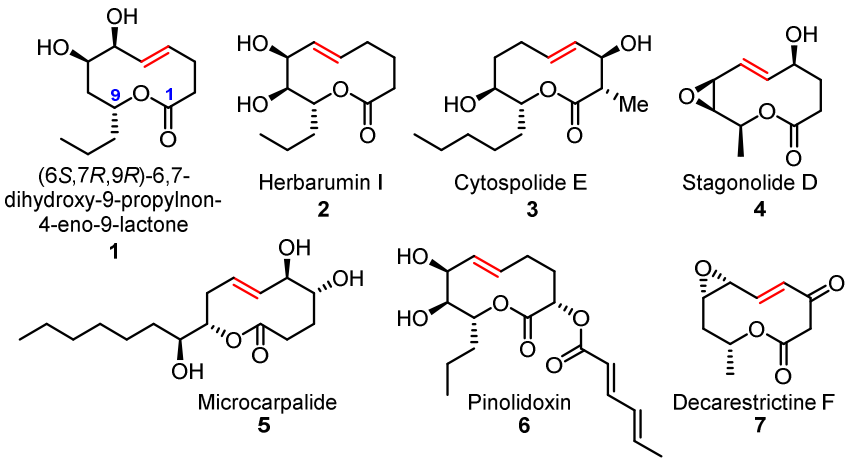


Figure 1. Few representative 10-membered lactones of nonenolide family

On the basis of characteristic structural element, the most commonly encountered 10-membered lactones in nature have been classified into monocyclic polyketides, oxylipins, bicyclic aliphatic and aromatic 10-membered lactones. Representative examples, their sources and bio-activities are presented below.

I. Polyketides

Polyketides are the secondary metabolites isolated from fungi, bacteria and plants. Biosynthetically these 10-membered nonenolides are assembled using building blocks such as acetates, malonates and propionate etc with late stage macrocyclization and installation of double bond as seen for achaetolide **10**.[5] This can thus provide a valuable insight in strategic designing and proper choice of key reaction to construct the polyketide derived 10-membered lactones.

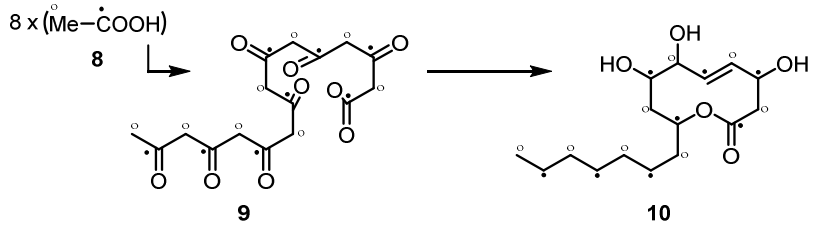


Figure 2. Biosynthetic incorporation of acetate units into achaetolide **10**

II. Oxylipins

Oxylipins are biologically active fatty acid metabolites. In plants, these are important class of signaling molecules also known as eicosanoid lactones, whose function is related to stress responses and innate immunity.[6] Biosynthetically they are produced from oxidation of polyunsaturated fatty acids containing a (1*Z*,4*Z*)-pentadiene system similar to arachidonic acid.[7] The best-characterized oxylipins are shown in Figure 3.

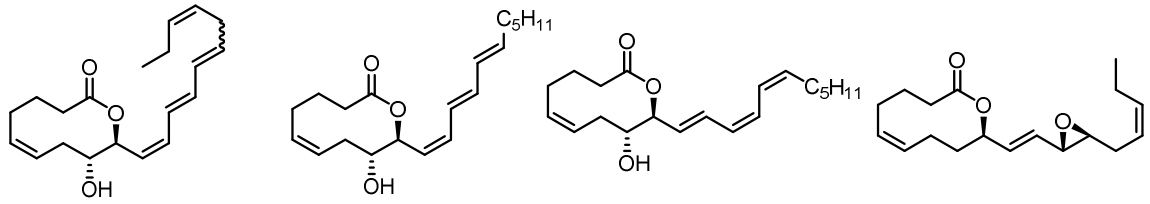


Figure 3. Eicosanoid Decanolactones

These eicosanoid lactones were found in the colonial marine tunicate. Didemnilactones A **11**, Didemnilactones B **12**, and neodidemnilactone **13** showed moderate inhibitory activity against lipoxygenase.[8] Similarly, the 18-carbon epoxy lactone **15** isolated from the cyanobacterium *Aphanizomenon flos-aquae* was found to be an inhibitor of fish development.[9]

III. Bicyclic 10-Membered Lactones

A relatively less number of structurally and stereochemically complex 10-membered macrolactones with additional rings have been isolated in the family of nonenolides (Figure 4). A valuable perfumery compound, (–)-jasmine ketolactone **16**, isolated from *Jasminum grandiflorum L*[10] and primase inhibitor, (+)-Sch 642305 **17** isolated from *Penicillium verrucosum*,[11] are among a few examples of aliphatic bicyclic 10-membered lactones. Whereas, Sporostatin **18** isolated from *Sporormiella sp.*[12] and Xestodecalactone A–C (**19-21**) isolated from the fungus *Penicillium cf. montanense,* found in the marine sponge *Xestospongia exigua*[13] are the few known examples of aromatic bicyclic 10-membered lactones containing fused 1,3-dihydroxybenzene motif.

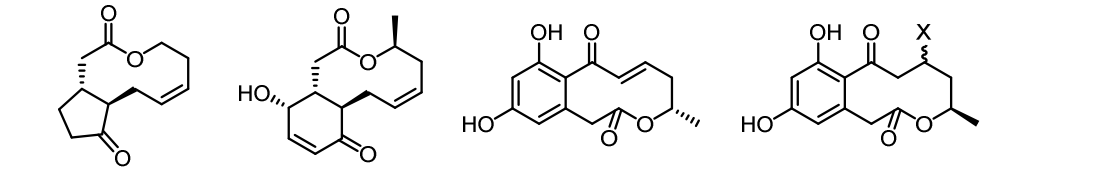


Figure 4. Representative examples of structurally diverse bicyclic 10-membered-ring lactones

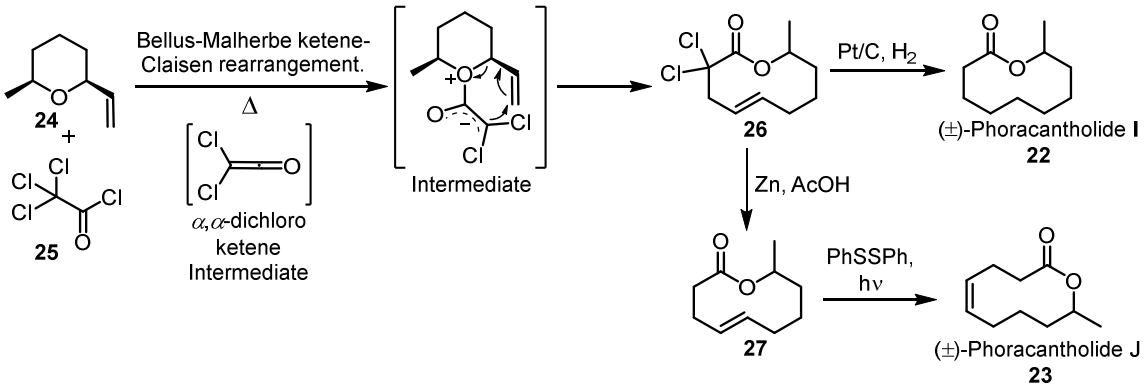
2.2. Synthetic Approaches for Constructing Naturally Occurring 10-Membered-Ring Lactones

The construction of medium-sized rings is an entropically disfavoured process and often leads to the formation of dimerized products due to intermolecular coupling. Therefore, lot of synthetic endeavor has been devoted towards the development of strategies for constructing medium-sized-ring systems. Based on the formation or cleavage of bond during the key reaction, the disconnection approach can be classified as follows:

1. Ring expansion
2. Ring contraction
3. Intramolecular ring closure

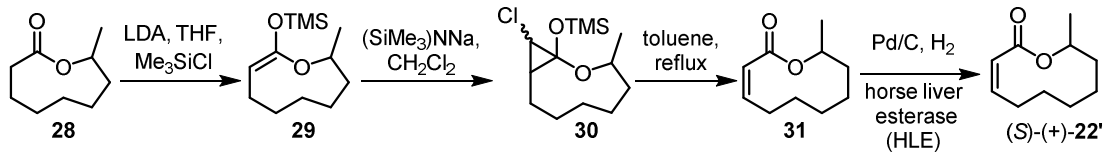
1. Ring Expansion Strategy

Belluš *et al.*[14] reported the ring expansion strategy between dichloroketene (formed *in situ* from trichloroacetyl chloride **25**) with 2-methyl-6-vinylpyran **24** giving rise to an *α*,*α*-dichloro 10-membered lactone, which proceeds through [3,3]-sigmatropic rearrangement of an oxonium dipolar intermediate as shown in Scheme 1. The rearranged product **26** on further functional group interconversion leads to the completion of total synthesis of (±)-phoracantholide I **22** and (±)-phoracantholide J **23**.



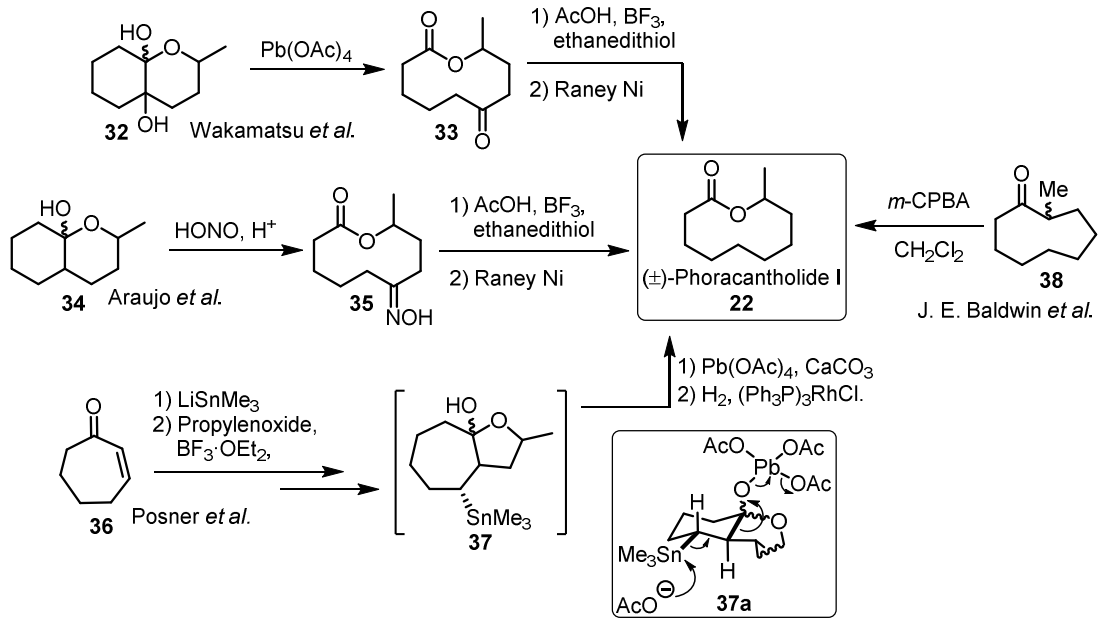
Scheme 1. Belluš-Claisen rearrangement in total synthesis of (±)-Phoracantholide I and J

Fouque and Rousseau[15] reported another efficient ring expansion strategy for the synthesis of (+)-phoracantholide I **22'** proceeding *via* rearrangement of bicyclic intermediate **30** obtained by addition of chlorocarbene to silyl enol ether **29** (Scheme 2).



Scheme 2. Total synthesis of (+)-Phoracantholide I **22'**

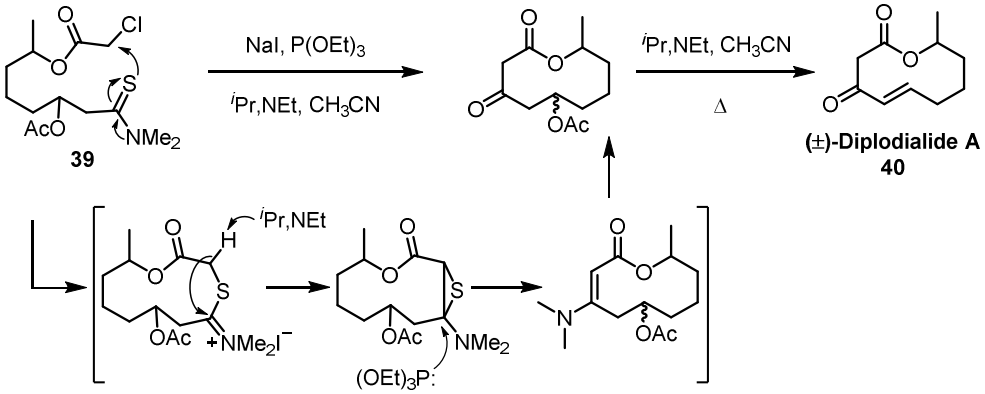
The various elegant ring expansion strategies *via* oxidative cleavage of bicyclic hemiketals as key intermediates have been developed by various groups such as Wakamatsu *et a.l*,[16] Araujo *et al.*[17] and Posner *et al.*[18] and has been exploited for the synthesis of (±)-phoracantholide I **22** as shown in Scheme 3. Baldwin and co-workers[19] have synthesized (±)-**22** using Baeyer-Villiger oxidative ring expansion of cyclic ketone **38**.



Scheme 3. Oxidative cleavage of bicyclic hemiketals in total synthesis of (±)-phoracantholide I **22**

2. Ring Contraction Strategy

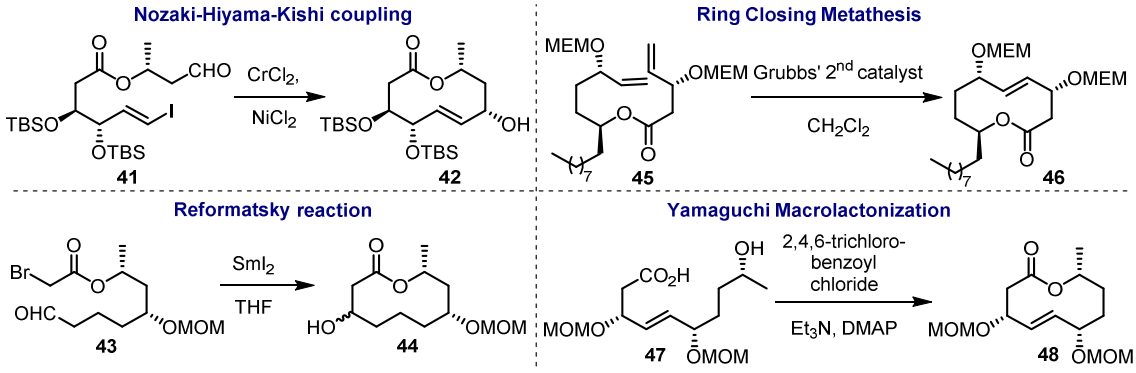
The syntheses of 10-membered macrolactones through ring contractions are relatively rare due to the problem of finding suitable large-ring precursors for the reactions. In 1979, Ireland and co-workers[20] accomplished the total synthesis of (±)-diplodialide A **40** through Eschenmoser sulfide contraction of 11-membered macrocycle formed *in situ* from **39** as shown in Scheme 4.



Scheme 4. Eschenmoser sulfide contraction for total synthesis of (±)-diplodialide A **40**

3. Intramolecular Ring Closure

The success of an intramolecular ring closing reaction involves a delicate balance of kinetic and thermodynamic parameters. In fact, the use of high-dilution conditions for macrocyclization reaction is based on kinetically favoring intramolecular versus intermolecular reactions. This fine tuning overcomes the unfavorable entropy factor involved in preorganization of open chain precursors by the favorable enthalpy associated with the presence of intramolecular electrostatic and other polar interactions such as H-bonding, π-interaction and steric interaction between the two reactive centers in close proximity thus enhancing the chance of a productive interaction.[21] The commonly employed methods for intramolecular ring closure in nonenolide synthesis are Nozaki-Hiyama-Kishi coupling (Decarestrictine D by Pilli *et al.*) **41** → **42**,[22] intramolecular Reformatsky reaction (Decarestrictine J by Oritani *et al.*) **43** → **44**,[23] Ring closing metathesis (Seimatopolide B by Kumar *et al.*) **45** → **46**,[24] Yamaguchi macrolactonization (Decarestrictine C_2 by Kibayashi) **47** → **48**[25] along with Shiina's macrolactonization (Seimatopolide A by Prasad *et al.*)[26] as shown in Scheme 5.



Scheme 5. Intramolecular ring closure by C–C bond forming processes

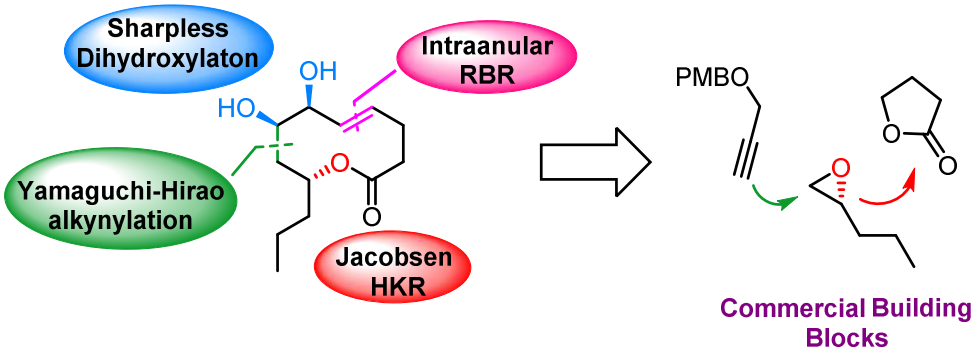
Inspite, of all the well established methods for macrocyclization documented in literature, the devise of new methods is always of general interest in order to tackle the problem of dimerization and *E*/*Z* ratio obtained during the course of reaction. The objective of this chapter is not only to present an overview of the macrocyclization in the total synthesis of natural products but to present other new effective procedures for the ring closure which has not yet been explored for the synthesis of 10-membered macrocyclic lactones.

"When the world says "give up", hope whispers "try one more time"

— Anonymous

Section A

Attempted Synthesis of 10-Membered Lactone using Intraannular Ramberg-Bäcklund Reaction as a Key Step



2.1.1. Nonenolide, (6*S*,7*R*,9*R*)-6,7-dihydroxy-9-propylnon-4-eno-9-lactone

2.1.1.1. Isolation, Biological activity and Characterization

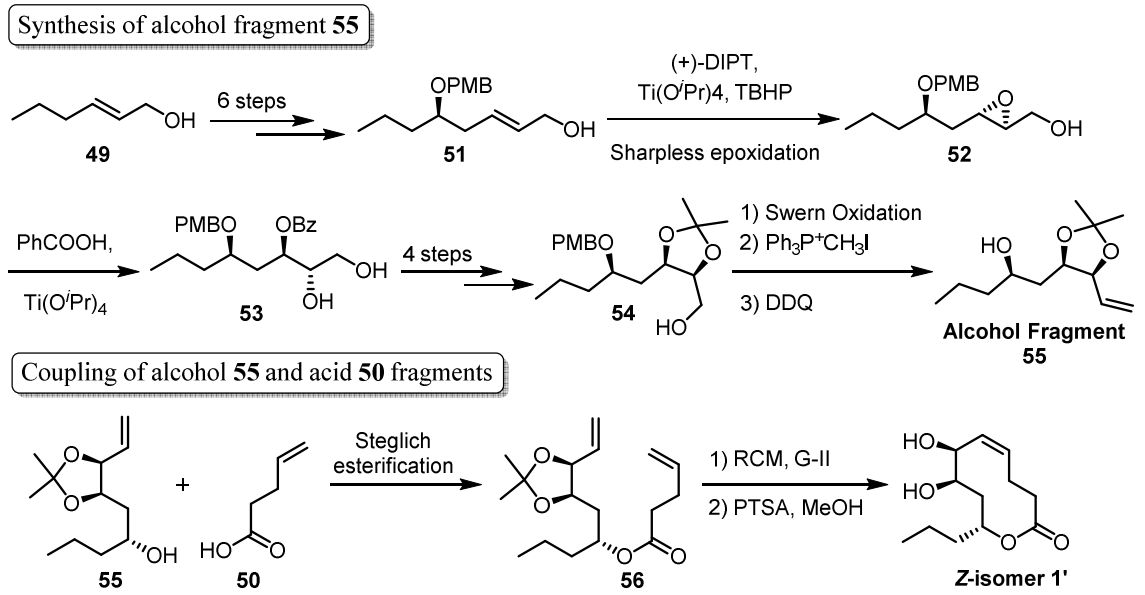
In 2012, Chen and co-workers [27] reported the isolation of a novel 10-membered nonenolide, (6*S*,7*R*,9*R*)-6,7-dihydroxy-9-propylnon-4-eno-9-lactone **1** from the solid cultures of the endophytic fungus *Phomopsis* strain HCCB03520. The compound **1** exhibited phytotoxic activity, with IC_{50} values of 15.8, 24.2 and 31.2 $\mu g.ml^{-1}$, for germination of *Medicago sativa*, *Trifolium hybridum* and *Buchloe dactyloides*, and 31.9, 63.3, 130.9 $\mu g.ml^{-1}$ for radical growth of these plants respectively. The structure of nonenolide **1** was elucidated by 1D and 2D NMR analyses which revealed the presence of one –Me group, five $-CH_2$, and three –OH groups, and two olefinic and one –COO– group. Further using CD spectrum, the absolute configuration of nonenolide **1** was assigned as 6*S*,7*R*,9*R*. The ^{1}H NMR analysis, of the coupling constant (J = 15.8 Hz) between H-4 and H-5 protons established the *E*-geometry of the double bond. The ^{13}C NMR analysis, δ 66.9 and δ 71.3 indicated the positions of two –OH group at C6 and C7 respectively. Finally the key HMBC and NOESY correlation signified the proper connection between C–C, C–H atoms thus confirming the structure.

2.1.2. Literature Review

The interesting structural features of 10-membered nonenolide **1**, is the presence of oxygenated macrolactone containing three stereogenic centers, (*E*)-double bond and an *n*-propyl carbon chain. Its remarkable biological activities and the scarcity of natural sources coupled with structural constraints in the selective construction of *E*-olefinic bond intrigued various synthetic chemists including us to choose (6*S*,7*R*,9*R*)-6,7-dihydroxy-9-propylnon-4-eno-9-lactone **1** as a synthetic target. In this direction, the attempts towards the total synthesis of *E*-nonenolide **1** by Radha Krishna *et al*.[28] and Das *et al*.[29] led to the formation of *Z*-isomer as the sole product. Both of these approaches to construct the C–C double bond relied on ring closing metathesis (RCM). A detailed report of their syntheses is described below.

2.1.2.1. Radha Krishna's Approach[28]

Radha Krishna and co-workers in 2013 accomplished the synthesis of the *Z*-isomer of (6*S*,7*R*,9*R*)-6,7-dihydroxy-9-propylnon-4-eno-9-lactone **1'** from *trans*-2-hexen-1-ol **49** and 4-pentenoic acid **50** using Sharpless asymmetric epoxidation, Steglich esterification and Ring-closing metathesis as the key steps.

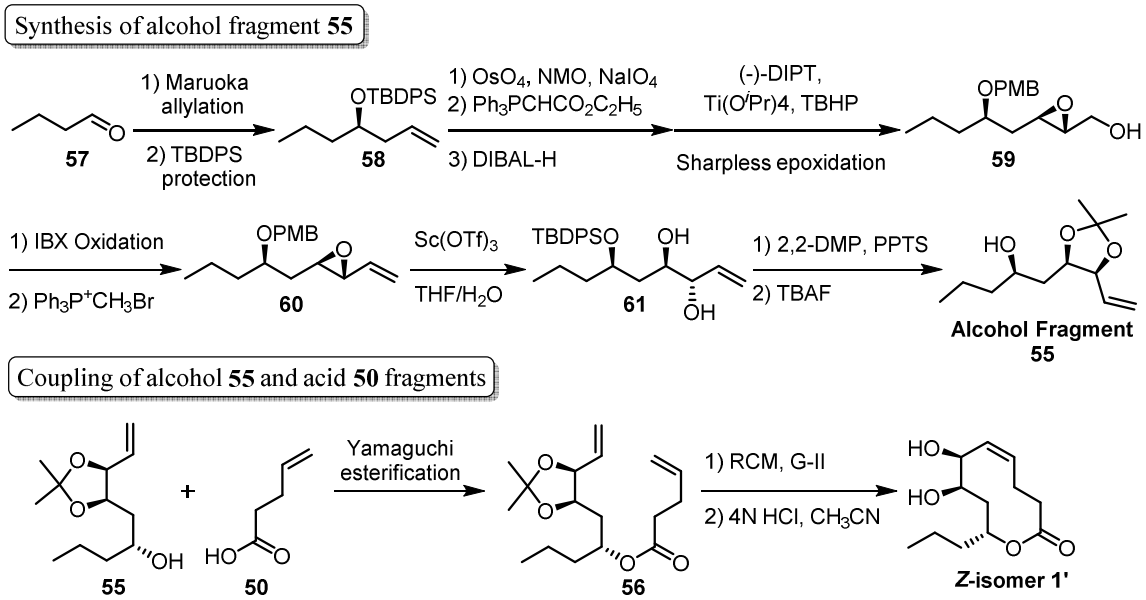


Scheme 2.1.1. Radha Krishna's synthesis of *Z*-isomer of (6*S*,7*R*,9*R*)-6,7-dihydroxy-9-propylnon-4-eno-9-lactone

Accordingly, the synthesis of **1'** starts with compound **49**, which was converted to the known allylic alcohol **51**, this was further converted into chiral epoxide **52** using (+)-DIPT under Sharpless epoxidation conditions. The Lewis acid mediated regioselective ring-opening of epoxide **52** using PhCOOH as the nucleophile furnished the dihydroxy benzoate **53**. The compound **53** was converted to **54** using 4 step protocol, which involves selective silylation of primary alcohol as its TBS ether, hydrolysis of benzoate group, acetonide protection followed by desilylation using TBAF. Next, the primary hydroxyl group in **54** was oxidized under Swern conditions, followed by one carbon Wittig olefination and subsequent PMB ether deprotection under standard DDQ conditions to furnish the alcohol fragment **55**. Under Steglich conditions the alcohol fragment **54** was coupled with commercially available 4-pentenoic acid **50** to give diene ester **56**. Finally RCM followed by acetonide deprotection afforded *Z*-isomer of the target molecule **1'** (Scheme 2.1.1).

2.1.2.2. Das's Approach[29]

Das and co-workers in 2014 accomplished the synthesis of the *Z*-isomer of (6*S*,7*R*,9*R*)-6,7-dihydroxy-9-propylnon-4-eno-9-lactone **1'** from butyraldehyde **57** and 4-pentenoic acid **50** using Sharpless asymmetric epoxidation, Yamaguchi esterification and ring-closing metathesis as the key steps.



Scheme 2.1.2. Das's synthesis of *Z*-isomer of (6*S*,7*R*,9*R*)-6,7-dihydroxy-9-propylnon-4-eno-9- lactone

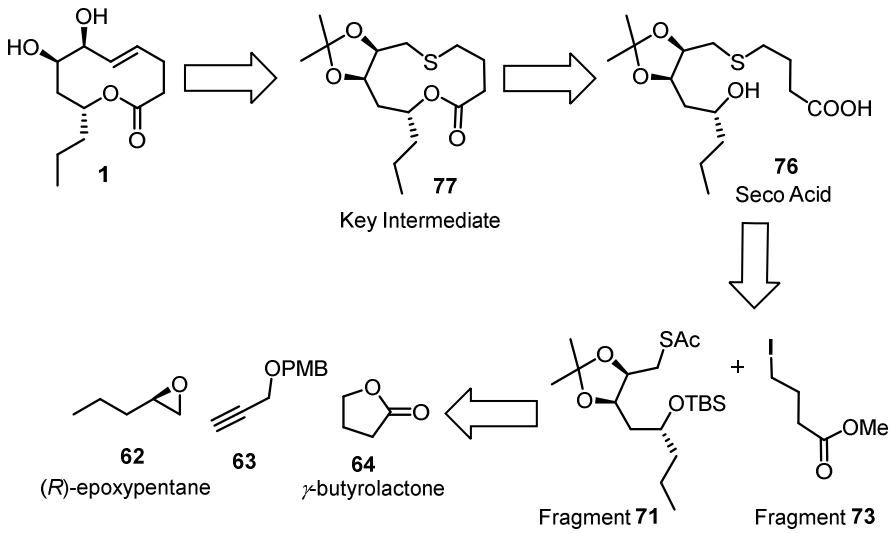
The synthesis commenced with butyraldehyde **57** as a starting material, which on enantioselective Maruoka allylation using allyltributyl tin and bidentate Ti(IV) binol ligand produced the known homoallylic alcohol, followed by its TBDPS ether protection gave the compound **58**. The oxidative cleavage of olefin **58**, C2 Wittig olefination and DIBAL-H reduction afforded the allylic alcohol, which under Sharpless asymmetric epoxidation using (–)-DIPT furnished chiral epoxy alcohol **59**. The alcohol **59** on IBX oxidation followed by C1 Wittig olefination yielded unsaturated epoxide **60**. The Lewis acid mediated ring-opening of epoxide **60** using H_2O as the nucleophile furnished diol **61**. Further acetonide protection and desilylation generated the alcohol fragment **55**. The alcohol **55** and 4-pentenoic acid **50** on Yamaguchi esterification afforded the desired diene ester **56**. Finally RCM followed by acetonide deprotection afforded *Z*-isomer of the target molecule **1'** (Scheme 2.1.2).

2.1.3. Present Work (Intra annular Ring Contraction Approach)

2.1.3.1. Objective

Literature survey revealed that the state-of-the-art disconnection strategy for macrocyclic lactones relies mainly on macrolactonization [30] or RCM as a key reaction.[31] The previous reports to access *E*-cytospolide **3**, a member from the same class of nonenolides family, was attempted by Ramana *et al*. using RCM approach but ended up with formation of *Z*-cytospolide, conversely when reversal of reaction sequence was attempted, *via*. cross metathesis followed by Shiina lactonization; ended up in dimerization.[32] Using computational methods during synthesis of herbarium I **2**, Fürstner *et al*. have elegantly shown that the *Z*-stereoisomer is thermodynamically more stable than the *E*-isomer by 3.5 kcal mol^{-1}.[33] As a part of our synthetic interest in nonenolide class of natural products,[34] and taking cue from the experimental observations as well as results of computational studies; we conceived to employ strategies other than RCM to make the skeletal framework with double bond having the desired *E*-geometry. We herein describe altogether different synthetic approach towards the total synthesis of *E*-nonenolide **1,** namely intraannular Ramberg-Bäcklund reaction (RBR) using sulfone substrate (masked alkene) in accordance with Meyers-modification [35] to explore an alternative to RCM-based synthesis of macrocycle. The details of the findings are reported below.

2.1.3.2. Retrosynthetic Analysis



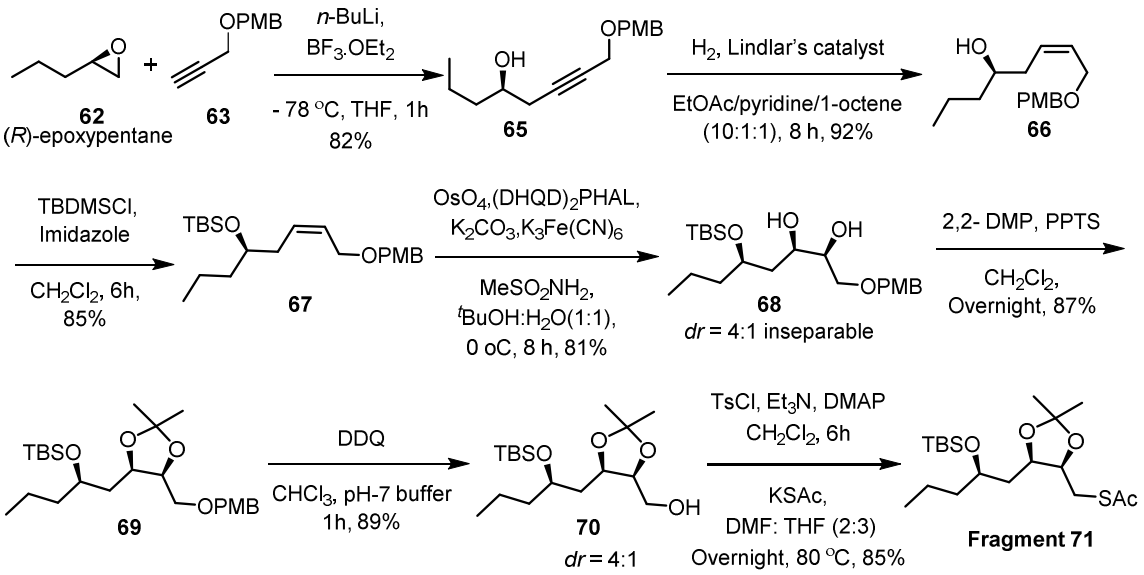
Scheme 2.1.3. Retrosynthetic analysis

Our retrosynthetic approach for the synthesis of *E*-nonenolide **1** is outlined in Scheme 2.1.3. The late stage incorporation of *trans* C4–C5 olefinic bond of macrolactone was hypothesized employing intramolecular RBR on the key intermediate **77**. The synthesis of **77** was envisaged by Yamaguchi macrolactonization of seco acid **76**, which in turn could be accessed from the coupling of thioacetate **71** and iodoester **73**. The compound **71** and **73**, in turn, could be synthesized from the commercially available building blocks (*R*)-1,2-epoxypentane **62**, PMB-protected propargylic alcohol **63** and γ-butyrolactone **64**.

2.1.3.3. Results and Discussion

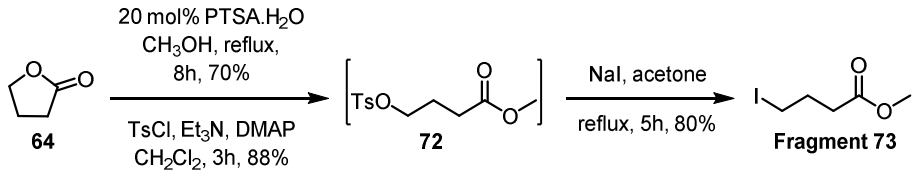
Accordingly, the synthetic sequence for thioacetate **71** commenced with Yamaguchi–Hirao alkynylation protocol of Lewis acid mediated opening of (*R*)-1,2-epoxypentane **62** with lithiated homopropargyl alcohol **63** to provide alkyne **65** in 82% yield. The IR spectrum of **65** gave broad hydroxyl absorption at 3414 cm^{-1}. The ^{1}H NMR signals at δ 3.80 - 3.69 (m, 1 H) corresponds to the proton of secondary hydroxy group which has come from epoxide fragment. The ^{13}C NMR signals at δ 83.3 and 78.5 correspond to the –C≡C– bond. The alkyne **65** was subjected to *cis*-selective Lindlar reduction to afford homoallylic alcohol **66** in 92% yield. The ^{1}H NMR signal at δ 5.84 - 5.56 (m, 2 H) confirmed the presence of olefinic protons. The protection of hydroxyl group of alcohol **66** as its TBS ether gave compound **67** in 85% yield. The IR spectrum of **67** indicated absence of hydroxyl groups. The compound **67** on asymmetric Sharpless dihydroxylation in the presence of $(DHQD)_2PHAL$ ligand furnished diol **68** in 81% yield as an inseparable diastereomeric mixture (dr ~ 4:1, *β*:*α*, confirmed by HPLC analysis). The ^{1}H NMR spectrum showed two chiral protons at δ 3.70 - 3.66 (m, 1 H) and 3.65 - 3.63 (m, 1 H). The diastereoselectivity observed here is particularly gratifying because *cis*-disubstituted alkenes are generally poor substrates for Sharpless asymmetric dihydroxylation.[36] The diol **68** was then treated with 2,2-dimethoxypropane in the presence of catalytic PPTS to furnish 1,2-acetonide **69** in 87% yield. The acetonide methyl protons appeared at δ 1.42 (s, 3 H) and 1.34 (s, 3 H) in the ^{1}H NMR spectrum and typical quaternary carbon of acetonide appeared at 107.9, 107.8 (2 signals correspond to *dr* ~ 4:1) in the ^{13}C NMR spectrum. The compound **69** on PMB deprotection using DDQ furnished the primary alcohol **70** in 89% yield. IR spectrum of **70** gave hydroxyl absorption at 3414 cm^{-1} as also revealed by the disappearance of aromatic protons in

^{1}H NMR spectrum corresponding to the PMB group protons. The primary alcohol **70** on tosylation followed by treatment with Potassium thioacetate (KSAc) in DMF: THF afforded the thioacetate coupling fragment **71** in 85% yield as shown in Scheme 2.1.4. The ^{1}H NMR spectrum showed peak at δ 2.35 (s, 3 H) corresponding to methyl protons of thioacetate group and signal at δ 195.3 in ^{13}C NMR corresponds to thioacetate carbon.



Scheme 2.1.4. Synthesis of thioacetate fragment **71**

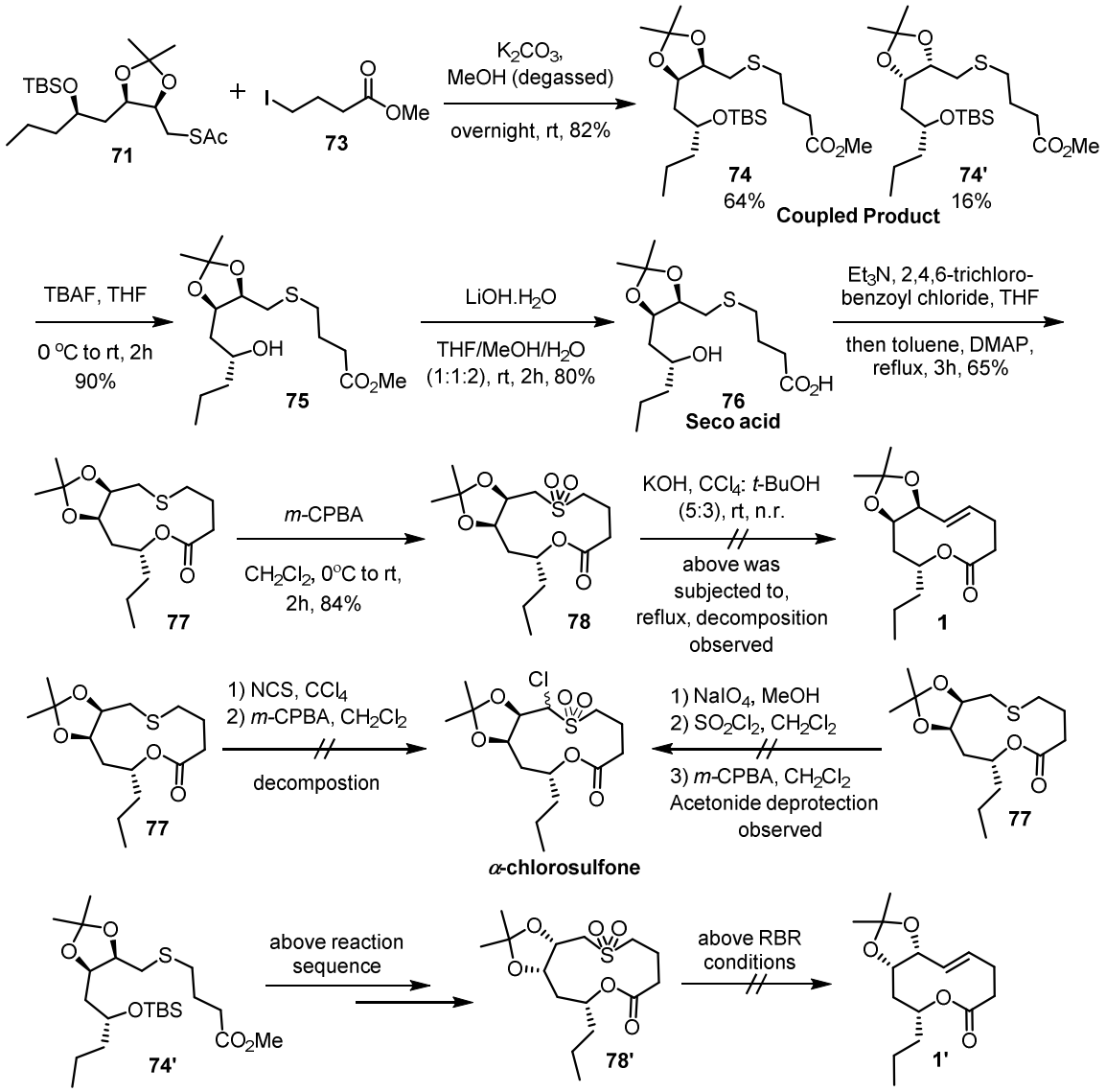
Our efforts were then directed toward the synthesis of iodoester fragment **73** which was accomplished as described below.



Scheme 2.1.5. Synthesis of iodoester fragment **73**

As illustrated in Scheme 2.1.5, γ-butyrolactone **64**, underwent transesterification in methanol under reflux condition in the presence of catalytic *p*-TSA.H_2O to give alcohol. This crude alcohol without any further purification was transformed to iodoester **73** in 80% overall yield, following a two-step reaction sequence involving tosylation with concomitant displacement using NaI in acetone under reflux condition as shown in Scheme 2.1.5. The shielded signal at δ 5.4 in ^{13}C NMR spectrum corresponds to $-CH_2-I$ carbon atom. It was further confirmed by HRMS (ESI^+) peak at 228.9716 corresponding to formula $C_5H_9O_2I$ $[M + H]^+$ (calculated value 228.9720).

Having synthesized both the fragments, we envisaged S_N2 nucleophilic substitution of iodoester **73** with the resulting thiolate anion generated *in situ* through methanolysis of thioacetate **71**, to get the coupled thioether product (Scheme 2.1.6). At this stage, both the diastereomers got separated on column chromatography furnishing major isomer **74** with desired stereochemistry in 64% yield and minor isomer **74'** in 16% yield.



Scheme 2.1.6. Coupling of fragments **71** and **73** and key RBR attempts on **77**

The characteristic signals of both the fragments in major diastereomers **74** can be seen from ^{1}H NMR spectrum at δ 3.68 (s, 3 H) corresponding to protons of methyl ester and δ 1.45 (s, 3 H), 1.34 (s, 3 H) corresponding to acetonide methyl protons. The ^{13}C NMR signal at δ 173.5 (–CO_2–) and 108.0 (quaternary carbon of acetonide) further confirmed the formation of desired product **74**. The yields were based on the diastereomeric ratio

(4:1) of thioacetate **71**. Major isomer **74** was carried forward, desilylation of which using TBAF gave hydroxy ester **75** in 90% yield. The IR spectrum of **75** showed strong hydroxyl absorption at 3458 cm^{-1}. The hydrolysis of methyl ester **75** using $LiOH.H_2O$ in aqueous THF at room temperature furnished the seco-acid **76** in 80% yield. The IR spectrum showed broad signal for carboxylic acid (–O–H) at 3445-2956 cm^{-1}. The ^1H NMR spectrum of **76** showed disappearance of methyl ester proton peaks which are further supported by ^{13}C NMR signal slightly shifted downfield at δ 177.9. The resultant seco-acid **76** under Yamaguchi macrolactonization with 2,4,6-trichlorobenzoyl chloride and DMAP in refluxing toluene gave 11-membered macrolactone **77** in 65% yield over two steps. The IR spectra of **77** showed ester carbonyl at 1725 cm^{-1}, as also supported by ^{13}C NMR peak owing to ester carbonyl carbon which shifted upfield at δ 173.1 in comparison to its seco-acid **76**. The macrocyclic thioether **77** on *m*-CPBA oxidation gave corresponding sulfone **78** in 84% yield. The HRMS (ESI^+) peak at 357.1335 corresponding to formula $C_{15}H_{26}O_6S$ $[M + Na]^+$ (calculated value 357.1342) showed incorporation of two addition "O" atoms in the molecule. A similar sequence of reactions was also executed for the synthesis of **77'** to be used for the preparation of the unnatural diastereomer starting for the compound **74'**, as shown in Scheme 4. All the intermediates from (**74'** → **78'**) were well characterized by ^1H NMR, ^{13}C NMR, HRMS and IR spectral analysis. The (7*S*,8*S*,10*R*) stereochemistry of **77'** was further confirmed by using 2D NMR experiments. In HMBC H10 proton at δ 5.08 showed two bond heteronuclear correlation with the carbonyl carbon C1 at δ 172.0, whereas H7 proton at δ 4.05 showed a cross peak with H8 proton at δ 4.18 in COSY suggesting both are adjacent to each other. In addition, H8 and H10 proton showed NOESY correlations thus indicating both the protons are on same side.

Attempts for crucial ring contraction reaction on macrocyclic sulfone **78** with KOH flakes in CCl_4: ^{t}BuOH, a Meyers' modified protocol of Ramberg-Bäcklund rearrangment[37] were found to be futile (Scheme 2.1.6). The failure of ring contraction reaction may be accounted to the labile lactone ester group which is susceptible to hydrolysis under basic reaction conditions. Taking some lead from a previous report of a similar RBR on a medium ring thioether by De Voss *et al.*,[38] we thought of carrying out the reaction in a stepwise manner, which involves *α*-chlorination of sulfide **77** using *N*-chlorosuccinimide (NCS) followed by its direct oxidation using *m*-CPBA to give

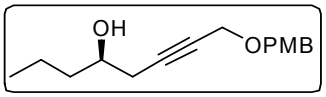
intermediate α-chlorosulfone, but this too resulted in the decomposition of the reaction mixture. To our dismay, even when similar sets of reactions were performed by oxidizing **77** to its corresponding sulphoxide using $NaIO_4$, complete decomposition was observed yet again. All attempts to induce the skeletal change under Ramberg-Bäcklund reaction conditions led to decomposition. The substrate that was subjected to Ramberg-Bäcklund ring contraction in the report by De Voss *et al*. had more robust ether-thioether functional groups. However, the sulphide **77** which was a key intermediate in our scheme had a more labile lactone which could be one of the reasons why the strategy failed to work. Having attempted different reaction conditions to afford the Ramberg-Bäcklund ring contraction on the key intermediate **77** with no success, we abandoned this strategy, and envisioned an intramolecular HWE approach to access the nonenolide **1** whose details are presented in **Chapter 2B**.

2.1.4. Conclusion

In conclusion, a systematic study towards the total synthesis of 10-membered macrolactone core using Ramberg-Bäcklund ring contraction was attempted, which didn't deliver the desired nonenolide **1** under the conditions employed. Developing new alternative methodologies other than metathesis and ring contraction to access this class of macrolactones may be a feasible and a viable option.

2.1.5. Experimental Section

(*R*)-8-((4-Methoxybenzyl)oxy)oct-6-yn-4-ol (65):



To a solution of alkyne **63** (8.2 g, 46.44 mmol, 2 equiv.) in THF (80 mL) at −78 ^{o}C, *n*-BuLi (29 mL, 46.44 mmol, 2 equiv.) was added dropwise and the resulting solution was stirred for 30 min followed by dropwise addition of $BF_3.Et_2O$ (5.7 mL, 46.44 mmol, 2 equiv.). After 15 minutes of stirring, a solution of the epoxide (2 g, 23.22 mmol, 1 equiv.) in THF (20 mL) was added and stirring continued for another 1h at −78 °C and then quenched with saturated aqueous NH_4Cl (20 mL). The reaction mixture was allowed to reach rt and partitioned between ethyl acetate (50 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 50 mL) and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced

pressure. The crude product was purified by flash column chromatography using petroleum ether/EtOAc (3:1) as eluent to give alkynol **65** as a pale yellow liquid.

Yield = 4.9 g, 82%;

R_f = 0.26 (petroleum ether/EtOAc, 4:1);

$[\alpha]_D^{25}$ = –1.8 (*c* 2.3, $CHCl_3$);

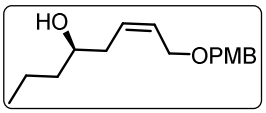
IR ($CHCl_3$): ν_{max} = 3414, 2925, 2865, 1611, 1513, 1456, 1355, 1248, 1175, 1069, 1031, 821, 768 cm^{-1};

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 8.6 Hz, 2 H), 6.89 (d, *J* = 8.6 Hz, 2 H), 4.53 (s, 2 H), 4.15 (s, 2 H), 3.81 (s, 3 H), 3.80 - 3.69 (m, 1 H), 2.58 - 2.29 (m, 2 H), 1.97 (br. s., 1 H), 1.62 - 1.26 (m, 4 H), 0.95 (t, *J* = 6.7 Hz, 3 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.3, 129.7, 129.5, 113.8, 83.3, 78.5, 71.1, 69.7, 57.3, 55.2, 38.4, 27.8, 18.8, 13.9;

HRMS (ESI^+) *m/z* = calcd for $C_{16}H_{22}O_3$ $[M + Na]^+$ 285.1461; found 285.1459.

(*R*,*Z*)-8-((4-Methoxybenzyl)oxy)oct-6-en-4-ol (66):



To a solution of **65** (4.8 g, 18.30 mmol) in 20 mL of ethyl acetate/pyridine/1-octene (10:1:1) was added Lindlar's catalyst (500 mg, Pd-$CaCO_3$). The reaction mixture was stirred for 8 h under a balloon of H_2 at room temperature. After completion of reaction as monitored by TLC, the reaction mixture was filtered through a celite pad. The filtrate was concentrated in *vacuo* and the residue was purified by flash column chromatography using petroleum ether/EtOAc (3:1) as eluent to give **66** as a colourless liquid.

Yield = 4.4 g, 92%;

R_f = 0.26 (petroleum ether/EtOAc, 4:1);

$[\alpha]_D^{25}$ = + 0.68 (*c* 4.3, $CHCl_3$);

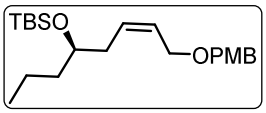
IR ($CHCl_3$): ν_{max} = 3424, 3010, 2951, 2866, 1612, 1513, 1457, 1247, 1076, 1034, 825, 758 cm^{-1};

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.6 Hz, 2 H), 6.85 (d, *J* = 8.6 Hz, 2 H), 5.84 - 5.56 (m, 2 H), 4.43 (s, 2 H), 4.00 (d, *J* = 5.9 Hz, 2 H), 3.77 (s, 3 H), 3.59 (br. s., 1 H), 2.19 (t, *J* = 6.8 Hz, 2 H), 1.50 - 1.23 (m, 4 H), 0.90 (t, *J* = 6.8 Hz, 3 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.1, 130.0, 129.9, 129.4, 128.6, 113.6, 71.9, 70.5, 65.0, 55.1, 39.0, 35.5, 18.7, 13.9;

HRMS (ESI^+) *m/z* = calcd for $C_{16}H_{24}O_3$ $[M + Na]^+$ 287.1618; found 287.1616.

(*R*,*Z*)-*tert*-Butyl((8-((4-methoxybenzyl)oxy)oct-6-en-4-yl)oxy)dimethylsilane (67):



To a stirred solution of alcohol **66** (4.3 g, 16.25 mmol, 1 equiv.) in CH_2Cl_2 (25 mL) was added imidazole (1.8 g, 26.84 mmol, 1.5 equiv.). To this solution *t*-butyldimethylchlorosilane (2.7 g, 17.89 mmol, 1.1 equiv.) was added at 0 ^oC and reaction was allowed to stir at room temperature for 6 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (3 x 50 mL). The extract was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography of the crude product using petroleum ether/EtOAc (19:1) as eluent provided **67** as a colorless liquid.

Yield = 5.2 g, 85%;

R_f = 0.69 (petroleum ether/EtOAc, 17:3);

$[\alpha]_D^{25}$ = + 9.8 (*c* 1.0, $CHCl_3$);

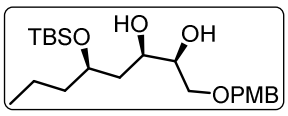
IR ($CHCl_3$): ν_{max} = 3011, 2945, 2859, 1612, 1513, 1461, 1249, 1089, 1043, 830, 772 cm^{-1};

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.7 Hz, 2 H), 6.85 (d, *J* = 8.7 Hz, 2 H), 5.73 - 5.53 (m, 2 H), 4.42 (s, 2 H), 4.13 - 3.91 (m, 2 H), 3.78 (s, 3 H), 3.71 - 3.60 (m, 1 H), 2.17 (t, *J* = 5.9 Hz, 2 H), 1.44 - 1.23 (m, 4 H), 0.93 - 0.80 (m, 12 H), 0.01 (s, 6 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.1, 130.4, 129.8, 129.3, 127.7, 113.7, 71.8, 65.6, 55.2, 39.2, 35.5, 25.8, 18.6, 18.1, 14.2, -4.4, -4.6;

HRMS (ESI^+) *m/z* = calcd for $C_{22}H_{38}O_3Si$ $[M + Na]^+$ 401.2482; found 401.2481.

(2*S*,3*R*,5*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-1-((4-methoxybenzyl)oxy)octane-2,3-diol (68):



To a mixture of $K_3[Fe(CN)_6]$ (5.2 g, 15.85 mmol, 3 equiv.), K_2CO_3 (2.2 g, 15.85 mmol, 3 equiv), $MeSO_2NH_2$ (502 mg, 5.28 mmol, 1 equiv.) and $(DHQD)_2PHAL$ (41 mg, 0.053 mmol, 1mol%) in $^tBuOH:H_2O$ (1:1, 100 mL) was added OsO_4 (2.1 mL, 0.1M soln in toluene, 0.4 mol%). The reaction mixture was stirred at 0 ^oC for 15 min and the olefin **67** (2 g, 5.28 mmol, 1 equiv.) was added in one portion. After stirring for 8 h at 0 ^oC the reaction mixture was quenched by adding solid Na_2SO_3 (5 g) and stirred for 15 min. The aqueous layer was separated and extracted with EtOAc (5 x 100mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography using petroleum ether/EtOAc (7:3) to give inseparable mixture (4:1, α:β, HPLC analysis) of diol **68** in excellent yield as a colorless liquid.

Yield = 1.76 g, 81%;

$\boldsymbol{R_f}$ = 0.35 (petroleum ether/EtOAc, 17:3);

$\boldsymbol{[\alpha]_D^{25}}$ = – 2.168 (*c* 7.7, $CHCl_3$);

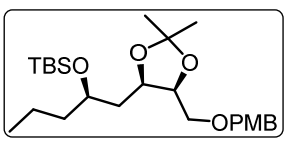
IR ($CHCl_3$): ν_{max} = 3457, 2946, 2864 1613, 1513, 1461, 1373, 1249, 1069, 1047,831, 769 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.4 Hz, 2 H), 6.88 (d, *J* = 8.4 Hz, 2 H), 4.49 (s, 2 H), 4.08 - 4.00 (m, 1 H), 3.99 - 3.92 (m, 1 H), 3.81 (s, 3 H), 3.71 (br. s., 1 H), 3.70 - 3.66 (m, 1 H), 3.65 - 3.63 (m, 1 H), 3.59 - 3.51 (m, 1 H), 1.75 - 1.67 (m, 1 H), 1.66 - 1.47 (m, 3 H), 1.36 - 1.26 (m, 2 H), 0.94 - 0.90 (m, 12 H), 0.13 - 0.07 (m, 6 H);

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.2, 129.9, 129.4, 113.8, 73.1, 73.0, 72.9, 72.8, 72.1, 71.3, 71.0, 70.8, 69.5, 55.2, 39.9, 38.8, 38.5, 37.0, 25.8, 18.8, 17.9, 17.8, 14.2, 14.1, -4.2, -4.6, -4.7, -4.8;

HRMS (ESI^+) *m*/*z* = calcd for $C_{22}H_{40}O_5Si$ $[M + Na]^+$ 435.2537; found 435.2531.

***tert*-Butyl(((*R*)-1-((4*R*,5*S*)-5-(((4-methoxybenzyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pentan-2-yl)oxy)dimethylsilane (69)**:



To a solution of 1,2-diol **68** (1.50 g, 3.64 mmol, 1 eq.) in 15 mL of anhydrous CH_2Cl_2 was added 2,2-DMP (4.5 mL, 36.4 mmol, 10 eq.) followed by catalytic amount of PPTS (457 mg, 1.82 mmol, 0.5 eq.) at rt and stirred overnight, under N_2 atmosphere. After

completion of reaction CH_2Cl_2 was evaporated in *vacuo* to get the crude product which upon purification by flash column chromatography using petroleum ether/EtOAc (24:1) as eluent gave an inseparable mixture (4:1, by HPLC analysis) of compound **69** as colorless liquid.

Yield = 1.43 g, 87%;

R_f = 0.48 (petroleum ether/EtOAc, 19:1);

$[\alpha]_D^{25}$ = – 10.0 (*c* 1.0, $CHCl_3$);

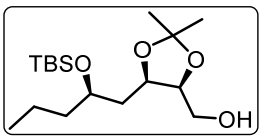
IR ($CHCl_3$): ν_{max} = 2926, 2866, 1694, 1652, 1586, 1444, 1346, 1253, 1177, 1139, 1095, 857, 809, 747 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 8.6 Hz, 2 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 4.53 (d, *J* = 11.7 Hz, 1 H), 4.45 (d, *J* = 11.7 Hz, 1 H), 4.35 - 4.30 (m, 1 H), 4.26 - 4.21 (m, 1 H), 3.91 - 3.82 (m, 1 H), 3.81 (s, 3 H), 3.48 - 3.39 (m, 2 H), 1.55 - 1.51 (m, 2 H), 1.49 - 1.43 (m, 2 H), 1.42 (s, 3 H), 1.41 - 1.35 (m, 1 H), 1.34 (s, 3 H), 1.32 - 1.26 (m, 1 H), 0.93 - 0.89 (m, 12 H), 0.07 - 0.05 (m, 6 H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2, 159.1, 130.1, 130.0, 129.4, 129.3, 113.8, 113.7, 107.9, 107.8, 76.4, 76.2, 74.1, 73.6, 73.1, 73.0, 69.5, 68.9, 55.2, 40.7, 38.8, 36.7, 36.2, 28.3, 28.2, 25.9, 25.8, 25.6, 25.5, 18.2, 18.0, 17.7, 14.4, 14.3, -4.3, -4.4, -4.5, -4.7;

HRMS (ESI^+) *m*/*z* = calcd for $C_{25}H_{44}O_5Si$ $[M + Na]^+$ 475.2850; found 475.2854.

((4*S*,5*R*)-5-((*R*)-2-((*tert*-Butyldimethylsilyl)oxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (70):



To a solution of compound **69** (1.2 g, 2.65 mmol, 1 equiv.) in a mixture of $CHCl_3$: pH = 7 phosphate buffer (20:1) (20 mL) at 0 ^oC, was added DDQ (1.8 g, 7.95 mmol, 3 equiv.), and the resultant mixture was stirred at room temperature for 1 h. After completion as indicated by TLC, the reaction was quenched with saturated aqueous solution of $NaHCO_3$ (10 mL) and Na_2SO_3 (10 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography of the crude product using petroleum ether/EtOAc (23:2) as

eluent gave inseparable mixture (4:1, by HPLC analysis) of alcohol **70** as a colorless liquid.

Yield = 785 mg, 89%;

R_f = 0.43 (petroleum ether/EtOAc, 17:3);

$[\alpha]_D^{25}$ = – 5.3 (*c* 1.7, $CHCl_3$);

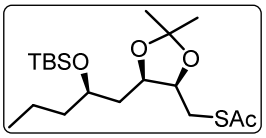
IR ($CHCl_3$): ν_{max} = 3414, 2945, 2863, 1593, 1463, 1375, 1252, 1217, 1037, 838, 761 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.37 - 4.28 (m, 1 H), 4.16 - 4.12 (m, 1 H), 3.92 - 3.79 (m, 1 H), 3.64 - 3.54 (m, 2 H), 2.10 (br. s., 1 H), 1.72 - 1.66 (m, 1 H), 1.60 - 1.53 (m, 1 H), 1.51 - 1.47 (m, 2 H), 1.46 (s, 3 H), 1.43-1.36 (m, 4 H), 1.34 - 1.27 (m, 1 H), 0.92 - 0.89 (m, 12 H), 0.08 - 0.06 (m, 6 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ = 108.0, 107.7, 77.9, 77.8, 73.8, 73.6, 69.6, 69.4, 61.9, 61.8, 40.6, 38.9, 36.1, 35.7, 28.3, 28.2, 25.9, 25.5, 18.4, 18.1, 17.7, 14.3, -4.3, -4.4, -4.5, -4.6;

HRMS (ESI^+) *m*/*z* = calcd for $C_{17}H_{36}O_4Si$ $[M + Na]^+$ 355.2275; found 355.2274.

***S*-(((4*R*,5*R*)-5-((*R*)-2-((*tert*-Butyldimethylsilyl)oxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl) ethanethioate (71)**:



To a stirred solution of alcohol **70** (700 mg, 2.10 mmol, 1 equiv.) in CH_2Cl_2 (15 mL) was added triethyl amine (0.58 mL, 4.20 mmol, 2 equiv.) at 0 ^oC, followed by tosyl chloride (482 mg, 2.53 mmol, 1.2 equiv.) and catalytic amount of DMAP. After being stirred at room temperature for 4 h under nitrogen atmosphere, the reaction mixture was diluted with H_2O, and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude tosylate was used in next step without any further purification.

To a solution of crude *O*-tosylate (880 mg, 1.81 mmole, 1 equiv.) in anhydrous DMF (4 mL) and anhydrous THF (6 mL) was added potassium thioacetate (310 mg, 2.71 mmol, 1.5 equiv.) and the reaction mixture was stirred overnight at 80 ^oC under nitrogen atmosphere. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature, diluted with water (10 mL) and extracted with ethyl

acetate (3 x 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography using petroleum ether/EtOAc (49:1) to afford inseparable diastereomeric mixture of thioacetate **71** as a colourless liquid.

Yield = 600 mg, 85%;

R_f = 0.67 (petroleum ether/EtOAc, 9:1);

$[\alpha]_D^{25}$ = 8.4 (*c* 1.73, $CHCl_3$);

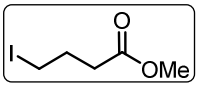
IR ($CHCl_3$): ν_{max} = 2945, 2864, 1694, 1463, 1373, 1251, 1220, 1128, 1051, 835, 762 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.33 (ddd, *J* = 3.4, 6.0, 9.4 Hz, 1 H), 4.10 (ddd, *J* = 3.7, 6.0, 9.6 Hz, 1 H), 3.94 - 3.86 (m, 1 H), 3.13 - 3.08 (m, 1 H), 2.88 - 2.79 (m, 1 H), 2.35 (s, 3 H), 1.64 - 1.57 (m, 2 H), 1.52 - 1.45 (m, 2 H), 1.43 (s, 3 H), 1.41 - 1.33 (m, 2 H), 1.32 (s, 3 H), 0.95 - 0.89 (m, 12 H), 0.07 (app. d, *J* = 1.8 Hz, 6 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ = 195.3, 108.1, 76.6, 76.5, 74.5, 74.2, 69.5, 68.9, 40.6, 39.0, 36.7, 36.4, 30.7, 30.5, 30.4, 28.3, 25.9, 25.7, 18.3, 18.0, 17.7, 14.3, 14.2, -4.3, -4.4, -4.5, -4.6;

HRMS (ESI^+) *m/z* = calcd for $C_{19}H_{38}O_4SSi$ $[M + Na]^+$ 413.2152; found 413.2151.

Methyl 4-iodobutanoate (73):



To a γ-butyrolactone **64** (1g, 11.62 mmole, 1 equiv.) in MeOH (20.0 mL) under argon was added *p*-TSA.H_2O (1.1 g, 5.81 mmol, 0.5 equiv.), and the reaction mixture was refluxed for 8h. After the completion of reaction as monitored by TLC, the reaction was cooled, and methanol was removed under *vacuo*. The reaction mixture was washed with saturated solution of $NaHCO_3$ (10 mL), water (10 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude alcohol as colorless oil, which was used without further purification.

To a stirred solution of crude alcohol (900 mg, 7.62 mmol, 1 equiv.) in dry CH_2Cl_2 (15 ml) was added Et_3N (2.1 mL, 15.24 mmol, 2 equiv.) at 0 ^oC, followed by addition of tosyl chloride (1.8 g, 9.14 mmol, 1.2 equiv.) and DMAP (cat.). The reaction mixture was stirred for 3 h under nitrogen atmosphere. After completion of the reaction

(monitored by TLC), the reaction mixture was washed with saturated solution of $NaHCO_3$ (10 mL), water (10 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude *O*-tosyl compound **72** (1.8 g, 88%) as a colorless oil.

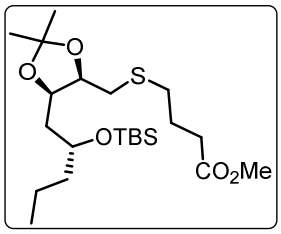
The crude tosylated compound **72** (1.2 g, 4.41 mmol, 1 equiv.) was dissolved under argon in dry acetone (30 mL) and was treated with NaI (6.6 g, 44.1 mmol). The reaction mixture was refluxed for 5 h. After cooling to room temperature the volatiles were removed under reduced pressure. Flash column chromatography of the crude product using petroleum ether/EtOAc (23:2) as eluent gave iodo compound **73** as a pale yellow liquid.

Yield = 804 mg, 80%;
$\boldsymbol{R_f}$ = 0.77 (petroleum ether/EtOAc, 4:1);
IR ($CHCl_3$): ν_{max} = 2951, 2848, 1735, 1436, 1366, 1206, 1122, 1017, 869, 764 cm^{-1};
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.67 (s, 3 H), 3.22 (t, *J* = 6.9 Hz, 2 H), 2.44 (t, *J* = 7.2 Hz, 2 H), 2.11 (quin, *J* = 6.9 Hz, 2 H);
^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.7, 51.6, 34.4, 28.3, 5.4;
HRMS (ESI^+) *m*/*z* = calcd for $C_5H_9O_2I$ $[M + H]^+$ 228.9720; found 228.9716.

Coupling of Fragments 71 and Fragments 73:

A solution of thioacetate **71** (500 mg, 1.28 mmol, 1 equiv.) and iodo **73** (321 mg, 1.41 mmol, 1.1 equiv.) in dry MeOH (25 mL) was degassed by bubbling dry argon through the solution for 10 min. After this time, K_2CO_3 (531 mg, 3.84 mmol, 3 equiv.) was added, and the reaction was stirred overnight at rt. After consumption of iodo **73** by TLC, the solvent was removed to dryness. The residue was dissolved in EtOAc (20 mL), and saturated aqueous NH_4Cl solution (10 mL) was added. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 25 mL). The organic layers were combined, washed with brine, dried with Na_2SO_4, filtered and reduced to dryness. The crude residue was purified using flash column chromatography using petroleum ether/EtOAc (97:3) to yield coupled product **74** as major isomer, followed by minor isomer **74'** as a colorless liquid.

Data of methyl-4-((((4*R*,5*R*)-5-((*R*)-2-((*tert*-butyldimethylsilyl)oxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)thio)butanoate (74):



Yield = 368 mg, 64%;

R_f = 0.46 (petroleum ether/EtOAc, 19:1);

$[\alpha]_D^{25}$ = + 0.76 (*c* 1.8, $CHCl_3$);

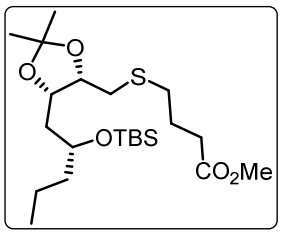
IR ($CHCl_3$): ν_{max} = 2938, 2859, 1736, 1652, 1446, 1369, 1253, 1217, 1136, 1052, 845, 769 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.26 - 4.15 (m, 2 H), 3.93 - 3.82 (m, 1 H), 3.68 (s, 3 H), 2.68 - 2.53 (m, 4 H), 2.49 - 2.40 (m, 2 H), 1.97 – 1.90 (m, 2 H), 1.76 - 1.67 (m, 1 H), 1.61 - 1.47 (m, 2 H), 1.45 (s, 3 H), 1.44 - 1.35 (m, 3 H), 1.34 (s, 3 H), 0.94 - 0.85 (m, 12 H), 0.06 (s, 6 H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5, 108.0, 77.5, 74.6, 69.5, 51.6, 38.7, 36.9, 32.7, 32.4, 32.1, 28.4, 25.9, 25.7, 24.7, 18.2, 18.1, 14.3, -4.4, -4.5;

HRMS (ESI^+) *m*/*z* = calcd for $C_{22}H_{44}O_5SSi$ $[M + Na]^+$ 471.2571; found 471.2563.

Data of methyl-4-((((4*S*,5*S*)-5-((*R*)-2-((t*ert*-butyldimethylsilyl)oxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)thio)butanoate (74'):



Yield = 92 mg, 16%;

R_f = 0.31 (petroleum ether/EtOAc, 19:1);

$[\alpha]_D^{25}$: – 1.2 (*c* 1.3, $CHCl_3$);

IR ($CHCl_3$,): ν_{max} 2945, 2862, 1739, 1646, 1454, 1372, 1250, 1215, 1132, 1047, 834, 772 cm^{-1};

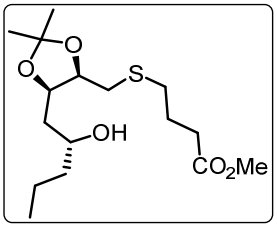
^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.31 (ddd, *J* = 3.1, 6.1, 9.5 Hz, 1 H), 4.19 (ddd, *J* = 5.7, 5.7, 8.0 Hz, 1 H), 3.93 - 3.86 (m, 1 H), 3.68 (s, 3 H), 2.69 - 2.53 (m, 4 H), 2.45 (t, *J*

= 7.2 Hz, 2 H), 1.93 (quin, *J* = 7.2 Hz, 2 H), 1.60 - 1.50 (m, 2 H), 1.50 - 1.45 (m, 2 H), 1.44 (s, 3 H), 1.40 - 1.34 (m, 1 H), 1.33 (s, 3 H), 1.32 - 1.27 (m, 1 H), 0.94 - 0.90 (m, 12 H), 0.07 (s, 6 H);

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.5, 107.9, 77.7, 74.4, 69.0, 51.6, 40.7, 36.6, 32.9, 32.7, 32.1, 28.4, 25.9, 25.8, 24.7, 18.1, 17.8, 14.3, -4.2, -4.6;

HRMS (ESI^+) *m*/*z* = calcd for $C_{22}H_{44}O_5SSi$ $[M + Na]^+$ 471.2571; found 471.2563.

Methyl-4-((((4*R*,5*R*)-5-((*R*)-2-hydroxypentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)thio)butanoate (75):



To a solution of ester **74** (350 mg, 0.78 mmol, 1 equiv.) in THF (7 mL) was added TBAF (1.2 mL, 1.17 mmol, 1.0 M solution in THF) at 0 ^oC. The reaction mixture was stirred for 2 h at room temperature and then diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent gave alcohol **75** as a colorless liquid.

Yield = 235 mg, 90%;

***R*$_f$** = 0.58 (petroleum ether/EtOAc, 7:3);

$[\alpha]_D^{25}$ = + 1.8 (*c* 1.2, $CHCl_3$);

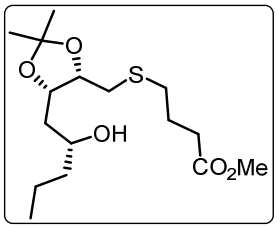
IR ($CHCl_3$): ν_{max} = 3458, 3015, 2958, 1732, 1428, 1369, 1215, 1165, 1052, 766 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.36 - 4.27 (m, 1 H), 4.25 - 4.21 (m, 1 H), 3.82 (app. s., 1 H), 3.66 (s, 3 H), 3.30 (br. s., 1 H), 2.68 - 2.52 (m, 4 H), 2.42 (t, *J* = 7.3 Hz, 2 H), 1.91 (quin, *J* = 7.3 Hz, 2 H), 1.66 - 1.48 (m, 3 H), 1.46 (s, 3 H), 1.44 - 1.36 (m, 3 H), 1.34 (s, 3 H), 0.92 (t, *J* = 6.7 Hz, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.4, 108.7, 78.2, 77.5, 71.1, 51.6, 39.6, 36.1, 32.6, 32.0, 31.9, 28.1, 25.6, 24.6, 18.6, 14 .0;

HRMS (ESI^+) *m*/*z* = calcd for $C_{16}H_{30}O_5S$ $[M + Na]^+$ 357.1706; found 357.1704.

Methyl-4-((((4*S*,5*S*)-5-((*R*)-2-hydroxypentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)thio)butanoate (75'):



Compound **74'** (80 mg, 0.178 mmol, 1 equiv.) was treated with TBAF (0.27 mL, 0.267 mmol, 1.5 equiv.) in THF (1 mL) under the same conditions as described for the synthesis of **75** to give compound **75'**, obtained as a colorless liquid after flash column chromatography using petroleum ether/EtOAc (4:1) as eluent.

Yield = 52 mg, 88 %;

R_f = 0.45 (petroleum ether/EtOAc, 7:3);

$[\alpha]_D^{25}$ = – 1.4 (*c* 0.3, $CHCl_3$);

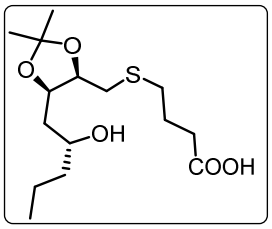
IR ($CHCl_3$): ν_{max} = 3448, 3010, 2950, 1730, 1431, 1373 1217, 1169, 1058, 758 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.44 (ddd, *J* = 3.4, 5.7, 9.5 Hz, 1 H), 4.27 - 4.23 (m, 1 H), 3.88 - 3.81 (m, 1 H), 3.68 (s, 3 H), 2.68 - 2.57 (m, 4 H), 2.44 (t, *J* = 7.2 Hz, 2 H), 2.01 (br. s., 1 H), 1.93 (quin, *J* = 7.2 Hz, 2 H), 1.69 (ddd, *J* = 2.7, 10.3, 13.6 Hz, 1 H), 1.57 - 1.46 (m, 4 H), 1.45 (s, 3 H), 1.43 - 1.37 (m, 1 H), 1.36 (s, 3 H), 0.94 (t, *J* = 6.9 Hz, 3 H);

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.5, 108.1, 77.5, 74.7, 68.8, 51.6, 40.1, 36.2, 32.7, 32.2, 32.0, 28.3, 25.7, 24.6, 18.9, 14.0;

HRMS (ESI^+) *m/z* = calcd for $C_{16}H_{30}O_5S$ $[M + Na]^+$ 357.1706; found 357.1705.

4-((((4*R*,5*R*)-5-((*R*)-2-Hydroxypentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)thio)butanoic acid (76):



To a solution of compound **75** (220 mg, 0.658 mmol, 1 eq.) in 6 mL of THF/MeOH/H_2O (1:1:2) was added LiOH.H_2O (138 mg, 3.29 mmol, 5 eq.) in one portion at 0 °C and stirred to rt for 3h. MeOH and THF were removed in *vacuo* and the aqueous layer was

extracted with Et_2O. The aqueous layer was acidified with 10% aq. citric acid solution (~5 mL) at 0 °C and extracted with EtOAc (5 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in *vacuo*. Flash column chromatography using petroleum ether/EtOAc (1:1) as eluent gave seco acid **76** as a colorless liquid.

Yield = 169 mg, 80%;

R_f = 0.24 (EtOAc);

$[\alpha]_D^{25}$ = + 0.83 (*c* 0.7, $CHCl_3$);

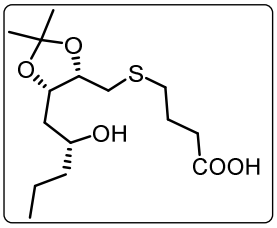
IR ($CHCl_3$): ν_{max} = 3445, 2956, 1718, 1372, 1212, 1158, 1056, 755 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.37 - 4.33 (m, 1 H), 4.28 - 4.24 (m, 1 H), 3.89 - 3.84 (m, 1 H), 2.70 - 2.56 (m, 4 H), 2.50 (t, *J* = 7.2 Hz, 2 H), 1.94 (quin, *J* = 7.2 Hz, 2 H), 1.67 - 1.62 (m, 1 H), 1.62 - 1.57 (m, 1 H), 1.57 - 1.50 (m, 1 H), 1.49 (s, 3 H), 1.45 - 1.42 (m, 1 H), 1.42 - 1.40 (m, 1 H), 1.40 - 1.38 (m, 1 H), 1.36 (s, 3 H), 0.94 (t, *J* = 7.1 Hz, 3 H);

^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.9, 108.9, 78.2, 77.6, 71.3, 39.6, 36.0, 32.5, 32.0, 31.9, 28.2, 25.7, 24.3, 18.6, 14.1;

HRMS (ESI^+) *m*/*z*: calcd for $C_{15}H_{28}O_5S$ $[M + Na]^+$ 343.1550; found 343.1541.

4-((((4*S*,5*S*)-5-((*R*)-2-hydroxypentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)thio)butanoic acid (76'):



Compound **75'** (45 mg, 0.135 mmol, 1 equiv.) was treated with $LiOH.H_2O$ (28 mg, 0.673 mmol, 5 eq.) under the same conditions as described for the synthesis of **76** to give compound **76'** as a colorless liquid, after flash column chromatography using petroleum ether/EtOAc (1:1) as eluent.

Yield = 35 mg, 81 %;

R_f = 0.22 (EtOAc);

$[\alpha]_D^{25}$ = – 3.4 (*c* 1.6, $CHCl_3$);

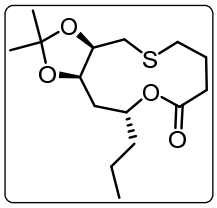
IR ($CHCl_3$): ν_{max} = 3423, 2929, 1714, 1377, 1218, 1164, 1046, 749 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.44 (ddd, *J* = 3.4, 6.0, 10.0 Hz, 1 H), 4.29 - 4.25 (m, 1 H), 3.89 - 3.84 (m, 1 H), 2.71 - 2.58 (m, 4 H), 2.49 (t, *J* = 7.1 Hz, 2 H), 1.94 (quin, *J* = 7.2 Hz, 2 H), 1.73 - 1.66 (m, 1 H), 1.59 - 1.46 (m, 4 H), 1.45 (s, 3 H), 1.44 - 1.37 (m, 1 H), 1.36 (s, 3 H), 0.94 (t, *J* = 6.9 Hz, 3 H);

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.2, 108.2, 77.5, 74.7, 68.9, 40.0, 36.1, 32.5, 32.1, 31.9, 28.3, 25.7, 24.4, 18.9, 14.0;

HRMS (ESI^+) *m*/*z* = calcd for $C_{15}H_{28}O_5S$ $[M + Na]^+$ 343.1550; found 343.1541.

(3a*R*,11*R*,12a*R*)-2,2-Dimethyl-11-propylhexahydro-4*H*-[1,3]dioxolo[4,5-*h*][1]oxa[6]thiacycloundecin-9(6*H*)-one (77):



To a solution of seco acid **76** (150 mg, 0.47 mmol, 1 equiv.) in THF (4 mL) were added Et_3N (0.11 mL, 0.79 mmol, 1.7 equiv.) and 2,4,6-trichlorobenzoyl chloride (73 μL, 0.47 mmol, 1 equiv.) and the reaction mixture was stirred overnight at room temperature under argon atmosphere and then diluted with toluene (150 mL). The resulting reaction mixture was added dropwise to a refluxing solution of DMAP (287 mg, 2.35 mmol, 5 equiv.) in toluene (20 mL) over a period of 6 h. After completion of addition, the reaction mixture was stirred for additional 3 h. Toluene was evaporated in *vacuo* and the residue was diluted with 10 mL of EtOAc, washed successively with saturated aqueous $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4 and concentrated. Flash column chromatography of the crude product using petroleum ether/EtOAc (23:2) as eluent provided the lactone **77** as a colorless liquid.

Yield = 92 mg, 65%;

R_f = 0.62 (petroleum ether/EtOAc, 7:3);

$[\alpha]_D^{25}$ = – 1.9 (*c* 0.8, $CHCl_3$);

IR ($CHCl_3$): ν_{max} = 2928, 2876, 1725, 1456, 1369, 1238, 1129, 1048, 878, 752 cm^{-1};

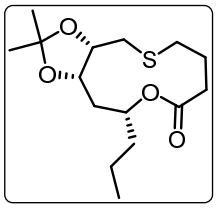
^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.44 - 5.37 (m, 1 H), 4.49 - 4.43 (m, 1 H), 4.43 - 4.38 (m, 1 H), 2.85 (ddd, *J* = 3.8, 9.5, 14.5 Hz, 1 H), 2.67 - 2.60 (m, 3 H), 2.55 (ddd, *J* = 5.3, 11.1, 14.9 Hz, 1 H), 2.43 - 2.32 (m, 2 H), 2.17 - 2.07 (m, 1 H), 1.98 - 1.89 (m, 1 H), 1.86

- 1.76 (m, 2 H), 1.60 - 1.52 (m, 1 H), 1.42 (s, 3 H), 1.38 - 1.31 (m, 5 H), 0.95 (t, *J* = 7.4 Hz, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1, 106.5, 76.6, 73.9, 70.0, 35.1, 35.0, 33.6, 33.2, 29.8, 28.6, 26.1, 26.0, 19.2, 13.8;

HRMS (ESI^+) *m*/*z* = calcd for $C_{15}H_{26}O_4S$ $[M + Na]^+$ 325.1444; found 325.1436.

(3a*S*,11*R*,12a*S*)-2,2-dimethyl-11-propylhexahydro-4*H*-[1,3]dioxolo[4,5-*h*][1]oxa[6]thiacycloundecin-9(6*H*)-one (77'):



Compound **76'** (30 mg, 0.0936 mmol, 1 equiv.) was treated with 2,4,6-trichlorobenzoyl chloride (15 μL, 0.0936 mmol, 1 equiv.) and Et_3N (22 μL, 0.159 mmol, 1.7 equiv.) in THF (2 mL) followed by its subsequent addition to a refluxing solution of DMAP (58 mg, 0.468 mmol, 5 equiv.) in toluene (30 mL) under the same reaction conditions as described for the synthesis of **77** to give compound **77'** as a pale yellow solid, after flash column chromatography using petroleum ether/EtOAc (47:3) as eluent.

Yield = 18 mg, 65%;

R_f = 0.61 (petroleum ether/EtOAc, 7:3);

mp = 60-61 ^oC;

$[\alpha]_D^{25}$ = – 0.8 (*c* 0.85, $CHCl_3$);

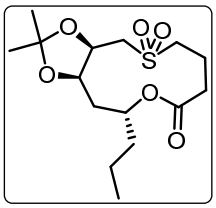
IR ($CHCl_3$): ν_{max} = 2931, 2870, 1727, 1450, 1372, 1232, 1138, 1047, 871, 750 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.11 - 5.05 (m, 1 H), 4.21 - 4.16 (m, 1 H), 4.07 - 4.04 (m, 1 H), 3.08 (dd, *J* = 6.1, 12.6 Hz, 1 H), 2.77 - 2.70 (m, 1 H), 2.55 (dd, *J* = 5.7, 12.6 Hz, 1 H), 2.53 - 2.48 (m, 1 H), 2.41 - 2.34 (m, 1 H), 2.27 - 2.21 (m, 1 H), 2.21 - 2.13 (m, 1 H), 2.13 - 2.05 (m, 1 H), 2.00 - 1.92 (m, 1 H), 1.91 - 1.86 (m, 1 H), 1.63 - 1.49 (m, 2 H), 1.43 (s, 3 H), 1.37 - 1.29 (m, 5 H), 0.91 (t, *J* = 7.2 Hz, 3 H);

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.0, 107.4, 78.3, 75.5, 72.7, 38.1, 35.8, 35.1, 29.5, 28.8, 28.3, 25.9, 22.6, 18.3, 13.9;

HRMS (ESI^+) *m*/*z* = calcd for $C_{15}H_{26}O_4S$ $[M + Na]^+$ 325.1444; found 325.1437.

(3a*R*,11*R*,12a*R*)-2,2-Dimethyl-11-propylhexahydro-4*H*-[1,3]dioxolo[4,5-*h*][1]oxa[6]thiacycloundecin-9(6*H*)-one 5,5-dioxide (78):



To a solution of thioether **77** (40 mg, 0.132 mmol, 1 equiv.) in CH_2Cl_2 (5 mL) at 0 °C was added 75% *m*-CPBA (76 mg, 0.331mmol, 2.5 equiv.). The reaction was allowed to warm to rt while stirring for 2 h. The reaction was quenched with the addition of saturated aqueous Na_2SO_3 solution (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ solution (10 mL), dried over Na_2SO_4, filtered, and reduced in *vacuo*. The product was purified by flash column chromatography using petroleum ether/EtOAc (3:2) to yield the title compound **78** as white solid.

Yield = 37 mg, 84%;

R_f = 0.35 (petroleum ether/EtOAc, 1:1);

mp = 110 ^{o}C;

$[\alpha]_D^{25}$ = – 1.6 (*c* 1.1, $CHCl_3$);

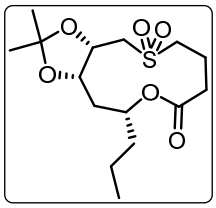
IR ($CHCl_3$): ν_{max} = 2951, 2879, 1729, 1456, 1376, 1307, 1243, 1121, 1048, 903, 795, 774 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.27 - 5.22 (m, 1 H), 4.59 - 4.53 (m, 1 H), 4.43 - 4.39 (m, 1 H), 3.45 - 3.29 (m, 2 H), 3.27 - 3.20 (m, 2 H), 2.57 - 2.45 (m, 2 H), 2.28 - 2.18 (m, 1 H), 2.13 - 1.97 (m, 3 H), 1.76 - 1.68 (m, 1 H), 1.59 - 1.52 (m, 4 H), 1.40 (s, 3 H), 1.38 - 1.33 (m, 2 H), 0.96 (t, *J* = 7.3 Hz, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 109.0, 73.9, 72.5, 71.8, 51.7, 51.2, 35.4, 33.7, 32.2, 27.4, 25.5, 18.8, 18.3, 13.8;

HRMS (ESI^+) *m/z* = calcd for $C_{15}H_{26}O_6S$ $[M + Na]^+$ 357.1342; found 357.1335.

(3a*S*,11*R*,12a*S*)-2,2-dimethyl-11-propylhexahydro-4*H*-[1,3]dioxolo[4,5-*h*][1]oxa[6]thiacycloundecin-9(6*H*)-one 5,5-dioxide (78'):



Compound **77'** (15 mg, 0.0495 mmol, 1 equiv.) was treated with 75% *m*-CPBA (29 mg, 0.124 mmol, 2.5 equiv.) under the same conditions as described for the synthesis of **78** to give compound **78'** as a white solid, after flash column chromatography using petroleum ether/EtOAc (1:1) as eluent.

Yield = 14 mg, 85 %;

R_f = 0.22 (petroleum ether/EtOAc, 3:2);

mp = 126-128 ^{o}C;

$[\alpha]_D^{25}$ = – 1.5 (*c* 0.5, $CHCl_3$);

IR ($CHCl_3$): ν_{max} = 2955, 2872, 1730, 1455, 1377, 1305, 1236, 1123, 1052, 908, 755 cm^{-1};

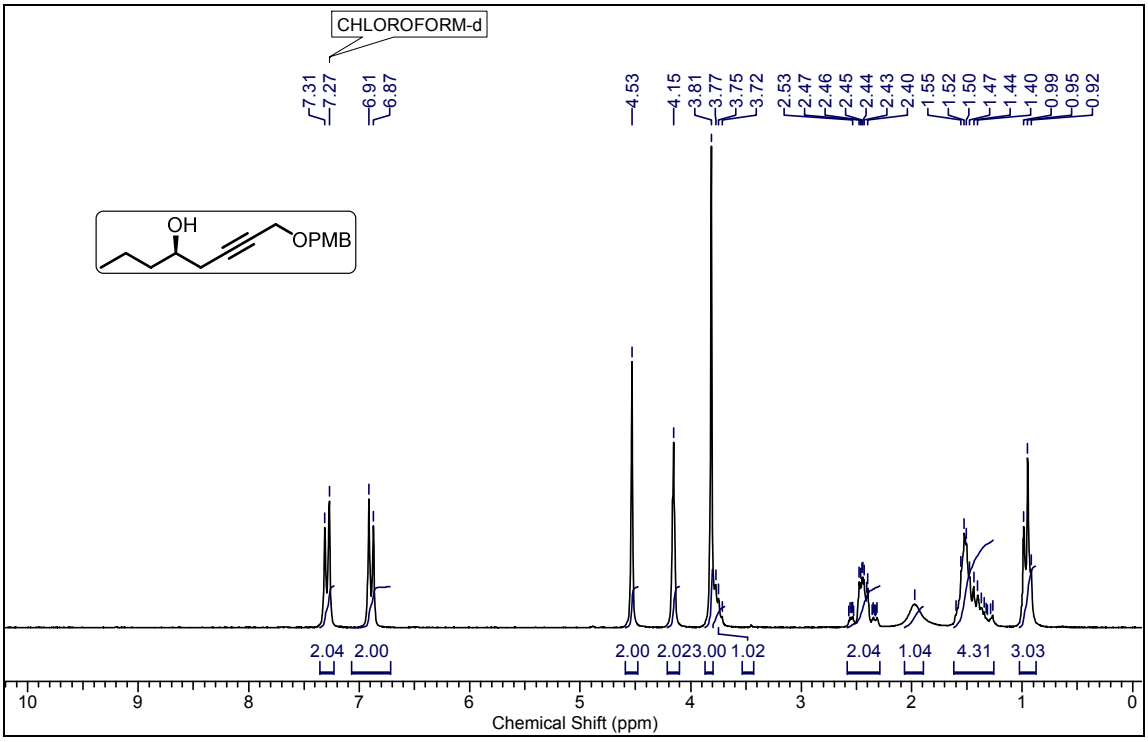
^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.15 - 5.09 (m, 1 H), 4.34 - 4.28 (m, 2 H), 3.88 (d, *J* = 15.3 Hz, 1 H), 3.20 - 3.13 (m, 1 H), 2.94 (ddd, *J* = 5.0, 5.0, 16.0 Hz, 1 H), 2.89 - 2.81 (m, 1 H), 2.66 (ddd, *J* = 4.2, 4.2, 16.4 Hz, 1 H), 2.41 (ddd, J = 8.2, 8.2, 16.4 Hz, 1 H), 2.22 - 2.14 (m, 3 H), 2.05 - 1.95 (m, 1 H), 1.69 - 1.61 (m, 1 H), 1.59 - 1.53 (m, 1 H), 1.50 (s, 3 H), 1.37 (s, 3 H), 1.36 - 1.31 (m, 2 H), 0.94 (t, *J* = 7.2 Hz, 3 H);

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.2, 108.7, 77.3, 73.5, 72.6, 51.2, 49.2, 37.5, 34.2, 28.2, 25.6, 18.3, 18.0, 13.8;

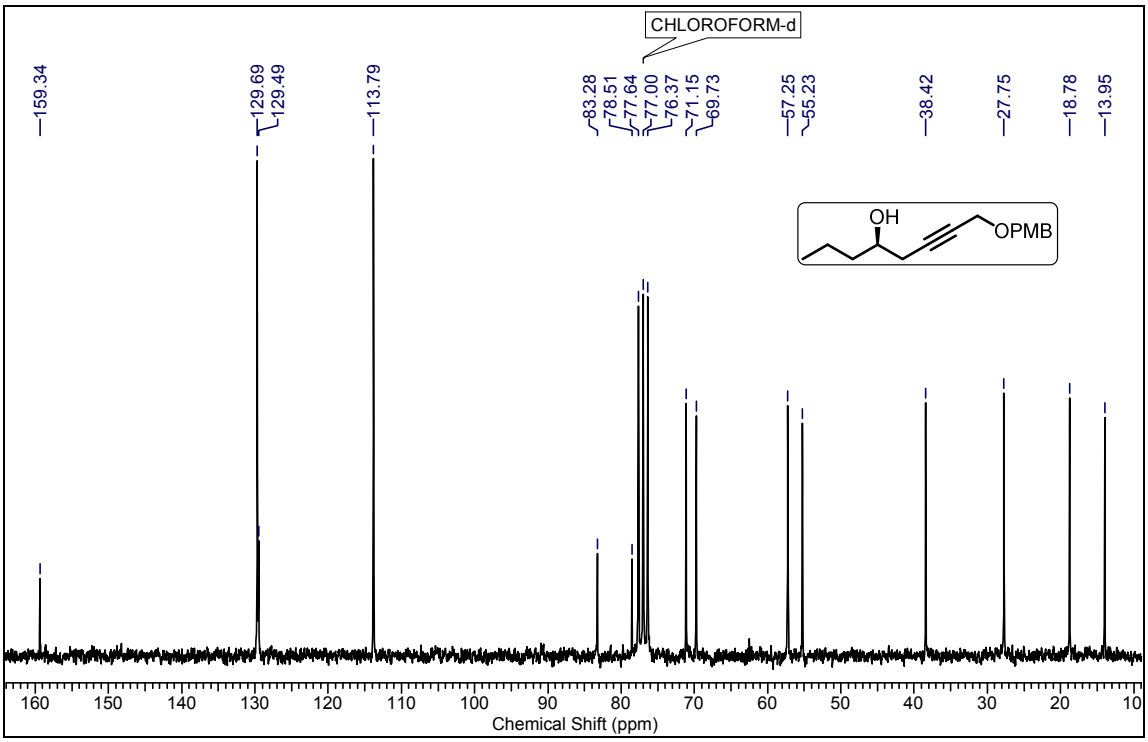
HRMS (ESI^+) *m*/*z* = calcd for $C_{15}H_{26}O_6S$ $[M + Na]^+$ 357.1342; found 357.1331.

2.1.6. Spectral Data

^{1}H NMR spectrum of compound **65** ($CDCl_3$, 200 MHz):

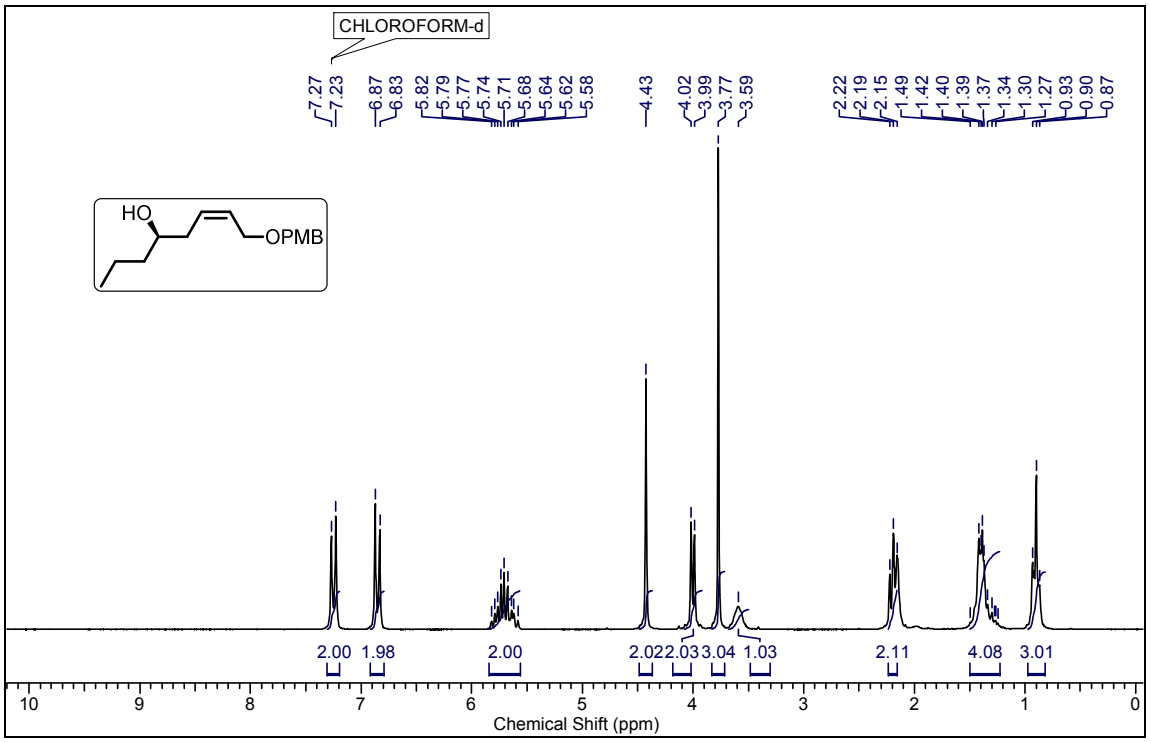


^{13}C NMR spectrum of compound **65** ($CDCl_3$, 50 MHz):

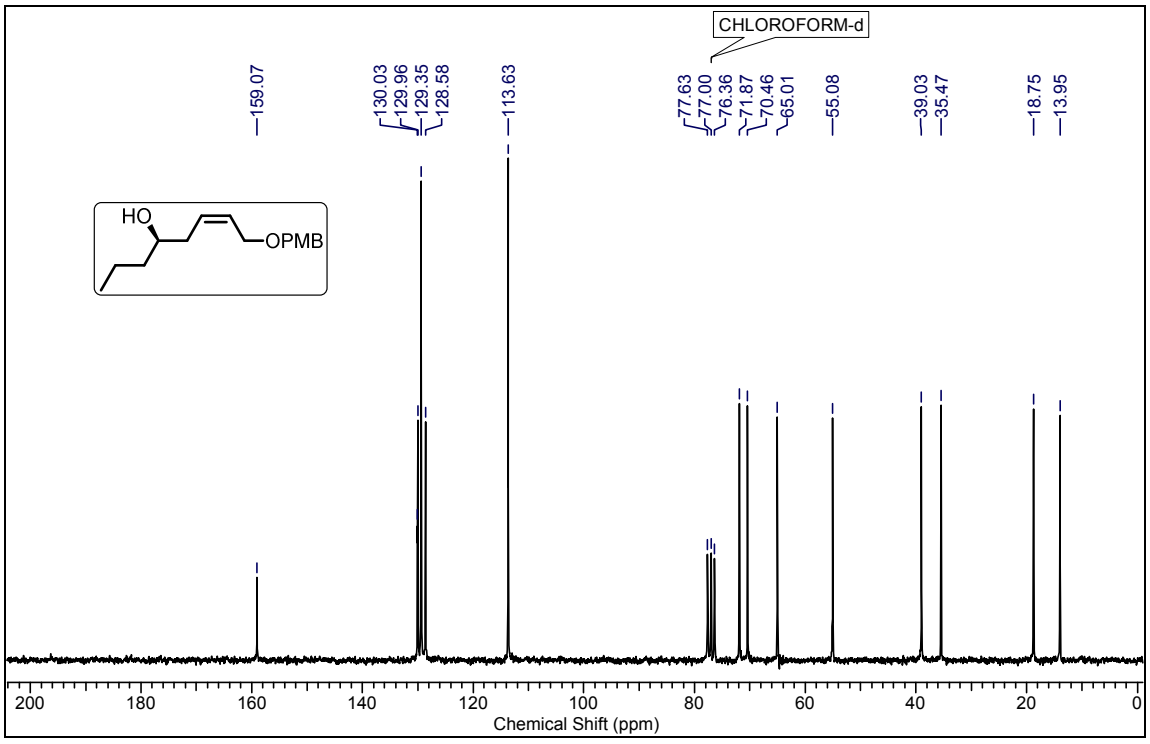


Spectra

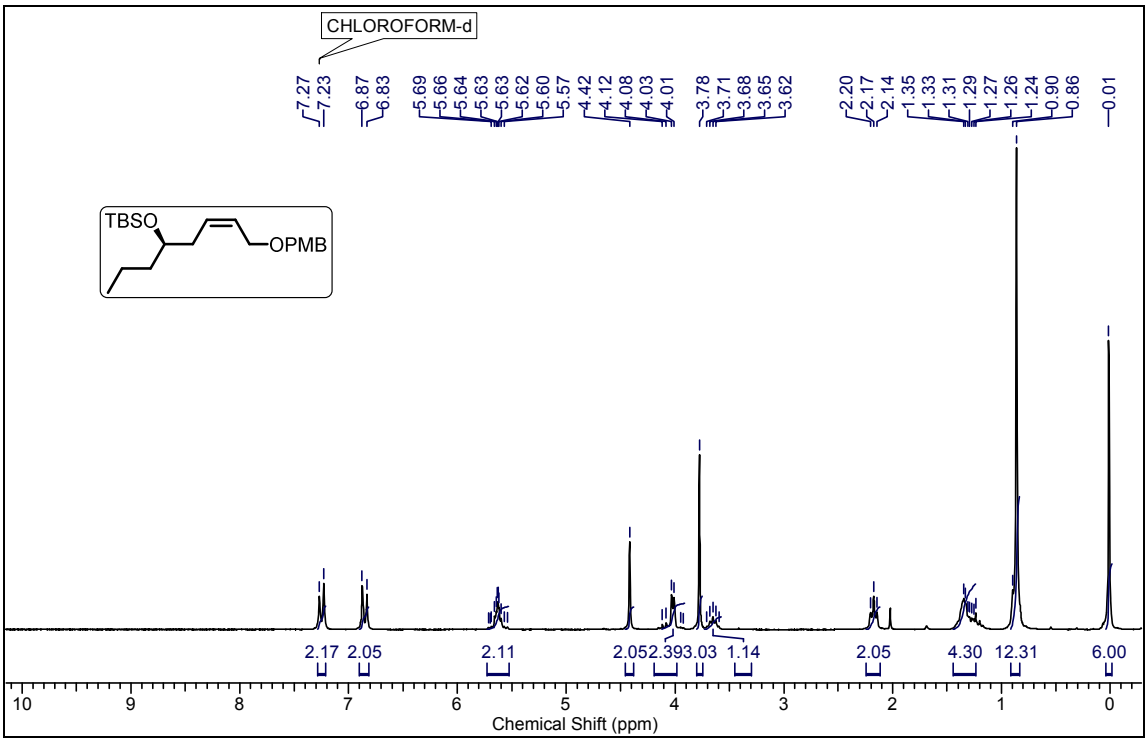
^{1}H NMR spectrum of compound **66** ($CDCl_3$, 200 MHz):



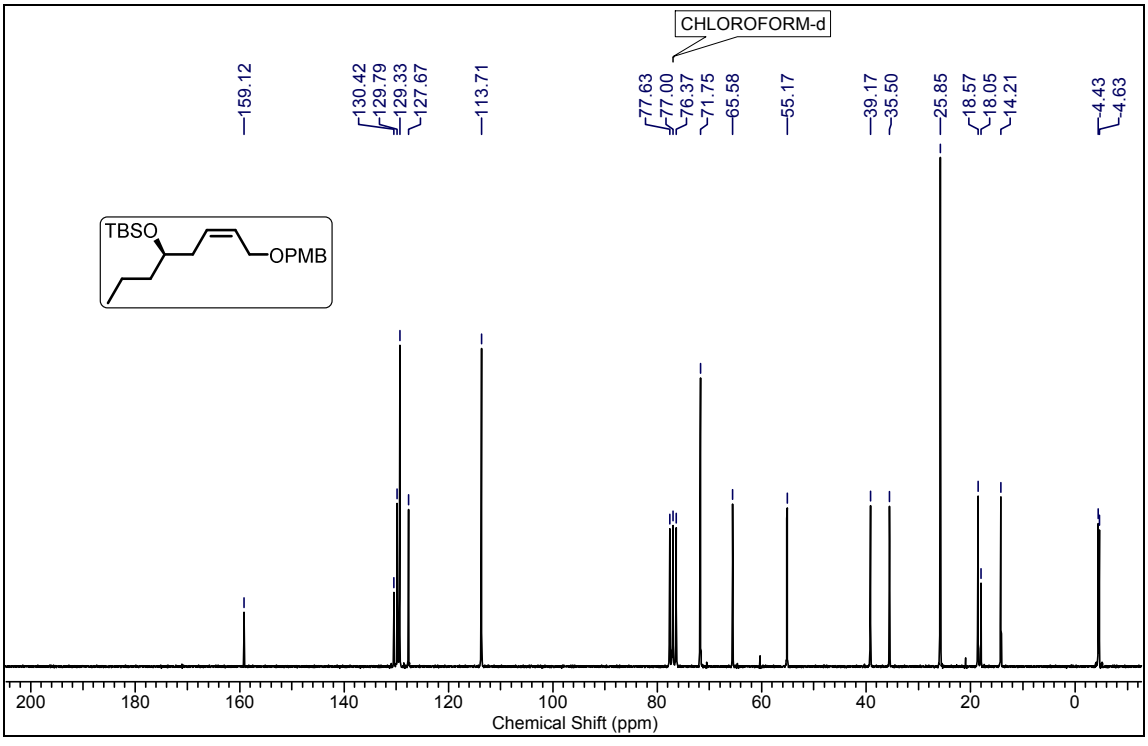
^{13}C NMR spectrum of compound **66** ($CDCl_3$, 50 MHz):



^{1}H NMR spectrum of compound **67** ($CDCl_3$, 200 MHz):

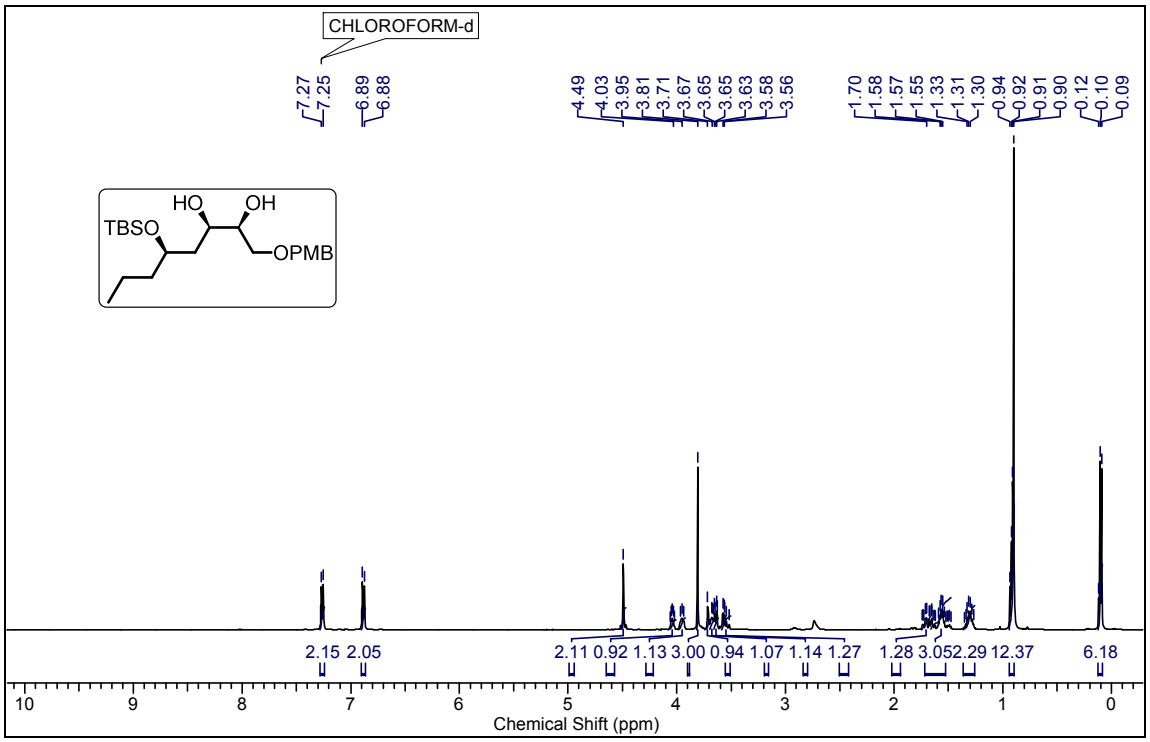


^{13}C NMR spectrum of compound **67** ($CDCl_3$, 50 MHz):

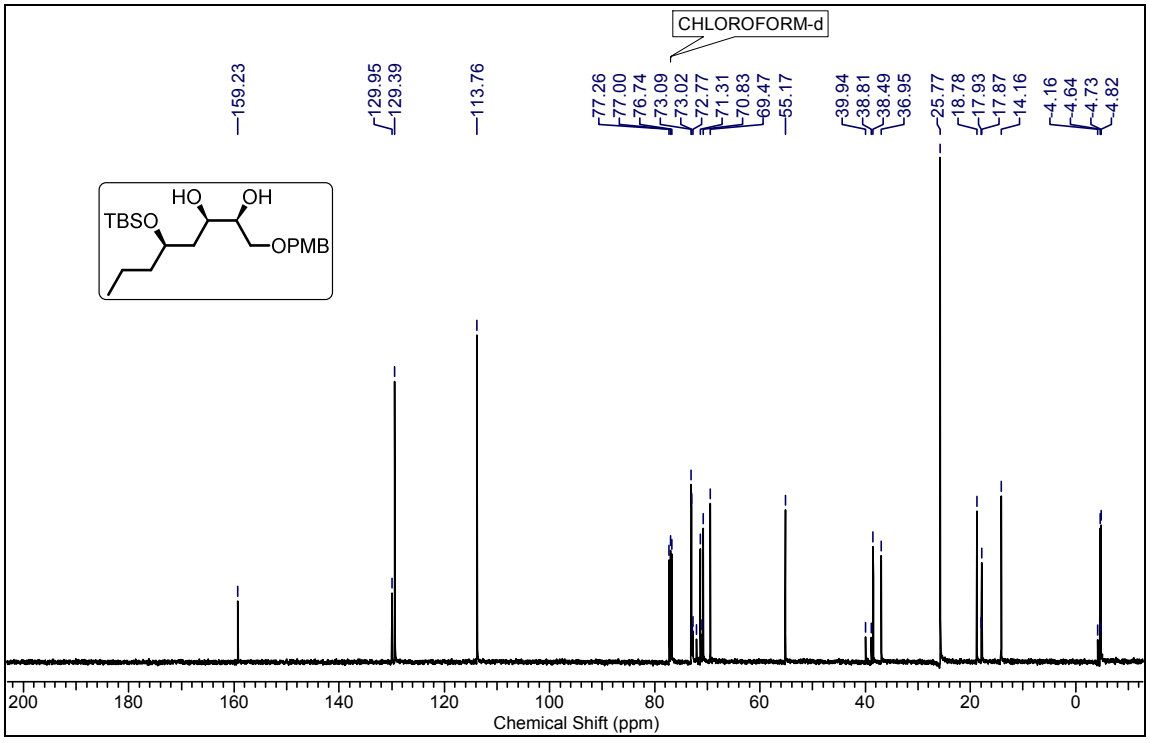


Spectra

^{1}H NMR spectrum of compound **68** ($CDCl_3$, 500 MHz):



^{13}C NMR spectrum of compound **68** ($CDCl_3$, 125 MHz):



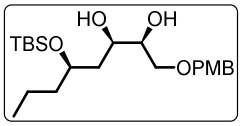
HPLC (*dr*) of the compound **68**:

D-7000 HPLC System Manager Report

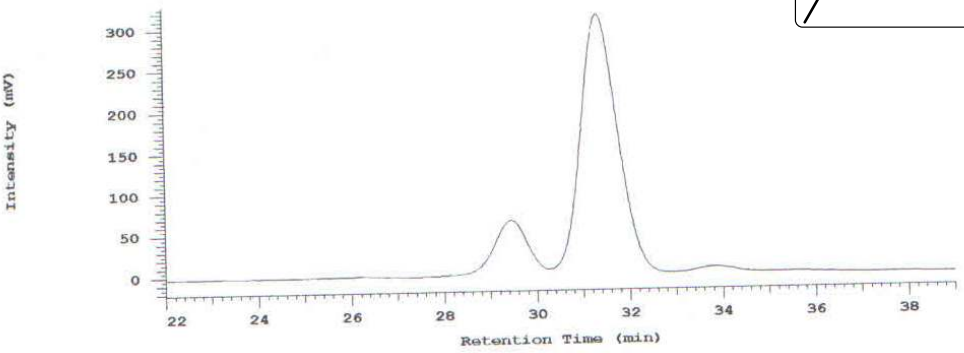
Analyzed: 08/02/17 02:46 PM
Reported: 08/03/17 11:28 AM
Processed: 08/03/17 11:27 AM

Data Path: C:\WIN32APP\HSM\HPLC\DATA\9677\
Processing Method: cal
System(acquisition): Sys 1
Application: HPLC
Sample Name: J-1
Injection from this vial: 1 of 1
Sample Description: MEOH:H2O(75:25)

Series:9677
Volume: 10.0 ul



Chrom Type: HPLC Channel : 1



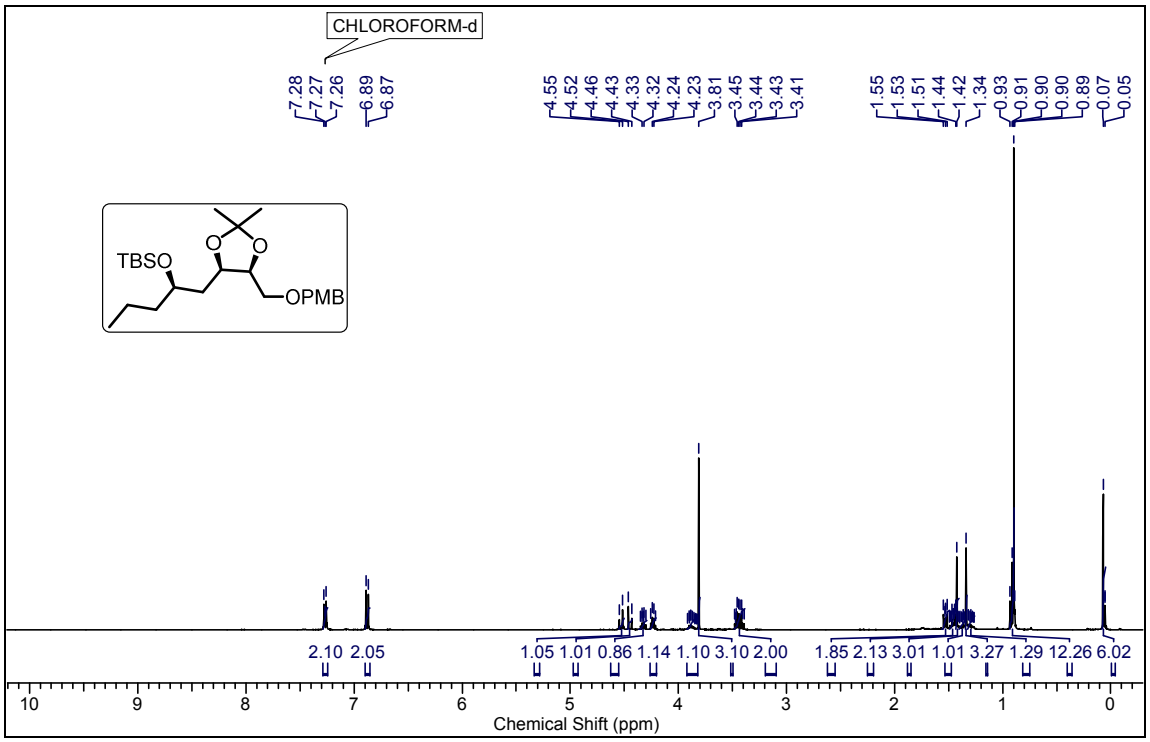
No.	RT	Area	Conc 1	BC
1	29.45	3058392	15.097	BV
2	31.35	17199224	84.903	VB
		20257616	100.000	

Peak rejection level: 0

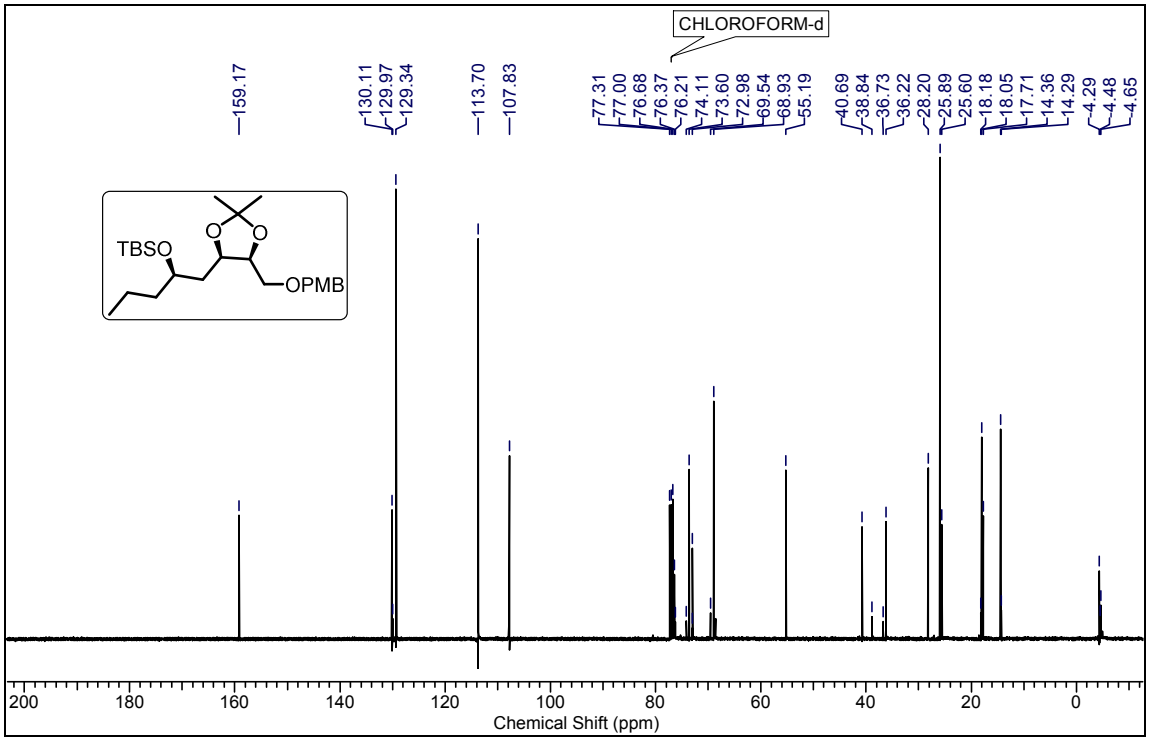
Project Leader: Dr.Tripathi P.K.
Column :Kromasil RP-18 (150 mmx4.6mm)
Mobile Ph : MEOH:H2O(75:25)
Wavelength : 230nm
Flow : 1.0 ml/min.
Inject vol: 5ul

Spectra

^{1}H NMR spectrum of compound **69** ($CDCl_3$, 400 MHz):



^{13}C NMR spectrum of compound **69** ($CDCl_3$, 100 MHz):



HPLC (*dr*) of the compound **69**:

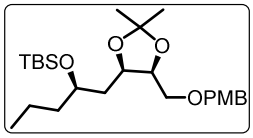
D-7000 HPLC System Manager Report

Analyzed: 08/02/17 01:20 PM
Reported: 08/03/17 10:51 AM
Processed: 08/03/17 10:51 AM

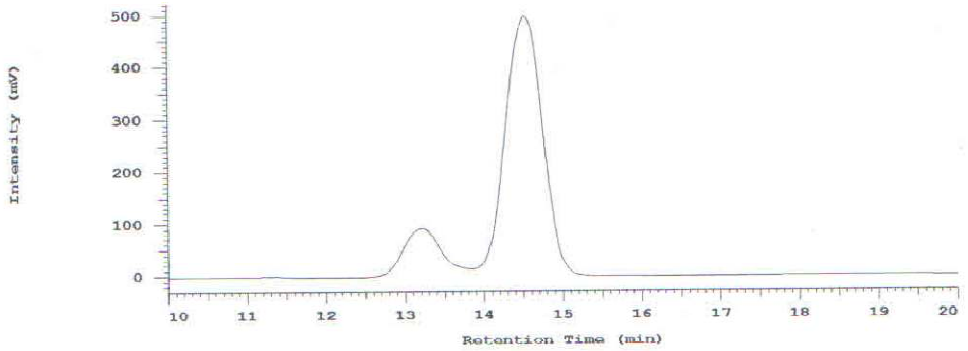
Data Path: C:\WIN32APP\HSM\HPLC\DATA\9674\
Processing Method: cal

System(acquisition): Sys 1
Application: HPLC
Sample Name: J-2
Injection from this vial: 1 of 1
Sample Description: MEOH:H2O(90:10)

Series:9674
Volume: 10.0 ul



Chrom Type: HPLC Channel : 1



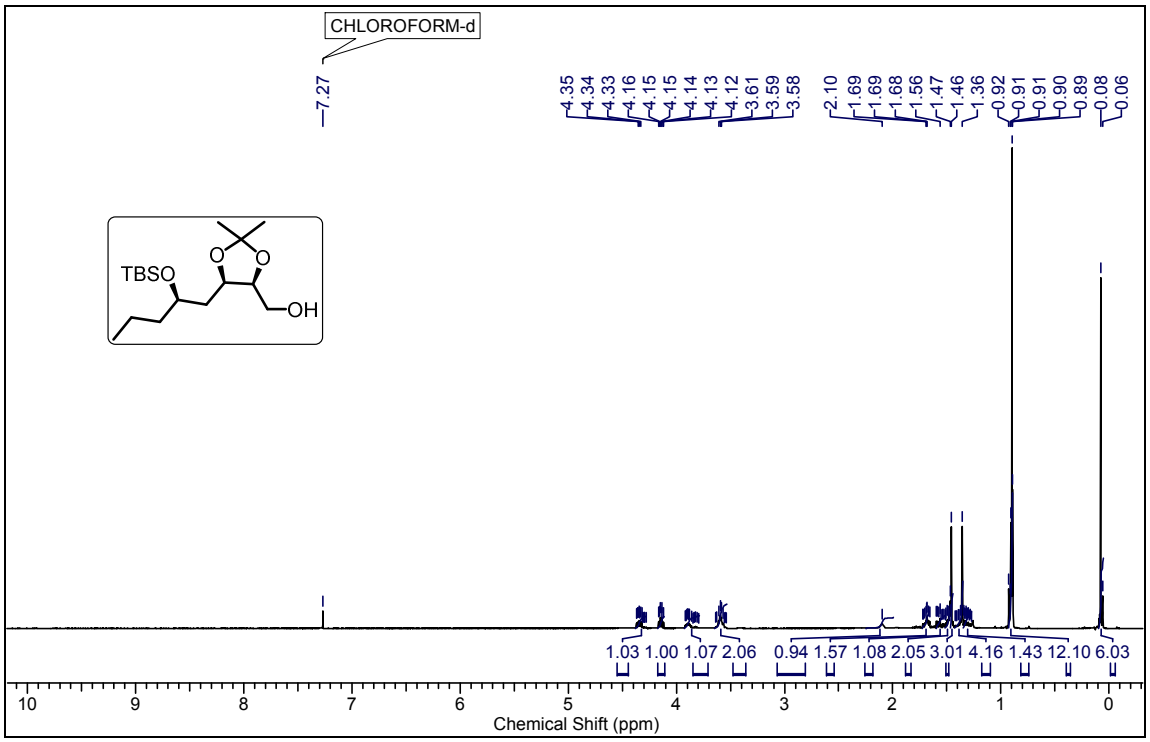
No.	RT	Area	Conc 1	BC
1	13.21	3058931	15.847	BV
2	14.53	16244078	84.153	VB
		19303009	100.000	

Peak rejection level: 0

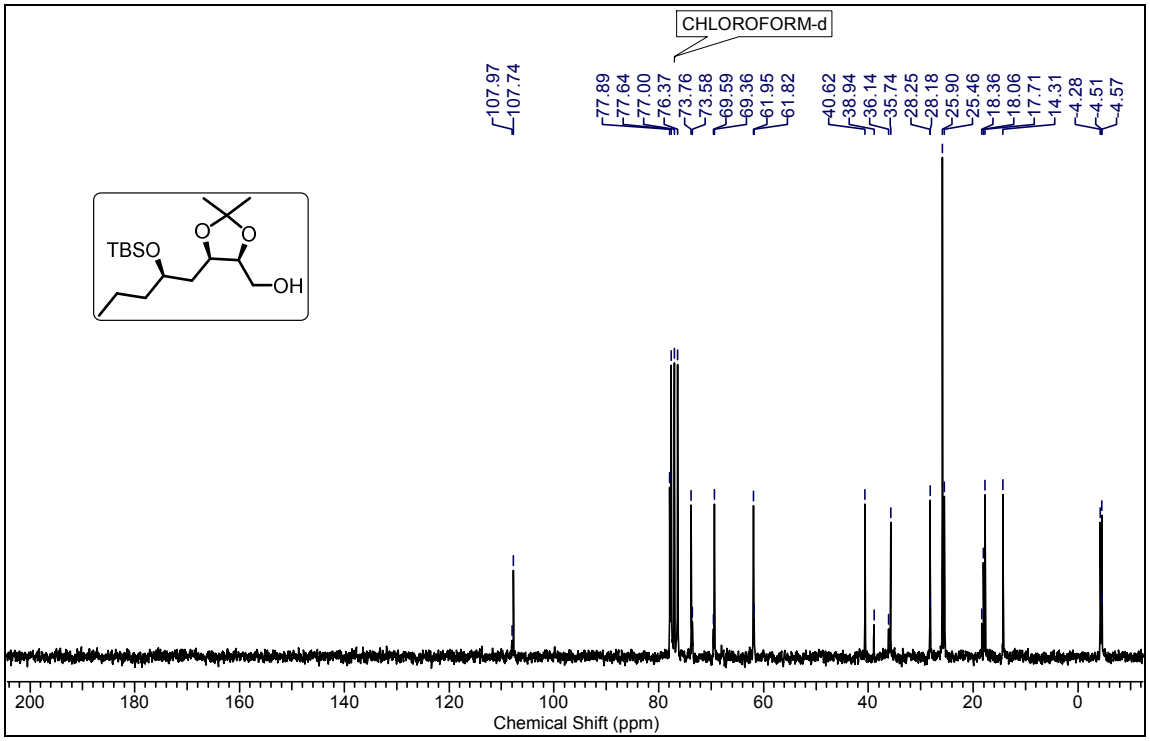
Project Leader: Dr.Tripathi P.K.
Column :Kromasil RP-18 (150 mmx4.6mm)
Mobile Ph : MEOH:H2O(90:10)
Wavelength : 230nm
Flow : 1.0 ml/min.
Inject vol: 5ul

Spectra

^{1}H NMR spectrum of compound **70** ($CDCl_3$, 400 MHz):



^{13}C NMR spectrum of compound **70** ($CDCl_3$, 50 MHz):



HPLC (*dr*) of the compound **70**:

D-7000 HPLC System Manager Report

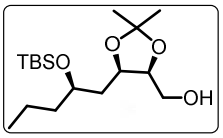
Analyzed: 08/02/17 04:51 PM

Reported: 08/02/17 05:10 PM
Processed: 08/02/17 05:10 PM

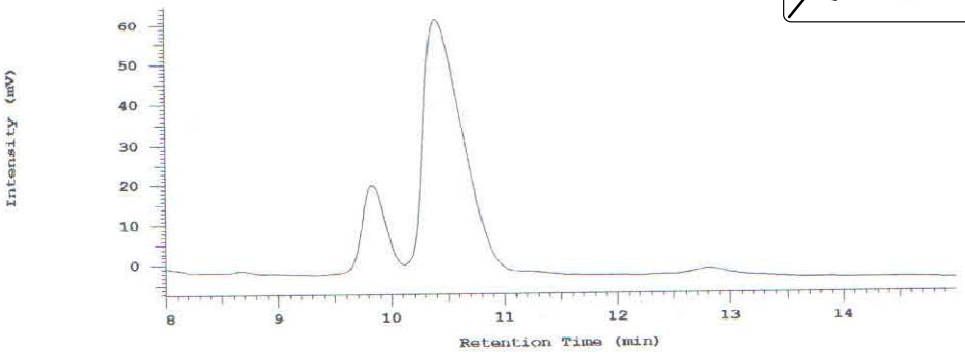
Data Path: C:\WIN32APP\HSM\HPLC\DATA\9680\
Processing Method: cal

System(acquisition): Sys 1
Application: HPLC
Sample Name: J-3
Injection from this vial: 1 of 1
Sample Description: ACN:H2O(80:20)

Series:9680
Volume: 10.0 ul



Chrom Type: HPLC Channel : 1



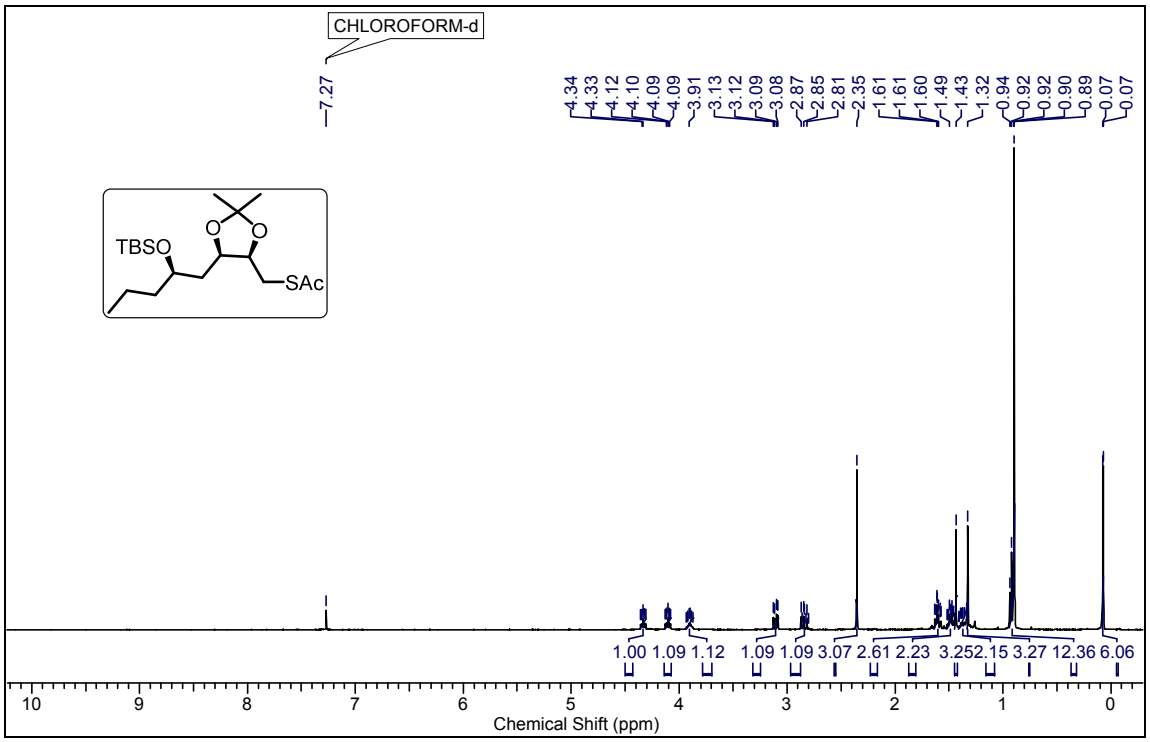
No.	RT	Area	Conc 1	BC
1	9.83	306861	17.080	BV
2	10.40	1489727	82.920	VB
		1796588	100.000	

Peak rejection level: 0

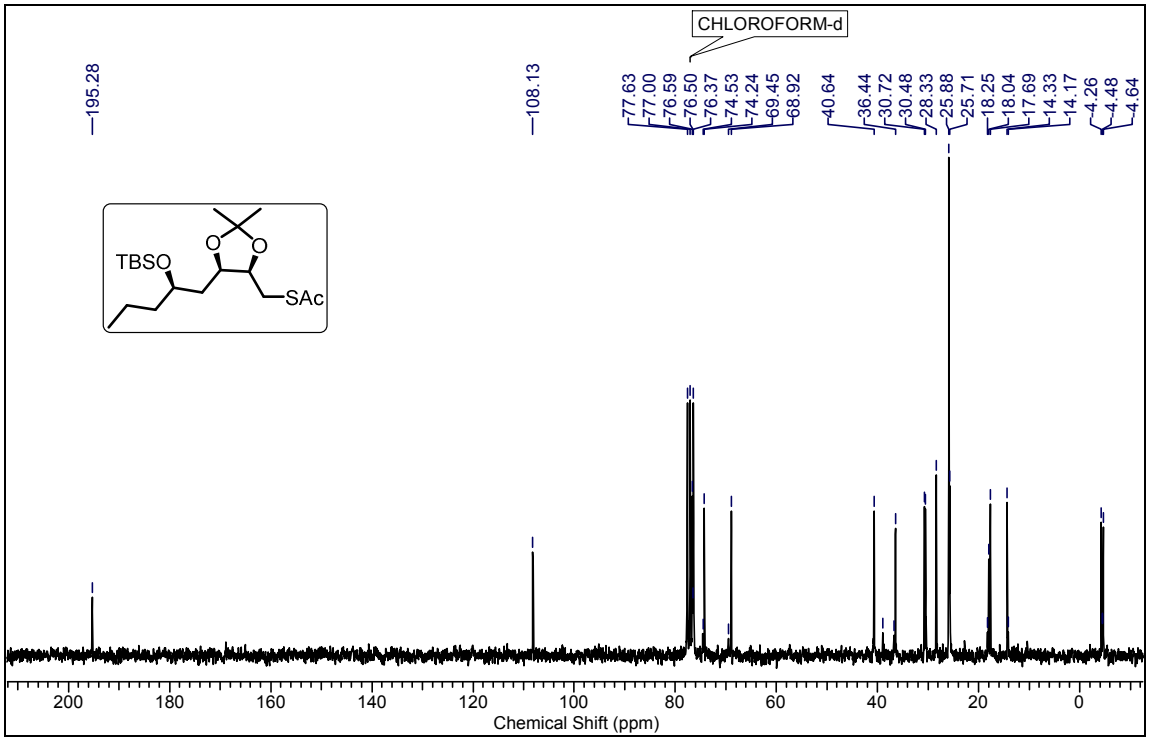
Project Leader: Dr.Tripathi P.K.
Column :Kromasil RP-18 (150 mmx4.6mm)
Mobile Ph : ACN:H2O(80:20)
Wavelength : 210nm
Flow : 1.0 ml/min.
Inject vol: 10ul

Spectra

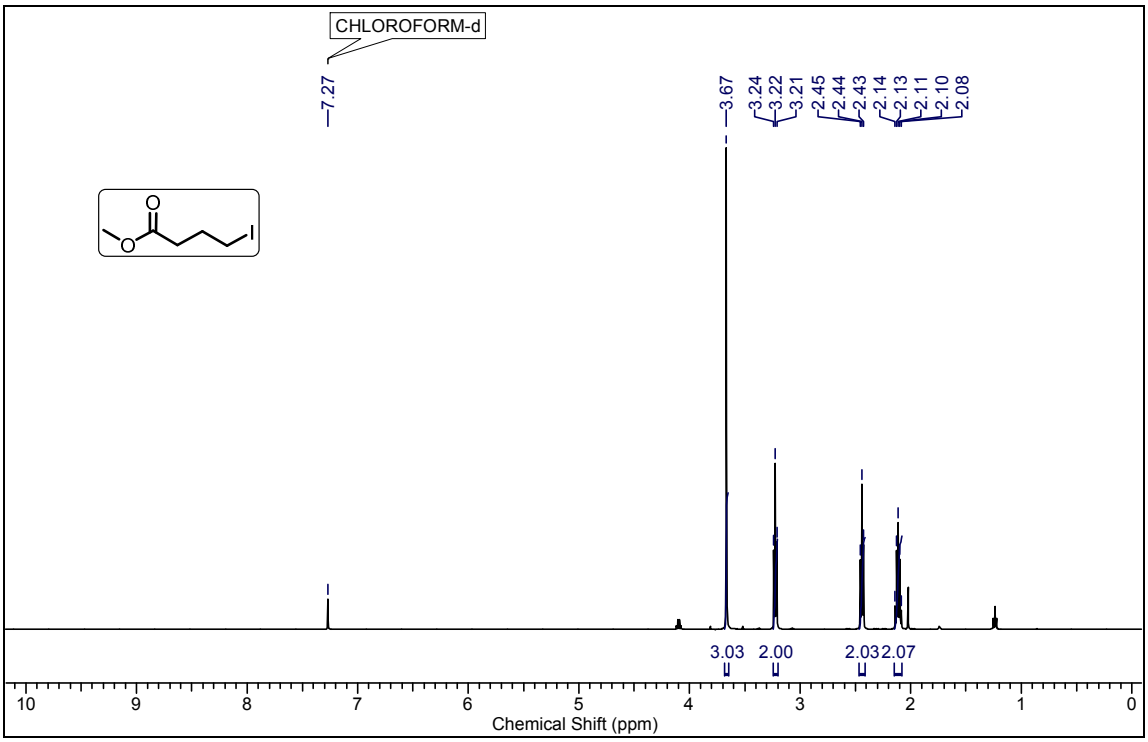
^{1}H NMR spectrum of compound **71** ($CDCl_3$, 400 MHz):



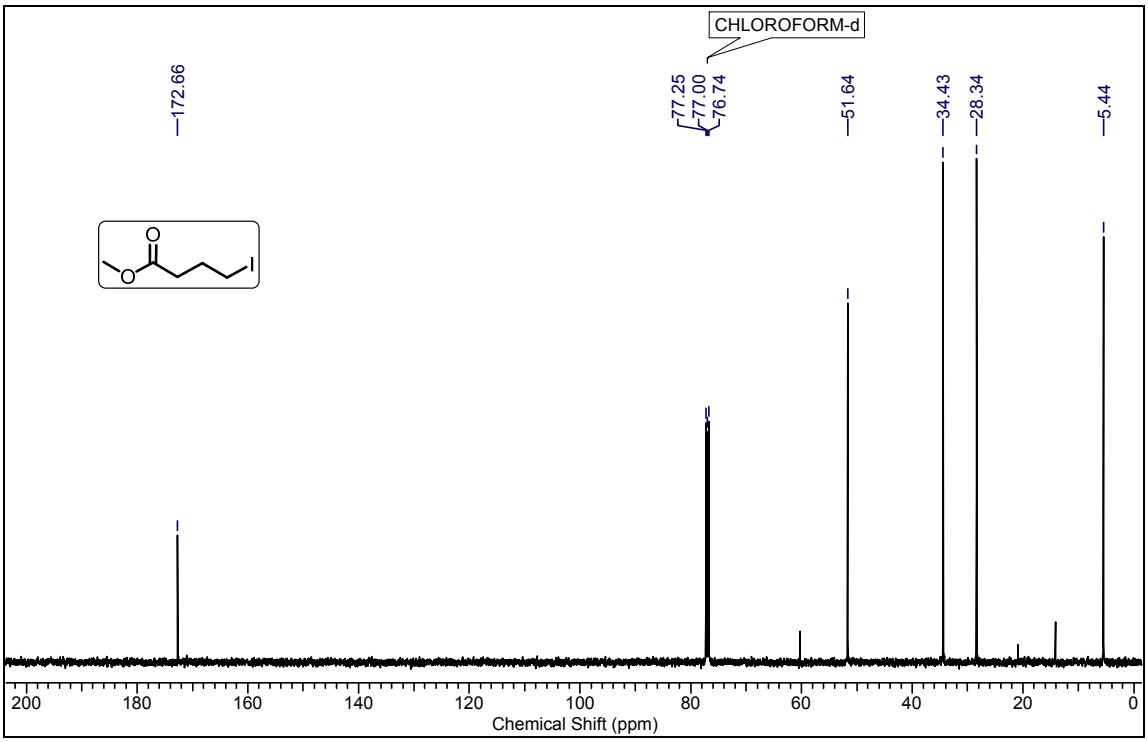
^{13}C NMR spectrum of compound **71** ($CDCl_3$, 50 MHz):



^{1}H NMR spectrum of compound **73** ($CDCl_3$, 500 MHz):

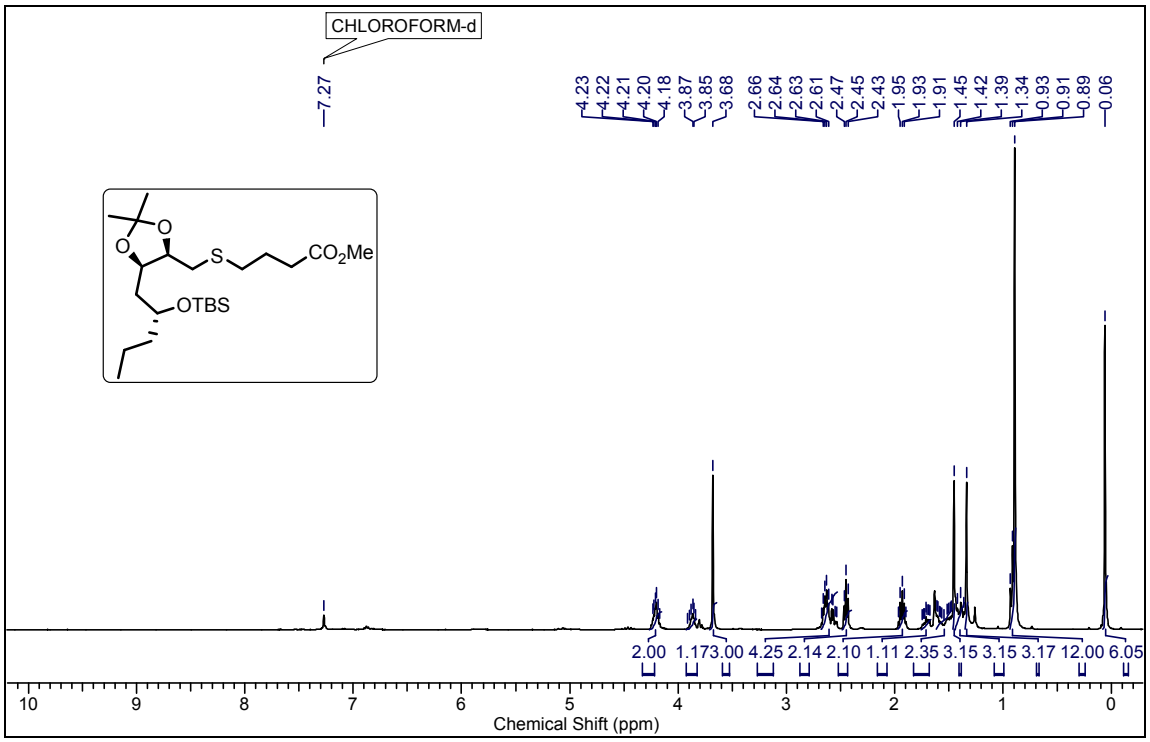


^{13}C NMR spectrum of compound **73** ($CDCl_3$, 125 MHz):

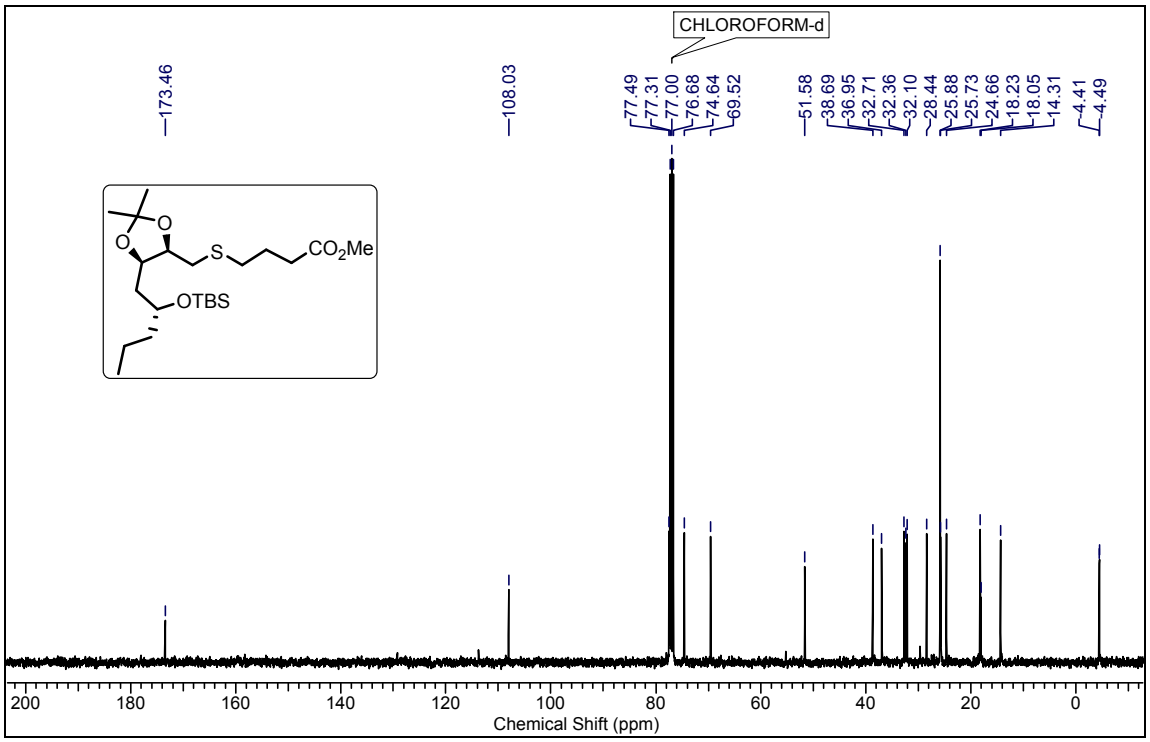


Spectra

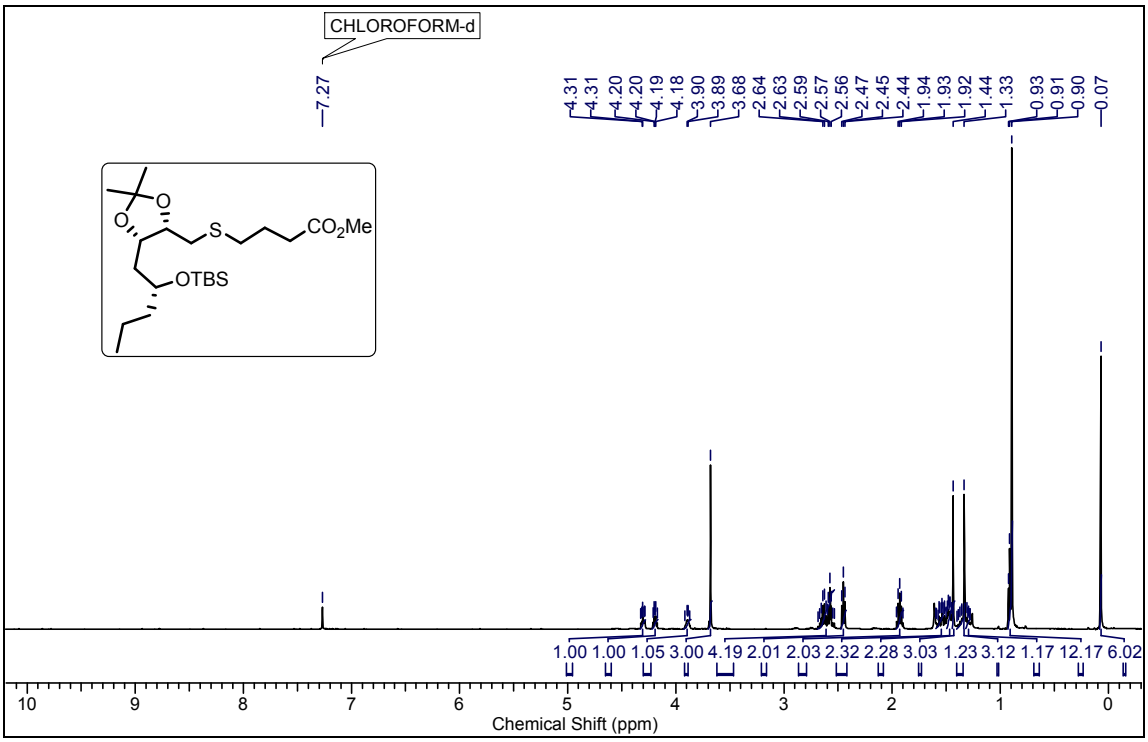
^{1}H NMR spectrum of compound **74** ($CDCl_3$, 400 MHz):



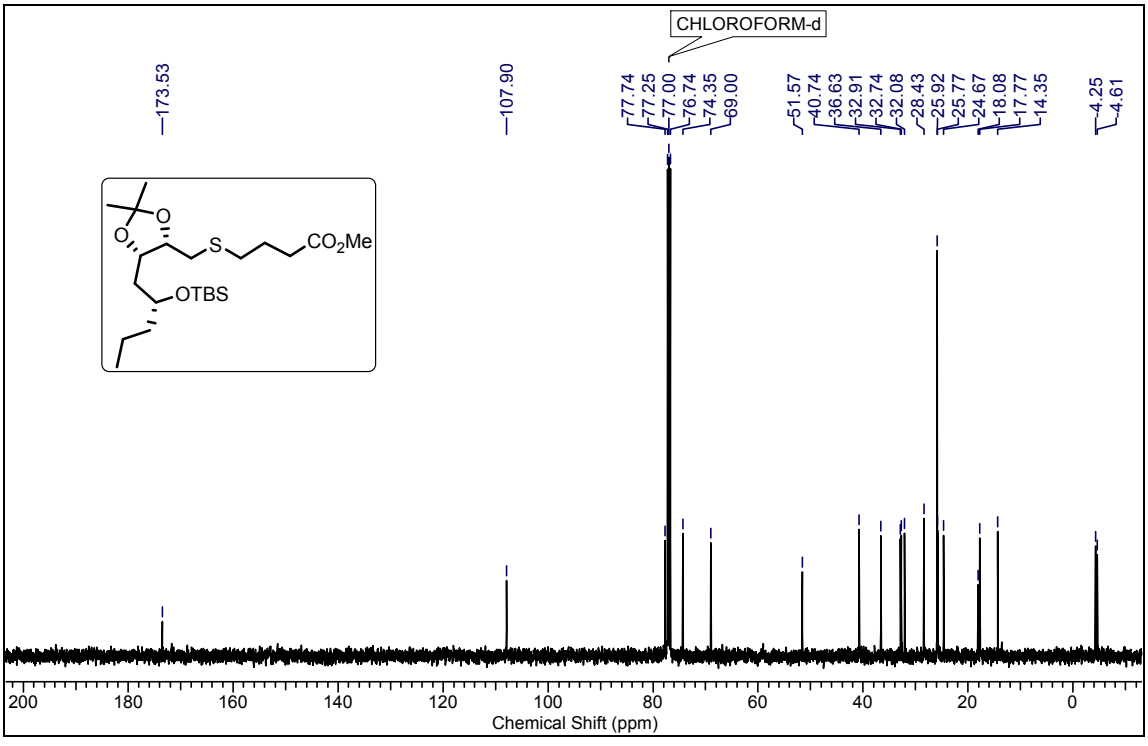
^{13}C NMR spectrum of compound **74** ($CDCl_3$, 100 MHz):



^{1}H NMR spectrum of compound **74'** ($CDCl_3$, 500 MHz):

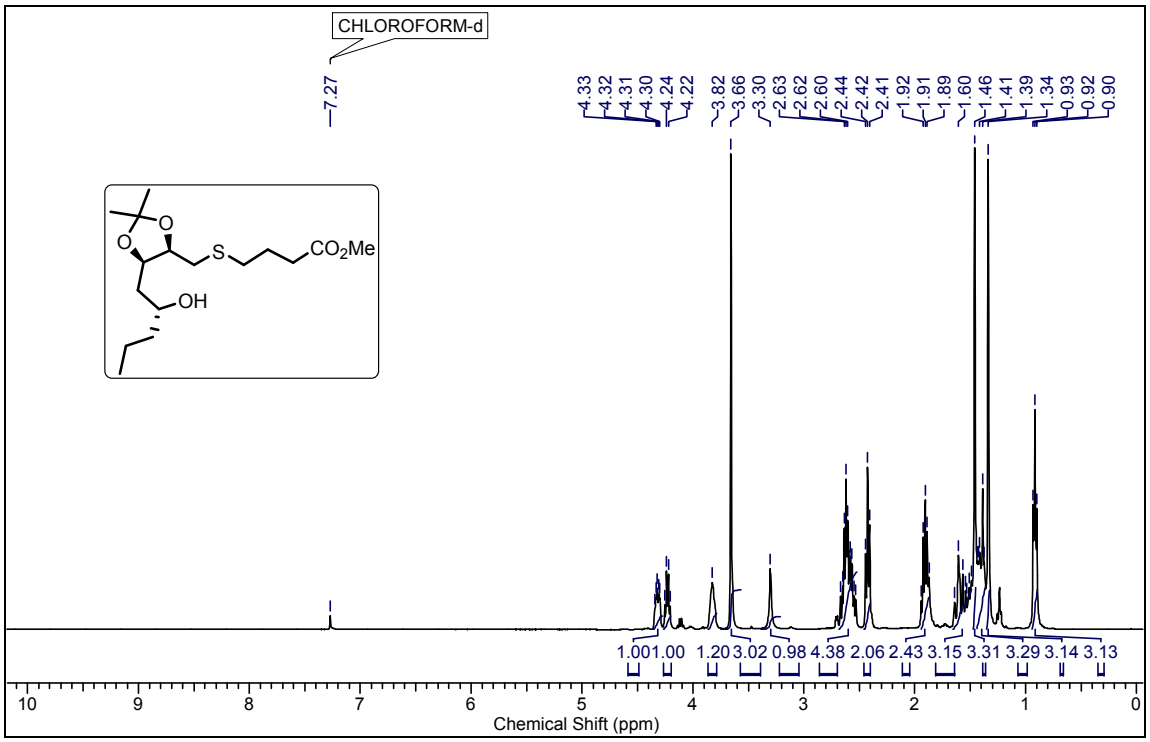


^{13}C NMR spectrum of compound **74'** ($CDCl_3$, 125 MHz):

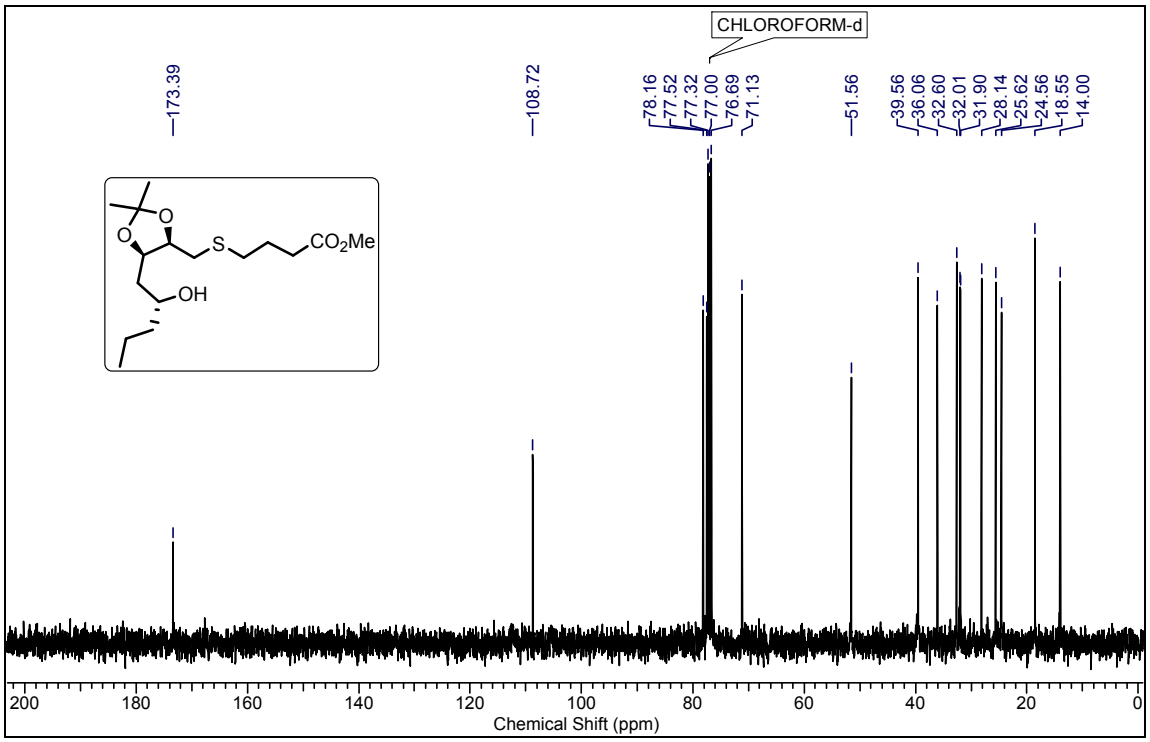


Spectra

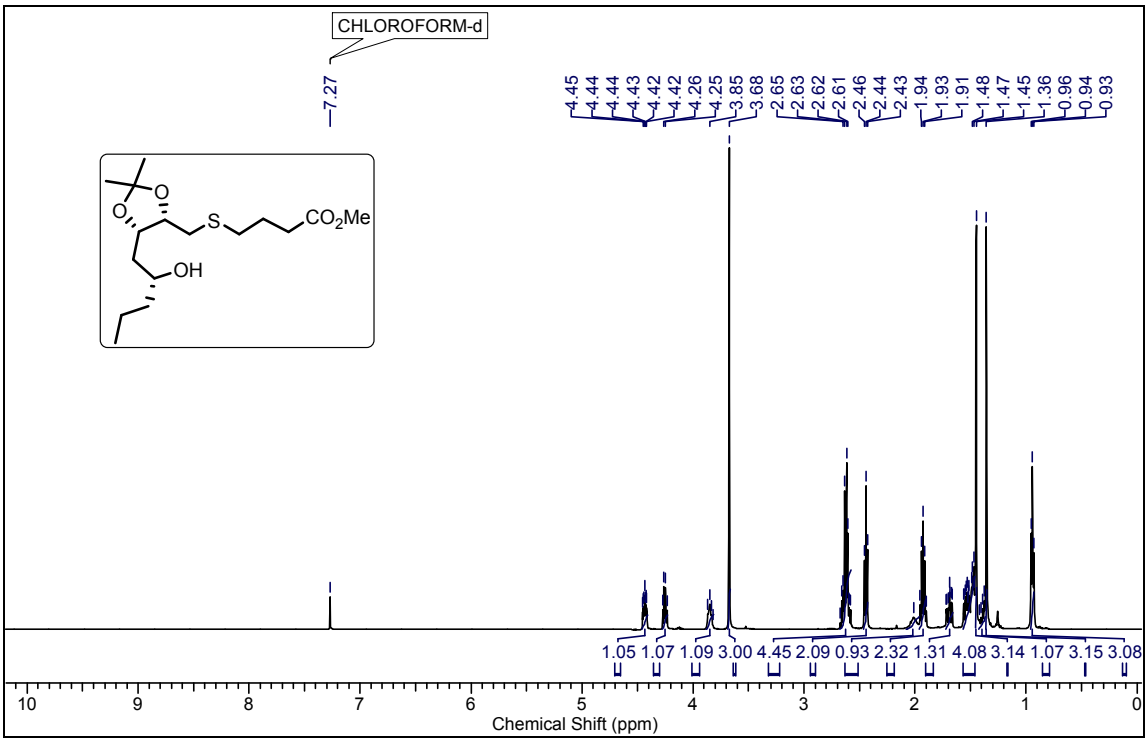
^{1}H NMR spectrum of compound **75** ($CDCl_3$, 400 MHz):



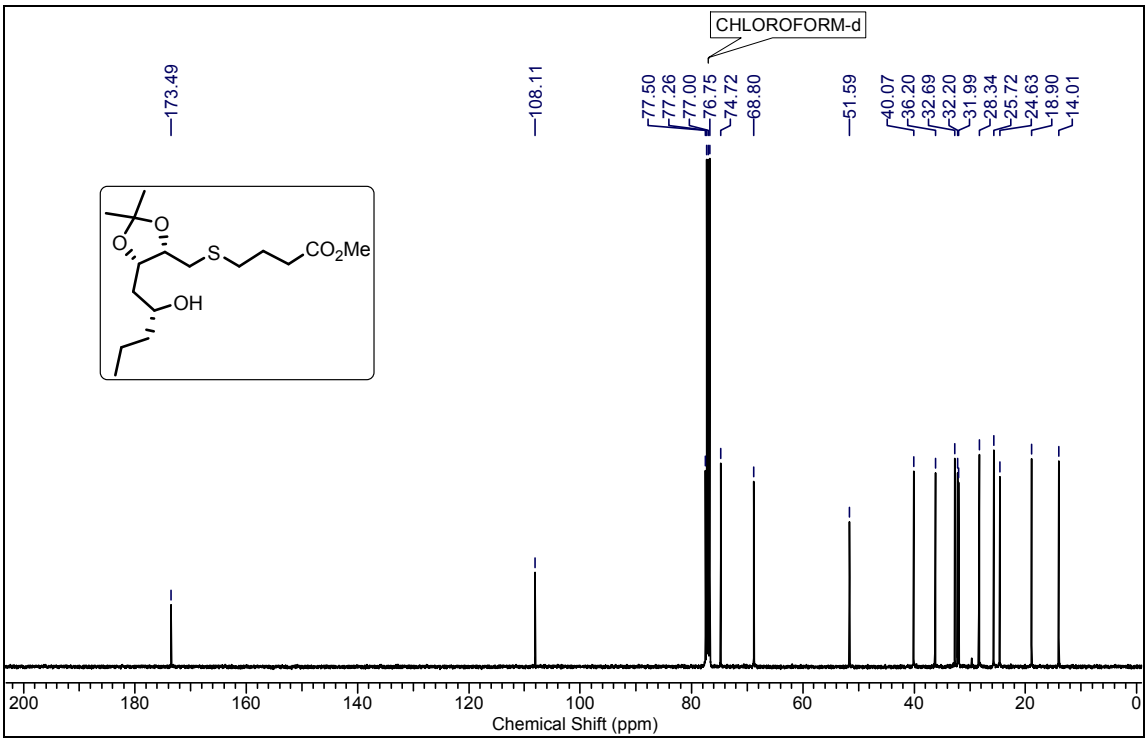
^{13}C NMR spectrum of compound **75** ($CDCl_3$, 100 MHz):



^{1}H NMR spectrum of compound **75'** ($CDCl_3$, 500 MHz):

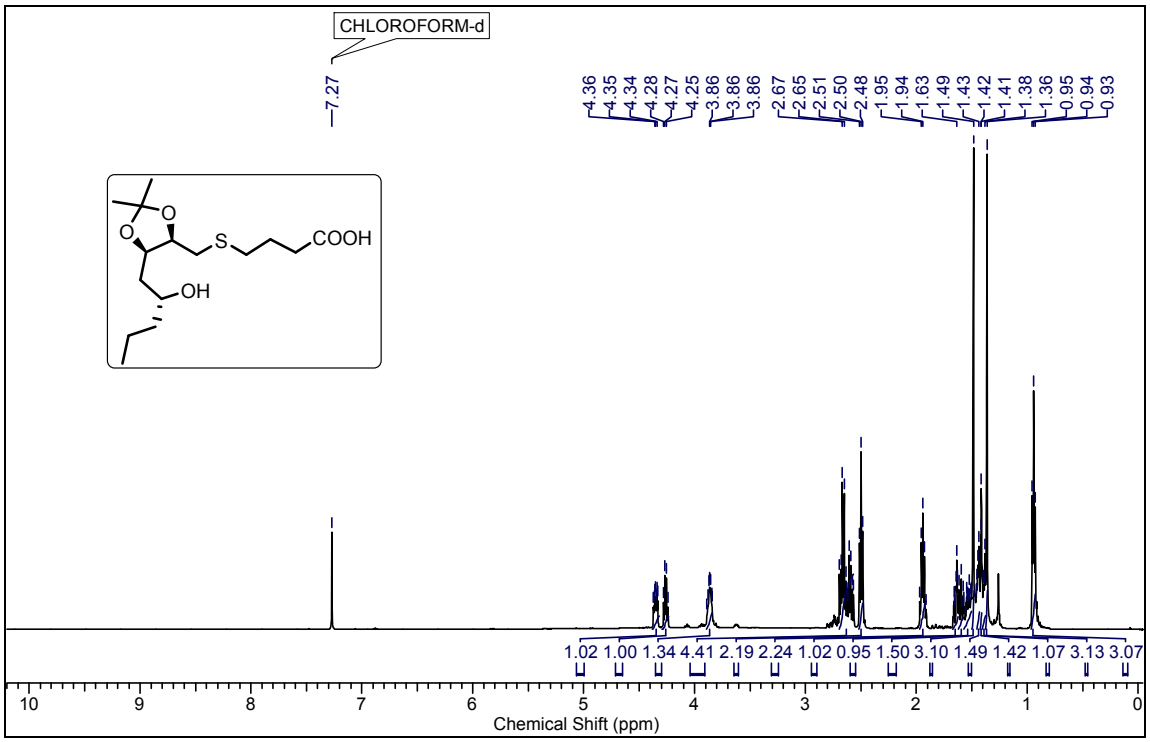


^{13}C NMR spectrum of compound **75'** ($CDCl_3$, 125 MHz):

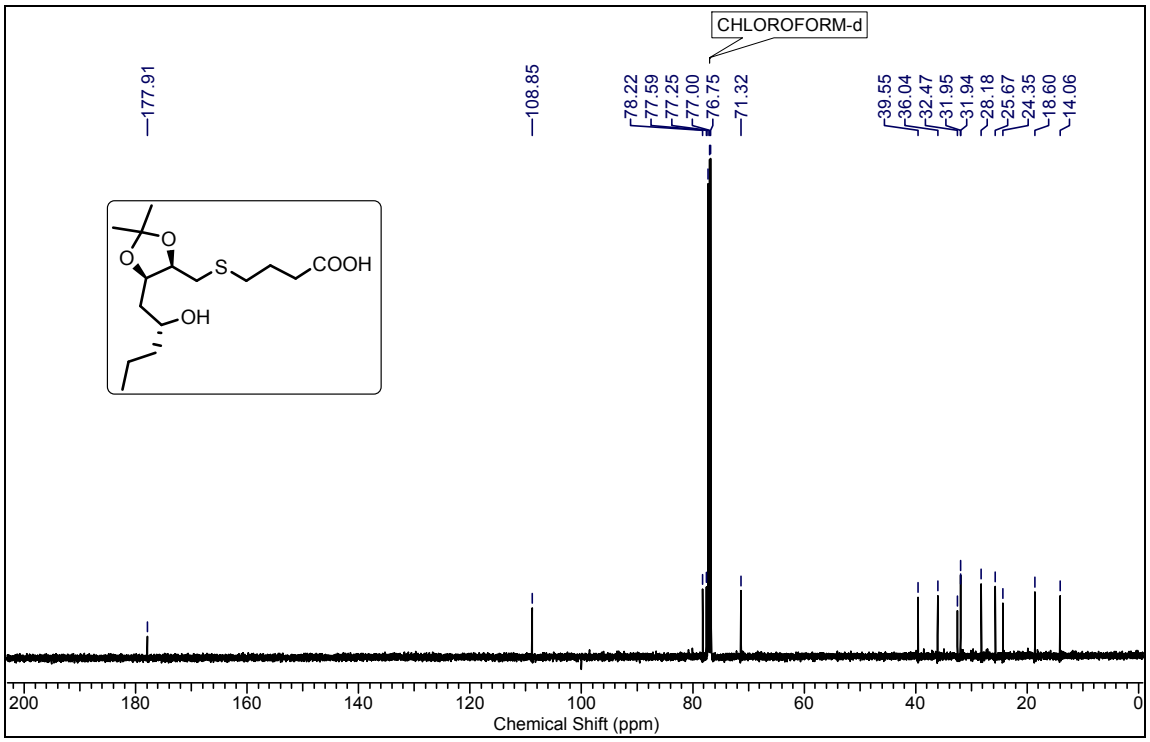


Spectra

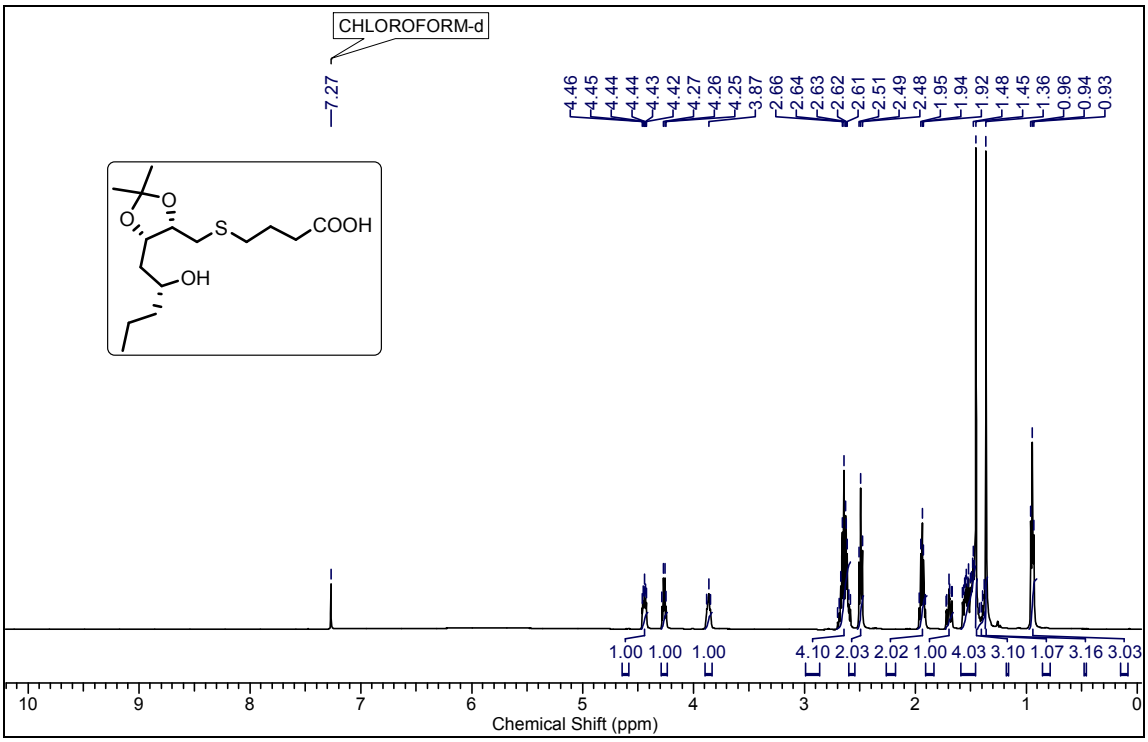
^{1}H NMR spectrum of compound **76** ($CDCl_3$, 500 MHz):



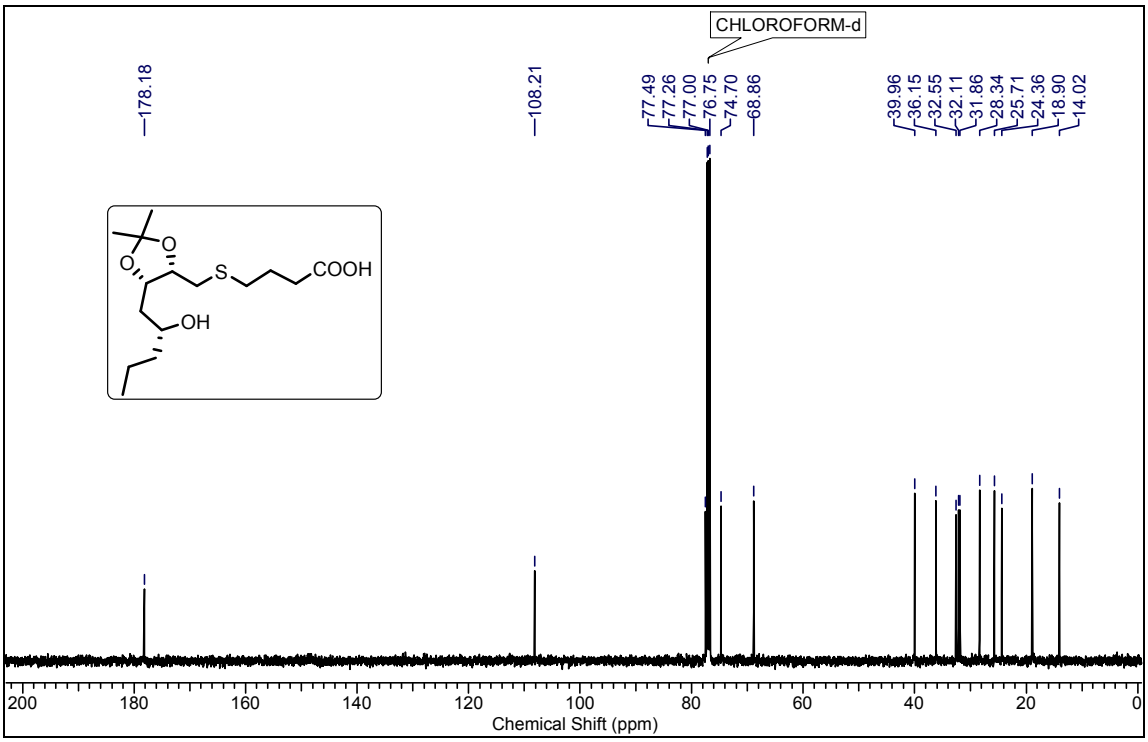
^{13}C NMR spectrum of compound **76** ($CDCl_3$, 125 MHz):



^{1}H NMR spectrum of compound **76'** ($CDCl_3$, 500 MHz):

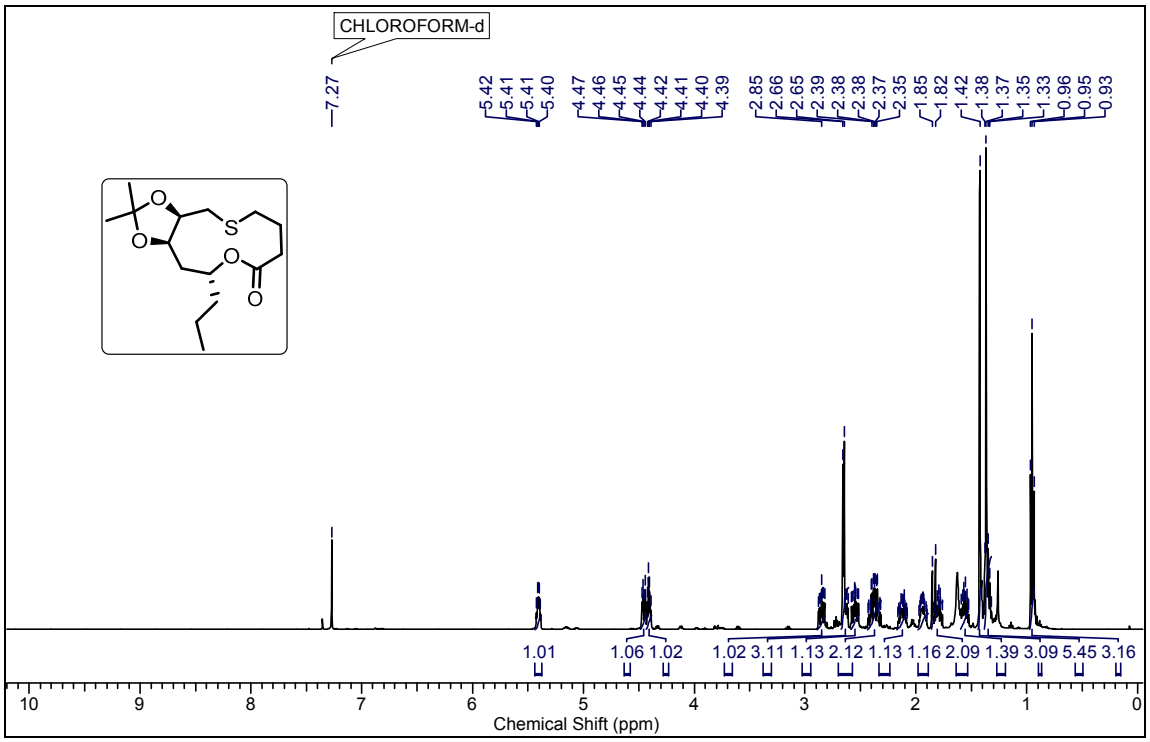


^{13}C NMR spectrum of compound **76'** ($CDCl_3$, 125 MHz):

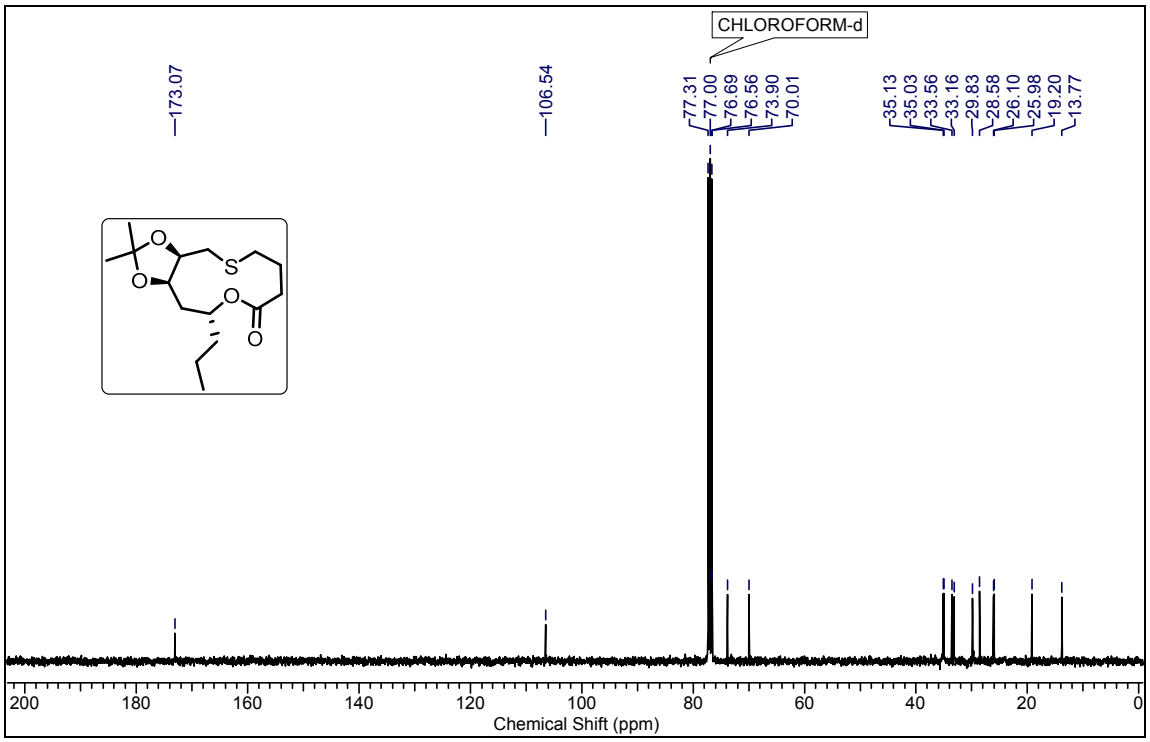


Spectra

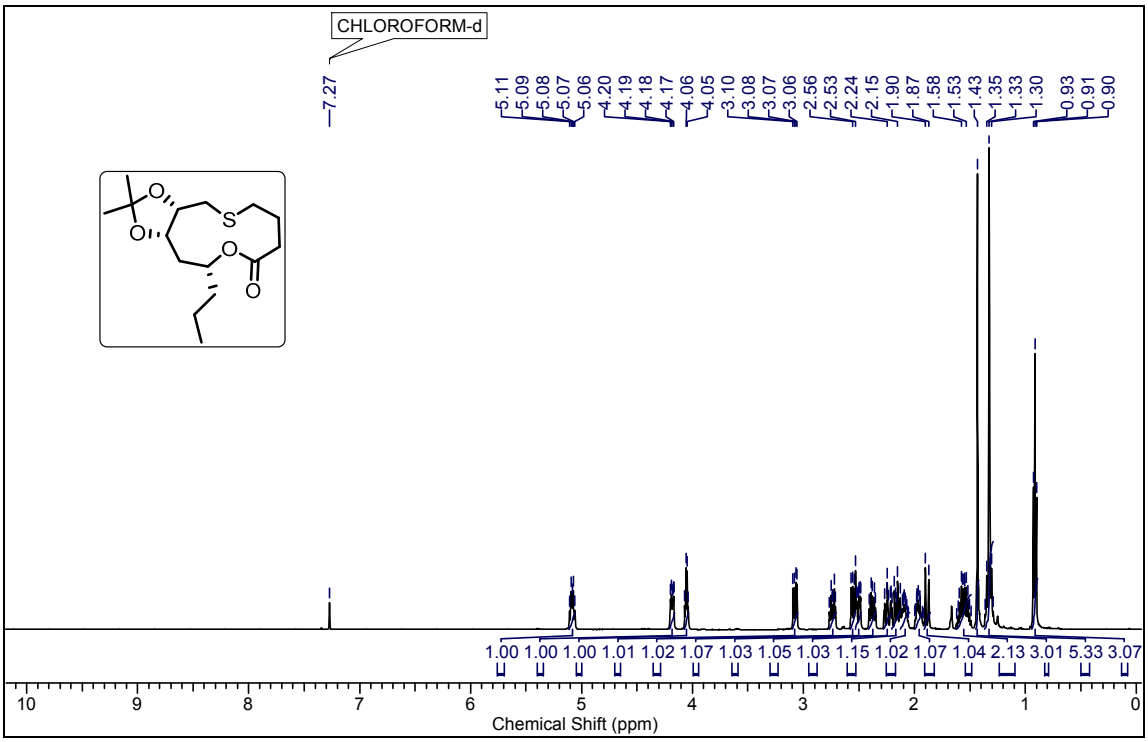
^{1}H NMR spectrum of compound **77** ($CDCl_3$, 500 MHz):



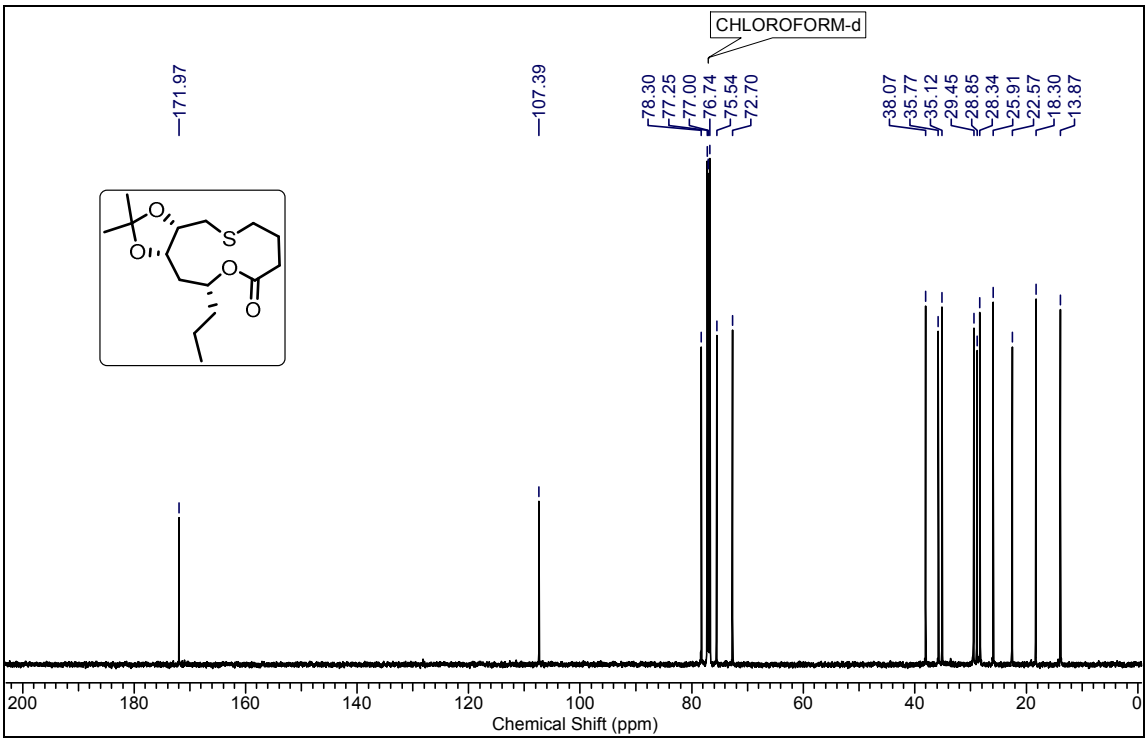
^{13}C NMR spectrum of compound **77** ($CDCl_3$, 100 MHz):



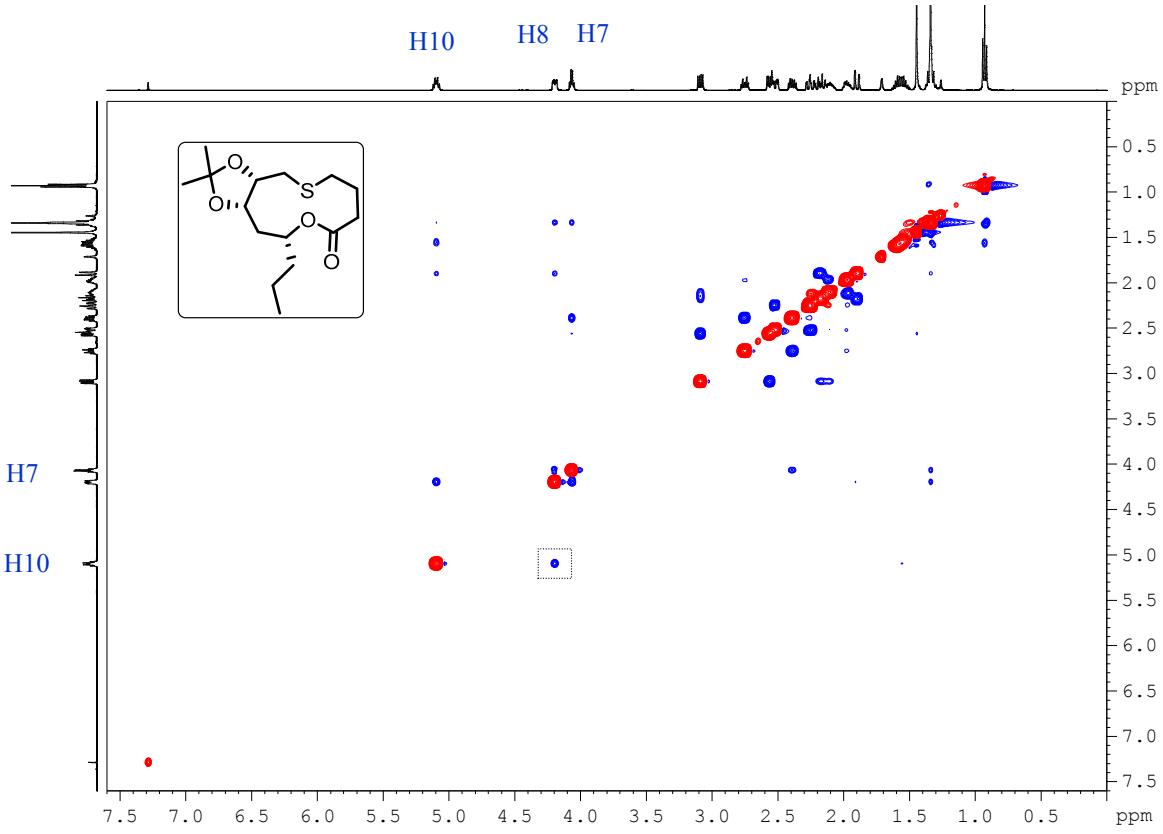
^{1}H NMR spectrum of compound **77'** ($CDCl_3$, 500 MHz):



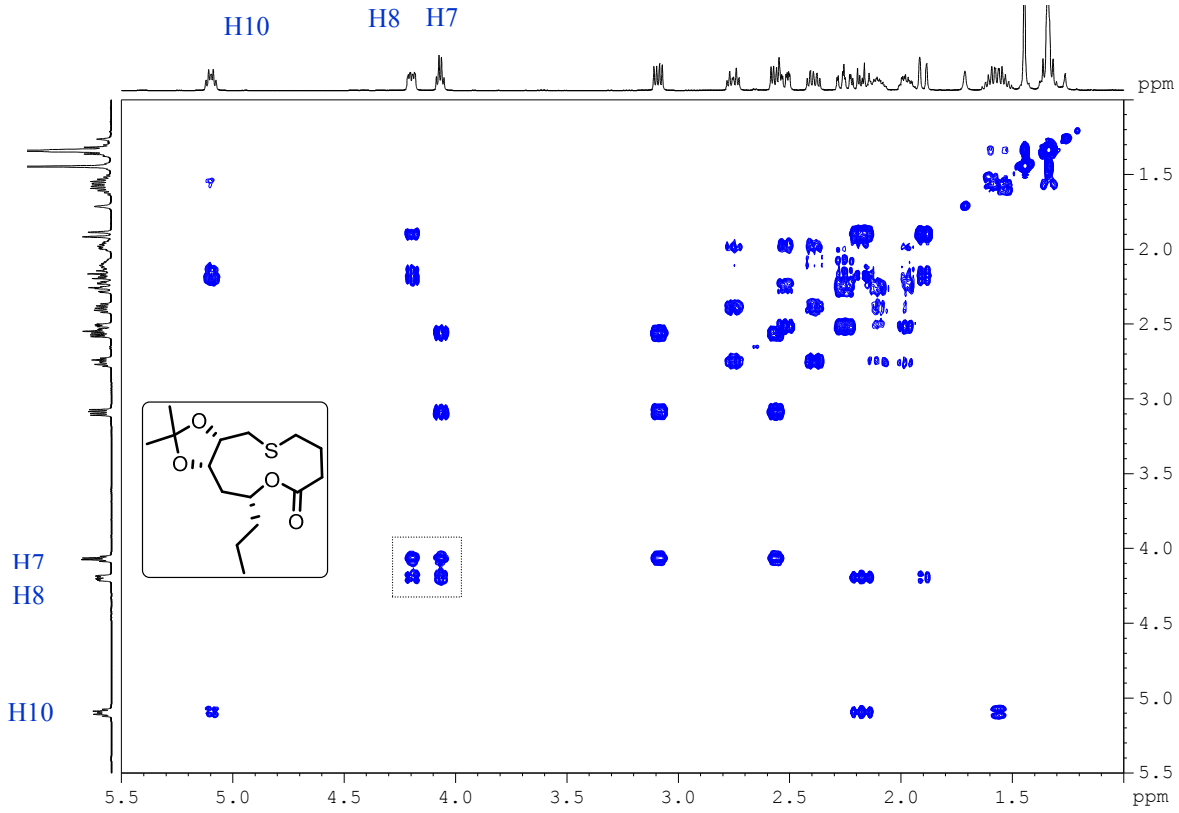
^{13}C NMR spectrum of compound **77'** ($CDCl_3$, 125 MHz):



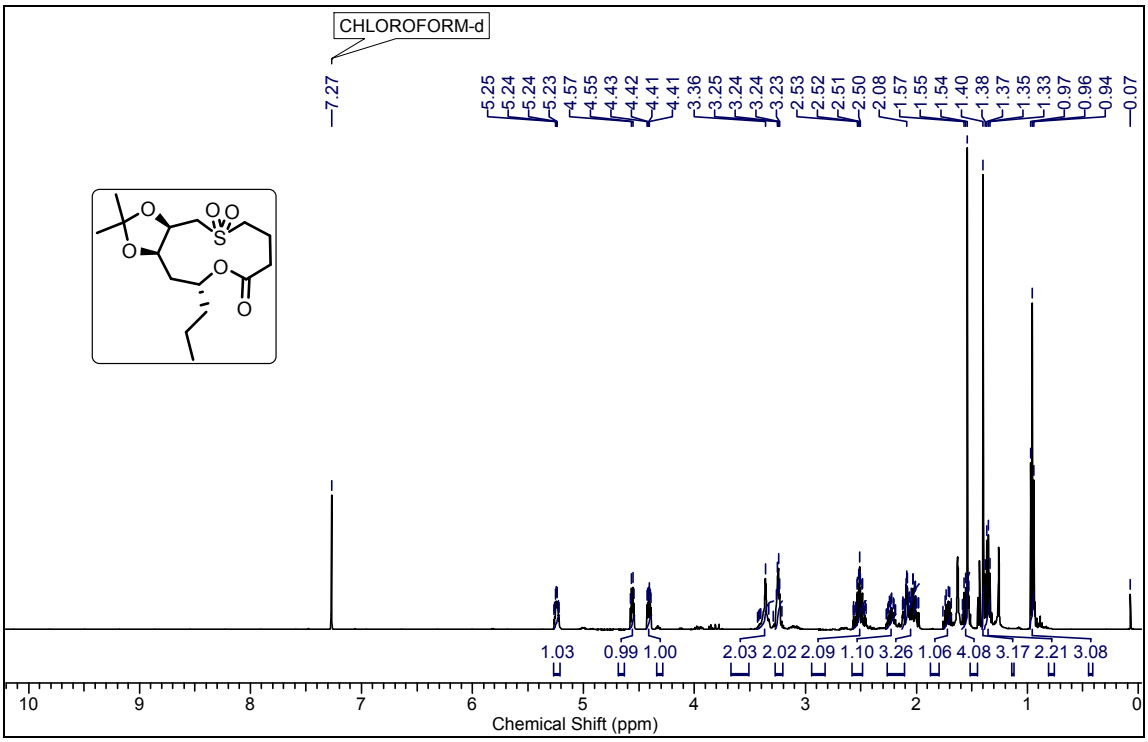
NOESY spectrum of compound **77'** ($CDCl_3$, 500 MHz):



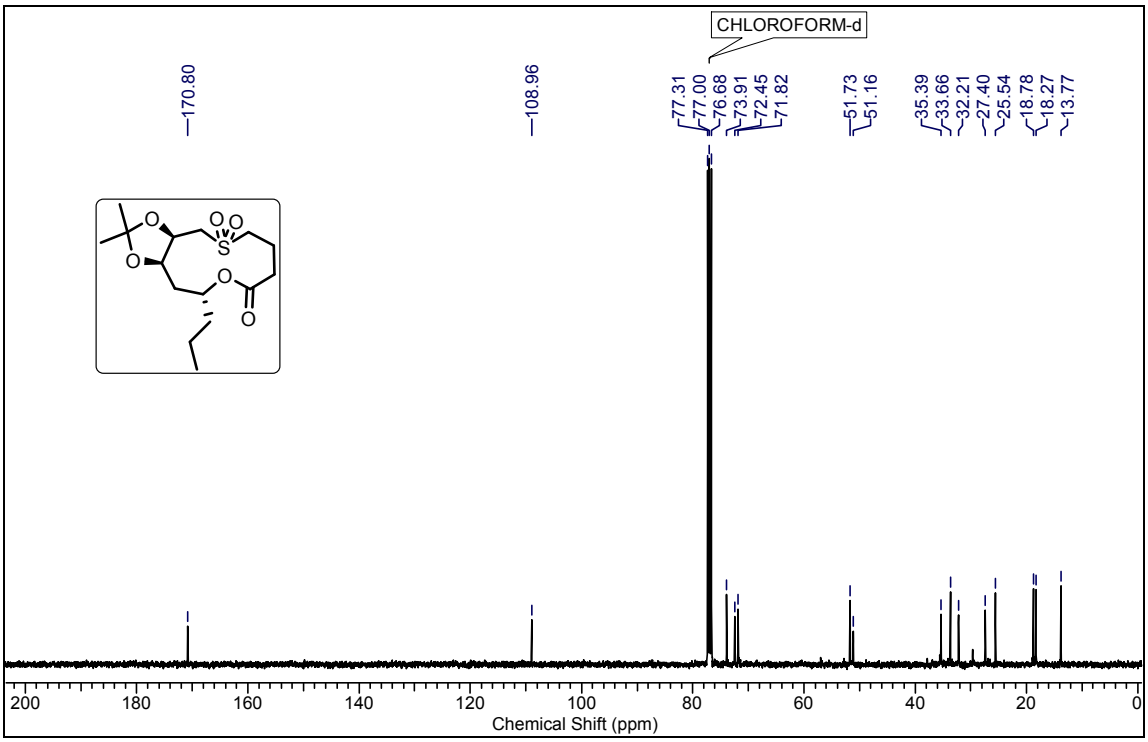
COSY spectrum of compound **77'** ($CDCl_3$, 500 MHz):



^{1}H NMR spectrum of compound **78** ($CDCl_3$, 500 MHz):

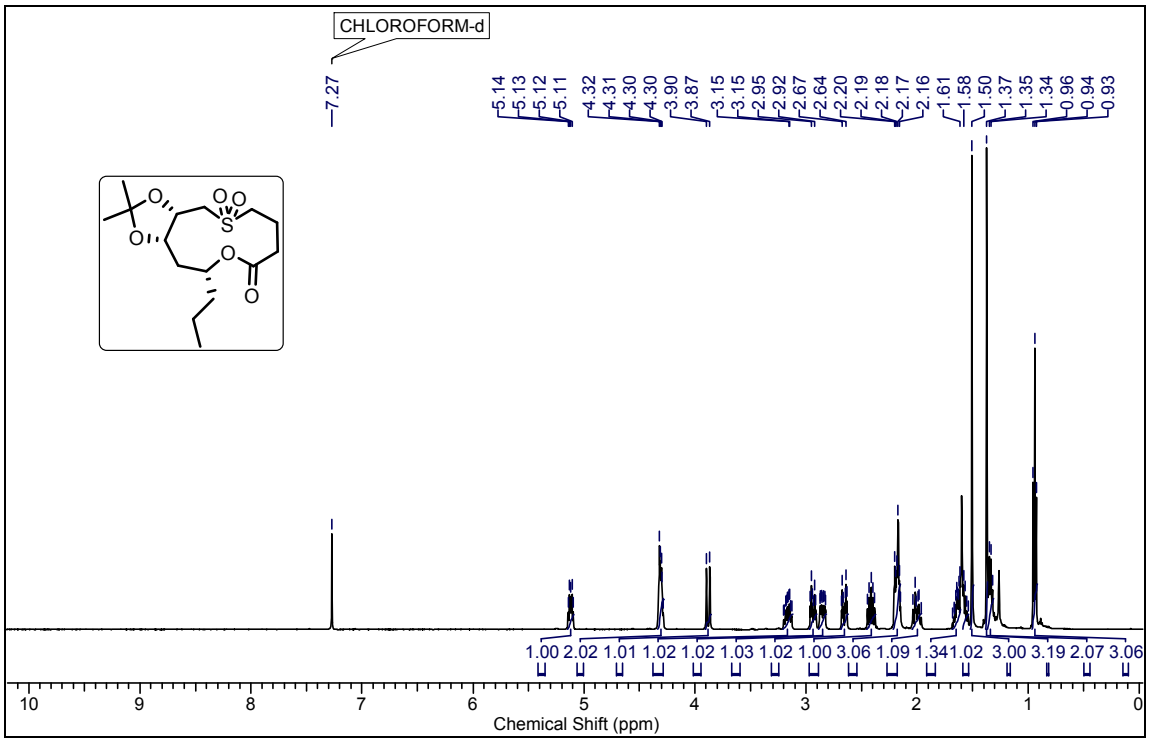


^{13}C NMR spectrum of compound **78** ($CDCl_3$, 100 MHz):

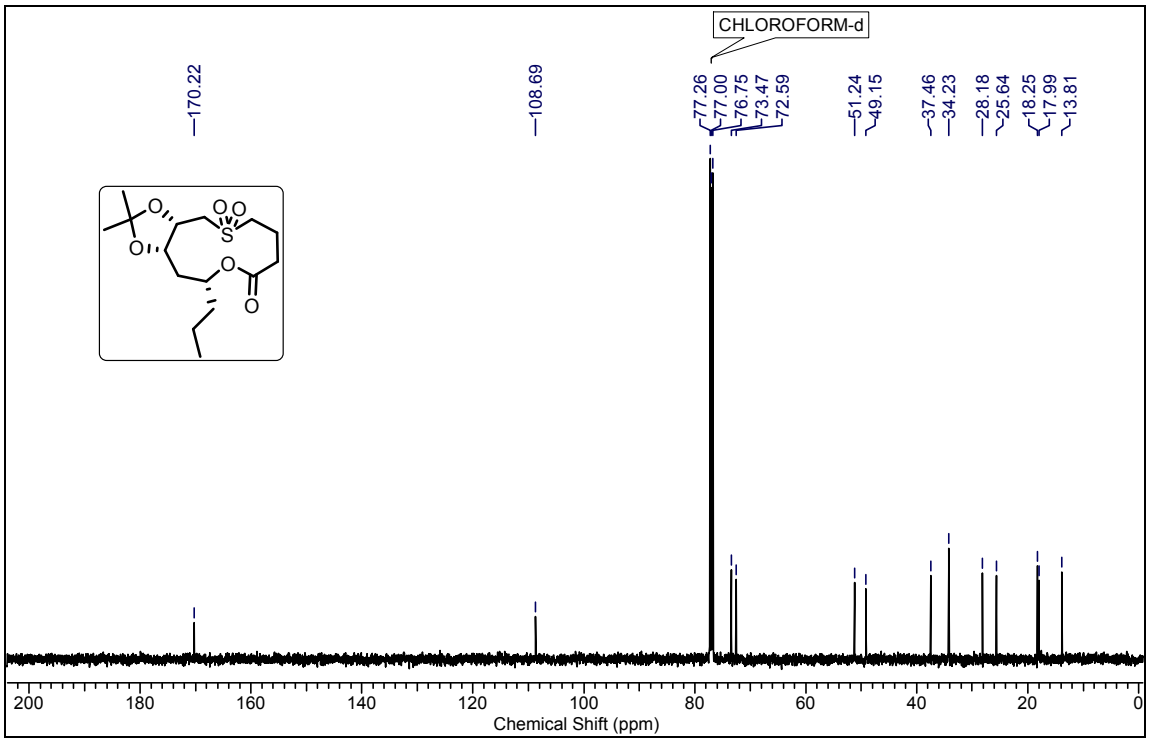


Spectra

^{1}H NMR spectrum of compound **78'** ($CDCl_3$, 500 MHz):



^{13}C NMR spectrum of compound **78'** ($CDCl_3$, 125 MHz):

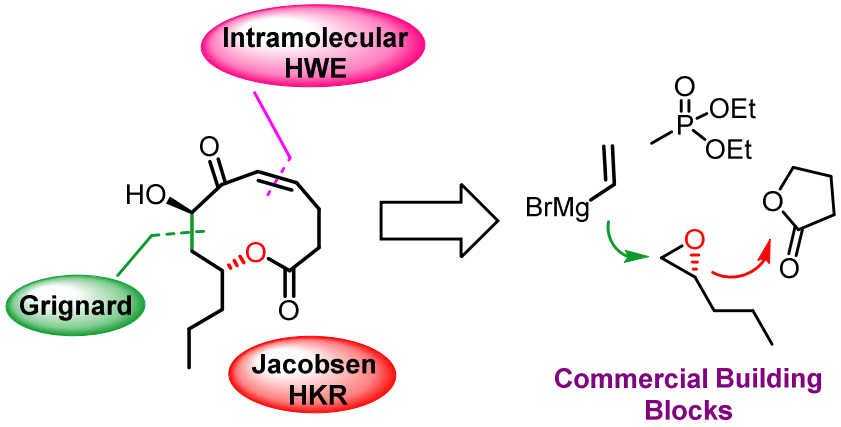


“Experience is not what happens to a man; it is what a man does with what happens to him.”

— Aldous Huxley

Section B

Intramolecular Horner-Wadsworth-Emmons Approach Towards the Total Synthesis of 10-Membered Lactone



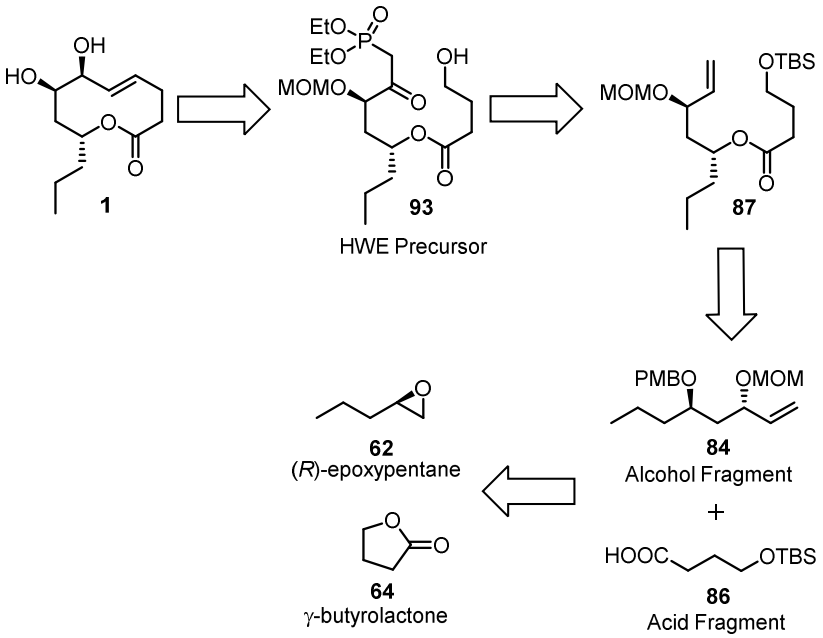
2.2.1. Present Work (Intramolecular Horner–Wadsworth–Emmons Macrocyclization Approach)

2.2.1.1. Objective

The intramolecular Horner-Wadsworth-Emmons (HWE) reaction has become a *de novo* tool for construction of –C=C– bond in macrocyclization reaction[39] since the pioneering work in 1979 by Stork and Nakamura[40] and Nicolaou *et al*.[41] The reaction has further been elegantly extended by many research groups for the synthesis of 12 to 21 membered macrolactones. In general, the HWE reaction offers a broad scope of reaction conditions which predominantly yields the more stable *E*-*α*,*β*-unsaturated lactones with high selectivity, depending upon the choice of phosphonates and base (NaH/THF, K_2CO_3 and 18-crown-6 in toluene, LiCl/DBN/CH_3CN) used, aiding trial of different conditions for a given substrate. The use of bis(2,2,2-trifluorethyl)phosphonoacetates developed by Still and Gennari[42] or bis(*O*-aryl)phosphonates proposed by Ando are known to give *Z*-selectivity.[43] Thus, it gives a "freedom of choice" for the reaction conditions to be selected during the key step to assemble highly functionalized advanced synthetic precursors. Following an unsuccessful attempts to synthesize nonenolide **1** *vi*a intra annular Ramberg-Bäcklund strategy (**Chapter II: Section A**), and the quest for *E*-selectivity; we further envisaged constructing C4–C5 olefinic bond of *E*-nonenolide **1** employing a unique intramolecular Horner–Wadsworth–Emmons (HWE) macrocyclization as the key reaction to access the 10-membered macrocyclic lactone.

2.2.1.2. Retrosynthetic Analysis

Our revised retrosynthetic disconnection was expected to deliver (*E*)-C4–C5 double bond through HWE-olefination of **93**, which in turn could be derived from ester **87**, obtained by the coupling of alcohol **84** and acid **86**. These fragments, in turn, could easily be accessed from the commercially available building blocks such as (*R*)-1,2-epoxypentane **62** and *γ*-butyrolactone **64** respectively as shown in Scheme 2.2.1.

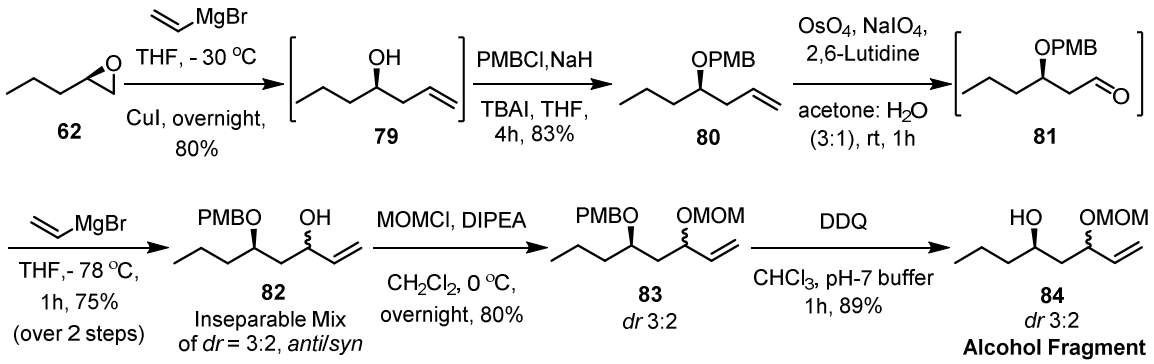


Scheme 2.2.1. Revised retrosynthetic analysis

2.2.1.3. Results and Discussion

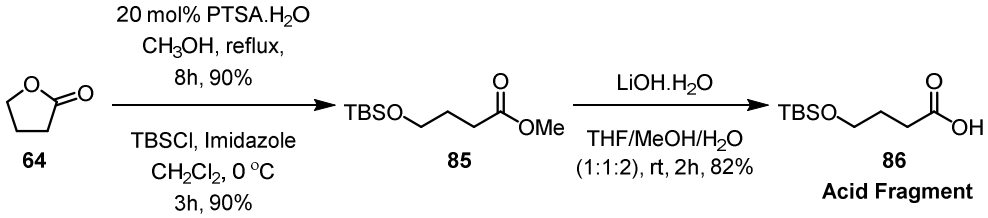
As illustrated in Scheme 2.2.2, the synthesis of alcohol fragment **84** started from (*R*)-1,2-epoxypentane **62**, which upon treatment with vinylmagnesium bromide in the presence of CuI in THF at –30 ^{o}C gave homoallylic alcohol **79** in 80% yield. Due to the low boiling point, the crude alcohol **79**, was protected as its PMB ether to give compound **80** in 83% yield. The ^{1}H NMR spectrum of **80** gave olefin peaks at δ 5.83 (dddd, *J* = 7.1, 7.1, 10.2, 17.1 Hz, 1 H), 5.13 - 4.98 (m, 2 H) and PMB group peaks at δ 3.78 (s, 3 H). The oxidative cleavage of resulting olefin **80** gave aldehyde **81**, which on subsequent treatment with vinylmagnesium bromide at –78 °C gave compound **82** as an inseparable diastereomeric mixture (3:2, *anti*/*syn* ^{1}H-NMR analysis) in 75 % yield over the two steps. The IR spectrum of **82** gave hydroxyl absorption at 3454 cm^{-1}. The ^{1}H NMR signals of vinylic protons at δ 5.91 - 5.78 (m, 1 H), 5.28 - 5.19 (m, 1 H) and 5.10 - 5.04 (m, 1 H) further confirmed the structure of **82**. The alcohol **82** was further converted to its MOM ether **83** in 80% yield. The ^{1}H NMR spectrum of **83** showed methoxy protons at δ 3.37 - 3.26 (m, 3 H) and the presence of methyleneoxy carbon was confirmed by its distinct signal at δ 94.2, 93.6 (2 signals correspond to *dr* ~ 3:2) in ^{13}C NMR. The DDQ mediated deprotection of the PMB group afforded the required alcohol **84** in 89 % yield. IR spectrum of **84** gave hydroxyl absorption bands at 3455 cm^{-1} and ^{1}H NMR spectrum

showed the disappearance of aromatic and methoxy peaks at δ 7.30 - 7.18 (m, 2 H), 6.89 - 6.78 (m, 2 H) and 3.75 (s, 3 H) w.r.t starting material **83**.



Scheme 2.2.2. Synthesis of alcohol fragment **84**

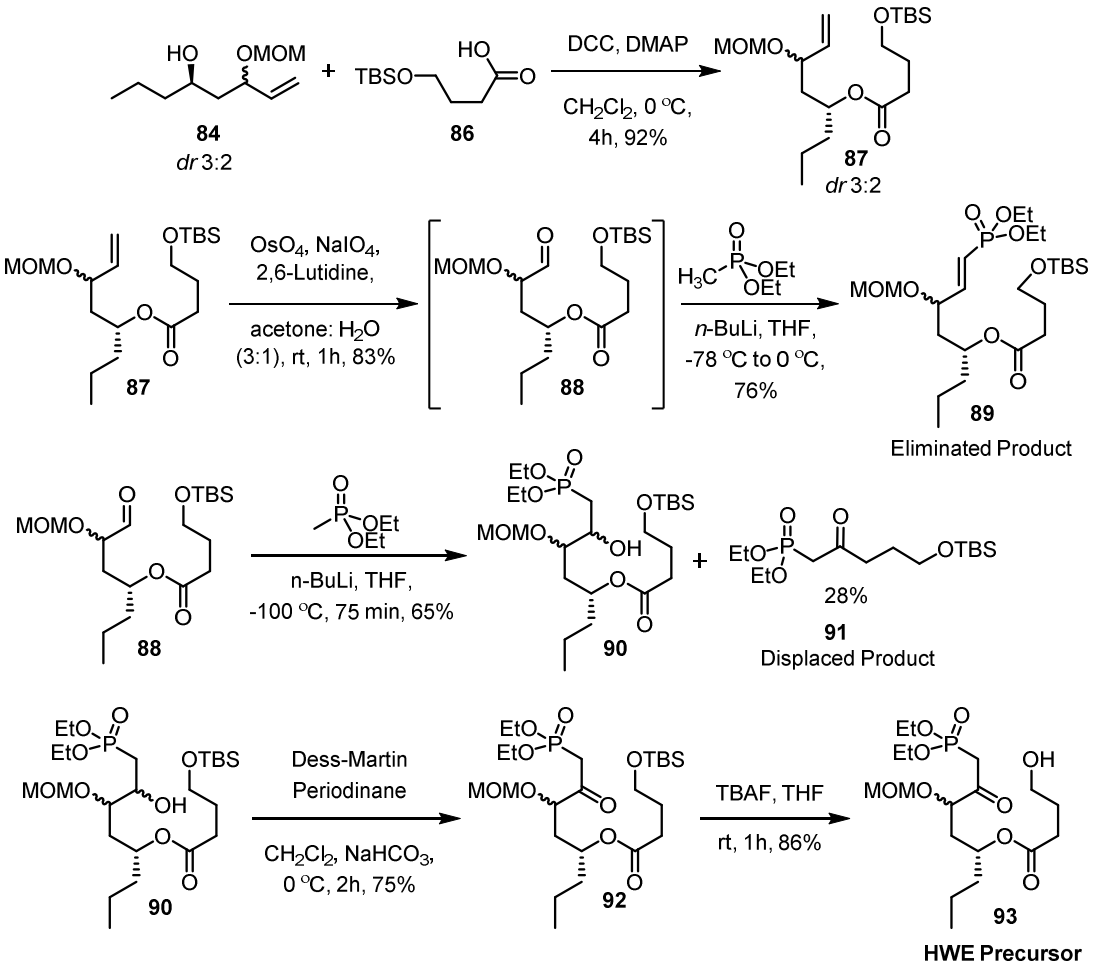
We next focused on the synthesis of the acid fragment **86** as described in Scheme 2.2.3. Starting from γ-butyrolactone **64**, which was converted to alcohol (as mentioned in previous section, Scheme 2.1.5), was subjected to its TBS ether protection to give compound **85** in 90% yield. The IR spectrum of acyclic ester **85** showed band at lower ν_{max} 1731 cm^{-1} compared to its cyclic form at 1775 cm^{-1}. The ^{1}H NMR spectrum showed the presence of methyl ester protons (–CO_2Me) peaks at δ 3.66 (s, 3 H) and ^{13}C NMR signals for ester carbonyl at δ 174.0. The base hydrolysis of methyl ester of **85** delivered the required acid fragment **86** in 82% yield. The ^{1}H NMR of **86** showed the disappearance of methyl ester protons.



Scheme 2.2.3. Synthesis of acid fragment **86**

With both the fragments in hand, the alcohol **84** and acid **86** were coupled under Steglich conditions[44] using DCC/DMAP in CH_2Cl_2 to afford the ester **87** in 92% yield. In the IR spectrum, absorption band at 1727 cm^{-1} showed the presence of ester functionality. In ^{1}H NMR, peak owing to olefin protons was present at δ 5.71 - 5.58 (m, 1 H), 5.22 - 5.14 (m, 2 H) and signal at δ 2.38 - 2.33 (m, 2 H) corresponds to the protons next to ester group. In ^{13}C NMR, peaks due to carbonyl carbon was present at δ 173.1, 173.0 (2 signals correspond to *dr* ~ 3:2). The $OsO_4/NaIO_4$-mediated one-pot oxidative cleavage of alkene

87 followed by treatment of resultant crude aldehyde **88** with the lithium carbanion of $(EtO)_2P(O)CH_2CH_3$ at 0 °C resulted in the exclusive formation of eliminated product **89**. The peak at δ 6.68 - 6.54 (m, 1 H) and 5.84 (m, 1 H) in ^{1}H NMR spectrum confirmed the presence of double bond. The HRMS (ESI^+) peak at 525.3008 corresponds to formula $C_{24}H_{49}O_8PSi$ $[M + H]^+$ (calculated value 525.3007). On the other hand, when the same aldol reaction was performed at −100 °C, it resulted in the formation of *β*-hydroxy phosphonates **90** as an inconsequential mixture of diastereomers in 65% yield along with displaced product **91** in 28% yield. The ^{1}H NMR spectrum of **90** showed signal at δ 3.58 - 3.48 (m, 1 H) which corresponds to proton of newly generated hydroxyl center. Further efforts to improve the yield of compound **90** by variation in the stoichiometry of the phosphonate reagent or temperature were futile.

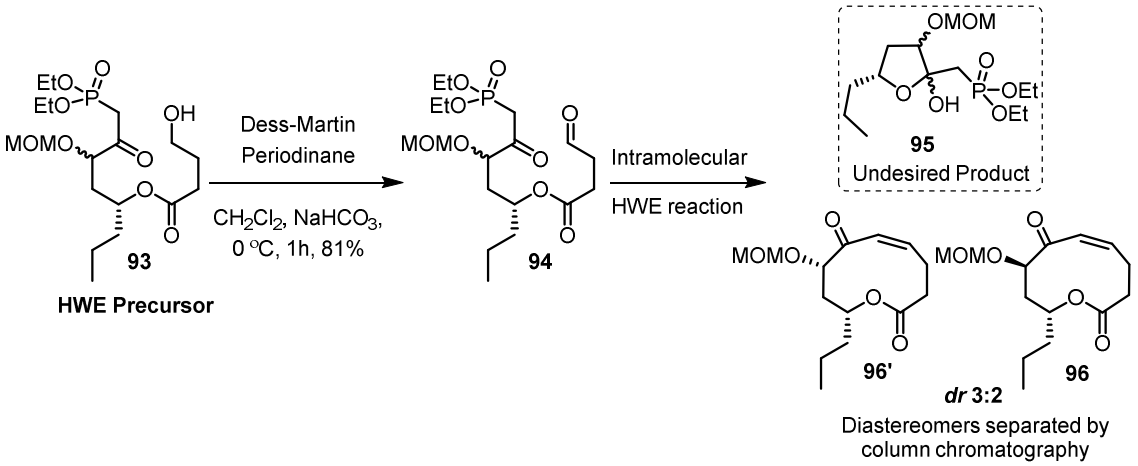


Scheme 2.2.4. Synthesis of HWE precursor **38**

Subsequent oxidation of **90** using Dess–Martin periodinane resulted in the formation of *β*-ketophosphonate **92** in 75% yield. The ^{1}H NMR showed the characteristic signal of

active methylene [–C(O)–CH_2–P(O)$(OEt)_2$] flanked on each side by carbonyl and phosphonate at δ 3.34 - 3.14 (m, 2 H). The ^{13}C NMR signal at δ 203.0, 202.9, 202.0 and 201.9 corresponds to ketone functionality (4 signals are due to *dr* ~ 3:2, –C–P coupling) whereas, signal at δ 173.3, 173.0 corresponds to ester carbonyl. The compound **92** on TBS deprotection using TBAF furnished the key HWE precursor **93** in 86% yield as a pale yellow liquid. The IR spectrum showed the hydroxyl absorption signal at 2954 cm^{-1}. The alcohol **93** was further oxidized to its corresponding aldehyde using DMP to give aldehyde **94** in 81% yield.

Thus, after having the desired key fragment in hand, intramolecular HWE reaction was attempted to stitch both the ends of the compound **94** to build the *E*-selective macrocyclic core of nonenolide **1**.



Sr.No	Conditions	Temp °C	Time h	Yields %	
				39	**40**
1	LiCl, DBU, MeCN	25	8	61	–
2	LiBr, DBU, MeCN	25	8	43	–
3	LiHMDS, THF	25	15	72	–
4	**K_2CO_3/18-Crown-6**	**60**	**8**	**–**	**63**

Table 2.2.1. Synthesis of macrocyclic core

Unfortunately, our first efforts in that direction led to the formation of undesired cyclized product **95** in 65% yield (Table 2.2.1, Entry 1). The ^{1}H NMR signal showed four protons less, which occurred due to complete displacement of ester fragment. The characteristic peaks in ^{13}C NMR of ester carbonyl at δ 173.5, 173.2 along with ketone group

disappeared, with the generation of signal at δ 104.2, 104.1, 104.0, 100.6, 100.5 corresponding to anomeric carbon. The HRMS (ESI^+) peak at 363.1536 corresponds to formula $C_{14}H_{29}O_7P$ $[M + Na]^+$ (calculated value 363.1543) are well in agreement with the structure assigned to compound **95**. The formation of the compound **95** can be justified on the basis of LiCl mediated ester hydrolysis followed by activation of carbonyl carbon towards hydroxyl attack due to Lewis acidic nature of Li^+ cation.[45] Other reported conditions such as LiBr–DBU/CH_3CN devised by Masamune and Roush[46] as well as the one developed by Stork and Nakamura using LiHMDS[40] for getting *E*-selectivity were also found to be ineffective in fetching required macrocyclic core of the nonenolide **1** and ended in the formation of undesired product **95** (Table 2.2.1, Entry 2-3).

As mentioned by Stork, the least-substituted precursors are associated with more degrees of freedom, so their cyclization is quite difficult.[40] To circumvent this unforeseen challenge, we tried standard conditions developed by Aristoff's *et al.*[47] for the intramolecular HWE reaction, K_2CO_3/18-crown-6 in toluene to check the feasibility of the macrocyclization reaction and its *E*/*Z* ratio. To our delight, reaction went smoothly to furnish the *α*,*β*-unsaturated macrocyclic lactone moiety **96** (Table 2.2.1, Entry 4). But to our dismay, the conditions of HWE macrocyclization led to the formation of the *Z*-isomer exclusively as revealed by ^{1}H-NMR analysis of macrolactone core of nonenolide **1**. The IR spectrum showed ester carbonyl at 1728 cm^{-1} and *α*,*β*-unsaturated ketone at 1629 cm^{-1}. The ^{1}H NMR spectrum showed signal of double bond protons at δ 6.37 (d, *J* = 11.8 Hz, 1 H) and 5.93 (ddd, *J* = 5.4, 11.8, 11.8 Hz, 1 H) having coupling constant *J* = 11.8 Hz, indicating *Z*-geometry. In ^{13}C NMR, a peak at δ 202.7 was observed belonging to ketone group while the peak for ester carbonyl appeared at δ 170.8. The HRMS (ESI^+) peak at 293.1356 corresponding to formula $C_{14}H_{22}O_5$ $[M + Na]^+$ (calculated value 293.1359) are in well accordance with the structure **96**. The (7*S*,9*R*) stereochemistry of lactone **96'** was fully assigned by using 2D-NMR experiments. The H9 proton at δ 5.06 and H7 proton at δ 4.16 showed NOESY correlation; in addition H8$_\beta$ proton at δ 2.11 also showed NOESY correlation with H7 proton thus suggesting the protons are on same side. The position of H9 was confirmed from HSQC and HMBC. The subsequent synthetic route involving carbonyl reduction and deprotection was not pursued further. The exclusive formation of *Z*-diastereomer reinstates its thermodynamic stability over

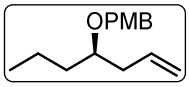
the *E*-isomer for this class of compounds. HWE reactions also offer a broad scope in terms of reagents and reaction conditions. Hence the standard reaction conditions which operate under kinetic control need to be investigated and is currently underway in our laboratory.

2.2.2. Conclusion and Prospect

In conclusion, the approach involving an intramolecular Horner–Wadsworth–Emmons reaction for the C4−C5 bond formation led to the *Z*-configured macrolactone core of a truncated analogue in the hunt for the synthesis of (*E*)-nonenolide 1. Successful approach for assembling the macrocyclic core with *Z*-double bond at C4–C5 position was accomplished from the key fragments which were synthesized from commercially available building blocks (*R*)-1,2-epoxypentane and γ-butyrolactone following simple synthetic transformations. Overall, synthetic investigations reveal that the requisite *E*-isomer of nonenolide **1** may not be accessed by late stage construction of C4−C5 bond by approaches that were employed as key disconnecting tools. This reflects on the biosynthetic design of the best chemist-nature, which must be accomplished through disconnection at an alternative site to construct the core framework. Alternative approaches to accomplish the total synthesis of nonenolide **1** are currently under progress in our laboratory.

2.2.3. Experimental Section

(*R*)-1-((Hept-1-en-4-yloxy)methyl)-4-methoxybenzene (80):



A round bottom flask was charged with copper(I)iodide (221 mg, 1.16 mmol, 5 mol%), gently heated under vacuum and slowly cooled with a flow of argon. After the addition of THF (20 mL), this suspension was cooled to –30 ^{o}C, stirred and vinylmagnesium bromide (47 mL, 46.44 mmol, 1M in THF, 2 equiv.) was added to it. After 30 min, the solution of epoxide **62** (2.0 g, 23.22 mmol, 1 equiv.) in THF (20 mL) was added dropwise to the reaction mixture at –30 ^{o}C and stirred overnight. After consumption of starting material, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl. The water layer was extracted with diethyl ether (3 x 50 mL). The combined organic layer was washed with brine, dried over Na_2SO_4. Evaporation of the solvent gave

crude alcohol **79** (2.1 g, 80%) as a yellow liquid, which was used in subsequent step without any further purification due to volatility.

Sodium hydride 60 wt% (1.5 g, 36.78 mmol, 2 equiv.) was suspended in 20 mL of THF, and the resulting slurry was cooled to 0 ^{o}C. A solution of alcohol **79** (2.1 g, 18.39 mmol, 1 equiv.) in 30 mL of THF was added dropwise with H_2 evolution. After 30 min, PMBCl (3.7 mL, 27.59 mmol, 1.5 equiv.) in 10 mL THF was added slowly, followed by catalytic amount of TBAI. After being stirred at room temperature for 4 h under nitrogen atmosphere, the reaction was quenched by saturated solution of $NaHCO_3$. The aqueous layer was extracted with ethyl acetate and the combined organic layer was dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography using petroleum ether, as eluent to afford desired PMB-ether **80** as a yellow liquid.

Yield = 3.6 g, 83%;

R_f = 0.43 (petroleum ether/EtOAc, 49:1);

$[\alpha]_D^{25}$ = + 7.8 (*c* 1.0, $CHCl_3$);

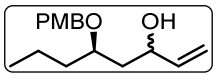
IR ($CHCl_3$): ν_{max} = 3415, 3010, 2949, 2867, 1643, 1512, 1456, 1247, 1174, 1041, 758 cm^{-1};

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.3 Hz, 2 H), 6.85 (d, *J* = 8.3 Hz, 2 H), 5.83 (dddd, *J* = 7.1, 7.1, 10.2, 17.1 Hz, 1 H), 5.13 - 4.98 (m, 2 H), 4.52 - 4.36 (m, 2 H), 3.78 (s, 3 H), 3.48 - 3.33 (m, 1 H), 2.29 (t, *J* = 6.2 Hz, 2 H), 1.53 - 1.28 (m, 4 H), 0.87 (t, *J* = 6.9 Hz, 3 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.0, 135.2, 131.0, 129.3, 116.7, 113.7, 78.0, 70.5, 55.2, 38.3, 36.1, 18.6, 14.2;

HRMS (ESI^+) *m/z* = calcd for $C_{15}H_{22}O_2$ $[M + Na]^+$ 257.1512; found 257.1510.

(5*R*)-5-((4-Methoxybenzyl)oxy)oct-1-en-3-ol (82):



To a cooled (0 °C) solution of **80** (3.2 g, 13.65 mmol, 1 equiv.) in acetone-water (3:1, 30 mL) OsO_4 (0.1M in toluene, 14 mL, 1.37 mmol, 10 mol%), $NaIO_4$ (11.7 g, 54.62 mmol, 4 equiv.) and 2,6-lutidine (3.2 mL, 27.3 mmol, 2 equiv.) were added. The reaction mixture was stirred overnight at room temperature, filtered, and concentrated under vacuum. The residue obtained was taken up in ethyl acetate (50 mL), washed with aq.$Na_2S_2O_3$ (10 mL) followed by brine (10 mL), dried over anhydrous Na_2SO_4, and

concentrated under reduced pressure to afford crude aldehyde **81** (2.8 g, 88%) as a pale yellow liquid, which was used in subsequent step without any further purification.

To a precooled (–78 °C) solution of **81** (2.8 g, 11.85 mmol, 1 equiv.) in dry THF (30 mL) was added vinylmagnesium bromide in THF (14.2 mL, 14.22 mmol, 1.2 equiv, 1M) under an argon atmosphere. The mixture was stirred at –78 °C for 1 h. The reaction was then cautiously quenched by the addition of saturated solution of NH_4Cl (20 mL) and the mixture was poured into H_2O (20 mL). The mixture was extracted with Et_2O (3 x 40 mL) and the extracts were washed with brine (2 x 10 mL) and dried over Na_2SO_4. Removal of solvent under reduced pressure gave a crude residue with diastereomeric ratio (3:2, ^{1}H-NMR analysis). Flash column chromatography using petroleum ether /EtOAc (41:9) furnished inseperable mixture of diastereomeric alcohol **82** as a colorless liquid.

Yield = 2.7 g, 75%;

R_f = 0.41 (petroleum ether /EtOAc, 4:1);

$[\alpha]_D^{25}$ = – 21.4 (*c* 1.0, $CHCl_3$);

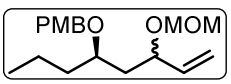
IR ($CHCl_3$): ν_{max} = 3454, 3075, 2947, 2868, 1613, 1513, 1456, 1247, 1174, 1038, 819, 765 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.2 Hz, 2 H), 6.87 (d, *J* = 8.2 Hz, 2 H), 5.91 - 5.78 (m, 1 H), 5.28 - 5.19 (m, 1 H), 5.10 - 5.04 (m, 1 H), 4.56 (d, *J* = 11.0 Hz, 0.6 H), 4.50 (d, *J* = 11.0 Hz, 0.4 H), 4.45 - 4.24 (m, 2 H), 3.79 (s, 3 H), 3.74 - 3.64 (m, 1 H), 1.78 - 1.65 (m, 2 H), 1.65 - 1.46 (m, 2 H), 1.43 - 1.30 (m, 2 H), 0.95 - 0.91 (m, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2, 159.1, 141.1, 140.7, 130.4, 130.1, 129.5, 114.0, 113.8, 113.7, 78.8, 76.3, 72.4, 70.7, 70.2, 69.8, 55.2, 41.1, 39.8, 35.7, 35.6, 18.5, 17.9, 14.3, 14.2;

HRMS (ESI^+) *m/z* = calcd for $C_{16}H_{24}O_3$ $[M + Na]^+$ 287.1618; found 287.1615.

1-Methoxy-4-((((4*R*)-6-(methoxymethoxy)oct-7-en-4-yl)oxy)methyl)benzene (83):



To a solution of **82** (2.5 g, 9.46 mmol, 1 equiv.) in dry CH_2Cl_2 (25 mL) was added DIPEA (8.2 mL, 47.3 mmol, 5 equiv.) at 0 ^oC. To this mixture MOM chloride (2.1 mL, 28.37 mmol, 3 equiv.) was added slowly and the reaction stirred overnight at room temperature. The reaction mixture was quenched with addition of cold water at 0 ^oC. The

two phases were separated and the aqueous phase was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with water (2 x 10 mL), brine, dried over Na_2SO_4 and concentrated. The residual oil was purified by flash column chromatography using petroleum ether/EtOAc (47:3) as eluent to furnish the inseparable, (3:2, ^{1}H-NMR analysis) diastereomeric mixture of MOM ether **83** as a colorless liquid.

Yield = 2.3 g, 80%;

R_f = 0.67 (petroleum ether/EtOAc, 4:1);

$[\alpha]_D^{25}$ = + 1.4 (*c* 6.8, $CHCl_3$);

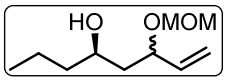
IR ($CHCl_3$): ν_{max} = 2999, 2947, 1613, 1513, 1457, 1247, 1159, 1088, 1036, 926, 819, 757 cm^{-1};

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.30 - 7.18 (m, 2 H), 6.89 - 6.78 (m, 2 H), 5.77 - 5.51 (m, 1 H), 5.24 - 5.05 (m, 2 H), 4.67 - 4.64 (m, 1 H), 4.52 - 4.29 (m, 3 H), 4.27 - 4.05 (m, 1 H), 3.75 (s, 3 H), 3.66 - 3.55 (m, 0.4 H), 3.48 - 3.39 (m, 0.6 H), 3.37 - 3.26 (m, 3 H), 2.06 - 1.70 (m, 1 H), 1.70 - 1.57 (m, 1 H), 1.57 - 1.44 (m, 2 H), 1.44 - 1.20 (m, 2 H), 0.92 - 0.84 (m, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1, 159.0, 138.7, 138.1, 131.0, 130.9, 129.3, 117.6, 116.5, 113.7, 113.6, 94.2, 93.6, 75.2, 74.8, 74.7, 70.5, 70.1, 55.6, 55.4, 55.2, 40.9, 40.1, 36.3, 36.0, 18.3, 18.1, 14.3, 14.2;

HRMS (ESI^+) *m/z* = calcd for $C_{18}H_{28}O_4$ $[M + Na]^+$ 331.1880; found 331.1880.

(4*R*)-6-(Methoxymethoxy)oct-7-en-4-ol (84):



To a solution of compound **83** (2.0 g, 6.48 mmol, 1 equiv) in $CHCl_3$: pH 7 buffer mixture (20:1) (20 mL), was added DDQ (4.4 g, 19.45 mmol, 3 equiv) and stirred at room temperature for 1 h. The reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ (20 mL) and Na_2SO_3 (20 mL), the organic layer was separated, washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and purified by flash column chromatography using petroleum ether/EtOAc (23:2) as eluent to afford (3:2, ^{1}H-NMR analysis) diastereomeric mixture of compound **84** as a colorless liquid.

Yield = 1.1 g, 89%;

R_f = 0.23 (petroleum ether/EtOAc, 17:3);

$[\alpha]_D^{25}$ = + 12.5 (*c* 1.3, $CHCl_3$);

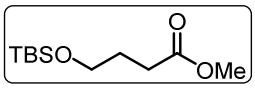
IR ($CHCl_3$): ν_{max} = 3455, 2947, 1689, 1597, 1511, 1458, 1425, 1259, 1155, 1097, 1031, 924, 838 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.83 - 5.63 (m, 1 H), 5.29 - 5.18 (m, 2 H), 4.73 (d, *J* = 6.9 Hz, 0.6 H), 4.73 (d, *J* = 6.9 Hz, 0.4 H), 4.57 (d, *J* = 6.9 Hz, 0.4 H), 4.57 (d, *J* = 6.9 Hz, 0.6 H), 4.36 - 4.31 (m, 0.4 H), 4.30 - 4.25 (m, 0.6 H), 3.94 - 3.88 (m, 0.4 H), 3.87 - 3.80 (m, 0.6 H), 3.41 (d like, *J* = 1.4 Hz, 3 H), 1.78 - 1.69 (m, 1 H), 1.68 - 1.63 (m, 1 H), 1.53 - 1.34 (m, 4 H), 0.94 (t, *J* = 7.1 Hz, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.8, 137.5, 118.0, 116.7, 94.4, 93.4, 77.7, 75.4, 70.6, 67.8, 55.8, 42.4, 42.2, 39.7, 39.6, 18.8, 18.6, 14.1;

HRMS (ESI^+) *m/z* = calcd for $C_{10}H_{20}O_3$ $[M + Na]^+$ 211.1505; found 211.1504.

Methyl 4-((*tert*-butyldimethylsilyl)oxy)butanoate (85):



To a stirred solution of *γ*–butyrolactone derived alcohol (900 mg, 7.62 mmol, 1 equiv.) (refer Scheme 2.1.5) in CH_2Cl_2 (15 mL), imidazole (1.0 g, 15.24 mmol, 2 equiv.) was added. To this solution *t*-butylchlorodimethyl silane (1.7 g, 11.43 mmol, 1.5 equiv.) was added at 0 ^oC and reaction was stirred at room temperature for 3 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (3 x 30 mL). The extract was washed with brine, dried (Na_2SO_4) and concentrated. Flash column chromatography of the crude product using petroleum ether/EtOAc (23:2) as eluent provided compound **85** as a colorless liquid.

Yield = 1.6 g, 90%;

R_f = 0.70 (petroleum ether/EtOAc, 7:3);

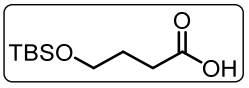
IR ($CHCl_3$): ν_{max} = 3022, 2946, 2862, 1731, 1464, 1371, 1253, 1216, 1101, 967, 840, 768, 670 cm^{-1};

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.66 (s, 3 H), 3.65 - 3.58 (m, 2 H), 2.39 (t, *J* = 7.3 Hz, 2 H), 1.90 - 1.74 (m, 2 H), 0.88 (s, 9 H), 0.03 (s, 6 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.0, 61.9, 51.4, 30.4, 27.8, 25.8, 18.2, -5.5;

HRMS (ESI^+) *m/z* = calcd for $C_{11}H_{24}O_3Si$ $[M + Na]^+$ 255.1387; found 255.1385.

4-((*tert*-Butyldimethylsilyl)oxy)butanoic acid (86):



To a solution of compound **85** (1.5 g, 6.46 mmol, 1 equiv.) in 15 mL of THF/MeOH/H_2O (1:1:2) was added LiOH.H_2O (1.3 g, 32.31 mmol, 5 equiv.) in one portion at 0 °C and stirred at rt for 2 h. After completion of the reaction as indicated by TLC, the solvents MeOH and THF were removed in *vacuo* and the aqueous layer was extracted with Et_2O. The aqueous layer was acidified with 10% aq. citric acid solution (~10 mL) at 0 °C and extracted with EtOAc (5 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in *vacuo* to get the crude product, which on flash column chromatographic purification using petroleum ether/EtOAc (4:1) as eluent provided acid **86** as a colorless liquid.

Yield = 1.1 g, 82%;

R_f = 0.48 (petroleum ether/EtOAc, 7:3);

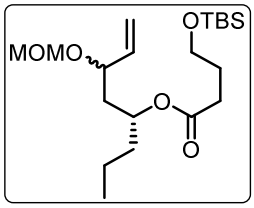
IR ($CHCl_3$): ν_{max} = 3736, 2944, 2863, 1710, 1516, 1463, 1417, 1256, 1103, 969, 838, 772 cm^{-1};

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.68 (t, *J* = 5.9 Hz, 2 H), 2.47 (t, *J* = 7.2 Hz, 2 H), 1.93 - 1.79 (m, 2 H), 0.90 (s, 9 H), 0.06 (s, 6 H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.0, 62.0, 30.7, 27.6, 25.9, 18.2, -5.5;

HRMS (ESI^+) *m/z* = calcd for $C_{10}H_{22}O_3Si$ $[M + Na]^+$ 241.1230; found 241.1229.

(4*R*)-6-(Methoxymethoxy)oct-7-en-4-yl-4-((*tert*-butyldimethylsilyl)oxy)butanoate (87):



To a stirred solution of acid **86** (1 g, 4.78 mmol, 2 equiv.) in dry CH_2Cl_2 (10 mL) at 0 ^oC, DCC (1.7 g, 8.36 mmol, 3.5 equiv.) was added in portion-wise resulting in formation of white precipitate. Then catalytic amount of DMAP was added followed by dropwise addition of alcohol **84** (450 mg, 2.39 mmol, 1 equiv.) in dry CH_2Cl_2 (10mL). The resultant solution was stirred at room temperature for 4h. The reaction mixture was evaporated to dryness. The crude product was purified by flash column chromatography

using petroleum ether/EtOAc (19:1) as an eluent to afford (3:2, ^{1}H-NMR analysis) diastereomeric mixture of ester **87** as a colorless liquid.

Yield = 855 mg, 92%;

R_f = 0.52 (petroleum ether/EtOAc, 9:1);

$[\alpha]_D^{25}$ = + 4.9 (*c* 1.0, $CHCl_3$);

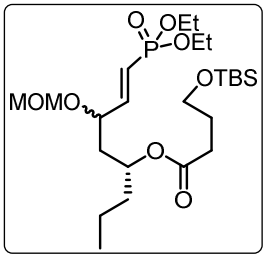
IR ($CHCl_3$): ν_{max} = 3016, 2945, 2865, 1727, 1640, 1462, 1376, 1252, 1218, 1101, 1034, 840, 760 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.71 - 5.58 (m, 1 H), 5.22 - 5.14 (m, 2 H), 5.11 - 5.04 (m, 0.4 H), 5.01 - 4.94 (m, 0.6 H), 4.65 (d, *J* = 6.4 Hz, 1 H), 4.49 (d, *J* = 6.9 Hz, 0.6 H), 4.46 (d, *J* = 6.9 Hz, 0.4 H), 4.05 - 3.97 (m, 1 H), 3.64 - 3.60 (m, 2 H), 3.34 (s, 1.8 H), 3.32 (s, 1.2 H), 2.38 - 2.33 (m, 2 H), 1.99 - 1.87 (m, 1 H), 1.82 - 1.78 (m, 1 H), 1.78 - 1.63 (m, 2 H), 1.58 - 1.50 (m, 2 H), 1.35 - 1.26 (m, 2 H), 0.91 - 0.86 (m, 12 H), 0.02 (s, 6 H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1, 173.0, 138.1, 137.4, 118.0, 117.2, 93.9, 93.6, 74.5, 74.0, 70.8, 70.6, 61.9, 55.7, 55.4, 40.2, 39.8, 36.9, 36.4, 30.8, 28.1, 28.0, 25.9, 25.8, 18.3, 18.2, 18.1, 14.0, 13.9, -5.4;

HRMS (ESI^+) *m/z* = calcd for $C_{20}H_{40}O_5Si$ $[M + Na]^+$ 411.2537; found 411.2534.

(4*R*,*E*)-8-(Diethoxyphosphoryl)-6-(methoxymethoxy)oct-7-en-4-yl-4-((*tert*-butyldimethylsilyl)oxy)butanoate (89):



To a cooled (0 °C) solution of ester **87** (800 mg, 2.06 mmol, 1 equiv.) in acetone-water (3:1, 10 mL) OsO_4 (0.1M in toluene, 2.06 mL, 0.206 mmol, 10 mol%), $NaIO_4$ (1.8 g, 8.24 mmol, 4 equiv.) and 2,6-lutidine (0.48 mL, 4.12 mmol, 2 equiv.) were added. The reaction mixture was stirred overnight at room temperature, filtered, and concentrated under vacuum. The residue obtained was taken up in ethyl acetate (20 mL), washed with aq.$Na_2S_2O_3$ (5 mL) followed by brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford crude aldehyde **88** (667 mg, 83%) as a pale yellow liquid, which was used in subsequent step without any further purification.

To a solution of diethyl methylphosphonate (28 μL, 0.192 mmol, 1.5 equiv) in dry THF (4 mL) at −78 °C was added *n*-BuLi (0.1 mL, 0.154 mmol, 1.6 M in hexane, 1.2 equiv). The resultant solution was stirred at −78 °C to 0 °C for 1 h, then cooled back to −78 °C and a solution of crude aldehyde **88** (50 mg, 0.128 mmol, 1.0 equiv) in THF (2 mL) was added. This mixture was stirred at −78 °C for 1 h. It was then quenched with sat. aq. NH_4Cl (5 mL) and the solution was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography using petroleum ether/EtOAc (3:2) as eluent to give eliminated product **89** as pale yellow liquid, diastereomeric mixture (3:2, ^{1}H-NMR analysis).

Yield = 51 mg, 76%;

R_f = 0.53 (petroleum ether/EtOAc, 1:4);

$[\alpha]_D^{25}$ = – 0.63 (*c* 1.0, $CHCl_3$);

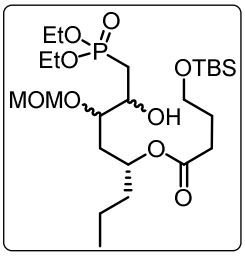
IR ($CHCl_3$): ν_{max} = 3015, 2947, 1724, 1637, 1463, 1217, 1100, 1031, 841, 759 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.68 - 6.54 (m, 1 H), 5.84 (m, 1 H), 5.09 - 4.91 (m, 1 H), 4.56 (t, *J* = 6.9 Hz, 1.3 H), 4.51 (t, *J* = 6.9 Hz, 0.7 H), 4.21 - 4.11 (m, 1 H), 4.10 - 4.00 (m, 4 H), 3.63 - 3.59 (m, 2 H), 3.34 (s, 1.2 H), 3.31 (s, 1.8 H), 2.38 - 2.32 (m, 2 H), 1.96 - 1.65 (m, 4 H), 1.60 - 1.42 (m, 2 H), 1.33 - 1.25 (m, 8 H), 0.89 - 0.86 (m, 3 H), 0.86 (d like, *J* = 1.4 Hz, 9 H), 0.01 (d, *J* = 1.4 Hz, 6 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.1, 173.0, 151.9, 151.8, 151.1, 151.0, 120.2, 119.6, 116.5, 115.8, 95.2, 94.6, 73.9, 73.6, 73.4, 73.1, 70.2, 61.9, 61.8, 61.7, 61.6, 56.0, 55.6, 39.4, 39.2, 36.8, 36.2, 30.7, 29.6, 28.0, 27.9, 25.8, 18.3, 18.2, 16.3, 16.2, 13.8, 13.8, -5.5;

HRMS (ESI^+) *m/z* = calcd for $C_{24}H_{49}O_8PSi$ $[M + H]^+$ 525.3007; found 525.3008.

(4*R*)-8-(Diethoxyphosphoryl)-7-hydroxy-6-(methoxymethoxy)octan-4-yl-4-((*tert*-butyldimethylsilyl)oxy)butanoate (90):



A flask containing diethyl methyl phosphonate (0.42 mL, 2.82 mmole, 2.2 equiv.) and 15 mL anhydrous THF was cooled to –100 ºC. *n*-BuLi (1.6 mL, 2.56 mmole; 1.6 M in

hexanes, 2 equiv.) was added dropwise to the solution over 10 min. The resulting mixture was allowed to stir for 1 h at –100 ºC. The aldehyde **88** (500 mg, 1.28 mmole, 1 equiv.) prepared in the previous step was dissolved in 10 mL THF and added slowly to the lithiated phosphonate solution over a period of 10 min. After stirring at –100 ^{o}C for an additional 5 minutes the reaction mixture was quenched with saturated $NaHCO_3$. The solution was diluted with EtOAc and the organic layer was separated. The aqueous layer was extracted with EtOAc (5 x 20 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in *vacuo*. Purification by flash chromatography using petroleum ether/EtOAc (11:9) as eluent gave desired phosphonate **90** as a mixture of *β*-hydroxy epimers as a colorless liquid along with undesired displaced product **91** as a colorless liquid.

Yield = 451 mg, 65%;

R_f = 0.36 (petroleum ether/EtOAc, 1:4);

$[\alpha]_D^{25}$ = + 1.1 (*c* 1.2, $CHCl_3$);

IR ($CHCl_3$): ν_{max} = 3398, 2943, 2864, 1728, 1647, 1461, 1385, 1247, 1166, 1099, 1032, 964, 838, 774 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.08 - 4.97 (m, 1 H), 4.74 - 4.55 (m, 2 H), 4.17 - 4.07 (m, 4 H), 4.01 - 3.72 (m, 1 H), 3.63 - 3.60 (m, 2 H), 3.58 - 3.48 (m, 1 H), 3.40 - 3.34 (m, 3 H), 2.41 - 2.30 (m, 2 H), 2.08 - 1.90 (m, 2 H), 1.87 - 1.70 (m, 3 H), 1.70 - 1.58 (m, 1 H), 1.58 - 1.43 (m, 2 H), 1.34 - 1.29 (m, 8 H), 0.91 - 0.84 (m, 12 H), 0.02 (s, 6 H);

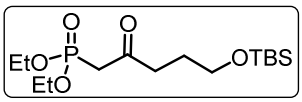
^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.4, 173.3, 173.2, 173.1, 98.0, 97.9, 96.9, 96.5, 80.2, 80.1, 79.3, 79.2, 78.0, 77.9, 71.3, 71.2, 70.5, 68.8, 68.7, 68.0, 67.9, 67.2, 67.1, 62.0, 61.9, 61.8, 61.7, 61.6, 56.0, 55.9, 37.1, 36.3, 36.0, 35.8, 35.7, 34.6, 34.3, 30.8, 29.6, 29.5, 29.2, 29.1, 28.4, 28.1, 28.0, 27.9, 27.8, 25.8, 18.4, 18.2, 16.4, 16.3, 13.8, -5.4;

HRMS (ESI^+) *m/z* = calcd for $C_{24}H_{51}O_9PSi$ $[M + Na]^+$ 565.2932; found 565.2929.

Undesired product **91** was obtained after flash column chromatography using petroleum ether/EtOAc (3:2) as eluent.

Characterization:

Diethyl(5-((*tert*-butyldimethylsilyl)oxy)-2-oxopentyl)phosphonate (91):



Yield = 126 mg, 28%;

R_f = 0.47 (petroleum ether/EtOAc, 1:4);

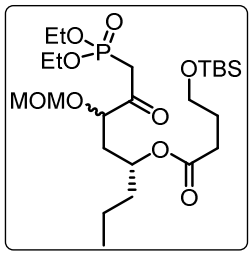
IR ($CHCl_3$): ν_{max} = 2996, 2943, 2863, 1714, 1638, 1465, 1397, 1252, 1099, 1028, 966, 837, 758 cm^{-1};

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.20 - 4.05 (m, 4 H), 3.59 (t, *J* = 6.1 Hz, 2 H), 3.13 (s, 1 H), 3.02 (s, 1 H), 2.68 (t, *J* = 7.2 Hz, 2 H), 1.84 - 1.71 (m, 2 H), 1.31 (t, *J* = 7.1 Hz, 6 H), 0.86 (s, 9 H), 0.01 (s, 6 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ = 202.0, 201.8, 62.5, 62.4, 61.9, 43.6, 41.1, 40.5, 26.6, 25.8, 18.2, 16.3, 16.2, -5.5;

HRMS (ESI^+) *m/z* = calcd for $C_{15}H_{33}O_5PSi$ $[M + H]^+$ 353.1908; found 353.1904.

(4*R*)-8-(Diethoxyphosphoryl)-6-(methoxymethoxy)-7-oxooctan-4-yl-4-((*tert*-butyldimethylsilyl)oxy)butanoate (92):



Dess–Martin periodinane (938 mg, 2.21 mmol, 3 equiv.) was added to a solution of *β*-hydroxy phosphonates **90** (400 mg, 0.74 mmol, 1 equiv.) in CH_2Cl_2 (10 ml) containing solid $NaHCO_3$ (249 mg, 2.96 mmol, 4 equiv.) at 0 ^oC. The reaction was stirred at 0 ^oC for 2 h, before being quenched with saturated aqueous $Na_2S_2O_3$ (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Flash column chromatography of the crude product using petroleum ether/EtOAc (11:9) as eluent gave ketophosphonate **92** as a colorless liquid, diastereomeric mixture (3:2, ^{1}H-NMR analysis).

Yield = 299 mg, 75%;

R_f = 0.63 (EtOAc);

$[\alpha]_D^{25}$ = + 2.9 (*c* 1.2, $CHCl_3$);

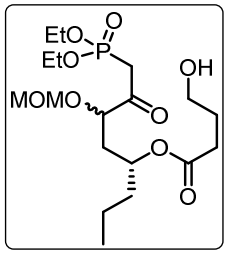
IR ($CHCl_3$): ν_{max} = 3007, 2947, 2865, 1725, 1641, 1462, 1385, 1252, 1166, 1101, 1027, 967, 839, 759 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.12 - 5.01 (m, 1 H), 4.68 - 4.58 (m, 2 H), 4.26 - 4.06 (m, 5 H), 3.67 - 3.61 (m, 2 H), 3.39 (s, 1.8 H), 3.35 (s, 1.2 H), 3.34 - 3.14 (m, 2 H), 2.46 - 2.28 (m, 2 H), 2.09 - 1.78 (m, 4 H), 1.61 - 1.54 (m, 2 H), 1.37 - 1.28 (m, 8 H), 0.94 - 0.88 (m, 12 H), 0.06 - 0.03 (m, 6 H);

^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.0, 202.9, 202.0, 201.9, 173.3, 173.0, 97.3, 96.7, 80.1, 79.7, 70.4, 70.1, 62.7, 62.6, 62.5, 62.0, 56.4, 56.2, 38.4, 38.0, 37.3, 36.9, 36.2, 36.0, 35.7, 30.8, 30.7, 28.1, 27.9, 25.9, 18.4, 18.3, 18.2, 16.3, 16.2, 13.9, 13.8, -5.4, -5.3;

HRMS (ESI^+) *m/z* = calcd for $C_{24}H_{49}O_9PSi$ $[M + Na]^+$ 563.2776; found 563.2772.

(4*R*)-8-(Diethoxyphosphoryl)-6-(methoxymethoxy)-7-oxooctan-4-yl 4-hydroxybutanoate (93):



To a solution of ketophosphonate **92** (250 mg, 0.462 mmol, 1 equiv.) in THF (5 mL) was added TBAF (0.7 mL, 0.693 mmol, 1.0 M solution in THF, 1.5 equiv) at 0 ^oC. The reaction mixture was stirred for 1 h and then diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. Flash column chromatography of the crude product using CH_2Cl_2/MeOH (49:1) as eluent gave alcohol **93** as a colorless liquid.

Yield = 170 mg, 86%;

R_f = 0.43 (CH_2Cl_2/MeOH, 19:1);

$[\alpha]_D^{25}$ = + 4.1 (*c* 1.0, $CHCl_3$);

IR ($CHCl_3$): ν_{max} = 2954, 1726, 1452, 1382, 1245, 1162, 1025, 968, 807 cm^{-1};

^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.20 - 4.95 (m, 1 H), 4.64 (d, *J* = 8.1 Hz, 2 H), 4.34 - 4.04 (m, 5 H), 3.69 - 3.64 (m, 2 H), 3.36 (d, *J* = 8.2 Hz, 3 H), 3.30 - 3.12 (m, 2 H), 2.57 - 2.34 (m, 2 H), 2.07 - 2.01 (m, 1 H), 1.98 - 1.75 (m, 3 H), 1.64 - 1.48 (m, 2 H), 1.48 - 1.28 (m, 8 H), 1.00 - 0.80 (t, *J* = 7.1 Hz, 3 H);

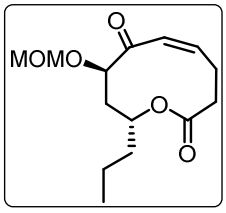
^{13}C NMR (50 MHz, $CDCl_3$): δ = 202.4, 202.3, 202.0, 201.9, 173.5, 173.2, 97.3, 96.6, 79.7, 79.2, 79.1, 70.4, 70.2, 62.9, 62.8, 62.7, 62.6, 61.5, 56.3, 56.2, 39.4, 39.3, 37.0, 36.8, 36.7, 36.3, 36.2, 35.5, 31.0, 30.8, 27.7, 27.5, 18.4, 16.4, 16.2, 13.9;
HRMS (ESI^+) *m/z* = calcd for $C_{18}H_{35}O_9P$ $[M + Na]^+$ 449.1911; found 449.1906.

***Z*-isomer of ten membered nonenolide core of (6*S*,7*R*,9*R*)-6,7-dihydroxy-9-propylnon-4-eno-9-lactone**:

Dess–Martin periodinane (448 mg, 1.06 mmol, 3 equiv.) was added to a solution of alcohol **93** (150 mg, 0.351 mmol, 1 equiv.) in CH_2Cl_2 (10 ml) containing solid $NaHCO_3$ (118 mg, 1.40 mmol, 4 equiv.) at 0 ^oC. The reaction was stirred at 0 ^oC for 1 h, before being quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The crude product aldehyde **94** (121 mg, 81%) obtained as a pale yellow liquid was used in next step without any further purification.

To a solution of K_2CO_3 (98 mg, 0.707 mmol, 6.0 equiv) and 18-crown-6 (374 mg, 1.416 mmol, 12.0 equiv) in toluene (100 mL) at 60 ^oC was added a solution of crude aldehyde **94** (50 mg, 0.118 mmol, 1 equiv.) in toluene (10 mL) over a period of 4 h. The resulting solution was stirred overnight at 60 ^oC. It was then quenched with sat. aq. NH_4Cl (10 mL) and the solution was extracted with EtOAc (5 x 25 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. Removal of solvent under reduced pressure gave the crude residue as a diastereomeric mixture (*β*/*α* 2:3). At this stage, both the diastereomers finally got separated by flash column chromatography (petroleum ether/EtOAc, 17:3) to afford compound **96** as a pale yellow liquid and **96'** (petroleum ether/EtOAc, 17:3) as a pale yellow liquid.

Data for (8*R*,10*R*,*Z*)-8-(methoxymethoxy)-10-propyl-3,4,9,10-tetrahydro-2*H*-oxecine-2,7(8*H*)-dione (96):



Yield = 7.5 mg, 36%;
***R*$_f$** = 0.5 (petroleum ether/EtOAc, 7:3);

$[\alpha]_D^{25}$ = + 4.6 (*c* 0.3, $CHCl_3$);

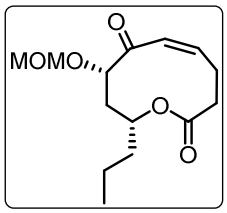
IR ($CHCl_3$): ν_{max} = 3016, 2926, 2858, 1728, 1629, 1458, 1224, 1153, 1046, 753 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.37 (d, *J* = 11.8 Hz, 1 H), 5.93 (ddd, *J* = 5.4, 11.8, 11.8 Hz, 1 H), 4.98 - 4.91 (m, 1 H), 4.71 (d, *J* = 6.9 Hz, 1 H), 4.61 (d, *J* = 6.9 Hz, 1 H), 4.12 (dd, *J* = 3.1, 9.2 Hz, 1 H), 3.31 (s, 3 H), 3.20 - 3.12 (m, 1 H), 2.58 (ddd, *J* = 4.6, 4.6, 15.3 Hz, 1 H), 2.32 - 2.24 (m, 2 H), 2.22 - 2.11 (m, 2 H), 1.73 - 1.69 (m, 1 H), 1.59 - 1.54 (m, 1 H), 1.32 - 1.28 (m, 2 H), 0.91 (t, *J* = 7.2 Hz, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.7, 170.8, 138.3, 132.3, 96.5, 78.7, 72.2, 55.8, 37.2, 36.4, 34.8, 22.7, 18.7, 13.8;

HRMS (ESI^+) *m/z* = calcd for $C_{14}H_{22}O_5$ $[M + Na]^+$ 293.1359; found 293.1356.

Data for (8*S*,10*R*,*Z*)-8-(methoxymethoxy)-10-propyl-3,4,9,10-tetrahydro-2*H*-oxecine-2,7(8*H*)-dione (96'):



Yield = 12 mg, 57 %;

***R*$_f$** = 0.56 (petroleum ether/EtOAc, 7:3);

$[\alpha]_D^{25}$ = + 18.9 (*c* 0.4, $CHCl_3$);

IR ($CHCl_3$): ν_{max} = 3019, 2930, 1730, 1628, 1457, 1395, 1248, 1155, 1047, 970, 759 cm^{-1};

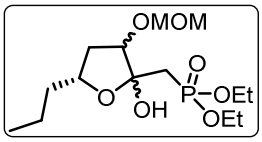
^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.55 (d, *J* = 11.8 Hz, 1 H), 5.93 (ddd, *J* = 5.7, 11.8, 11.8 Hz, 1 H), 5.12 - 5.05 (m, 1 H), 4.74 - 4.69 (m, 2 H), 4.19 (dd, *J* = 1.9, 6.9 Hz, 1 H), 3.41 (s, 3 H), 3.18 - 3.08 (m, 1 H), 2.58 (ddd, *J* = 4.2, 4.2, 15.3 Hz, 1 H), 2.34 - 2.26 (m, 2 H), 2.18 - 2.08 (m, 2 H), 1.67 - 1.60 (m, 1 H), 1.55 - 1.47 (m, 1 H), 1.34 - 1.29 (m, 2 H), 0.92 (t, *J* = 7.2 Hz, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.8, 170.5, 137.2, 131.5, 96.0, 79.6, 70.0, 56.1, 37.2, 36.2, 35.3, 22.2, 18.5, 13.9;

HRMS (ESI^+) *m/z* = calcd for $C_{14}H_{22}O_5$ $[M + Na]^+$ 293.1359; found 293.1357.

During the optimization of intramolecular HWE reaction undesired product **95** was also formed which was isolated and characterized as follows.

(((5*R*)-2-hydroxy-3-(methoxymethoxy)-5-propyltetrahydrofuran-2-yl)methyl)phosphonate (95):



To a stirred suspension of LiCl (15 mg, 0.353 mmol, 3 equiv.), DBU (53 μL, 0.353 mmol, 3 equiv.) in anhydrous MeCN (60 mL) was added the solution of crude aldehyde **94** (50 mg, 0.118 mmol, 1 equiv.) in MeCN (10 mL) dropwise over a period of 15 min. The reaction mixture was stirred overnight at room temperature. After completion, the reaction mixture was concentrated; and washed with water and extracted with EtOAc (3 x 20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography on silica gel (petroleum ether/EtOAc, 11:9) afforded compound **95** as a colorless liquid.

Yield = 24 mg, 61%;

R_f : 0.41 (petroleum ether/EtOAc, 1:1);

$[\alpha]_D^{25}$ = – 0.66 (*c* 1.1, $CHCl_3$);

IR ($CHCl_3$): ν_{max} = 3410, 2928, 1724, 1643, 1451, 1389, 1222, 1152, 1034, 967, 812 cm^{-1};

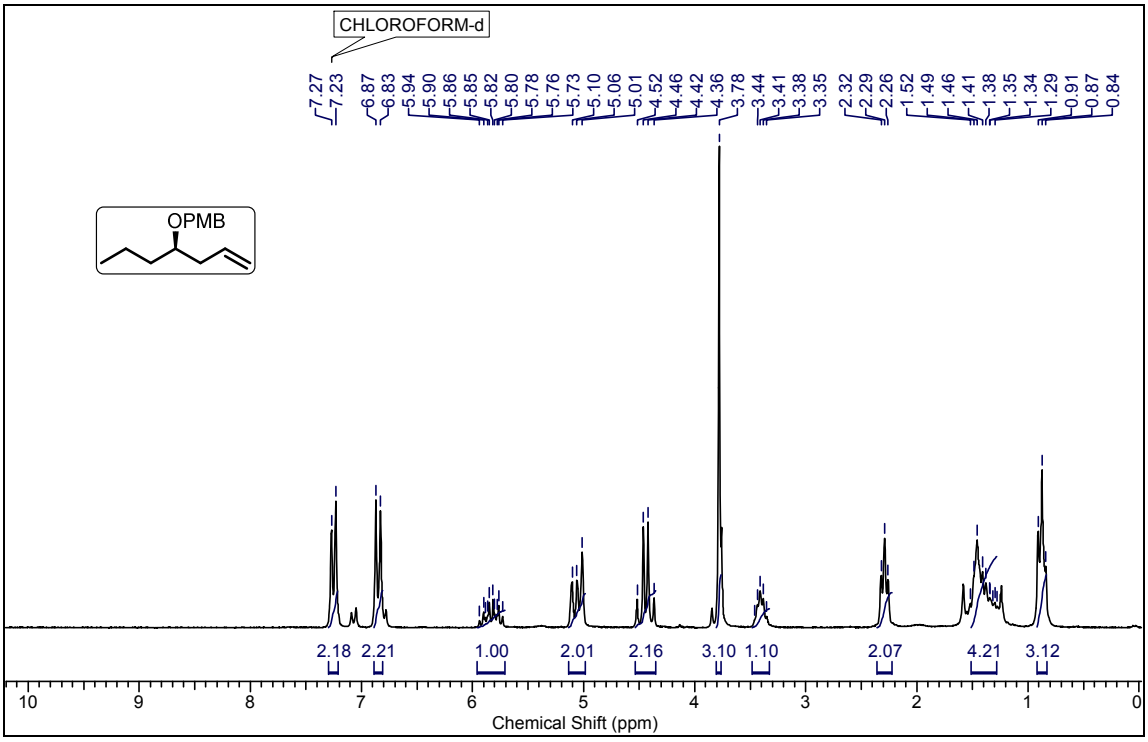
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.52 - 5.14 (m, 1 H), 4.77 - 4.59 (m, 2 H), 4.31 - 3.98 (m, 6 H), 3.42 - 3.33 (m, 3 H), 2.53 - 2.36 (m, 1 H), 2.27 - 2.09 (m, 1 H), 2.09 - 1.82 (m, 1 H), 1.74 - 1.59 (m, 1 H), 1.57 - 1.37 (m, 3 H), 1.33 (t, *J* = 6.7 Hz, 7 H), 0.91 (t, *J* = 6.7 Hz, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 104.2, 104.1, 104.0, 100.6, 100.5, 99.7, 99.6, 96.5, 96.4, 95.5, 95.4, 82.7, 82.6, 82.5, 82.4, 81.9, 81.8, 81.2, 81.1, 79.4, 76.9, 76.4, 75.8, 63.0, 62.9, 62.8, 62.6, 62.5, 62.5, 61.6, 61.5, 61.4, 61.3, 61.2, 55.7, 55.6, 40.0, 39.9, 38.3, 38.2, 36.8, 36.2, 35.5, 35.4, 35.1, 34.1, 33.8, 32.5, 32.2, 31.9, 31.2, 30.8, 29.7, 22.7, 19.4, 19.2, 19.1, 18.8, 16.5, 16.4, 16.3, 16.2, 14.1, 14.0, 13.9;

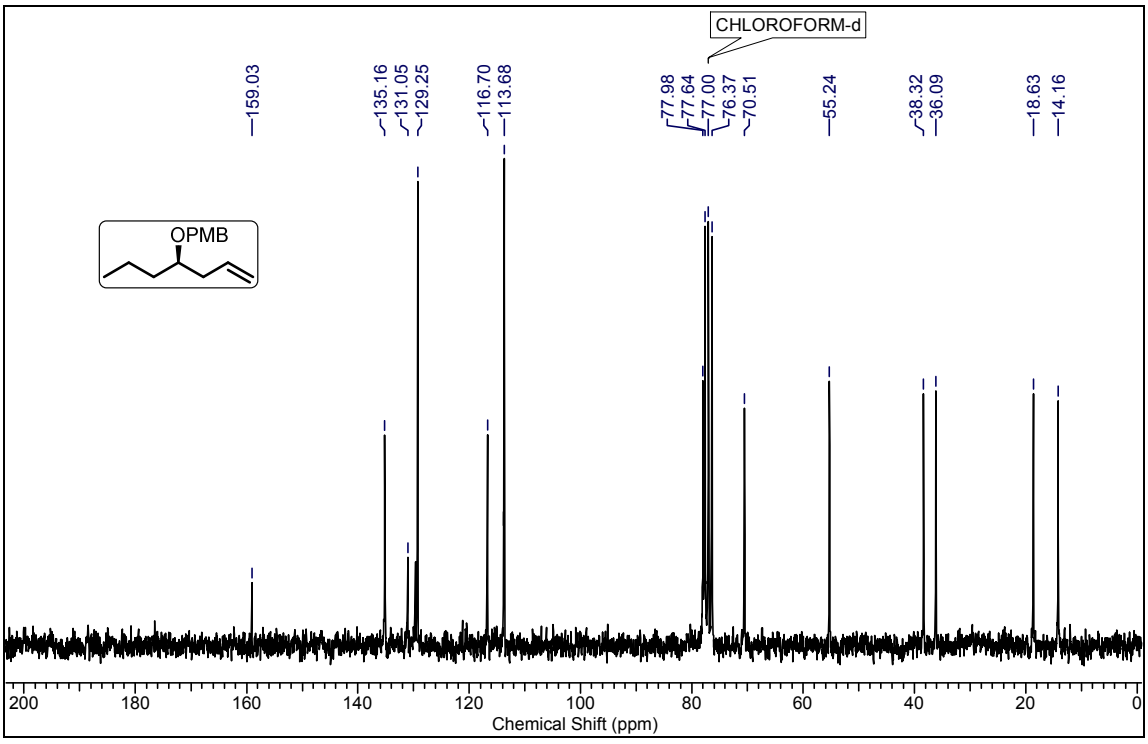
HRMS (ESI^+) *m/z* = calcd for $C_{14}H_{29}O_7P$ $[M + Na]^+$ 363.1543; found 363.1536.

2.2.4. Spectral Data

^{1}H NMR spectrum of compound **80** ($CDCl_3$, 200 MHz):

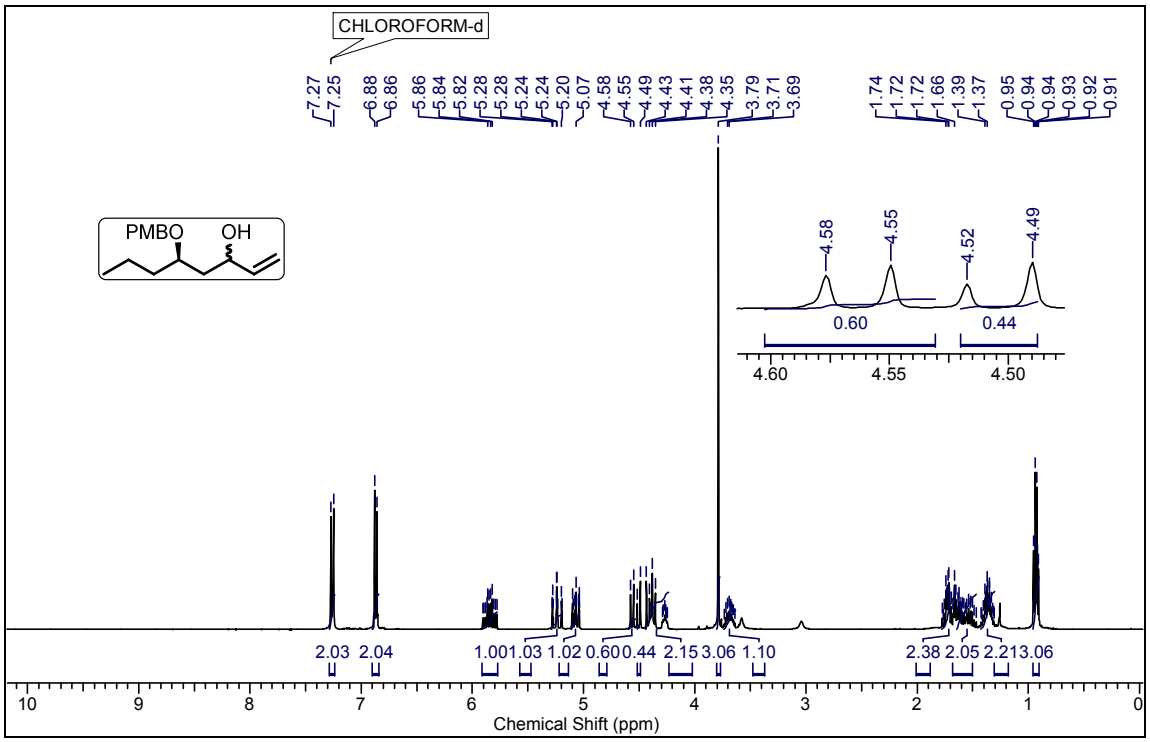


^{13}C NMR spectrum of compound **80** ($CDCl_3$, 50 MHz):

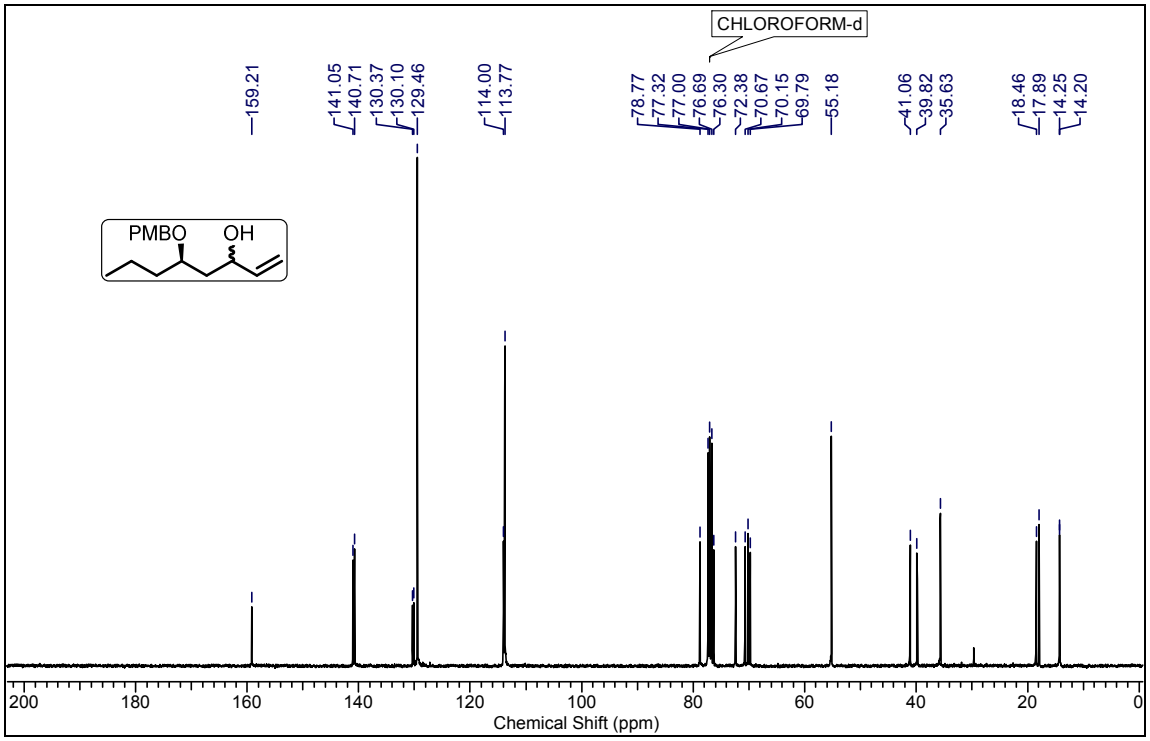


Spectra

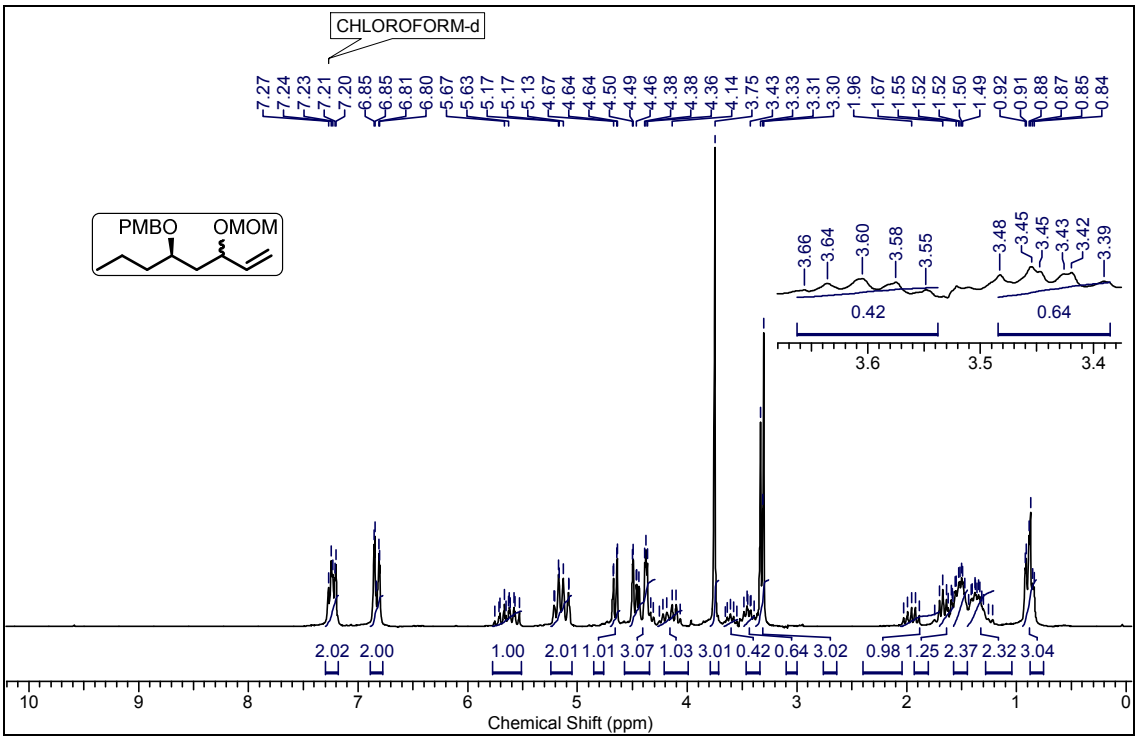
^{1}H NMR spectrum of compound **82** ($CDCl_3$, 400 MHz):



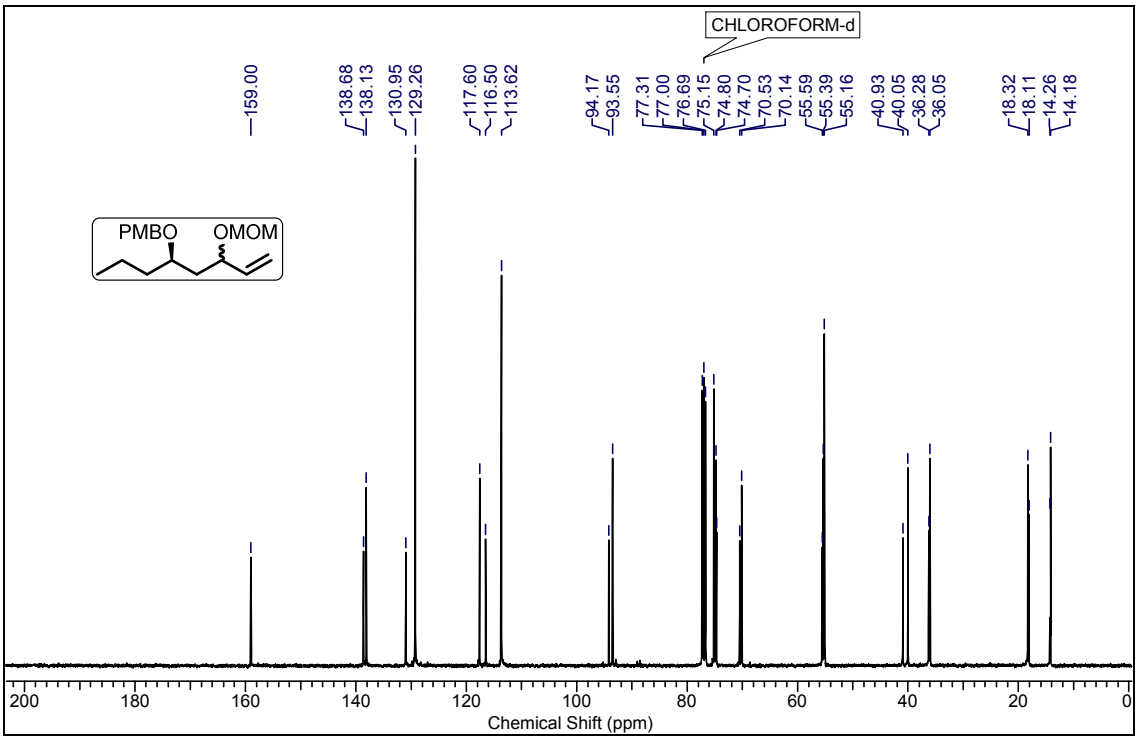
^{13}C NMR spectrum of compound **82** ($CDCl_3$, 100 MHz):



^{1}H NMR spectrum of compound **83** ($CDCl_3$, 200 MHz):

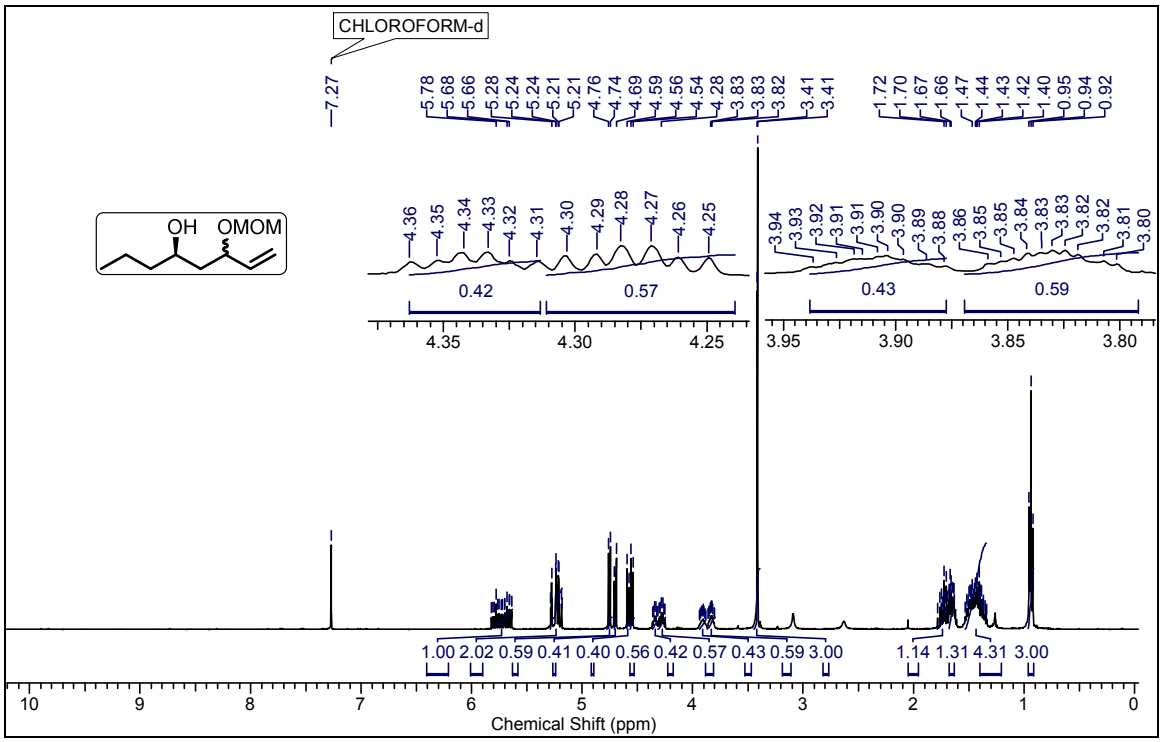


^{13}C NMR spectrum of compound **83** ($CDCl_3$, 100 MHz):

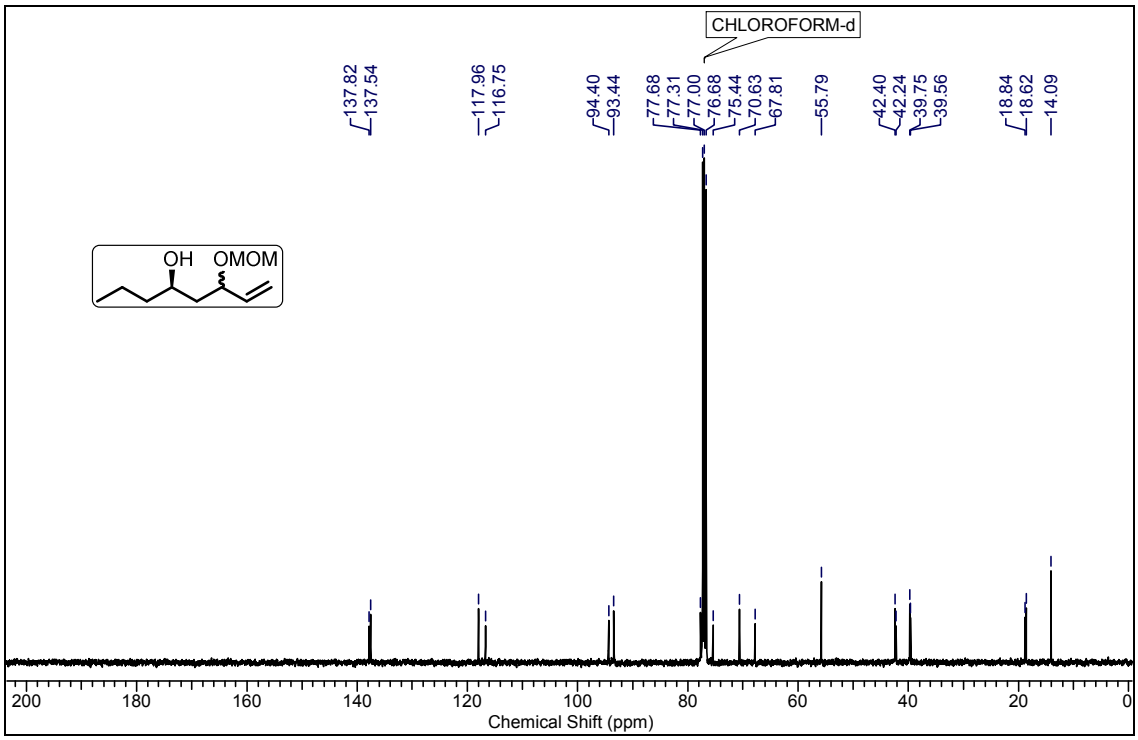


Spectra

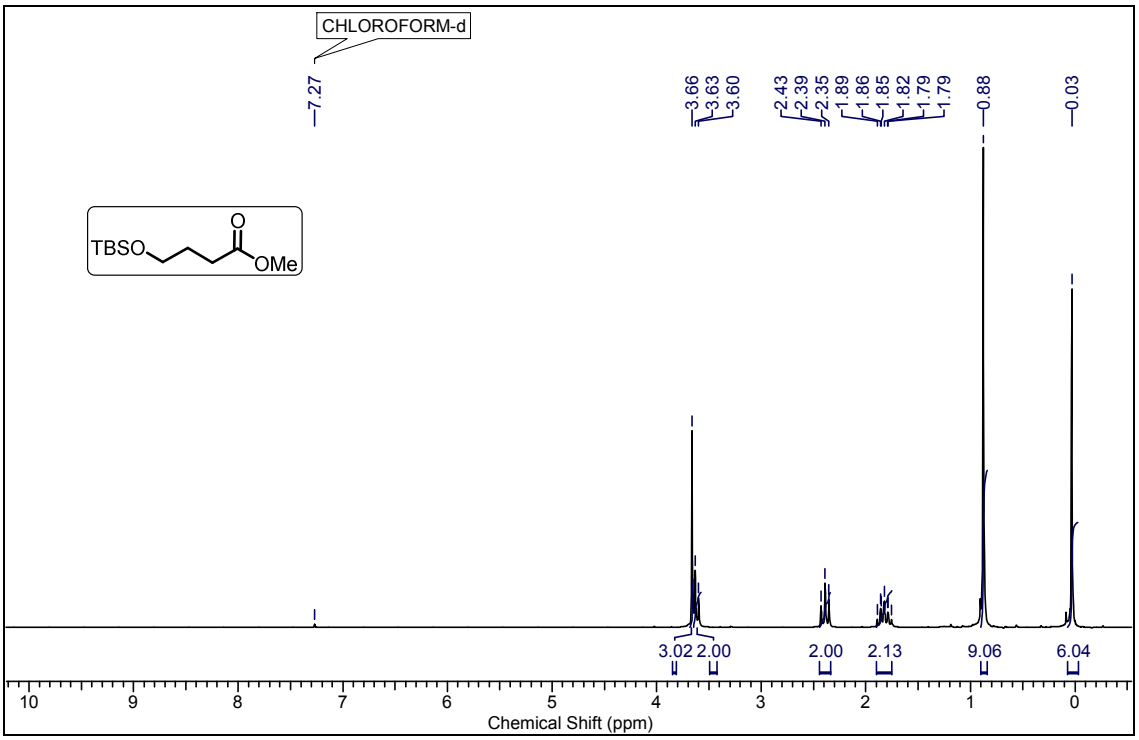
^{1}H NMR spectrum of compound **84** ($CDCl_3$, 400 MHz):



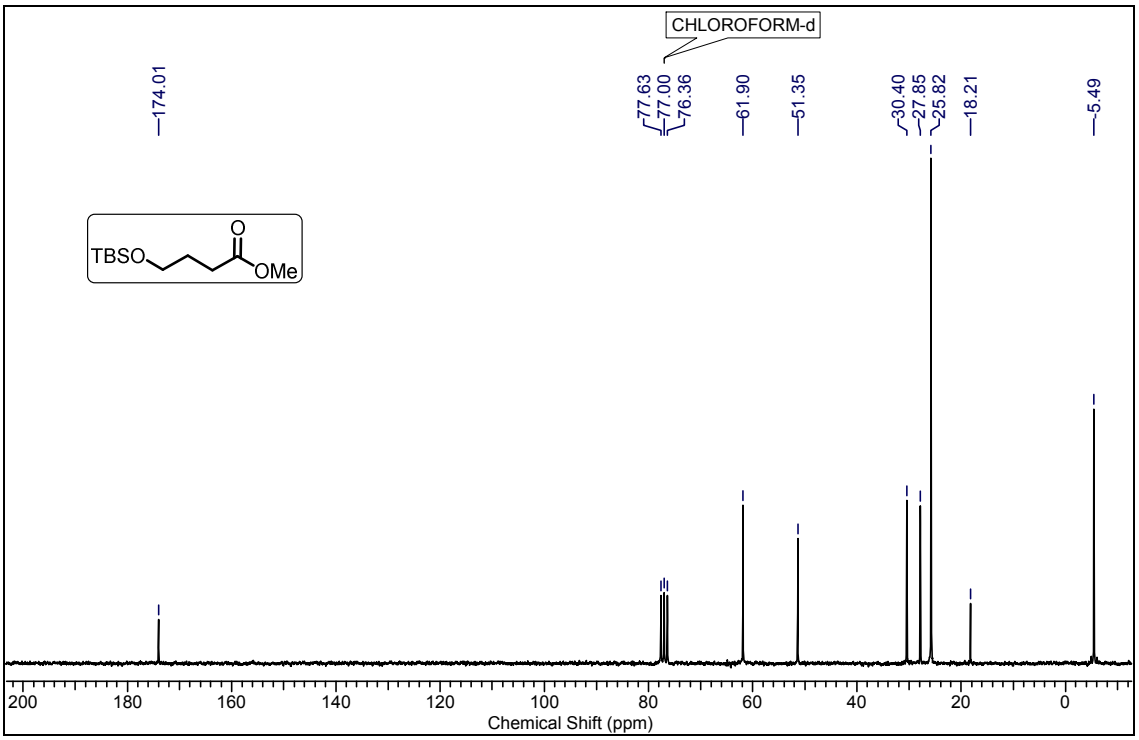
^{13}C NMR spectrum of compound **84** ($CDCl_3$, 100 MHz):



^{1}H NMR spectrum of compound **85** ($CDCl_3$, 200 MHz):

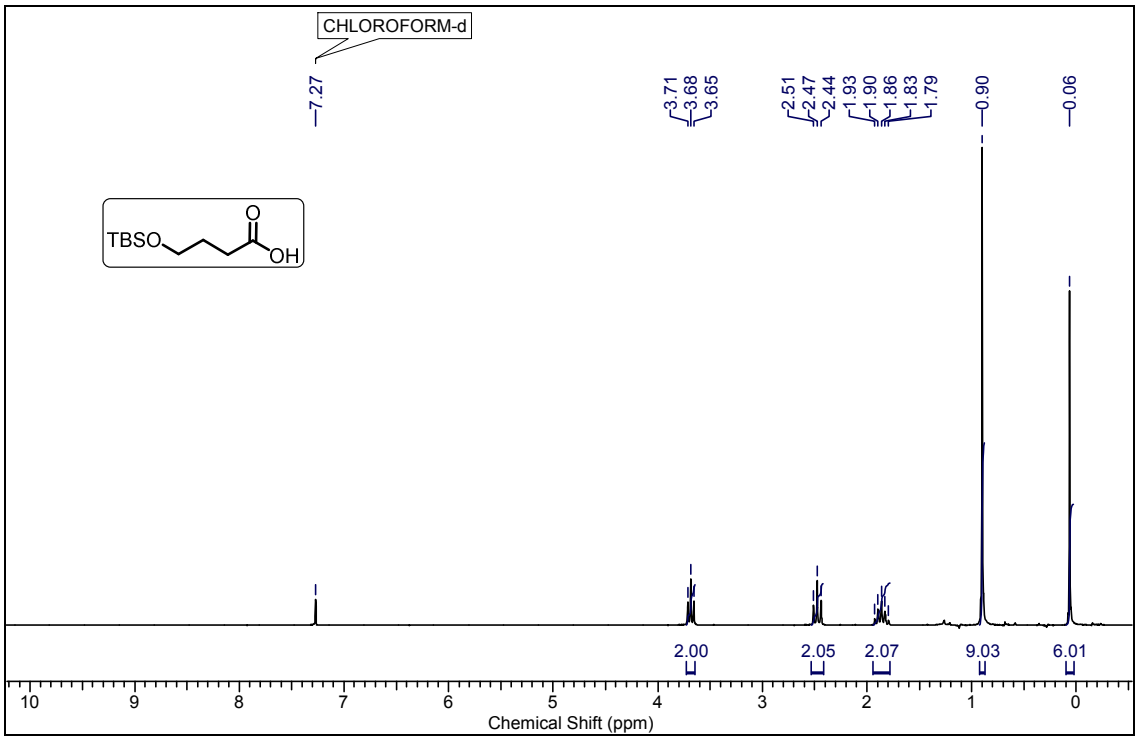


^{13}C NMR spectrum of compound **85** ($CDCl_3$, 50 MHz):

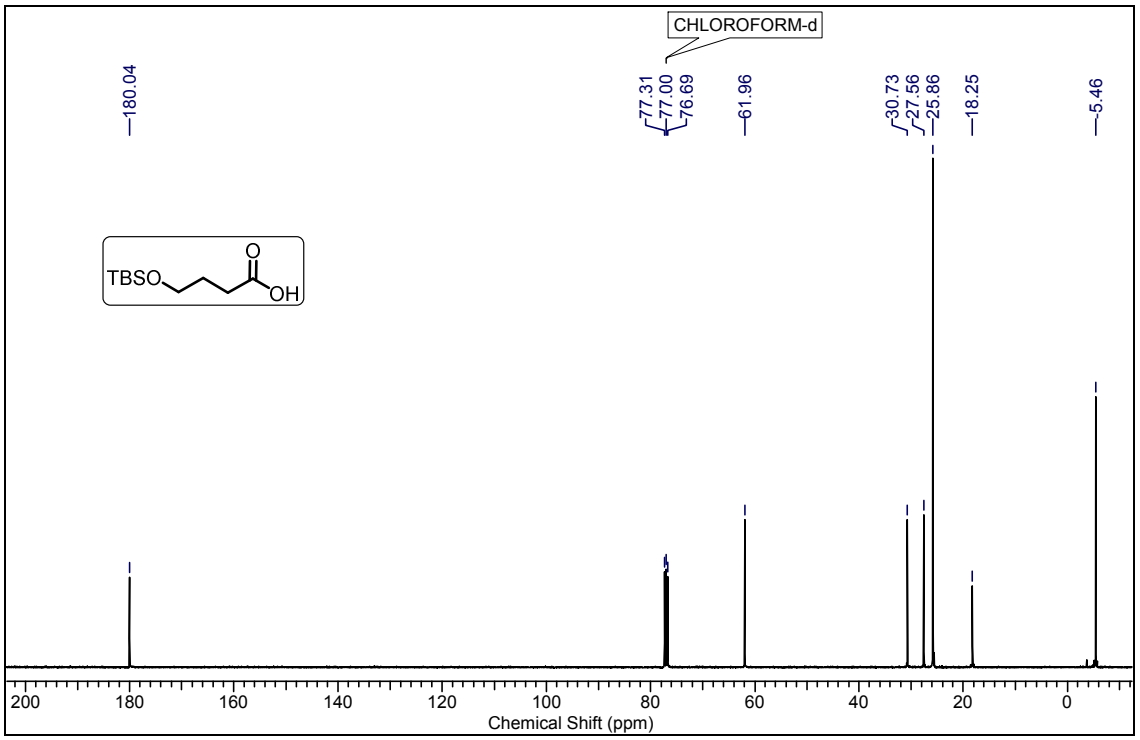


Spectra

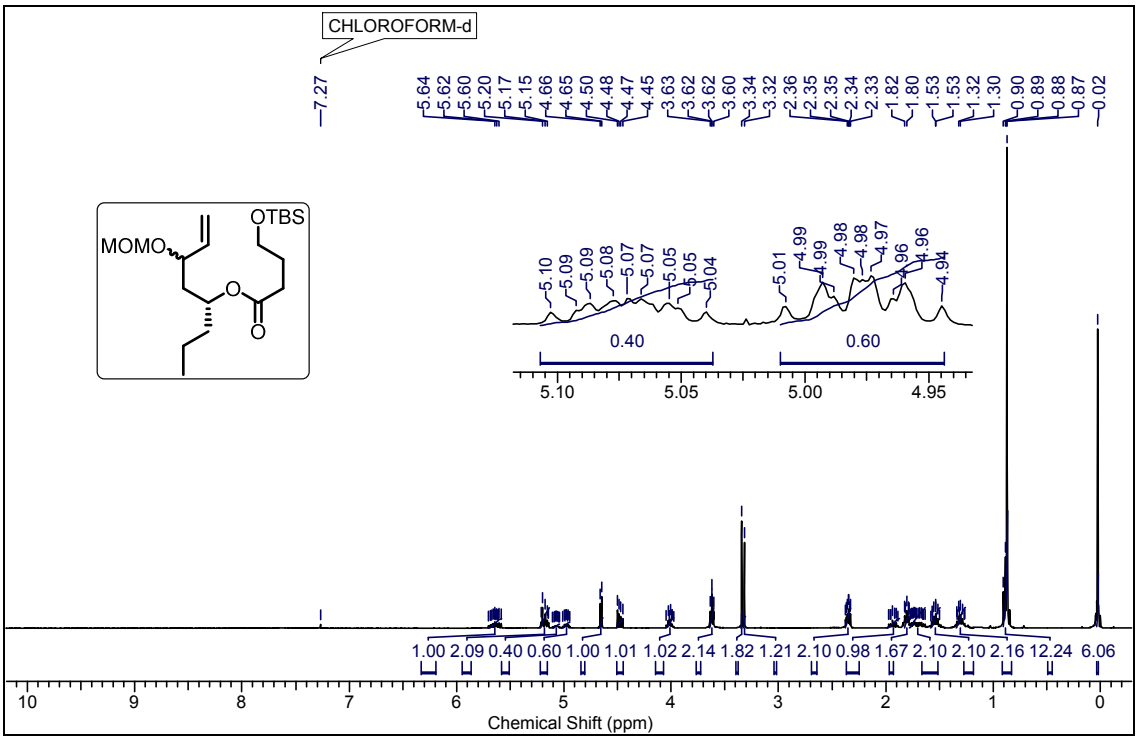
^{1}H NMR spectrum of compound **86** ($CDCl_3$, 200 MHz):



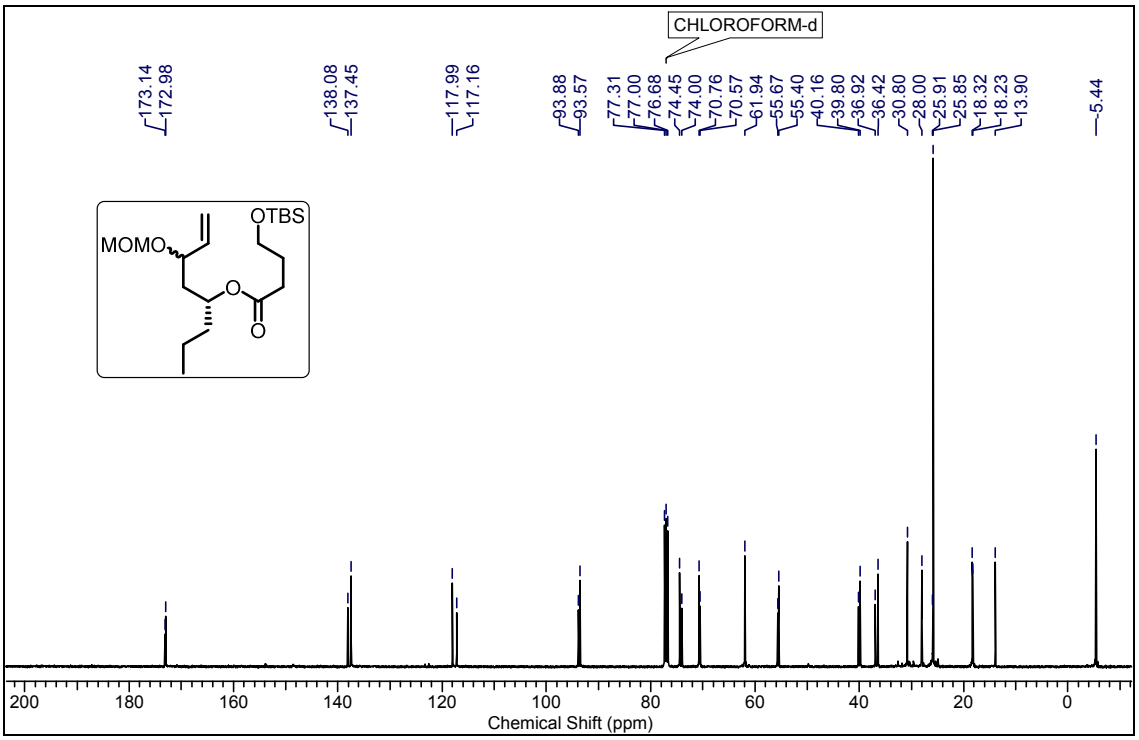
^{13}C NMR spectrum of compound **86** ($CDCl_3$, 100 MHz):



^{1}H NMR spectrum of compound **87** ($CDCl_3$, 400 MHz):

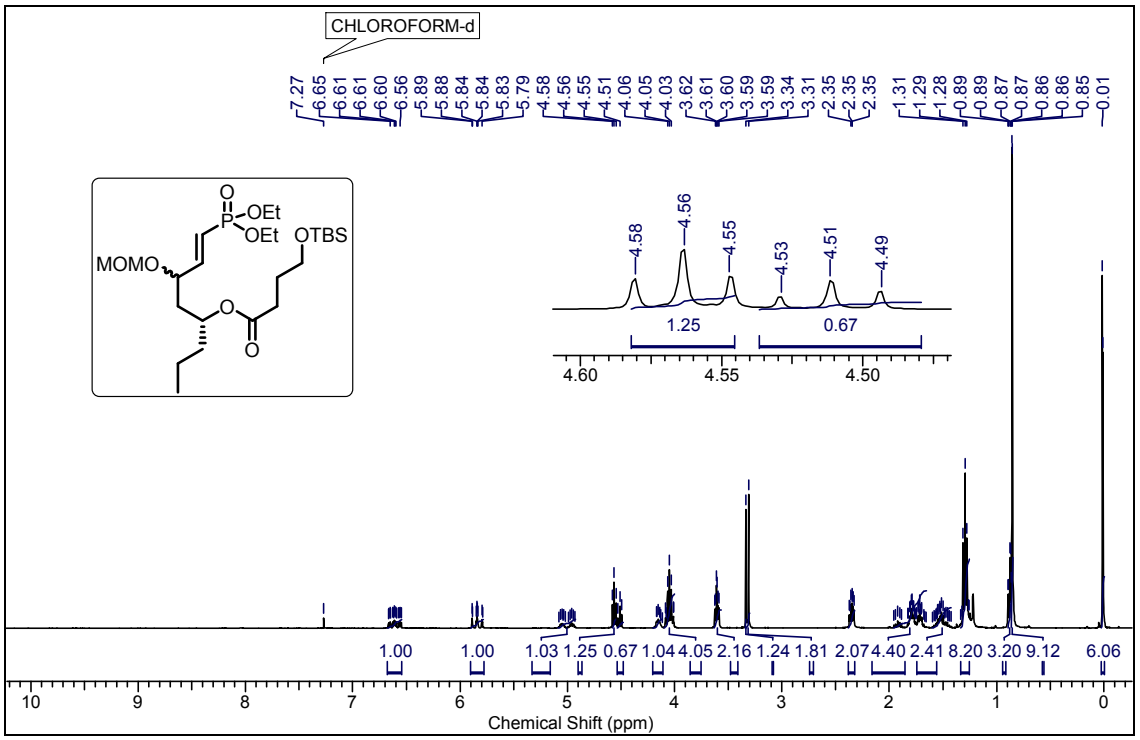


^{13}C NMR spectrum of compound **87** ($CDCl_3$, 100 MHz):

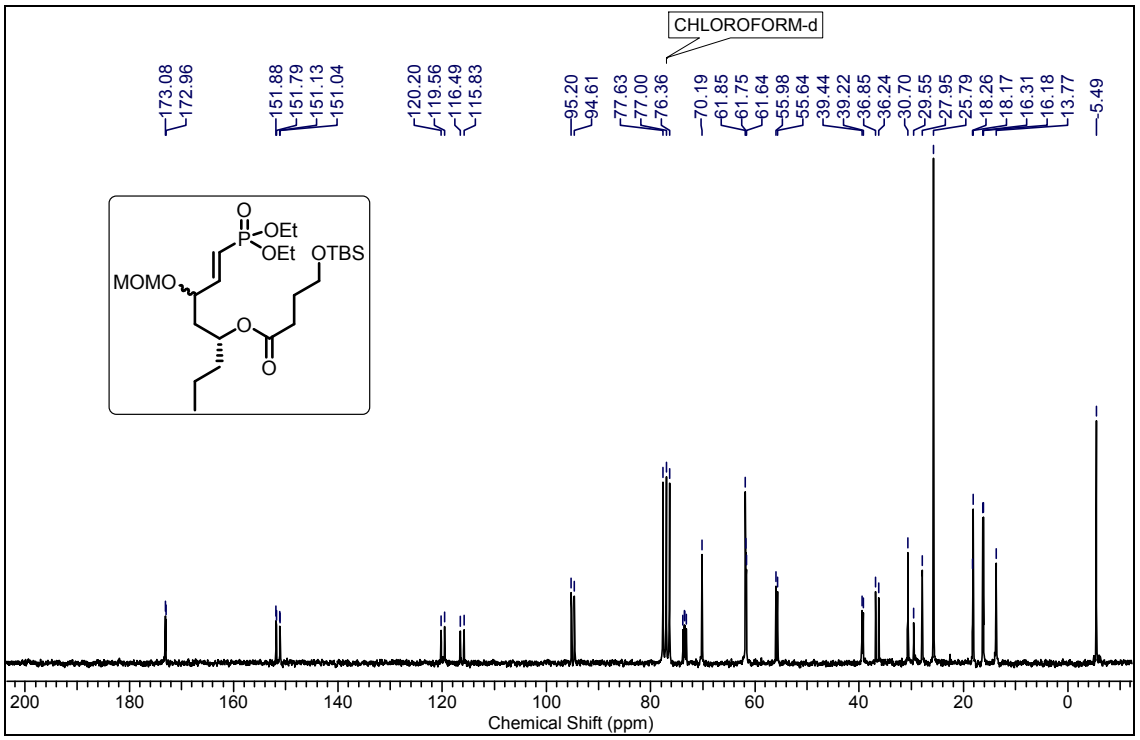


Spectra

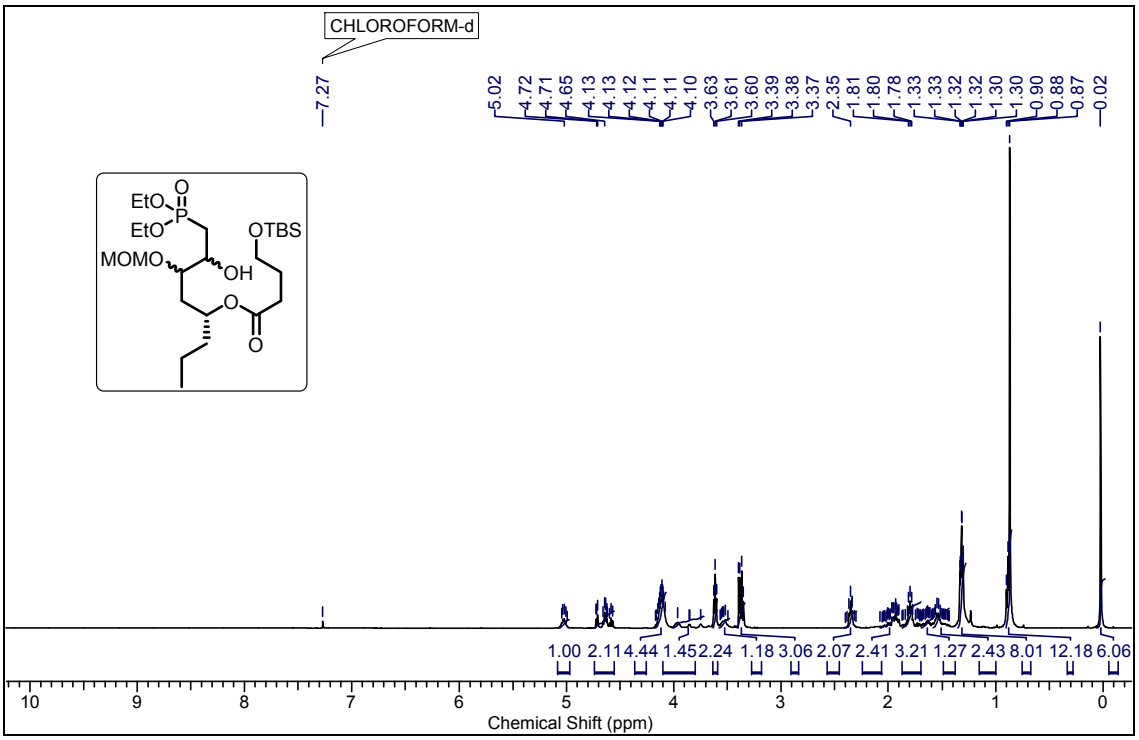
^{1}H NMR spectrum of compound **89** ($CDCl_3$, 400 MHz):



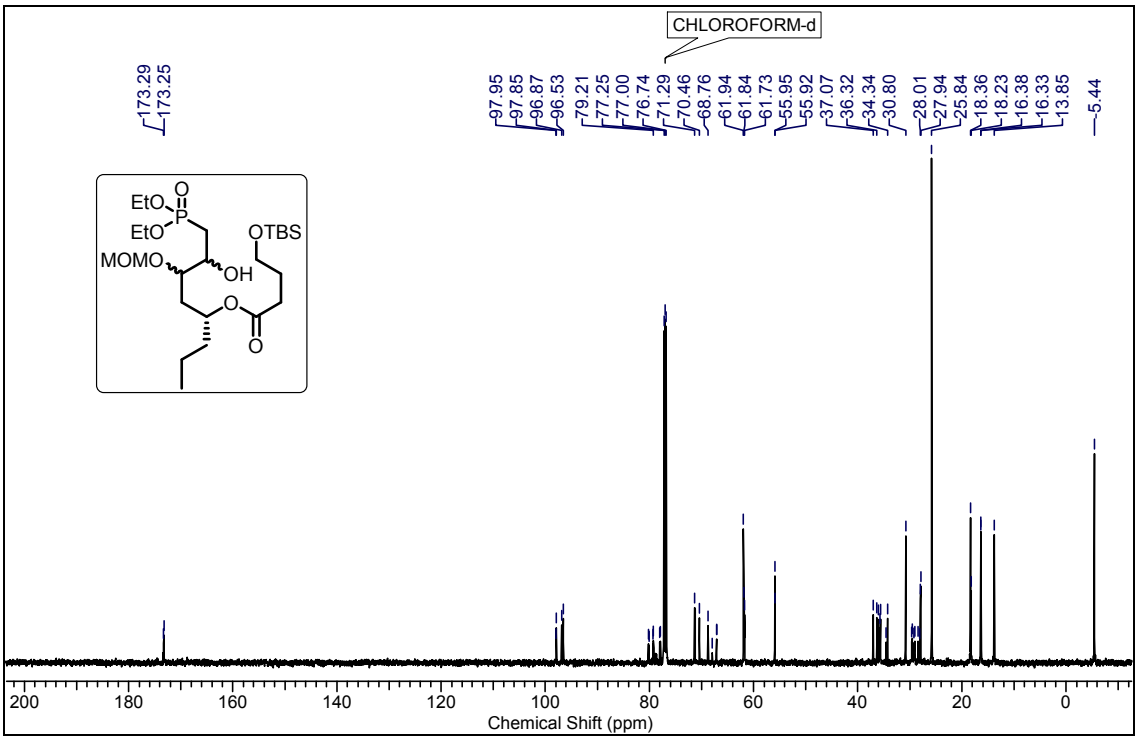
^{13}C NMR spectrum of compound **89** ($CDCl_3$, 50 MHz):



^{1}H NMR spectrum of compound **90** ($CDCl_3$, 500 MHz):

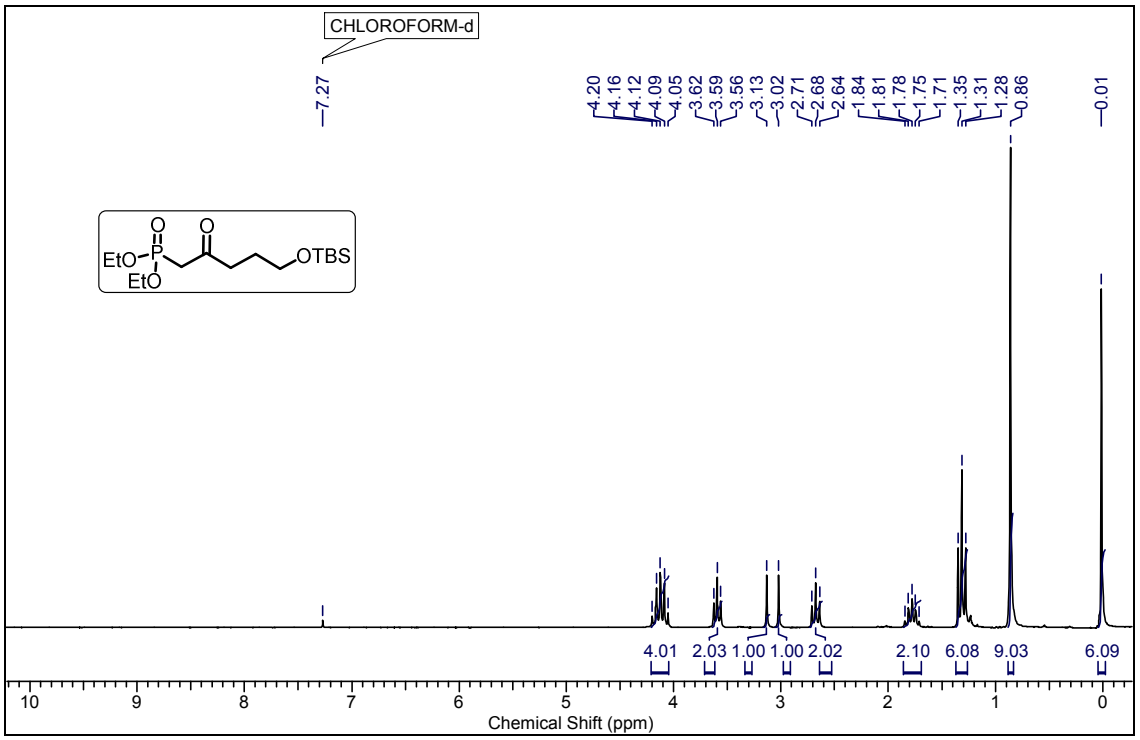


^{13}C NMR spectrum of compound **90** ($CDCl_3$, 125 MHz):

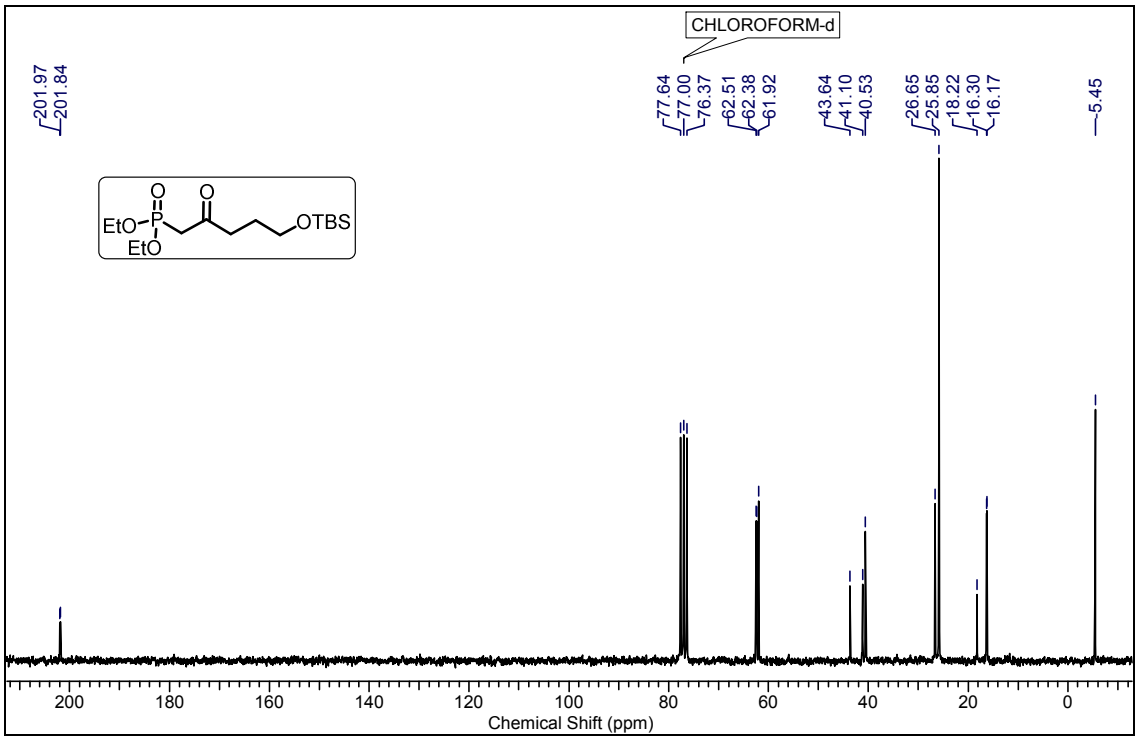


Spectra

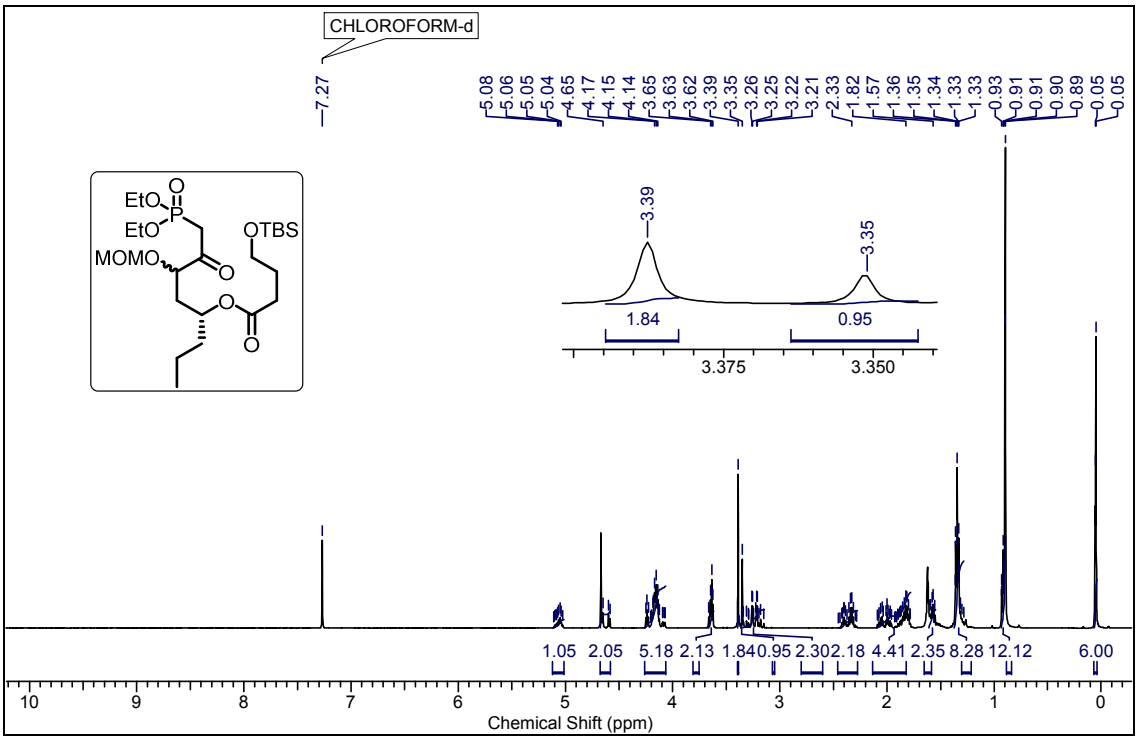
^{1}H NMR spectrum of compound **91** ($CDCl_3$, 200 MHz):



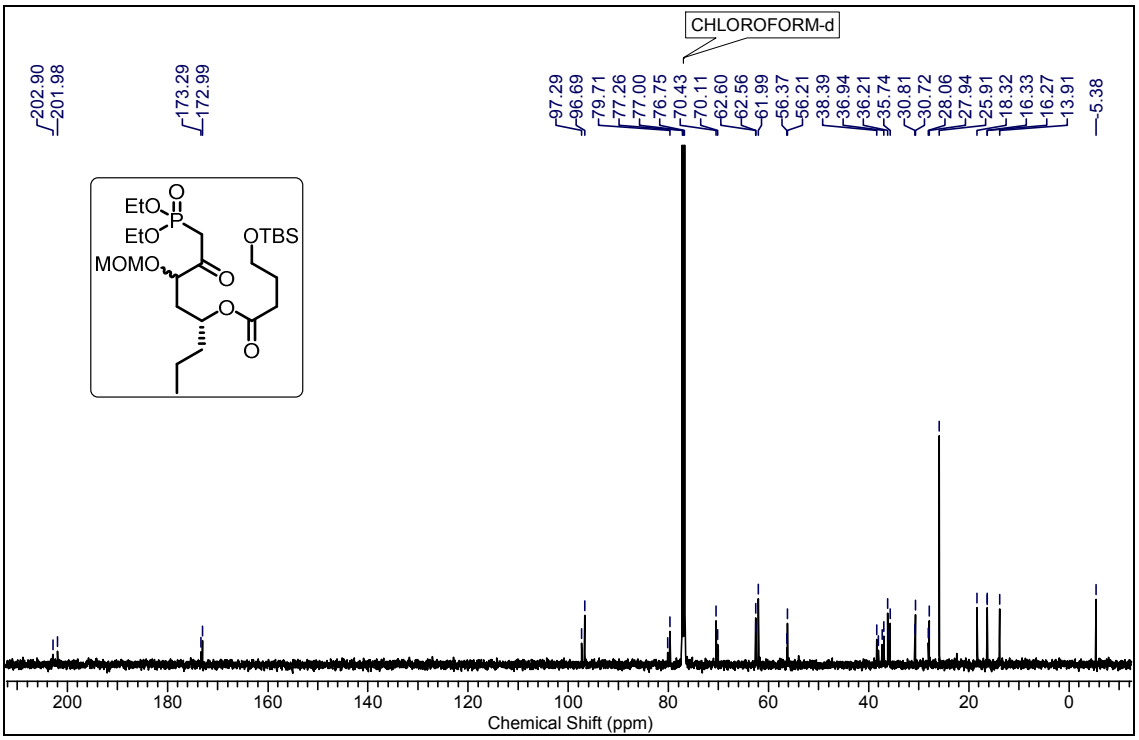
^{13}C NMR spectrum of compound **91** ($CDCl_3$, 50 MHz):



^{1}H NMR spectrum of compound **92** ($CDCl_3$, 500 MHz):

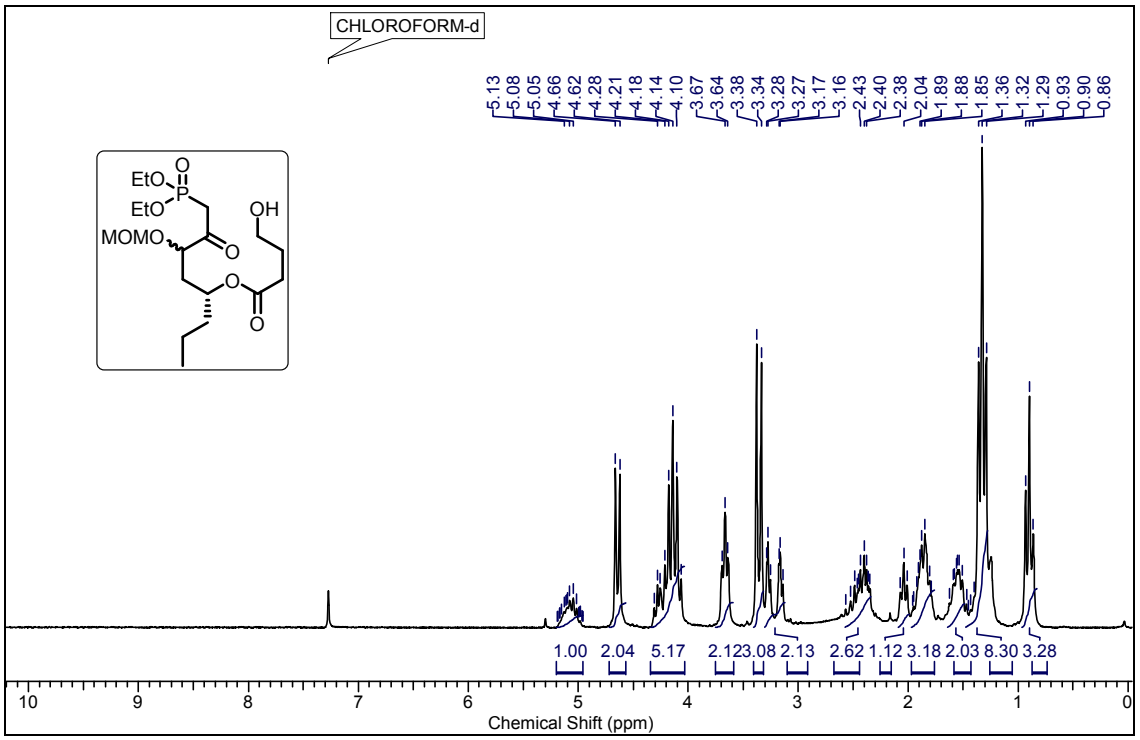


^{13}C NMR spectrum of compound **92** ($CDCl_3$, 125 MHz):

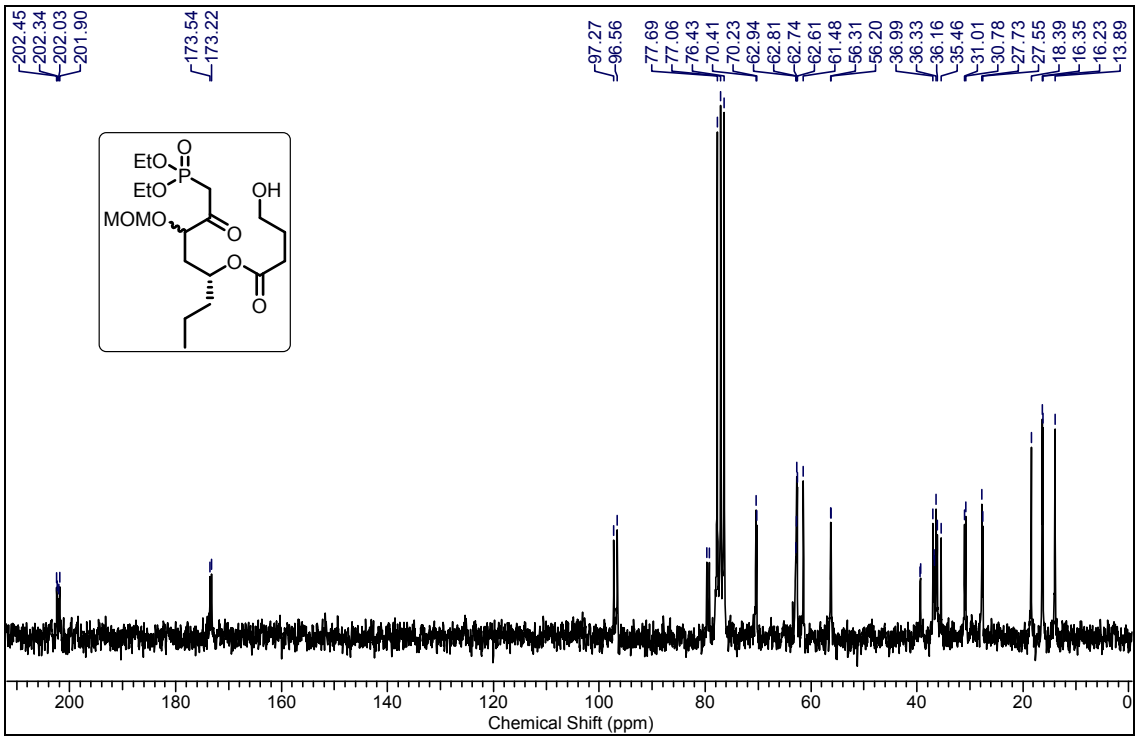


Spectra

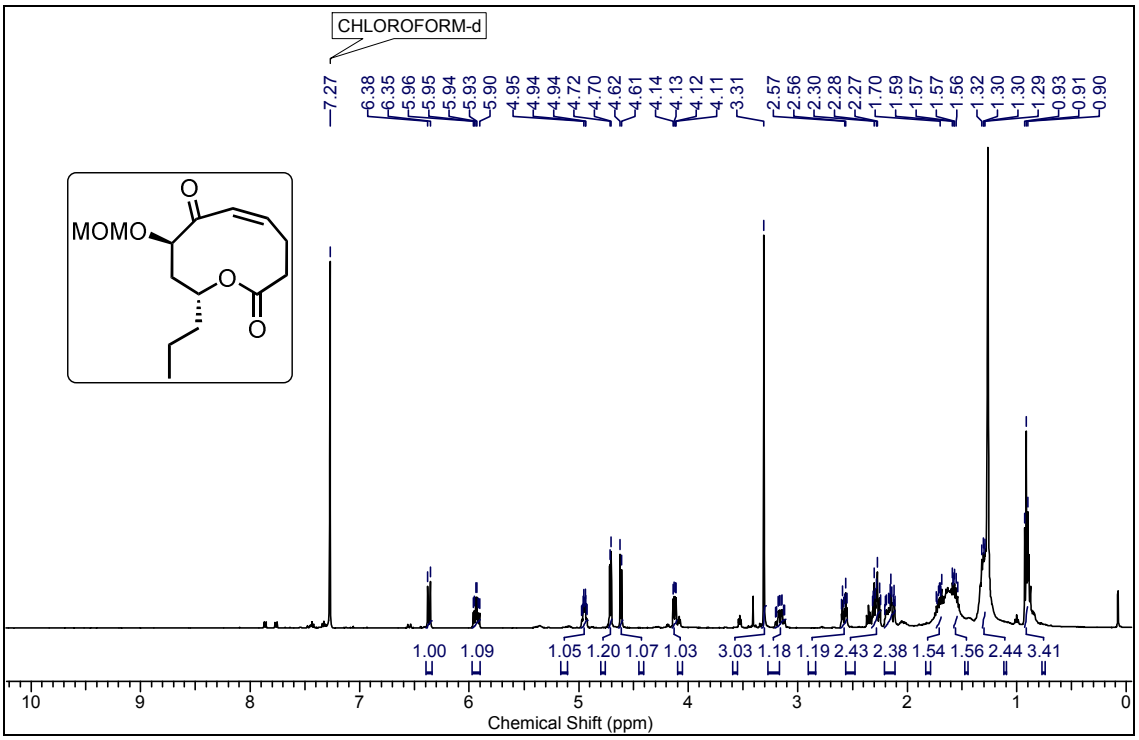
^{1}H NMR spectrum of compound **93** ($CDCl_3$, 200 MHz):



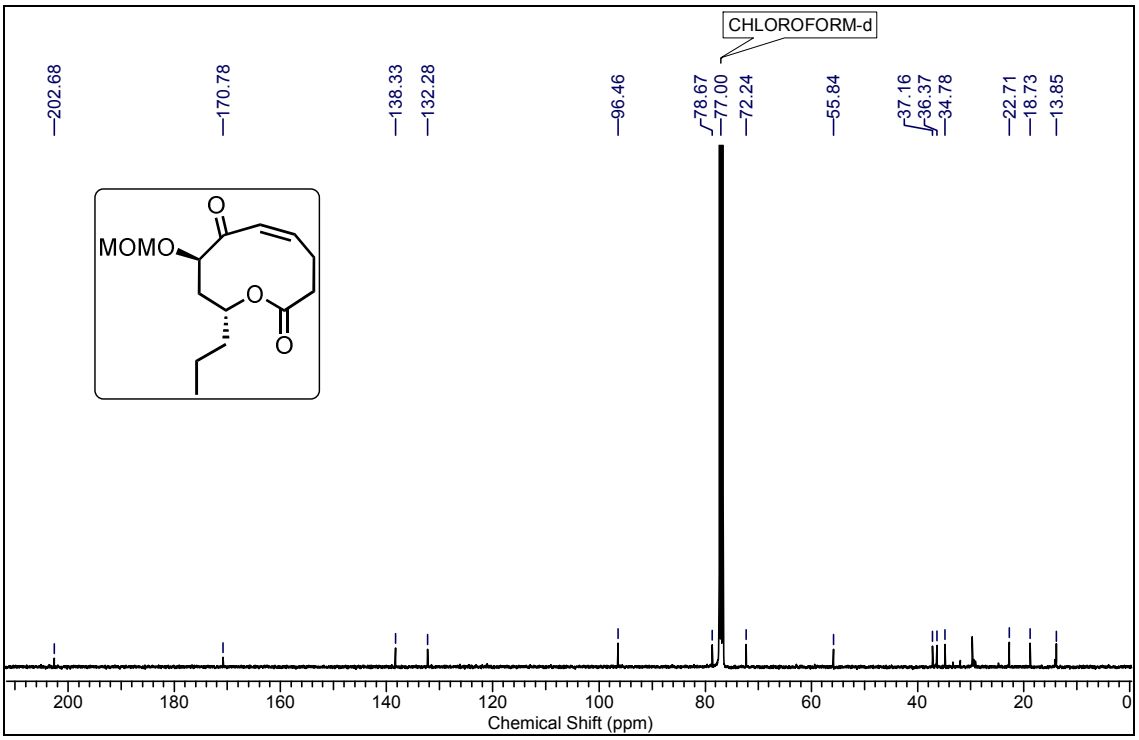
^{13}C NMR spectrum of compound **93** ($CDCl_3$, 50 MHz):



^{1}H NMR spectrum of compound **96** ($CDCl_3$, 500 MHz):

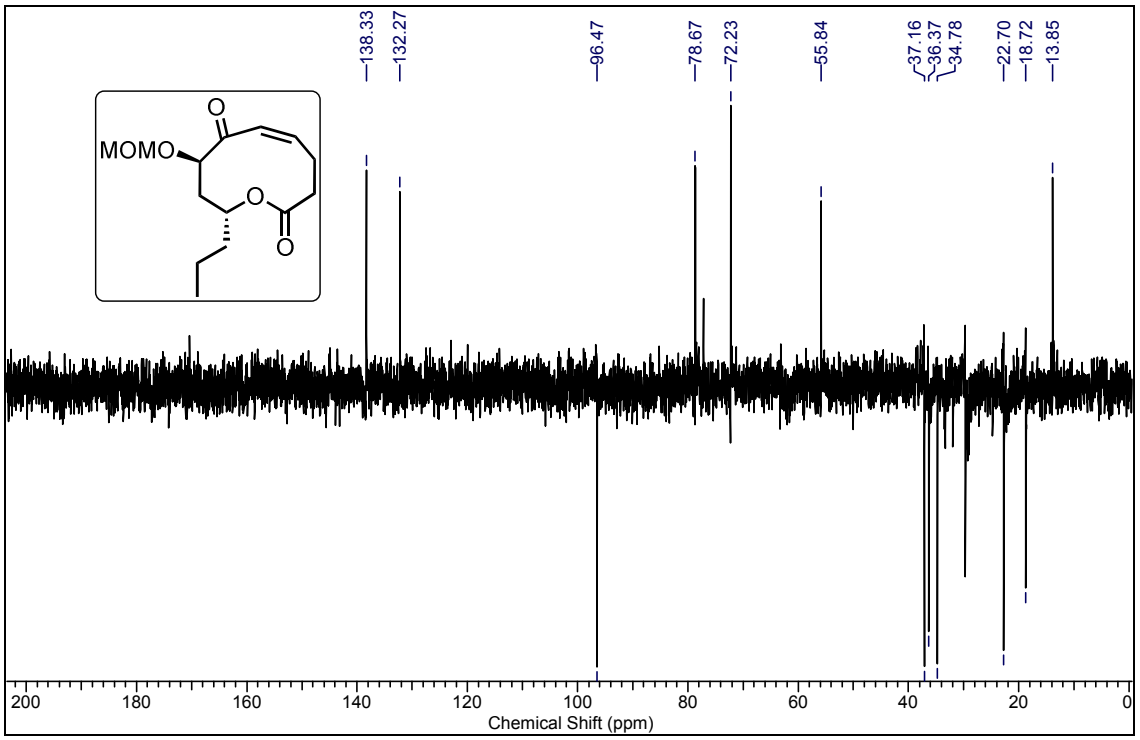


^{13}C NMR spectrum of compound **96** ($CDCl_3$, 100 MHz):

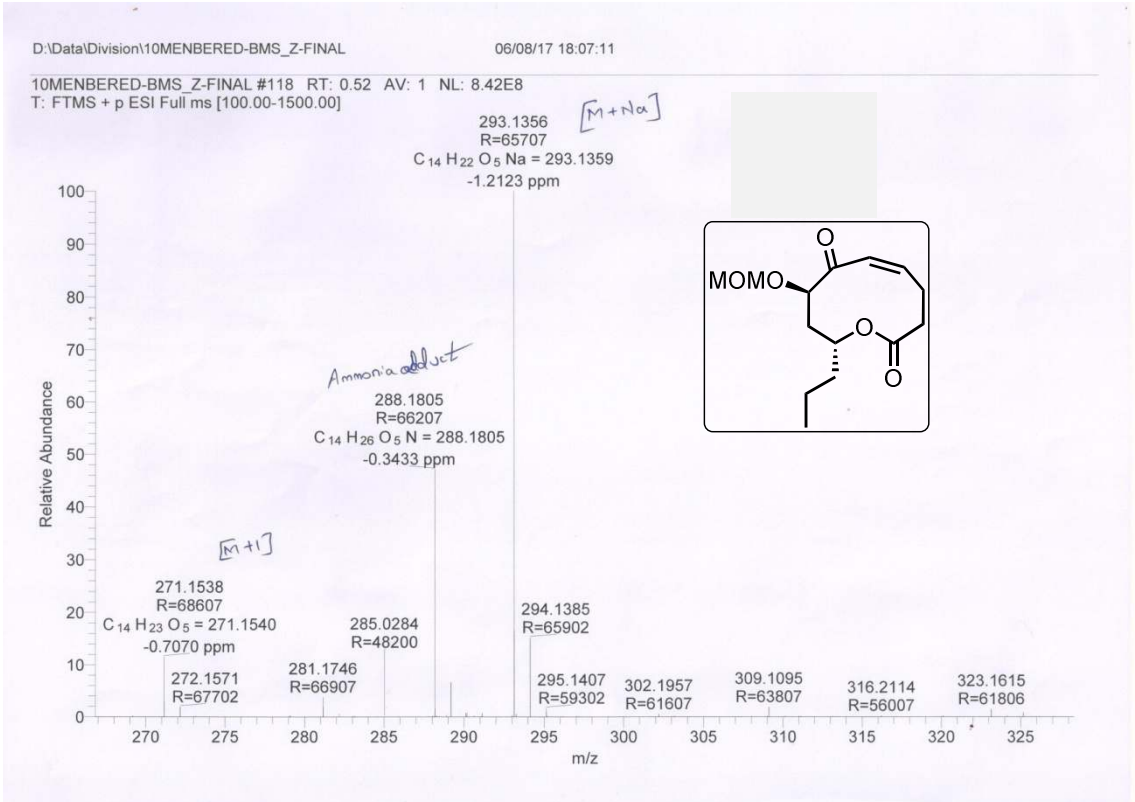


Spectra

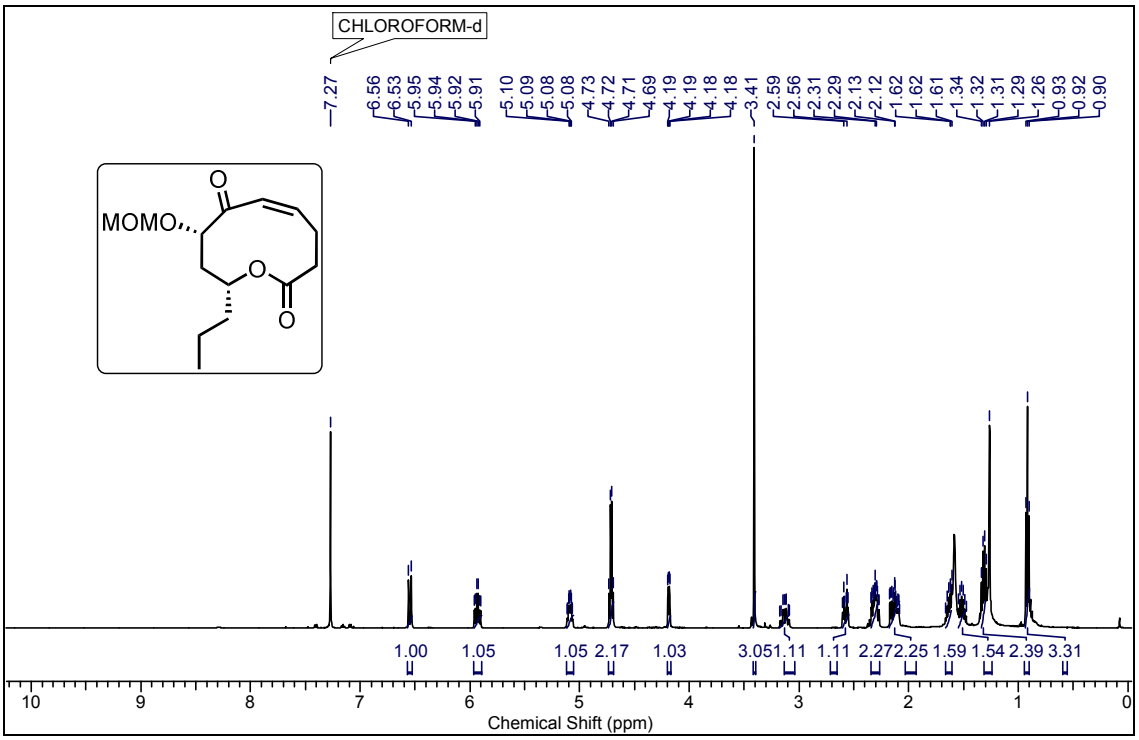
DEPT-135 NMR spectrum of compound **96** ($CDCl_3$, 100 MHz):



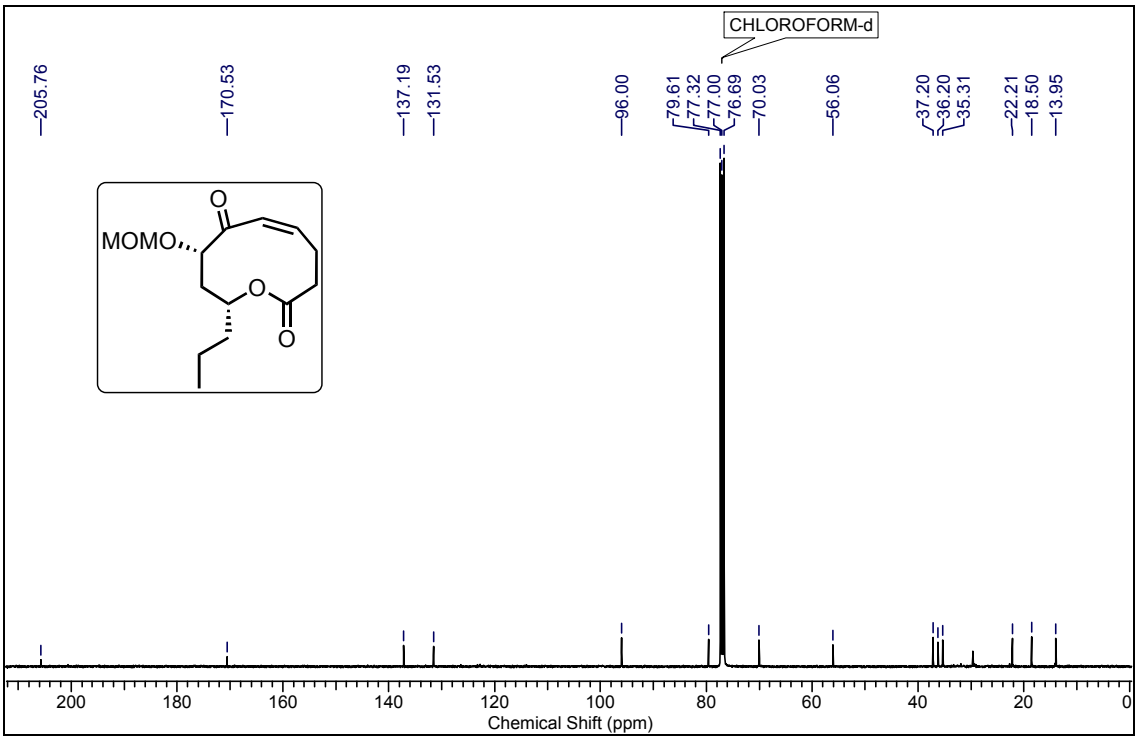
HR-ESI(+)-MS spectrum of compound **96**:



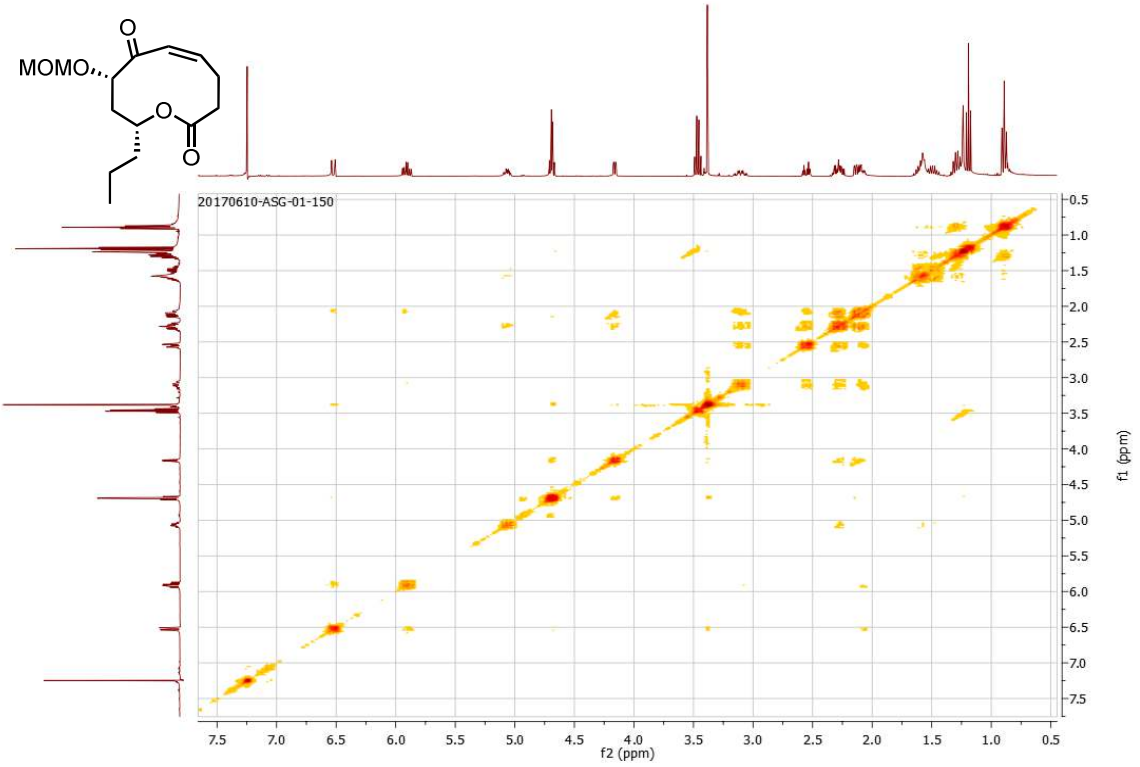
^{1}H NMR spectrum of compound **96'** ($CDCl_3$, 500 MHz):



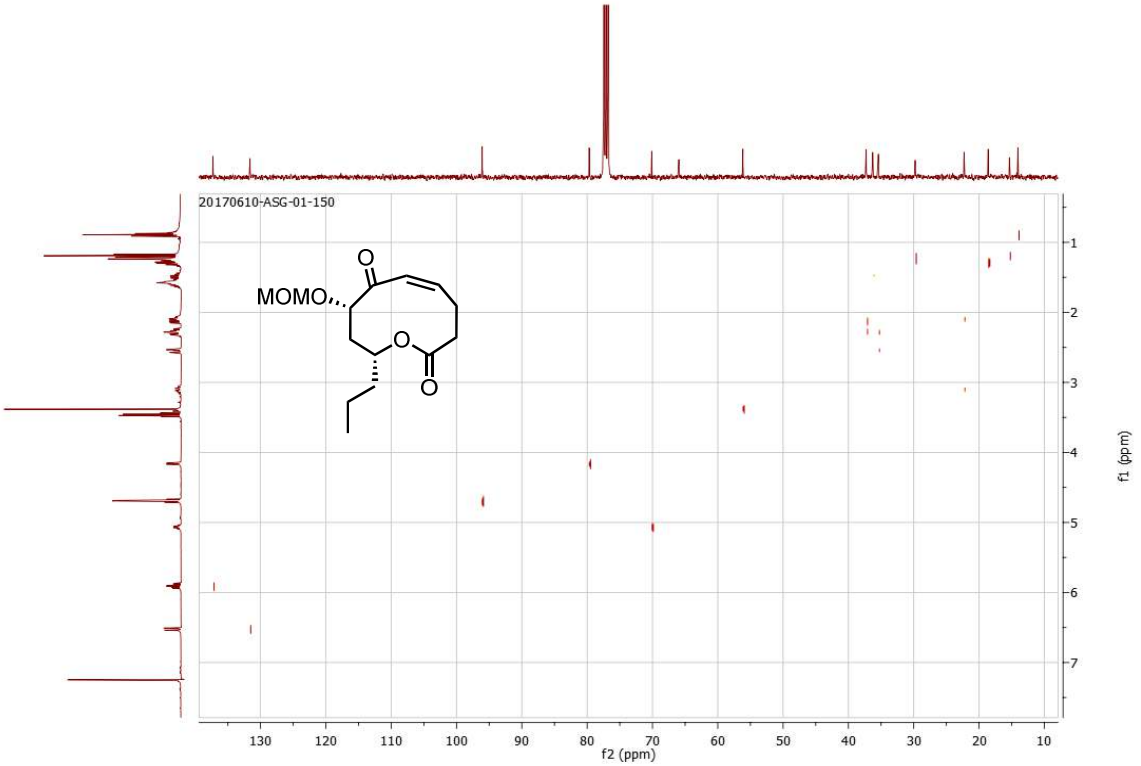
^{13}C NMR spectrum of compound **96'** ($CDCl_3$, 100 MHz):



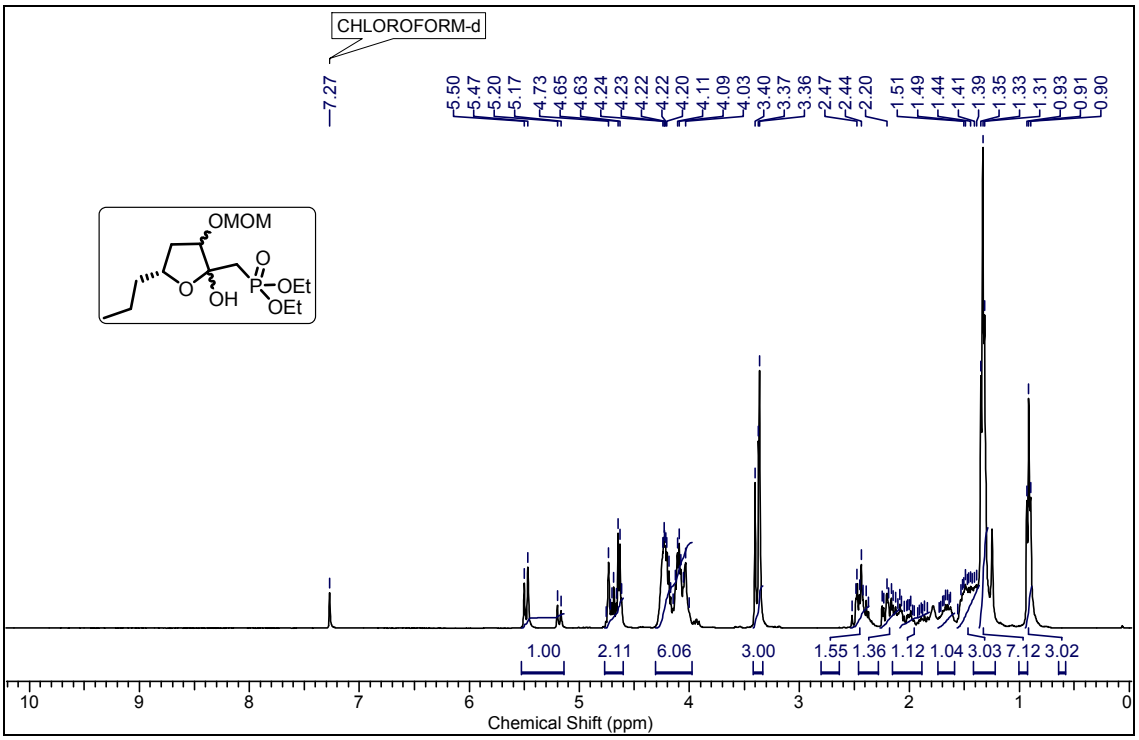
NOESY spectrum of compound **96'** ($CDCl_3$, 400 MHz):



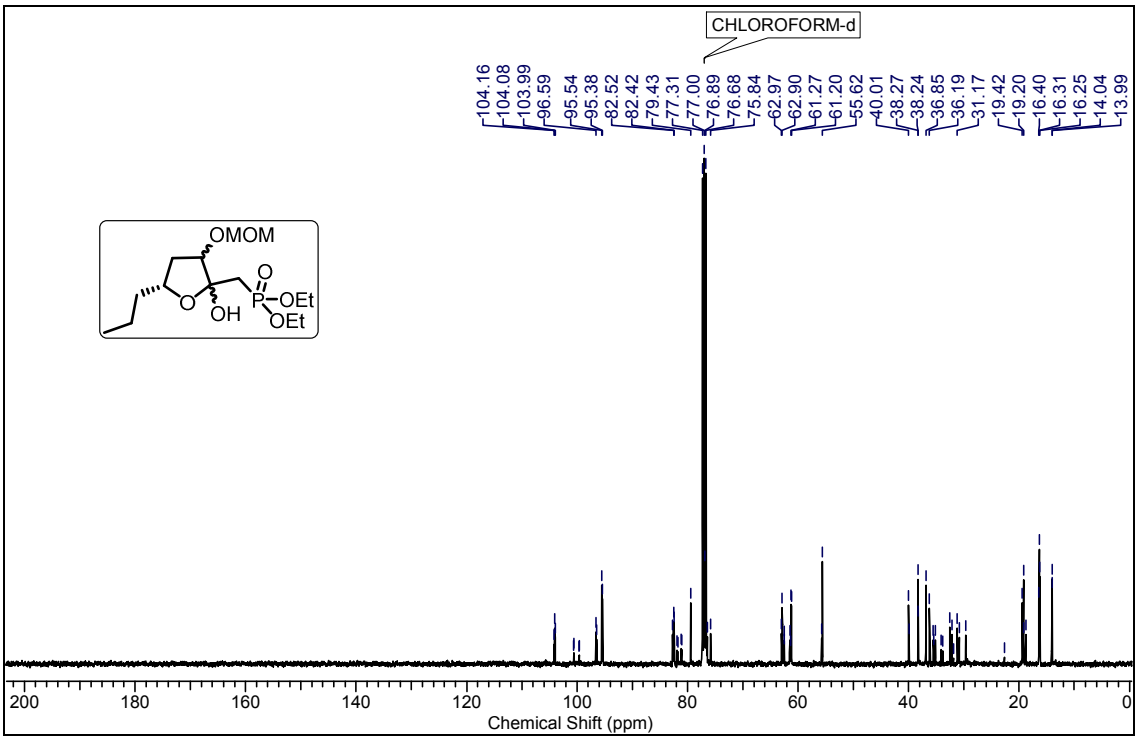
HSQC spectrum of compound **96'** ($CDCl_3$, 400 MHz):



^{1}H NMR spectrum of compound **95** ($CDCl_3$, 400 MHz):



^{13}C NMR spectrum of compound **95** ($CDCl_3$, 100 MHz):



2.3. References

(1) Sun, P.; Lu, S.; V Ree, T.; Krohn, K.; Li, L.; Zhang, W. *Curr. Med. Chem.* **2012**, *19*, 3417.

(2) Rousseau, G. *Tetrahedron* **1995**, *51*, 2777.

(3) Back, T. G. *Tetrahedron* **1977**, *33*, 3041.

(4) a) Dräger, G.; Kirschning, A.; Thiericke, R.; Zerlin, M. *Nat. Prod. Rep.* **1996**, *13*, 365; b) Ferraz, H. M.; Bombonato, F. I.; Longo Jr, L. S. *Synthesis* **2007**, *2007*, 3261; c) Riatto, V. B.; Pilli, R. A.; Victor, M. M. *Tetrahedron* **2008**, *64*, 2279.

(5) Bodo, B.; Molho, L.; Davoust, D.; Molho, D. *Phytochemistry* **1983**, *22*, 447.

(6) Barbosa, M.; Valentão, P.; Andrade, P. B. *Mar. Drugs* **2016**, *14*, 23.

(7) a) Gerwick, W. H. *Chem. Rev.* **1993**, *93*, 1807; b) Noverr, M. C.; Erb-Downward, J. R.; Huffnagle, G. B. *Clin. Microbiol. Rev.* **2003**, *16*, 517.

(8) a) Niwa, H.; Inagaki, H.; Yamada, K. *Tetrahedron Lett.* **1991**, *32*, 5127; b) Niwa, H.; Watanabe, M.; Inagaki, H.; Yamada, K. *Tetrahedron* **1994**, *50*, 7385.

(9) a) Papendorf, O.; König, G. M.; Wright, A. D.; Chorus, I.; Oberemm, A. *J. Nat. Prod.* **1997**, *60*, 1298; b) Stierle, D. B.; Stierle, A. A.; Bugni, T.; Loewen, G. *J. Nat. Prod.* **1998**, *61*, 251.

(10) Demole, E.; Willhalm, B.; Stoll, M. *Helv. Chim. Acta* **1964**, *47*, 1152.

(11) Chu, M.; Mierzwa, R.; Xu, L.; He, L.; Terracciano, J.; Patel, M.; Gullo, V.; Black, T.; Zhao, W.; Chan, T.-M.; McPhail, A. T. *J. Nat. Prod.* **2003**, *66*, 1527.

(12) Kinoshita, K.; Sasaki, T.; Awata, M.; Takada, M.; Yaginuma, S. *J. Antibiot.* **1997**, *50*, 961.

(13) Edrada, R. A.; Heubes, M.; Brauers, G.; Wray, V.; Berg, A.; Gräfe, U.; Wohlfarth, M.; Mühlbacher, J.; Schaumann, K.; Sudarsono; Bringmann, G.; Proksch, P. *J. Nat. Prod.* **2002**, *65*, 1598.

(14) Malherbe, R.; Rist, G.; Bellus, D. *J. Org. Chem.* **1983**, *48*, 860.

(15) Fouque, E.; Rousseau, G. *Synthesis* **1989**, *1989*, 661.

(16) a) Wakamatsu, T.; Akasaka, K.; Ban, Y. *Tetrahedron Lett.* **1977**, *18*, 2755; b) Wakamatsu, T.; Akasaka, K.; Ban, Y. *J. Org. Chem.* **1979**, *44*, 2008.

(17) Mahajan, J. R.; De Araújo, H. C. *Synthesis* **1981**, *1981*, 49.

(18) Posner, G. H.; Wang, Q.; Halford, B. A.; Elias, J. S.; Maxwell, J. P. *Tetrahedron Lett.* **2000**, *41*, 9655.

(19) Baldwin, J. E.; Adlington, R. M.; Singh, R. *Tetrahedron* **1992**, *48*, 3385.

(20) Ireland, R. E.; Brown Jr, F. R. *J. Org. Chem.* **1980**, *45*, 1868.

(21) Martí-Centelles, V.; Pandey, M. D.; Burguete, M. I.; Luis, S. V. *Chem. Rev* **2015**, *115*, 8736.

(22) Pilli, R. A.; Victor, M. M. *Tetrahedron Lett.* **1998**, *39*, 4421.

(23) Yamada, S.; Tanaka, A.; Oritani, T. *Biosci., Biotechnol., Biochem.* **1995**, *59*, 1657.

(24) Nookaraju, U.; Harbindu, A.; Bhise, A. D.; Sharma, B. M.; Kumar, P. *RSC Adv.* **2012**, *2*, 11231.

(25) Arai, M.; Morita, N.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **2000**, *41*, 1199.

(26) Prasad, K. R.; Revu, O. *J. Org. Chem.* **2014**, *79*, 1461.

(27) Yang, Z.; Ge, M.; Yin, Y.; Chen, Y.; Luo, M.; Chen, D. *Chem. Biodiversity* **2012**, *9*, 403.

(28) Krishna, P. R.; Prabhakar, S.; Krishna, K. V. R. *RSC Adv.* **2013**, *3*, 23343.

(29) Reddy, C. R.; Das, B. *Tetrahedron Lett.* **2014**, *55*, 67.

(30) a) Parenty, A.; Moreau, X.; Niel, G.; Campagne, J. M. *Chem. Rev.* **2013**, *113*, PR1; b) Cordes, M.; Kalesse, M. Synthesis of 12-to 16-Membered-Ring Lactones. In *Synthesis of Saturated Oxygenated Heterocycles II*, Springer, **2014**; pp 369.

(31) a) Gradillas, A.; Pérez-Castells, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6086; b) Nicolaou, K.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490; c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012.

(32) Vadhadiya, P. M.; Rout, J. K.; Ramana, C. *Tetrahedron* **2015**, *71*, 9088.

(33) Fürstner, A.; Radkowski, K.; Wirtz, C.; Goddard, R.; Lehmann, C. W.; Mynott, R. *J. Am. Chem. Soc.* **2002**, *124*, 7061.

(34) a) Kumar, P.; Naidu, S. V. *J. Org. Chem.* **2005**, *70*, 4207; b) Gupta, P.; Kumar, P. *Eur. J. Org. Chem.* **2008**, *2008*, 1195; c) Gupta, P.; Kumar, P. *Tetrahedron: Asymmetry* **2007**, *18*, 1688; d) Chowdhury, P. S.; Gupta, P.; Kumar, P. *Tetrahedron Lett.* **2009**, *50*, 7018; e) Chowdhury, P. S.; Gupta, P.; Kumar, P. *Tetrahedron Lett.* **2009**, *50*, 7188.

(35) a) Baird, L. J.; Timmer, M. S.; Teesdale-Spittle, P. H.; Harvey, J. E. *J. Org. Chem.* **2009**, *74*, 2271; b) Nicolaou, K. e. C.; Sarlah, D.; Wu, T. R.; Zhan, W.

Angew. Chem., Int. Ed. **2009**, *48*, 6870; c) MaGee, D. I.; Beck, E. J. *Can. J. Chem.* **2000**, *78*, 1060.

(36) a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483; b) Wang, L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7568.

(37) Meyers, C. Y.; Malte, A. M.; Matthews, W. S. *J. Am. Chem. Soc.* **1969**, *91*, 7510.

(38) Coster, M. J.; De Voss, J. J. *Org. Lett.* **2002**, *4*, 3047.

(39) a) Ando, K.; Narumiya, K.; Takada, H.; Teruya, T. *Org. Lett.* **2010**, *12*, 1460; b) Nicolaou, K.; Sun, Y.-P.; Guduru, R.; Banerji, B.; Chen, D. Y.-K. *J. Am. Chem. Soc.* **2008**, *130*, 3633; c) Morin-Fox, M. L.; Lipton, M. A. *Tetrahedron Lett.* **1993**, *34*, 7899.

(40) Stork, G.; Nakamura, E. *J. Org. Chem.* **1979**, *44*, 4010.

(41) Nicolaou, K.; Seitz, S.; Pavia, M.; Petasis, N. *J. Org. Chem.* **1979**, *44*, 4011

(42) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

(43) a) Ando, K. *J. Org. Chem.* **1997**, *62*, 1934; b) Ando, K. *J. Org. Chem.* **1998**, *63*, 8411; c) Ando, K. *J. Org. Chem.* **1999**, *64*, 8406; d) Ando, K.; Oishi, T.; Hirama, M.; Ohno, H.; Ibuka, T. *J. Org. Chem.* **2000**, *65*, 4745.

(44) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed.* **1978**, *17*, 522.

(45) Mattsson, S.; Dahlström, M.; Karlsson, S. *Tetrahedron Lett.* **2007**, *48*, 2497.

(46) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

(47) Aristoff, P. A. *J. Org. Chem.* **1981**, *46*, 1954.

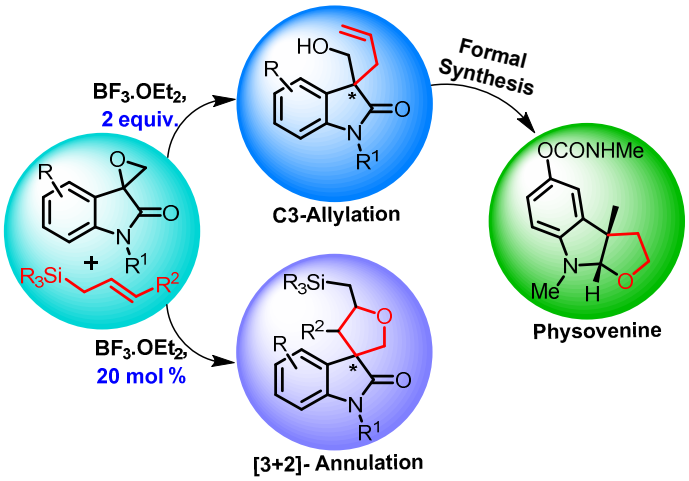
"There is no denying (nor should there be any need to deny!) that the sheer sense of challenge posed by a complex molecular target serves to stimulate the creative impulses of the synthetic chemist"

— S. J. Danishefsky

Chapter III– Lewis Acid Mediated Regioselective C–C Bond Formation

Section A

Unified Approach for Fused and Spirocyclic Oxindoles *via* Lewis Acid Promoted Opening of Spiro-epoxyoxindoles with Allylsilanes



3.1.1. Introduction

3.1.1.1. C-3 Quaternary Oxindole Motifs

Oxindoles with a C-3 quaternary framework have found a renewed synthetic interest due to their widespread presence in natural products.[1] Among such oxindole derivatives, 3-allyl-3-(hydroxymethyl)-oxindole **1** containing an all-carbon quaternary centre is at the core of several pharmaceutically and naturally important alkaloids, such as physovenine **3**, physostigmine **4** and oxaline **7** (Figure 3.1.1), with a wide range of biological activites.[2] At the same time, spirooxindole moiety **2** has been recognized as the key structural motif in a wide array of biologically active compounds, including aspergillines A and B **9** and XEN402 **10**.[3] Unnatural spirooxindoles containing silane in their structure have also been found to exhibit excellent anti-tumour activity **8** by Schreiber *et al.*[4] (Figure 3.1.1).

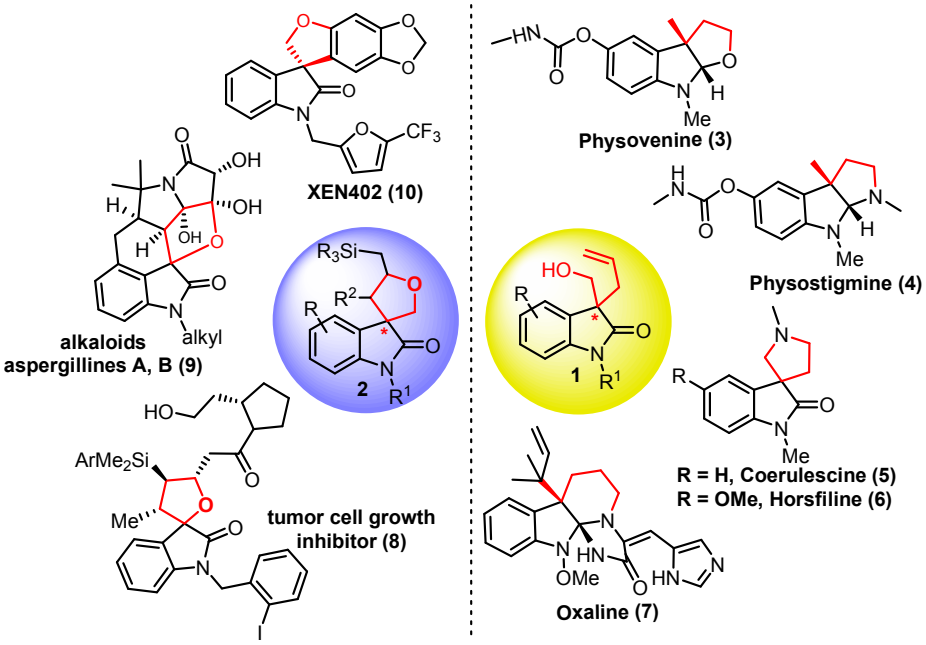


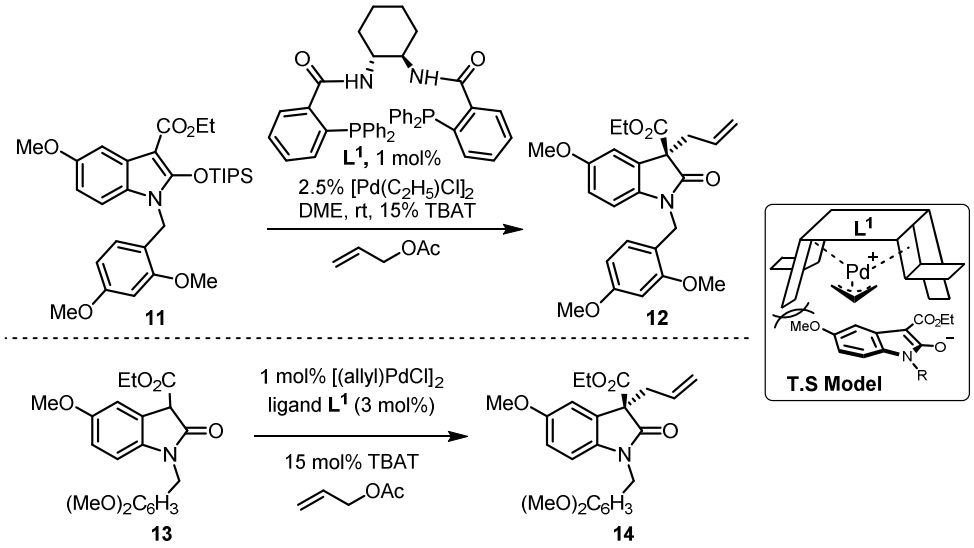
Figure 3.1.1. A schematic representation of natural and unnatural oxindole compounds.

Smith and co-workers have accomplished the synthesis of alkaloids belonging to this class e.g., (±)-coerulescine **5** and (±)-horsfiline **6** *via* **1** as a key intermediate.[5] The challenge for synthesizing 2-oxindoles containing an all-carbon quaternary at C-3 position continues to inspire ingenious solutions for bond formation.

3.1.2. Literature Review

Several synthetic approaches have been proposed in the literature for the construction of 3,3-disubstituted oxindoles over the past decade. Few notable among them are encapsulated below:

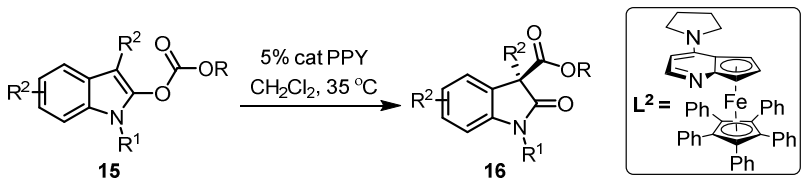
I. Pd-catalyzed Trost's Asymmetric Allylation [6]



Scheme 3.1.1. C-3 quaternary oxindole using Pd-AAA

Trost *et al*. in 2005 reported Pd-catalyzed asymmetric allylic alkylation (AAA) reaction of oxindole **11**/**13** and allyl acetate in presence of tetrabutylammonium difluorotriphenylsilicate (TBAT) as an additive to form 3-alkyl-3-aryl oxindole **12** with 84% *ee* and **14** up to 97% *ee*. The enantioselectivity of Pd-AAA reaction can be rationalized on the basis of nucleophilic attack preferring underneath the flap of chiral ligand $\mathbf{L^1}$ so as to minimize steric repulsion as shown using T.S model (Scheme 3.1.1).

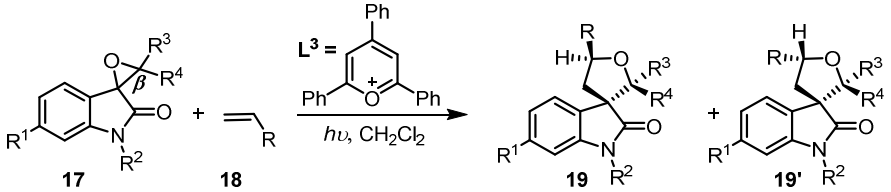
II. Fu's Enantioselective Black Rearrangement Approach [7]



Scheme 3.1.2. C-3 quaternary oxindole using Black rearrangement

Fu *et al*. in 2003 reported PPY (4-(Pyrrolidino)pyridine) **L[2]** derived catalytic enantioselective O-to-C Black rearrangement of *O*-acylated oxindoles **15** to give *C*-acylated oxindoles **16** with high enantioselectivity (up to 98% *ee*) (Scheme 3.1.2).

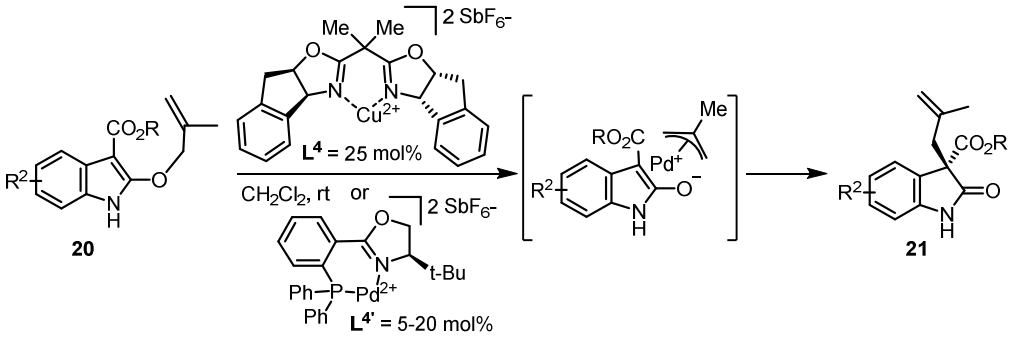
III. Photoinduced Electron Transfer (PET)-Catalyzed [3+2] Reactions [8]



Scheme 3.1.3. C-3 quaternary oxindole using photoinduced electron transfer

Zhang *et al*. in 2012 reported photoinduced electron transfer reaction *via* 2,4,6-triphenylpyrylium tetarfluoroborate (TPT, **L[3]**) sensitized C_β–O bond cleavage of substituted spiro[indoline-3,20-oxiran]-2-ones **17** and its subsequent [3+2] cycloaddition reaction with olefins **18** to give spiro[furan-2',3-indolin]-2-ones **19** and **19'** as a diastereomeric mixture (Scheme 3.1.3).

IV. Cu- and Pd-Catalyzed Claisen Rearrangement of Allyloxy- and Propargyloxy-indoles [9]

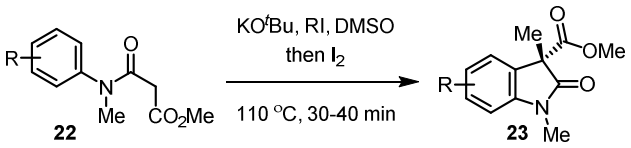


Scheme 3.1.4. C-3 quaternary oxindole using Cu- and Pd-catalyzed Claisen rearrangement

Kozlowski *et al*. in 2012 reported catalytic enantioselective Meerwein−Eschenmoser Claisen rearrangement of allyloxindole **20** using Cu–indanol bisoxazoline catalysts **L[4]** to construct a range of oxindoles bearing an allyl-substituted C3-quaternary center **21** with 81% *ee* (Scheme 3.1.4). Switching to Pd–BINAP or Pd–*t*-BuPHOX **L[4']** based catalytic system improved the selectivity (85-92% *ee*) and catalytic

turnover no. The major difference between Cu(II) and Pd(II) lies in the turnover, which is attributed to the larger size and weaker O–coordinating ability of the palladium.

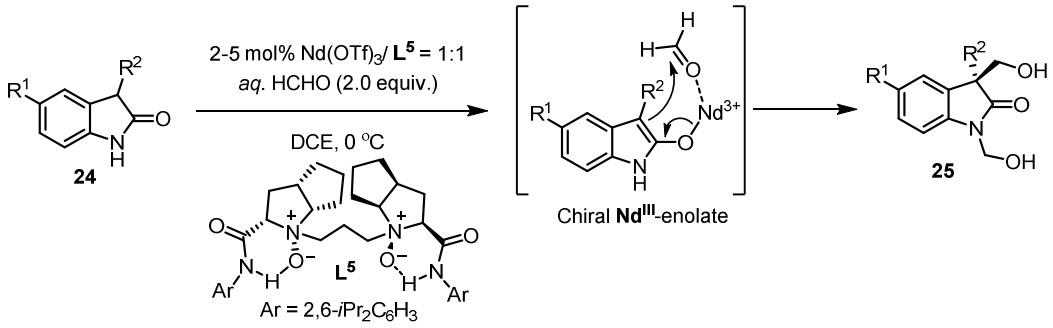
V. Intramolecular Dehydrogenative Coupling [10]



Scheme 3.1.5. C-3 quaternary oxindole using intramolecular-dehydrogenative coupling

Bisai *et al*. in 2012 reported transition metal free intramolecular-dehydrogenative coupling (IDC) strategy (Scheme 3.1.5), which involves one-pot *C*-alkylation of **22** using KO^{t}Bu followed by oxidative coupling in the presence of stoichiometric I_2 via single electron transfer (SET) process, for constructing 2-oxindoles **23** bearing an all-carbon quaternary stereocenter.

VI. Nd^{III}-N,N'-Dioxide Mediated Synthesis [11]

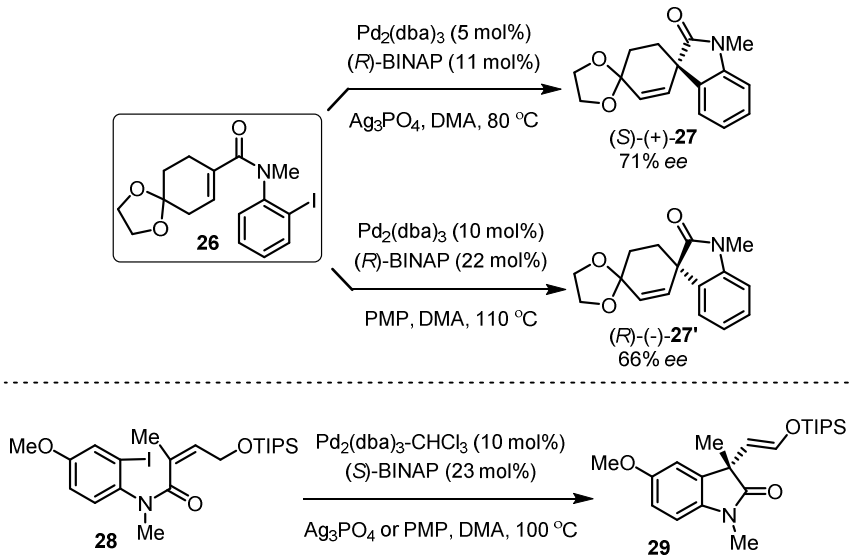


Scheme 3.1.6. C-3 quaternary oxindole using chiral neodymium complex

Feng *et al*. in 2010 reported synthesis of 1,3-bis(hydroxymethyl)-2-oxindoles **25** with formalin and oxindole **24** with >99% *ee* using chiral Nd^{III}-N,N'-dioxide catalyst through an *in situ* generated *O*-bond Nd^{III}-enolate (Scheme 3.1.6).

VII. Overman's Pd-Catalyzed Asymmetric Heck Cyclization Approach [12]

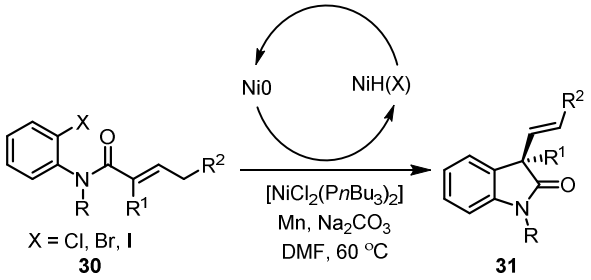
Overmann *et al*. in 1998 reported the effect of solvent and HI scavenger [Ag_3PO_4 or 1,2,2,6,6-pentamethylpiperidine (PMP)] used on Pd-BINAP-catalyzed intramolecular Heck reactions of (*Z*)-*α,β*-unsaturated 2-iodoanilides **26** to afford enantioenriched 3,3-disubstituted 2-oxindole **27** or **27'** with reversed stereoinduction (Scheme 3.1.7).



Scheme 3.1.7. C-3 quaternary oxindole using Pd- catalyzed asymmetric Heck cyclization

Whereas, methoxy-(*Z*)-2-butenanilides **28** in the presence of either Ag_3PO_4 or 1,2,2,6,6-pentamethylpiperidine (PMP) furnished (*R*)- enol ether oxindole **29**. Thus these studies unambiguously demonstrated that, with certain substrates, and also depending upon how HI is scavenged high enantioselection could be achieved.

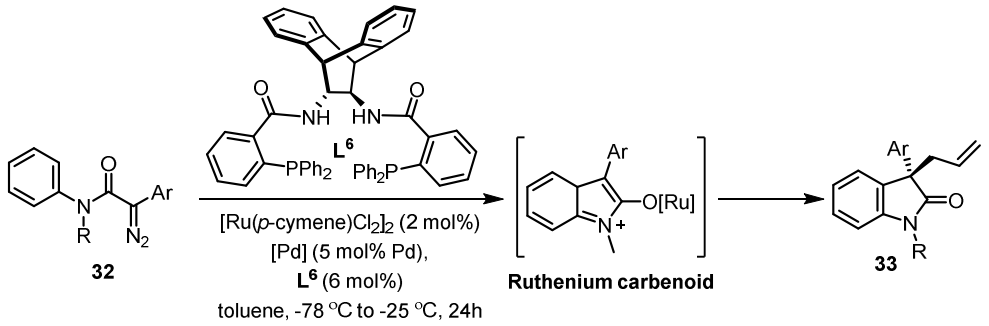
VIII. Garg's Ni-Catalyzed Heck Cyclization Approach [13]



Scheme 3.1.8. C-3 quaternary oxindole using Ni- catalyzed asymmetric Heck cyclization

Later Garg *et al*. in 2016 reported nickel-catalyzed Heck reaction of 2-halo-anilides **30** to give 3,3-disubstituted oxindole **31** (Scheme 3.1.8), by overcoming the problem of protonolysis or dimerization of organonickel intermediate using $[NiCl_2(PnBu_3)_2]$, Mn (reducing agent) and inorganic base (K_2CO_3/Na_2CO_3).

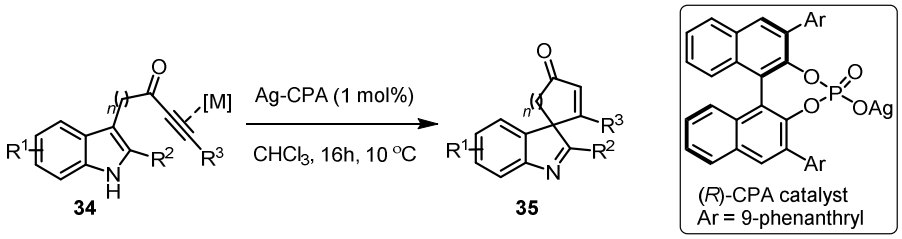
IX. Lauten's Ru-Catalyzed C-H Functionalization with Pd-Catalyzed Asymmetric Allylic Alkylation [14]



Scheme 3.1.9. C-3 quaternary oxindole using C−H Functionalization/AAA

Lauten *et al*. in 2016 reported one-pot Ru(II)metal-catalyzed C−H functionalization of phenyl-substituted *α*-diazoamide **32** followed by Pd metal-catalyzed asymmetric allylic alkylation in toluene at -78 ^{o}C to afford chiral 3-allyl-3-aryl oxindoles **33** up to 99% yield and up to 85% *ee*. The reaction proceeded *via* ruthenium carbenoid and an allylpalladium complex to form two new C−C bonds (Scheme 3.1.9).

X. Dearomatization Approach [15]



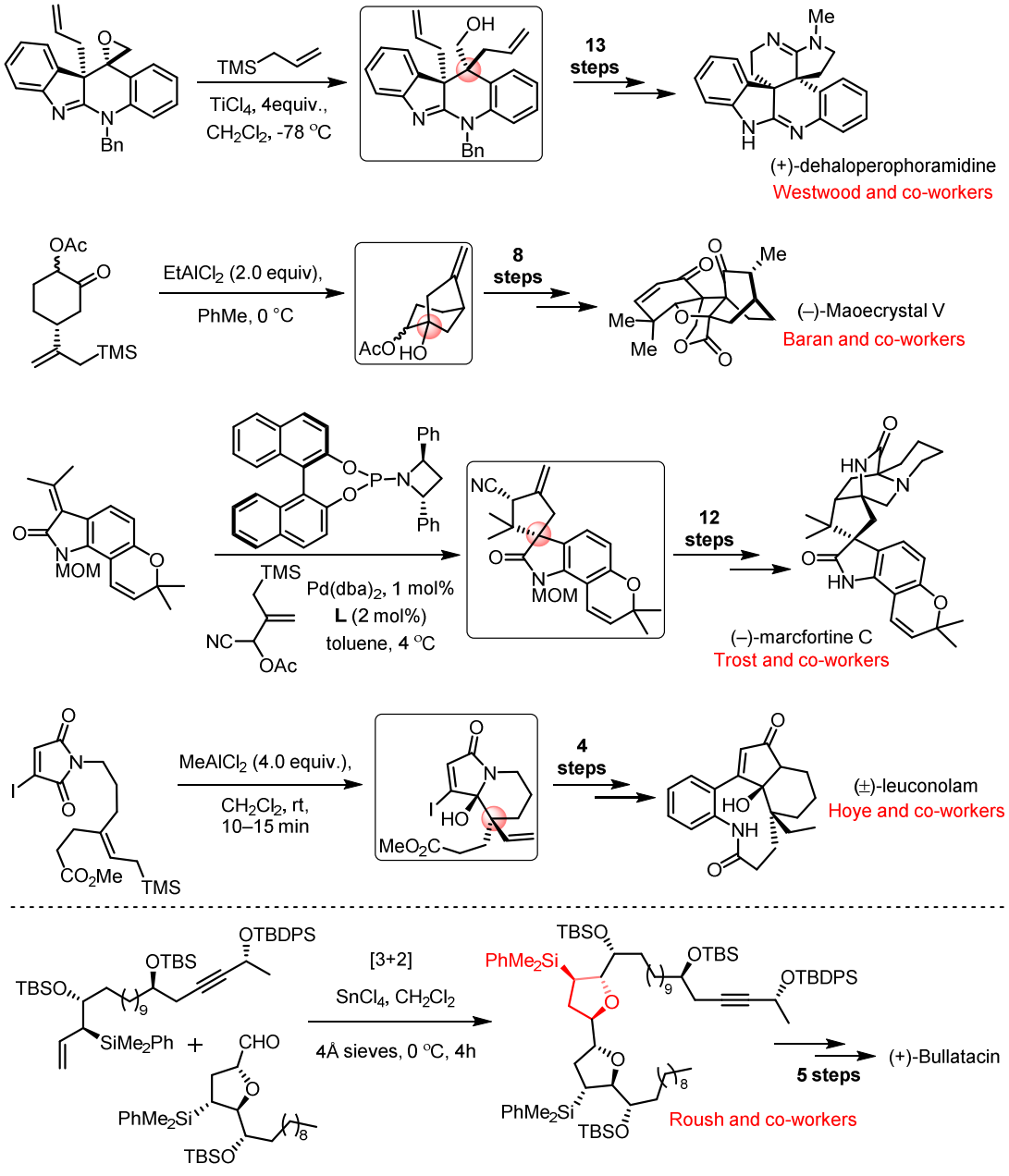
Scheme 3.1.10. C-3 quaternary oxindole using dearomative spirocyclization strategy

Taylor *et al*. in 2015 reported asymmetric dearomative spirocyclization strategy on aromatic ynones **34** using Ag(I) salts of BINOL-based chiral phosphoric acid to give spirocyclic indolenines **35** in up to 89:11 *e.r* (Scheme 3.1.10).

XI. Hosomi-Sakurai Approach

Furthermore, the generation of quaternary carbon centers using allylsilanes through the Hosomi-Sakurai reaction[16] and [3+2] annulation reactions[17] has been used by numerous synthetic groups, in the synthesis of a number of biologically active compounds in recent years.[18] Few remarkable accomplishments in these directions from

the laboratory of Westwood,[19] Baran,[20] Trost,[21] Hoye,[22] and Roush[23] have been documented in Scheme 3.1.11. Thus, Lewis acid catalyzed C-C bond formation using allylsilane reagents to access fused and spirocyclic oxindole structures containing an all-carbon quaternary centre has been demonstrated to be a new & promising approach to the synthesis of this class of alkaloids.

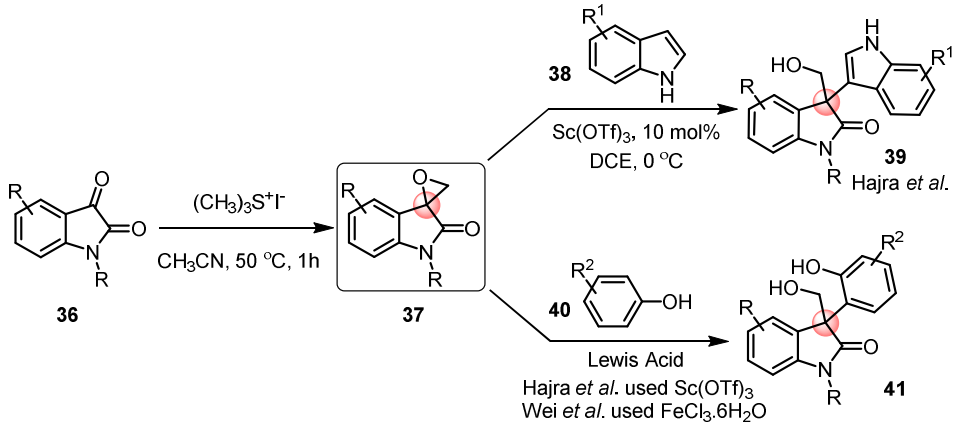


Scheme 3.1.11. Application of Hosomi-Sakurai reaction in natural product synthesis

3.1.3. Present Work

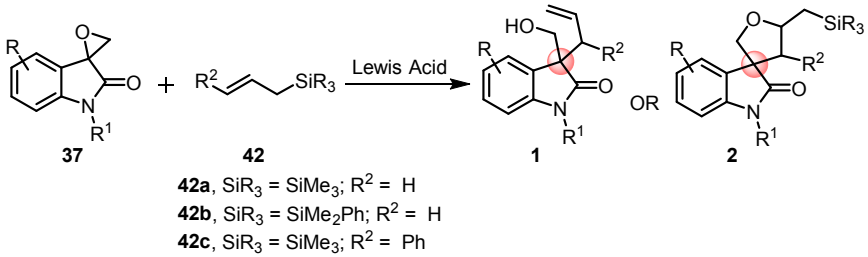
3.1.3.1. Objective

The above mentioned protocols showcase the importance of C-3-allyl oxindole or the corresponding ester as a versatile synthon. However, in all these approaches, several steps are required for the synthesis of highly functionalized starting material, especially 2-acyloxindole or phenyl-substituted α-diazoamide precursor. Recently, the pioneering work by Hajra and Wei *et al.*[24] on Lewis acid catalyzed opening of spiro-epoxyoxindoles **37** using indole **38** and phenol **40** as a nucleophile, demonstrated a straight forward method in the direction for generation of all-carbon quaternary centers at C-3 position of oxindole **39** and **41**, starting from *N*-protected isatin **36** (Scheme 3.1.12).



Scheme 3.1.12. Lewis acid catalyzed regioselective opening of spiroepoxyoxindole **37**

In the light of above literature reports, we considered examining the Lewis-acid-mediated reactions of spiroepoxyoxindoles **37** with allylsilanes as the nucleophilic source which could eventually give either allylation product **1** or [3+2] annulation product **2**, depending on the reaction conditions and the stoichiometry used (Scheme 3.1.13).

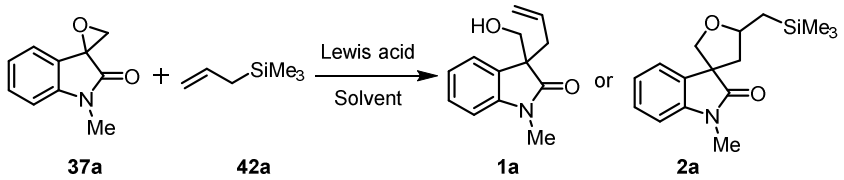


Scheme 3.1.13. Proposed concept for the generation of quaternary carbon atoms

The formation of [3+2] annulated product can be rationalized on the basis of existing literature, which suggests that Lewis-acid-mediated allylation reactions of allylsilanes often favour the competing annulation pathway, due to the stereoelectronic environment of different silyl groups.[25] The synthetic potential of this route was demonstrated through its successful application to the formal synthesis of (±)-physovenine.

3.1.3.2. Results and Discussion

Table 3.1.1. Optimization studies[a]



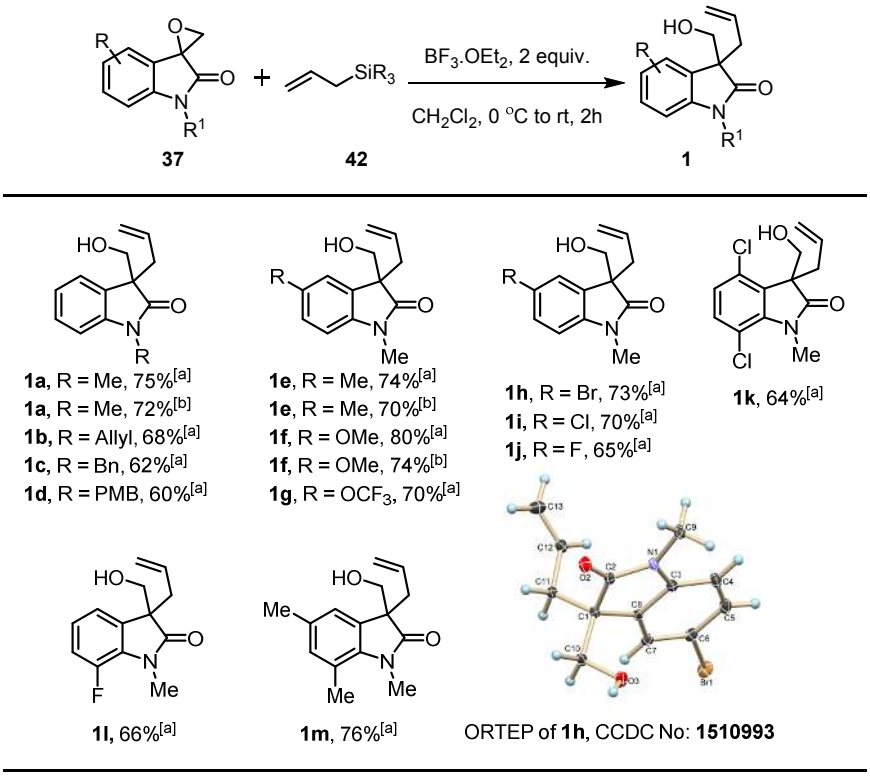
37a **42a** **1a** **2a**

Entry	Lewis acid	Solvent	*T* [°C]	*t* [h]	Yield[b] (%)	
					1a	**2a**
1	$Sc(OTf)_3$	DCE	0 °C	1	–	65
2	$Sc(OTf)_3$	CH_2Cl_2	0 °C	1	15	55
3	$Sc(OTf)_3$	CH_2Cl_2	25 °C	8	25	45
4	$Cu(OTf)_3$	CH_2Cl_2	25 °C	8	10	60
5	$Bi(OTf)_3$	CH_2Cl_2	25 °C	8	20	40
6	$FeCl_3$	CH_2Cl_2	0 °C	1	10	50
7	**$BF_3.OEt_2$**	**CH_2Cl_2**	**0 °C**	**0.5**	**–**	**72**[c]
8	$BF_3.OEt_2$	CH_2Cl_2	rt	24	10	65
9[d]	$BF_3.OEt_2$	CH_2Cl_2	0 °C	5 min	–	70
10[d]	$BF_3.OEt_2$	CH_2Cl_2	rt	25	58	20
11[e]	**$BF_3.OEt_2$**	**CH_2Cl_2**	**0 °C**	**2**	**75**	**–**
12[e, f]	$BF_3.OEt_2$	THF	rt	6	N.R	N.R
13[e]	$BF_3.OEt_2$	Toluene	0 °C	2	30	–
14[e]	$BF_3.OEt_2$	DCE	rt	8	15	52

[a] *N*-Methyl spiro-epoxyoxindole **37a** (0.28 mmol), Trimethylallylsilane **42a** (0.56 mmol), and Lewis acid (20 mol%) in solvent (1 mL) were stirred at specified temperature. [b] Isolated yield. [c] *dr* determined by ^1H NMR analysis. [d] 1 equiv. of $BF_3.OEt_2$ was used. [e] 2 equiv. of $BF_3.OEt_2$ was used. [f] 5 equiv. of $BF_3.OEt_2$, decomposition of **37a** was observed. NR: No reaction.

To validate our proposed design, we started our investigation by testing whether various Lewis acids could promote the regioselective ring-opening reaction, using *N*-methylspiroepoxyoxindole **37a** and allyltrimethylsilane (**42a**) as model substrates (Table 3.1.1). When the reaction was carried out with 20 mol% $Sc(OTf)_3$ in 1,2-dichloroethane at 0 ^oC, the spiro-annulated product **2a** was obtained in 65% yield (Table 3.1.1, Entry 1). On the other hand, when CH_2Cl_2 was used as solvent at 0 ^oC, the reaction gave **2a** in 55% yield, and allylated product **1a** in 15% yield (Table 3.1.1, Entry 2). The 3-allyl-3-(hydroxymethyl)oxindole (**1a**) was formed through a Hosomi–Sakurai-type reaction, whereas the formation of spirooxindole **2a** proceeded through trapping of a transient *β*-silyl-stabilized carbocation.[26] Even when the reaction time was increased to 8 h at room temperature, no improvement to the yield or selectivity of **1a** and **2a** was observed (Table 3.1.1, Entry 3). Next, we attempted to optimize the formation of allylation product **1a** and spiro-annulation product **2a** in a stepwise manner. A screening of different Lewis acids, including $Cu(OTf)_2$, $Bi(OTf)_3$, and $FeCl_3$, was ineffective in terms of product selectivity (Table 3.1.1, Entries 4–6). We found that the use of $BF_3{\cdot}OEt_2$ resulted in the exclusive formation of spirooxindole **2a** in 72% yield when the reaction was run at 0 ^oC for about 30 min (Table 3.1.1, Entry 7). These results prompted us to monitor the reaction for longer time under similar reaction conditions, but spirooxindole **2a** was still observed as one of the major products (Table 3.1.1, Entry 8). Gratifyingly, when the reaction was carried out using 1 equiv. of $BF_3{\cdot}OEt_2$, a switch in the selectivity was observed (Table 3.1.1, Entry 10), and allyloxindole product **1a** was formed in 58% yield. Interestingly, when 2 equiv. of $BF_3{\cdot}OEt_2$ was used at 0 ^oC, 3-allyl-3-(hydroxymethyl)oxindole was obtained exclusively in 75% yield (Table 3.1.1, Entry 11). Thus, a slight modification in the stoichiometry of $BF_3{\cdot}OEt_2$ resulted in tuning of the product selectivity. A screening of solvents indicated that CH_2Cl_2 gave better results than toluene and DCE (Table 3.3.1, Entries 13 and 14); no reaction was observed in THF (Entry 12).

The generality and scope of this method for allylation and spiro-annulation reactions was explored using an array of spiroepoxyoxindoles **37** and allylsilanes **42** under the optimized reaction conditions. First, we evaluated the scope of the allylation reaction (Scheme 3.1.14) with a series of spiroepoxyoxindoles bearing *N*-methyl, *N*-(*para*-methoxybenzyl), *N*-benzyl, and *N*-allyl substituents.

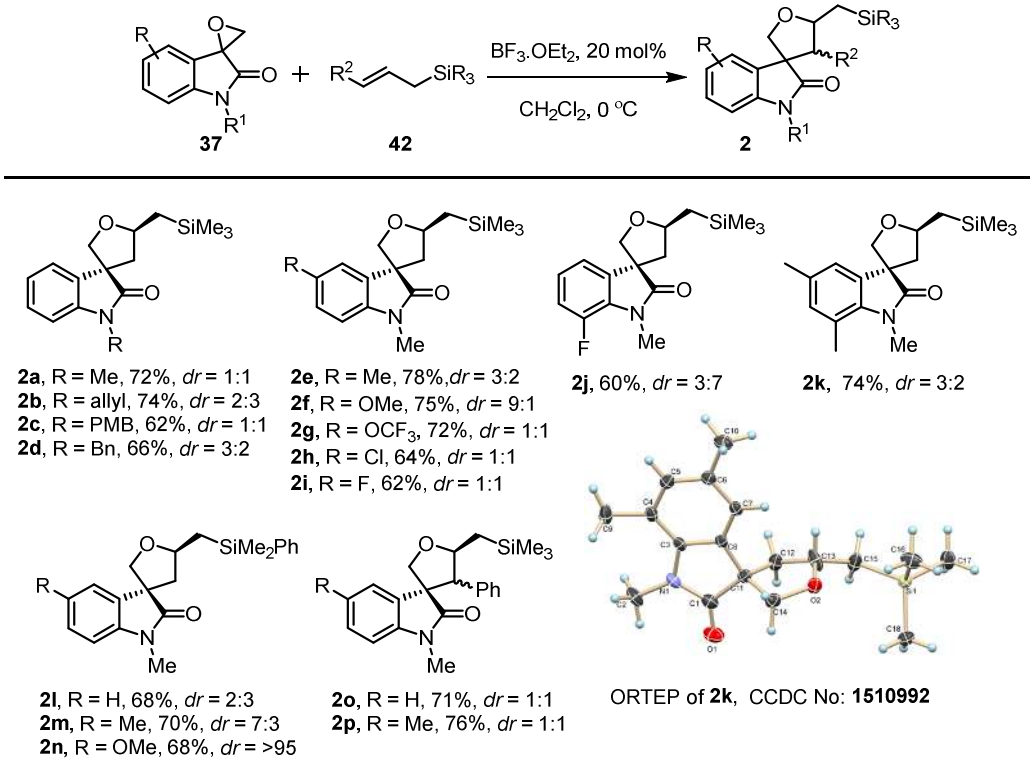


[a] Yields using (-$SiMe_3$) allylsilane and [b] Yields using (-$SiMe_2Ph$) allylsilane.

Scheme 3.1.14. Allylation reaction: Scope of spiro-epoxyoxindoles and allylsilanes

These substrates were found to be compatible with the reaction conditions, and they reacted smoothly with allyltrimethylsilane (**42a**) to give the desired Hosomi–Sakurai type products **1a**–**1m** in good to excellent yields (60–80%). The electronic properties of the substituents at C-5 and C-7 of the spiroepoxyoxindoles have little or no impact on the yields, for both electron-donating and electron-withdrawing substituents. The structure of product **1h** was confirmed by single-crystal X-ray analysis. We went on to study the scope of the reaction with allyldimethyl(phenyl)silane (–$SiMe_2Ph$, **42b**). This worked equally well and underwent the Hosomi–Sakurai-type reaction to give the expected product in good yield. The IR spectrum of compound **1a** showed hydroxyl absorption at 3444 cm^{-1}. The ^1H NMR signals at δ 5.46 (dddd, J = 7.8, 7.8, 10.1, 17.2 Hz, 1 H), 5.08 - 5.01 (m, 1 H), 4.98 - 4.92 (m, 1 H) correspond to the double bond protons. The ^{13}C NMR signal at δ 54.0 corresponds to the C-3 quaternary carbon, as also confirmed by DEPT-135 spectrum which showed no signal at δ 54.0. The HRMS (ESI^+) peak at 218.1176 corresponding to formula $C_{13}H_{15}NO_2$ $[M + H]^+$ (calculated value 218.1172) showed the

incorporation of allyl moiey. Similarly 3-allyl-3-(hydroxymethyl)oxindoles (**1b-1m**) were characterized by ^{1}H NMR, ^{13}C NMR, HRMS and IR spectral analysis.

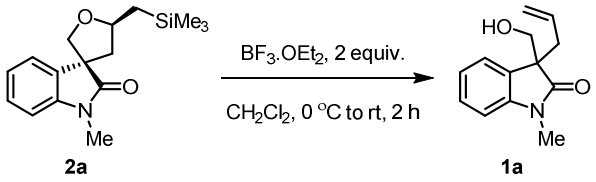


Scheme 3.1.15. Spirocyclization reaction: Scope of spiro-epoxyoxindoles and allylsilanes

The scope of the spiro-annulation reaction using substituted and unsubstituted allylsilanes **42** with spiroepoxyoxindoles **37** was then examined (Scheme 3.1.15) in order to determine the influence of the silyl group on the yield of the products and the diastereoselectivity of the reaction. Thus, we screened different allylsilanes that favour the annulation pathway and also contain an oxidizable silane group with different steric and electronic properties. Under $BF_3{\cdot}OEt_2$ catalysed conditions, electronically dissimilar allylsilanes with different substitution patterns at the silane motif [–$SiMe_3$ (**42a**), –$SiMe_2Ph$ (**42b**)], added smoothly to spiroepoxyoxindoles to give the new silicon-containing spirocyclic oxindoles as diastereomeric mixtures in good yields (60–78%). With substituted allylsilanes **42c**, three contiguous stereocentres (as in **2o** and **2p**) were generated with a diastereomeric ratio of 1:1. The structure of spirocyclic oxindole **2k** was further confirmed by single-crystal X-ray analysis. The IR spectrum of compound

2a showed the absence of free hydroxyl group. The ^{1}H NMR spectrum showed signals at 4.48 (ddt, *J* = 6.1, 8.5, 14.7 Hz, 0.5 H), 4.36 (ddt, *J* = 6.1, 9.8, 14.7 Hz, 0.5 H), 4.21 (d, *J* = 8.5 Hz, 0.5 H), 4.00 - 3.93 (m, 1 H), 3.82 (d, *J* = 8.5 Hz, 0.5 H) corresponding to the protons attached to the hydroxyl group and the incorporation of (–$SiMe_3$) group was confirmed by the signal at δ 0.07 (s, 9 H), with (*dr* ~ 1:1). The HRMS (ESI$^+$) peak of **2a** at 290.1571 corresponding to formula $C_{16}H_{23}NO_2Si$ $[M + H]^+$ (calculated value 290.1565) validated the presence of "Si" group. Similarly all the spirocyclic oxindoles (**2b**-**2p**) were characterized by ^{1}H NMR, ^{13}C NMR, HRMS and IR spectral analysis.

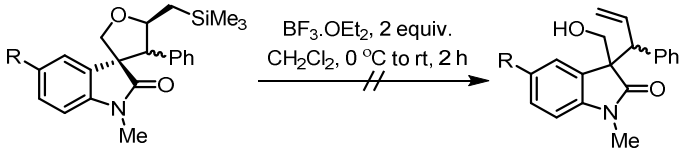
To gain mechanistic insight into this transformation, we carried out control experiments on a few spirocyclic oxindoles **2a**, **2o**, and **2p**. When spirooxindole **2a** was treated with $BF_3{\cdot}OEt_2$ (2 equiv.), it gave the desired allylated product **1a** (Scheme 3.1.16a).



2a **1a**

Scheme 3.1.16a. Control experiment using unsubstituted spirocyclic oxindole

On the other hand, when spirooxindole **2o** was treated with $BF_3{\cdot}OEt_2$ (2–5 equiv.), it did not give the allyl product **1o**, and the starting material was either recovered or decomposed. Even desilylation failed to occur in the presence of 4 equiv. of TBAF. A similar set of results was obtained when the 5-methyl analogue, spirooxindole **2p**, was used (Scheme 3.1.16b).



2o, R = H
2p, R = Me

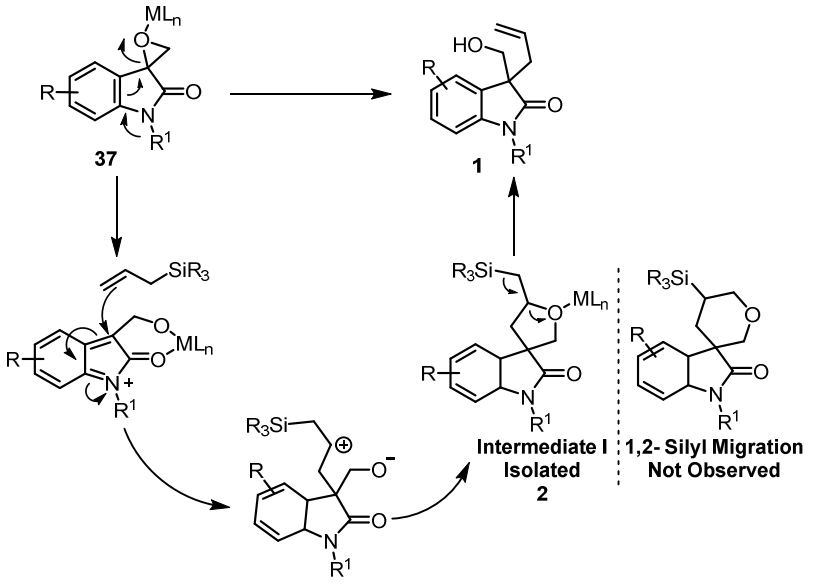
1o and **1p**
Not Observed

Scheme 3.1.16b. Control experiment using C-3 substituted spirocyclic oxindoles

Thus, spiro-annulated compound **2a**, without any substituent at the C-3 position of the THF ring, easily underwent the ring-opening reaction, as shown in Scheme 3.1.16a. But when there was a substituent at the C-3 position, as in **2o** and **2p**, it was difficult to eliminate the silyl group, even in the presence of an excess of the Lewis acid and a fluoride source (Scheme 3.1.16b). This suggests that the phenyl substituent plays a role

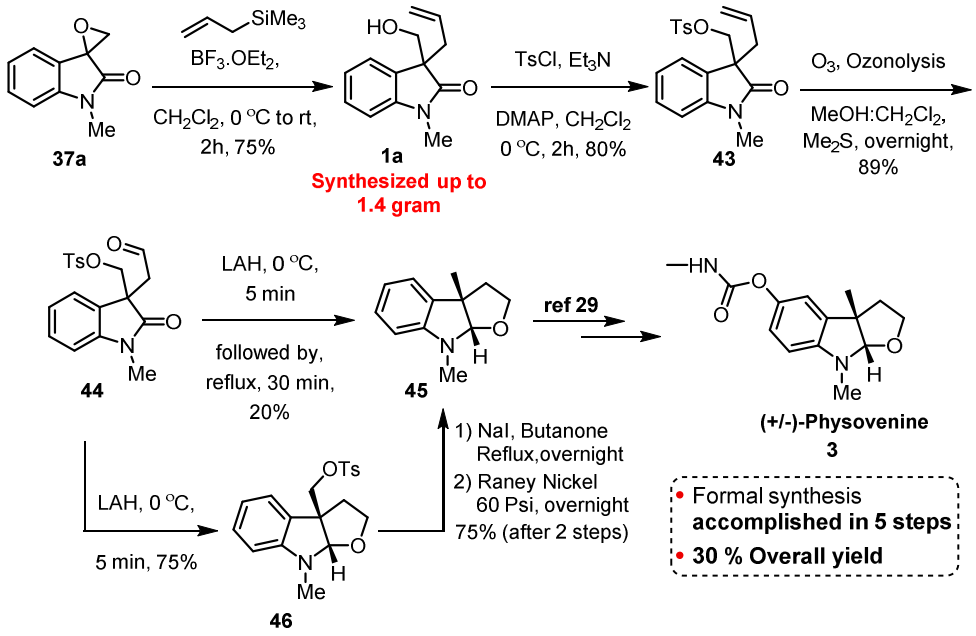
in stabilizing the *β*-carbocation. However, the exact role of the C-3 substituent is not clear at this stage, and further investigations are in progress.

Based on the above results, a plausible mechanism for the Lewis-acid-mediated opening of spiroepoxyoxindoles is given in Scheme 3.1.17. Hosomi–Sakurai-type reaction of spiroepoxide **37** with allylsilane **42** could be triggered by chelation with Lewis acid $BF_3{\cdot}OEt_2$. This would increase the electrophilicity of the spiroepoxyoxindole, making it more susceptible to attack by the allylsilane. The addition may lead to the formation of a *β*-silyl-stabilized carbocation, as perceived through classical silicon chemistry. Although elimination of the silyl group from the carbocation would give allylation product **1** in the classical cascade, it was observed that the cation was intercepted by the nucleophilic oxygen atom[27] to give spirocyclic oxindole intermediate **I**. This intermediate was isolated, and the structure of its 5,7-dimethyl analogue **2k** was conclusively established by single-crystal X-ray analysis. The annulation reaction, according to literature precedence, should proceed by a 1,2-silyl migration[28] in the presence of bulky silyl groups. We observed no 1,2-silyl migration, even with a bulky (–$SiMe_2Ph$) silyl group.



Scheme 3.1.17. Plausible mechanism of Lewis acid-catalyzed spiro-epoxyoxindoles ring opening

The synthetic potential and utility of this method was further demonstrated through the formal synthesis of (±)-physovenine **3** (Scheme 3.1.18).

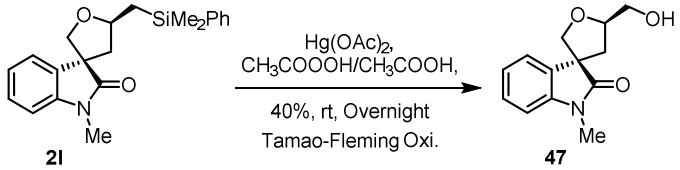


Scheme 3.1.18. Formal synthesis of (±)-physovenine **3**

Our synthetic journey began with the gram-scale ring-opening reaction of racemic spiroepoxyoxindole **37a** with allyltrimethylsilane **42a** in the presence of $BF_3 \cdot OEt_2$ to give Hosomi–Sakurai-type product **1a** in 75% yield with high regioselectivity. Tosylation of the primary hydroxy group gave compound **43** in 80% yield. The IR spectrum showed the disappearance of absorption band of hydroxyl group. The compound **43** was then subjected to ozonolysis conditions to give the key precursor spirooxindole aldehyde **44** in 89% yield. The ^{1}H NMR spectrum showed the signal at δ 9.40 (s, 1 H) corresponding to aldehyde proton. ^{13}C NMR spectrum gave signal at δ 196.9 indicating the (–CHO) aldehyde functionality. Finally, cyclization followed by displacement of the tosyl group in one pot using $LiAlH_4$ under reflux gave intermediate **45** in 20% yield. In order to improve the yield of **45**, we conceptualized a stepwise transformation. Thus, compound **44** was treated with $LiAlH_4$ (4 equiv.) at 0 °C to give fused compound **46** in 75% yield. The ^{1}H NMR signal at δ 5.15 confirmed the formation of the tetrahydrofuro[2,3-b]indole ring system. The ^{13}C NMR signal at δ 100.4 corresponds to carbon of *N*,*O*-acetal (–N–C–O–). Displacement of the tosylate using NaI, under reflux in butanone, gave the iodo compound, which was then subjected to

hydrogenation without any purification to give final intermediate **45** in 75% yield over two steps. The ^{1}H NMR signal at δ 1.5 corresponds to the formation of $–CH_3$ group at C-3 quaternary carbon as also confirmed by signal at δ 24.7 in ^{13}C NMR. The HRMS (ESI^+) peak of **45** at 190.1226 corresponds to formula $C_{12}H_{15}NO$ $[M + H]^+$ (calculated value 190.1225). In two more steps, intermediate **45** could be transformed into (±)-physovenine,[29] thus completing the formal synthesis of target molecule **3** in five steps with an overall yield of 30%, starting from spiroepoxyoxindole **37a**.

Silicon-containing spirocyclic oxindoles serve as potential building blocks for the synthesis of various biologically active compounds. To demonstrate the synthetic utility that may be derived from oxidation of the C–Si bond,[30] an interesting organic transformation using the Tamao–Fleming oxidation was carried out to functionalize the silyl group (i.e., to access the corresponding alcohol **47**) using compound **2l**, as shown in Scheme 3.1.19. This product can serve as important building block.[31]



Scheme 3.1.19. Synthetic utility of spiro-annulated silyl product

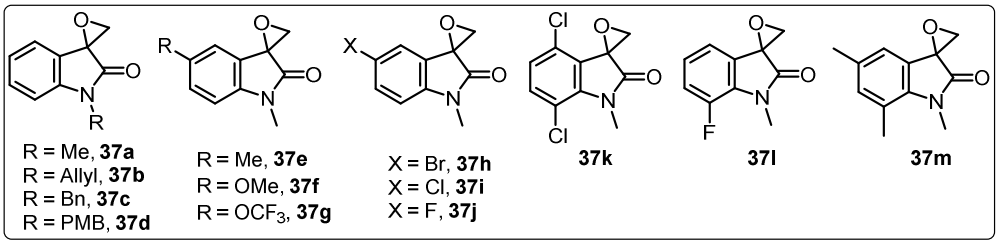
3.1.4. Conclusions and Prospect

We have developed a versatile and highly regioselective strategy for the synthesis of 3-allyl-3-(hydroxymethyl)oxindoles, as well as new silicon-containing spirocyclic oxindoles through the Lewis-acid-mediated ring opening of spiroepoxyoxindoles with allylsilanes. Whether the allylated or the annulated product is formed depends solely on the stoichiometry of the Lewis acid used. Substituted allylsilanes give access to spirocyclic oxindoles having three contiguous stereocentres. These products show an unusual stability towards Lewis acids, which is one of the important key findings of our work. A formal synthesis of (±)-physovenine was achieved in five steps starting from cheap and easily accessible spiroepoxyoxindole **37a**. Further studies on asymmetric ring-opening of spiro-epoxyoxindoles and its applications are currently being investigated in our laboratory.

3.1.5. Experimental Section

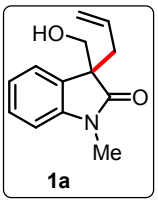
I. General Procedure for Synthesis of Spiro-epoxyoxindole 37a-37m:

All the substrates **37a-37m** were prepared according to literature reported procedure.[32] In a flame dried round bottomed flask trimethylsulphonium iodide (2.53 g, 12.41 mmol) and cesium carbonate (8.086 g, 12.41 mmol) were taken in dry acetonitrile (10 mL). The resulting mixture was stirred at 50 ^{o}C for 1h under argon atmosphere. To this, a solution of *N*-Methylisatin **36a** (1.0 g, 6.205mmol) in dry acetonitrile(10 mL) was added slowly over 15min. After completion of reaction (monitored by TLC), the mixture was filtered through a celite bed. The filtrate was evaporated to dryness. The crude product was purified by column chromatography (basic alumina) using petroleum ether/ethyl acetate, (4:1) mixture as an eluent to afford the pure product **37a** (0.934 g, 86%).



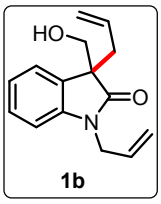
II. General Procedure for the Allylation Reaction of Spiroepoxyoxindoles with Allylsilanes. General Procedure A:

$BF_3{\cdot}OEt_2$ (0.56 mmol, 2 equiv.) was added dropwise to a stirred solution of spiroepoxyoxindoles **37** (0.28 mmol, 1.0 equiv.) and allyllsilane **42** (0.56 mmol, 2.0 equiv.) in CH_2Cl_2 (1.0 mL) at 0 ^{o}C, and the reaction mixture was stirred at room temperature for 2 h. When TLC showed that the reaction was complete, the reaction was quenched with water, and the mixture was sequentially washed with brine (2 mL), and saturated. aq. $NaHCO_3$ (2 x 2 ml). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated in *vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate) gave product **1a**–**1m**.



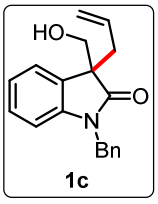
1a

Compound **1a** was obtained as pale yellow solid in 75% and 72% yields using allylsilane reagent **42a** and **42b** respectively. **mp** = 74 ºC; R_f = 0.25 (pet. ether/ethyl acetate = 1:1); **IR** ($CHCl_3$): ν_{max} = 3444, 3018, 2934, 1698, 1612, 1470, 1378, 1216, 926, 768 cm^{-1}; **^{1}H NMR** (400 MHz , $CDCl_3$) δ = 7.32 (t, *J* = 7.8 Hz, 1 H), 7.24 (d, *J* = 6.9 Hz, 1 H), 7.10 (t, *J* = 7.8 Hz, 1 H), 6.88 (d, *J* = 7.8 Hz, 1 H), 5.46 (dddd, *J* = 7.8, 7.8, 10.1, 17.2 Hz, 1 H), 5.08 - 5.01 (m, 1 H), 4.98 - 4.92 (m, 1 H), 3.92 (t, *J* = 10.1 Hz, 1 H), 3.77 (dd, *J* = 2.8, 11.0 Hz, 1 H), 3.23 (s, 3 H), 2.73 - 2.60 (dddd, *J* = 8.2, 14.7, 14.7 Hz, 2 H), 2.40 (dd, *J* = 3.7, 9.6 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 178.9, 144.0, 131.8, 129.4, 128.5, 123.3, 122.6, 119.1, 108.2, 66.4, 54.0, 37.3, 26.1; **HRMS** (ESI^+) *m/z* = calcd for $C_{13}H_{15}NO_2$ $[M + H]^+$ 218.1172, found 218.1176.



1b

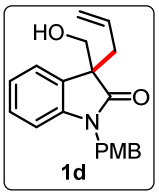
Compound **1b** was obtained as colourless liquid in 68% yield. R_f = 0.5 (pet. ether/ethyl acetate = 1:1); **IR** ($CHCl_3$): ν_{max} = 3419, 32923, 1698, 1643, 1489, 1364, 1182, 1071, 990, 922, 755 cm^{-1}; **^{1}H NMR** (400 MHz , $CDCl_3$) δ = 7.29 - 7.24 (m, 2 H), 7.11 - 7.06 (m, 1 H), 6.84 (d, *J* = 7.8 Hz, 1 H), 5.85 - 5.76 (m, 1 H), 5.49 - 5.39 (m, 1 H), 5.22 - 5.20 (m, 1 H), 5.19 - 5.17 (m, 1 H), 5.05 - 5.01 (m, 1 H), 4.95 - 4.92 (m, 1 H), 4.43 - 4.24 (m, 2 H), 3.92 (d, *J* = 11.0 Hz, 1 H), 3.79 (d, *J* = 11.0 Hz, 1 H), 2.70 (dd, *J* = 7.8, 13.7 Hz, 1 H), 2.61 (dd, *J* = 6.9, 13.7 Hz, 1 H), 2.46 (br. s., 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 178.6, 143.2, 131.7, 131.1, 129.4, 128.3, 123.3, 122.6, 119.1, 117.3, 109.1, 66.5, 54.2, 42.1, 37.3; **HRMS** (ESI^+) *m/z* = calcd for $C_{15}H_{17}NO_2$ $[M + H]^+$ 244.1326, found 244.1332.



1c

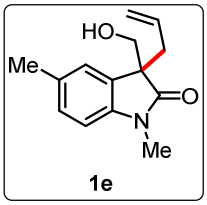
Compound **1c** was obtained as colourless solid in 62% yield. **mp** = 148 ºC; R_f = 0.50 (pet. ether/ethyl acetate = 1:1); **IR** ($CHCl_3$): ν_{max} = 3430, 3019, 2923, 1689, 1611, 1490, 1463, 1377, 1217, 927, 760 cm^{-1}; **^{1}H NMR** (400 MHz , $CDCl_3$) δ = 7.31 - 7.21 (m, 6 H), 7.16 (ddd, *J* = 1.1, 7.8, 7.8 Hz, 1 H), 7.04 (ddd, *J* = 1.0, 7.8, 7.8 Hz, 1 H), 6.70 (d, *J* = 7.8 Hz, 1 H), 5.45 (dddd, *J* = 6.9, 8.2, 10.1, 16.9 Hz, 1 H), 5.09 - 5.03 (m, 1 H), 5.00 - 4.92 (m, 2 H), 4.85 (d, *J* = 16.0 Hz, 1 H), 4.00 - 3.91 (m, 1 H), 3.82 (d, *J* = 11.0 Hz, 1 H), 2.74 (dd, *J* = 8.2, 13.3 Hz, 1 H), 2.65 (dd, *J* = 6.9, 13.3 Hz, 1 H), 2.46 (br. s., 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 178.9, 143.2, 135.6, 131.8, 129.4, 128.7, 128.3, 127.5, 127.2, 123.3, 122.6, 119.2, 109.3,

66.7, 54.3, 43.6, 37.4; **HRMS** (ESI^+) *m/z* = calcd for $C_{19}H_{19}NO_2$ $[M + H]^+$ 294.1484, found 294.1489.



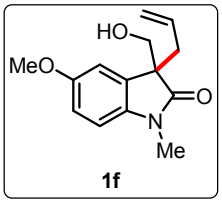
1d

Compound **1d** was obtained as yellow solid in 60% yield. **mp** = 110 ºC; $\boldsymbol{R_f}$ = 0.40 (pet. ether/ethyl acetate = 1:1); **IR** ($CHCl_3$): ν_{max} = 3433, 3012, 2930, 1697, 1612, 1513, 1465, 1360, 1247, 1217, 1035, 924, 754 cm^{-1}; **^{1}H NMR** (400 MHz , $CDCl_3$) δ = 7.25 - 7.17 (m, 4 H), 7.06 (ddd, *J* = 0.9, 7.8, 7.8 Hz, 1 H), 6.83 (d, *J* = 8.7 Hz, 2 H), 6.75 (d, *J* = 7.8 Hz, 1 H), 5.46 (dddd, *J* = 6.9, 8.2, 10.1, 16.9 Hz, 1 H), 5.10 - 5.05 (m, 1 H), 4.98 - 4.90 (m, 2 H), 4.80 (d, *J* = 15.6 Hz, 1 H), 3.97 (br. d., *J* = 11.0 Hz, 1 H), 3.82 (d, *J* = 11.0 Hz, 1 H), 3.77 (s, 3 H), 2.76 (dd, *J* = 7.8, 13.7 Hz, 1 H), 2.66 (dd, *J* = 6.9, 13.7 Hz, 1 H), 2.39 (br. s., 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 178.9, 159.0, 143.2, 131.8, 129.4, 128.6, 128.3, 127.6, 123.3, 122.6, 119.2, 114.1, 109.4, 66.7, 55.2, 54.2, 43.1, 37.3; **HRMS** (ESI^+) *m/z* = calcd for $C_{20}H_{21}NO_3$ $[M + H]^+$ 324.1597, found 324.1594.



1e

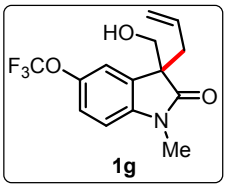
Compound **1e** was obtained as colourless solid in 74% and 70% yields using allylsilane reagent **42a** and **42b** respectively. **mp** = 101 ºC; $\boldsymbol{R_f}$ = 0.48 (pet. ether/ethyl acetate = 1:1); **IR** ($CHCl_3$): ν_{max} = 3417, 3017, 2926, 1694, 1622, 1499, 1366, 1216, 925, 758 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.09 (d, *J* = 7.2 Hz, 1 H), 7.05 (s, 1 H), 6.74 (d, *J* = 7.6 Hz, 1 H), 5.49 - 5.37 (m, 1 H), 5.02 (d, *J* = 17.2 Hz, 1 H), 4.92 (d, *J* = 10.3 Hz, 1 H), 3.88 (d, *J* = 10.7 Hz, 1 H), 3.74 (d, *J* = 10.7 Hz, 1 H), 3.17 (s, 3 H), 2.71 (br. s., 1 H), 2.68 - 2.56 (m, 2 H), 2.35 (s, 3 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 178.7, 141.6, 132.1, 131.9, 129.6, 128.5, 124.1, 118.8, 107.8, 66.4, 54.2, 37.2, 26.1, 21.1; **HRMS** (ESI^+) *m/z* = calcd for $C_{14}H_{17}NO_2$ $[M + H]^+$ 232.1328, found 232.1332.



1f

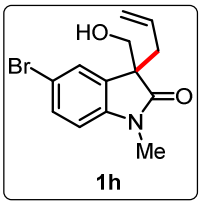
Compound **1f** was obtained as colourless liquid in 80% and 74% yields using allylsilane reagent **42a** and **42b** respectively. $\boldsymbol{R_f}$ = 0.30 (pet. ether/ethyl acetate = 1:1); **IR** ($CHCl_3$): ν_{max} = 3422, 3077, 2932, 1690, 1602, 1497, 1368, 1232, 1035, 756 cm^{-1}; **^{1}H NMR** (500 MHz , $CDCl_3$) δ = 6.85 (d, *J* = 2.3 Hz, 1 H), 6.81 (dd, *J* = 2.3, 8.8 Hz, 1 H), 6.75 (d, *J* = 8.8 Hz, 1 H), 5.43 (dddd, *J* = 7.6, 7.6, 9.9, 16.8 Hz, 1 H), 5.01 (d, *J* = 16.8 Hz, 1 H), 4.92 (d, *J* = 10.3 Hz, 1 H), 3.87 (br. d., *J* = 10.7 Hz, 1 H), 3.79 (s, 3 H), 3.74 (d, *J* = 11.1 Hz, 1 H), 3.17 (s, 3 H), 2.78 (br. s., 1 H), 2.63 (dd, *J* = 7.6, 13.7 Hz, 1 H), 2.57 (dd, *J* = 6.9, 13.7

Hz, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 178.4, 156.0, 137.5, 131.7, 131.0, 118.9, 112.2, 111.0, 108.4, 66.3, 55.7, 54.6, 37.2, 26.1; **HRMS** (ESI^+) *m/z* = calcd for $C_{14}H_{17}NO_3$ $[M + H]^+$ 248.1276, found 248.1281.



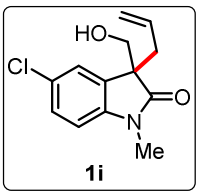
1g

Compound **1g** was obtained as colourless liquid in 70% yield. R_f = 0.65 (pet. ether/ethyl acetate = 1:1); **IR** ($CHCl_3$): ν_{max} = 3399, 3013, 2927, 1705, 1621, 1469, 1368, 1219, 766 cm^{-1}; **^{1}H NMR** (500 MHz , $CDCl_3$) δ = 7.18 (d, *J* = 8.4 Hz, 1 H), 7.14 (s, 1 H), 6.84 (d, *J* = 8.4 Hz, 1 H), 5.43 (dddd, *J* = 7.2, 7.2, 10.3, 17.1 Hz, 1 H), 5.01 (d, *J* = 16.8 Hz, 1 H), 4.96 (d, *J* = 10.3 Hz, 1 H), 3.90 (br. d., *J* = 10.7 Hz, 1 H), 3.80 (d, *J* = 11.1 Hz, 1 H), 3.21 (s, 3 H), 2.61 (d, *J* = 7.2 Hz, 2 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 178.5, 144.7, 142.7, 131.3, 131.1, 121.4, 119.6, 117.5, 108.5, 66.1, 54.7, 37.3, 26.3; **HRMS** (ESI^+) *m/z* = calcd for $C_{14}H_{14}F_3NO_3$ $[M + H]^+$ 302.0991, found 302.0999.



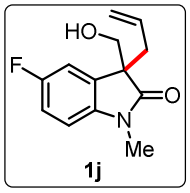
1h

Compound **1h** was obtained as colourless solid in 73% yield. **mp** = 130 ºC; R_f = 0.45 (pet. ether/ethyl acetate = 1:1); **IR** ($CHCl_3$): ν_{max} = 3381, 3020, 2929, 1705, 1608, 1488, 1216, 928, 758 cm^{-1}; **^{1}H NMR** (500 MHz , $CDCl_3$) δ = 7.44 (d, *J* = 8.0 Hz, 1 H), 7.36 (s, 1 H), 6.74 (d, *J* = 7.6 Hz, 1 H), 5.49 - 5.37 (m, 1 H), 5.05 (d, *J* = 17.2 Hz, 1 H), 4.97 (d, *J* = 9.9 Hz, 1 H), 3.93 - 3.87 (m, *J* = 7.2 Hz, 1 H), 3.78 (d, *J* = 11.1 Hz, 1 H), 3.19 (s, 3 H), 2.68 - 2.56 (m, 2 H), 2.37 (br. s., 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 178.1, 143.1, 131.8, 131.2, 126.6, 119.5, 115.3, 109.6, 66.2, 54.5, 37.2, 26.2; **HRMS** (ESI^+) *m/z* = calcd for $C_{13}H_{14}BrNO_2$ $[M + H]^+$ 296.0276, found 296.0281.



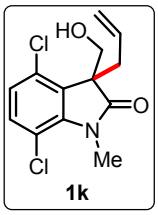
1i

Compound **1i** was obtained as colourless solid in 70% yield. **mp** = 128 ºC; R_f = 0.35 (pet. ether/ethyl acetate = 1:1); **IR** ($CHCl_3$): ν_{max} = 3419, 3017, 2929, 1705, 1611, 1490, 1363, 1216, 1097, 765 cm^{-1}; **^{1}H NMR** (400 MHz , $CDCl_3$) δ = 7.29 (dd, *J* = 1.8, 8.2 Hz, 1 H), 7.23 (d, *J* = 1.8 Hz, 1 H), 6.79 (d, *J* = 8.2 Hz, 1 H), 5.44 (dddd, *J* = 7.8, 7.8, 10.1, 16.9 Hz, 1 H), 5.05 (dd, *J* = 1.4, 16.9 Hz, 1 H), 4.97 (dd, *J* = 1.4, 10.1 Hz, 1 H), 3.90 (dd, *J* = 8.2, 11.0 Hz, 1 H), 3.78 (dd, *J* = 8.2, 11.0 Hz , 1 H), 3.20 (s, 3 H), 2.69 - 2.56 (m, 2 H), 2.38 (br. s., 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 178.3, 142.6, 131.4, 131.2, 128.3, 128.0, 123.9, 119.5, 109.1, 66.2, 54.5, 37.2, 26.2; **HRMS** (ESI^+) *m/z* = calcd for $C_{13}H_{14}ClNO_2$ $[M + H]^+$ 252.0792, found 252.0786.



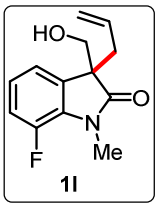
1j

Compound **1j** was obtained as colourless solid in 65% yield. **mp** = 105 ºC; R_f = 0.40 (pet. ether/ethyl acetate = 1:1); **IR** ($CHCl_3$): ν_{max} = 3422, 3018, 2929, 1701, 1618, 1494, 1365, 1216, 925, 766 cm^{-1}; **^{1}H NMR** (400 MHz , $CDCl_3$) δ = 7.04 - 6.97 (m, 2 H), 6.81 - 6.75 (m, 1 H), 5.48 - 5.36 (m, 1 H), 5.05 - 5.00 (m, 1 H), 4.97 - 4.94 (m, 1 H), 3.89 (d, *J* = 11.0 Hz, 1 H), 3.77 (d, *J* = 11.0 Hz,1 H), 3.21 - 3.18 (m, 3 H), 2.74 - 2.54 (m, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 178.5, 159.2 (d, J_{C-F} = 241.5 Hz), 139.9, 131.4 (d, J_{C-F} = 8.6 Hz), 131.3, 119.4, 114.5 (d, J_{C-F} = 23.0 Hz), 111.6 (d, J_{C-F} = 24.9 Hz), 108.6 (d, J_{C-F} = 7.8 Hz), 66.2, 54.7, 37.2, 26.2; **HRMS** (ESI^+) *m*/*z* = calcd for $C_{13}H_{14}FNO_2$ $[M + H]^+$ 236.1077, found 236.1081.



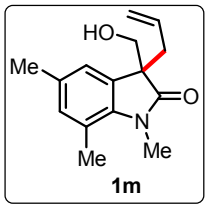
1k

Compound **1k** was obtained as yellow liquid in 64% yield. R_f = 0.70 (pet. ether/ethyl acetate = 1:1); **IR** ($CHCl_3$): ν_{max} = 3430, 3080, 2925, 1706, 1596, 1454, 1372, 1102, 924, 759 cm^{-1}; **^{1}H NMR** (500 MHz , $CDCl_3$) δ = 7.16 (d, *J* = 8.8 Hz, 1 H), 6.93 (d, *J* = 8.8 Hz, 1 H), 5.25 (dddd, *J* = 7.2, 7.2, 9.9, 17.2 Hz, 1 H), 5.02 (d, *J* = 17.2 Hz, 1 H), 4.87 (d, *J* = 9.9 Hz, 1 H), 4.17 (d, *J* = 11.1 Hz, 1 H), 4.08 (d, *J* = 10.7 Hz, 1 H), 3.57 (s, 3 H), 2.94 (dd, *J* = 7.2, 13.4 Hz, 1 H), 2.67 (dd, *J* = 7.2, 13.4 Hz, 1 H), 2.31 (br. s., 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 178.5, 141.9, 131.9, 130.9, 129.2, 128.1, 124.3, 119.1, 114.3, 64.3, 57.0, 34.5, 29.6; **HRMS** (ESI^+) *m*/*z* = calcd for $C_{13}H_{13}Cl_2NO_2$ $[M + H]^+$ 286.0391, found 286.0396.



1l

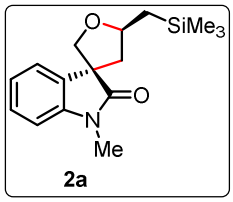
Compound **1l** was obtained as yellow liquid in 66% yield. R_f = 0.60 (pet. ether/ethyl acetate = 1:1); **IR** ($CHCl_3$): ν_{max} = 3421, 3078, 2924, 1702, 1631, 1482, 1240, 996, 772 cm^{-1}; **^{1}H NMR** (500 MHz , $CDCl_3$) δ = 7.05 - 6.99 (m, 3 H), 5.41 (ddd, *J* = 7.6, 9.9, 16.9 Hz, 1 H), 5.01 (d, *J* = 16.4 Hz, 1 H), 4.95 (d, *J* = 9.9 Hz, 1 H), 3.90 - 3.88 (m, 1 H), 3.77 (d, *J* = 11.1 Hz, 1 H), 3.41 (d, *J* = 2.3 Hz, 3 H), 2.65 (dd, *J* = 7.6, 13.4 Hz, 1 H), 2.59 - 2.55 (m, 2 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 178.4, 147.8 (d, J_{C-F} = 244.1 Hz), 132.6 (d, J_{C-F} = 2.9 Hz), 131.4, 130.6 (d, J_{C-F} = 8.6 Hz), 123.2 (d, J_{C-F} = 6.7 Hz), 119.3, 119.1 (d, J_{C-F} = 2.9 Hz), 116.4 (d, J_{C-F} = 19.1 Hz), 66.4, 54.7, 37.5, 28.5 (d, J_{C-F} = 5.7 Hz)**;** **HRMS** (ESI^+) *m*/*z* = calcd for $C_{13}H_{14}FNO_2$ $[M + H]^+$ 236.1077, found 236.1081.



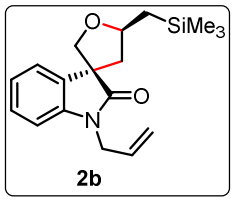
Compound **1m** was obtained as colourless solid in 76% yield. **mp** = 122 ºC; R_f = 0.50 (pet. ether/ethyl acetate = 1:1); **IR** ($CHCl_3$): ν_{max} = 3423, 3077, 3008, 2923, 2868, 1690, 1603, 1477, 1359, 1093, 919, 753 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 6.86 (s, 1 H), 6.83 (s, 1 H), 5.48 - 5.36 (m, 1 H), 5.02 (d, *J* = 17.2 Hz, 1 H), 4.93 (d, *J* = 9.9 Hz, 1 H), 3.85 (br. s., 1 H), 3.70 (d, *J* = 10.7 Hz, 1 H), 3.46 (s, 3 H), 2.71 - 2.64 (m, 1 H), 2.60 (br. s., 1 H), 2.57 - 2.54 (m, 1 H), 2.53 (s, 3 H), 2.30 (s, 3 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 179.6, 139.3, 132.7, 132.0, 131.9, 130.1, 121.8, 119.5, 118.8, 66.8, 53.3, 37.6, 29.4, 20.8, 18.9; **HRMS** (ESI^+) *m/z* = calcd for $C_{15}H_{19}NO_2$ $[M + H]^+$ 246.1483, found 246.1489.

III. General Procedure for the Annulation Reaction of Spiroepoxyoxindoles with Allylsilanes. General Procedure B:

A mixture of spiroepoxyoxindole **37** (0.28 mmol, 1.0 equiv.), allylsilane **42** (0.56 mmol, 2.0 equiv.), and $BF_3{\cdot}OEt_2$ (0.056 mmol, 20 mol%) in CH_2Cl_2 (1.0 mL) was stirred at 0 °C for 0.5 h except for spiroepoxyoxindoles **37b**, **37d**, **37e**, **37f**, **37j** (reaction time only 5 min). When TLC showed the consumption of spiroepoxyoxindole **37**, the reaction mixture was directly loaded onto a silica gel column and eluted with petroleum ether/ethyl acetate to give product **2a**–**2p**.

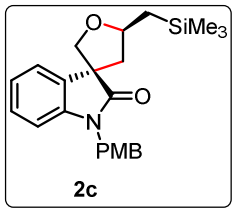


Compound **2a** was obtained as colourless liquid in 72% yield (*dr* ~ 1:1 by ^{1}H NMR). R_f = 0.50 (pet. ether/ethyl acetate = 4:1); **IR** ($CHCl_3$): ν_{max} = 3396, 2953, 1715, 1613, 1492, 1348, 1219, 1670, 690 cm^{-1}; **^{1}H NMR** (400 MHz , $CDCl_3$) δ = 7.40 - 7.28 (m, 2 H), 7.10 (t, *J* = 7.3 Hz, 1 H), 6.85 (t, *J* = 8.5 Hz, 1 H), 4.48 (ddt, *J* = 6.1, 8.5, 14.7 Hz, 0.5 H), 4.36 (ddt, *J* = 6.1, 9.8, 14.7 Hz, 0.5 H), 4.21 (d, *J* = 8.5 Hz, 0.5 H), 4.00 - 3.93 (m, 1 H), 3.82 (d, *J* = 8.5 Hz, 0.5 H), 3.23 (d, *J* = 3.7 Hz, 3 H), 2.22 - 2.10 (m, 1 H), 1.72 (dd, *J* = 9.2, 12.8 Hz, 1 H), 1.31 (ddd, *J* = 6.1, 9.8, 14.6 Hz, 1 H), 1.09 (dd, *J* = 8.5, 14.0 Hz, 0.5 H), 1.01 (dd, *J* = 9.2, 14.0 Hz, 0.5 H), 0.07 (s, 9 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 178.8, 178.3, 142.9, 142.8, 135.2, 134.0, 128.0, 127.9, 123.0, 122.9, 122.7, 122.6, 108.0, 107.9, 79.1, 76.5, 75.4, 55.5, 55.3, 47.1, 46.9, 26.4, 26.3, 24.1, 24.0, -0.9, -1.0; **HRMS** (ESI^+) *m/z* = calcd for $C_{16}H_{23}NO_2Si$ $[M + H]^+$ 290.1565, found 290.1571.



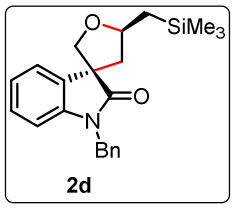
2b

Compound **2b** was obtained as colourless liquid in 74% yield. (*dr* ~ 2:3 by ^{1}H NMR) R_f = 0.65 (pet. ether/ethyl acetate = 4:1); **IR** ($CHCl_3$): ν_{max} = 3414, 3057, 2953, 1715, 1612, 1487, 1358, 1218, 839, 770 cm^{-1}; **^{1}H NMR** (500 MHz , $CDCl_3$) δ = 7.37 (dd, *J* = 7.3, 16.8 Hz, 1 H), 7.29 - 7.23 (m, 1 H), 7.09 (t, *J* = 7.3 Hz, 1 H), 6.85 (dd, *J* = 8.0, 11.4 Hz, 1 H), 5.86 (ddd, *J* = 5.3, 10.3, 16.0 Hz, 1 H), 5.27 - 5.19 (m, 2 H), 4.54 - 4.35 (m, 3 H), 4.24 (d, *J* = 8.4 Hz, 0.5 H), 4.02 - 3.97 (m, 1 H), 3.84 (d, *J* = 8.4 Hz, 1 H), 2.62 - 2.15 (m, 1 H), 1.78 - 1.73 (m, 1 H), 1.32 (ddd, *J* = 6.1, 14.5, 14.5 Hz, 1 H), 1.11 (dd, *J* = 8.4, 14.1 Hz, 0.44 H), 1.03 (dd, *J* = 8.8, 14.1 Hz, 0.61 H), 0.08 (s, 9 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 178.5, 178.0, 142.1, 142.0, 135.1, 134.0, 131.4, 127.9, 127.7, 123.0, 122.9, 122.8, 122.7, 117.6, 108.9, 108.7, 79.1, 76.6, 75.6, 55.4, 55.2, 47.3, 47.0, 42.5, 42.4, 24.1, 24.0, -0.9, -1.0; **HRMS** (ESI^+) *m/z* = calcd for $C_{18}H_{25}NO_2Si$ $[M + H]^+$ 316.1721, found 316.1727.



2c

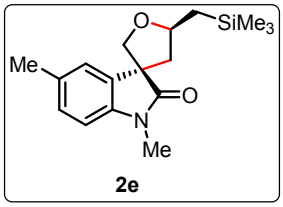
Compound **2c** was obtained as colourless liquid in 62% yield. (*dr* ~ 1:1 by ^{1}H NMR) R_f = 0.55 (pet. ether/ethyl acetate = 4:1); **IR** ($CHCl_3$): ν_{max} = 3425, 2953, 1711, 1612, 1486, 1357, 1248, 838, 769 cm^{-1}; **^{1}H NMR** (500 MHz , $CDCl_3$) δ = 7.34 (dd, *J* = 7.3, 17.2 Hz, 1 H), 7.23 (d, *J* = 8.8 Hz, 2 H), 7.18 (q, *J* = 7.6 Hz, 1 H), 7.05 (t, *J* = 7.6 Hz, 1 H), 6.85 (d, *J* = 8.4 Hz, 2 H), 6.76 (dd, *J* = 8.0, 10.7 Hz, 1 H), 4.86 (d, *J* = 5.3 Hz, 2 H), 4.50 (ddt, *J* = 6.1, 8.8, 14.9 Hz, 0.5 H), 4.40 (ddt, *J* = 6.1, 8.8, 14.9 Hz, 0.5 H), 4.27 (d, *J* = 8.8 Hz, 0.5 H), 4.06 - 3.98 (m, 1 H), 3.85 (d, *J* = 8.8 Hz, 1 H), 3.78 (s, 3 H), 2.64 - 2.19 (m, 1 H), 1.79 - 1.69 (m, 1 H), 1.37 - 1.28 (m, 1 H), 1.12 (dd, *J* = 8.8, 14.1 Hz, 0.5 H), 1.03 (dd, *J* = 8.8, 14.1 Hz, 0.5 H), 0.08 (s, 9 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 178.9, 178.5, 159.1, 142.0, 141.9, 135.1, 134.0, 128.7, 127.9, 127.7, 123.0, 122.9, 122.8, 122.7, 114.2, 109.0, 108.9, 79.2, 79.1, 76.6, 75.6, 55.5, 55.3, 55.2, 47.3, 47.0, 43.4, 43.3, 24.2, 24.0, -0.92, -0.93; **HRMS** (ESI^+) *m/z* = calcd for $C_{23}H_{29}NO_3Si$ $[M + H]^+$ 396.1981, found 396.1989.



2d

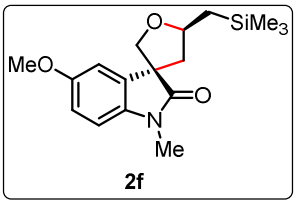
Compound **2d** was obtained as colourless liquid in 66% yield. (*dr* ~ 3:2 by ^{1}H NMR) R_f = 0.65 (pet. ether/ethyl acetate = 4:1); **IR** ($CHCl_3$): ν_{max} = 3414, 3032, 2952, 1714, 1611, 1488, 1358, 1248, 1070, 861, 752 cm^{-1}; **^{1}H NMR** (500 MHz , $CDCl_3$) δ = 7.39 - 7.27

(m, 6 H), 7.17 (q, *J* = 7.6 Hz, 1 H), 7.06 (t, *J* = 7.6 Hz, 1 H), 6.74 (dd, *J* = 8.0, 10.3 Hz, 1 H), 4.93 (d, *J* = 5.0 Hz, 2 H), 4.51 (ddt, *J* = 6.1, 8.8, 14.9 Hz, 0.6 H), 4.41 (ddt, *J* = 6.1, 9.2, 14.9 Hz, 0.4 H), 4.29 (d, *J* = 8.4 Hz, 1 H), 4.07 - 4.00 (m, 1 H), 3.87 (d, *J* = 8.8 Hz, 1 H), 2.66 - 2.22 (m, 1 H), 1.81 - 1.72 (m, 1 H), 1.37- 1.29 (m, 1 H), 1.14 (dd, *J* = 8.8, 14.1 Hz, 0.6 H), 1.04 (dd, *J* = 8.4, 14.1 Hz, 0.4 H), 0.09 (s, 9 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 179.0, 178.5, 142.0, 141.9, 135.82, 135.8, 135.0, 133.9, 128.8, 127.9, 127.8, 127.6, 127.3, 123.1, 122.9, 122.8, 122.7, 109.0, 108.9, 79.2, 79.1, 76.6, 75.7, 55.5, 55.3, 47.3, 47.0, 44.0, 43.9, 24.2, 24.0, -0.92, -0.93; **HRMS** (ESI^+) *m/z* = calcd for $C_{22}H_{27}NO_2Si$ $[M + H]^+$ 366.1879, found 366.1884.



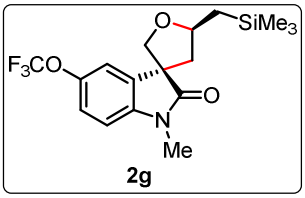
2e

Compound **2e** was obtained as colourless solid in 78% yield. (*dr* ~ 3:2 by ^{1}H NMR) **mp** = 52 ºC; ***R*$_f$** = 0.60 (pet. ether/ethyl acetate = 4:1); **IR** ($CHCl_3$): ν_{max} = 3426, 2952, 1708, 1643, 1475, 1350, 1247, 1065, 859, 771 cm^{-1}; **^{1}H NMR** (500 MHz , $CDCl_3$) δ = 7.19 - 7.13 (m, 1 H), 7.08 (t, *J* = 8.4.0 Hz, 1 H), 6.73 (dd, *J* = 8.0, 11.8 Hz, 1 H), 4.49 (ddt, *J* = 6.1, 8.8, 14.9 Hz, 0.6 H), 4.34 (ddt, *J* = 6.1, 8.8, 14.9 Hz, 0.4 H), 4.19 (d, *J* = 8.8 Hz, 0.5 H), 3.95 (s, 1 H), 3.80 (d, *J* = 8.8 Hz, 0.5 H), 3.20 (d, *J* = 5.0 Hz, 3 H), 2.57 - 2.10 (m, 5 H), 1.74 - 1.28 (m, 1 H), 1.10 (dd, *J* = 8.8, 14.1 Hz, 0.6 H), 1.01 (dd, *J* = 8.8, 14.1 Hz, 0.4 H), 0.07 (s, 9 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 178.8, 178.1, 140.5, 140.4, 135.2, 134.1, 132.6, 132.5, 128.2, 128.0, 123.5, 123.4, 107.7, 107.6, 79.1, 79.0, 76.5, 75.4, 55.6, 55.3, 47.1, 46.9, 26.4, 26.3, 24.3, 24.0, 21.1, 21.0, -0.9, -1.0; **HRMS** (ESI^+) *m/z* = calcd for $C_{17}H_{25}NO_2Si$ $[M + H]^+$ 304.1719, found 304.1727.



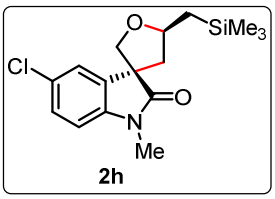
2f

Compound **2f** was obtained as colourless liquid in 75% yield. (*dr* ~ 9:1 by ^{1}H NMR) ***R*$_f$** = 0.35 (pet. ether/ethyl acetate = 4:1); **IR** ($CHCl_3$): ν_{max} = 3399, 2951, 1710, 1600, 1497, 1362, 1248, 1033, 804, 693 cm^{-1}; **^{1}H NMR** (500 MHz , $CDCl_3$) δ = 6.95 (d, *J* = 2.7 Hz, 1 H), 6.82 (dd, *J* = 2.7, 8.4 Hz, 1 H), 6.75 (d, *J* = 8.4 Hz, 1 H), 4.47 (ddt, *J* = 6.1, 8.8, 14.5 Hz, 1 H), 4.20 (d, *J* = 8.8 Hz, 1 H), 3.83 - 3.79 (m, 4 H), 3.21 (s, 3 H), 2.20 - 2.11 (m, 2 H), 1.32 (dd, *J* = 5.7, 14.1 Hz, 1 H), 1.09 (dd, *J* = 8.8, 14.1 Hz, 1 H), 0.06 (s, 9 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 177.9, 156.3, 136.4, 135.4, 111.9, 110.6, 108.2, 79.0, 75.4, 55.9, 55.8, 46.9, 26.5, 24.2, -0.9; **HRMS** (ESI^+) *m/z* = calcd for $C_{17}H_{25}NO_3Si$ $[M + H]^+$ 320.1667, found 320.1676.



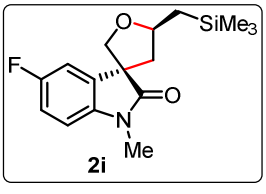
2g

Compound **2g** was obtained as colourless liquid in 72% yield. (*dr* ~ 1:1 by ^{1}H NMR) $\boldsymbol{R_f}$ = 0.60 (pet. ether/ethyl acetate = 4:1); **IR** ($CHCl_3$): ν_{max} = 2954, 1721, 1620, 1496, 1349, 1254, 1164, 861, 769 cm^{-1}; **^{1}H NMR** (500 MHz , $CDCl_3$) δ = 7.26 - 7.19 (m, 1 H), 7.19 - 7.14 (m, 1 H), 6.82 (dd, *J* = 8.4, 11.8 Hz, 1 H), 4.46 (ddt, *J* = 6.1, 8.4, 14.9 Hz, 0.5 H), 4.33 (ddt, *J* = 6.1, 8.8, 14.9 Hz, 0.5 H), 4.20 (d, *J* = 8.4 Hz, 0.5 H), 3.99 - 3.92 (m, 1 H), 3.81 (d, *J* = 8.4 Hz, 0.5 H), 3.23 (d, *J* = 5.0 Hz, 3 H), 2.62 - 2.12 (m, 1 H), 1.71 - 1.69 (m, 1 H), 1.33 - 1.27 (m, 1 H), 1.09 (dd, *J* = 8.4, 14.1 Hz, 0.5 H), 1.00 (dd, *J* = 8.4, 14.1 Hz, 0.5 H), 0.07 (s, 9 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 178.4, 177.9, 145.1, 145.0, 141.5, 141.4, 136.7, 135.4, 121.1, 120.9, 116.8, 116.7, 108.3, 108.2, 79.1, 79.0, 76.4, 75.1, 55.8, 55.5, 47.2, 46.8, 26.6, 26.5, 24.2, 24.0, -0.9, -1.0; **HRMS** (ESI^+) *m/z* = calcd for $C_{17}H_{22}F_3NO_3Si$ $[M + H]^+$ 374.1385, found 374.1394.



2h

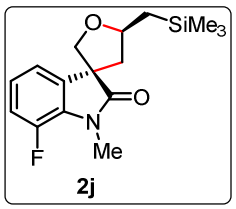
Compound **2h** was obtained as colourless liquid in 64% yield. (*dr* ~ 1:1 by ^{1}H NMR) $\boldsymbol{R_f}$= 0.45 (pet. ether/ethyl acetate = 4:1); **IR** ($CHCl_3$): ν_{max} = 3395, 2953, 1717, 1611, 1489, 1346, 1248, 1066, 860, 766 cm^{-1}; **^{1}H NMR** (500 MHz , $CDCl_3$) δ = 7.32 (dd, *J* = 2.0, 18.3 Hz, 1 H), 7.29 - 7.24 (m, 1 H), 6.76 (dd, *J* = 8.4, 11.4 Hz, 1 H), 4.47 (ddt, *J* = 6.1, 8.8, 14.9 Hz, 0.5 H), 4.32 (ddt, *J* = 6.1, 8.8, 14.9 Hz, 0.5 H), 4.19 (d, *J* = 8.4 Hz, 0.5 H), 3.97 - 3.90 (m, 1 H), 3.79 (d, *J* = 8.4 Hz, 0.5 H), 3.21 (d, *J* = 4.6 Hz, 3 H), 2.60 - 2.12 (m, 1 H), 1.72 - 1.64 (m, 1 H), 1.30 (ddd, *J* = 6.1, 6.1, 14.1 Hz, 1 H), 1.09 (dd, *J* = 8.4, 14.1 Hz, 0.5 H), 1.01 (dd, *J* = 8.8, 14.1 Hz, 0.5 H), 0.08 (s, 9 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 178.2, 177.7, 141.4, 141.3, 137.0, 135.6, 128.4, 128.2, 127.9, 127.8, 123.3, 123.2, 108.9, 108.8, 79.2, 79.0, 76.4, 75.2, 55.7, 55.5, 47.1, 46.8, 26.6, 26.5, 24.3, 24.0, -0.9, -1.0; **HRMS** (ESI^+) *m/z* = calcd for $C_{16}H_{22}ClNO_2Si$ $[M + H]^+$ 324.1174, found 324.1181.



2i

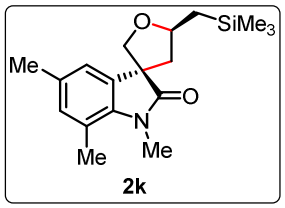
Compound **2i** was obtained as colourless liquid in 62% yield. (*dr* ~ 1:1 by ^{1}H NMR) $\boldsymbol{R_f}$ = 0.50 (pet. ether/ethyl acetate = 4:1); **IR** ($CHCl_3$): ν_{max} = 3419, 2953, 2858, 1715, 1617, 1494, 1353, 1248, 1068, 861, 763 cm^{-1}; **^{1}H NMR** (500 MHz , $CDCl_3$) δ = 7.09 (ddd, *J* = 2.3, 8.0, 17.6 Hz, 1 H), 7.02 - 6.94 (m, 1 H), 6.75 (ddd, *J* = 3.8, 8.4, 12.2 Hz, 1 H), 4.45 (ddt, *J* = 6.1, 8.4, 14.9 Hz, 0.5 H), 4.32 (ddt, *J* = 6.4, 8.7, 14.9 Hz, 0.5 H), 4.19 (d, *J*

= 8.4 Hz, 0.5 H), 3.94 (s, 1 H), 3.79 (d, *J* = 8.4 Hz, 0.5 H), 3.21 (d, *J* = 4.6 Hz, 3 H), 2.61 - 2.14 (m, 1 H), 1.71 - 1.27 (m, 1 H), 1.08 (dd, *J* = 8.4, 14.1 Hz, 0.5 H), 1.00 (dd, *J* = 8.4, 14.1 Hz, 0.5 H), 0.07 (s, 9 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 178.3, 177.8, 160.5 (d, J_{C-F} = 16.2 Hz), 158.6 (d, J_{C-F} = 16.2 Hz), 138.7 (d, J_{C-F} = 11.4 Hz), 136.9 (d, J_{C-F} = 8.6 Hz), 135.5 (d, J_{C-F} = 7.6 Hz), 114.1 (d, J_{C-F} = 20.0 Hz), 113.9 (d, J_{C-F} = 19.1 Hz), 111.0 (d, J_{C-F} = 20.0 Hz), 110.8 (d, J_{C-F} = 20.0 Hz), 108.4 (d, J_{C-F} = 7.6 Hz), 108.3 (d, J_{C-F} = 7.6 Hz), 79.1, 78.9, 76.4, 75.2, 56.0, 55.7, 47.1, 46.8, 26.6, 26.5, 24.2, 24.0, -0.9, -1.0; **HRMS** (ESI^+) *m/z* = calcd for $C_{16}H_{22}FNO_2Si$ $[M + H]^+$308.1469, found 308.1477.



2j

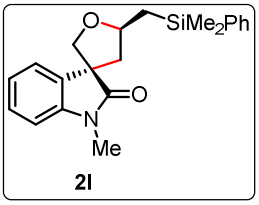
Compound **2j** was obtained as colourless liquid in 60% yield. (*dr* ~ 3:7 by ^{1}H NMR) R_f = 0.70 (pet. ether/ethyl acetate = 4:1); **IR** ($CHCl_3$): ν_{max} = 3043, 2858, 1721, 1631, 1482, 1371, 1241, 1053, 860, 733 cm^{-1}; **^{1}H NMR** (400 MHz , $CDCl_3$) δ = 7.18 - 7.09 (m, 1 H), 7.06 - 6.96 (m, 2 H), 4.50 - 4.41 (m, 0.3 H), 4.38 - 4.28 (m, 0.7 H), 4.20 (d, *J* = 8.5 Hz, 0.5 H), 3.94 (s, 1 H), 3.80 (d, *J* = 8.5 Hz, 0.5 H), 3.46 - 3.38 (m, 3 H), 2.61 - 2.09 (m, 1 H), 1.69 (dd, *J* = 8.5, 11.6 Hz, 1 H), 1.34 - 1.26 (m, 1 H), 1.08 (dd, *J* = 8.5, 14.0 Hz, 0.3 H), 0.99 (dd, *J* = 9.2, 14.0 Hz, 0.7 H), 0.06 (s, 9 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 178.4, 177.9, 148.7 (d, J_{C-F} = 12.3 Hz), 146.3 (d, J_{C-F} = 12.3 Hz), 138.2 (d, J_{C-F} = 3.1 Hz), 136.9 (d, J_{C-F} = 3.1 Hz), 129.50 - 129.31 (m), 123.6 (d, J_{C-F} = 6.9 Hz), 123.5 (d, J_{C-F} = 6.9 Hz), 118.5 (d, J_{C-F} = 3.1 Hz), 118.4 (d, J_{C-F} = 3.1 Hz), 116.0 (d, J_{C-F} = 19.3 Hz), 115.8 (d, J_{C-F} = 19.3 Hz), 79.1, 79.0, 75.5, 55.8 (d, J_{C-F} = 1.5 Hz), 55.6 (d, J_{C-F} = 1.5 Hz), 47.5, 47.2, 28.9 (d, J_{C-F} = 5.4 Hz), 28.8 (d, J_{C-F} = 5.4 Hz), 24.1, 23.9, -0.9, -1.0; **HRMS** (ESI^+) *m/z* = calcd for $C_{16}H_{22}FNO_2Si$ $[M + H]^+$ 308.1472, found 308.1477.



2k

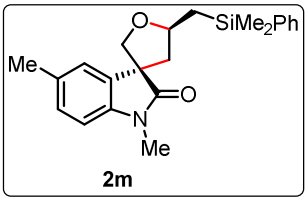
Compound **2k** was obtained as colourless solid in 74% yield. (*dr* ~ 3:2 by ^{1}H NMR) **mp** = 72 ºC; R_f = 0.52 (pet. ether/ethyl acetate = 4:1); **IR** ($CHCl_3$): ν_{max} = 3426, 2952, 1708, 1643, 1475, 1350, 1247, 1065, 859, 771 cm^{-1}; **^{1}H NMR** (500 MHz , $CDCl_3$) δ = 7.04 - 6.96 (m, 1 H), 6.85 - 6.79 (m, 1 H), 4.47 (br. s., 0.6 H), 4.33 (br. s., 0.4 H), 4.18 (d, *J* = 8.0 Hz, 0.5 H), 3.93 (br. s., 1 H), 3.77 (d, *J* = 8.0 Hz, 0.5 H), 3.48 (br. s., 3 H), 2.57 - 2.27 (m, 7 H), 2.19 - 2.09 (m, 1 H), 1.35 - 1.27 (m, 1 H), 1.13 - 1.06 (m, 0.6 H), 1.04 - 0.97 (m, 0.4 H), 0.07 (s, 9 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 179.6, 179.1, 138.2, 138.1, 136.1, 134.9, 132.6, 132.4, 132.1, 131.9, 121.4, 121.2, 119.3, 119.2, 79.2,

79.1, 76.9, 75.9, 55.1, 54.8, 47.8, 47.3, 29.8, 29.6, 24.3, 23.9, 20.8, 18.8, 18.7, -0.9, -1.0; **HRMS** (ESI^+) *m/z* = calcd for $C_{18}H_{27}NO_2Si$ $[M + H]^+$ 318.1879, found 318.1884.



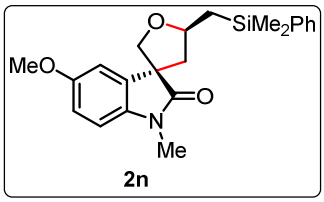
2l

Compound **2l** was obtained as colourless liquid in 68% yield. (*dr* ~ 2:3 by ^1H NMR) R_f = 0.45 (pet. ether/ethyl acetate = 4:1); **IR** ($CHCl_3$): ν_{max} = 2955, 2854, 1715, 1612, 1492, 1374, 1251, 1069, 834, 751 cm^{-1}; **^{1}H NMR** (400 MHz , $CDCl_3$) δ = 7.60 - 7.50 (m, 2 H), 7.38 - 7.21 (m, 5 H), 7.07 (q, *J* = 7.3 Hz, 1 H), 6.83 (t, *J* = 7.3 Hz, 1 H), 4.47 - 4.40 (m, 0.4 H), 4.40 - 4.32 (ddt, *J* = 6.1, 8.5, 14.7 Hz, 0.6 H), 4.20 (d, *J* = 8.5 Hz, 0.5 H), 3.98 - 3.90 (m, 1 H), 3.79 (d, *J* = 8.5 Hz, 0.5 H), 3.21 (d, *J* = 4.3 Hz, 3 H), 2.53 - 2.07 (m, 1 H), 1.67 (dd, *J* = 9.2, 12.8 Hz, 1 H), 1.58 - 1.50 (m, 1 H), 1.36 - 1.23 (m, 1 H), 0.38 - 0.34 (m, 6 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 178.7, 178.3, 142.9, 142.8, 138.6, 135.1, 134.0, 133.6, 133.5, 129.1, 129.0, 128.0, 127.9, 127.8, 123.0, 122.9, 122.7, 122.6, 108.0, 107.8, 78.9, 78.8, 76.6, 75.5, 55.5, 55.3, 47.0, 46.9, 26.4, 26.3, 23.3, -2.1, -2.2, -2.4, -2.5; **HRMS** (ESI^+) *m/z* = calcd for $C_{21}H_{25}NO_2Si$ $[M + H]^+$ 352.1722, found 352.1727.

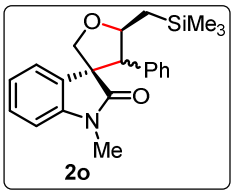


2m

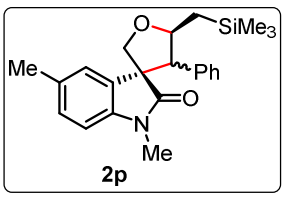
Compound **2m** was obtained as colourless liquid in 70% yield. (*dr* ~ 7:3 by ^1H NMR) R_f = 0.45 (pet. ether/ethyl acetate = 4:1); **IR** ($CHCl_3$): ν_{max} = 3400, 2924, 1712, 1621, 1498, 1355, 1249, 1066, 832, 756 cm^{-1}; **^{1}H NMR** (500 MHz , $CDCl_3$) δ = 7.63 - 7.48 (m, 2 H), 7.46 - 7.29 (m, 3 H), 7.20 - 7.01 (m, 2 H), 6.74 - 6.69 (m, 1 H), 4.43 (ddt, *J* = 6.5, 8.4, 14.5 Hz, 0.7 H), 4.35 (ddt, *J* = 6.1, 8.4, 14.5 Hz, 0.3 H), 4.20 - 3.74 (m, 2 H), 3.21 - 3.17 (m, 3 H), 2.37 - 2.33 (m, 3 H), 2.13 - 2.08 (m, 1 H), 1.67 (d, *J* = 16.4 Hz, 1 H), 1.55 (ddd, *J* = 6.1, 14.1, 14.1 Hz, 1 H), 1.32 (dd, *J* = 8.4, 14.1 Hz, 1 H), 0.39 - 0.34 (m, 6 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 178.6, 178.1, 140.5, 138.7, 134.1, 133.6, 133.5, 132.6, 132.5, 129.1, 129.0, 128.2, 128.0, 127.9, 127.8, 123.6, 123.4, 107.7, 107.6, 78.8, 76.6, 75.5, 55.5, 55.3, 47.1, 46.8, 26.4, 26.3, 23.4, 23.3, 21.1, -2.1, -2.2, -2.3, -2.5; **HRMS** (ESI^+) *m/z* = calcd for $C_{22}H_{27}NO_2Si$ $[M + H]^+$ 366.1880, found 366.1884.



Compound **2n** was obtained as colourless liquid in 68% yield. (*dr* > 99 by ^{1}H NMR) R_f = 0.25 (pet. ether/ethyl acetate = 4:1); **IR** ($CHCl_3$): ν_{max} = 3394, 2952, 2854, 1708, 1600, 1497, 1364, 1251, 1065, 833, 756 cm^{-1}; **^{1}H NMR** (500 MHz , $CDCl_3$) δ = 7.59 - 7.50 (m, 2 H), 7.50 - 7.33 (m, 3 H), 6.84 (d, *J* = 2.3 Hz, 1 H), 6.80 (dd, *J* = 2.3, 8.4 Hz, 1 H), 6.73 (d, *J* = 8.4 Hz, 1 H), 4.42 (ddt, *J* = 6.1, 8.4, 14.5 Hz, 1 H), 4.19 (d, *J* = 8.4 Hz, 1 H), 3.78 (s, 3 H), 3.19 (s, 3 H), 2.14 - 2.05 (m, 1 H), 1.56 (dd, *J* = 6.1, 14.5 Hz, 1 H), 1.32 (dd, *J* = 8.4, 14.5 Hz, 1 H), 0.36 (s, 3 H), 0.35 (s, 3 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 177.9, 156.3, 138.6, 136.4, 135.3, 133.6, 129.0, 127.8, 112.1, 110.3, 108.2, 78.8, 75.5, 55.9, 55.8, 46.8, 26.5, 23.4, -2.2, -2.3; **HRMS** (ESI^+) *m/z* = calcd for $C_{22}H_{27}NO_3Si$ $[M + H]^+$ 382.1826, found 382.1833.



Compound **2o** was obtained as colourless solid in 71% yield. (*dr* ~ 1:1 by ^{1}H NMR) **mp** = 122 ºC; R_f = 0.36 (pet. ether/ethyl acetate = 85:15); **IR** ($CHCl_3$): ν_{max} = 3407, 3059, 3032, 1713, 1611, 1470, 1418, 1349, 1249, 1066, 843, 491 cm^{-1}; **^{1}H NMR** (200 MHz , $CDCl_3$) δ = 7.42 - 7.13 (m, 7 H), 7.02 (ddd, *J* = 1.0, 7.5, 15.0 Hz, 1 H), 6.74 (dd, *J* = 7.7, 12.3 Hz, 1 H), 4.89 (d, *J* = 10.0 Hz, 0.5 H), 4.66 (d, *J* = 10.1 Hz, 0.5 H), 4.41 (d, *J* = 8.3 Hz, 0.5 H), 4.24 - 4.10 (m, 1 H), 3.93 (d, *J* = 8.3 Hz, 0.5 H), 3.11 (d, *J* = 0.9 Hz, 3 H), 2.78 (ddd, *J* = 4.5, 7.7, 10.1 Hz, 0.5 H), 2.46 (ddd, *J* = 4.8, 7.7, 10.0 Hz, 0.5 H), 2.46 (ddd, *J* = 4.9, 7.7, 10.0 Hz, 1 H), 0.61 - 0.34 (m, 1 H), 0.30 - 0.02 (m, 1 H), 0.56 (s, 4 H), 0.72 (s, 5 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 177.9, 176.8, 143.9, 143.5, 140.2, 139.5, 131.1, 130.6, 128.5, 128.4, 128.3, 127.4, 127.3, 124.6, 122.9, 122.7, 122.5, 108.2, 108.1, 90.0, 88.8, 76.4, 59.9, 59.3, 54.6, 52.8, 26.4, 26.1, 13.0, 12.2, -1.7, -1.8; **HRMS** (ESI^+) *m/z* = calcd for $C_{22}H_{27}NO_2Si$ $[M +H]^+$ 366.1877, found 366.1884.

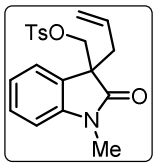


Compound **2p** was obtained as colourless liquid in 76% yield. (*dr* ~ 1:1 by ^{1}H NMR); R_f = 0.60 (pet. ether/ethyl acetate = 4:1); **IR** ($CHCl_3$): ν_{max} = 3402, 2951, 2870, 1709, 1620, 1498, 1354, 1249, 1072, 809, 758 cm^{-1}; **^{1}H NMR** (400 MHz , $CDCl_3$) δ = 7.55 - 7.46 (m, 2 H), 7.40 (t, *J* = 7.3 Hz, 2 H), 7.36 - 7.29 (m, 1 H), 7.29 - 7.18 (m, 1 H), 7.18 - 7.07 (m, 1 H), 6.84 - 6.69 (m, 1 H), 5.02 (d, *J* = 9.8 Hz, 0.5 H), 4.80 (d, *J* = 9.8 Hz, 0.5 H), 4.53 (d, *J* = 8.5 Hz, 0.5 H), 4.29 (q, *J* = 8.5 Hz, 1 H), 4.05 (d, *J* = 8.5 Hz, 0.5 H),

3.22 (s, 3 H), 2.95 - 2.87 (m, 0.5 H), 2.61 - 2.52 (m, 0.5 H), 2.41 (d like., 3 H), 0.68 - 0.50 (m, 1 H), 0.36 (dd, *J* = 4.3, 15.3 Hz, 0.5 H), 0.20 (dd, *J* = 7.9, 15.3 Hz, 0.5 H), 0.42 (s, 5 H), 0.59 (s, 4 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 178.8, 178.1, 140.5, 140.4, 135.2, 134.1, 132.6, 132.5, 128.2, 128.0, 123.5, 123.4, 107.7, 107.6, 79.1, 79.0, 76.5, 75.4, 55.6, 55.3, 47.1, 46.9, 26.4, 26.3, 24.3, 24.0, 21.1, 21.0, -0.9, -1.0; **HRMS** (ESI^+) *m*/*z* = calcd for $C_{23}H_{29}NO_2Si$ $[M + H]^+$ 380.2037, found 380.2040.

IV. Formal Synthesis of (±)-Physovenine:

(3-Allyl-1-methyl-2-oxoindolin-3-yl)methyl 4-Methylbenzenesulfonate (43):



Compound **1a** (1 g, 4.60 mmol) was dissolved in dry CH_2Cl_2 (10 mL) under argon, and the solution was treated with TsCl (1.1 g, 5.52 mmol), Et_3N (1.6 mL, 11.51 mmol), and a catalytic amount of DMAP. The reaction mixture was stirred at room temperature for 2 h, and then it was quenched with water. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL), and the combined organic layers were washed with brine and concentrated. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 4:1) to give **43** as a pale yellow solid.

Yield = 1.370 g, 80 %;

m.p = 83 °C;

R_f = 0.63 (petroleum ether/ethyl acetate, 3:2);

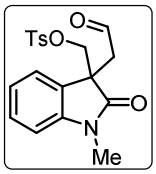
IR ($CHCl_3$) ν_{max} = 3423, 3017, 2936, 1718, 1612, 1469, 1359, 1181, 1096, 984, 837, 754 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.63 (d, *J* = 8.2 Hz, 2 H), 7.33 - 7.28 (m, 3 H), 7.19 (dd, *J* = 0.9, 7.8 Hz, 1 H), 7.04 (ddd, *J* = 0.9, 7.8, 7.8 Hz, 1 H), 6.82 (d, *J* = 7.8 Hz, 1 H), 5.32 (dddd, *J* = 6.9, 7.8, 10.1, 16.9 Hz, 1 H), 5.01 - 4.95 (m, 1 H), 4.93 - 4.89 (m, 1H), 4.28 (d, *J* = 9.2 Hz, 1 H), 4.14 (d, *J* = 9.2 Hz, 1 H), 3.16 (s, 3 H), 2.56 (dd, *J* = 6.9, 13.7 Hz, 1 H), 2.51 - 2.45 (m, 1 H), 2.45 (s, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.6, 144.9, 143.7, 132.3, 130.5, 129.8, 128.7, 128.1, 127.9, 123.9, 122.7, 119.7, 108.2, 72.0, 52.1, 37.8, 26.2, 21.6;

HRMS (ESI^+) *m*/*z* = calcd for $C_{20}H_{21}NO_4S$ $[M + H]^+$ 372.1256; found 372.1264.

[1-Methyl-2-oxo-3-(2-oxoethyl)indolin-3-yl]methyl 4-Methylbenzenesulfonate (44):



Ozone was bubbled through a solution of **43** (1 g, 2.69 mmol) in CH_2Cl_2 (50 mL) and MeOH (50 mL) at –78 ^oC until the colour of the solution turned violet. Oxygen gas was then bubbled through the reaction mixture for 5 min. After this, Me_2S (0.5 mL, 6.73 mmol) was added, and the mixture was warmed to room temperature, stirred overnight, and then concentrated to dryness under reduced pressure using a rotavapor. The resulting crude aldehyde was purified by flash silica gel column chromatography (petroleum ether/ethyl acetate, 3:2) to give compound **44** as a colourless solid.

Yield = 895 mg, 89 %;

m.p = 110 °C;

R_f = 0.32 (petroleum ether/ethyl acetate, 1:1);

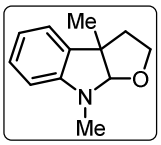
IR ($CHCl_3$) ν_{max} = 3424, 3022, 1714, 1617, 1494, 1372, 1217, 988, 760 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.40 (s, 1H), 7.61 (d, *J* = 7.9 Hz, 2 H), 7.30 - 7.21 (m, 3 H), 7.16 (d, *J* = 7.3 Hz, 1 H), 6.97 (t, *J* = 7.3 Hz, 1 H), 6.82 (d, *J* = 7.3 Hz, 1 H), 4.23 (d, *J* = 9.8 Hz, 1 H), 3.93 (d, *J* = 9.2 Hz, 1 H), 3.18 (s, 3 H), 3.13 (d, *J* = 18.3 Hz, 1 H), 2.95 (d, *J* = 18.3 Hz, 1 H), 2.40 (s, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.9, 175.0, 145.2, 143.8, 132.1, 129.9, 129.2, 127.9, 127.7, 123.8, 122.9, 108.6, 72.2, 48.6, 46.3, 26.6, 21.6;

HRMS (ESI^+) *m*/*z* = calcd for $C_{19}H_{19}NO_5S$ $[M + H]^+$ 374.1052; found 374.1057.

3a,8-Dimethyl-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]indole (45):



Solid $LiAlH_4$ (255 mg, 6.69 mmol) was added to a solution of aldehyde **44** (500 mg, 1.34 mmol) in THF (10 mL) at 0 ^oC. When TLC showed that the reaction was complete (5 min), the same reaction mixture was further heated at reflux for 2 h. The mixture was

then cooled to room temperature, and the excess hydride was decomposed through the dropwise addition of EtOAc (15 mL). Saturated aqueous $NaHCO_3$ (15 ml) was added, the phases were separated. The aqueous layer was extracted with EtOAc (2 x 15 mL), and the combined organic extracts were washed with brine (14 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 98:2) to give fused compound **45** as a pale yellow liquid.

Yield = 50 mg, 20 %;

R_f = 0.41 (petroleum ether/ethyl acetate, 95:5);

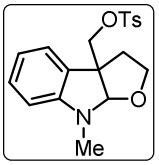
IR ($CHCl_3$) ν_{max} = 3447, 3052, 2959, 1608, 1494, 1388, 1300, 1123, 1013, 918, 740 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.11 (ddd, *J* = 1.1, 7.6, 7.6 Hz, 1 H), 7.05 (dd, *J* = 1.1, 7.3 Hz, 1 H), 6.69 (ddd, *J* = 1.1, 7.3, 7.3 Hz, 1 H), 6.38 (d, *J* = 7.6 Hz, 1 H), 5.08 (s, 1 H), 3.96 (ddd, *J* = 1.5, 7.3, 8.7 Hz, 1 H), 3.47 (ddd, *J* = 5.3, 8.7, 11.4 Hz, 1 H), 2.93 (s, 3 H), 2.14 (ddd, *J* = 1.5, 5.3, 11.8 Hz, 1 H), 2.06 (ddd, *J* = 7.3, 11.8, 11.8 Hz, 1 H), 1.47 (s, 3 H);

^{13}C NMR (125 MHz, $CDCl_3$) δ = 150.4, 134.5, 128.1, 122.4, 117.3, 105.0, 104.8, 67.3, 52.3, 41.7, 30.9, 24.7;

HRMS (ESI^+) *m*/*z* = calcd for $C_{12}H_{15}NO$ $[M + H]^+$ 190.1225; found 190.1226.

(8-Methyl-2,3,8,8a-tetrahydro-3a*H*-furo[2,3-*b*]indol-3a-yl)methyl-4-Methylbenzenesulfonate (46):



A solution of compound **44** (200 g, 0.54 mmol) in THF (5 mL) in a two-necked round-bottomed flask (50 mL) was cooled to 0 ^oC. $LiAlH_4$ (0.082 g, 2.14 mmol) was added to the reaction mixture under argon, and the mixture was stirred at 0 ^oC for 5 min. EtOAc (10 mL) was then added, followed by saturated. aq. NaCl (5 mL). The organic layers were washed with water and brine, dried with Na_2SO_4, and concentrated. The resulting crude product was purified by flash column chromatography (petroleum ether/ethyl acetate, 85:15) to give **46** as a colourless liquid.

Yield = 144 mg, 75 %;

R_f = 0.23 (petroleum ether/ethyl acetate, 4:1);

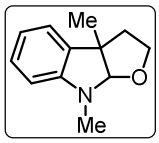
IR ($CHCl_3$) ν_{max} = 3449, 3053, 2941, 1606, 1495, 1361, 1179, 1020, 853, 747 cm^{-1};

^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.65 (d, *J* = 8.3 Hz, 2 H), 7.25 (d, *J* = 8.0 Hz, 2 H), 7.05 (ddd, *J* = 1.3, 7.6, 7.6 Hz, 1 H), 6.88 (dd, *J* = 0.9, 7.3, 7.3 Hz, 1 H), 6.54 (ddd, *J* = 0.9, 7.3, 7.3 Hz, 1 H), 6.28 (d, *J* = 7.8 Hz, 1 H), 5.12 (s, 1 H), 4.14 (d, *J* = 9.6 Hz, 1 H), 4.02 (d, *J* = 9.7 Hz, 1 H), 3.89 (ddd, *J* = 1.5, 7.5, 8.7 Hz, 1 H), 3.41 (ddd, *J* = 5.3, 8.7, 11.0 Hz, 1 H), 2.80 (s, 3 H), 2.38 (s, 3 H), 2.17 (ddd, *J* = 7.5, 11.0, 11.0 Hz, 1 H), 1.95 (ddd, *J* = 1.5, 5.3, 11.0 Hz, 1 H);

^{13}C NMR (125 MHz, $CDCl_3$) δ = 151.0, 144.9, 132.6, 129.9, 129.3, 128.1, 127.9, 123.4, 117.4, 105.3, 100.4, 71.8, 66.8, 56.3, 36.4, 30.7, 21.6;

HRMS (ESI^+) *m*/*z* = calcd for $C_{19}H_{21}NO_4S$ $[M + H]^+$ 360.1264; found 360.1264.

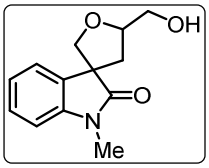
3a,8-Dimethyl-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]indole (45):



Tosylate **46** (100 mg, 0.278 mmol) was heated with sodium iodide (0.417 g, 2.782 mmol) in refluxing 2-butanone (10 mL) for 6 h. After the reaction was complete, the cooled mixture was filtered through a pad of Celite. Concentration of the filtrate under reduced pressure gave the crude iodo compound (88 %). The crude iodo compound and triethylamine (590 mg, 58.4 mmol) were dissolved in dry methanol, and freshly prepared Raney nickel (0.05 g) was added. The reaction mixture was stirred under H_2 (60 psi) at 25 ^oC overnight. When TLC showed that the reaction was complete, the reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The reduced compound was purified by flash column chromatography (petroleum ether/ethyl acetate, 98:2) to give fused compound **45** (39 mg, 75 % over two steps) as a pale yellow liquid. R_f = 0.41 (petroleum ether/ethyl acetate, 95:5).

V. Synthetic Utility of the Product:

5-(Hydroxymethyl)-1′-methyl-4,5-dihydro-2*H*-spiro[furan-3,3′-indolin]-2′-one (47):



Mercuric acetate (27 mg, 0.085 mmol) was added to a stirred solution of compound **2l** (20 mg, 0.27 mmol) in peracetic acid (15 % solution in acetic acid, containing 1 % sulfuric acid; 0.72 mL, 1.482 mmol), and the mixture was stirred at room temperature for 8 h. Diethyl ether (5 mL) was then added, and the solution was washed with sodium thiosulfate solution, water, sodium hydrogen carbonate solution, and brine. The solution was then dried (Na_2SO_4), and the solvents were evaporated in *vacuo*. The resulting oil was purified by flash silica gel column chromatography (petroleum ether/ethyl acetate, 30:70) to give compound **47** (*dr* ~ 1:1 by NMR spectroscopy) as a colourless liquid.

Yield = 5 mg, 40 %;

R_f = 0.52(ethyl acetate);

IR ($CHCl_3$) ν_{max} = 3426, 2924, 2855, 1697, 1613, 1469, 1353, 1257, 1110, 756 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37 - 7.27 (m, 2 H), 7.17 - 7.06 (q, *J* = 7.9 Hz, 1 H), 6.86 (dd, *J* = 7.9, 13.4 Hz, 1 H), 4.61 - 4.53 (m, 0.5 H), 4.53 - 4.44 (m, 0.5 H), 4.19 - 3.88 (m, 3 H), 3.83 - 3.72 (m, 1 H), 3.24 (d, *J* = 3.7 Hz, 3 H), 2.44 (ddd, *J* = 4.8, 7.3, 12.2 Hz, 1 H), 2.20 (dd, *J* = 7.3, 12.8 Hz, 1 H), 2.11 (dd, *J* = 9.2, 12.8 Hz, 1 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ = 178.6, 178.3, 143.1, 143.0, 133.5, 132.1, 128.4, 128.2, 123.1, 122.7, 122.6, 108.3, 108.0, 80.9, 80.8, 77.2, 76.1, 64.1, 63.8, 54.7, 54.6, 39.4, 38.5, 26.5, 26.4;

HRMS (ESI^+) *m*/*z* = calcd for $C_{13}H_{15}NO_3$ $[M + H]^+$ 234.1125; found 234.1125.

VI. X-ray Crystallography:

X-ray intensity data measurements of compounds **1h** and **2k** were carried out on a Bruker D8 VENTURE Kappa Duo PHOTON II CPAD diffractometer equipped with Incoatech multilayer mirrors optics. The intensity measurements were carried out with Mo micro-focus sealed tube diffraction source (MoK_α= 0.71073 Å) at 100(2) K temperature. The X-ray generator was operated at 50 kV and 1.1 mA. A preliminary set of cell constants and an orientation matrix were calculated from three sets of 36 frames. Data were collected with ω scan width of 0.5° at different settings of φ and 2θ keeping the sample-to-detector distance fixed at 5.00 cm. The X-ray data collection was monitored by APEX3 program (Bruker, 2016).[33] All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs (Bruker, 2016). SHELX-97 was used for structure solution and full matrix least-squares refinement on F^2.[34] All the hydrogen atoms were placed in geometrically idealized positions (C-H = 0.95 Å, C-H = 0.99 Å and C-H = 0.98 Å for the phenyl, methylene and methyl H atoms respectively) and constrained to ride on their parent atoms [Uiso(H) = 1.2Ueq(C) for phenyl, methylene groups and Uiso(H) = 1.5Ueq(C) for methyl group]. An *ORTEP* III[35] view of both compounds were drawn with 50% probability displacement ellipsoids and H atoms are shown as small spheres of arbitrary radii. The tetrahydrofuran and ethyltrimethylsilane groups diaplayed statistical disorder over two positions having occuancies 0.6 and 0.4 (for tetrahydrofuran moiety) and 0.9 and 0.1 for (ethyltrimethylsinale group) respectively.

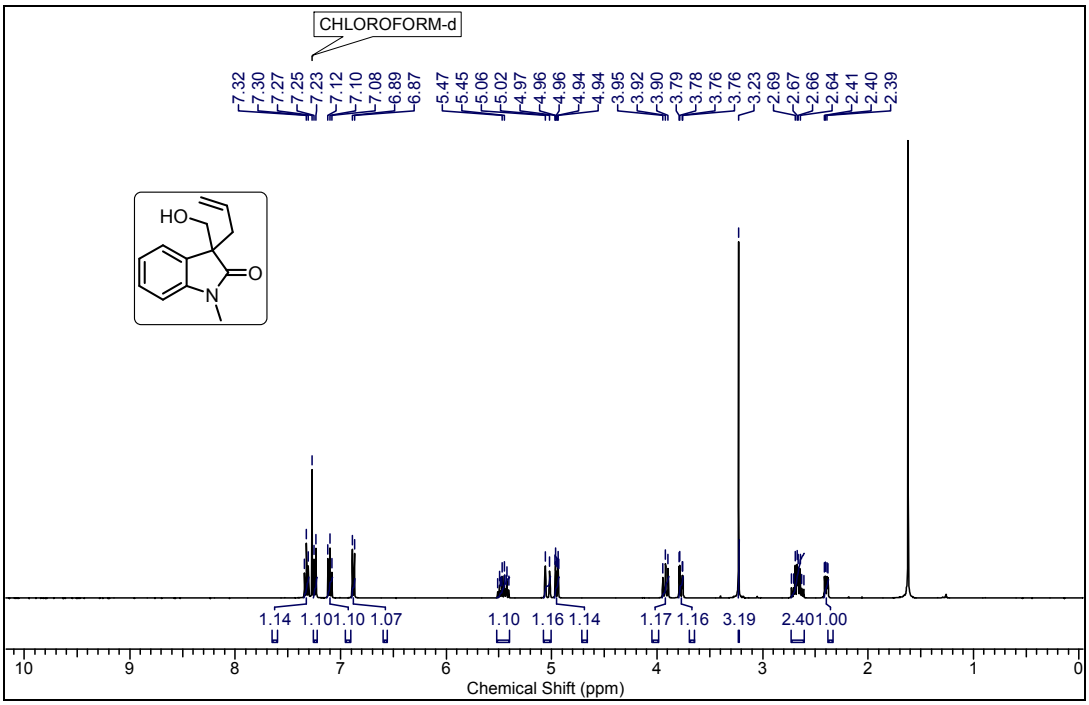
Crystal Data	**1h**	**2k**
Formula	$C_{13}H_{14}BrNO_2$	$C_{18}H_{27}NO_2Si$
Mr	296.16	317.49
Crystal Size (mm)	0.32 x 0.19 x 0.09	0.49 x 0.18 x 0.07
Temp. (K)	100(2) K	100(2) K
Crystal Syst., Sp. Gr.	monoclinic, $P2_1/c$	monoclinic, $P2_1/c$
a/Å	11.8013(5)	18.0157(7)
b/Å	13.5736(6)	6.1437(3)
c/Å	8.1920(4)	16.6073(7)

$\beta/^0$	106.915(2)	105.874(2)
Volume ($Å^3$)	1255.47(10)	1768.05(13)
Z	4	4
D_c, *g* cm^{-3}	1.567	1.193
μ/mm^{-1}	3.263	0.140
F(000)	600	688.0
Ab. Correct.	multi-scan	multi-scan
T_{min}	0.422	0.935
T_{max}	0.758	0.990
θ_{max}	29.991	31.095
Completeness at θ_{max}	99.8%	99.5%
h, k, l (min, max)	(16, -16), (19, -19), (11, -11)	(26, -26), (8, -8), (24, -24)
Number of reflections	97726	121926
unique reflections	3659	5631
Observed reflections	3502	5358
R_{int}	0.0110	0.0166
R_{sig}	0.0430	0.0519
Number of parameters	156	271
Number of restraints	0	94
R1[I>2σ(I)]	0.0185	0.0714
wR2[I>2σ(I)]	0.0473	0.1656
R1_all data	0.0196	0.0740
*wR2*_all data	0.0479	0.1669
Goodness-of-fit (S)	1.046	1.204
$\Delta\rho_{max}$, $\Delta\rho_{min}$($eÅ^{-3}$)	+0.485, -0.359	+0.597, -0.414
CCDC No.	1510993	1510992

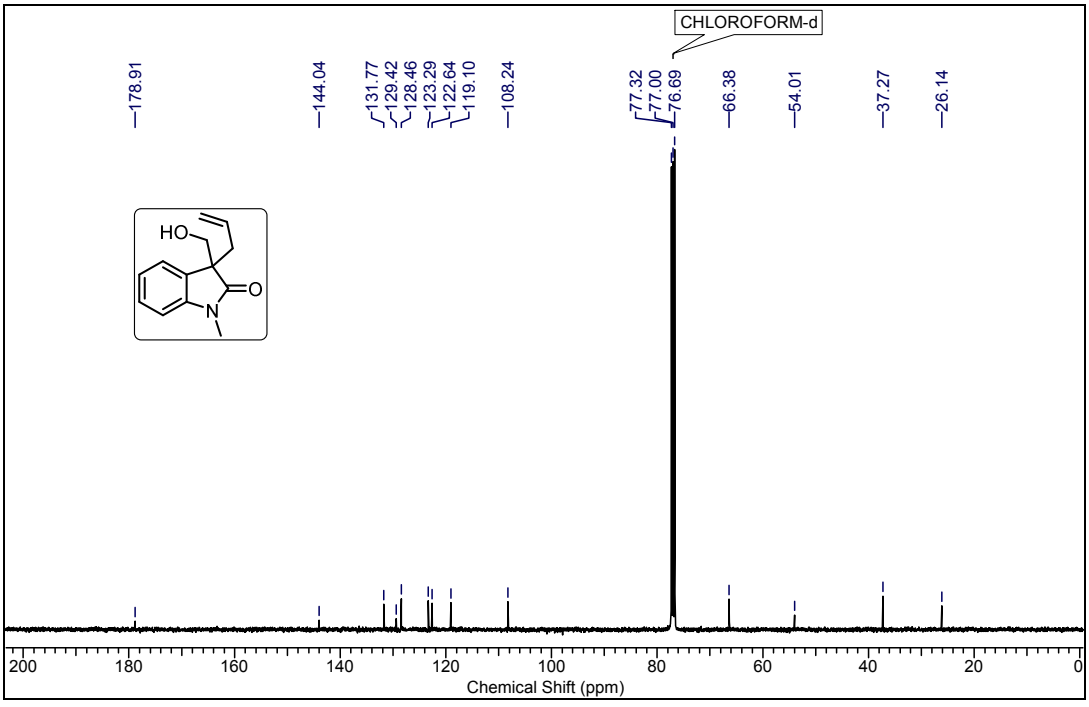
3.1.6. Spectral Data

Spectra

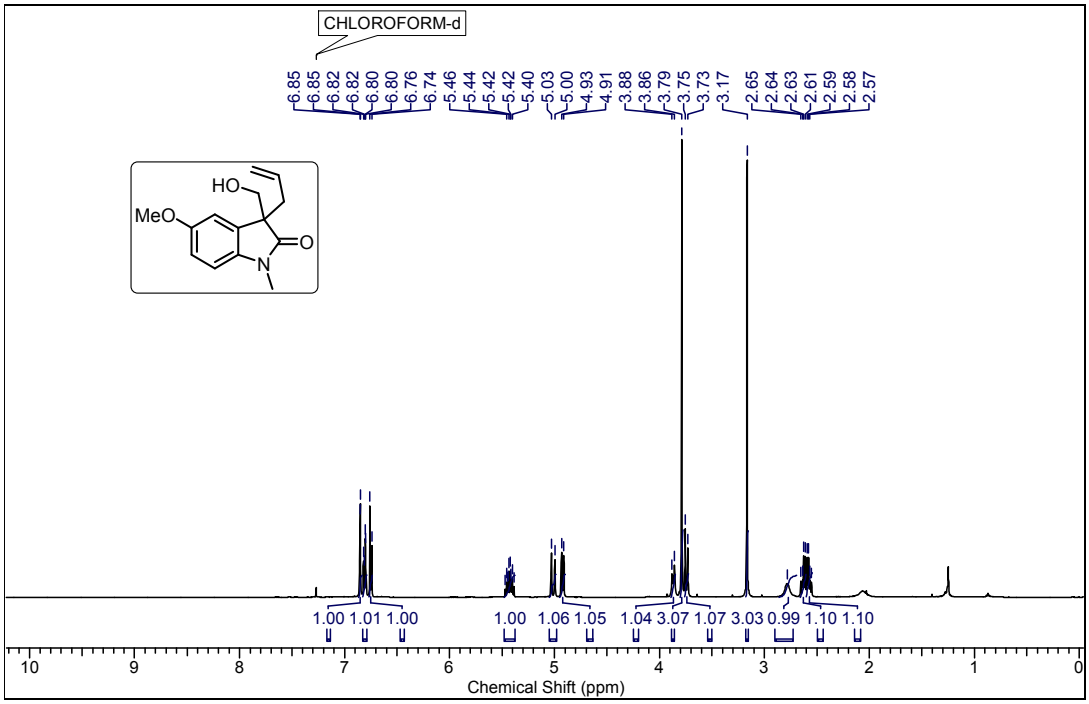
^{1}H NMR spectrum of compound **1a** ($CDCl_3$, 400 MHz):



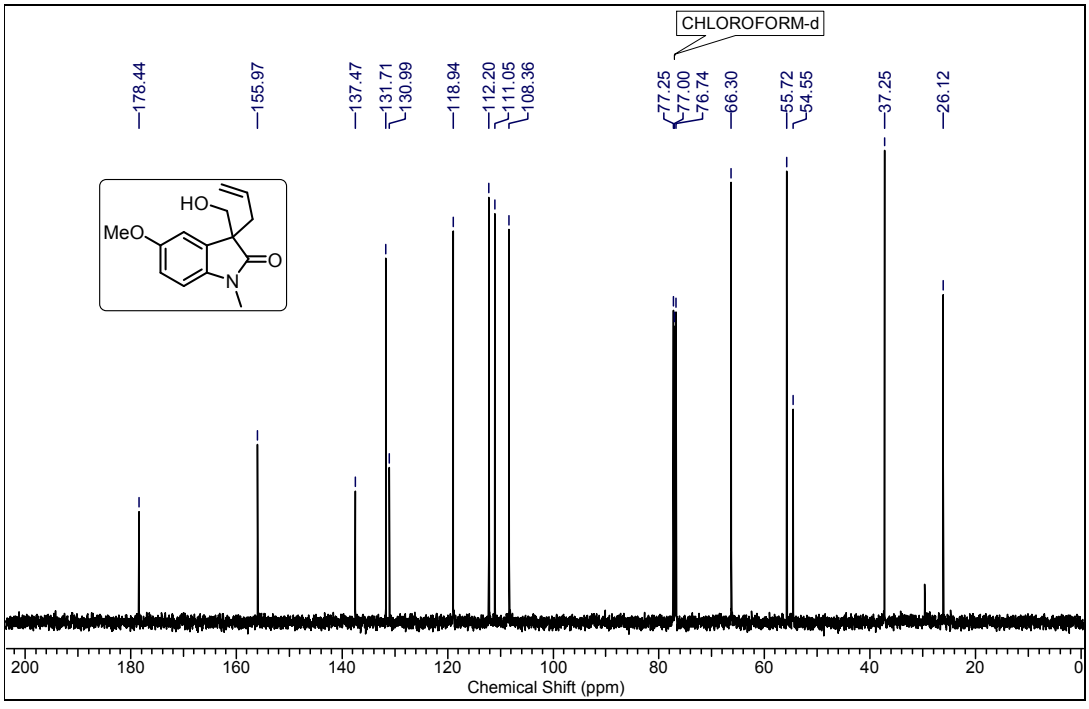
^{13}C NMR spectrum of compound **1a** ($CDCl_3$, 100 MHz):



^{1}H NMR spectrum of compound **1f** ($CDCl_3$, 500 MHz):

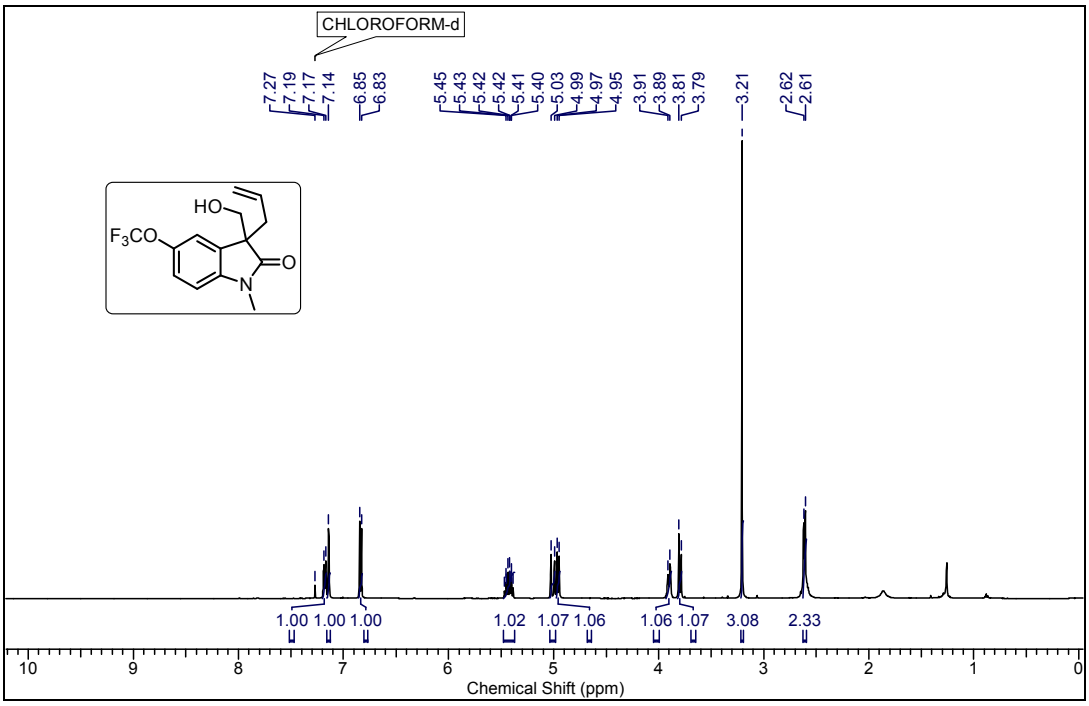


^{13}C NMR spectrum of compound **1f** ($CDCl_3$, 125 MHz):

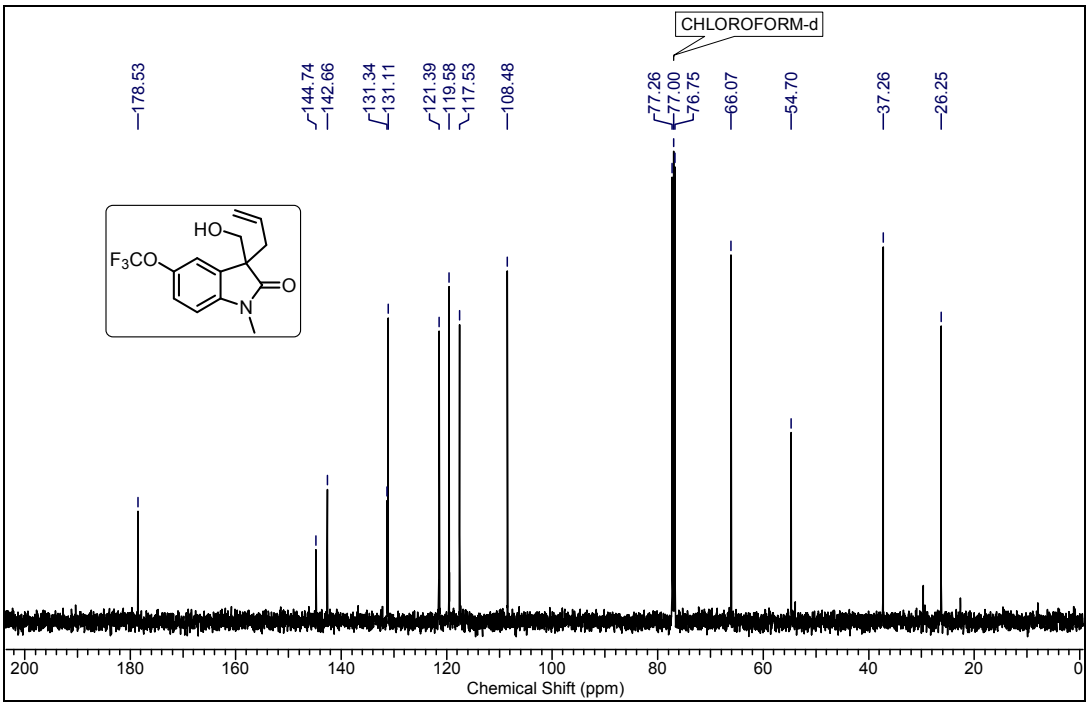


Spectra

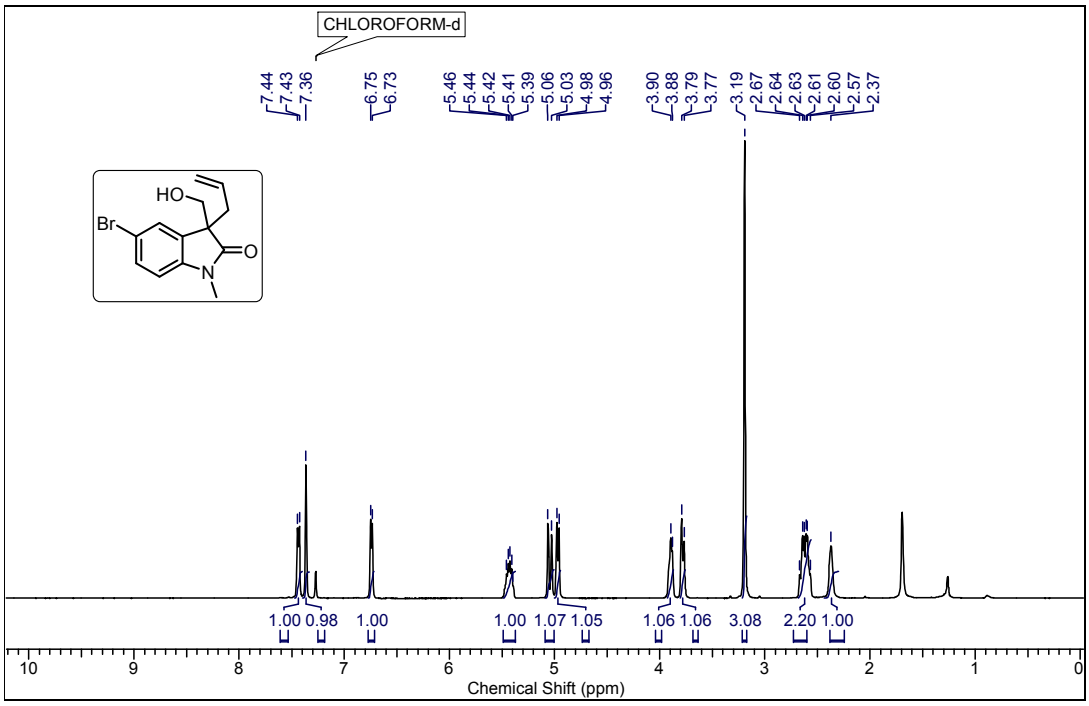
^{1}H NMR spectrum of compound **1g** ($CDCl_3$, 500 MHz):



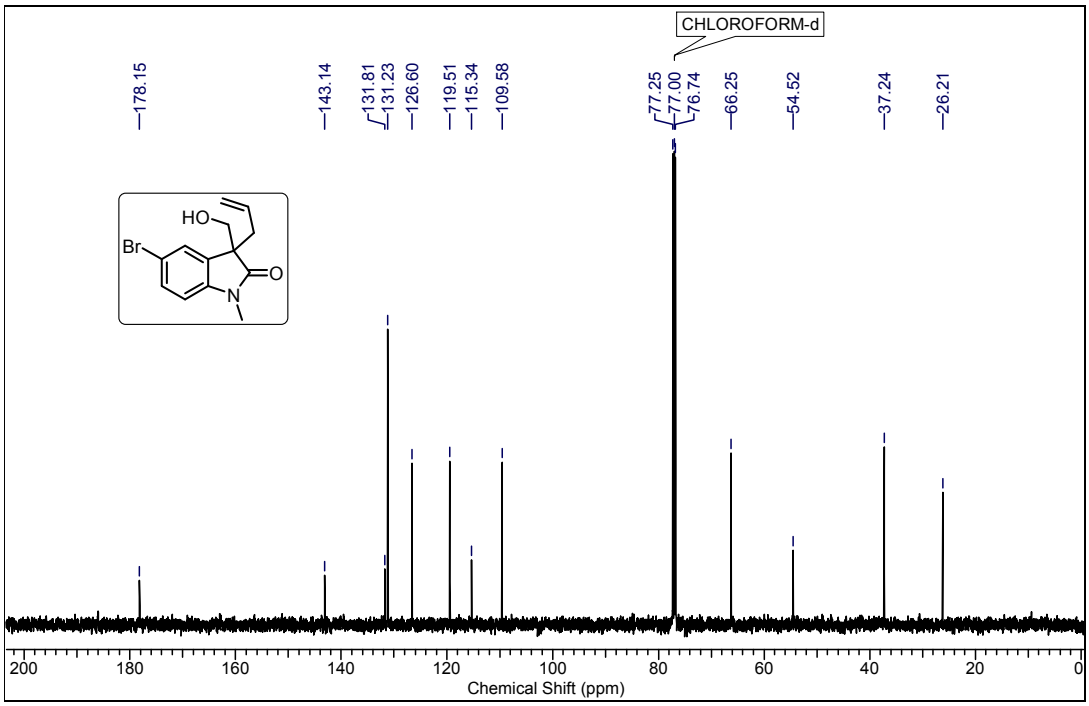
^{13}C NMR spectrum of compound **1g** ($CDCl_3$, 125 MHz):



^{1}H NMR spectrum of compound **1h** ($CDCl_3$, 500 MHz):

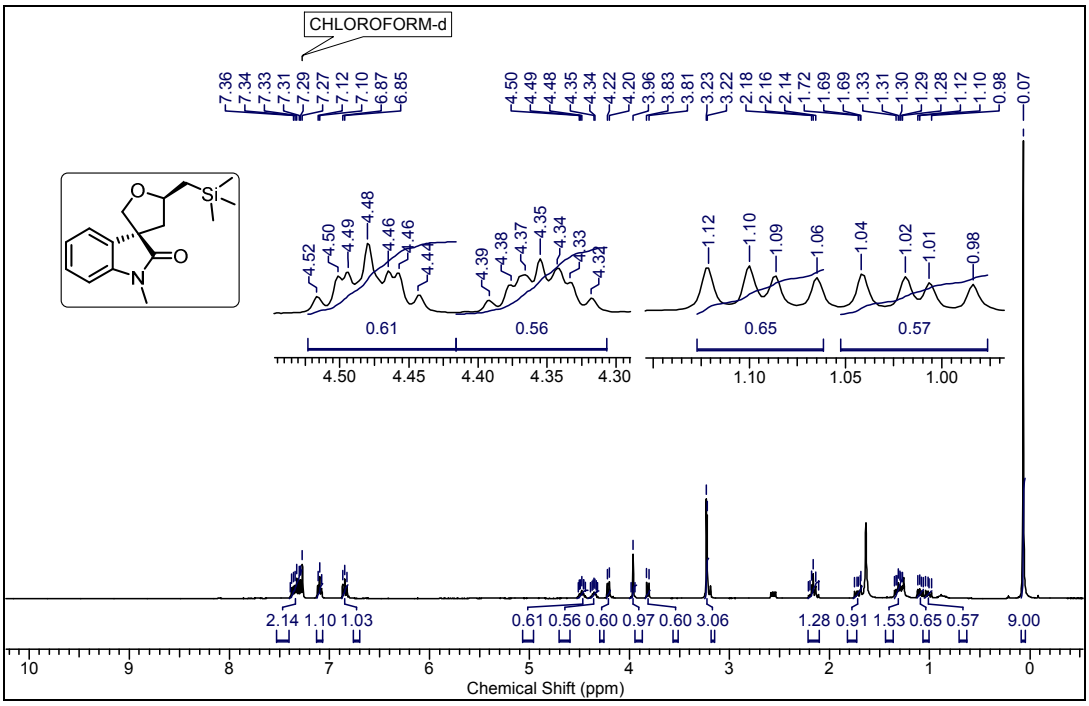


^{13}C NMR spectrum of compound **1h** ($CDCl_3$, 125 MHz):

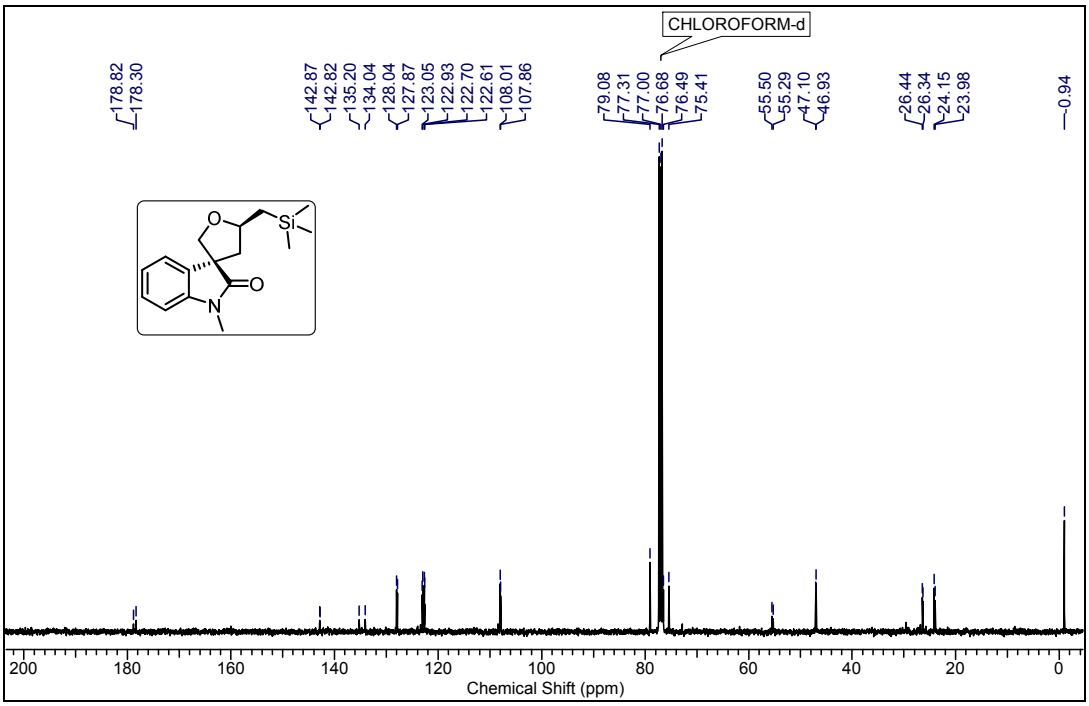


Spectra

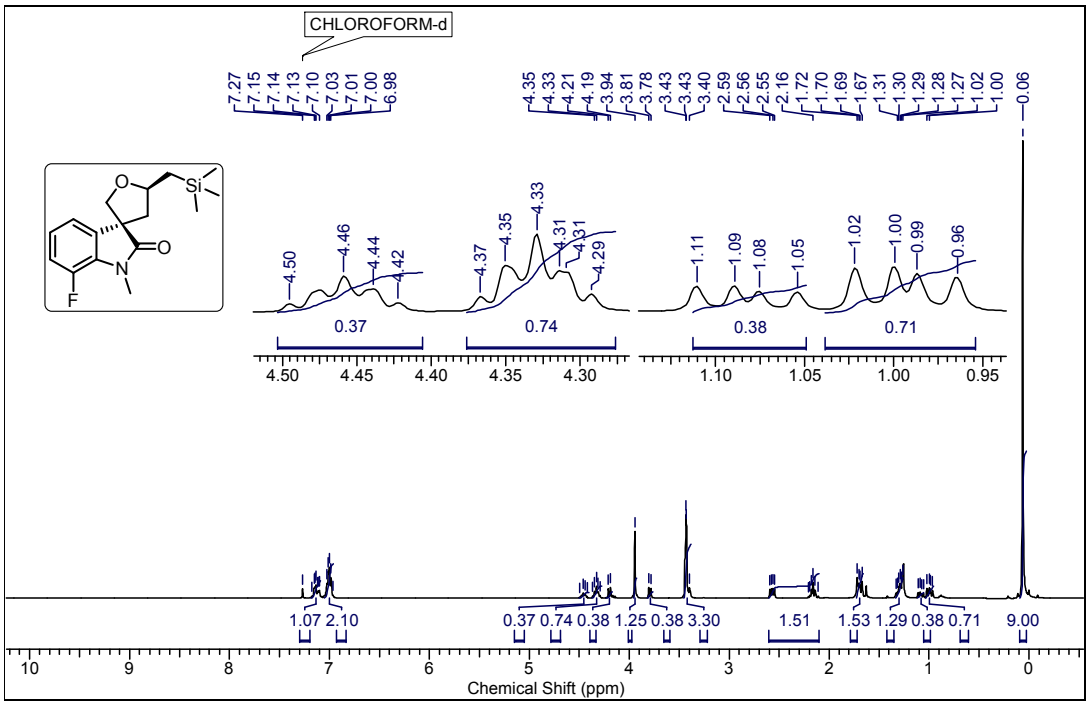
^{1}H NMR spectrum of compound **2a** ($CDCl_3$, 400 MHz):



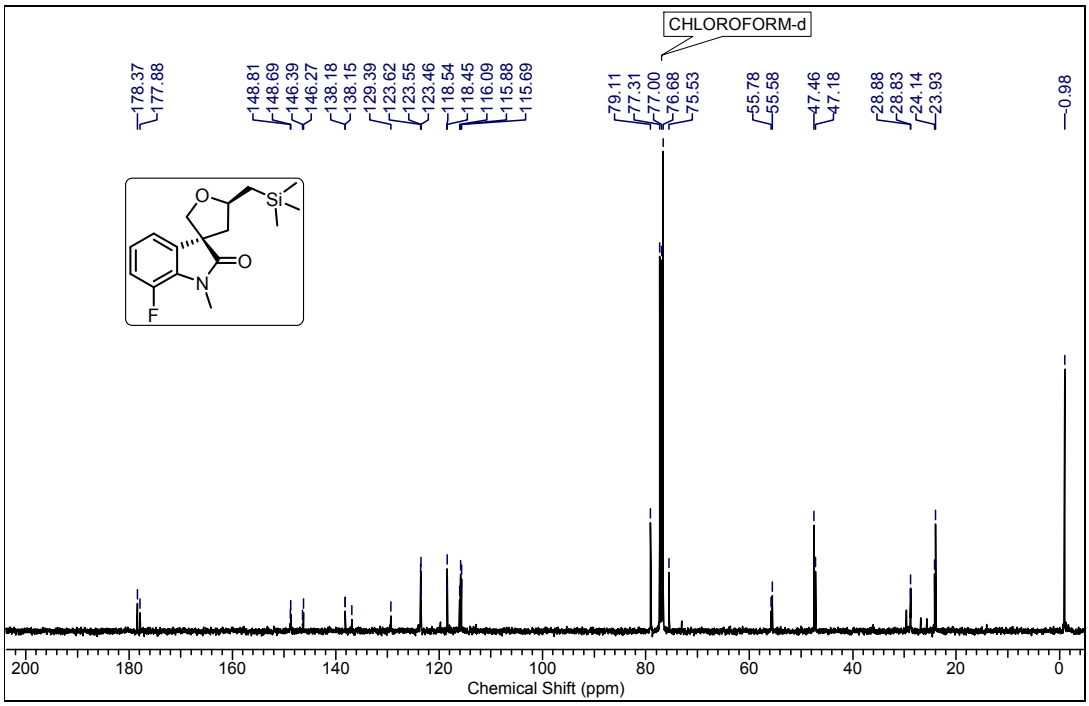
^{13}C NMR spectrum of compound **2a** ($CDCl_3$, 100 MHz):



^{1}H NMR spectrum of compound **2j** ($CDCl_3$, 400 MHz):

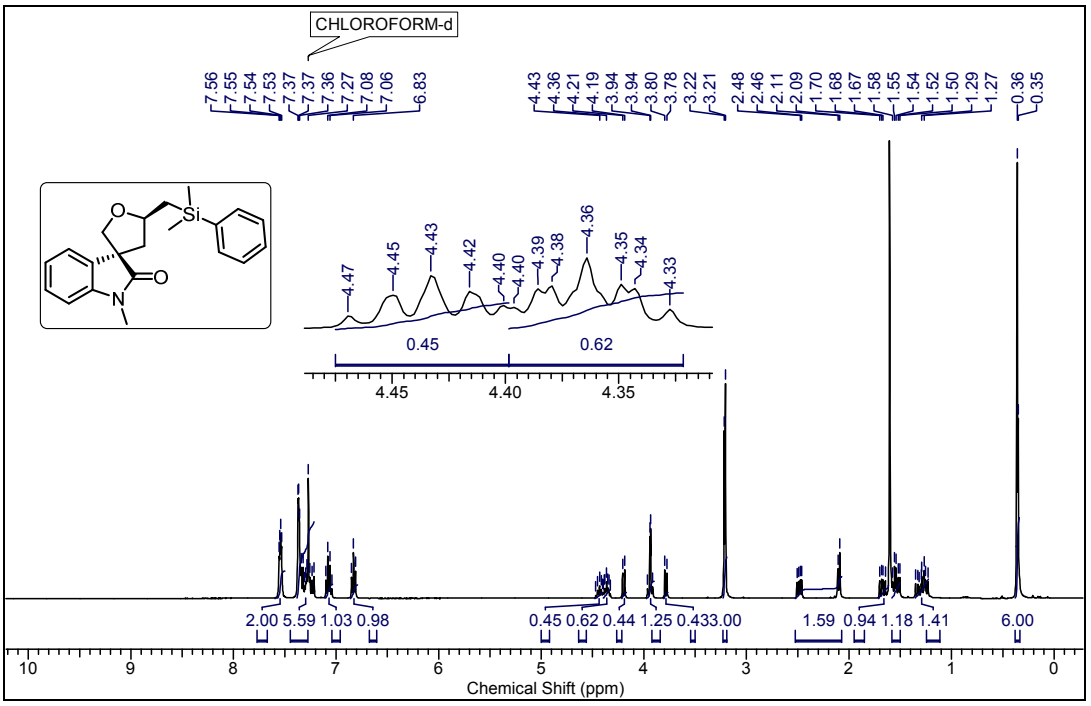


^{13}C NMR spectrum of compound **2j** ($CDCl_3$, 100 MHz):

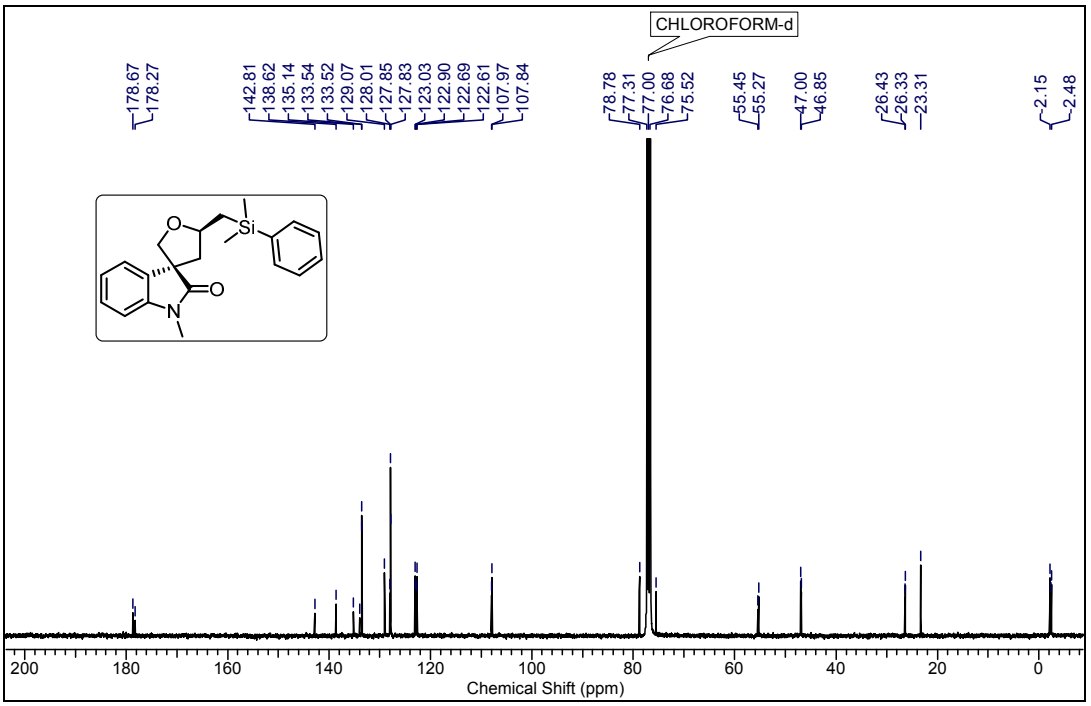


Spectra

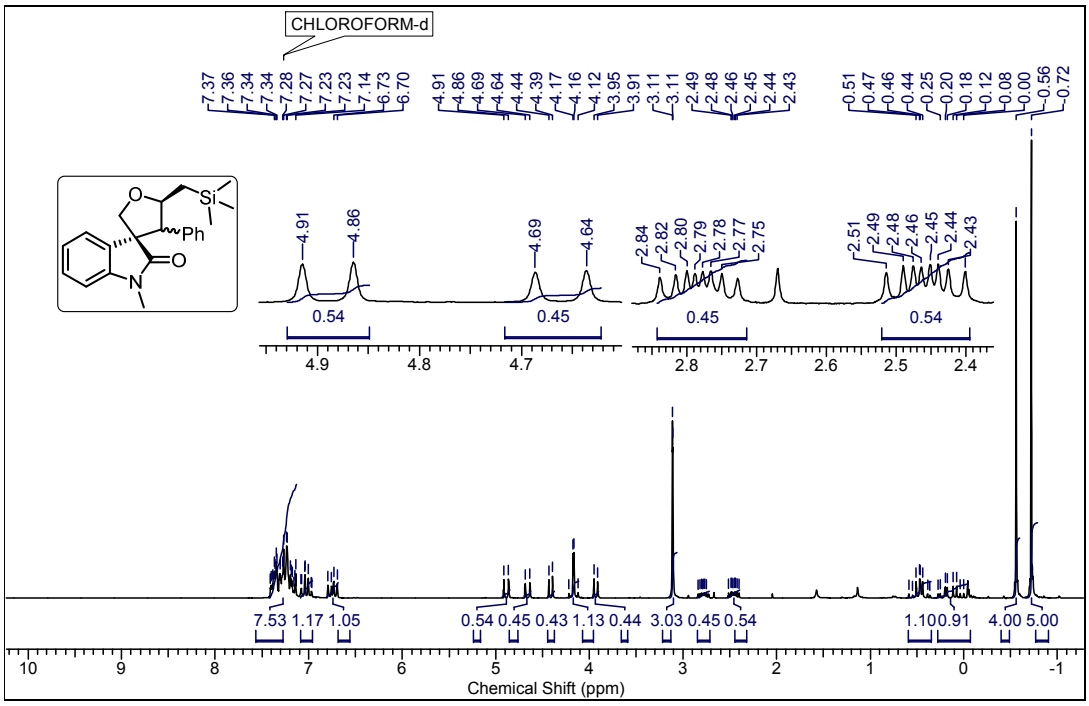
^{1}H NMR spectrum of compound **2l** ($CDCl_3$, 400 MHz):



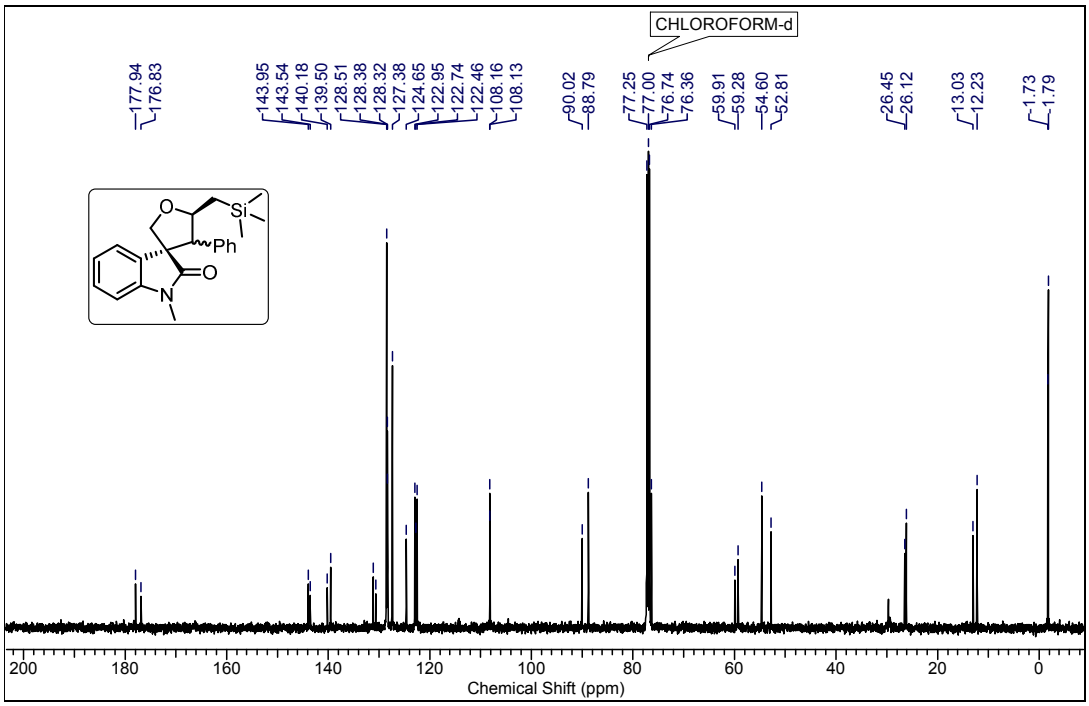
^{13}C NMR spectrum of compound **2l** ($CDCl_3$, 100 MHz):



^{1}H NMR spectrum of compound **2o** ($CDCl_3$, 200 MHz):

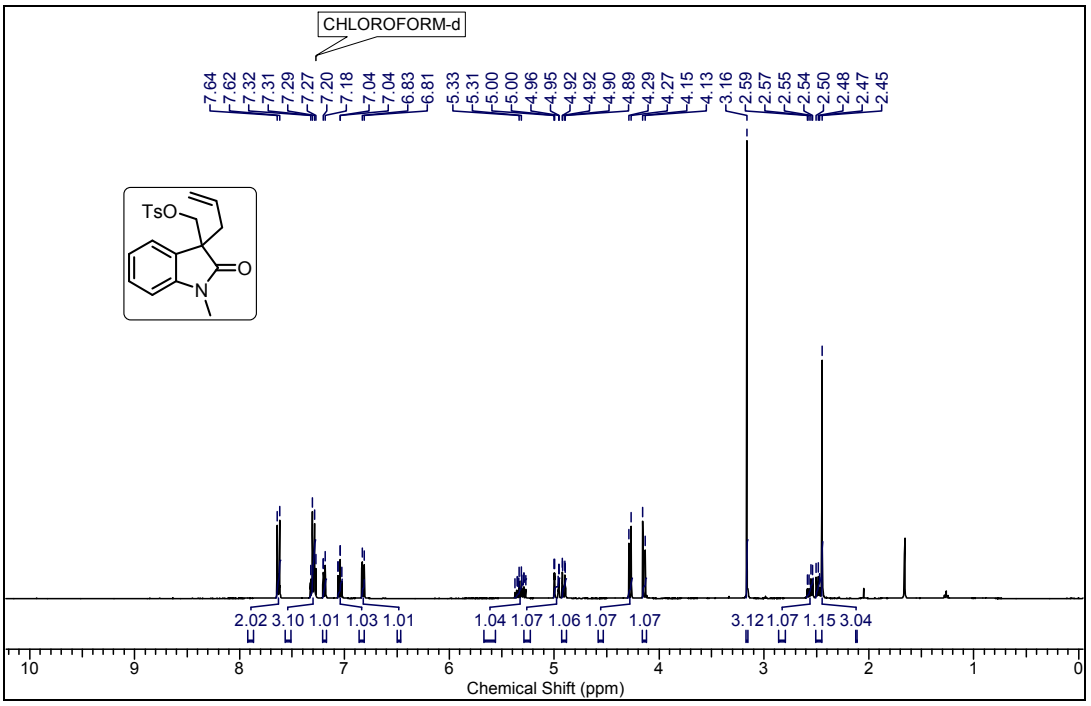


^{13}C NMR spectrum of compound **2o** ($CDCl_3$, 125 MHz):

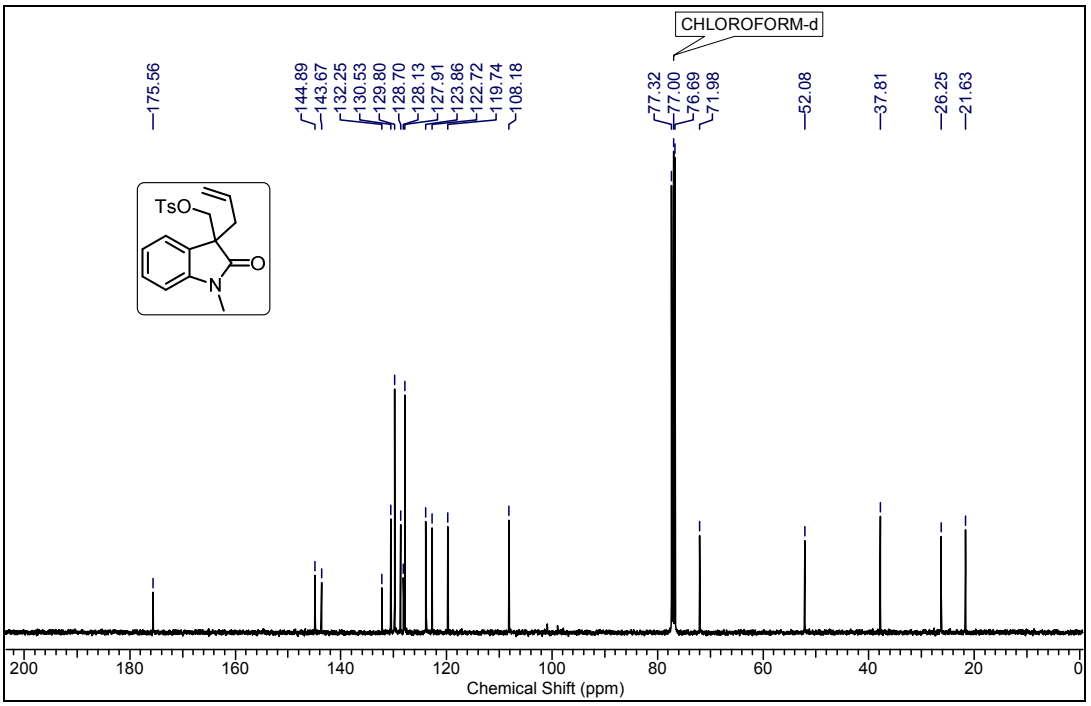


Spectra

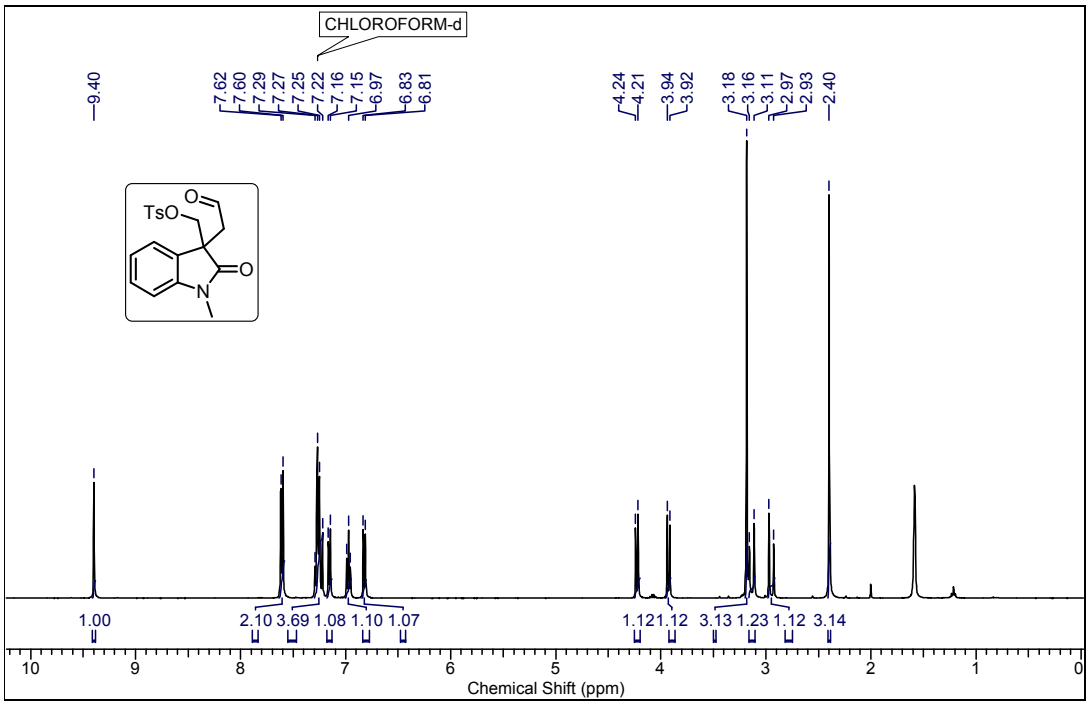
^{1}H NMR spectrum of compound **43** ($CDCl_3$, 400 MHz):



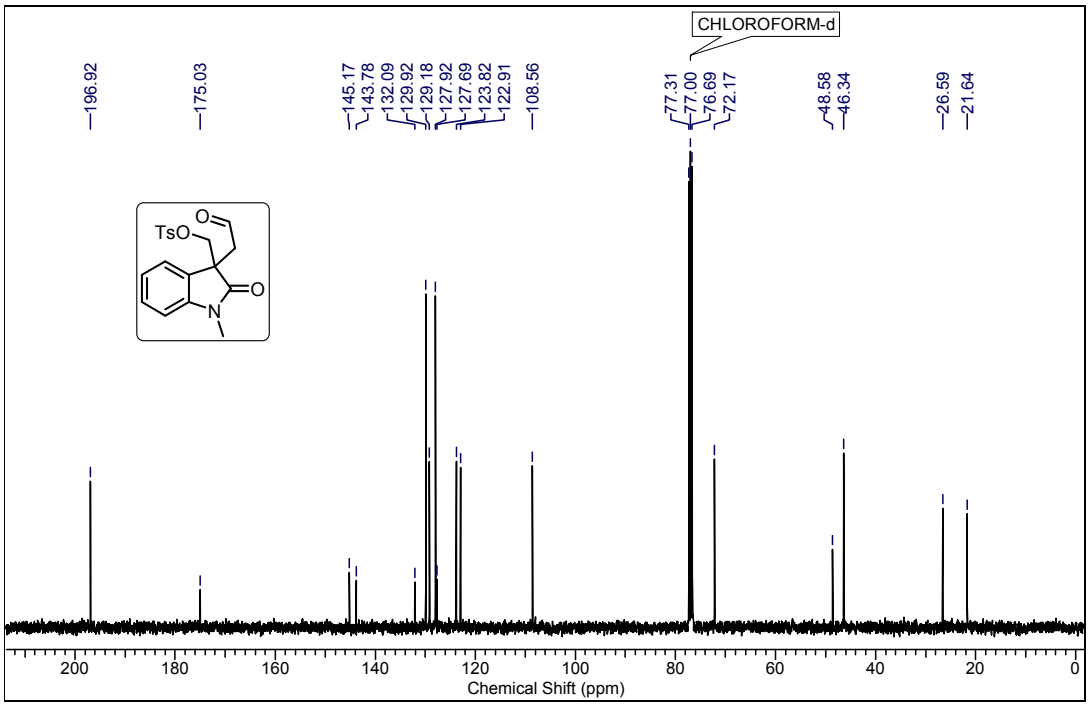
^{13}C NMR spectrum of compound **43** ($CDCl_3$, 100 MHz):



^{1}H NMR spectrum of compound **44** ($CDCl_3$, 400 MHz):

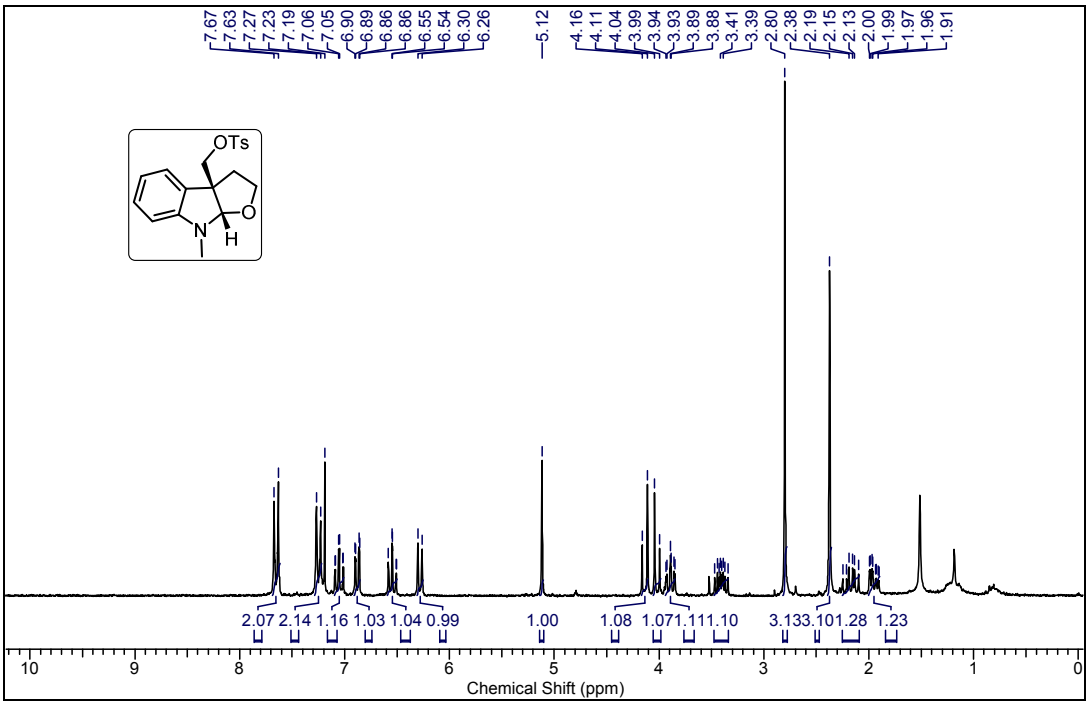


^{13}C NMR spectrum of compound **44** ($CDCl_3$, 100 MHz):

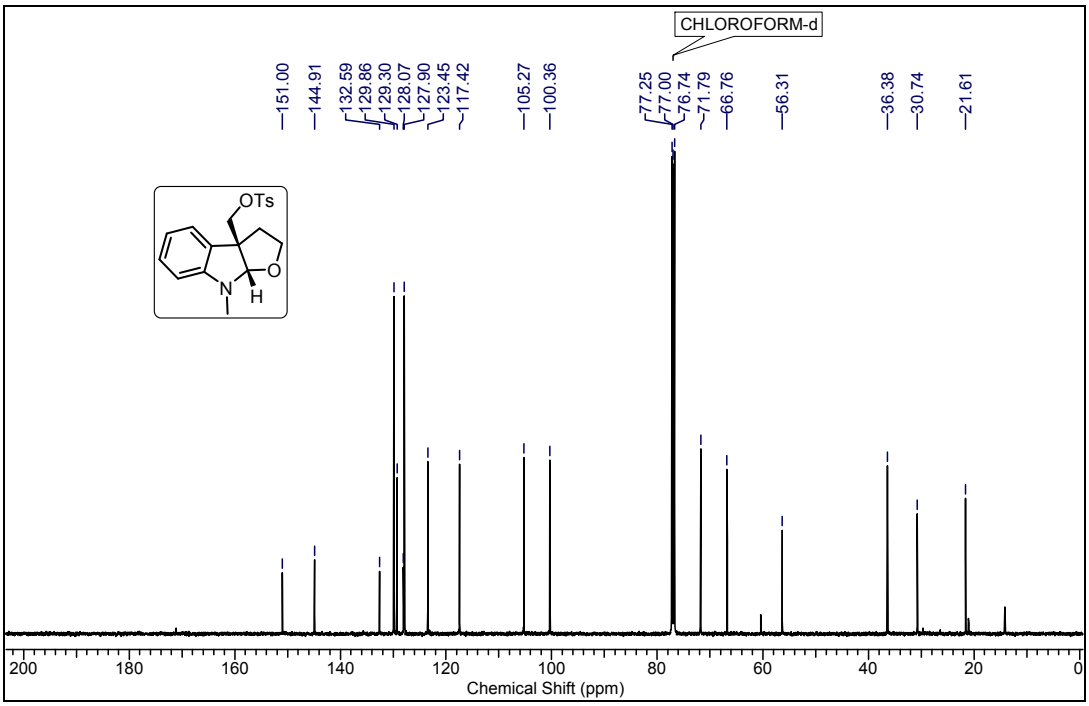


Spectra

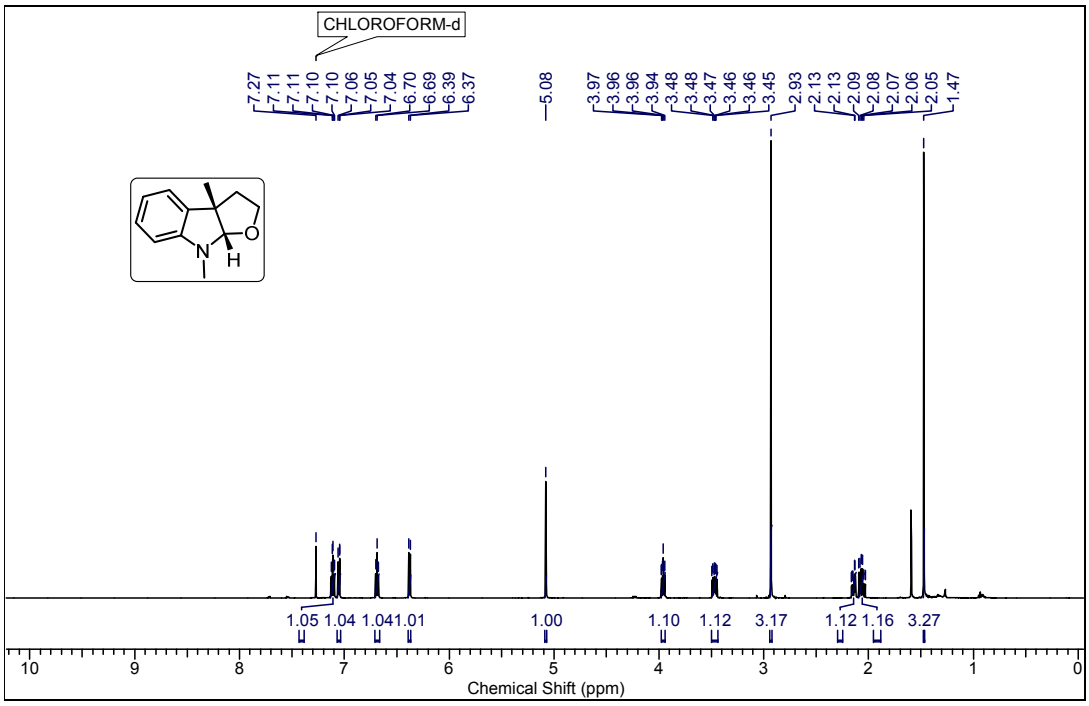
^{1}H NMR spectrum of compound **46** ($CDCl_3$, 200 MHz):



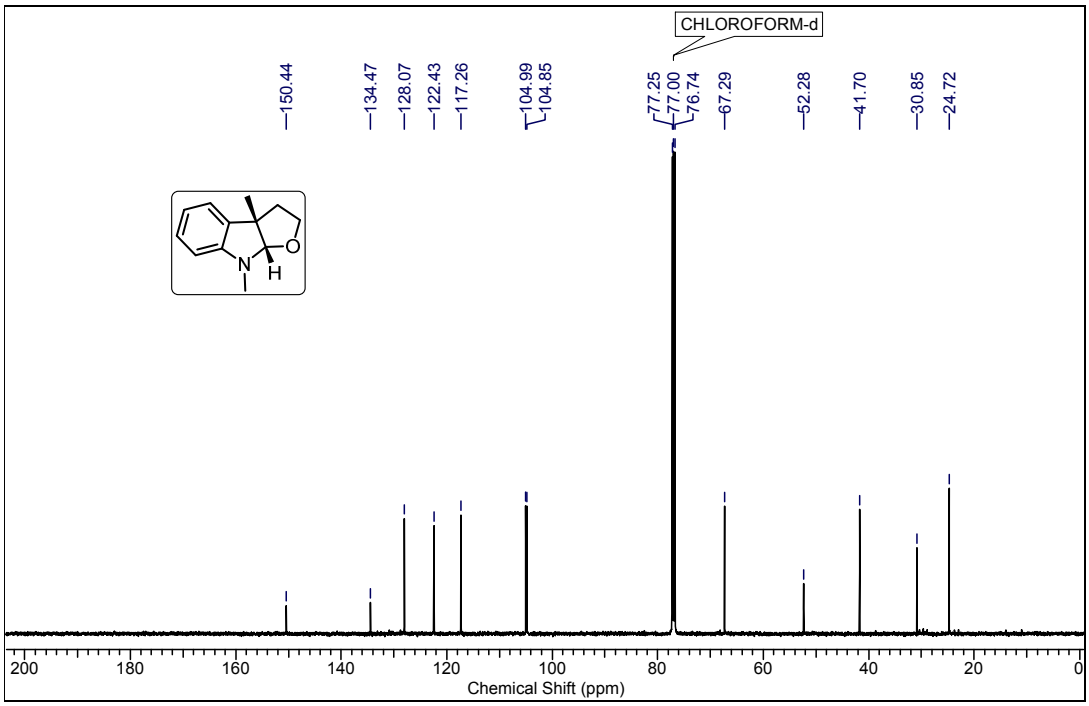
^{13}C NMR spectrum of compound **46** ($CDCl_3$, 125 MHz):



^{1}H NMR spectrum of compound **45** ($CDCl_3$, 500 MHz):

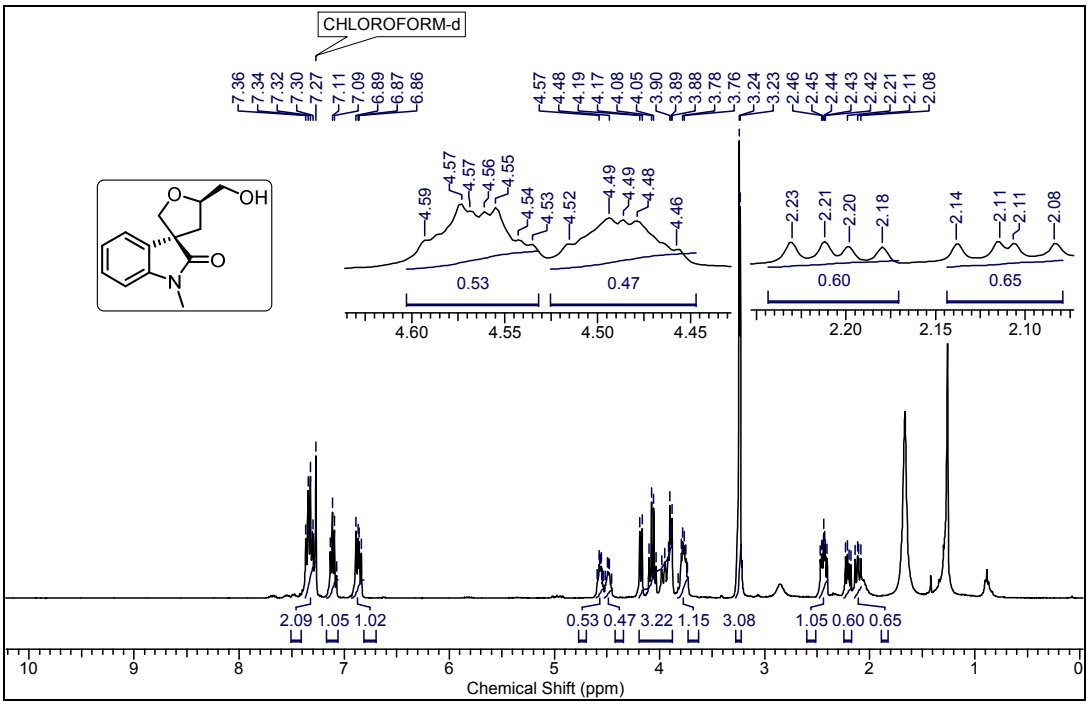


^{13}C NMR spectrum of compound **45** ($CDCl_3$, 125 MHz):



Spectra

^{1}H NMR spectrum of compound **47** ($CDCl_3$, 400 MHz):



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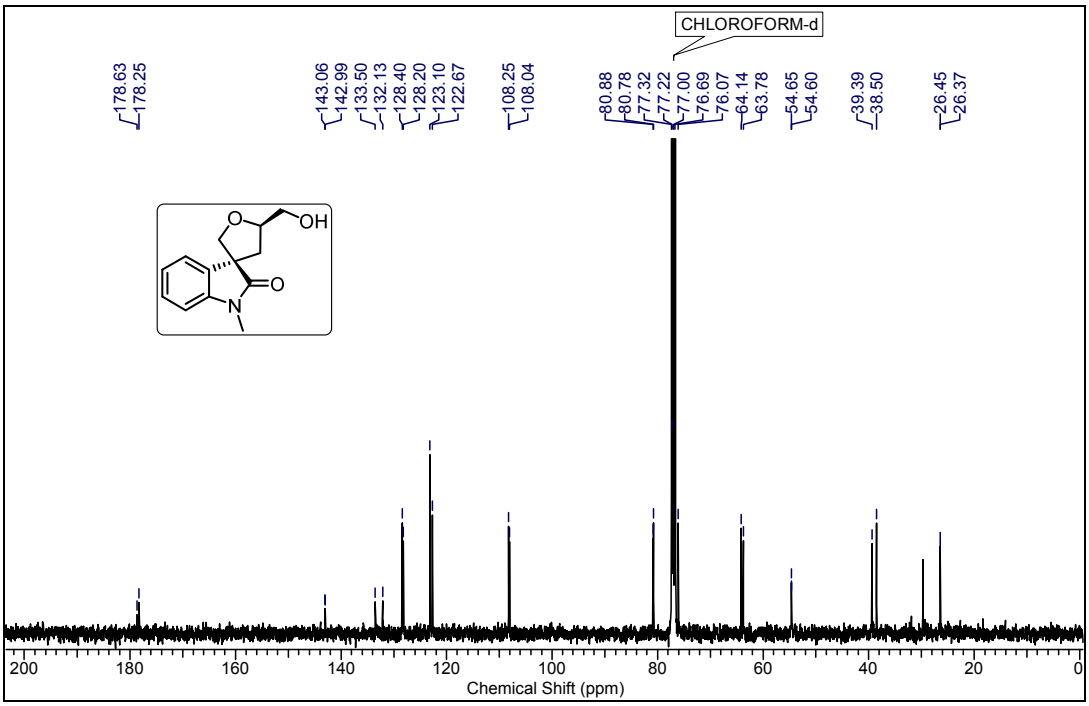


3.1.7. References

(1) a) Galliford, C. V.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 8748; b) Hong, L.; Wang, R. *Adv. Synth. Catal.* **2013**, *355*, 1023; c) Chen, J.-R.; Yu, X.-Y.; Xiao, W.-J. *Synthesis* **2015**, *47*, 604; d) Singh, G. S.; Desta, Z. Y. *Chem. Rev.* **2012**, *112*, 6104.

(2) Ozturk, T. In *The Alkaloids: Chemistry and Pharmacology*; Geoffrey, A. C., Ed.; Academic Press: **1997**; Vol. 49, p 79.

(3) a) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209; b) Dalpozzo, R.; Bartoli, G.; Bencivenni, G. *Chem. Soc. Rev.* **2012**, *41*, 7247; c) Pavlovska, T. L.; Redkin, R. G.; Lipson, V. V.; Atamanuk, D. V. *Mol. Diversity* **2016**, *20*, 299.

(4) Franz, A. K.; Dreyfuss, P. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 1020.

(5) Thomson, J. E.; Kyle, A. F.; Ling, K. B.; Smith, S. R.; Slawin, A. M.; Smith, A. D. *Tetrahedron* **2010**, *66*, 3801.

(6) a) Trost, B. M.; Brennan, M. K. *Org. Lett.* **2006**, *8*, 2027; b) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2007**, *129*, 14548; c) Trost, B. M.; Frederiksen, M. U. *Angew. Chem. Int. Ed.* **2005**, *44*, 308.

(7) Hills, I. D.; Fu, G. C. *Angew. Chem. Int. Ed.* **2003**, *42*, 3921.

(8) Wang, L.; Li, Z.; Lu, L.; Zhang, W. *Tetrahedron* **2012**, *68*, 1483.

(9) Cao, T.; Linton, E. C.; Deitch, J.; Berritt, S.; Kozlowski, M. C. *J. Org. Chem.* **2012**, *77*, 11034.

(10) De, S.; Das, M. K.; Bhunia, S.; Bisai, A. *Org. Lett.* **2015**, *17*, 5922.

(11) Shen, K.; Liu, X.; Wang, W.; Wang, G.; Cao, W.; Li, W.; Hu, X.; Lin, L.; Feng, X. *Chem. Sci.* **2010**, *1*, 590.

(12) a) Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477; b) Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488.

(13) Desrosiers, J.-N.; Hie, L.; Biswas, S.; Zatolochnaya, O. V.; Rodriguez, S.; Lee, H.; Grinberg, N.; Haddad, N.; Yee, N. K.; Garg, N. K.; Senanayake, C. H. *Angew. Chem. Int. Ed.* **2016**, *55*, 11921.

(14) Yamamoto, K.; Qureshi, Z.; Tsoung, J.; Pisella, G.; Lautens, M. *Org. Lett.* **2016**.

(15) a) James, M. J.; Cuthbertson, J. D.; O'Brien, P.; Taylor, R. J.; Unsworth, W. P. *Angew. Chem. Int. Ed.* **2015**, *54*, 7640; b) Liddon, J. T.; Clarke, A. K.; Taylor, R. J.; Unsworth, W. P. *Org. Lett.* **2016**, *18*, 6328.

(16) a) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, *17*, 1295; b) Hosomi, A. *Acc. Chem. Res.* **1988**, *21*, 200.

(17) a) Brengel, G. P.; Meyers, A. *J. Org. Chem.* **1996**, *61*, 3230; b) Danheiser, R. L.; Dixon, B. R.; Gleason, R. W. *J. Org. Chem.* **1992**, *57*, 6094; c) Sugita, Y.; Kimura, Y.; Yokoe, I. *Tetrahedron Lett.* **1999**, *40*, 5877.

(18) a) Langkopf, E.; Schinzer, D. *Chem. Rev.* **1995**, *95*, 1375; b) Chabaud, L.; James, P.; Landais, Y. *Eur. J. Org. Chem.* **2004**, *2004*, 3173.

(19) Wilkie, R. P.; Neal, A. R.; Johnston, C. A.; Voute, N.; Lancefield, C. S.; Stell, M. D.; Medda, F.; Makiyi, E. F.; Turner, E. M.; Stephen Ojo, O.; Slawin, A. M. Z.; Lebl, T.; Mullen, P.; Harrison, D. J.; Ireland, C. M.; Westwood, N. J. *Chem. Commun.* **2016**, *52*, 10747.

(20) Cernijenko, A.; Risgaard, R.; Baran, P. S. *J. Am. Chem. Soc.* **2016**, *138*, 9425.

(21) Trost, B. M.; Bringley, D. A.; Zhang, T.; Cramer, N. *J. Am. Chem. Soc.* **2013**, *135*, 16720.

(22) Izgu, E. C.; Hoye, T. R. *Chem. Sci.* **2013**, *4*, 2262.

(23) Tinsley, J. M.; Mertz, E.; Chong, P. Y.; Rarig, R.-A. F.; Roush, W. R. *Org. Lett.* **2005**, *7*, 4245.

(24) a) Hajra, S.; Maity, S.; Maity, R. *Org. Lett.* **2015**, *17*, 3430; b) Hajra, S.; Maity, S.; Roy, S. *Adv. Synth. Catal.* **2016**, *358*, 2300; c) Luo, M.; Yuan, R.; Liu, X.; Yu, L.; Wei, W. *Chem. Eur. J.* **2016**, *22*, 9797.

(25) Knölker, H. J.; Foitzik, N.; Graf, R.; Goesmann, H. *Angew. Chem. Int. Ed.* **1993**, *32*, 1081.

(26) a) Lambert, J. B.; Zhao, Y. *J. Am. Chem. Soc.* **1996**, *118*, 7867; b) Creary, X.; Kochly, E. D. *J. Org. Chem.* **2009**, *74*, 2134; c) Lambert, J. B.; Zhao, Y.; Emblidge, R. W.; Salvador, L. A.; Liu, X.; So, J.-H.; Chelius, E. C. *Acc. Chem. Res.* **1999**, *32*, 183.

(27) Shupe, B. H.; Allen, E. E.; MacDonald, J. P.; Wilson, S. O.; Franz, A. K. *Org. Lett.* **2013**, *15*, 3218.

(28) a) Hanhan, N. V.; Ball-Jones, N. R.; Tran, N. T.; Franz, A. K. *Angew. Chem. Int. Ed.* **2012**, *51*, 989; b) Akiyama, T.; Kirino, M. *Chem. Lett.* **1995**, 723.

(29) Kulkarni, M. G.; Dhondge, A. P.; Borhade, A. S.; Gaikwad, D. D.; Chavhan, S. W.; Shaikh, Y. B.; Nigdale, V. B.; Desai, M. P.; Birhade, D. R.; Shinde, M. P. *Eur. J. Org. Chem.* **2009**, 3875.

(30) Fleming, I.; Sanderson, P. E. *Tetrahedron Lett.* **1987**, *28*, 4229.

(31) Nair, V.; Treesa, P.; Rath, N. P.; Kunwar, A.; KiranKumar, K.; RaviSankar, A.; Vairamani, M.; Prabhakar, S. *Tetrahedron* **2002**, *58*, 7221.

(32) Chouhan, M.; Senwar, K. R.; Sharma, R.; Grover, V.; Nair, V. A. *Green Chemistry* **2011**, *13*, 2553.

(33) Bruker (2016). *APEX3*, *SAINT* and *SADABS*. Bruker AXS Inc., Madison, Wisconsin, USA.

(34) Sheldrick, G. M. *Acta Crystallogr*. **2008**, *A64*, 112.

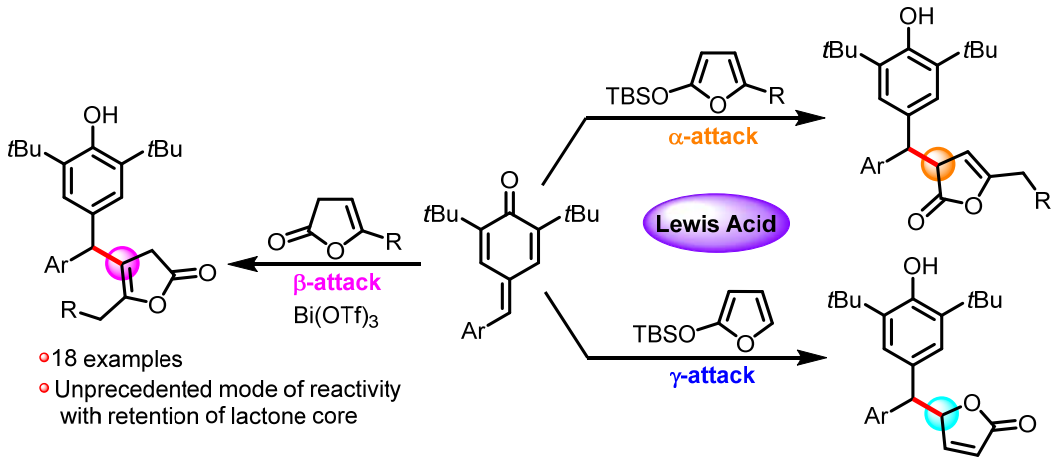
(35) Farrugia, L. J. *J. Appl. Cryst.* **1997**, *30*, 565.

"The meeting of two personalities is like the contact of two chemical substances: if there is any reaction, both are transformed"

— C.G. Jung

Section B

Unraveling the Nucleophilicity of Butenolides for 1,6-Conjugate Addition to *p*-QMs - A Direct Access to Diversely Substituted Butenolide-derived Diarylmethanes



3.2.1. Introduction

3.2.1.1. Butenolides

Butenolides are structurally important scaffolds in various biologically active molecules, natural products, and synthetic intermediates.[1] Among various unsaturated γ-lactone derivatives, butenolide-derived diarylmethane unit appears as privileged structural motif in various complex lignans and secolignans.[2] The diarylmethane derived regioselectively functionalized sites of butenolides constitute an important class of structural features present in a diverse range of natural and unnatural products, exhibiting a wide spectrum of biological activities (Figure 3.2.1).

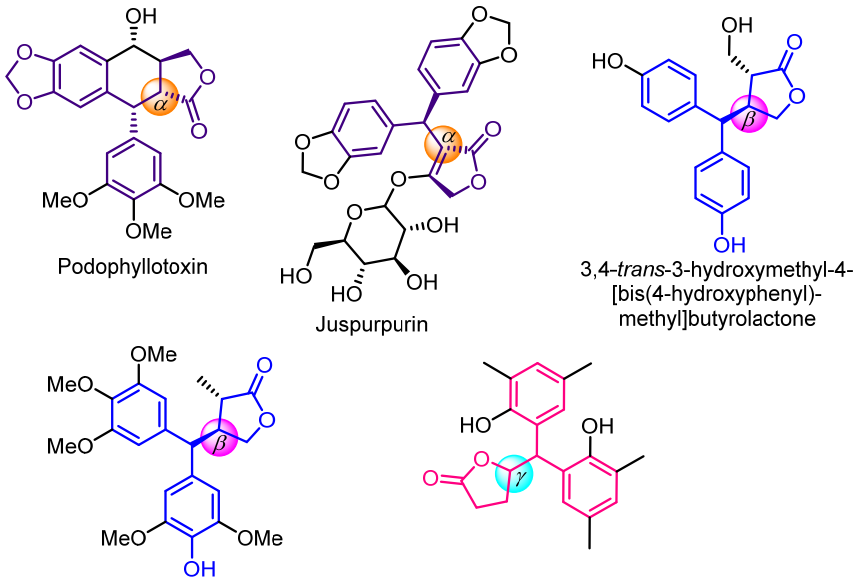


Figure 3.2.1. Natural and unnatural products containing γ-butenolides/γ-butyrolactones derived diarylmethane scaffolds

Owing to the prevalence and significance of butenolides and its congeners, the development of streamlined strategies to exploit the nucleophilicity of all the positions (α, β, γ) of butenolide regioselectively remains an active area in the realm of exploratory synthetic research.[3]

3.2.1.2. Literature Review

I. Lewis Acid Catalyzed Vinylogous Mukaiyama–Michael reactions (VMMRs)

Enolate-based reactions have become a staple method for C–C bond formation to furnish highly functionalized natural products of great value.[4] Mukaiyama and co-workers in 1974 reported a Lewis acid-catalysed Michael type reaction between silyl enol ethers and α,β–conjugated carbonyl compounds.[5] Over the decades of development by several groups, the reactivity of silyl enol ether moiety was further extended by a conjugated vinyl group, which tuned the polarity and reactivity of the new vinylogous dienol silyl ether towards broad range of electrophiles from the γ- rather than at the α-position (Figure 3.2.2a).[6] Thus, the nucleophilicity of vinylogous silyl ketene acetals at the γ-position, in contrast with the corresponding metal dienolates, can be rationalized on the basis of different HOMO coefficients and/or electrophilic susceptibility (Figure 3.2.2b).[7] As a consequence, various strategies for the exploitation of vinylogous reactivity of different classes of vinylogous nucleophiles (Figure 3.2.2c) have been developed by different research groups.

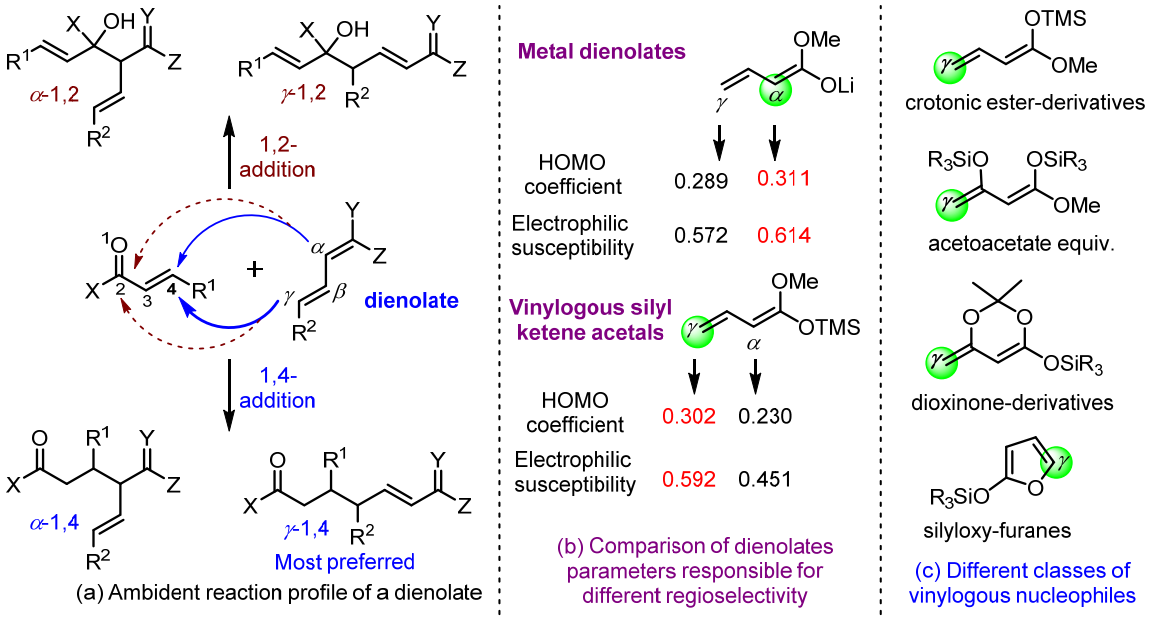


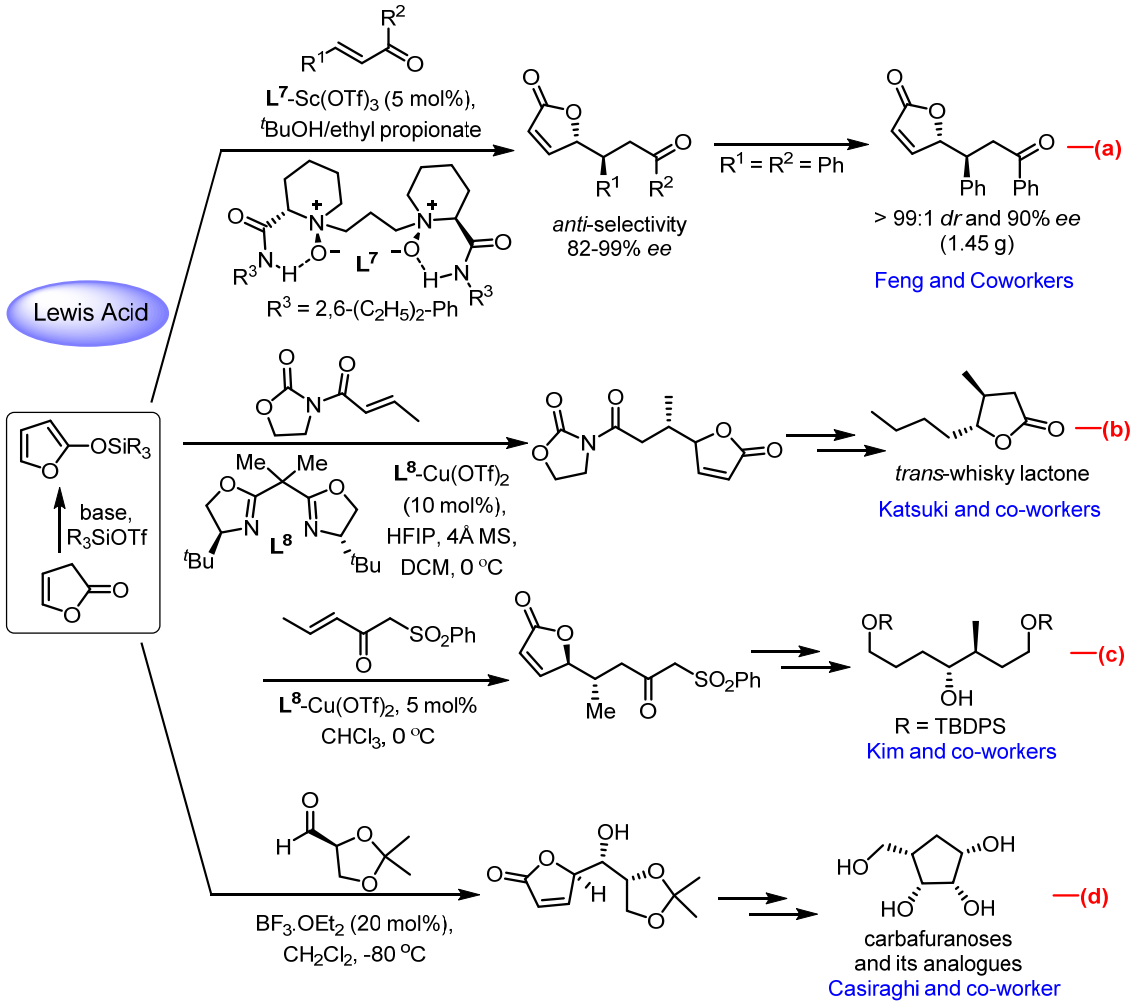
Figure 3.2.2. Vinylogous reactivity parameters of dienolates

In this section, we will be focusing only on Lewis acid catalyzed vinylogous Mukaiyama–Michael reactions of silyloxyfurans nucleophile and *in situ* generated vinylogous nucleophile of deconjugated butenolides from their γ-positions and

applications thereof in natural product synthesis (Scheme 3.2.1 and 3.2.2). A few reports on Mukaiyama–Michael addition of silyloxyfurans and vinylogous reactivity of deconjugated butenolides form α-position has also been summarized (Scheme 3.2.3).

II. Lewis Acid Catalyzed Vinylogous Mukaiyama-Michael Addition of Silyloxyfurans from γ-position

A variety of Lewis acid catalyzed diastereoselective methods have been developed for the stereoselective and regioselective formation of γ-butenolides. These examples illustrate the significance of vinylogous Mukaiyama-Michael reactions in current synthetic chemistry.

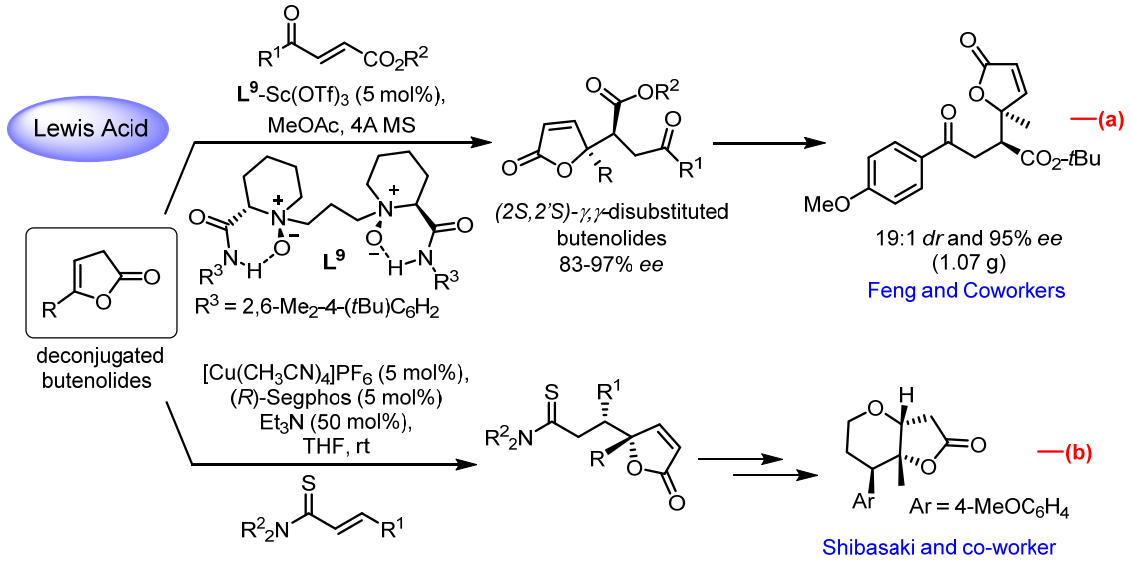


Scheme 3.2.1. γ-Attack of silyloxyfurans

Feng and co-workers [8] showed the application of weak chelating chalcones in the asymmetric vinylogous Mukaiyama−Michael reaction of 2-(trimethylsilyloxy)furan using chiral N,N′-dioxide $\mathbf{L}^7$−scandium(III) catalytic system (Scheme 3.2.1a). In 1998,

Katsuki and co-workers[9] reported the chiral Lewis acid mediated Mukaiyama−Michael reaction of 2-trimethylsilyloxyfurans and oxazolidinone enolates in presence of **L**[8]/Cu(OTf)$_2$, and further utilized in a short synthesis of (+)-whisky lactone (Scheme 3.2.1b). Later, Kim and co-workers[10] in 2003 used the same catalytic system, which was developed by Katsuki, to disclose the reaction of α'-phenylsulfonyl enones with 2-(trimethylsilyloxy)furan with exclusive *anti* selective β-methyl substituted enone, which was further converted into a number of valuable building blocks (Scheme 3.2.1c). Analogously, $BF_3.OEt_2$ catalyzed diastereoselective vinylogous reaction of 2-(trimethylsilyloxy)furan and aldehydes developed by Casiraghi and co-workers[11] has served as an intermediate in the syntheses of a variety of furanose derivatives (Scheme 3.2.1d).

III. Lewis Acid Catalyzed Direct Vinylogous Michael Addition of Deconjugated Butenolides from γ-position

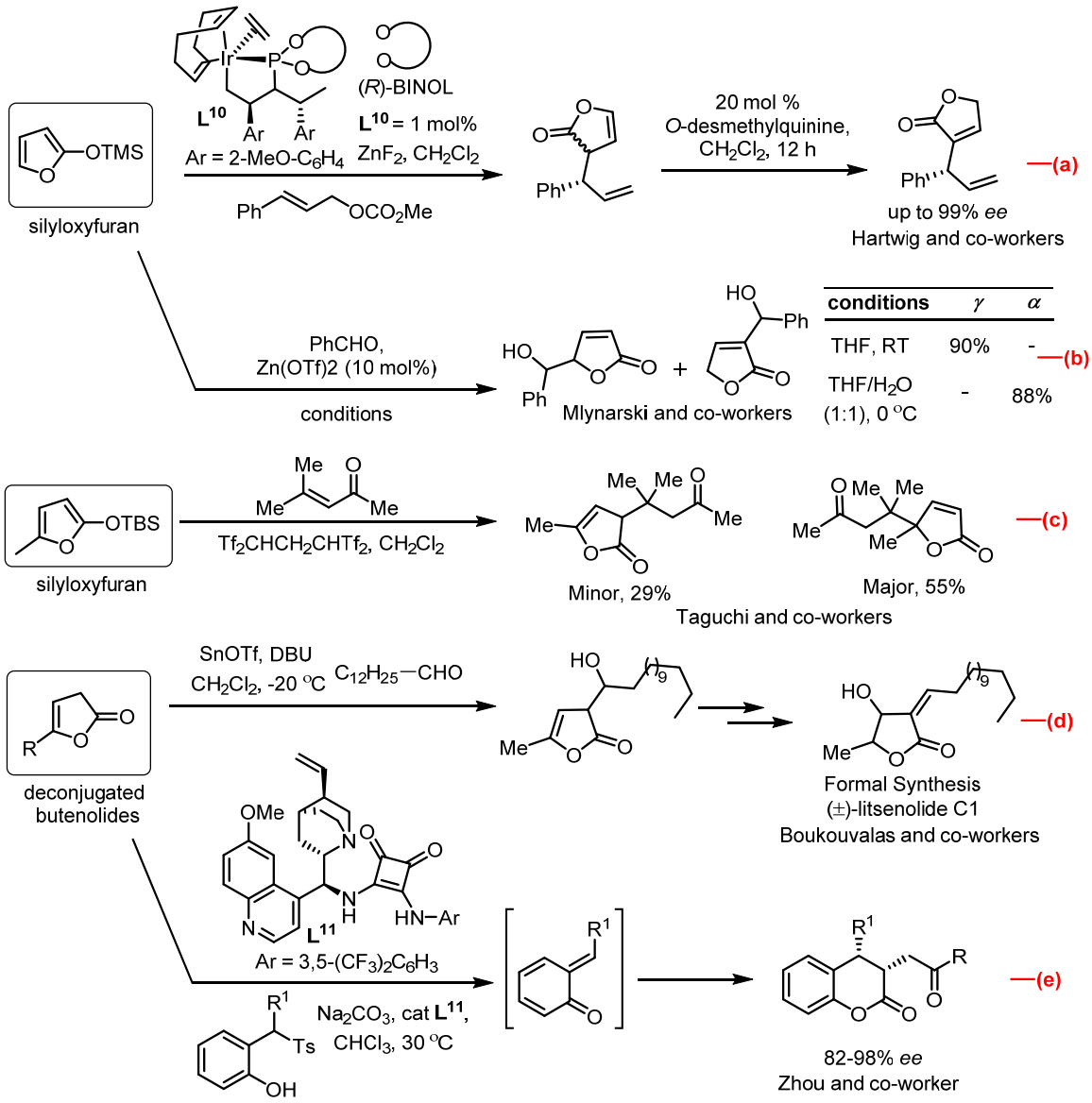


Scheme 3.2.2. γ-Attack of deconjugated butenolide

Feng and co-workers[12] in 2013 developed an efficient *N*,*N*′-dioxide **L**[9]–scandium(III) complex catalytic system for asymmetric vinylogous Michael reaction of α-angelica lactone and its derivatives to α,β-unsaturated γ-keto esters, to furnish corresponding γ,γ-disubstituted butenolides with high *dr* (up to >19:1) and *ee* (up to 97%) (Scheme 3.2.2a). Later in 2014, Shibasaki and co-workers[13] reported soft Lewis acid/Brønsted base cooperative catalysts enabled direct asymmetric vinylogous conjugate addition of

deconjugated butenolides to α,β-unsaturated thioamides and further demonstrated the synthetic utility of product by transforming it to bicyclic compound (Scheme 3.2.2b).

IV. Lewis Acid Catalyzed Vinylogous Mukaiyama-Michael of Silyloxyfurans and Direct Vinylogus Michael Addition of Deconjugated Butenolides form α-position

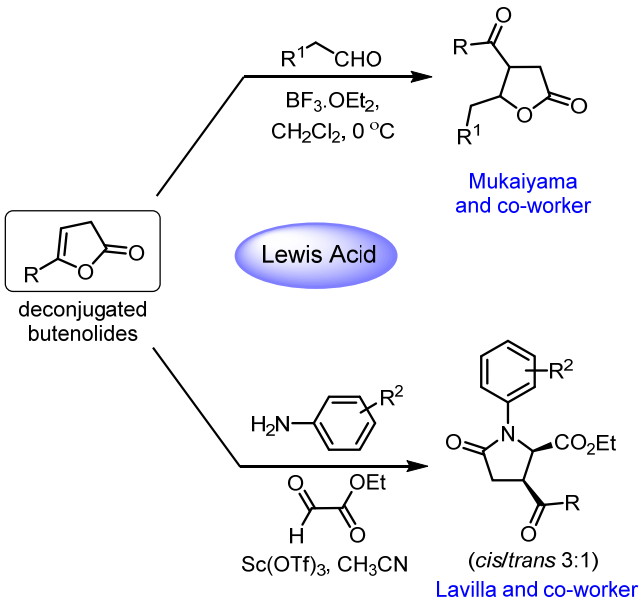


Scheme 3.2.3. α-Attackof silyoxyfurans/deconjugated butenolides

Among various reports on α-addition,[14] only a few were based on Lewis acid catalyzed α-addition with retention of a double bond without isomerization towards more stable α,β-unsaturated butenolide. Towards this goal, Hartwig and co-workers exquisitely demonstrated **L**^{10}-Ir-catalyzed regio and enantioselective α-allylation of

trimethylsilyloxyfuran (Scheme 3.2.3a).[15] Mlynarski and co-workers[16] in 2012 demonstrated a regioselective switch in the addition of 2-(trimethylsiloxy)-furan on aldehyde in presence of $Zn(OTf)_2$ to afford C-3 subsituted α-butenolides under aqueous condition (Scheme 3.2.3b). In fact, in a few synthetic methodologies, α-addition with silyloxyfurans was reported, as a minor product but not explored to a large extent as shown by Taguchi and co-workers (Scheme 3.2.3c).[17] Boukouvalas *et al.*[18] have successfully achieved the α-addition of 2-furanolates regioselectively using Sn-enolate-based chelation controlled strategy and the methodology was exquisitely utilized for the formal synthesis of (±)-litsenolide C1 and (±)-dihydromahubanolide (Scheme 3.2.3d). Recently, Zhou and co-workers reported a quinine-squaramide **L**[11] catalyzed enantioselective α-addition/transesterification of deconjugated butenolides with *o*-quinone methides (Scheme 3.2.3e).[19]

In contrast to the well explored γ-attack of deconjugated butenolides or silyloxyfurans, only two reports by Mukaiyama[20] and Lavilla[21] were found for nucleophilic attack of α-angelica lactone from β-position. However, the initial attack from β-position in both the reports led to skeletal rearrangements of butenolide framework in a reaction cascade (Scheme 3.2.4).



Scheme 3.2.4. Skeletal rearrangement of β,γ-deconjugated butenolides

3.2.1.3. *para*-Quinone Methides (*p*-QMs)

para-Quinone methides and their derivatives are common constituents of biological systems. Quinone methides occur in nature both as fungal metabolites, and as wood pigments. A plethora of natural products, with prominent biological activities, such as kendomycin **48** (anti-tumor and anti-bacterial),[22] taxodone **49** (anti-cancer)[23] and celastrol **50** (anti-oxidant and anti-inflammatory)[24] contain *p*-quinone methide system (Figure 3.2.3). Quinone methides (*o*-QM, *p*-QM and *m*-QM) are highly electrophilic and transient intermediates thought to be formed either by tautomeric rearrangement of quinones or by oxidation of phenols in a large number of biological processes[25] such as DNA-alkylation[26] and enzyme inhibition.[27] Regarding enzyme inhibition, they have been shown to particularly inhibit *β*- lactamase, serine hydrolase,[28] phosphatase and ribonuclease.[29]

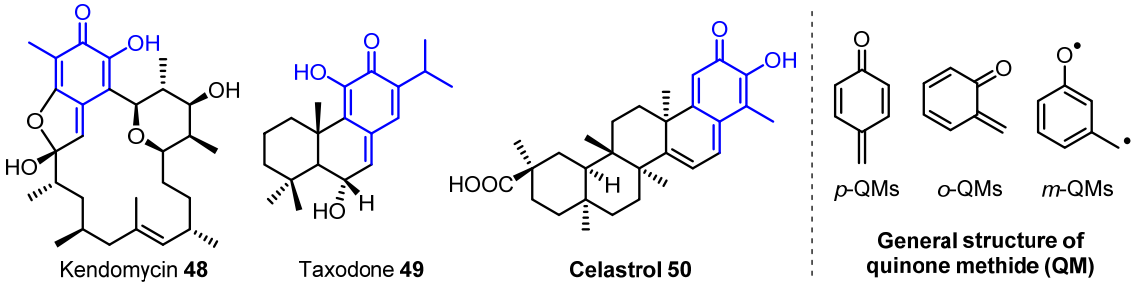
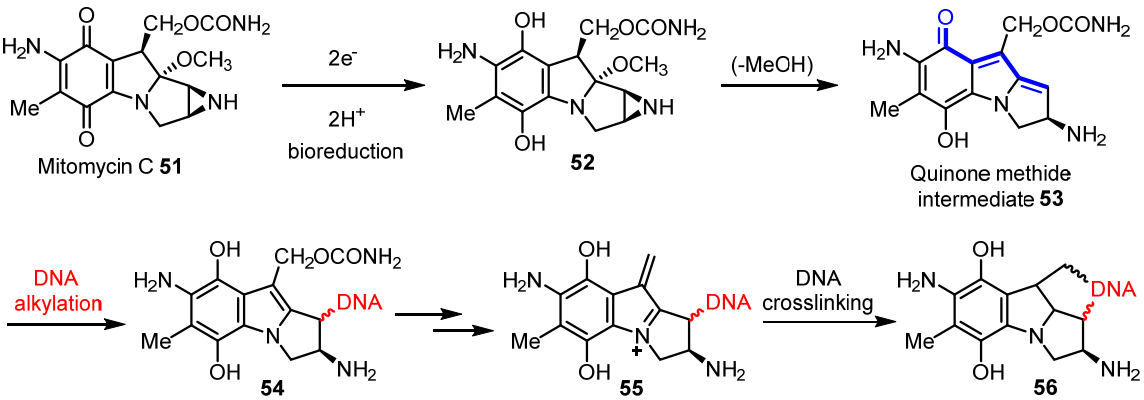


Figure 3.2.3. Few representative *p*-QMs core containing natural products

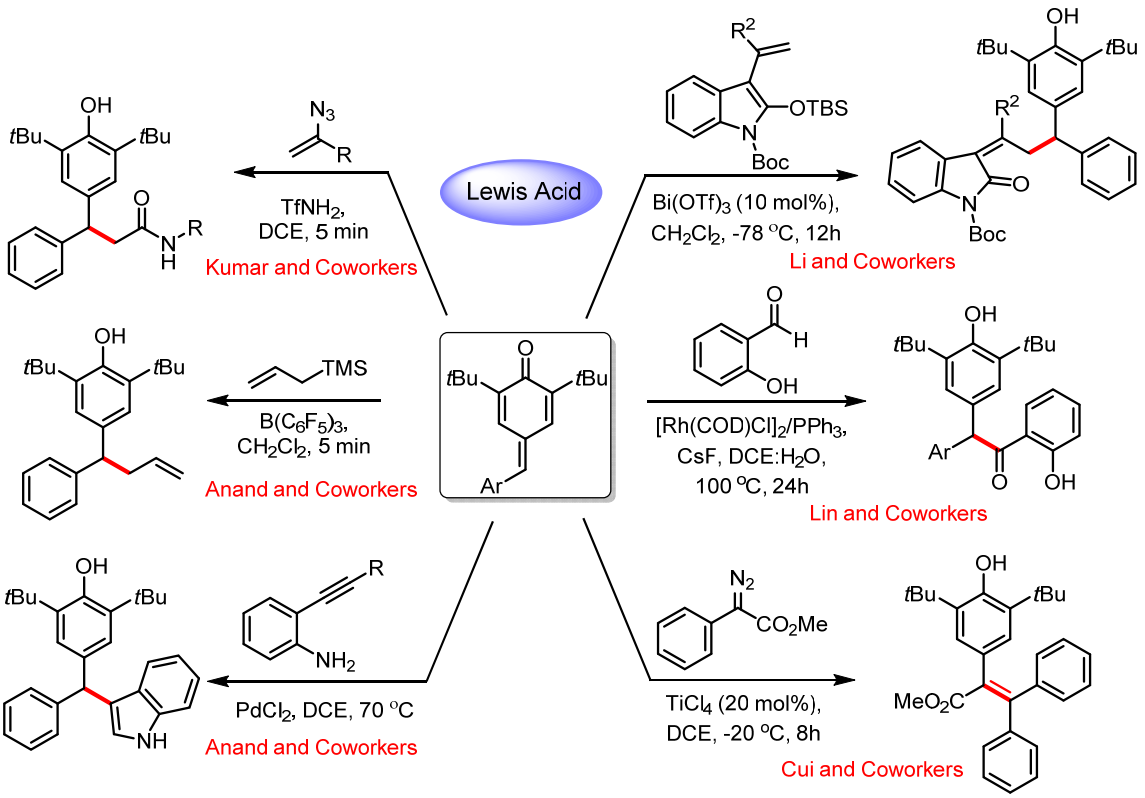
The most famous example is that of mitomycin C **51**, a clinically used anticancer drug. Its mode of action involves bioreductive step followed by loss of methanol and opening of the aziridine ring to generate quinone methide intermediate **53**, which is the active species responsible for alkylation of DNA **54** causing cross-linkage **56** (Scheme 3.2.5).[30]



Scheme 3.2.5. Mechanism of mitomycin C with DNA

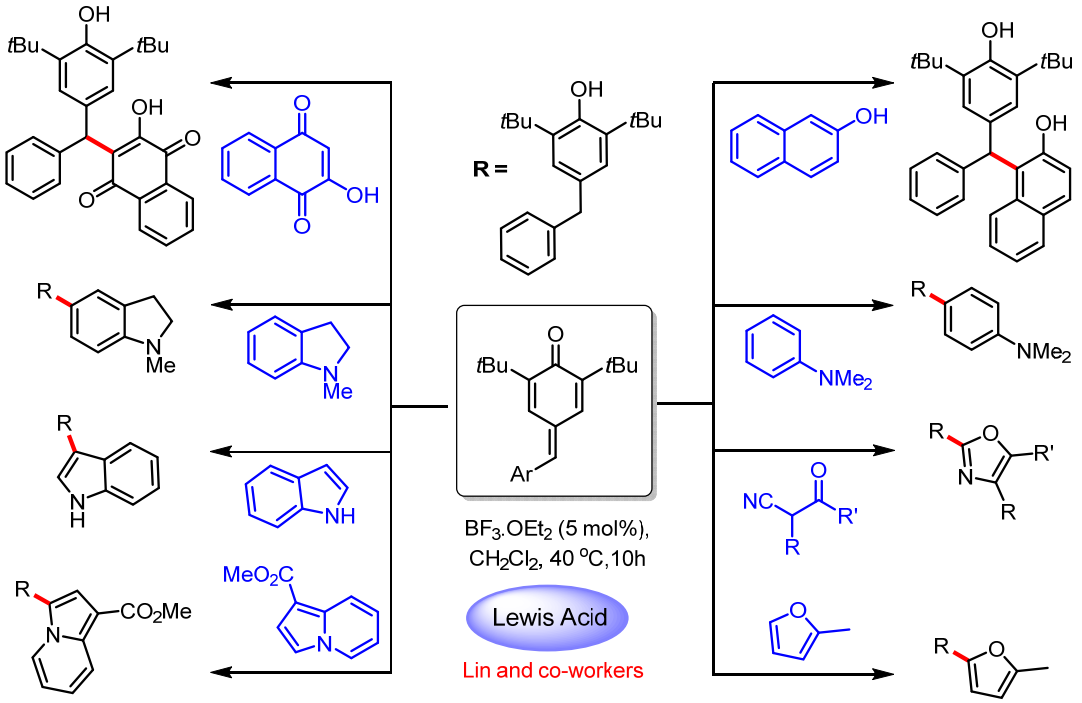
3.2.1.4. Lewis Acid Catalyzed Reactivity of *p*-QMs: A literature Review

These reactive *p*-QMs intermediates have gained credence partly because many of them exist in stable forms. The reactivity and thus the stability of quinone methides can be influenced by the presence of electron withdrawing or donating sunstituents on the ring (relative to the carbonyl oxygen).[31] In recent years, *para*-quinone methides have been explored extensively by various groups of Anand,[32] Tortosa,[33] Lin,[34] Cui[35] and Li [36] including our group[37] due to its unique ability as powerful Michael acceptors with a variety of nucleophiles (Scheme 3.2.6).[38] Quinone methides are more reactive than vinyl ketones, owing to the additional driving force of aromatisation which characterises all their reactions.[39]



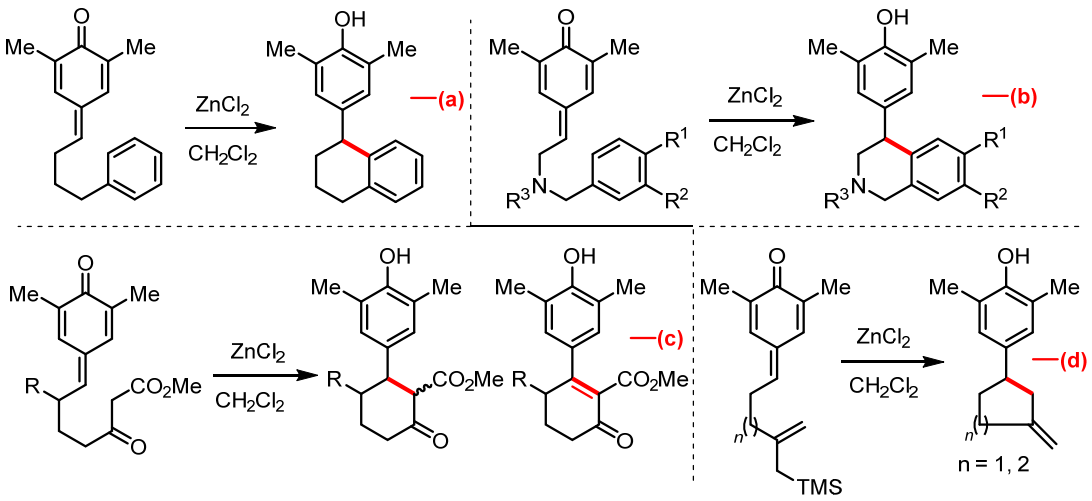
Scheme 3.2.6. Intermolecular 1,6-conjugate addition on *p*-QMs

In 2016, Lin and co-workers [40] demonstrated $BF_3{\cdot}OEt_2$ catalyzed metal-free intermolecular 1,6- addition arylation of *p*-QMs with electron-rich aromatic compounds. Thus, allowing direct synthesis of unsymmetrical triarylmethanes in good to excellent yields under mild conditions, good functional-group tolerance and scalability up to gram scale (Scheme 3.2.7).



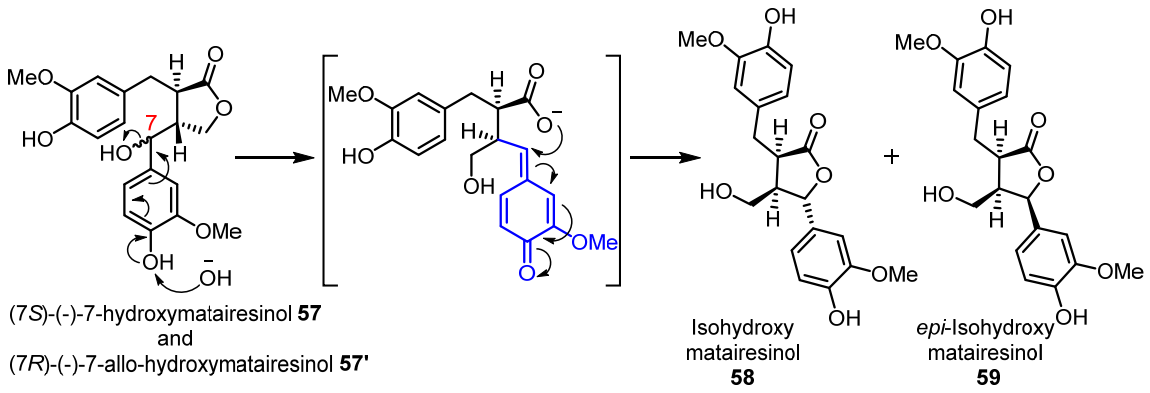
Scheme 3.2.7. $BF_3 \cdot OEt_2$ catalyzed the inter molecular 1,6-nucleophilic addition arylation of *p*-QMs with electron rich arenes

Angle [41] and China Raju [42] exquisitely demonstrated the viability of *para*-quinone methides as cyclization initiators in intramolecular electrophilic aromatic substitution reaction by an atom appended to the *p*-QMs (pyrrole, furan and benzene as a nucleophile) as depicted in Scheme 3.2.8a-b. Also other cyclization terminators such as allyl silanes and *β*-keto esters have also been explored (Scheme 3.2.8c-d).



Scheme 3.2.8. Intramolecular 1,6-conjugate addition on *p*-QMs

In 2004 Eklund and co-workers[43] have elegantly shown the oxidative metabolism of plant lignans hydroxymatairesinol (**57** and **57'**) to its corresponding butyrolactone lignin, isohydroxymatairesinol **58** and *epi*-isohydroxymatairesinol **59** *via* a *p*-QMs intermediate (Scheme 3.2.9).



Scheme 3.2.9. Oxidative metabolism of lignans *via para*-Quinone Methide Intermediate

Recently our group has also reported Tf_2NH catalyzed 1,6-conjugate addition reaction of *p*-QMs with vinyl azide.[37] In continuation we have further explored a highly efficient and regioselective 1,6-conjugate addition of deconjugated butenolides and silyloxyfurans to *p*-QMs catalyzed by Lewis acid leading to diversely substituted butenolide derived diarylmethane scaffold.

3.2.2. Present Work

3.2.2.1. Objective

A deconjugated butenolide, α-angelica lactone has emerged as a valuable building block for the construction of butenolide derivatives.[44] It has been synthetically exploited through *in situ* conversion to dienolate intermediates and silyloxyfurans for the electrophilic attack at the γ-position. A few reports for α-attack of silyloxyfurans are also available in the literature. However, the nucleophilicity of β-position has not been explored rigorously (Figure 3.2.4). With our ongoing interest and endeavor in butenolide chemistry,[45] we envisioned a regioselective β-attack of deconjugated butenolides in enol ester type reactivity (unexplored). To the best of our knowledge, there is no report of Lewis acid catalyzed nucleophilic addition from α, β, γ-positions of butenolides on a *p*-QMs as a single substrate.

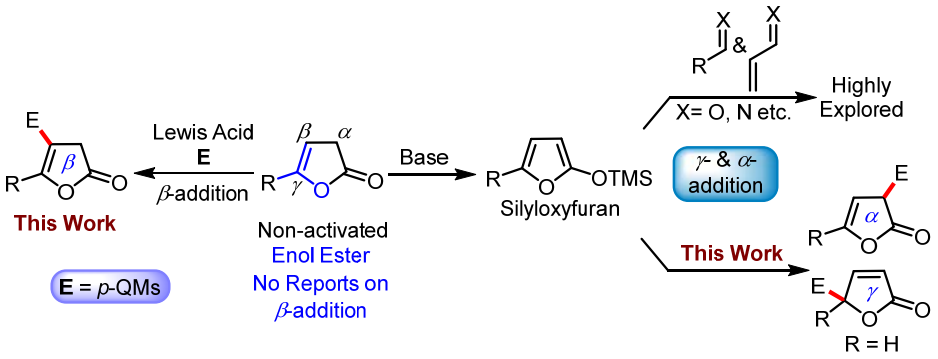
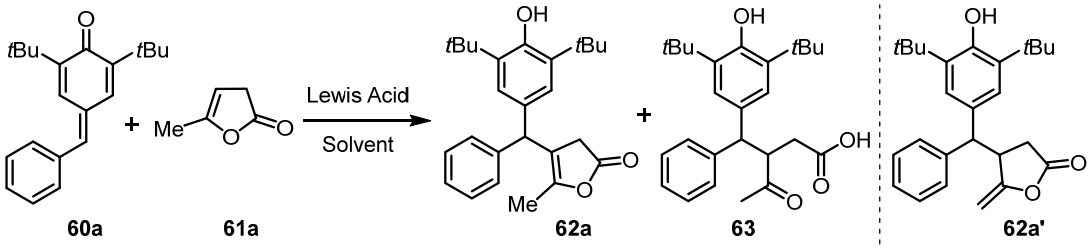


Figure 3.2.4. Regioselectivity of deconjugated butenolides and silyloxyfurans towards 1,6-conjugate addition reaction

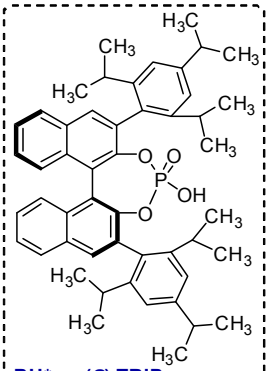
3.2.2.2. Results and Discussion

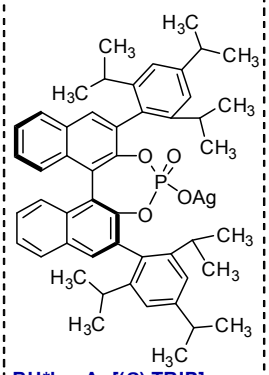
To investigate our hypothesis, we started our exploration of *β*-addition reaction using *α*-angelica lactone **61a**, and *p*-QMs **60a** as a model substrate. **Table 3.2.1** summarizes the effect of several parameters on this reaction. Initially when 20 mol% of $BF_3.OEt_2$ was used to catalyze the reaction between **60a** and **61a** in CH_2Cl_2 at 0 ^oC; it resulted in the formation of undesired hydrolyzed product **63** exclusively in 5 min only *via* *β*-attack (Table 3.2.1, entry 1). The formation of product **63** gave us the idea about reaction proceeding *via* enol ester type reactivity. The intermediate oxonium ion thus formed was quenched due to the presence of traces of moisture, thus accounting for the formation of hydrolyzed product **63**. To rationalize our concept and to minimize the side product, we attempted the reaction, using activated molecular sieves (Table 3.2.1, entry 2). Though this has resulted in the formation of desired product **62a** in 33% yield along with product **62a'** having an isomerised *exo*-double bond in 11% yield (*dr* ~ 4:1 ^1H NMR); the formation of hydrolyzed product **63** in 37% yield, couldn't be suppressed. Use of other Lewis acids seemed to be the best alternative for improving yields and selectivity of product **62a**. Interestingly, 20 mol% of $Bi(OTf)_3$ afforded 74% yield of product **62a** with the formation of trace amounts of **63** (Table 3.2.1, entry 3). Screening of other Lewis acids such as $Cu(OTf)_2$, $Sc(OTf)_3$, AgOTf and $La(OTf)_3$ was ineffective in terms of product selectivity and yields (Table 3.2.1, entries 4-7). With the promising result of $Bi(OTf)_3$, we further screened its efficacy in other solvents like THF and CH_3CN but ended with unsatisfactory results (Table 3.2.1, entries 8 and 9).

Table 3.2.1. Optimization studies for *β*-attack[a]



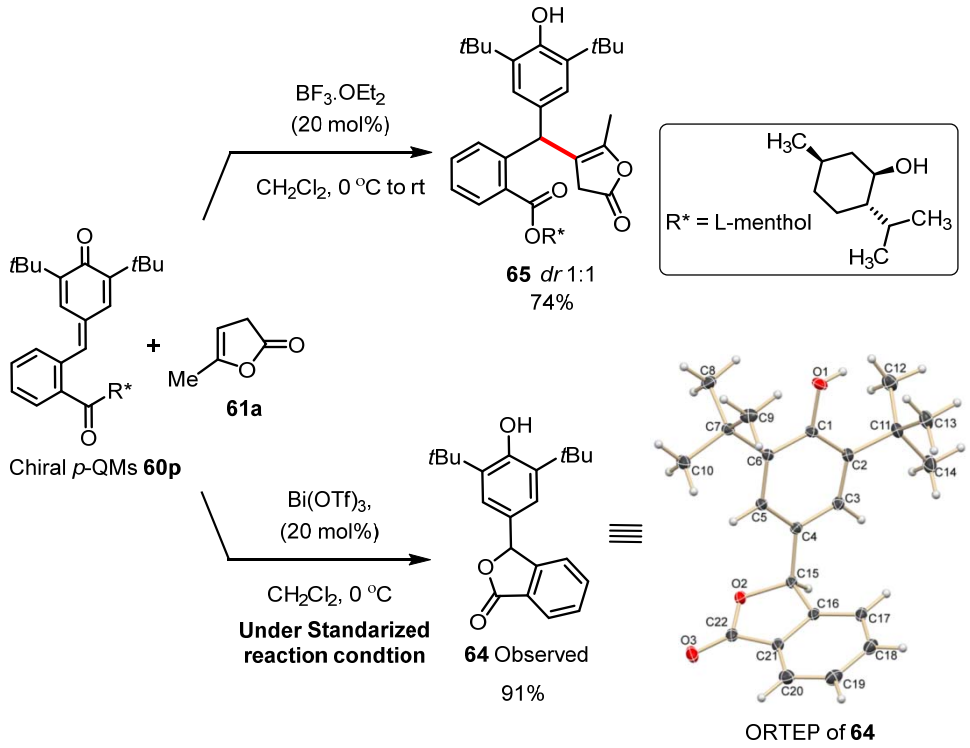
Entry	Catalyst	solvent	T [°C]	time (min)	yield[b] 3a	4
1	$BF_3.OEt_2$	CH_2Cl_2	0	5	–	83
2[c,d]	$BF_3.OEt_2$	CH_2Cl_2	0	15	33	37
3[e]	$Bi(OTf)_3$	CH_2Cl_2	0	5	74	<5
4	$Cu(OTf)_2$	CH_2Cl_2	0	15	45	28
5	$Sc(OTf)_3$	CH_2Cl_2	0	5	–	67
6	AgOTf	CH_2Cl_2	0	10	8	78
7[f]	$La(OTf)_3$	CH_2Cl_2	0	15	6	14
8	$Bi(OTf)_3$	THF	0	15	12	69
9	$Bi(OTf)_3$	CH_3CN	0	5	–	86
10	BH*a	toluene	25	24h	N.R	
11	BH*a	toluene	60	24h	N.R	
12	BH*b	toluene	25	24h	N.R	





[a] Unless and otherwise stated the reaction was performed with *p*-QMs **60a** (0.17 mmol, 50 mg), *α*-angelica lactone **61a** (0.17 mmol, 15 µL) and Lewis acid/BH* (20 mol%) in 2 ml of solvent at the specified temperature. [b] Isolated yields. [c] 4 Å molecular sieves (50 mg). [d] Formation of **62a'** was observed in 11% yield. [e] No reaction when performed in the presence of 4 Å molecular sieves. [f] yields b.r.s.m **60a**. N.R = No reaction. BH* = Appropriate chiral phosphoric acid.

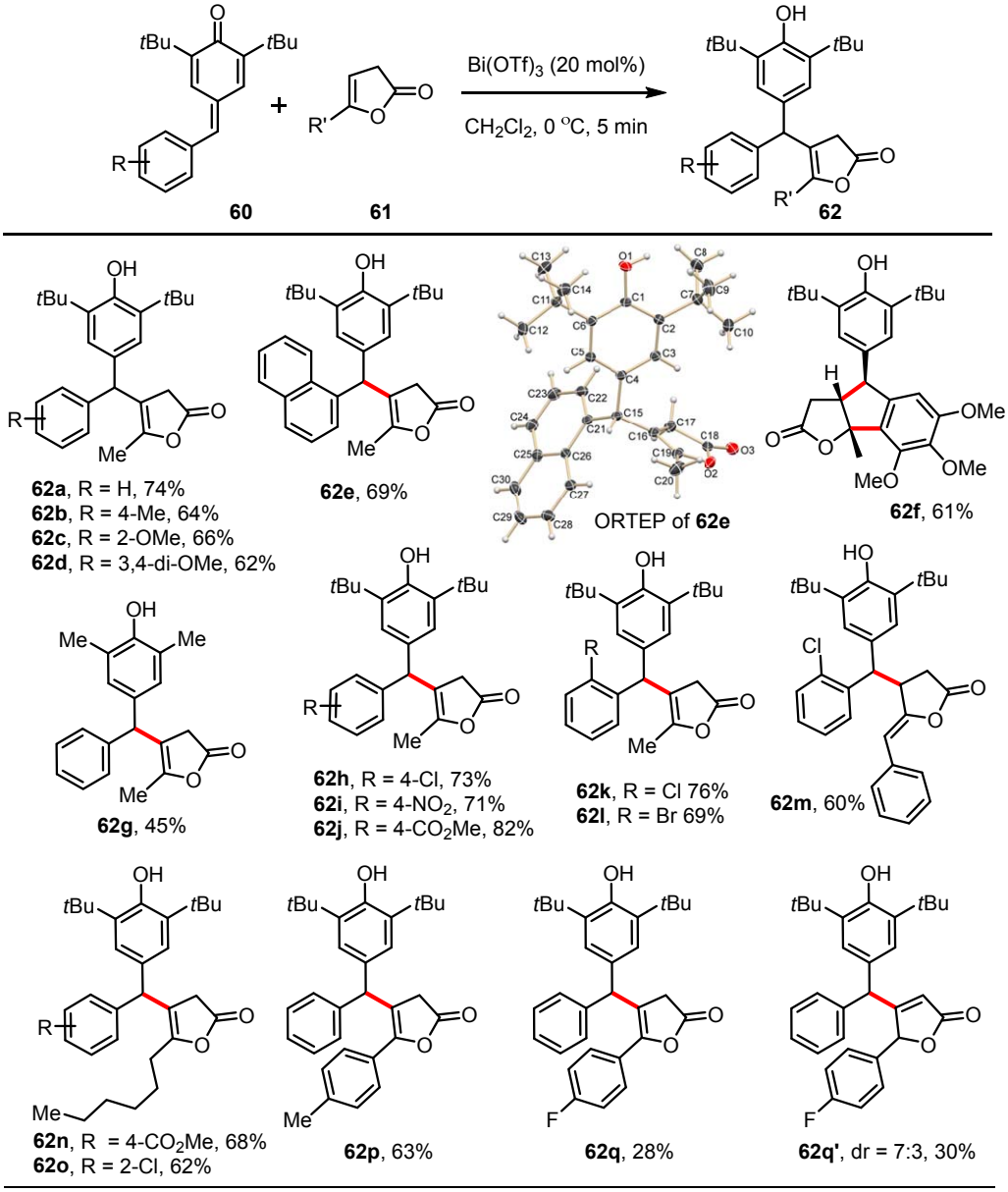
As this reaction led to the formation of product **62a** in a nearly racemic form, we considered attempting the asymmetric version of same. To this end, we tested chiral phosphoric acids containing bulky groups on the BINOL backbone such as (*S*)-TRIP catalyst, but unfortunately the reaction didn't work (Table 3.2.1, entries 10 and 11). This could probably be attributed to the inefficiency of the catalyst to activate *p*-QMs towards nucleophilic attack. A similar set of disappointing results was obtained on switching to chiral metal phosphates with a view to activate *p*-QMs through the interaction of its lone pair with the Lewis acidic metal (Table 3.2.1, entry 12). After having attempted the chiral



Scheme 3.2.10. Attempts for Chiral Induction

catalysts in triggering the *β*-addition, we considered inducing chirality employing chiral auxiliary. Accordingly, we prepared (–)-Menthol incorporated *p*-QMs[46] and subjected it to standardized reaction conditions, but to our dismay, we ended up getting the undesired auxiliary cleaved product **64** in 91% yield. The formation of **64** may be attributed to steric crowding towards incoming nucleophile, thus facilitating intramolecular 1,6-conjugate addition by ester carbonyl followed by elimination of the menthol moiety (Scheme 3.2.10). On the other hand, $BF_3.OEt_2$ worked well in case of chiral *p*-QMs to deliver the required product **65** in 74% yield with *dr* ~ 1:1 (^{1}H NMR analysis). The effect of temperature on 1,6-conjugate addition reactions was also studied. To our surprise, the reaction did not work at lower temperature (-78 ^{o}C). Interestingly, though the reaction at 0 ^{o}C for more than 2 days failed to proceed but as soon as this was brought to room temperature, the formation of product **65** was observed within 5 min. Thus we observed that the influence of chiral auxiliary on the reactive site is minimal which can be attributed not only to the presence of spacer (–CO_2–) thus orienting the auxiliary away from the reactive site but also to the short reaction time giving no scope for chiral induction.

The reaction of butenolides with diversely substituted *p*-QMs **60a-60l** was examined, for both compatibility and wide substrate applicability under the reaction condition. The reaction was found to be very facile with *α*-angelica lactone and its derivatives (Scheme 3.2.11).



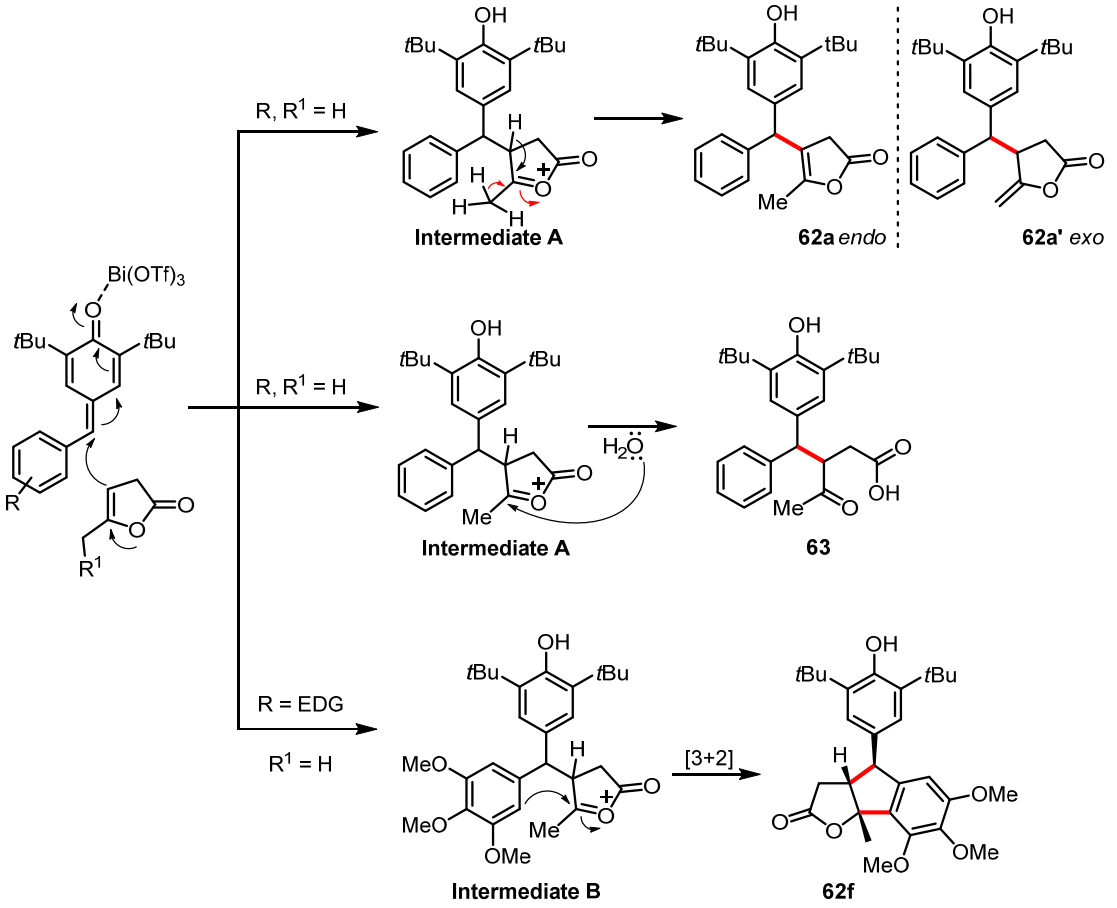
Scheme 3.2.11. Substrate Scope for *β*–addition

Interestingly, *p*-QMs with electron-withdrawing substituents **60h−60l** furnished the desired products **62h-62l** in good yields (69–82%), in comparison with electron-donating substituents, which gave only moderate yields (45–74%) of the products **62a-62g**. In case, of 3,4,5-trimethoxy substituted *p*-QMs **60f**, product with tricyclic core **62f** was obtained in 61% yield, and the structure was further confirmed by single-crystal X-ray

analysis. The formation of tricyclic product can be attributed to [3+2] cycloaddition of the oxonium ion formed after an initial *β*-attack. The characterization of this product validates the enol-ester type reactivity of the butenolide. Surprisingly, when the *tert*-butyl groups at 2 and 6-position of phenol was replaced with methyl group to give *p*-QMs **60q**, yields of product **62g** reduced drastically to 45%, suggesting that bulky substituents are crucial for the stability of *p*-QM. The scope of the reaction was further investigated with *α*-angelica lactones bearing different substituents at *γ*-position. Both electron-donating and electron-withdrawing groups on the aryl ring attached to *α*-angelica lactone, as well as alkyl substituents, were well suited to furnish the products **62m–62q** in (58–68%) yields. It is noteworthy that $–CH_2Ph$ substituted lactone resulted in the formation of product **62m** with *exo* double bond in 60% yield due to the elimination of competing acidic proton at benzylic position. Moreover, lactone **61e** having –F group gave **62q** in a crude yield of 66%. However, attempts to purify **62q** on a column gave two fractions of **62q** and **62q'** in 28% and 30% yields respectively. This was probably due to epimerization of acidic proton at the *α*-position of the product during silica gel column chromatography due to –ve inductive effect of –F group. The structure of products **62e** and **62m** was further confirmed by single-crystal X-ray analysis. The band at 1793 cm^{-1} in IR spectrum of **62a** corresponds to unsaturated cyclic ester. The ^1H NMR spectrum of **62a** showed signal at δ 5.16 (s, 1 H) corresponds to the phenolic (–OH) protons as confirmed by D_2O exchange and signal at δ 3.11 - 3.08 (m, 2 H) corresponds to the allylic ($–CH_2–$) protons of lactone ring, which was further validated by DEPT-135 NMR signal at δ 35.4. The ^{13}C NMR signals at δ 136.0 and 114.8 correspond to the *β*,*γ*-enol ether carbon of the lactone ring. The HRMS (ESI^+) peak of **62a** at 415.2246 corresponding to formula $C_{26}H_{32}O_3$ $[M + Na]^+$ (calculated value 415.2244).

Based on the experimental results, a plausible mechanism for the formation of various products during *β*–addition is proposed. $Bi(OTf)_3$ catalyzed activation of *p*-QMs followed by 1,6-conjugate addition by deconjugated butenolides, when R, R^1 = H; leads to the formation of oxonium **intermediate A**, which undergoes deprotonation affording product **62a** (*endo* double bond) and **62a'** (*exo*). On the other hand, if oxonium **intermediate A** is quenched by moisture it leads to the formation of undesired hydrolyzed product **63**. Finally the [3+2]-cycloaddition on deconjugated butenolides takes place when oxonium ion of **intermediate B** is intercepted with highly electron

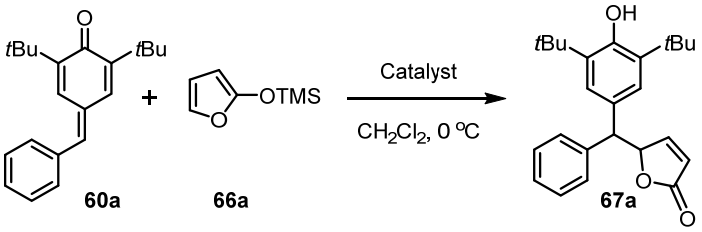
donating aromatic ring of *p*-QMs to give tricyclic product **62f** as shown in Scheme 3.2.12.



Scheme 3.2.12. Plausible Reaction Mechanism

After having explored the *β*-attack, we sought to access the *γ*-position of butenolides *via* Lewis acid catalyzed vinylogous Mukaiyama-Michael reaction [47] of *γ*-unsubstituted silyloxyfurans on *p*-QMs. After screening various Lewis acids (Table 3.2.2) $BF_3.OEt_2$ gave good yield of **67a**. The yields with $Sc(OTf)_3$ were also comparable to $BF_3.OEt_2$ but it was found incompatible with electron donating groups such as –OMe. Also the chiral phosphoric acid were found ineffective in trigging the *γ*-addition reaction. Among the solvents (THF, 1,2-dichloroethane, CH_2Cl_2 and toluene) screened in presence of $BF_3.OEt_2$, dichloromethane was found to be the best.

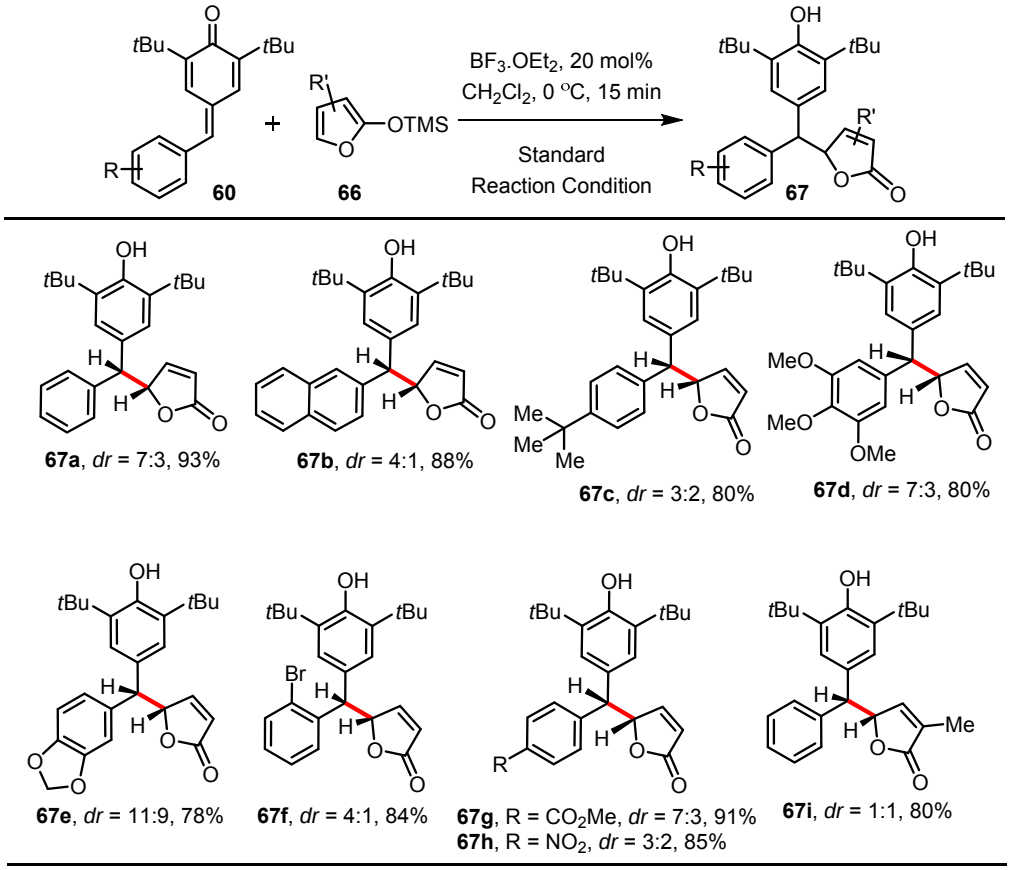
Table 3.2.2. Optimization studies for *γ*-attack[a]



Entry [c]	Catalyst	*t*ime [min]	Yield [b] (%) **67a**
1	$Bi(OTf)_3$	20	81
2	$Cu(OTf)_2$	30	78
3 [d]	$Sc(OTf)_3$	10	88
4	$BF_3.OEt_2$	15	93
5	$La(OTf)_3$	25	75
6	AgOTf	15	80
7	BH*a	25h	N.R
8	BH*b	25h	N.R

[a] Unless and otherwise stated the reaction was performed with *p*-QMs **60a** (0.17 mmol, 50 mg), silyoxyfuran **66a** (0.17 mmol, 30 µL) and Lewis acid/BH* (20 mol%) in 2 ml of solvent at the specified temperature. [b] Isolated yields. [c] When the reaction was carried at -78 °C it took longer time ranging from 1h to 4h depending on the Lewis acid used, without much change in yield and *dr* ratio of **67a**. [d] Reaction was found sluggish with other *p*-QMs having –OMe groups. BH* = Appropriate chiral phosphoric acid.

After having standardized the reaction conditions (Table 3.2.2); we studied the substrate scope of the *p*-QMs and silyloxyfurans (Scheme 3.2.13). The presence of electron-donating and electron-withdrawing substituents on *p*-QMs and silyloxyfurans have very little impact on the product **67a**–**67i** yields (78–93%) and diastereoselectivity. The structure of product **67b** was further confirmed by single-crystal X-ray analysis. The IR spectrum of **67a** showed absorption at 1755 cm^{-1}corresponding to cyclic *α,β*-unsaturated ester. The ^1H NMR spectrum of **67a** showed signals at δ 5.18 (s, 0.3 H), 5.13 (s, 0.7 H) corresponds to the phenolic (–OH) proton as confirmed by D_2O exchange and the signals at δ 6.08 - 6.03 (m, 1 H) correspond to the *α*-protons of *α,β*-unsaturated lactone and (*dr* ~ 7:3). The ^{13}C NMR and DEPT-135 spectrum showed signals at δ 156.0, 155.9 (2 signals represents 2 diastereomers) corresponding to the *β*-carbon of *α,β*-unsaturated lactone ring. The HRMS (ESI^+) peak of **67a** at 401.2086 corresponds to formula $C_{25}H_{30}O_3$ $[M + Na]^+$ (calculated value 401.2087).

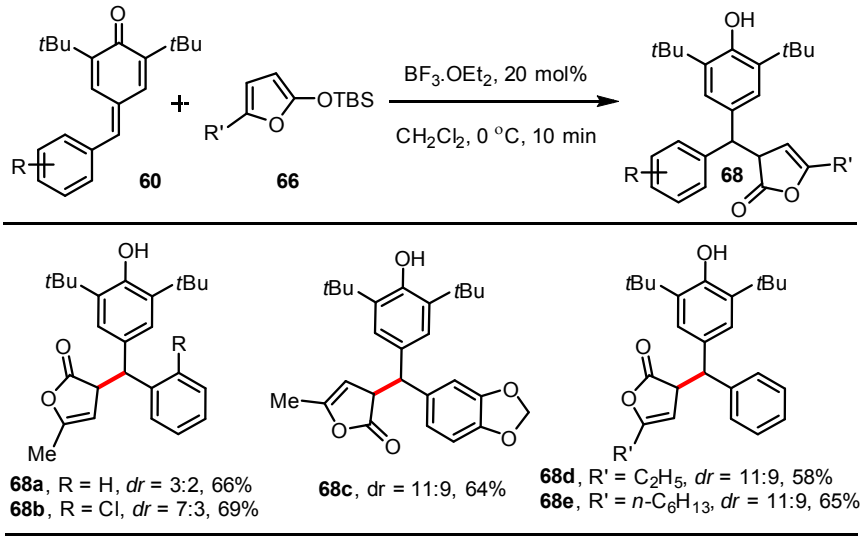


[a] *tert*-Butyldimethylsilylfuran **66b** was used in case of **67i**.

Scheme 3.2.13. Substrate Scope for *γ*–addition[a]

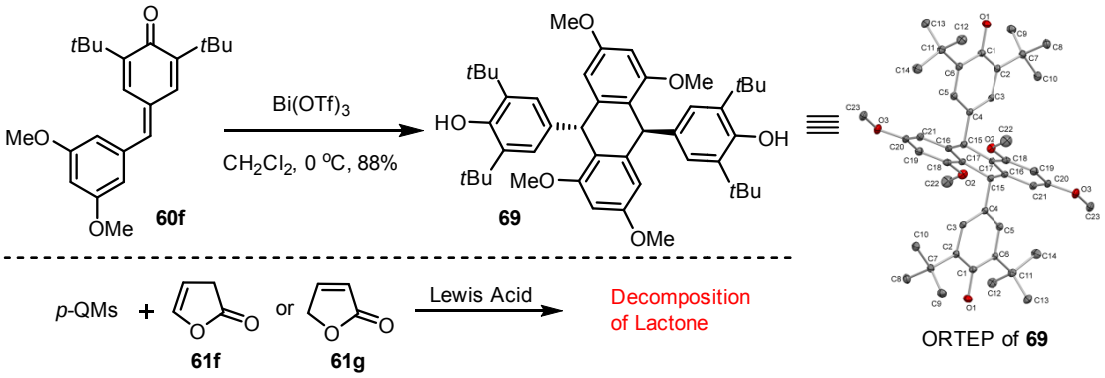
Structural variation in the silyloxyfuran system at *γ*-position gave surprising results with exclusive *α*-attack (Scheme 3.2.14), which has not been observed with other electrophiles, with *γ* being the preferred site of the attack. Thus it gives us deeper insights and the need towards better understanding of the reactivity and substrate selectivity of *p*-QMs. A series of substrates having linear alkyl groups attached to the *γ*-position of silyloxyfuran moiety readily underwent efficient Mukaiyama-Michael reaction under the optimised reaction conditions to furnish the product **68a**-**68e** in good yields (58−69%). The band at 1778 cm^{-1} in IR spectrum of **68a** corresponds to unsaturated cyclic ester. The ^{1}H NMR spectrum of **68a** showed signal at δ 5.13 (s, 0.4 H), 5.09 (s, 0.6 H) corresponding to the phenolic (–OH) protons as confirmed by D_2O exchange and signal at δ 5.23 (s, 0.4 H), 5.20 (s, 0.6 H) corresponds to the *β*-proton of *β*,*γ*-unsaturated lactone ring and (*dr* ~ 3:2). The ^{13}C NMR signals at δ 102.9 and 102.6 (2 signals represents 2 diastereomers) correspond to the *β*-carbon of the *β*,*γ*-unsaturated

lactone ring. The HRMS (ESI^+) peak of **68a** at 393.2415 corresponds to formula $C_{26}H_{32}O_3$ $[M + H]^+$ (calculated value 393.2424).



Scheme 3.2.14. Substrate Scope for *α*–addition

Inspite of all the above advantages, this method has some defined limitations (Scheme 3.2.15). For example, *p*-QMs **60f** underwent homodimerization[48] under the reaction conditions to give product **69** in 88% yield.



Scheme 3.2.15. Unsuccessful Substrate

These results were consistent even in the presence of other Lewis acids such as $BF_3.OEt_2$ and Tf_2NH. The structure of product **69** was further confirmed by single-crystal X-ray analysis. Highly reactive butenolides such as furan-2(3*H*)-one **61f** and furan-2(5*H*)-one **61g**, underwent decomposition under the reaction conditions.

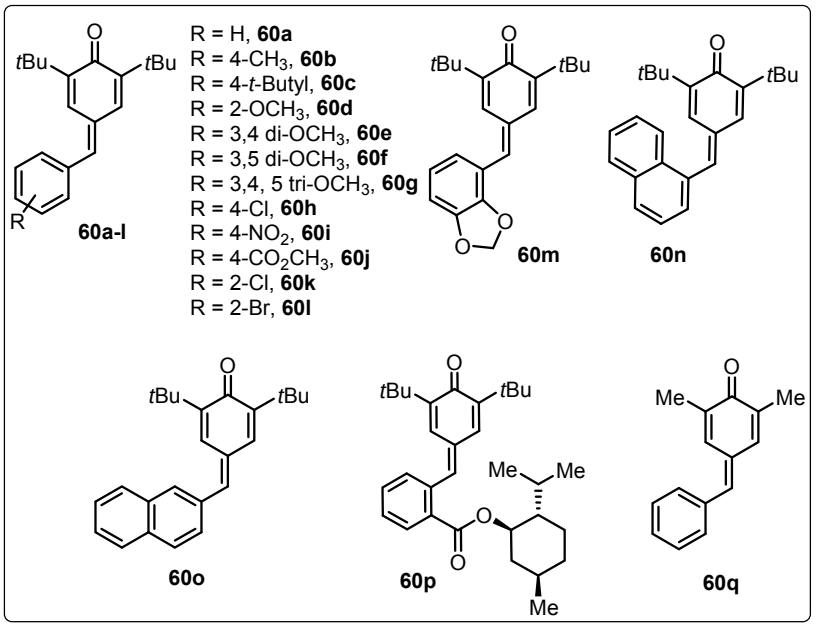
3.2.3. Conclusion and Prospect

In conclusion, we have explored the electrophile driven selectivity of *p*-QMs towards nucleophilic reactivity of α, β & γ-positions of butenolides. This protocol allows synthesis of diversely substituted butenolide derived diarylmethane units embedded in various natural products belonging to lignan and secolignan families. The enol ester reactivity of butenolide was one of the key findings of this work. Further efforts toward asymmetric induction in the unexplored β-attack and [3+2]-cycloaddition reactions of deconjugated butenolides and its applications in organic synthesis are currently under progress.

3.2.4. Experimental Section

General Procedure

I. Synthesis of *p*-Quinone Methide 60a-60p:[49]

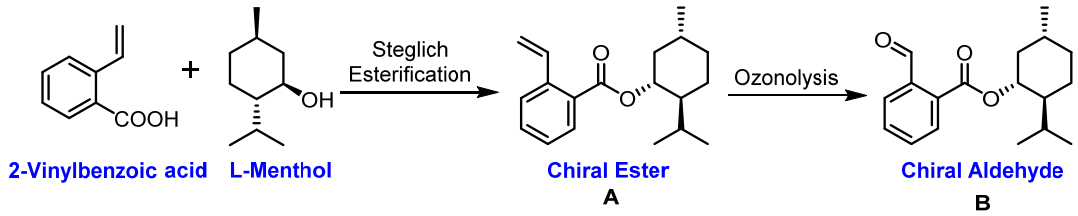


In an oven dried Dean-Stark apparatus, phenol (25.0 mmol) and the corresponding aldehyde (25.0 mmol) were taken in toluene (100 mL), the reaction mixture was heated to reflux followed by dropwise addition of piperidine (50.0 mmol, 4.94 mL) within 1 h. The reaction mixture was continued to reflux for 6 hours. After cooling just below the boiling point of the reaction mixture, acetic anhydride (50.0 mmol, 2.55 g) was added and stirring was continued for 30 min. Then the reaction mixture was poured on ice-

water (500 mL) and extracted with CH_2Cl_2 (4 x 200 mL). The combined organic phase was dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography and further recrystallized from *n*-hexane, affording *p*-quinone methide in good yields.

Compound **60q** was prepared according to literature report.[50]

II. Preparation of Chiral Aldehyde Used for the Synthesis of *p*-QM 60p:



2-Vinylbenzoic acid was prepared according to literature report.[51]

To a stirred solution of 2-vinylbenzoic acid (0.567 g, 3.84 mmol) in dry CH_2Cl_2 (5 mL) at 0 ^oC, DCC (1.85 g, 8.96 mmol) was added in portion-wise resulting in formation of white precipitate. Then catalytic amount of DMAP was added followed by dropwise addition of L-menthol (0.400 g, 2.56 mmol) in dry CH_2Cl_2 (5 mL). The resultant solution was stirred overnight at room temperature. The reaction mixture was evaporated to dryness. The crude product was purified by flash column chromatography using petroleum ether/EtOAc (98:2) as an eluent to afford chiral ester **A** as a colorless liquid.

Yield = 87%;

R_f = 0.52 (pet. ether);

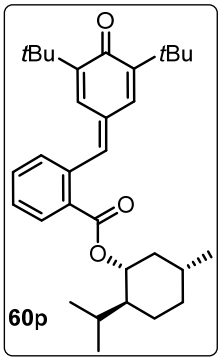
^{1}H NMR (400MHz, $CDCl_3$) δ = 7.87 (d, *J* = 7.9 Hz, 1 H), 7.59 (d, *J* = 7.9 Hz, 1 H), 7.53 - 7.42 (m, 2 H), 7.33 (t, *J* = 7.3 Hz, 1 H), 5.66 (d, *J* = 17.7 Hz, 1 H), 5.36 (d, *J* = 11.0 Hz, 1 H), 4.95 (ddd, *J* = 4.3, 11.0, 11.0 Hz, 1 H), 2.17 (d, *J* = 11.6 Hz, 1 H), 2.06 - 1.96 (m, 1 H), 1.78 - 1.68 (m, 2 H), 1.64 - 1.50 (m, 2 H), 1.20 - 1.07 (m, 2 H), 0.94 (t, *J* = 6.7 Hz, 7 H), 0.82 (d, *J* = 6.7 Hz, 3 H)**;**

^{13}C NMR (100MHz, $CDCl_3$) δ = 166.9, 139.4, 135.9, 131.7, 129.9, 129.4, 127.3, 127.1, 116.1, 74.9, 47.2, 40.9, 34.2, 31.4, 26.3, 23.3, 22.0, 20.8, 16.2;

HRMS (ESI^+) *m/z* = calcd for $C_{19}H_{26}O_2$ $[M + Na]^+$ 309.1825, found 309.1821.

Ozone was bubbled through a solution of **A** (300 mg, 1.05 mmol) in CH_2Cl_2 (30 mL) at –78 ^oC until the solution colour turned to violet. Oxygen gas was bubbled into the

reaction mixture for 5 min. After Me_2S (0.19 mL, 2.63 mmol) was added, the mixture was warmed to room temperature, stirred overnight, and then concentrated. The remaining solvents were removed using rotavapour under reduced pressure to afford the crude aldehyde in 93% yield, which was used directly in next step without any further purification for the synthesis of ***p*-QM 60p**.

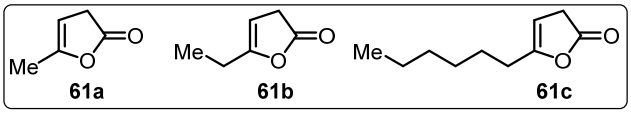


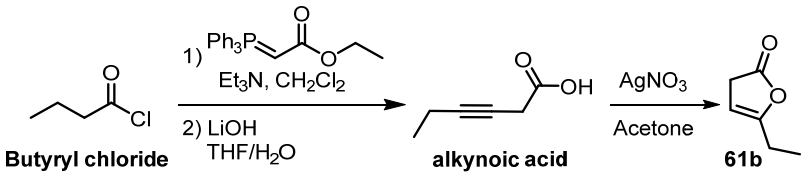
Compound **60p** was prepared according to general procedure I. After column purification the product was obtained as yellow solid in 84% yield. **mp** = 128-130 ºC; $\boldsymbol{R_f}$ = 0.42 (pet. ether); IR ($CHCl_3$): ν_{max} = 3019, 2955, 1704, 1611, 1464, 1261, 1219, 1133, 1078, 761 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.12 (d, *J* = 7.9 Hz, 1 H), 7.75 (s, 1 H), 7.60 (t, *J* = 7.3 Hz, 1 H), 7.49 (t, *J* = 7.3 Hz, 1 H), 7.36 (d, *J* = 7.3 Hz, 1 H), 7.19 (d like, *J* = 1.8 Hz, 1 H), 7.12 (s, 1 H), 4.91 (ddd, *J* = 4.3, 11.0, 11.0 Hz, 1 H), 2.14 (d, *J* = 11.6 Hz, 1 H), 2.01 - 1.89 (m, 1 H), 1.75 (s, 1 H), 1.72 (s, 1 H), 1.62 (s, 1 H), 1.58 - 1.49 (m, 2 H), 1.34 (s, 9 H), 1.24 (s, 9 H), 1.15 - 1.03 (m, 2 H), 0.92 (t, *J* = 7.3 Hz, 6 H), 0.79 (d, *J* = 6.7 Hz, 3 H)**; ^{13}C NMR** (100 MHz, $CDCl_3$) δ = 186.6, 166.0, 149.0, 147.8, 143.1, 137.3, 135.0, 132.2, 131.7, 131.2, 131.0, 130.3, 128.7, 128.1, 75.5, 47.3, 41.0, 35.3, 35.0, 34.3, 31.5, 29.5, 29.4, 26.4, 23.5, 22.0, 20.9, 16.4; **HRMS** (ESI^+) *m/z* = calcd for $C_{32}H_{44}O_3$ $[M + H]^+$ 477.3363, found 477.3358.

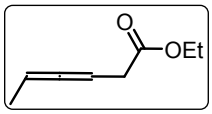
III. Synthesis of *α,β* and *β,γ*-Unsaturated Butenolides:

➢ Preparation of the Starting Material 5-ethylfuran-2(3*H*)-one (61b):

α-Angelica lactone **61a** was purchased from Aldrich Inc. and used without further purification. **61b** and **61c** were prepared according to slightly modified Marshall's method as described below.[52]

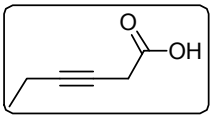




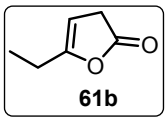


Step I. Ethyl (triphenylphosphoranylidene)acetate (6.3 g, 18.8 mmol, 1 equiv.) was stirred with triethylamine (2.6 ml, 18.8 mmol, 1 equiv.) in dry CH_2Cl_2 (20 mL, 1 mL per 1 g of acetate) with ice-bath cooling. Butyryl chloride (2 mL, 18.8 mmol, 1 equiv.) was added dropwise and the mixture was allowed to warm to room temperature then stirred for 24 hours. The solvent was evaporated and due to low boiling nature of compound, the crude residue was purified by flash chromatography on silica using pentane/ diethyl ether (9:1) to give 1.9 g (15.1 mmol) of the expected product.

Yield: 80%.



Step II. The ester (1.9 g, 15.1 mmol, 1 equiv.) was dissolved in 25 mL of THF and saponified by treatment with monohydrate $LiOH.H_2O$ (3.2 g, 75.5 mmol, 5 equiv.) in 25 mL of water for 1 hour. The mixture was then washed with 50 mL of diethyl ether. The aqueous phase was acidified with 1M HCl solution and extracted with 50 mL of diethyl ether twice. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to furnish the desired alkynoic acid, containing ~ 30% of allenoic acid. It was subjected to next step without further purification.

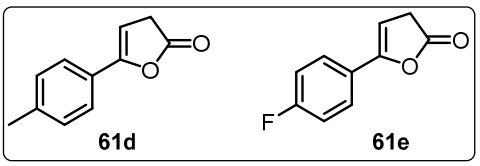


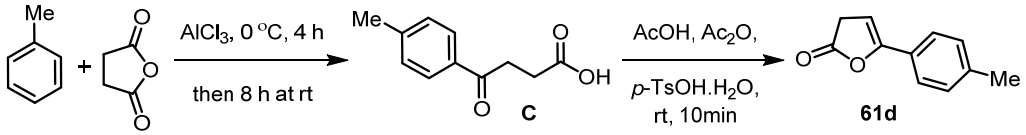
Step III. The alkynoic acid (1.7 g, 15.1 mmol, 1 equiv.) was stirred in acetone (17 mL, 10mL per 1g of acid) covered with silver foils and treated with silver nitrate (513 mg, 3.02 mmol, 0.2 equiv.) at room temperature. After 24 hours, the mixture was concentrated *in vacuo* and the crude residue was purified by flash chromatography on silica (pentane/ diethyl ether, 9:1) to give the desired lactone **61b** (233 mg, 2.08 mmol).

Yield: 14% (two steps).

- **Preparation of the Starting Material 5-(*p*-tolyl)furan-2(3*H*)-one (61d)**:

Butenolides **61d** and **61e** were synthesized by slightly modifying the protocol developed by Dixon *et.al* and Yuan *et.al*.[53] for better yields and reproducibility as mentioned below.

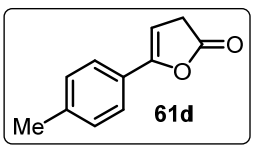




Step I: A 100-mL, three-necked, round-bottomed flask is charged with Succinic anhydride (1.0 equiv.) and toluene (1.0 equiv.) under dry nitrogen. The resulting white mixture was cooled to 0 ^{o}C before anhydrous aluminum trichloride (1.2 equiv.) was added in portion wise manner and the reaction started immediately with the evolution of HCl gas. The reaction mixture was stirred over a period of 4 h at 0 ^{o}C followed by stirring it at room temperature for 8 h. The reaction was poured into ice, and 10 mL of 1N hydrochloric acid was added under stirring at 0 ^{o}C. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 twice. The combined organic layers were washed with water, dried over Na_2SO_4 and concentrated. The crude product **C** was used as such in the next step without further purification.

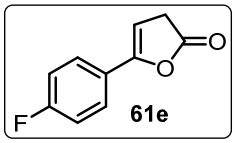
Step II: A dried 100 mL round flask was charged with 4-oxo-4-(*p*-tolyl)butanoic acid **C** (4.4 g), acetic anhydride (5 mL), acetic acid (3 mL) followed by addition of *p*-TSA.H_2O (2 mol%, only) at room temperature. The slurry was allowed to stir for 10 min at room temperature during which the solid was dissolved followed by precipitation of solid after another 5 min indicating the completion of the reaction. To the reaction mixture, ice pieces were added and stirred for 15 min. The product was collected by filtration to give an off white crystalline solid which was washed with an excess of water to remove AcOH and Ac_2O. The crude product was crystallized using benzene and diethyl ether (1:1) under the slight heating condition to yield *β,γ*-lactone **61d** in 75% yield.

Note: Avoid purification of *β,γ*-lactone by silica gel chromatography otherwise, it results in the formation of pink colored impurity (Pechmann dye)[54] which comes along with the product, as well as the product is also obtained in poor yield.



Compound **61d** was obtained as a pale yellow solid in 75% yields after re-crystallization. **mp** = 110 ºC; $\boldsymbol{R_f}$ = 0.37 (pet. ether/ethyl acetate = 9:1); **IR** ($CHCl_3$): ν_{max} = 3113, 3030, 2930, 1797, 1653, 1509, 1404, 1307, 1249, 1117, 1024, 999, 893, 826, 753 cm^{-1}; **^{1}H NMR** (500MHz , $CDCl_3$) δ = 7.55 (d, *J* = 8.4 Hz, 2 H), 7.26 (d, *J* = 8.0 Hz, 2 H), 5.77 (t, *J* = 2.7 Hz, 1 H), 3.44 (d, *J* = 2.7 Hz, 2 H), 2.43 (s, 3 H)**; ^{13}C NMR** (125MHz, $CDCl_3$) δ = 175.9, 153.9,

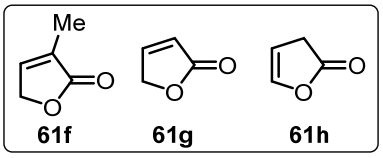
139.6, 129.2, 125.6, 124.5, 96.6, 34.4, 21.2; **HRMS** (ESI^+) *m/z* = calcd for $C_{11}H_{10}O_2$ $[M + H]^+$ 175.0754, found 175.0751.



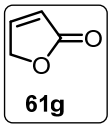
Compound **61e** was obtained as a pale orange solid in 72% yield after re-crystallization. **mp** = 109-110 ºC; $\boldsymbol{R_f}$ = 0.30 (pet. ether/ethyl acetate = 9:1); **IR** ($CHCl_3$): ν_{max} = 3115, 2925, 2856, 1787, 1596, 1502, 1382, 1222, 1111, 1019, 993, 837, 767 cm^{-1}; **^{1}H NMR** (400MHz , $CDCl_3$) δ = 7.49 (dd, *J* = 5.5, 8.5 Hz, 2 H), 7.00 (t, *J* = 8.5 Hz, 2 H), 5.65 (s, 1 H), 3.32 (d like, *J* = 2.4 Hz, 2 H)**; ^{13}C NMR** (100MHz, $CDCl_3$) δ = 175.4, 164.3, 161.8, 152.7, 126.5 (d, $J_{C\text{-}F}$ = 8.5 Hz), 124.6 (d, $J_{C\text{-}F}$ = 3.1 Hz), 115.6 (d, $J_{C\text{-}F}$ = 21.6 Hz), 97.3 (d like, $J_{C\text{-}F}$ = 1.5 Hz), 34.4; **HRMS** (ESI^+) *m/z* = calcd for $C_{10}H_7FO_2$ $[M + Na]^+$ 201.0322, found 201.0321.

- **Preparation of Butenolides 61g and 61h**:

Butenolide **61f** was purchased from TCI chemicals and used without further purification. Butenolides **61g** and **61h** were prepared according to literature method as described below.[55, 56]



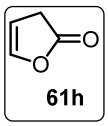
Furan-2(5*H*)-one (61g):



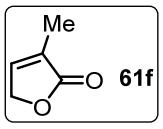
A 500 mL, three-necked, round-bottomed flask equipped with two condensers and a dropping funnel is charged with 42 mL (0.5 mol, 1 equiv.) of furfural and 200 mL of CH_2Cl_2. The addition of 20 g of sodium sulfate and 17 mL of *N,N*-dimethylethanolamine in one portion each, is followed immediately by 38 mL (1 mol, 2 equiv.) of formic acid (98%), carefully added in portions over a period of 2 min, after which 10 mL of 30% hydrogen peroxide is added in one portion. The mixture is stirred vigorously. After 5 min the mixture will reflux (exothermic reaction) and another 80 mL of 30% H_2O_2 is added dropwise during 9 hr while stirring is continued. When the addition is complete, the mixture is vigorously stirred as long as it refluxes and then stirred gently overnight. The organic phase is separated, and the water phase is extracted with the 20 mL of CH_2Cl_2.

The CH_2Cl_2 phase is washed with two 20 mL portions of saturated sodium disulfite ($Na_2S_2O_5$) solution to remove traces of furfural and dried over Na_2SO_4. The crude product was distilled at 85–85 ^oC (13 mmHg) to give butenolide **61g** as a colorless to pale yellow liquid (17 g) in 41% yield, which is further stored at 2-8 ^oC. The compound **61g** becomes yellow on standing: redistillation affords coloreless **61g**.

Furan-2(3*H*)-one (61h):



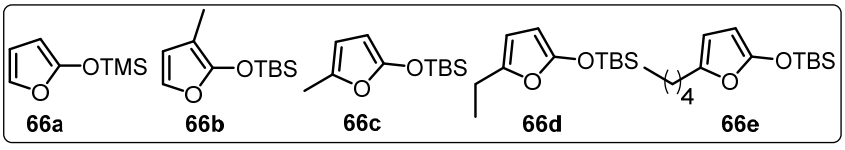
A 500 mL, three-necked, round-bottomed flask equipped with condensers and a dropping funnel is charged with 42 mL (0.5 mol, 1 equiv.) of furfural, 200 mL of CH_2Cl_2, formic acid (98%, 29 ml, 0.75 mol, 1.5 equiv.), and 30% hydrogen peroxide 38 mL is added in one portion. Vigorous stirring is continued for 30-45 min after which time the mixture refluxes gently. Then, 30% hydrogen peroxide 75 mL is added dropwise with continued stirring over a period of 3h. The mixture is allowed to cool to room temperature with continued stirring for 10h. The organic phase is separated, and the water phase is extracted with the 50 mL of CH_2Cl_2. The CH_2Cl_2 phase is washed with two 20 mL portions of saturated sodium disulfite ($Na_2S_2O_5$) solution and dried over Na_2SO_4. The crude product was distilled at 43–45 ^oC (13 mmHg) to give butenolide **61h** as a colorless to pale yellow liquid (18 g) in 21% yield. The compound **61h** isomerizes to **61g** on standing at room temperature, so it should be stored at 2-8 ^oC.



Butenolide **61f** was purchased from TCI chemicals India Pvt. Ltd. and used without further purification.

IV. Preparation of Silyloxyfurans *tert*-Butyldimethyl((3-methylfuran-2-yl)oxy)silane 66b:

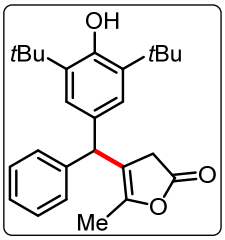
2-Trimethylsilyloxy furan **66a** were purchased from Aldrich and used without further purification. *tert*-Butyldimethylsilyloxy furans (**66b-66e)** were prepared by slightly modifying the literature methods as described below. [57]



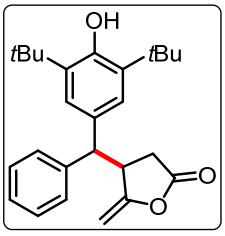
tert-Butyldimethylsilyl trifluoromethanesulfonate (TBSOTf, 0.56 mL, 2.44 mmol, 1.2 equiv.) was added dropwise to a stirred solution of butenolide **66b** (200 mg, 2 mmole, 1 equiv.) and Et_3N (0.57 mL, 4.1 mmole, 2 equiv.) in 2 ml CH_2Cl_2 at 0 ^oC. The mixture was stirred for 1h at 0 ^oC, and then 3h at rt. The solution was diluted with cold pentane (5 ml x 2) and the pentane layer was decanted and concentrated and used as such in next step without any further purification.

V. General Procedure for *β*-addition of *α*-Angelica Lactone derivatives (61a-61e) to *p*-QMs:

To a stirring solution of *para*-quinone methides (*p*-QMs) **60** (0.17 mmol, 1 equiv.) and *α*-Angelica Lactone derivatives **61** (0.17 mmol, 1 equiv.) in dry CH_2Cl_2 (2mL) at 0 ^oC (immersion bath) was added Bismuth triflate (20 mol%). The resulting solution was stirred at the same temperature until the yellow-orange color of reaction mixture disappears as also indicated by TLC. After completion of the reaction, a pinch of solid $NaHCO_3$ was added and stirred for 5 min followed by evaporation of the solvent. The purification of crude residue on flash silica gel chromatography using petroleum ether/ethyl acetate furnished the desired product **62a-62q**.

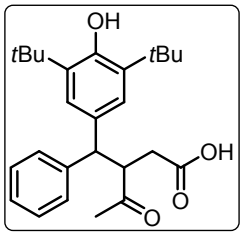


Compound **62a** was obtained as white solid in 74% yield. **mp** = 114-115 ºC; R_f = 0.55 (pet. ether/ethyl acetate = 4:1); **IR** ($CHCl_3$): ν_{max} = 3634, 2958, 1793, 1596, 1480, 1437, 1388, 1225, 1150, 1047, 756, 703 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.36 - 7.30 (m, 2 H), 7.28 - 7.23 (m, 1 H), 7.16 - 7.12 (m, 2 H), 6.89 (s, 2 H), 5.16 (s, 1 H), 4.96 (s, 1 H), 3.11 - 3.08 (m, 2 H), 1.91 (t, *J* = 2.5 Hz, 3 H), 1.40 (s, 18 H)**; ^{13}C NMR** (100 MHz, $CDCl_3$) δ = 175.9, 152.5, 147.7, 142.0, 136.0, 131.7, 128.5, 128.4, 126.7, 125.1, 114.8, 47.7, 35.4, 34.3, 30.3, 11.5; **HRMS** (ESI^+) calcd for $C_{26}H_{32}O_3$ $[M + Na]^+$ 415.2244, found 415.2246.

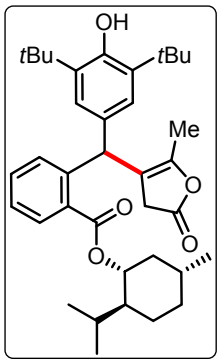


Compound **62a'** was obtained as white solid in 11% yield. (*dr* ~ 4:1 by ^{1}H-NMR); **mp** = 103-104 ºC; R_f = 0.41 (pet. ether/ethyl acetate = 4:1); **IR** ($CHCl_3$): ν_{max} = 3631, 2956, 1803, 1666, 1438, 1238, 1144, 977, 852, 759 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.36 - 7.31 (m, 2 H), 7.30 - 7.22 (m, 3 H), 7.07 (s, 1.66 H), 7.03 (s, 0.34 H), 5.14 - 5.11 (m, 1 H), 4.63 (br. s., 1 H), 3.96 - 3.91 (m, 1 H), 3.91 - 3.83 (m, 1 H), 3.68 (s, 0.17

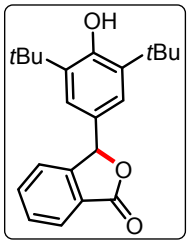
H), 3.61 (s, 0.83 H), 2.81 - 2.72 (m, 1 H), 2.51 - 2.38 (m, 1 H), 1.43 (s, 18 H)**;** ^{13}**C NMR** (100 MHz, $CDCl_3$) δ = 173.6, 157.9, 152.7, 142.1, 136.2, 136.0, 132.1, 132.0, 128.8, 128.6, 128.1, 128.0, 126.9, 126.8, 124.8, 124.4, 91.1, 91.0, 55.6, 55.5, 42.6, 42.5, 34.4, 34.1, 34.0, 30.3; **HRMS** (ESI^+) *m*/*z* = calcd for $C_{26}H_{32}O_3$ $[M + Na]^+$ 415.2244, found 415.2236.



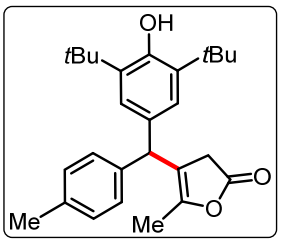
Compound **63** was obtained as white solid in 86% yield. (*dr* ~ 4:1 by ^{1}H-NMR); **mp** = 197-199 ºC; R_f = 0.56 (pet. ether/ethyl acetate = 1:1); **IR** ($CHCl_3$): ν_{max} = 3691, 3638, 2958, 1710, 1434, 1359, 1228, 1161, 931, 761 cm^{-1}; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ = 7.32 - 7.29 (m, 3 H), 7.27 - 7.14 (m, 2 H), 7.06 (s, 0.4 H), 7.03 (s, 1.6 H), 5.10 - 5.05 (m, 1 H), 3.82 - 3.77 (m, 2 H), 2.85 - 2.72 (m, 1 H), 2.45 - 2.39 (m, 0.2 H), 2.37 - 2.32 (m, 0.8 H), 1.76 (s, 0.6 H), 1.70 (s, 2.4 H), 1.41 (s, 3.6 H), 1.38 (s, 14.4 H)**;** ^{13}**C NMR** (125 MHz, $CDCl_3$) δ = 212.6, 212.5, 178.4, 178.3, 152.7, 152.6, 141.7, 136.2, 136.1, 131.9, 131.5, 128.9, 128.7, 128.0, 127.8, 126.9, 126.8, 124.5, 124.3, 54.7, 52.4, 52.2, 36.2, 36.1, 34.3, 32.4, 30.3, 30.2; **HRMS** (ESI^+) calcd for $C_{26}H_{34}O_4$ $[M + Na]^+$ 433.2349, found 433.2350.



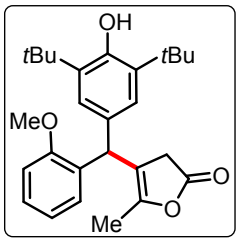
Compound **65** was obtained as pale yellow liquid in 74% yield. (*dr* ~ 1:1 by ^{1}H-NMR); R_f = 0.43 (pet. ether/ethyl acetate = 9:1); **IR** ($CHCl_3$): ν_{max} = 3636, 3020, 2958, 2870, 1783, 1704, 1439, 1376, 1265, 1221, 1139, 1047, 963, 759 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ = 7.80 (dd, *J* = 7.9, 12.8 Hz, 1 H), 7.45 - 7.37 (m, 1 H), 7.35 - 7.26 (m, 1 H), 7.03 (d, *J* = 7.9 Hz, 0.5 H), 6.98 (d, *J* = 7.9 Hz, 0.5 H), 6.85 (s, 2 H), 6.05 (s, 0.5 H), 5.98 (s, 0.5 H), 5.14 (s, 1 H), 4.90 - 4.80 (m, 1 H), 3.22 - 2.95 (m, 2 H), 2.04 - 1.80 (m, 2 H), 1.72 (d like, *J* = 11.0 Hz, 2 H), 1.66 (d like, *J* = 1.2 Hz, 3 H), 1.57 - 1.43 (m, 2 H), 1.39 (s, 18 H), 1.16 - 0.97 (m, 2 H), 0.94 (s, 1 H), 0.94 - 0.87 (m, 6 H), 0.78 (d, *J* = 7.3 Hz, 1.5 H), 0.73 (d, *J* = 6.7 Hz, 1.5 H)**;** ^{13}**C NMR** (100 MHz, $CDCl_3$) δ = 176.0, 175.9, 167.5, 167.3, 152.5, 152.4, 148.2, 148.1, 143.5, 143.3, 135.9, 135.8, 131.6, 131.5, 131.4, 131.3, 131.2, 131.1, 130.4, 130.1, 129.4, 126.5, 125.2, 125.1, 115.4, 115.2, 74.9, 74.7, 47.1, 43.6, 40.8, 40.7, 37.0, 36.8, 34.3, 34.2, 34.1, 31.5, 31.4, 30.3, 26.5, 26.4, 23.3, 23.2, 22.0, 21.9, 20.8, 20.7, 16.2, 16.1, 11.7, 11.6; **HRMS** (ESI^+) calcd for $C_{37}H_{50}O_5$ $[M + Na]^+$ 597.3550, found 597.3551.



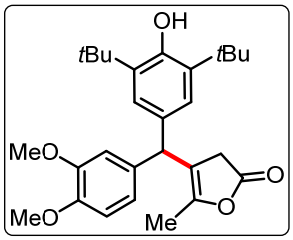
Compound **64** was obtained as white solid in 91% yield. **mp** = 164-165 ºC; R_f = 0.28 (pet. ether/ethyl acetate = 9:1); **IR** ($CHCl_3$): ν_{max} = 3627, 2960, 1760, 1606, 1437, 1290, 1239, 1065, 944, 753 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.97 (d, *J* = 7.3 Hz, 1 H), 7.68 (t, *J* = 7.9 Hz, 1 H), 7.57 (t, *J* = 7.3 Hz, 1 H), 7.39 (d, *J* = 7.9 Hz, 1 H), 7.03 (s, 2 H), 6.38 (s, 1 H), 5.35 (s, 1 H), 1.40 (s, 18 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 170.6, 154.7, 149.6, 136.4, 134.0, 129.2, 126.7, 126.2, 125.5, 124.4, 123.1, 83.8, 34.3, 30.1; **HRMS** (ESI^+) calcd for $C_{22}H_{26}O_3$ $[M + H]^+$ 339.1955, found 339.1956.



Compound **62b** was obtained as colourless liquid in 64% yield. R_f = 0.31 (pet. ether/ethyl acetate = 19:1); **IR** ($CHCl_3$): ν_{max} = 3634, 3011, 2959, 2876, 1791, 1436, 1224, 1151, 1052, 961, 759 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.14 (d, *J* = 7.9 Hz, 2 H), 7.03 (d, *J* = 7.9 Hz, 2 H), 6.91 (s, 2 H), 5.16 (s, 1 H), 4.93 (s, 1 H), 3.09 (d like, *J* = 1.8 Hz, 2 H), 2.36 (s, 3 H), 1.91 (t like, *J* = 2.1 Hz, 3 H), 1.41 (s, 18 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 176.0, 152.5, 147.5, 138.9, 136.2, 136.0, 131.8, 129.2, 128.3, 125.0, 115.0, 47.4, 35.4, 34.3, 30.3, 21.0, 11.5; **HRMS** (ESI^+) calcd for $C_{27}H_{34}O_3$ $[M + Na]^+$ 429.2400, found 429.2391.

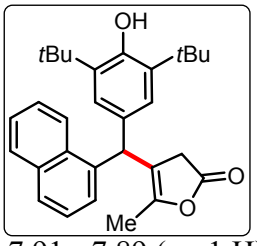


Compound **62c** obtained as pale yellow solid in 66% yield. **mp** = 141-142 ºC; R_f = 0.43 (pet. ether/ethyl acetate = 17:3); **IR** ($CHCl_3$): ν_{max} = 3634, 2956, 1793, 1591, 1477, 1436, 1237, 1150, 1037, 962, 754 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.26 - 7.21 (m, 1 H), 6.97 - 6.88 (m, 5 H), 5.35 (s, 1 H), 5.12 (s, 1 H), 3.82 (s, 3 H), 3.21 - 3.13 (m, 1 H), 3.04 - 2.95 (m, 1 H), 1.84 - 1.80 (m, 3 H), 1.40 (s, 18 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 176.3, 157.1, 152.3, 147.9, 135.8, 131.4, 130.7, 129.3, 127.8, 124.9, 120.4, 114.4, 110.7, 55.5, 40.7, 36.0, 34.3, 30.3, 11.5; **HRMS** (ESI^+) *m/z* = calcd for $C_{27}H_{34}O_4$ $[M + Na]^+$ 445.2349, found 445.2341.

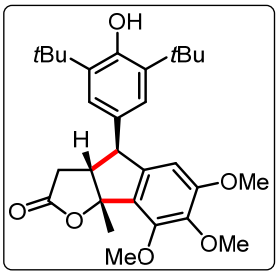


Compound **62d** was obtained as orange liquid in 62% yield. R_f = 0.34 (pet. ether/ethyl acetate = 4:1); **IR** ($CHCl_3$): ν_{max} = 3634, 3017, 2959, 1790, 1513, 1435, 1224, 1146, 1030, 962, 758 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.91 (s, 2 H), 6.83 (d, *J* = 8.2

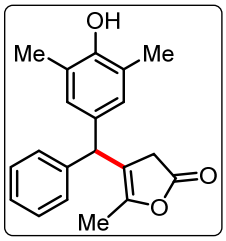
Hz, 1 H), 6.69 - 6.63 (m, 2 H), 5.17 (s, 1 H), 4.90 (s, 1 H), 3.89 (s, 3 H), 3.80 (s, 3 H), 3.09 - 3.07 (m, 2 H), 1.89 (t, J = 2.3 Hz, 3 H), 1.40 (s, 18 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 175.9, 152.5, 148.9, 147.7, 147.5, 136.0, 134.4, 131.7, 124.9, 120.5, 115.1, 111.8, 111.0, 55.9, 55.8, 47.3, 35.5, 34.3, 30.3, 11.5; **HRMS** (ESI^+) calcd for $C_{28}H_{36}O_5$ $[M + Na]^+$ 475.2455, found 475.2446.



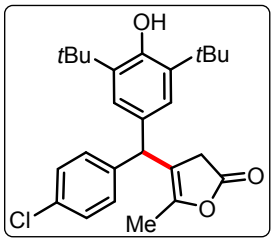
Compound **62e** was obtained as white solid in 69% yield. **mp** = 160-162 ºC; $\boldsymbol{R_f}$ = 0.21 (pet. ether/ethyl acetate = 19:1); **IR** ($CHCl_3$): ν_{max} = 3630, 3056, 2958, 1793, 1434, 1389, 1223, 1149, 1056, 961, 760 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.98 - 7.96 (m, 1 H), 7.91 - 7.89 (m, 1 H), 7.79 (d, J = 8.5 Hz, 1 H), 7.54 - 7.48 (m, 2 H), 7.42 (t, J = 7.6 Hz, 1 H), 7.11 (d, J = 7.3 Hz, 1 H), 6.96 (s, 2 H), 5.66 (s, 1 H), 5.17 (s, 1 H), 3.22 - 3.10 (m, 1 H), 3.02 - 2.92 (m, 1 H), 1.71 (s, 3 H), 1.40 (s, 18 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 175.8, 152.6, 148.3, 138.3, 136.1, 134.0, 131.7, 131.6, 128.9, 127.6, 126.3, 126.2, 125.6, 125.3, 125.1, 123.3, 114.7, 44.2, 36.7, 34.3, 30.3, 11.6; **HRMS** (ESI^+) calcd for $C_{30}H_{34}O_3$ $[M + Na]^+$ 465.2400, found 465.2397.



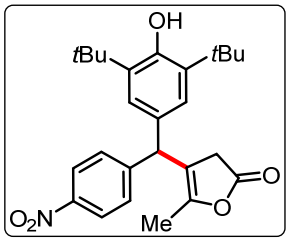
Compound **62f** was obtained as white solid in 61% yield. (*dr* ~ 1:1 by ^{1}H-NMR); **mp** = 165-166 ºC; $\boldsymbol{R_f}$ = 0.31 (pet. ether/ethyl acetate = 7:3); **IR** ($CHCl_3$): ν_{max} = 3631, 2956, 1764, 1594, 1472, 1334, 1233, 1112, 1024, 926, 758 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.93 (s, 1 H), 6.89 (s, 1 H), 6.34 (s, 0.5 H), 6.28 (s, 0.5 H), 5.18 (s, 1 H), 4.04 - 3.74 (m, 11 H), 3.10 (d like, J = 1.8 Hz, 0.5 H), 2.99 (dd, J = 9.2, 18.3 Hz, 0.5 H), 2.78 - 2.73 (m, 0.5 H), 2.72 - 2.66 (m, 0.5 H), 1.90 (s, 3 H), 1.42 (s, 9 H), 1.41 (s, 9 H)**;** **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 176.3, 175.8, 155.9, 153.2, 152.8, 152.6, 151.1, 147.7, 141.9, 141.8, 137.5, 136.8, 136.2, 136.1, 133.0, 131.2, 127.1, 125.3, 125.0, 124.3, 114.9, 105.7, 103.8, 95.3, 61.6, 61.0, 60.9, 57.2, 56.2, 56.1, 55.7, 48.0, 35.6, 35.5, 34.4, 34.3, 30.3, 25.0, 11.6; **HRMS** (ESI^+) calcd for $C_{29}H_{38}O_6$ $[M+ H]^+$ 483.2741, found 483.2741.



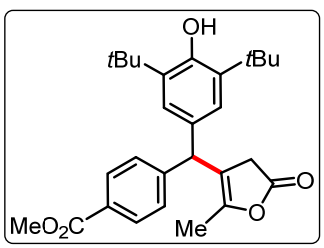
Compound **62g** was obtained as sticky yellow solid in 45% yield. R_f = 0.34 (pet. ether/ethyl acetate = 4:1); **IR** ($CHCl_3$): ν_{max} = 3635, 3019, 2925, 2859, 1751, 1596, 1486, 1446, 1206, 1144, 1026, 950, 755, 703 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.35 - 7.30 (m, 2 H), 7.27 - 7.24 (m, 1 H), 7.12 (d, *J* = 7.6 Hz, 2 H), 6.71 (s, 2 H), 4.94 (s, 1 H), 4.65 (br. s., 1 H), 3.07 (s, 2 H), 2.22 (s, 6 H), 1.91 (s, 3 H)**; ^{13}C NMR** (125 MHz, $CDCl_3$) = 175.9, 151.1, 147.8, 142.0, 132.9, 131.5, 129.7, 128.6, 128.4, 128.1, 126.7, 123.2, 114.4, 47.0, 35.5, 16.0, 11.5; **HRMS** (ESI^+) calcd for $C_{20}H_{20}O_3$ $[M + Na]^+$ 331.1305, found 331.1299.



Compound **62h** was obtained as white solid in 73% yield. **mp** = 94-95 ºC; R_f = 0.35 (pet. ether/ethyl acetate = 9:1); **IR** ($CHCl_3$): ν_{max} = 3633, 2957, 1795, 1483, 1436, 1225, 1149, 961, 758 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.30 (d, *J* = 8.5 Hz, 2 H), 7.08 (d, *J* = 8.5 Hz, 2 H), 6.86 (s, 2 H), 5.18 (s, 1 H), 4.93 (s, 1 H), 3.07 - 3.04 (m, 2 H), 1.91 (s, 3 H), 1.40 (s, 18 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 175.5, 152.7, 148.0, 140.6, 136.2, 132.5, 131.2, 129.8, 128.7, 125.0, 114.3, 47.2, 35.3, 34.3, 30.3, 11.5; **HRMS** (ESI^+) calcd for $C_{26}H_{31}ClO_3$ $[M + Na]^+$ 449.1854, found 449.1844.

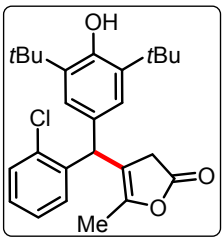


Compound **62i** was obtained as yellow solid in 71% yield. **mp** = 74 ºC; R_f = 0.5 (pet. ether/ethyl acetate = 4:1); **IR** ($CHCl_3$): ν_{max} = 3626, 2956, 1792, 1596, 1520, 1432, 1348, 1228, 1150, 1051, 963, 763 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.20 (d, *J* = 8.5 Hz, 2 H), 7.32 (d, *J* = 8.5 Hz, 2 H), 6.84 (s, 2 H), 5.23 (s, 1 H), 5.05 (s, 1 H), 3.06 (s, 2 H), 1.93 (s, 3 H), 1.40 (s, 18 H)**; ^{13}C NMR** (100 MHz, $CDCl_3$) δ = 175.1, 153.0, 149.8, 148.7, 146.8, 136.5, 130.3, 129.2, 124.9, 123.8, 113.3, 47.7, 35.2, 34.4, 30.2, 11.6; **HRMS** (ESI^+) calcd for $C_{26}H_{31}NO_5$ $[M + Na]^+$ 460.2094, found 460.2084.

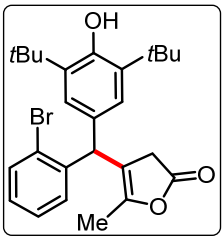


Compound **62j** was obtained as reddish yellow liquid in 82% yield. R_f = 0.20 (pet. ether/ethyl acetate = 9:1); **IR** ($CHCl_3$): ν_{max} = 3632, 2958, 1792, 1718, 1609, 1437, 1282, 1228, 1115, 1054, 961, 757 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 8.00 (d,

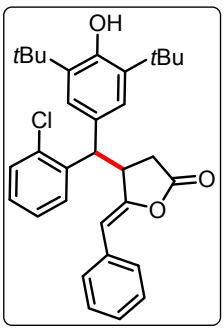
J = 8.5 Hz, 2 H), 7.23 (d, *J* = 7.9 Hz, 2 H), 6.86 (s, 2 H), 5.20 (s, 1 H), 5.01 (s, 1 H), 3.93 (s, 3 H), 3.09 - 3.05 (m, 2 H), 1.93 - 1.89 (m, 3 H), 1.39 (s, 18 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 175.5, 166.8, 152.7, 148.2, 147.4, 136.3, 131.0, 129.8, 128.7, 128.5, 125.0, 114.0, 52.1, 47.8, 35.4, 34.3, 30.2, 11.5; **HRMS** (ESI^+) calcd for $C_{28}H_{34}O_5$ $[M + Na]^+$ 473.2298, found 473.2290.



Compound **62k** was obtained as pale yellow solid in 76% yield. **mp** = 138-140 ºC; R_f = 0.37 (pet. ether/ethyl acetate = 9:1); **IR** ($CHCl_3$): ν_{max} = 3632, 3056, 2956, 1795, 1435, 1388, 1224, 1149, 1047, 963, 757 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.45 - 7.39 (m, 1 H), 7.22 -7.20 (m, 2 H), 7.04 - 6.99 (m, 1 H), 6.90 (s, 2 H), 5.39 (s, 1 H), 5.19 (s, 1 H), 3.22 - 3.14 (m, 1 H), 2.99 - 2.91 (m, 1 H), 1.83 (s, 3 H), 1.41 (s, 18 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 175.7, 152.6, 148.8, 140.1, 136.1, 134.3, 130.4, 130.0, 129.8, 128.1, 126.7, 124.9, 113.0, 44.4, 35.9, 34.3, 30.2, 11.7; **HRMS** (ESI^+) calcd for $C_{26}H_{31}ClO_3$ $[M + Na]^+$ 449.1854, found 449.1848.

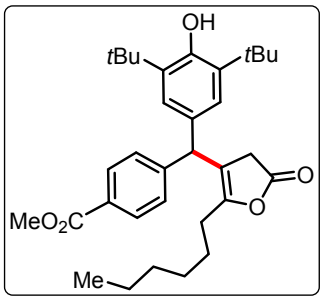


Compound **62l** was obtained as white solid in 69% yield. **mp** = 150-151 ºC; R_f = 0.52 (pet. ether/ethyl acetate = 9:1); **IR** ($CHCl_3$): ν_{max} = 3633, 2959, 1795, 1434, 1388, 1224, 1150, 1054, 963, 757 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.63 (d, *J* = 7.9 Hz, 1 H), 7.30 - 7.24 (m, 1 H), 7.17 - 7.11 (m, 1 H), 7.01 (d, *J* = 6.7 Hz, 1 H), 6.92 (s, 2 H), 5.37 (s, 1 H), 5.20 (s, 1 H), 3.25 - 3.16 (m, 1 H), 3.00 - 2.91 (m, 1 H), 1.85 (s, 3 H), 1.42 (s, 18 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 175.7, 152.6, 148.9, 141.8, 136.1, 133.2, 130.5, 130.2, 128.3, 127.4, 125.1, 124.9, 113.0, 47.2, 36.0, 34.3, 30.3, 11.8; **HRMS** (ESI^+) calcd for $C_{26}H_{31}BrO_3$ $[M + Na]^+$ 493.1349, found 493.1342.

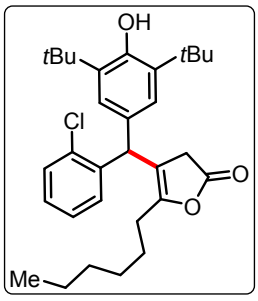


Compound **62m** was obtained as white solid in 60% yield. **mp** = 215-216 ºC; R_f = 0.36 (pet. ether/ethyl acetate = 9:1); **IR** ($CHCl_3$): ν_{max} = 3629, 3015, 2958, 1803, 1726, 1437, 1358, 1227, 1115, 1037, 951, 757 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.43 (d, J = 8.0 Hz, 1 H), 7.40 (d, J = 8.5 Hz, 1 H), 7.34 - 7.28 (m, 3 H), 7.27 - 7.20 (m, 3 H), 7.19 - 7.14 (m, 1 H), 7.10 (s, 2 H), 5.15 (s, 1 H), 4.53 - 4.47 (m, 2 H), 4.00 - 3.91 (m, 1 H), 2.86 (dd, J = 9.2, 18.3 Hz, 1 H), 2.35 (dd, J = 3.7, 18.3 Hz, 1 H), 1.37 (s, 18 H)**;** **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 173.6, 152.9, 149.1, 139.6, 136.0,

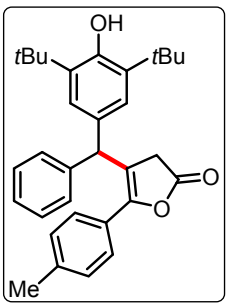
134.7, 133.6, 130.3, 128.5, 128.3, 128.1, 128.0, 127.1, 126.8, 125.7, 107.7, 51.2, 43.4, 34.3, 33.4, 30.3; **HRMS** (ESI^+) calcd for $C_{32}H_{35}ClO_3$ $[M + Na]^+$ 525.2167, found 525.2168.



Compound **62n** was obtained as pale yellow liquid in 68% yield. R_f = 0.23 (pet. ether/ethyl acetate = 9:1); **IR** ($CHCl_3$): ν_{max} = 3634, 2956, 2866, 1793, 1719, 1608, 1438, 1364, 1283, 1229, 1149, 1115, 1015, 974, 758 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 8.00 (d, *J* = 7.9 Hz, 2 H), 7.23 (d, *J* = 8.5 Hz, 2 H), 6.85 (s, 2 H), 5.18 (s, 1 H), 5.04 (s, 1 H), 3.93 (s, 3 H), 3.07 (s, 2 H), 2.27 (t, *J* = 7.0 Hz, 2 H), 1.57 - 1.49 (m, 2 H), 1.39 (s, 18 H), 1.31 - 1.21 (m, 6 H), 0.86 (t, *J* = 6.7 Hz, 3 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 175.7, 166.8, 152.7, 152.1, 147.5, 136.2, 131.1, 129.8, 128.7, 128.5, 125.0, 113.8, 52.1, 47.6, 35.2, 34.3, 31.4, 30.2, 28.9, 26.6, 25.7, 22.5, 14.0; **HRMS** (ESI^+) calcd for $C_{33}H_{44}O_5$ $[M + Na]^+$ 543.3081, found 543.3088.

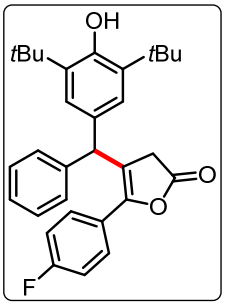


Compound **62o** was obtained as white solid in 62% yield. **mp** = 68-69 ºC; R_f = 0.33 (pet. ether/ethyl acetate = 9:1); **IR** ($CHCl_3$): ν_{max} = 3634, 3066, 2955, 2866, 1796, 1436, 1230, 1149, 1034, 981, 756 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.44 - 7.38 (m, 1 H), 7.23 - 7.18 (m, 2 H), 7.02- 7.00 (m, 1 H), 6.89 (s, 2 H), 5.40 (s, 1 H), 5.16 (s, 1 H), 3.21 - 3.13 (m, 1 H), 2.99 - 2.92 (m, 1 H), 2.23 - 2.08 (m, 2 H), 1.46 - 1.43 (m, 2 H), 1.39 (s, 18 H), 1.24 - 1.21 (m, 2 H), 1.19 - 1.18 (m, 4 H), 0.85 (t, *J* = 7.0 Hz, 3 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 175.9, 152.7, 152.6, 140.2, 136.0, 134.3, 130.5, 130.1, 129.9, 128.1, 126.7, 124.9, 112.8, 44.4, 36.0, 34.4, 31.4, 30.3, 28.9, 26.5, 26.0, 22.4, 14.0; **HRMS** (ESI^+) calcd for $C_{31}H_{41}ClO_3$ $[M + Na]^+$ 519.2636, found 519.2631.

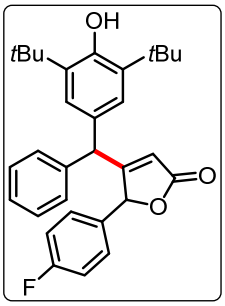


Compound **62p** was obtained as pale yellow solid in 63% yield. **mp** = 130-132 ºC; R_f = 0.40 (pet. ether/ethyl acetate = 9:1); **IR** ($CHCl_3$): ν_{max} = 3632, 2958, 1798, 1599, 1436, 1229, 1164, 1036, 819, 757 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 7.45 (d, *J* = 8.1 Hz, 2 H), 7.41 - 7.28 (m, 3 H), 7.26 - 7.20 (m, 3 H), 7.17 (br. s., 1 H), 6.91 (s, 2 H), 5.35 (s, 1 H), 5.19 (s, 1 H), 3.27 (d like, *J* = 2.3 Hz, 2 H), 2.40 (s, 3

H), 1.40 (s, 18 H)**;** ^{13}**C NMR** (50 MHz, $CDCl_3$) δ = 175.4, 152.6, 148.5, 142.1, 139.5, 136.0, 132.0, 129.3, 128.6, 128.5, 127.3, 126.7, 125.9, 125.2, 115.4, 47.9, 36.4, 34.3, 30.3, 21.4; **HRMS** (ESI^+) *m/z* = calcd for $C_{32}H_{36}O_3$ $[M + Na]^+$ 491.2557, found 491.2548.



Compound **62q** was obtained as pale yellow solid in 63% yield. **mp** = 69 ºC; $\boldsymbol{R_f}$ = 0.35 (pet. ether/ethyl acetate = 9:1); **IR** ($CHCl_3$): ν_{max} = 3632, 2958, 1797, 1600, 1504, 1437, 1233, 1159, 1037, 836, 758 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ = 7.51 (dd, *J* = 5.5, 8.5 Hz, 2 H), 7.38 - 7.31 (m, 2 H), 7.31 - 7.26 (m, 1 H), 7.16 (d, *J* = 7.3 Hz, 2 H), 7.09 (t, *J* = 8.5 Hz, 2 H), 6.87 (s, 2 H), 5.27 (s, 1 H), 5.17 (s, 1 H), 3.34 - 3.17 (m, 2 H), 1.38 (s, 18 H)**;** ^{13}**C NMR** (100MHz, $CDCl_3$) δ = 175.0, 152.7, 147.5, 141.9, 136.2, 131.8, 129.4, 129.3, 128.7, 128.5, 126.9, 125.1, 116.1, 115.9, 115.6, 48.0, 36.4, 34.3, 30.3; **HRMS** (ESI^+) *m/z* = calcd for $C_{31}H_{33}FO_3$ $[M + Na]^+$ 495.2306, found 495.2298.

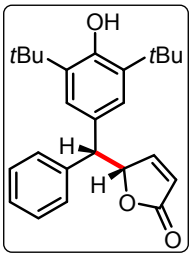


Compound **62q'** was obtained as colourless liquid after column purification in 30% yield. (*dr* ~ 7:3 by ^{1}H-NMR); $\boldsymbol{R_f}$ = 0.23 (pet. ether/ethyl acetate = 9:1); **IR** ($CHCl_3$): ν_{max} = 3631, 2958, 1755, 1599, 1506, 1436, 1228, 1158, 1013, 835, 706 cm^{-1}; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ = 7.45 - 7.28 (m, 2 H), 7.27 - 7.14 (m, 2 H), 7.12 - 6.98 (m, 4 H), 6.91 (s, 0.6 H), 6.73 (s, 1.4 H), 5.82 - 5.64 (m, 2 H), 5.27 (s, 0.3 H), 5.14 (s, 0.7 H), 4.44 (s, 0.7 H), 4.41 (s, 0.3 H), 1.43 (s, 5.4 H), 1.35 (s, 12.6 H)**;** ^{13}**C NMR** (100 MHz, $CDCl_3$) δ = 176.0, 175.8, 172.8, 172.7, 164.5, 164.4, 162.0, 153.3, 152.8, 140.2, 139.2, 136.7, 136.1, 130.4, 130.3, 130.2, 130.1, 129.1, 128.9, 128.8, 128.7, 128.6, 128.2, 127.6, 127.2, 125.6, 124.7, 118.0, 117.3, 116.2, 116.1, 115.9, 115.8, 84.6, 84.5, 51.2, 51.0, 34.4, 34.3, 30.3, 30.1; **HRMS** (ESI^+) *m/z* = calcd for $C_{31}H_{33}FO_3$ $[M + H]^+$ 473.2486, found 473.2478.

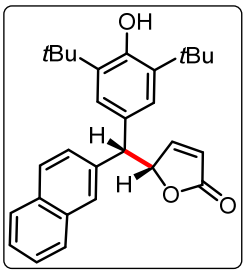
VI. General Procedure for γ-addition of γ-unsubstituted Silyloxyfuran derivatives (66a & 66b) to *p*-QMs:

To a solution of *p*-QMs **60** (0.17 mmol, 1 equiv.) and silyloxyfuran derivatives **66** (0.17 mmol, 1 equiv.) in CH_2Cl_2 (2 mL) cooled to 0 °C was added $BF_3.OEt_2$ (20 mol%). The resulting mixture was stirred for 15 min at that temperature until the yellow-orange color

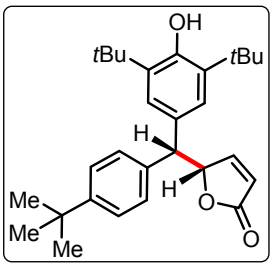
of reaction mixture disappears as also indicated by TLC. After completion of the reaction, the solvent was concentrated in *vacuo*, and the residue was subjected to flash silica gel chromatography (ethyl acetate/hexane) to give desired products **67a-67i**.



Compound **67a** was obtained as pale yellow liquid in 93% yield. (*dr* ~ 7:3 by ^{1}H-NMR); R_f = 0.32 (pet. ether/ethyl acetate = 9:1); **IR** ($CHCl_3$): ν_{max} = 3633, 2959, 1755, 1595, 1438, 1360, 1314, 1228, 1160, 1099, 1035, 897, 757, 702 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.36 - 7.33 (m, 3 H), 7.32 - 7.29 (m, 2 H), 7.28 - 7.22 (m, 1 H), 7.09 (s, 0.6 H), 7.08 (s, 1.4 H), 6.08 - 6.03 (m, 1 H), 5.71 - 5.66 (m, 1 H), 5.18 (s, 0.3 H), 5.13 (s, 0.7 H), 4.07 - 4.01 (m, 1 H), 1.42 (s, 6 H), 1.41 (s, 12 H)**; ^{13}C NMR** (100 MHz, $CDCl_3$) δ = 172.9, 172.8, 156.0, 155.9, 152.9, 152.8, 140.5, 139.7, 136.2, 135.7, 130.4, 129.6, 128.8, 128.4, 128.3, 128.2, 127.2, 127.0, 124.8, 124.7, 122.1, 122.0, 85.3, 85.2, 55.1, 34.4, 34.3, 30.2; **HRMS** (ESI^+) calcd for $C_{25}H_{30}O_3$ $[M + Na]^+$ 401.2087, found 401.2086.

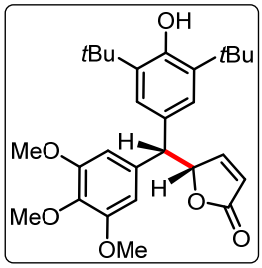


Compound **67b** was obtained as white solid in 88% yield. (*dr* ~ 4:1 by ^{1}H-NMR); **mp** = 172-175 ºC; R_f = 0.54 (pet. ether/ethyl acetate = 4:1); **IR** ($CHCl_3$): ν_{max} = 3628, 3012, 2959, 1754, 1636, 1436, 1361, 1227, 1158, 1104, 1034, 892, 815, 756 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.86 - 7.81 (m, 3 H), 7.81 - 7.77 (m, 1 H), 7.53 - 7.40 (m, 3 H), 7.39 (d, *J* = 5.3 Hz, 0.3 H), 7.32 (d, *J* = 5.3 Hz, 0.7 H), 7.15 (s, 0.6 H), 7.14 (s, 1.4 H), 6.08 - 6.03 (m, 1 H), 5.84 - 5.78 (m, 1 H), 5.19 (s, 0.3 H), 5.14 (s, 0.7 H), 4.25 - 4.20 (m, 1 H), 1.43 (s, 5.4 H), 1.43 (s, 12.6 H)**; ^{13}C NMR** (125 MHz, $CDCl_3$) δ = 172.9, 172.8, 156.0, 155.8, 153.0, 152.9, 138.0, 137.3, 136.3, 135.8, 133.4, 133.3, 132.4, 130.3, 129.4, 128.5, 128.1, 127.9, 127.6, 127.6, 126.8, 126.8, 126.7, 126.4, 126.3, 126.0, 126.0, 125.8, 125.0, 124.8, 122.1, 122.1, 85.2, 85.1, 55.2, 55.1, 34.4, 34.3, 30.2; **HRMS** (ESI^+) calcd for $C_{29}H_{32}O_3$ $[M + H]^+$ 429.2424, found 429.2420.

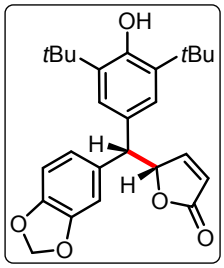


Compound **67c** was obtained as white solid in 80% yield. (*dr* ~ 3:2 by ^{1}H-NMR); **mp** = 143-145 ºC; R_f = 0.48 (pet. ether/ethyl acetate = 4:1); **IR** ($CHCl_3$): ν_{max} = 3631, 2958, 2909, 1754, 1434, 1362, 1223, 1158, 1103, 895, 813, 760 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.38 - 7.30 (m, 3 H), 7.29 - 7.25 (m, 2 H), 7.10 (s, 2 H), 6.07 (dd, *J* = 1.7, 5.5 Hz, 0.4 H), 6.04 (dd, *J* = 1.5, 5.7 Hz, 0.6 H), 5.69 - 5.64 (m, 1

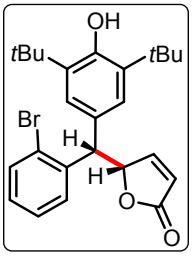
H), 5.17 (s, 0.4 H), 5.12 (s, 0.6 H), 4.02 - 3.96 (m, 1 H), 1.43 (s, 7.2 H), 1.44 (m, 10.8 H), 1.32 (s, 5.4 H), 1.31 (m, 3.6 H)**;** ^{13}**C NMR** (125 MHz, $CDCl_3$) δ = 173.0, 172.9, 156.2, 156.1, 152.9, 152.8, 150.0, 149.7, 137.4, 136.8, 136.2, 135.7, 130.5, 129.9, 127.8, 127.7, 125.7, 125.4, 124.8, 124.7, 122.0, 121.9, 85.7, 85.6, 54.9, 34.5, 34.4, 34.3, 31.3, 30.3; **HRMS** (ESI^+) calcd for $C_{29}H_{38}O_3$ $[M + H]^+$ 435.2894, found 435.2891.



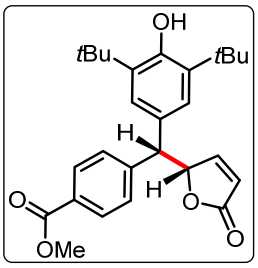
Compound **67d** was obtained as orange liquid in 80% yield. (*dr* ~ 7:3 by ^{1}H-NMR); R_f = 0.42 (pet. ether/ethyl acetate = 7:3); **IR** ($CHCl_3$): ν_{max} = 3633, 3010, 2958, 1754, 1592, 1504, 1432, 1326, 1232, 1125, 1035, 895 817, 757 cm^{-1}; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ = 7.33 (dd, *J* = 1.1, 5.7 Hz, 0.7 H), 7.31 (dd, *J* = 1.1, 5.7 Hz, 0.3 H), 7.13 (s, 0.6 H), 7.11 (s, 1.4 H), 6.58 (s, 1.4 H), 6.55 (s, 0.6 H), 6.07 (dd, *J* = 1.9, 5.7 Hz, 0.3 H), 6.04 (dd, *J* = 1.9, 5.7 Hz, 0.7 H), 5.65 - 5.59 (m, 1 H), 5.20 (s, 0.3 H), 5.15 (s, 0.7 H), 3.97 (d, *J* = 7.3 Hz, 0.7 H), 3.94 (d, *J* = 8.0 Hz, 0.3 H), 3.88 - 3.81 (m, 9 H), 1.43 (s, 5.4 H), 1.42 (s, 12.6 H)**;** ^{13}**C NMR** (125 MHz, $CDCl_3$) δ = 172.9, 172.8, 155.9, 155.8, 153.3, 153.1, 153.0, 152.9, 137.1, 137.0, 136.2, 136.1, 135.7, 135.3, 130.1, 129.2, 124.8, 124.6, 122.1, 122.0, 105.5, 105.3, 85.6, 85.5, 60.8, 60.7, 56.1, 56.0, 55.3, 55.2, 34.4, 34.3, 30.2; **HRMS** (ESI^+) calcd for $C_{28}H_{36}O_6$ $[M + Na]^+$ 491.2404, found 491.2393.



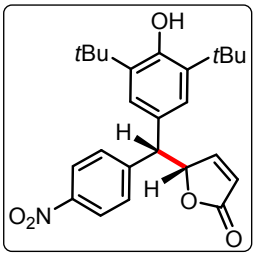
Compound **67e** was obtained as pale yellow solid in 78% yield. (*dr* ~ 11:9 by ^{1}H-NMR); **mp** = 128-131 ºC; R_f = 0.24 (pet. ether/ethyl acetate = 9:1); **IR** ($CHCl_3$): ν_{max} = 3628, 2959, 2909, 1754, 1491, 1438, 1360, 1241, 1161, 1104, 931, 813, 758 cm^{-1}; ^{1}**H NMR** (500 MHz , $CDCl_3$) δ = 7.32 (d, *J* = 5.7 Hz, 1 H), 7.08 (s, 1 H), 7.06 (s, 1 H), 6.83 - 6.72 (m, 3 H), 6.06 (dd, *J* = 1.9, 5.7 Hz, 0.55 H), 6.04 (dd, *J* = 1.9, 5.7 Hz, 0.45 H), 5.95 (s, 1 H), 5.93 (s, 1 H), 5.65 - 5.58 (m, 1 H), 5.18 (s, 0.55 H), 5.13 (s, 0.45 H), 3.96 (dd, *J* = 8.0, 10.3 Hz, 1 H), 1.43 (s, 9.9 H), 1.42 (s, 8.1 H)**;** ^{13}**C NMR** (125 MHz, $CDCl_3$) δ = 172.9, 172.8, 156.0, 155.8, 153.0, 152.9, 147.9, 147.7, 146.6, 146.5, 136.3, 135.8, 134.4, 133.7, 130.6, 129.8, 124.7, 124.6, 122.1, 122.0, 121.5, 121.4, 109.0, 108.7, 108.5, 108.1, 101.1, 101.0, 85.4, 85.2, 54.8, 54.7, 34.4, 34.3, 30.3; **HRMS** (ESI^+) calcd for $C_{26}H_{30}O_5$ $[M + H]^+$ 423.2166, found 423.2163.



Compound **67f** was obtained as pale yellow solid in 84% yield. (*dr* ~ 4:1 by ^{1}H-NMR); **mp** = 136-138 ºC; $\boldsymbol{R_f}$ = 0.52 (pet. ether/ethyl acetate = 3:1); IR ($CHCl_3$): ν_{max} = 3622, 2957, 1755, 1591, 1434, 1362, 1224, 1158, 1107, 1031, 769 cm^{-1}; **^{1}H NMR** (500 MHz , $CDCl_3$) δ = 7.67 - 7.58 (m, 1 H), 7.56 - 7.43 (m, 1 H), 7.35 (t, *J* = 7.6 Hz, 1 H), 7.29 (dd like, *J* = 1.1, 5.7 Hz, 1 H), 7.19 - 7.06 (m, 3 H), 6.08 - 6.02 (m, 1 H), 5.73 (d, *J* = 7.2 Hz, 0.2 H), 5.67 (d, *J* = 6.5 Hz, 0.8 H), 5.19 (s, 0.2 H), 5.12 (s, 0.8 H), 4.72 (d, *J* = 6.9 Hz, 0.2 H), 4.65 (d, *J* = 6.9 Hz, 0.8 H), 1.42 (s, 3.6 H), 1.40 (s, 14.4 H)**; ^{13}C NMR** (125 MHz, $CDCl_3$) δ = 172.8, 172.7, 155.5, 155.4, 153.0, 152.9, 140.2, 136.2, 135.6, 133.4, 133.0, 129.7, 129.6, 129.3, 128.6, 128.5, 128.0, 127.9, 127.5, 125.4, 125.0, 124.7, 122.4, 122.1, 84.9, 84.6, 52.8, 52.6, 34.4, 34.3, 30.2; **HRMS** (ESI^+) calcd for $C_{25}H_{29}BrO_3$ $[M + H]^+$ 457.1370, found 457.1373.

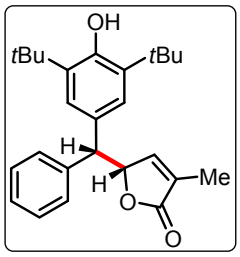


Compound **67g** was obtained as reddish yellow solid in 91% yield. (*dr* ~ 7:3 by ^{1}H-NMR); **mp** = 64-65 ºC; $\boldsymbol{R_f}$ = 0.37 (pet. ether/ethyl acetate = 7:3); **IR** ($CHCl_3$): ν_{max} = 3631, 2985, 1758, 1719, 1609, 1436, 1284, 1234, 1160, 1108, 1031, 897, 816, 757 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 8.02 (d, *J* = 8.4 Hz, 1.4 H), 7.99 (d, *J* = 8.4 Hz, 0.6 H), 7.44 (d, *J* = 8.4 Hz, 1.4 H), 7.39 (d, *J* = 8.4 Hz, 0.6 H), 7.33 (d, *J* = 5.7 Hz, 0.3 H), 7.30 (d, *J* = 5.7 Hz, 0.7 H), 7.05 (s, 0.6 H), 7.03 (s, 1.4 H), 6.08 (dd, *J* = 1.9, 5.7 Hz, 0.3 H), 6.03 (dd, *J* = 1.9, 5.7 Hz, 0.7 H), 5.73 - 5.67 (m, 1 H), 5.21 (s, 0.3 H), 5.16 (s, 0.7 H), 4.17 (d, *J* = 6.5 Hz, 0.7 H), 4.06 (d, *J* = 8.0 Hz, 0.3 H), 3.92 (s, 2.1 H), 3.90 (s, 0.9 H), 1.41 (s, 5.4 H), 1.40 (s, 12.6 H)**; ^{13}C NMR** (125 MHz, $CDCl_3$) δ = 172.6, 166.8, 166.7, 155.7, 155.2, 153.2, 153.0, 145.7, 145.1, 136.5, 135.9, 130.1, 129.8, 129.6, 129.0, 128.8, 128.5, 128.4, 125.0, 124.7, 122.5, 122.2, 84.7, 84.6, 55.1, 54.7, 52.1, 52.0, 34.4, 34.3, 30.2; **HRMS** (ESI^+) calcd for $C_{27}H_{32}O_5$ $[M + Na]^+$ 459.2142, found 459.2133.



Compound **67h** was obtained as pale yellow solid in 85% yield. (*dr* ~ 3:2 by ^{1}H-NMR); **mp** = 182-185 ºC; $\boldsymbol{R_f}$ = 0.29 (pet. ether/ethyl acetate = 4:1); **IR** ($CHCl_3$): ν_{max} = 3630, 3020, 2961, 1758, 1600, 1521, 1436, 1349, 1220, 1159, 1106, 759 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 8.24 - 8.15 (m, 2 H), 7.58 (d, *J* = 8.8 Hz, 1.2 H), 7.49 (d, *J* = 8.4 Hz, 0.8 H), 7.34 (d, *J* = 5.7 Hz, 1 H), 7.05 (s, 0.8 H), 6.98 (s, 1.2 H), 6.13

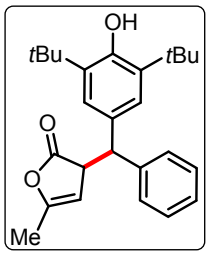
(dd, *J* = 1.5, 5.7 Hz, 0.4 H), 6.03 (dd, *J* = 1.5, 5.7 Hz, 0.6 H), 5.72 (d, *J* = 5.3 Hz, 0.6 H), 5.69 (d, *J* = 8.4 Hz, 0.4 H), 5.26 (s, 0.4 H), 5.20 (s, 0.6 H), 4.31 (d, *J* = 5.3 Hz, 0.6 H), 4.09 (d, *J* = 8.4 Hz, 0.4 H), 1.42 (s, 7.2 H), 1.40 (s, 10.8 H)**;** ^{13}**C NMR** (125 MHz, $CDCl_3$) δ = 172.2, 155.4, 154.7, 153.4, 153.3, 148.0, 147.4, 147.0, 146.9, 136.8, 136.2, 129.3, 129.2, 129.0, 127.4, 125.1, 124.6, 123.9, 123.7, 122.8, 122.5, 84.3, 84.0, 55.0, 54.1, 34.4, 34.3, 30.2; **HRMS** (ESI^+) calcd for $C_{25}H_{29}NO_5$ $[M + Na]^+$ 446.1938, found 446.1935.



Compound **67i** was obtained as pale yellow solid in 80% yield. (*dr* ~ 1:1 by ^{1}H-NMR); **mp** = 126-128 ºC; R_f = 0.42 (pet. ether/ethyl acetate = 9:1); **IR** ($CHCl_3$): ν_{max} = 3628, 2958, 1754, 1652, 1438, 1360, 1229, 1154, 1101, 1055. 886, 760, 701 cm^{-1}; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ = 7.31 (s, 1 H), 7.30 (s, 1 H), 7.29 - 7.27 (m, 1 H), 7.27 - 7.15 (m, 2 H), 7.04 (s, 1 H), 7.03 (s, 1 H), 6.90 (s, 0.5 H), 6.84 (s, 0.5 H), 5.54 - 5.47 (m, 1 H), 5.13 (s, 0.5 H), 5.08 (s, 0.5 H), 3.95 (s, 0.5 H), 3.93 (s, 0.5 H), 1.81 (s, 1.5 H), 1.78 (s, 1.5 H), 1.39 (s, 9 H), 1.37 (s, 9 H)**;** ^{13}**C NMR** (125 MHz, $CDCl_3$) δ = 174.0, 173.9, 152.8, 152.7, 148.3, 148.2, 140.7, 140.1, 136.1, 135.6, 130.5, 130.4, 129.9, 128.7, 128.4, 128.3, 128.2, 127.0, 126.8, 124.8, 124.7, 83.0, 82.9, 55.3, 55.2, 34.3, 34.2, 30.2, 10.6, 10.5; **HRMS** (ESI^+) calcd for $C_{26}H_{32}O_3$ $[M + H]^+$ 393.2424, found 393.2420.

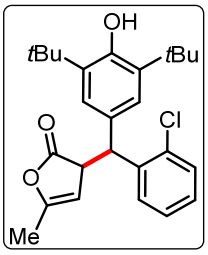
VII. General Procedure for *α*-addition of *γ*-substituted Silyloxyfuran derivatives (66c-66e) to *p*-QMs:

The desired products **68a-68e** was prepared as per the general procedure VI.

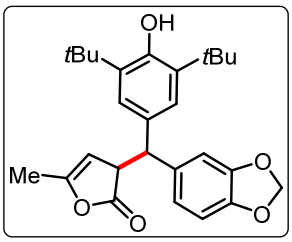


Compound **68a** was obtained as pale yellow solid in 66% yield. (*dr* ~ 3:2 by ^{1}H-NMR); **mp** = 53-56 ºC; R_f = 0.38 (pet. ether/ethyl acetate = 19:1); **IR** ($CHCl_3$): ν_{max} = 3632, 2959, 1778, 1601, 1438, 1370, 759, 700, 1288, 1234, 1155, 1120, 1042, 936 cm^{-1}; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ = 7.35 - 7.30 (m, 1 H), 7.28 - 7.17 (m, 4 H), 7.04 (s, 1 H), 6.98 (s, 1 H), 5.23 (s, 0.4 H), 5.20 (s, 0.6 H), 5.13 (s, 0.4 H), 5.09 (s, 0.6 H), 4.56 (d, *J* = 5.0 Hz, 0.4 H), 4.51 (d, *J* = 5.3 Hz, 0.6 H), 4.05 - 4.0 (m, 1 H), 1.90 (s, 1.8 H), 1.88 (s, 1.2 H), 1.42 (s, 7.2 H), 1.39 (s, 10.8 H); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ = 177.9, 177.7, 152.6, 152.4, 152.3, 152.2, 142.2, 140.6, 135.7, 135.4, 132.0, 130.5, 128.9, 128.4, 128.1,

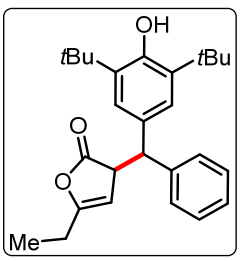
128.0, 126.8, 126.5, 125.4, 124.6, 102.9, 102.6, 51.4, 51.3, 50.9, 34.4, 34.3, 30.3, 30.2, 13.9, 13.8; **HRMS** (ESI^+) calcd for $C_{26}H_{32}O_3$ $[M + H]^+$ 393.2424, found 393.2415.



Compound **68b** was obtained as pale yellow solid in 69% yield. (*dr* ~ 3:2 by HPLC); **mp** = 57-57 ºC; $\boldsymbol{R_f}$ = 0.33 (pet. ether/ethyl acetate = 19:1); **IR** ($CHCl_3$): ν_{max} = 3631, 2958, 1787, 1470, 1436, 1371, 1233, 1156, 1118, 1042, 889, 758 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.49 - 7.35 (m, 1 H), 7.27 - 7.15 (m, 3 H), 7.06 - 6.99 (m, 2 H), 5.14 - 5.08 (m, 2 H), 4.97 - 4.92 (m, 1 H), 4.09 - 4.04 (m, 1 H), 1.98 - 1.93 (m, 3 H), 1.40 (s, 18 H)**; ^{13}C NMR** (125 MHz, $CDCl_3$) δ = 177.1, 176.9, 152.7, 152.6, 152.2, 152.1, 139.7, 139.3, 135.7, 135.6, 134.1, 133.8, 130.2, 130.0, 129.9, 129.8, 129.5, 129.3, 127.9, 127.8, 126.8, 126.6, 125.0, 124.9, 103.4, 103.2, 49.7, 49.1, 47.4, 47.2, 34.4, 34.3, 30.3, 14.1, 14.0; **HRMS** (ESI^+) calcd for $C_{26}H_{31}ClO_3$ $[M + H]^+$ 427.2034, found 427.2028.

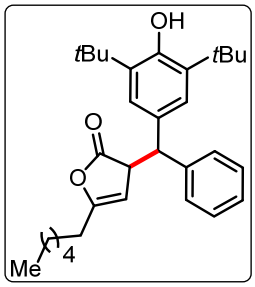


Compound **68c** was obtained as pale yellow solid in 64% yield. (*dr* ~ 11:9 by ^{1}H-NMR); **mp** = 60-61 ºC; $\boldsymbol{R_f}$ = 0.34 (pet. ether/ethyl acetate = 19:1); **IR** ($CHCl_3$): ν_{max} = 3632, 2957, 1767, 1646, 1490, 1436, 1238, 1115, 1039, 932, 767 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.02 (s, 1 H), 6.97 (s, 1 H), 6.77 - 6.64 (m, 3 H), 5.94 (s, 1 H), 5.92 (d like, *J* = 1.9 Hz, 1 H), 5.24 (s, 0.45 H), 5.18 (s, 0.55 H), 5.13 (s, 0.45 H), 5.09 (s, 0.55 H), 4.50 (d, *J* = 4.6 Hz, 0.45 H), 4.39 (d, *J* = 5.7 Hz, 0.55 H), 4.01 - 3.97 (m, 0.45 H), 3.96 - 3.94 (m, 1 H), 1.91 (s, 3 H), 1.42 (s, 8 H), 1.39 (s, 10 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 177.9, 177.5, 152.6, 152.5, 152.4, 152.2, 147.7, 147.3, 146.3, 146.1, 136.2, 135.7, 135.5, 134.6, 132.2, 130.8, 125.2, 124.9, 124.4, 122.2, 120.9, 109.4, 108.6, 108.0, 107.9, 102.9, 102.5, 101.0, 100.8, 51.1, 51.0, 50.9, 50.8, 34.4, 34.3, 30.3, 30.2, 14.0; **HRMS** (ESI^+) calcd for $C_{27}H_{32}O_5$ $[M + Na]^+$ 459.2142, found 459.2132.

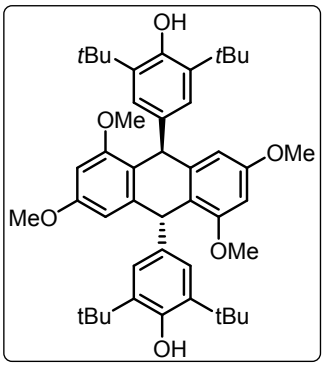


Compound **68d** was obtained as pale yellow liquid in 58% yield. (*dr* ~ 11:9 by ^{1}H-NMR); $\boldsymbol{R_f}$ = 0.45 (pet. ether/ethyl acetate = 19:1); **IR** ($CHCl_3$): ν_{max} = 3631, 2959, 1783, 1438, 1362, 1233, 1152, 1120, 761, 701 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.36 - 7.30 (m, 1 H), 7.30 - 7.23 (m, 3 H), 7.22 - 7.17 (m, 1 H), 7.05 (s, 1 H), 6.95 (s, 1 H), 5.21 (s, 0.45 H), 5.18 (d like, *J* = 1.2 Hz, 0.55 H), 5.14 (s, 0.45 H), 5.09 (s, 0.55 H), 4.57

(t, *J* = 4.6 Hz, 1 H), 4.05 - 3.99 (m, 1 H), 2.24 - 2.12 (m, 2 H), 1.42 (s, 8.1 H), 1.38 (s, 9.9 H), 1.04 - 0.96 (m, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 178.1, 178.0, 157.6, 157.4, 152.6, 152.4, 142.2, 140.5, 135.7, 135.3, 132.0, 130.5, 129.0, 128.4, 128.0, 127.9, 126.8, 126.6, 125.5, 124.6, 101.0, 100.9, 51.5, 51.4, 50.5, 50.4, 34.4, 34.2, 30.3, 21.4, 10.2, 10.0; **HRMS** (ESI^+) calcd for $C_{27}H_{34}O_3$ $[M + Na]^+$ 429.2400, found 429.2395.

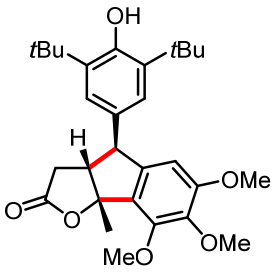
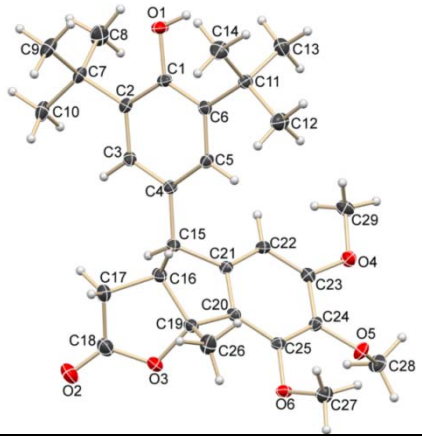
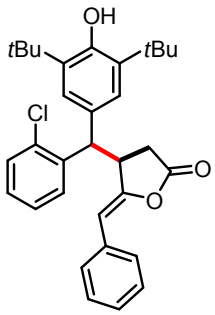
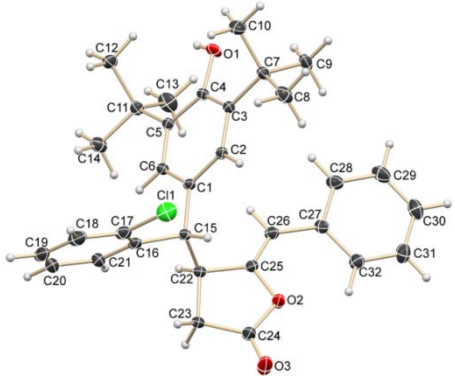
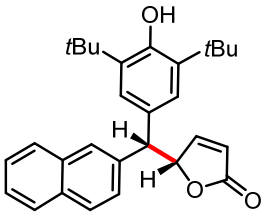
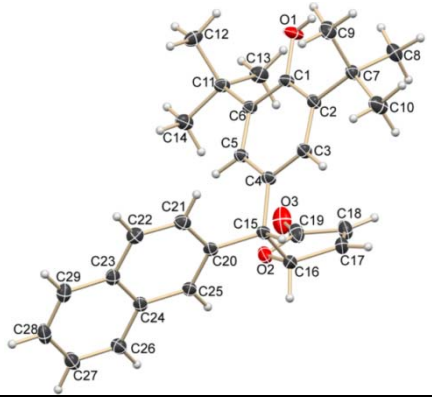


Compound **68e** was obtained as colourless liquid in 65% yield. (*dr* ~ 11:9 by ^{1}H-NMR); ***R*$_f$** = 0.51 (pet. ether/ethyl acetate = 9:1); **IR** ($CHCl_3$): ν_{max} = 3630, 2925, 2861, 1783, 1438, 1369, 1232, 1118, 767, 702 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.35 - 7.30 (m, 1 H), 7.29 - 7.27 (m, 1 H), 7.27 - 7.19 (m, 2 H), 7.19 - 7.15 (m, 1 H), 7.05 (s, 1 H), 6.94 (s, 1 H), 5.22 (s, 0.45 H), 5.17 (s, 0.55 H), 5.13 (s, 0.45 H), 5.08 (s, 0.55 H), 4.58 (d, *J* = 4.3 Hz, 0.45 H), 4.55 (d, *J* = 4.9 Hz, 0.55 H), 4.04 - 3.99 (m, 1 H), 2.15 (t, *J* = 7.0 Hz, 2 H), 1.42 (s, 8.1 H), 1.38 (s, 9.9 H), 1.31 - 1.21 (m, 8 H), 0.89 - 0.86 (m, 3 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 178.2, 178.0, 156.4, 156.3, 152.6, 152.4, 142.2, 140.6, 135.7, 135.3, 132.1, 130.7, 129.0, 128.4, 128.1, 128.0, 126.8, 126.5, 125.5, 124.6, 101.8, 101.7, 98.1, 51.5, 51.4, 50.6, 50.5, 34.4, 34.3, 33.9, 31.5, 31.4, 31.3, 30.3, 28.6, 28.4, 28.3, 28.2, 28.1, 25.7, 25.6, 22.5, 22.4, 22.3, 14.1, 14.0; **HRMS** (ESI^+) calcd for $C_{31}H_{42}O_3$ $[M + Na]^+$ 485.3018, found 485.3026.



Compound **69** was obtained as white solid in 88% yield. **mp** = 259-260 ºC; ***R*$_f$** = 0.40 (pet. ether/ethyl acetate = 19:1); **IR** ($CHCl_3$): ν_{max} = 3636, 2955, 1600, 1467, 1432, 1316, 1205, 1145, 1104, 1057, 759 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.86 (s, 2 H), 6.67 (s, 2 H), 6.57 (s, 1 H), 6.52 (s, 1 H), 6.34 (d like, *J* = 1.8 Hz, 1 H), 6.20 (d like, *J* = 1.8 Hz, 1 H), 5.61 (s, 1 H), 5.29 (s, 1 H), 4.89 (s, 1 H), 4.75 (s, 1 H), 3.94 (s, 3 H), 3.81 (s, 3 H), 3.68 (s, 3 H), 3.44 (s, 3 H), 1.35 (s, 18 H), 1.13 (s, 18 H)**;** **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 158.8, 158.3, 158.0, 157.2, 151.1, 150.9, 142.1, 140.5, 139.3, 134.8, 134.3, 133.8, 124.7, 124.6, 123.1, 120.1, 105.5, 105.3, 97.4, 97.1, 55.6, 55.5, 55.4, 55.0, 44.7, 43.2, 34.2, 34.1, 30.5, 30.2; **HRMS** (ESI^+) calcd for $C_{46}H_{60}O_6$ $[M + H]^+$ 709.4463, found 709.4461.

VIII. X-ray Crystallography

Comp. No	Compound Structure	ORTEP Diagram
62f		
62m		
67b		

X-ray intensity data measurements of all the compounds were carried out on a Bruker D8 VENTURE Kappa Duo PHOTON II CPAD diffractometer equipped with Incoatech multilayer mirrors optics or on a Bruker SMART APEX II CCD diffractometer with graphite-monochromatized radiation. The intensity measurements were carried out with Mo micro-focus/fine-focus sealed tube diffraction source

(MoK$_\alpha$= 0.71073Å) at 100(2) K temperature or Cu micro-focussealed tube diffraction source (CuK$_\alpha$= 1.54184Å). The X-ray generator was operated at 50 kV and 1.1 mA for Cu source and 50 kV and 1.4 mA. For Mo source. The X-ray generator power setting for the data collected on a Bruker SMART APEX II CCD was 50 kV and 30 mA. A preliminary set of cell constants and an orientation matrix were calculated from three sets of 36/40 frames.Data were collected with ωscan width of 0.5° at different settings of φ and 2θ keeping the sample-to-detector distance fixed at 5.00 cm. The X-ray data collection was monitored by APEX3 program (Bruker, 2016). All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs (Bruker, 2016). SHELX-97 was used for structure solution and full matrix least-squares refinement on F^2. All the hydrogen atoms were placed in geometrically idealized positions and constrained to ride on their parent atoms. An*ORTEP* III view of both compounds were drawn with 50% probability displacement ellipsoids and H atoms are shown as small spheres of arbitrary radii.

Crystal Data	**62e**	**62f**
Formula	C_{30} H_{34} O_3	C_{29} H_{38} O_6
Mr	442.57	482.59
Temp. (K)	100(2) K	100(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal Syst., Sp. Gr	Monoclinic, *P 2$_1$/n*	Monoclinic, *P 2$_1$/c*
Unit cell dimensions	a = 10.8677(3) Å; α= 90^o b = 10.6208(3) Å; β=98.2830(10)^o c = 22.1502(6) Å; γ = 90^o	a = 11.6430(9) Å; α= 90^o b = 9.9000(8) Å; β = 94.4560(10)^o c = 23.0736(18) Å; γ = 90^o
Volume (Å^3)	2529.99(12)	2651.6(4)
Z	4	4
D$_c$, Mg/m^3	1.162	1.209
μ/mm^{-1}	0.073	0.083
F(000)	952	1040
Crystal size (mm^3)	0.190 x 0.180 x 0.150	0.340 x 0.210 x 0.080

$\theta_{min\text{-}max}$	2.671 to 30.513°	2.240 to 28.000°
h, k, l (min, max)	(-15, 15), (-15, 15), (-31, 31)	(-15, 15), (-13, 13), (-30, 30)
Number of reflections	39402	33670
unique reflections	7594 [R(int) = 0.0275]	6384 [R(int) = 0.0349]
Completeness at θ_{max}	99.8 %	99.7 %
Ab. Correct.	multi-scan	multi-scan
T_{min}	0.986	0.972
T_{max}	0.989	0.993
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Number of parameters	306	327
Goodness-of-fit (S)	1.027	1.164
Final R indices [I>2sigma(I)]	R1 = 0.0446, wR2 = 0.1123	R1 = 0.0561, wR2 = 0.1328
R indices (all data)	R1 = 0.0528, wR2 = 0.1173	R1 = 0.0629, wR2 = 0.1364
$\Delta\rho_{max}$, $\Delta\rho_{min}$(eÅ^{-3})	+0.323, -0.302 e.Å^{-3}	+0.402, -0.233 e.Å^{-3}

Crystal Data	**62m**	**67b**
Formula	C_{32} H_{35} Cl O_3	C_{29} H_{32} O_3
Mr	503.05	428.54
Temp. (K)	100(2) K	100(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal Syst., Sp. Gr	Monoclinic, *C 2/c*	Monoclinic, *P 2$_1$/c*
Unit cell dimensions	a = 27.2646(7) Å; α= 90° b = 9.7962(2) Å; β = 90.0190(10)° c = 21.4240(5) Å; γ = 90°	a = 10.3404(5) Å; α= 90° b = 13.3275(6) Å; β = 94.178(2)° c = 17.2980(7) Å; γ = 90°
Volume (Å^3)	5722.1(2)	2377.53(18)

Z	8	4
D_c, Mg/m^3	1.168	1.197
μ/mm^{-1}	0.163	0.076
F(000)	2144	920
Crystal size (mm^3)	0.340 x 0.240 x 0.200	0.202 x 0.158 x 0.072
$\theta_{min\text{-}max}$	2.209 to 30.522°	2.497 to 30.533°
h, k, l (min, max)	(-38, 38), (-12, 13), (-30, 29)	(-14, 14), (-18, 19), (-24, 24)
Number of reflections	53277	39196
unique reflections	8708 [R(int) = 0.0216]	7232 [R(int) = 0.0327]
Completeness at θ_{max}	99.7 %	99.7 %
Ab. Correct.	multi-scan	multi-scan
T_{min}	0.947	0.985
T_{max}	0.968	0.995
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Number of parameters	333	296
Goodness-of-fit (S)	1.092	1.017
Final R indices [I>2sigma(I)]	R1 = 0.0456, wR2 = 0.1317	R1 = 0.0436, wR2 = 0.1158
R indices (all data)	R1 = 0.0502, wR2 = 0.1370	R1 = 0.0496, wR2 = 0.1205
$\Delta\rho_{max}$, $\Delta\rho_{min}$($eÅ^{-3}$)	+1.230, -0.690 $e.Å^{-3}$	+0.356, -0.268 $e.Å^{-3}$

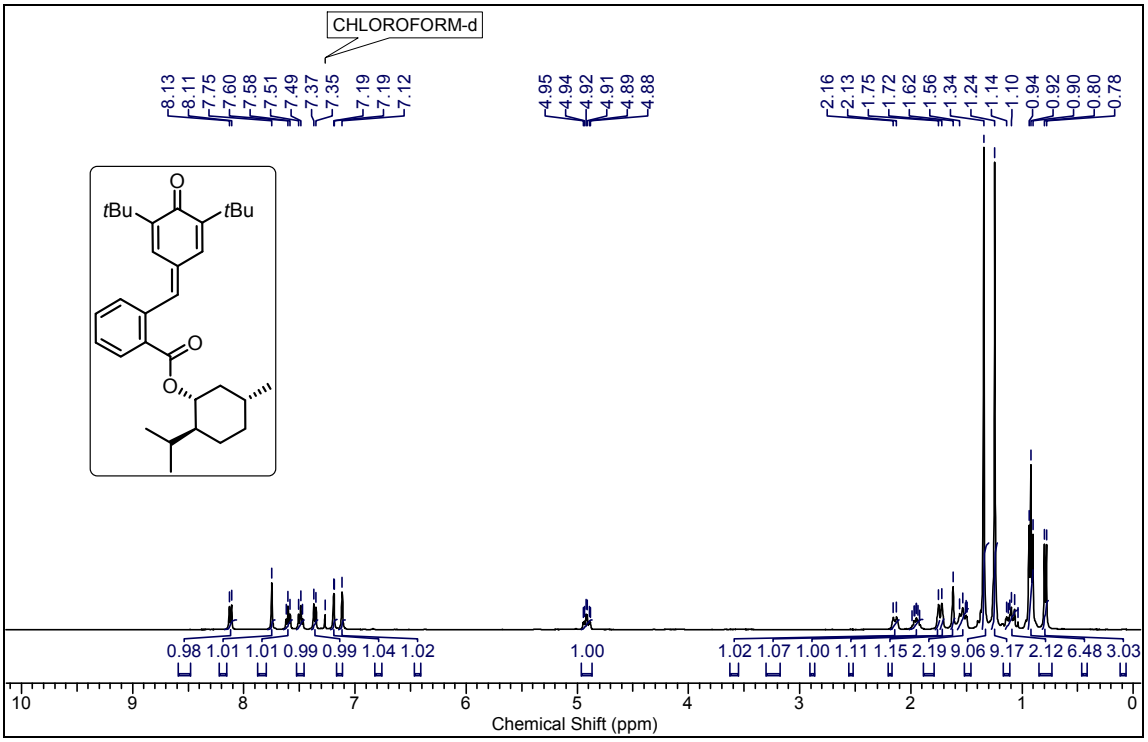
Crystal Data	**69**	**64**
Formula	C_{23} H_{30} O_3	C_{22} H_{26} O_3
Mr	354.47	338.43
Temp. (K)	100(2) K	100(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal Syst., Sp. Gr	Triclinic, *P -1*	Monoclinic, *P* $2_1/c$

Unit cell dimensions	a = 7.6850(6) Å; α= 96.035(3)° b = 10.0553(8) Å; β= 98.763(3)° c = 15.0472(11) Å; γ = 110.728(3)°	a = 14.4184(5) Å; α= 90° b = 15.8907(6) Å; β= 92.8930(10)° c = 8.0161(3) Å; γ = 90°
Volume ($Å^3$)	1058.78(14)	1834.30(12)
Z	2	4
D_c, Mg/m^3	1.112	1.225
μ/mm^{-1}	0.072	0.080
F(000)	384	728
Crystal size (mm^3)	0.450 x 0.300 x 0.220	0.450 x 0.320 x 0.260
$\theta_{min-max}$	2.390 to 30.548°	2.563 to 30.549°
h, k, l (min, max)	(-10, 8), (-14, 14), (-21, 21)	(-20, 20), (-22, 22), (-10, 11)
Number of reflections	25303	74505
unique reflections	6431 [R(int) = 0.0301]	5601 [R(int) = 0.0282]
Completeness at θ_{max}	99.7%	99.9 %
Ab. Correct.	multi-scan	multi-scan
T_{min}	0.968	0.965
T_{max}	0.984	0.980
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Number of parameters	244	233
Goodness-of-fit (S)	1.039	1.033
Final R indices [I>2sigma(I)]	R1 = 0.0403, wR2 = 0.1050	R1 = 0.0396, wR2 = 0.1126
R indices (all data)	R1 = 0.0530, wR2 = 0.1139	R1 = 0.0441, wR2 = 0.1215
$\Delta\rho_{max}$, $\Delta\rho_{min}$($eÅ^{-3}$)	+0.379, -0.244 $e.Å^{-3}$	+0.462, -0.653 $e.Å^{-3}$

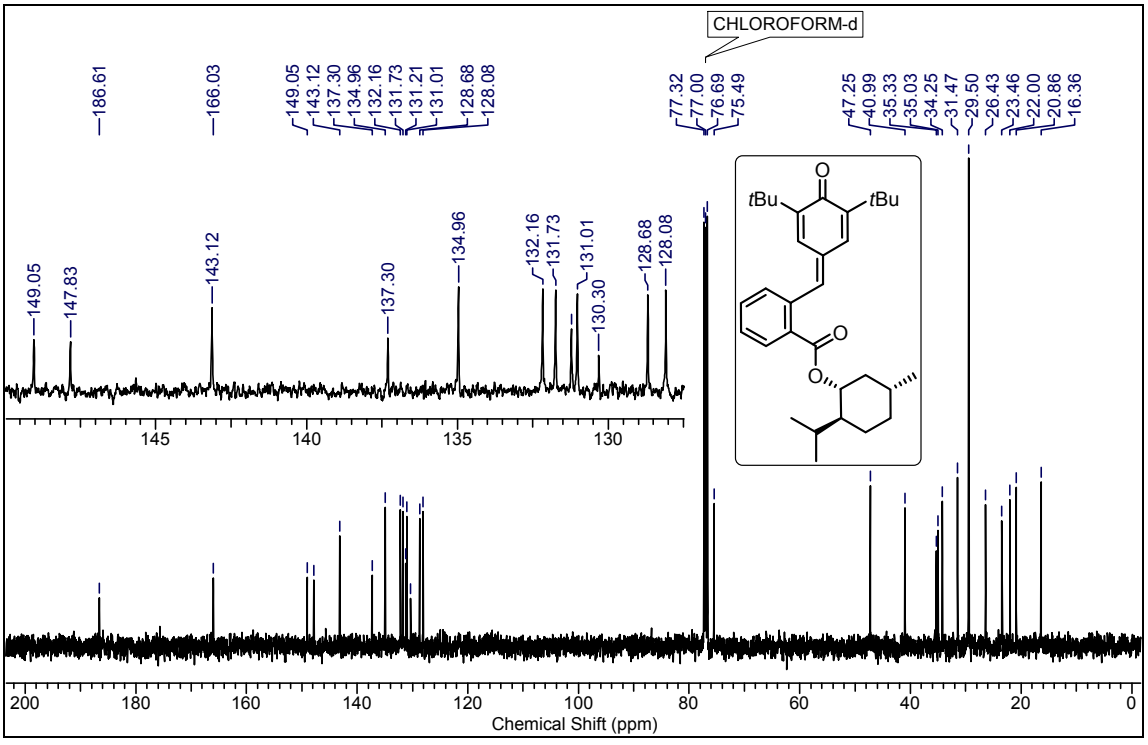
3.2.5. Spectral Data

Spectra

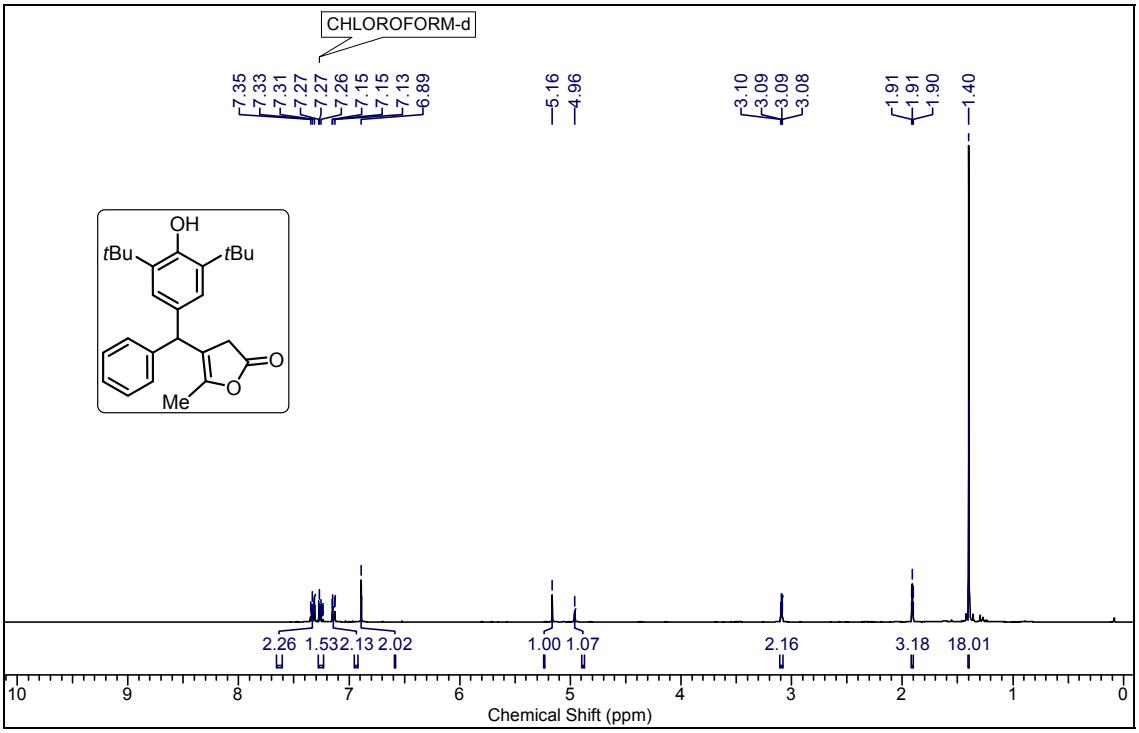
^{1}H NMR spectrum of compound **60p** ($CDCl_3$, 400 MHz):



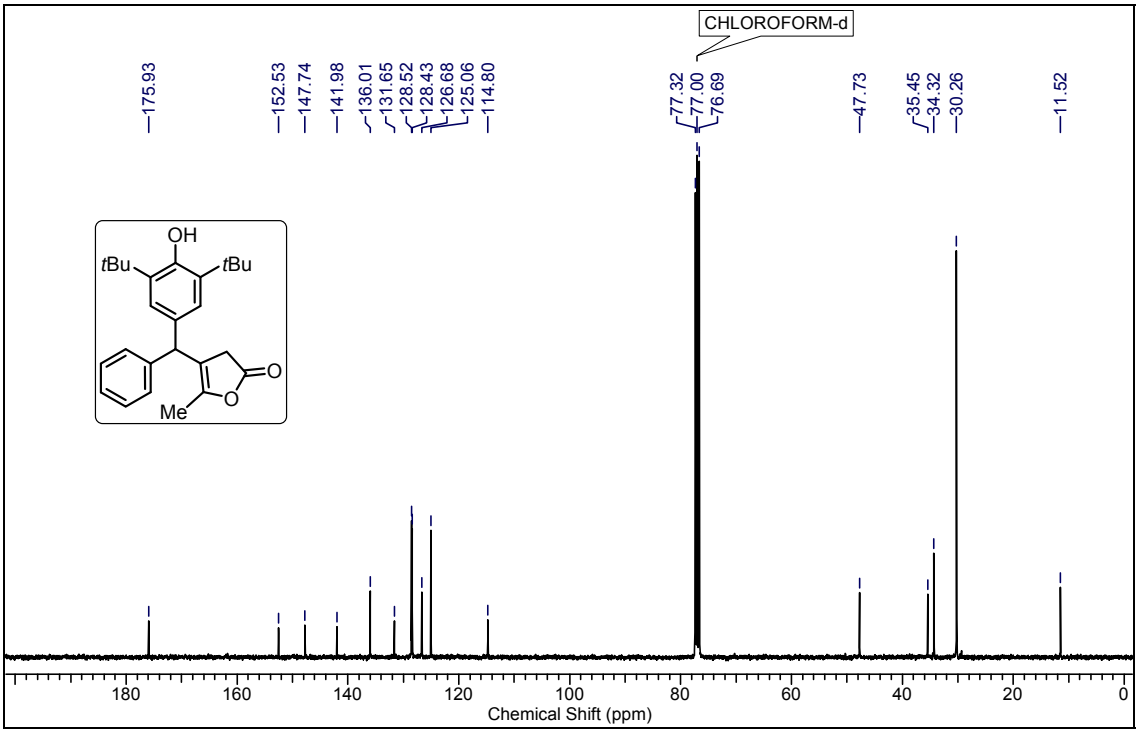
^{13}C NMR spectrum of compound **60p** ($CDCl_3$, 100 MHz):



^{1}H NMR spectrum of compound **62a** ($CDCl_3$, 400 MHz):

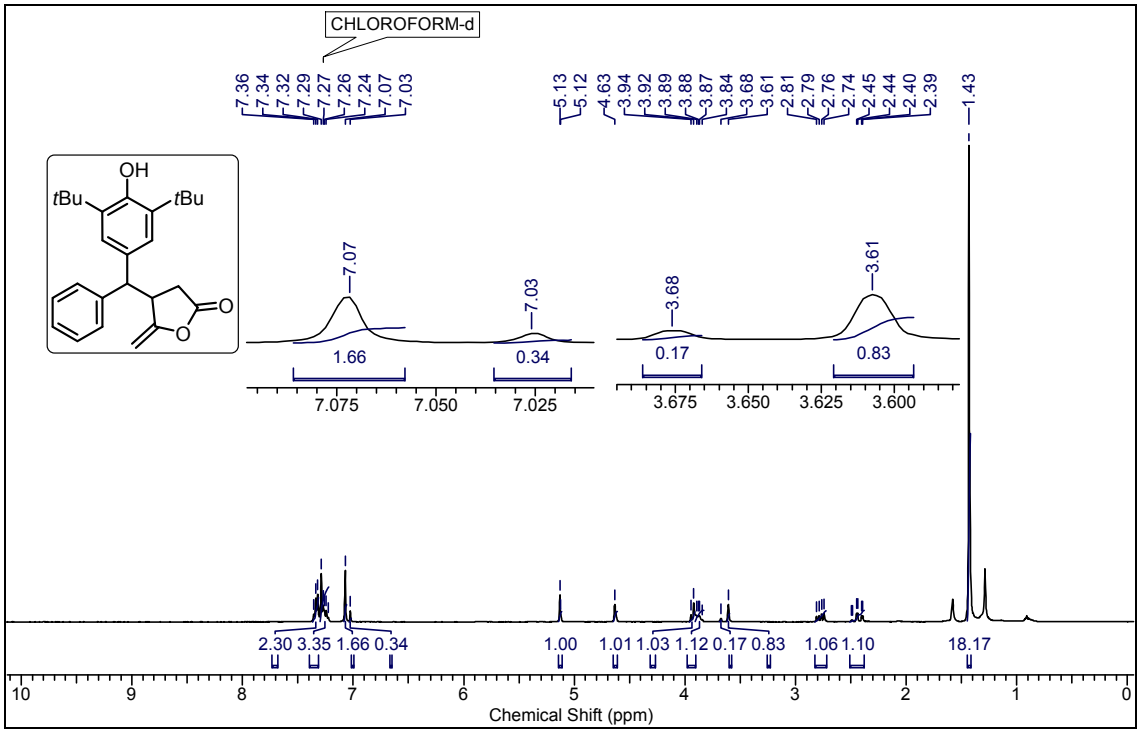


^{13}C NMR spectrum of compound **62a** ($CDCl_3$, 100 MHz):

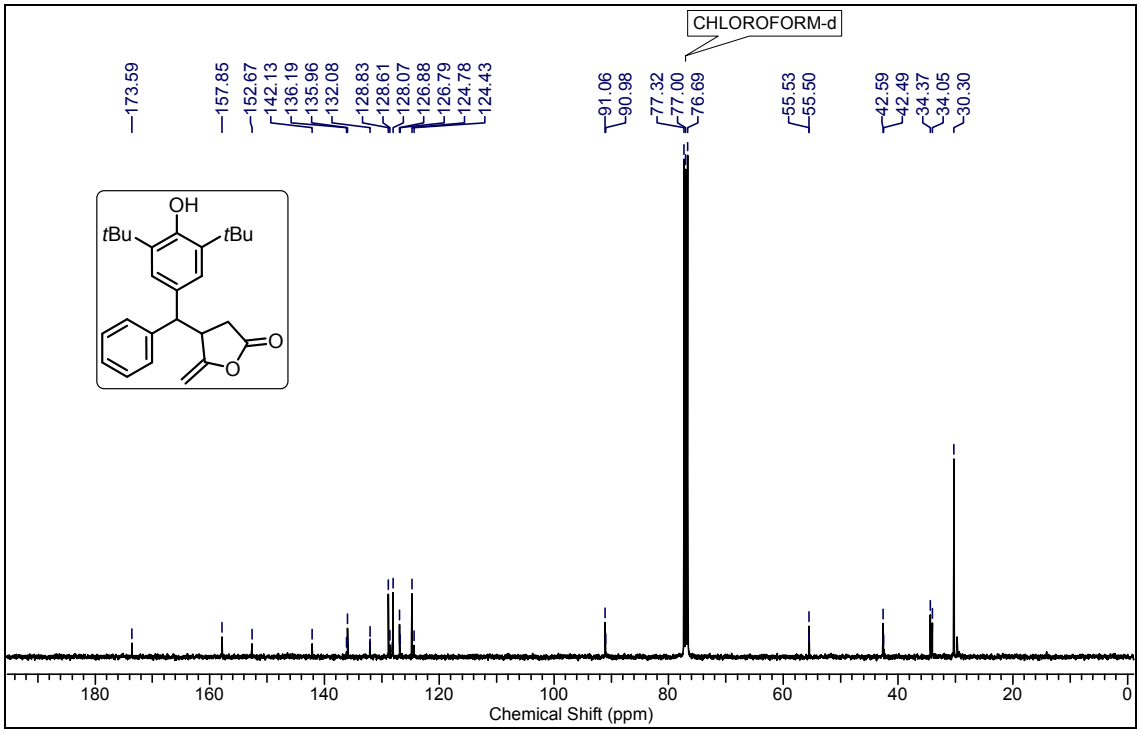


Spectra

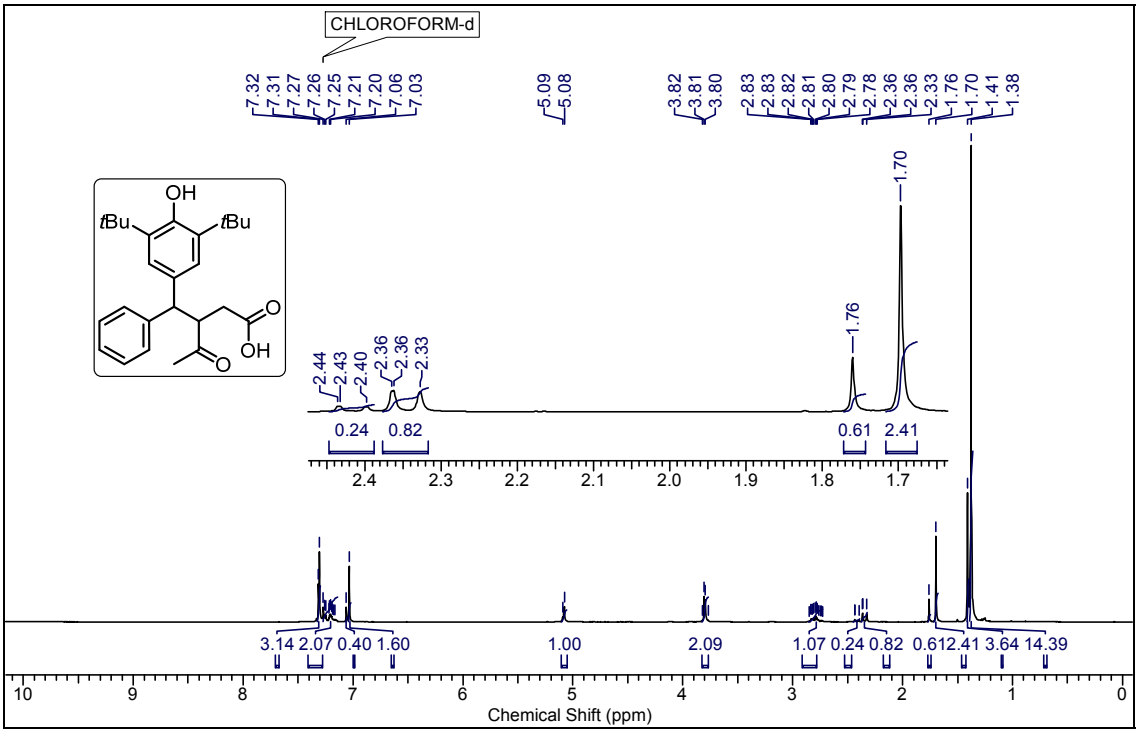
^{1}H NMR spectrum of compound **62a'** ($CDCl_3$, 400 MHz):



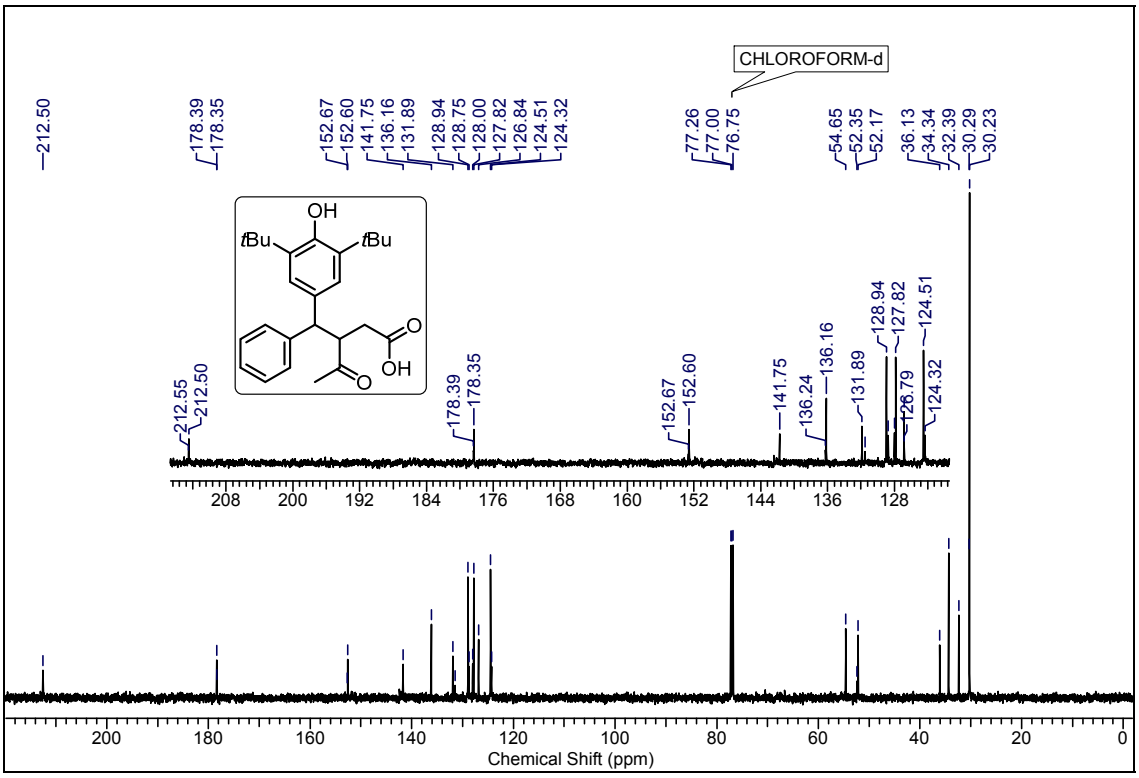
^{13}C NMR spectrum of compound **62a'** ($CDCl_3$, 100 MHz):



^{1}H NMR spectrum of compound **63** ($CDCl_3$, 500 MHz):

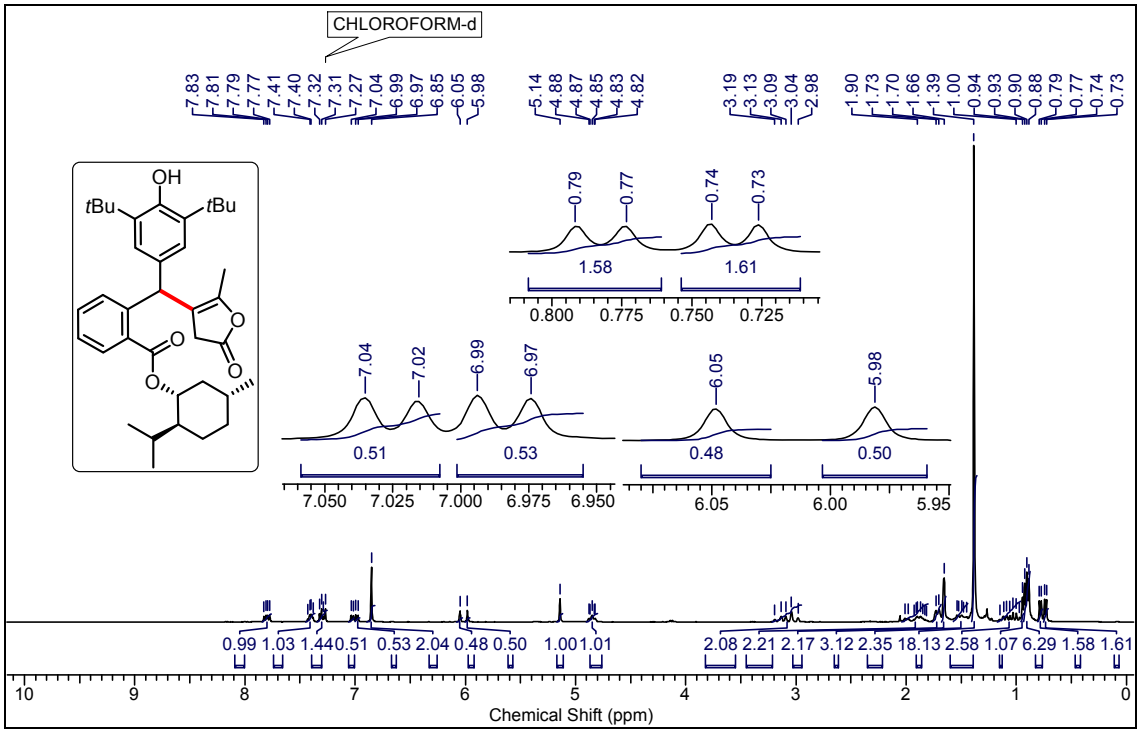


^{13}C NMR spectrum of compound **63** ($CDCl_3$, 125 MHz):

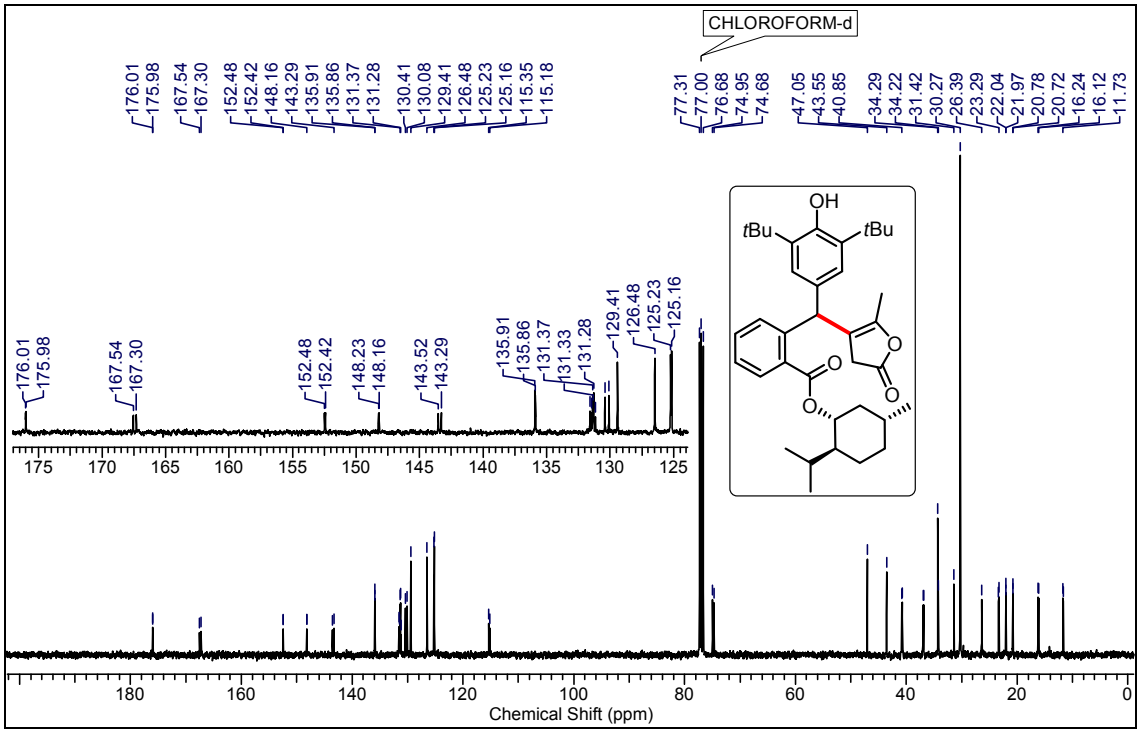


Spectra

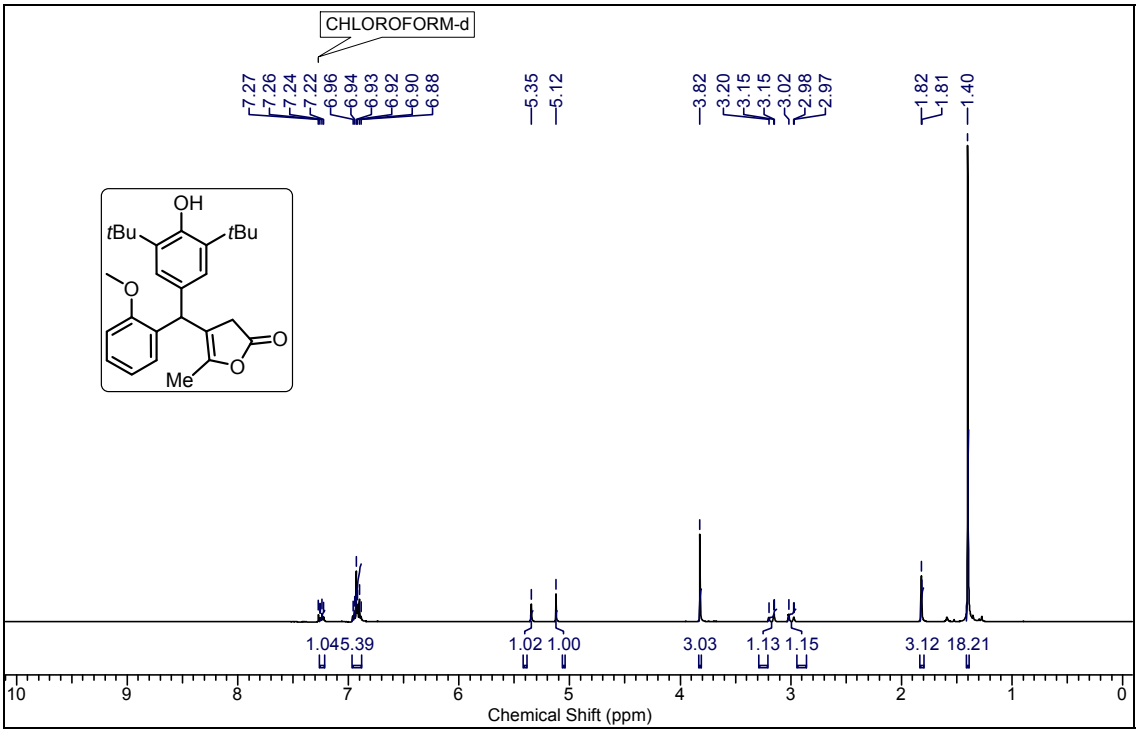
^{1}H NMR spectrum of compound **65** ($CDCl_3$, 400 MHz):



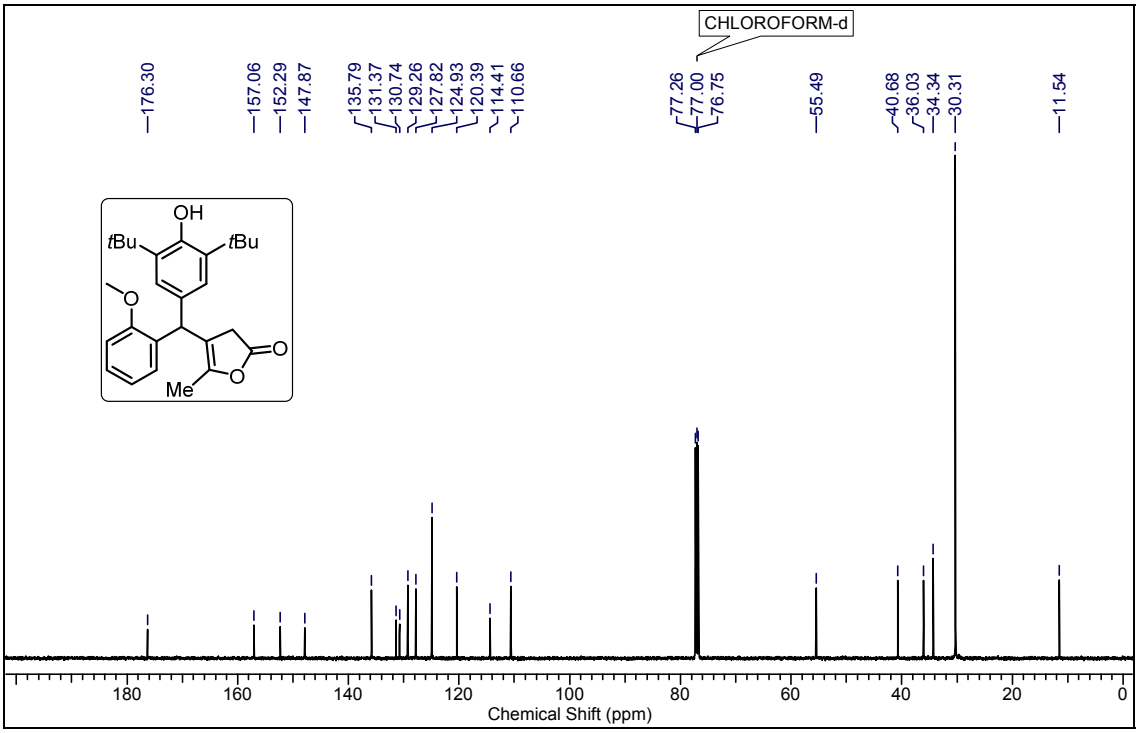
^{13}C NMR spectrum of compound **65** ($CDCl_3$, 100 MHz):



^{1}H NMR spectrum of compound **62c** ($CDCl_3$, 500 MHz):

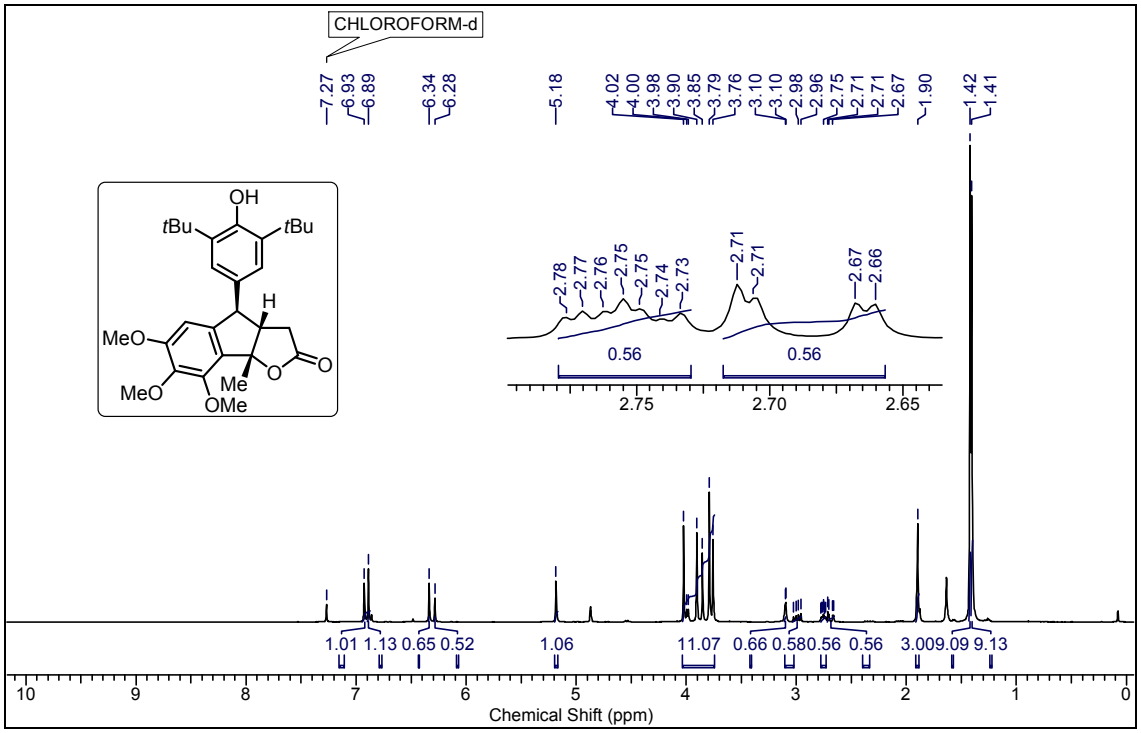


^{13}C NMR spectrum of compound **62c** ($CDCl_3$, 125 MHz):

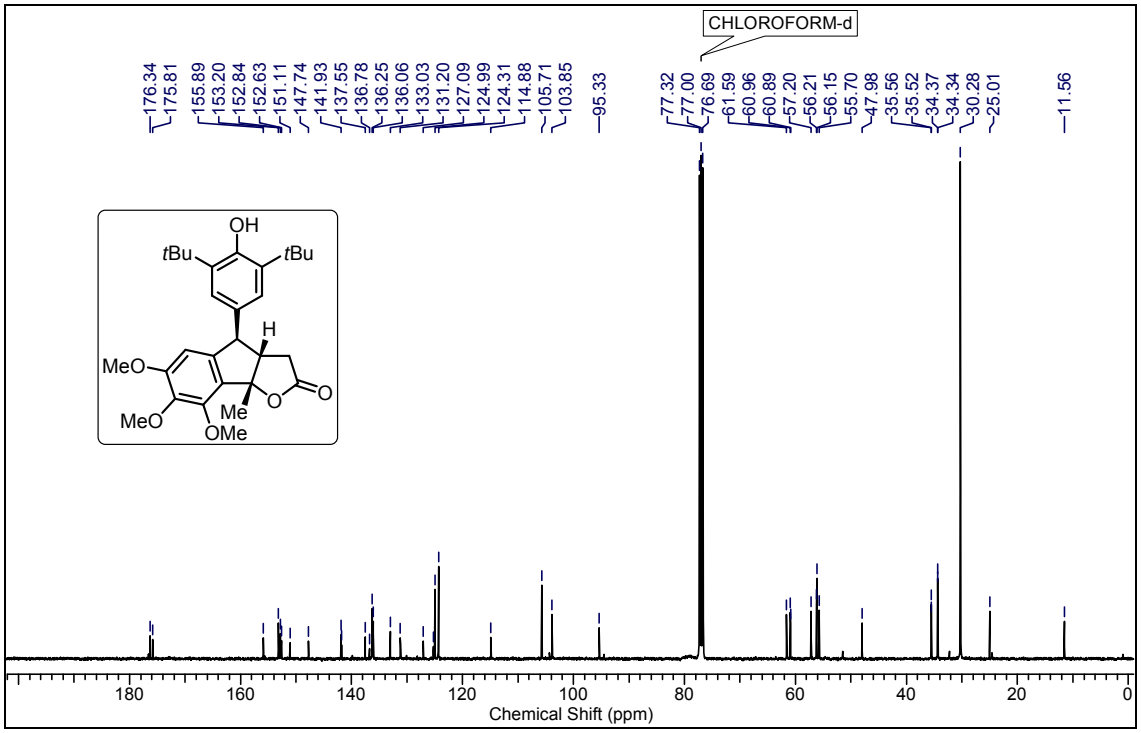


Spectra

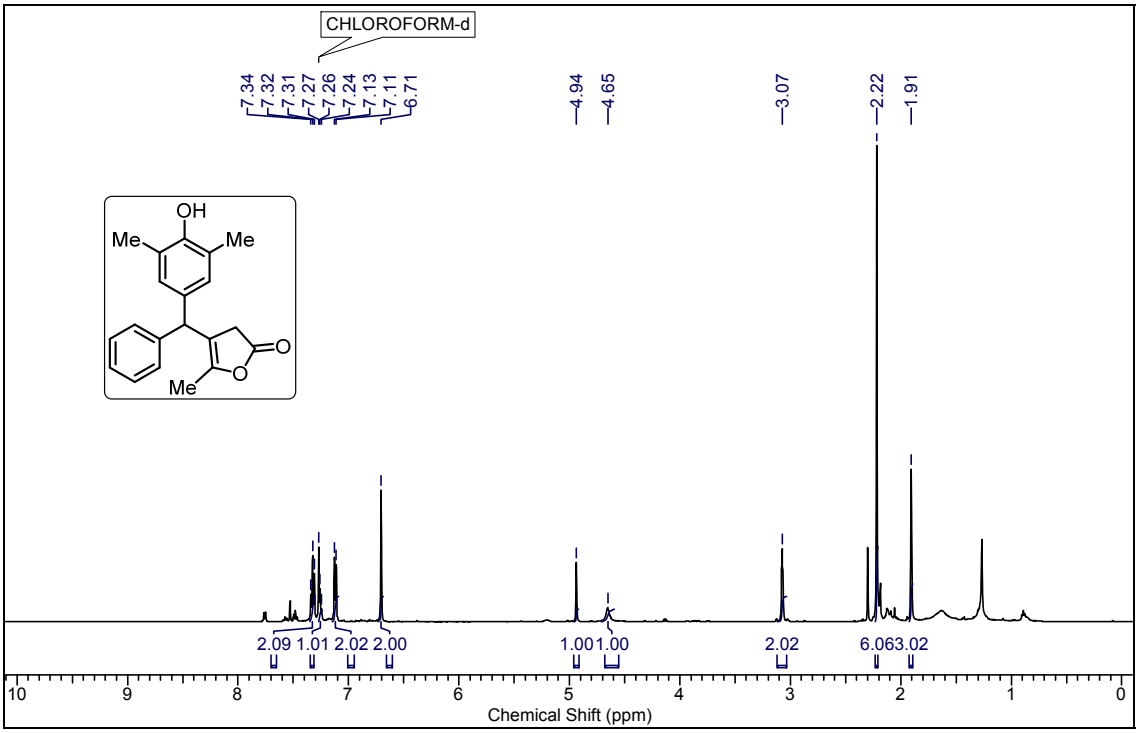
^{1}H NMR spectrum of compound **62f** ($CDCl_3$, 400 MHz):



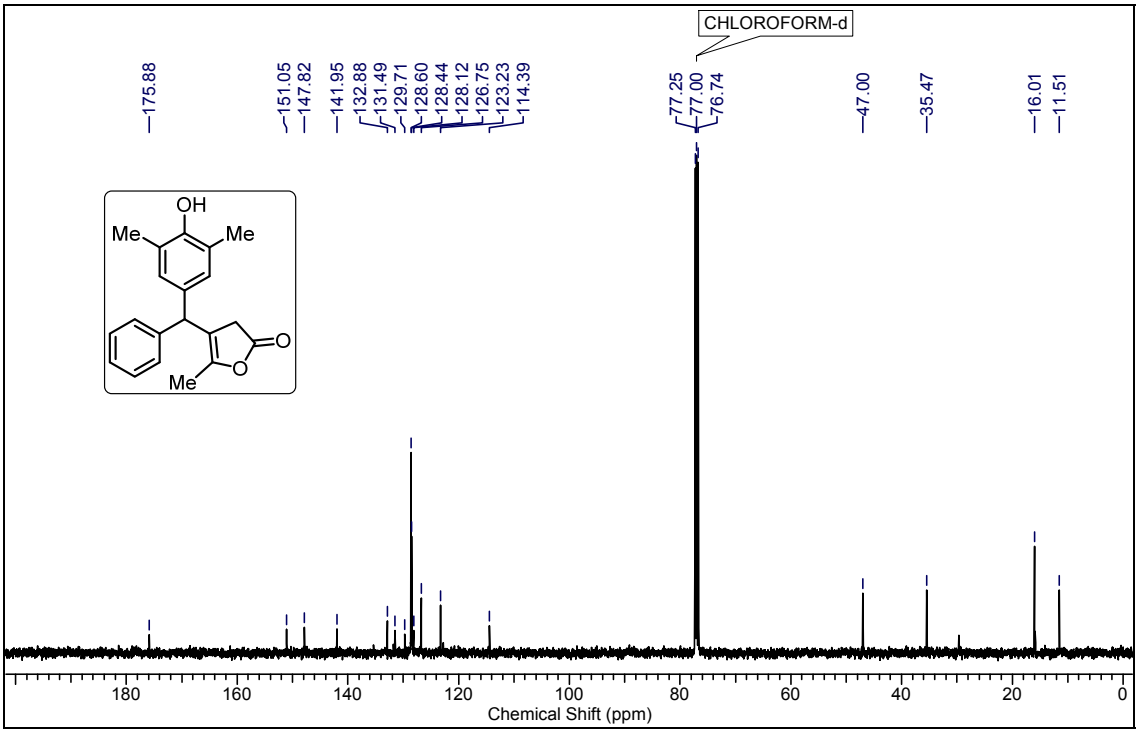
^{13}C NMR spectrum of compound **62f** ($CDCl_3$, 100 MHz):



^{1}H NMR spectrum of compound **62g** ($CDCl_3$, 500 MHz):

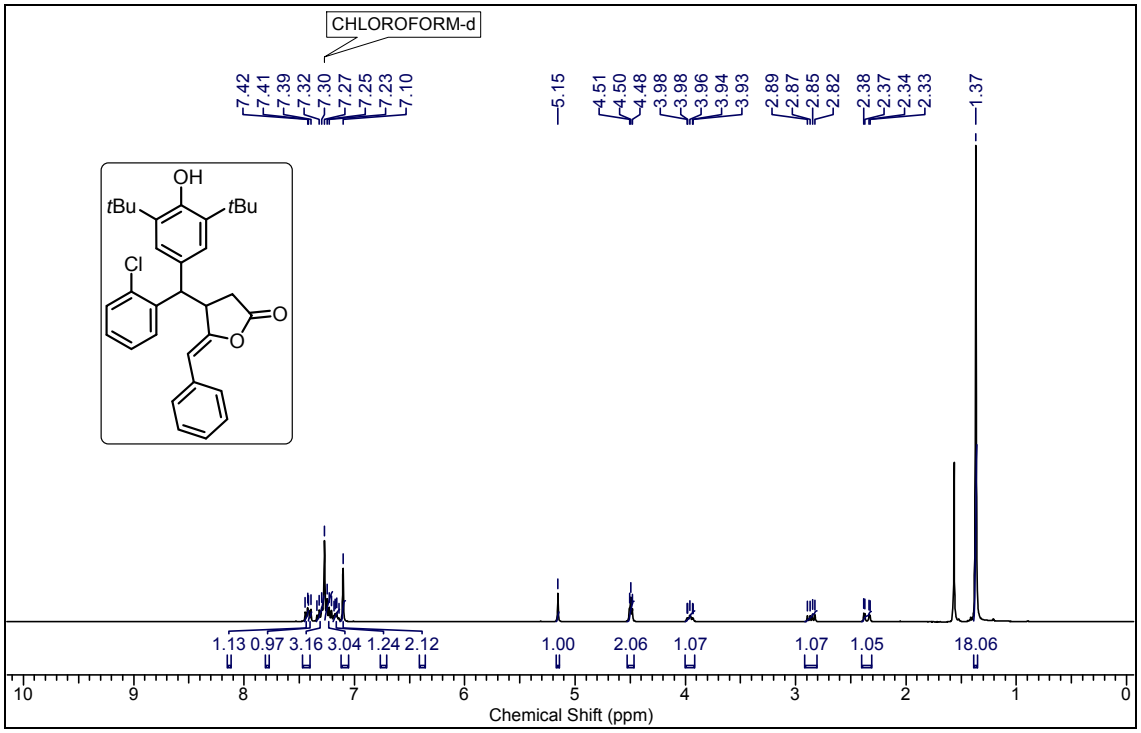


^{13}C NMR spectrum of compound **62g** ($CDCl_3$, 125 MHz):

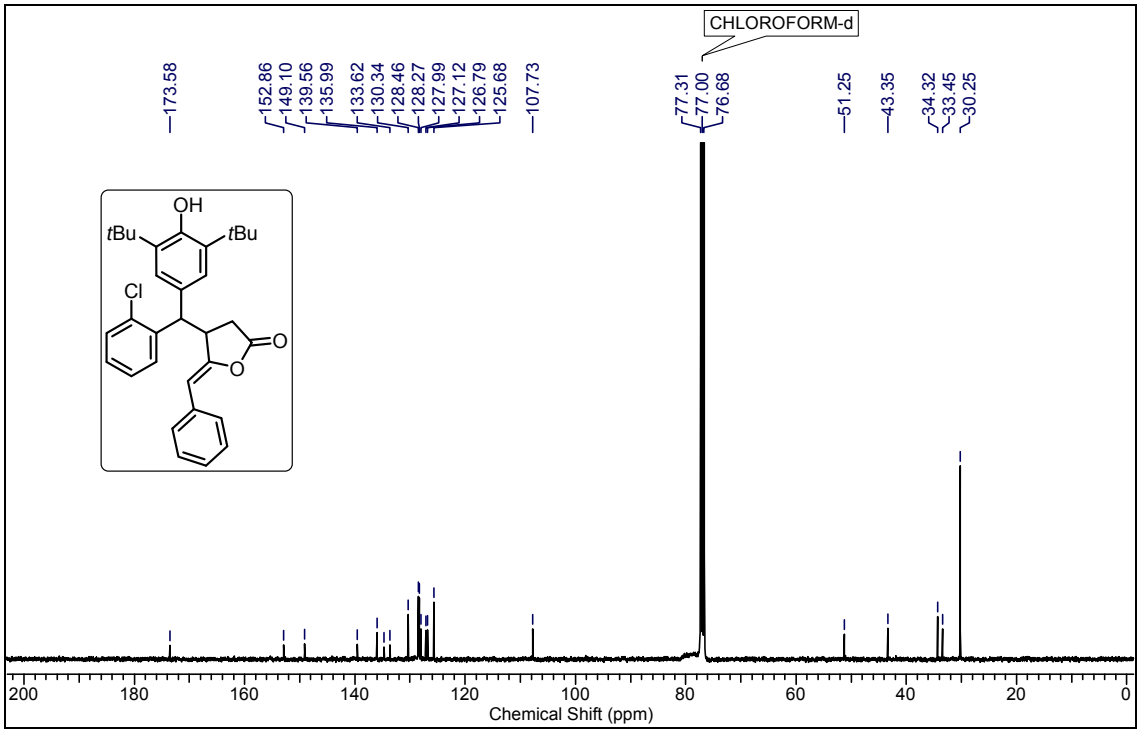


Spectra

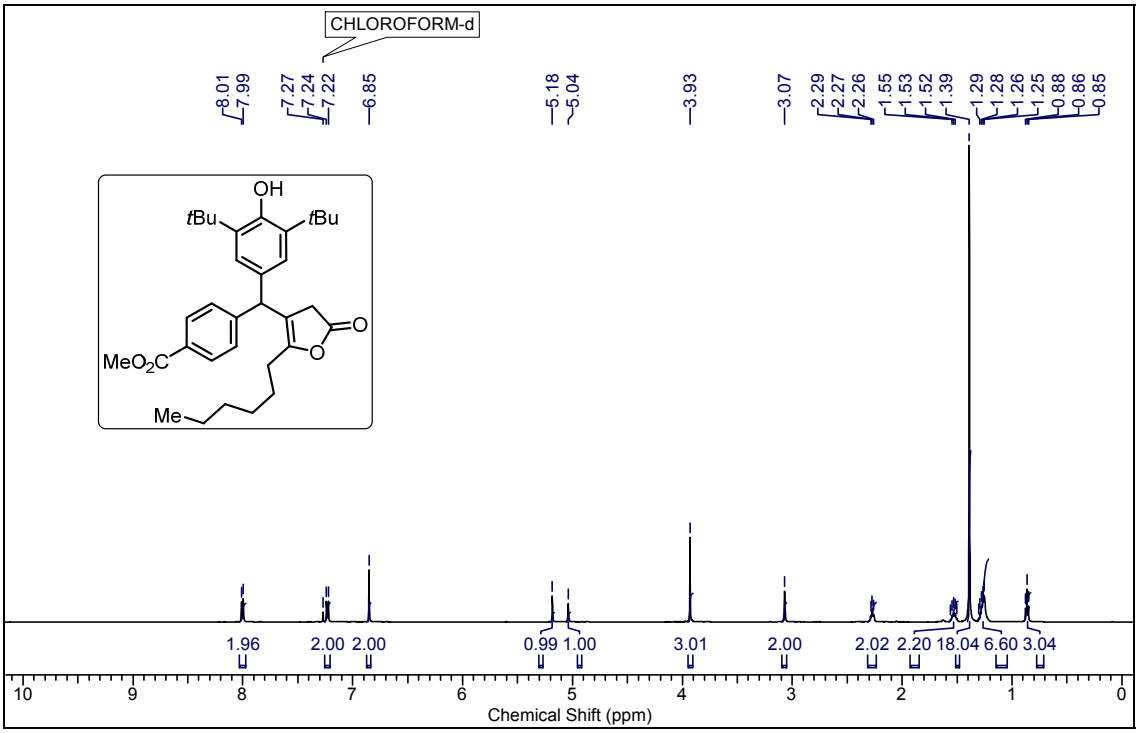
^{1}H NMR spectrum of compound **62m** ($CDCl_3$, 400 MHz):



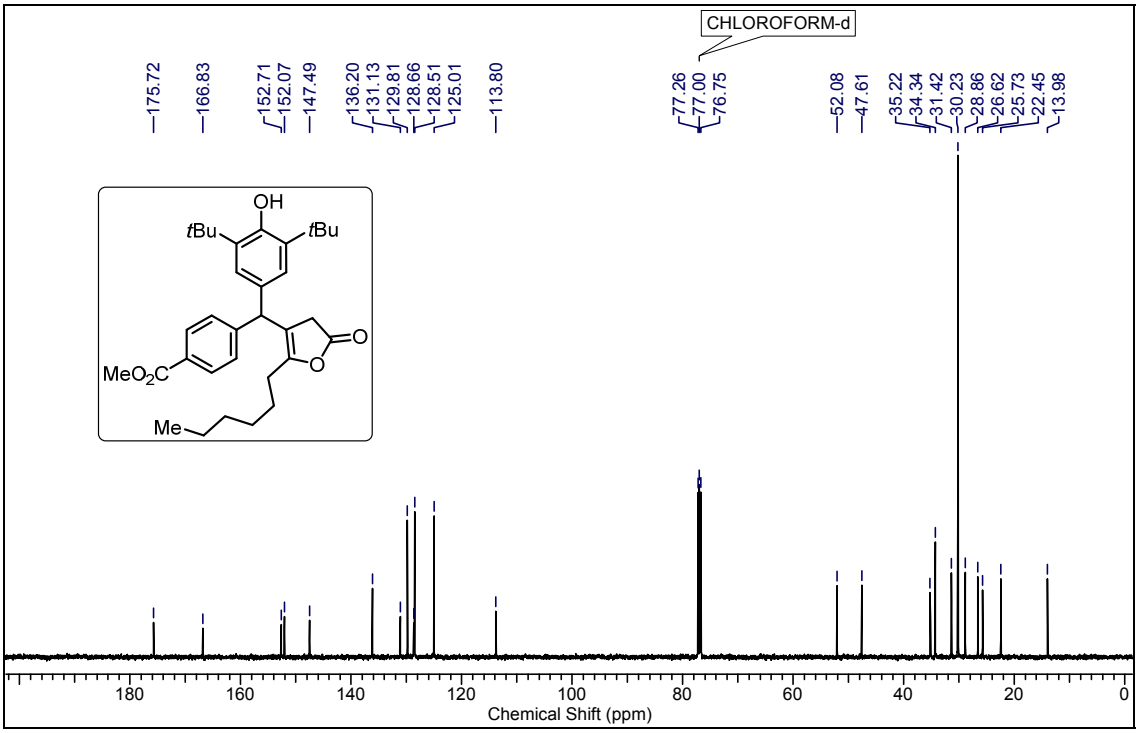
^{13}C NMR spectrum of compound **62m** ($CDCl_3$, 100 MHz):



^{1}H NMR spectrum of compound **62n** ($CDCl_3$, 500 MHz):

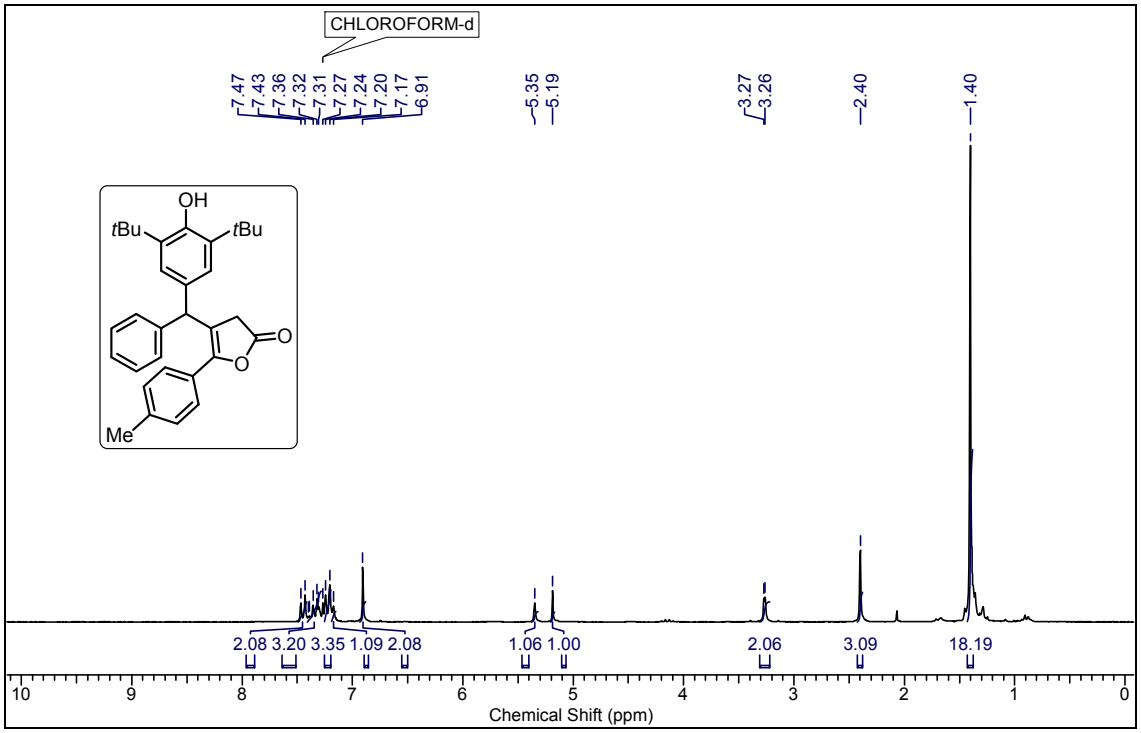


^{13}C NMR spectrum of compound **62n** ($CDCl_3$, 125 MHz):

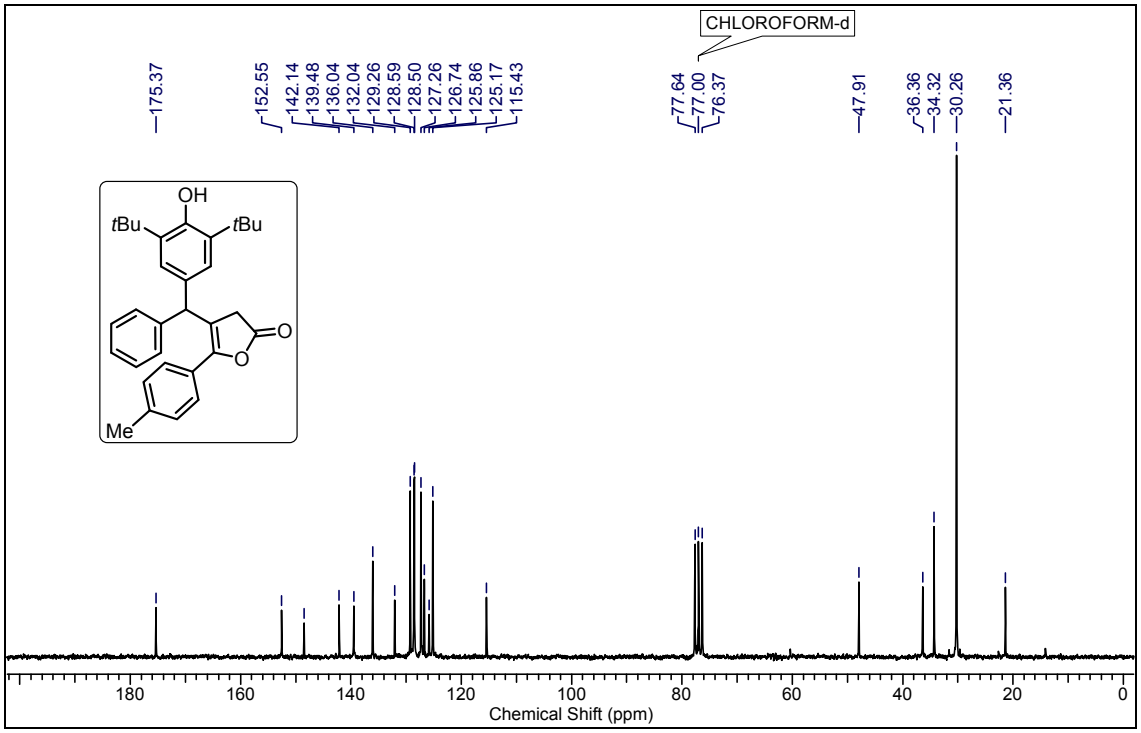


Spectra

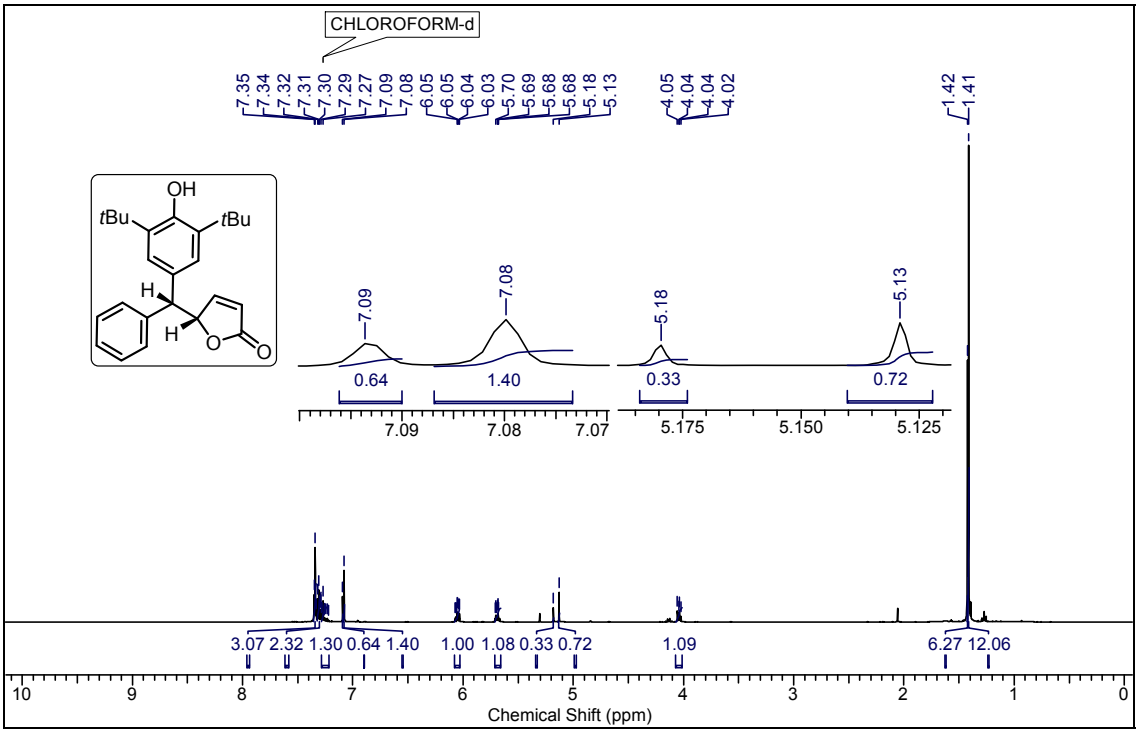
^{1}H NMR spectrum of compound **62p** ($CDCl_3$, 200 MHz):



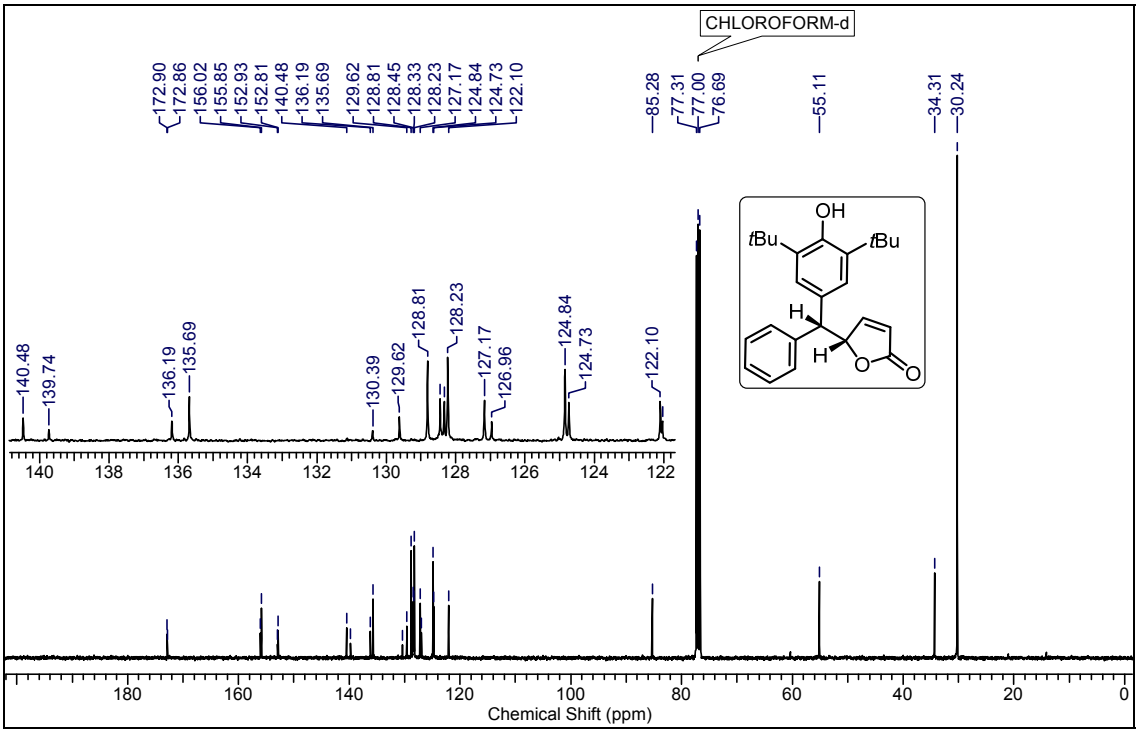
^{13}C NMR spectrum of compound **62p** ($CDCl_3$, 50 MHz):



^{1}H NMR spectrum of compound **67a** ($CDCl_3$, 400 MHz):

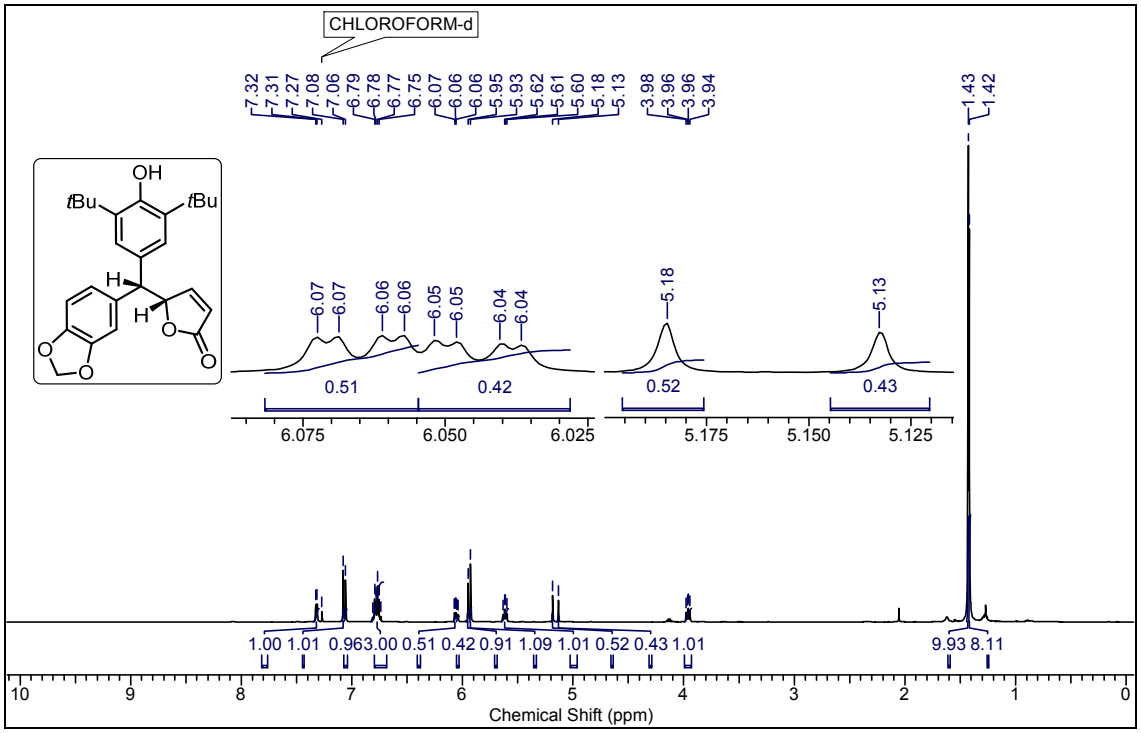


^{13}C NMR spectrum of compound **67a** ($CDCl_3$, 100 MHz):

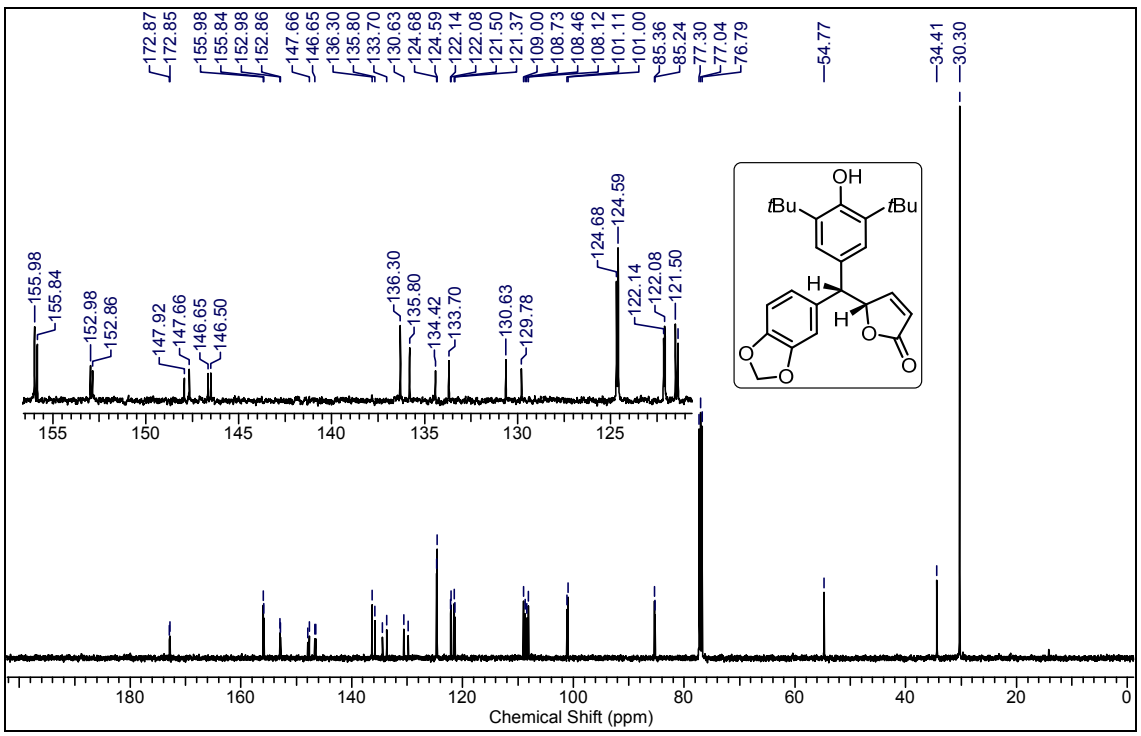


Spectra

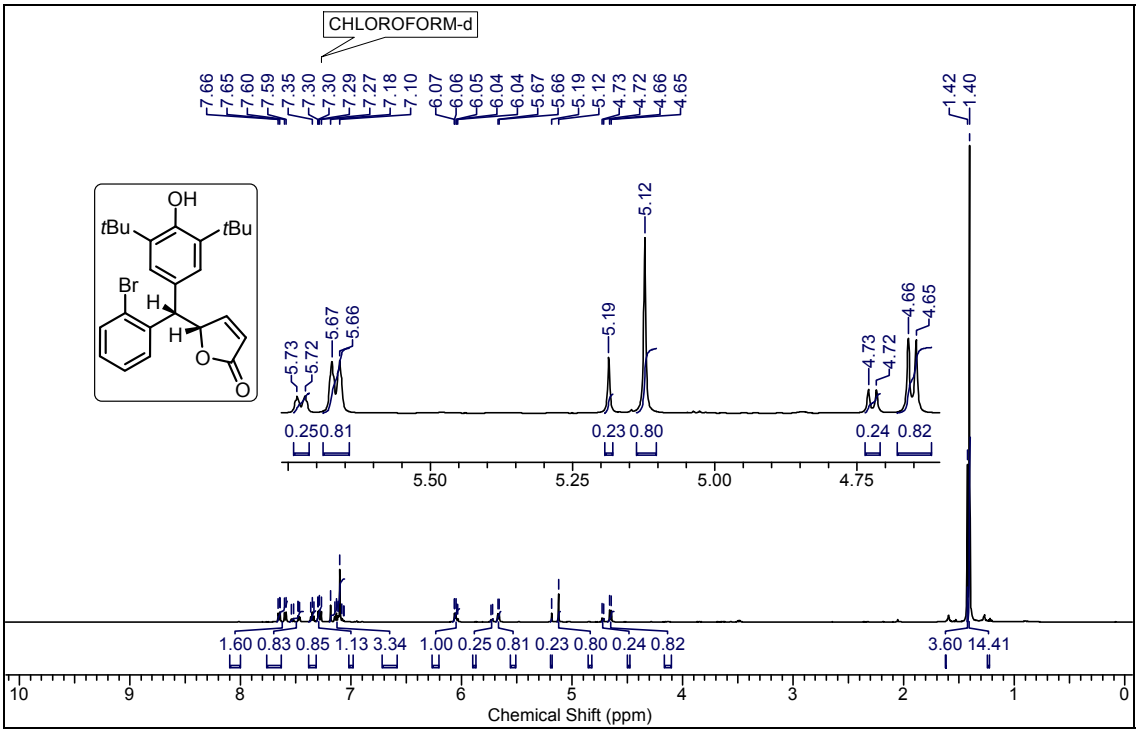
^{1}H NMR spectrum of compound **67e** ($CDCl_3$, 500 MHz):



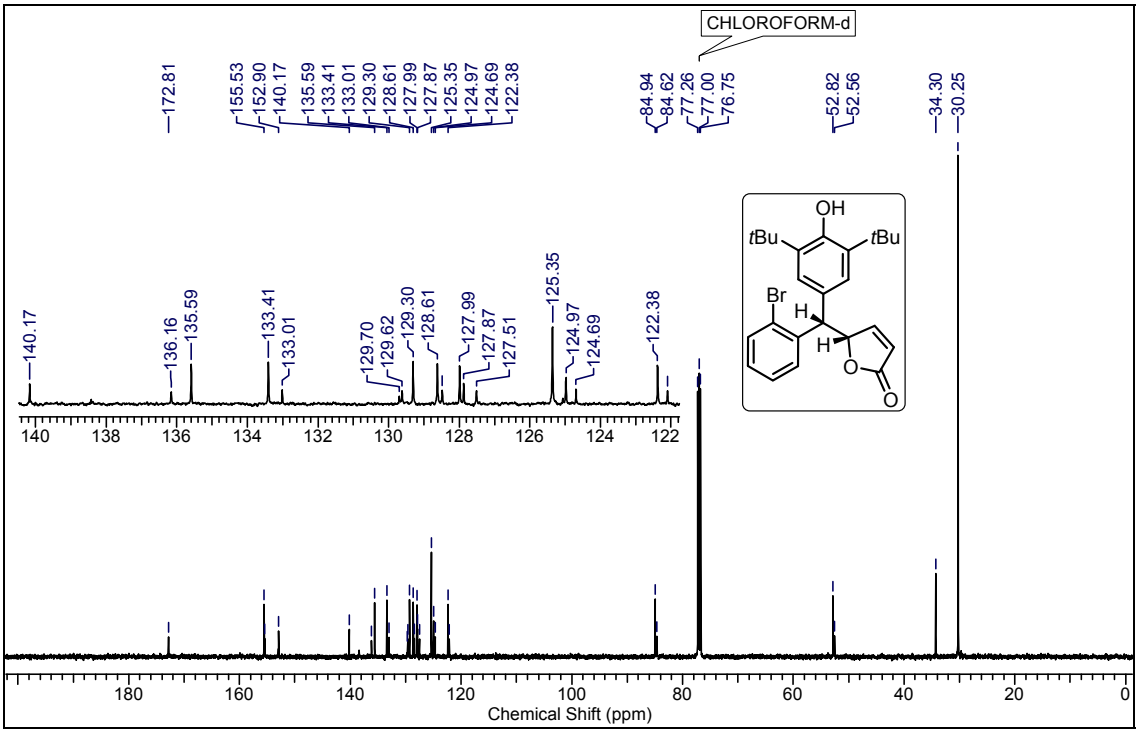
^{13}C NMR spectrum of compound **67e** ($CDCl_3$, 125 MHz):



^{1}H NMR spectrum of compound **67f** ($CDCl_3$, 500 MHz):

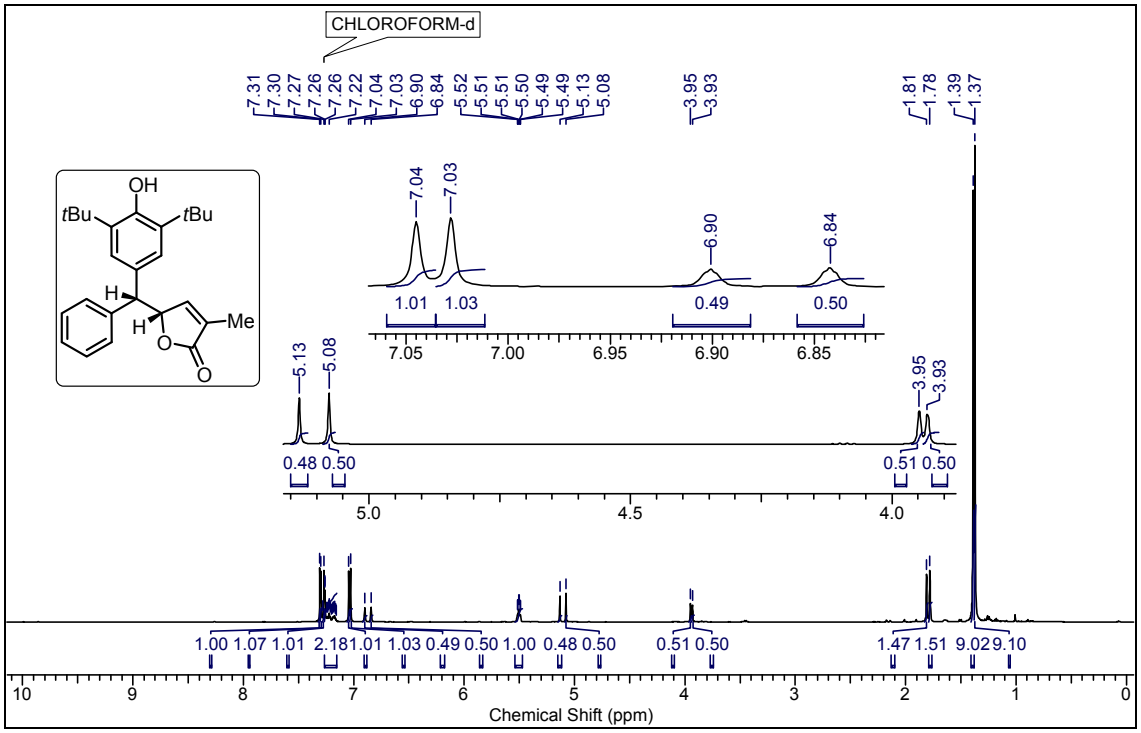


^{13}C NMR spectrum of compound **67f** ($CDCl_3$, 125 MHz):

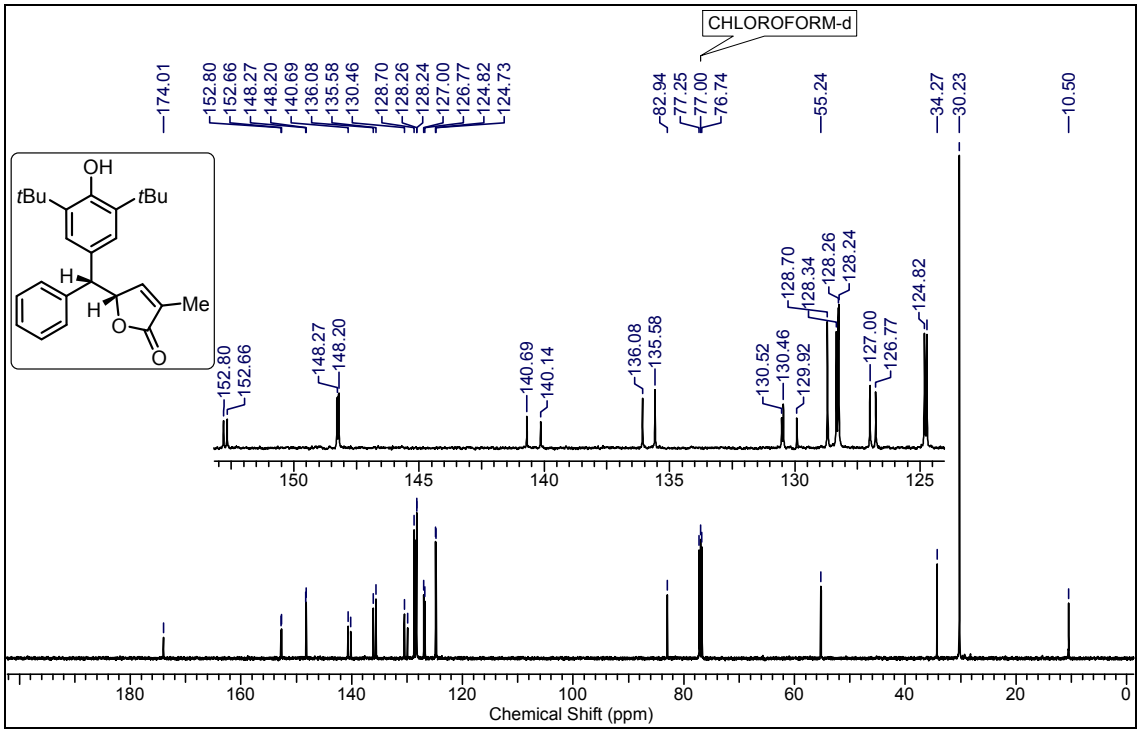


Spectra

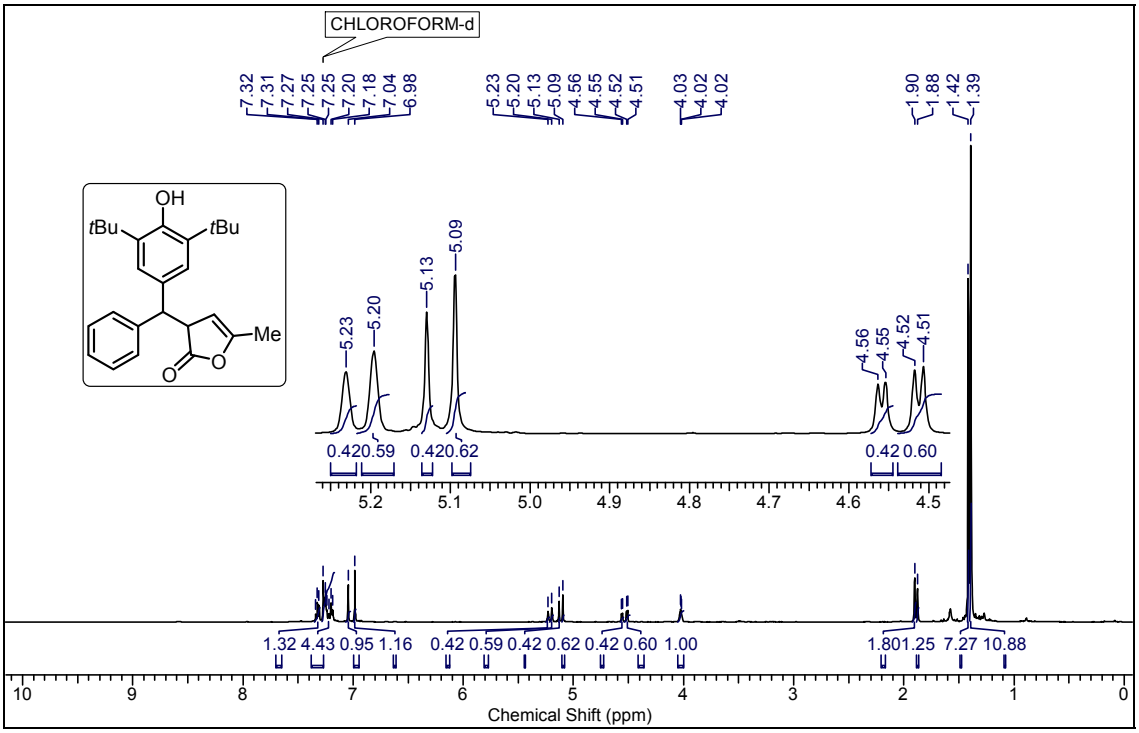
^{1}H NMR spectrum of compound **67i** ($CDCl_3$, 500 MHz):



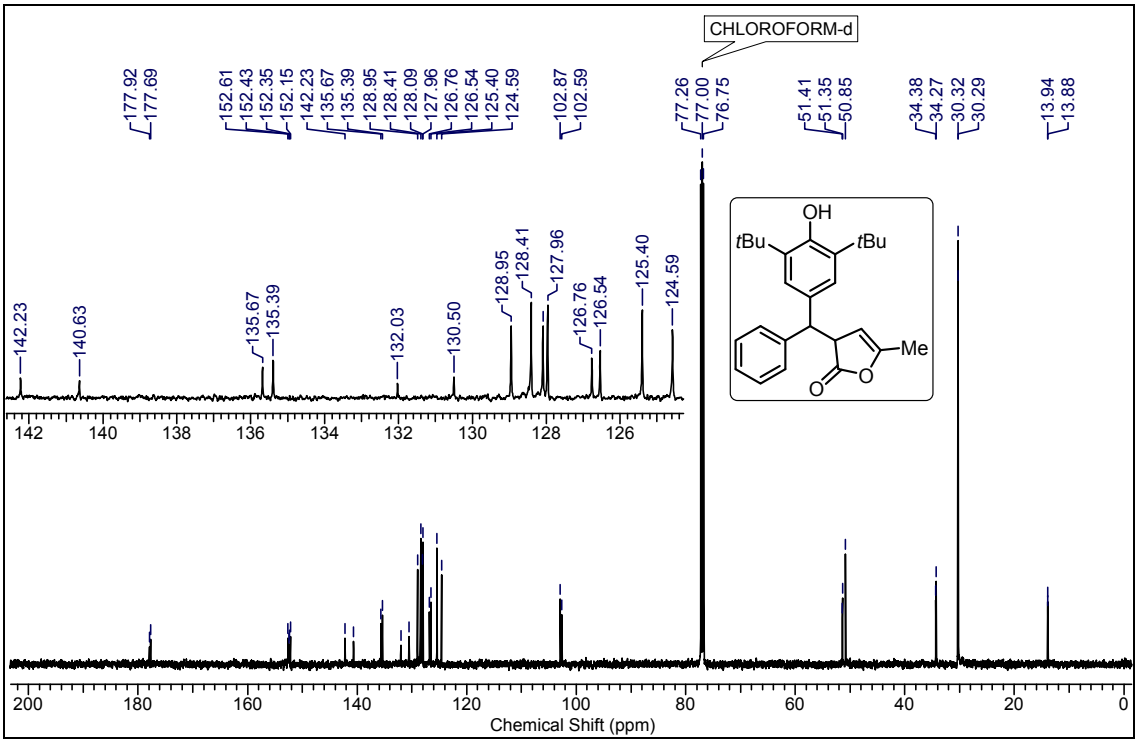
^{13}C NMR spectrum of compound **67i** ($CDCl_3$, 125 MHz):



^{1}H NMR spectrum of compound **68a** ($CDCl_3$, 500 MHz):

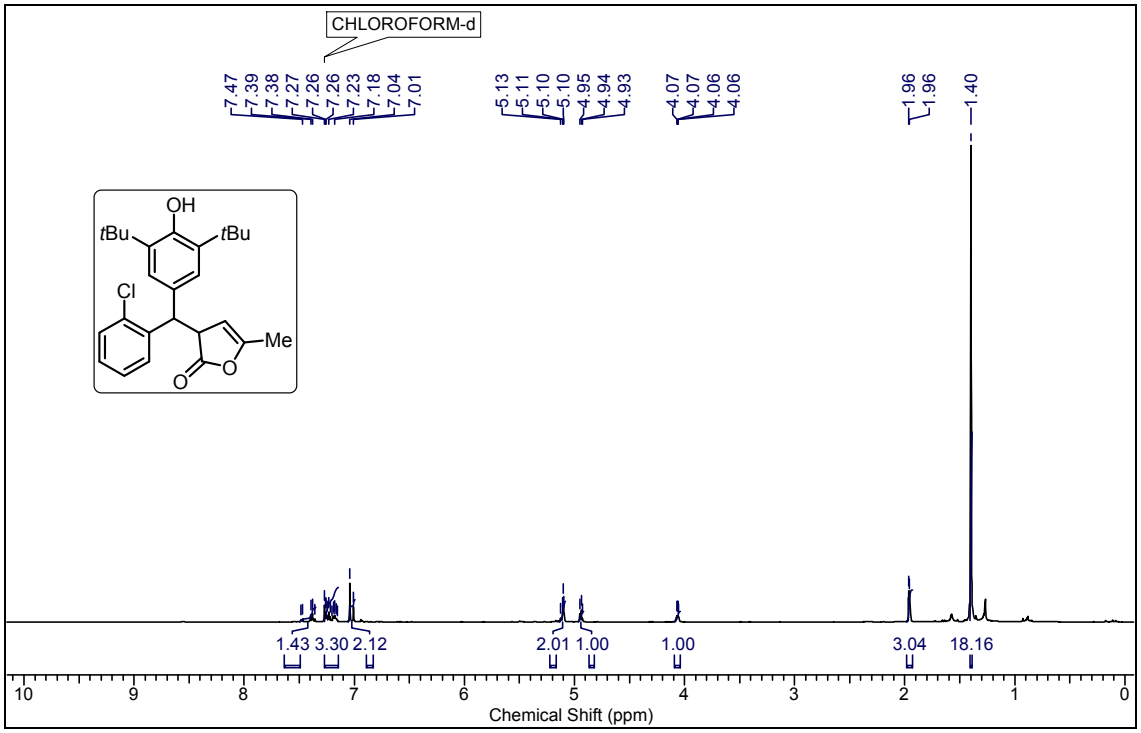


^{13}C NMR spectrum of compound **68a** ($CDCl_3$, 125 MHz):

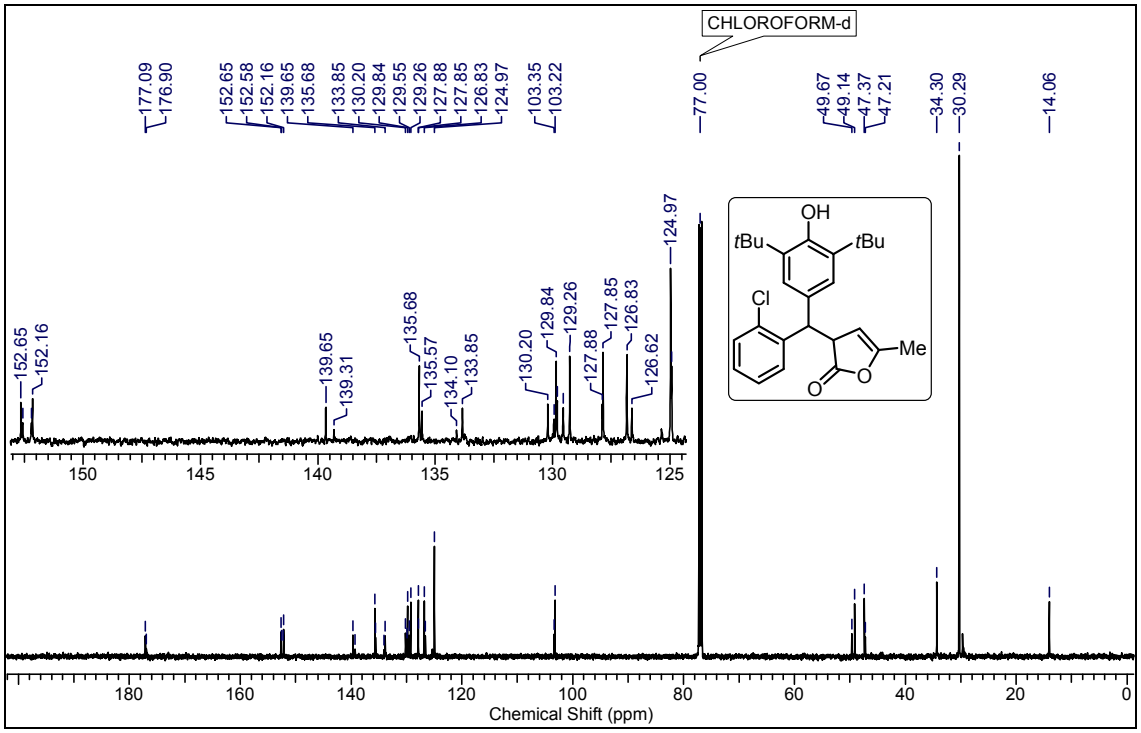


Spectra

^{1}H NMR spectrum of compound **68b** ($CDCl_3$, 500 MHz):



^{13}C NMR spectrum of compound **68b** ($CDCl_3$, 125 MHz):



HPLC (*dr*) of compound **68b**:

D-7000 HPLC System Manager Report

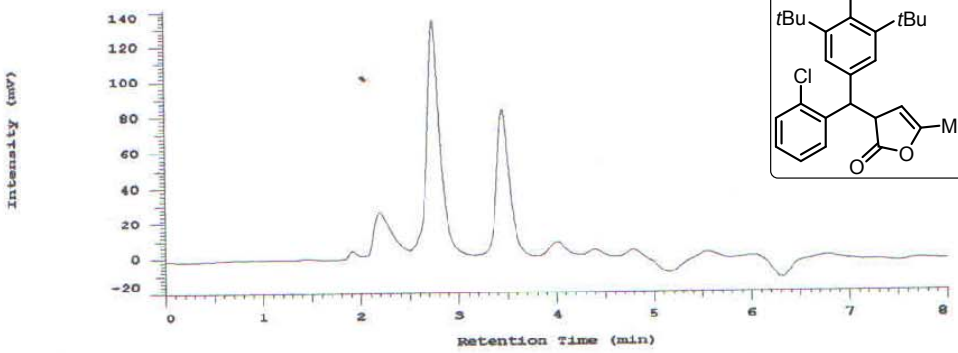
Analyzed: 08/14/17 04:27 PM

Reported: 08/14/17 04:48 PM
Processed: 08/14/17 04:47 PM

Data Path: C:\WIN32APP\HSM\HPLC\DATA\9708\
Processing Method: cal
System(acquisition): Sys 1
Application: HPLC
Sample Name: L-26
Injection from this vial: 1 of 1
Sample Description: PE:IPA(98:02)

Series:9708
Volume: 10.0 ul

Chrom Type: HPLC Channel : 1



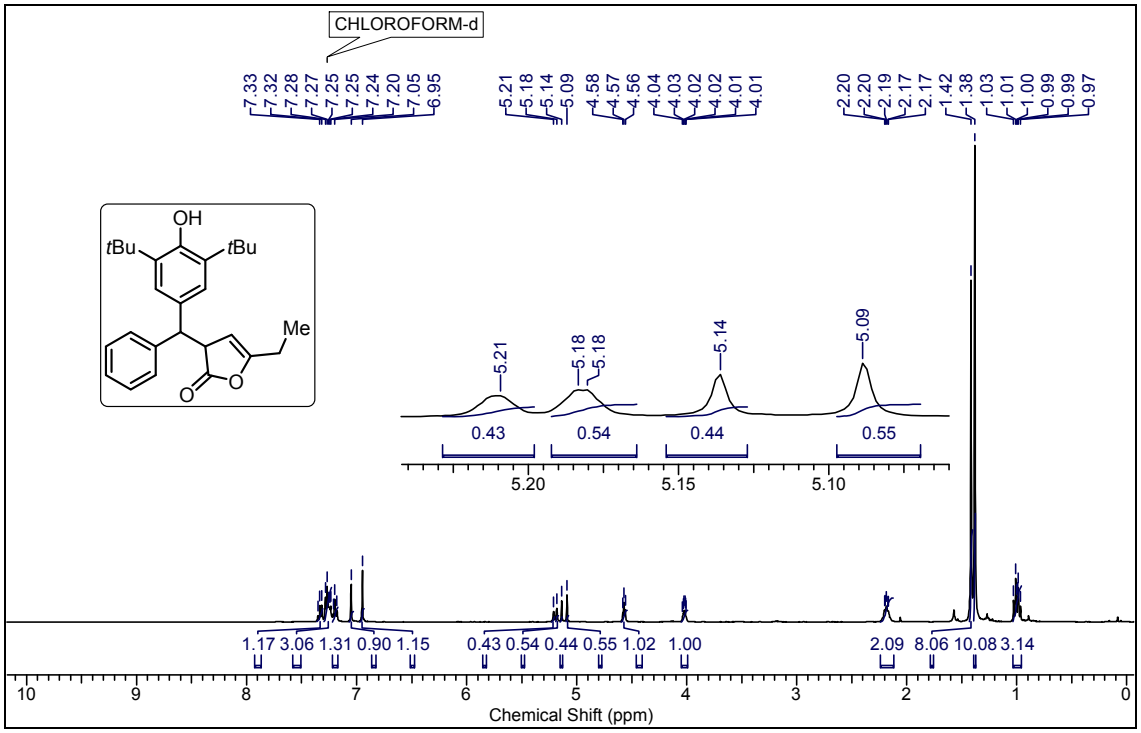
No.	RT	Area	Conc 1	BC
1	2.75	1194079	61.030	BB
2	3.45	762463	38.970	BB
		1956542	100.000	

Peak rejection level: 0

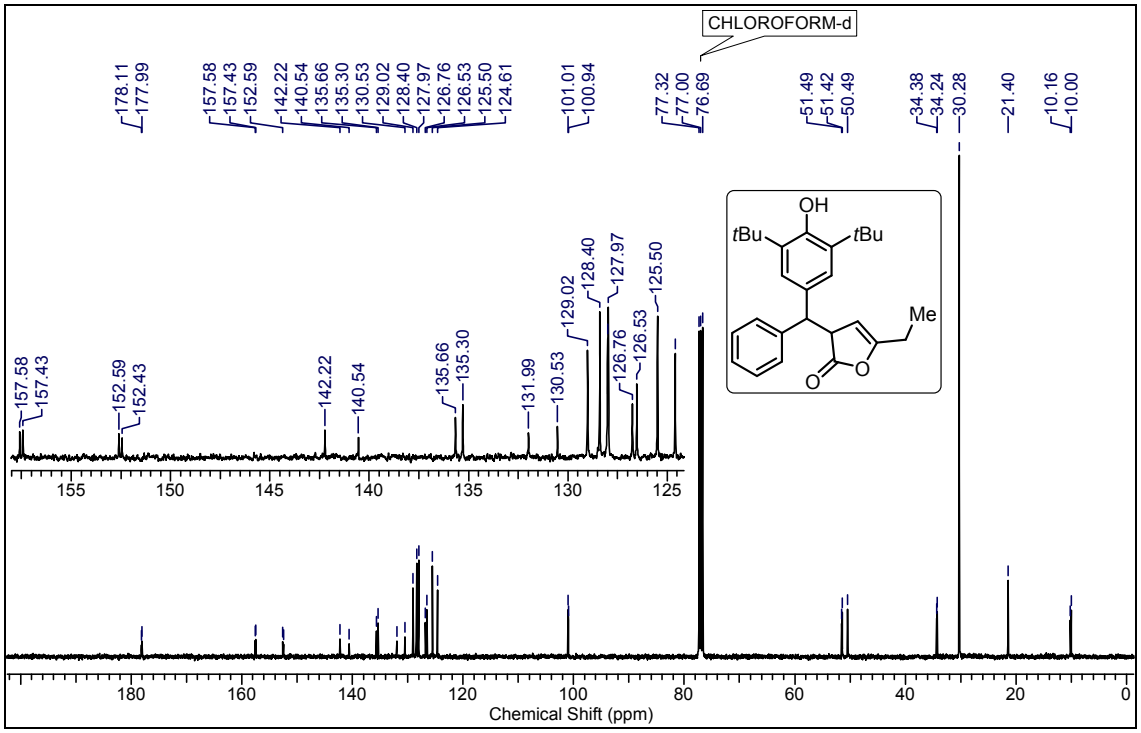
Project Leader: Dr.P.K.Tripathi
Column :Chiralpak IA(150 mmx4.6mm)
Mobile Ph : IPA:PE(02:98)
Wavelength : 220nm
Flow : 1.0 ml/min.
Inject vol: 2ul

Spectra

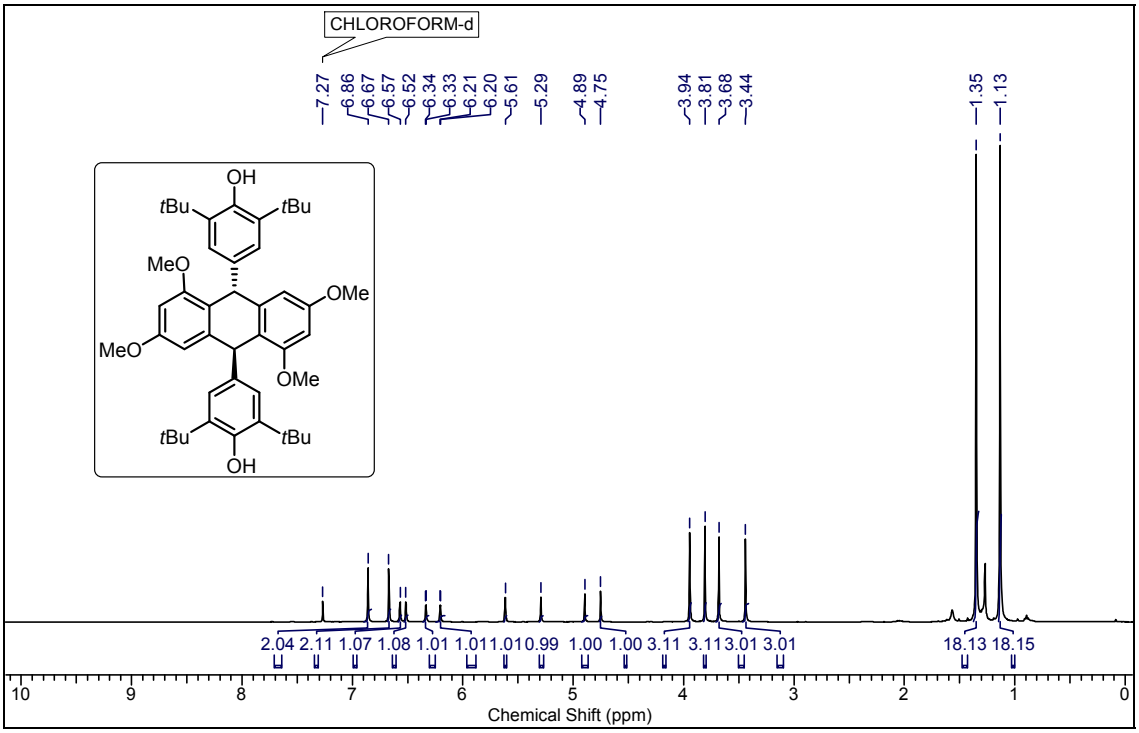
^{1}H NMR spectrum of compound **68d** ($CDCl_3$, 400 MHz):



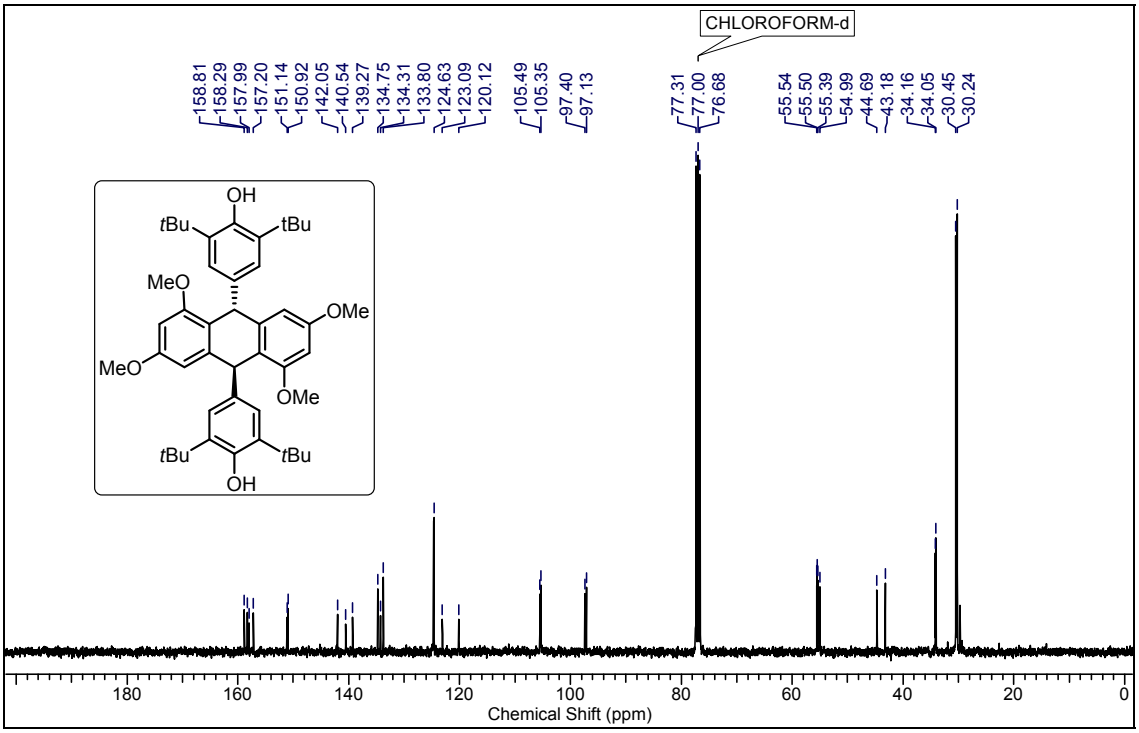
^{13}C NMR spectrum of compound **68d** ($CDCl_3$, 100 MHz):



^{1}H NMR spectrum of compound **69** ($CDCl_3$, 400 MHz):



^{13}C NMR spectrum of compound **69** ($CDCl_3$, 100 MHz):



3.2.6. References

(1) a) Rao, Y. S. *Chem. Rev.* **1964**, *64*, 353; b) Bandichhor, R.; Nosse, B.; Reiser, O. In *Natural Product Synthesis I: Targets, Methods, Concepts*; Springer Berlin Heidelberg: Berlin, Heidelberg, **2005**, p 43; c) Kitson, R. R. A.; Millemaggi, A.; Taylor, R. J. K. *Angew. Chem. Int. Ed.* **2009**, *48*, 9426; d) Guo, F.; Li, Z.; Xu, X.; Wang, K.; Shao, M.; Zhao, F.; Wang, H.; Hua, H.; Pei, Y.; Bai, J. *Fitoterapia* **2016**, *113*, 44.

(2) a) Wu, J.-l.; Li, N.; Hasegawa, T.; Sakai, J.-i.; Mitsui, T.; Ogura, H.; Kataoka, T.; Oka, S.; Kiuchi, M.; Tomida, A.; Turuo, T.; Li, M.; Tang, W.; Ando, M. *J. Nat. Prod.* **2006**, *69*, 790; b) Yu, X.; Che, Z.; Xu, H. *Chem. Eur. J.* **2017**, *23*, 4467; c) Kavitha, J.; Gopalaiah, K.; Rajasekhar, D.; Subbaraju, G. V. *J. Nat. Prod.* **2003**, *66*, 1113; d) Feng, W.-S.; Chen, H.; Zheng, X.-K.; Wang, Y.-Z.; Gao, L.; Li, H.-W. *J. Asian Nat. Prod. Res.* **2009**, *11*, 658.

(3) a) Mao, B.; Fañanás-Mastral, M.; Feringa, B. L. *Chem. Rev.* **2017**, *117*, 10502; b) Knight, D. W. *Contemp. Org. Synth.* **1994**, *1*, 287; c) Negishi, E.-i.; Kotora, M. *Tetrahedron* **1997**, *53*, 6707; d) Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev.* **2011**, *111*, 3076.

(4) Machajewski, T. D.; Wong, C. H. *Angew. Chem. Int. Ed.* **2000**, *39*, 1352.

(5) Narasaka, K.; Soai, K.; Mukaiyama, T. *Chem. Lett.* **1974**, *3*, 1223.

(6) Schneider, C.; Abels, F. *Org. Biomol. Chem.* **2014**, *12*, 3531.

(7) a) Kalesse, M.; Cordes, M.; Symkenberg, G.; Lu, H.-H. *Nat. Prod. Rep.* **2014**, *31*, 563; b) Denmark, S. E.; Heemstra, J. R.; Beutner, G. L. *Angew. Chem. Int. Ed.* **2005**, *44*, 4682.

(8) Zhang, Q.; Xiao, X.; Lin, L.; Liu, X.; Feng, X. *Org. Biomol. Chem.* **2011**, *9*, 5748.

(9) Nishikori, H.; Ito, K.; Katsuki, T. *Tetrahedron: Asymmetry* **1998**, *9*, 1165.

(10) Yang, H.; Kim, S. *Synlett* **2008**, 555.

(11) Rassu, G.; Auzzas, L.; Pinna, L.; Zambrano, V.; Battistini, L.; Zanardi, F.; Marzocchi, L.; Acquotti, D.; Casiraghi, G. *J. Org. Chem.* **2001**, *66*, 8070.

(12) Ji, J.; Lin, L.; Zhou, L.; Zhang, Y.; Liu, Y.; Liu, X.; Feng, X. *Adv. Synth. Catal.* **2013**, *355*, 2764.

(13) Yin, L.; Takada, H.; Lin, S.; Kumagai, N.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 5327.

(14) a) Egorova, A. Y.; Timofeeva, Z. Y. *Russ. J. Gen. Chem.* **2003**, *73*, 655; b) Mao, B.; Ji, Y.; Fañanás-Mastral, M.; Caroli, G.; Meetsma, A.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2012**, *51*, 3168.

(15) Chen, W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 15249.

(16) Woyciechowska, M.; Forcher, G.; Buda, S.; Mlynarski, J. *Chem. Commun.* **2012**, *48*, 11029.

(17) Takahashi, A.; Yanai, H.; Zhang, M.; Sonoda, T.; Mishima, M.; Taguchi, T. *J. Org. Chem.* **2010**, *75*, 1259.

(18) Jefford, C. W.; Jaggi, D.; Boukouvalas, J. *J. Chem. Soc., Chem. Commun.,* **1988**, 1595.

(19) Wu, B.; Yu, Z.; Gao, X.; Lan, Y.; Zhou, Y.-G. *Angew. Chem. Int. Ed.* **2017**, *56*, 4006.

(20) Sato, T.; Hanna, J.; Nakamura, H.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1055.

(21) Isambert, N.; Cruz, M.; Arévalo, M. J.; Gomez, E.; Lavilla, R. *Org. Lett.* **2007**, *9*, 4199.

(22) Bode, H. B.; Zeeck, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 323.

(23) Kupchan, S. M.; Karim, A.; Marcks, C. *J. Am. Chem. Soc.* **1968**, *90*, 5923.

(24) a) Allison, A. C.; Cacabelos, R.; Lombardi, V. R. M.; Álvarez, X. A.; Vigo, C. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **2001**, *25*, 1341; b) Kim, D. H.; Shin, E. K.; Kim, Y. H.; Lee, B. W.; Jun, J. G.; Park, J. H. Y.; Kim, J. K. *Eur. J. Clin. Invest.* **2009**, *39*, 819.

(25) a) Peter, M. G. *Angew. Chem. Int. Ed.* **1989**, *28*, 555; b) Van De Water, R. W.; Pettus, T. R. *Tetrahedron* **2002**, *58*, 5367.

(26) Rajski, S. R.; Williams, R. M. *Chem. Rev.* **1998**, *98*, 2723.

(27) Myers, J. K.; Cohen, J. D.; Widlanski, T. S. *J. Am. Chem. Soc.* **1995**, *117*, 11049.

(28) Nguyen, C.; Blanco, J.; Mazaleyrat, J.-P.; Krust, B.; Callebaut, C.; Jacotot, E.; Hovanessian, A. G.; Wakselman, M. *J. Med. Chem.* **1998**, *41*, 2100.

(29) Stowell, J. K.; Widlanski, T. S.; Kutateladze, T. G.; Raines, R. T. *J. Org. Chem.* **1995**, *60*, 6930.

(30) Wang, P.; Song, Y.; Zhang, L.; He, H.; Zhou, X. *Curr. Med. Chem.* **2005**, *12*, 2893.

(31) Thompson, D. C.; Thompson, J. A.; Sugumaran, M.; Moldéus, P. *Chem.-Biol. Interact.* **1992**, *86*, 129.

(32) a) Mahesh, S.; Kant, G.; Anand, R. V. *RSC Advances* **2016**, *6*, 80718; b) Reddy, V.; Vijaya Anand, R. *Org. Lett.* **2015**, *17*, 3390.

(33) Jarava-Barrera, C.; Parra, A.; López, A.; Cruz-Acosta, F.; Collado-Sanz, D.; Cárdenas, D. J.; Tortosa, M. *ACS Catal.* **2016**, *6*, 442.

(34) Yang, C.; Gao, S.; Yao, H.; Lin, A. *J. Org. Chem.* **2016**, *81*, 11956.

(35) Huang, B.; Shen, Y.; Mao, Z.; Liu, Y.; Cui, S. *Org. Lett.* **2016**, *18*, 4888.

(36) Xie, K.-X.; Zhang, Z.-P.; Li, X. *Org. Lett.* **2017**.

(37) Rathod, J.; Sharma, B. M.; Mali, P. S.; Kumar, P. *Synthesis* **2017**, *49*, 5224.

(38) a) Toteva, M. M.; Richard, J. P. In *Advances in Physical Organic Chemistry*; John, P. R., Ed.; Academic Press: **2011**; Vol. 45, p 39; b) Angle, S. R.; Arnaiz, D. O. *J. Org. Chem.* **1990**, *55*, 3708.

(39) Turner, A. B. *Q. Rev., Chem. Soc.* **1964**, *18*, 347.

(40) Gao, S.; Xu, X.; Yuan, Z.; Zhou, H.; Yao, H.; Lin, A. *Eur. J. Org. Chem.* **2016**, 3006.

(41) a) Angle, S. R.; Turnbull, K. D. *J. Am. Chem. Soc.* **1989**, *111*, 1136; b) Angle, S. R.; Louie, M. S.; Mattson, H. L.; Yang, W. *Tetrahedron Lett.* **1989**, *30*, 1193.

(42) China Raju, B.; Neelakantan, P.; Bhalerao, U. T. *Tetrahedron Lett.* **2004**, *45*, 7487.

(43) Eklund, P. C.; Willför, S. M.; Smeds, A. I.; Sundell, F. J.; Sjöholm, R. E.; Holmbom, B. R. *J. Nat. Prod.* **2004**, *67*, 927.

(44) Zhou, L.; Lin, L.; Ji, J.; Xie, M.; Liu, X.; Feng, X. *Org. Lett.* **2011**, *13*, 3056.

(45) a) Kumar, P.; Naidu, S. V.; Gupta, P. *J. Org. Chem.* **2005**, *70*, 2843; b) Show, K.; Kumar, P. *Eur. J. Org. Chem.* **2016**, 4696.

(46) Oertling, H.; Reckziegel, A.; Surburg, H.; Bertram, H.-J. *Chem. Rev.* **2007**, *107*, 2136.

(47) a) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192; b) Jusseau, X.; Chabaud, L.; Guillou, C. *Tetrahedron* **2014**, *70*, 2595;

c) Jadhav, A. P.; Rao, V. B.; Singh, P.; Gonnade, R.; Singh, R. P. *Chem. Commun.* **2015**, *51*, 13941.

(48) Snyder, S. A.; ElSohly, A. M.; Kontes, F. *Nat. Prod. Rep.* **2011**, *28*, 897.

(49) Chu, W. D.; Zhang, L. F.; Bao, X.; Zhao, X. H.; Zeng, C.; Du, J. Y.; Zhang, G. B.; Wang, F. X.; Ma, X. Y.; Fan, C. A. *Angew. Chem. Int. Ed.* **2013**, *52*, 9229.

(50) Jarava-Barrera, C.; Parra, A.; López, A.; Cruz-Acosta, F.; Collado-Sanz, D.; Cárdenas, D. J.; Tortosa, M. *ACS Catal.* **2015**, *6*, 442.

(51) Hewitt, J. F.; Williams, L.; Aggarwal, P.; Smith, C. D.; France, D. J. *Chem. Sci.* **2013**, *4*, 3538.

(52) a) Marshall, J. A.; Wolf, M. A.; Wallace, E. M. *J. Org. Chem.* **1997**, *62*, 367; b) Quintard, A.; Lefranc, A.; Alexakis, A. *Org. Lett.* **2011**, *13*, 1540; c) Wu, Y.; Singh, R. P.; Deng, L. *J. Am. Chem. Soc.* **2011**, *133*, 12458.

(53) a) Li, X.; Lu, M.; Dong, Y.; Wu, W.; Qian, Q.; Ye, J.; Dixon, D. J. *Nat. Commun.* **2014**, *5*, 4479; b) Wang, Z.-H.; Wu, Z.-J.; Huang, X.-Q.; Yue, D.-F.; You, Y.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. *Chem. Commun.* **2015**, *51*, 15835.

(54) Tsolomitis, A.; Sandris, C. *J. Heterocycl. Chem.* **1983**, *20*, 1545.

(55) Nasman, J. *Org. Synth.* **1990**, *68*, 162.

(56) Näsman, J.-A. H.; Pensar, K. G. *Synthesis* **1985**, 786.

(57) a) Martin, S. F.; Barr, K. J.; Smith, D. W.; Bur, S. K. *J. Am. Chem. Soc.* **1999**, *121*, 6990; b) Yang, Y.; Li, Y. *J. Chem. Res.* **2006**, 758.

Publications

1. "First total synthesis of seimatopolide B" U. Nookaraju, Anand Harbindu, Ankushkumar D. Bhise, **Brijesh M. Sharma**, Pradeep Kumar*, *RSC Adv.* **2012**, *2*, 11231.

2. "Asymmetric routes to pentadec-1-en-4-ol: application to the syntheses of aculeatins F and *epi*-F, *(R)*- and *(S)*-5-hexadecanolide and a formal synthesis of solenopsin" Anand Harbindu, **Brijesh M. Sharma**, Pradeep Kumar*, *Tetrahedron: Asymmetry*, **2013**, *24*, 305.

3. "Enantioselective modular total synthesis of macrolides Sch725674 and C-4-*epi*-Sch725674." **Brijesh M. Sharma**, Arjun Gontala, Pradeep Kumar*, *Eur. J. Org. Chem*. **2016**, 1215.

4. "Transition metal catalysis — a unique road map in the stereoselective synthesis of 1,3-polyols." Divya Tripathi, **Brijesh M. Sharma,** Namrata Dwivedi, Pradeep Kumar*, *Org. Biomol. Chem.* **2017,** 733.

5. Unified Approach to Fused and Spirocyclic Oxindoles through Lewis-Acid-Promoted Opening of Spiroepoxyoxindoles with Allylsilanes: Application to the Formal Synthesis of (±)-Physovenine. **Brijesh M. Sharma**, Mahesh Yadav, Rajesh G. Gonnade, Pradeep Kumar*, *Eur. J. Org. Chem.* **2017**, 2603.

6. Tf_2NH Catalyzed 1,6-Conjugate Addition of Vinyl azide with *p*-Quinone Methides: A Mild and Efficient Method for Synthesis of *β*-Bis-Arylamides. Jayant B. Rathod, **Brijesh M. Sharma,** Pramod S. Mali, Pradeep Kumar*, *Synthesis.* **2017**, *49*, 5224.

7. Ramberg-Bäcklund and Intramolecular HWE Approach Towards Macrocyclization for the Synthesis of *Z*-isomer of ten membered nonenolide core of (6S,7R,9R)-6,7-dihydroxy-9-propylnon-4-eno-9-lactone. **Brijesh M. Sharma**, Pradeep Kumar* (*Manuscript under preparation*).

8. Unraveling the Nucleophilicity of Butenolides for 1,6-Conjugate Addition to *p*-Quinone Methides: A Direct Access to Diversely Substituted Butenolide-Derived

Diarylmethanes. **Brijesh M. Sharma**, Dinesh. Shinde, Ruchi Jain, Eeshwaraiah Begari, Shruti Satbhaiya, Rajesh G. Gonnade, Pradeep Kumar * *Org. Lett.* **2018**, 20, 2787.

9. Harnessing Nucleophilicity of Allenol Ester with *p*-Quinone Methides *via* Gold Catalysis: Application to the Synthesis of Diarylmethine-Substituted Enones. **Brijesh M. Sharma,** Jayant B. Rathod, Rajesh G. Gonnade, Pradeep Kumar * (***Just Accepted,*** *J. Org. Chem. jo-2018-012944*).

10. Proline Catalyzed Asymmetric *α*-Amination in the Synthesis of Bioactive Molecules. Pradeep Kumar *, **Brijesh M. Sharma** (**Accounts**, ***Just Accepted,*** *Synlett, ST-2018-02-0117-A*).

Patents:

11. Substituted sugar derived 1,2,3- triazole compounds and their dimmers and a process for the preparation thereof. Anand Harbindu, **Brijesh M. Sharma**, Pradeep Kumar***, WO2014/132273 A1**.

12. Triazine compounds and a process for preparation thereof. Anand Harbindu, **Brijesh M. Sharma**, Pradeep Kumar***, WO2014/115171 A1**.

Authors Profile

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Brijesh M. Sharma was born in 1989 in Khopoli (Maharashtra), India. He completed his B.Sc. chemistry from K. M. C College Khopoli, in the year 2009 and M.Sc in Organic Chemistry from Department of Chemistry, the University of Mumbai in 2011. He has been awarded National fellowship for pursuing his doctoral studies in CSIR-National Chemical Laboratory under the supervision of Dr. Pradeep Kumar. His research interest centers around the development of highly selective C−C bond-forming reactions and total synthesis of biologically active natural products and drugs such as, Aculeatins F and *epi*-F, (*R*)- and (*S*)-5-hexadecanolide and a formal synthesis of solenopsin, Seimatopolide B, Sch725674 and C-4-*epi*-Sch725674, formal synthesis of (±)-Physovenine, 10-Memered core of Nonenolide (Completed). Total synthesis of (−)-Bitungolide F (under progress).

Supervised/Trained

Trained 2 graduate and 3 post graduate students in my PhD tenture:

- **Mr. Mahesh Yadav**, currently pursuing PhD with Dr. Narshinha P. Argade (CSIR-NCL)
- **Mr. Arjun Gontala**, currently pursuing PhD with Prof. Sang Kook Woo (South Korea)
- **Mr. Mahesh S. Kutwal**, currently pursuing PhD with Prof. Chandrakumar Appayee (IIT- Gandhinagar)

CSIR-NCL Main Building

NCL-Research Scholar Meet – 2014 "A Memorable Occasion"

Reunion Eve of Dr. P. K. T's Group at Hotel Seasons

Reprint of Publications

ChemPubSoc Europe

DOI: 10.1002/ejoc.201501531

EurJOC European Journal of Organic Chemistry

Full Paper

Total Synthesis

Enantioselective Modular Total Synthesis of Macrolides Sch725674 and C-4-*epi*-Sch725674

Brijesh M. Sharma,[a] Arjun Gontala,[a] and Pradeep Kumar*[a]

Abstract: The convergent total synthesis of Sch725674 has been accomplished by starting from (*R*)-1,2-epoxyheptane and assembling five modules in a highly stereoselective manner to give the final product in 6.6 % overall yield. The same strategy was extended to the synthesis of its C-4 epimer. Key reactions of the synthetic pathway include a Jacobsen hydrolytic kinetic resolution of an epoxide followed by its regioselective opening through a Yamaguchi–Hirao alkynylation, and ring-closing metathesis reaction to furnish the unique 14-membered ring macrolactone. In addition, the influence of protecting groups on the efficiency of the ring-closing metathesis (RCM) macrocyclization has been studied to maximize its yields.

Introduction

Fourteen-membered ring macrolides have been research targets because of their exceptional biological activity and have been subjected to chemical modifications to establish structure–activity relationships for more than five decades.[1] The most distinguished feature of macrolides is their antimicrobial activity. However, their use has resulted in macrolide resistance in many organisms, which fuels the quest for newer potentially active macrolides. A new Sch725674 macrolide was recently isolated by Yang et al. from an *Aspergillus* sp., which has good antifungal activity against *S. cereviceae* and *C. albicans* with minimum inhibitory concentrations (MICs) of 8 and 32 μg mL^{-1} respectively.[2]

Additionally, this molecule can be converted into products that contain the structural scaffolds of pyran and furan rings[3] by using a simple intramolecular transannular oxy-Michael reaction to afford compounds that resemble those with established antineoplastic activity (Figure 1). Such transformations would help to tune the biological activity of a lead structure by incorporating activity-determining structural features. Hence, the total synthesis of Sch725674 can lead to a plethora of opportunities in terms of achieving a function-oriented synthesis of new macrolides.[4]

This structurally and stereochemically complex 14-membered ring macrolactone is comprised of an oxygenated hydrocarbon skeleton that contains four stereogenic centers, an α,β-unsaturated ester, and an unusual *n*-pentyl carbon chain. Because of its distinctive framework, Sch725674 has gained rapid intrigue among synthetic organic chemists. The first total synthesis of Sch725674 along with its 16 stereoisomeric analogues was reported by Curran et al. using a fluorous-tagging strategy.[5] A few more total syntheses of the same macrolactone were reported by Prasad et al.[6] and Kaliappan et al.[7] During the preparation of our manuscript, Reddy et al.[8] reported the formal total synthesis of Sch725674 (**1**).

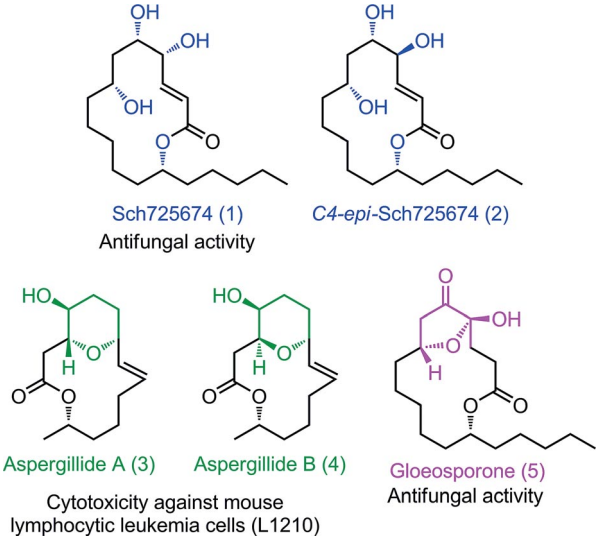

Figure 1. Structures of some representative macrolides.

For the synthesis of a library of compounds in terms of functional groups and stereochemical diversity,[9] an modular synthesis was envisioned as optimal to allow for maximum variability. This approach allows for parallel combinatorial and synthetic strategies. Thus, a convergent approach amenable for the easy synthesis of Sch725674 and C-4-*epi*-Sch725674 was designed, which was comprised of the assembly of five modules through sequential Jacobsen hydrolytic kinetic resolution,[10] Yamaguchi–Hirao alkynylation,[11] and ring-closing metathesis (RCM) steps to construct the core skeleton of the macrolide as shown in Scheme 1.

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Indole Derivatives

Unified Approach to Fused and Spirocyclic Oxindoles through Lewis-Acid-Promoted Opening of Spiroepoxyoxindoles with Allylsilanes: Application to the Formal Synthesis of (±)-Physovenine

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Abstract: A protocol for the construction of oxindoles containing all-carbon quaternary centres in a highly regioselective manner has been developed. The reaction involves opening of spiroepoxyoxindoles with allylsilanes to give Hosomi–Sakurai-type products as well as new silicon-containing spirocyclic oxindoles. A formal synthesis of (±)-physovenine was accomplished in five steps using this protocol.

Introduction

Oxindoles with a C-3 quaternary framework have found a renewed synthetic interest due to their widespread presence in natural products.[1] Among such oxindole derivatives, 3-allyl-3-(hydroxymethyl)oxindole **1**, which contains an all-carbon quaternary centre, is at the core of several pharmaceutically and naturally important alkaloids, such as physovenine, physostigmine, and oxaline (Figure 1), with a wide range of biological activites.[2] At the same time, spirooxindole moiety **2** has been recognized as the key structural motif in a wide array of biologically active compounds, including aspergillines A and B and XEN402.[3] Unnatural spirooxindoles containing silane in their structure have also been found to show excellent antitumour activity by Schreiber et al.[4] (Figure 1).

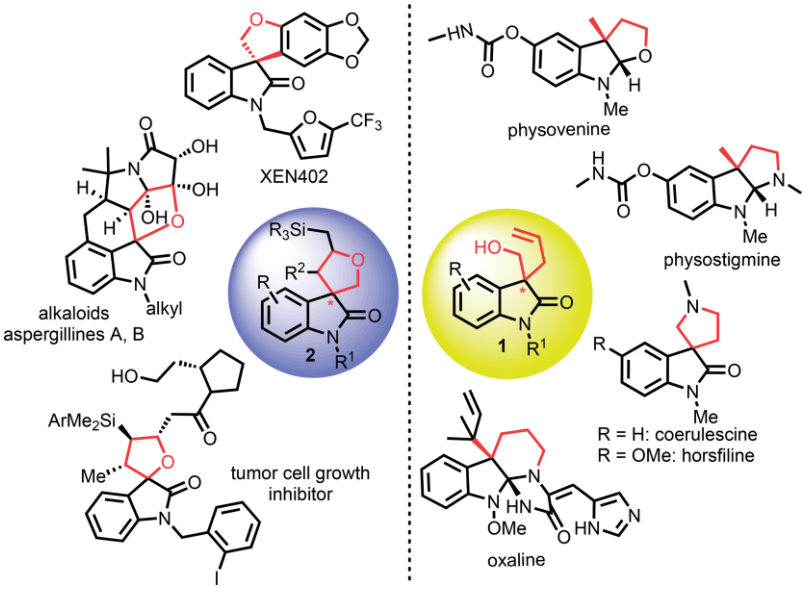

Figure 1. Some natural and unnatural oxindole compounds.

Smith and co-workers have accomplished the synthesis of alkaloids belonging to this class [e.g., (±)-coerulescine and (±)-

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Transition metal catalysis—a unique road map in the stereoselective synthesis of 1,3-polyols†

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The present review summarizes recent diverse reactions employed in the formation of 1,3-polyols providing an overview of the mechanistic pathway and the enantioselectivity obtained, in terms of the properties of transition metals directly involved in the catalytic transformations and their interaction with various ligands.

1. Introduction

The search for novel and proficient asymmetric catalysts has been a constant endeavor for scientists and has resulted in rapid expansion and investigations in the field of asymmetric syntheses.[1] Catalyst-controlled asymmetric reactions have presented a new paradigm shift over traditional substrate controlled asymmetric inductions.[2] In this context, transition metal catalysis has been exploited extensively in the field of organic chemistry for the synthesis of polyols. The asymmetric 1,3-polyol framework[3] can be ubiquitously seen in nature's vast repertoire of biologically active natural products which possess copious medicinal properties and intriguing structural complexity thus making the pursuit of transition metal catalyzed synthesis of 1,3-polyols a voracious quest. The study of 1,3-polyol scaffolds present in complex polyketides[4] is an important research goal not only to enhance the often sparse natural supply of these compounds and to support further biological applications, but also to enable structure–activity relationship studies (SAR) and for unambiguous stereochemical assignments.

Transition metals with variable oxidation states, comparable d-orbital energies and fine tunable ligands have rendered them as facile tools for accessing all stereoisomers of not only 1,3-polyol natural products, but also their analogues. The nature of the ligand bound to the metal centre influences the rates and selectivities of any organic transformation (Fig. 1). Hence the combined techniques of organic synthesis and

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†This article is dedicated to Professor Goverdhan Mehta in recognition of his seminal and outstanding contributions to so many aspects of organic chemistry.

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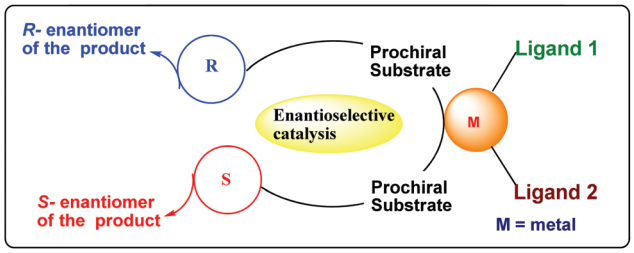

Fig. 1 Parameters involved in asymmetric catalysis.

organometallic chemistry can effectively address the challenge of enantioselectivity in a product for the development of more efficient catalytic transformations.

2. Tracing the past: roads travelled by

Nature's ability to functionalize various bonds has inspired and motivated organic chemists to closely examine the biosynthetic pathways and modify, fine-tune and redesign them for the construction of various natural products.[5] Working along these lines, many eminent chemists have engaged themselves in the construction of 1,3-oriented hydroxy groups in a stereocontrolled manner.[6]

Some of the previously reported landmark transition metal catalyzed reactions for the construction of 1,3-polyols employing stereoselective bond formation (C–C,[7] C–H,[8] and C–O[9]), have been recapitulated in Fig. 2.

An updated review on the synthesis of polyols appeared in 2006,[10] however to the best of our knowledge, there is no known review till date which deals exclusively with transition metal catalyzed 1,3-polyol synthesis along with their mechanistic studies. The present review will summarize recent diverse reactions employed in the formation of 1,3-polyols providing an overview of the concept, design, enantioselectivity and mechanistic pathway. Transmission of chirality from the catalyst to the product will be rationalized on the basis of certain transition states to establish the correlation between the structure and the stereochemistry of the product.

This review will encompass recent reports on the catalytic activity of transition metal complexes and their interactions with chiral ligands. The major transition metals used in 1,3-polyol synthesis, their respective benefits and disadvantages along with other relevant properties are also reviewed. However, 1,3-polyol methodologies leading to alternate methyl and hydroxyl groups or derivatives of 1,3-polyols have not been dealt with in this review as it is quite a vast topic and needs separate discussion. The review is organized as follows: Ti, Cr, Co, Ni, Cu, Ru, Rh, Pd, Os, Pt, Fe, Au/Bi, Ag and Re transition metal mediated synthesis of 1,3-polyols, the mechanistic rationale and reason for selectivity.

3. Titanium mediated synthesis of 1,3-polyols

3.1. Regiodivergent epoxide opening

In general, the use of the titanocenes in catalytic amounts is attractive especially for reagent controlled radical reactions. In relation to titanocene-mediated epoxide deoxygenation, RajanBabu and co-workers first introduced low-valent $Cp_2Ti(III)Cl$ to function as subtle and extremely chemoselective reagents for epoxide opening through electron-transfer.[11] Based on these seminal findings, Gansäuer and co-workers[12] devised regiodivergent epoxide opening (REO) of epoxide **1** to form 1,3-diols (**3**, **5**) and 1,4-diols (**2**, **4**) (Scheme 1) by employing electron transfer using Kagan's titanocene(III) complexes (**A** or ***ent*-A**).[13] This protocol has been further extended for the synthesis of 1,3-polyols.

3.1.1. Mechanistic rationale for high selectivity in REO. Even though the catalyst's reactive site is rather loose, the

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Organic LETTERS

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Unravelling the Nucleophilicity of Butenolides for 1,6-Conjugate Addition to *p*-Quinone Methides: A Direct Access to Diversely Substituted Butenolide-Derived Diarylmethanes

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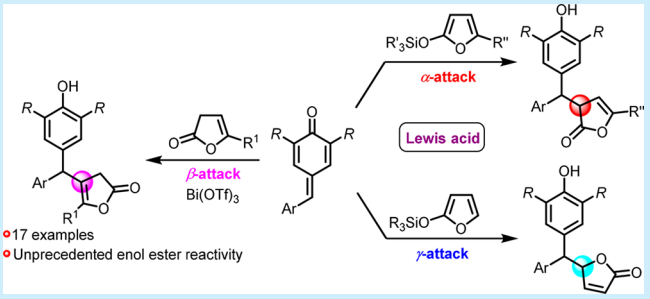
Supporting Information

ABSTRACT: A Lewis acid catalyzed regioselective C−C bond is constructed through β-addition of deconjugated butenolides with *p*-quinone methides in a 1,6-conjugate addition manner. Interestingly, Lewis acid catalyzed vinylogous Mukaiyama−Michael reaction of silyloxyfurans with *p*-QMs proceeds selectively through the α or γ position exclusively. The reaction is mild with broad substrate scope, thus allowing easy access to a wide range of bis-arylated α-/β-/γ-substituted butenolides.



Butenolides are structurally important scaffolds in various biologically active molecules, natural products, and synthetic intermediates.[1] Among various unsaturated γ-lactone derivatives, the butenolide-derived diarylmethane unit appears as a privileged structural motif in various complex lignans and secolignans.[2] The regioselectively functionalized sites of butenolide-derived diarylmethane constitutes an important structural feature of a diverse range of natural and unnatural products, exhibiting a wide spectrum of biological activities (Figure 1). Owing to the prevalence and significance of butenolides and its congeners, the development of streamlined strategies to exploit the nucleophilicity of all the positions (α, β, γ) of butenolide regioselectively remains an active area in the realm of exploratory synthetic research.[3]

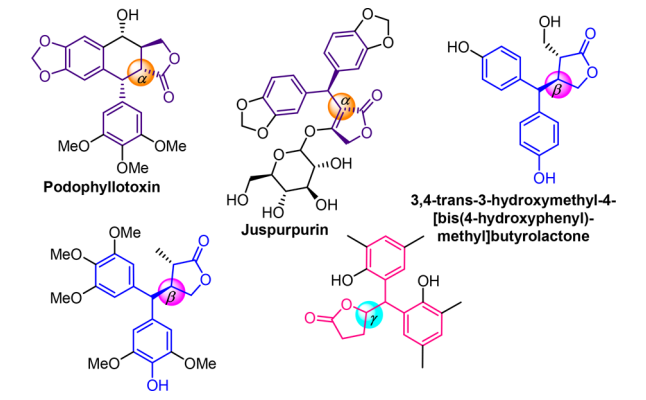
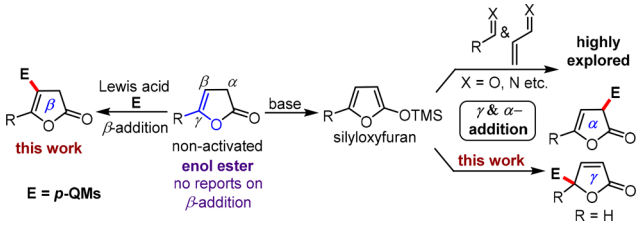


Figure 1. Natural and unnatural products containing γ-butenolide-/γ-butyrolactone-derived diarylmethane scaffolds.

A deconjugated butenolide, α-angelica lactone, has emerged as a valuable building block for the construction of butenolide derivatives.[4] It has been synthetically exploited through in situ conversion to dienolate intermediates and silyloxyfurans for the electrophilic attack at the γ-position. A few reports for α-attack of silyloxyfurans are also available in the literature. However, the nucleophilicity of the β-position has not been explored rigorously (Scheme 1).

In contrast to the well explored γ-attack of deconjugated butenolides or silyloxyfurans, only two reports by Mukaiyama[5] and Lavilla[6] were found for nucleophilic attack of α-angelica

Scheme 1. Regioselectivity of Deconjugated Butenolides and Silyloxyfurans toward 1,6-Conjugate Addition Reaction



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