SELECTIVE CARBON–CARBON COUPLING REACTIONS OF PHTHALIDES: SYNTHESIS OF anti-HELICOBACTER PYLORI AGENTS THE CJ-MOLECULES AND OXYGEN CONTAINING BIOACTIVE NATURAL PRODUCTS

THESIS

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By

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AUGUST 2012

Dedicated to…..

Dhan Baba Lakho

&

my Family

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "***Selective Carbon-Carbon Coupling Reactions of Phthalides: Synthesis of anti-Helicobacter Pylori Agents the CJ-Molecules and Oxygen Containing Bioactive Natural Products***" which is being submitted to the ***University of Pune*** for the award of ***Doctor of Philosophy*** in ***Chemistry*** by ***Mr. Mandeep Singh*** was carried out by him under my supervision at the National Chemical Laboratory, Pune. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

August 2012
Pune

Dr. N. P. Argade
(Research Guide)

Candidate's Declaration

I hereby declare that the research work incorporated in the thesis entitled "***Selective Carbon-Carbon Coupling Reactions of Phthalides: Synthesis of anti-Helicobacter Pylori Agents the CJ-Molecules and Oxygen Containing Bioactive Natural Products***" submitted for the degree of ***Doctor of Philosophy*** in ***Chemistry*** to the ***University of Pune***, has been carried out by me at the Division of Organic Chemistry, National Chemical Laboratory, Pune, India, from August 2007 to August 2012 under the supervision of Dr. Narshinha P. Argade. This work has not been submitted in part or full by me for a degree or diploma to this or any other University or Institution.

August 2012
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Arup, Ramesh, Mahesh, Abasaheb, Kishor, Lalit, Rahul, Sujit, Swaroop, Kannan to name just a few. I am also thankful to my friends Sangram, Tukaram, Roshana, Kheria, Nilesh, Sumanta, Prakash, Pradeep, Sutar, Anand, Ankush, Krishanu, Pankaj & Pankaj, Ranjeet, Jyoti, Laha, Krunal, Rishi, Anuj, Ajay, Anil, Rupesh, Dipesh, Maidul, Roshan, Saikat, Somesh & all my other colleagues for their cheerful support, co-operation and making my stay at NCL very comfortable and memorable one.

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I wish to express my gratitude towards "God-almighty", who gave me the strength and courage to fulfil my dreams and has showered upon me his choicest blessings.

.....Mandeep

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General Remarks

- All the solvents used were purified using the known literature procedures.
- Petroleum ether used in the experiments was of 60-80 °C boiling range.
- Silica gel column chromatographic separations were carried out by gradient elution with light petroleum ether-ethyl acetate mixture, unless otherwise mentioned (silica gel, 60-120 mesh/100-200 mesh/230-400 mesh).
- TLC was performed on E-Merck pre-coated 60 F_{254} plates and the spots were rendered visible by exposing to UV light, iodine, *p*-anisaldehyde (in ethanol), bromocresol green (in ethanol) and ninhydrin (in ethanol).
- IR spectra were recorded on Shimadzu FTIR instrument, for solid either as nujol mull or in chloroform solution (concentration 0.05 to 10%) and neat in case of liquid compounds.
- NMR spectra were recorded on Brucker ACF 200 (200 MHz for ^{1}H NMR and 50 MHz for ^{13}C NMR), ACF 400 (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR) and DRX 500 (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR) spectrometers. Chemical shifts (δ) reported are referred to internal reference tetramethyl silane.
- Mass spectra were taken on MS-TOF mass spectrometer.
- HRMS (ESI) were taken on Orbitrap (quadrupole plus ion trap) and TOF mass analyzer.
- Microanalysis data were obtained using Flash EA 1112 series and Elementar Vario EL analyzer.
- All the melting points reported are uncorrected and were recorded using an electro-thermal melting point apparatus.
- All the compounds previously known in the literature were characterized by comparison of IR and NMR spectra as well as melting point with authentic samples.
- All the new experiments were repeated two or more times.
- Starting materials were obtained from commercial sources or prepared using known procedures.

Abbreviations

Å	Angstrom
Aq.	Aqueous
AIBN	2,2'-Azobisisobutyronitrile
BAIB	Bis(acetoxy)iodobenzene
(+)-BINOL	(+)-1,1'-Bi-2-naphthol
BOMCl	Benzyl chloromethyl ether
CAN	Ceric ammonium nitrate
cat.	Catalytic
CSA	(1*R*)-(−)-Camphor-10-sulfonic acid
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
DEPT	Distortionless enhancement by polarization transfer
DIBAL-H	Diisobutylaluminium hydride
DIPEA	Diisopropyl ethyl amine
(−)-DIPT	(−)-Diisopropyl tartrate
DMA	*N*,*N*'-Dimethylaniline
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulphoxide
DMP	Dess–Martin periodinane
dppb	1,4-Bis(diphenylphosphino)butane
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
EDCI	*N*-Ethyl-*N*'-(3-dimethylaminopropyl)carbodimide hydrochloride
ee	Enantiomeric excess
ESI	Electro spray ionization
eq.	Equation
equiv	Equivalent
h	Hour(s)
HMPA	Hexamethylphosphoramide
HOBt	1-Hydroxybenzotriazole
HRMS	High resolution mass spectra
HPLC	High performance liquid chromatography
Hz	Hertz
IC	Inhibitory concentration
IR	Infra Red
KHMDS	Potassium bis(trimethylsilyl)amide
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
m-CPBA	*m*-Chloroperbenzoic acid

MHz	Megahertz
(*R*)-MeCBS	(*R*)-2-Methyl-CBS-Oxazaborolidine
min.	Minute(s)
mL	Millilitre(s)
MOMCl	Chloromethyl methyl ether
mmol	Millimole(s)
Mp	Melting point
MS	Mass Spectrum
MsCl	Methanesulfonyl chloride
NBS	*N*-Bromosuccinimide
NaHMDS	Sodium bis(trimethylsilyl)amide
NMO	4-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
PMBCl	*p*-Methoxybenzyl chloride
p-TsOH	*p*-Toluenesulfonic acid
p-TsCl	*p*-Toluenesulfonyl chloride
PPTS	Pyridinium *p*-toluenesulfonate
Py	Pyridine
rt	Room temperature
TBAF	Tetra-*n*-butylammonium fluoride
TBAI	Tetra-*n*-butylammonium iodide
TBHP	*tert*-Butyl hydroperoxide
TBSCl	tert-Butyldimethylsilyl chloride
TBDPSCl	tert-Butyldiphenylsilyl chloride
TMSCl	Trimethylsilyl chloride
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TFA	Trifluoroacetic acid
TIPSOTf	Triisopropyl trifluoromethane sulfonate
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMU	1,1,3,3-Tetramethylurea
TMEDA	Tetramethylethylenediamine
TPAP	Tetrapropylammonium perruthenate
TPP	Triphenylphosphine
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

Abstract

The present dissertation is divided into three chapters. The first chapter portrays a contemporary literature account of 1(*3H*)-isobenzofuranones (phthalides). In second chapter, a brief account of anti-*Helicobacter pylori agents* has been illustrated coupled with our contribution towards the synthesis of several anti-*Helicobacter pylori agents* and the enantiomerically pure spiroketal segment of (+)-spiroxaline methyl ether. In third chapter, concise account on chemistry of naturally occurring pawhuskins, schweinfurthins, NG-121 and stachybotrins has been described along with our results on the synthesis of pawhuskin C, schweinfurtin J and NG-121 methyl ether (Figure).

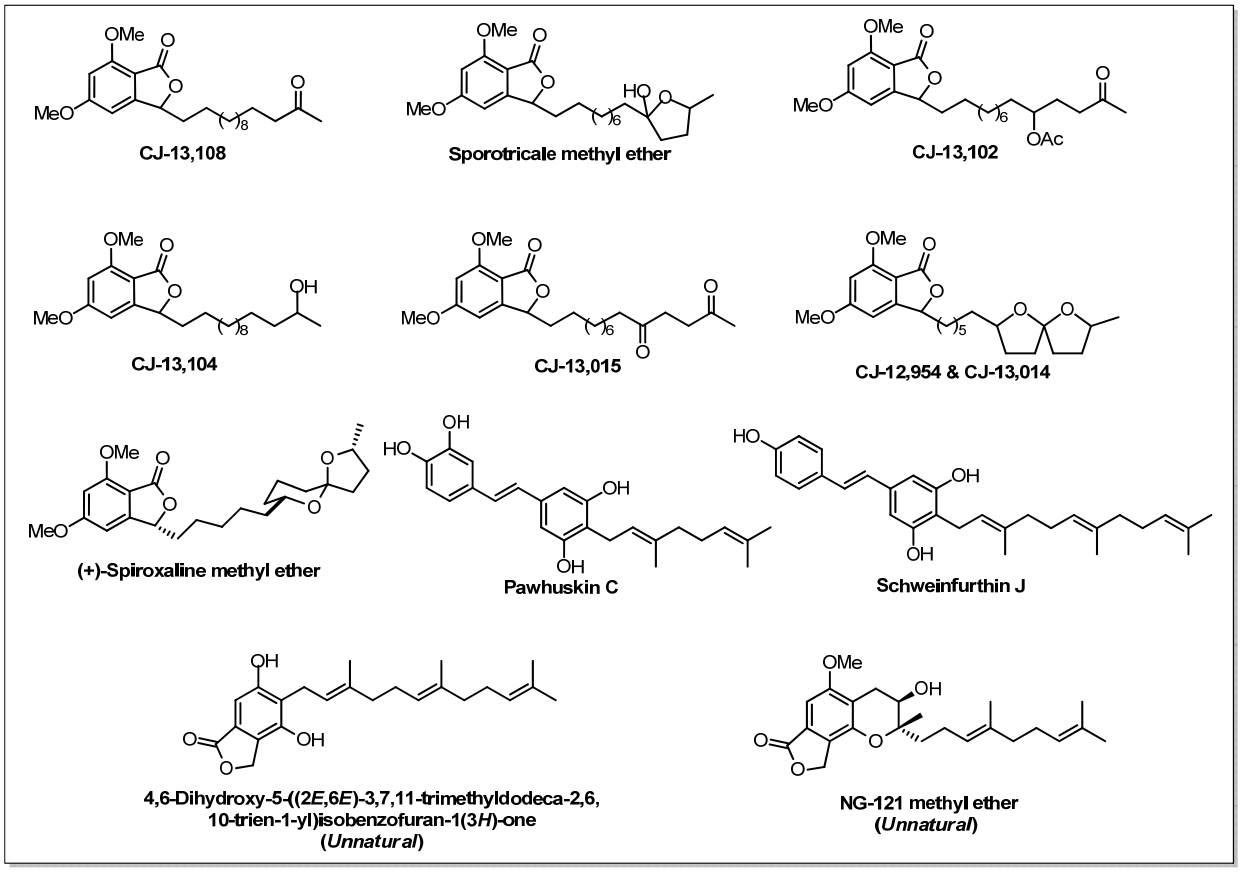


Figure. Oxygen containing bioactive natural and unnatural products synthesized

Chapter 1. A Brief Review on the Chemistry of 1(*3H*)-Isobenzofuranones (Phthalides)

1(*3H*)-Isobenzofuranones (phthalides) are the prominent class of natural products by virtue of their significantly varied biological properties (Figure 1). They are of interest to synthetic organic chemists from both basic and applied point of view. Depending on the structural features, multiple electrophilic and nucleophilic reactive sites are available on phthalides and hence they serve as pivotal synthetic building blocks. This chapter presents concise recent literature account of phthalides illustrating

isolation, bioactivity and synthesis of phthalide based natural products with an emphasis on new synthetic routes and strategies.

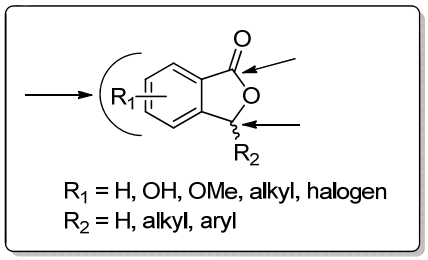
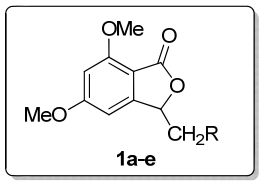


Figure 1. 1(*3H*)-Isobenzofuranones (phthalides) and their derivatives

Chapter 2. Synthesis of Naturally Occurring Remotely Functionalized anti-*Helicobacter pylori* Antibiotics

This chapter is divided into two sections. Section A presents a brief literature account on *Helicobacter pylori* antibiotics, the CJ-molecules and sporotricale methyl ether. The section B describes our contribution towards the synthesis of these imperative target compounds.

Section A: A Concise Literature Account of anti-*Helicobacter pylori* Agents



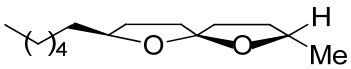
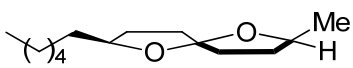
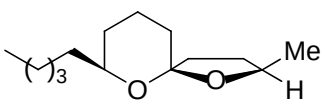
Compound	R	Activity (μg/disk that gives a 15 mm zone)
CJ-13,015 (**1a**)	$-(CH_2)_8COCH_2CH_2COCH_3$	2
CJ-13,102 (**1b**)	$-(CH_2)_8CH(OAc)CH_2CH_2COCH_3$	0.5
CJ-13,103 (**1c**)	$-(CH_2)_{10}COCH_2CH_2COCH_3$	50
CJ-13,104 (**1d**)	$-(CH_2)_{11}CH(OH)CH_3$	500
CJ-13,108 (**1e**)	$-(CH_2)_{11}COCH_3$	10
CJ-12,954 (**1f**)		0.02
CJ-13,014 (**1g**)		0.02
Spirolaxine methyl ether (**1h**)		Not determined

Figure 2. New microbial secondary metabolites and helicobactericidal activities

Gastric and duodenal ulcers affect a significant portion of the human population worldwide. The root cause of gastric and duodenal ulcers is the presence of the microaerophilic Gram-negative bacterium *Helicobacter pylori*, which appear to live beneath the mucus layer of the stomach. There is a need for a safe and effective treatment with a compound having an excellent anti-*H*. *pylori* activity. Dekker et al. isolated the new phthalides **1a**-**h** from the basidiomycete *Phanerochaerte velutina* with promising anti-*H*. *pylori* activity (Figure 2). Recently, Brimble et al. have reported the synthesis of five CJ-compounds **1a**-**e** using an intrinsic flexible approach. Soon after, Dallavalle et al. reported the synthesis of analogues natural product sporotricale methyl ether. An attractive syntheses of enantiomerically pure (–)-spiroxaline methyl ether have been recently reported by employing the Diels–Alder reaction, Julia olefination, Prins cyclization, cyclopropanol based and an alkyne-based strategies. As an introduction part the chemistry of CJ-targets has been summarized in the present section.

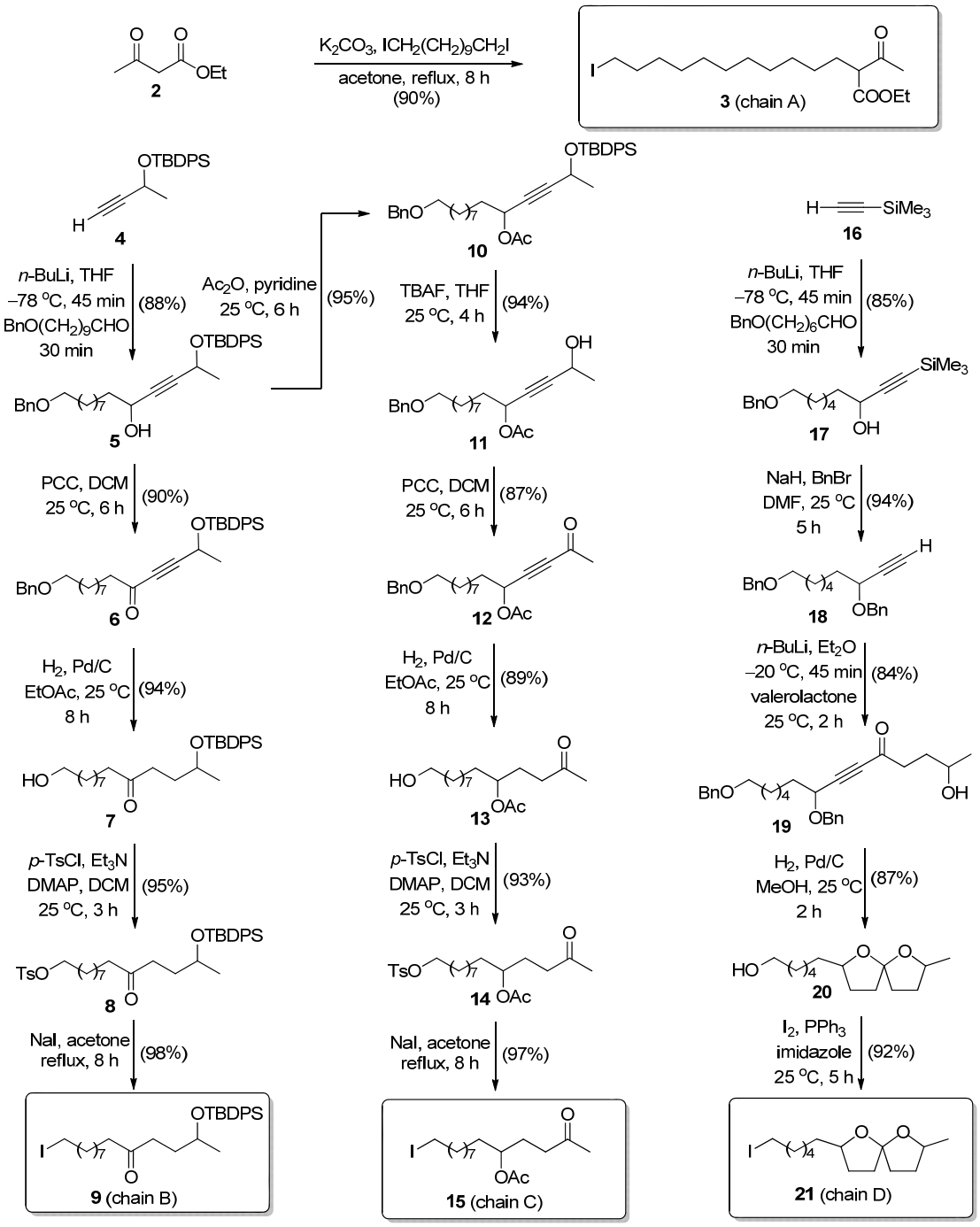
Section B: Facile Racemic Synthesis of *Helicobacter Pylori* Antibiotics and An Efficient Convergent Access to Spiroketal Segment of (+)-Spiroxaline Methyl Ether

In the present part our contribution towards the racemic and enantiomerically pure target compounds has been described in details.

2B.2.1 Chemoselective Coupling Reactions of 5,7-Dimethoxyphthalide with the Remotely Functionalized Alkyl Iodides: Facile Racemic Synthesis of *Helicobacter pylori* Antibiotics

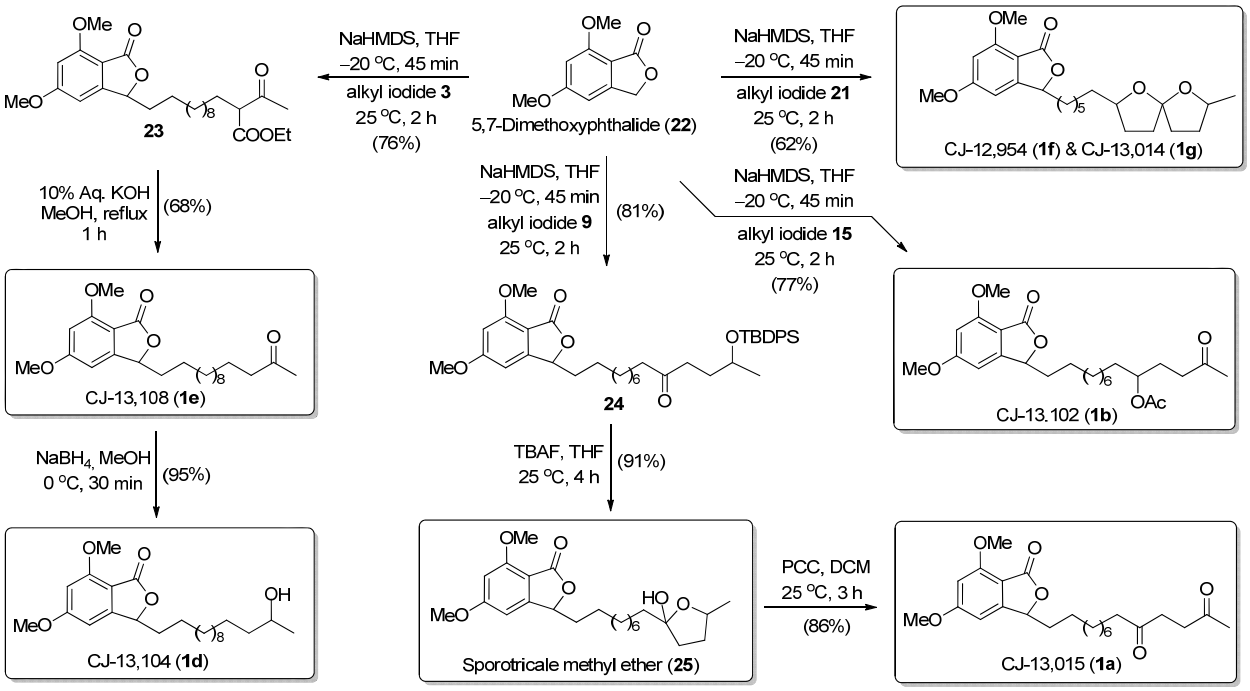
A careful scrutiny of structures of all the CJ-molecules revealed that they are the remotely mono-functionalized, bi-functionalized and latent tri-functionalized 3-alkyl substituted 5,7-dimethoxyphthalides. We envisaged the stepwise preparation of the desired long chain alkyl iodides (**A**-**D**) starting from ethyl acetoacetate (**2**) and two different suitably substituted acetylene derivatives **4**/**16** via the alkylation/condensation with aliphatic aldehydes, followed by the systematic functional group interconversions (Scheme 1).

The preferred reactivity of phthalide carbanions towards S_N2-displacements of halides versus addition to the carbonyl groups has not been studied previously. We developed a systematic plan to generate a 5,7-dimethoxyphthalide carbanion and study its chemoselective coupling reactions with the primary alkyl iodide chains **A**-**D** (Scheme 2). The chemoselective reaction of benzylic carbanion from 5,7-dimethoxyphthalide (1.00 equiv.), generated by using NaHMDS (1.10 equiv.) as the base, with alkyl iodide chain **A** (1.00 equiv.) exclusively furnished the expected coupled product **23** in 76% yield via the S_N2-displacement pathway. The base catalyzed hydrolysis of ester moiety in compound **23** followed by an in situ decarboxylation of the intermediate β-keto acid furnished CJ-13,108 (**1e**) in 68% yield. Chemoselective $NaBH_4$-reduction of the ketone moiety in **1e** furnished CJ-13,104 (**1d**) in 95% yield.



Scheme 1. Synthesis of Remotely Functionalized Long Chain Alkyl Iodides A-D

Similarly, the chemoselective reaction of benzylic carbanion from 5,7-dimethoxyphthalide with the chain **B** furnished the product **24**, which on desilylation gave sporotricale methyl ether (**25**). The compound **25** on PCC-oxidation provided the CJ-13,015 (**1a**) in very good yield. Finally, the chemoselective couplings of the phthalide carbanion with chain **C** and chain **D**, respectively furnished the desired products the CJ-13,102 (**1b**) and diastereomeric mixture of CJ-12,954/CJ-13,014 (**1f**)/(**1g**). These results clearly demonstrate the preferential S_N2 displacement ability of the NaHMDS-generated phthalide carbanion



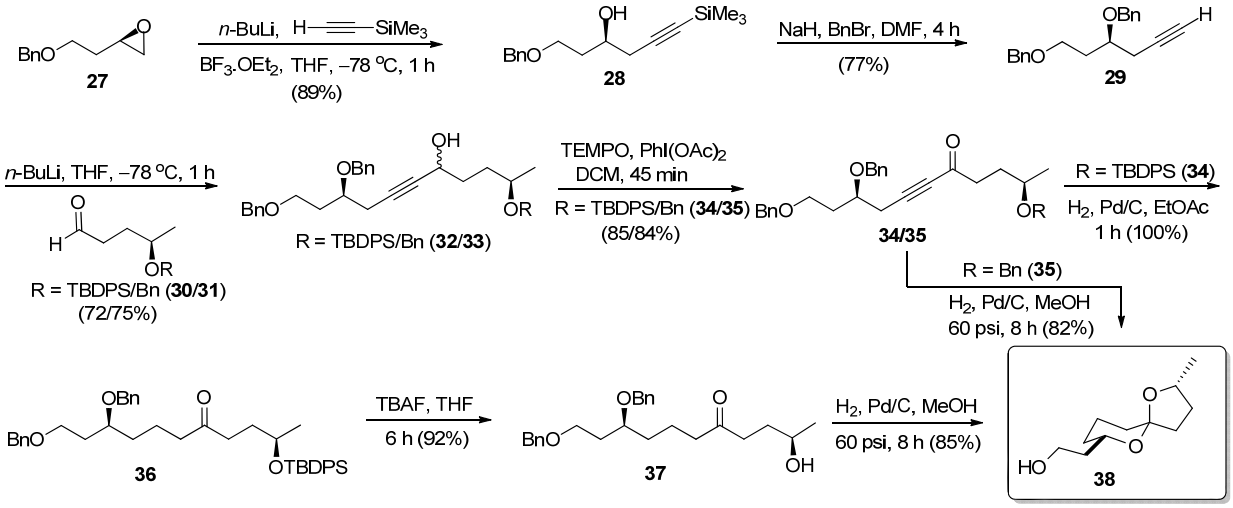
Scheme 2. Chemoselective Alkylation of 5,7-Dimethoxyphthalide: Synthesis of CJ-Compounds

over the 1,2-addition to carbonyl groups. Overall we have demonstrated a practical synthesis of remotely functionalized important natural products, the CJ-molecules by taking the advantage of highly chemoselective carbon–carbon bond forming reactions of phthalide with the functionalized alkyl iodides.

2B.2.2 An Efficient Convergent Access to Spiroketal Segment of (+)-Spiroxaline Methyl Ether

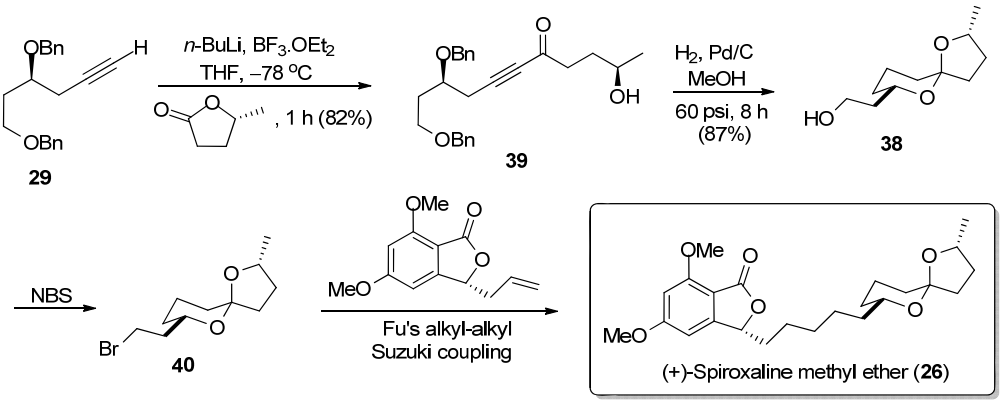
At this stage we prepared a plan to synthesize enantiomerically pure (+)-spiroxaline methyl ether (**26**). Regioselective ring opening of (*R*)-oxirane **27** (~100% ee, by chiral HPLC) with the trimethylsilylacetylene carbanion exclusively provided the required alkynol **28** in 89% yield (Scheme 3). Chemoselective *O*-benzyl protection of the formed secondary alcohol **28** directly furnished an in situ desilylated required acetylene derivative **29** in 77% yield. Condensation of the acetylenic carbanion of **29** with TBDPS-protected aldehyde **30** furnished compound **32** in 72% yield. TEMPO-oxidation of obtained secondary alcohol **32** supplied the required alkynone **34** in 85% yield. Chemoselective reduction of the carbon–carbon triple bond in the alkyne **34** under very mild catalytic hydrogenation conditions provided the desired single product **36** in ~100% yield, which was followed by the TBDPS group deprotection of **36** to furnish the stable compound **37** in 92% yield. The compound **37** on catalytic hydrogenation underwent regio- and stereoselective spiroketalization to furnish the essential product (+)-**38** in 85% yield. At this stage we could sense that it would be feasible to curtail down the two steps in the above mentioned synthesis progression by avoiding the TBDPS protection. Thus, the reaction of an alkyne carbanion of **29**

was performed with benzyl-protected aldehyde **31** yielding compound **33** in 75% yield. The obtained product **33** on TEMPO oxidation (84%), followed by simultaneous catalytic hydrogenation directly furnished the enantiomerically and diastereomerically pure compound (+)-**38** in 82% yield.



Scheme 3. Syntheses of (+)-Spiroketal Segment via Two Partially Separate Routes

Finally, the reaction of an acetylenic carbanion of **29** with commercially available enantiomerically pure (*R*)-*γ*-valerolactone also provided the stable alkynonol **39** in 82% yield via the nucleophilic lactone ring opening (Scheme 4). Alkynonol **39** under the catalytic hydrogenation conditions, once again directly



Scheme 4. Concise and Efficent Formal Synthesis of (+)-Spiroxaline Methyl Ether

furnished the enantiomerically and diastereomerically pure compound (+)-**38** in 87% yield. The quantitative NBS-induced conversion of spiroalcohol **38** to spiro-bromide **40** and its Fu et al. alkyl–alkyl Suzuki coupling with the enantiomerically pure (*R*)-3-allyl-5,7-dimethoxyisobenzofuran-1(3*H*)-one that delivers the final product, the (+)-spiroxaline methyl ether (**26**) have been well established in the literature.

<u>Chapter 3.</u> Palladium-Catalyzed Routes to Geranylated/Farnesylated Phenolic Systems: Total Synthesis of Naturally Occurring Pawhuskin C, Schweinfurthin J and NG-121 Methyl Ether

This chapter is also divided into two sections. Section A presents a concise literature account on pawhuskins, schweinfurthins, NG-121 and stachybotrins. The section B describes highly efficient palladium-catalyzed routes to geranylated/farnesylated phenolic substrates and their applications in the synthesis of pawhuskin C and schweinfurthin J. The present chemistry has been then logically extended further to accomplish the first diastereoselective total synthesis of phthalide based architecture NG-121 methyl ether.

<u>Section A:</u> A Concise Literature Account of Pawhuskins, Schweinfurthins, NG-121 and Stachybotrins

A large number of prenylated, geranylated and farnesylated phenolic compounds exist in Nature and they constitute structurally interesting and biologically important benzopyran architectures. A few representative examples of such naturally occurring bioactive phenolic stilbenes have been depicted in figure 1. The naturally occurring novel multifunctional phthalide NG-121 and their nitrogen analogs, the stachybotrins have been reported in figure 2. The total synthesis of these bioactive target compounds are imperative from advance biological screenings point of view. As an introduction a concise account of known chemistry of these target compounds has been described in the present section.

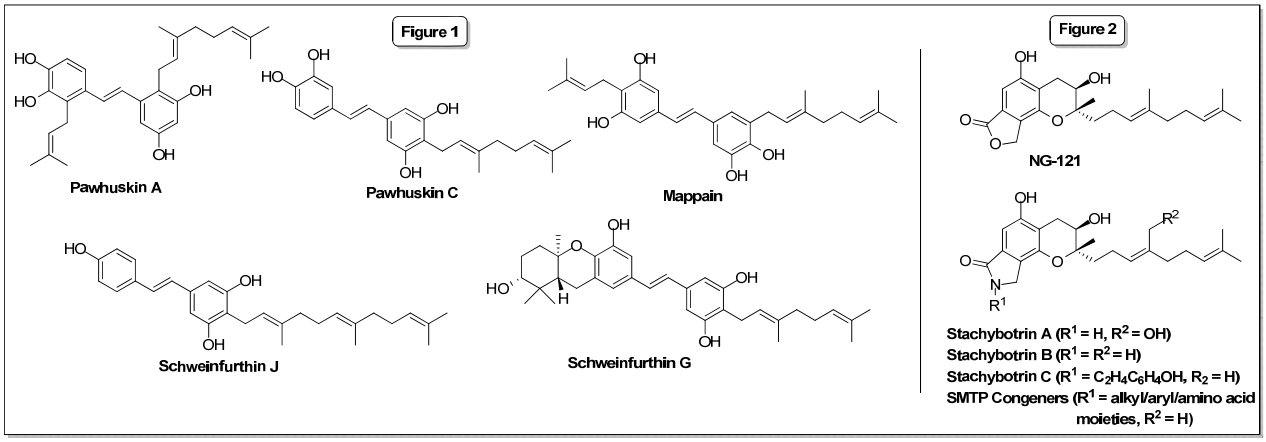


Figure 1. Naturally occurring prenylated/geranylated/farnesylated phenolic stilbenes

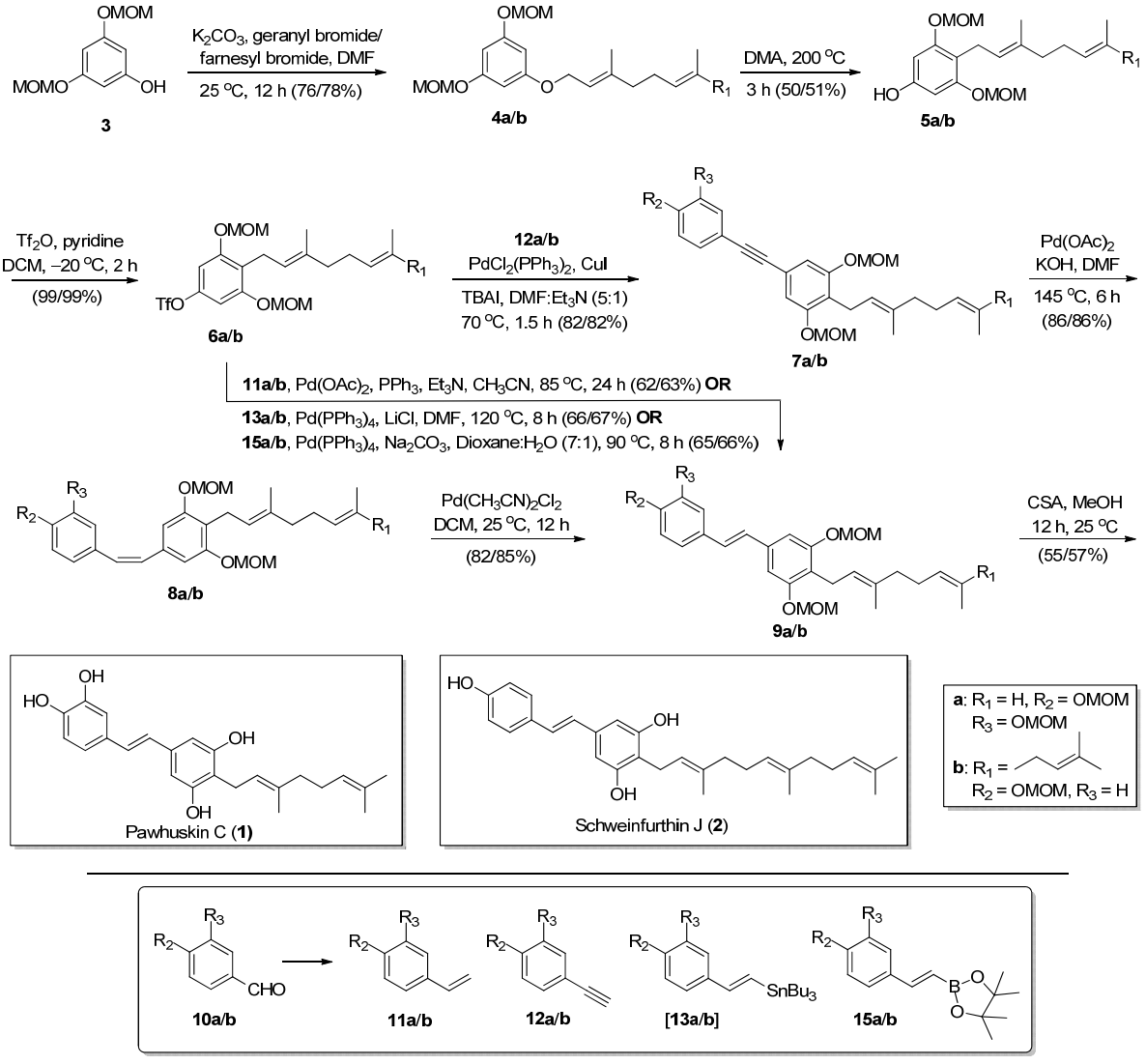
Figure 2. Naturally occurring multifunctional bioactive chromanols

<u>Section B:</u> Total Synthesis of Naturally Occurring Pawhuskin C, Schweinfurthin J and NG-121 Methyl Ether

In this present part our contribution towards the synthesis of pawhuskin C, schweinfurthin J and NG-121 methyl ether has been described in details.

3B.2.1 Palladium-Catalyzed Routes to Geranylated/Farnesylated Phenolic Stilbenes: Synthesis of Pawhuskin C and Schweinfurthin J

In the synthesis of target compounds holding free prenyl/geranyl/farnesyl chains; formation of benzofurans/benzopyrans, cycloaddition products, regioisomeric mixtures and polymeric gums are the common difficulties. The natural products pawhuskin C (**1**) and schweinfurthin J (**2**) possessing such chains have been respectively isolated from *Dalea purpurea* and *Macaranga Schweinfurthii* and they are known to respectively exhibit opioid and anticancer activity. To date, only one synthesis of pawhuskin C (**1**) is known in the literature. The palladium catalyzed carbon–carbon coupling reactions of substrates



Scheme 1. Synthesis of Bioactive Natural and Unnatural Geranylated/Farnesylated Phenolic Stilbenes

bearing prenylated/geranylated/farnesylated phenolic segments to form the stilbenes are not known in the literature. We realized that the synthesis of natural products **1** and **2** would be feasible via the

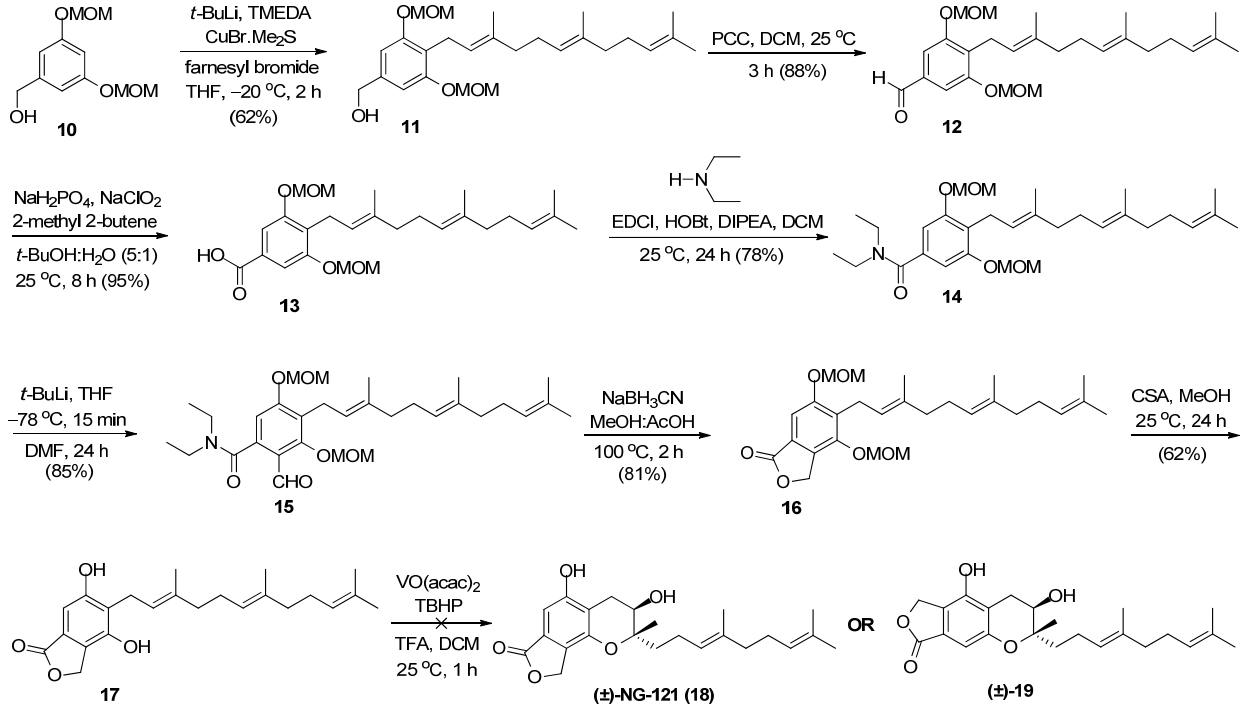
uncommon aromatic Claisen rearrangement of geranyl/farnesyl unit followed by Heck/Stille/Suzuki/Sonogashira coupling reactions pathways (Schemes 1).

The double MOM-protected symmetrical phenol **3** on reaction with geranyl bromide/farnesyl bromide in the presence of K_2CO_3 in DMF provided the expected *O*-geranylated/farnesylated products **4a**/**b** in 76/78% yields. The products **4a**/**b** in refluxing *N*,*N*-dimethylaniline (DMA) underwent a defined Claisen rearrangement and furnished only the corresponding *para*-geranylated/farnesylated *trans* products **5a**/**b** in 50/51% yields. The free phenolic groups in compounds **5a**/**b** were transformed to good leaving group –OTf by treatment with Tf_2O/pyridine to obtain **6a**/**b** in 99% yields. Subsequently, the Heck, Stille and Suzuki coupling reactions of the building blocks **6a**/**b** with an appropriate coupling partners were deliberated to obtain the products **9a**/**b** in good yields (62-67%). A systematic study of Sonogashira coupling of **6a** was also planned to selectively provide both the *cis*- and *trans*-stilbenes. Sonogashira coupling reaction of the two electron rich segments **6a**/**b** using Boger et al approach yielded the desired products **7a**/**b** in 82% yields. At this stage, the recently reported palladium-catalyzed transfer semi-hydrogenation conditions for the reduction of the triple bond to double bond were sought. The reaction of alkynes **7a**/**b** with DMF and KOH in the presence of $Pd(OAc)_2$ exclusively supplied the corresponding *cis*-stilbenes **8a**/**b** in 86% yields. Using the method reported by Spencer et al, Pd(II)-catalyzed *cis* to *trans* isomerization of carbon–carbon double bond in compounds **8a**/**b** formed the required products **9a**/**b** in 82/85% yields. Finally, the acid-catalyzed global deprotection of MOM-groups in **9a**/**b** delivered the desired natural products pawhuskin C (**1**) and schweinfurthin J (**2**) in 55/57% yields.

3B.2.2 Synthetic Studies Towards NG-121: Diastereoselective Access to NG-121 Methyl Ether

The naturally occurring novel multifunctional NG-121 and stachybotrin C have been isolated from the culture broth of *Stachybotrys parvispora* F-4708. The NG-121 has been suggested to be effective against Alzheimer's disease, while stachybotrin C prevents hypoxic neuronal injury caused by ischemia. The real challenge in synthesis of these natural products is in (i) regioselective introduction of farnesyl unit, (ii) stereoselective creation of two adjacent asymmetric carbon centers in chroman ring, (iii) lactonization with the regioselective introduction of a formyl group and (iv) the preservation of carbon–carbon double bonds throughout the reaction sequence. As described in scheme 2, the symmetrically double MOM-protected benzyl alcohol **10** on selective *o*-lithiation followed by the reaction with farnesyl bromide gave the desired coupling product **11** in 62% yield. The PCC oxidation of the benzyl alcohol **11** to the corresponding aldehyde **12** (88%) and its subsequent Pinnick oxidation ($NaClO_2$/NaH_2PO_4) provided the carboxylic acid **13** in 95% yield. At this stage it appeared appropriate to generate the lactone ring first by applying the *o*-formylation strategy. The carboxylic acid **13** on EDCI induced coupling with diethylamine gave an appropriate amide **14** as a suitable substrate for the introduction of the

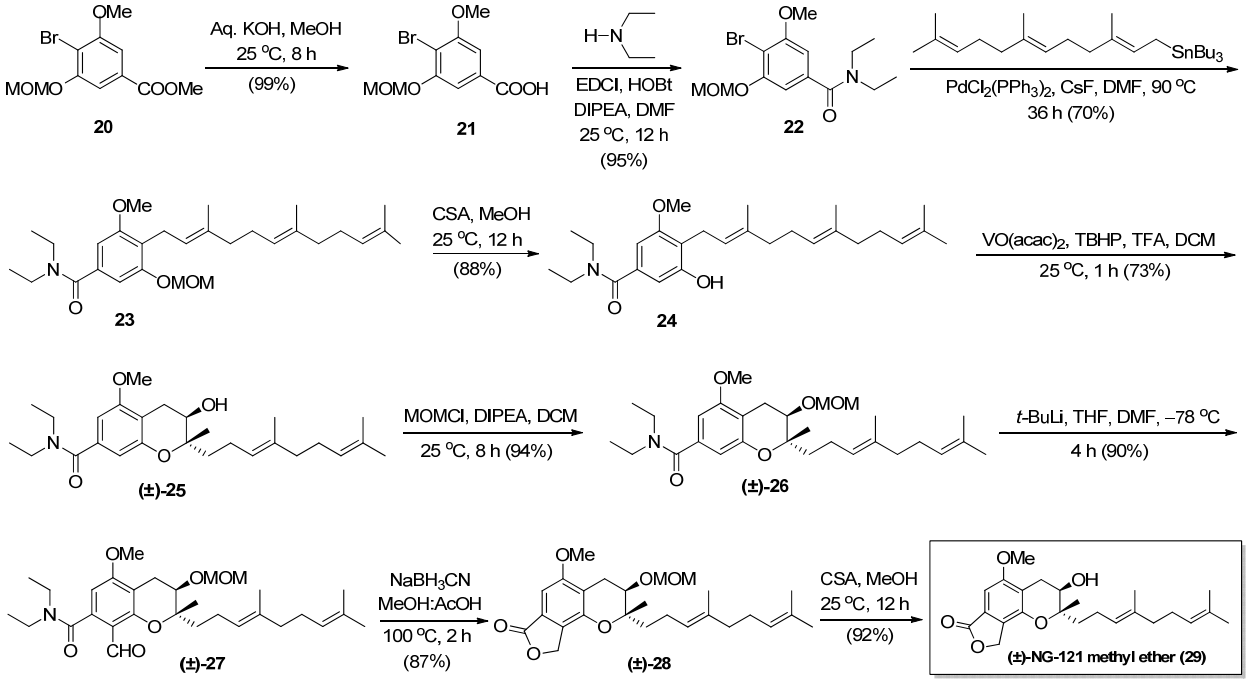
formyl unit. The *t*-BuLi/DMF induced formylation of the amide **14** yielded the benzaldehyde derivative **15** in 85% yield. The $NaBH_3CN$ reduction of the benzaldehyde derivative **15** to the corresponding intermediate benzyl alcohol and an in situ lactonization furnished the required phthalide **16** in 81% yield. A selective mono-MOM deprotection of compound **16** was unsuccessful and we always ended up with double-MOM deprotection to yield the farnesylated dihydroxyphthalide **17** in 62% yield. The hydroxy directed $VO(acac)_2$-catalyzed selective epoxidation to obtain the chromanol was extended for the biphenolic compound **17** to diastereoselectively obtain either the (±)-NG-121 (**18**) or its regioisomer **19**. Unfortunately, all attempts met with failure and the highly reactive biphenolic substrate **17** always underwent an excessive decomposition.



Scheme 2. An Attempted Synthesis of Chromanol (±)-NG-121

To circumvent the above mentioned difficulty involved in the selective MOM-deprotection, we decided to commence the synthesis with the unsymmetrical methyl benzoate derivative **20** having two different protecting groups, the –OMe and –OMOM (Scheme 3). The base catalyzed hydrolysis of ester **20** to the corresponding carboxylic acid **21** (99%) followed by the EDCI induced coupling with diethylamine provided the appropriate amide **22** in 95% yield. The palladium-catalyzed Stille coupling reaction of electron rich bromoresorcinol derivative **22** with the farnesyl tributyltin using CsF (2.00 equiv) as an accelerator provided the coupling product **23** in 70% yield. The camphorsulfonic acid driven selective MOM-deprotection of compound **23** gave the desired phenol **24** in 88% yield. The hydroxy directed $VO(acac)_2$/*tert*- butyl hydroperoxide (TBHP) induced regioselective epoxidation of 2-position

carbon–carbon double bond in the farnesyl chain followed by concomitant regio- and diastereoselective intramolecular oxirane ring opening exclusively formed the pair of chromanol enantiomers (±)-**25** in 73% yield. The *cis*-orientation of secondary hydroxyl group and the tertiary methyl group in compound (±)-**25** was established on the basis of NOESY studies. The formed free secondary hydroxyl group in compound (±)-**25** was MOM-protected to obtain product (±)-**26** in 94% yield. The *t*-BuLi/DMF stimulated *o*-formylation of (±)-**26** was completely regioselective and exclusively furnished the requisite benzaldehyde derivative (±)-**27** in 90% yield. The $NaBH_3CN$ reduction of aldehyde (±)-**27** and an in situ lactonization furnished the phthalide (±)-**28** in 87% yield. The MOM-deprotection in product (±)-**28** furnished the NG-121 methyl ether (±)-**29** in 92% yield. We carefully studied the demethylation of



Scheme 3. Diastereoselective Total Synthesis of NG-121 Methyl Ether

compound (±)-**29** to get the actual natural product NG-121 under different set of reaction conditions, but always ended up with the recovery of starting material and/or decomposition. Hence at this stage, what we have accomplished is the diastereoselective total synthesis of methyl ether of the natural product NG-121. The demethylation of NG-121 methyl ether to natural product NG-121 still remains the challenging task of our current interest. Further studies for the demethylation of compound (±)-**29** are in active process in our laboratory.

Note: Compound, scheme and figure numbers in the abstract are different from those in the thesis.

CHAPTER 1

A Brief Review on the Chemistry of 1(*3H*)-Isobenzofuranones (Phthalides)

This chapter features the following topics:

1.1 Introduction

The 1(3*H*)-Isobenzofuranones (phthalides) are prominent class of natural products by virtue of their significantly varied biological properties. The basic core structure of phthalide is 1(3*H*)-isobenzofuranone, which contains a benzene ring fused with a γ-lactone between carbon atoms 1 and 3 (Figure 1).[1] All the known phthalide compounds have been identified as derivatives of 1(3*H*)-isobenzofuranone. To date, most of the known phthalides have been identified from plant genesis. Phthalides are also found in fungi, bacteria and liverworts. More than 180 naturally occurring phthalide derivatives have been identified, among them nearly 140 phthalides were isolated from wide variety of plant species. Most of the naturally occurring phthalides have been biologically active and they display wide range of pharmacological properties, including actions on the central nervous system, anti-angina, anti-platelet aggregation, anti-smooth muscle proliferation, anti-thrombosis, cardiac function modulation and protection cerebral ischemia.[2]

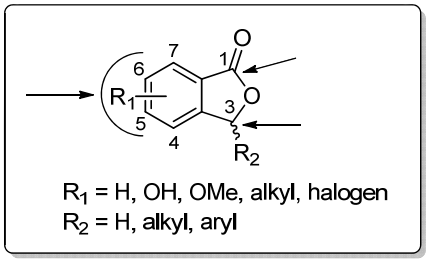


Figure 1. 1(3*H*)-Isobenzofuranones (phthalides) and their derivatives

Phthalides are versatile building blocks for the synthesis of biologically active compounds and have been proven to be useful in the treatment of circulatory and heart diseases.[3] 3-Butylphthalide (**1**), a component in the Chinese folk medicine extracted from celery seed oil, is in phase II clinical trials in China and potentially can be used for the treatment of stroke. Moreover, it is employed for seasoning and flavoring purposes, shows anticonvulsant action, increases the duration of anesthesia and exhibits cerebral anti-ischemic action.[4] Fuscinarin (**2**) is a potent human CCR5 antagonist, effectively blocking HIV entry into host cells.[5] However, the bioactivities of (–)-typhaphthalide (**3**),[6] (+)-spiroxaline (**4**)[7] and monascodilone (**5**)[8] are still not known (Figure 2). 1(3*H*)-Isobenzofuranones (phthalides) have number of reactive sites available and all the sites have been explored i.e., nucleophilic attack on C_1 carbonyl group, nucleophilic substitution reactions with the C_3 position carbanion and reactions on C_4, C_5, C_6 and C_7 positions of the phthalide.[9] The 1(3*H*)-isobenzofuranone was prepared for the first time in 1922 by Perkin and co-workers,[10] by thermal decomposition of ethyl 2-(bromomethyl)benzoate. Later in 1955, Eliel and co-workers[11] performed the reduction of

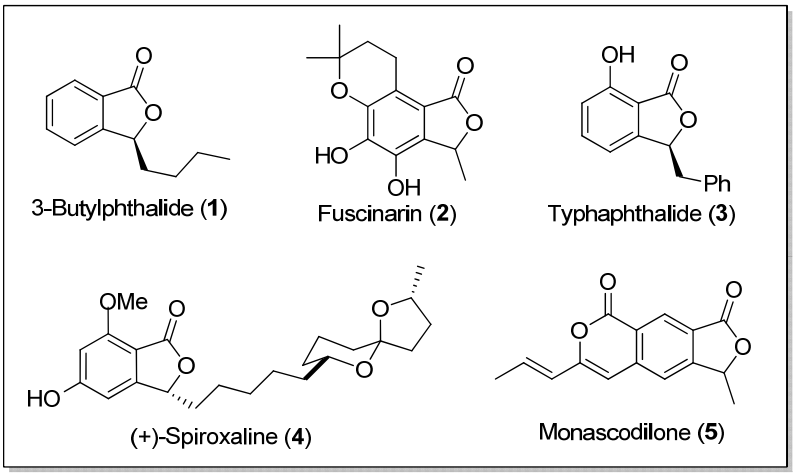


Figure 2. Natural occurring 1(3*H*)-isobenzofuranones

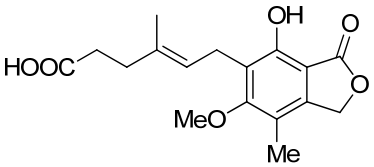
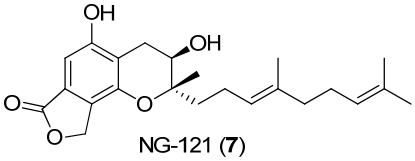
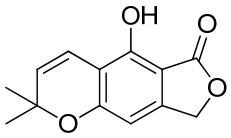
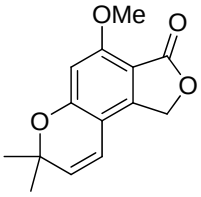
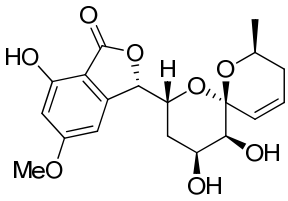
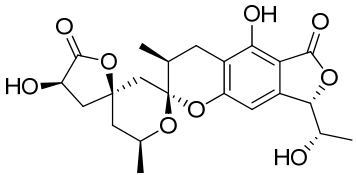
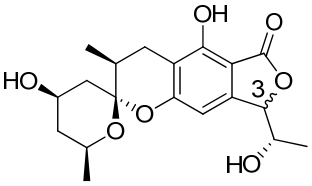
methyl phthalate to phthalide in good yield using $LiAlH_4$. In 1989, Watanabe and co-workers[12] utilized Diels-Alder reaction between substituted furanones and silyloxydienes to provide substituted phthalides in moderate to good yields. Recently, directed *ortho*-metallation,[13] reaction between homophthalic anhydride and benzil,[14] Heck-Matsuda reaction[15] and many more methods have been developed for the synthesis of substituted phthalides.

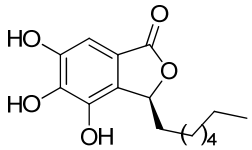
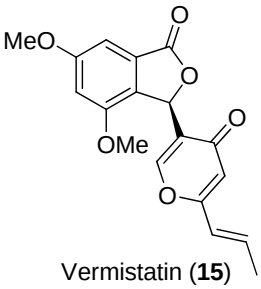
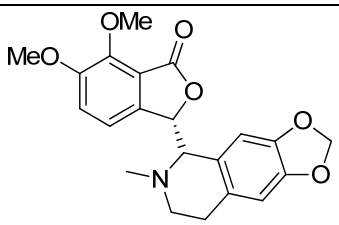
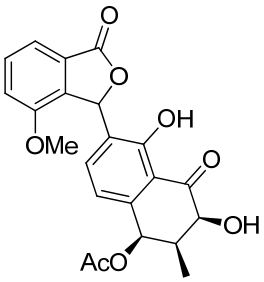
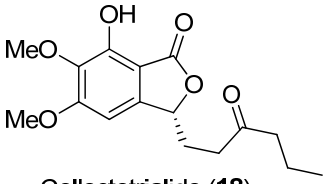
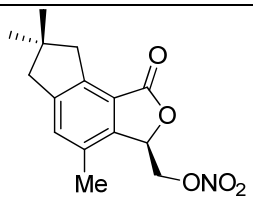
In the present chapter, we have described a concise account on isolation, bioactivity and synthesis of recently isolated, 1(3*H*)-isobenzofuranones (phthalides) and their derivatives with an emphasis on new synthetic routes and strategies. Related representative examples have been choosen for this purpose. Since large amount of data is available in the literature, no pretension of completeness has been claimed.

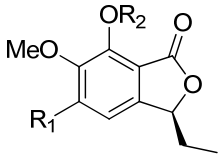
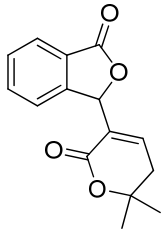
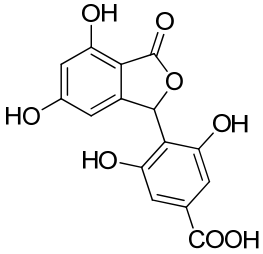
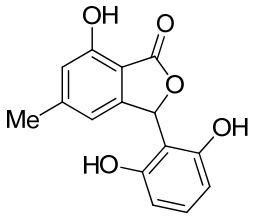
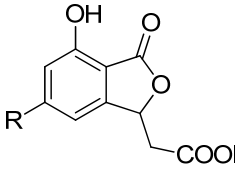
1.2 Mini-Glossary of Natural Products Bearing 1(3*H*)-Isobenzofuranone Backbone

Some of the representative examples of 1(3*H*)-isobenzofuranones, 3-substituted 1(3*H*)-isobenzofuranones and 3,3'-disubstituted 1(3*H*)-isobenzofuranones have been listed in Table 1 along with their structure, name, isolation source, synthesis and bioactivity.

Sr. No.	Natural Product	Isolation Source (Synthesis Known)	Activity	Ref.

1	 Mycophenolic acid (**6**)	*Penicillium spp* (Eight total and eight formal synthesis)	Anti-fungal, anti-viral, anti-bacterial and immunosuppressive	16
2	 NG-121 (**7**)	*Stachybotrys parvispora* F-4708 (Not known)	Alzheimer's disease	17
3	 Salfredin B_{11} (**8**)	*Crucibulum sp. RF-3817* (Two)	Aldose reductase inhibitor	18
4	 Phthalidochromene (**9**)	*Helichrysum platypterum* (One)	Not known	19
5	 (+)-Aigialospirol (**10**)	*Aigialus parvus* BCC 5311 (One)	Not known	20
6	 Virgatolide A (**11**)	*Pestalotiopsis virgatula* (Not known)	Cytotoxic against HeLa (cervical epithelium) cells	21
7	 (i) Virgatolide B (**12**, $C_3 = \alpha$) (ii) Virgatolide C (**13**, $C_3 = \beta$)	*Pestalotiopsis virgatula* (Not known)	Cytotoxic against HeLa (cervical epithelium) cells	21

8	 Cytosporone E (**14**)	*Cytospora Sp.* CR200 (Not known)	Anti-microbial	22
9	 Vermistatin (**15**)	*Penicillium vermiculatum* DANG (Not known)	Cytotoxic against tumor cells	23
10	 (–)-Hydrastine (**16**)	*Corydalis stricta* (Not known)	Antipaclitaxel-resistant human ovarian cancer activity	24
11	 Rubiginone (**17**) (Sterochemistry at C-3 position unknown)	*Streptomyces sp.* (strain GÖ NI/5) (Not known)	Inhibits the growth of some Gram-positive bacteria and cytotoxic against different tumor cells	25
12	 Collectotrialide (**18**)	*Colletotrichum sp*. CRI535-02 (Not known)	Potential cancer chemopreventive properties	26
13	 Alcyopterosin E (**19**)	*Alcyonium paessleri* (One)	Cytotoxicity toward Hep-2 (human larynx carcinoma) cell line	27

14	 (i) $R_1 = R_2 = H$ (**20**) (ii) $R_1 = OMe$, $R_2 = H$ (**21**) (iii) $R_1 = OMe$, $R_2 = Me$ (**22**)	*Pittosporum illicioides* (Not known)	*In vitro* inhibitory activity on neutrophil pro-inflammatory responses	28
15	 Catalpalactone (**23**)	*Catalpa ouata* G. Don (Three)	Not known	29
16	 Cryphonectric acid (**24**)	*Cryphonectrica parasitica* (One)	Inhibits the formation of tomato seedlings	30
17	 Isopestacin (**25**)	*Pestalopsis microspore* (Two)	Anti-fungal activity, anti-oxidant toward both superoxide radical and hydroxyl free radicals	30
18	 (i) R = H, Isoochracinic acid (**26**) (ii) R = OH, Herbaric acid (**27**)	*Alternaria kikuchiana* (isoochracinic acid) (Two) *Cladosporium herbarum* (Herbaric acid) (One)	Anti-bacterial and antibiotic	31

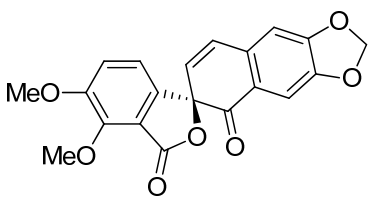
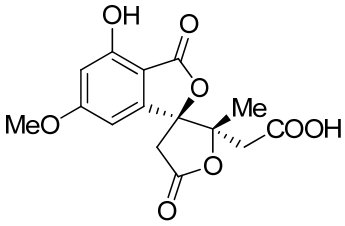
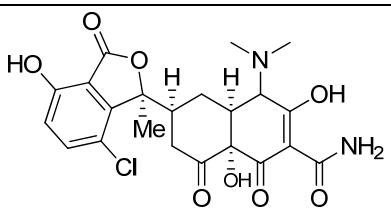
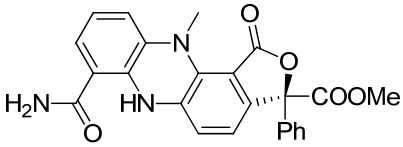
19	 (–)-Arnottin II (**28**)	*Xanthoxylum arnottianum* (Two)	Not known	32
20	 Altenuic acid II (**29**)	*Alternaria tenuis* (Not known)	Not known	33
21	 Isochlorotetracycline (**30**)	*Synthetic* (One)	Plant growth stimulator	34
22	 Dermacozine D (**31**)	*Dermacoccus abyssi* (Not known)	Cytotoxic against different tumor cell lines	35

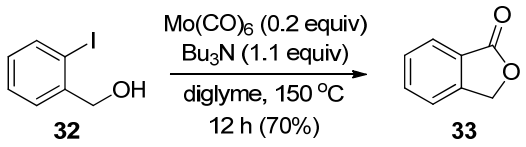
Table 1. Naturally Occurring 1(3*H*)-Isobenzofuranones and their Derivatives

1.3 Recent Methodologies for the Synthesis of 1(3*H*)-Isobenzofuranone

During past ten years remarkable progress on synthetic methodologies applicable for the synthesis of imperative 1(3*H*)-isobenzofuranone has been reported in the literature. Some of the recent important methodologies reported for the synthesis of 1(3*H*)-isobenzofuranone have been described in this section.

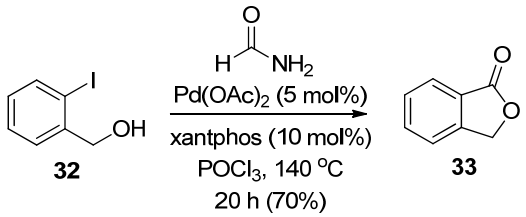
Yamane and co-workers[36] developed a $Mo(CO)_6$-mediated alkoxycarbonylation of aryl halides with alcohols to afford arenecarboxylic acid esters. The molybdenum carbonyl complexes act as the catalyst and the source with carbon monoxide. The intramolecular alkoxycarbonylation of (2-

iodophenyl)methanol (**32**) with $Mo(CO)_6$ under the specified conditions provided 1(3*H*)-isobenzofuranone (**33**) in 70% yield (Scheme 1).



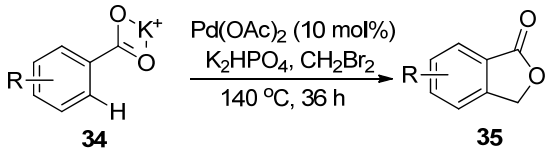
Scheme 1. $Mo(CO)_6$-Mediated Alkoxycarbonylation of Alkyl Iodide

Bhanage and co-workers[37] developed a new carbon monoxide-free, solvent-free, single step protocol for the synthesis of isoindole-1,3-diones from *o*-haloarenes using formamide, palladium acetate and xantphos catalysis. They further extended their synthetic methodology for the synthesis of 1(3*H*)-isobenzofuranone (**33**) from *o*-iodobenzyl alcohol (**32**) (Scheme 2).



Scheme 2. Palladium-Catalyzed CO-Free Synthesis of 1(3*H*)-Isobenzofuranone

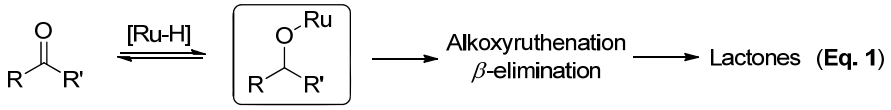
The Pd-catalyzed arylation of C–H bonds with aryl halides was among the earliest examples of Pd-catalyzed C–H activation/arylation chemistry. Yu and co-workers[38] developed a novel Pd(II)-catalyzed intermolecular alkylation of C–H bonds with alkyl halides. Reaction of benzoic acid derivatives **34** with 10 mol% $Pd(OAc)_2$, K_2HPO_4 as a base and CH_2Br_2 as alkyl iodide source at 140 °C provided the 1(3*H*)-isobenzofuranone derivatives **35** in good yields (Scheme 3).



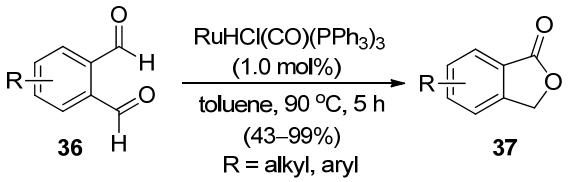
R = H, Me, F, Cl, Br, CF_3, COPh, COOMe, aryl

Scheme 3. Palladium-Catalyzed Alkylation of Aryl C–H Bond

During the course of studies on ruthenium-catalyzed transformations, Ryu and co-workers[39] developed novel catalytic transformations where ruthenium hydride complex, $RuHCl(CO)(PPh_3)_3$, serves as an excellent catalyst for variety of atom-economical transformations with the aldehydes.

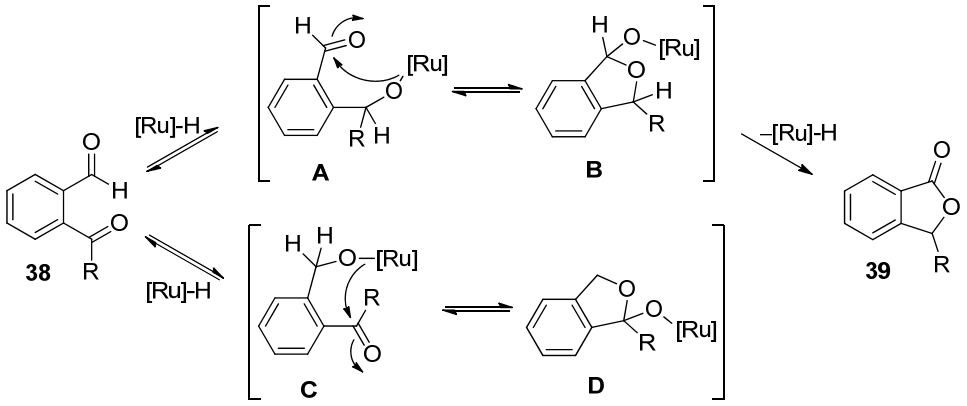


R = H, alkyl, aryl
R' = alkyl containing a formyl group



Scheme 4. Ruthenium Hydride Catalyzed Lactonization of Dialdehydes

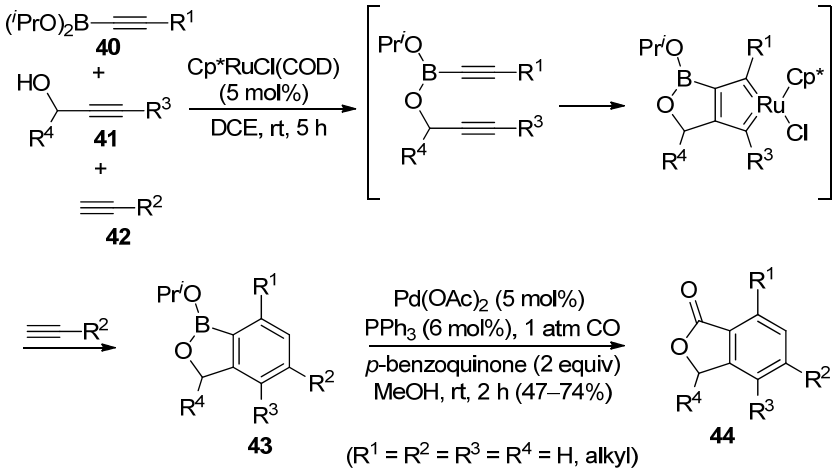
This led them to consider the potential of ruthenium hydrides for an hydroruthenation–intramolecular alkoxy-ruthenation sequence (Eq. 1) which would lead to an intramolecular Tishchenko type lactonization reaction. The lactonizations of both dialdehydes and keto aldehydes were affected by using $RuHCl(CO)(PPh_3)_3$ as the catalyst, providing both the 1(3*H*)-isobenzofuranones (**37**) and 3-substituted phthalide derivatives in good to excellent yields (Scheme 4).



Scheme 5. Proposed Mechanism for Lactonization of the Dialdehyde and Keto Aldehyde

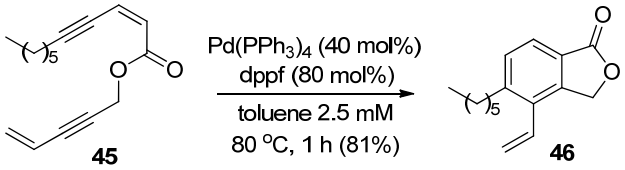
A likely reaction mechanism is proposed with an example of a keto aldehyde **38**. The hydroruthenation gives two types of acetal-type Ruthenium complex, **B** and **D**. Ruthenium complex **D**, which arises from hydroruthenation to an aldehyde group cannot undergo β-hydride elimination, hence reverts back to **A** via **38**. Eventually, the Ru-complex **B** overall arising from the hydroruthenation of a ketone carbonyl undergoes cyclization and β-elimination to form lactone **39** (Scheme 5).

Yamamoto and co-workers[40] have described an efficient regioselective four-component coupling approach to highly substituted 1(3*H*)-isobenzofuranones **44** via sequential Cp*RuCl-catalyzed cyclotrimerization of alkynylboronates **40**, propargyl alcohols **41** and terminal alkynes **42** followed by palladium(II)-catalyzed carbonylation of the resultant arylboronates **43** (Scheme 6).



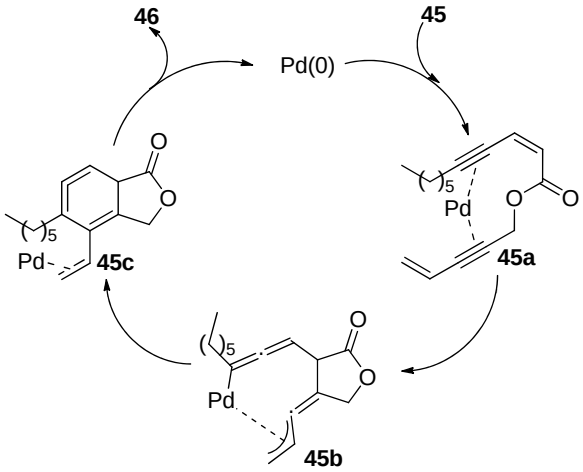
Scheme 6. Synthesis of 1(3*H*)-Isobenzofuranones via Sequential Four-Component Couplings

Yamamoto and co-workers[41] also described a novel method for the synthesis of 1(3*H*)-Isobenzofuranones via the palladium-catalyzed intramolecular benzannulation of bis-enyne and enyne-diyne systems. Bis-enyne **45** on exposure to $Pd(PPh_3)_4$/dppf in toluene underwent a smooth and precise intramolecular benzannulation to provide 1(3*H*)-isobenzofuranone **46** in 81% yield (Scheme 7).



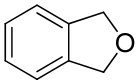
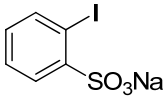
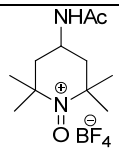
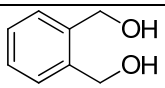
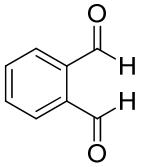
Scheme 7. Palladium-Catalyzed Intramolecular Benzannulation

A proposed mechanism involves the coordination of Pd(0) to alkyne moiety of the bis-enyne **45** which would form the palladacycle **45b** through **45a**. The reductive elimination of Pd(0) from the complex **45c** provides the isobenzofuranone **46** (Scheme 8).



Scheme 8. Proposed Mechanism for Intramolecular Benzannulation

Apart from the methods mentioned above for the synthesis of 1(3*H*)-isobenzofuranone (**33**), it has also been synthesized by chemoselective benzylic oxidation of 1,3-dihydroisobenzofuran (**47**), selective benzylic oxidation of 1,2-phenylenedimethanol (**48**) followed by lactonization, Tishchenko type reactions of phthalaldehyde (**49**) and chemoselective reduction of phthalic anhydride (**50**). The details about these transformations have been listed in Table 2.

Starting Material	Conditions	Yield	Reference
 1,3-Dihydroiso-benzofuran (**47**)	$ReOCl_3(OPPh_3)(SMe_2)$ (5 mol%), TBHP (2 equiv), 90 °C, 20 h	76	42
”	 (5 mol%) n-Bu_4NHSO_4 (20 mol%), oxone (3 equiv), CH_3CN, 60 °C, 5 h	80	43
”	 (1 equiv) CH_3CN:H_2O (9:1), rt, 8 h	91	44
”	$KAuCl_4.0.5H_2O$ (5 mol%), pyridine (5 mol%), TBHP (2 equiv), air, 24 h, 90 °C	65	45
 1,2-Phenylene-dimethanol (**48**)	$WO_3.H_2O$ (5 mol%), H_2O_2, t-BuOH, 80 °C, 24 h	90	46
”	$BaMnO_4$ (3 equiv), μω, CH_3CN, 1 h	88	47
”	$[IrCl(coe)_2]_2$ (3 mol%), neat, 95 °C, 15 h, open air	86	48
”	PCC (2 mol%), H_5IO_6 (1.05 equiv), CH_3CN, rt, 2 h	99	49
 Phthalaldehyde (**49**)	NaH (5 mol%), toluene, rt, 24 h	94	50
”	LiBr (0.5 equiv), Et_3N (1.5 equiv), rt, 2 days	96	51

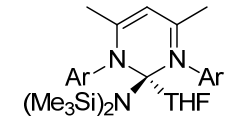
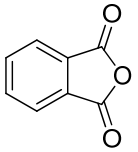
”	(1 mol%)  Ar = 2,6-Diisopropylphenyl benzene, rt, 24 h	81	52
”	$MgBr_2.Et_2O$, Et_3N, DCM, rt, 2 days	92	53
 Phthalic anhydride (**50**)	$NaBH_4$, MeOH, 0–10 °C, 3 h	70	54

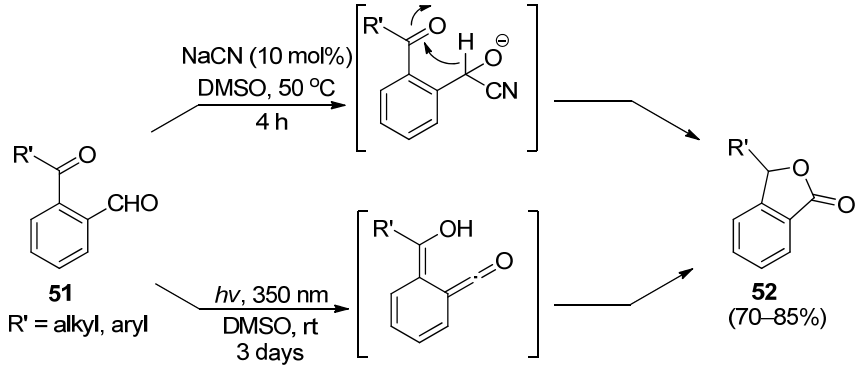
Table 2. Recently Reported Methods for the Synthesis of 1(3*H*)-Isobenzofuranone

1.4 Recent Methodologies for the Synthesis of 3-Substituted 1(3*H*)-Isobenzofuranones

There are large numbers of phthalide derived natural products having substitution at C-3 position. Because of their promising bioactivities, remarkable progress on synthetic methodologies applicable for the synthesis of 3-substituted 1(3*H*)-isobenzofuranones has been described in the literature. Some of the recently reported methodologies for the synthesis of 3-substituted 1(3*H*)-isobenzofuranones have been described in this section.

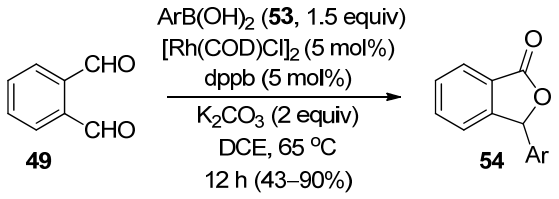
1.4.1 Recent Methodologies for the Synthesis of 3-Substituted (±)-1(3*H*)-Isobenzofuranones

Schmalz and co-workers[55] observed a facile conversion (isomerization) of 2-formyl-arylketones into 3-substituted 1(3*H*)-isobenzofuranones **52** and it was further investigated by using a series of simple 2-acylbenzaldehydes **51** as the substrates. The transformation generally proceeds smoothly in DMSO, either in a Cannizarro–Tishchenko type reaction under the nucleophile catalysis (NaCN) or under photochemical conditions (DMSO, 350 nm) (Scheme 9).



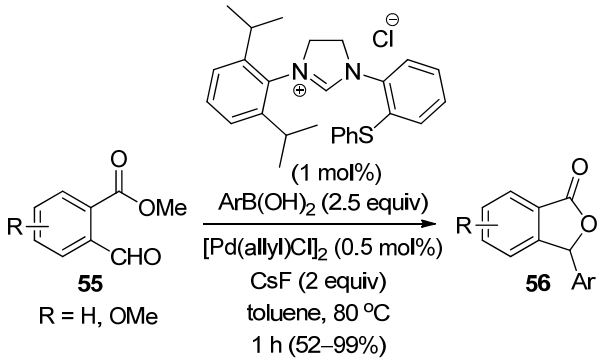
Scheme 9. Facile Rearrangement of 2-Acylbenzaldehydes to Phthalides

Cheng and co-workers[56] have developed an efficient rhodium-catalyzed cascade aryl addition/intramolecular esterification of phthalaldehyde (**49**) with arylboronic acids **53**, affording the 3-aryl and alkenyl 1(3*H*)-isobenzofuranones **54** in moderate to good yields (Scheme 10).



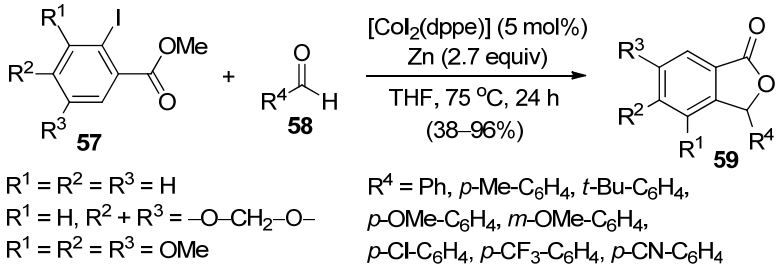
Scheme 10. Reaction of Phthalaldehyde with Arylboronic Acids

Onomura and co-workers[57] have synthesized 3-aryl 1(3*H*)-isobenzofuranones **56** in good to excellent yields via palladium-catalyzed arylation of ester-aldehydes **55** with organoboronic acids using the thioether-imidazolinium carbene ligand with 1.0 mol% of the catalyst loading and high substrate tolerance (Scheme 11).



Scheme 11. Synthesis of 3-Arylphthalides via the Palladium-Catalyzed Arylation of Aldehydes

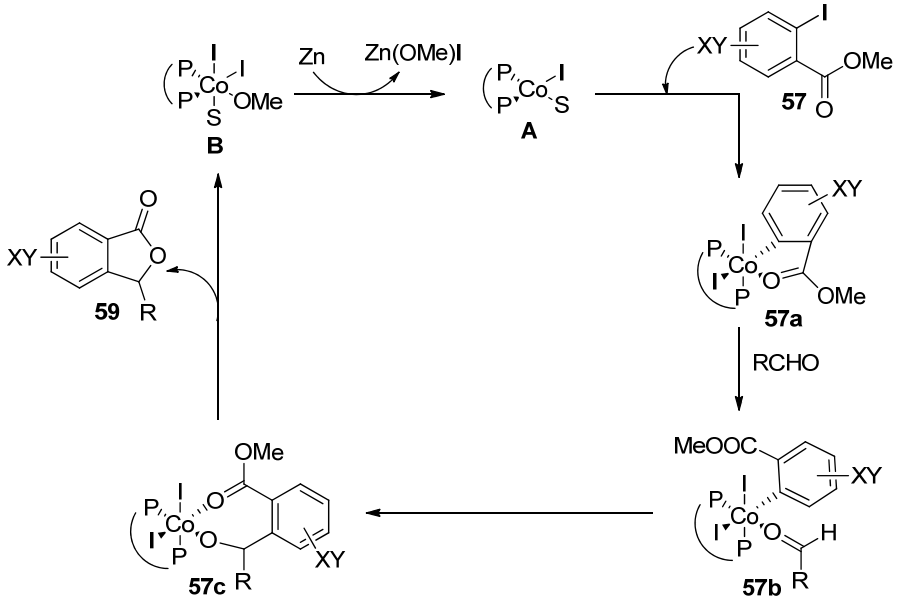
Cheng and co-workers[58] have developed a cobalt-catalyzed cocyclization reaction of 2-iodobenzoates **57** with aldehydes **58** to afford substituted 1(3*H*)-isobenzofuranone derivatives **59** in one pot under mild reaction conditions with good to excellent yields (Scheme 12).



Scheme 12. Cobalt-Catalyzed Cyclization Reaction of *o*-Iodobenzoates with Aldehydes

Based on the known chemistry of cobalt and zinc, a plausible general mechanism has been proposed in scheme 13. Reduction of cobalt(II) to (I) by Zn metal likely initiates the catalytic reaction. Oxidative

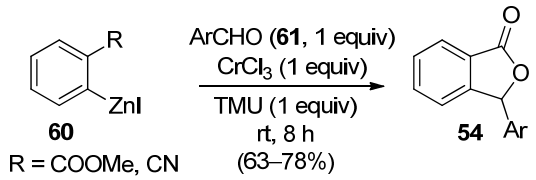
addition of methyl 2-iodobenzoate **57** with the cobalt(I) species yields an *o*-metalated methybenzoate complex **57a** with both the *o*-carbon atom and the ester oxygen atom bonded to the cobalt center. Coordination of the aldehyde molecule to the cobalt center adjacent to the *o*-metalated methyl benzoate group to give **57b**, followed by insertion of the cobalt–carbon bond to the aldehyde affords cobalt–alkoxide intermediate **57c**. Intramolecular nucleophilic addition of the coordinated alkoxy group in **57c** to the ester group gives the final product **59** and a cobalt (III) species. The latter cobalt species is reduced by zinc metal to regenerate the active cobalt(I) species.



Scheme 13. Plausible Mechanism for the Cobalt-Catalyzed Cyclization Reaction

Cheng and co-workers[59] have also shown the efficiency of nickel complexes to catalyze the cyclization between *o*-bromobenzoate and aldehydes to afford 1(3*H*)-isobenzofuranone derivatives in excellent yields.

Takagi and co-workers[60] studied the effect of transition metal complexes for the nucleophilic addition to aldehyde **61** using arylzinc compound **60**, which was prepared from the corresponding aryl iodide

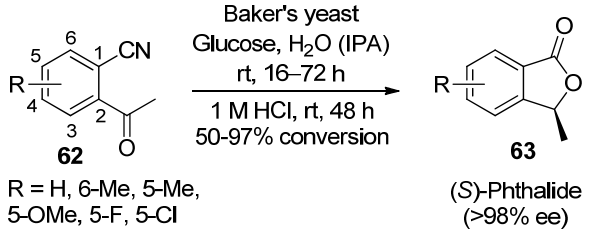


Scheme 14. The $CrCl_3$-Mediated Synthesis of 3-Aryl-1(3*H*)-Isobenzofuranones

and zinc powder in 1,1,3,3-tetramethylurea (TMU). Among various transition metal complexes, $CrCl_3$ most efficiently promoted the reaction to form the product 3-aryl-1(3*H*)-isobenzofuranones **54** in 63–78% yields (Scheme 14).

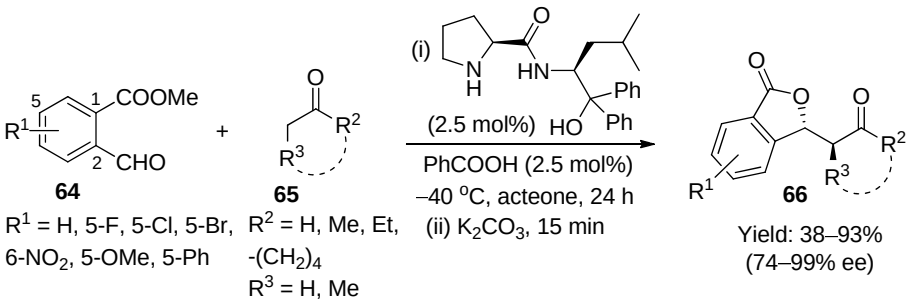
1.4.2 Recent Methodologies for the Synthesis of Enantiomerically Pure 3-Substituted 1(3*H*)-Isobenzofuranones

Gotor and co-workers[61] have developed a straightforward synthesis of (*S*)-3-methylphthalides **63**, with bio-reduction of 2-acetylbenzonitriles **62** being the key asymmetric step. The enzymatic processes are highly dependent on the pH value and acidic conditions were required to avoid undesired side reactions. Baker's yeast was found to be the best biocatalyst acting in a highly stereoselective fashion. The simple treatment of the reaction crudes with aqueous HCl has provided access to enantiopure (*S*)-3-methylphthalides in moderate to excellent yields (Scheme 15).



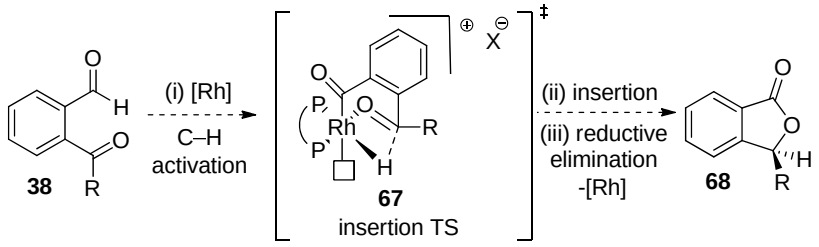
Scheme 15. Enzymatic Approach to Enantiopure (*S*)-Phthalides

Wang and co-workers[62] have described an unprecedented organocatalytic asymmetric aldol-lactonization reaction of 2-formylbenzoic esters **64** with ketones/aldehydes **65** for convenient construction of the enantioenriched "privileged" scaffold **66**. Due to the sensitive nature of substrate structures of an organocatalytic enantioselective aldol reaction, after extensive optimization of reaction conditions, catalyst L-prolinamide alcohol was identified as the best promoter. Interestingly, it was found that addition of an acid additive $PhCO_2H$ in the reaction, could significantly enhance reaction efficiency with use of 2.5 mol % catalyst for the process. Moreover, due to the sensitivity of reaction conditions toward a sequential aldol-lactonization process without affecting enantioselectivity and avoiding racemization, it is essential to remove the catalyst for the subsequent K_2CO_3 induced facile lactonization reaction. The aldol-lactonization process was applied for a three step catalytic asymmetric synthesis of the natural product of 3-butylphthalide (**1**) (Scheme 16).



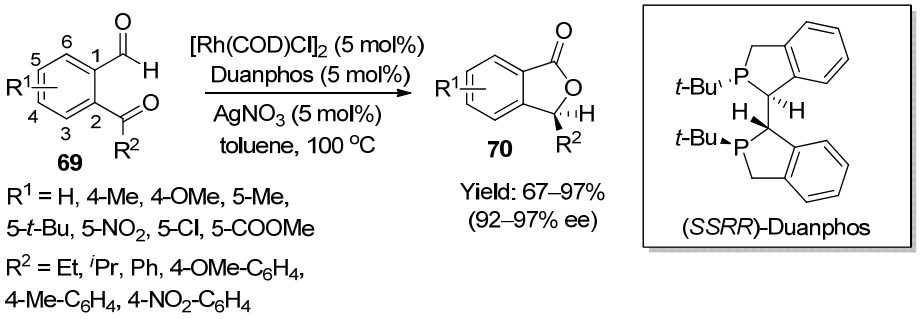
Scheme 16. New Organocatalytic Approach to Chiral 3-Substituted Phthalides

Over the years significant efforts have been focused on the synthesis of phthalides, but most asymmetric methods require chiral auxiliaries or chiral organometallics and few are catalytic.[63] To address this challenge, Dong and co-workers[64] reported an efficient and complementary route to phthalides **68** by enantioselective ketone hydroacylation. From mechanistic studies it was reasoned



Scheme 17. Mechanistic Rationale for Ketone Hydroacylation

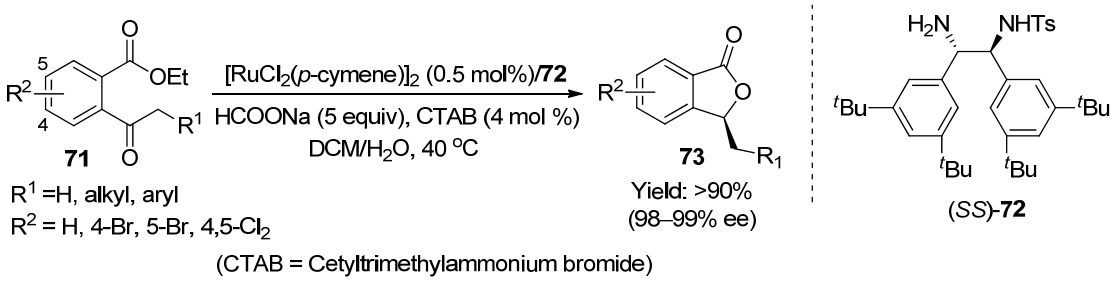
that 2-ketobenzaldehydes **38** would be undergoing hydroacylation to form phthalides **68** by an analogous pathway via a distinct transition state **67**. In **67**, one coordination site would be available for solvent, ligand or counterion binding. After evaluating many chiral phosphines, Duanphos was found to be a promising ligand. With this bulky electron-rich phosphine, the counterions with various



Scheme 18. Rhodium-Catalyzed Hydroacylation of Substituted Ketoaldehydes

coordinating strengths (SbF_6^- < BF_4^- < ^-OTf < ^-OMs < NO_3^-< Cl^-) were studied. The study revealed a marked counterion effects on reactivity. Catalysts with more strongly coordinating counterions gave better selectivity for hydroacylation over decarbonylation, with yields increasing from 30 to 97%. They applied their approach for the synthesis of (*S*)-3-butylphthalide (**1**) (97% ee) (Scheme 17 and 18).

Lin and co-workers[65] developed a new diamine ligand TsDBuPEN, **72** for asymmetric transfer hydrogenation (ATH). The reductive cyclization of 2-acylarylcarboxylates **71** was found to proceed with high stereoselectively by the new diamine TsDBuPEN, **72**/Ru(II) catalyst and subsequent in situ lactonization under the aqueous conditions. It enables the efficient access to a wide range of 3-substituted isobenzofuranones **73** in enantiomerically pure form (Scheme 19).



Scheme 19. Asymmetric Synthesis of 3-Substituted Isobenzofuranones via Transfer Hydrogenation

The origin of excellent stereocontrol came from more preferable chirality-determining transition state of the Ru-TsDBuPEN **72** complex with the ethyl 2-acylarylcarboxylate substrates **71**. There is a possible hydrogen bonding involvement of the neighboring ester function group of the 2-acylarylcarboxylate substrate, which might be responsible for the observed selectivity. It was also found that the enantiomeric excess (ee) dramatically dropped with 2-methylacetophenone as substrate, which has an *ortho*-methyl group at the place of alkoxycarbonyl group. Moreover, phthalide was the only product observed during the reaction, suggesting a very good cooperative processing of the asymmetric reduction and lactonization (Figure 3).

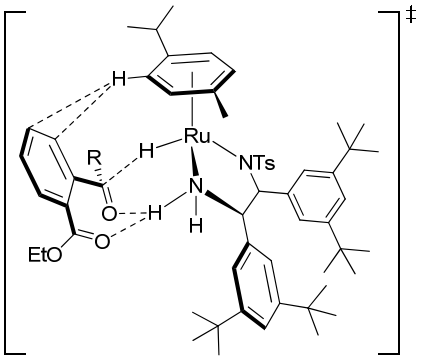


Figure 3. Proposed transition state

Recently, Dudding and co-workers[66] have also reported an elegant one-pot synthesis of chiral C(3)-substituted phthalides via an indium-mediated allylation/transesterification reaction.

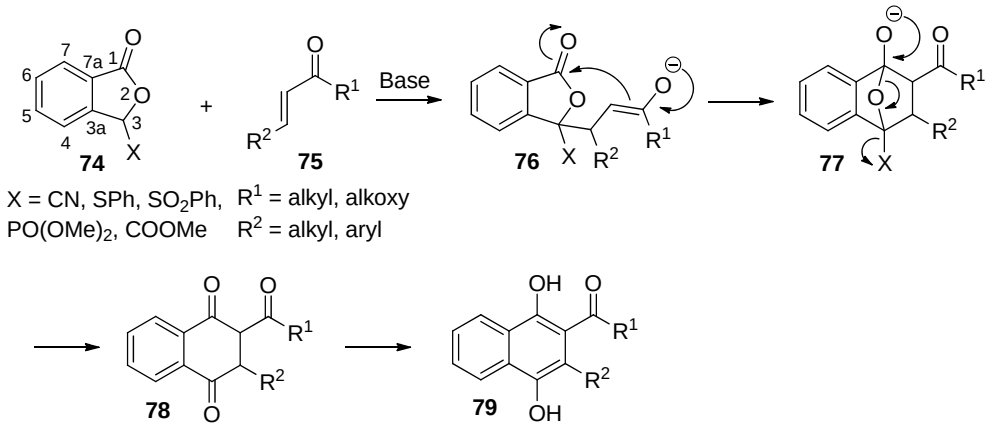
1.5 Application of 1(3*H*)-Isobenzofuranone Motifs in the Total Synthesis of Natural Products

1.5.1 Annulations with Stabilized Phthalide Anions and Michael Acceptors

Annulation with stabilized phthalide anions and Michael acceptors provides a powerful tool for the synthesis of quinoid natural products. The quinone unit is a common feature in many natural products. The interesting structures and exciting biological activities[67] of these natural products have provided a strong forum for synthetic organic chemists to enter this field of endeavor. Whilst many

strategies exist for the synthesis of quinones, the annulation of stabilized phthalide anions with Michael acceptors is a widely accepted tool. The general prototype for this reaction was developed simultaneously by Hauser[68] and Kraus[69] in the late 1970s.

The phthalide annulation procedure involves deprotonation of a suitable stabilized phthalide **74** by a strong base, Michael addition to an appropriate acceptor **75** followed by Dieckmann-like condensation to afford a bicyclic system **77** (Scheme 20).



Scheme 20. Annulation of Stabilized Phthalide Anions with Michael Acceptors

K1115 B_1 (**81**) (BE-41956A, alnumycin) was isolated as an antitumor antibiotic independently by Banyu & co-workers (as BE-41956A in 1997),[70] Bieber & co-workers (as alnumycin in 1998)[71] and Eisai & co-workers (as K1115 B1 in 1998).[72] Tatsuta and co-workers[73] have synthesized four stereoisomers of K1115 B_1 and compared the ^{1}H NMR spectra with that of the natural product isolated from the culture broth of *Streptomyces griseorubiginosus*. Consequently, they found that a red spot on TLC, of which R_f value was the same as the literature,[72] contained two compounds as a diastereomeric mixture. The mixture composed of 1.25:1 ratio of the compounds, which have been named K1115 $B_{1\alpha}$ and K1115 $B_{1\beta}$, respectively.

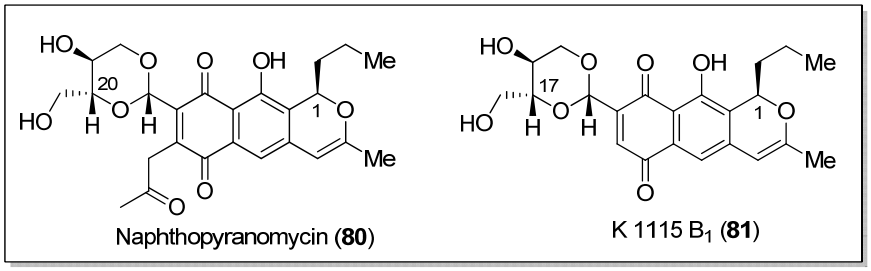
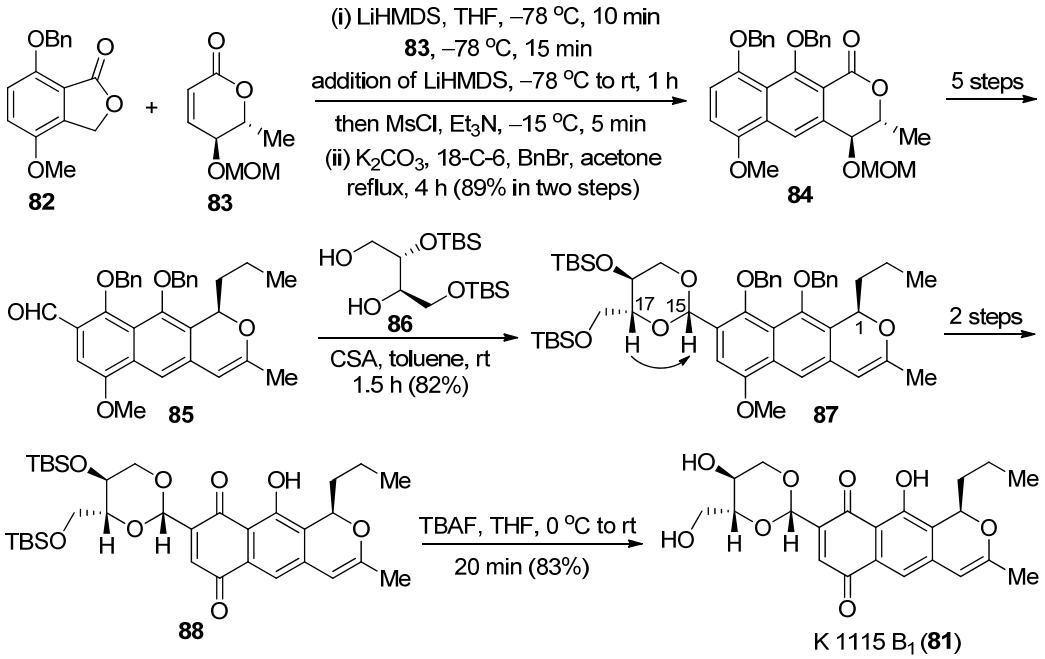


Figure 4. Structure of K1115 B_1

Although the relative stereochemistry of the 1,3-dioxane moiety of K1115 B_1 has not been disclosed, similarity of the ^{1}H NMR data (chemical shifts & coupling constants) between K1115 B_1 (**81**) and

alnumycin **80** reveals that the 1,3-dioxane moiety of K1115 B1 should have the same relative stereochemistry that of alnumycin (Figure 4). Difficulty of the structural determination of K1115 B_1 is due to the distance of chiral centers between the C1 position and 1,3-dioxane. These compounds are generally crystalline solid in nature and the relative structural assignment would be possible on the basis of single crystal X-ray analysis data.

Coupling of isobenzofuranone **82** and rhamnose derivative **83** was carried out by Michael–Dieckmann type cyclization (Scheme 21). Treatment of isobenzofuranone **82** with LHMDS (1.1 equiv) in THF at −78 °C for 10 min and addition of α,β-unsaturated lactone **83** to the resulting mixture (at



Scheme 21. Annulation of Stabilized Phthalide Anions with Michael Acceptors

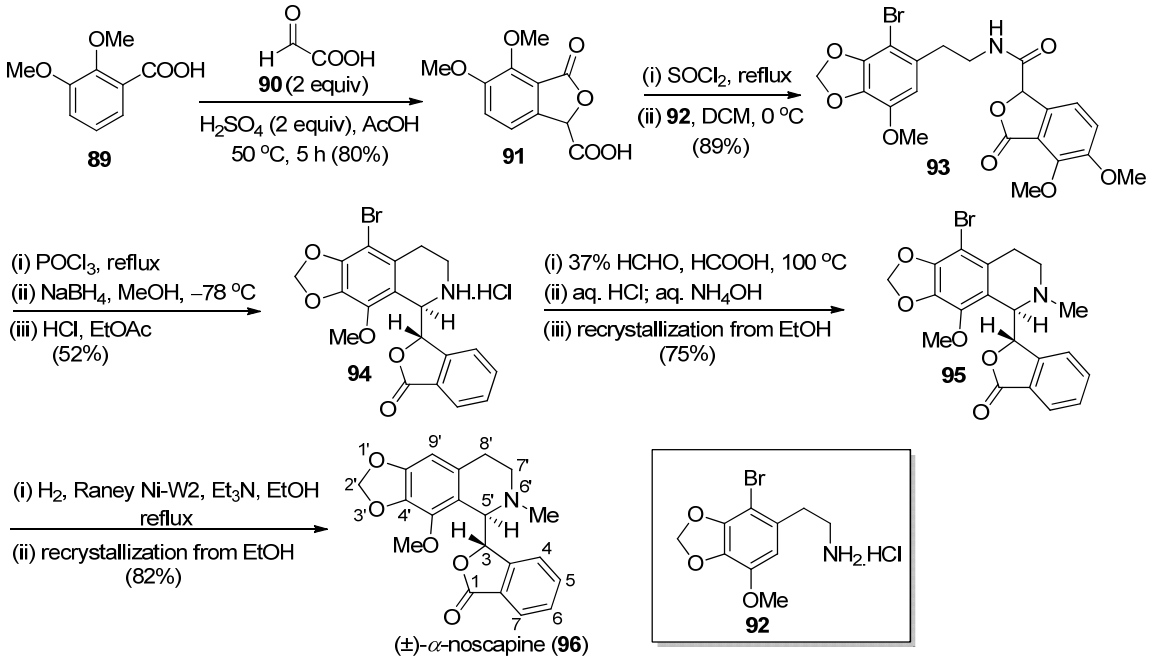
−78 °C for 15 min) gave Michael addition adduct, to which was added another 1.1 equiv of LHMDS and the reaction mixture was stirred at room temperature for 1 h to complete Dieckmann condensation. Further addition of triethylamine and mesylchloride to the reaction mixture at −15 °C proceeded aromatization to give a pyranonaphthalene, which was protected as benzyl ether to afford pyranonaphthalene **84** in high yield. The next five step sequence afforded vinyl ether **85**. Acetalization of **85** with diol **86** gave 1,3-dioxane **87** as a single isomer. The stereochemistry of the C15 position of **87** was determined by NOE (12.5% to C17). Treatment of **87** with Raney nickel in ethanol gave the labile hydroquinone monomethyl ether, which was found to be difficult to subject the direct oxidation into the corresponding quinone. After numerous experiments, it was found that the unstable quinone monoacetal was obtained in good yield by submitting the filtrate of the Raney nickel reduction to the direct oxidation with [bis(trifluoroacetoxy)iodo]-benzene (PIFA). Successive

hydrolysis of quinone monoacetal afforded quinone **88**. De-*O*-silylation of **88** with TBAF gave (1*R*,17*R*)-K1115 B_1 (**81**).

The annulation of stabilized phthalide anions with Michael acceptors has been used widely in synthesis tri- and tetracyclic natural products, such as anthracycline antibiotics.[74] The chemistry of annulation reactions of stabilized phthalide anion has been well documented in two reviews.[75,76]

1.5.2 Diastereoselective Total Synthesis of (±)-α-Noscapine

Opium alkaloid (–)-α-noscapine (narcotine), which was originally isolated from *Papaver somniferum L.*,[77] is a classical non-addictive antitussive agent without significant toxicity.[78] It has been found that (–)-α-noscapine also displays other potential clinical utilities[79] for the treatment of cancer, stroke, anxiety and cerebral edema. Natural noscapine (α- or *erythro*-form) contains two adjacent chiral carbon centers: C-5' at tetrahydroisoquinoline ring and C-3 at phthalide framework. So far, the total synthesis of (–)-α-noscapine have been known but to the limited extend. The pioneer work was reported by Robinson and Perkin[80] who constructed C5'–C3 bond through direct condensation between cortanine and meconine, which were produced by degradation of natural (–)-α-noscapine. Shono et al.[81] developed zinc-promoted reductive coupling of 3-bromo-econine to the iminium salt of



Scheme 22. Total Synthesis of (±)-α-Noscapine

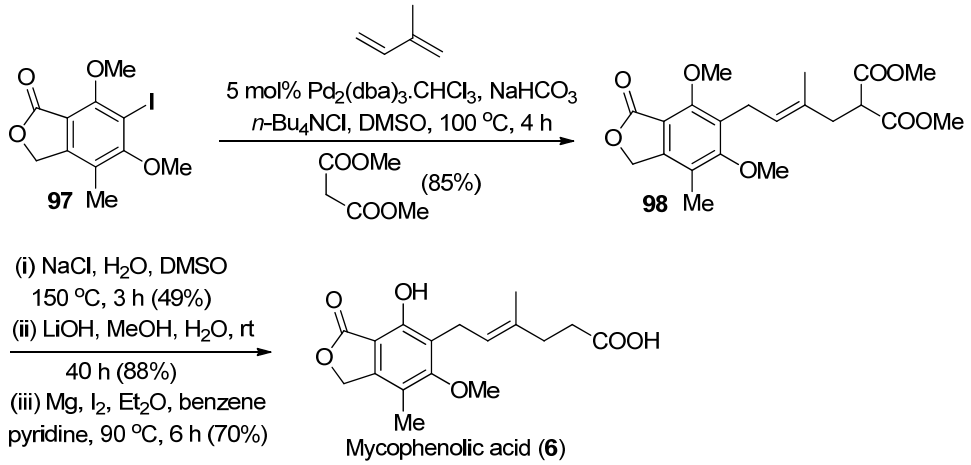
cotarnine to construct C5'–C3 bond. Alternatively, Kerekes & Bognár[82] and Szántay & co-workers[83] synthesized tetrahydroisoquinoline skeleton through Bischler-Napieralski reaction after formation of C5'–C3 bond. However, the main problem for these procedures was formation of nearly equivalent (±)-β-noscapine and/or other regioisomers. It was envisioned that by installing a removable blocking

group (such as Br) onto C-9' position, the formation of undesired regioisomers (C5'–C3 connection) would be completely avoided during Bischler-Napieralski cyclization.

Xu and co-workers[84] approach commenced with the synthesis of meconine-3-carboxylic acid (**91**) which could be easily prepared from simple 2,3-dimethoxybenzoic acid (**89**) and glyoxylic acid (**90**) in the presence of concentrated sulfuric acid with acetic acid as solvent at 50 °C in one-pot. While the amine functionality **92** could be easily prepared from gallic acid over a nine step sequence. With the meconine-3-carboxylic acid (**91**) and hydrochloride **92** in hand, the amide bond was formed (C5'–C3 bond formation) from the acyl chloride of **91** and free amine **92** in 89% yield (Scheme 22). The next step was typical Bischler-Napieralski reaction in the presence of $POCl_3$. As expected, cyclization smoothly occurred to afford labile imine, which was then directly reduced to generate tetrahydroisoquinoline **94**. After extensive tuning of $NaBH_4$/$NaBH_3CN$ reduction, it was found that low reaction temperature was crucial for the high diastereoselectivity and relatively high yields. Subsequently, Eschweiler-Clarke reaction was used to furnish *N*-methylated compound, **95** in 75% yield. Finally, the tetrahydroisoquinoline underwent hydrogenation in the presence of Raney Ni-W2 to remove cleanly the blocking Br-group. Further recrystallization afforded pure (±)-α-noscapine (**96**).

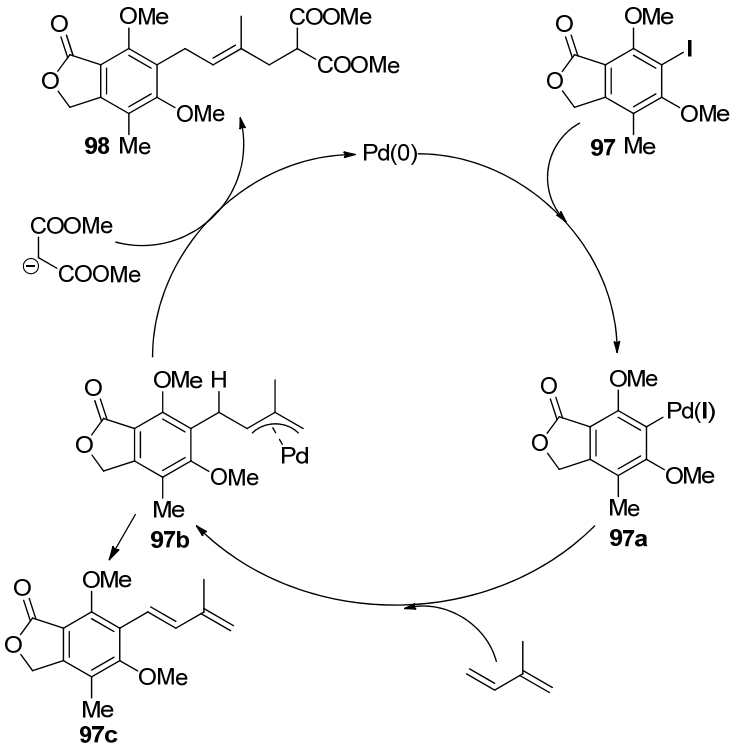
1.5.3 Palladium-Catalyzed Three Component Coupling Reaction: Total Synthesis of Mycophenolic Acid

Mycophenolic acid (MPA, **6**) is produced by the fermentation of a number of penicillium species.[85] Recently this compound and its analogs have been found to possess several significant biological activities, such as anti-neoplastic, anti-parastic, anti-viral, and immunosuppressive activities.[86] The synthesis of **6** was first reported by Birch[87] and later several other methods were reported. Shimizu



Scheme 23. Palladium-Catalyzed Three Component Coupling Reaction

and co-workers[88] focused on the palladium-catalyzed three component coupling reaction consisting of aromatic halides, 1,3-dienes and nulceophiles developed by Heck.[89] Reaction of phthalide **97**, isoprene, and dimethyl malonate was carried out under various conditions. Among various solvents investigated, the best result was obtained when the reaction was carried out in DMSO at 100 °C to give **98** in 85% as an 82:18 mixture of *E*:*Z* isomers. The choice of base is important for the three component coupling, thus, $NaHCO_3$ was found to be a suitable base whereas Et_3N, K_2CO_3 and NaH did not give the satisfactory results. The coupling product **98** was converted to mycophenolic acid (**6**) in three steps via Krapcho decarboxylation, hydrolysis of ester moiety followed by selective demethylation (Scheme 23).



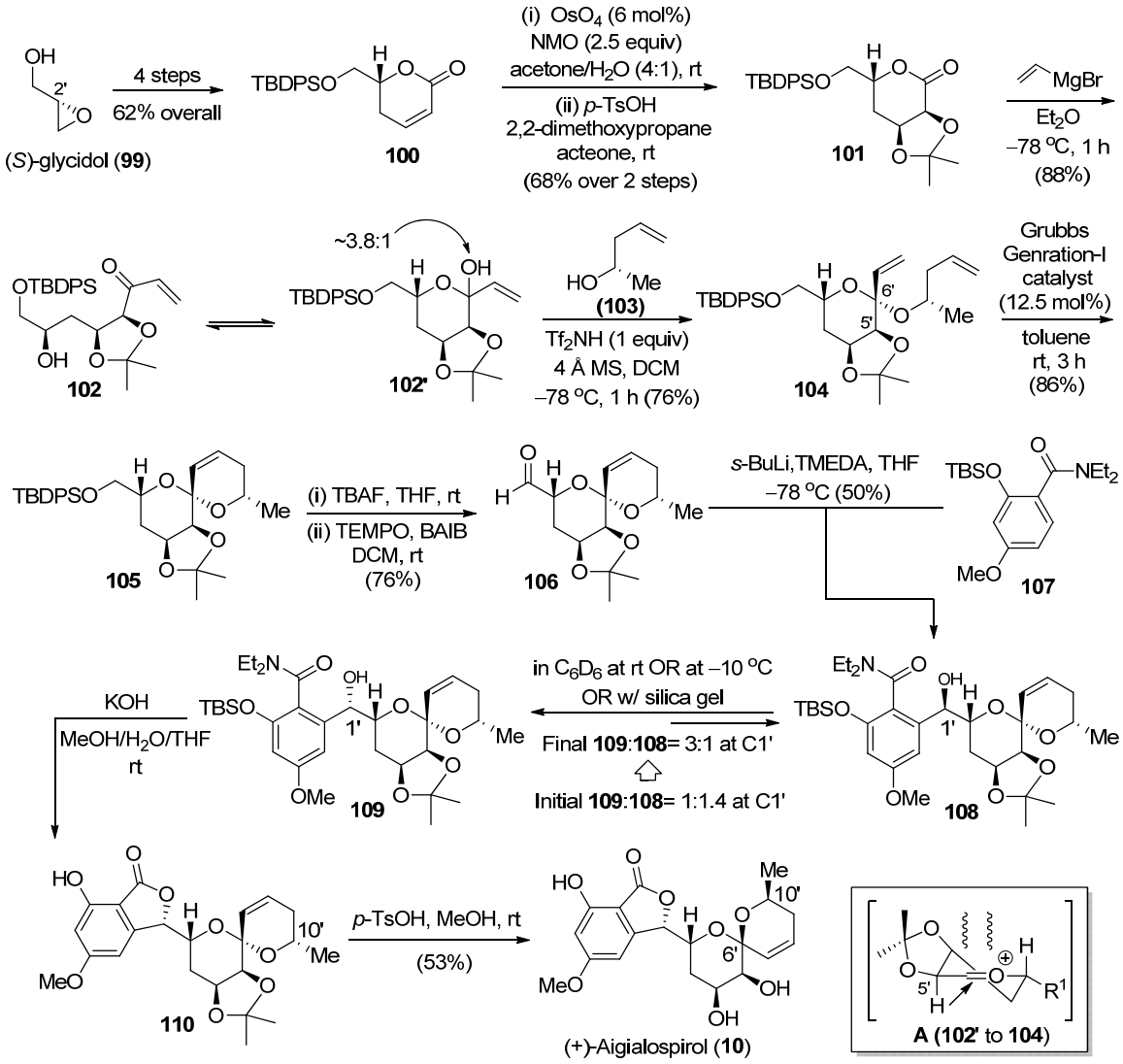
Scheme 24. A Plausible Mechanism For **97** to **98** Transformation

The reaction mechanism can be explained as shown in scheme 24. Oxidative addition of the aryl iodide **97** to Pd(0) species gives the aryl palladium complex **97a**, which reacts with isoprene to give the π-allylpalladium intermediate **97b** by an insertion reaction at the less hindered double bond of isoprene. Nucleophilic attack of the malonate anion at the terminal carbon of the η^3-allylpalladium intermediate **97b** gives the three components coupling product **98** and the palladium(0) species is regenerated to carry on the catalytic cycle. When β-elimination reaction from the η^3-allylpalladium intermediate takes place prior to the expected nucleophilic reaction, the undesired diene **97c** is

formed. This method provides a useful means for syntheses of not only mycophenolic acid but also of other related isoprenoid substituted aromatic compounds.

1.5.4 An Enantioselective Total Synthesis of (+)-Aigialospirol

Recently, Isaka[90] reported the isolation of (+)-aigialospirol (**10**), which was obtained after an extended fermentation of the marine fungus *Aigialus parvus* BCC 5311 that was found in the mangrove Ascomycete. Although biological activities of **10** are not known, natural products of marine fungi origins in general represent medicinally significant structural scaffolds.[91] Hsung and co-workers[92] recent interest in developing cyclic ketal-tethered methods for constructing spiroketals[93,94]



Scheme 24. Total Synthesis of (+)-Aigialospirol (**10**)

led them to (+)-aigialospirol (**10**).[20] They recognized that **10** represents a unique opportunity to demonstrate the expediency of a cyclic ketal tethered ring-closing metathesis (RCM) as a strategy

inthe total synthesis of spiroketal-containing natural products and that it can challenge the classical approach using keto diols in the spiroketal synthesis.

The synthesis commenced with (*S*)-glycidol (**99**) as the Chiron source for the C2' stereocenter and prepared the known dihydro-*R*-pyrone **100** in 62% yield over four steps (Scheme 25). Dihydroxylation of **100** followed by acetonide formation gave δ-lactone (**101**), and addition of vinyl Grignard to **101** gave an equilibrating mixture of lactol **102'** and vinyl ketone **102** in 88% overall yield. After being exposed to 1.00 equiv of Tf_2NH at -78 °C for 1 h, the key formation of cyclic ketal **104** was accomplished in 76% yield from the lactol ketone mixture and the chiral homoallylic alcohol **103**. While the C6' stereochemistry was confirmed at a later stage, cyclic ketal **104** was isolated as a single diastereomer. The overall sequence leading to the key RCM precursor **104** is short. The ring-closing metathesis of cyclic ketal **104** proceeded smoothly to give spiroketal **105** in 86% yield employing 12.5 mol % of Grubb's first generation catalyst. However, at this stage, NOE experiments using **105** confirmed earlier fear when examining NOEs of **104**, which only hinted that the stereochemistry at the C6' spiroketal center could be wrong. The assignment of **105** implies that the alcohol **103** had added to the oxocarbenium ion **A** (**102'** to **104**) in an equatorial manner *anti* to the C5' oxygen (see Scheme 25). Fortuitously, when the acetonide group was removed under acidic conditions, the spiroketal center had completely epimerized to the desired C6' stereocenter which was evident by both NOE and X-ray structure of diol derived from **105**. To complete the total synthesis, spiroketal **105** was elected and the epimerization of C6' spiroketal center was choosen to pursue at the very end. Desilylation and oxidation of **105** gave aldehyde **106**. Subsequent addition of the aryl lithium intermediate, generated via a Snieckus's directed *ortho*-metalation of amide **107** afforded a readily separable mixture of alcohols **109** and **108** with an isomeric ratio 1:1.4. It was uncertain which was the desired C1' epimer, they pursued with the lactone formation employing both alcohols **108** and **109**. Intriguingly, it was found that both **108** and **109** led to the same lactone **110** (with loss of the TBS group). Lactone **110** was taken to (+)-aigialospirol (**10**) after removal of the acetonide group concomitant with C6'epimerization.

1.6 Summary

In summary, we have presented a concise account on the synthesis of 1(3H)-isobenzofuranones (phthalides) with their isolation and bioactivity data. Various synthetic methodologies to the 1(3H)-isobenzofuranone motif and related derivatives reported by different research groups have been presented. Emphasis has been placed on recent developments of synthetic methodologies for 1(3H)-isobenzofuranone compounds, including $Mo(CO)_6$-Mediated alkoxycarbonylation of alkyl Iodide, palladium-catalyzed alkylation of aryl C–H bond, ruthenium hydride catalyzed lactonization of dialdehydes, ruthenium-catalyzed sequential four-component coupling, palladium-catalyzed intramolecular benzannulation, chemoselective benzylic oxidation of 1,3-dihydroisobenzofuran, selective benzylic oxidation of 1,2-phenylenedimethanol followed by lactonization, Tishchenko type reactions of phthalaldehyde, chemoselective reduction of phthalic anhydride, palladium-catalyzed arylation of aldehydes with organoboronic acids, cobalt-catalyzed cyclization reaction of o-iodobenzoates with aldehydes, $CrCl_3$-mediated synthesis of 3-aryl-1(3H)-isobenzofuranones, enzymatic reduction of ketones, organocatalytic asymmetric aldol-lactonization reaction and rhodium-catalyzed hydroacylation. Number of research groups have reported variety of synthetic approaches to biologically active natural/synthetic 1(3H)-isobenzofuranones (phthalides). All the information collected and presented here has been well supported by the provision of more than 150 references from various monographs and international journals. We also foresee the huge amount of imperative complete information available about this scaffold in the literature.

Given the advances in synthetic methodology and technology in recent years and the continued interest in the 1(3H)-isobenzofuranone (phthalide) skeleton in medicinal chemistry and drug development, the development of new efficient methods for the construction of these target molecules will ensure that it is an active and important area of research.

We strongly believe that the broad field of 1(3H)-isobenzofuranones (phthalides) will be of continuing interest to both the synthetic and medicinal chemists and positively there will be interminable promising advancements in the knowledge. In this context, as part of this present dissertation, we have synthesized two unnatural 1(3H)-isobenzofuranones, six natural 3-substituted 1(3H)-isobenzofuranones and two natural geranylated/farnesylated phenolic stilbenes. Our synthetic studies towards the synthesis of these natural/unnatural products will be discussed in details in the second and third chapter of the present dissertation.

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CHAPTER 2

Synthesis of Naturally Occurring Remotely Functionalized anti-*Helicobacter pylori* Antibiotics

This chapter features the following topics:

Note: An independent figure, table, scheme, structure and reference numbers have been used for the each section.

This chapter is divided into two sections. The section A presents a concise literature account on the synthesis of CJ-13,015, CJ-13,102, CJ-13,103, CJ-13,104, CJ-13,108, CJ-12,954/CJ-13,014, sporotricale methyl ether and (+)-spirolaxine methyl ether (Figure). The section B describes a highly chemoselective coupling reactions of 5,7-dimethoxyphthalide carbanion with the remotely functionalized long chain alkyl iodides and its application in the synthesis of CJ-13,015, CJ-13,102, CJ-13,103, CJ-13,104, CJ-13,108, CJ-12,954/CJ-13,014 and sporotricale methyl ether. This section also describes the synthesis of pivotal spiroketal segment of (+)-spirolaxine methyl ether via a stepwise alkylation and acylation of an alkyne with two different readily available chiral building blocks followed by the reductive in situ regio- and stereoselective spiroketalization pathway. The detailed experimental procedures, complete tabulated analytical and spectral data and some selected NMR spectra have been appropriately included at the end part of section B.

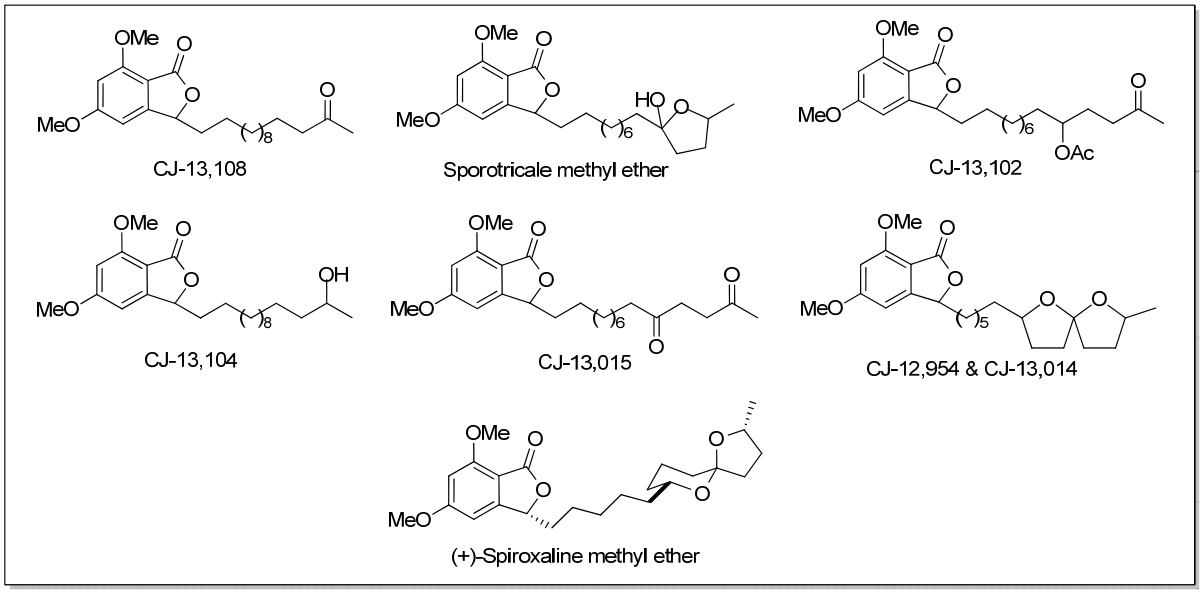


Figure. Oxygen containing bioactive natural products synthesized

CHAPTER 2: SECTION A

A Concise Literature Account of anti-*Helicobacter pylori* Agents

This section A of chapter 2 features the following topics:

2A.1. Background

Gastric and duodenal ulcers affect a significant portion of the human population worldwide. The root cause of gastric and duodenal ulcers is the presence of the microaerophilic Gram-negative bacterium *Helicobacter pylori*, which appear to live beneath the mucus layer of the stomach (Figure 1).[1,2] Infection has been associated with chronic superficial gastritis, chronic active gastritis, peptic ulcer disease and gastric cancer in humans.[3] As a result, the International Agency for Research in Cancer classified *Helicobacter pylori* as a class I carcinogen in the year 1994.[4]

The current first-line triple-therapy for *Helicobacter pylori*-associated gastrointestinal diseases using a combination of antibiotics with a proton-pump inhibitor fails to fully eradicate *Helicobacter pylori* in approximately 10-23% of patients and relapse is a problem.[1,2] However, long-term treatment with current therapies is not recommended and accordingly, second-line or rescue treatments are often required.[5] Treatment failure is associated with the emergence of *Helicobacter pylori* strains that are resistant to the broad-spectrum antibiotics used.[4] Consequently, there is an urgent need for a safe and effective treatment with a compound having an excellent anti-*Helicobacter pylori* activity. Recently, in a screening program designed to discover such compounds, Dekker et al.[6] isolated the new phthalides **1**-**7** from the basidiomycete *Phanerochaerte velutina* with promising anti-*Helicobacter pylori* activity (Figure 2). The secondary metabolites **1**-**7** were isolated in very small amounts and a realistic supply of these natural products for further biological evaluation is necessary. The (+)-spirolaxine methyl ether (**8**) has been isolated from various strains of white rot fungi genera *Sporotrichum* and *Phanerochaetei* and the stereochemical structural assignment has been done on the basis of single-crystal X-ray analysis data.[7,8] It exhibits various biological activities such as cholesterol lowering, cytotoxic towards endothelial cells (BMEC and Huvec) and variety of tumor cell lines (LoVo and HL60).[9,10] More specifically, they possess prominent and highly selective activity against the gastric and duodenal ulcers inducing microaerophilic Gram-negative bacterium *Helicobacter pylori*. (+)-Sporotricale methyl ether (**9**) is a polyketide-derived natural product that was isolated from a culture of the fungus *Sporotrichum laxum* (basidiomycetae). Depending on the solvent it exists in two different equilibrium forms, the epimeric hemiketal and the open hydroxy ketone [Hemi-ketal (chloroform)/Hydroxyketone (acetone)] (Figure 3).[7] Sporotricale methyl ether belongs to a small group of fungal metabolites that have received attention for their inhibitory activity against *Helicobacter pylori*[11] and therefore may become leading compounds for the development of drugs for the treatment of gastroduodenal disorders and prevention of gastric cancer.

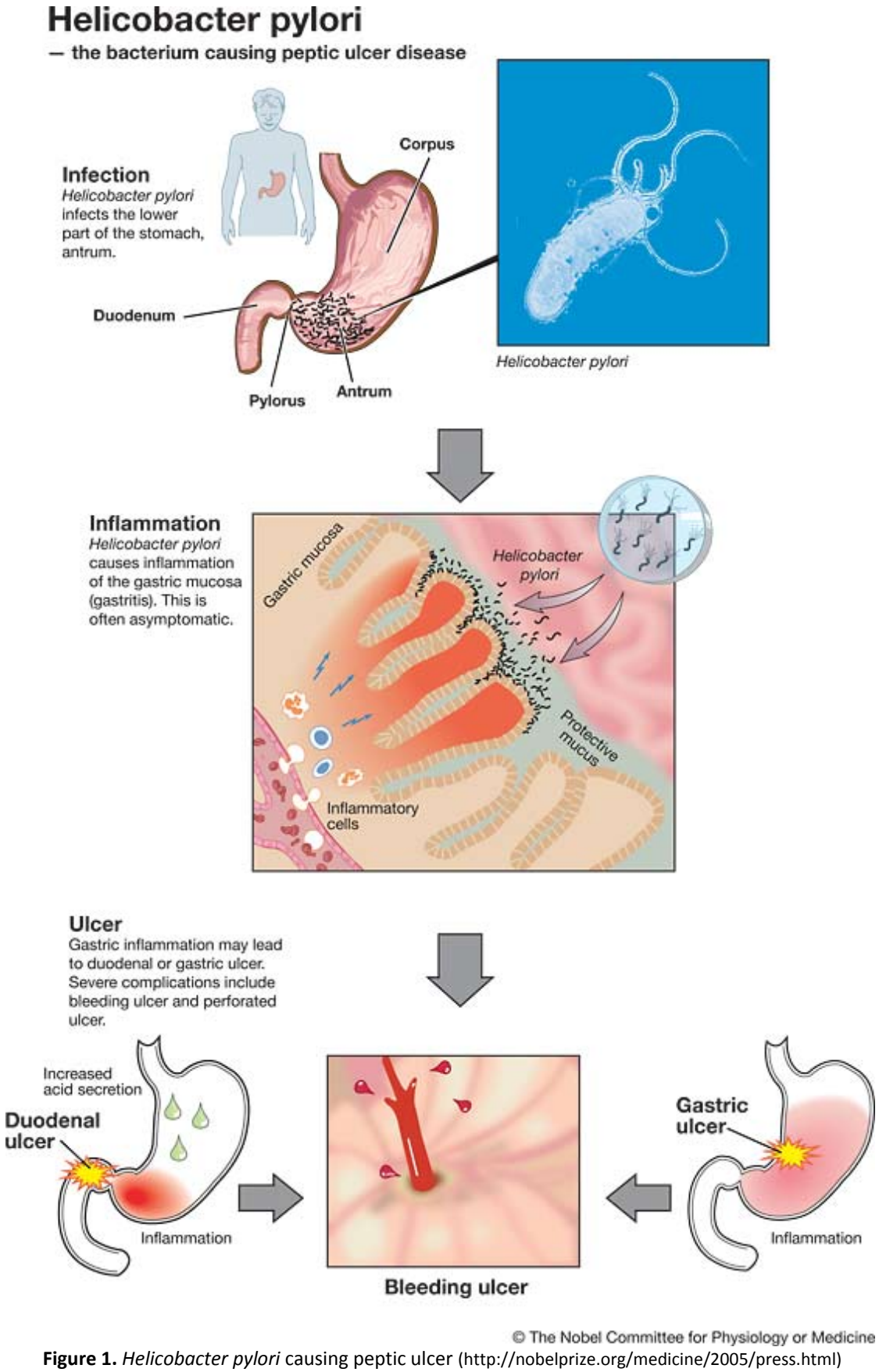
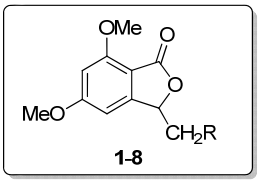


Figure 1. *Helicobacter pylori* causing peptic ulcer (http://nobelprize.org/medicine/2005/press.html)



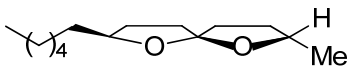
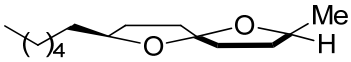
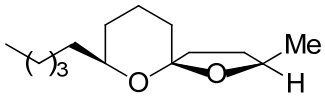
Compound	R	Activity (μg/disk that gives a 15 mm zone)
CJ-13,015 (**1**)	$-(CH_2)_8COCH_2CH_2COCH_3$	2
CJ-13,102 (**2**)	$-(CH_2)_8CH(OAc)CH_2CH_2COCH_3$	0.5
CJ-13,103 (**3**)	$-(CH_2)_{10}COCH_2CH_2COCH_3$	50
CJ-13,104 (**4**)	$-(CH_2)_{11}CH(OH)CH_3$	500
CJ-13,108 (**5**)	$-(CH_2)_{11}COCH_3$	10
CJ-12,954 (**6**)		0.02
CJ-13,014 (**7**)		0.02
Spirolaxine methyl ether (**8**)		Not determined

Figure 2. New microbial secondary metabolites and helicobactericidal activities

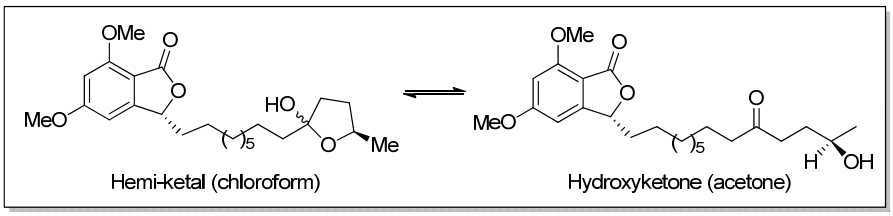


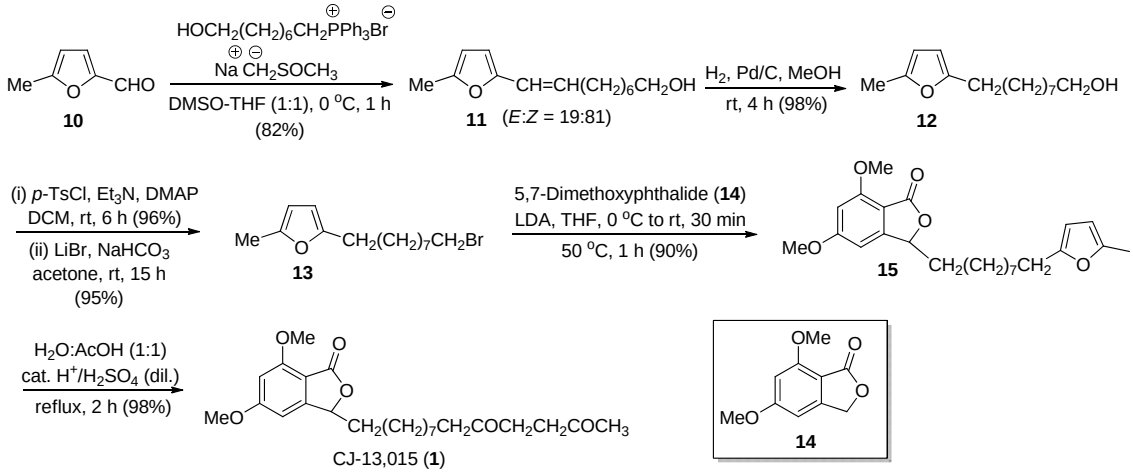
Figure 3. Ring-chain tautomerism in (+)-sporotricale methyl ether (**9**)

2A.2 Synthetic Approaches Towards anti-*Helicobacter pylori* Natural Products

The clinical potential of the microbial secondary metabolites CJ-13,015 (**1**), CJ-13,102 (**2**), CJ-13,103 (**3**), CJ-13,104 (**4**), CJ-13,108 (**5**), CJ-12,954 (**6**)/CJ-13,014 (**7**), (+)-spirolaxine methyl ether (**8**) and sporotricale methyl ether (**9**) has led to great interest in developing new syntheses and reported synthetic approaches have been illustrated in this section.

2A.2.1 Argade's Approach Towards the Synthesis of CJ-13,015

Argade and co-workers[12] reported a six-step first synthesis of an anti-*Helicobacter pylori* secondary metabolite, CJ-13,015 (**1**) via the coupling of anion of 5,7-dimethoxyphthalide (**14**) with bromo compound **13**, using 5-methylfuran as the latent source of 1,4-dicarbonyl system. The retrosynthetic analysis of the microbial secondary metabolite CJ-13,015 revealed that 5-methylfurfural (**10**), 8-bromo-1-octanol and 5,7-dimethoxyphthalide (**14**) would be suitable building blocks to access **1** (Scheme 1). The Wittig reaction of 5-methylfurfural (**10**) with the ylide generated in situ from the reaction of (8-hydroxyoctyl)triphenylphosphonium bromide and sodium methylsulfinylmethanide in

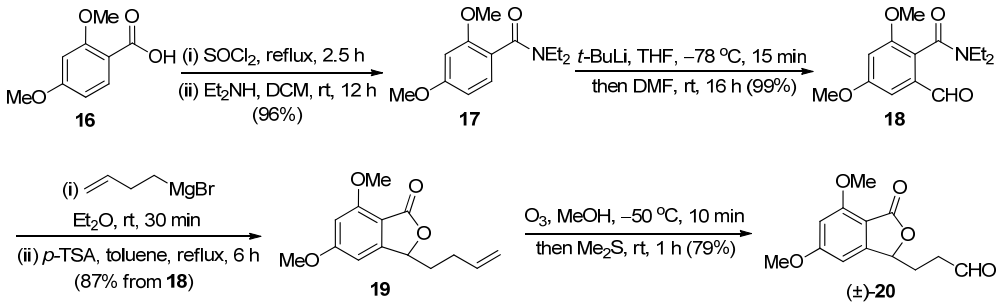


Scheme 1. Synthesis of CJ-13,015 via S_N2 Displacement Reaction

a mixture of DMSO–THF (1:1) furnished the mixture *E*- and *Z*-isomers **11** in an 82% yield. Palladium on charcoal induced selective catalytic hydrogenation of the newly generated carbon–carbon double bond in **11** gave the furan derivative **12** in quantitative yield. The primary alcohol **12** was treated with *p*-toluenesulfonyl chloride to form the corresponding tosylate (96% yield) which on reaction with lithium bromide, yielded the desired furan containing alkyl bromide **13** in 95% yield. The bromide **13** underwent a smooth S_N2 substitution reaction with the anion of 5,7-dimethoxyphthalide (**14**) in THF at 50 °C to yield the desired coupling product **15** in 90% yield. The furan moiety in compound **15** underwent a clean chemoselective hydrolysis in a refluxing acetic acid–water mixture (1:1) in the presence of a catalytic amount of dilute sulfuric acid to exclusively furnish the desired bioactive natural product CJ-13,015 (**1**) in quantitative yield.

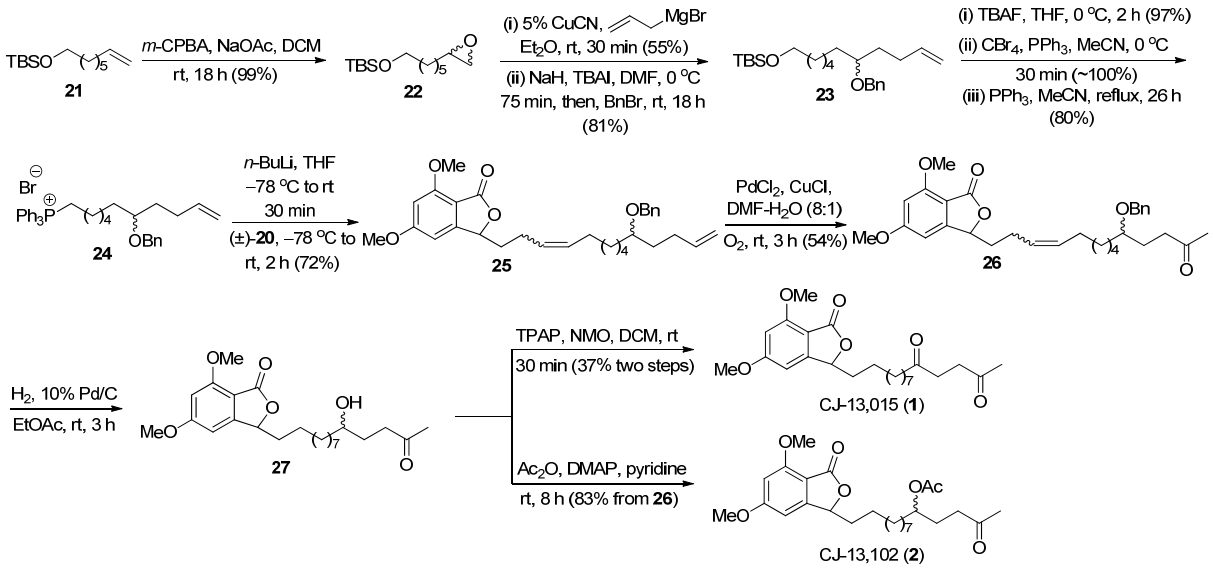
2A.2.2 Brimble's Approach Towards CJ-13,015, CJ-13,102, CJ-13,103, CJ-13,104 and CJ-13,108

Brimble and co-workers[13] reported a multistep synthesis of CJ-13,015 (**1**), CJ-13,102 (**2**), CJ-13,103 (**3**), CJ-13,104 (**4**) and CJ-13,108 (**5**) using the Wittig reaction of a key phthalide-aldehyde (±)-**20** with



Scheme 2. Synthesis of Phthalide-Aldehyde (±)-**20**

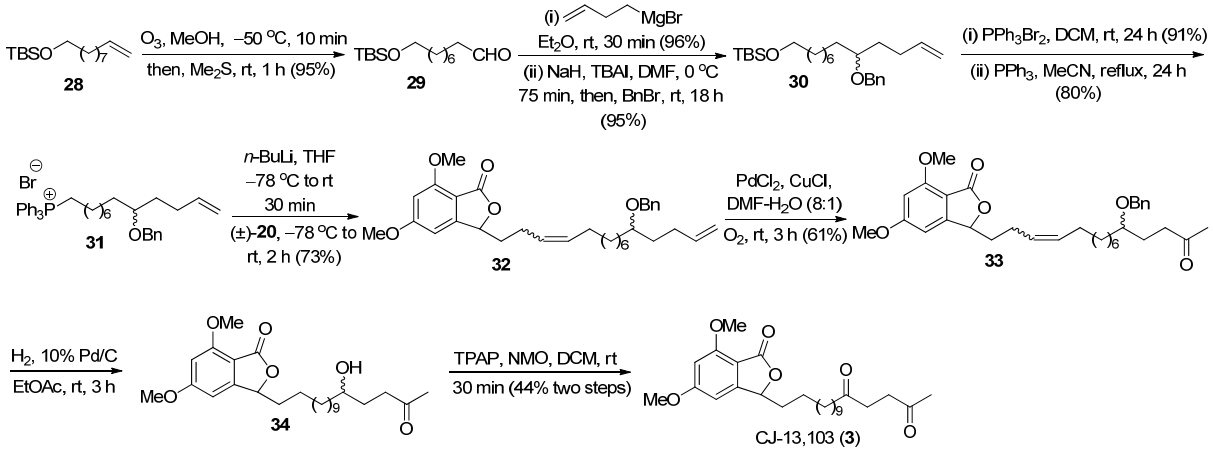
the ylide generated from the appropriate phosphonium salts (Schemes 2 to 5). The building block phthalide-aldehydes (±)-**20** was prepared from 2,4-dimethoxybenzoic acid (**16**), firstly by conversion to the corresponding amide **17**. *ortho*-Lithiation followed by formylation provided aldehyde **18**. Compound **18** on treatment with but-3-en-1-ylmagnesium bromide furnished the alcohol derivative which on acid-catalyzed cyclization furnished phthalide **19**, that upon ozonolysis of the terminal olefin gave the desired phthalide-aldehyde (±)-**20** in 65% overall yield (Scheme 2). The required side chain for CJ- 13,015 (**1**) and CJ-13,102 (**2**) was synthesized from 7-octen-1-ol (Scheme 3). Epoxidation of terminal olefin in TBS-protected ether **21** furnished the oxirane **22**. Ring opening of the epoxide using higher-order allyl-cuprate afforded the secondary alcohol, which was protected as benzyl ether



Scheme 3. Synthesis of CJ-13,015 and CJ-13,102

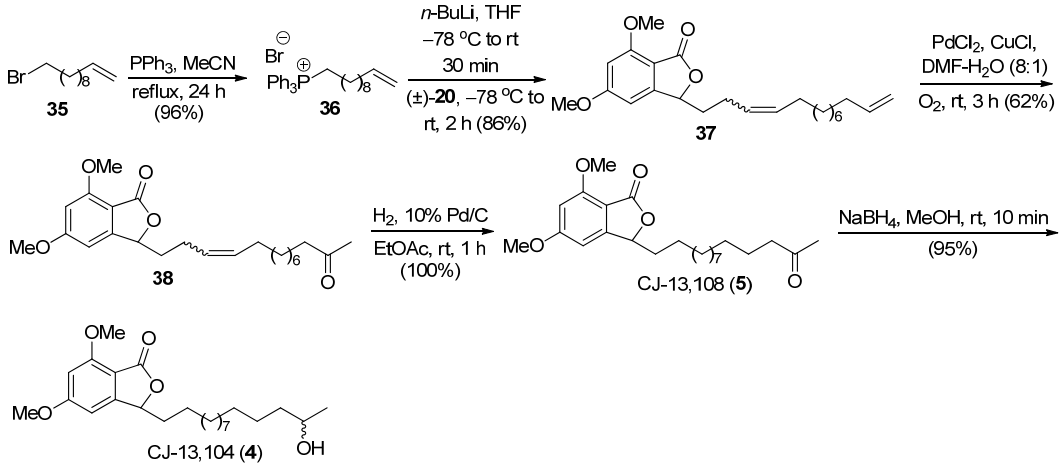
23. Desilylation of the TBS ether **23** gave alcohol which was converted to bromocompound followed by its reaction with triphenylphosphine gave the desired phosphonium salt **24** in 34% overall yield (seven steps). Wittig reaction of the ylide generated from phosphonium salt **24** with phthalide aldehyde (±)-**20** gave compound **25** in 72% yields as a mixture of *E*- and *Z*-isomers. Selective Wacker oxidation of the terminal olefin **25** to ketone **26** followed by hydrogenation of the internal olefin with

the simultaneous removal of benzyl group furnished hydroxyketone **27** which on TPAP oxidation produced the natural product CJ-13,015 (**1**). Direct acylation of the alcohol **27** provided another natural product CJ-13, 102 (**2**).



Scheme 4. Synthesis of CJ-13,103

Using the same strategy, CJ-13,103 (**3**) was synthesized from TBS-protected 9-decen-1-ol **28** (Scheme 4). TBS ether **28** on ozonolysis of the terminal olefin furnished the aldehyde **29**. Reaction of **29** with but-3-en-1-ylmagnesium bromide gave secondary alcohol which was protected as benzyl ether **30**. One pot desilylation-bromination of **30** gave the bromide which on treatment with triphenylphosphine furnished the desired phosphonium salt **31**. The Wittig reaction of the ylide generated from **31** with (±)-**20** furnished olefin **32** as a mixture of *E*- and *Z*-isomers. Selective Wacker oxidation of the terminal olefin **32** to ketone **33** followed by simultaneous hydrogenation of internal olefin and hydrogenation of benzyl ether to hydroxyketone **34** and finally oxidation of the alcohol furnished the natural product CJ-13,103 (**3**).

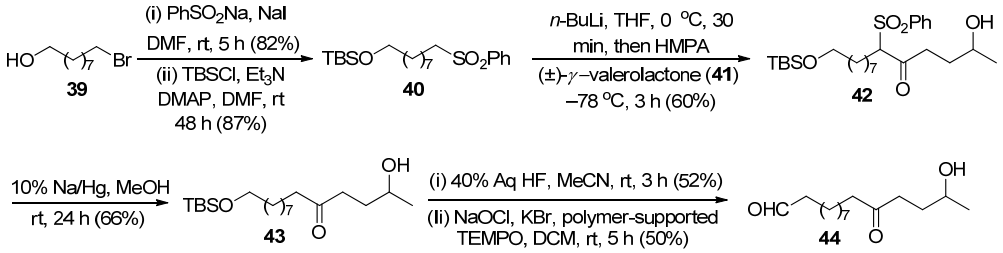


Scheme 5. Synthesis of CJ-13,108 and CJ-13,104

Both the natural products CJ-13,104 (**4**) and CJ-13-108 (**5**) were synthesized from the phosphonium salt of commercially available 10-undecen-1-ylbromide (**35**). Wittig reaction of the ylide generated from phosphonium salt **36** with the aldehyde (±)-**20** gave the desired product **37** as a mixture of *E*- and *Z*-isomers. Selective Wacker oxidation of the terminal olefin **37** gave the methyl ketone **38** which upon hydrogenation of the internal olefin furnished the natural product CJ-13,108 (**5**). Reduction of the ketone in **5** with sodium borohydride gave another natural product CJ-13,104 (**4**) (Scheme 5).

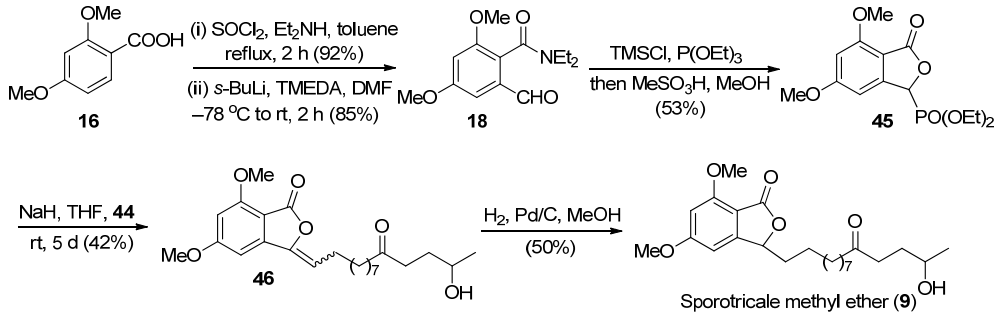
2A.2.3 Dallavalle's Approach Towards Sporotricale Methyl Ether

Dallavalle and co-workers[14] reported the synthesis of sporotricale methyl ether (**9**) utilizing Horner–Wadsworth–Emmons condensation of 13-hydroxy-10-oxotetradecanal (**44**) with diethyl 5,7-dimethoxyphthalide-3-phosphonate (**45**) followed by hydrogenation of the obtained alkene (Scheme 6 and 7). Reaction of 9-bromononan-1-ol (**39**) with sodium benzenesulfinate gave the sulfone which



Scheme 6. Synthesis of Requisite Aldehyde **44**

on silylation gave TBS protected sulfone **40**. Treatment of **40** with *n*-BuLi gave the soluble lithio-derivative. Addition of a small amount of hexamethylphosphoramide followed by the stoichiometric amount of (±)-γ-valerolactone (**41**) at –78 °C afforded **42** in a 60% yield. Sulfone cleavage was accomplished with Na/Hg amalgam in methanol to give the silylated hydroxyketone **43**. Desilylation



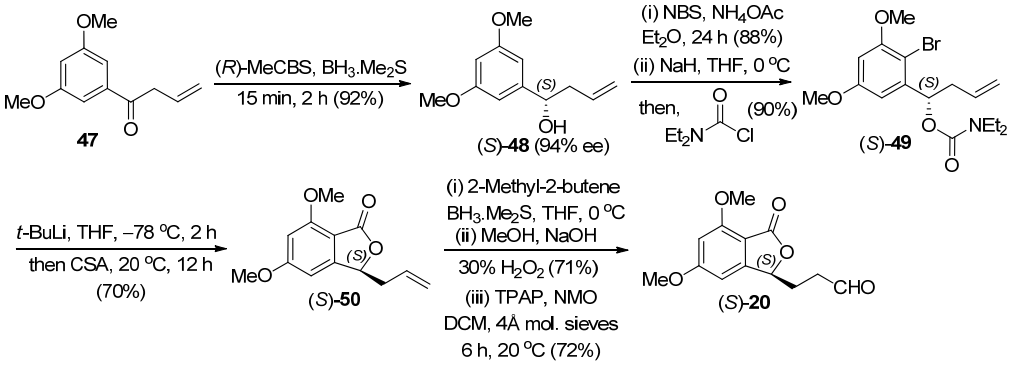
Scheme 7. Synthesis of Sporotricale Methyl Ether

of **43** with aqueous HF gave the primary alcohol which was oxidized to the aldehyde **44** with polymer-supported TEMPO (Scheme 6). Compound **45** was prepared following a procedure described by Watanabe[15] for the synthesis of various diethyl phthalide-3-phosphonates, that requires the

reaction of appropriate diethyl-2-formylbenzamides with *tert*-butyldimethylsilyldimethylphosphite. The phosphonate **45** was prepared by direct treatment of **18** with chlorotrimethylsilane and triethylphosphite followed by desilylation and cyclization using methanesulfonic acid (Scheme 7). The Horner–Wadsworth–Emmons reaction between **44** and **45** in the presence of NaH gave the expected alkene **46** as a mixture of *E*/*Z* isomers. Hydrogenation of the exocyclic double bond of **46** in methanol using 10% Pd/C as a catalyst gave sporotricale methyl ether (**9**) in 50% yield.

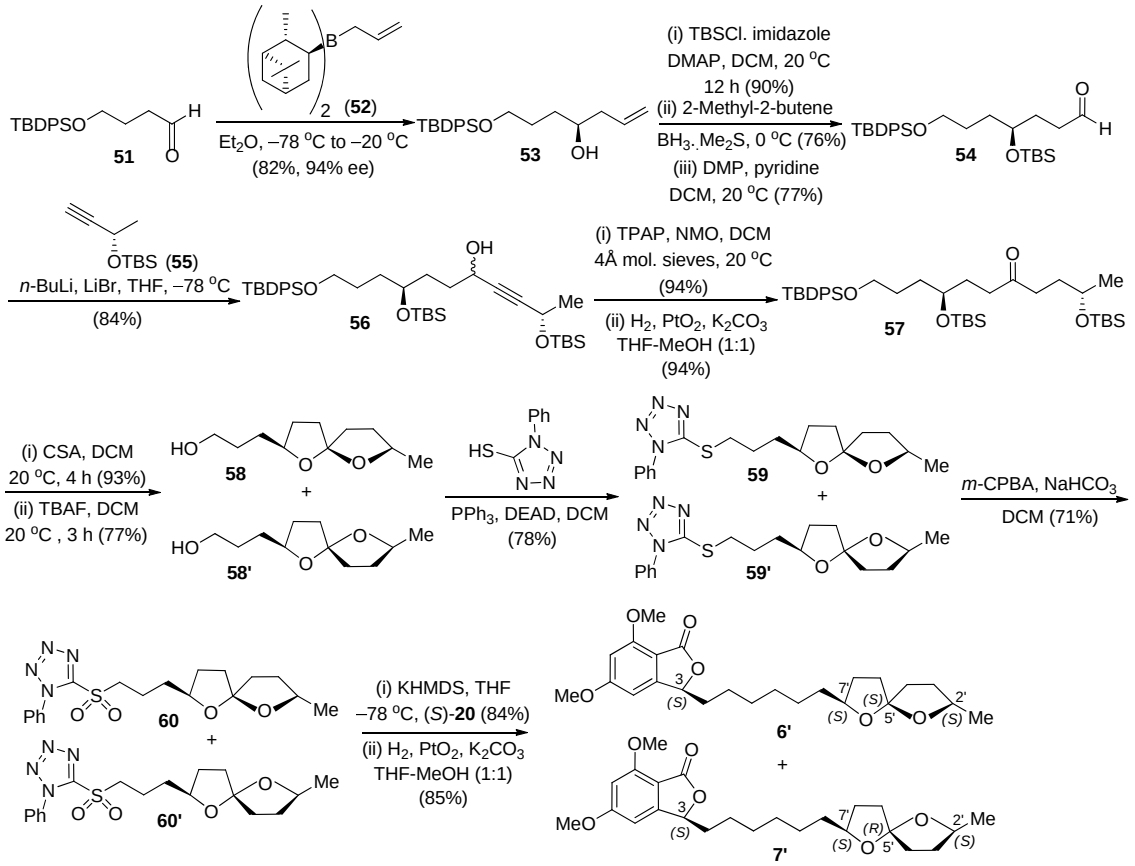
2A.2.4 Brimble's Approach Towards the Enantiomers of CJ-12,954 and CJ-13,014

Brimble and co-workers[16] reported total synthesis of the enantiomers of the CJ-12,954 (**6**) and CJ-13,014 (**7**) (Scheme 8 and 9). They have synthesized the (*S*)-phthalide-aldehyde **20** by asymmetric reduction of the ketone **47** using (*R*)-2-Me-CBS-oxazaborolidine and boran-dimethyl sulfide affording benzyl alcohol (*S*)-**48** (94% ee). The alcohol (*S*)-**48** on regioselective bromination and subsequent conversion to diethyl carbamate (*S*)-**49** followed by lithium-halogen exchange and intramolecular cyclization furnished the phthalide (*S*)-**50**. Hydroboration of the allyl group followed by oxidation furnished the desired (*S*)-phthalide-aldehyde **20** (Scheme 8).



Scheme 8. Synthesis of Enanatiomerically Pure Aldehyde Segment (*S*)-**20**

The required side chain fragment was synthesized from aldehyde **51**. Addition of (+)-*B*-allyldiisopinocamphenylborane (**52**) to the aldehyde **51** afforded (*S*)-homoallyl alcohol **53** in 82% yield (94% ee). Silyl ether formation followed by hydroboration and oxidation of the resultant primary alcohol gave aldehyde **54**. Addition of aldehyde **54** to lithium TBS ether of (*S*)-but-3-yn-2-ol (**55**) at –78 °C provided alcohol **56** as a mixture of diastereoisomers which was oxidized to ketone using TPAP/NMO and the subsequent reduction of the acetylene unit furnished **57**. Compound **57** underwent smooth spirocyclization using camphorsulfonic acid in dichloromethane and afforded an inseparable 1 : 1 mixture of spiroacetals **58** and **58'** after the cleavage of TBDPS ether. Mitsunobu displacement of hydroxyspiroacetals **58** and **58'** with 1-phenyl-1*H*-tetrazole-5-thiol afforded sulfides



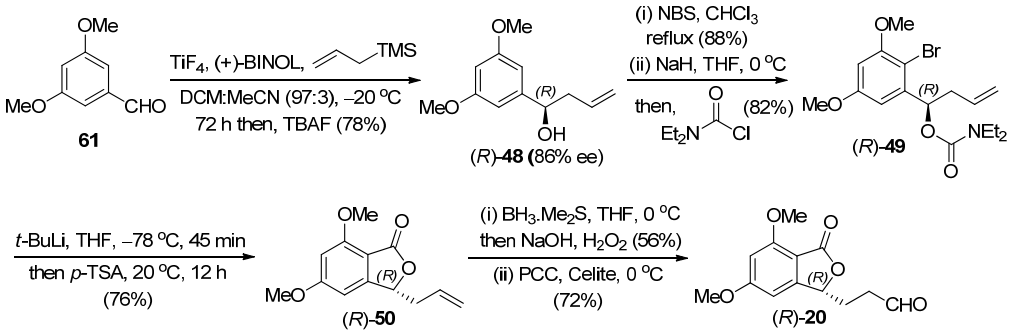
Scheme 9. Synthesis of CJ-12,954 and CJ-13,014 via Heterocycle-Activated Julia-Kocienski Olefination

59 and **59'**, which underwent oxidation to form the inseparable mixture of sulfones **60** and **60'**. Finally the modified Julia olefination of the mixture **60** and **60'** with (*S*)-**20** followed by catalytic hydrogenation furnished 1:1 mixture of phthalide-spiroacetals (3*S*,2'*S*,5'*S*,7'*S*)-**6'** and (3*S*,2'*S*,5'*R*,7'*S*)-**7'**. Comparison of the HPLC retention time and $[\alpha]_D$ value of the mixture **6'** and **7'** with the mixture of natural products **6** and **7**, established that **6'** and **7'** are enantiomers of **6** and **7** respectively and the absolute configuration of the natural product CJ-12,954 (**6**) is (3*R*,2'*R*,5'*R*,7'*R*) and that of CJ-13,014 (**7**) is (3*R*,2'*R*,5'*S*,7'*R*) (Scheme 9).

2A.2.5 Brimble's Approach Towards (+)-Spirolaxine Methyl Ether

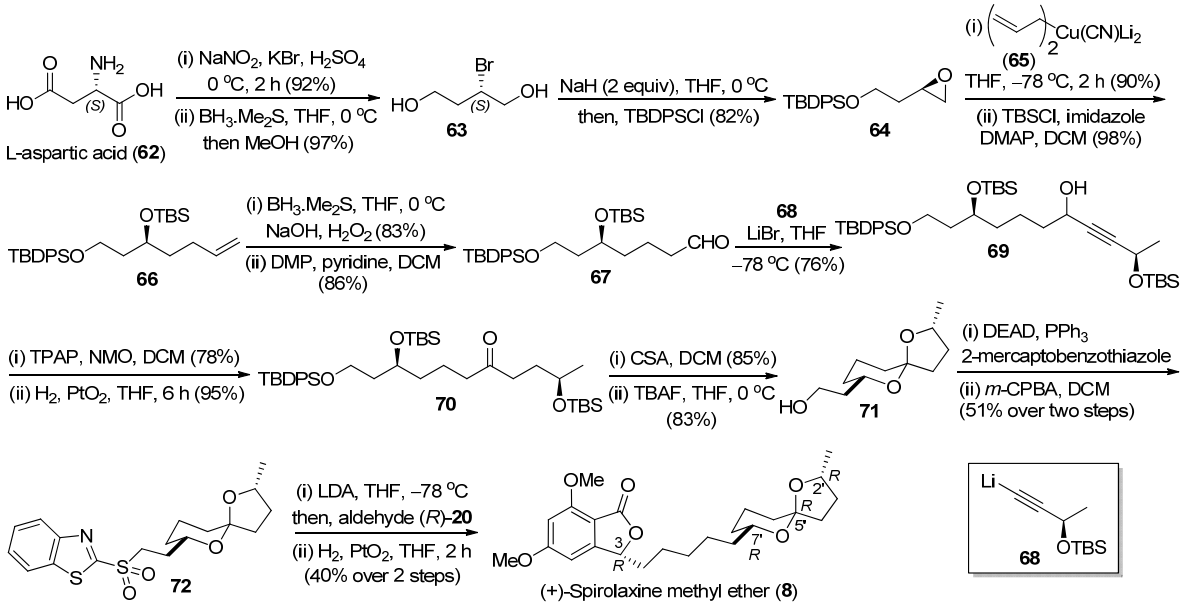
Brimble and co-workers[17] reported the first enantioselective synthesis of the anti-*Helicobacter pylori* agent (+)-spirolaxine methyl ether (**8**) in a convergent fashion by heterocycle-activated Julia olefination of a spiroacetal-containing sulfone fragment with a phthalide containing aldehyde fragment. The total synthesis of (+)-spirolaxine methyl ether (**8**) also establishes the absolute stereochemistry of the natural product to be (3*R*,2'*R*,5'*R*,7'*R*) (Scheme 10 and 11). The (3*R*)-stereochemistry in phthalide-aldehyde **20** was set up via titanium (+)-BINOL mediated asymmetric

allylation of 3,5-dimethoxybenzaldehyde (**61**) providing (*R*)-homoallylic alcohol **48** in 78% yield (86% ee). Regioselective bromination of the aromatic ring using NBS afforded the desired bromo-compound. Attempts to effect direct carboxylation of bromide proved fruitless. Hence the alcohol was converted to diethylcarbamate (*R*)-**49** with subsequent lithium-halogen exchange followed by intramolecular acylation and lactonisation provided phthalide the (*R*)-**50**. Elaboration of the allyl



Scheme 10. Synthesis of Enanatiomerically Pure Aldehyde Segment (*R*)-**20**

group via hydroboration and oxidation then provided the desired phthalide-aldehyde (*R*)-**20** (Scheme 10). For the synthesis of spiroketal sulfone **72** with the (2*R*',7*S*') configuration it was noted that (*R*)-epoxide **64** would a suitable starting material for introduction of the (*S*)-stereochemistry at C-7'. Additionally, lithium (*R*)-acetylide **68** can be used to form C-2 of the spiroketal ring with the desired (*R*)-stereochemistry (Scheme 11). Brominative diazotisation of L-aspartic acid (**62**) followed by



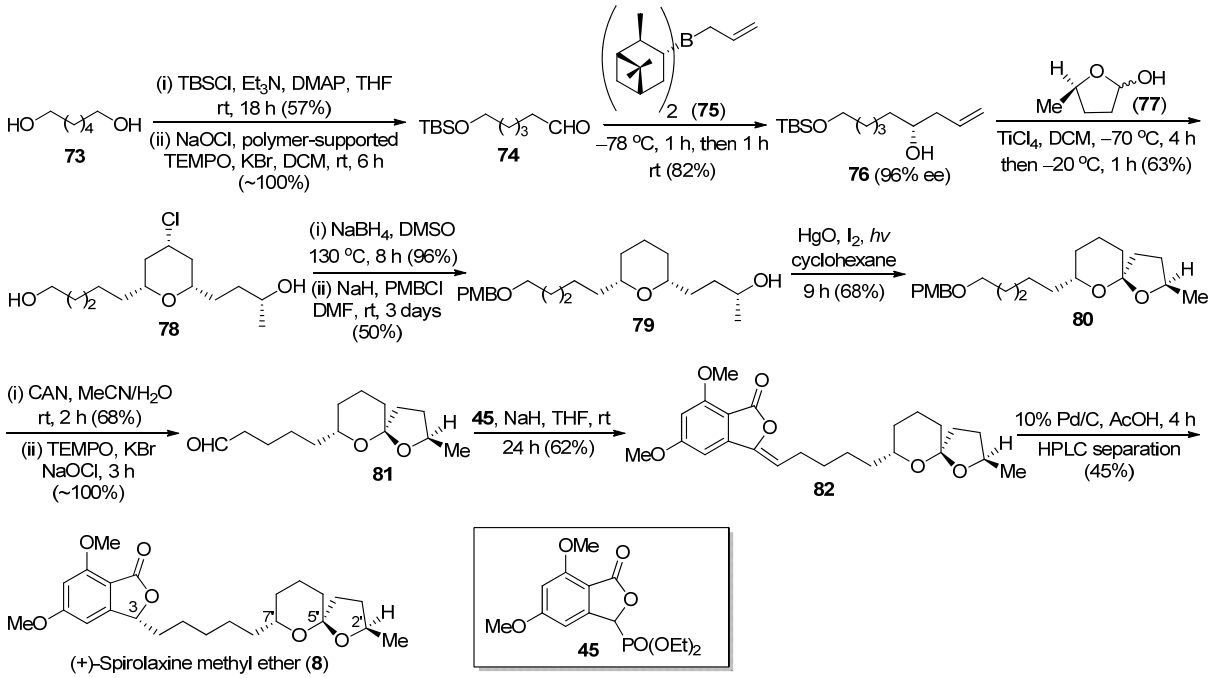
Scheme 11. Synthesis of (+)-Spirolaxine Methyl Ether via Heterocycle-Activated Julia-Kocienski Olefination

reduction of the carboxylic acid groups gave bromo-diol **63**. One-pot intramolecular cyclization of bromo-diol **63** and the subsequent protection of the primary alcohol as a silyl ether gave (*R*)-epoxide

64. Treatment of (*R*)-epoxide **64** with allyl cuprate **65** afforded a secondary alcohol that was protected as TBS-ether **66**. Subsequent hydroboration and oxidation of the resultant primary alcohol using Dess–Martin periodinane afforded aldehyde **67**. Addition of aldehyde **67** to lithium acetylide **68** at −78 °C in the presence of LiBr provided alcohol **69** in 76% yield. Oxidation of the alcohol to a ketone using TPAP/NMO, followed by reduction of the acetylene afforded the protected dihydroxyketone **70**. Deprotection of the TBS-ethers and facile spirocyclization was then readily effected using CSA to give spiroacetal, which was followed by cleavage of the TBDPS-ether with TBAF to form **71**. The bis-axial stereochemical orientation of spiroacetal **71** is the major thermodynamically-favoured isomer due to its stabilization by the anomeric affect. Conversion of the side chain alcohol group in spiroacetal **71** to sulfone **72** proceeded readily in two steps by treatment with mercaptobenzothiazole, PPh_3 and DEAD followed by oxidation using *m*-CPBA. With phthalide-aldehyde (*R*)-**20** and sulfone **72** in hand the key heterocycle-activated modified Julia-Kocienski olefination was undertaken. Thus treatment of sulfone **72** with LDA at −78 °C followed by the addition of phthalide-aldehyde (*R*)-**20** provided the olefin which on hydrogenation over PtO_2 gave (+)-spirolaxine methyl ether (**8**) in 40% yield.

2A.2.6 Dallavalle's Approach Towards (+)-Spirolaxine Methyl Ether

Dallavalle and co-workers[18] synthesized (+)-spirolaxine methyl ether (**8**) by taking advantage of Prins cyclization, to obtain the [6,5]-spiroketal system and a Wadsworth-Emmons condensation for the installation of the polymethylene chain on the phthalide moiety (Scheme 12). The spiroketal system was obtained by an oxidative cyclization of a hydroxyl alkyl-substituted tetrahydropyran **78** via Prins cyclization, which is a powerful synthetic route for the construction of these six-membered tetrahydropyran derivatives. The aldehyde **81** was prepared by protection of 1,6-hexanediol (**73**) to give the mono-silyl derivative which on oxidation with polymer-supported TEMPO gave aldehyde **74**. The (−)-*B*-allyldiisopinocamphenylborane (**75**) was obtained by treatment of (−)-Ipc_2OMe with allylmagnesium bromide at −78 °C. It was immediately subjected to a condensation with **74** at −78 °C to furnish the secondary homoallylic alcohol **76** in 82% yield [ee >96% confirmed by ^1H NMR in the presence of the chiral shift reagent $Eu(hfc)_3$]. With homoallylic alcohol **76** in hand, next focus was the preparation of chiral aldehyde **77** as a second building block for the introduction of the proper stereochemistry at C-2', which was easily obtained by the reduction of (*R*)-γ-valerolactone with *i*-Bu_2AlH. Prins cyclization between **76** and **77** was performed by using different Lewis acids, the use of $TiCl_4$ in dichloromethane at a low temperature afforded better yields and clean reaction mixture, leading to the desired chlorotetrahydropyran **78** with a 63% yield. Reductive dechlorination using the

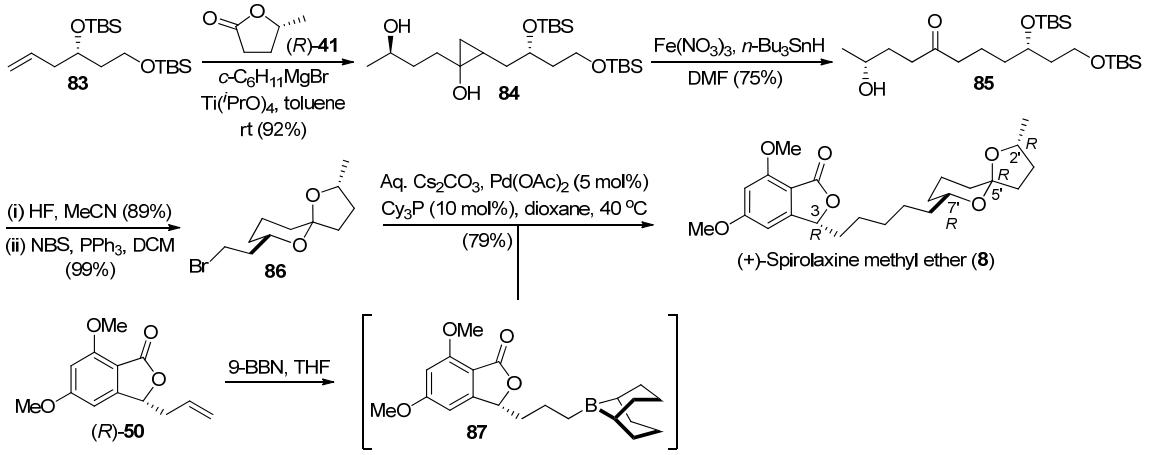


Scheme 12. Synthesis of (+)-Spirolaxine Methyl Ether via Wadsworth-Emmons condensation

Hutchins protocol ($NaBH_4$ in DMSO) gave required tetrahydropyran in good yield (96%). The primary alcohol was protected as a PMB-ether **79**, followed by HgO/I_2 mediated oxidative cyclization gave the desired spiroketal **80** in 68% yield. Deprotection of the PMB group gave the free hydroxyl moiety which was oxidized with TEMPO to obtain the desired aldehyde **81**. The condensation of the aldehyde **81** with phthalide **45** afforded the alkene **82** as a mixture of *E*/*Z* stereoisomers. Finally, reduction of the double bond in AcOH using Pd/C (10%) as a catalyst led to a mixture of two diastereoisomers, from which (+)-spirolaxine methyl ether (**8**) was separated by preparative HPLC.

2A.2.7 Phillips's Approach Towards (+)-Spirolaxine Methyl Ether

Phillips and co-workers[19] reported the synthesis of (+)-spirolaxine methyl ether (**8**) via a Kulinkovich cyclopropanation and subsequent cyclopropanol opening followed by Fu's alkyl-alkyl Suzuki coupling (Scheme 13). The synthesis commences with the coupling of readily available olefin **83** with commercially available (*R*)-γ-valerolactone (**41**) in the presence of cyclohexylmagnesium bromide and Ti(*i*-PrO)$_4$ in toluene at room temperature to afford Kulinkovich cyclopropanation product **84** in 92% yield. Immediate exposure of cyclopropanol **84** to $Fe(NO_3)_3$ and *n*-Bu_3SnH provided ketone **85** in 75% yield. Deprotection of the TBS group and concomitant spiroketal formation proceeded smoothly upon exposure of **85** to HF to yield spiroketal alcohol in 89% yield. Subsequent Appel reaction of alcohol with NBS and PPh_3 proceeded in quantitative yield to give primary bromide **86**. At this juncture, the alkyl-alkyl Suzuki coupling recently reported by Fu[20] was sought for the union of the two

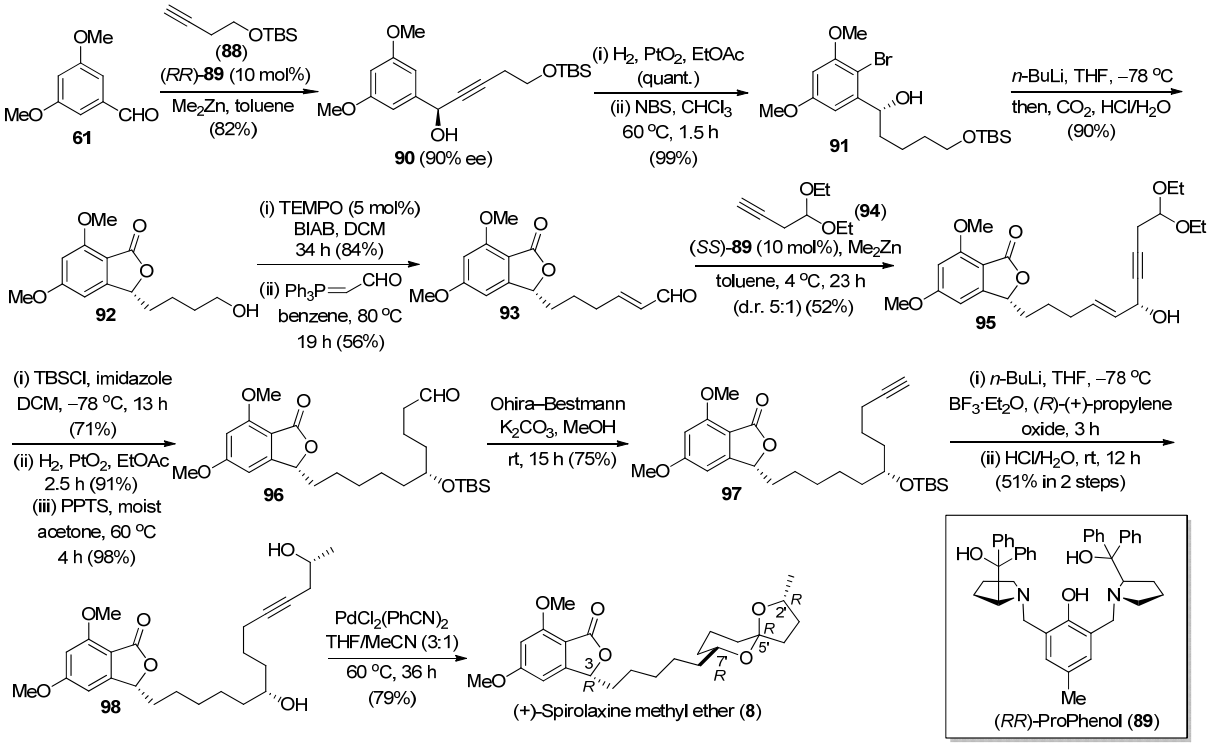


Scheme 13. Synthesis of (+)-Spirolaxine Methyl Ether via Fu's Alkyl-Alkyl Coupling

halves of the target. A solution of olefin (*R*)-**50** in THF (prepared by Brimble's route)[17] was treated with 9-BBN at 25 °C to yield intermediate borane **87**, which was coupled with alkyl bromide **86** in the presence of aqueous Cs_2CO_3, $Pd(OAc)_2$ (5 mol %) and Cy_3P (10 mol %) in dioxane to directly yield (+)-spirolaxine methyl ether (**8**) in 79% yield.

2A.2.8 Trost's Approach Towards (+)-Spirolaxine Methyl Ether

Trost and co-workers[21] synthesized (+)-spirolaxine methyl ether (**8**) in 13 steps using an alkyne-based strategy. The stereochemistry in both the phthalide portion and the spiroketal portion were established by ProPhenol catalyst (**89**) controlled asymmetric alkynylation chemistry (Scheme 14). The enantioselective addition of terminal alkynes to aldehydes is an active field of research and many efficient and complimentary catalyst systems have been designed. The ProPhenol-catalyzed addition of 4-(tert-butyldimethylsilyloxy)-1-butyne (**88**) to 3,5-dimethoxybenzaldehyde (**61**) led to high yield and enantiomeric excess of the desired propargylic alcohol **90** (82% yield, 89–90% ee). Mild hydrogenation of alkyne **90** with the Adams catalyst in ethyl acetate furnished the saturated alkane followed by its regioselective bromination gave **91** in nearly quantitative yield. Bromo alcohol **91** on treatment with *n*-BuLi (2.2 equiv) at −78 °C for one minute then, rapidly flushing the reaction with CO_2 gas to trap the aryl lithium species followed by acidic workup gave phthalide **92** in high yield (90%) with concomitant cleavage of silyl group. Oxidation of the primary alcohol **92** and homologation using Wittig olefination gave access to enal **93**. At this stage, a second ProPhenol-catalyzed asymmetric alkynylation was employed to set the stereochemistry of the distal stereogenic center and to construct the carbon skeleton. Catalyst-controlled diastereoselective alkynylation of enal **93** with 4,4-diethoxybut-1-yne (**94**) gave access to the desired propargylic alcohol **95** without disturbing the relatively sensitive phthalide group. The diastereomeric ratio and absolute config-

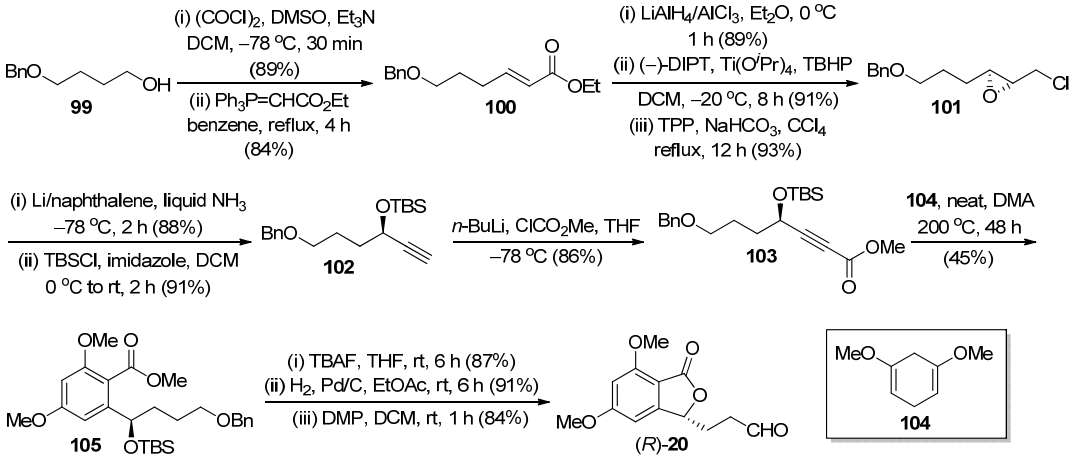


Scheme 14. Synthesis of (+)-Spirolaxine Methyl Ether

uration of this new stereocenter was determined by formation of the mandelate ester. Alcohol **95** was silylated, which was followed by the complete reduction to the fully saturated chain. Hydrolysis of the diethyl acetal furnished the silyl protected alkoxy aldehyde **96**. Homologation of aldehyde **96** to the terminal alkyne **97** with preservation of the phthalide was accomplished by the mild Ohira–Bestmann alkynylation. Addition of the alkyne **97** to *R*-(+)-propylene oxide assisted by a Lewis acid gave the corresponding homopropargylic alcohol and subsequent treatment with HCl effectively removed the TBS group to furnish the diol **98**. The spiroketalization of **98** was promoted by $PdCl_2(PhCN)_2$ which gave the desired natural product (+)-spirolaxine methyl ether (**8**) in 79% yield.

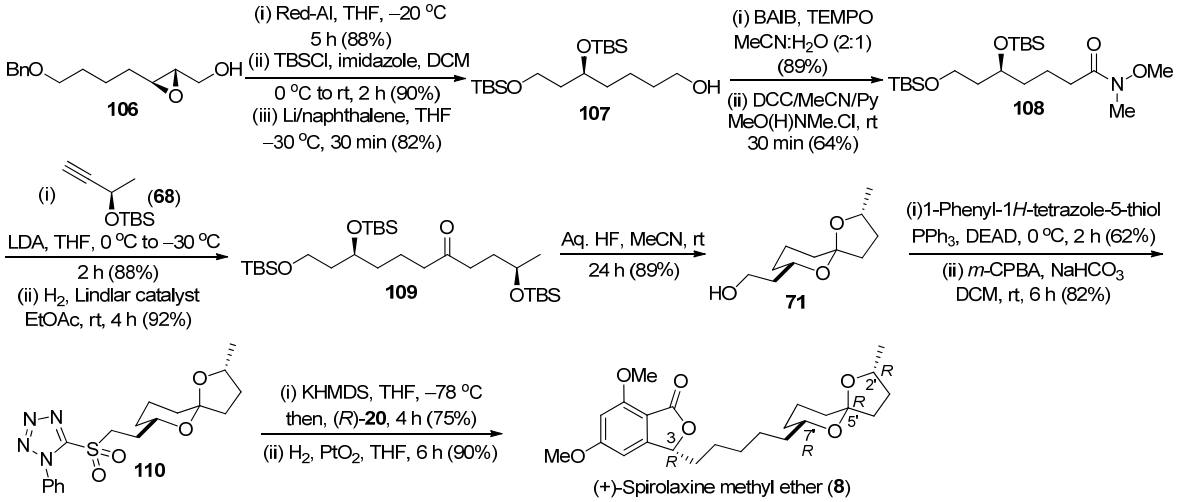
2A.2.9 Yadav's Approach Towards (+)-Spirolaxine Methyl Ether

Yadav and co-workers[22] reported the total synthesis of (+)-spirolaxine methyl ether (**8**) in which phthalide-aldehyde (*R*)-**20** has been prepared via the Diels-Alder reaction between 1,4-unconjugated diene **104** and a long-chain acetylenic dienophile **103**. The carbon framework of spiroketal sulfone **110** has been constructed from monobenzyl protected 1,5-pentanediol and the stereochemistry in both the phthalide portion (*R*)-**20** and the spiroketal portion **71** has been established by the Sharpless asymmetric epoxidation (Scheme 15 and 16). The synthesis of phthalide-aldehyde (*R*)-**20** started from a known monobenzyl ether **99**, which was oxidized to the corresponding aldehyde and further homologated by a two-carbon Wittig olefination to afford α,β-unsaturated ester (*E*-isomer) **100** as



Scheme 15. Synthesis of Phthalide Aldehyde (*R*)-**20** via Diels-Alder Reaction

the sole product. Reduction of compound **100** with $LiAlH_4/AlCl_3$ afforded an allylic alcohol in 87% yield, which on Sharpless asymmetric epoxidation with (–)-DIPT, $Ti(iPrO)_4$ and TBHP at –20 °C furnished epoxy alcohol in 91% yield (94% ee) and its subsequent reaction with PPh_3 in CCl_4 gave **101** in 93% yield. The compound **101** on base-induced dehydrohalogenation gave alkynol which on silylation gave **102**. Treatment of the TBS protected alkyne **102** with *n*-BuLi followed by addition of methyl chloroformate gave a long-chain acetylenic ester **103** in 84% yield. Subsequently Alder-Rickert reaction of diene **104** with acetylenic dienophile **103** was carried out by heating 2:1 ratio of diene **104** and acetylenic dienophile **103** in a sealed tube at 200 °C in the presence of a catalytic amount of *N*,*N*'-dimethylaniline to obtain the aromatic precursor **105** in 45% yield. The amount of *N*,*N*'-dimethylaniline plays a crucial role in the Diels-Alder reaction, notably the use of a very minute quantity of *N*,*N*'-dimethylaniline affords the product in higher yield. Surprisingly, no Diels-Alder



Scheme 16. Synthesis of (+)-Spirolaxine Methyl Ether

reaction was observed in the absence of *N*,*N*'-dimethylaniline. Deprotection of silyl ether with TBAF in THF gave the benzyl-protected phthalide-alcohol, which on debenzylation followed by oxidation with Dess-Martin periodinane gave the phthalide-aldehyde (*R*)-**20** in 84% yield (Scheme 15). For the synthesis of spiroketal part, **106** was synthesized via Sharpless asymmetric epoxidation of the corresponding allyl alcohol. Reductive opening of epoxy alcohol **106** with Red-Al afforded diol in good yield. The diol was protected as silyl ether and then subjected to debenzylation to give alcohol **107**, which on subsequent oxidation with TEMPO/BAIB gave acid which was converted into its Weinreb amide **108**. Treatment of the alkyne **68** with LDA followed by addition of the Weinreb amide **108** and a subsequent hydrogenation with the Lindlar catalyst gave the corresponding ketone **109** in excellent yield. Compound **109** was subjected to TBS-ether deprotection and a subsequent spiroketolization by treatment with aqueous HF in acetonitrile to give thermodynamically stable 6,5-spiroketal **71** in 84% yield. Conversion of the side chain alcohol of spiroketal **71** into sulfone **110** proceeded readily in two steps by treatment with 1-phenyl-1H-tetrazole-5-thiol, PPh_3 and DEAD followed by oxidation with *m*-CPBA. The key heterocycle-activated modified Julia olefination was carried out with phthalide-aldehyde (*R*)-**20** and sulfone **110**. Thus treatment of sulfone **110** with phthalide-aldehyde (*R*)-**20** in the presence of KHMDS at −78 °C gave the olefin as a mixture of *trans*- and *cis*-isomers. Reduction of olefin (*trans*/*cis*) with PtO_2 under H_2 atmosphere gave the target (+)-spirolaxine methyl ether (**8**) in 72% yield (Scheme 16).

2A.3 Summary

In summary, we have presented a concise literature account on the synthesis of CJ-13,015, CJ-13,102, CJ-13,103, CJ-13,104, CJ-13,108, CJ-12,954/CJ-13,014, sporotricale methyl ether and (+)-spirolaxine methyl ether. The key reactions that were employed to efficiently accomplish the synthesis of above mentioned bioactive natural products were S_N2 coupling reactions of 5,7-dimethoxyphthalide carbanion, Wittig reaction of a key phthalide-aldehyde with the ylide, heterocycle-activated Julia-Kocienski olefination, Wadsworth-Emmons condensation, Fu's alkyl-alkyl coupling, ProPhenol catalyst controlled asymmetric alkynylation and Sharpless asymmetric epoxidation. Overall, several remarkable approaches to these target compounds have been known in the literature. Our synthetic studies towards the synthesis of these natural products have been discussed in details in the section B of the present chapter.

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CHAPTER 2: SECTION B

Facile Racemic Synthesis of *Helicobacter Pylori* Antibiotics and An Efficient Convergent Access to Spiroketal Segment of (+)-Spiroxaline Methyl Ether

This section B of chapter 2 features the following topics:

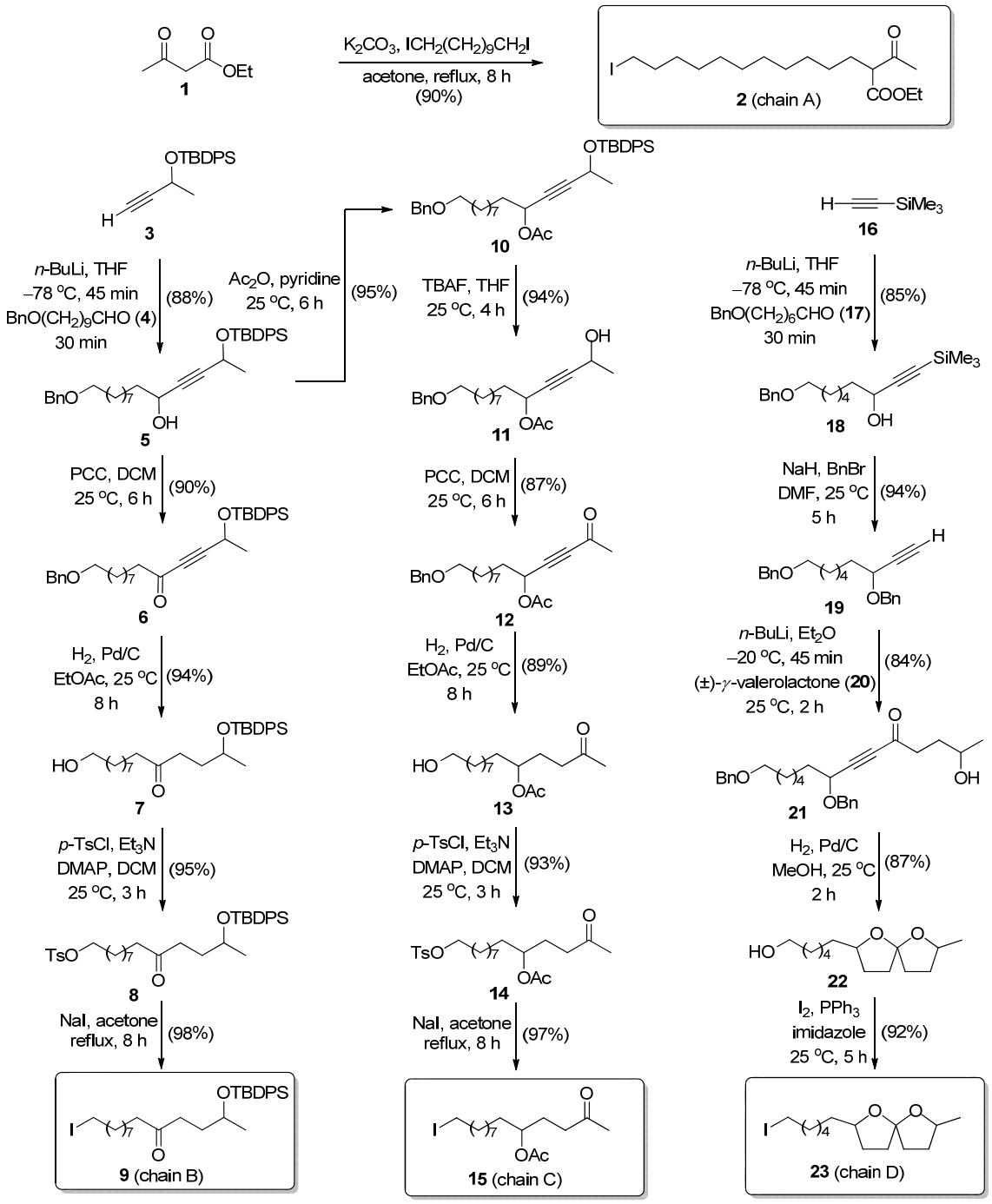
2B.1 Rationale of the Present Work

It is evident from the discussion in section A that the novel microbial secondary metabolites CJ-13,015, CJ-13,102, CJ-13,103, CJ-13,104, CJ-13,108, CJ-12,954/CJ-13,014, sporotricale methyl ether and (+)-spirolaxine methyl ether provide promising new leads for the treatment of *Helicobacter pylori*-related diseases. The high clinical potential of these natural products makes them an attractive synthetic target and the provision of short and efficient synthetic routes to these target molecules is an imperative task of current interest. In continuation of our ongoing work on bioactive natural product synthesis, we have designed an efficient synthetic route to CJ-13,015, CJ-13,102, CJ-13,104, CJ-13,108, CJ-12,954/CJ-13,014 and sporotricale methyl ether via a highly chemoselective coupling reactions of 5,7-dimethoxyphthalide carbanion with the remotely functionalized long chain alkyl iodides. The synthesis of pivotal spiroketal segment of (+)-spirolaxine methyl ether has been accomplished via a stepwise alkylation and acylation of an alkyne with two different readily available chiral building blocks followed by the reductive in situ regio- and stereoselective spiroketalization pathway.

2B.2 Results and Discussion

2B.2.1 Chemoselective Coupling Reactions of 5,7-Dimethoxyphthalide with the Remotely Functionalized Alkyl Iodides: Facile Racemic Synthesis of *Helicobacter pylori* Antibiotics

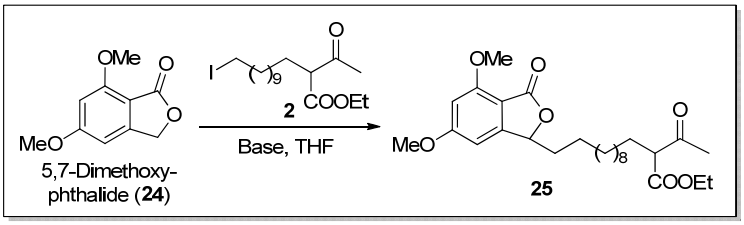
A careful scrutiny of structures of all the CJ-molecules revealed that they are the remotely monofunctionalized, bifunctionalized, and latent trifunctionalized 3-alkyl-substituted 5,7-dimethoxyphthalides. We envisaged the stepwise preparation of the desired long chain alkyl iodides (**A**-**D**) starting from ethyl acetoacetate (**1**) and two different suitably substituted acetylene derivatives **3**/**16** via the alkylation/condensation with aliphatic aldehydes, followed by the systematic functional group interconversions (Scheme 1). The base-catalyzed selective mono coupling of ethyl acetoacetate (**1**) with 1,11-diiodoundecane in refluxing acetone furnished the desired chain A (**2**) in 90% yield. The base-catalyzed coupling of TBDPS protected acetylene derivative **3** with the *ω*-*O*-benzyl protected aliphatic aldehyde **4** followed by the PCC-oxidation of thus formed secondary alcohol furnished the ketone **6**. The ketone **6** on catalytic hydrogenation underwent both the debenzylation and reduction of carbon–carbon triple bond in one pot to provide the reduced desired product **7**. The silyl-protected keto-alcohol **7** on tosylation followed by treatment with sodium iodide gave the desired chain B (**9**) with 69% overall yield in five steps. The common intermediate **5** on acylation gave **10**, then followed by desilylation provided the secondary alcohol **11** which on PCC-



Scheme 1. Synthesis of Remotely Functionalized Long Chain Alkyl Iodides A-D

oxidation gave the ketone **12**. The ketone **12** on catalytic hydrogenation gave the expected debenzylated reduced product **13**, which on tosylation followed by treatment with sodium iodide gave the desired chain C (**15**) with 51% overall yield in seven steps. Trimethylsilylacetylene (**16**) on reaction with the *O*-benzyl protected requisite aliphatic aldehyde **17** followed by benzyl protection of the formed secondary alcohol **18** directly furnished an in situ desilylated acetylene derivative **19**. Compound **19** on base-catalyzed condensation with the (±)-γ-valerolactone (**20**) provided the keto-

alcohol **21**. The product **21** on catalytic hydrogenation formed the double debenzylated saturated ketone as an unstable intermediate, which on rapid intramolecular dehydrative double cyclization provided the spiro-alcohol **22**. The alcohol **22** on treatment with iodine and triphenylphosphine gave the desired chain D (**23**) with 54% overall yield in five steps. Thus we accomplished the smooth preparation of the desired remotely functionalized alkyl iodide long chains A-D in a concise and efficient fashion via the appropriate functional group interconversion pathways.



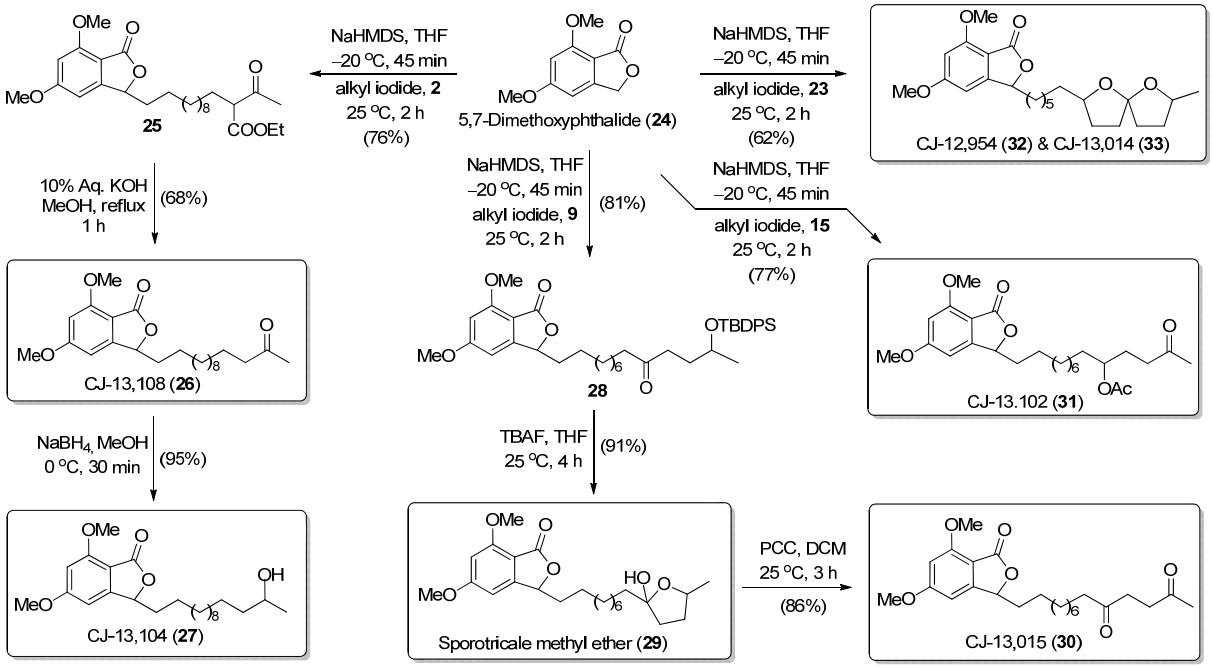
Sr. No.	Base	Additive	Temp. °C	% Yield
1	DBU	–	0	NR[a]
2	Et_3N	–	0	NR[a]
3	NaH	–	0	NR[a]
4	*n*-BuLi	–	–78 to 0	NR[a]
5	*s*-BuLi	–	–78	5
6	LDA	–	–78	41
7	LDA	HMPA	–78	40
8	LDA	DMPU	–78	38
9	NaHMDS (1 M in THF)	–	–78	55
10	NaHMDS (1 M in THF)	–	–20	76
11	LiHMDS (1 M in THF)	–	–20	NR[a]
12	KHMDS (0.5 M in toluene)	–	–20	NR[a]

[a]No reaction

Table 1. Optimization of Coupling Reaction Conditions

The phthalides are widely used building blocks in organic synthesis and the generated benzylic carbanions on them are known to react with acid chlorides, imines, alkyl halides, aldehydes and esters.[1,2] The preferred reactivity of phthalide carbanions toward S_N2-displacements of halides versus addition to the carbonyl groups has not been studied previously. The alkyl iodide chains A-D contain remotely placed ketone/ester, silyloxyketone, acetoxyketone and spiroketal units respectively. We developed a systematic plan to generate a 5,7-dimethoxyphthalide carbanion and study its chemoselective coupling reactions with the primary alkyl iodide chains A-D with the expectation that the stabilized benzylic carbanion will be competing for an S_N2 substitution reaction over the 1,2-addition reactions. We screened bases such as triethylamine, DBU, NaH, *n*-BuLi, *s*-BuLi, LDA, NaHMDS, LiHMDS and KHMDS for the generation of the necessary benzylic carbanion on 5,7-dimethoxyphthalide (**24**) and studied the chemoselective coupling reactions with the primary alkyl

iodide chain A (**2**) (Table 1). In our hands the bases triethylamine, DBU, NaH, and *n*-BuLi (entries 1-4) were ineffective in inducing the coupling of 5,7-dimethoxyphthalide (**24**) with the alkyl iodide chain A (**2**). The use of *s*-BuLi (entry 5) as the base for the coupling of **24** with iodide **2** gave the desired product **25**, but only in 5-6% yield. The use of LDA (entry 6) also gave the desired product in 41% yield along with the formation of side products. It is well known that the use of additives such as HMPA and DMPU can increase the state of aggregation around the carbocation (by coordination with the counter cation; $Li^+/Na^+/K^+$) and thus can make carbanion more reactive for the nucleophilic attack. However, in our case the use of HMPA and DMPU (entry 7 and 8) did not reflect any marked change on the yields. By changing the base from LDA to NaHMDS (entry 9) we observed slight increase in the yield from 41% to 55%. At this stage we decided to increase the temperature from −78 to −20 °C and this proved to be the decisive factor as we obtained the coupling product **25** in 76% yield (entry 10). However, no coupling product **25** was observed when LiHMDS or KHMDS (entry 11 and 12) was used as a base.



Scheme 2. Chemoselective Alkylation of 5,7-Dimethoxyphthalide: Synthesis of CJ-Compounds

The chemoselective reaction of benzylic carbanion from 5,7-dimethoxyphthalide (**24**, 1.00 equiv), generated by using NaHMDS (1.10 equiv) as the base, with alkyl iodide chain A (**2**) (1.00 equiv) exclusively furnished the expected coupled product **25** in 76% yield via the S_N2-displacement pathway (Scheme 2). On the basis of formation of product **25**, we feel that the S_N2-displacement of primary alkyl iodide in chain A with the benzylic carbanion of phthalide **24** is faster than the deprotonation of the acidic methine proton in chain A by the phthalide carbanion. The base-

catalyzed hydrolysis of ester moiety in compound **25** followed an in situ decarboxylation of the intermediate β-keto acid furnished the desired bioactive natural product CJ-13,108 (**26**) in 68% yield.

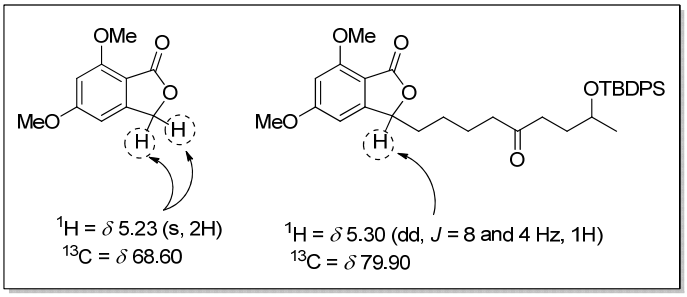
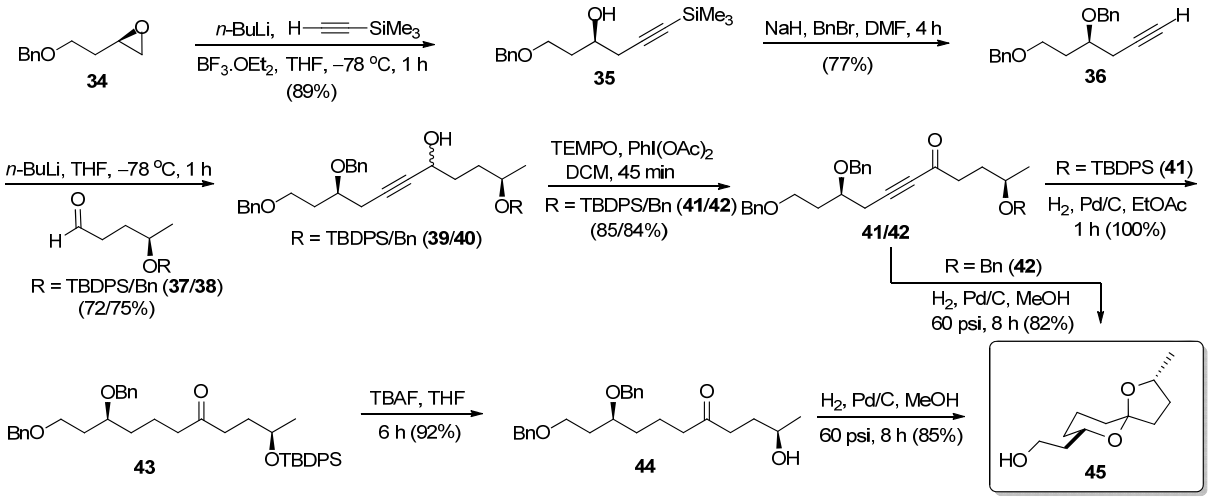


Figure 1. Comparison of ^{1}H and ^{13}C NMR values

Chemoselective $NaBH_4$-reduction of the ketone moiety in **26** furnished the desired bioactive natural product in the series, the CJ-13,104 (**27**) in 95% yield. Similarly, the chemoselective reaction of benzylic carbanion from 5,7-dimethoxyphthalide (**24**) with chain B (**9**) furnished the product **28**, which on desilylation gave the natural product sporotricale methyl ether (**29**). In solution the compound **29** displays a ring-chain tautomerism, chloroform (hemiketal)/acetone (hydroxyketone). Compound **29** on PCC-oxidation provided the CJ-13,015 (**30**) in very good yield. Finally, the chemoselective couplings of the phthalide carbanion with chain C (**15**) and chain D (**23**) respectively furnished the desired products CJ-13,102 (**31**) and a diastereomeric mixture of CJ-12,954/CJ-13,014 (**32**)/(**33**). The formation of these coupling products was supported by change in the ^{1}H and ^{13} C NMR values of starting material and coupling products. The benzylic proton (C–H) in coupling product shows a characteristic dd at δ5.30 in ^{1}H NMR, whereas in ^{13}C NMR a peak δ79.90 is characteristic of benzylic carbon (Figure 1). The analytical and spectral data obtained for CJ-13,015 (**30**), CJ-13,102 (**31**), CJ-13,104 (**27**), CJ-13,108 (**26**), CJ-12,954/CJ-13,014 (**32**)/(**33**) and sporotricle methyl ether (**29**) were in complete agreement with the reported data[3,4] and were obtained in one to three steps with very good overall yields. These results clearly demonstrate the preferential S_N2 displacement ability of the NaHMDS-generated phthalide carbanion over the 1,2-addition to carbonyl groups.

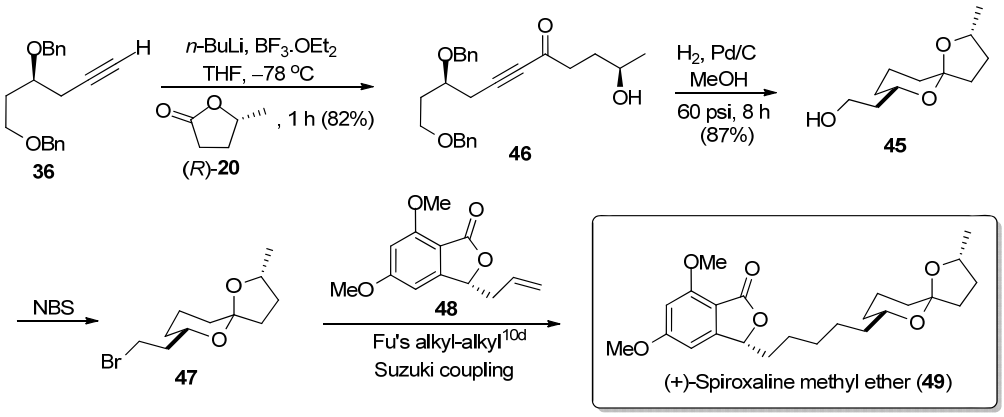
2B.2.2 An Efficient Convergent Access to Spiroketal Segment of (+)-Spiroxaline Methyl Ether

Complementary to Trost and Weiss alkyne strategy, our synthesis of important spiroketal system also began with TMS-protected acetylene. Regioselective ring opening of an enantiomerically pure (*R*)-oxirane **34** (~100% ee)[5] with the trimethylsilylacetylene carbanion exclusively provided the required alkynol **35** in 89% yield (Scheme 3). Chemoselective *O*-benzyl protection of the formed secondary alcohol **35** directly furnished the in situ desilylated required acetylene derivative **36** in 77% yield. Condensation of the acetylenic carbanion of **36** with the enantiomerically pure TBDPS-protected



Scheme 3. Syntheses of (+)-Spiroketal Segment via Two Partially Separate Routes

aldehyde **37**[6] yielded the chromatographically inseparable diastereomeric mixture of **39** (~1:1, by NMR spectroscopy) in 72% yield. TEMPO-oxidation of obtained secondary alcohol **39** supplied the required alkynone **41** in 85% yield. Unfortunately, all our attempts for the TBAF-induced deprotection of TBDPS group in compound **41** failed and we always ended up with the formation of decomposed materials. Assuming that the alkyne unit in compound **41** is not stable to our TBDPS-deprotection conditions, the chemoselective carbon–carbon triple bond reduction in the alkyne **41** was attempted under very mild catalytic hydrogenation conditions, and fortunately it provided the



Scheme 4. Concise and Efficent Formal Synthesis of (+)-Spiroxaline Methyl Ether

desired single product **43** in ~100% yield. Our speculation about the triple bond delicacy was true and the TBDPS group deprotection in the corresponding reduction product **43** made available the stable compound **44** in 92% yield. The compound **44** on catalytic hydrogenolysis of two *O*-benzyl groups underwent regio- and stereoselective concomitant spiroketalization to furnish the essential product (+)-**45** in 85% yield. At this stage we could sense that it would be feasible to curtail down the two steps in the above mentioned synthesis progression by avoiding the TBDPS protection. Thus, the

reaction of an alkyne carbanion of **36** was performed with the enantiomerically pure benzyl-protected aldehyde **38**[7] yielding the column inseparable diastereomeric mixture **40** (~2:3, by ^{1}H NMR spectroscopy) in 75% yield. The obtained product **40** on TEMPO oxidation (84%) followed by simultaneous catalytic hydrogenation of triple bond and hydrogenolysis of three *O*-benzyl groups again directly furnished the diastereomerically pure compound (+)-**45** in 82% yield.

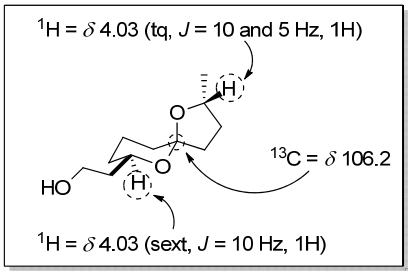


Figure 2. ^{1}H and ^{13} C NMR values of (+)-spiroketal segment

Finally, we deliberated for the acylation of alkyne **36** with the appropriate chiral lactone to avoid the involved secondary alcohol to ketone TEMPO-oxidation step in Scheme 3 to formulate the still one step shorter execution of spiroketal **45** synthesis (Scheme 4). Indeed the reaction of an acetylenic carbanion of **36** with commercially available enantiomerically pure (*R*)-γ-valerolactone (**20**) provided the stable alkynonol **46** in 82% yield via the nucleophilic lactone ring opening. Alkynonol **46** under the catalytic hydrogenation conditions, once again directly furnished the diastereomerically pure compound (+)-**45** in 87% yield. Characteristic ^{1}H and ^{13}C NMR values of spiroketal segment of (+)-spirolaxine methyl ether have been shown in Figure 2. Thus starting from oxirane **34**, the desired (+)-spiroketal **45** was obtained in just four steps in 49% overall yield and the obtained analytical and spectral data for (+)-**45** were in complete agreement with the reported data.[8,9,10] The quantitative NBS-induced conversion of spiroalcohol **45** to spiro-bromide **47** and its alkyl–alkyl Suzuki coupling with the enantiomerically pure (*R*)-3-allyl-5,7-dimethoxyisobenzofuran-(3*H*)-one (**48**)[10f] that delivered the final product, the (+)-spiroxaline methyl ether (**49**) with 79% yield have been well established in the literature.[10d]

2B.3 Summary

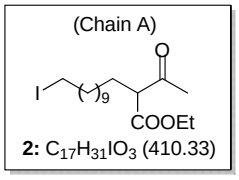
In summary, we have reported a practical synthesis of remotely functionalized important natural products, the CJ-molecules, by taking advantage of highly chemoselective carbon–carbon bond forming reactions of phthalide with the functionalized alkyl iodides. We feel that in the present approach, the remarkably chemoselective displacements of primary iodides by the 5,7-dimethoxyphthalide carbanion, specifically in the presence of a free ketone and ester moieties are noteworthy.

We have also accomplished a concise and efficient formal synthesis of the enantiomerically and diastereomerically pure bioactive natural product (+)-spiroxaline methyl ether by using readily available appropriate chiral building blocks, utilizing the most promising alkynes reactivity paradigm. In the present four-step approach variety of desired bond forming and bond breaking processes take place under the set of our applied four reaction conditions and hence represents a nice illustration of bond-forming bond-cleaving economy. Our approach is general in nature and will be useful in designing a focused minilibrary of analogous and congeners of CJ-molecules for SAR studies.

2B.4 Experimental Section

Commercially available NaHMDS, $NaBH_4$, ethyl acetoacetate, *n*-BuLi, pyridinium chlorochromate, Pd on charcoal (10 wt%), *p*-toluenesulfonyl chloride, tetrabutylammonium fluoride, sodium hydride, benzyl bromide, (±)-γ-valerlactone, iodine, triphenylphosphine, trimethylsilylacetylene, $BF_3{\cdot}OEt_2$, TEMPO, iodobis(acetoxy)benzene, (*R*)-γ-valerolactone were used. 5,7-Dimethoxyphthalide (**24**) and (*R*)-2-[2-(Benzyloxy)ethyl]oxirane (**34**) were prepared using the known procedures.[11,5]

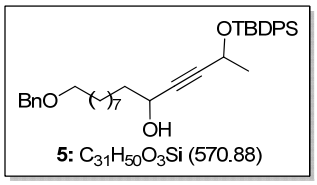
Ethyl 2-acetyl-13-iodotridecanoate (Chain A, 2). Powdered K_2CO_3 (1.21 g, 8.82 mmol) was added to a stirred solution of 1,11-diiodoundecane (1.00 g, 2.45 mmol) and ethyl acetoacetate (**1**, 0.40 mL, 3.18 mmol) in acetone (25 mL). The reaction mixture was stirred and heated under reflux for 8 h under nitrogen and then concentrated in vacuo to remove acetone. The obtained residue was diluted with water and extracted with ethyl acetate (2 X 20 mL). The combined ethyl acetate extract was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (95:5) as an eluent afforded pure product **2** (side chain A) as a thick oil (904 mg, 90%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.15–1.50 (m, 19H), 1.65–1.93 (m, 4H), 2.23 (s, 3H), 3.19 (t, *J* = 8 Hz, 2H), 3.40 (t, *J* = 8 Hz, 1H), 4.20 (q, *J* = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 7.3, 14.1, 27.3, 28.1, 28.5,



2: $C_{17}H_{31}IO_3$ (410.33)

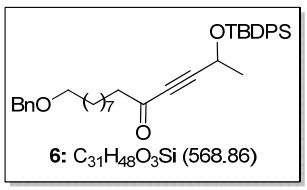
28.7, 29.23, 29.24, 29.3, 29.42, 29.44, 30.4, 33.5, 59.9, 61.2, 169.9, 203.4; Anal. Calcd for $C_{17}H_{31}IO_3$: C, 49.76; H, 7.61. Found: C, 49.93; H, 7.85; IR ($CHCl_3$) ν_{max} 3436, 1738, 1713 cm^{-1}.

14-Benzyloxy-2-(*tert*-butyldiphenylsilanyloxy)tetradec-3-ynol (5). *n*-BuLi (1.60 M in hexane, 8.01 mL) was added to a stirred solution of alkyne **3** (3.94 g, 12.82 mmol) in THF (30 mL) at –78 °C and stirred further for 45 min, followed by the addition of 10-benzyloxy-decanal (**4**, 2.80 g, 10.68 mmol) in THF (10 mL). The reaction mixture was stirred at –78 °C for 30 min. The reaction was quenched with saturated NH_4Cl solution (5 mL) and then concentrated in vacuo. To the obtained residue was added ethyl acetate (50 mL) and the separated organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (9:1) as an eluent afforded pure product **5** as a thick oil (5.30 g, 88%). ^{1}H NMR ($CDCl_3$, 200 MHz) (diastereomeric mixture) δ 1.06 (s, 9H), 1.26 (br s, 12H), 1.41 (d, *J* = 8 Hz, 3H), 1.45–1.55 (m, 2H), 1.61 (quintet, *J* = 6 Hz, 2H), 3.46 (t, *J* = 6 Hz, 2H), 4.08–4.25 (m, 1H), 4.50 (s, 2H), 4.53 (q, *J* = 6 Hz, 1H), 7.25–7.50 (m, 11H), 7.63–7.80 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.1, 25.0, 25.1, 26.2, 26.8, 29.2, 29.4, 29.5, 29.8, 37.5, 59.9, 62.3, 70.5, 72.8, 84.9, 87.1, 127.4, 127.6, 128.3, 129.6, 133.7, 134.0, 135.8, 136.0, 138.7; ESIMS (*m*/*z*) 593 $[M+Na]^+$; Anal. Calcd for $C_{31}H_{50}O_3Si$: C, 77.84; H, 8.83. Found: C, 77.50; H, 8.75; IR ($CHCl_3$) ν_{max} 3606, 2253 cm^{-1}.



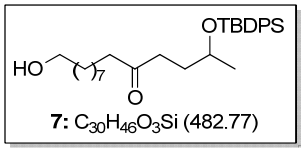
5: $C_{31}H_{50}O_3Si$ (570.88)

14-Benzyloxy-2-(*tert*-butyldiphenylsilanyloxy)tetradec-3-yn-5-one (6). To a stirred suspension of pyridinium chlorochromate (1.13 g, 5.26 mmol) and 4 Å molecular sieves in dichloromethane (40 mL) at 0 °C was added alcohol **5** (2.00 g, 3.50 mmol) in dichloromethane (10 mL). After 6 h of stirring at 25 °C, the reaction mixture was diluted with diethyl ether (10 mL). The resulting reaction mixture was filtered through Celite pad and the filtrate was concentrated in vacuo. Silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (95:5) as an eluent afforded pure product **6** as a thick oil (1.87 g, 90%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.07 (s, 9H), 1.27 (br s, 10H), 1.46 (d, *J* = 6 Hz, 3H), 1.50–1.70 (m, 4H), 2.36 (t, *J* = 8 Hz, 2H), 3.46 (t, *J* = 6 Hz, 2H), 4.50 (s, 2H), 4.59 (q, *J* = 6 Hz, 1H), 7.25–7.50 (m, 11H), 7.63–7.78 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.1, 23.8, 24.3, 26.2, 26.7, 28.9, 29.36, 29.39, 29.7, 45.2, 59.7, 70.5, 72.8, 82.7, 93.4, 127.4, 127.6, 128.3, 129.85, 129.94, 133.1, 135.7, 135.9, 138.7, 187.9; ESIMS (*m*/*z*) 591 $[M+Na]^+$; HRMS (ESI) calcd for $C_{31}H_{48}O_3SiNa^+$ 591.3270, found 591.3276; IR ($CHCl_3$) ν_{max} 2254, 1673 cm^{-1}.



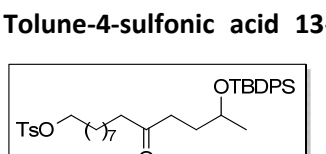
6: $C_{31}H_{48}O_3Si$ (568.86)

2-(*tert*-Butyldiphenylsilanyloxy)-14-hydroxytetradecan-5-one (7). Palladium on carbon (10 wt%) was added to the stirred solution of compound **6** (2.30 g, 4.04 mmol) in ethyl acetate (20 mL) at 25 °C. The reaction mixture was stirred under H_2 atmosphere (50 psi) for 8 h and filtered through a pad of Celite. Removal of the solvent in vacuo followed by the silica gel column chromatography of the obtained residue using petroleum ether–ethyl acetate (85:15) as an eluent afforded pure product **7** as a thick oil (1.83 g, 94%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.05 (s, 9H), 1.06 (d, *J* = 6 Hz, 3H), 1.15–1.40 (m, 10H), 1.40–1.85 (m, 7H), 2.30 (t, *J* = 8 Hz, 2H), 2.35–2.50 (m, 2H), 3.63 (t, *J* = 6 Hz, 2H), 3.89 (sextet, *J* = 6 Hz, 1H), 7.30–7.50 (m, 6H), 7.60–7.70 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.2, 23.2, 23.8, 25.6, 27.0, 29.1, 29.2, 29.3, 32.7, 32.9, 38.3, 42.7, 62.9, 68.7, 127.4, 129.5, 134.1, 134.5, 135.8, 211.5; ESIMS (*m*/*z*) 505 $[M+Na]^+$; HRMS (ESI) calcd for $C_{30}H_{46}O_3SiNa^+$ 505.3113, found 505.3126; IR ($CHCl_3$) ν_{max} 3410, 1710 cm^{-1}.



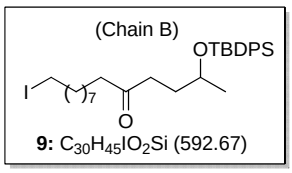
7: $C_{30}H_{46}O_3Si$ (482.77)

Tolune-4-sulfonic acid 13-(*tert*-butyldiphenylsilanyloxy)-10-oxotetradecyl ester (8). To a stirred solution of compound **7** (500 mg, 1.03 mmol) in dichloromethane (15 mL) at 0 °C was added triethylamine (0.43 mL, 3.11 mmol), *p*-toluenesulfonyl chloride (295 mg, 1.55 mmol) and DMAP (cat.). The reaction mixture was stirred for 3 h at 25 °C. It was then diluted with dichloromethane (10 mL) and the organic layer was washed with water, 5% aqueous $NaHCO_3$, brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by the silica gel column chromatography of the obtained residue using petroleum ether–ethyl acetate (9:1) as an eluent afforded pure product **8** as a thick oil (626 mg, 95%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.04 (s, 9H), 1.05 (d, *J* = 6 Hz, 3H), 1.10–1.35 (m, 10H), 1.35–1.75 (m, 6H), 2.29 (t, *J* = 8 Hz, 2H), 2.35–2.48 (m, 2H), 2.44 (s, 3H), 3.91 (sextet, *J* = 6 Hz, 1H), 4.01 (t, *J* = 6 Hz, 2H), 7.30–7.45 (m, 8H), 7.60–7.70 (m, 4H), 7.79 (d, *J* = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.2, 21.6, 23.2, 23.7, 25.2, 27.0, 28.7, 28.8, 29.0, 29.1, 32.9, 38.3, 42.6, 68.7, 70.6, 127.4, 127.5, 127.8, 129.47, 129.54, 129.8, 133.2, 134.2, 134.6, 135.76, 135.81, 144.6, 211.2; ESIMS (*m*/*z*) 659 $[M+Na]^+$; Anal. Calcd for $C_{37}H_{52}O_5SSi$: C, 69.77; H, 8.23. Found: C, 69.73; H, 8.52; IR ($CHCl_3$) ν_{max} 1708 cm^{-1}.



8: $C_{37}H_{52}O_5SSi$ (636.96)

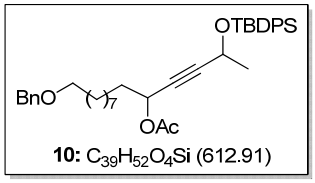
2-(*tert*-Butyldiphenylsilanyloxy)-14-iodotetradecan-5-one (Chain B, 9). To a stirred mixture of sodium iodide (235 mg, 1.57 mmol) in acetone (10 mL), a solution of tosylate **8** (0.50 g, 0.786 mmol) in acetone (5 mL) was added and the reaction mixture was stirred and heated under reflux for 8 h under nitrogen atmosphere and then concentrated in vacuo to remove the acetone. The obtained residue was diluted with water and extracted with ethyl acetate (2 X 10 mL). The combined ethyl acetate



9: $C_{30}H_{45}IO_2Si$ (592.67)

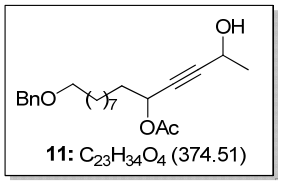
extract was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (95:5) as an eluent afforded pure product **9** (side chain B) as a thick oil (526 mg, 98%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.05 (s, 9H), 1.05 (d, *J* = 6 Hz, 3H), 1.15–1.45 (m, 10H), 1.45–1.90 (m, 6H), 2.30 (t, *J* = 8 Hz, 2H), 2.35–2.50 (m, 2H), 3.19 (t, *J* = 6 Hz, 2H), 3.88 (sextet, *J* = 6 Hz, 1H), 7.30–7.50 (m, 6H), 7.60–7.70 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 7.3, 19.3, 23.2, 23.8, 27.0, 28.5, 29.16, 29.20, 29.3, 30.4, 33.0, 33.5, 38.4, 42.7, 68.8, 127.4, 127.6, 129.5, 134.2, 134.6, 135.8, 211.3; Anal. Calcd for $C_{30}H_{45}IO_2Si$: C, 60.80; H, 7.65. Found: C, 60.80; H, 7.69; IR ($CHCl_3$) ν_{max} 1709 cm^{-1}.

Acetic acid 10-benzyloxy-1-[3-(*tert*-butyldiphenylsilanyloxy)but-1-ynyl]decyl ester (10). Acetic anhydride (5 mL, 52.63 mmol) was added to a stirred reaction mixture of compound **5** (3.00 g, 5.26 mmol) in pyridine (2 mL) at 25 ^{o}C. The reaction mixture was stirred for 6 h and then concentrated in vacuo. Silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (95:5) as an eluent afforded pure product **10** as a thick oil (3.05 g, 95%). ^{1}H NMR ($CDCl_3$, 200 MHz) (diastereomeric mixture) δ 1.06 (s, 9H), 1.26 (br s, 12H), 1.39 (d, *J* = 6 Hz, 3H), 1.61 (br s, 4H), 2.03 (s, 1.50H), 2.05 (s, 1.50H), 3.46 (t, *J* = 6 Hz, 2H), 4.49 (q, *J* = 6 Hz, 1H), 4.50 (s, 2H), 5.29 (t, *J* = 8 Hz, 1H), 7.20–7.50 (m, 11H), 7.60–7.80 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.2, 21.04, 21.06, 24.9, 24.98, 25.00, 26.2, 26.8, 29.1, 29.38, 29.44, 29.5, 29.8, 34.6, 59.9, 64.03, 64.06, 70.5, 72.8, 81.1, 87.5, 87.6, 127.4, 127.56, 127.60, 128.3, 129.6, 129.7, 133.6, 133.7, 135.7, 135.9, 138.7, 169.89, 169.91; ESIMS (*m*/*z*) 635 [M+Na]$^+$; Anal. Calcd for $C_{39}H_{52}O_4Si$: C, 76.43; H, 8.55. Found: C, 75.99; H, 8.71; IR ($CHCl_3$) ν_{max} 2254, 1732 cm^{-1}.



10: $C_{39}H_{52}O_4Si$ (612.91)

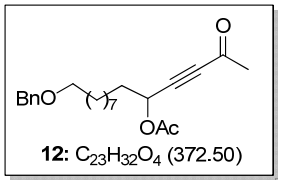
Acetic acid 10-benzyloxy-1-(3-hydroxybut-1-ynyl)decyl ester (11). Tetrabutylammonium fluoride (1 M in THF, 5.61 mL, 5.61 mmol) was added to a stirred solution of compound **10** (2.29 g, 3.74 mmol) in THF (20 mL) at 0 ^{o}C and the reaction mixture was stirred for 4 h at 25 ^{o}C. To the reaction mixture was added saturated NH_4Cl solution (5 mL) and THF was removed in vacuo. Ethyl acetate (20 mL) was added to the reaction mixture and the separated organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (9:1) as an eluent afforded pure product **11** as a thick oil (1.31 g, 94%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.28 (br s, 12H), 1.44 (d, *J* = 6 Hz, 3H), 1.50–1.80 (m, 4H), 2.07 (s, 3H), 3.46 (t, *J* = 8 Hz, 2H), 4.50 (s, 2H), 4.55 (q, *J* = 6 Hz, 1H), 5.36



11: $C_{23}H_{34}O_4$ (374.51)

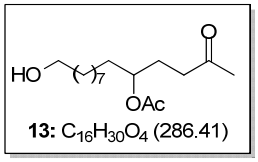
(t, *J* = 8 Hz, 1H), 7.20–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.1, 24.1, 24.9, 26.1, 29.0, 29.3, 29.4, 29.7, 34.6, 58.2, 64.0, 70.4, 72.8, 81.4, 87.2, 127.4, 127.6, 128.3, 138.6, 170.1; ESIMS (*m/z*) 397 $[M+Na]^+$; Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.48; H, 8.76; IR ($CHCl_3$) ν_{max} 3444, 2254, 1732 cm^{-1}.

Acetic acid 10-benzyloxy-1-(3-oxobut-1-ynyl)decyl ester (12). It was obtained from compound **11** using the same procedure as described for compound **6**, as a thick oil (865 mg, 87%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.20–1.50 (br s, 12H), 1.50–1.70 (m, 2H), 1.74–1.88 (m, 2H), 2.10 (s, 3H), 2.34 (s, 3H), 3.46 (t, *J* = 6 Hz, 2H), 4.50 (s, 2H), 5.45 (t, *J* = 6 Hz, 1H), 7.20–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.8, 24.9, 26.1, 28.9, 29.2, 29.4, 29.7, 32.5, 33.9, 63.2, 70.4, 72.8, 84.1, 88.3, 127.4, 127.6, 128.3, 138.6, 169.7, 183.9; ESIMS (*m/z*) 395 $[M+Na]^+$; HRMS (ESI) calcd for $C_{23}H_{32}O_4Na^+$ 395.2198, found 395.2199; IR ($CHCl_3$) ν_{max} 2254, 1741, 1679 cm^{-1}.



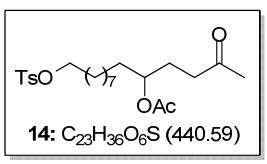
12: $C_{23}H_{32}O_4$ (372.50)

Acetic acid 10-hydroxy-1-(3-oxobutyl)decyl ester (13). It was obtained from compound **12** using the same procedure as described for compound **7**, as a thick oil (658 mg, 89%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.27 (br s, 12H), 1.45–1.65 (m, 4H), 1.65–2.00 (m, 2H), 2.05 (s, 3H), 2.15 (s, 3H), 2.46 (t, *J* = 8 Hz, 2H), 3.64 (t, *J* = 8 Hz, 2H), 4.77–4.92 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.1, 25.2, 25.6, 27.9, 29.3, 29.4, 29.9, 32.7, 34.2, 39.5, 62.9, 73.5, 170.9, 208.0; ESIMS (*m/z*) 309 $[M+Na]^+$, 325 $[M+K]^+$; Anal. Calcd for $C_{16}H_{30}O_4$: C, 67.10; H, 10.56. Found: C, 66.85; H, 10.39; IR ($CHCl_3$) ν_{max} 3423, 1742, 1717 cm^{-1}.



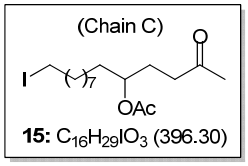
13: $C_{16}H_{30}O_4$ (286.41)

Acetic acid 1-(3-oxobutyl)-10-(toluene-4-sulfonyloxy)decyl ester (14). It was obtained from compound **13** using the same procedure as described for compound **8**, as a thick oil (858 mg, 93%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.22 (br s, 10H), 1.40–2.00 (m, 8H), 2.04 (s, 3H), 2.14 (s, 3H), 2.45 (s, 3H), 2.45 (t, *J* = 6 Hz, 2H), 4.01 (t, *J* = 6 Hz, 2H), 4.75–4.92 (m, 1H), 7.35 (d, *J* = 8 Hz, 2H), 7.79 (d, *J* = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.2, 21.6, 25.2, 25.3, 27.9, 28.77, 28.83, 29.2, 29.27, 29.31, 29.9, 34.2, 39.5, 70.7, 73.5, 127.8, 129.8, 133.2, 144.6, 170.9, 207.9; ESIMS (*m/z*) 463 $[M+Na]^+$, 479 $[M+K]^+$; Anal. Calcd for $C_{23}H_{36}O_6S$: C, 62.70; H, 8.24. Found: C, 63.00; H, 7.79; IR ($CHCl_3$) ν_{max} 1745, 1718 cm^{-1}.



14: $C_{23}H_{36}O_6S$ (440.59)

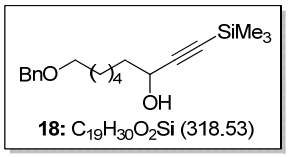
Acetic acid 10-iodo-1-(3-oxobutyl)decyl ester (Chain C, 15). It was obtained from compound **14** using the same procedure as described for compound **9**, as a thick oil (541 mg, 97%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.27 (br s, 12H), 1.45–1.60 (br s, 2H), 1.65–2.00 (m,



15: $C_{16}H_{29}IO_3$ (396.30)

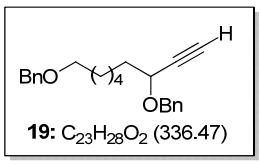
4H), 2.05 (s, 3H), 2.15 (s, 3H), 2.46 (t, *J* = 6 Hz, 2H), 3.19 (t, *J* = 8 Hz, 2H), 4.75–4.94 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) 7.3, 21.2, 25.2, 27.9, 28.4, 29.25, 29.33, 29.9, 30.4, 33.5, 34.2, 39.5, 73.5, 170.9, 207.9; Anal. Calcd for $C_{16}H_{29}IO_3$: C, 48.49; H, 7.38. Found: C, 48.40; H 7.18; IR ($CHCl_3$) ν_{max} 1744, 1718 cm^{-1}.

9-Benzyloxy-1-trimethylsilanylnon-1-yn-3-ol (18). *n*-BuLi (1.60 M in hexane, 12.27 mL, 19.63 mmol) was added to a stirred solution of alkyne **16** (2.77 mL, 19.63 mmol) in THF (40 mL) at –78 °C and stirred further for 45 min, followed by the addition of 7-benzyloxyheptanal (**17**, 3.60 g, 16.36 mmol) in THF (15 mL). The reaction mixture was stirred at –78 °C for 45 min. The reaction was quenched with saturated NH_4Cl solution (5 mL) and THF was removed in vacuo. To the reaction mixture was added ethyl acetate (50 mL) and the separated organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (9:1) as an eluent afforded pure product **18** as a thick oil (4.42 g, 85%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.17 (s, 9H), 1.20–1.50 (m, 6H), 1.50–1.75 (m, 4H), 3.46 (t, *J* = 8 Hz, 2H), 4.34 (t, *J* = 6 Hz, 1H), 4.50 (s, 2H), 7.25–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 0.1, 25.0, 26.1, 29.0, 29.6, 37.6, 62.8, 70.4, 72.8, 89.3, 106.8, 127.5, 127.6, 128.3, 138.6; ESIMS (*m*/*z*) 341 [M+Na]$^+$, 357 [M+K]$^+$; Anal. Calcd for $C_{19}H_{30}O_2Si$: C, 71.64; H, 9.49. Found: C, 71.47; H, 9.06; IR ($CHCl_3$) ν_{max} 3601, 2253 cm^{-1}.



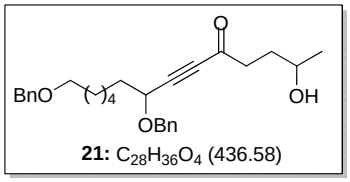
18: $C_{19}H_{30}O_2Si$ (318.53)

1-[(7-(Benzyloxy)non-8-ynyloxy)methyl]benzene (19). To a stirred suspension of sodium hydride (60% dispersion in mineral oil, 1.09 g, 22.83 mmol) in *N*,*N*-dimethylformamide (40 mL) was added alcohol **18** (3.30 g, 10.37 mmol) in *N*,*N*-dimethylformamide (15 mL) at 0 °C. After 45 min, benzyl bromide (3.08 mL, 25.94 mmol) was added to the reaction mixture and stirred at 25 °C for 5 h. The reaction was quenched with saturated NH_4Cl solution (5 mL) and the reaction mixture was extracted with ethyl acetate (100 mL). The organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (97:3) as an eluent afforded pure product **19** as a thick oil (3.27 g, 94%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.20–1.85 (m, 10H), 2.46 (d, *J* = 2 Hz, 1H), 3.44 (t, *J* = 6 Hz, 2H), 4.06 (dt, *J* = 8 and 2 Hz, 1H), 4.48 (s, 2H), 4.49 (d, *J* = 12 Hz, 1H), 4.80 (d, *J* = 12 Hz, 1H), 7.20–7.40 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.0, 26.0, 29.0, 29.6, 35.5, 68.3, 70.3, 70.4, 72.8, 73.8, 82.9, 127.4, 127.5, 127.6, 127.9, 128.26, 128.28, 137.8, 138.6; ESIMS (*m*/*z*) 359 [M+Na]$^+$; HRMS (ESI) calcd for $C_{23}H_{28}O_2Na^+$ 359.1987, found 359.1983; IR ($CHCl_3$) ν_{max} 3306, 2251 cm^{-1}.



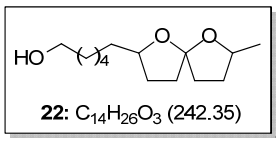
19: $C_{23}H_{28}O_2$ (336.47)

8,14-*Bis*-benzyloxy-2-hydroxytetradec-6-yn-5-one (21). *n*-BuLi (1.60 M in hexane, 3.05 mL, 4.88 mmol) was added to the stirring solution of compound **19** (1.64 g, 4.88 mmol) in Et_2O (20 mL) at –20 °C. After stirring for 45 min, (±)-γ-valerolactone (**20**, 0.46 mL, 4.88 mmol) was added dropwise. The reaction mixture was allowed to reach 25 °C and further stirred for 2 h. The reaction was quenched with saturated NH_4Cl (5 mL) and Et_2O was removed in vacuo. To the reaction mixture was added ethyl acetate (25 mL) and the separated organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (3:1) as an eluent afforded pure product **21** as a thick oil (1.78 g, 84%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22 (d, *J* = 8 Hz, 3H), 1.25–1.45 (m, 2H), 1.45–1.55 (m, 2H), 1.62 (quintet, *J* = 8 Hz, 2H), 1.68–1.90 (m, 6H), 2.65–2.80 (m, 2H), 3.46 (t, *J* = 8 Hz, 2H), 3.77–3.87 (m, 1H), 4.22 (t, *J* = 8 Hz, 1H), 4.49 (s, 2H), 4.50 (d, *J* = 12 Hz, 1H), 4.78 (d, *J* = 12 Hz, 1H), 7.25–7.40 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.7, 25.0, 25.8, 29.6, 32.7, 35.0, 42.0, 67.1, 68.4, 70.2, 71.1, 72.9, 84.7, 91.1, 127.5, 127.6, 127.9, 128.0, 128.4, 128.5, 137.3, 138.6, 187.5; ESIMS (*m*/*z*) 459 $[M+Na]^+$; Anal. Calcd for $C_{28}H_{36}O_4$: C, 77.03; H, 8.31. Found: C, 76.61; H, 8.33; IR ($CHCl_3$) ν_{max} 3462, 2212, 1664 cm^{-1}.



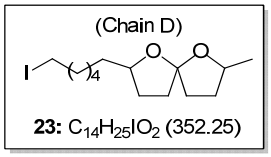
21: $C_{28}H_{36}O_4$ (436.58)

6-(7-Methyl-1,6-dioxaspiro[4.4]non-2-yl)hexan-1-ol (22). Palladium on carbon (10 wt%) was added to a stirred solution of compound **21** (1.48 g, 3.39 mmol) in methanol (10 mL) at 25 °C. The reaction mixture was stirred under an atmosphere of hydrogen for 8 h and filtered through a pad of Celite. Removal of the solvent in vacuo followed by the silica gel column chromatography using petroleum ether–ethyl acetate (7:3) as an eluent afforded pure product **22** as a thick oil (714 mg, 87%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.15–2.16 (m, 21H), 3.59 (t, *J* = 8 Hz, 2H), 3.88–4.25 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.0, 21.2, 25.5, 25.7, 30.1, 30.7, 31.7, 32.1, 32.5, 32.6, 35.0, 35.6, 37.2, 62.6, 73.8, 74.0, 75.7, 75.8, 77.2, 77.8, 78.0, 79.8, 79.9, 114.2, 114.4, 114.7; ESIMS (*m*/*z*) 265 $[M+Na]^+$, 281 $[M+K]^+$; HRMS (ESI) calcd for $C_{14}H_{26}O_3Na^+$ 265.1779, found 265.1788; IR (neat) ν_{max} 3412, 1460 cm^{-1}.



22: $C_{14}H_{26}O_3$ (242.35)

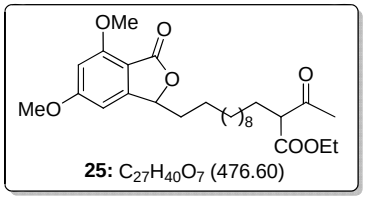
2-(6-Iodohexyl)-7-methyl-1,6-dioxaspiro[4.4]nonane (Chain D, 23). To a stirred mixture of iodine (627 mg, 2.47 mmol), triphenylphosphine (595 mg, 2.27 mmol) and imidazole (154 mg, 2.27 mmol) in dichloromethane (30 mL) at 0 °C was added alcohol **22** (500 mg, 2.06 mmol) in dichloromethane (10 mL). The reaction mixture was stirred at 25 °C for 5 h. It was then diluted with dichloromethane (20 mL) and the organic layer was washed with water, brine and dried over Na_2SO_4. Removal of the solvent in



23: $C_{14}H_{25}IO_2$ (352.25)

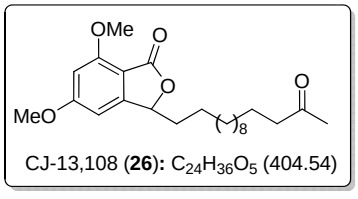
vacuo followed by the silica gel column chromatography of the obtained residue using petroleum ether–ethyl acetate (95:5) as an eluent afforded pure product **23** (chain D) as a thick oil (669 mg, 92%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.15–2.18 (m, 21H), 3.18 (t, *J* = 8 Hz, 2H), 3.89–4.32 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 7.1, 7.2, 21.1, 21.3, 24.8, 25.0, 30.2, 30.5, 30.8, 31.8, 32.2, 32.5, 33.4, 35.4, 35.6, 37.1, 73.8, 74.0, 75.7, 77.7, 77.9, 79.7, 114.3, 114.5, 114.7; Anal. Calcd for $C_{14}H_{25}IO_2$: C, 47.74; H, 7.15;. Found: C, 48.40; H, 7.18; IR (neat) ν_{max} 1459 cm^{-1}.

Ethyl 2-acetyl-13-(4,6-dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl) tridecanoate (25). To a stirred solution of 5,7-dimethoxyphthalide (**24**, 500 mg, 2.57 mmol) in THF (25 mL) at −20 °C was added NaHMDS (1 M in THF, 2.83 mL, 2.83 mmol) and the reaction mixture was stirred at −20 °C for 45 min, which was followed by the dropwise addition of alkyl iodide **2** (chain A, 1.05 g, 2.57 mmol) in THF (8 mL) at −20 °C. The reaction mixture was allowed to attain room temperature. Saturated NH_4Cl solution (5 mL) was added to the reaction mixture and THF was removed in vacuo. To the reaction mixture was added ethyl acetate (20 mL) and the separated organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (65:35) as an eluent afforded pure product **25** as a thick oil (932 mg, 76%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.24 (br s, 14H), 1.28 (t, *J* = 8 Hz, 3H), 1.26–1.38 (m, 2H), 1.38–1.52 (m, 2H), 1.62–1.74 (m, 1H), 1.77–1.91 (m, 2H), 1.93–2.05 (m, 1H), 2.23 (s, 3H), 3.40 (t, *J* = 8 Hz, 1H), 3.90 (s, 3H), 3.95 (s, 3H), 4.20 (q, *J* = 8 Hz, 2H), 5.30 (dd, *J* = 8 and 2 Hz, 1H), 6.42 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 24.5, 27.3, 28.1, 28.7, 29.2, 29.3, 29.36, 29.42, 34.7, 55.8, 55.9, 59.8, 61.1, 79.9, 97.3, 98.5, 106.7, 155.1, 159.4, 166.6, 168.5, 169.8, 203.4; Anal. Calcd for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46. Found: C, 67.71; H, 8.60; IR ($CHCl_3$) ν_{max} 1746, 1721, 1712, 1605 cm^{-1}.



25: $C_{27}H_{40}O_7$ (476.60)

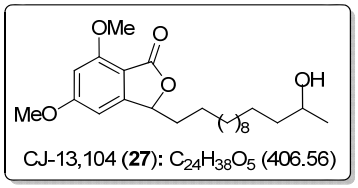
5,7-Dimethoxy-3-(13-oxotetradecyl)isobenzofuran-1(3*H*)-one [(±)-CJ-13,108 (26)]. The compound **25** (120 mg) was added to the mixture of 10% aqueous solution of KOH (10 mL) and MeOH (10 mL). The reaction mixture was stirred and heated under reflux for 1 h and then allowed to attain the room temperature. The reaction mixture was concentrated in vacuo. The residue was dissolved in ethyl acetate (20 mL) and washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (3:2) as an eluent afforded pure product (±)-CJ-13,108 (**26**, 70 mg, 68%) as a white solid. Mp 105 °C (lit.[4] 104-106 °C); ^{1}H NMR



CJ-13,108 (**26**)**:** $C_{24}H_{36}O_5$ (404.54)

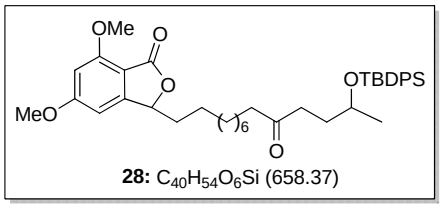
($CDCl_3$, 200 MHz) δ 1.24 (br s, 18H), 1.50–1.80 (m, 3H), 1.89–2.05 (m, 1H), 2.14 (s, 3H), 2.42 (t, *J* = 8 Hz, 2H), 3.90 (s, 3H), 3.95 (s, 3H), 5.30 (dd, *J* = 8 and 2 Hz, 1H), 6.41 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.8, 24.6, 29.1, 29.28, 29.34, 29.39, 29.44, 29.5, 29.6, 29.8, 34.8, 43.8, 55.8, 55.9, 79.9, 97.4, 98.6, 106.9, 155.2, 159.6, 166.6, 168.5, 209.4; ESIMS (*m*/*z*) 427 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1748, 1709, 1605 cm^{-1}.

3-(13-Hydroxytetradecyl)-5,7-dimethoxyisobenzofuran-1(3*H*)-one [(±)-CJ-13,104 (27)]. Sodium borohydride (10 mg, 0.28 mmol) was added in one lot to a stirred solution of **26** (30 mg, 0.07 mmol) in MeOH (5 mL) at 0 °C. The reaction mixture was stirred at room temperature under the nitrogen atmosphere for 30 min and the solvent was removed in vacuo. The residue was dissolved in ethyl acetate (15 mL) and the organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (1:1) as an eluent afforded pure product (±) CJ-13,104 (**27**, 29 mg, 95%) as a white solid. Mp 103-105 °C (lit.[4] 100-102 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.18 (d, *J* = 6 Hz, 3H), 1.23 (br s, 18H), 1.30–1.55 (m, 4H), 1.55–1.80 (m, 1H), 1.85–2.10 (m, 1H), 3.79 (sextet, *J* = 6 Hz, 1H), 3.88 (s, 3H), 3.94 (s, 3H), 5.29 (dd, *J* = 8 and 2 Hz, 1H), 6.40 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 23.4, 24.6, 25.7, 29.3, 29.5, 34.8, 39.3, 55.8, 55.9, 68.1, 79.9, 97.3, 98.5, 106.8, 155.1, 159.5, 166.6, 168.5; ESIMS (*m*/*z*) 429 $[M+Na]^+$, 445 $[M+K]^+$; IR ($CHCl_3$) ν_{max} 3400, 1748, 1605 cm^{-1}.



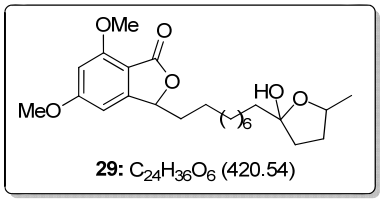
CJ-13,104 (**27**): $C_{24}H_{38}O_5$ (406.56)

3-[13-(*tert*-Butyldiphenylsilanyloxy)-10-oxotetradecyl]-5,7-dimethoxy-3*H*-isobenzofuran-1-one (28). It was obtained from 5,7-dimethoxyphthalide (**24**, 100 mg, 0.51 mmol), NaHMDS (1 M in THF, 0.56 mL, 0.56 mmol) and alkyl iodide **9** (chain B, 305 mg, 0.51 mmol), using the same procedure as described for compound **25**, as a thick oil (274 mg, 81%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.05 (s, 9H), 1.06 (d, *J* = 8 Hz, 3H), 1.15–1.75 (m, 16H), 1.90–2.10 (m, 2H), 2.25–2.50 (m, 4H), 3.85–3.90 (m, 1H), 3.89 (s, 3H), 3.95 (s, 3H), 5.30 (dd, *J* = 8 and 4 Hz, 1H), 6.41 (s, 1H), 6.42 (s, 1H), 7.33–7.46 (m, 6H), 7.63–7.70 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.2, 23.2, 23.8, 24.6, 27.0, 29.2, 29.29, 29.31, 29.7, 32.9, 34.8, 38.3, 42.7, 55.9, 56.0, 68.7, 79.9, 97.4, 98.6, 106.9, 127.4, 127.5, 129.5, 129.6, 134.2, 134.6, 135.78, 135.83, 155.2, 159.6, 166.6, 168.6, 211.4; Anal. Calcd for $C_{40}H_{54}O_6Si$: C, 72.91; H, 8.26. Found: C, 73.21; H, 8.76; IR ($CHCl_3$) ν_{max} 1748, 1720 cm^{-1}.



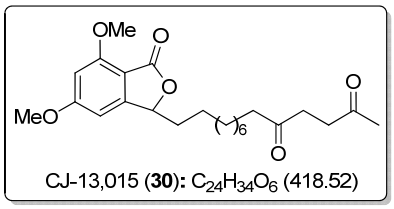
28: $C_{40}H_{54}O_6Si$ (658.37)

3-(13-Hydroxy-10-oxotetradecyl)-5,7-dimethoxy-3*H*-isobenzofuran-1-one [sporotricale methyl ether (29)]. Tetrabutylammonium fluoride (1 M in THF, 0.11 mL, 0.11 mmol) was added to a stirred solution of compound **28** (50 mg, 0.07 mmol) in THF (5 mL) at 0 °C and the reaction mixture was stirred for 4 h at 25 °C. Saturated NH_4Cl solution (5 mL) was added to the reaction mixture and THF was removed in vacuo. Ethyl acetate (20 mL) was added to the reaction mixture and the separated organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (2:3) as an eluent afforded pure product, sporotricale methyl ether (**29**, 29 mg, 91%) as a gummy solid. ^{1}H NMR (acetone-d_6, 400 MHz) δ 1.12 (d, *J* = 8 Hz, 3H), 1.20–1.45 (m, 14H), 1.50–1.75 (m, 4H), 2.45 (t, *J* = 8 Hz, 2H), 2.50–2.58 (m, 2H), 3.70 (sextet, *J* = 8 Hz, 1H), 3.93 (s, 3H), 3.94 (s, 3H), 5.36 (dd, *J* = 8 and 4 Hz, 1H), 6.59 (s, 1H), 6.72 (s, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 24.0, 24.5, 25.4, 29.0–31.0, 33.8, 35.4, 39.4, 42.9, 56.1, 56.4, 66.8, 80.1, 98.9, 99.4, 107.4, 156.2, 160.4, 167.6, 167.7, 210.7. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.20 (d, *J* = 8 Hz, 3H), 1.26 (br s, 12H), 1.28–2.10 (m, 6H), 2.43 (t, *J* = 8 Hz, 2H), 2.57 (t, *J* = 8 Hz, 2H), 3.75–3.84 (m, 1H), 3.90 (s, 3H), 3.95 (s, 3H), 5.30 (dd, *J* = 8 and 4 Hz, 1H), 6.41 (s, 1H), 6.42 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.7, 23.8, 24.6, 29.1, 29.2, 29.3, 29.7, 32.6, 34.8, 39.1, 42.9, 55.9, 56.0, 67.6, 79.9, 97.3, 98.6, 106.9, 155.2, 159.6, 166.7, 168.6, 212.2; ESIMS (*m*/*z*) 443 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 3445, 1747, 1712 cm^{-1}.



29: $C_{24}H_{36}O_6$ (420.54)

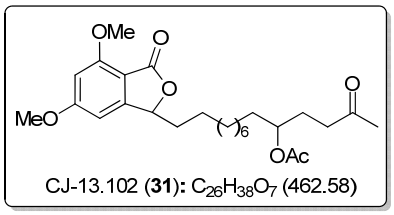
14-(4,6-Dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)tetradecane-2,5-dione [(±)-CJ-13,105 (30)]. To a stirred suspension of pyridinium chlorochromate (15 mg, 0.07 mmol) and 4 Å molecular sieves in dichloromethane (5 mL) at 0 °C was added alcohol **29** (20 mg, 0.04 mmol) in dichloromethane (1 mL). After 3 h of stirring at 25 °C, the reaction mixture was diluted with diethyl ether (3 mL). The resulting reaction mixture was filtered through Celite pad and the filtrate was concentrated in vacuo. Silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (1:1) as an eluent afforded pure product (±)-CJ-13,015 (**30**, 17 mg, 86 %) as a white solid. Mp 104–106 °C (lit.[4] 104-106 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.25 (s, 8H), 1.25–1.37 (m, 2H), 1.37–1.50 (m, 2H), 1.55 (quintet, *J* = 10 Hz, 2H), 1.63–1.73 (m, 1H), 1.92–2.01 (m, 1H), 2.17 (s, 3H), 2.43 (t, *J* = 10 Hz, 2H), 2.63–2.72 (m, 4H), 3.89 (s, 3H), 3.94 (s, 3H), 5.28 (m, 1H), 6.40 (s, 1H), 6.41 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.8, 24.6, 29.1, 29.2, 29.8,



CJ-13,015 (**30**)**:** $C_{24}H_{34}O_6$ (418.52)

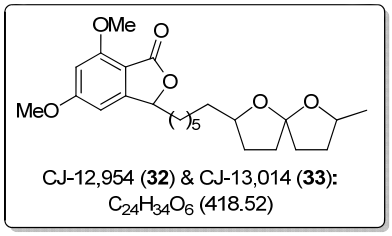
34.8, 36.0, 36.9, 42.8, 55.9, 56.0, 79.8, 97.5, 98.7, 107.1, 155.2, 159.7, 166.7, 168.3, 207.0, 209.5; ESIMS (*m*/*z*) 419 $[M+H]^+$, IR (Nujol) ν_{max} 1759, 1697, 1614, 1601, 1468, 837 cm^{-1}.

Acetic acid 10-(4,6-dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-1-(3-oxobutyl)decyl ester [(±)-CJ-13,102 (31)]. It was obtained from 5,7-dimethoxyphthalide (**24**, 50 mg, 0.25 mmol), NaHMDS (1 M in THF, 0.28 mL, 0.28 mmol) and alkyl iodide **15** (chain C, 102 mg, 0.25 mmol), using the same procedure as described for compound **25**, as a thick oil [CJ-13,102 (**31**)] (91 mg, 77%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.26 (s, 10H), 1.35–2.04 (m, 10H), 2.05 (s, 3H), 2.15 (s, 3H), 2.46 (t, *J* = 10 Hz, 2H), 3.90 (s, 3H), 3.95 (s, 3H), 4.80–4.89 (m, 1H), 5.31 (dd, *J* = 10 and 5 Hz, 1H), 6.41 (s, 1H), 6.42 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.2, 24.6, 25.2, 27.9, 29.26, 29.31, 29.33, 29.7, 30.0, 34.2, 34.8, 39.5, 55.9, 56.0, 73.5, 79.9, 97.4, 98.6, 106.9, 155.2, 159.6, 166.7, 168.6, 171.0, 208.0; ESIMS (*m*/*z*) 485 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1747, 1732, 1720 cm^{-1}.



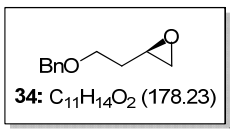
CJ-13.102 (**31**): $C_{26}H_{38}O_7$ (462.58)

5,7-Dimethoxy-3-[6-(7-methyl-1,6-dioxaspiro[4.4]non-2-yl)hexyl]-3*H*-isobenzofuran-1-one [CJ-12,954 (32) & CJ-13,014 (33)]. It was obtained from 5,7-dimethoxyphthalide (**24**, 50 mg, 0.25 mmol), NaHMDS (1 M in THF, 0.28 mL, 0.28 mmol) and alkyl iodide **23** (chain D, 90 mg, 0.25 mmol), using the same procedure as described for compound **25**, as a thick oil [CJ-12,954 (**32**) & CJ-13,014 (**33**)] (66 mg, 62%). ^{1}H NMR ($CDCl_3$, 500 MHz) (diastereomeric mixture) δ 1.18–2.19 (m, 23H), 3.90 (s, 3H), 3.95 (s, 3H), 4.00–4.27 (m, 2H), 5.30 (dd, *J* = 10 and 5 Hz, 1H), 6.41 (s, 1H), 6.42 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.1, 21.3, 24.6, 25.7, 29.3, 29.5, 30.2, 30.8, 31.8, 32.2, 34.8, 35.2, 35.6, 36.4, 37.3, 56.0, 73.8, 74.0, 77.9, 78.1, 79.9, 97.3, 98.6, 106.9, 114.46, 114.49, 114.7, 155.2, 159.6, 166.7, 168.6; ESIMS (*m*/*z*) 441 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1750, 1605 cm^{-1}.



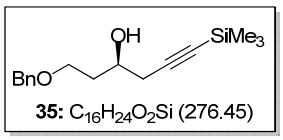
CJ-12,954 (**32**) & CJ-13,014 (**33**): $C_{24}H_{34}O_6$ (418.52)

(*R*)-2-[2-(Benzyloxy)ethyl]oxirane (34).[5] $[\alpha]_D^{25}$ +16.2 (*c* 2.0 $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.65–2.03 (m, 2H), 2.52 (dd, *J* = 6 and 2 Hz, 1H), 2.77 (t, *J* = 4 Hz, 1H), 3.00–3.11 (m, 1H), 3.62 (t, *J* = 4 Hz, 2H), 4.52 (s, 2H), 7.20–7.40 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 32.8, 46.9, 49.9, 66.9, 72.9, 127.4 (2 carbons), 128.2, 138.1; ESIMS (*m*/*z*) 201 $[M + Na]^+$; IR (neat) ν_{max} 1601 cm^{-1}.



34: $C_{11}H_{14}O_2$ (178.23)

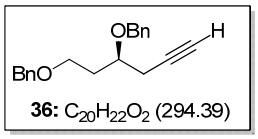
(*S*)-1-(Benzyloxy)-6-(trimethylsilyl)hex-5-yn-3-ol (35). To a stirred solution of trimethylsilylacetylene



35: $C_{16}H_{24}O_2Si$ (276.45)

(7.14 mL, 50.56 mmol) in THF (60 mL) at –78 °C was added *n*-BuLi (1.60 M in hexane, 30.54 mL, 48.87 mmol) and the reaction mixture was stirred for 30 min. To the above mixture was added dropwise $BF_3.OEt_2$ (6.44 mL, 52.24 mmol) at –78 °C, the stirring continued for 10 min and then the epoxide **34** (3.00 g, 16.85 mmol) in THF (10 mL) was added dropwise to the above mixture. The mixture was stirred further for 1 h at –78 °C and quenched with sat. aq NH_4Cl (5 mL). The mixture was concentrated in vacuo and the obtained residue was dissolved in EtOAc (60 mL). The organic layer was washed with H_2O (15 mL), brine (15 mL), and dried (Na_2SO_4). Removal of the solvent in vacuo followed by silica gel column chromatography of the resulting residue using petroleum ether–ethyl acetate (92:8) as an eluent afforded pure product **35** as a thick oil (4.13 g, 89%)[12] $[\alpha]_D^{25}$ +3.4 (*c* 1.0 $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.15 (s, 9H), 1.70–2.00 (m, 2H), 2.44 (dd, *J* = 8 and 2 Hz, 2H), 3.07 (br s, 1H), 3.57–3.80 (m, 2H), 3.87–4.04 (m, 1H), 4.52 (s, 2H), 7.20–7.40 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 0.02, 28.5, 35.3, 68.5, 69.3, 73.2, 87.0, 103.3, 127.6, 127.7, 128.4, 137.8; ESIMS (*m*/*z*) 277 $[M + H]^+$, 299 $[M + Na]^+$, 315 $[M + K]^+$; IR (neat) ν_{max} 3444, 2176 cm^{-1}.

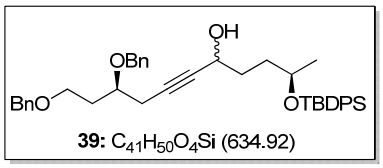
1-{[(*S*)-1-(Benzyloxy)hex-5-yn-3-yloxy]methyl}benzene (36). To a stirred suspension of NaH (60%



36: $C_{20}H_{22}O_2$ (294.39)

dispersion in mineral oil, 1.33 g, 27.89 mmol) in DMF (40 mL) was added alcohol **35** (3.50 g, 12.68mmol) in DMF (15 mL) at 0 °C. At the end of 45 min, benzyl bromide (1.50 mL, 27.89 mmol) was added to the reaction mixture and further stirred at 25°C for 4 h. The mixture was quenched with sat. aq NH_4Cl (5 mL) and extracted with EtOAc (100 mL). The organic layer was washed with brine (25 mL) and dried (Na_2SO_4). Removal of the solvent in vacuo followed by silica gel column chromatography of the resulting residue using petroleum ether–ethyl acetate (95:5) as an eluent afforded pure product **36** as a thick oil (4.13 g, 89%).[13] $[\alpha]_D^{25}$ +43.2 (*c* 1.7 $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.81–2.10 (m, 2H), 2.01 (t, *J* = 4 Hz, 1H), 2.47 (dd, *J* = 6 and 2 Hz, 2H), 3.48–3.67 (m, 2H), 3.67–3.85 (m, 1H), 4.38–4.51 (m, 2H), 4.46 (d, *J* = 12 Hz, 1H), 4.66 (d, *J* = 12 Hz, 1H), 7.15–7.45 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.0, 34.3, 66.5, 70.2, 71.6, 72.9, 74.1, 80.9, 127.5, 127.6, 127.7, 127.8, 128.3 (2 carbons), 138.3, 138.4; ESIMS (*m*/*z*) 295 $[M + H]^+$, 317 $[M + Na]^+$; IR (neat) ν_{max} 3306, 2120 cm^{-1}.

(2*R*,9*S*)-9,11-Bis(benzyloxy)-2-[(*tert*-butyldiphenylsilyl)oxy]undec-6-yn-5-ol (39). To a stirred

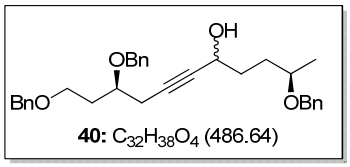


39: $C_{41}H_{50}O_4Si$ (634.92)

solution of **36** (1.03 g, 3.52 mmol) in THF (30 mL) at –78 °C was added *n*-BuLi (1.60 M in hexane, 2.20 mL, 3.52 mmol) and the

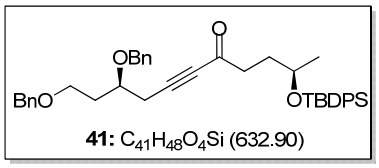
reaction mixture was stirred for 45 min. A solution of aldehyde **37** (1.00 g, 2.94 mmol) in THF (10 mL) was added dropwise to the above mixture and it was further stirred at –78 °C for 1 h. The reaction was quenched with sat. aq NH_4Cl (5 mL) and the THF was removed in vacuo. The obtained residue was dissolved in EtOAc (50 mL) and the organic layer was washed with H_2O (15 mL), brine (15 mL), and dried (Na_2SO_4). Removal of the solvent in vacuo followed by silica gel column chromatography of the resulting residue using petroleum ether–ethyl acetate (9:1) as an eluent afforded pure product **39** as a thick oil (1.34 g, 72%). $[\alpha]_D^{25}$ +23.0 (*c* 0.6 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (d, *J* = 8 Hz, 3H), 1.05 (s, 9H), 1.55–1.77 (m, 4H), 1.82–2.03 (m, 2H), 2.41–2.55 (m, 2H), 3.51–3.66 (m, 2H), 3.69–3.79 (m, 1H), 3.90 (sept, *J* = 8 Hz, 1H), 4.22–4.33 (m, 1H), 4.40–4.51 (m, 3H), 4.59–4.66 (m, 1H), 7.20–7.45 (m, 16H), 7.65–7.72 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 22.8, 22.9, 24.3, 27.0, 33.3, 33.5, 34.4, 34.5, 34.8, 62.5, 62.7, 66.5, 69.09, 69.13, 71.6, 72.9, 74.47, 74.50, 81.6, 81.7, 83.10, 83.13, 127.4, 127.52, 127.54, 127.6, 127.7, 127.8, 128.3, 129.45, 129.54, 134.1, 134.2, 134.6, 135.9, 138.4; ESIMS (*m*/*z*) 657 $[M + Na]^+$; Anal. Calcd for $C_{41}H_{50}O_4Si$: C, 77.56; H, 7.94. Found: C, 77.27; H, 8.36; IR ($CHCl_3$) ν_{max} 3367, 2251, 1611 cm^{-1}.

(2*R*,9*S*)-2,9,11-Tris(benzyloxy)undec-6-yn-5-ol (40). Similarly, starting from compound **36** (918 mg, 3.12 mmol) and using the benzyl-protected **38** (500 mg, 2.60 mmol), product **40** was obtained as thick oil (949 mg, 75%) following the above procedure. $[\alpha]_D^{25}$ +23.1 (*c* 0.5 $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.21 (d, *J* = 6 Hz, 3H), 1.55–2.10 (m, 6H), 2.51 (d, *J* = 6 Hz, 2H), 2.62 (br s, 1H), 3.40–3.65 (m, 3H), 3.65–3.85 (m, 1H), 4.30–4.55 (m, 6H), 4.64 (d, *J* = 12 Hz, 1H), 7.20–7.40 (m, 15H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.3, 19.5, 24.3, 31.9, 32.1, 33.7, 33.9, 34.4, 62.4, 66.5, 70.2, 71.6, 72.9, 74.4, 74.5, 81.6, 83.1, 127.45, 127.53, 127.6, 127.7, 127.8, 128.3, 138.3, 138.6; ESIMS (*m*/*z*) 504 $[M + NH_4]^+$, 509 $[M + Na]^+$, 525 $[M + K]^+$; HRMS (ESI) (*m*/*z*) calcd for $C_{32}H_{38}O_4Na$ $[M + Na]^+$ 509.2667; found: 509.2648; IR ($CHCl_3$) ν_{max} 3433, 2252 cm^{-1}.



40: $C_{32}H_{38}O_4$ (486.64)

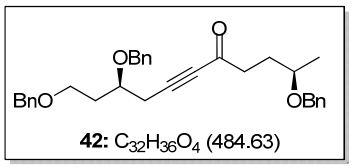
(2*R*,9*S*)-9,11-Bis(benzyloxy)-2-[(*tert*-butyldiphenylsilyl)oxy]undec-6-yn-5-one (41). To a stirred solution of alcohol **39** (1.00 g, 1.57 mmol) in DCM (1.50 mL) at 25 °C was added TEMPO (24 mg, 0.15 mmol) and reaction the mixture was further stirred for 10 min, followed by the addition of iodobis(acetoxy)benzene (558 mg, 1.73 mmol). The mixture was stirred for 45 min and then diluted with DCM (5 mL). The mixture was washed with sat. aq $Na_2S_2O_3$ (5 mL) and extracted with DCM (3 × 5 mL). The combined organic extracts were washed with sat. aq $NaHCO_3$ (2 mL), brine (2 mL) and dried (Na_2SO_4). Removal of the solvent in vacuo followed by silica gel column chromatography of the



41: $C_{41}H_{48}O_4Si$ (632.90)

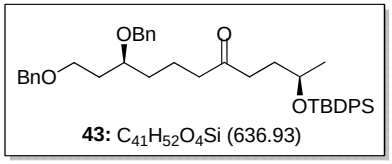
resulting residue using petroleum ether–ethyl acetate (93:7) as an eluent afforded pure product **41** as a thick oil (847 mg, 85%). $[\alpha]_D^{25}$ +24.5 (*c* 0.6 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (d, *J* = 8 Hz, 3H), 1.04 (s, 9H), 1.70–1.87 (m, 2H), 1.87–2.00 (m, 2H), 2.50–2.70 (m, 4H), 3.50–3.65 (m, 2H), 3.79–3.95 (m, 2H), 4.40–4.50 (m, 3H), 4.63 (d, *J* = 12 Hz, 1H), 7.20–7.45 (m, 16H), 7.60–7.70 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 23.0, 24.7, 27.0, 33.0, 34.6, 41.2, 66.2, 68.4, 71.9, 73.0, 73.8, 82.2, 90.4, 127.4, 127.57, 127.60, 127.68, 127.73, 127.8, 128.36, 128.38, 129.5, 129.6, 134.0, 134.5, 135.77, 135.81, 138.0, 138.3, 187.8; ESIMS (*m*/*z*) 655 $[M + Na]^+$; HRMS (ESI) (*m*/*z*) calcd for $C_{41}H_{48}O_4SiNa$ $[M + Na]^+$: 655.3219; found: 655.3194; IR ($CHCl_3$) ν_{max} 2214, 1715, 1671, 1610 cm^{-1}.

(2*R*,9*S*)-2,9,11-Tris(benzyloxy)undec-6-yn-5-one (42). Similarly, starting from compound **40** (510 mg, 1.04 mmol), product **42** was obtained as thick oil, (426 mg, 84%) following the above procedure. $[\alpha]_D^{25}$ +29.7 (*c* 0.5 $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.18 (d, *J* = 6 Hz, 3H), 1.93 (sext, *J* = 6 Hz, 4H), 2.50–2.78 (m, 4H), 3.42–3.65 (m, 3H), 3.83 (dquint, *J* = 6 and 2 Hz, 1H), 4.39 (d, *J* = 12 Hz, 1H), 4.41–4.59 (m, 4H), 4.63 (d, *J* = 10 Hz, 1H), 7.15–7.40 (m, 15H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.4, 24.7, 30.5, 34.5, 41.4, 66.2, 70.3, 71.8, 72.9, 73.5, 73.8, 82.1, 90.5, 127.4, 127.55, 127.61, 127.67, 127.73, 128.25, 128.31, 138.0, 138.2, 138.6, 187.7; ESIMS (*m*/*z*) 507 $[M + Na]^+$, 523 $[M + K]^+$; Anal. Calcd for $C_{32}H_{36}O_4$: C, 79.31; H, 7.49. Found: C, 79.47; H, 7.85; IR ($CHCl_3$) ν_{max} 2253, 2215, 1670 cm^{-1}.



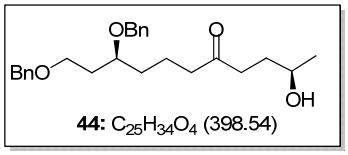
42: $C_{32}H_{36}O_4$ (484.63)

(2*R*,9*S*)-9,11-Bis(benzyloxy)-2-[(*tert*-butyldiphenylsilyl)oxy]undecan-5-one (43). To a stirred solution of **41** (0.50 g, 0.79 mmol) in EtOAc (10 mL) at 25 °C was added 10% Pd/C (50 mg). The reaction mixture was stirred under H_2 atmosphere at balloon pressure for 1 h and filtered through a pad of Celite. Removal of the solvent in vacuo followed by silica gel column chromatography of the residue using petroleum ether–ethyl acetate (93:7) as an eluent afforded pure product **43** as a thick oil (500 mg, ~100%). $[\alpha]_D^{25}$ +11.5 (*c* 1.1 $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.04 (d, *J* = 8 Hz, 3H), 1.04 (s, 9H), 1.40–1.80 (m, 6H), 1.84 (q, *J* = 6 Hz, 2H), 2.22–2.55 (m, 4H), 3.47–3.70 (m, 3H), 3.88 (sext, *J* = 6 Hz, 1H), 4.48 (s, 4H), 7.20–7.50 (m, 16H), 7.60–7.75 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.2, 19.4, 23.2, 27.0, 32.9, 33.6, 34.2, 38.3, 42.6, 66.8, 68.7, 71.1, 73.0, 75.8, 127.4, 127.45, 127.53, 127.7, 127.8, 128.29, 128.31, 129.5, 129.6, 134.2, 134.5, 135.76, 135.81, 138.4, 138.7, 210.8; ESIMS (*m*/*z*) 654 $[M + NH_4]^+$, 659 $[M + Na]^+$; Anal. Calcd for $C_{41}H_{52}O_4Si$: C, 77.31; H, 8.23. Found: C, 77.64; H, 8.37. IR ($CHCl_3$) ν_{max} 1713 cm^{-1}.



43: $C_{41}H_{52}O_4Si$ (636.93)

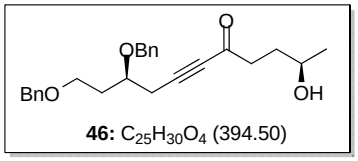
(2*R*,9*S*)-9,11-Bis(benzyloxy)-2-hydroxyundecan-5-one (44). To a stirred solution of compound **43**



44: $C_{25}H_{34}O_4$ (398.54)

(400 mg, 0.63 mmol) in THF (5 mL) at 0 °C was added TBAF (1 M in THF, 1.25 mL, 1.25 mmol) and the reaction mixture was stirred for 6 h at 25 °C. To the mixture was added sat. aq NH_4Cl (5 mL) and the THF was removed in vacuo. The obtained residue was dissolved in EtOAc (20 mL), and the organic layer was washed with brine (5 mL) and dried (Na_2SO_4). Removal of the solvent in vacuo followed by silica gel column chromatography of the resulting residue using petroleum ether–ethyl acetate (7:3) as an eluent afforded pure product **44** as a thick oil (230 mg, 92%). $[\alpha]_D^{25}$ +8.0 (*c* 1.16 $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.17 (d, *J* = 6 Hz, 3H), 1.40–1.95 (m, 8H), 2.10 (br s, 1H), 2.41 (t, *J* = 8 Hz, 2H), 2.50 (t, *J* = 8 Hz, 2H), 3.45–3.68 (m, 3H), 3.68–3.82 (m, 1H), 4.40–4.55 (m, 4H), 7.20–7.40 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.4, 23.6, 32.5, 33.4, 34.2, 38.9, 42.7, 66.8, 67.3, 71.1, 72.9, 75.8, 127.4, 127.5, 127.6, 127.8, 128.2, 128.3, 138.3, 138.7, 211.6; ESIMS (*m*/*z*) 421 $[M + Na]^+$, 437 $[M + K]^+$; Anal. Calcd for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found: C, 75.29; H, 8.23; IR (neat) ν_{max} 3445, 1712 cm^{-1}.

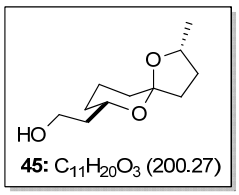
(2*R*,9*S*)-9,11-Bis(benzyloxy)-2-hydroxyundec-6-yn-5-one (46). To a stirred solution of alkyne **36** (100



46: $C_{25}H_{30}O_4$ (394.50)

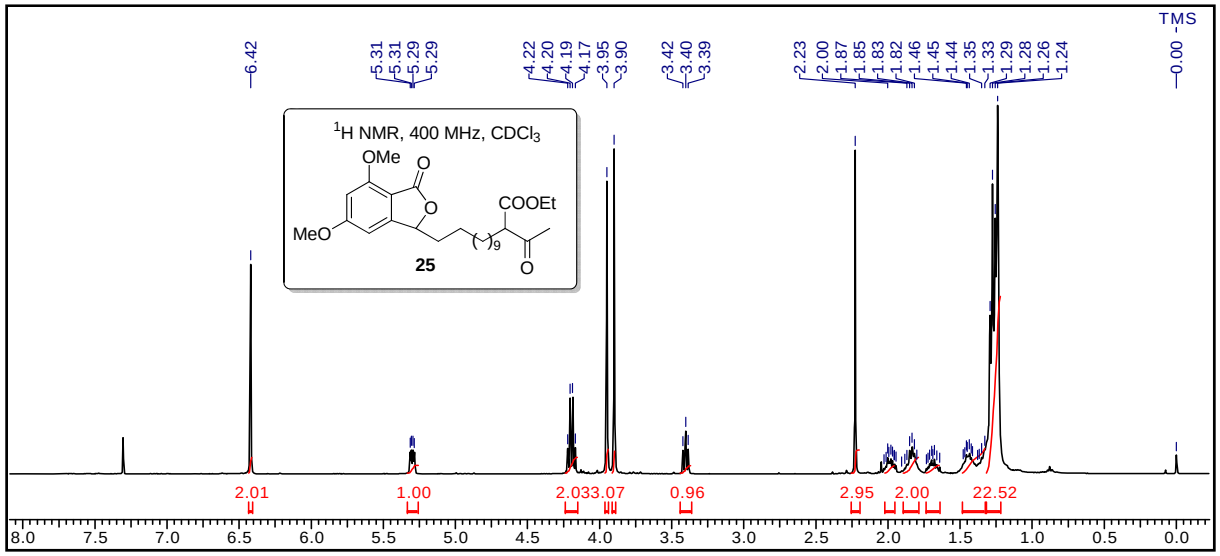
mg, 0.34 mmol) in THF (5 mL) at –78 °C was added *n*-BuLi (1.60 M in hexane, 0.21 mL, 0.34 mmol) and the reaction mixture was stirred for 30 min. To the above mixture was added dropwise $BF_3.OEt_2$ (0.04 mL, 0.34 mmol) at –78 °C and the stirring was further continued for 10 min, followed by the dropwise addition of (*R*)-γ-valerolactone (**20**, 0.03 mL, 0.34 mmol). The mixture was stirred further for 1 h at –78 °C and then quenched with sat. aq NH_4Cl (1 mL) and the THF was removed in vacuo. To the obtained residue was added EtOAc (10 mL) and the organic layer was washed with water (4 mL), brine (4 mL) and dried (Na_2SO_4). Removal of the solvent in vacuo followed by silica gel column chromatography of the resulting residue using petroleum ether–ethyl acetate (4:1) as an eluent afforded pure product **46** as a thick oil (109 mg, 82%). $[\alpha]_D^{25}$ +28.1 (*c* 0.72 $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.17 (d, *J* = 6 Hz, 3H), 1.60–2.05 (m, 4H), 2.65 (d, *J* = 6 Hz, 2H), 2.66 (t, *J* = 6 Hz, 2H), 3.50–3.65 (m, 2H), 3.65–3.90 (m, 2H), 4.40–4.55 (m, 2H), 4.50 (d, *J* = 10 Hz, 1H), 4.64 (d, *J* = 10 Hz, 1H), 7.20–7.40 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.4, 24.6, 32.9, 34.6, 41.9, 66.2, 66.9, 71.8, 73.0, 73.8, 82.1, 91.0, 127.6, 127.68, 127.74, 127.8, 28.3 (2 carbons), 138.0, 138.2, 188.0; ESIMS (*m*/*z*) 417 $[M + Na]^+$, 433 $[M + K]^+$; Anal. Calcd for $C_{25}H_{30}O_4$: C, 76.11; H, 7.66. Found: C, 76.22; H, 7.61; IR (neat) ν_{max} 3463, 2213, 1715, 1671 cm^{-1}.

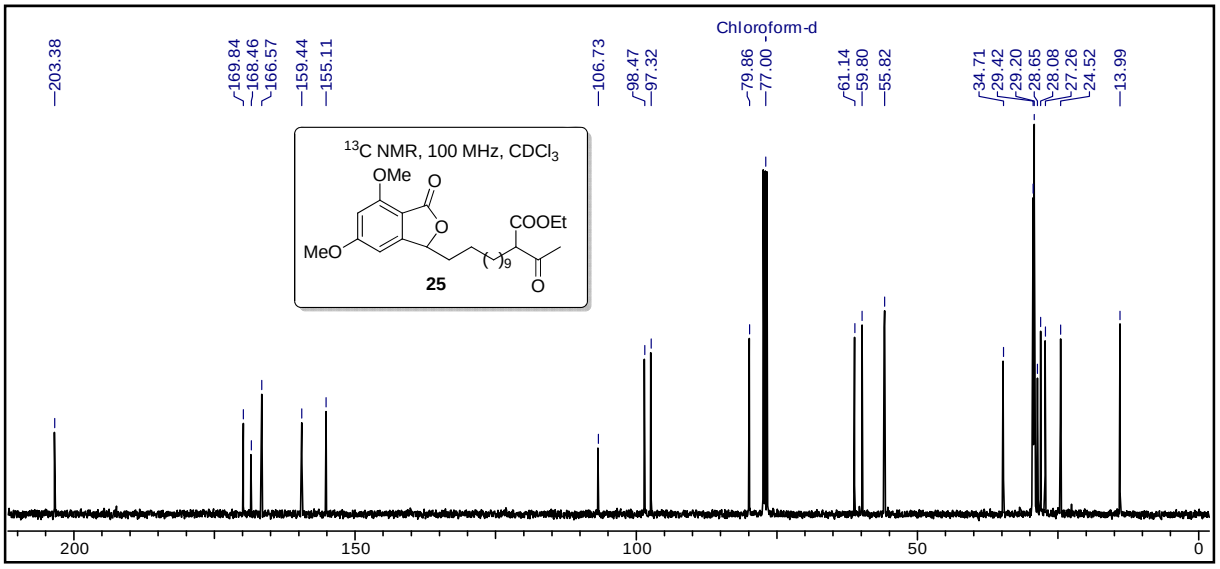
2-[(2*R*,5*R*,7*R*)-2-Methyl-1,6-dioxaspiro[4.5]decan-7-yl]ethanol (45). To a stirred solution of **42** (150 mg, 0.30 mmol)/**44** (200 mg, 0.50 mmol)/**46** (100 mg, 0.25 mmol) in MeOH (5 mL) at 25 °C was added 10% Pd/C (20 mg). The reaction mixture was stirred under an atmosphere of H_2 at 60 psi pressure for 8 h and filtered through a pad of Celite. Removal of the solvent in vacuo followed by silica gel column chromatography of the resulting residue using petroleum ether–ethyl acetate (3:1) as an eluent afforded pure product **45** as a thick oil [50/85/44 mg (82/85/87%)]. $[\alpha]_D^{25}$ +65.4 (*c* 0.76 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (d, *J* = 5 Hz, 3H), 1.27–1.37 (m, 1H), 1.40–1.48 (m, 1H), 1.51–1.56 (m, 1H), 1.62–1.93 (m, 8H), 2.04–2.18 (m, 1H), 3.03 (br s, 1H), 3.72–3.80 (m, 2H), 4.03 (tq, *J* = 10 and 5 Hz, 1H), 4.03 (sext, *J* = 10 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.1, 21.2, 30.8, 31.1, 33.2, 37.6, 38.0, 62.2, 71.8, 74.0, 106.2; ESIMS (*m*/*z*) 223 $[M + Na]^+$; IR ($CHCl_3$) ν_{max} 3368, 1613 cm^{-1}.

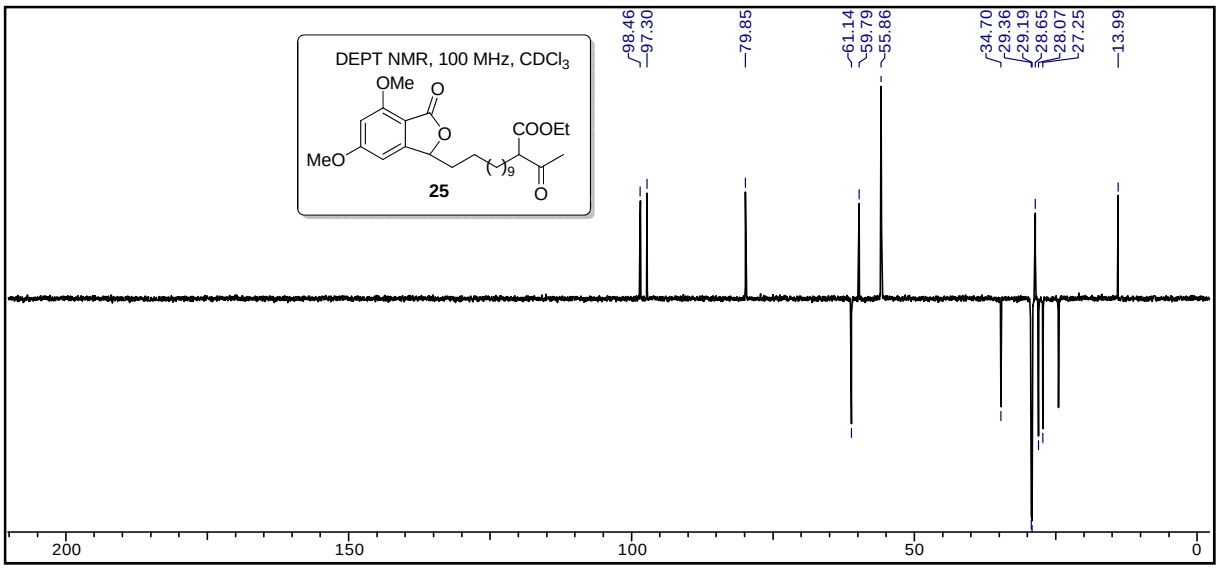


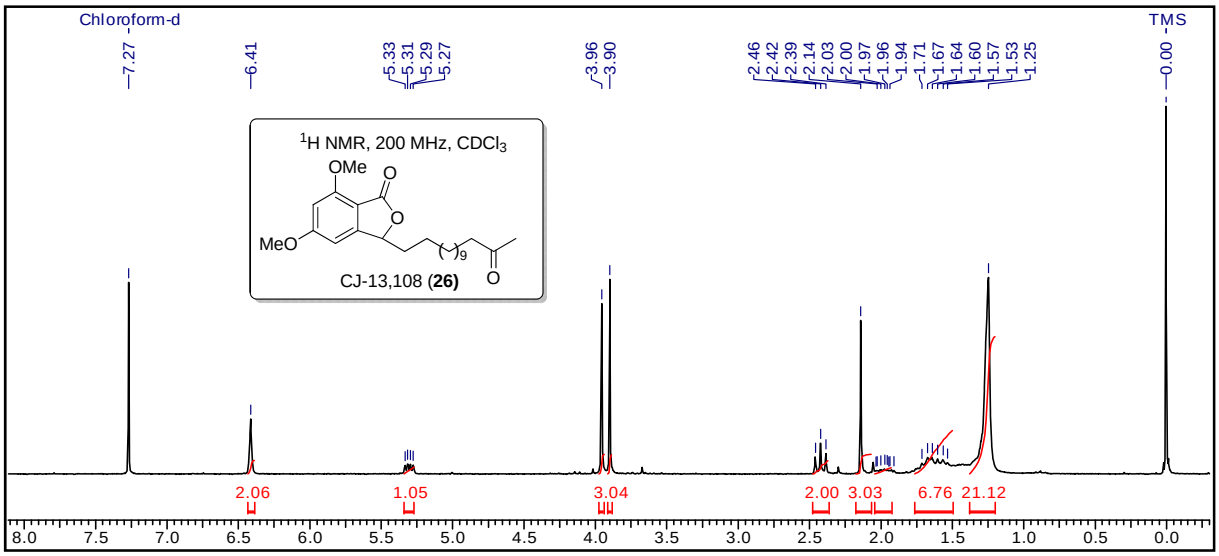
45: $C_{11}H_{20}O_3$ (200.27)

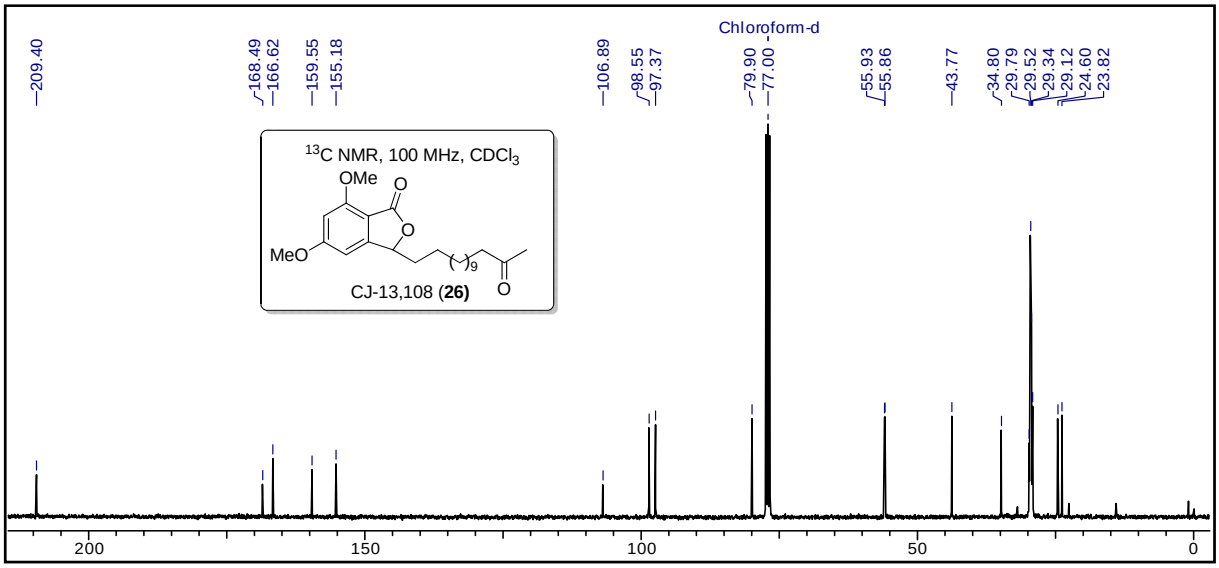
2B.5 Selected Spectra

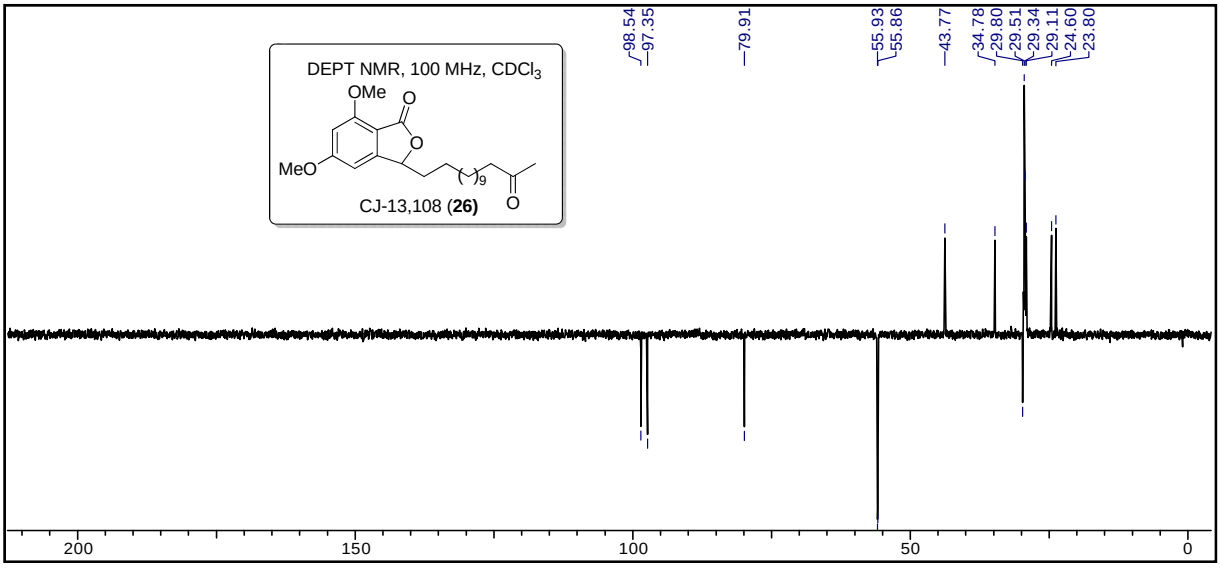

TMS
6.42
5.31
5.31
5.29
5.29
4.22
4.20
4.19
4.17
3.95
3.90
3.42
3.40
3.39
2.23
2.00
1.87
1.85
1.83
1.82
1.46
1.45
1.44
1.35
1.33
1.29
1.28
1.26
1.24
0.00
^{1}H NMR, 400 MHz, $CDCl_3$
OMe
O
O
COOEt
MeO
9
25
O
2.01
1.00
2.03
3.07
0.96
2.95
2.00
22.52
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

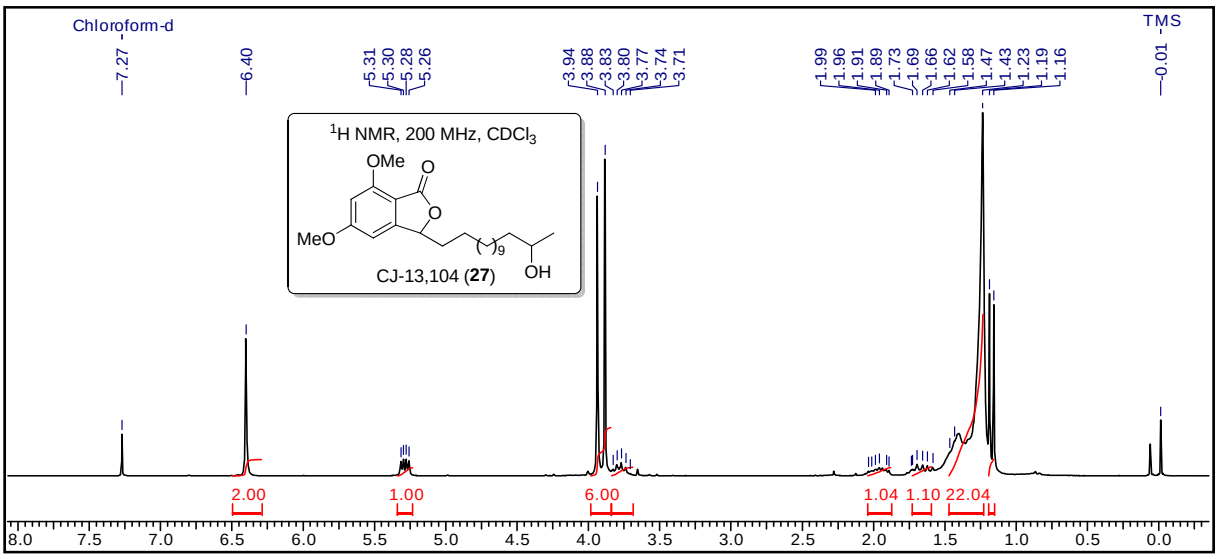

Chloroform-d
203.38
169.84
168.46
166.57
159.44
155.11
106.73
98.47
97.32
79.86
77.00
61.14
59.80
55.82
34.71
29.42
29.20
28.65
28.08
27.26
24.52
13.99
^{13}C NMR, 100 MHz, $CDCl_3$
OMe
O
O
COOEt
MeO
9
25
O
200
150
100
50
0

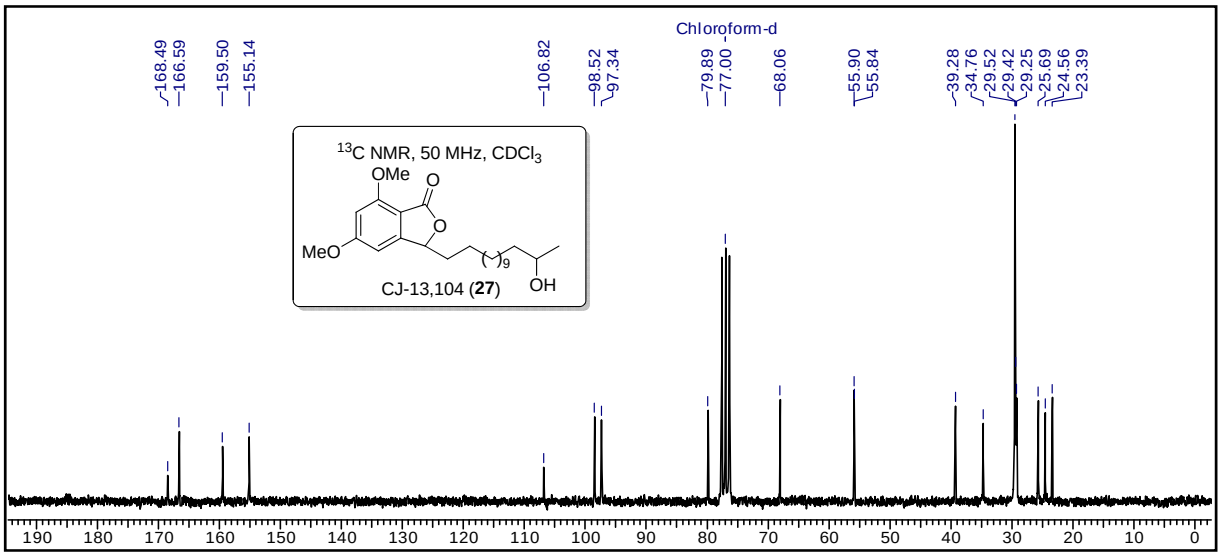

98.46
97.30
79.85
61.14
59.79
55.86
34.70
29.36
29.19
28.65
28.07
27.25
13.99
DEPT NMR, 100 MHz, $CDCl_3$
OMe
O
O
COOEt
MeO
9
25
O
200
150
100
50
0

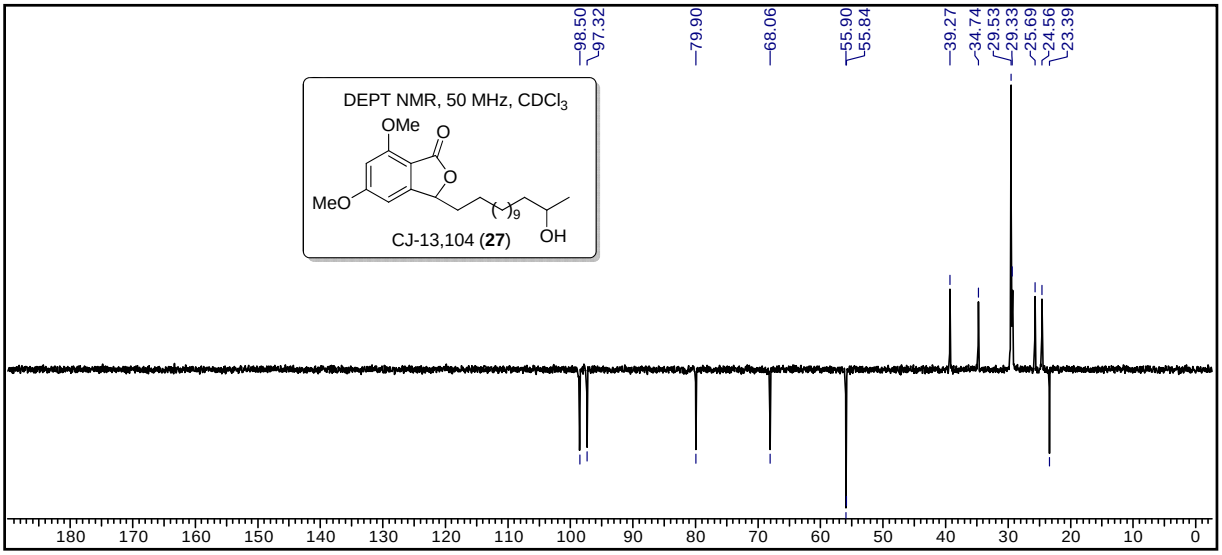

Chloroform-d
TMS
7.27
6.41
5.33
5.31
5.29
5.27
3.96
3.90
2.46
2.42
2.39
2.14
2.03
2.00
1.97
1.96
1.94
1.71
1.67
1.64
1.60
1.57
1.53
1.25
0.00
^{1}H NMR, 200 MHz, $CDCl_3$
OMe
O
O
MeO
9
O
CJ-13,108 (**26**)
2.06
1.05
3.04
2.00
3.03
6.76
21.12
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

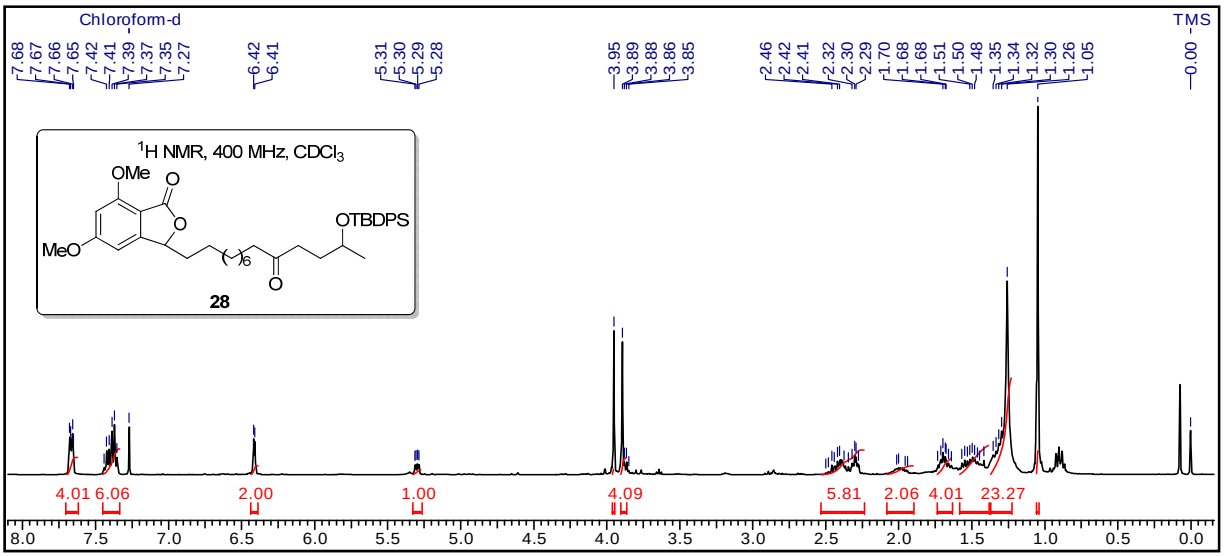

Chloroform-d
209.40
168.49
166.62
159.55
155.18
106.89
98.55
97.37
79.90
77.00
55.93
55.86
43.77
34.80
29.79
29.52
29.34
29.12
24.60
23.82
^{13}C NMR, 100 MHz, $CDCl_3$
OMe
O
O
MeO
9
O
CJ-13,108 (**26**)
200
150
100
50
0

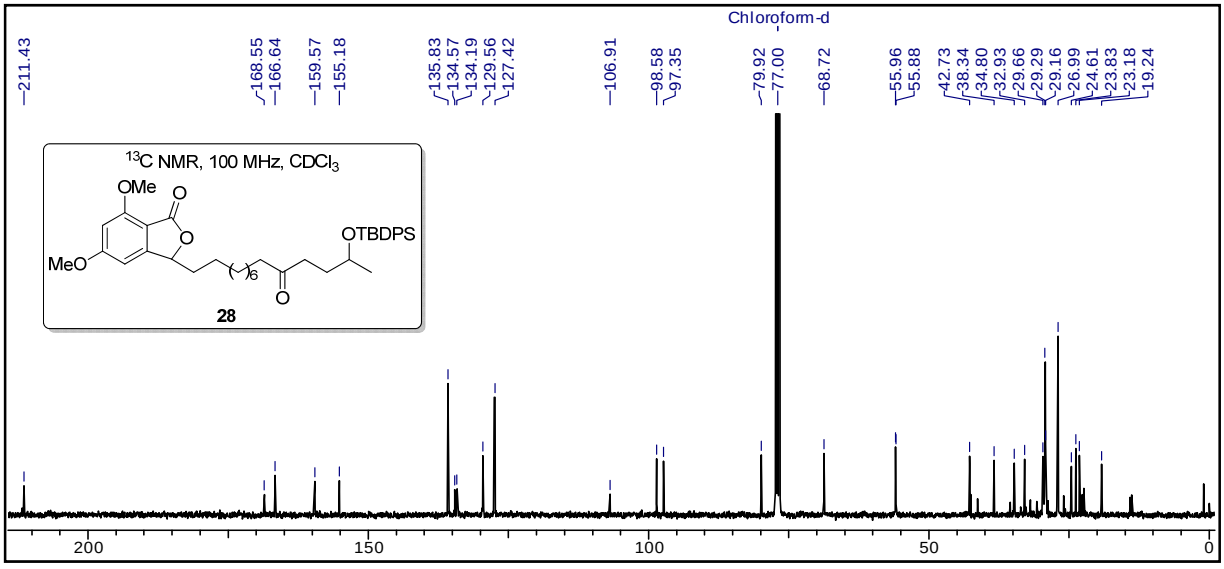

98.54
97.35
79.91
55.93
55.86
43.77
34.78
29.80
29.51
29.34
29.11
24.60
23.80
DEPT NMR, 100 MHz, $CDCl_3$
OMe
O
O
MeO
9
O
CJ-13,108 (**26**)
200
150
100
50
0

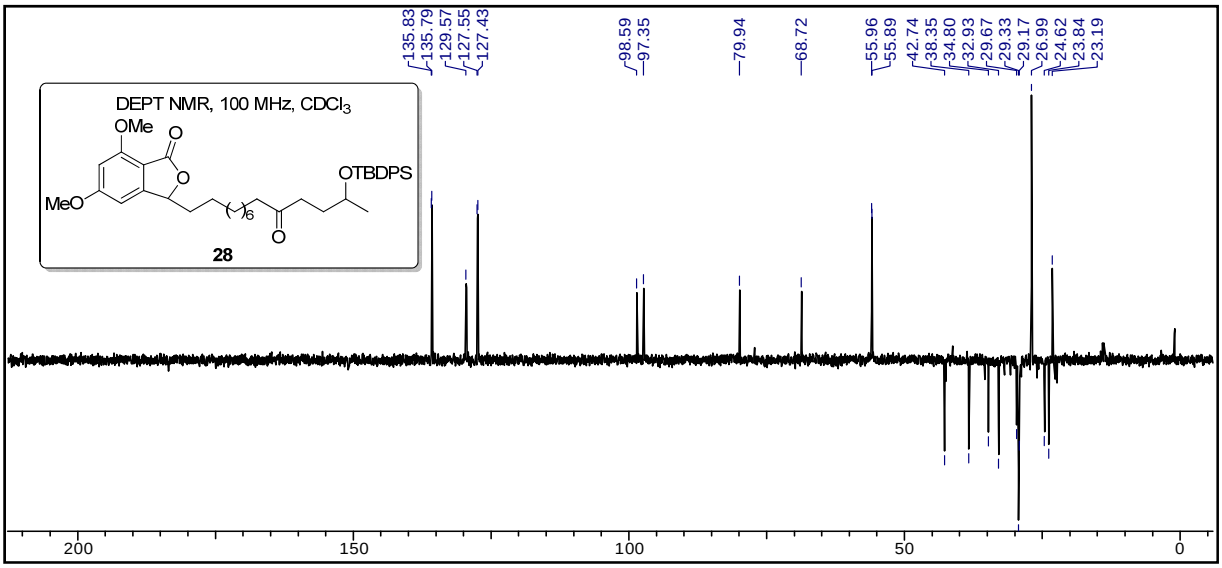

Chloroform-d
TMS
7.27
6.40
5.31
5.30
5.28
5.26
3.94
3.88
3.83
3.80
3.77
3.74
3.71
1.99
1.96
1.91
1.89
1.73
1.69
1.66
1.62
1.58
1.47
1.43
1.23
1.19
1.16
0.01
1H NMR, 200 MHz, CDCl3
OMe
O
O
MeO
9
OH
CJ-13,104 (27)
2.00
1.00
6.00
1.04
1.10
22.04
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

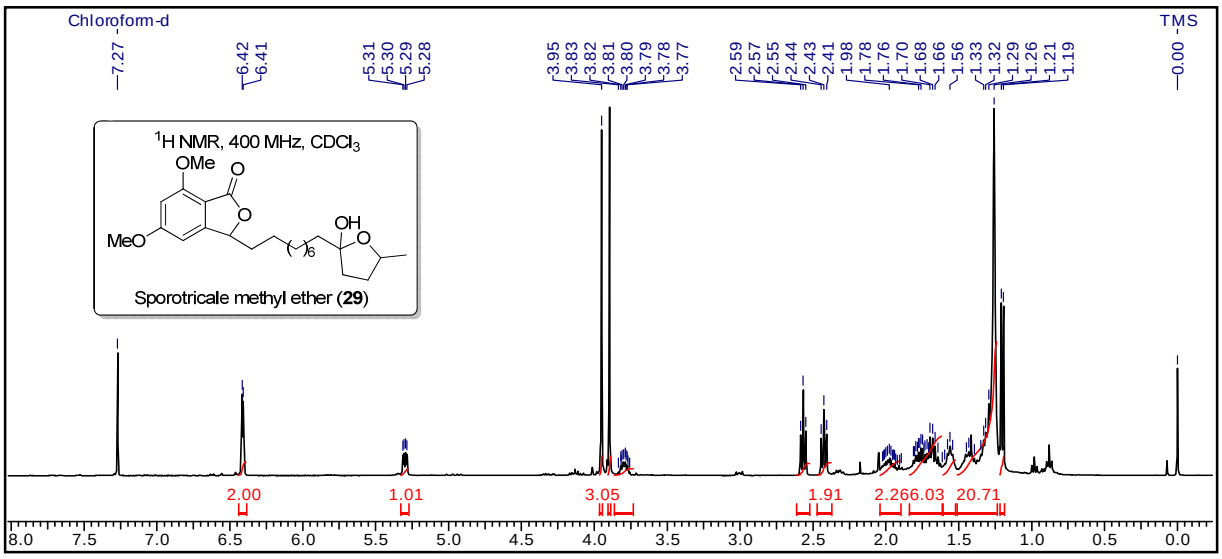

Chloroform-d
168.49
166.59
159.50
155.14
106.82
98.52
97.34
79.89
77.00
68.06
55.90
55.84
39.28
34.76
29.52
29.42
29.25
25.69
24.56
23.39
13C NMR, 50 MHz, CDCl3
OMe
O
O
MeO
9
OH
CJ-13,104 (27)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

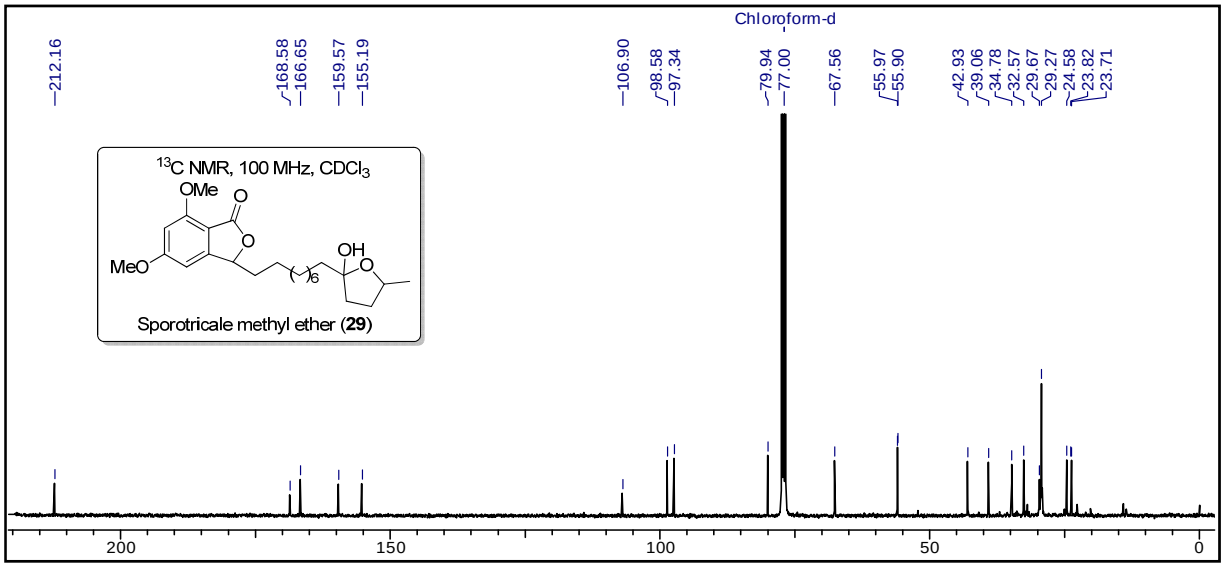

98.50
97.32
79.90
68.06
55.90
55.84
39.27
34.74
29.53
29.33
25.69
24.56
23.39
DEPT NMR, 50 MHz, CDCl3
OMe
O
O
MeO
9
OH
CJ-13,104 (27)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

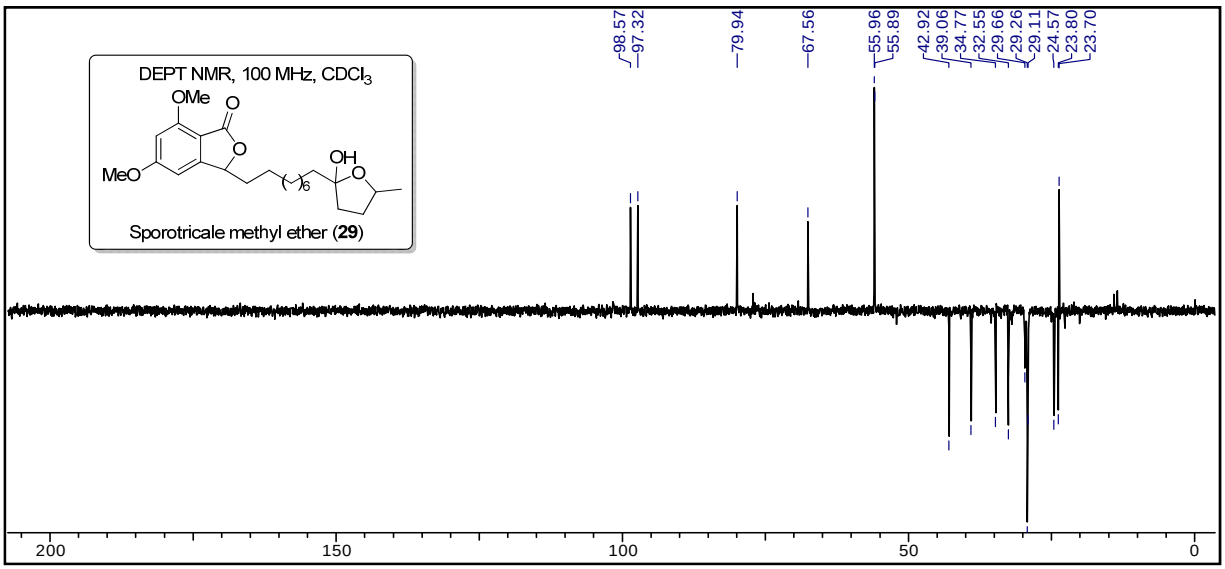

Chloroform-d
TMS
7.68 7.67 7.66 7.65 7.42 7.41 7.39 7.37 7.35 7.27
6.42 6.41
5.31 5.30 5.29 5.28
3.95 3.89 3.88 3.86 3.85
2.46 2.42 2.41 2.32 2.30 2.29
1.70 1.68 1.51 1.50 1.48 1.35 1.34 1.32 1.30 1.26 1.05
0.00
^{1}H NMR, 400 MHz, $CDCl_3$
OMe
MeO
OTBDPS
28
4.01 6.06 2.00 1.00 4.09 5.81 2.06 4.01 23.27
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

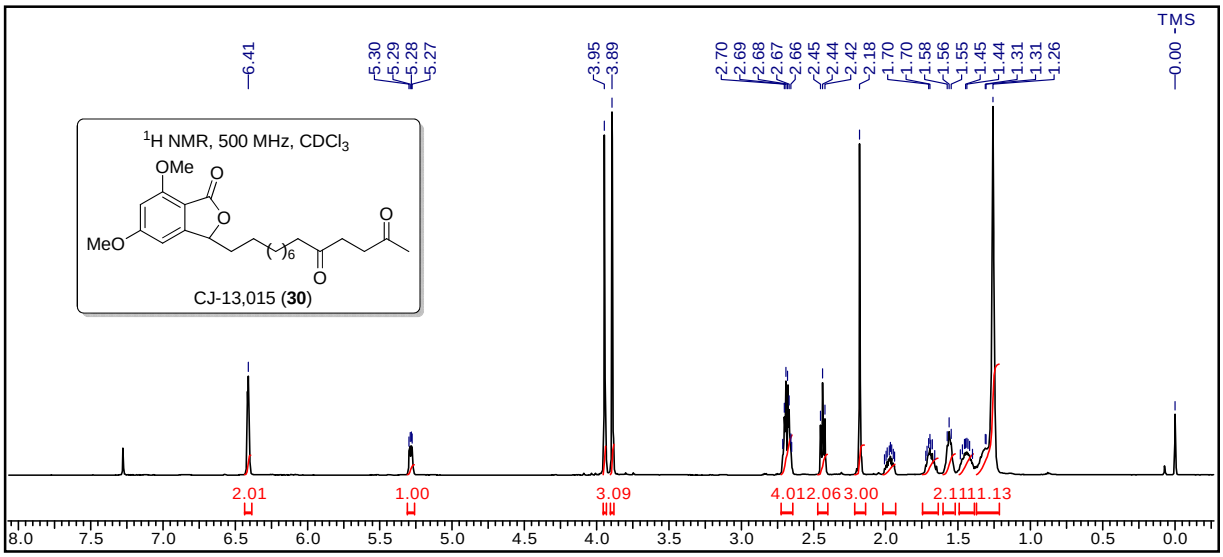

Chloroform-d
211.43
168.55 166.64 159.57 155.18
135.83 134.57 134.19 129.56 127.42
106.91
98.58 97.35
79.92 77.00
68.72
55.96 55.88
42.73 38.34 34.80 32.93 29.66 29.29 29.16 26.99 24.61 23.83 23.18 19.24
^{13}C NMR, 100 MHz, $CDCl_3$
OMe
MeO
OTBDPS
28
200 150 100 50 0

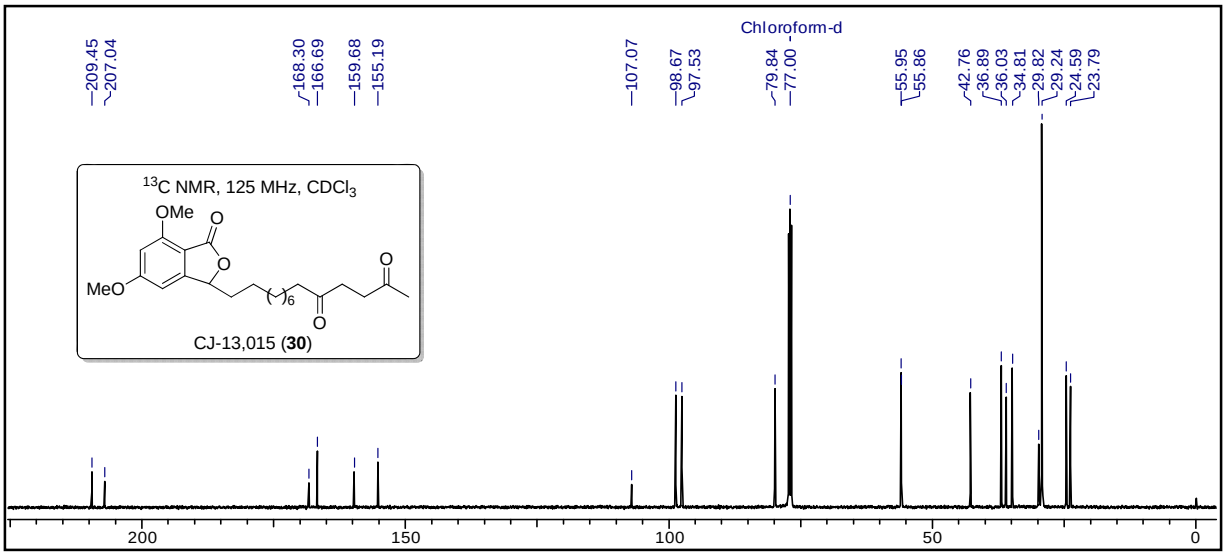

135.83 135.79 129.57 127.55 127.43
98.59 97.35
79.94
68.72
55.96 55.89
42.74 38.35 34.80 32.93 29.67 29.33 29.17 26.99 24.62 23.84 23.19
DEPT NMR, 100 MHz, $CDCl_3$
OMe
MeO
OTBDPS
28
200 150 100 50 0

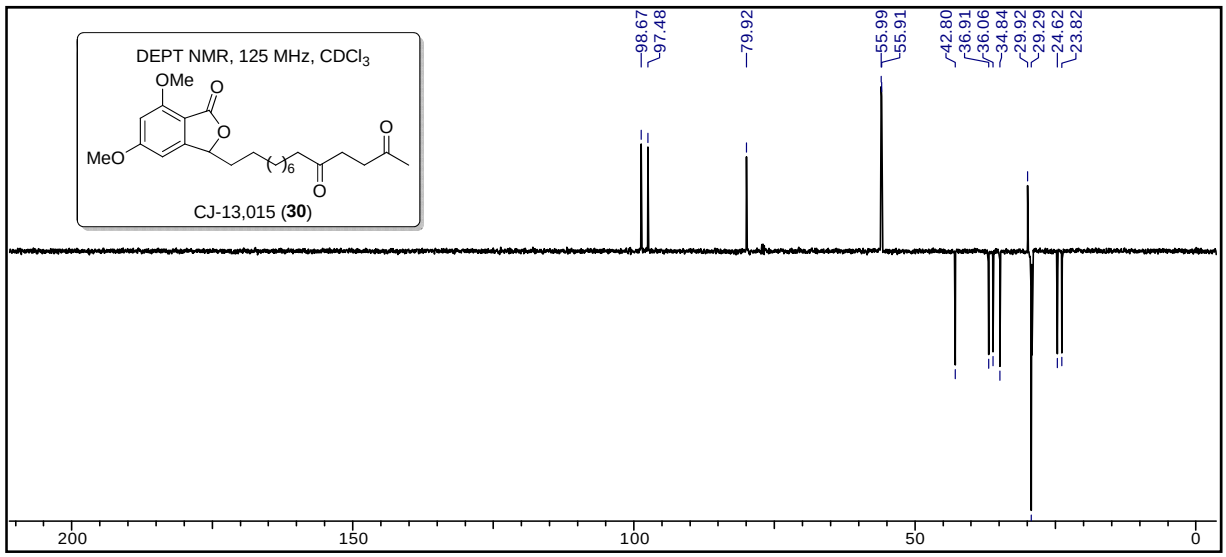

Chloroform-d
TMS
7.27
6.42
6.41
5.31
5.30
5.29
5.28
3.95
3.83
3.82
3.81
3.80
3.79
3.78
3.77
2.59
2.57
2.55
2.44
2.43
2.41
1.98
1.78
1.76
1.70
1.68
1.66
1.56
1.33
1.32
1.29
1.26
1.21
1.19
0.00
^{1}H NMR, 400 MHz, CDCl$_3$
OMe
O
O
MeO
OH
O
6
Sporotricale methyl ether (29)
2.00
1.01
3.05
1.91
2.26
6.03
20.71
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

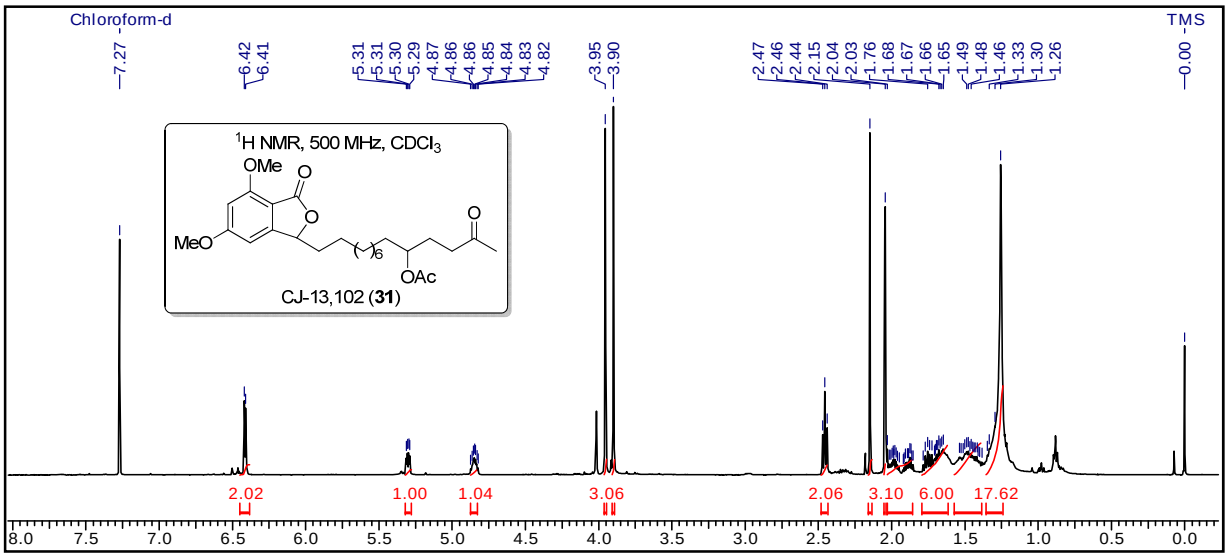

Chloroform-d
212.16
168.58
166.65
159.57
155.19
106.90
98.58
97.34
79.94
77.00
67.56
55.97
55.90
42.93
39.06
34.78
32.57
29.67
29.27
24.58
23.82
23.71
^{13}C NMR, 100 MHz, CDCl$_3$
OMe
O
O
MeO
OH
O
6
Sporotricale methyl ether (29)
200
150
100
50
0

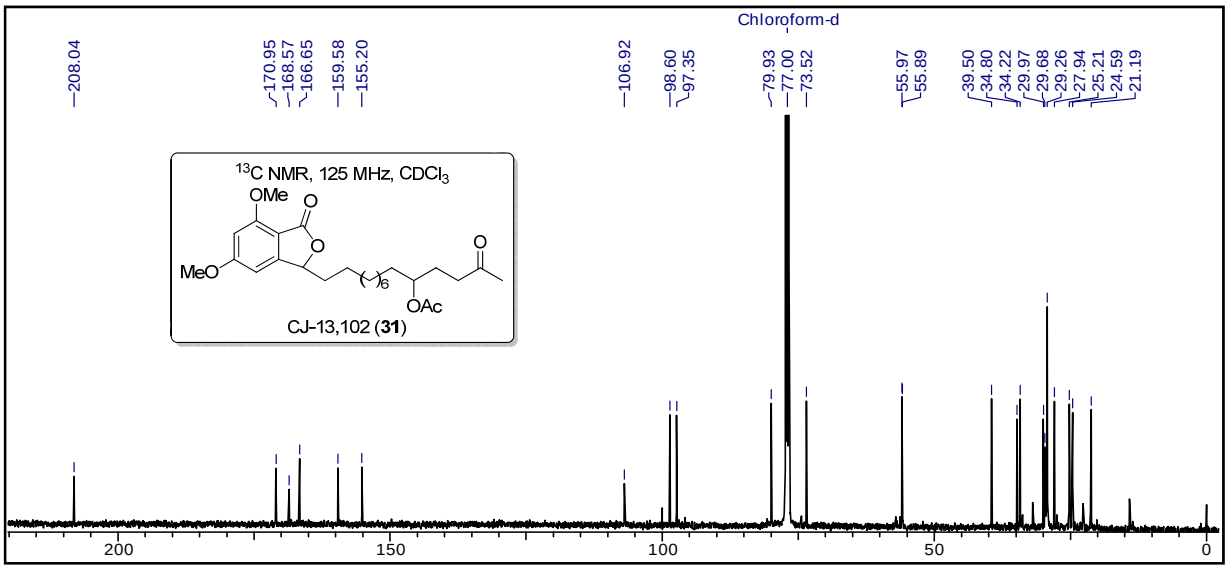

98.57
97.32
79.94
67.56
55.96
55.89
42.92
39.06
34.77
32.55
29.66
29.26
29.11
24.57
23.80
23.70
DEPT NMR, 100 MHz, CDCl$_3$
OMe
O
O
MeO
OH
O
6
Sporotricale methyl ether (29)
200
150
100
50
0

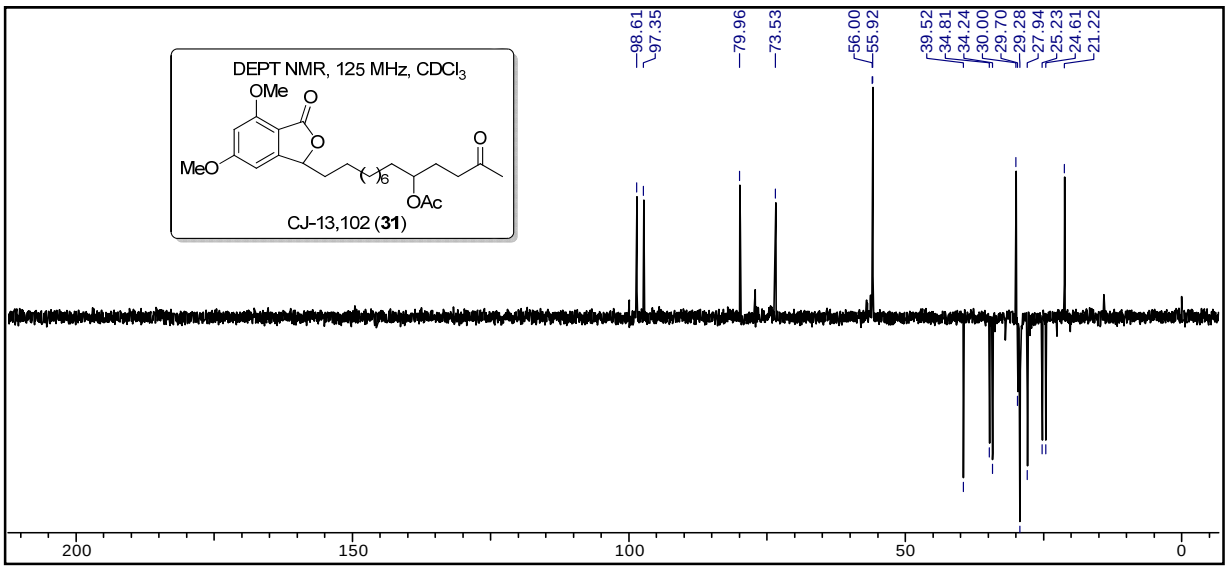

TMS
6.41
5.30
5.29
5.28
5.27
3.95
3.89
2.70
2.69
2.68
2.67
2.66
2.45
2.44
2.42
2.18
1.70
1.70
1.58
1.56
1.55
1.45
1.44
1.31
1.31
1.26
0.00
^{1}H NMR, 500 MHz, $CDCl_3$
OMe
MeO
CJ-13,015 (**30**)
2.01
1.00
3.09
4.01
2.06
3.00
2.11
11.13
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

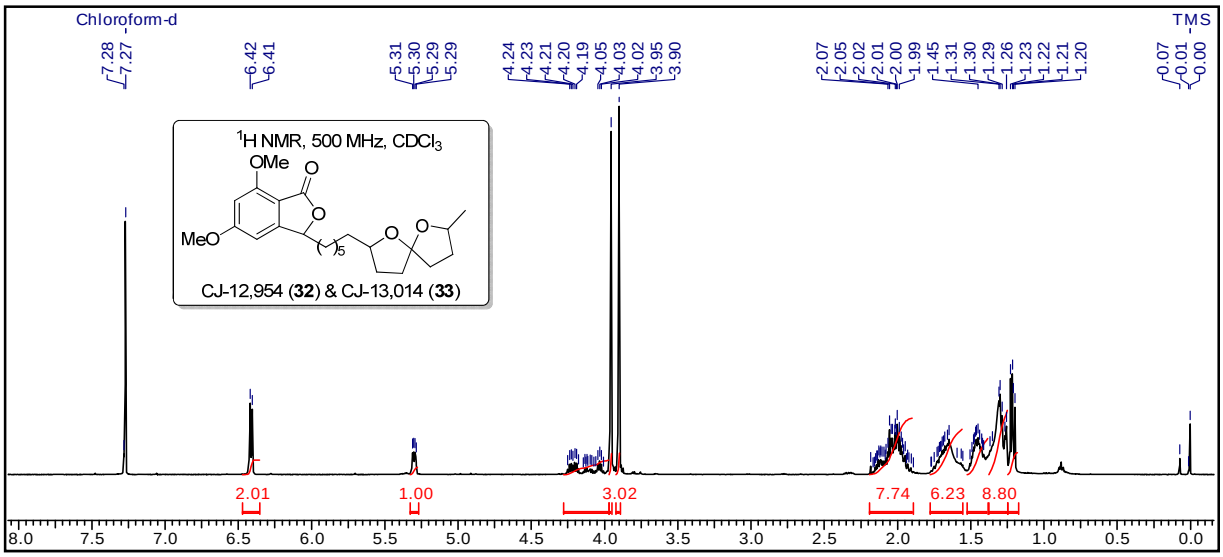

Chloroform-d
209.45
207.04
168.30
166.69
159.68
155.19
107.07
98.67
97.53
79.84
77.00
55.95
55.86
42.76
36.89
36.03
34.81
29.82
29.24
24.59
23.79
^{13}C NMR, 125 MHz, $CDCl_3$
OMe
MeO
CJ-13,015 (**30**)
200
150
100
50
0

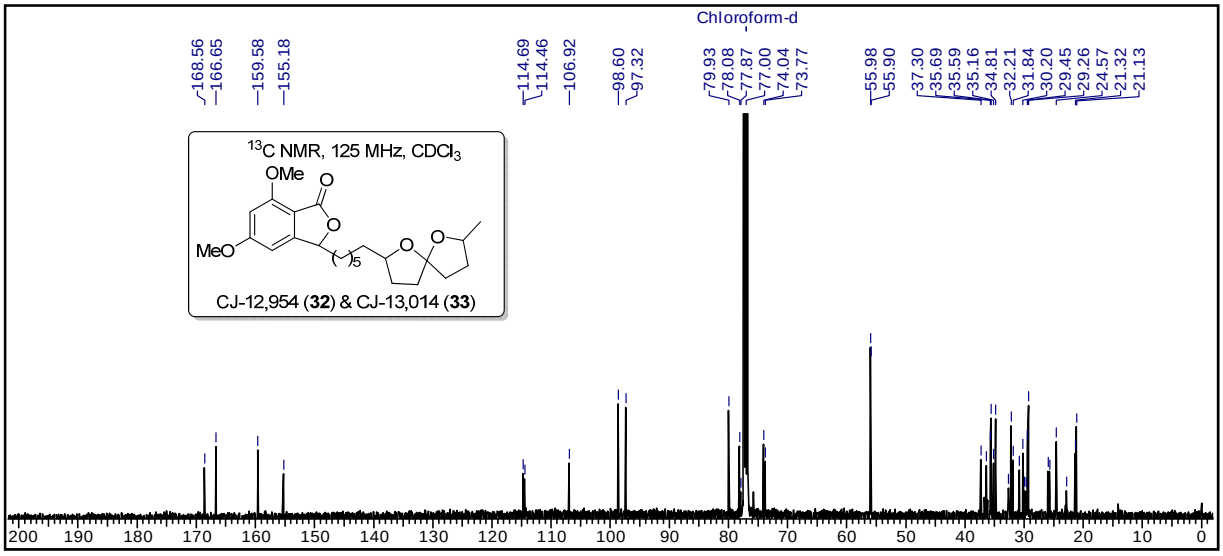

98.67
97.48
79.92
55.99
55.91
42.80
36.91
36.06
34.84
29.92
29.29
24.62
23.82
DEPT NMR, 125 MHz, $CDCl_3$
OMe
MeO
CJ-13,015 (**30**)
200
150
100
50
0

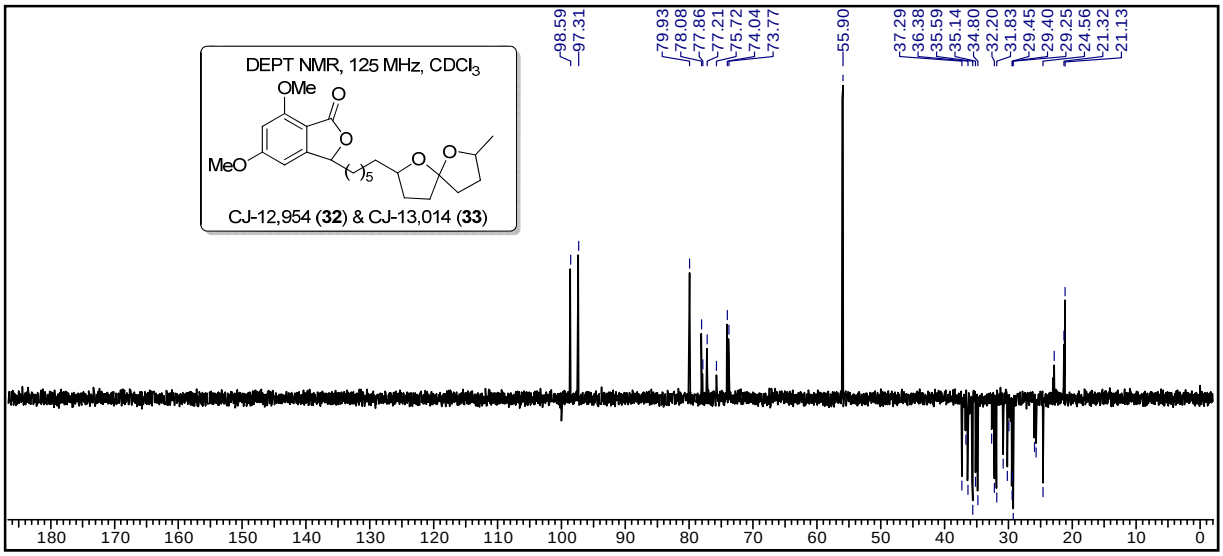

Chloroform-d
TMS
7.27
6.42
6.41
5.31
5.31
5.30
5.29
4.87
4.86
4.86
4.85
4.84
4.83
4.82
3.95
3.90
2.47
2.46
2.44
2.15
2.04
2.03
1.76
1.68
1.67
1.66
1.65
1.49
1.48
1.46
1.33
1.30
1.26
0.00
^{1}H NMR, 500 MHz, CDCl$_3$
OMe
O
O
MeO
6
O
OAc
CJ-13,102 (31)
2.02
1.00
1.04
3.06
2.06
3.10
6.00
17.62
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


Chloroform-d
208.04
170.95
168.57
166.65
159.58
155.20
106.92
98.60
97.35
79.93
77.00
73.52
55.97
55.89
39.50
34.80
34.22
29.97
29.68
29.26
27.94
25.21
24.59
21.19
^{13}C NMR, 125 MHz, CDCl$_3$
OMe
O
O
MeO
6
O
OAc
CJ-13,102 (31)
200
150
100
50
0

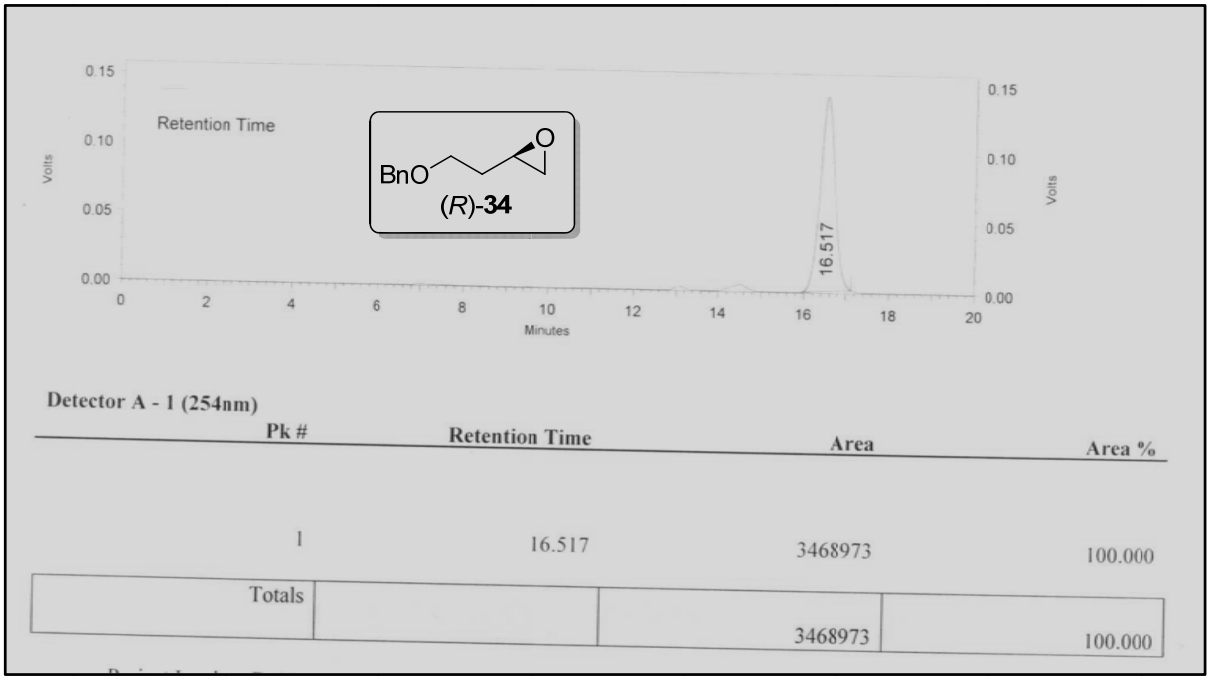

98.61
97.35
79.96
73.53
56.00
55.92
39.52
34.81
34.24
30.00
29.70
29.28
27.94
25.23
24.61
21.22
DEPT NMR, 125 MHz, CDCl$_3$
OMe
O
O
MeO
6
O
OAc
CJ-13,102 (31)
200
150
100
50
0


Chloroform-d
TMS
7.28
7.27
6.42
6.41
5.31
5.30
5.29
5.29
4.24
4.23
4.21
4.20
4.19
4.05
4.03
4.02
3.95
3.90
2.07
2.05
2.02
2.01
2.00
1.99
1.45
1.31
1.30
1.29
1.26
1.23
1.22
1.21
1.20
0.07
0.01
0.00
^{1}H NMR, 500 MHz, CDCl$_3$
OMe
MeO
CJ-12,954 (32) & CJ-13,014 (33)
2.01
1.00
3.02
7.74
6.23
8.80
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


Chloroform-d
168.56
166.65
159.58
155.18
114.69
114.46
106.92
98.60
97.32
79.93
78.08
77.87
77.00
74.04
73.77
55.98
55.90
37.30
35.69
35.59
35.16
34.81
32.21
31.84
30.20
29.45
29.26
24.57
21.32
21.13
^{13}C NMR, 125 MHz, CDCl$_3$
OMe
MeO
CJ-12,954 (32) & CJ-13,014 (33)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

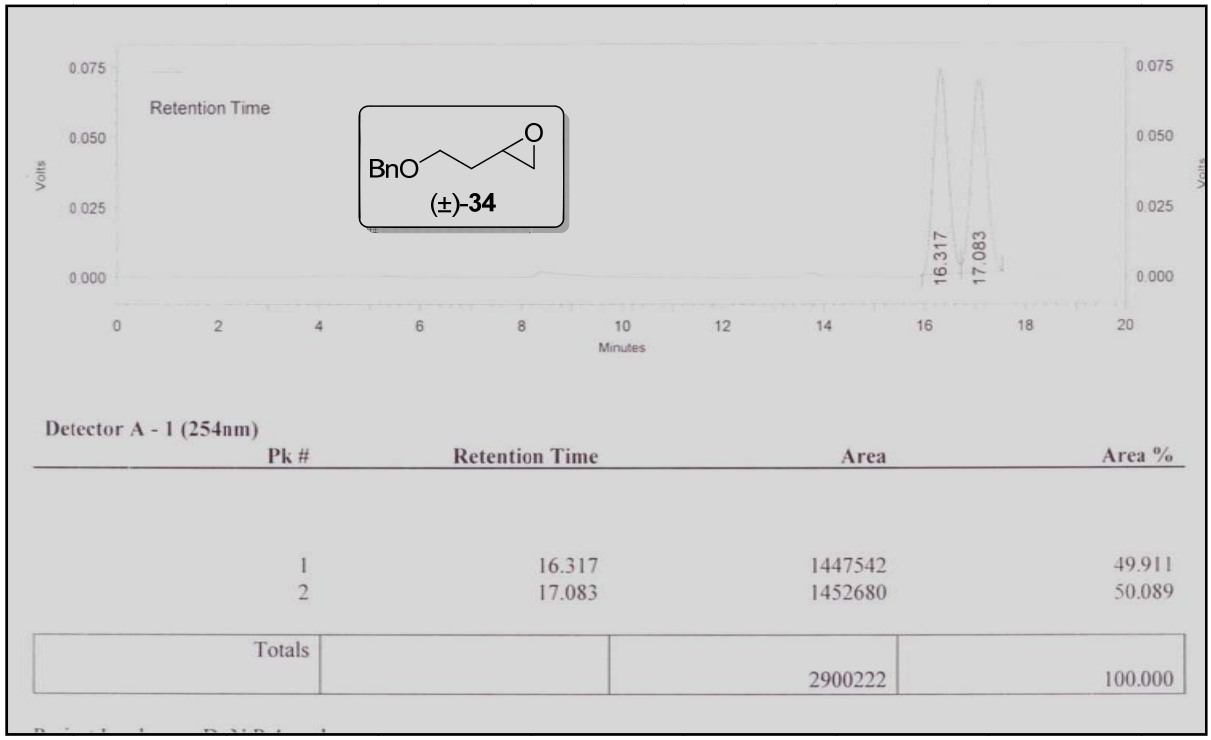

98.59
97.31
79.93
78.08
77.86
77.21
75.72
74.04
73.77
55.90
37.29
36.38
35.59
35.14
34.80
32.20
31.83
29.45
29.40
29.25
24.56
21.32
21.13
DEPT NMR, 125 MHz, CDCl$_3$
OMe
MeO
CJ-12,954 (32) & CJ-13,014 (33)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

Column: Chiralcel OD-H (250 x 4.6 mm)
Mobile Phase: IPA:PE (1.5:98.5)
Wavelength: 254 nm
Flow Rate: 0.5 mL/min (286 psi)
Sample Conc.: 1 mg/1.0 mL



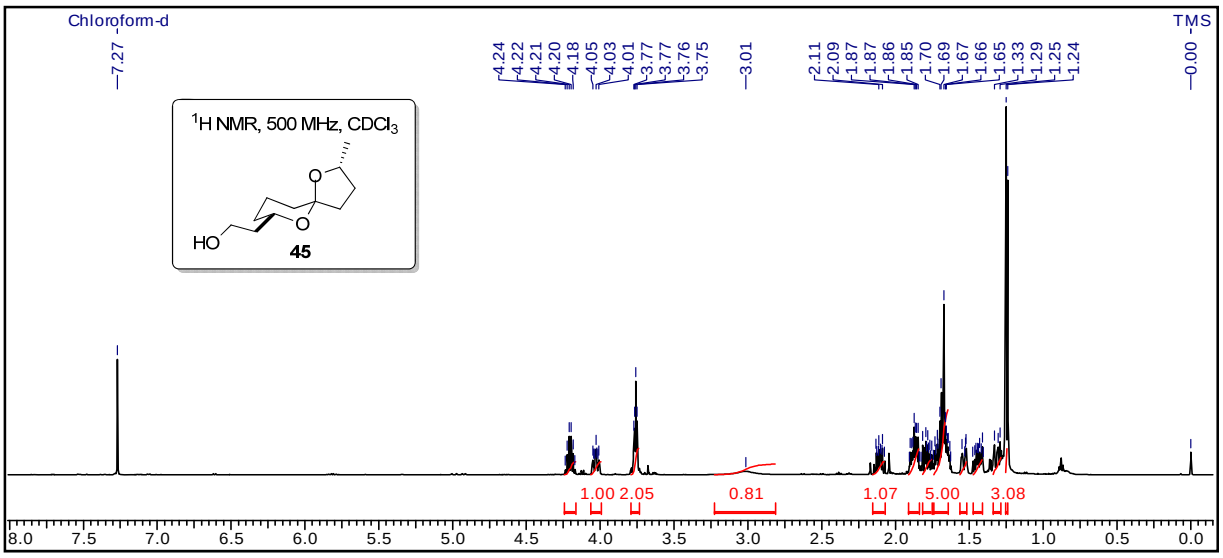
Detector A - 1 (254nm)

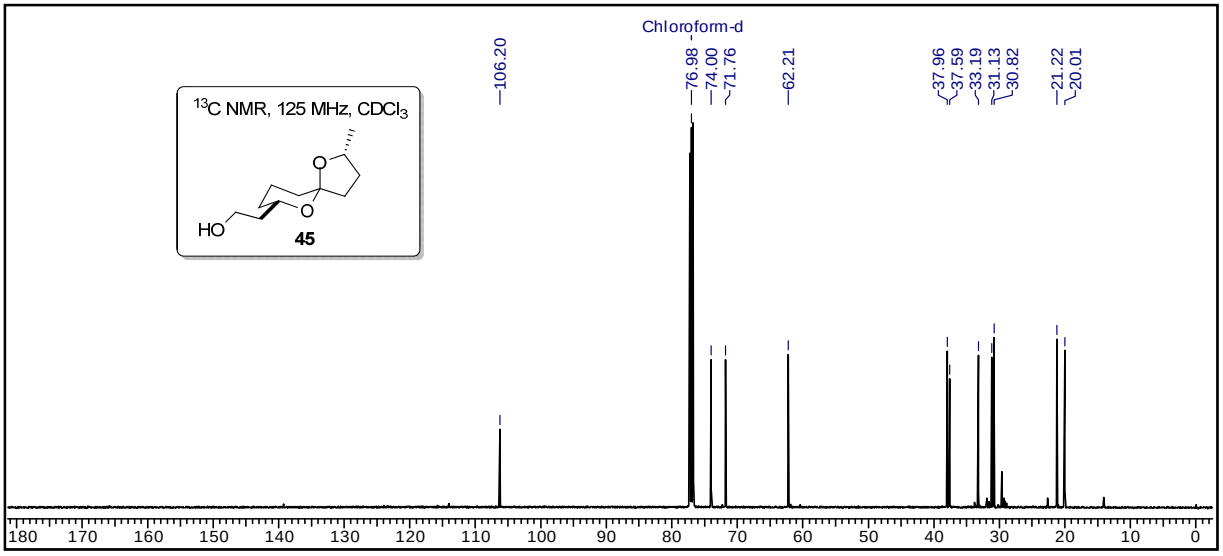
Pk #	Retention Time	Area	Area %
1	16.517	3468973	100.000
Totals		3468973	100.000

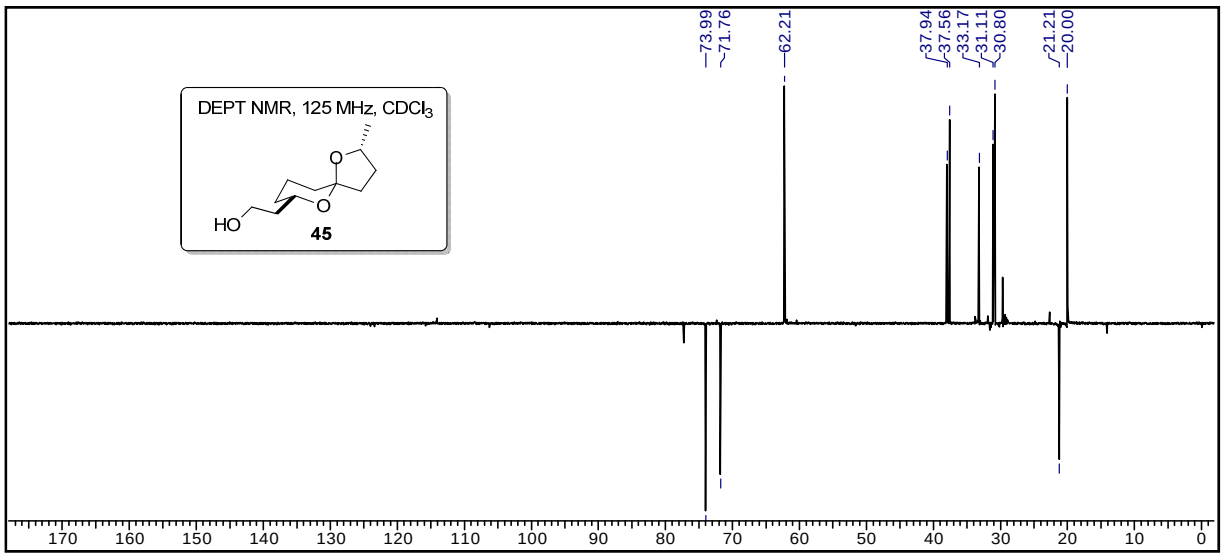


Detector A - 1 (254nm)

Pk #	Retention Time	Area	Area %
1	16.317	1447542	49.911
2	17.083	1452680	50.089
Totals		2900222	100.000


Chloroform-d
TMS
7.27
4.24
4.22
4.21
4.20
4.18
4.05
4.03
4.01
3.77
3.77
3.76
3.75
3.01
2.11
2.09
1.87
1.87
1.86
1.85
1.70
1.69
1.67
1.66
1.65
1.33
1.29
1.25
1.24
0.00
1H NMR, 500 MHz, CDCl3
HO
45
1.00 2.05 0.81 1.07 5.00 3.08


Chloroform-d
106.20
76.98
74.00
71.76
62.21
37.96
37.59
33.19
31.13
30.82
21.22
20.01
13C NMR, 125 MHz, CDCl3
HO
45


73.99
71.76
62.21
37.94
37.56
33.17
31.11
30.80
21.21
20.00
DEPT NMR, 125 MHz, CDCl3
HO
45

2B.6 References

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CHAPTER 3

Palladium-Catalyzed Routes to Geranylated/Farnesylated Phenolic Systems: Total Synthesis of Naturally Occurring Pawhuskin C, Schweinfurthin J and NG-121 Methyl Ether

This chapter features the following topics:

Note: An independent figure, table, scheme, structure and reference numbers have been used for the each section.

This chapter is divided into two sections. The Section A presents a concise literature account of isolation, biological activity and synthesis of pawhuskins, schweinfurthins, NG-121 and stachybotrins (Figure). The Section B describes the total synthesis of naturally occurring pawhuskin C and schweinfurthin J utilizing Heck/Stille/Suzuki coupling reactions of two different electron rich phenolic segments bearing geranylated/farnesylated units. The Sonogashira coupling reaction followed by palladium catalyzed chemo- and stereoselective *cis*-reduction of an alkyne unit and the subsequent isomerization to desired natural products has been also described. This section also features the total synthesis of NG-121 methyl ether via a Stille coupling reaction of farnesyl unit with electron rich phenolic segment, hydroxy directed selective epoxidation of farnesyl chain with the concomitant phenol driven intramolecular regio- and diastereoselective ring closure to the corresponding hydroxybenzopyran and the regioselective formylation followed by reductive an in situ lactonization pathway. The detailed experimental procedures, complete tabulated analytical and spectral data and some selected NMR spectra have been appropriately included at the end part of Section B.

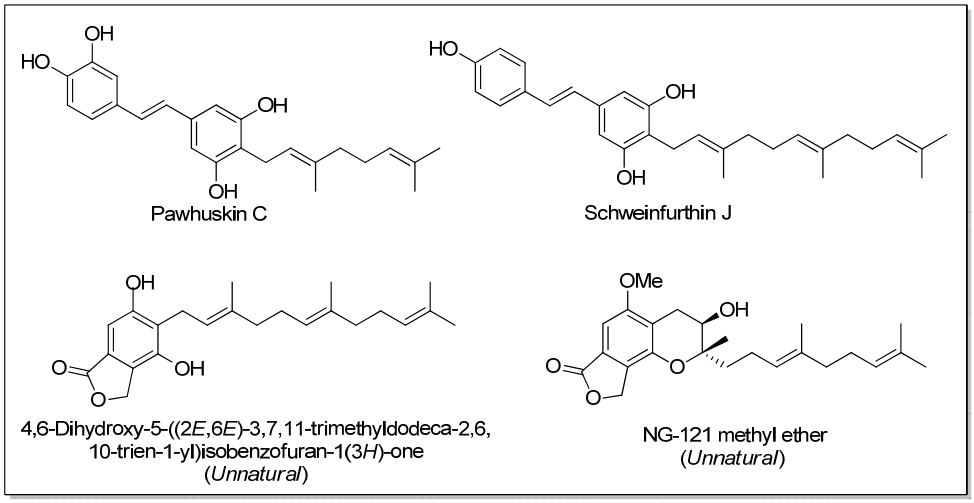


Figure. Oxygen containing bioactive natural and unnatural products synthesized

CHAPTER 3: SECTION A

A Concise Literature Account of Pawhuskins, Schweinfurthins, NG-121 and Stachybotrins

This section A of chapter 3 features the following topics:

3A.1. Background

Belofsky and co-workers[1] reported the isolation of several compounds from *Dalea purpurea*, including three new isoprenylated stilbenes named pawhuskins A-C (Figure 1, **1**-**3**). These three compounds were shown to have affinity for the opioid receptor in bioassays that quantified displacement of ^{3}Hnaloxone from a preparation of rat striatal tissue that included the α, κ, and μ receptors.[2] Pawhuskin A is the most active with respect to opioid receptor binding and its substitution pattern differs from that of pawhuskin C or synthetic schweinfurthins. During the past few years, it has been recognized that non-nitrogenous compounds can bind at the opioid receptors and demonstrate activity or block the binding of active agents.[3] The diterpenoid salvinorin A[4] was found to be a κ selective agonist and then more recently the pawhuskins have been reported to bind at opioid receptors although their specificity has not been established. However, there are compelling needs for new analgesics for treatment of pain as well as for compounds that block opiate binding for use in pharmacological interventions in the cases of stimulant abuse.[5] Apart from pawhuskins, artochamins F (**4**), artochamins G (**5**)[6] and mappin (**6**)[7] are the other representative examples of prenylated/geranylated phenolic stilbenes isolated from *Artocarpus chama* and *Macaranga mappa* respectively (Figure 1). Artochamins F and G possess interesting biological activities such as cytotoxicity, antibacterial effects against cariogenic bacteria and cyclooxygenase, and tyrosinase inhibitory activities. Whereas, mappin displays significant cytotoxicity against both drug resistant (SKVLB-1) and drug-sensitive (SK-OV-3) ovarian cancer cell lines (IC_{50} of 3.5μg/mL).

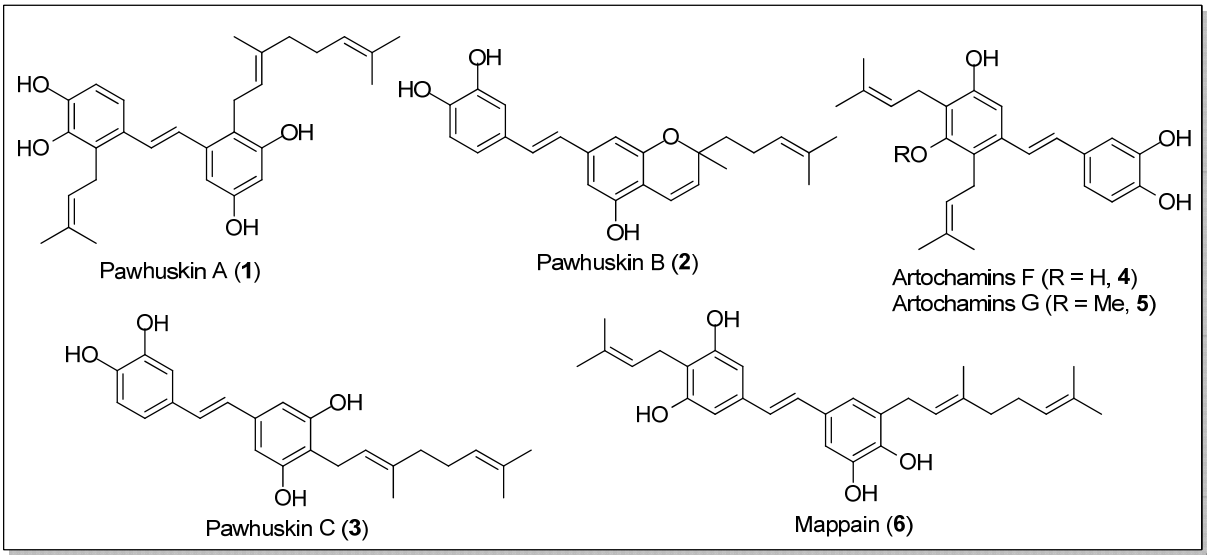


Figure 1. Naturally occurring pawhuskins and related natural products

Schweinfurthins and the closely related compound vedelianin (**18**) belong to a small family of isoprene substituted stilbenes (Figure 2, **7**-**17**).[8] These natural products have been isolated from

various *Macaranga* species in small and in some cases not easily reproducible quantities. Schweinfurthins display significant and differential cytotoxicity, based on the National Cancer Institutes's (NCI) 60-cell line assay report.[8a] Although compounds are known with greater potency, only the stellettins,[9] cephalostatins[10] and OSW-112[11] display a similar pattern of activity in the 60-cell line assay. Furthermore the schweinfurthins do not correlate through the COMPARE statistical analysis[12] to any clinical agent in NCI's standard agent database which suggests that they attack a new target or have a novel mode of action. At present no mechanism has been determined to account for their biological activity. Schweinfurthins, which may be the synthetically accessible of these families, show special potency toward central nervous system-derived cell lines including those from glioblastoma multiforme (e.g., SF-295, <10 nM GI_{50}) for which there is no effective clinical treatment.

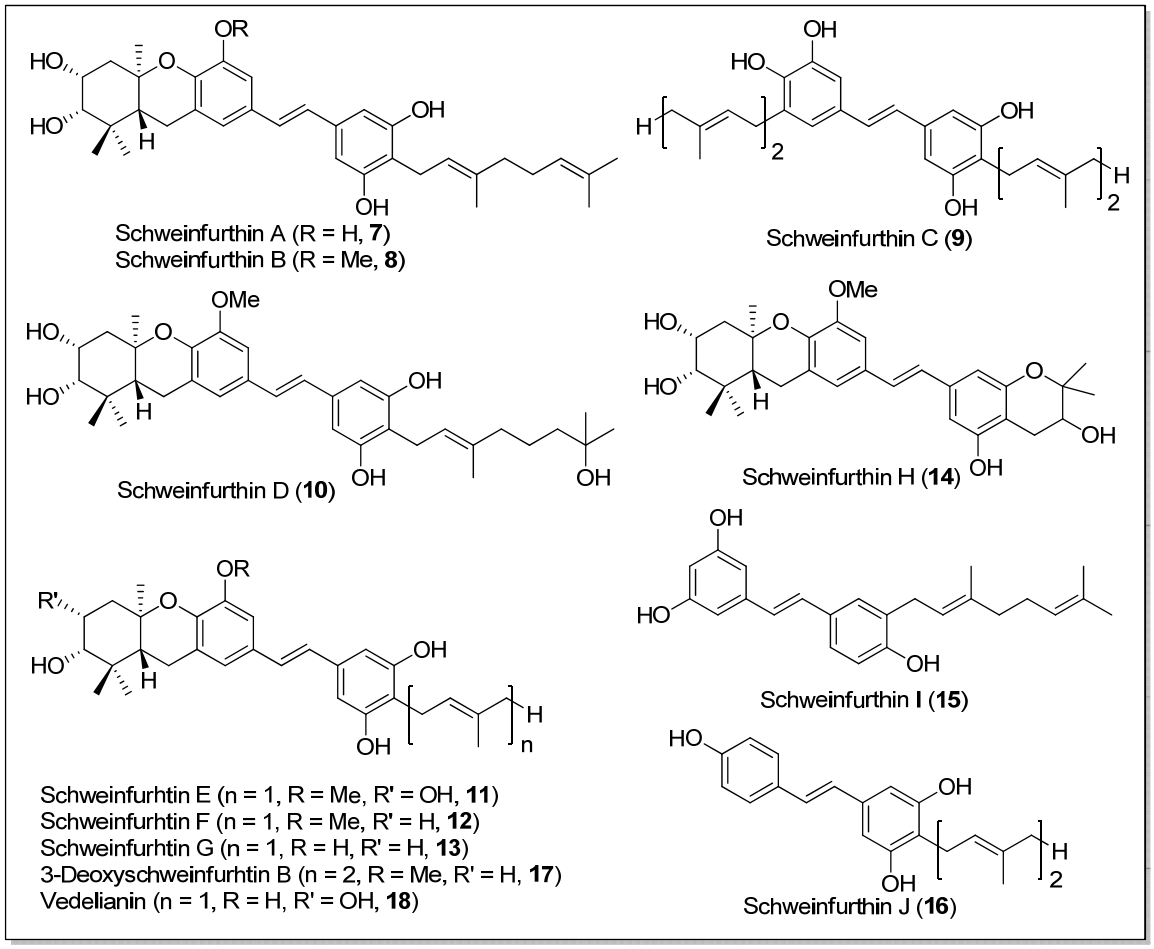


Figure 2. Naturally occurring schweinfurthins

A large number of structurally interesting and biologically important natural and unnatural benzopyrans are known in the literature.[13] The naturally occurring novel multifunctional NG-121 (**19**) and stachybotrin C (**22**) were isolated from the culture broth of *Stachybotrys parvispora* F-4708[14,15]

(Figure 3). The NG-121 has been suggested to be effective against Alzheimer's disease, while stachybotrin C prevents hypoxic neuronal injury caused by ischemia.[14,15] The stachybotrin A (**20**) and B (**21**) were isolated from *Stachybotrys* (SC-710-1) and possess anti-bacterial and anti-fungal activities.[16] SMTP congeners were isolated from *Stachybotrys microspora* and are effective plasminogen modulators.[17,18]

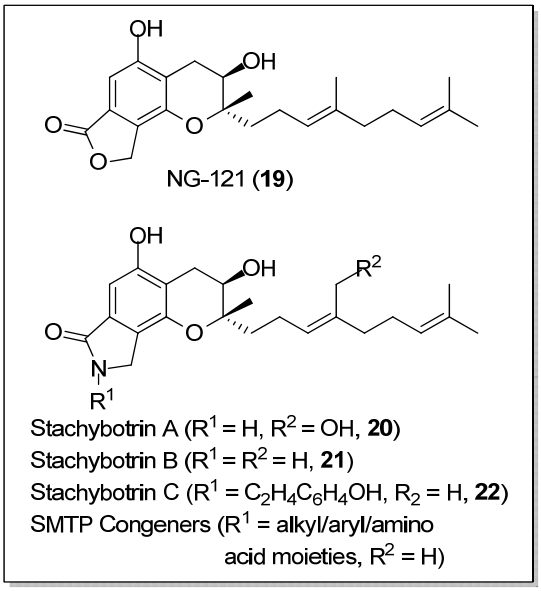


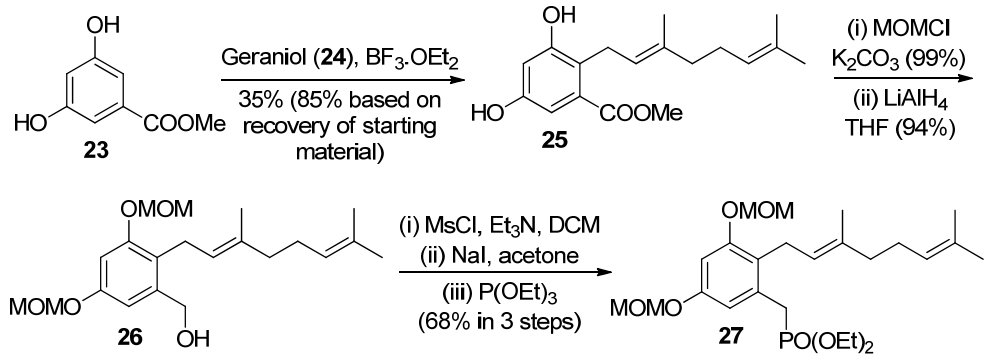
Figure 3. Naturally occurring multifunctional bioactive chromanols

3A.2 Synthetic Approaches Towards Pawhuskins, Schweinfurthins and NG-121 Model Compound

The combination of interesting biological activity and the need for different protocols for introduction of the isoprenoid substituents led to an interest in the preparation of these compounds and various elegant approaches have been reported in the literature for the synthesis of pawhuskins, schweinfurthins and NG-121 model compound. The common strategy applied for the synthesis of pawhuskin A, pawhuskin C and schweinfurthin C involves *ortho*-lithiation to install the geranyl chain and the subsequent appropriate Horner-Wadworth-Emmons condensation to form the desired *trans*-stilbene. The $BF_3.OEt_2$ mediated cascade cyclization strategy is applied for the synthesis of schweinfurthin B, E, F and G. The latter strategy was further extended for the synthesis of schweinfurthin A. In the present section these elegant literature approaches have been discussed in a concise fashion.

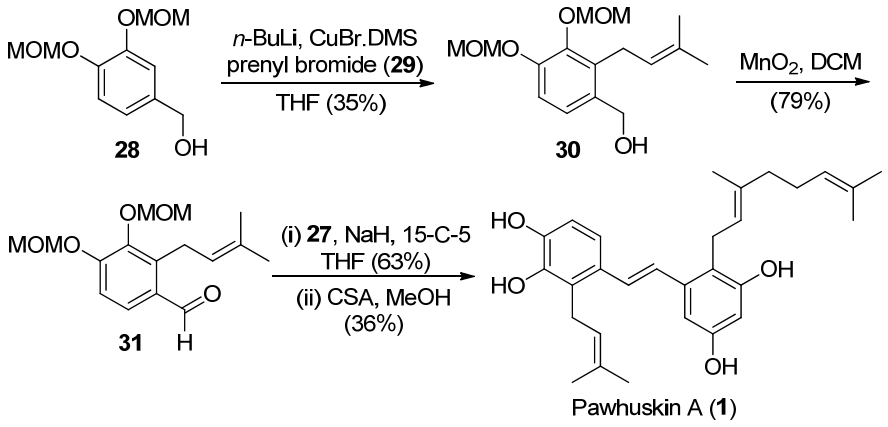
3A.2.1 Wiemer's Approach Towards the Synthesis of Pawhuskin A

Weimer and co-workers[19] reported a nice approach to pawhuskin A (**1**) in which a geranylated phosphonate **27** and a prenylated aldehyde **31** were coupled using stereoselective Horner-Wadsworth-Emmons condensation to afford the target *trans*-olefin isomer. For the synthesis of phosphonate **27**, the ester **23** was treated with geraniol (**24**) and $BF_3{\cdot}OEt_2$ to obtain the target carbon skeleton **25** in 35% yield with a substantial recovery of starting material. Subsequent protection with the MOM groups and reduction with $LiAlH_4$ proceeded smoothly to afford the benzylic alcohol **26** in a good yield. Conversion of alcohol **26** to the corresponding phosphonate **27** also proceeded smoothly through formation of the mesylate, displacement with NaI and the final reaction with $P(OEt)_3$ (Scheme 1).



Scheme 1. Synthesis of Phosphonate **27**

The synthesis of the aldehyde **31** required for the anticipated HWE condensation is shown in scheme 2. 3,4-Dihydroxybenzaldehyde was readily converted to the MOM-protected benzyl alcohol **28**. Treatment of alcohol **28** with excess *n*-BuLi and CuBr.DMS followed by reaction with prenyl bromide



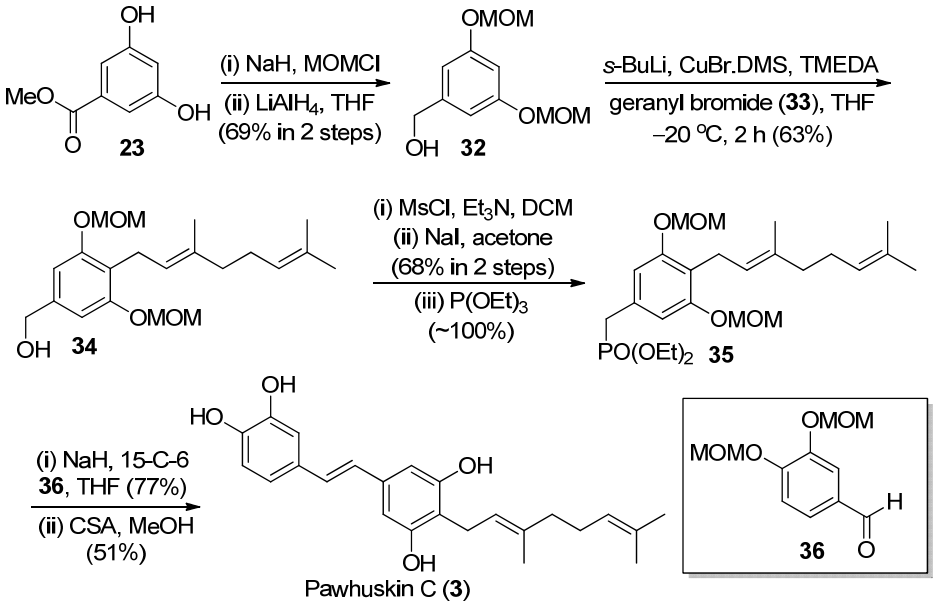
Scheme 2. Synthesis of Pawhuskin A

(**29**) afforded **30**. Oxidation of the benzylic alcohol **30** to the corresponding aldehyde **31** occurred readily upon treatment with MnO_2. The HWE condensation of phosphonate **27** and aldehyde **31**

smoothly provided the *trans*-stilbene with no trace of the isomeric *cis*-product. Deprotection of the four MOM groups was accomplished with CSA in MeOH to afford pawhuskin A (**1**) in 36% yield.

3A.2.2 Wiemer's Approach Towards the Synthesis of Pawhuskin C

Weimer and co-workers[20] reported the first synthesis of pawhuskin C (**3**). The reaction of the MOM protected compound **32** with *s*-BuLi and TMEDA followed by treatment with copper bromide–dimethyl sulfide and geranyl bromide (**33**) at −20 °C gave the alkylated benzylic alcohol **34** in 63% yield. Conversion of alcohol **34** to the corresponding phosphonate **35** also proceeded smoothly through formation of the mesylate, displacement with NaI and a final reaction with $P(OEt)_3$ (Scheme 3).



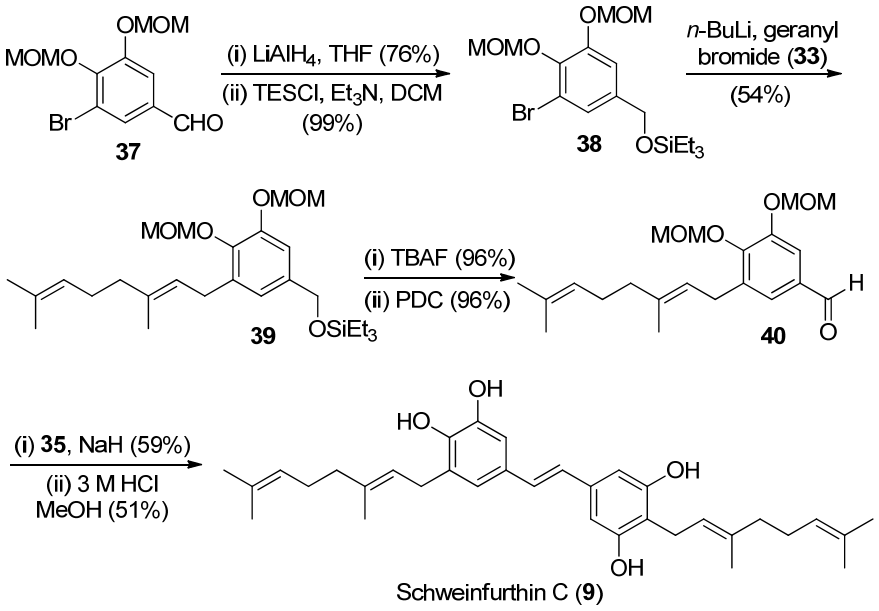
Scheme 3. Synthesis of Pawhuskin C

To complete the synthesis of pawhuskin C, the phosphonate **35** was treated with known benzaldehyde **36** and sodium hydride in the presence of catalytic 15-crown-5 to afford the *trans*-stilbene in good yield, which was subjected for MOM-deprotection using CSA to furnish the natural product pawhuskin C (**3**) in moderate 51% yield.

3A.2.3 Wiemer's Approach Towards the Synthesis of Schweinfurthin C

Weimer and co-workers[21] reported the synthesis of schweinfurthin C (**9**) via *ortho*-lithiation and HWE olefination strategy. The synthesis started from vanillin which was converted to the aldehyde **37** using known protocols. Aldehyde **37** on reduction with $LiAlH_4$ and the subsequent protection of the resulting alcohol with TESCl gave the silyl ether **38**. Compound **38** on treatment with *n*-BuLi followed

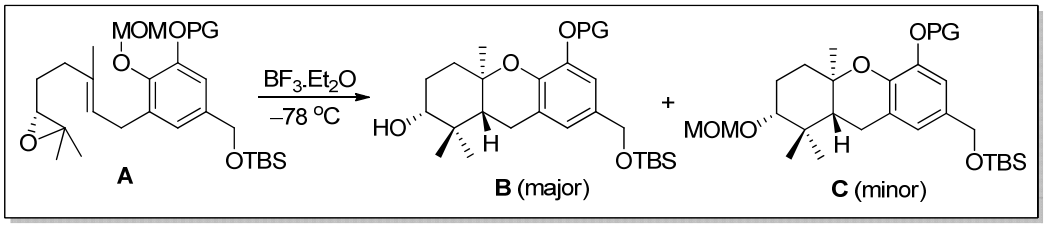
by geranyl bromide (**33**) gave the desired coupling product **39** in 54% yield. Cleavage of the silyl ether followed by oxidation with PDC gave the aromatic aldehyde **40**. Condensation of phosphonate **35** and aldehyde **40** gave the desired *trans*-stilbene as a single isomer. Deprotection of all four MOM group of the resulting olefin using 3 M HCl in methanol gave the schweinfurthin C (**9**) 51% yield (Scheme 4).



Scheme 4. Synthesis of Schweinfurthin C

3A.2.4 Wiemer's Approach Towards the Synthesis of Schweinfurthin F and G

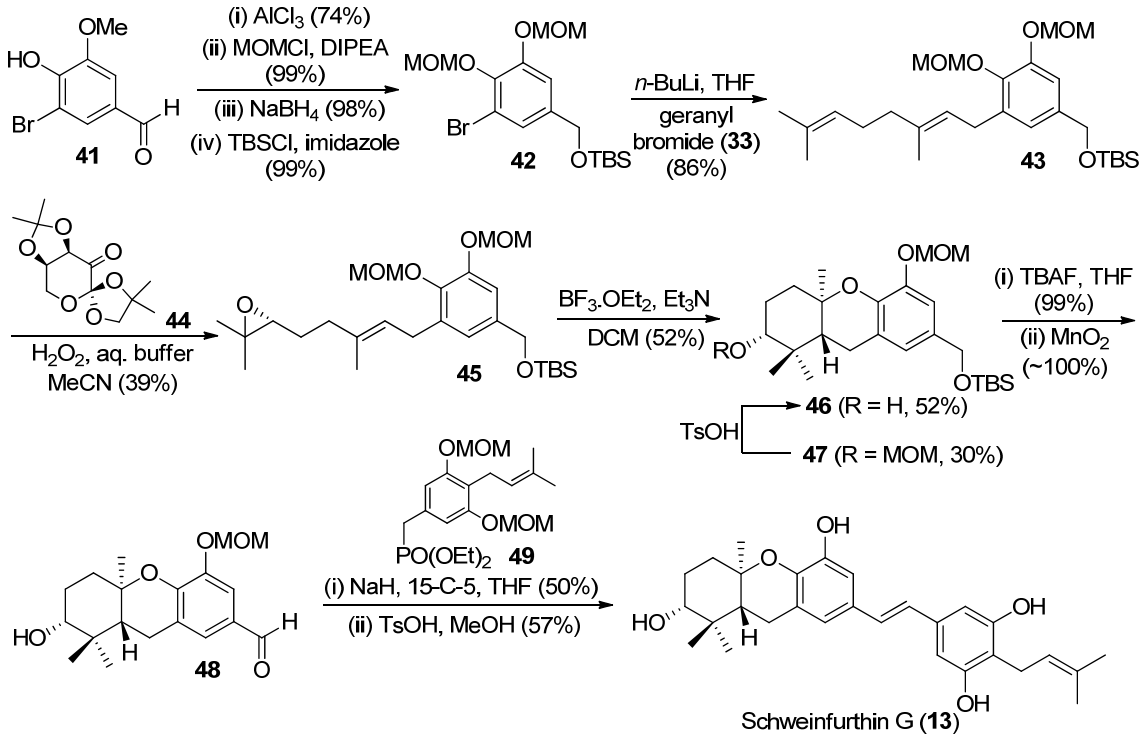
Weimer and co-workers developed an efficient $BF_3.Et_2O$ mediated cationic cascade cyclization protocol as represented in scheme 5. This cascade process is initiated by Lewis acid promoted ring opening of an epoxide and terminated through a novel reaction with phenolic oxygen "protected" as



Scheme 5. $BF_3.Et_2O$ Mediated Cyclization of Epoxide

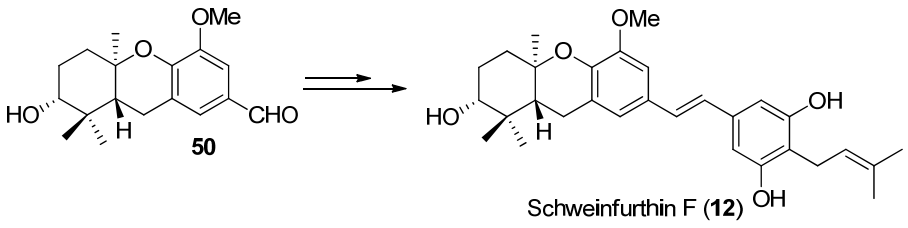
its MOM ether. Several Lewis acids were examined for their ability to induce this reaction and $BF_3.Et_2O$ was found to be the most effective. The only byproduct formed under these conditions was the MOM ether derivative **C**. This byproduct was converted to the original target compound through hydrolysis. The formation of this hexahydroxanthene framework has been further utilized for the synthesis of schweinfurthin B, E, F and G.

Weimer and co-workers[22] reported the first total synthesis of both schweinfurthin F (**12**) and G (**13**) via a $BF_3.OEt_2$ mediated cascade cyclization of the epoxide to furnish hexahydroxanthene framework (Scheme 6). Bromovanillin **41** on treatment with $AlCl_3$ gave catechol which on MOM-protection followed by reduction of the aldehyde and its protection as TBS ether gave bromo compound **42**. Treatment of **42** with *n*-BuLi enacted halogen metal exchange and subsequent reaction with geranyl bromide (**33**) installed the geranyl chain to provide compound **43** in 86% yield. A Shi epoxidation of geranylated arene **43** by treatment with hydrogen peroxide in the presence of sugar catalyst **44** and acetonitrile in buffered solution afforded epoxide **45** in a 39% yield but with excellent enantioselectivity. The application of the Shi epoxidation generally results in recovery of 33-54% of the starting olefin, so yields based on recovered starting material have been very attractive. With epoxide **45** in hand, the stage was set for Lewis acid mediated cascade cyclizations. Compound **45** on brief treatment with $BF_3.Et_2O$ afforded tricycle **46** in a 52% yield along with tricycle **47** in 30% yield representing very efficient formation of the tricyclic system. Removal of the silyl protecting group of tricycle **46** was successful using standard conditions and oxidation with MnO_2 gave the aldehyde **48**. The HWE condensation of aldehyde **48** and known phosphonate **49** provided the *trans*-stilbene which on acidic hydrolysis of the three MOM ethers gave schweinfurthin G (**13**) in 57% yield.



Scheme 6. Synthesis of Schweinfurthin G

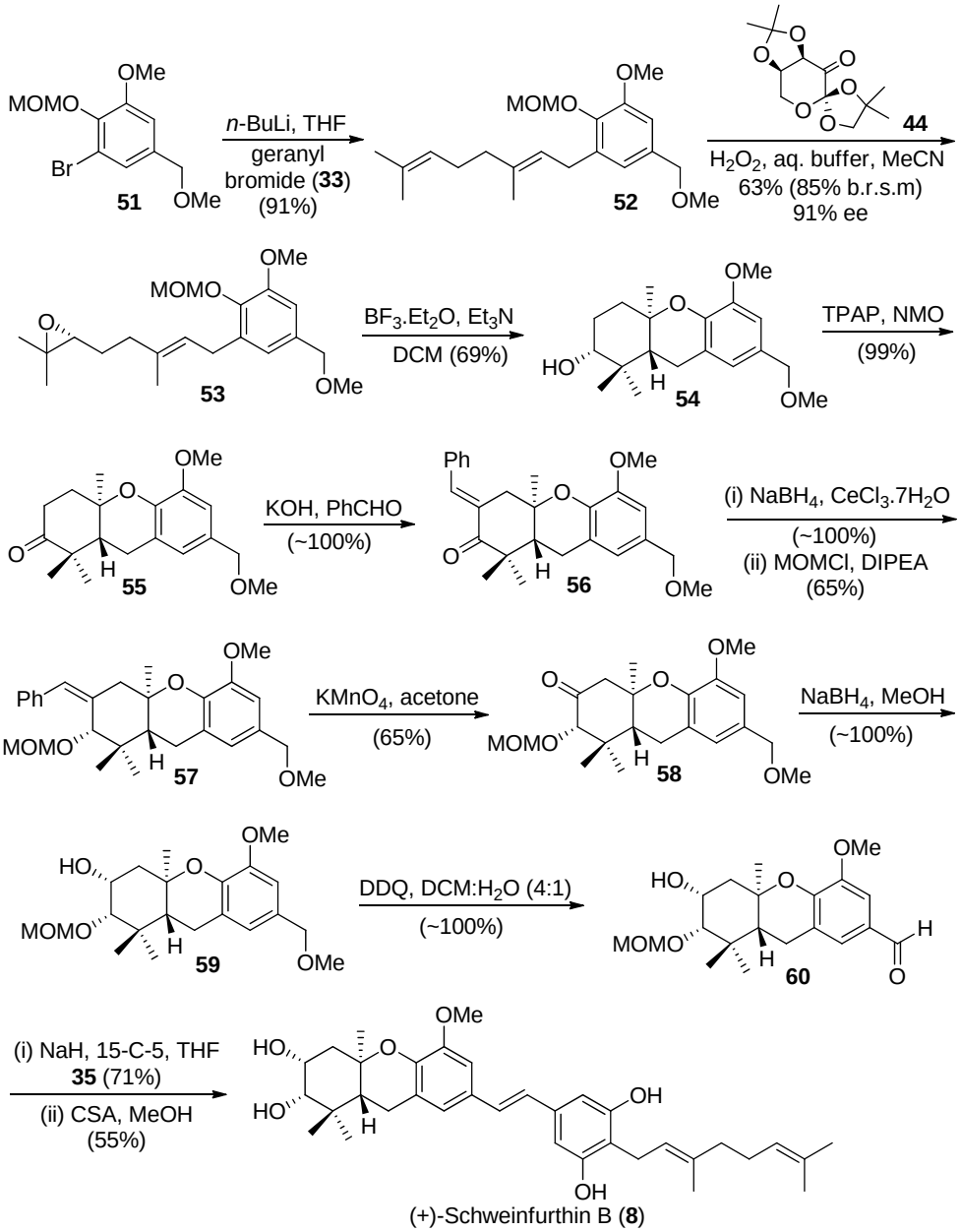
Similarly, the tricycle **50** was prepared. The HWE olefination of **49** with **50** and deprotection of all MOM groups completed the synthesis of schweinfurthin F (**12**) (Scheme 7).



Scheme 7. Synthesis of Schweinfurthin F

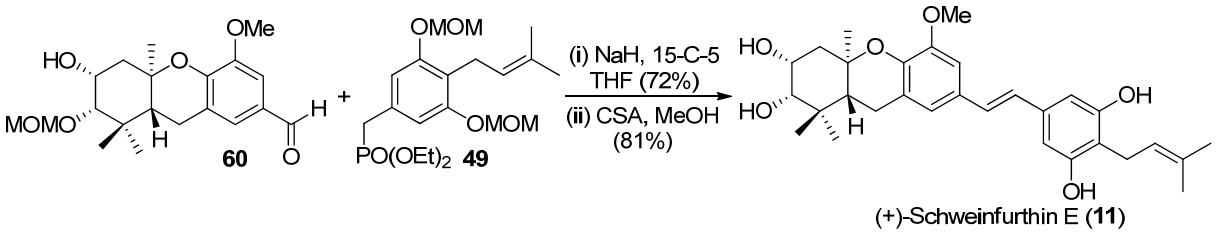
3A.2.5 Wiemer's Approach Towards the Synthesis of (+)-Schweinfurthin B and E

Weimer and co-workers[23] reported the first total synthesis of (+)-schweinfurthin B (**8**) and E (**11**) via a



Scheme 8. Synthesis of (+)-Schweinfurthin B

Shi epoxidation and an efficient cascade cyclization initiated by treatment of the resulting epoxide with $BF_3.OEt_2$ (Scheme 8). The compound **51** was treated with *n*-BuLi to induce halogen-metal exchange. Reaction of the resulting aryl anion with geranyl bromide (**33**) furnished **52** in excellent overall yield. Compound **52** was epoxidized under Shi's conditions with the sugar derivative **44**. This protocol consistently produced epoxide **53** in greater than 90% ee (by chiral HPLC). Cyclization of epoxide **52** occurred upon brief exposure to $BF_3.Et_2O$ and gave compound **54**. Oxidation of hexahydroxanthene **54** under Ley's conditions afforded ketone **55** in excellent yield. The limited success of direct methods for oxidation of ketone **55** led to consider less straightforward strategies for preparation of the A-ring *cis*-diol. Brief exposure of ketone **55** to benzaldehyde and KOH in ethanol produced enone **56** in quantitative yield. Reduction of the α,β-unsaturated ketone **56** under Luche conditions afforded alcohol which was protected as a MOM ether to give compound **57** in moderate yield. Initial attempts of oxidative cleavage of the olefin via reaction with $OsO_4/NaIO_4$ did provide ketone **58** in 32% yield. Addition of excess $NaIO_4$, use of longer reaction time and application of a higher reaction temperature all failed to effect a complete conversion. However, the use of excess of $KMnO_4$ (10 equiv) provided of the desired ketone **58** in satisfactory yield. The $NaBH_4$ reduction of ketone **58** afforded alcohol **59** in quantitative yield as the single diastereomer. Exposure of compound **59** to DDQ afforded aldehyde **60** from the methyl ether. Phosphonate **35** was then coupled with aldehyde **60** under standard HWE conditions to yield *trans*-stilbene. Which on acidic hydrolysis of the three MOM groups using CSA provided (+)-schweinfurthin B (**8**) in moderate yield.

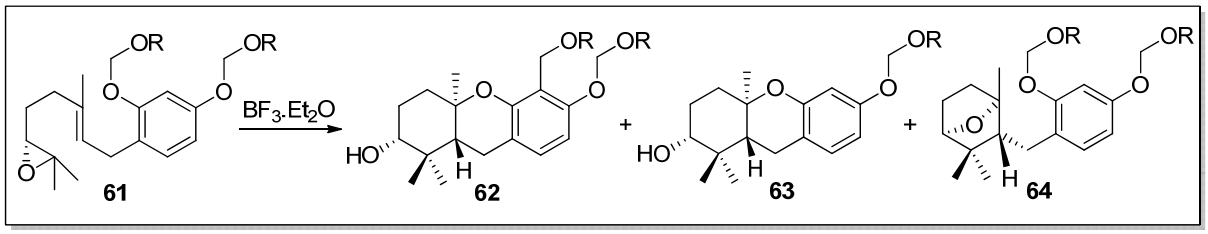


Scheme 9. Synthesis of (+)-Schweinfurthin E

One key advantage of the present approach to the schweinfurthins is that both the aldehyde and phosphonate subunits can be employed in a divergent fashion to afford multiple products efficiently. The phosphonate **49** was coupled with aldehyde **60** (Scheme 9) to afford *trans*-stilbene which on CSA catalyzed deprotection of MOM units gave (+)-schweinfurthin E (**11**) in excellent yield.

Weimer and co-workers[24,25] have described a epoxide-initiated cascade cyclizations with a range of "protected" phenols. When the protecting group can be relived as a stabilized electrophile, the cascade process continues beyond ring closure to afford products which have undergone a tandem electrophilic aromatic substitution. A number of functional groups have proven viable in the cascade

process and the regiochemistry of their substitution reactions has been studied (Table 1). This methodology has been successfully applied for the first total synthesis of (+)-schweinfurthin A.



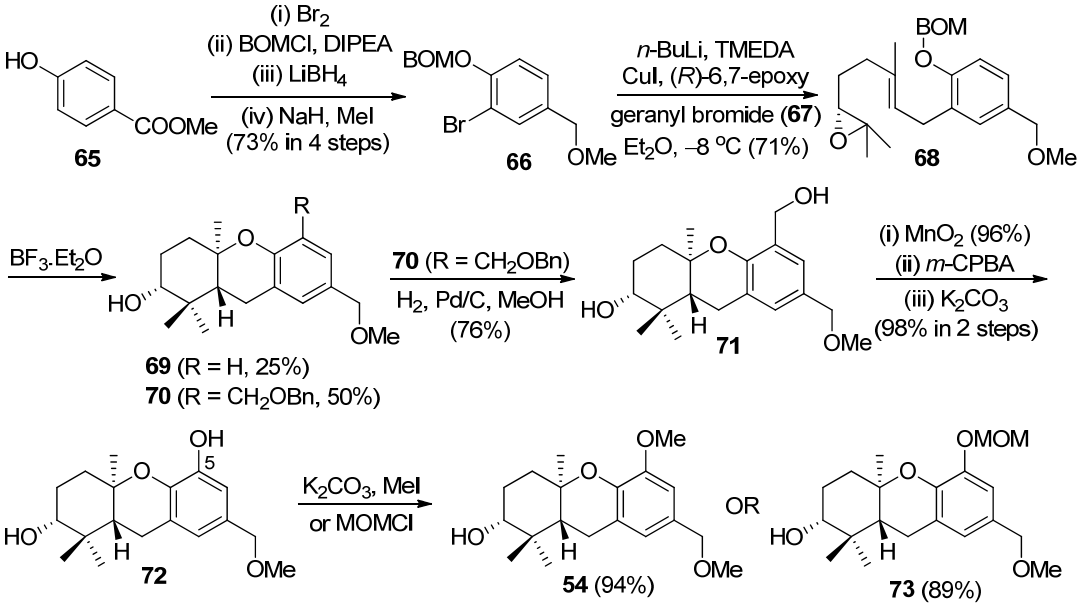
Entry	R	% Yield 62	% Yield 63	% Yield 64
1	Me	52	30	--
2	Bn	62	--	--
3	CH_2CH_2TMS	57	--	--
4	CH_2CH_2OMe	53	28	--
5	$COCMe_3$	--	--	47
6	4-Cl-C_6H_4	--	56	37

Table 1. Cascade Cyclization/Aromatic Substitution of Alkoxymethyl Substituted Phenols

3A.2.6 Wiemer's Approach Towards the Synthesis of (+)-Schweinfurthin A

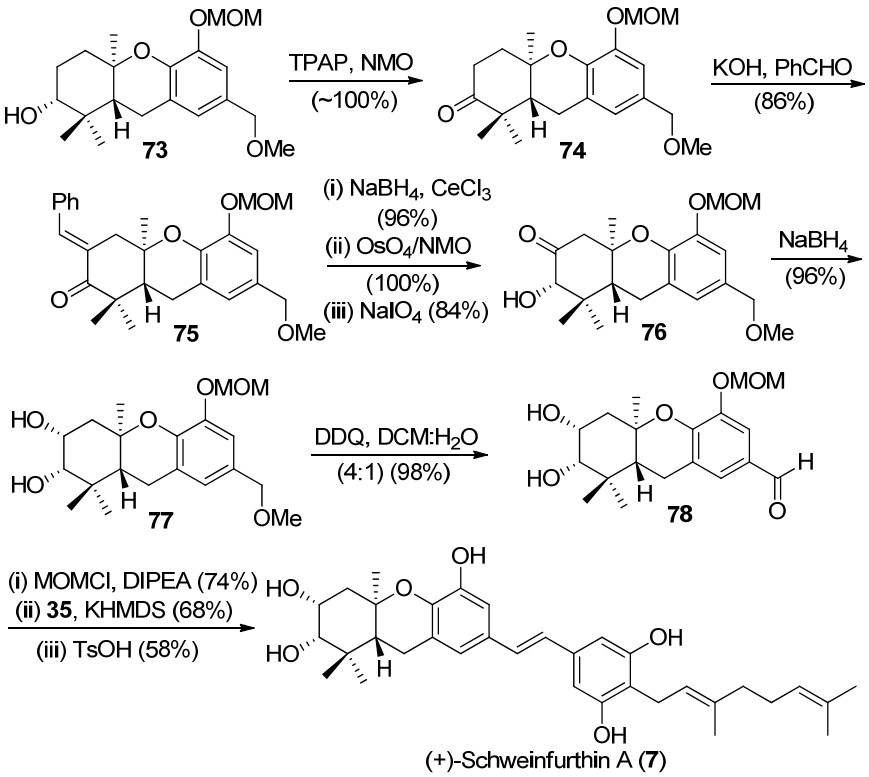
Weimer and co-workers[25] reported the synthesis of (+)-schweinfurthin A (**7**) via a $BF_3.Et_2O$ mediated cascade cyclization and a tandem electrophilic aromatic substitution (Scheme 10 and 11). The synthetic sequence started with bromination of methyl 4-hydroxybenzoate (**65**) followed by BOM protection. Reduction of the intermediate ester and methylation afforded arene **66** in 73% overall yield. Arene **66** on halogen metal exchange followed by addition of (*R*)-6,7-epoxygeranyl bromide (**67**) (up to 93% ee) afforded epoxide **68** in 71% yield. The crucial cascade cyclization/aromatic substitution proceeded smoothly to afford the desired tricycle **70** along with the unsubstituted analogue **69**. Although compounds **69** and **70** were obtained as an inseparable mixture, both were single regio- and diastereoisomers. Separation of these products was readily accomplished after selective hydrogenolysis, which afforded the benzylic alcohol **71** and recovered hexahydroxanthene **69**. The alcohol **71** in hand, installation of the requisite C-5 phenol proceeded smoothly (Scheme 10). Chemoselective oxidation of benzyl alcohol **71** to the corresponding aldehyde was accomplished

upon treatment with MnO_2 and its subsequent Baeyer-Villiger oxidation with *m*-CPBA followed by hydrolysis of the resultant formate provided phenol **72** in excellent yield. This reaction sequence extends cascade cyclization/aromatic substitution strategy to allow the introduction of the C-5 phenol central to the schweinfurthins. The phenol **72** serves as the divergent intermediate for the synthesis of schweinfurthins. Alkylation of phenol **72** with either methyl iodide or MOMCl proceeded with excellent selectivity to afford intermediates **54** and **73** respectively. The synthesis of compound **54** constitutes a formal synthesis of schweinfurthins B, E, and F.



Scheme 10. Synthesis of Hexahydroxanthene **54** and **73**

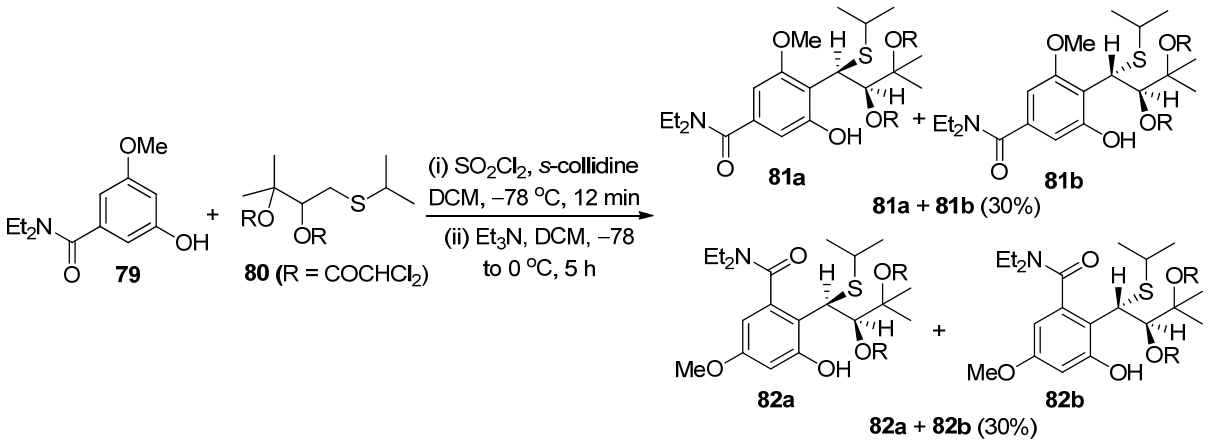
On having intermediate **73** in hand, the total synthesis of (+)-schweinfurthin A was pursued (Scheme 11). Intermediate **73** was oxidized with TPAP/NMO to provide the ketone **74**. Condensation of ketone **74** with benzaldehyde provided enone **75**, which was to be utilized as a latent carbonyl group. Reduction proceeded smoothly under Luche conditions to afford alcohol which was subjected to Upjohn dihydroxylation to provide triol and its subsequent glycolytic cleavage with $NaIO_4$ gave ketone **76** in very good yield. Diastereoselective reduction of ketone **76** provided diol **77**. Treatment of benzyl ether **77** with DDQ provided aldehyde **78**. Direct HWE condensation of phosphonate **35** with aldehyde **78** proved troublesome. To circumvent this problem, the diol unit in aldehyde **78** was protected by treatment with excess MOMCl and base. Subsequent attempts at the HWE condensation of phosphonate **35** with MOM-protected aldehyde in the presence of KHMDS afforded *trans*-stilbene in moderate yield and subsequent global hydrolysis of the MOM ethers provided (+)-schweinfurthin A (**7**) in 58% yield.



Scheme 11. Synthesis of (+)-Schweinfurthin A

3A.2.7 Inoue's Approach Towards the Synthesis of NG-121 Model Compound

The total synthesis of NG-121 and stachybotrins has not been accomplished till date[14,15] and is imperative from advance biological screenings point of view. Inoue and co-workers[26] reported the synthesis of NG-121 model compound. The key steps were *ortho*-alkylation of the phenol via [2,3]-sigmatropic rearrangement of a sulfur ylide and the regioselective construction of the attached

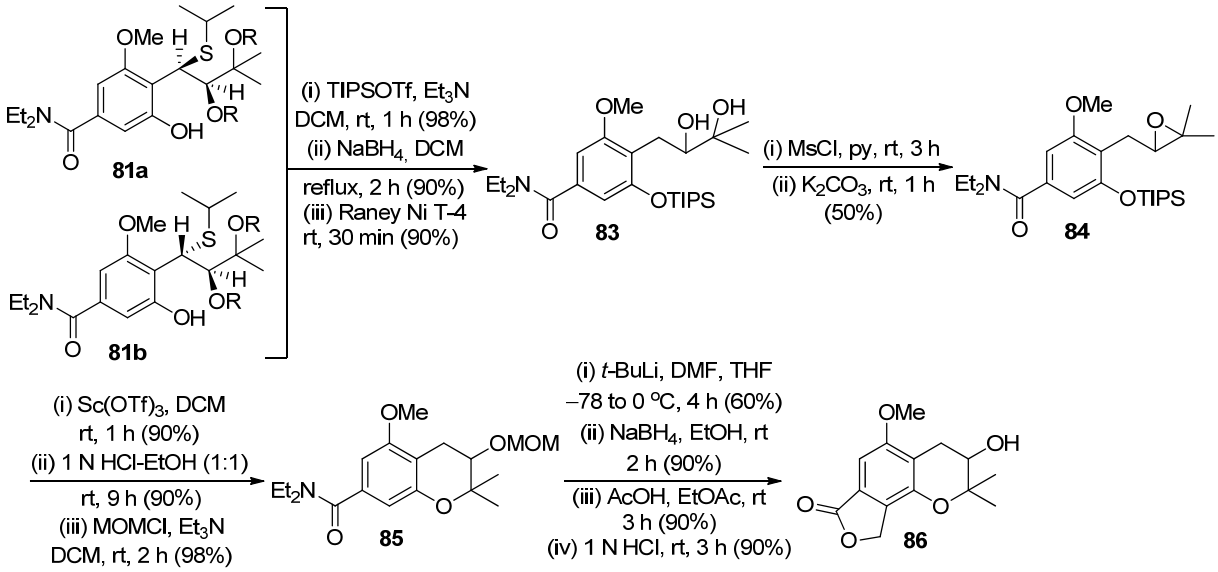


Scheme 12. Reaction of *N*,*N*'-Diethylbenzamide with Sulfide

lactone ring (Scheme 12 and 13). *N*,*N*'-Diethylbenzamide **79** was reacted with sulfide **80** to give the desired *ortho*-alkylphenols **81a** and **81b** along with the regioisomers **82a** and **82b** in moderate yields

in a 1:1 ratio (Scheme 12). Fortunately, the desired benzamides **81a** and **81b** and the regioisomers **82a** and **82b** were separable by column chromatography on silica gel.

Subsequently, the phenolic hydroxyl groups of **81a** and **81b** were protected with a TIPS group (Scheme 13). Then the dichloroacetyl groups were removed, which was followed by the deprotection of isopropylsulfanyl groups by hydrogenolysis with freshly prepared Raney Ni (T-4) in ethanol to obtain alcohol **83**. The secondary hydroxyl group in **83** was selectively mesylated and the conversion of mesylate into epoxide **84** was done by treatment with potassium carbonate. The TIPS group was



Scheme 13. Synthesis of NG-121 Model Compound

cleanly cleaved by $Sc(OTf)_3$ followed by treatment with 1 N HCl at room temperature to furnish 2,2-dimethylchroman-3-ol and then it was protected as a MOM ether **85**. Chroman **85** was lithiated with *t*-BuLi and the resulting *o*-lithioamide was quenched with DMF to afford aldehyde as the sole product then it was subjected for $NaBH_4$ reduction to provide the alcohol, which cyclized to the tricyclic compound in excellent yield. Finally the deprotection of MOM group gave the tricyclic chroman model compound **86**.

3A.3 Summary

In summary, we have presented a concise literature account on the isolation, bioactivity and synthesis of pawhuskin A, pawhuskin C, schweinfurthin C, schweinfurthin F & G, (+)-schweinfurthin B & E and (+)-schweinfurthin A. The key reactions that were employed to efficiently accomplish the synthesis of above mentioned bioactive natural products were ortho-lithiation to install the prenyl/geranyl chains and the subsequent appropriate Horner-Wadworth-Emmons condensation to form the desired trans-stilbene, an efficient $BF_3.Et_2O$ mediated cationic cascade cyclization, a tandem cascade cyclization and electrophilic aromatic substitutions. Overall, several remarkable approaches to these target compounds and related natural products have been known in the literature. Our synthetic studies towards the synthesis of these natural products have been discussed in details in the section B of the present chapter.

3A.4 References

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CHAPTER 3: SECTION B

Total Synthesis of Naturally Occurring Pawhuskin C, Schweinfurthin J and NG-121 Methyl Ether

This section B of chapter 3 features the following topics:

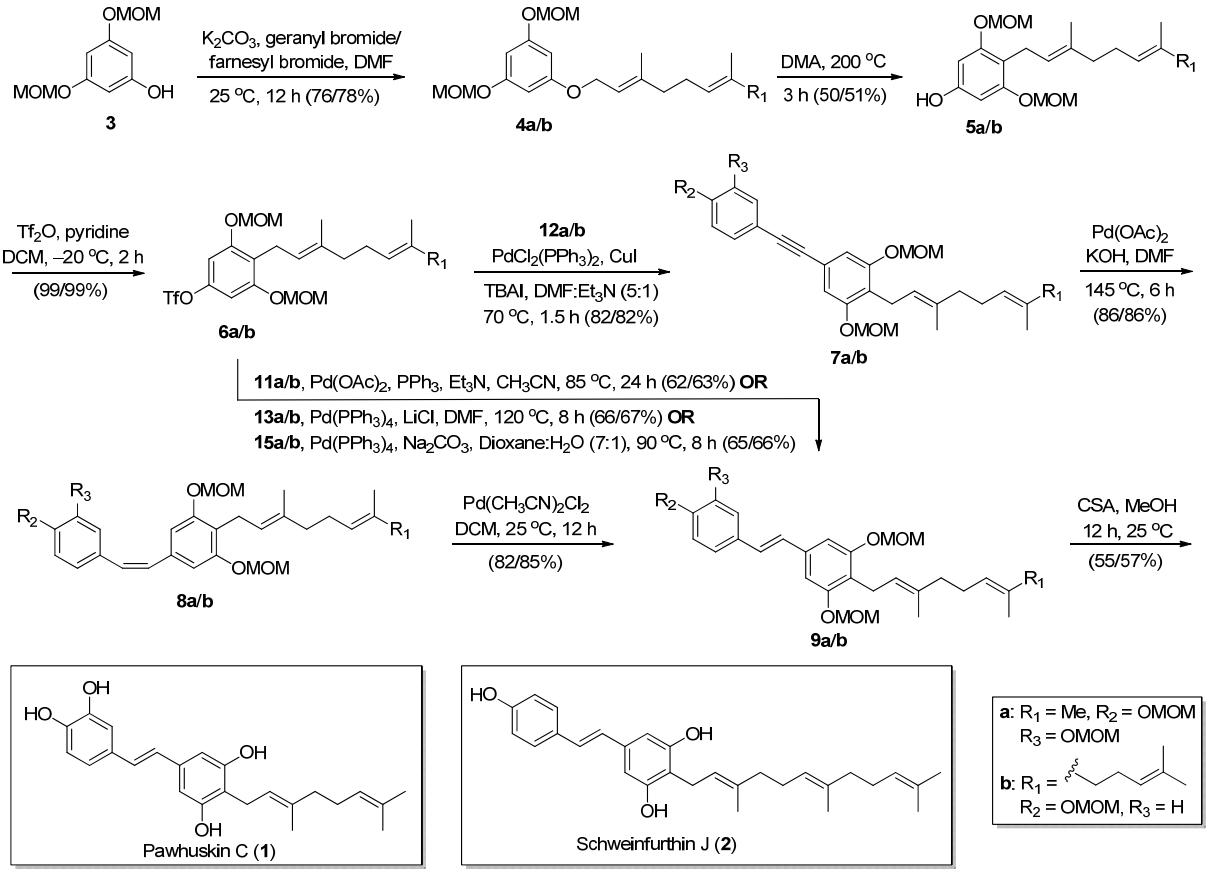
3B.1 Rationale of the Present Work

It is evident from the discussion in section A that the pawhuskins, schweinfurthins, NG-121 and stachybotrins are structurally interesting and they possess a wide range of biological activities. The unique structural architecture and exotic bioactivities of these natural products makes them an attractive synthetic targets. The provision of short and efficient synthetic routes to these target molecules is an imperative task of current interest. In continuation of our ongoing work on bioactive natural product synthesis, we have designed an efficient synthetic route to naturally occuring pawhuskin C and schweinfurthin J utilizing Heck/Stille/Suzuki coupling reactions of two different electron rich phenolic segments bearing geranylated/farnesylated units. The Sonogashira coupling reaction followed by palladium catalyzed chemo- and stereoselective *cis*-reduction of an alkyne unit and the subsequent isomerization to desired natural products has been also described. The total synthesis of NG-121 methyl ether has also been accomplished via a Stille coupling reaction of farnesyl unit with electron rich phenolic segment, hydroxy directed selective epoxidation of farnesyl chain with the concomitant phenol driven intramolecular regio- and diastereoselective ring closure to the corresponding hydroxybenzopyran and the regioselective formylation followed by reductive an in situ lactonization pathway.

3B.2 Results and Discussion

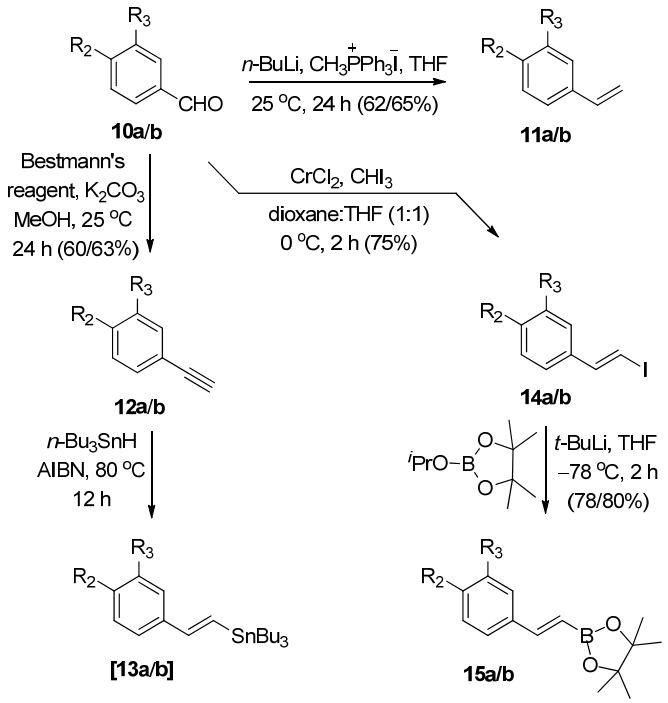
3B.2.1 Palladium-Catalyzed Routes to Geranylated/Farnesylated Phenolic Stilbenes: Synthesis of Pawhuskin C and Schweinfurthin J

The palladium catalyzed carbon–carbon coupling reactions of substrates bearing prenylated/geranylated/farnesylated phenolic segments to form the stilbenes are not known in the literature.[1] The synthesis of natural products **1** and **2** would be feasible via the uncommon aromatic Claisen rearrangement of geranyl/farnesyl unit followed by Heck/Stille/Suzuki/Sonogashira coupling reactions pathways (Scheme 1 and 2). The double MOM-protected symmetrical phenol **3**[2] on reaction with geranyl bromide/farnesyl bromide in the presence of K_2CO_3 in DMF provided the expected *O*-geranylated/farnesylated products **4a**/**b** in 76/78% yields (Scheme 1). The products **4a**/**b** in refluxing *N*,*N*-dimethylaniline (DMA) underwent a defined Claisen rearrangement and furnished only the corresponding *para*-geranylated/farnesylated *trans*-products **5a**/**b** in 50/51% yields along with 30-35% recovery of the starting material. In the above reaction we also noticed the decomposition of the starting material to the extent of 10-15%, while under the forced conditions we



Scheme 1. Synthesis of Bioactive Natural and Unnatural Geranylated/Farnesylated Phenolic Stilbenes

noticed the excessive decomposition. To the best of our knowledge, very few examples of such aromatic Claisen rearrangement to install the geranyl/farnesyl unit are known in literature.[3] The free phenolic groups in compounds **5a**/**b** were transformed to good leaving group –OTf by treatment with Tf_2O/pyridine to obtain **6a**/**b** in 99% yields. Subsequently, the Heck, Stille and Suzuki coupling reactions of the building blocks **6a**/**b** with appropriate coupling partners from scheme 2 were deliberated to obtain the products **9a**/**b**.[4] As depicted in scheme 2, the Heck and Sonogashira coupling partners **11** and **12** were respectively prepared from **10a**/**b** by using Wittig and Ohira-Bestmann's reagents.[5] The radical hydrostannation of **12a**/**b** provided the desired Stille coupling regioisomers **13a/b** and were used as such for the next step.[6] The Suzuki coupling partners were also obtained from **10a**/**b** via the Takai olefination to form vinyl iodides **14a**/**b** and subsequent conversion to vinyl pinacol boronates **15a**/**b**.[7] The above mentioned palladium catalyzed Heck/Stille/Suzuki coupling reactions of **6a**/**b** with **11a**/**b**, **13a**/**b** and **15a**/**b** were selective and exclusively provided the desired products **9a**/**b** in good yields (62-67%). Interestingly, all the above mentioned palladium catalyzed coupling reactions involving electron-rich substrates were equally efficient in yielding the



Scheme 2. Synthesis of Heck, Sonogashira, Stille and Suzuki Coupling Blocks

desired *trans*-stilbenes. A systematic study of Sonogashira coupling between **6a** and **12a** was also planned to selectively provide both the *cis*- and *trans*-stilbenes.[8] Initial attempts to couple the phenolic compounds **6a** and **12a** under standard coupling conditions resulted in dimerization of an alkyne unit. A literature search revealed that the present observation matches with the report of Boger et al[9] that such type of electron rich compounds are relatively less reactive. An in situ exchange of –OTf to iodide using excess of tetrabutylammonium iodide was necessary for Sonogashira coupling reactions of the two electron rich segments **6a**/**b** and **12a**/**b**. Fortunately, the above mentioned coupling conditions yielded the desired products **7a**/**b** in 82% yields. Efforts to convert the alkyne unit in **7a**/**b** to *trans*-**9a**/**b** using DIBAL were unsuccessful and lead to the recovery of starting materials.[10] At this stage, the recently reported palladium-catalyzed transfer semihydrogenation conditions for the reduction of the triple bond to double bond were sought.[11] The reaction of alkynes

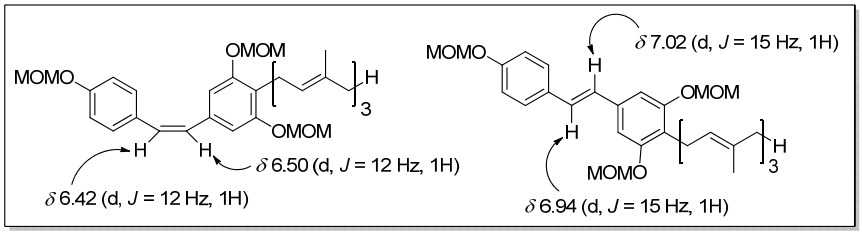
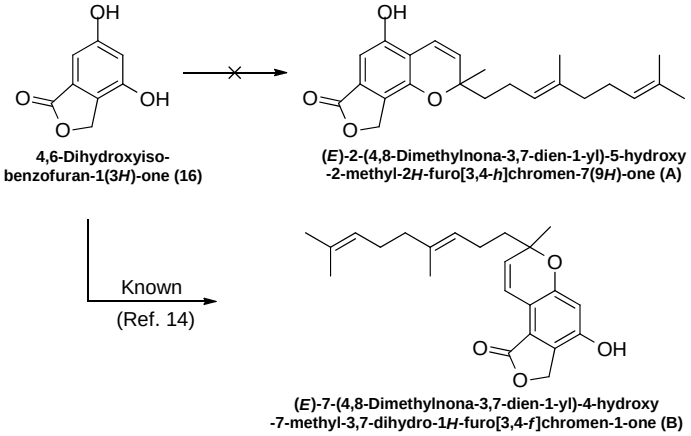


Figure 1. ^{1}H NMR values and coupling constant in *cis*- and *trans*-stilbenes

7a/**b** with DMF and KOH in the presence of $Pd(OAc)_2$ exclusively supplied the corresponding *cis*-isomerization (allylic rearrangement). Finally, the acid-catalyzed global deprotection of MOM-groups in **9a**/**b** delivered the stilbenes **8a**/**b** in 86% yields. The *cis*-geometry of carbon–carbon double bond in products **8a**/**b** was confirmed on the basis of δ-values and coupling constants of the corresponding vinylic protons (Figure 1). Using the method reported by Spencer et al,[12a] Pd(II)-catalyzed *cis* to *trans* isomerization of carbon–carbon double bond in compounds **8a**/**b** formed the required products **9a**/**b** in 82/85% yields. On the basis of Sen et al.[12b,c] reports, we feel that neryl substituted analogs of compound **8a** will also form the corresponding product **9a** via the *Z*- to *E*- carbon–carbon double bond desired natural products pawhuskin C (**1**) and schweinfurthin J (**2**) in 55/57% yields. The obtained analytical and spectral data for the natural products **1** and **2** were in complete agreement with the reported data.[13] The natural products **1** and **2** were obtained via partially separate routes in five and seven linear steps with 14/15% and 12/14% overall yields.

3B.2.2 Synthetic Studies Towards NG-121: Diastereoselective Access to NG-121 Methyl Ether

The real challenge in synthesis of natural products, NG-121 and stachybotrins lies in (i) regioselective introduction of farnesyl unit, (ii) stereoselective creation of two adjacent asymmetric carbon centers in chroman ring, (iii) lactonization with the regioselective introduction of a formyl group and (iv) the preservation of carbon–carbon double bonds throughout the reactions sequence. Retro-synthetically, the regioselective condensation of 4,6-dihydroxyphthalide (**16**) with farnesal would constitute benzopyran **A** from scheme 3, followed by the selective hydroxy-directed epoxidation and oxirane ring opening with the metal hydride would formulate the concise approach to NG-121. However, as depicted in scheme 3, the reaction of 4,6-dihydroxyphthalide with farnesal is known to produce the different regioisomer **B**.[14]



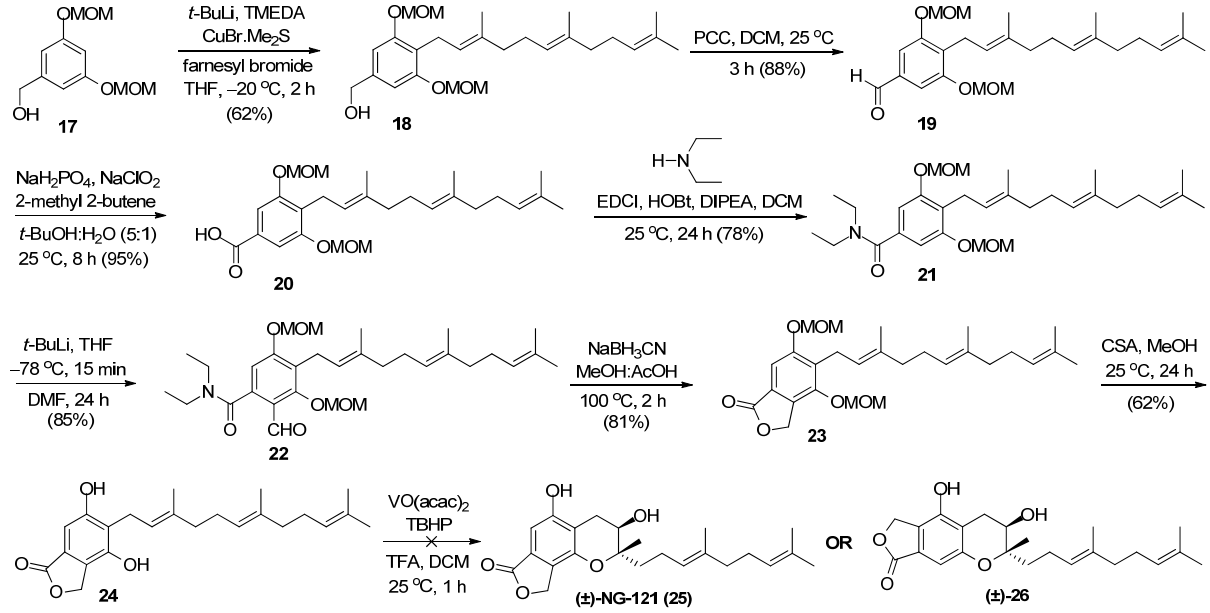
4,6-Dihydroxyiso-benzofuran-1(3*H*)-one (16)

(*E*)-2-(4,8-Dimethylnona-3,7-dien-1-yl)-5-hydroxy -2-methyl-2*H*-furo[3,4-*h*]chromen-7(9*H*)-one (A)

(*E*)-7-(4,8-Dimethylnona-3,7-dien-1-yl)-4-hydroxy -7-methyl-3,7-dihydro-1*H*-furo[3,4-*f*]chromen-1-one (B)

Scheme 3. Reported Regioselective Coupling of 4,6-Dihydroxyphthalide and Farnesal

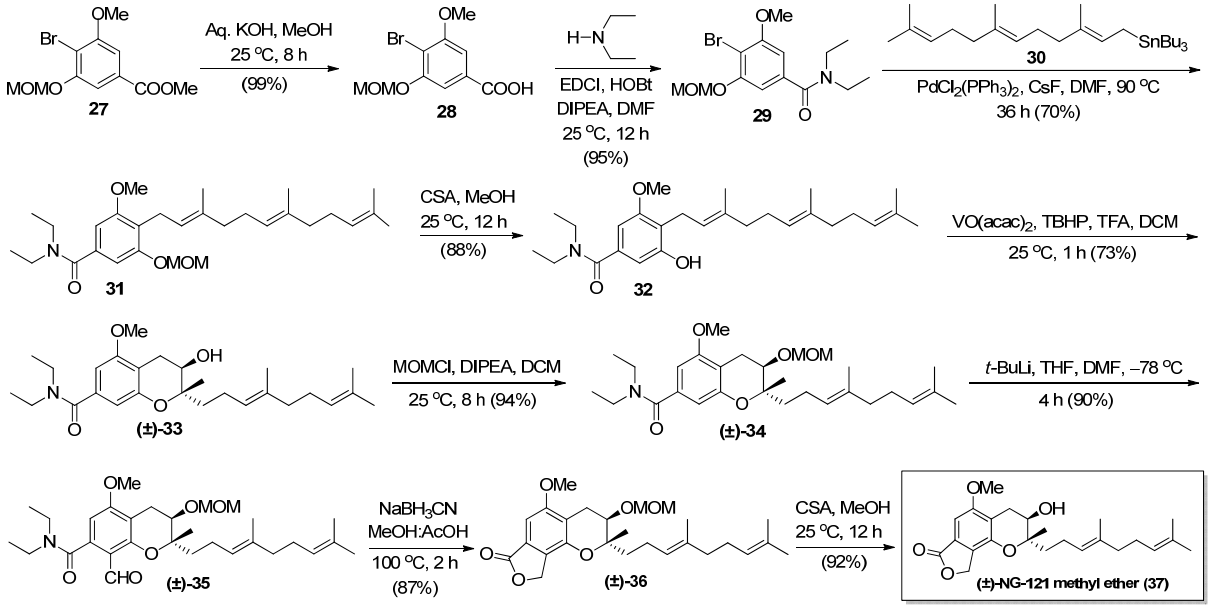
Hence, alternatively we decided to initiate our synthesis with an appropriate resorcinol derivative with introduction of the farnesyl unit first and then the stepwise lactonization followed by chromanol generation (Scheme 4). The symmetrically double MOM-protected benzyl alcohol **17** on selective *o*-lithiation using *t*-BuLi as the base followed by the reaction with farnesyl bromide gave the desired coupling product **18** in 62% yield. The PCC oxidation of benzyl alcohol **18** to the corresponding aldehyde **19** (88%) and its subsequent Pinnick oxidation ($NaClO_2/NaH_2PO_4$)[15] provided the carboxylic acid **20** in 95% yield. At this stage, for selectivity reasons it appeared appropriate to generate the lactone ring first by applying the *o*-formylation strategy. The carboxylic acid **20** on EDCI induced coupling with diethylamine gave an appropriate amide **21** for the introduction of the formyl unit. The reaction of symmetrical amide **21** with *t*-BuLi/DMF selectively yielded the desired mono-formylated benzaldehyde derivative **22** in 85% yield. The sodium cyanoborohydride reduction of benzaldehyde derivative **22** to the corresponding intermediate benzyl alcohol and an in situ lactonization furnished the required phthalide **23** in 81% yield. A selective mono-MOM deprotection of compound **23** was studied using the known literature protocols (CSA/MeOH, 2 N HCl/MeOH, CBr_4/*i*PrOH,[16] I_2/MeOH[17]). Unfortunately, all the attempts were unsuccessful and ended up with double-MOM deprotection to yield the farnesylated dihydroxyphthalide **24** in 62% yield. Herein it appears that mono-MOM deprotected intermediate under goes the second deprotection at the faster rate than the starting material itself. Alas, the mono-MOM protection of biphenolic compound **24** using different molar concentrations of MOMCl also majorly resulted in the double-MOM protected compound **23**. The hydroxyl directed $VO(acac)_2$-catalyzed selective epoxidation condition developed by Lattanzi et al[18] to



Scheme 4. An Attempted Synthesis of Chromanol (±)-NG-121

obtain the chromanol was extended to the biphenolic compound **24** to diastereoselectively obtain either the (±)-NG-121 (**25**) or its regioisomer **26**. All attempts met with failure and the highly reactive biphenolic substrate **24** instantaneously underwent an excessive decomposition.

To circumvent the above mentioned difficulty involved in the selective MOM-deprotection, we once again altered our plan and decided to commence the synthesis with unsymmetrical methyl benzoate derivative **27** having two different protecting groups, the –OMe and –OMOM (Scheme 5). The base catalyzed hydrolysis of ester **27** to corresponding carboxylic acid **28** (99%) followed by the EDCI induced coupling with diethylamine provided an appropriate amide **29** in 95% yield. The palladium-catalyzed Stille coupling reaction of electron rich bromoresorcinol derivative **29** with farnesyl tributyltin (**30**) furnished the coupling product **31** in 10–15% yield only.[19] However as per the literature report,[20] the addition of CsF (2.00 equiv) as an accelerator to a reaction mixture improved the yield of desired Stille coupling product **31** upto 70%. As described in scheme 4, similarly at this point the *o*-formylation of compound **31** was planned for the generation of requisite *γ*-lactone moiety. However, the *t*-BuLi/DMF driven *o*-formylation of –OMe and –OMOM protected unsymmetrical amide **31** was not selective and ended up with the mixture of corresponding desired and undesired isomeric benzaldehyde derivatives utilizing both the available *o*-positions (3:2, by ^{1}H NMR). Hence the deprotection of the MOM-group was planned to generate the chromanol and then the introduction the formyl unit. The camphorsulfonic acid driven selective MOM-deprotection of compound **31** gave the desired phenol **32** in 88% yield. The hydroxy directed $VO(acac)_2$/*tert*-butyl hydroperoxide (TBHP) mediated regioselective epoxidation of 2-position carbon–carbon double bond in the farnesyl chain followed by concomitant



Scheme 5. Diastereoselective Synthesis of NG-121 Methyl Ether

regio- and diastereoselective intramolecular oxirane ring opening exclusively formed the pair of chromanol enantiomers (±)-**33** in 73% yield. A pseudo-S_N2 epoxide opening resulted in *cis*-orientation of secondary hydroxyl group and the tertiary methyl group in compound (±)-**33**, which was established on the basis of NOESY studies and we feel that the outcome could be due the thermodynamic stability reason (Figure 2).[21]

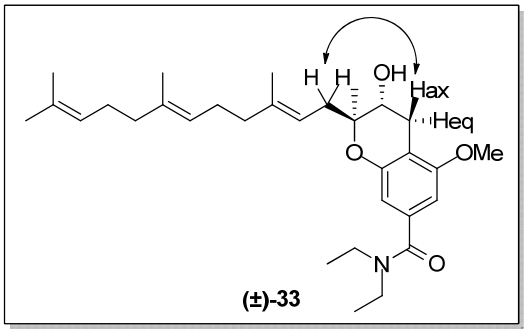


Figure 2. NOESY interaction between H_{axial} and methylene protons

The formed free secondary hydroxyl group in compound (±)-**33** was MOM-protected to obtain product (±)-**34** in 94% yield. Fortunately, the *t*-BuLi/DMF stimulated *o*-formylation of (±)-**34** was completely regioselective and exclusively furnished the requisite benzaldehyde derivative (±)-**35** in 90% yield. The presence of formyl group at 8-position in compound (±)-**35** was confirmed on the basis of NOESY studies. The NOESY data revealed the interaction of –OMe group with an adjacent aromatic proton through space. Herein the exclusive formylation at 8-position in the starting material (±)-**34** could be due to the effective participation of locked ring oxygen atom of the chromane system in *o*-lithiation step. The sodium cyanoborohydride reduction of aldehyde (±)-**35** and an in situ lactonization gave the phthalide (±)-**36** in 87% yield. The MOM-deprotection in product (±)-**36** provided the NG-121 methyl ether (±)-**37** in 92% yield. The obtained spectral data for NG-121 methyl ether (±)-**37** was in concurrence with the data reported for the model compound.[22] We carefully studied the demethylation of compound (±)-**37** to get the actual natural product NG-121, using BCl_3, BBr_3, TMSI/DCM,[23] LiCl/DMF,[24] EtSNa/HMPA[25] and BuSLi/HMPA[26] under different set of reaction conditions, but always ended up with the recovery of starting material and/or decomposition. Hence what we have accomplished is the diastereoselective synthesis of methyl ether of the natural product NG-121. Further studies for the demethylation of compound (±)-**37** are in active process in our laboratory.

3B.3 Summary

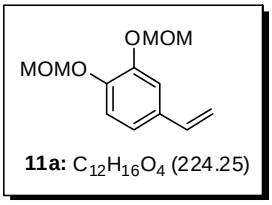
In summary, we have demonstrated a new route to bioactive polyene natural products pawhuskin C and schweinfurthin J by using Heck/Stille/Suzuki/Sonogashira coupling reactions as the key steps. The present approach provides an easy access to the both geometrically pure cis- and trans-stilbene isomers. We feel that Heck/Stille/Suzuki coupling reactions will provide an access to nerylated trans-stilbenes and the Sonogashira coupling reaction will provide an access to nerylated cis-stilbenes. Hence the described synthetic strategy is general in nature and will be useful to prepare some of the desired natural and unnatural stilbene analogs, congeners and the corresponding benzofuran/benzopyran architectures.

We have also accomplished the diastereoselective first synthesis of methyl ether of natural product NG-121 in nine steps with 29% overall yield (an average of 88% yield each step) using an appropriate reactions sequence and the essential protecting groups. The Stille coupling to introduce farnesyl chain on electron rich phenolic system, regio- and diastereoselective ring closure with the generation of two adjacent chiral centres and selective o-formylation were the involved key steps. We feel that our present approach to NG-121 methyl ether would be useful to access the NG-121 and stachybotrin analogs and SMTP congeners for SAR studies.

3B.4 Experimental Section

Commercially available *n*-BuLi, $CrCl_2$, CHI_3, *n*-Bu_3SnH, AIBN, isopropyl pinacol borane, *N*,*N*-dimethylaniline (DMA), Tf_2O, TBAI, $PdCl_2(PPh_3)_2$, $Pd(OAc)_2$, $Pd(PPh_3)_4$, $Pd(CH_3CN)_2Cl_2$, *t*-BuLi, farnesyl bromide, TMEDA, $CuBr.Me_2S$, PCC, 2-methyl 2-butene, *N*,*N*'-diethylamine hydrochloride, EDCI, HOBt, CsF, camphorsulfonic acid (CSA), $VO(acac)_2$, MOMCl, TBHP and $NaBH_3CN$ were used. The starting materials (3,5-bis(methoxymethoxy)phenyl)methanol (**17**), methyl 4-bromo-3-methoxy-5-(methoxymethoxy)benzoate (**27**) and farnesyl tributyltin (**30**) were prepared by using the known procedures.[27]

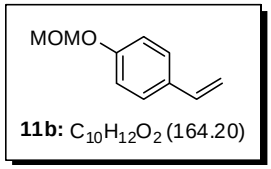
1,2-Bis(methoxymethoxy)-4-vinylbenzene (11a). To a stirred solution of methyltriphenylphosphonium iodide (2.68 g, 6.63 mmol) in THF (30 mL) at 0 ^oC was added *n*-BuLi (1.60 M in hexane, 4.0 mL, 6.41 mmol) and the reaction mixture was stirred for 45 min under argon atmosphere. A solution of aldehyde **10a** (500 mg, 2.21 mmol) in THF (10 mL) was added dropwise to the above reaction mixture and further stirred at 25 ^oC for 24 h. The reaction was quenched with saturated NH_4Cl (5 mL) and THF was removed in vacuo. The obtained residue was dissolved in ethyl



11a: $C_{12}H_{16}O_4$ (224.25)

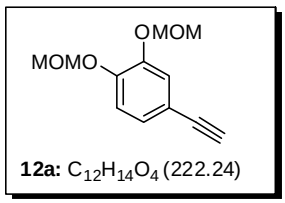
acetate (25 mL) and the organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (9:1) as an eluent afforded pure product **11a** as a thick oil (307 mg, 62%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.51 (s, 3H), 3.53 (s, 3H), 5.16 (dd, *J* = 10 and 2 Hz, 1H), 5.23 (s, 2H), 5.25 (s, 2H), 5.62 (dd, *J* = 18 and 2 Hz, 1H), 6.64 (dd, *J* = 18 and 10 Hz, 1H), 7.01 (dd, *J* = 8 and 2 Hz, 1H), 7.12 (d, *J* = 8 Hz, 1H), 7.25 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 56.21, 56.23, 95.4, 95.5, 112.7, 114.2, 116.5, 120.7, 132.5, 136.2, 147.0, 147.3; ESIMS (*m*/*z*) 247 $[M+Na]^+$; IR (neat) ν_{max} 1631, 1603 cm^{-1}.

1-(Methoxymethoxy)-4-vinylbenzene (11b). It was obtained from compound **10b** (500 mg, 3.01 mmol), methyltriphenylphosphonium iodide (3.65 g, 9.03 mmol), *n*-BuLi (1.60 M in hexane, 5.45 mL, 8.73 mmol) using the same procedure described above for **11a**, as a thick oil (329 mg, 65%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.48 (s, 3H), 5.16 (d, *J* = 10 Hz, 1H), 5.18 (s, 2H), 5.64 (d, *J* = 18 Hz, 1H), 6.68 (dd, *J* = 18 and 10 Hz, 1H), 7.00 (d, *J* = 8 Hz, 2H), 7.35 (d, *J* = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 56.0, 94.4, 112.1, 116.2, 127.3, 131.5, 136.1, 156.9; ESIMS (*m*/*z*) 165 $[M+H]^+$; IR (neat) ν_{max} 1629, 1606 cm^{-1}.



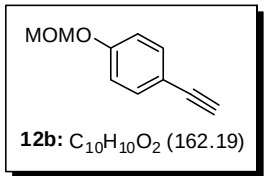
11b: $C_{10}H_{12}O_2$ (164.20)

4-Ethynyl-1,2-bis(methoxymethoxy)benzene (12a). To a stirred solution of compound **10a** (3.00 g, 13.27 mmol) and Ohira-Bestmann's reagent (6.41 g, 39.82 mmol) in MeOH (80 mL) was added K_2CO_3 (9.17 g, 66.37 mmol) and the reaction mixture was stirred at 25 °C for 24 h under argon atmosphere. The reaction mixture was concentrated in vacuo. To the obtained residue was added ethyl acetate (50 mL) and the organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (9:1) as an eluent afforded pure product alkyne **12a** as a thick oil (1.76 g, 60%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.01 (s, 1H), 3.51 (s, 3H), 3.52 (s, 3H), 5.23 (s, 2H), 5.25 (s, 2H), 7.09–7.14 (m, 2H), 7.31 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 56.2 (2 carbons), 76.1, 83.3, 95.1, 95.4, 115.9, 116.0, 120.2, 126.8, 146.7, 148.0; ESIMS (*m*/*z*) 223 $[M+H]^+$, 245 $[M+Na]^+$; HRMS (ESI) calcd for $C_{12}H_{14}O_4$ $[M+Na]^+$ 245.0790, found 245.0784; IR (neat) ν_{max} 3286, 2105, 1600 cm^{-1}.



12a: $C_{12}H_{14}O_4$ (222.24)

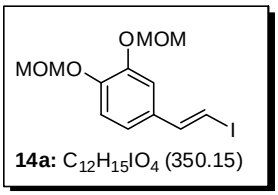
1-Ethynyl-4-(methoxymethoxy)benzene (12b). It was obtained from compound **10b** (3.00 g, 18.07 mmol), Ohira-Bestmann's reagent (8.72 g, 54.21 mmol), K_2CO_3 (12.48 g, 90.36 mmol) using the same procedure described above for **12a**, as a thick oil (1.84



12b: $C_{10}H_{10}O_2$ (162.19)

g, 63%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.01 (s, 1H), 3.47 (s, 3H), 5.18 (s, 2H), 6.93–7.03 (m, 2H), 7.38–7.47 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 56.1, 76.0, 83.5, 94.2, 115.3, 116.1, 133.5, 157.5; ESIMS (*m*/*z*) 163 $[M+H]^+$, 185 $[M+Na]^+$; IR (neat) ν_{max} 3288, 2107, 1604 cm^{-1}.

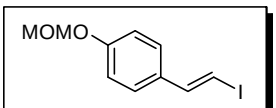
(*E*)-4-(2-Iodovinyl)-1,2-bis(methoxymethoxy)benzene (14a). To a vigorously stirred suspension of



14a: $C_{12}H_{15}IO_4$ (350.15)

$CrCl_2$ (4.35 g, 35.39 mmol) in THF:dioxane (60 mL, 1:1) at 0 °C was added a solution of aldehyde **10a** (1.00 g, 4.42 mmol) in THF:dioxane (20 mL, 1:1) under argon atmosphere. After 5 min, CHI_3 (6.09 g, 15.48 mmol) solution in THF:dioxane (10 mL, 1:1) was added to the reaction mixture. After 2 h at 0 °C, water (80 mL) and ethyl acetate (80 mL) were added to the reaction mixture and the organic layer was separated. The aqueous layer was extracted with EtOAc (40 mL X 2) and the combined organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (19:1) as an eluent afforded pure product (*E*)-vinyl iodide **14a** as a thick oil (1.16 g, 75%). ^{1}H NMR ($CDCl_3$, 200 MHz) (*E*:*Z* = 94:6) δ 3.51 (s, 3H), 3.52 (s, 3H), 5.23 (s, 4H), 6.68 (d, *J* = 14 Hz, 1H), 6.89 (dd, *J* = 8 and 2 Hz, 1H), 7.10 (d, *J* = 8 Hz, 1H), 7.13 (d, *J* = 2 Hz, 1H), 7.33 (d, *J* = 16 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 56.2 (2 carbons), 75.0, 95.3, 95.5, 113.9, 116.4, 120.6, 132.5, 144.2, 147.3, 147.5; ESIMS (*m*/*z*) 373 $[M+Na]^+$; HRMS (ESI) calcd for $C_{12}H_{15}IO_4$ $[M+Na]^+$ 372.9913, found 372.9904; IR ($CHCl_3$) ν_{max} 1601 cm^{-1}.

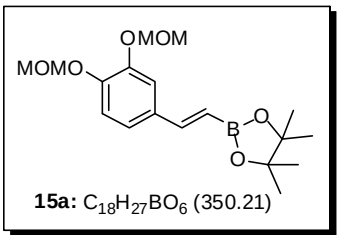
(*E*)-1-(2-Iodovinyl)-4-(methoxymethoxy)benzene (14b). It was obtained from compound $CrCl_2$ (5.92



14b: $C_{10}H_{11}IO_2$ (290.10)

g, 48.19 mmol), aldehyde **10b** (1.00 g, 6.02 mmol), CHI_3 (8.30 g, 21.08 mmol) using the same procedure described above for **14a**, as a thick oil (1.31 g, 75%). ^{1}H NMR ($CDCl_3$, 200 MHz) (*E*:*Z* = 93:7) δ 3.47 (s, 3H), 5.17 (s, 2H), 6.66 (d, *J* = 14 Hz, 1H), 6.94–7.04 (m, 2H), 7.18–7.29 (m, 2H), 7.36 (d, *J* = 16 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 56.1, 74.2, 94.3, 116.3, 127.2, 131.8, 144.2, 157.3; ESIMS (*m*/*z*) 313 $[M+Na]^+$; HRMS (ESI) calcd for $C_{10}H_{11}IO_2$ $[M+H]^+$ 290.9882, found 290.9871; IR ($CHCl_3$) ν_{max} 1605 cm^{-1}.

(*E*)-2-(3,4-Bis(methoxymethoxy)styryl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (15a). To a stirred

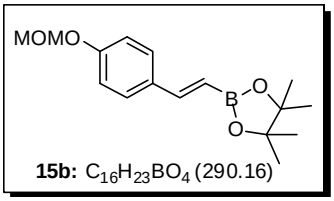


15a: $C_{18}H_{27}BO_6$ (350.21)

solution of vinyl iodide **14a** (500 mg, 1.42 mmol) in THF (10 mL) at –78 °C was added *t*-BuLi (1.30 M in hexane, 1.53 mL, 1.99 mmol) and the reaction mixture was stirred for 45 min under argon atmosphere. Isopropyl pinacol borane (0.32 mL, 1.99 mmol) was added dropwise to the above reaction mixture and further stirred at –78 °C for 2 h. The reaction was quenched with saturated NH_4Cl (2 mL) and THF was removed in vacuo. The obtained

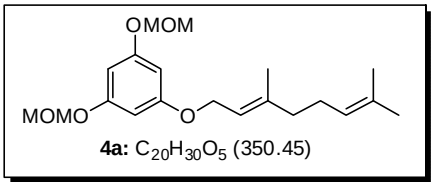
residue was dissolved in ethyl acetate (25 mL) and the organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (9:1) as an eluent afforded pure product vinyl boronate **15a** as a thick oil (390 mg, 78%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.24 (s, 12H), 3.44 (s, 6H), 5.16 (s, 2H), 5.17 (s, 2H), 5.98 (d, *J* = 18 Hz, 1H), 7.04 (s, 2H), 7.18–7.32 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.8, 56.1, 56.2, 83.3, 95.2, 95.5, 115.0, 116.1, 121.9, 132.2, 147.2, 148.0, 148.9; ESIMS (*m*/*z*) 351 $[M+H]^+$, 373 $[M+Na]^+$; HRMS (ESI) calcd for $C_{18}H_{27}BO_6$ $[M+Na]^+$ 373.1798, found 373.1800; IR (neat) ν_{max} 1625, 1602 cm^{-1}.

(*E*)-2-(4-(Methoxymethoxy)styryl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (15b). It was obtained from vinyl iodide **14b** (500 mg, 1.72 mmol), *t*-BuLi (1.30 M in hexane, 1.85 mL, 2.41 mmol), isopropyl pinacol borane (0.49 mL, 2.41 mmol) using the same procedure described above for **15a**, as a thick oil (400 mg, 80%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.28 (s, 12H), 3.44 (s, 3H), 5.15 (s, 2H), 6.00 (d, *J* = 18 Hz, 1H), 6.97 (d, *J* = 10 Hz, 2H), 7.32 (d, *J* = 20 Hz, 1H), 7.40 (d, *J* = 10 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.8, 56.0, 83.2, 94.3, 116.2, 128.4, 130.2, 131.5, 148.9, 157.9; ESIMS (*m*/*z*) 291 $[M+H]^+$, 313 $[M+Na]^+$; HRMS (ESI) calcd for $C_{16}H_{23}BO_4$ $[M+H]^+$ 291.1768, found 291.1750; IR ($CHCl_3$) ν_{max} 1626, 1604 cm^{-1}.



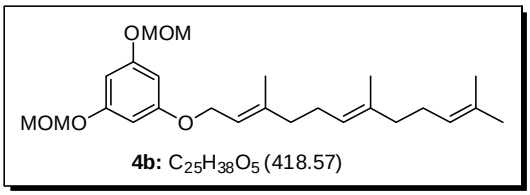
15b: $C_{16}H_{23}BO_4$ (290.16)

(*E*)-1-((3,7-Dimethylocta-2,6-dien-1-yl)oxy)-3,5-bis(methoxymethoxy)benzene (4a). To a stirred solution of compound **3** (2.00 g, 9.34 mmol) and geranyl bromide (4.05 g, 18.69 mmol) in DMF (40 mL) was added K_2CO_3 (6.45 g, 46.72 mmol) and the reaction mixture was stirred at 25 °C for 12 h under argon atmosphere. To the reaction mixture was added ethyl acetate (100 mL) and the organic layer was washed with brine (25 mL X 3) and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (19:1) as an eluent afforded pure product **4a** as a thick oil (2.48 g, 76%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.61 (s, 3H), 1.68 (s, 3H), 1.73 (s, 3H), 2.00–2.20 (m, 4H), 3.47 (s, 6H), 4.49 (d, *J* = 8 Hz, 2H), 5.00–5.20 (m, 1H), 5.13 (s, 4H), 5.47 (t, *J* = 6 Hz, 1H), 6.27–6.38 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.6, 17.7, 25.6, 26.3, 39.5, 56.0, 64.9, 94.5, 96.9, 97.2, 119.3, 123.8, 131.8, 141.3, 158.9, 160.6; ESIMS (*m*/*z*) 351 $[M+H]^+$, 373 $[M+Na]^+$; HRMS (ESI) calcd for $C_{20}H_{30}O_5$ $[M+H]^+$ 351.2171, found 351.2159; IR (neat) ν_{max} 1602 cm^{-1}.



4a: $C_{20}H_{30}O_5$ (350.45)

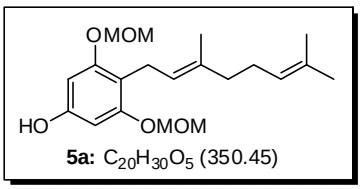
1,3-Bis(methoxymethoxy)-5-(((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)oxy)benzene (4b). It



4b: $C_{25}H_{38}O_5$ (418.57)

was obtained from compound **3** (2.00 g, 9.34 mmol), farnesyl bromide (5.32 g, 18.70 mmol) and K_2CO_3 (6.45 g, 46.72 mmol) using the same procedure described above for **4a**, as a thick oil (3.04 g, 78%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.60 (s, 6H), 1.68 (s, 3H), 1.73 (s, 3H), 1.90–2.20 (m, 8H), 3.47 (s, 6H), 4.49 (d, *J* = 6 Hz, 2H), 5.00–5.20 (m, 2H), 5.13 (s, 4H), 5.47 (t, *J* = 8 Hz, 1H), 6.27–6.38 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.0, 16.6, 17.7, 25.7, 26.2, 26.7, 39.5, 39.7, 56.0, 64.9, 94.4, 96.8, 97.2, 119.2, 123.7, 124.3, 131.3, 135.4, 141.3, 158.9, 160.6; ESIMS (*m*/*z*) 419 $[M+H]^+$, 441 $[M+Na]^+$; HRMS (ESI) calcd for $C_{25}H_{38}O_5$ $[M+Na]^+$ 441.2617, found 441.2607; IR (neat) ν_{max} 1603 cm^{-1}.

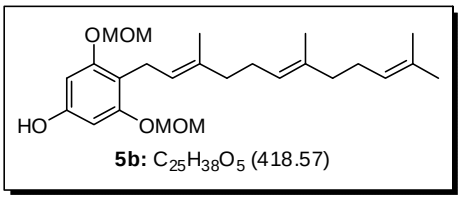
(*E*)-4-(3,7-Dimethylocta-2,6-dien-1-yl)-3,5-bis(methoxymethoxy)phenol (5a). *N*,*N*-Dimethylaniline (5



5a: $C_{20}H_{30}O_5$ (350.45)

mL) was added to the compound **4a** (500 mg, 1.43 mmol) and the reaction mixture was refluxed for 3 h under argon atmosphere. The reaction mixture was allowed to attain room temperature. To the reaction mixture was added ethyl acetate (40 mL) and it was washed with dil. HCl (10 mL X 2), water (10 mL X 3), brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (4:1) as an eluent afforded pure product **5a** as a thick oil (250 mg, 50%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.57 (s, 3H), 1.65 (s, 3H), 1.76 (s, 3H), 1.85–2.20 (m, 4H), 3.30 (d, *J* = 8 Hz, 2H), 3.46 (s, 6H), 5.00–5.25 (m, 2H), 5.14 (s, 4H), 5.48 (br s, 1H), 6.31 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.0, 17.6, 22.1, 25.7, 26.7, 39.8, 55.9, 94.3, 96.0, 112.4, 123.2, 124.4, 131.2, 134.2, 154.8, 156.2; ESIMS (*m*/*z*) 373 $[M+Na]^+$; HRMS (ESI) calcd for $C_{20}H_{30}O_5$ $[M+H]^+$ 351.2171, found 351.2172; IR ($CHCl_3$) ν_{max} 3394, 1603 cm^{-1}.

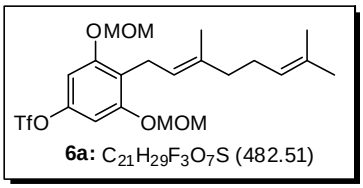
3,5-Bis(methoxymethoxy)-4-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)phenol (5b). It was



5b: $C_{25}H_{38}O_5$ (418.57)

obtained from compound **4b** (500 mg, 1.19 mmol) using the same procedure described above for **5a**, as a thick oil (255 mg, 51%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.57 (s, 3H), 1.59 (s, 3H), 1.67 (s, 3H), 1.76 (s, 3H), 1.85–2.15 (m, 8H), 3.31 (d, *J* = 6 Hz, 2H), 3.46 (s, 6H), 5.00–5.25 (m, 3H), 5.14 (s, 4H), 6.31 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.9, 16.0, 17.7, 22.1, 25.7, 26.66, 26.71, 39.7, 39.8, 55.9, 94.3, 96.0, 112.4, 123.2, 124.3, 124.4, 131.3, 134.2, 134.8, 154.8, 156.2; ESIMS (*m*/*z*) 419 $[M+H]^+$, 441 $[M+Na]^+$; HRMS (ESI) calcd for $C_{25}H_{38}O_5$ $[M+H]^+$ 419.2797, found 419.2798; IR (neat) ν_{max} 3398, 1606 cm^{-1}.

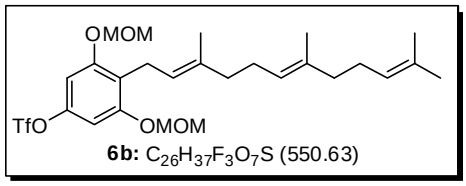
(*E*)-4-(3,7-Dimethylocta-2,6-dien-1-yl)-3,5-bis(methoxymethoxy)phenyl trifluoromethanesulfonate



6a: $C_{21}H_{29}F_3O_7S$ (482.51)

(6a). To a stirred solution of compound **5a** (250 mg, 0.71 mmol) in DCM (5 mL) at –20 °C was added pyridine (0.11 mL, 1.42 mmol) in a dropwise fashion under argon atmosphere and the reaction mixture was stirred at –20 °C for 30 min which was followed by the addition of Tf_2O (0.18 mL, 1.07 mmol). After 2 h of stirring at –20 °C the reaction was quenched with ice-cooled water. The reaction mixture was extracted with DCM (10 mL X 3) and the organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (97:3) as an eluent afforded pure product triflate **6a** as a thick oil (340 mg, 99%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.56 (s, 3H), 1.64 (s, 3H), 1.77 (s, 3H), 1.85–2.15 (m, 4H), 3.36 (d, *J* = 8 Hz, 2H), 3.46 (s, 6H), 5.05 (t, *J* = 6 Hz, 1H), 5.15 (t, *J* = 6 Hz, 1H), 5.18 (s, 4H), 6.72 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.0, 17.6, 22.5, 25.6, 26.6, 39.7, 56.1, 94.6, 101.7, 120.3, 121.6, 124.2, 131.4, 135.4, 148.0, 156.0; ESIMS (*m*/*z*) 505 $[M+Na]^+$; HRMS (ESI) calcd for $C_{21}H_{29}F_3O_7S$ $[M+Na]^+$ 505.1484, found 505.1498; IR (neat) ν_{max} 1612 cm^{-1}.

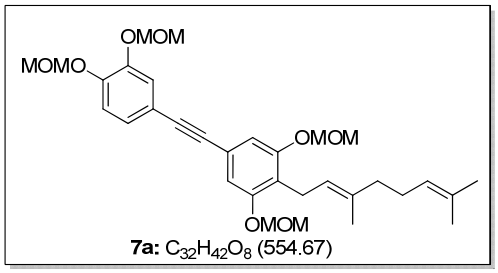
3,5-Bis(methoxymethoxy)-4-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)phenyl



6b: $C_{26}H_{37}F_3O_7S$ (550.63)

trifluoromethanesulfonate (6b). It was obtained from compound **5b** (250 mg, 0.59 mmol), pyridine (0.09 mL, 1.19 mmol) and Tf_2O (0.15 mL, 0.89 mmol) using the same procedure described above for **6a**, as a thick oil (325 mg, 99%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.57 (s, 6H), 1.68 (s, 3H), 1.77 (s, 3H), 1.85–2.20 (m, 8H), 3.37 (d, *J* = 6 Hz, 2H), 3.46 (s, 6H), 5.00–5.25 (m, 3H), 5.18 (s, 4H), 6.72 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.0, 16.1, 17.6, 22.5, 25.7, 26.6, 26.7, 39.7, 39.8, 56.1, 94.6, 101.7, 120.4, 121.6, 124.1, 124.3, 131.3, 135.0, 135.2, 135.5, 148.0, 156.0; ESIMS (*m*/*z*) 573 $[M+Na]^+$; HRMS (ESI) calcd for $C_{26}H_{37}F_3O_7S$ $[M+H]^+$ 551.2290, found 551.2296; IR (neat) ν_{max} 1612 cm^{-1}.

(*E*)-5-((3,4-Bis(methoxymethoxy)phenyl)ethynyl)-2-(3,7-dimethylocta-2,6-dien-1-yl)-1,3-

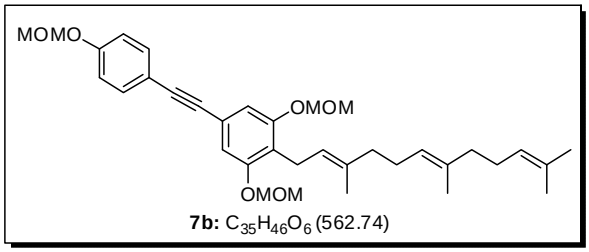


7a: $C_{32}H_{42}O_8$ (554.67)

bis(methoxymethoxy)benzene (7a). To a stirred solution of triflate **6a** (300 mg, 0.62 mmol), $PdCl_2(PPh_3)_2$ (43 mg, 10 mol%), CuI (35 mg, 30 mol%) and TBAI (689 mg, 1.86 mmol) in DMF:Et_3N (8 mL, 5:1) under argon atmosphere at 70 °C was added alkyne **12a** (193 mg, 0.87 mmol) in DMF:Et_3N (4 mL, 5:1) over a period of 1 h. The reaction mixture was allowed to stir for an additional

30 min and then it was cooled to 25 °C. The reaction mixture was diluted with ethyl acetate (50 mL) and the organic layer was washed with brine (20 mL X 3) and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (4:1) as an eluent afforded pure product **7a** as a thick oil (282 mg, 82%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.57 (s, 3H), 1.65 (s, 3H), 1.78 (s, 3H), 1.85–2.15 (m, 4H), 3.40 (d, *J* = 8 Hz, 2H), 3.48 (s, 6H), 3.52 (s, 3H), 3.54 (s, 3H), 5.06 (t, *J* = 6 Hz, 1H), 5.13–5.25 (m, 1H), 5.20 (s, 4H), 5.25 (s, 4H), 6.95 (s, 2H), 7.05–7.20 (m, 2H), 7.33 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.0, 17.6, 22.7, 25.6, 26.7, 39.8, 56.0, 56.2 (2 carbons), 88.3, 88.5, 94.4, 95.2, 95.4, 111.1, 116.2, 117.3, 119.6, 121.1, 121.5, 122.2, 124.3, 126.2, 131.2, 134.9, 146.8, 147.5, 155.4; ESIMS (*m*/*z*) 555 $[M+H]^+$, 577 $[M+Na]^+$; HRMS (ESI) calcd for $C_{32}H_{42}O_8$ $[M+Na]^+$ 577.2777, found 577.2770; IR ($CHCl_3$) ν_{max} 2401, 1597 cm^{-1}.

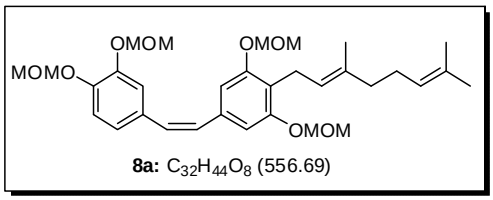
1,3-Bis(methoxymethoxy)-5-((4-(methoxymethoxy)phenyl)ethynyl)-2-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)benzene (7b).



7b: $C_{35}H_{46}O_6$ (562.74)

It was obtained from triflate **6b** (300 mg, 0.54 mmol), $PdCl_2(PPh_3)_2$ (38 mg, 10 mol%), CuI (31 mg, 30 mol%), TBAI (604 mg, 1.63 mmol), alkyne **12b** (123 mg, 0.76 mmol) using the same procedure described above for **7a**, as a thick oil (251 mg, 82%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.57 (s, 3H), 1.59 (s, 3H), 1.67 (s, 3H), 1.78 (s, 3H), 1.85–2.50 (m, 8H), 3.40 (d, *J* = 8 Hz, 2H), 3.48 (s, 9H), 5.08 (t, *J* = 6 Hz, 1H), 5.10–5.25 (m, 2H), 5.19 (s, 2H), 5.20 (s, 4H), 6.94 (s, 2H), 6.95–7.05 (m, 2H), 7.40–7.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.0, 16.1, 17.7, 22.7, 25.7, 26.6, 26.7, 39.7, 39.8, 56.0, 56.1, 88.4, 88.5, 94.3, 94.4, 111.1, 116.1, 116.7, 121.0, 121.7, 122.2, 124.2, 124.4, 131.3, 133.0, 135.0, 155.4, 157.1; ESIMS (*m*/*z*) 585 $[M+Na]^+$; HRMS (ESI) calcd for $C_{35}H_{46}O_6$ $[M+Na]^+$ 585.3192, found 585.3191; IR ($CHCl_3$) ν_{max} 2401, 1598 cm^{-1}.

5-((*Z*)-3,4-Bis(methoxymethoxy)styryl)-2-((*E*)-3,7-dimethylocta-2,6-dien-1-yl)-1,3-bis(methoxymethoxy)benzene (8a).

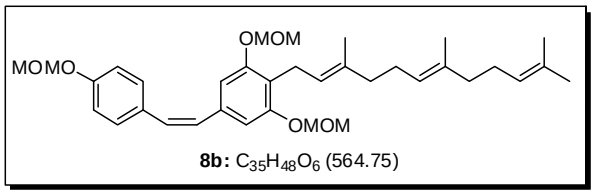


8a: $C_{32}H_{44}O_8$ (556.69)

Compound **7a** (200 mg, 0.36 mmol), KOH (30 mg, 0.54 mmol), $Pd(OAc)_2$ (4.0 mg, 5 mol%) and DMF (2 mL) were placed in a thick-walled Pyrex screw-cap tube (10 mL) under a argon atmosphere and the capped tube was heated in an oil bath at 145 °C under stirring for 6 h. After the reaction mixture was cooled to 25 °C, it was diluted with ethyl acetate (25 mL) and the organic layer was washed with brine (10 mL X 3) and dried over Na_2SO_4. The concentration of organic layer in vacuo

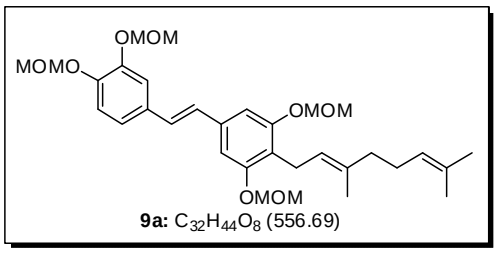
followed by silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (4:1) as an eluent afforded pure product *cis*-stilbene **8a** as a thick oil (172 mg, 86%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.50 (s, 3H), 1.58 (s, 3H), 1.69 (s, 3H), 1.80–2.05 (m, 4H), 3.29 (d, *J* = 8 Hz, 2H), 3.33 (s, 9H), 3.42 (s, 3H), 4.96 (s, 4H), 4.99 (s, 2H), 5.05–5.25 (m, 2H), 5.13 (s, 2H), 6.40 (s, 2H), 6.59 (s, 2H), 6.75–7.00 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.0, 17.6, 22.6, 25.6, 26.7, 39.8, 55.8, 56.0, 56.1, 94.5, 95.4 (2 carbons), 108.7, 116.4, 117.6, 119.3, 122.7, 123.3, 124.4, 129.5, 129.7, 131.2, 131.9, 134.5, 136.0, 146.3, 146.8, 155.4; ESIMS (*m*/*z*) 557 $[M+H]^+$, 579 $[M+Na]^+$; HRMS (ESI) calcd for $C_{32}H_{44}O_8$ $[M+Na]^+$ 579.2934, found 579.2924; IR ($CHCl_3$) ν_{max} 1638 cm^{-1}.

1,3-Bis(methoxymethoxy)-5-((*Z*)-4-(methoxymethoxy)styryl)-2-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)benzene (8b). It was obtained from compound **7b** (200 mg, 0.35 mmol), KOH (30 mg, 0.53 mmol), $Pd(OAc)_2$ (4.0 mg, 5 mol%) using the same procedure described above for **8a**, as a thick oil (172 mg, 86%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.57 (s, 3H), 1.59 (s, 3H), 1.67 (s, 3H), 1.77 (s, 3H), 1.85–2.15 (m, 8H), 3.36 (d, *J* = 6 Hz, 2H), 3.39 (s, 6H), 3.46 (s, 3H), 5.01 (s, 4H), 5.05–5.27 (m, 3H), 5.15 (s, 2H), 6.42 (d, *J* = 12 Hz, 1H), 6.50 (d, *J* = 12 Hz, 1H), 6.67 (s, 2H), 6.90 (d, *J* = 8 Hz, 2H), 7.22 (d, *J* = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.9, 16.1, 17.7, 22.6, 25.7, 26.65, 26.71, 39.7, 39.8, 55.8, 55.9, 94.3, 94.4, 108.8, 115.9, 119.3, 122.7, 124.3, 124.4, 129.2, 129.5, 130.2, 131.0, 131.2, 134.6, 134.8, 136.0, 155.4, 156.2; ESIMS (*m*/*z*) 565 $[M+H]^+$, 587 $[M+Na]^+$; HRMS (ESI) calcd for $C_{35}H_{48}O_6$ $[M+Na]^+$ 587.3349, found 587.3352; IR ($CHCl_3$) ν_{max} 1604 cm^{-1}.



8b: $C_{35}H_{48}O_6$ (564.75)

5-((*E*)-3,4-Bis(methoxymethoxy)styryl)-2-((*E*)-3,7-dimethylocta-2,6-dien-1-yl)-1,3-bis(methoxymethoxy)benzene (9a). To a stirred solution of the *cis*-stilbene **8a** (100 mg, 0.18 mmol) in DCM (0.4 mL) was added $PdCl_2(CH_3CN)_2$ (4.6 mg, 10 mol%) and the reaction mixture was stirred at 25 °C for 12 h under argon atmosphere. The reaction mixture was diluted with Et_2O (20 mL), filtered through a short pad of Celite and washed with diethyl ether. The solvent was removed in vacuo and the obtained residue was subjected for silica gel column chromatographic purification using petroleum ether–ethyl acetate (4:1) as an eluent to afford pure product *trans*-stilbene **9a** as a thick oil (82 mg, 82%).



9a: $C_{32}H_{44}O_8$ (556.69)

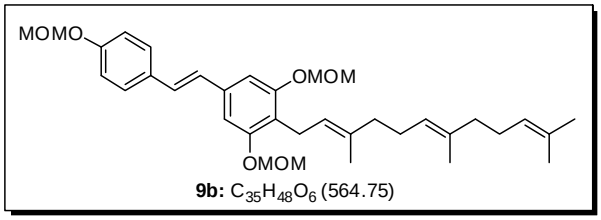
Heck Coupling: Triflate **6a** (100 mg, 0.20 mmol) and styrene **11a** (69 mg, 0.31 mmol) were dissolved in CH_3CN (2 ml). Et_3N (1 mL), $Pd(OAc)_2$ (4.6 mg, 10 mol%) and PPh_3 (27 mg, 50 mol%) were added to

the stirred reaction mixture. The reaction mixture was heated at 85 °C for 24 h under argon atmosphere. The reaction mixture was concentrated in vacuo and the obtained residue was subjected for silica gel column chromatographic purification using petroleum ether–ethyl acetate (4:1) as an eluent to afford pure product *trans*-stilbene **9a** as a thick oil (71 mg, 62%).

Stille Coupling: Triflate **6a** (100 mg, 0.20 mmol) and stannate **13a** (159 mg, 0.31 mmol) were dissolved in DMF (2 ml) in a thick-walled Pyrex screw-cap tube (10 mL) under argon atmosphere. $Pd(PPh_3)_4$ (12 mg, 5 mol%) and LiCl (44 mg, 1.031 mmol) were added to this reaction mixture and the capped tube was heated in an oil bath at 120 °C with stirring for 8 h. To the reaction mixture was added ethyl acetate (20 mL) and the organic layer was washed with brine (10 mL X 3) and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (4:1) as an eluent afforded pure product *trans*-stilbene **9a** as a thick oil (76 g, 66%).

Suzuki Coupling: To a mixture of triflate **6a** (100 mg, 0.20 mmol) and boronate **15a** (108 mg, 0.31 mmol) in dioxane:water (2 mL, 7:1) were added $Pd(PPh_3)_4$ (12 mg, 5 mol%) and Na_2CO_3 (109 mg, 1.037 mmol) in a thick-walled Pyrex screw-cap tube (10 mL). The reaction mixture was heated at 90 °C for 8 h. The reaction mixture was concentrated in vacuo. To the obtained residue was added ethyl acetate (20 mL) and the organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (4:1) as an eluent afforded pure product *trans*-stilbene **9a** as a thick oil (74 mg, 65%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.57 (s, 3H), 1.65 (s, 3H), 1.79 (s, 3H), 1.85–2.15 (m, 4H), 3.40 (d, J = 8 Hz, 2H), 3.50 (s, 6H), 3.53 (s, 3H), 3.56 (s, 3H), 5.00–5.15 (m, 1H), 5.15–5.30 (m, 1H), 5.24 (s, 4H), 5.25 (s, 2H), 5.29 (s, 2H), 6.92 (s, 2H), 6.90–7.18 (m, 4H), 7.33 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.0, 17.6, 22.7, 25.6, 26.7, 39.8, 56.0, 56.16, 56.19, 94.4, 95.4 (2 carbons), 106.0, 114.2, 116.5, 119.7, 120.9, 122.5, 124.3, 127.6, 127.7, 131.2, 132.1, 134.6, 136.7, 146.8, 147.4, 155.8; ESIMS (m/z) 579 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1599 cm^{-1}.

1,3-Bis(methoxymethoxy)-5-((*E*)-4-(methoxymethoxy)styryl)-2-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)benzene (9b). It was obtained from *cis*-stilbene **8b** (150 mg, 0.26 mmol), $PdCl_2(CH_3CN)_2$ (6.8 mg, 10 mol%) using the same procedure described above for **9a**, as a thick oil (127 mg, 85%).



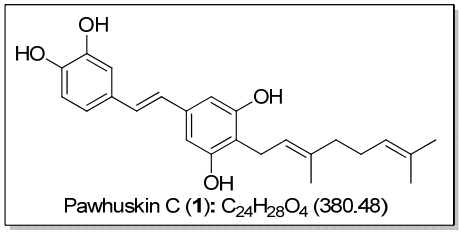
9b: $C_{35}H_{48}O_6$ (564.75)

Heck Coupling: It was obtained from triflate **6b** (100 mg, 0.18 mmol), styrene **11b** (45 mg, 0.27 mmol), Et_3N (1 mL), $Pd(OAc)_2$ (4.0 mg, 10 mol%), PPh_3 (24 mg, 50 mol%) using the same procedure described above for **9a**, as a thick oil (64 mg, 63%).

Stille Coupling: It was obtained from triflate **6b** (100 mg, 0.18 mmol), stannate **13b** (123 mg, 0.27 mmol), $Pd(PPh_3)_4$ (10 mg, 5 mol%), LiCl (39 mg, 0.90 mmol) using the same procedure described above for **9a**, as a thick oil (68 mg, 67%).

Suzuki Coupling: It was obtained from triflate **6b** (100 mg, 0.18 mmol), boronate **15b** (79 mg, 0.27 mmol), $Pd(PPh_3)_4$ (10 mg, 5 mol%), Na_2CO_3 (96 mg, 0.90 mmol) using the same procedure described above for **9a**, as a thick oil (67 mg, 66%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.59 (s, 3H), 1.60 (s, 3H), 1.68 (s, 3H), 1.81 (s, 3H), 1.92–2.00 (m, 4H), 2.00–2.11 (m, 4H), 3.43 (d, *J* = 5 Hz, 2H), 3.50 (s, 3H), 3.52 (s, 6H), 5.06–5.14 (m, 2H), 5.20 (s, 2H), 5.22–5.28 (m, 1H), 5.25 (s, 4H), 6.94 (d, *J* = 15 Hz, 1H), 6.94 (s, 2H), 7.02 (d, *J* = 15 Hz, 1H), 7.03 (d, *J* = 10 Hz, 2H), 7.45 (d, *J* = 10 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.9, 16.1, 17.6, 22.7, 25.6, 26.6, 26.7, 39.7, 39.8, 55.9 (2 carbons), 94.4, 94.5, 106.0, 116.4, 119.7, 122.6, 124.2, 124.4, 127.2, 127.6, 127.7, 131.2, 131.3, 134.6, 134.8, 136.5, 155.9, 156.8; ESIMS (*m*/*z*) 565 $[M+H]^+$; HRMS (ESI) calcd for $C_{35}H_{48}O_6$ $[M+Na]^+$ 587.3349, found 587.3358; IR ($CHCl_3$) ν_{max} 1601 cm^{-1}.

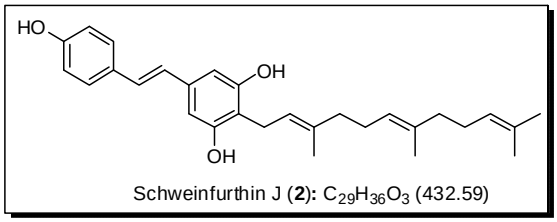
4-((*E*)-4-((*E*)-3,7-Dimethylocta-2,6-dien-1-yl)-3,5-dihydroxystyryl)benzene-1,2-diol (Pawhuskin C, 1).



Pawhuskin C (**1**): $C_{24}H_{28}O_4$ (380.48)

To a stirred solution of *trans*-stilbene **9a** (80 mg, 0.14 mmol) in MeOH (10 mL) was added a catalytic amount of camphorsulfonic acid (5 mg) and the reaction mixture was stirred at 25 °C for 12 h under argon atmosphere. The reaction was quenched by addition of sat. $NaHCO_3$ and concentrated in vacuo. To the obtained residue was added ethyl acetate (20 mL) and the organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (1:1) as an eluent afforded pure product pawhuskin C (**1**) as a yellow solid (30 mg, 55%). Mp 144–146 °C (lit.[13] 148-152 °C); ^{1}H NMR (acetone-d_6, 200 MHz) δ 1.57 (s, 3H), 1.62 (s, 3H), 1.78 (s, 3H), 1.90–2.15 (m, 4H), 3.37 (d, *J* = 8 Hz, 2H), 5.09 (t, *J* = 6 Hz, 1H), 5.33 (t, *J* = 6 Hz, 1H), 6.58 (s, 2H), 6.70–6.92 (m, 4H), 7.04 (d, *J* = 2 Hz, 1H), 7.75–8.15 (br s, 4H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 16.4, 17.9, 23.2, 26.0, 27.6, 40.8, 105.8, 113.8, 115.4, 116.4, 119.9, 124.4, 125.4, 127.1, 128.5, 131.0, 131.7, 134.7, 137.4, 146.1, 146.3, 157.2; ESIMS (*m*/*z*) 381 $[M+H]^+$, 403 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 3423, 1619 cm^{-1}.

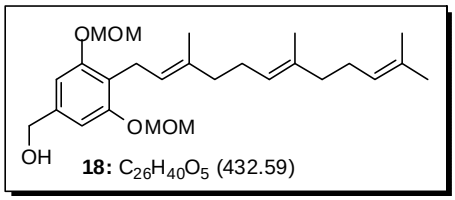
5-((*E*)-4-Hydroxystyryl)-2-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)benzene-1,3-diol



Schweinfurthin J (**2**): $C_{29}H_{36}O_3$ (432.59)

(Schweinfurthin J, **2).** It was obtained from compound **9b** (100 mg, 0.17 mmol) using the same procedure described above for **1**, as a yellow solid (43 mg, 57%). Mp 118**–**120 °C; ^{1}H NMR (CD_3OD, 500 MHz) δ 1.56 (s, 6H), 1.63 (s, 3H), 1.77 (s, 3H), 1.90 (t, *J* = 10 Hz, 2H), 1.96 (q, *J* = 10 Hz, 2H), 2.01 (t, *J* = 10 Hz, 2H), 2.07 (q, *J* = 10 Hz, 2H), 3.30 (d, *J* = 10 Hz, 2H), 5.03–5.10 (m, 1H), 5.08 (t, *J* = 10 Hz, 1H), 5.26 (t, *J* = 10 Hz, 1H), 6.46 (s, 2H), 6.75 (d, *J* = 15 Hz, 1H), 6.76 (d, *J* = 10 Hz, 2H), 6.90 (d, *J* = 15 Hz, 1H), 7.32 (d, *J* = 10 Hz, 2H); ^{13}C NMR (CD_3OD, 125 MHz) δ 16.1, 16.3, 17.8, 23.2, 25.9, 27.6, 27.8, 40.8, 41.0, 105.7, 115.8, 116.5, 124.7, 125.5, 125.6, 127.3, 128.2, 128.6, 130.7, 131.9, 134.7, 135.8, 137.6, 157.2, 158.1; ESIMS (*m*/*z*) 433 $[M+H]^+$, 455 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 3423, 1630, 1605 cm^{-1}.

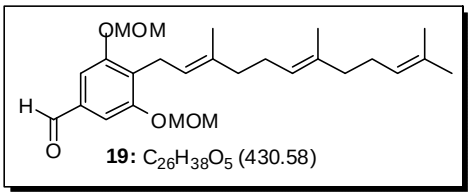
(3,5-Bis(methoxymethoxy)-4-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)phenyl)methanol



18: $C_{26}H_{40}O_5$ (432.59)

(18). A solution of *t*-BuLi in pentane (1.60 M, 30.15 mL, 48.24 mmol) was added dropwise to a solution of alcohol **17** (5.00 g, 21.92 mmol) and TMEDA (6.86 mL, 46.05 mmol) in THF (60 mL) at –20 °C under argon atmosphere and the reaction mixture was stirred at –20 °C for 1 h. This was followed by the addition of $CuBr.Me_2S$ (9.44 g, 46.05 mmol) and the reaction mixture was further stirred at –20 °C for 1 h. A solution of farnesyl bromide (6.87 g, 24.12 mmol) in THF (20 mL) was added dropwise to the above reaction mixture and it was stirred at –20 °C for 2 h. The reaction was quenched with saturated aq. NH_4Cl solution (10 mL) and then concentrated in vacuo. To the obtained residue was added ethyl acetate (80 mL) and the organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (1:1) as an eluent afforded pure product **18** as a thick oil (5.87 g, 62%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.56 (s, 3H), 1.59 (s, 3H), 1.67 (s, 3H), 1.78 (s, 3H), 1.80–2.14 (m, 8H), 3.39 (d, *J* = 8 Hz, 2H), 3.47 (s, 6H), 4.61 (s, 2H), 5.01–5.14 (m, 2H), 5.14–5.25 (m, 1H), 5.19 (s, 4H), 6.78 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.0, 16.1, 17.6, 22.5, 25.7, 26.6, 26.7, 39.7, 39.8, 56.0, 65.5, 94.4, 106.5, 119.5, 122.6, 124.2, 124.4, 131.3, 134.7, 134.9, 140.0, 155.7; ESIMS (*m*/*z*) 455 $[M+Na]^+$; HRMS (ESI) calcd for $C_{26}H_{40}O_5$ $[M+Na]^+$ 455.2773, found 455.2776; IR (neat) ν_{max} 3427, 1611, 1589 cm^{-1}.

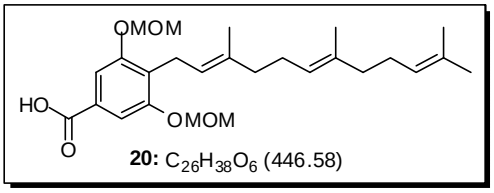
3,5-Bis(methoxymethoxy)-4-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)benzaldehyde (19).



19: $C_{26}H_{38}O_5$ (430.58)

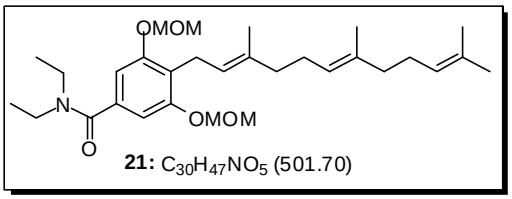
To a stirred suspension of PCC (3.74 g, 17.36 mmol) and 4 Å molecular sieves in dichloromethane (60 mL) at 0 °C was added solution of alcohol **18** (5.00 g, 11.57 mmol) in dichloromethane (20 mL) under argon atmosphere. After stirring at 25 °C for 3 h, the reaction mixture was diluted with diethyl ether (20 mL). The resulting reaction mixture was filtered through Celite pad and the filtrate was concentrated in vacuo. The silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (4:1) as an eluent afforded pure aldehyde **19** as a thick oil (4.37 g, 88%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.56 (s, 3H), 1.58 (s, 3H), 1.67 (s, 3H), 1.80 (s, 3H), 1.85–2.10 (m, 8H), 3.46 (d, *J* = 8 Hz, 2H), 3.48 (s, 6H), 5.06 (t, *J* = 8 Hz, 2H), 5.15–5.28 (m, 1H), 5.26 (s, 4H), 7.29 (s, 2H), 9.87 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.0, 16.1, 17.6, 23.2, 25.7, 26.5, 26.7, 39.7, 39.8, 56.1, 94.4, 108.9, 121.2, 124.0, 124.3, 127.5, 131.3, 135.0, 135.5, 135.7, 156.0, 191.6; ESIMS (*m*/*z*) 453 $[M+Na]^+$; HRMS (ESI) calcd for $C_{26}H_{38}O_5$ $[M+Na]^+$ 453.2617, found 453.2611; IR ($CHCl_3$) ν_{max} 2723, 1699, 1586 cm^{-1}.

3,5-Bis(methoxymethoxy)-4-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)benzoic Acid (20). To



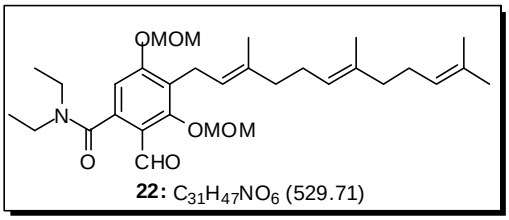
20: $C_{26}H_{38}O_6$ (446.58)

a stirred solution of aldehyde **19** (4.00 g, 9.30 mmol) in *t*-BuOH:H_2O (5:1, 40 mL) was added 2-methyl-2-butene (5.91 mL, 55.81 mmol) at 25 °C and the reaction mixture was stirred for 15 min which was followed by the addition of NaH_2PO_4 (1.67 g, 13.95 mmol). After stirring at 25 °C for 10 min, $NaClO_2$ (3.36 g, 37.20 mmol) was added to above reaction mixture and the stirring was continued for 8 h. The reaction mixture was concentrated in vacuo and to the obtained residue was added ethyl acetate (60 mL) and the organic layer was washed with brine (20 mL X 3) and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by the silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (2:3) as an eluent afforded pure product **20** as white solid (3.94 g, 95%). Mp 78–80 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.56 (s, 3H), 1.58 (s, 3H), 1.67 (s, 3H), 1.79 (s, 3H), 1.90–2.10 (m, 8H), 3.46 (d, *J* = 5 Hz, 2H), 3.48 (s, 6H), 5.07 (t, *J* = 10 Hz, 2H), 5.19 (t, *J* = 10 Hz, 1H), 5.25 (s, 4H), 7.49 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.0, 16.1, 17.6, 23.1, 25.7, 26.6, 26.7, 39.7, 39.8, 56.1, 94.5, 109.5, 121.5, 124.1, 124.3, 126.7, 127.9, 131.3, 135.0, 135.6, 155.4, 170.9; ESIMS (*m*/*z*) 447 $[M+H]^+$, 469 $[M+Na]^+$; HRMS (ESI) calcd for $C_{26}H_{38}O_6$ $[M+Na]^+$ 469.2566, found 469.2578; IR ($CHCl_3$) ν_{max} 1726, 1693, 1586 cm^{-1}.

***N*,*N*-Diethyl-3,5-bis(methoxymethoxy)-4-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)benzamide (21).** 

21: $C_{30}H_{47}NO_5$ (501.70)

A solution of EDCI (1.64 g, 8,63 mmol) and HOBt (1.32 g, 8.63 mmol) in DCM (20 mL) was added dropwise to a stirred suspension of acid **20** (3.50 g, 7.84 mmol) and *N*,*N*′-diethylamine hydrochloride (946 mg, 8,63 mmol) in DCM (40 mL) at 0 °C under argon atmosphere. DIPEA (2.95 mL, 17.26 mmol) was added dropwise to the above reaction mixture and it was stirred at 25 °C for 24 h. To the reaction mixture was added ethyl acetate (60 mL) and the organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by the silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (3:1) as an eluent afforded pure product **21** as a thick oil (3.06 g, 78%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.05–1.33 (m, 6H), 1.57 (s, 3H), 1.59 (s, 3H), 1.67 (s, 3H), 1.78 (s, 3H), 1.90–2.15 (m, 8H), 3.15–3.60 (m, 4H), 3.40 (d, *J* = 8 Hz, 2H), 3.46 (s, 6H), 5.00–5.28 (m, 3H), 5.18 (s, 4H), 6.79 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.9, 14.0, 15.9, 16.1, 17.6, 22.6, 25.6, 26.6, 26.7, 39.3, 39.7, 39.8, 43.3, 55.9, 94.5, 106.1, 121.1, 122.1, 124.2, 124.3, 131.2, 134.87, 134.93, 135.7, 155.5, 171.0; ESIMS (*m*/*z*) 524 $[M+Na]^+$; HRMS (ESI) calcd for $C_{30}H_{47}NO_5$ $[M+H]^+$ 502.3532, found 502.3529; IR ($CHCl_3$) ν_{max} 1732, 1619, 1581 cm^{-1}.

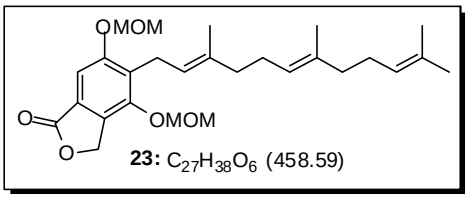
***N*,*N*-Diethyl-2-formyl-3,5-bis(methoxymethoxy)-4-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)benzamide (22).** 

22: $C_{31}H_{47}NO_6$ (529.71)

A solution of *t*-BuLi in pentane (1.60 M, 5.23 mL, 8.38 mmol) was added to a stirred solution of compound **21** (3.00 g, 5.98 mmol) in THF (30 mL) at –78 °C under argon atmosphere and stirred further for 15 min which was followed by the addition of DMF (2.31 mL, 29.94 mmol). The reaction mixture was allowed to attain 25 °C and stirred for 24 h. The reaction was quenched with saturated aq. NH_4Cl solution (10 mL) and then concentrated in vacuo. To the obtained residue was added ethyl acetate (50 mL) and the organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (3:2) as an eluent afforded pure product **22** as a thick oil (2.69 g, 85%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.03 (t, *J* = 10 Hz, 3H), 1.33 (t, *J* = 10 Hz, 3H), 1.58 (s, 3H), 1.60 (s, 3H), 1.68 (s, 3H), 1.79 (s, 3H), 1.93–2.11 (m, 8H), 3.09 (q, *J* = 10 Hz, 2H), 3.42 (d, *J* = 5 Hz, 2H), 3.45 (s, 3H), 3.53–3.64 (m, 2H), 3.59 (s, 3H), 5.06 (s, 2H), 5.08 (t, *J* = 5 Hz, 1H), 5.09 (t, *J* = 5 Hz, 1H), 5.16 (t, *J* = 10 Hz, 1H), 5.25 (s, 2H), 6.83 (s, 1H), 10.21 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz)

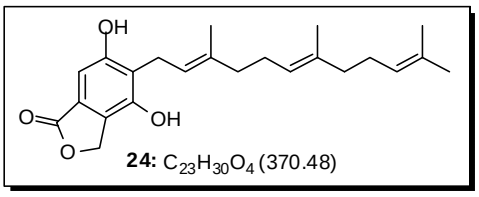
δ 12.1, 13.5, 16.0, 16.3, 17.7, 23.2, 25.7, 26.6, 26.7, 38.8, 39.7 (2 carbons), 42.5, 56.2, 58.0, 94.1, 101.6, 108.7, 120.8, 121.5, 124.0, 124.3, 125.1, 131.3, 135.2, 136.1, 138.6, 159.9, 160.5, 169.5, 189.0; ESIMS (*m*/*z*) 530 $[M+H]^+$, 552 $[M+Na]^+$; HRMS (ESI) calcd for $C_{31}H_{47}NO_6$ $[M+H]^+$ 530.3482, found 530.3484; IR ($CHCl_3$) ν_{max} 2857, 1740, 1684, 1634, 1594 cm^{-1}.

4,6-Bis(methoxymethoxy)-5-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)isobenzofuran-1(3H)-one (23). To a stirred solution of compound **22** (2.00 g, 3.78 mmol) in AcOH:MeOH (1:1, 20 mL) was added $NaBH_3CN$ (356 mg, 5.67 mmol) and the reaction mixture was heated at 100 °C for 2 h. The reaction was allowed to attain 25 °C and concentrated in vacuo. To the obtained residue was added ethyl acetate (40 mL) and the organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (9:1) as an eluent afforded pure product **23** as a thick oil (1.40 g, 81%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.56 (s, 3H), 1.58 (s, 3H), 1.67 (s, 3H), 1.80 (s, 3H), 1.90–2.12 (m, 8H), 3.47 (s, 3H), 3.48 (d, *J* = 8 Hz, 2H), 3.54 (s, 3H), 5.07 (s, 2H), 5.07 (t, *J* = 8 Hz, 2H), 5.14 (t, *J* = 8 Hz, 1H), 5.26 (s, 2H), 5.37 (s, 2H), 7.38 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.0, 16.2, 17.6, 23.8, 25.6, 26.4, 26.7, 39.6, 39.7, 56.1, 56.7, 69.0, 94.4, 97.1, 105.2, 121.2, 123.9, 124.2, 125.4, 129.5, 131.3, 135.1, 136.0, 150.3, 156.9, 171.0; ESIMS (*m*/*z*) 481 $[M+Na]^+$, 513 $[M+Na+MeOH]^+$; HRMS (ESI) calcd for $C_{27}H_{38}O_6$ $[M+Na]^+$ 481.2566, found 481.2566; IR ($CHCl_3$) ν_{max} 1768, 1619 cm^{-1}.



23: $C_{27}H_{38}O_6$ (458.59)

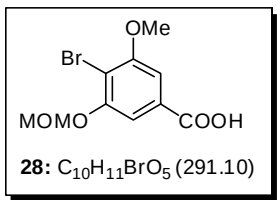
4,6-Dihydroxy-5-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)isobenzofuran-1(3H)-one (24). To a stirred solution of compound **23** (1.00 g, 2.18 mmol) in MeOH (30 mL) was added a catalytic amount of camphorsulfonic acid (50 mg) and the reaction mixture was stirred at 25 °C under argon atmosphere for 24 h. The reaction was quenched by addition of saturated aq. $NaHCO_3$ and concentrated in vacuo. To the obtained residue was added ethyl acetate (30 mL) and the organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (4:1) as an eluent afforded pure product **24** as a thick oil (500 mg, 62%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.58 (s, 3H), 1.59 (s, 3H), 1.67 (s, 3H), 1.84 (s, 3H), 1.90–2.20 (m, 8H), 3.55 (d, *J* = 8 Hz, 2H), 5.06 (t, *J* = 8 Hz, 1H), 5.07 (t, *J* = 8 Hz, 1H), 5.24 (s, 2H), 5.30 (t, *J* = 8 Hz, 1H), 6.48 (br s, 1H), 7.07 (s, 1H), 7.33 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.1, 16.3, 17.6, 23.1, 25.6, 26.1, 26.6, 39.6 (2 carbons), 68.8, 103.3, 120.3,



24: $C_{23}H_{30}O_4$ (370.48)

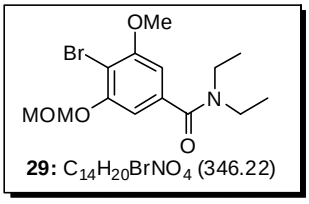
120.8, 123.3, 124.2, 124.4, 126.1, 131.4, 135.9, 140.7, 150.4, 156.4, 173.0; ESIMS (*m*/*z*) 393 $[M+Na]^+$; HRMS (ESI) calcd for $C_{23}H_{30}O_4$ $[M+Na]^+$ 393.2042, found 393.2041; IR ($CHCl_3$) ν_{max} 3380, 1735, 1618 cm^{-1}.

4-Bromo-3-methoxy-5-(methoxymethoxy)benzoic Acid (28). The ester **27** (5.00 g, 16.44 mmol) was added to the mixture of 10% aqueous solution of KOH (40 mL) and MeOH (40 mL) and the reaction mixture was stirred at 25 °C for 8 h. The reaction mixture was concentrated in vacuo. The residue was diluted with ethyl acetate (50 mL), acidified with 2 N HCl and extracted with ethyl acetate (20 mL X 3). The combined organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (2:3) as an eluent afforded pure product **28** as a white solid (4.72 g, 99%). Mp 160–162 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 3.41 (s, 3H), 3.90 (s, 3H), 5.33 (s, 2H), 7.24 (s, 1H), 7.37 (s, 1H), 13.26 (br s, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 56.1, 56.5, 94.8, 106.0, 106.6, 108.8, 131.3, 154.3, 156.6, 166.7; HRMS (ESI) calcd for $C_{10}H_{11}BrO_5$ $[M+Na]^+$ 312.9688, found 312.9695; IR (nujol) ν_{max} 2700–2500, 1687, 1588 cm^{-1}.



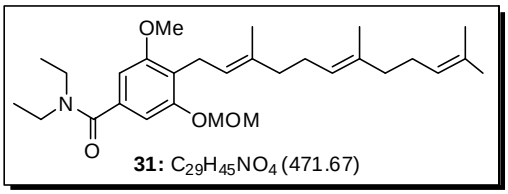
28: $C_{10}H_{11}BrO_5$ (291.10)

4-Bromo-*N*,*N*-diethyl-3-methoxy-5-(methoxymethoxy)benzamide (29). A solution of EDCI (3.26 g, 17.06 mmol) and HOBt (2.61 g, 17.06 mmol) in DMF (15 mL) was added dropwise to a stirred suspension of acid **28** (4.50 g, 15.51 mmol) and *N*,*N*′-diethylamine hydrochloride (1.87 g, 17.06 mmol) in DMF (30 mL) at 0 °C under argon atmosphere. DIPEA (5.84 mL, 34.13 mmol) was added dropwise to the above reaction mixture and it was stirred at 25 °C for 12 h. To the reaction mixture was added ethyl acetate (80 mL) and the organic layer was washed with brine (20 mL X 4) and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by the silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (3:2) as an eluent afforded pure product **29** as a thick oil (5.08 g, 95%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.05–1.35 (m, 6H), 3.15–3.35 (m, 2H), 3.40–3.60 (m, 2H) 3.49 (s, 3H), 3.91 (s, 3H), 5.25 (s, 2H), 6.62 (d, *J* = 2 Hz, 1H), 6.82 (d, *J* = 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.8, 14.1, 39.4, 43.3, 56.3, 56.5, 95.1, 103.0, 103.7, 106.3, 137.3, 154.8, 157.1, 170.1; ESIMS (*m*/*z*) 368 $[M+Na]^+$; HRMS (ESI) calcd for $C_{14}H_{20}BrNO_4$ $[M+Na]^+$ 368.0473, found 368.0471; IR (neat) ν_{max} 1634, 1581 cm^{-1}.



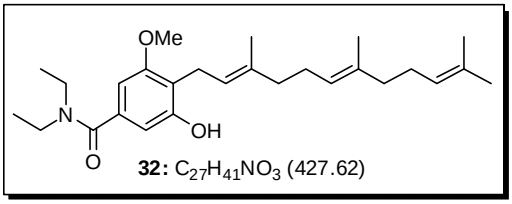
29: $C_{14}H_{20}BrNO_4$ (346.22)

***N*,*N*-Diethyl-3-methoxy-5-(methoxymethoxy)-4-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)benzamide (31).** $Pd(PPh_3)_2Cl_2$ (200 mg, 10 mol%) was added to a stirred solution of aryl bromide **29** (1.00 g, 2.89 mmol) and farnesyl tributyltin (**30**, 2.86 g, 5.79 mmol) in DMF (14.5 mL) at 25 °C under argon atmosphere. CsF (880 mg, 5.79 mmol) was added to the reaction mixture and it was heated at 90 °C for 36 h. To the reaction mixture was added ethyl acetate (60 mL) and insoluble residue was removed by filtration. The organic layer was washed with brine (20 mL X 4) and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by the silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (7:3) as an eluent afforded pure product **31** as a thick oil (955 mg, 70%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.05–1.35 (m, 6H), 1.56 (s, 3H), 1.58 (s, 3H), 1.66 (s, 3H), 1.76 (s, 3H), 1.85–2.12 (m, 8H), 3.15–3.60 (m, 4H), 3.36 (d, *J* = 6 Hz, 2H), 3.44 (s, 3H), 3.81 (s, 3H), 5.00–5.22 (m, 3H), 5.16 (s, 2H), 6.58 (s, 1H), 6.73 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.8, 14.1, 15.9, 16.0, 17.6, 22.3, 25.6, 26.6, 26.7, 39.2, 39.6, 39.7, 43.3, 55.7, 55.8, 94.5, 102.9, 105.2, 120.3, 122.2, 124.2, 124.3, 131.1, 134.75, 134.83, 135.6, 155.3, 158.1, 171.2; ESIMS (*m*/*z*) 494 $[M+Na]^+$; HRMS (ESI) calcd for $C_{29}H_{45}NO_4$ $[M+H]^+$ 472.3427, found 472.3424; IR (neat) ν_{max} 1636, 1581 cm^{-1}.



31: $C_{29}H_{45}NO_4$ (471.67)

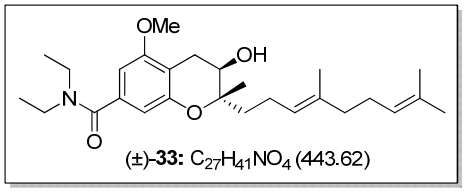
***N*,*N*-Diethyl-3-hydroxy-5-methoxy-4-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)benzamide (32).** To a stirred solution of compound **31** (2.00 g, 4.24 mmol) in MeOH (50 mL) was added camphorsulfonic acid (100 mg) and the reaction mixture was stirred at 25 °C under argon atmosphere for 12 h. The reaction was quenched by addition of saturated aq. $NaHCO_3$ solution and concentrated in vacuo. To the obtained residue was added ethyl acetate (50 mL) and the organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (2:1) as an eluent afforded pure product **32** as a thick oil (1.59 g, 88%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.00–1.35 (m, 6H), 1.57 (s, 3H), 1.58 (s, 3H), 1.66 (s, 3H), 1.76 (s, 3H), 1.35–2.15 (m, 8H), 3.20–3.40 (m, 2H), 3.40–3.60 (m, 2H), 3.33 (d, *J* = 8 Hz, 2H), 3.77 (s, 3H), 5.00 (t, *J* = 6 Hz, 1H), 5.08 (t, *J* = 6 Hz, 1H), 5.19 (t, *J* = 6 Hz, 1H), 6.37 (d, *J* = 2 Hz, 1H), 6.55 (d, *J* = 2 Hz, 1H), 7.35 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.8, 14.2, 15.9, 16.1, 17.6, 22.2, 25.6, 26.6, 26.7, 39.3, 39.7, 39.8, 43.3, 55.7, 100.5, 107.5, 117.4, 122.0, 124.1, 124.4,



32: $C_{27}H_{41}NO_3$ (427.62)

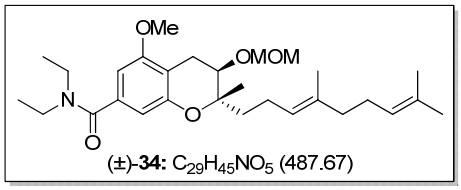
131.2, 134.9, 135.0, 136.3, 155.6, 158.0, 171.9; ESIMS (*m/z*) 450 $[M+Na]^+$; HRMS (ESI) calcd for $C_{27}H_{41}NO_3$ $[M+H]^+$ 428.3165, found 428.3154; IR ($CHCl_3$) ν_{max} 3272, 1615, 1586 cm^{-1}.

(±)-2-((*E*)-4,8-Dimethylnona-3,7-dien-1-yl)-*N*,*N*-diethyl-3-hydroxy-5-methoxy-2-methylchroman-7-carboxamide (33). The $VO(acac)_2$ (14 mg, 1.50 mol%) was added to a stirred solution of phenol **32** (1.50 g, 3.51 mmol) in DCM (20 mL) at 25 °C under argon atmosphere. After 15 min, a solution of TBHP in decane (~5.50 M, 0.83 mL, 4.56 mmol) was added to the above reaction mixture followed by the dropwise addition of TFA (0.05 mL, 20 mol%) and the reaction mixture was further stirred at 25 °C for 1 h. The reaction mixture was concentrated in vacuo and the silica gel column chromatographic purification of the obtained residue using petroleum ether–ethyl acetate (13:7) as an eluent afforded pure product chromanol **33** as a thick oil (1.13 g, 73%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.00–1.30 (m, 6H), 1.27 (s, 3H), 1.50–1.65 (m, 2H), 1.58 (s, 6H), 1.66 (s, 3H), 1.90–2.15 (m, 6H), 2.20–2.45 (br s, 1H), 2.61 (dd, *J* = 16 and 4 Hz, 1H), 2.81 (dd, *J* = 16 and 4 Hz, 1H), 3.20–3.40 (m, 2H), 3.40–3.60 (m, 2H), 3.73 (t, *J* = 8 Hz, 1H), 3.81 (s, 3H), 5.02–5.12 (m, 2H), 6.41 (s, 1H), 6.45 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.8, 14.3, 15.9, 17.6, 19.0, 21.5, 25.6, 26.2, 26.6, 36.9, 39.1, 39.6, 43.2, 55.5, 67.5, 78.7, 100.2, 107.8, 109.2, 123.8, 124.2, 131.4, 135.5, 136.5, 153.3, 158.2, 171.1; ESIMS (*m/z*) 466 $[M+Na]^+$, 482 $[M+K]^+$; HRMS (ESI) calcd for $C_{27}H_{41}NO_4$ $[M+H]^+$ 444.3114, found 444.3109; IR ($CHCl_3$) ν_{max} 3393, 1612, 1579 cm^{-1}.



(±)-**33:** $C_{27}H_{41}NO_4$ (443.62)

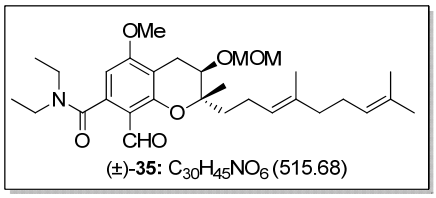
(±)-2-((*E*)-4,8-Dimethylnona-3,7-dien-1-yl)-*N*,*N*-diethyl-5-methoxy-3-(methoxymethoxy)-2-methylchroman-7-carboxamide (34). MOMCl (0.25 mL, 3.38 mmol) was added to a stirred solution of chromanol **33** (1.00 g, 2.25 mmol) in DCM (15 mL) at 0 °C under argon atmosphere. The reaction mixture was stirred for 30 min followed by the dropwise addition of DIPEA (0.77 mL, 4.51 mmol). The reaction mixture was further stirred at 25 °C for 8 h and then quenched with water (5 mL). The organic layer was separated and the aqueous layer was extracted with DCM (10 mL X 3). The combined organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (7:3) as an eluent afforded pure product **34** as a thick oil (1.03 g, 94%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.10–1.30 (m, 6H), 1.28 (s, 3H), 1.58 (s, 6H), 1.60–1.70 (m, 2H), 1.66 (s, 3H), 1.92–2.00 (m, 2H), 2.00–2.08 (m, 2H), 2.13 (q, *J* = 8 Hz, 2H), 2.65 (dd, *J* = 16 and 8 Hz, 1H), 2.93 (dd, *J* = 16 and 8 Hz, 1H), 3.20–3.40 (m, 2H), 3.40–3.60 (m, 2H), 3.40 (s, 3H), 3.81 (s, 3H), 3.81 (t, *J* = 8 Hz, 1H), 4.66 (d, *J* = 8 Hz,



(±)-**34:** $C_{29}H_{45}NO_5$ (487.67)

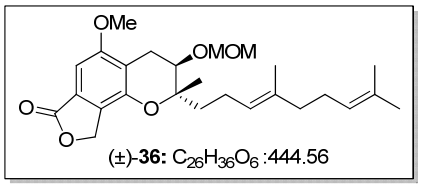
1H), 4.82 (d, *J* = 8 Hz, 1H), 5.07 (t, *J* = 8 Hz, 1H), 5.09 (t, *J* = 8 Hz, 1H), 6.41 (s, 1H), 6.46 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.8, 14.3, 15.9, 17.6, 19.0, 21.4, 23.2, 25.6, 26.6, 37.4, 39.0, 39.6, 43.2, 55.5, 55.8, 72.5, 77.9, 95.3, 100.0, 107.8, 109.4, 123.9, 124.2, 131.2, 135.3, 136.3, 153.3, 157.9, 171.1; ESIMS (*m*/*z*) 510 $[M+Na]^+$; HRMS (ESI) calcd for $C_{29}H_{45}NO_5$ $[M+H]^+$ 488.3376, found 488.3380; IR ($CHCl_3$) ν_{max} 1637, 1581 cm^{-1}.

(±)-2-((*E*)-4,8-Dimethylnona-3,7-dien-1-yl)-*N*,*N*-diethyl-8-formyl-5-methoxy-3-(methoxymethoxy)-2-methylchroman-7-carboxamide (35). A solution of *t*-BuLi in pentane (1.60 M, 0.89 mL, 1.43 mmol) was added to a stirred solution of compound **34** (500 mg, 1.02 mmol) in THF (10 mL) at –78 °C and stirred further for 15 min which was followed by the addition of DMF (0.39 mL, 5.13 mmol). The reaction mixture was allowed to attain 25 °C and stirred further for 4 h. The reaction mixture was quenched with saturated aq. NH_4Cl solution (5 mL) and then concentrated in vacuo. To the obtained residue was added ethyl acetate (20 mL) and the organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (3:2) as an eluent afforded pure product **35** as a thick oil (475 mg, 90%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.01 (t, *J* = 8 Hz, 3H), 1.25–1.42 (m, 6H), 1.59 (s, 6H), 1.67 (s, 3H), 1.65–1.80 (m, 2H), 1.90–2.25 (m, 6H), 2.55–2.75 (m, 1H), 2.85–3.05 (m, 1H), 3.08 (q, *J* = 6 Hz, 2H), 3.43 (s, 3H), 3.45–3.75 (m, 2H), 3.86 (t, *J* = 6 Hz, 1H), 3.88 (s, 3H), 4.69 (d, *J* = 8 Hz, 1H), 4.84 (d, *J* = 8 Hz, 1H), 5.00–5.20 (m, 2H), 6.31 (s, 1H), 10.35 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.1, 13.6, 16.0, 17.6, 21.5, 23.1, 25.6, 26.6, 37.6, 38.5, 39.6, 42.3, 55.87, 55.94, 72.1, 79.4, 95.5, 101.3, 115.0, 123.4, 124.2, 131.4, 135.8, 138.9, 157.0, 162.3, 170.1, 187.9; ESIMS (*m*/*z*) 538 $[M+Na]^+$; HRMS (ESI) calcd for $C_{30}H_{45}NO_6$ $[M+Na]^+$ 538.3145, found 538.3135; IR (neat) ν_{max} 1682, 1639, 1599 cm^{-1}.



(±)-**35:** $C_{30}H_{45}NO_6$ (515.68)

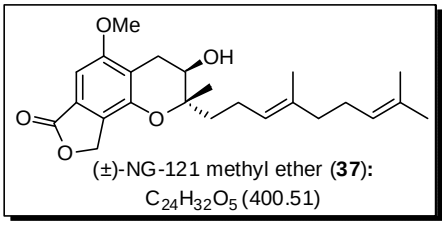
(±)-2-((*E*)-4,8-Dimethylnona-3,7-dien-1-yl)-5-methoxy-3-(methoxymethoxy)-2-methyl-3,4-dihydro-2*H*-furo[3,4-h]chromen-7(9*H*)-one (36). To a stirred solution of aldehyde **35** (400 mg, 0.77 mmol) in AcOH:MeOH (1:1, 10 mL) was added $NaBH_3CN$ (73 mg, 1.16 mmol) and the reaction mixture was heated at 100 °C for 2 h. The reaction was allowed to attain 25 °C and concentrated in vacuo. To the obtained residue was added ethyl acetate (25 mL) and the organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (2:1) as an eluent afforded pure product **36** as a thick oil



(±)-**36:** $C_{26}H_{36}O_6$:444.56

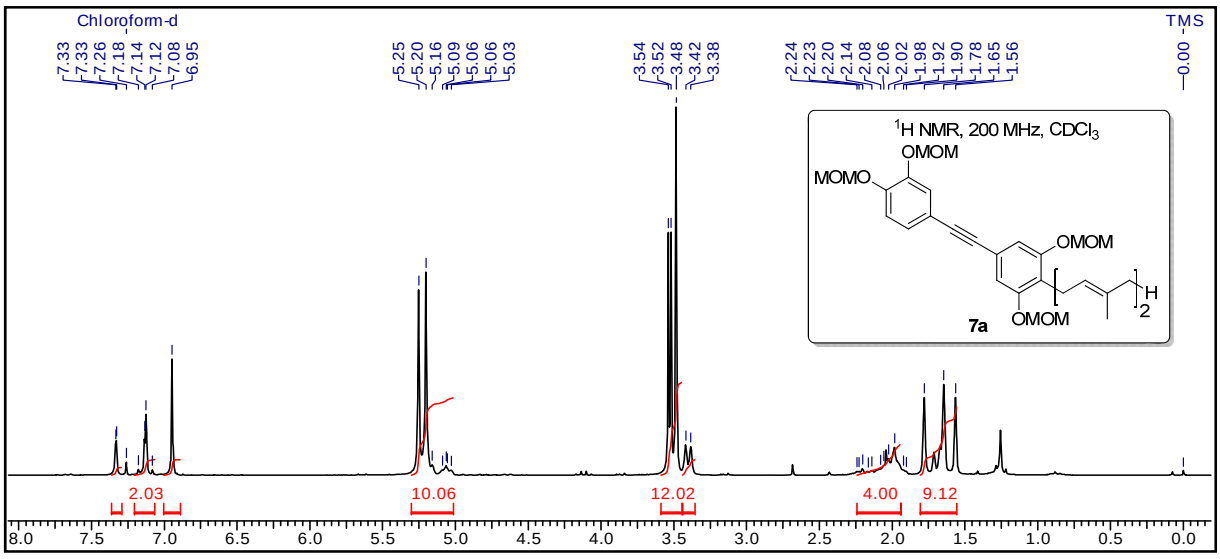
(300 mg, 87%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.35 (s, 3H), 1.58 (s, 6H), 1.55–1.75 (m, 2H), 1.66 (s, 3H), 1.90–2.22 (m, 6H), 2.78 (dd, *J* = 18 and 6 Hz, 1H), 2.99 (dd, *J* = 18 and 4 Hz, 1H), 3.42 (s, 3H), 3.88 (t, *J* = 8 Hz, 1H), 3.88 (s, 3H), 4.68 (d, *J* = 8 Hz, 1H), 4.84 (d, *J* = 8 Hz, 1H), 5.00–5.16 (m, 2H), 5.16 (d, *J* = 14 Hz, 1H), 5.25 (d, *J* = 14 Hz, 1H), 6.90 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.9, 17.6, 19.4, 21.5, 23.8, 25.6, 26.6, 37.3, 39.6, 55.93, 55.96, 68.0, 72.1, 78.9, 95.5, 97.1, 114.8, 123.4, 124.1, 125.3, 127.8, 131.4, 135.7, 148.0, 159.4, 171.7; ESIMS (*m*/*z*) 483 $[M+K]^+$, 499 $[M+Na+MeOH]^+$; HRMS (ESI) calcd for $C_{26}H_{36}O_6$ $[M+H]^+$ 445.2590, found 445.2585; IR ($CHCl_3$) ν_{max} 1770, 1619 cm^{-1}.

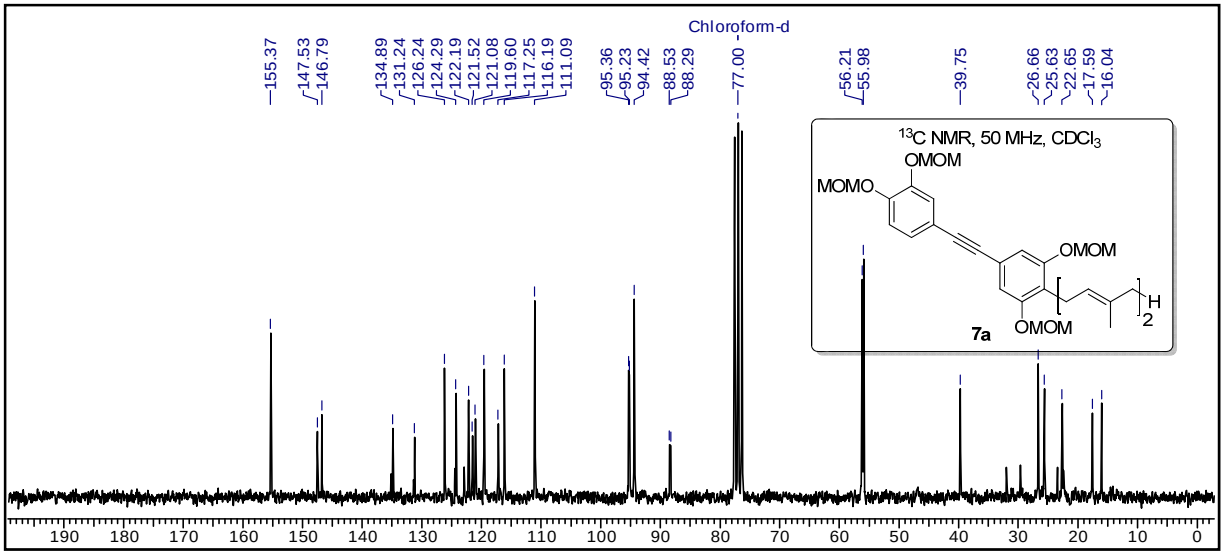
(±)-2-((*E*)-4,8-Dimethylnona-3,7-dien-1-yl)-3-hydroxy-5-methoxy-2-methyl-3,4-dihydro-2*H*-furo[3,4-h]chromen-7(9*H*)-one (NG-121 Methyl Ether, 37). The MOM-deprotection of compound **36** (250 mg, 0.56 mmol) using the experimental procedure described above for the preparation of compound **32** afforded pure product **37** as a thick oil (207 mg, 92%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.36 (s, 3H), 1.57 (s, 6H), 1.59–1.65 (m, 2H), 1.66 (s, 3H), 1.89 (br s, 1H), 1.92–2.18 (m, 4H), 2.13 (q, *J* = 8 Hz, 2H), 2.77 (dd, *J* = 18 and 4 Hz, 1H), 2.98 (dd, *J* = 18 and 4 Hz, 1H), 3.88 (s, 3H), 3.95 (s, 1H), 5.06 (t, *J* = 8 Hz, 1H), 5.08 (t, *J* = 8 Hz, 1H), 5.17 (d, *J* = 16 Hz, 1H), 5.22 (d, *J* = 16 Hz, 1H), 6.90 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.9, 17.6, 19.1, 21.5, 25.7, 26.6, 26.9, 36.9, 39.6, 55.9, 67.3, 68.0, 79.5, 97.2, 114.7, 123.4, 124.1, 125.4, 127.8, 131.5, 136.0, 147.9, 159.5, 171.7; ESIMS (*m*/*z*) 423 $[M+Na]^+$; HRMS (ESI) calcd for $C_{24}H_{32}O_5$ $[M+Na]^+$ 423.2147, found 423.2141; IR (neat) ν_{max} 3460, 1770, 1621 cm^{-1}.

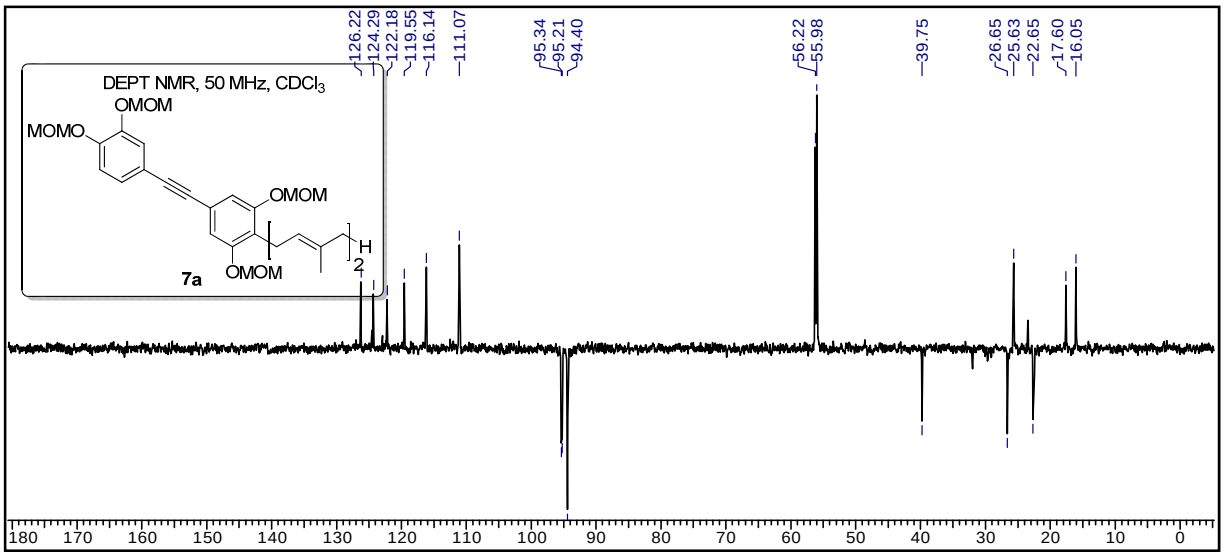


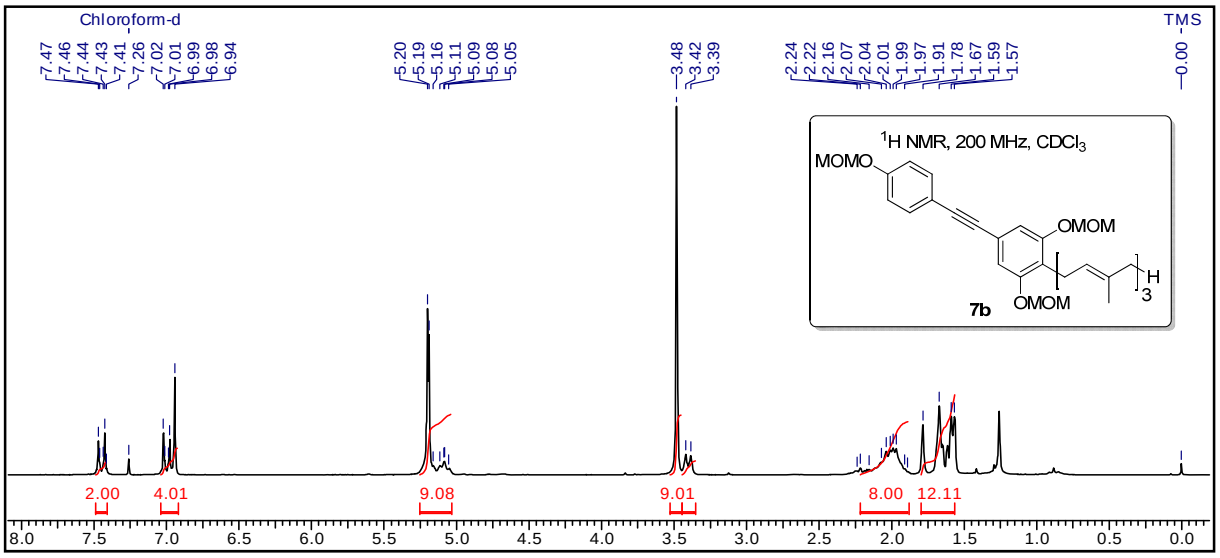
(±)-NG-121 methyl ether (**37**):
$C_{24}H_{32}O_5$ (400.51)

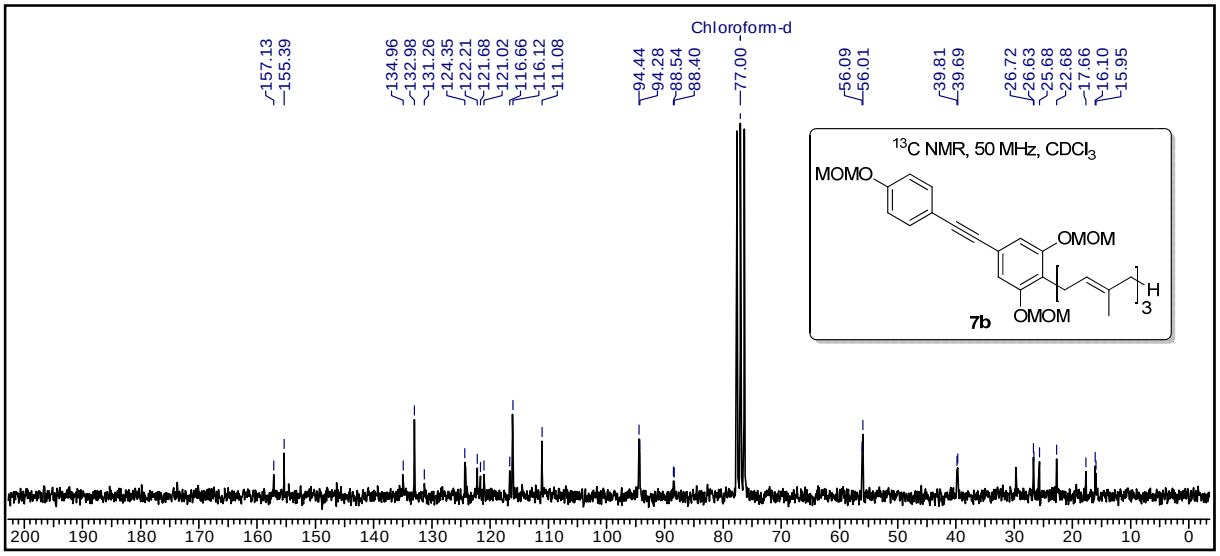
3B.5 Selected Spectra

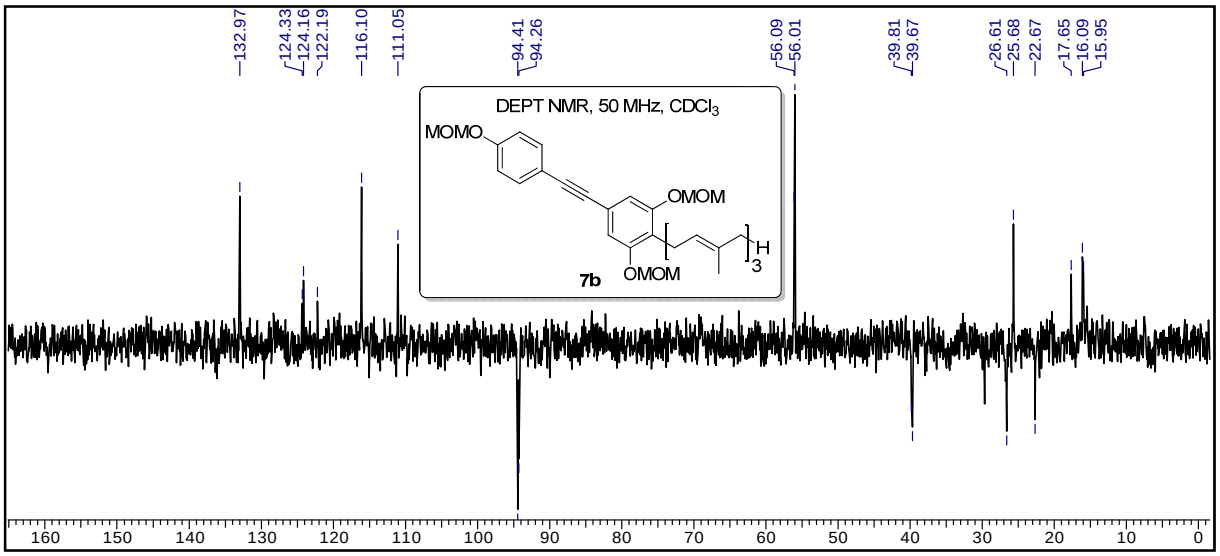

Chloroform-d
TMS
^{1}H NMR, 200 MHz, CDCl$_3$
OMOM
MOMO
OMOM
OMOM
H
2
7a
2.03
10.06
12.02
4.00
9.12

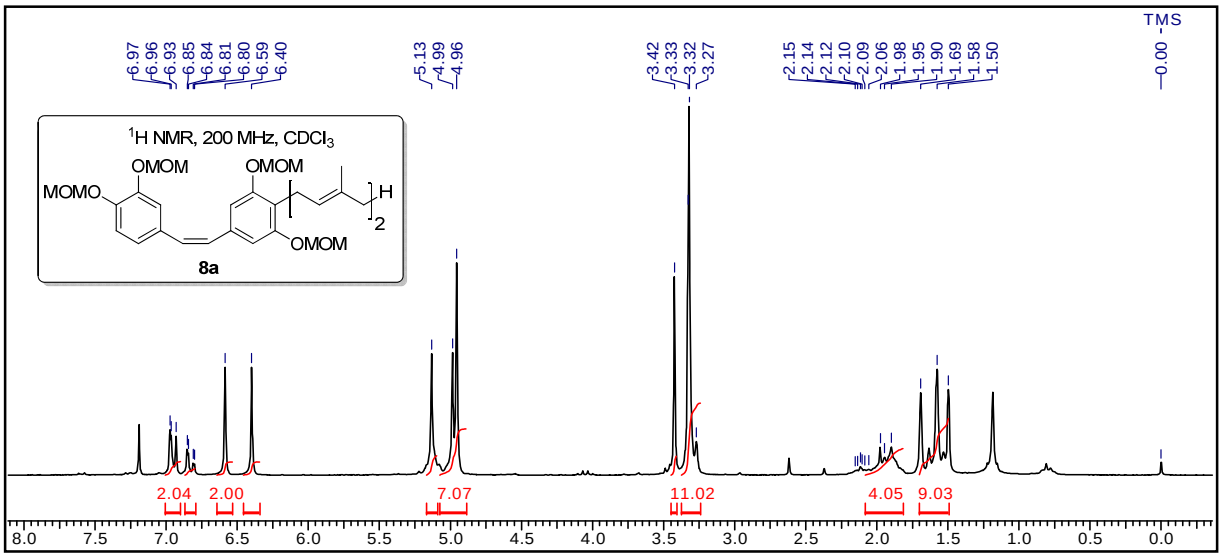

Chloroform-d
^{13}C NMR, 50 MHz, CDCl$_3$
OMOM
MOMO
OMOM
OMOM
H
2
7a

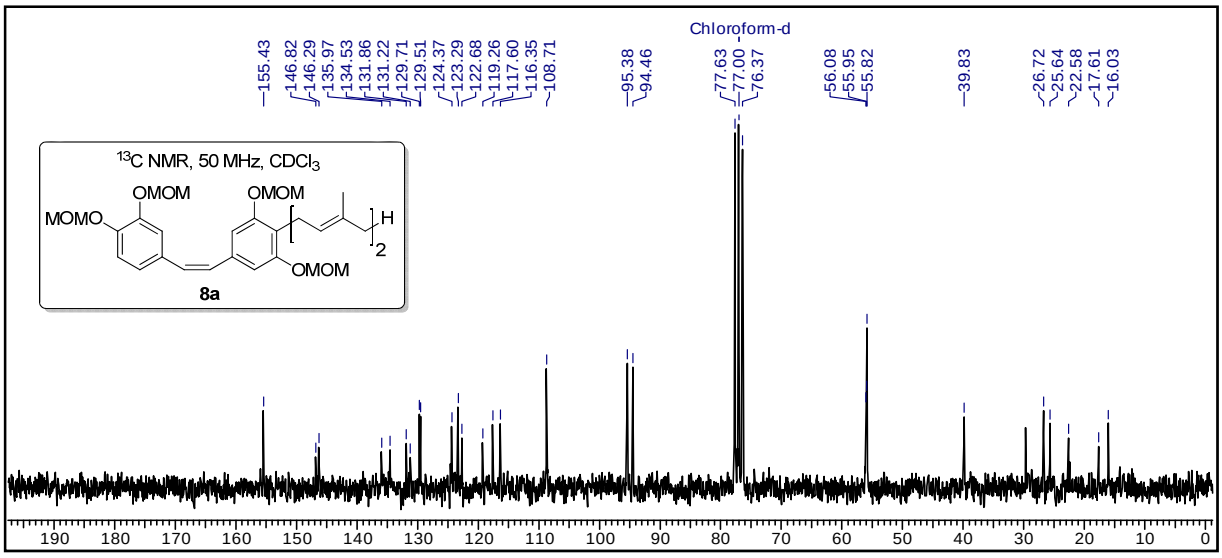

DEPT NMR, 50 MHz, CDCl$_3$
OMOM
MOMO
OMOM
OMOM
H
2
7a

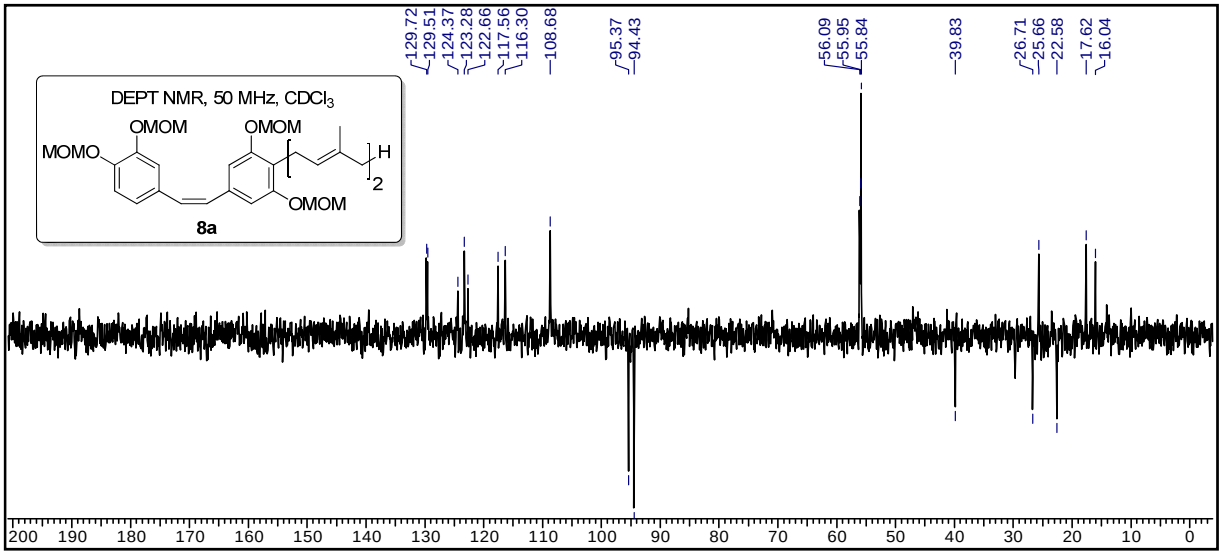

Chloroform-d
TMS
7.47
7.46
7.44
7.43
7.41
7.26
7.02
7.01
6.99
6.98
6.94
5.20
5.19
5.16
5.11
5.09
5.08
5.05
3.48
3.42
3.39
2.24
2.22
2.16
2.07
2.04
2.01
1.99
1.97
1.91
1.78
1.67
1.59
1.57
0.00
^{1}H NMR, 200 MHz, CDCl$_3$
MOMO
OMOM
OMOM
H
3
7b
2.00
4.01
9.08
9.01
8.00
12.11

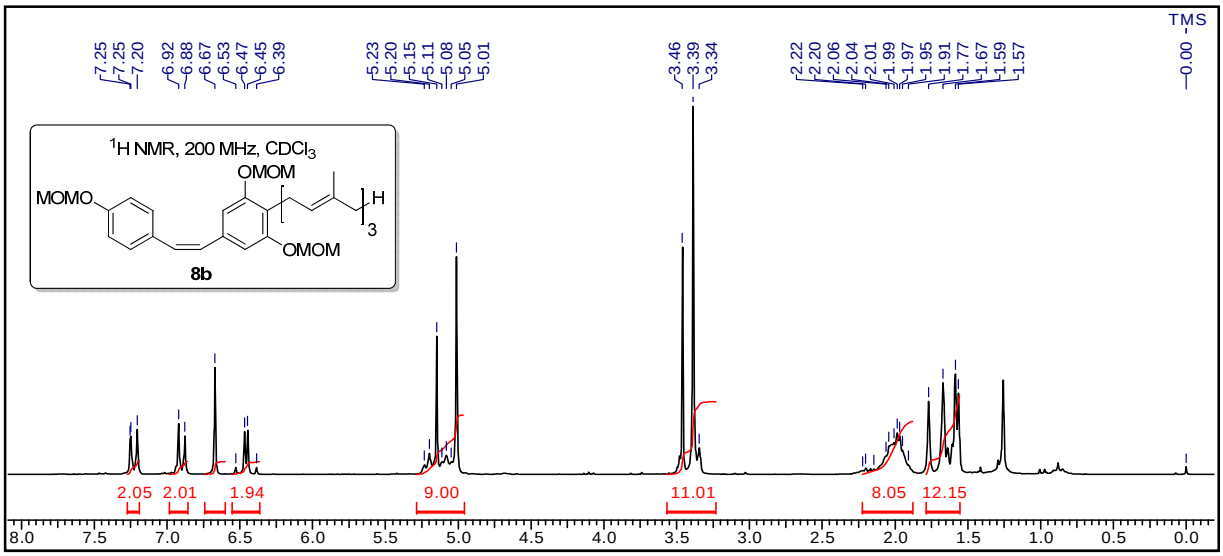

Chloroform-d
157.13
155.39
134.96
132.98
131.26
124.35
122.21
121.68
121.02
116.66
116.12
111.08
94.44
94.28
88.54
88.40
77.00
56.09
56.01
39.81
39.69
26.72
26.63
25.68
22.68
17.66
16.10
15.95
^{13}C NMR, 50 MHz, CDCl$_3$
MOMO
OMOM
OMOM
H
3
7b

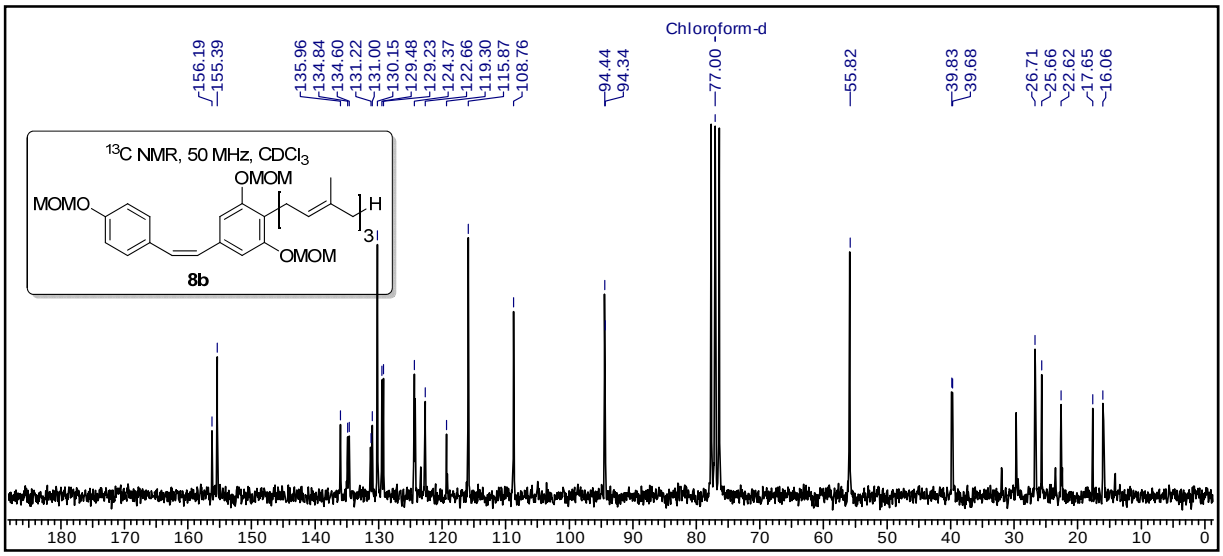

132.97
124.33
124.16
122.19
116.10
111.05
94.41
94.26
56.09
56.01
39.81
39.67
26.61
25.68
22.67
17.65
16.09
15.95
DEPT NMR, 50 MHz, CDCl$_3$
MOMO
OMOM
OMOM
H
3
7b

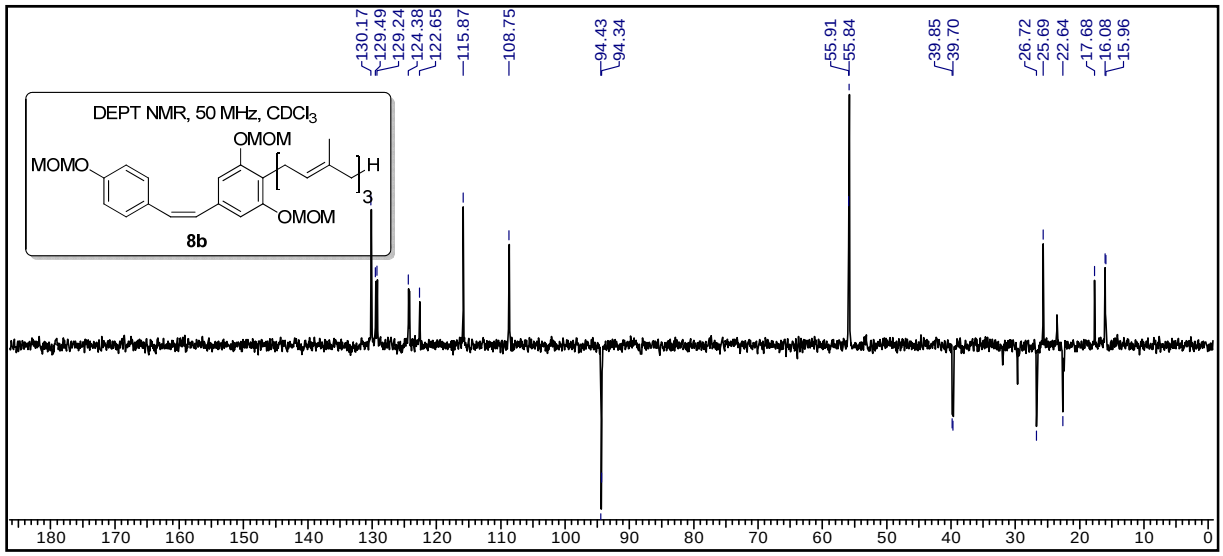

TMS
6.97
6.96
6.93
6.85
6.84
6.81
6.80
6.59
6.40
5.13
4.99
4.96
3.42
3.33
3.32
3.27
2.15
2.14
2.12
2.10
2.09
2.06
1.98
1.95
1.90
1.69
1.58
1.50
0.00
^{1}H NMR, 200 MHz, $CDCl_3$
OMOM
OMOM
MOMO
H
2
OMOM
8a
2.04
2.00
7.07
11.02
4.05
9.03
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

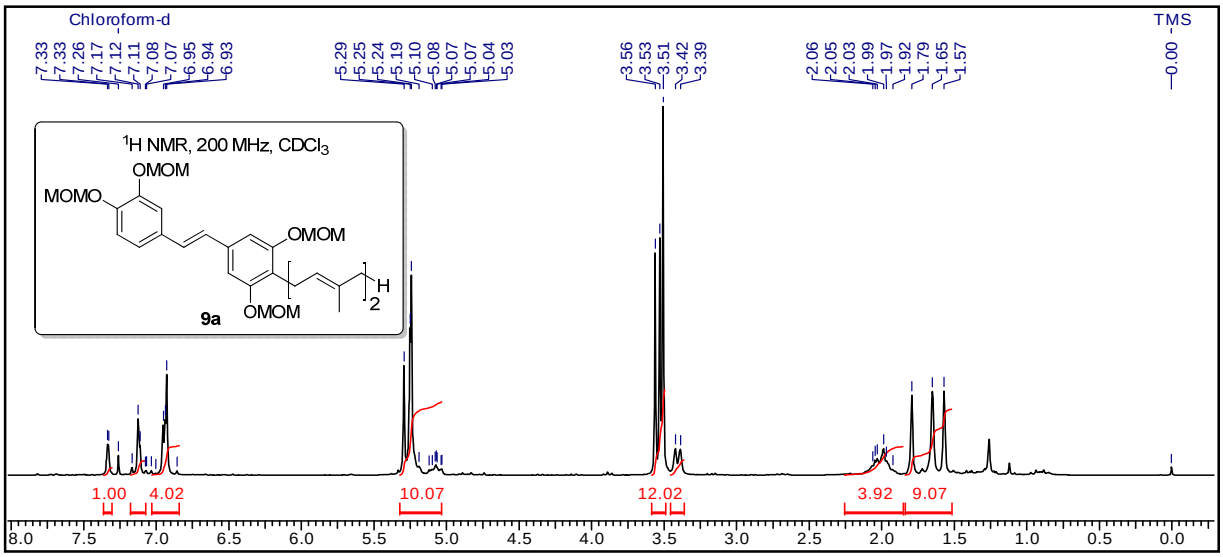

Chloroform-d
155.43
146.82
146.29
135.97
134.53
131.86
131.22
129.71
129.51
124.37
123.29
122.68
119.26
117.60
116.35
108.71
95.38
94.46
77.63
77.00
76.37
56.08
55.95
55.82
39.83
26.72
25.64
22.58
17.61
16.03
^{13}C NMR, 50 MHz, $CDCl_3$
OMOM
OMOM
MOMO
H
2
OMOM
8a
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

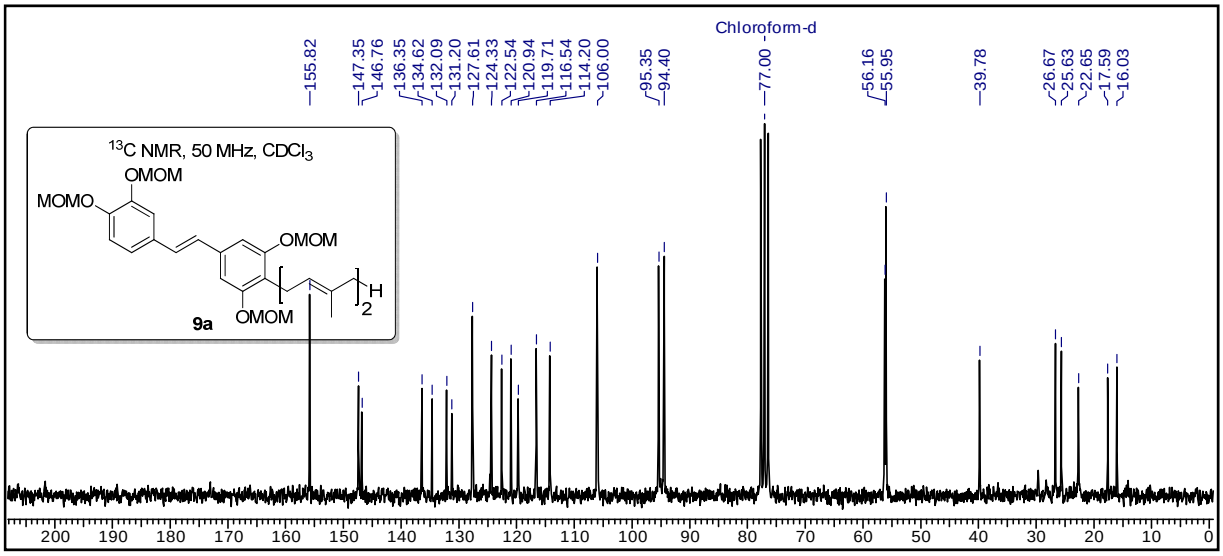

129.72
129.51
124.37
123.28
122.66
117.56
116.30
108.68
95.37
94.43
56.09
55.95
55.84
39.83
26.71
25.66
22.58
17.62
16.04
DEPT NMR, 50 MHz, $CDCl_3$
OMOM
OMOM
MOMO
H
2
OMOM
8a
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

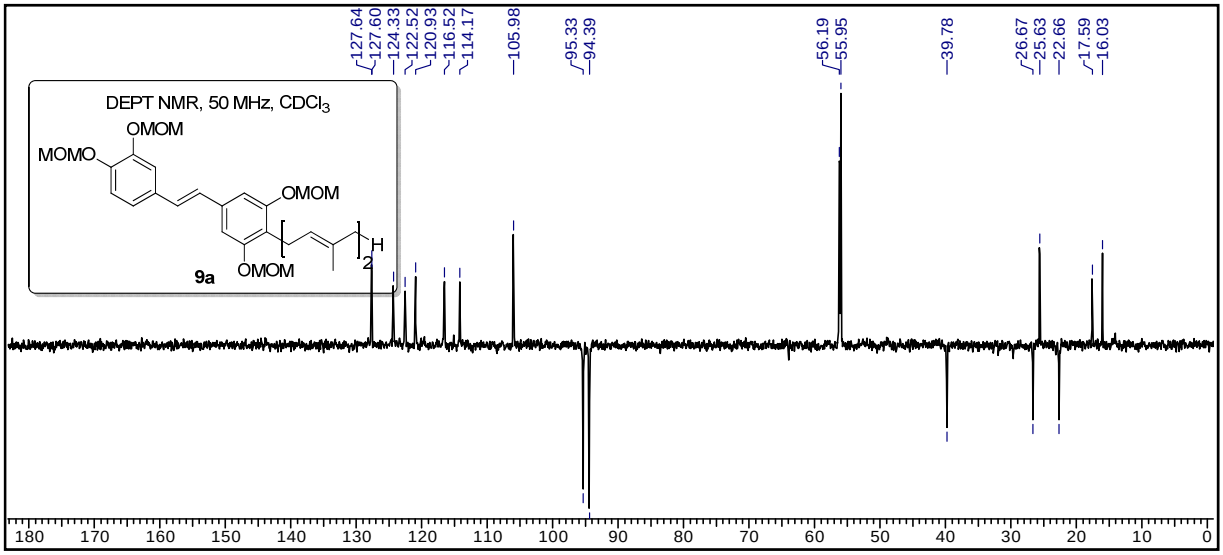

TMS
7.25
7.25
7.20
6.92
6.88
6.67
6.53
6.47
6.45
6.39
5.23
5.20
5.15
5.11
5.08
5.05
5.01
3.46
3.39
3.34
2.22
2.20
2.06
2.04
2.01
1.99
1.97
1.95
1.91
1.77
1.67
1.59
1.57
0.00
^{1}H NMR, 200 MHz, CDCl$_3$
MOMO
OMOM
OMOM
H
3
8b
2.05
2.01
1.94
9.00
11.01
8.05
12.15
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

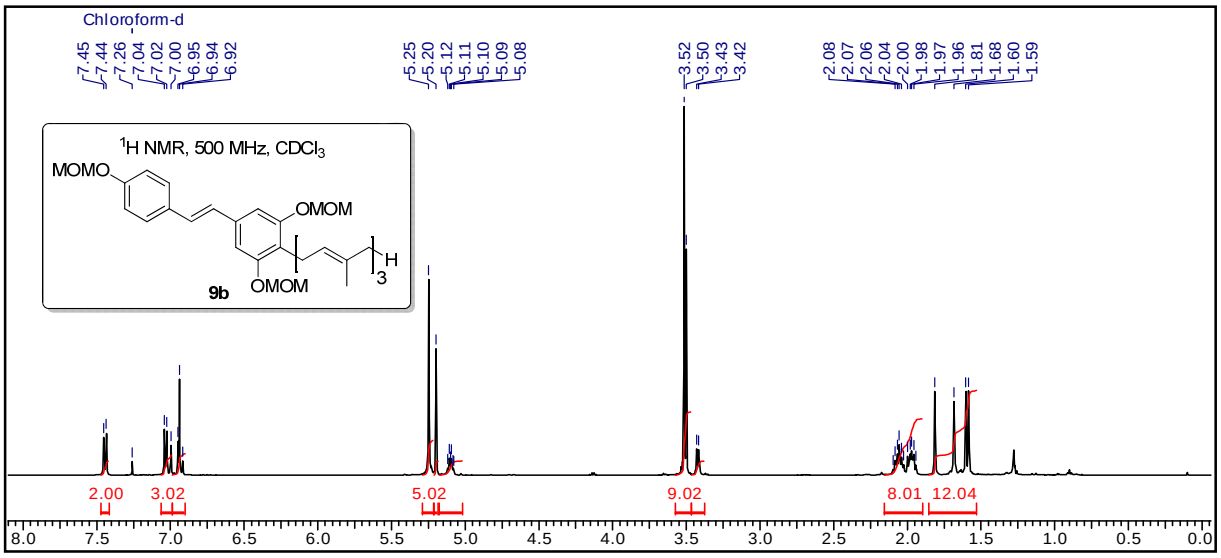

Chloroform-d
156.19
155.39
135.96
134.84
134.60
131.22
131.00
130.15
129.48
129.23
124.37
122.66
119.30
115.87
108.76
94.44
94.34
77.00
55.82
39.83
39.68
26.71
25.66
22.62
17.65
16.06
^{13}C NMR, 50 MHz, CDCl$_3$
MOMO
OMOM
OMOM
H
3
8b
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

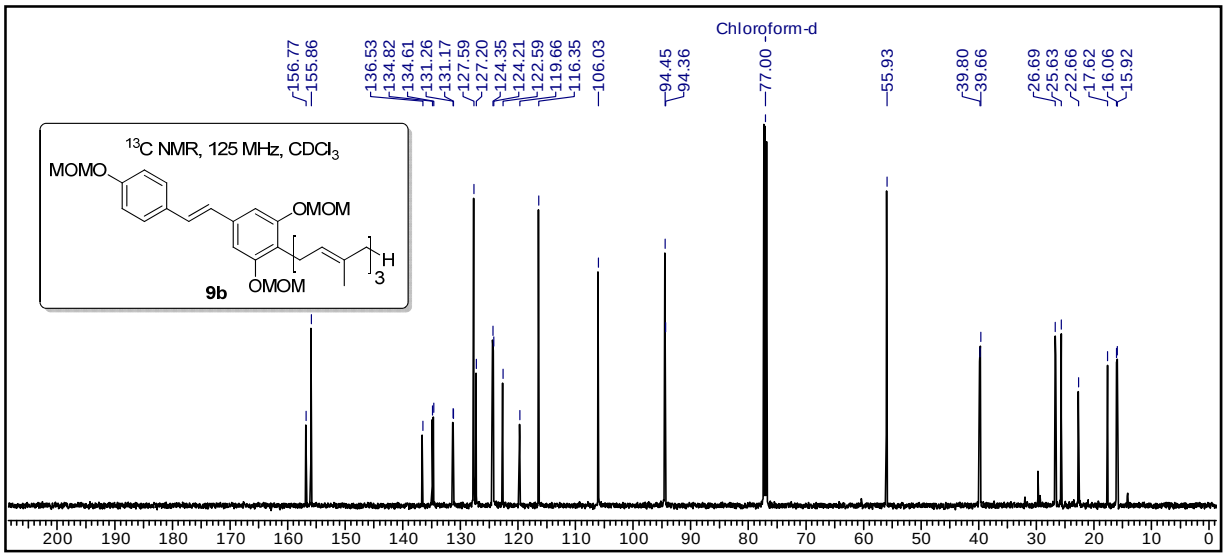

130.17
129.49
129.24
124.38
122.65
115.87
108.75
94.43
94.34
55.91
55.84
39.85
39.70
26.72
25.69
22.64
17.68
16.08
15.96
DEPT NMR, 50 MHz, CDCl$_3$
MOMO
OMOM
OMOM
H
3
8b
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

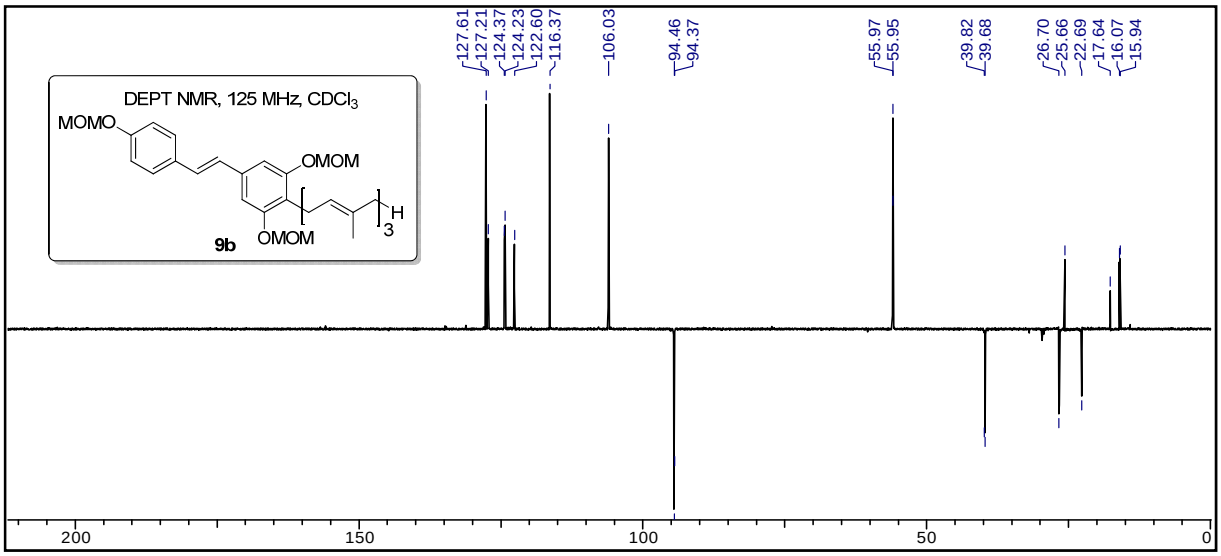

Chloroform-d
TMS
7.33
7.33
7.26
7.17
7.12
7.11
7.08
7.07
6.95
6.94
6.93
5.29
5.25
5.24
5.19
5.10
5.08
5.07
5.07
5.04
5.03
3.56
3.53
3.51
3.42
3.39
2.06
2.05
2.03
1.99
1.97
1.92
1.79
1.65
1.57
0.00
1H NMR, 200 MHz, CDCl3
OMOM
MOMO
OMOM
OMOM
H
2
9a
1.00
4.02
10.07
12.02
3.92
9.07
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

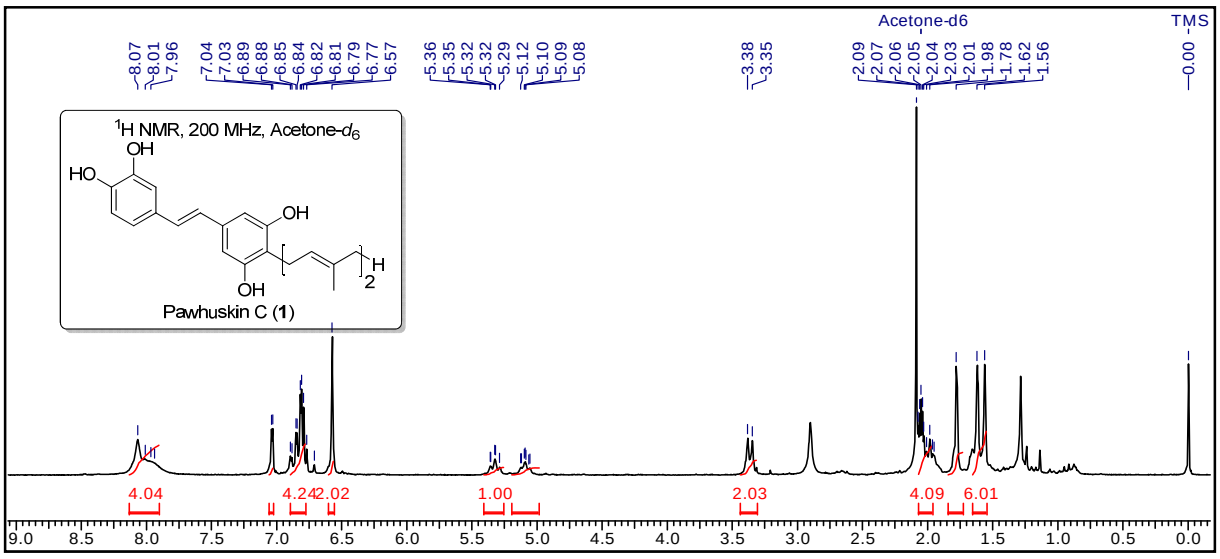

Chloroform-d
155.82
147.35
146.76
136.35
134.62
132.09
131.20
127.61
124.33
122.54
120.94
119.71
116.54
114.20
106.00
95.35
94.40
77.00
56.16
55.95
39.78
26.67
25.63
22.65
17.59
16.03
13C NMR, 50 MHz, CDCl3
OMOM
MOMO
OMOM
OMOM
H
2
9a
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

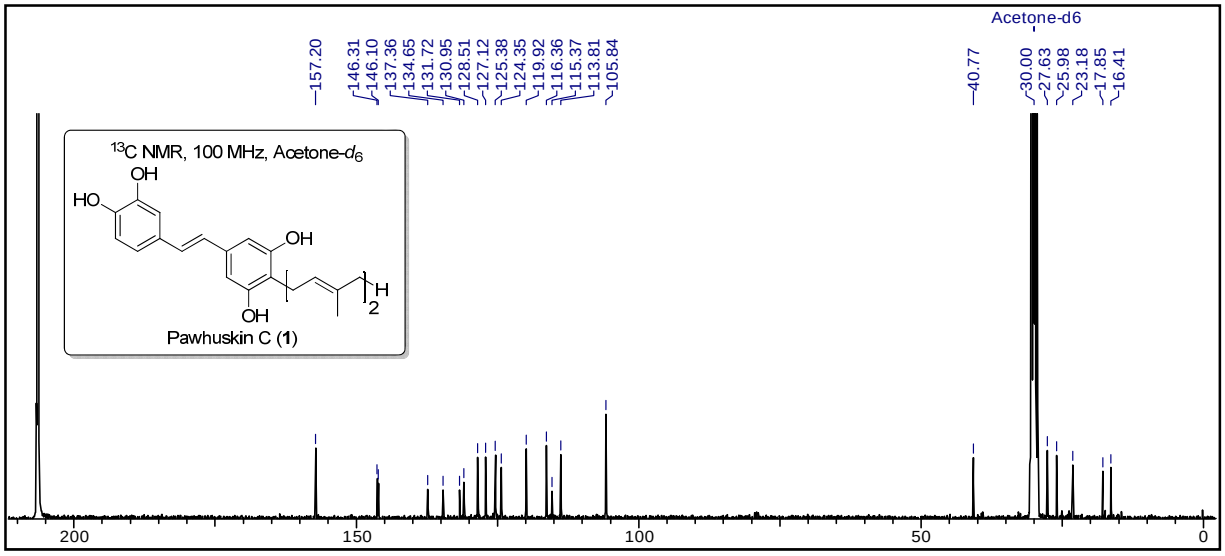

127.64
127.60
124.33
122.52
120.93
116.52
114.17
105.98
95.33
94.39
56.19
55.95
39.78
26.67
25.63
22.66
17.59
16.03
DEPT NMR, 50 MHz, CDCl3
OMOM
MOMO
OMOM
OMOM
H
2
9a
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

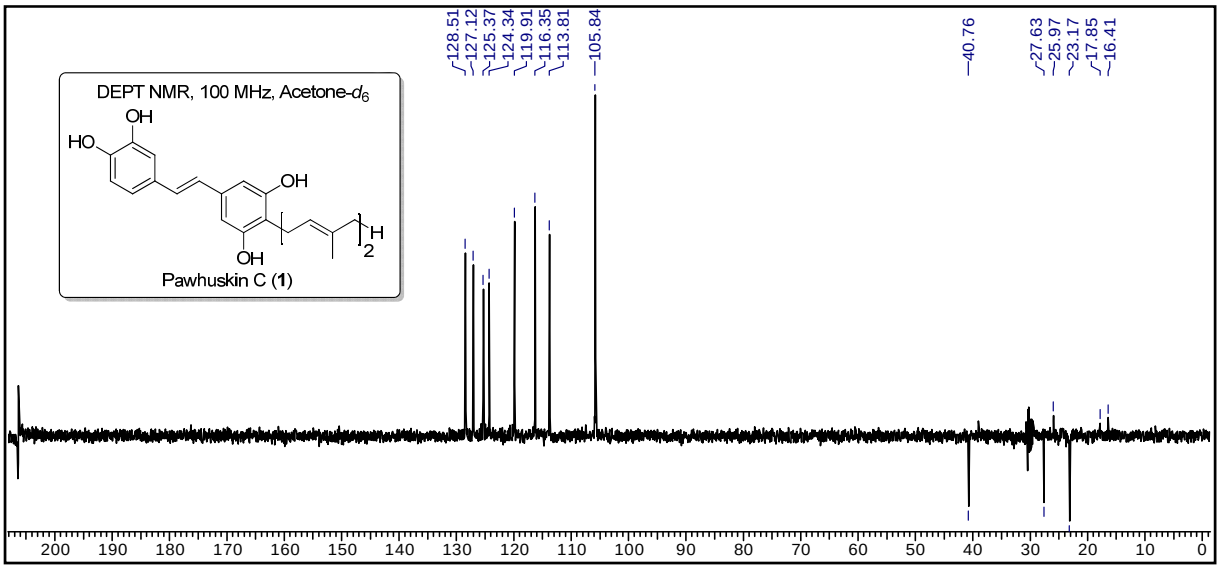

Chloroform-d
7.45
7.44
7.26
7.04
7.02
7.00
6.95
6.94
6.92
5.25
5.20
5.12
5.11
5.10
5.09
5.08
3.52
3.50
3.43
3.42
2.08
2.07
2.06
2.04
2.00
1.98
1.97
1.96
1.81
1.68
1.60
1.59
^{1}H NMR, 500 MHz, CDCl$_3$
MOMO
OMOM
OMOM
H
3
9b
2.00
3.02
5.02
9.02
8.01
12.04
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

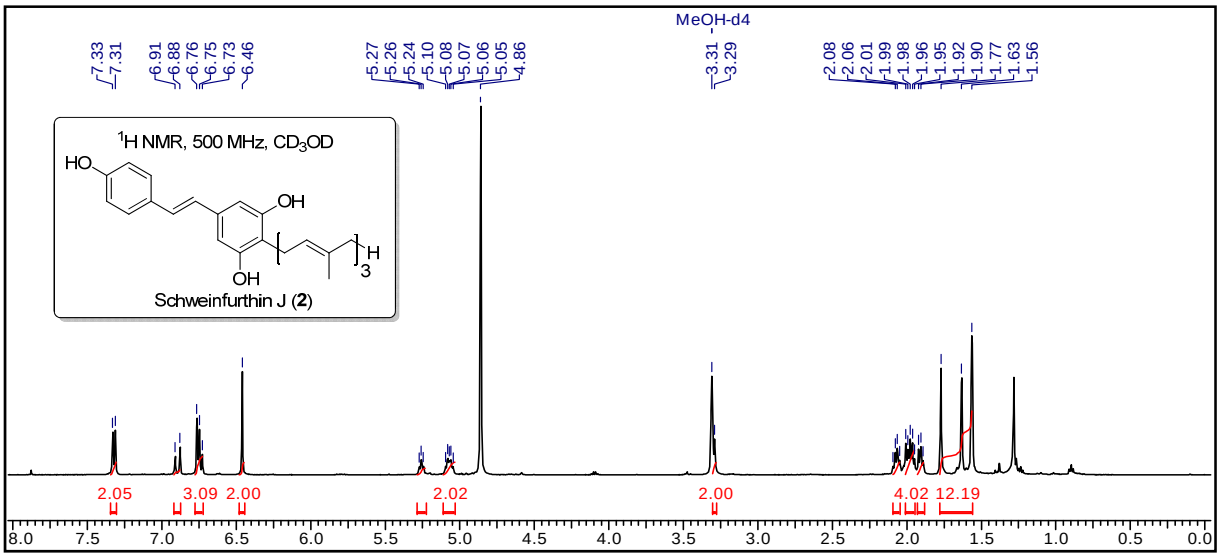

Chloroform-d
156.77
155.86
136.53
134.82
134.61
131.26
131.17
127.59
127.20
124.35
124.21
122.59
119.66
116.35
106.03
94.45
94.36
77.00
55.93
39.80
39.66
26.69
25.63
22.66
17.62
16.06
15.92
^{13}C NMR, 125 MHz, CDCl$_3$
MOMO
OMOM
OMOM
H
3
9b
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

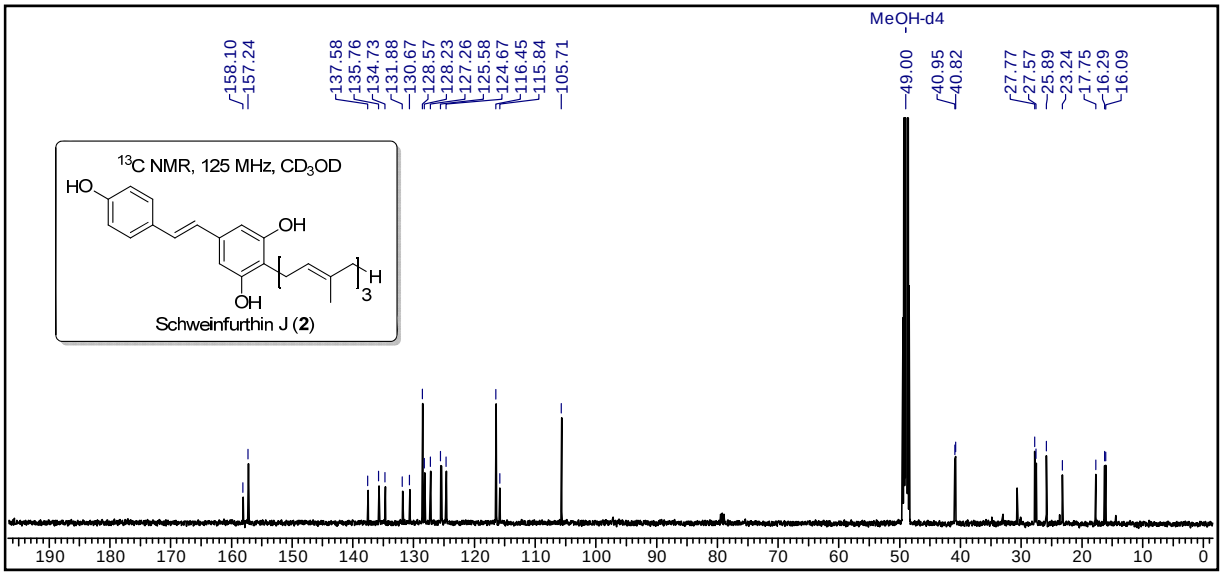

127.61
127.21
124.37
124.23
122.60
116.37
106.03
94.46
94.37
55.97
55.95
39.82
39.68
26.70
25.66
22.69
17.64
16.07
15.94
DEPT NMR, 125 MHz, CDCl$_3$
MOMO
OMOM
OMOM
H
3
9b
200
150
100
50
0

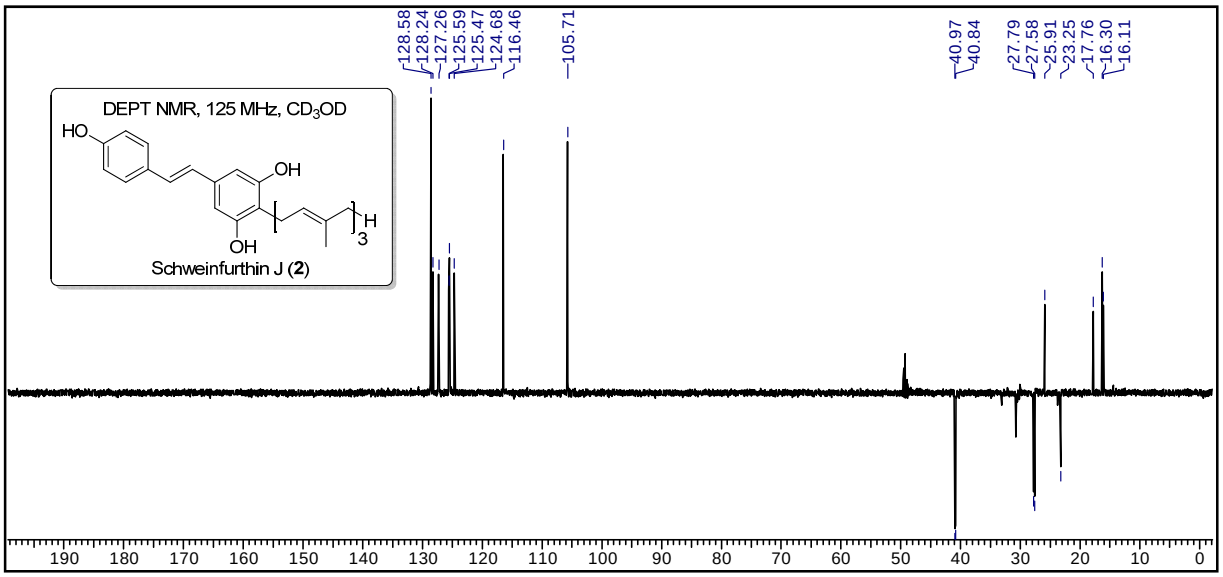

Acetone-d6
TMS
8.07
8.01
7.96
7.04
7.03
6.89
6.88
6.85
6.84
6.82
6.81
6.79
6.77
6.57
5.36
5.35
5.32
5.32
5.29
5.12
5.10
5.09
5.08
3.38
3.35
2.09
2.07
2.06
2.05
2.04
2.03
2.01
1.98
1.78
1.62
1.56
0.00
1H NMR, 200 MHz, Acetone-d6
OH
HO
OH
OH
H
2
Pawhuskin C (1)
4.04
4.24
2.02
1.00
2.03
4.09
6.01
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

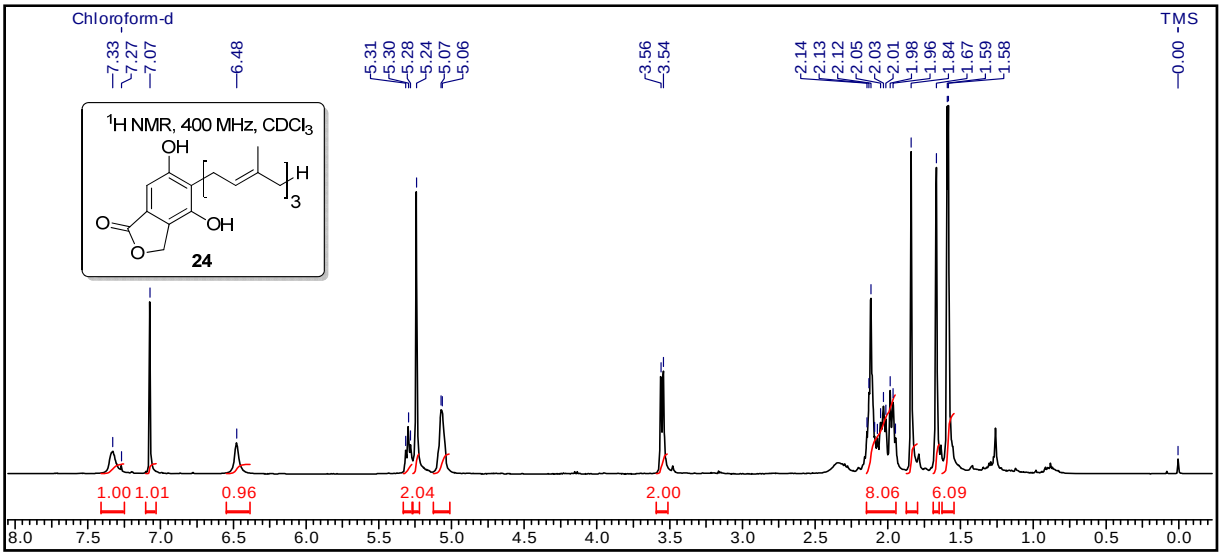

Acetone-d6
157.20
146.31
146.10
137.36
134.65
131.72
130.95
128.51
127.12
125.38
124.35
119.92
116.36
115.37
113.81
105.84
40.77
30.00
27.63
25.98
23.18
17.85
16.41
13C NMR, 100 MHz, Acetone-d6
OH
HO
OH
OH
H
2
Pawhuskin C (1)
200
150
100
50
0

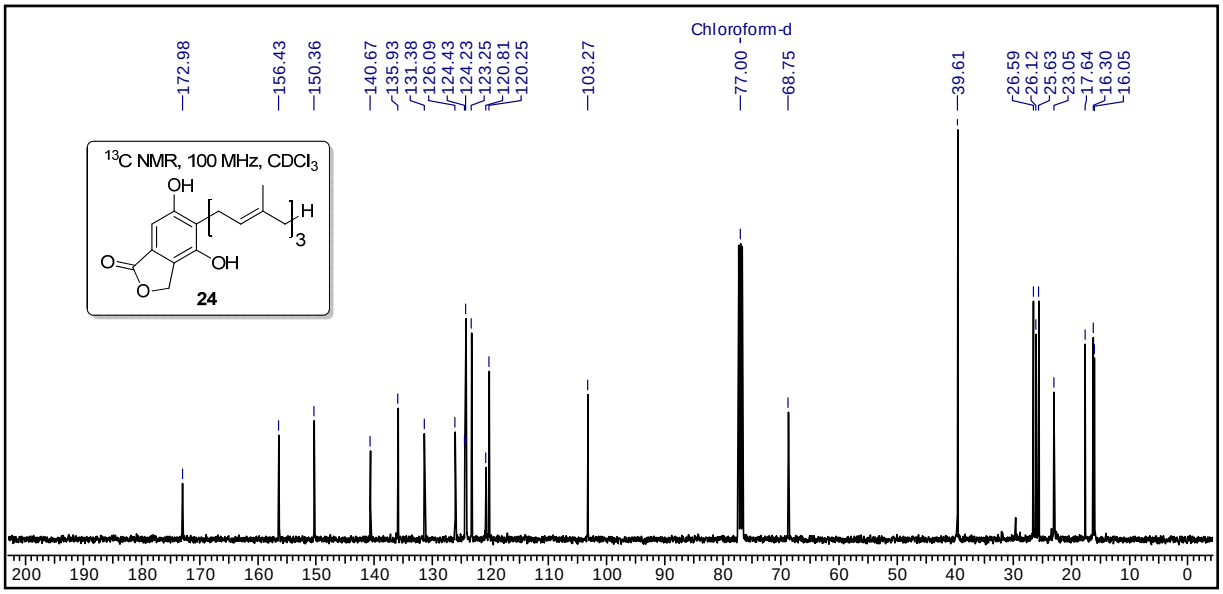

128.51
127.12
125.37
124.34
119.91
116.35
113.81
105.84
40.76
27.63
25.97
23.17
17.85
16.41
DEPT NMR, 100 MHz, Acetone-d6
OH
HO
OH
OH
H
2
Pawhuskin C (1)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

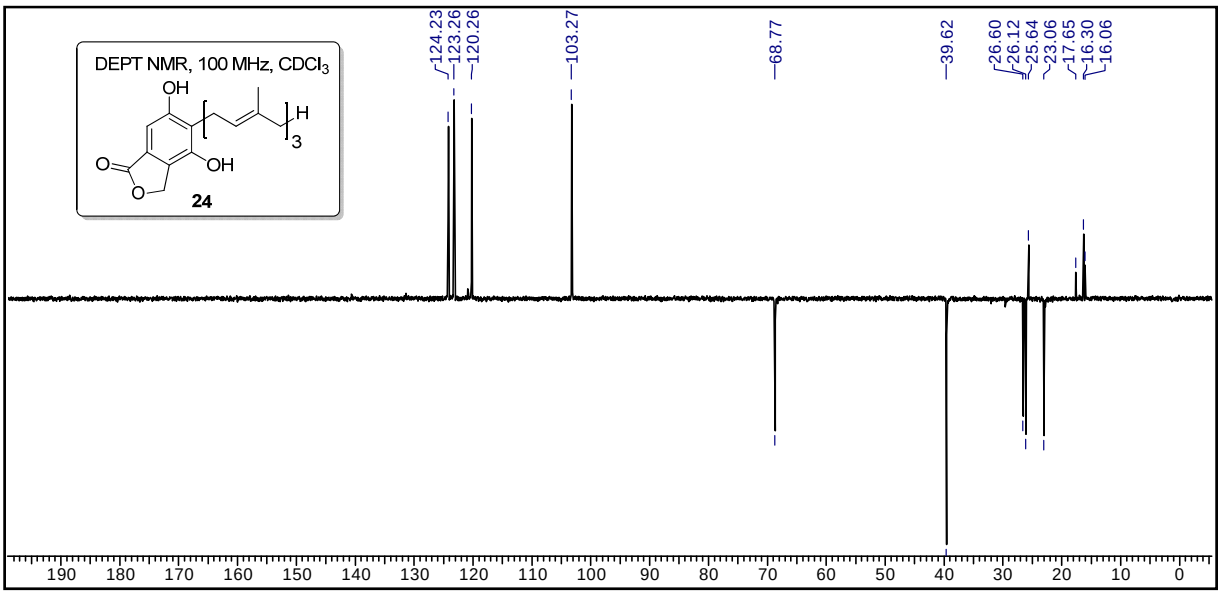

MeOH-d4
7.33
7.31
6.91
6.88
6.76
6.75
6.73
6.46
5.27
5.26
5.24
5.10
5.08
5.07
5.06
5.05
4.86
3.31
3.29
2.08
2.06
2.01
1.99
1.98
1.96
1.95
1.92
1.90
1.77
1.63
1.56
^{1}H NMR, 500 MHz, CD$_3$OD
HO
OH
OH
H
3
Schweinfurthin J (2)
2.05
3.09
2.00
2.02
2.00
4.02
12.19
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

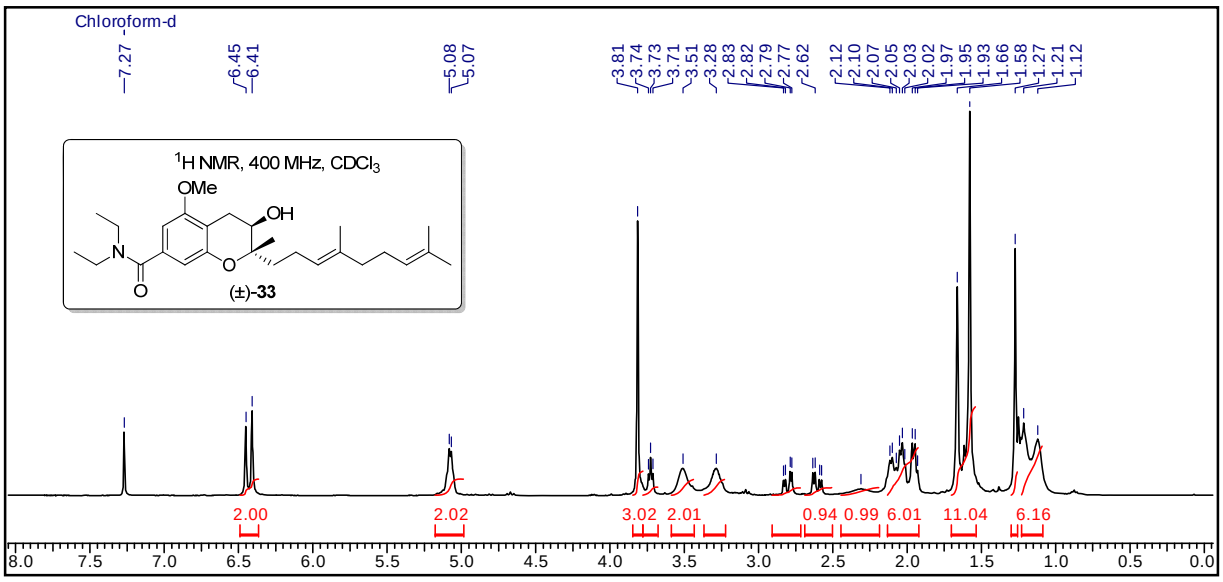

MeOH-d4
158.10
157.24
137.58
135.76
134.73
131.88
130.67
128.57
128.23
127.26
125.58
124.67
116.45
115.84
105.71
49.00
40.95
40.82
27.77
27.57
25.89
23.24
17.75
16.29
16.09
^{13}C NMR, 125 MHz, CD$_3$OD
HO
OH
OH
H
3
Schweinfurthin J (2)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

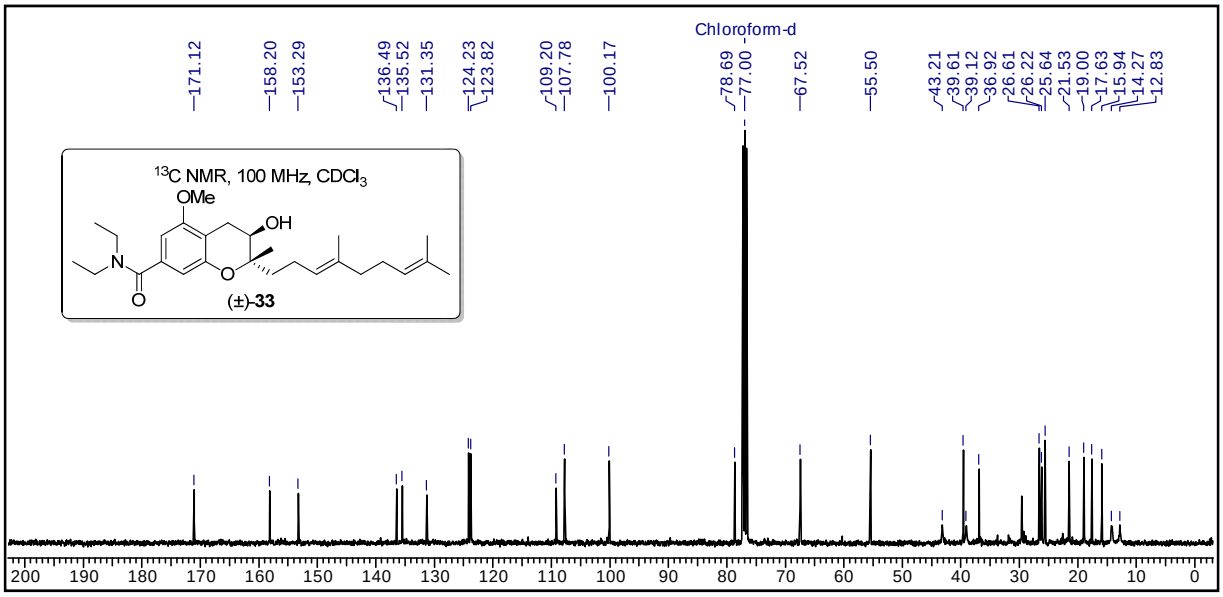

128.58
128.24
127.26
125.59
125.47
124.68
116.46
105.71
40.97
40.84
27.79
27.58
25.91
23.25
17.76
16.30
16.11
DEPT NMR, 125 MHz, CD$_3$OD
HO
OH
OH
H
3
Schweinfurthin J (2)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

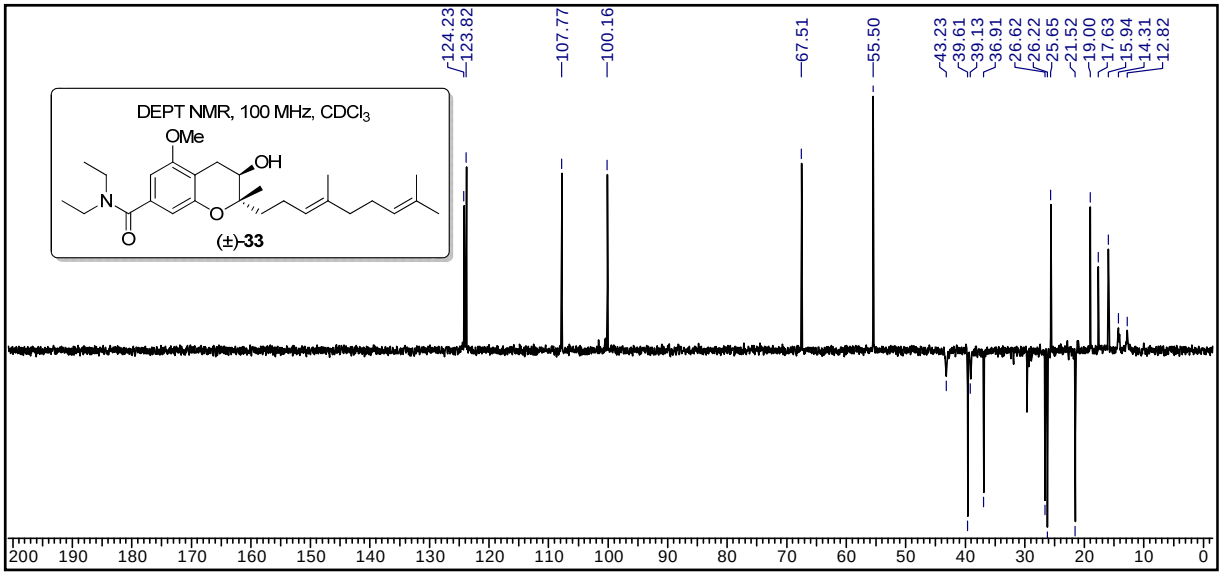

Chloroform-d
TMS
7.33
7.27
7.07
6.48
5.31
5.30
5.28
5.24
5.07
5.06
3.56
3.54
2.14
2.13
2.12
2.05
2.03
2.01
1.98
1.96
1.84
1.67
1.59
1.58
0.00
^{1}H NMR, 400 MHz, $CDCl_3$
OH
H
3
O
OH
O
24
1.00
1.01
0.96
2.04
2.00
8.06
6.09
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

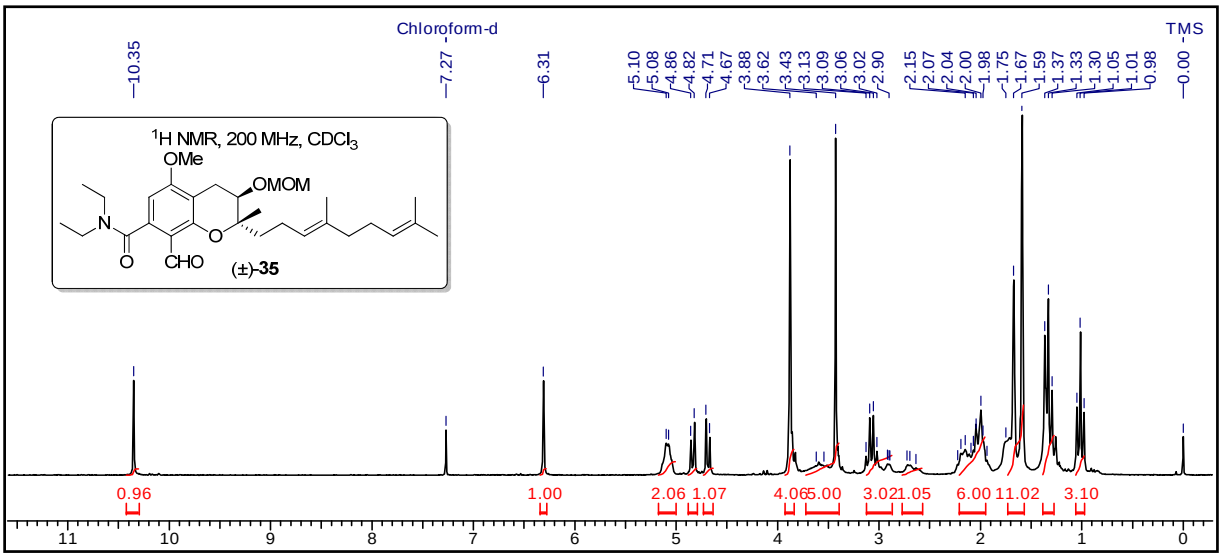

Chloroform-d
172.98
156.43
150.36
140.67
135.93
131.38
126.09
124.43
124.23
123.25
120.81
120.25
103.27
77.00
68.75
39.61
26.59
26.12
25.63
23.05
17.64
16.30
16.05
^{13}C NMR, 100 MHz, $CDCl_3$
OH
H
3
O
OH
O
24
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

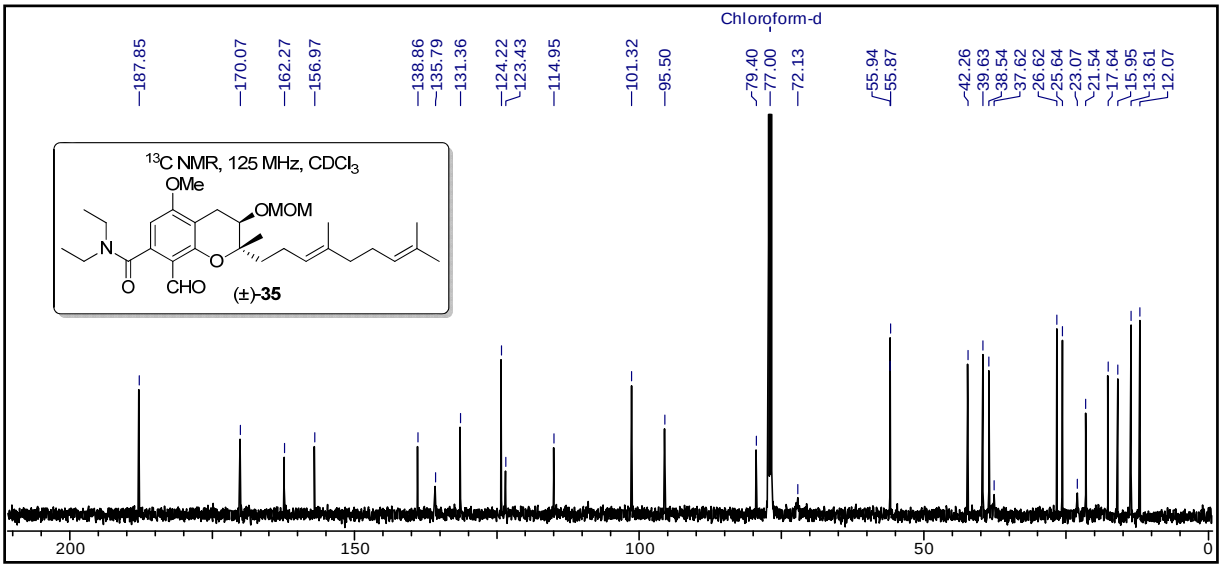

124.23
123.26
120.26
103.27
68.77
39.62
26.60
26.12
25.64
23.06
17.65
16.30
16.06
DEPT NMR, 100 MHz, $CDCl_3$
OH
H
3
O
OH
O
24
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

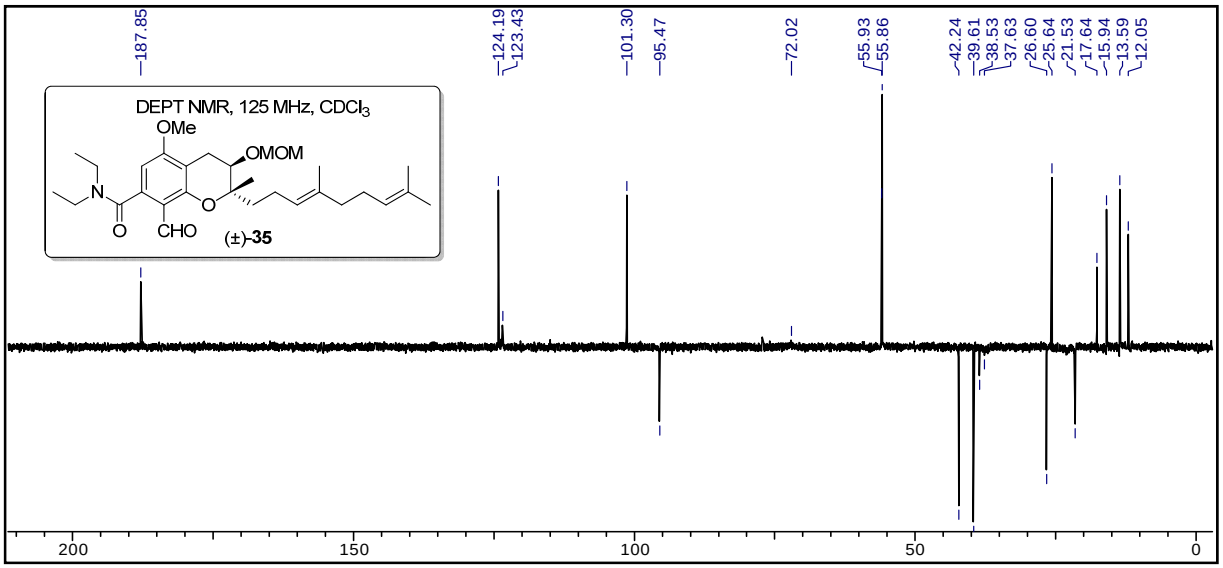

Chloroform-d
7.27
6.45
6.41
5.08
5.07
3.81
3.74
3.73
3.71
3.51
3.28
2.83
2.82
2.79
2.77
2.62
2.12
2.10
2.07
2.05
2.03
2.02
1.97
1.95
1.93
1.66
1.58
1.27
1.21
1.12
^{1}H NMR, 400 MHz, $CDCl_3$
OMe
OH
N
O
O
(±)-33
2.00
2.02
3.02
2.01
0.94
0.99
6.01
11.04
6.16
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

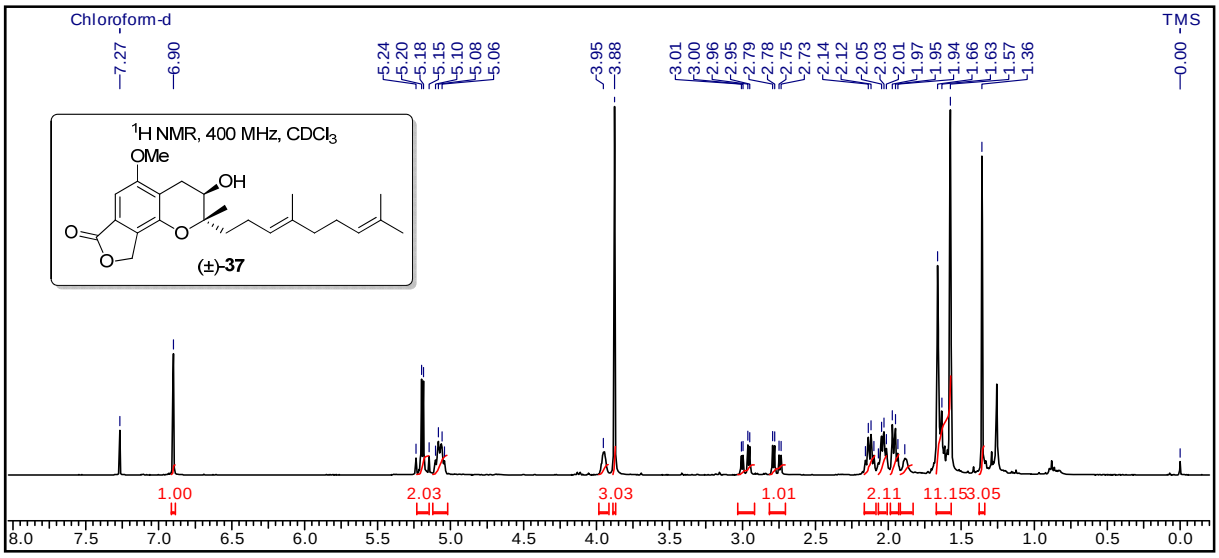

Chloroform-d
171.12
158.20
153.29
136.49
135.52
131.35
124.23
123.82
109.20
107.78
100.17
78.69
77.00
67.52
55.50
43.21
39.61
39.12
36.92
26.61
26.22
25.64
21.53
19.00
17.63
15.94
14.27
12.83
^{13}C NMR, 100 MHz, $CDCl_3$
OMe
OH
N
O
O
(±)-33
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


124.23
123.82
107.77
100.16
67.51
55.50
43.23
39.61
39.13
36.91
26.62
26.22
25.65
21.52
19.00
17.63
15.94
14.31
12.82
DEPT NMR, 100 MHz, $CDCl_3$
OMe
OH
N
O
O
(±)-33
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


Chloroform-d
TMS
10.35
7.27
6.31
5.10
5.08
4.86
4.82
4.71
4.67
3.88
3.62
3.43
3.13
3.09
3.06
3.02
2.90
2.15
2.07
2.04
2.00
1.98
1.75
1.67
1.59
1.37
1.33
1.30
1.05
1.01
0.98
0.00
^{1}H NMR, 200 MHz, CDCl$_3$
OMe
OMOM
N
O
O
CHO
(±)-35
0.96
1.00
2.06
1.07
4.06
5.00
3.02
1.05
6.00
11.02
3.10
11
10
9
8
7
6
5
4
3
2
1
0


Chloroform-d
187.85
170.07
162.27
156.97
138.86
135.79
131.36
124.22
123.43
114.95
101.32
95.50
79.40
77.00
72.13
55.94
55.87
42.26
39.63
38.54
37.62
26.62
25.64
23.07
21.54
17.64
15.95
13.61
12.07
^{13}C NMR, 125 MHz, CDCl$_3$
OMe
OMOM
N
O
O
CHO
(±)-35
200
150
100
50
0


187.85
124.19
123.43
101.30
95.47
72.02
55.93
55.86
42.24
39.61
38.53
37.63
26.60
25.64
21.53
17.64
15.94
13.59
12.05
DEPT NMR, 125 MHz, CDCl$_3$
OMe
OMOM
N
O
O
CHO
(±)-35
200
150
100
50
0


Chloroform-d
TMS
7.27
6.90
5.24
5.20
5.18
5.15
5.10
5.08
5.06
3.95
3.88
3.01
3.00
2.96
2.95
2.79
2.78
2.75
2.73
2.14
2.12
2.05
2.03
2.01
1.97
1.95
1.94
1.66
1.63
1.57
1.36
0.00
^{1}H NMR, 400 MHz, CDCl$_3$
OMe
OH
O
O
O
(±)-37
1.00
2.03
3.03
1.01
2.11
11.15
3.05
8.0
7.5
7.0
6.5
6.0
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2.5
2.0
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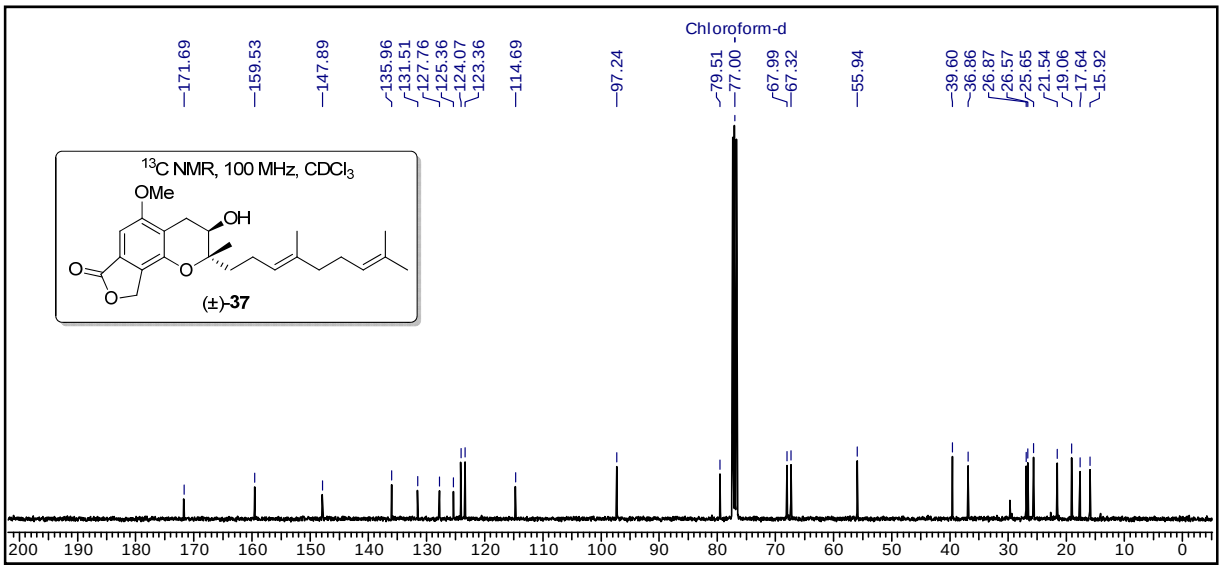
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97.24
79.51
77.00
67.99
67.32
55.94
39.60
36.86
26.87
26.57
25.65
21.54
19.06
17.64
15.92
^{13}C NMR, 100 MHz, CDCl$_3$
OMe
OH
O
O
O
(±)-37
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
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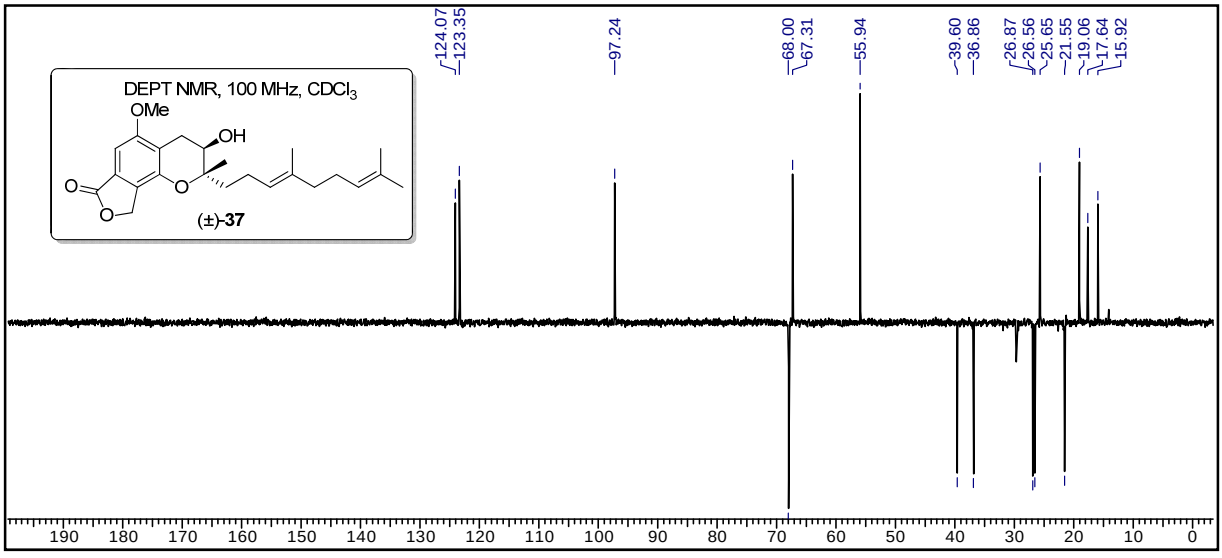
124.07
123.35
97.24
68.00
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26.56
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21.55
19.06
17.64
15.92
DEPT NMR, 100 MHz, CDCl$_3$
OMe
OH
O
O
O
(±)-37
190
180
170
160
150
140
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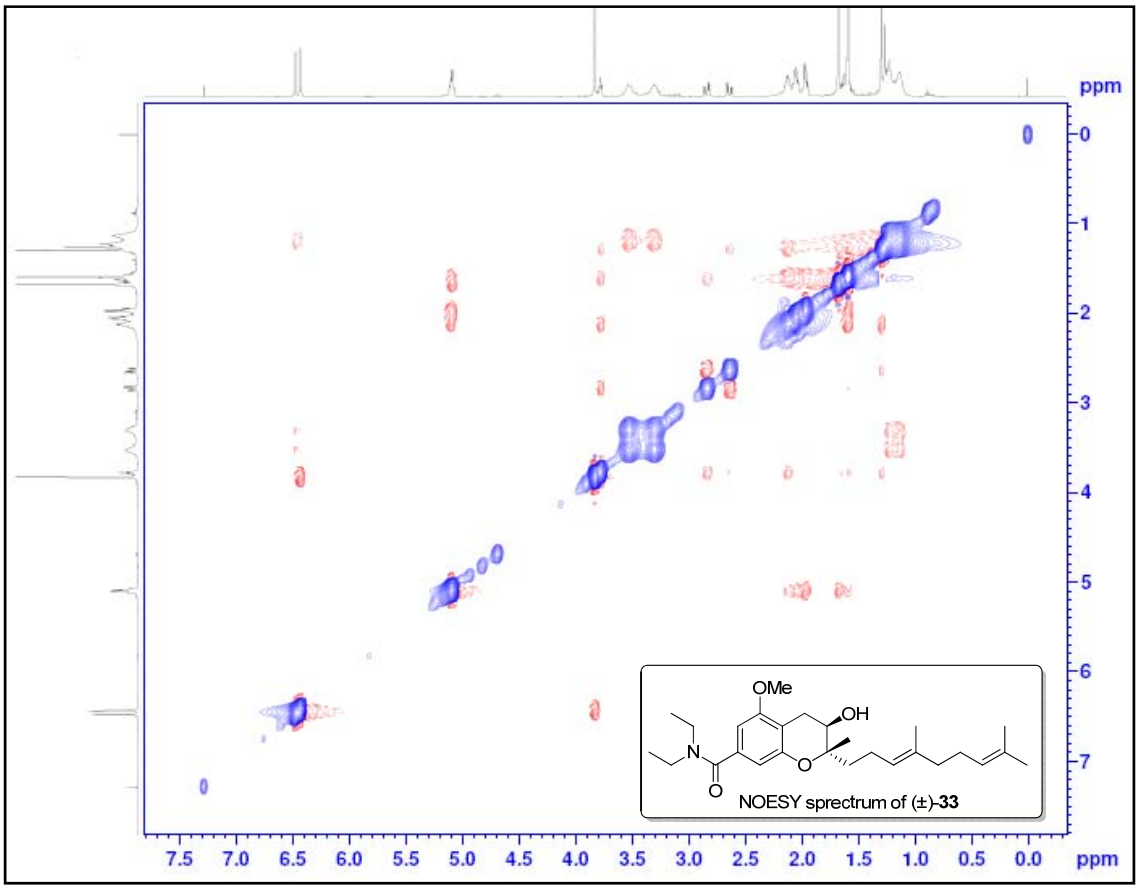
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2
3
4
5
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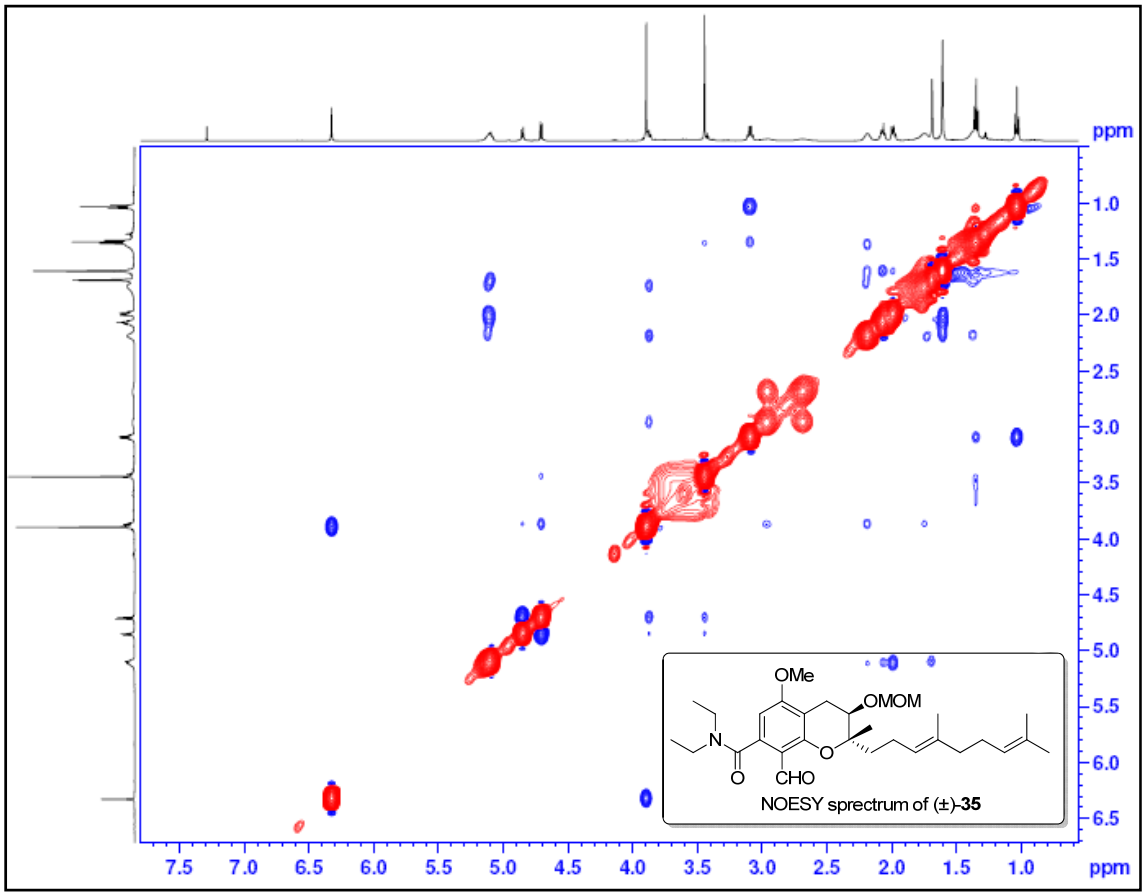
7
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm
OMe
OH
N
O
O
NOESY sprectrum of (±)-33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4.5
5.0
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7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm
OMe
OMOM
N
O
O
CHO
NOESY sprectrum of (±)-35

3B.6 References

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Overall Conclusion and Perspective

Present dissertation describes our concise and efficient approaches for the synthesis of various naturally occurring 1(3H)-Isobenzofuranones (phthalides) implementing novel synthetic routes. Various synthetic methodologies to the 1(3H)-Isobenzofuranones (phthalides) and related derivatives reported by different research groups have been presented. 1(3H)-Isobenzofuranones (phthalides) because of its fascinating structure and remarkable bioactivity has incited a lot of activity in the synthetic community towards its total synthesis.

We have presented a concise literature account on the synthesis of CJ-13,015, CJ-13,102, CJ-13,103, CJ-13,104, CJ-13,108, CJ-12,954/CJ-13,014, sporotricale methyl ether and (+)-spirolaxine methyl ether. We have reported a practical synthesis of remotely functionalized important natural products, the CJ-molecules, by taking advantage of highly chemoselective carbon–carbon bond forming reactions of phthalide with the functionalized alkyl iodides. We feel that in the present approach, the remarkably chemoselective displacements of primary iodides by the 5,7-dimethoxyphthalide carbanion, specifically in the presence of a free ketone and ester moieties are noteworthy. We have also accomplished a concise and efficient formal synthesis of the enantiomerically and diastereomerically pure bioactive natural product (+)-spiroxaline methyl ether by using readily available appropriate chiral building blocks, utilizing the most promising alkynes reactivity paradigm.

We have presented a concise literature account on the isolation, bioactivity and synthesis of pawhuskin A, pawhuskin C, schweinfurthin C, schweinfurthin F & G, (+)-schweinfurthin B & E and (+)-schweinfurthin A. We have demonstrated a new route to bioactive polyene natural products pawhuskin C and schweinfurthin J by using Heck/Stille/Suzuki/Sonogashira coupling reactions as the key steps. We have also accomplished the diastereoselective first synthesis of methyl ether of natural product NG-121 in nine steps with 29% overall yield (an average of 88% yield each step) using an appropriate reactions sequence and the essential protecting groups. We feel that our present approach to NG-121 methyl ether would be useful to access the NG-121 and stachybotrin analogs and SMTP congeners for SAR studies.

In short, we have accomplished a concise and efficient total synthesis of CJ-13,015, CJ-13,102, CJ-13,104, CJ-13,108, CJ-12,954/CJ-13,014, sporotricale methyl ether, (+)-spirolaxine methyl ether, pawhuskin C, schweinfurthin J and NG-121 methyl ether using different routes and strategies.

All these studies provided us a nice opportunity for learning a lot of new basic and applied chemistry not just from our work but also from the vast literature in this field. We also feel that the approaches which we have developed are quite general and biogenetic in nature and would be useful in designing several important complex natural products and natural product hybrids for structure activity relationship studies. A look at the recent literature also revealed that the histogram of the 1(3H)-Isobenzofuranones (phthalides) is in escalating slope and increasing medicinal and pharmaceutical demands for natural and designed 1(3H)-Isobenzofuranones (phthalides) would maintain the high positive slope in the present day world of medicinal and synthetic chemistry. As per our perception, a combination of natural and hybrid 1(3H)-Isobenzofuranones (phthalides) would serve as a launching pad to fight against new generation diseases. Finally, on the basis of exposure to the literature of 1(3H)-Isobenzofuranones (phthalides) and our contribution to the same, it can be said with assurance that this interesting discipline will spread the wings still wider in the field of organic and pharmaceutical chemistry in future.

List of Publications

1. Chemoselective Coupling Reactions of 5,7-Dimethoxyphthalide with the Remotely Functionalized Alkyl Iodides: Facile Racemic Synthesis of *Helicobacter pylori* Antibiotics
   Mandeep Singh and N. P. Argade*
   J. *Org*. *Chem*. **2010**, *75*, 3121.

2. An Efficient Convergent Access to Spiroketal Segment of (+)-Spiroxaline Methyl Ether
   Mandeep Singh and N. P. Argade*
   Synthesis **2011**, 1137.

3. Palladium-Catalyzed Routes to Geranylated/Farnesylated Phenolic Stilbenes: Synthesis of Pawhuskin C and Schweinfurthin J
   Mandeep Singh and N. P. Argade*
   Synthesis **2012**, *In Press*.

4. Synthetic studies towards NG-121: Diastereoselective access to NG-121 methyl ether
   Mandeep Singh and N. P. Argade*
   Manuscript Communicated.

Erratum