STUDIES TOWARD THE TOTAL SYNTHESES OF SKIPPED POLYOL NATURAL PRODUCTS: STRICTIFOLIONE, 6*R*-6-[(4*R*,6*R*)-4,6-DIHYDROXY-10-PHENYLDEC-1-ENYL]-5,6-DIHYDRO-2H-PYRAN-2-ONE, MARINOMYCIN A, (+)-CRYPTOCARYA DIACETATE

A THESIS

SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)

TO

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BY

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(Research Guide)

DIVISION OF ORGANIC CHEMISTRY
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AUGUST 2008

DEDICATED

TO

MY FAMILY

DECLARATION

The research work embodied in this thesis has been carried out at National Chemical Laboratory, Pune under the supervision of **Dr. M. K. Gurjar**, former HOD, Organic Chemistry Technology, National Chemical Laboratory, Pune - 411 008. This work is original and has not been submitted in part or full, for any degree or diploma of this or any other University.

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CERTIFICATE

The research work presented in thesis entitled **"Studies Toward the Total Syntheses of Skipped Polyol Natural Products: Strictifolione, 6*R*-6-[(4*R*,6*R*)-4,6-Dihydroxy-10-phenyldec-1-enyl]-5,6-dihydro-2H-pyran-2-one, Marinomycin A, Cryptocarya diacetate"** has been carried out under my supervision and is a bonafide work of **Mr N. Raghupathi**. This work is original and has not been submitted for any other degree or diploma of this or any other University.

Pune

Date: 16-08-2008

(Dr. M. K. Gurjar)
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- Raghupathi

DEFINITIONS AND ABBREVIATIONS

Ac	-	Acetyl
AcOH	-	Acetic acid
AIBN	-	Azoisobutyronitrile
Ac_2O	-	Acetic anhydride
BzCl	-	Benzoyl
t-BuOOH	-	*tert*-Butylhydroperoxide
$BF_3.Et_2O$	-	Boron trifluoride diethyl ether complex
n-BuLi	-	*n*-Butyl lithium
Bu_3SnH	-	Tributyltin hydride
Bu_2SnO/DBTO	-	Dibutyltin oxide
CS_2	-	Carbon disulfide
CSA	-	Camphor-10-sulphonic acid
CH_3CN	-	Acetonitrile
CCl_4	-	Carbon tetrachloride
$CeCl_3.7H_2O$	-	Cerium(III) chloride heptahydrate
DDQ	-	2,3-dichloro-5,6-dicyano 1,4-benzoquinone
DEAD	-	Diethyl azodicarboxylate
DIBAL-H	-	Diisobutylaluminiumhydride
DIPT	-	Diisopropyl tartrate
DIPEA		*N*,*N*-Diisopropylethylamine
2,2'-DMP	-	2,2'-Dimethoxypropane
DMP		Dess-Martin Periodinane
DMAP	-	4-Dimethylaminopyridine
DMSO	-	Dimethyl sulfoxide
Et_3N/TEA	-	Triethylamine
EtOAc	-	Ethyl acetate
EtOH	-	Ethanol
HMPA	-	Hexamethylphosphoramide
H_5IO_6	-	Periodic acid
Im	-	Imidazole
KHMDS	-	Potassium 1,1,1,3,3,3-hexamethyldisilazane
K_2CO_3	-	Potassium carbonate

LAH	-	Lithium aluminium hydride
LiOH	-	Lithium hydroxide
LiI	-	Lithium iodide
MeI	-	Methyl iodide
MeOH	-	Methanol
NaH	-	Sodium hydride
MsCl	-	Methanesulphonyl chloride
MOMCl	-	Methyl chloromethyl ether
$NaBH_4$	-	Sodium borohydride
$NaIO_4$	-	Sodium metaperiodate
NMO	-	N-Methyl morpholine N-oxide
NH_4Cl	-	Ammonium chloride
OsO_4	-	Osmium tetroxide
$PhI(COOCF_3)_2$	-	Phenyliodine(III) bis(trifluoroacetate)
PMB-Cl	-	*para*-Methoxy benzyl chloride
PPTS	-	Pyridine *p*-Toluenesulfonate
p-TSA	-	*para*-Toluenesulphonic acid
Red-Al	-	Sodium bis(2-methoxyethoxy)aluminium hydride
Selectride	-	Tri-*sec*-butylborohydride solution
THF	-	Tetrahydrofuran
TBAF	-	Tetrabutylammonium flouride
TBSOTf	-	*tert*-Butyldimethyl chlorosilane
TBDMSCl	-	*tert*-Butyldimethylsilyl triflouromethanesulphonate
TBDPS/TPS	-	*tert*-Butyldiphenyl chlorosilane
TFA	-	Trifluoroacetic acid
$Ti(O^iPr)_4$	-	Titaniumtetraisopropoxide
TPP/PPh_3	-	Triphenylphosphine
TsCl		*para*-Toluenesulphonyl chloride

-

GENERAL REMARKS

- ^{1}H NMR spectra were recorded on AV-200 MHz, AV-400 MHz, and DRX-500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C NMR spectra were recorded on AV-50 MHz, AV-100 MHz, and DRX-125 MHz spectrometer.
- EI Mass spectra were recorded on Finngan MAT-1020 spectrometer at 70 *eV* using a direct inlet system.
- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.
- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.
- Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected.
- All reactions are monitored by Thin Layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV light, I_2, and anisaldehyde in ethanol as developing agents.
- All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 40 °C unless otherwise specified.
- Silica gel (60–120), (100-200), and (230-400) mesh were used for column chromatography.
- Different numbers were assigned for compounds in Abstract and Chapters.

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ABSTRACT

ABSTRACT

The thesis entitled **"Studies Toward the Total Syntheses of Skipped Polyol Natural Products: Strictifolione, 6*R*-6-[(4*R*,6*R*)-4,6-Dihydroxy-10-phenyldec-1-enyl]-5,6-dihydro-2H-pyran-2-one, Marinomycin A, Cryptocarya diacetate"** consists of three chapters. First chapter gives an overview of the selected approaches from the literature for the stereoselective construction of 1,3-skipped polyols/diols and δ-lactones. Chapter two is divided into Section A and Section B. Section A describes a carbohydrate-based approach to the total synthesis of strictifolione, and Section B extends a similar carbohydrate-based approach towards the synthesis of (6*R*)-6-[(4*R*,6*R*)-4,6-dihydroxy-10-phenyldec-1-enyl]-5,6-dihydro-2H-pyran-2-one. Third chapter is also divided into Section A and Section B. Section A deals with the synthetic studies toward the key polyol unit of marinomycin A and a short total synthesis of (+)-cryptocarya diacetate is addressed in Section B.

Chapter I

Stereoselective construction of 1,3-skipped polyols/diols and δ-lactones

Nature has evolved a flexible and iterative approach for the synthesis of 1,3-polyols and aldol compounds possessing a broad structural diversity. Polyketide-derived natural products, many of which contain a *syn*- or *anti*-1,3-diol unit, have attracted much attention, particularly since they belong to the most potent class of biological compounds known. Description of some important methods for polyol synthesis like "C–C alkylations, asymmetric homogeneous and heterogeneous hydrogenation, diastereoselective reduction, chain elongations *via* desymmetrization, dynamic kinetic resolution, chiron and linchpin approaches" form the major content of the first chapter. Figure 1 summarizes selected synthetic approaches for stereoselective 1,3-diol synthesis.

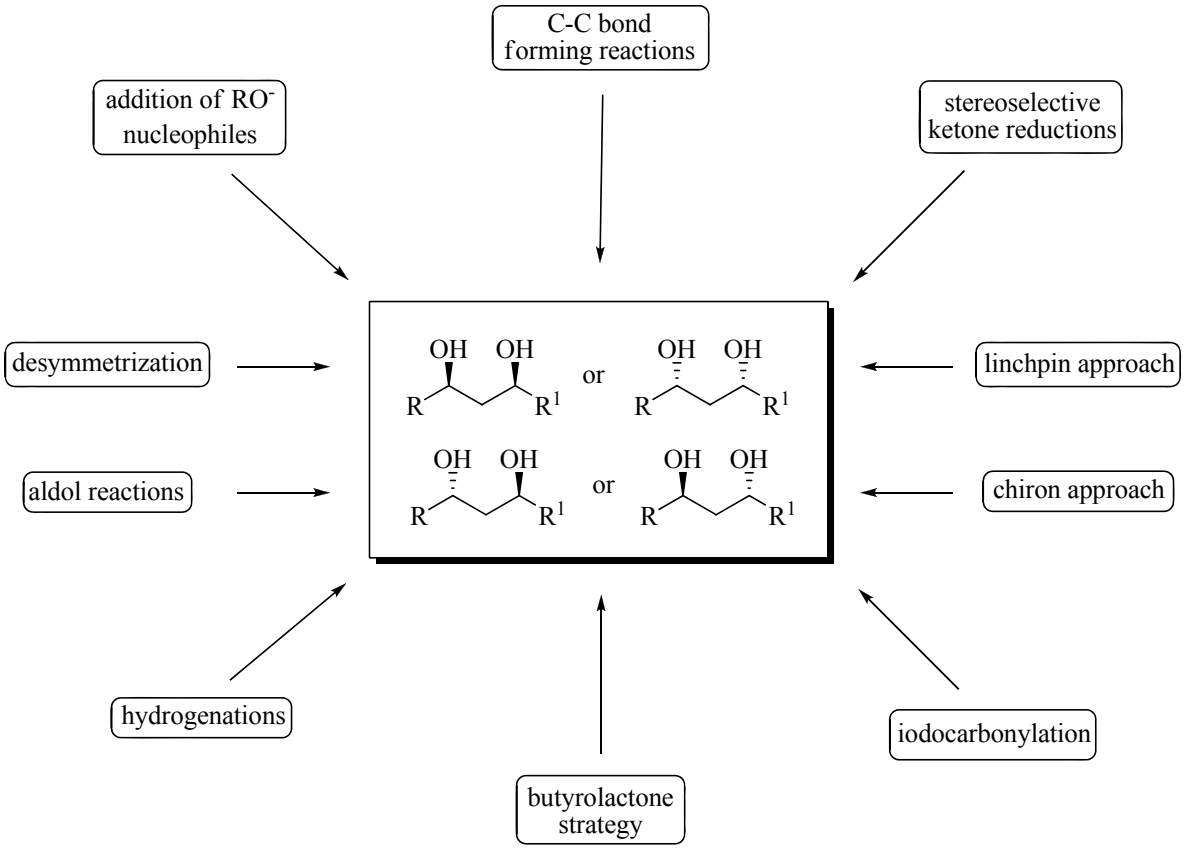
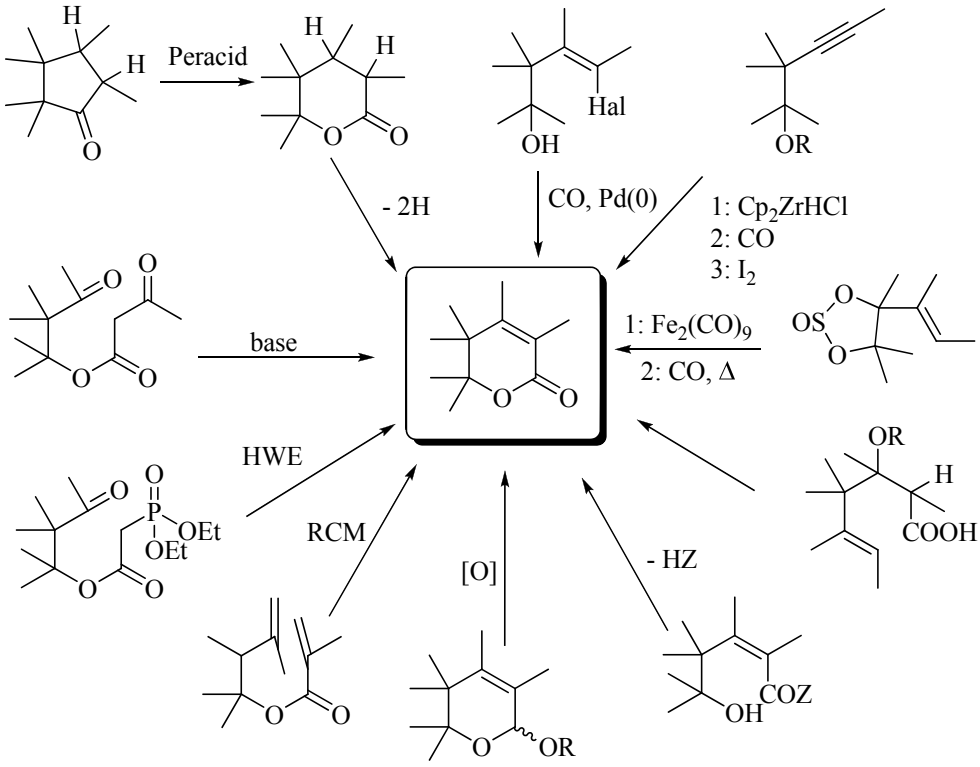


Figure 1. Selected approaches for the construction of 1,3-diols

As the key functional unit present in the selected targets of this thesis was a δ-lactone/5,6-dihydropyran-2-one moiety, a brief introduction to the available synthetic methods has been given according to the key transformation employed (Scheme 1).

- ❖ Lactonization of substituted δ-hydroxy acid derivatives
- ❖ Oxidation of substituted dihydropyran derivatives
- ❖ Ring closing metathesis
- ❖ Miscellaneous methods



Scheme 1.

Chapter II

<u>Section A</u>: <u>A carbohydrate-based approach to the total synthesis of strictifolione</u>

Strictifolione was isolated by Aimi and co-workers from the stem bark of *Cryptocarya strictifolia* that grows in the Indonesian tropical rainforests. The relative and the absolute configuration of strictifolione were revised by the same group after accomplishing its first total synthesis. Later, asymmetric syntheses, primarily with RCM as one of the key reactions, have been reported. As a part of our longstanding interest in the synthesis of bioactive natural products using the chiron approach, we have taken up the total synthesis of strictifolione **1** (Figure 2).

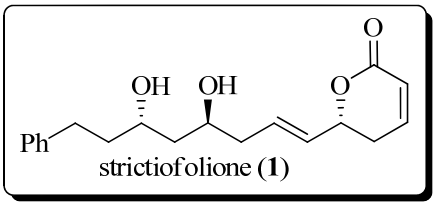


Figure 2.

Retrosynthetic Analysis

Our basic approach to the synthesis of strictifolione (**1**) features dissecting the molecule at two junctions as shown in Figure 3. One of the final key reaction will be the *Z*-selective witttig olefination and intramolecular lactonization leading to the α,β-unsaturated-δ-valerolactone of **1**. This led to the identification of **2** as a key intermediate in our total synthesis. The key intermediate **2**, in turn can be prepared by nucleophilic opening of a suitably protected epoxide **3** with lithium acetylide derivative of **4** using Yamaguchi protocol. In this context, a chiral pool approach starting from easily available D-glucose for the synthesis of **3** and a catalytic asymmetric epoxidation protocol for the synthesis of the alkyne **4** were planned to execute the synthesis of key intermediate **2**.

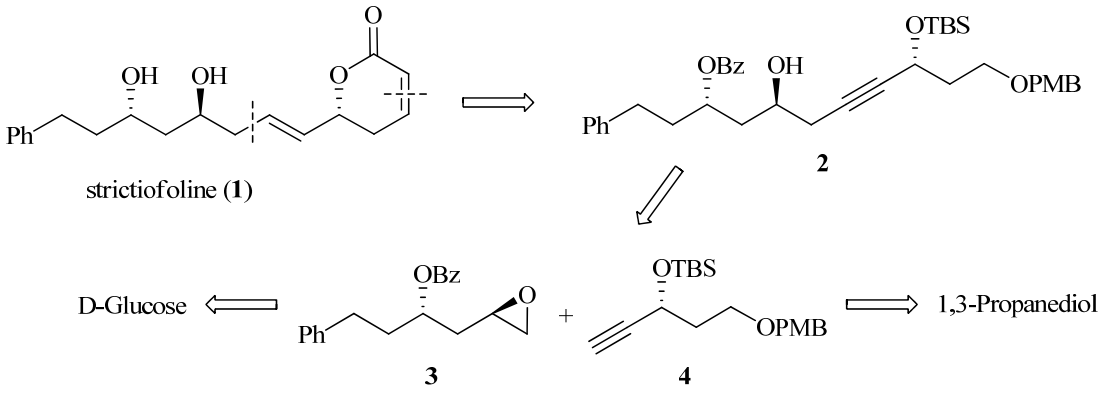
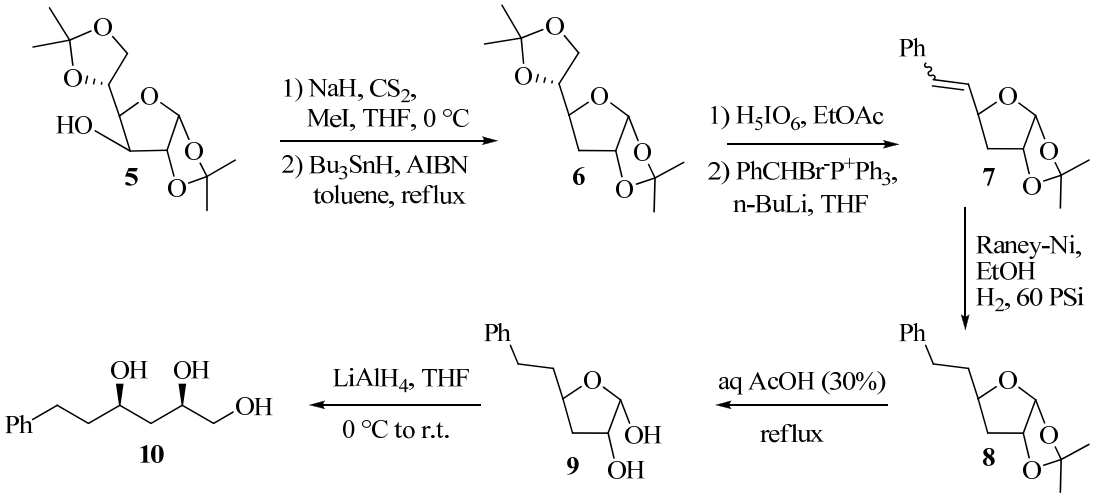


Figure 3.

Synthesis of epoxide 3

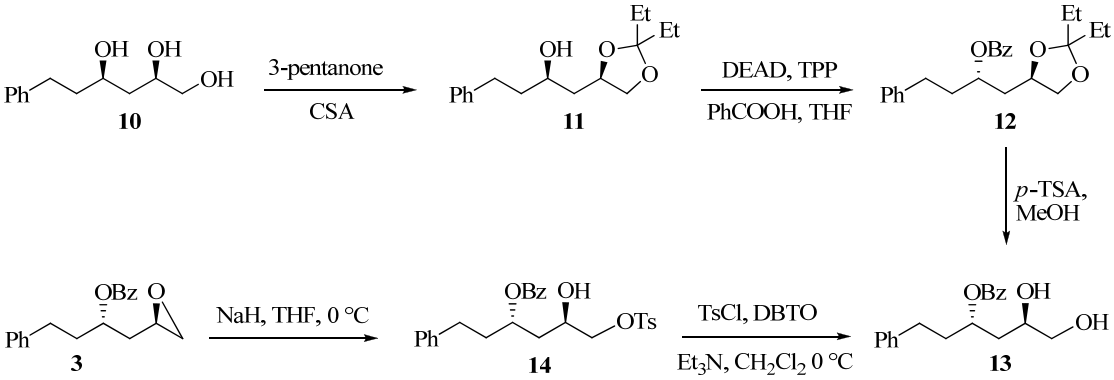
As intended, the synthesis of epoxide **3** was started from D-Glucose which was converted to the corresponding diacetonide **5** followed by its deoxygenation using Barton McCombie protocol *via* a xanthate ester formation. Periodic acid mediated oxidative cleavage of 5,6-isopropylidene group of **6** gave the corresponding furanoaldehyde which on wittig olefination with benzyl triphenylphosporane (generated from the corresponding phosphonium bromide using *n*-BuLi in THF) furnished an *E*/*Z*-mixture of β-styrene derivatives **7**. Hydrogenation of **7** using Raney-Ni in ethanol at 60 psi hydrogen pressure gave the saturated compound **8** in quantitative yield. Cleavage of 1,2-isopropylidene group was effected by refluxing **8**

in 30% AcOH to give lactol **9** which upon reduction with $LiAlH_4$ in THF yielded the triol **10** (Scheme 2).



Scheme 2.

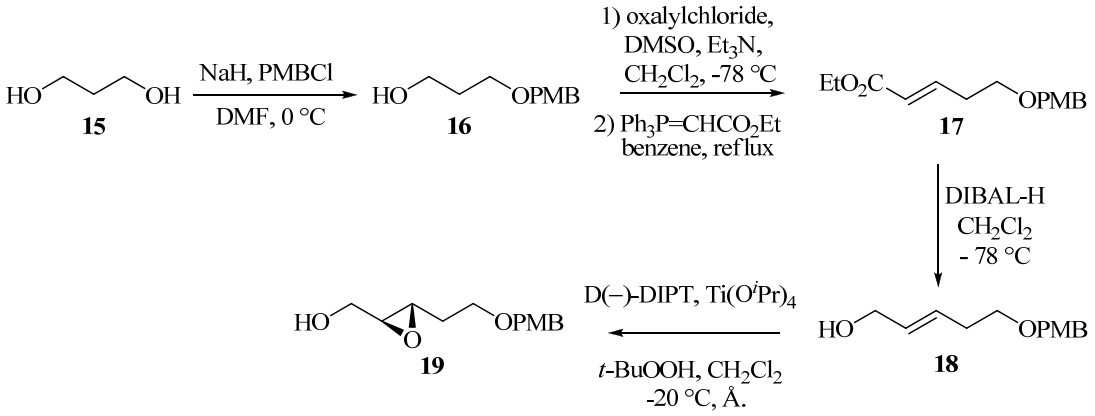
Selective 1,2-diol protection of **10** was carried out using 3-pentanone under acid catalyzed condition and the required five membered dioxalane derivative **11** was obtained exclusively leaving the 4-hydroxy intact which was inverted under Mitsunobu conditions to afford the benzoate **12**. Hydrolysis of dioxalane ketal in *p*-TSA, MeOH gave diol **13**. Selective 1°-OH tosylation and subsequent treatment with NaH in THF afforded the desired epoxide **3** (Scheme 3).



Scheme 3.

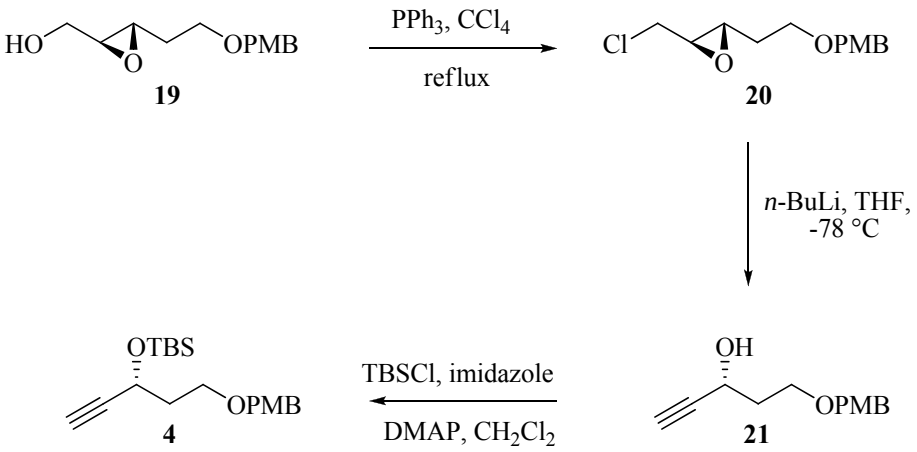
Synthesis of alkyne 4

Synthesis of alkyne fragment **4** was started with the selective mono protection of propane1,3-diol (**15**) as PMB ether by reacting with NaH, PMBCl in DMF to afford the compound **16** (Scheme 4). Oxidation of **16** under Swern conditions gave corresponding aldehyde which on 2C-Wittig olefination gave the *E*-unsaturated ester **17**. Selective carboxylate reduction using DIBAL-H in DCM at –78 °C provided allyl alcohol **18** in good yield. Sharpless asymmetric epoxidation of **18** was carried out using L-diisopropyl tartrate and titanium tetraisopropoxide in the presence of *t*-butylhydroperoxide in dry dichloromethane and the epoxide **19** was obtained in good yield with high enantiomeric excess (Scheme 4).



Scheme 4.

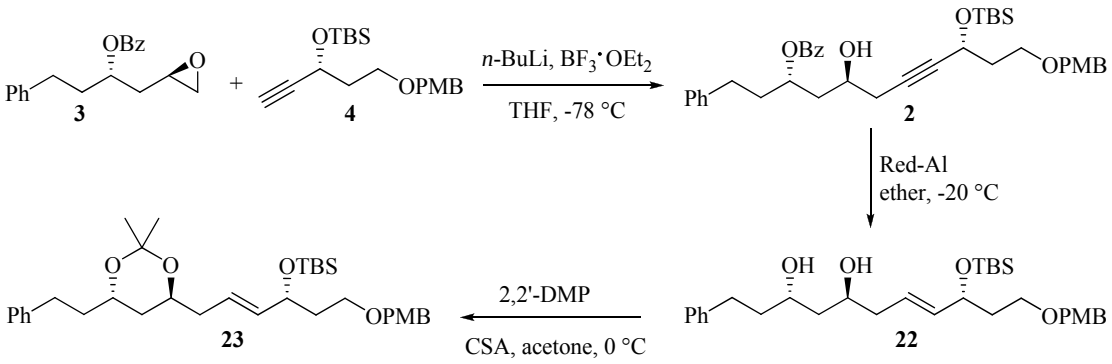
Refluxing **19** in CCl_4 in the presence of triphenyl phosphine gave the chloroepoxide **20** which on treatment with excess *n*-BuLi in THF at –40 °C provided the α-hydroxy alkyne **21** *via* a double elimination. Finally, protection of **21** as its TBS-ether using TBSCl and imidazole in CH_2Cl_2 resulted in the formation of desired alkyne **4** (Scheme 5).



Scheme 5.

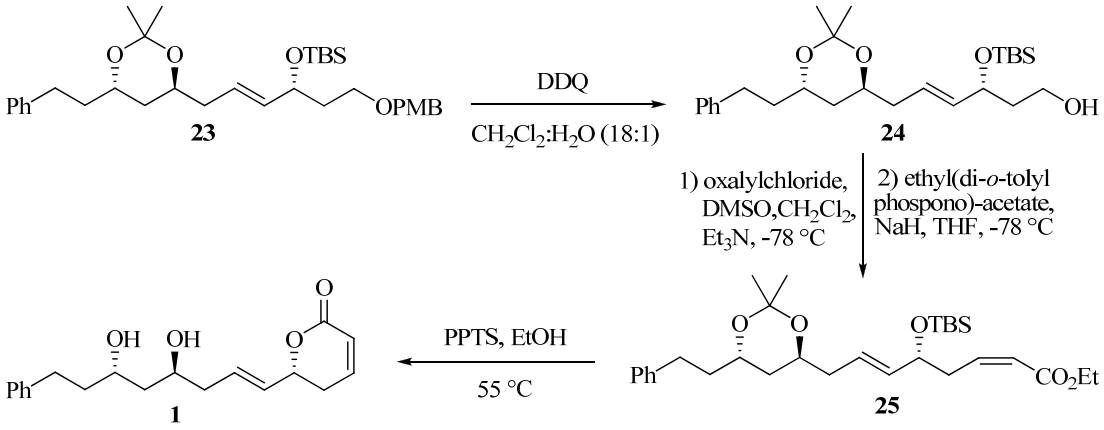
Coupling of epoxide with alkyne

Sequential treatment of alkyne **4** with *n*-BuLi, $BF_3.Et_2O$ followed by addition of epoxide **3** in THF at –78 °C resulted in the formation of β-hydroxy alkyne **2**. The reduction of C≡C to the corresponding *E*-Olefin with concomitant debenzoylation occurred when **2** was treated with Redal-H in ether at –20 °C. The resultant **22** was subsequently transformed into the corresponding isopropylidene derivative **23** by treating with 2,2'-DMP and catalytic CSA in acetone (Scheme 6).



Scheme 6.

Our next concern was to install dihydropyran ring. Cleavage of PMB ether using DDQ in 9:1 mixture of DCM and water gave the alcohol **24**. Swern oxidation of **24** followed by HWE reaction with ethyl (di-*o*-tolylphosphono) acetate and NaH, in THF furnished the ester **25** exclusively with *Z*-configuration.



Scheme 7.

Among a few reagents examined, PPTS in ethanol at 55 °C effectively deprotected both the TBS and acetonide groups. Moreover, the lactonization step also took place to complete the total synthesis of strictifolione (**1**) (Scheme 7).

In summary the total synthesis of strictifolione using a combination of chiral pool approach and an asymmetric epoxidation has been accomplished.

Section B: A carbohydrate-based approach towards the synthesis of (6*R*)-6-[(4*R*,6*R*)-4,6-dihydroxy-10-phenyldec-1-enyl]-5,6-dihydro-2H-pyran-2-one

The biologically active polyketide-δ-lactone (6*R*)-6-[(4*R*,6*R*)-4,6-dihydroxy-10-phenyldec-1-enyl]-5,6-dihydro-2H-pyran-2-one (**26**) and a structurally similar compound **27** were isolated from *Ravensara crassifolia* recently (Figure 4). Fascinated by its broad range of biological activity, structural diversity and also considering structural similarity with strictifolione (Section-A), we next aimed at the synthesis of **26** using the same strategy as discussed in the previous section originating from D-glucose.

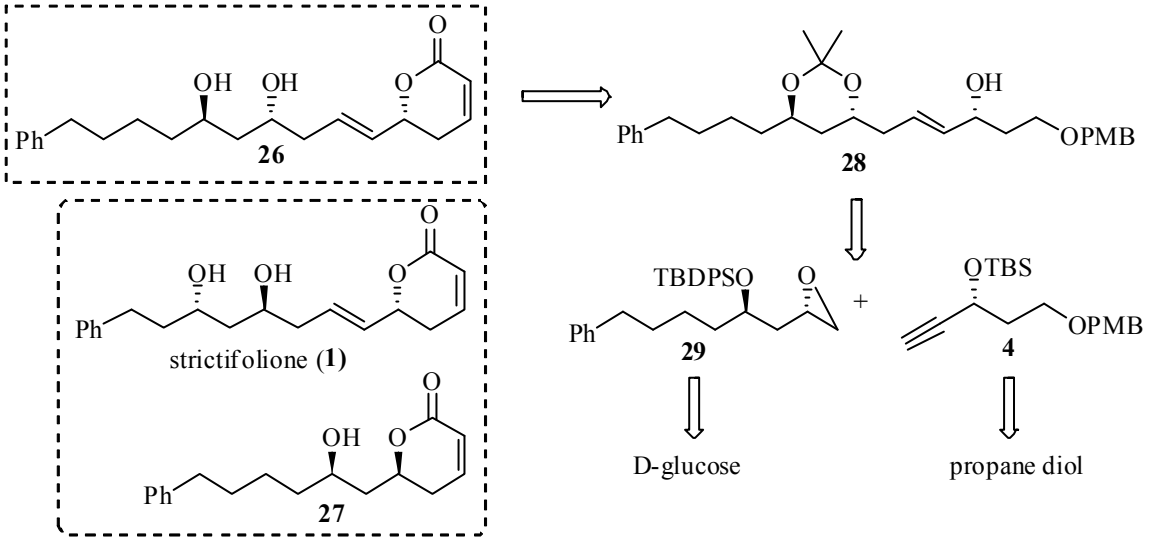
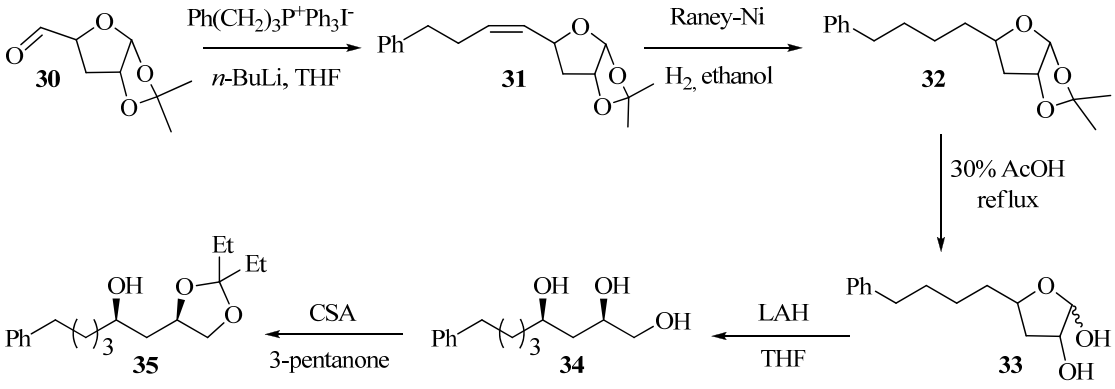


Figure 4. Newly isolated 5,6-dihydro-2H-pyran-2-one natural products **26** and **27** and the retrosynthetic strategy for **26**

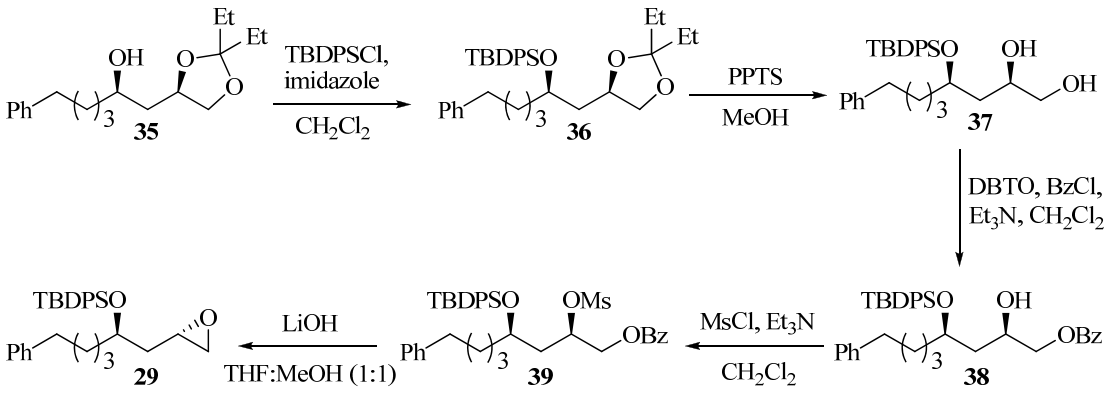
Our strategy is illustrated in Figure 4. Retrosynthetically we sought to address the synthesis of **28** by employing Yamaguchi protocol to couple epoxide **29** with lithium acetylide derivative of **4**, a key fragment we used in our synthesis of strictifolione (Section A) followed by a *trans*-selective reduction of the resulting alkyne. The requisite epoxide fragment **29** synthesis was planned from D-glucose.

The projected synthetic program commenced from the known aldehyde **30** prepared from D-glucose (3 steps, Section-A), which was treated with an ylide generated from $C_6H_5CH_2CH_2CH_2P^+Ph_3I^-$ using *n*-BuLi in THF to furnish the olefin **31**. The double bond was reduced using Raney-Ni under H_2 gas pressure (60 psi) to afford **32**. The cleavage of 1,2-acetonide was achieved by refluxing **32** in 30% aqueous AcOH to accomplish the anomeric mixture (α/β) of lactol **33**. The reductive opening of the furan ring with LAH in THF resulted in triol **34**. The 1,2-diol was selectively protected using 3-pentanone in the presence of CSA and the required five membered dioxalane derivative **35** was formed exclusively (Scheme 8).



Scheme 8.

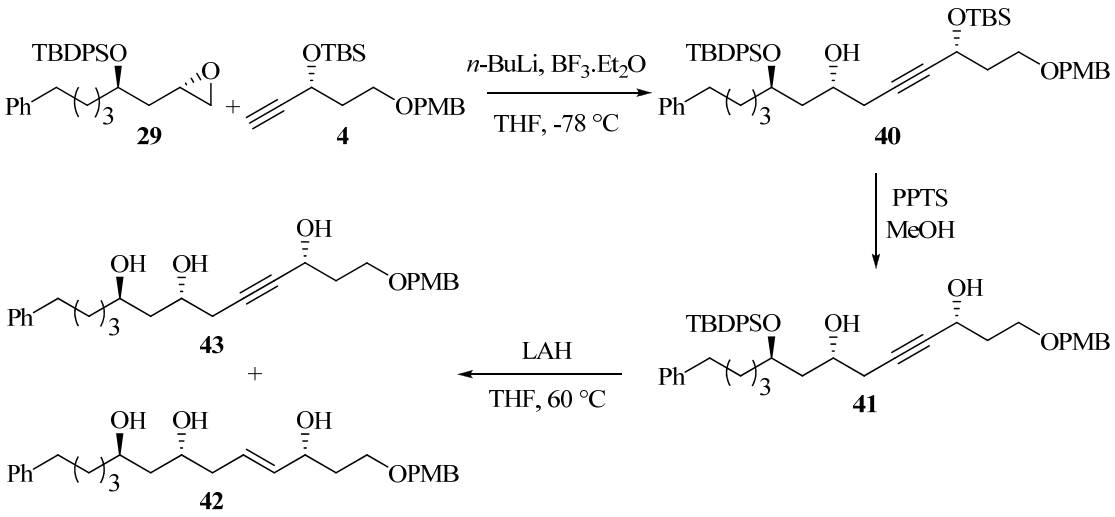
The C(4)-OH of **35** was then converted to its TBDPS ether **36** upon treatment with TBDPSCl, imidazole and catalytic DMAP using CH_2Cl_2 as solvent. Hydrolysis of the dioxalane ketal was achieved by the action of PPTS in MeOH to produce the diol **37**. The 1^o-OH of **37** was selectively protected as benzoate **38** with ($BzCl/Et_3N/CH_2Cl_2$/rt) followed by mesylation with ($MsCl/Et_3N/CH_2Cl_2$/DMAP/rt) gave the diprotected compound **39**. Base induced deprotection of the benzoate generated an alkoxide, which prompted simultaneous elimination of the mesylate and ring closure by an SN^2 mode to afford the desired epoxide **29** (Scheme 9).



Scheme 9.

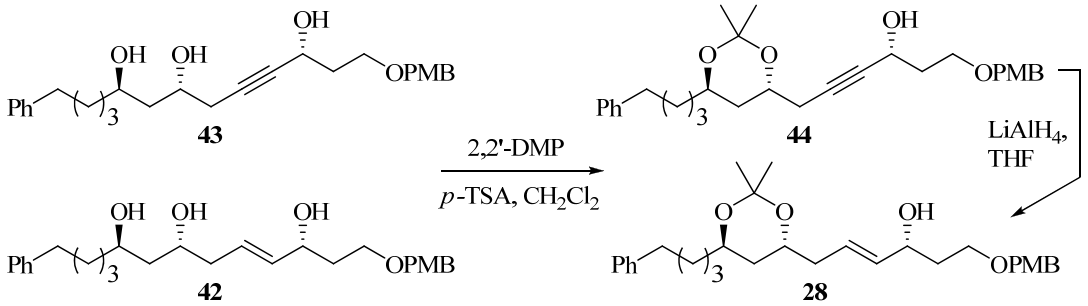
Reaction of **29** with the lithiated anion of **4** in presence of $BF_3.Et_2O$ in THF at –78 ^oC afforded the advanced intermediate **40**. The TBS group was selectively deprotected by treating **40** with PPTS in methanol at rt to procure the diol **41**. The

reduction of the alkyne proceeded smoothly when **41** was treated with LAH in THF at 60 °C producing the triols **42** and **43** with a concomitant deprotection of TBDPS group (Scheme 10).



Scheme 10.

Triols **42** and **43** were subsequently treated individually with 2,2'-DMP, *p*-TSA in CH_2Cl_2 to afford the corresponding 1,3-isopropylidene derivatives **28** and **44**. The desired **28** could also be resulted from **44** by LAH reduction to accomplish the formal total synthesis of **26** (Scheme 11).



Scheme 11.

All that remains in this synthetic sequence is the final refunctionalizations such as deprotection of PMB group, oxidation followed by Horner-Wordsworth-

Emmons homologation and lactonization to complete the total synthesis of **26**, like we executed in the total synthesis of strictifolione (**1**) and that was, however, reported exactly by Radhakrishna et al..

In summary a formal total synthesis of **26** was achieved starting from D-glucose. Notable features of this approach include a Yamaguchi coupling of epoxide **29** with alkyne **4** to give the advanced intermediate **40** with all the requisite stereocenters followed by reduction to establish the (*E*) double bond at $C_{1'}$–$C_{2'}$ of target molecule **26**.

Chapter III

Section A: Synthetic studies toward the key polyol unit of marinomycin A

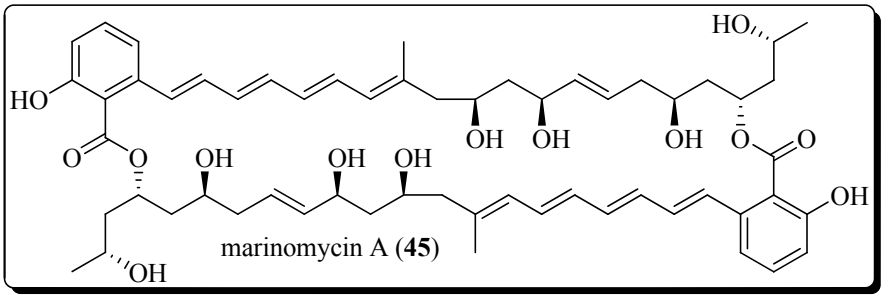


Figure 5.

Marinomycin A (**45**) is a dimeric polyene macrodiolide, recently isolated by Fenical et al. from the marine actinomycetes, named *Marinispora*. This novel macrodiolide exhibits significant cytotoxicities and antibiotic activity against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*. The challenging molecular architecture and impressive biological properties of this marine natural product coupled with our longstanding interest in synthesis of polyketide natural products impelled us to take on the synthesis of marinomycin A (**45**) (Figure 5).

Retrosynthesis

Retrosynthetically the polyol part **46** was traced back to the olefin **47** and the terminal olefin in **47** was to act as the surrogate to the ketone in **46** selecting Wacker oxidation transform. The olefinic part could be obtained by performing a

diastereoselective allylation on the advanced intermediates **48**, **49** or **50** whose origin was planned by the ring opening of epoxide **51** with alkynes **52**, **53** or **54** respectively (Figure 6). The requisite epoxide could be easily prepared by employing a multicomponent linchpin protocol of dithiane **55** with the commercially available epoxides **56** and **57**. The alkyne **52** would be accessed from D-glucose whereas alkynes **53** and **54** inturn could be synthesized from propane diol (chapter 2).

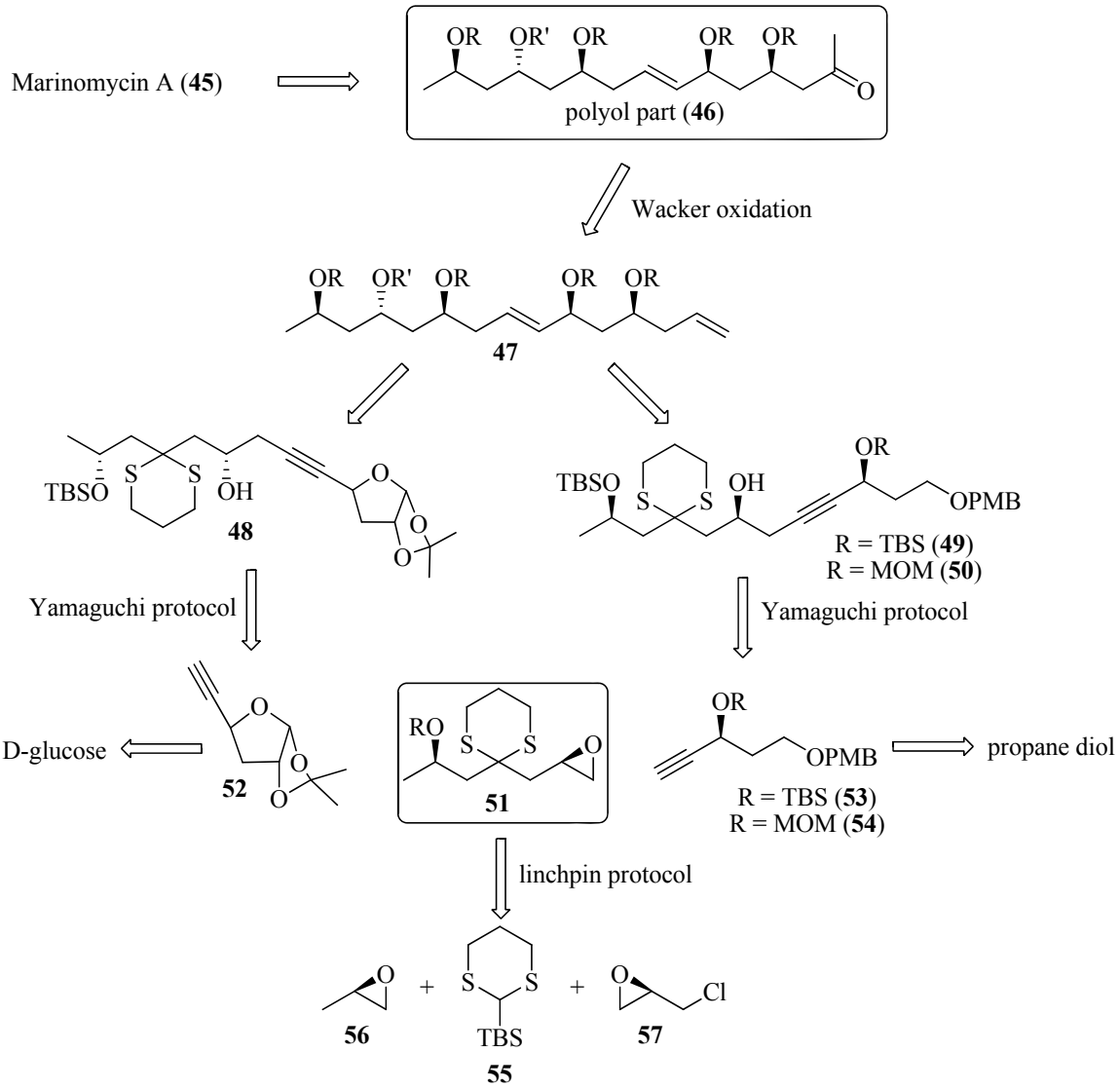
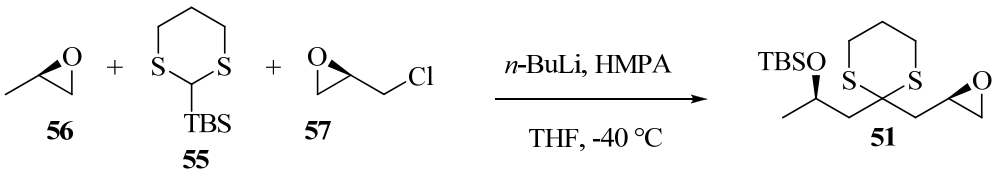


Figure 6.

The synthetic studies toward the polyol **46** were instigated by conducting a linchpin bis-alkylation of lithiated TBS-dithiane **55** with epoxides **56**, **57** using HMPA for triggering the Brook rearrangement to produce the required epoxide **51** with the desired stereogenic centers (Scheme 12).

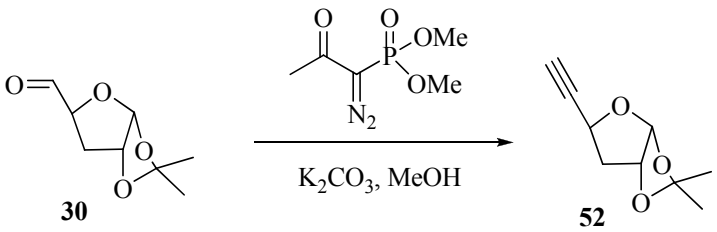


56 **55** **57** **51**

Scheme 12.

Synthesis of alkyne 52

Treatment of aldehyde **30** with Ohira-Bestmann reagent in the presence of K_2CO_3 in methanol furnished furano alkyne **52** (Scheme 13).

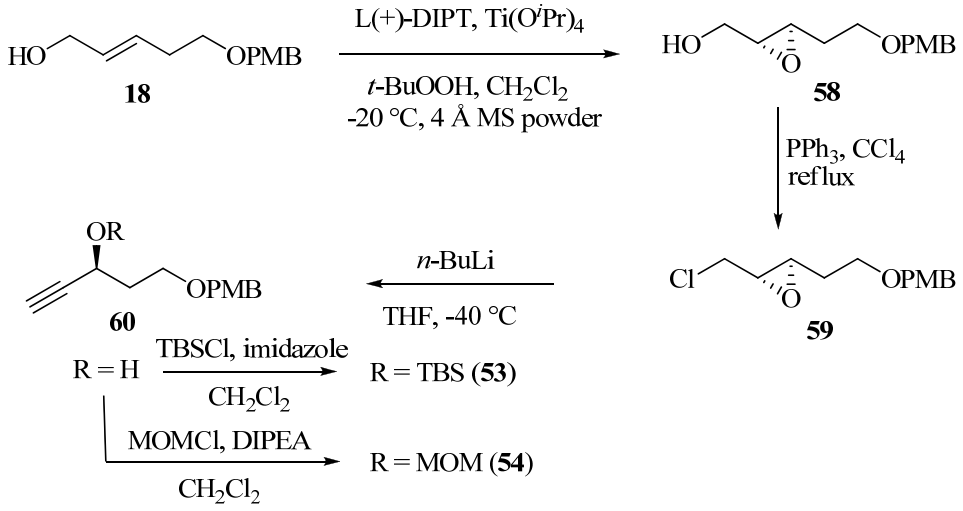


30 **52**

Scheme 13.

Synthesis of alkynes 53, **54**

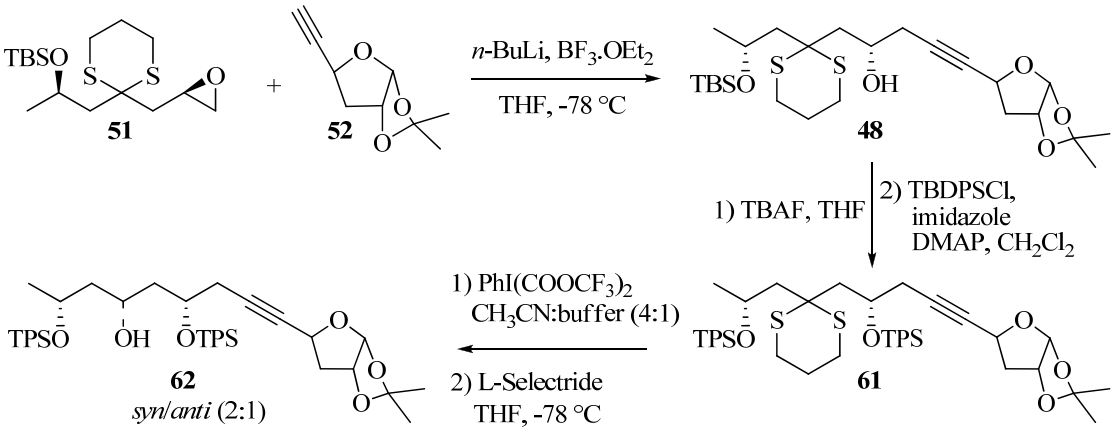
The alkyne fragments **53** and **54** were prepared by carrying out the Sharpless asymmetric epoxidation of **18** using L-(+)-diisopropyl tartrate and Titanium tetraisopropoxide in the presence of *t*-butylhydroperoxide in dry CH_2Cl_2 and the epoxide **58** was obtained in good yield. Refluxing **58** in CCl_4 in the presence of triphenyl phosphine gave the chlorooxirane **59** which on treatment with excess *n*-BuLi in THF at –40 °C provided the α-hydroxy alkyne **60**. Finally, protection of half the portion of **60** as its TBS-ether **53** using TBSCl and imidazole in CH_2Cl_2. The other half portion was converted to its MOM ether **54** by treating with MOMCl and Hunig's base in CH_2Cl_2 (Scheme 14).



Scheme 14.

Approach with sugar alkyne 52

The regioselective ring opening of epoxide **51** with lithium species derived from easily accessed alkyne **52** and *n*-BuLi in the presence of $BF_3 \cdot OEt_2$ was executed as the first stride of couplings which provided homopropargylic alcohol **48**.

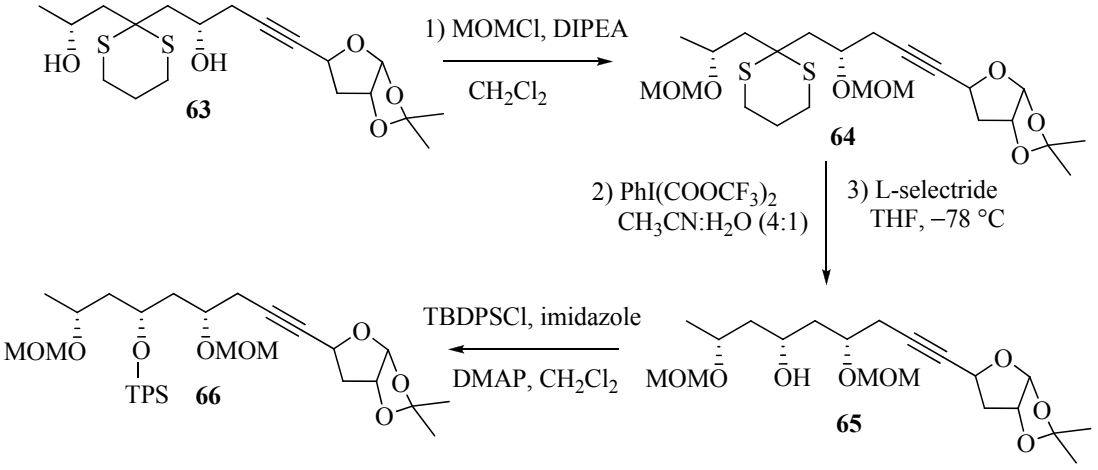


Scheme 15.

The TBS group was cleaved by treating **48** with TBAF in THF and the resulting diol was subsequently converted to the di-TPS ether **61** by reacting with (TBDPSCl/imidazole/DMAP/CH_2Cl_2). Hydrolysis of the dithioketal group was achieved by the action of $PhI(CF_3COO)_2$ in CH_3CN-buffer (4:1) to secure the corresponding ketone which upon diastereoselective reduction using L-selectride in

THF, at –78 °C furnished alcohol **62** in good yield but with a poor selectivity: *syn: anti* isomers in 2:1 ratio as an inseparable mixture (Scheme 15).

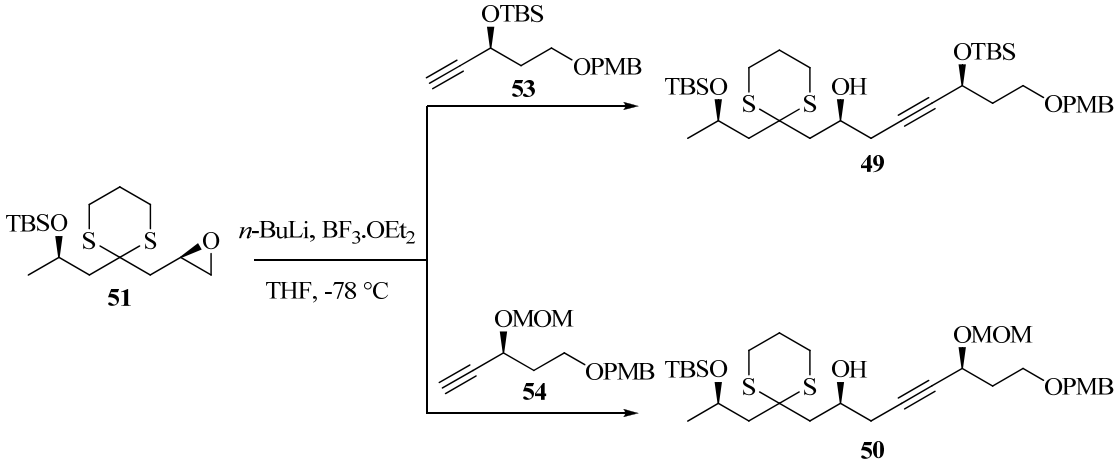
Speculating the bulky TBDPS groups may be the reason for the poor stereochemical outcome and seeking the betterment the diol **63** was converted to its di-MOM derivative **64** by treating with MOMCl and Hunig's base in CH_2Cl_2.



Scheme 16.

The hydrolysis of the dithioketal with $PhI(CF_3COO)_2$ produced the corresponding ketone which upon the projected reduction with L-Selectride in THF at –78 °C furnished the desired *syn* alcohol **65** exclusively as confirmed by NMR analysis of its TPS derivative **66** (Scheme 16).

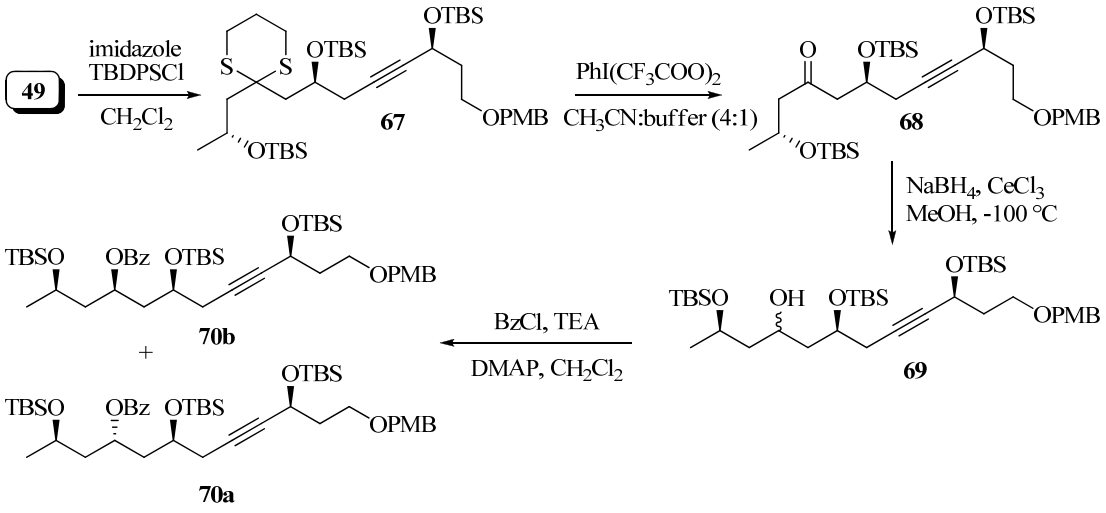
A parallel approach with alkynes 53 & 54



Scheme 17.

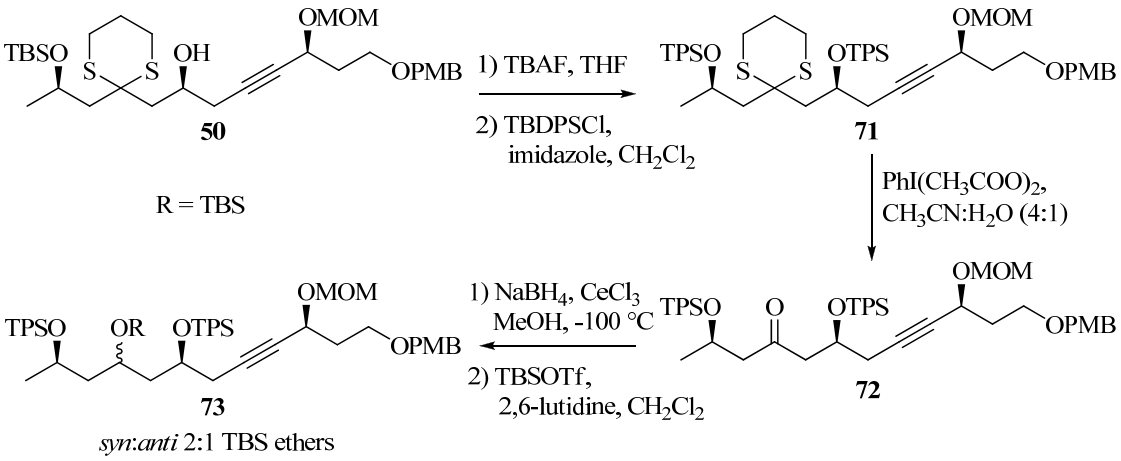
Alkynes **53** and **54** were coupled separately with the epoxide **51** employing the same Yamaguchi conditions to secure the homopropargyl alcohols **49** and **50**.

Conversion of homopropargylic alcohol **49** to the corresponding TBS ether **67** with TBSCl/imidazole/DMAP/CH_2Cl_2 followed by the dithio group cleavage with $PhI(CF_3COO)_2$ produced the ketone **68**. Reduction of ketone **68** under Luche's conditions using $NaBH_4$, and $CeCl_3$ as the chelating agent in methanol at –100 °C produced a 2:1 inseparable mixture of s*yn*/*anti* alcohols **69** which on exposure to benzoylchloride, triethylamine and catalytic DMAP in CH_2Cl_2 provided the easily separable benzoates **70a** and **70b** (Scheme 18).



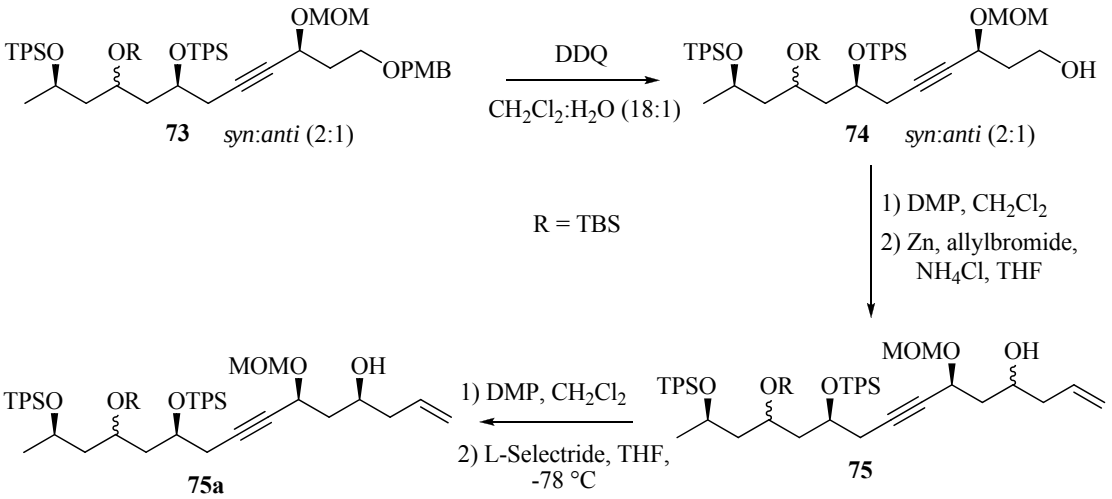
Scheme 18.

The conversion of homopropargylic alcohol **50** to di-TPS derivative **71** *via* a deprotection and protection sequence followed by the cleavage of dithiane group afforded the ketone **72**. The ketone **72** was subjected to Luche's reduction and the resulting alcohol was subsequently treated with TBSOTf, 2,6-lutidine in CH_2Cl_2 to furnish the *syn*/*anti* TBS ethers **73** in 2:1 diastereomeric ratio (Scheme 19).



Scheme 19.

Our next concern was the diastereoselective allylation. Cleavage of PMB ether was effected with DDQ in 18:1 mixture of DCM and water to afford the alcohol **74**. Successive oxidation of **74** with DMP followed by allylation in Barbier conditions furnished the homoallylic alcohols **75**. To improve the stereoselectivity for the desired *syn*-**75** we then decided to explore the oxidation/reduction sequence on the mixture of isomers of *syn*/*anti* **75**. Treatment of **75** with Dess-Martin reagent gave a clean conversion to the coprresponding ketone which was further subjected to the diastereoselective reduction using L-Selectride to accomplish the desired *syn* isomer **75a** (Scheme 20).

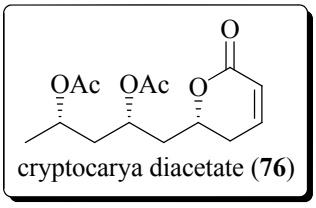


Scheme 20.

Overall a substantial synthetic work has been done for constructing the polyol unit of marinomycin A. Linchpin approach for epoxide construction, Yamaguchi protocol for regioselective ring opening of epoxide with different lithiated alkynes and diastereoselective keto reductions are the other notable reactions in our synthetic sequence. Attempts towards the total synthesis of marinomycin A is currently being pursued in our group.

Section B: A short total synthesis of (+)-cryptocarya diacetate

Cryptocarya diacetate (**76**) is a 6-substituted 5,6-dihydropyran-2-one, isolated by Horn et al. from *Cryptocarya latifolia.* It has shown promising anti bacterial and anti fungal activities. Simple structure and broad spectrum of biological activities of **76** have stimulated substantial synthetic work, culminating in several total syntheses (Figure 7).



cryptocarya diacetate (**76**)

Figure 7.

Retrosynthesis

Herein we document a short total synthesis of **76** exploiting a one-flask three-component linchpin coupling reaction for building the central carbon unit with requisite stereochemical features. A *Z*-selective Horner-Wadsworth-Emmons reaction (HWE reaction) of aldehyde **83** was opted for 5,6-dihydropyran-2-one construction. Considering an olefin group as surrogate for the requisite aldehyde, the advanced dithiane derivative **79** was identified as the key intermediate, which in turn can be obtained by linchpin coupling of dithiane **55** with known epoxides **77** and **78** (Figure 8).

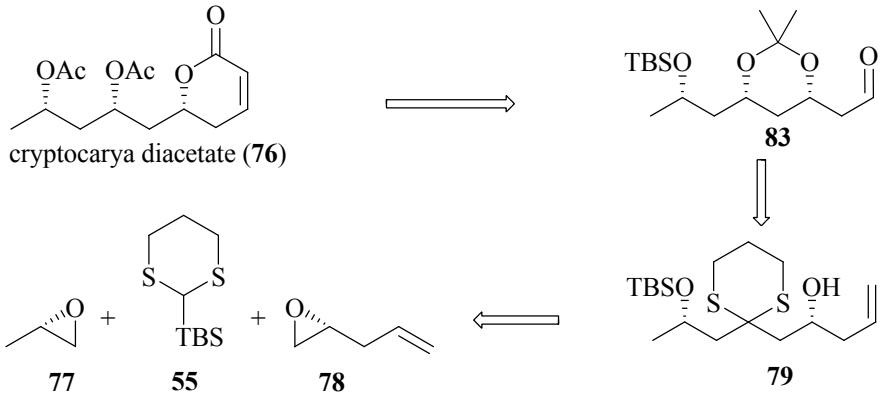
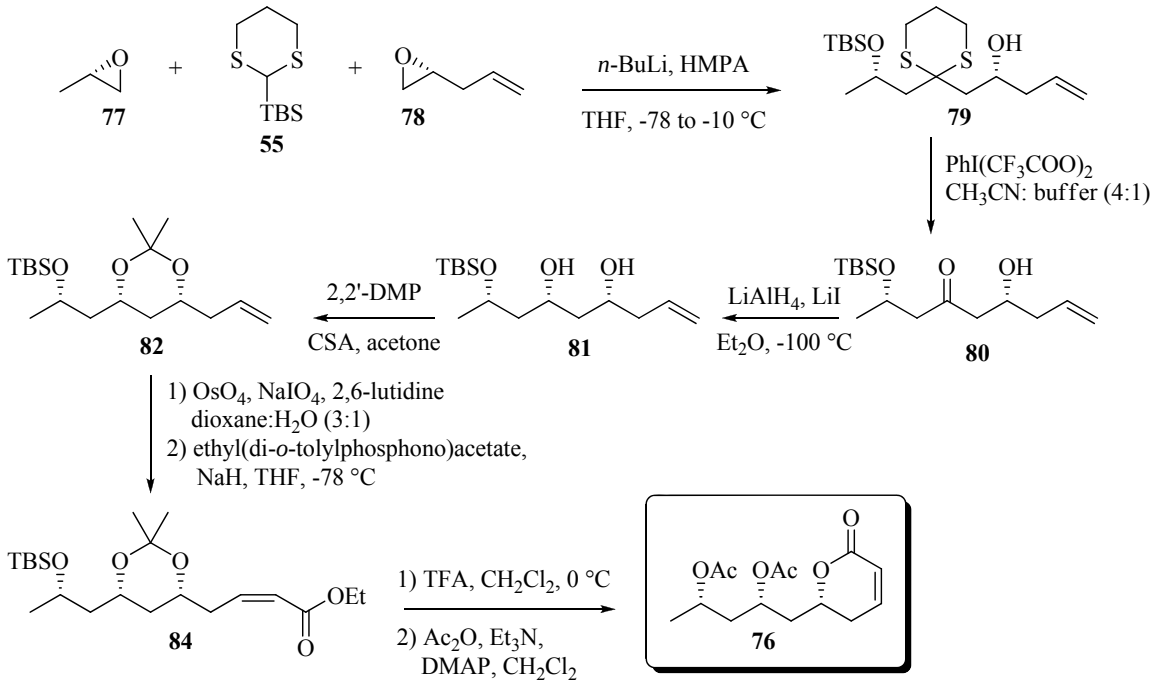


Figure 8.

The synthesis of **76** was started by performing a dialkylation reaction of lithiated dithiane **55** with epoxides **77** and **78** in the presence of HMPA to furnish **79**. Amongst a few reagents examined, $PhI(CF_3COO)_2$, in CH_3CN-phosphate buffer (pH 7.0) (4:1) effectively deprotected dithioketal to give the corresponding hydroxyketone **80**. The diastereoselective reduction of **80** with $LiAlH_4$ in the presence of LiI as a chelating agent in ether at –100 ^oC afforded diol **81** as the major product (*syn*/*anti* in 9:1 ratio). The diol **81** was subsequently transformed into the isopropylidene derivative **82** by treating with 2,2'-DMP-catalytic CSA in acetone. The oxidative cleavage of the terminal double bond of **82** using $OsO_4/NaIO_4$/2,6-lutidine in dioxane-H_2O followed by HWE reaction of the resulting aldehyde **83** with ethyl(di-*o*-tolylphosphono)acetate and NaH in THF gave *Z*-unsaturated ester **84** exclusively. After some experimentation with various acids, TFA in CH_2Cl_2 at 0 ^oC was found to be apt for the deprotection of TBS and acetonide groups with concomitant lactonization to afford the corresponding dihydroxy lactone which was acylated further by treating with Ac_2O, Et_3N–DMAP in CH_2Cl_2 to complete the synthesis of cryptocarya diacetate (**76**) (scheme 21).



Scheme 21.

A short synthesis of (+)-cryptocarya diacetate was achieved by employing three component linchpin coupling, diastereoselective reduction of β-hydroxyketone, and *Z*-selective HWE reaction as the key transformations.

CHAPTER-I

Stereoselective construction of 1,3-skipped polyols/diols and δ-lactones: A literature survey

Progress in the total synthesis of natural products since the synthesis of urea by Wohler in 1828 has been phenomenal. It is almost 65 years ago that Woodward and Deoring completed the total synthesis of quinine.[1] Even by today's standards such a molecule presents a substantial level of structural complexity and a veritable challenge. Considering the methods then available for stereocontrolled bond formation, and the lack of sophisticated spectroscopic techniques, the synthesis of quinine which is called as one of the classic total syntheses and taken as a representative example, is in fact an accomplishment.

With a constant flow of novel natural products that have intricate structures and interesting biological activities, every decade seems to have generated its own target molecules as challenges to the synthetic chemist. Armed with an impressive armamenthum of modern synthetic methods, and aided by state-of-the-art instrumental techniques, these challenges have been met head-on with extremely gratifying results. Complex frameworks of natural products with an abundance of stereogenic centers and seemingly untouchable concatenations of functionality have succumbed to the ingenuity and creativity of the synthetic organic chemist (Figure 1).[2]

The last century has seen the isolation and synthesis of a multitude of molecules with remarkable biological activity. Some of them represent milestones in chemical space and points of reference in the various disciplines of chemical synthesis, medicine, and biology that they beneficially impact. The notable history of natural products as antibiotics dates back to the 18th century. They continue to play an indispensable role in the advances that have been seen in the quality of life for the general population. This has come about because of the rich dialog that can be found at the interfaces between chemistry, biochemistry, biology, and medicine. Amphotericin B is an important representative of antibiotics with a long rich history.[3] Its impact continues to be felt today in its use in the clinic to combat fungal infections and unlike many other natural products, its impact has resonated across numerous disciplines in science. It is a natural product that remains in use in the clinic because of its indispensable, life-saving activity as an antifungal agent. Its unique structure and biological activity inspired a number of intriguing hypotheses in membrane

biology and biophysics in order to account for its mode of action. It kindled the development of novel effective approaches for its delivery as a drug. Moreover, the constellation of functionality and stereochemical patterns found adorning the macrocycle have also stimulated the field of natural products synthesis both in the development of innovative synthetic methods and at the level of synthetic strategy. Recent work in this area suggests that additional significant discoveries and advances are on the horizon.

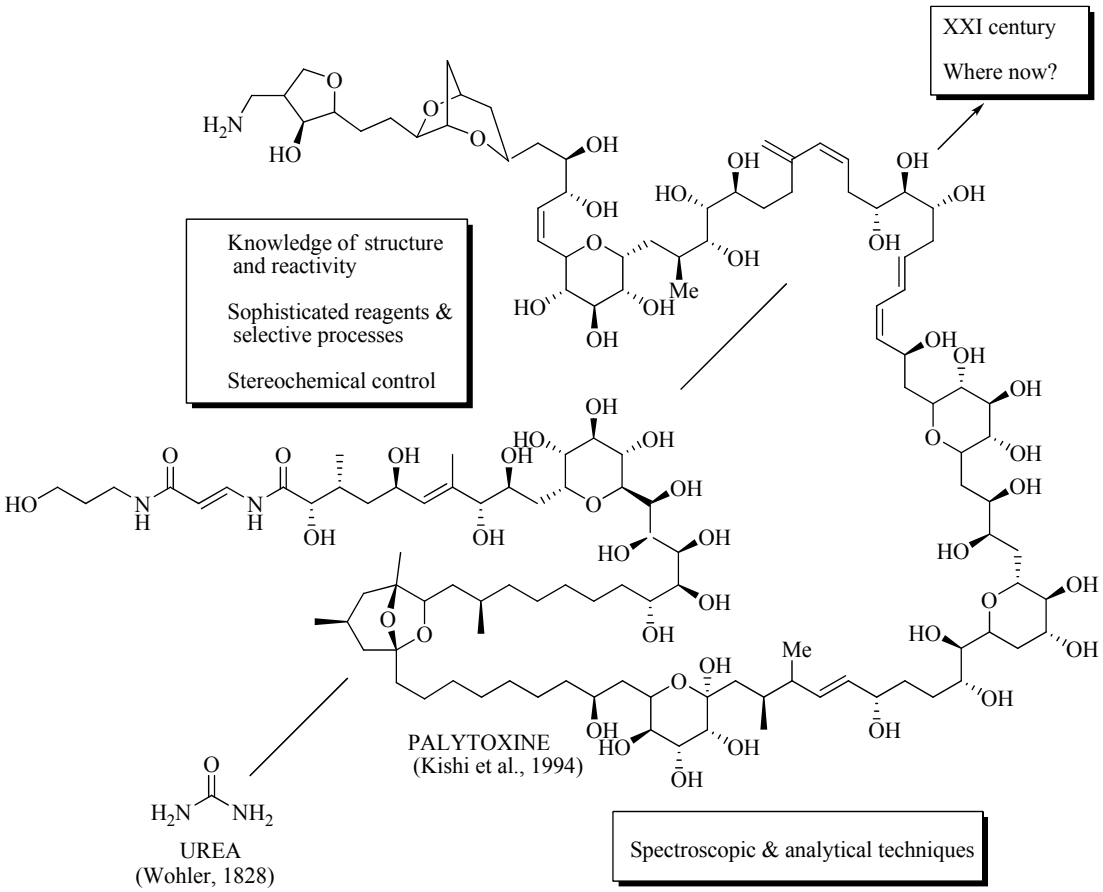


Figure 1. Conquest of natural products by synthesis – from urea the first and smallest organic natural product, to palytoxine, the largest but not the last…

For over a century, natural products have served as tools and leads for the development of new drugs. The initial focus on these compounds was their biological activity in assays and their evaluation was based on whether a particular natural product was able to provide a cure or atleast a relief of diseases. In the past two decades the focus was shifted to using natural products to probe critical cellular

events, and by doing so identifying promising targets has become more important than their actual use in the treatment of diseases. Thus natural products may not only interfere with their liganded protein target, but also help to unravel its cellular function. So far most of the small molecules used have been natural products or their variants and analogs. One of the early biological experiments that is used to provide a first insight of when and how a natural product interferes with the life cycle of cells is the cell cycle analysis, usually performed with the aid of flow cytometry.

These experiments help to distinguish four sequential phases of cell division. The cell prepares for DNA replication in the first gap phase (G1), the synthesis (S) phase is the period of DNA synthesis, the second gap phase (G2) is the period during which the cell prepares for division and in the final mitosis (M) phase where two copies of DNA are separated and the cell is divided into two daughter cells (Figure 2).

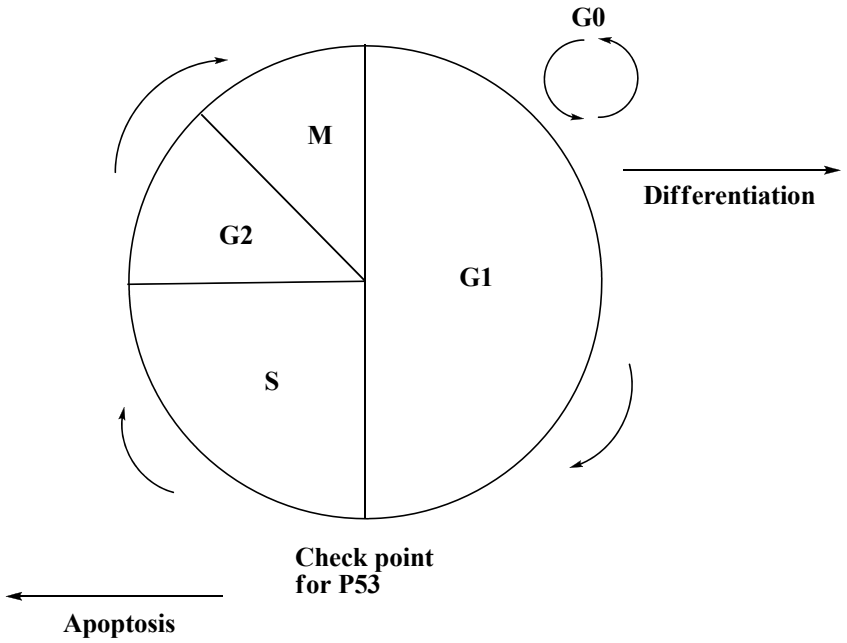


Figure 2. The cell cycle

Many natural products are known to be specific inhibitors of the cell cycle and these compounds have been classified according to their ability to selectively inhibit the individual phases.[4]

Another method of classification groups various natural products into 'families'. The individual members of each family typically have similar structures and/or functionalities. The structural similarity among compounds from different

sources might be the result of 'different solutions to one problem'. This is the case for a group of compounds which are referred to as the polyketide-δ-lactones, polyene macrolide antibiotics and marine macrolide antibiotics, a few to mention.

Polyketide-δ-lactones[5]

All members of this group share an unsaturated lactone moiety (C1–C5) attached to an alkyl side chain having polyol/diol/keto systems. Some of the structurally similar natural products of this group are leptomycin B (**1**), parasorbic acid (**2**), fostriecin (**3**), cryptofolione (**4**), pironetin (**5**) and passifloricin (**6**) (Figure 3). Even though these compounds were isolated from different plants or microorganisms inhabiting different ecosystems, they exhibit strikingly similar structural motifs with cytotoxic and antifungal biological activities.[6]

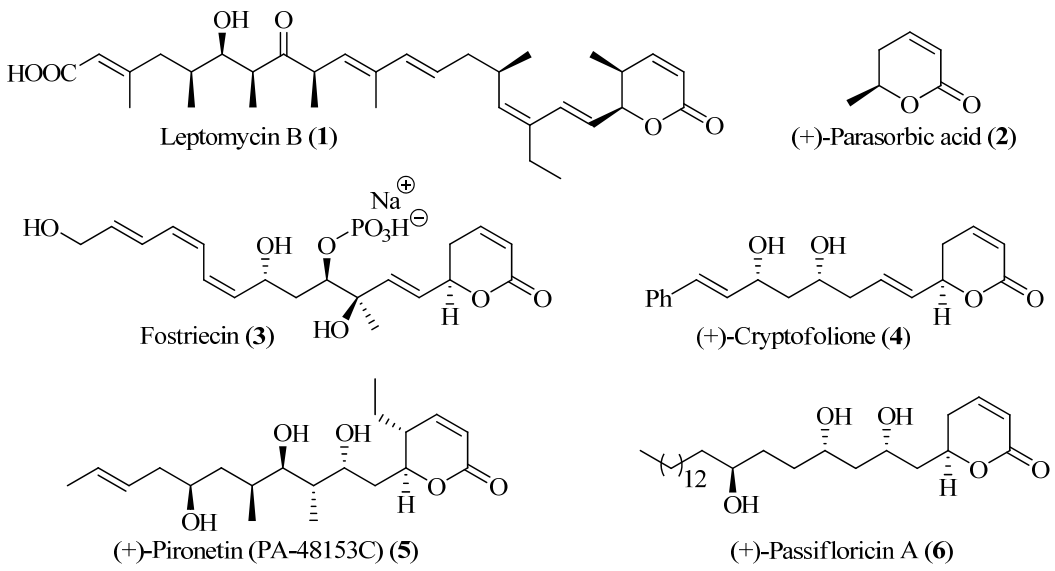


Figure 3. Some polyketide δ-lactone natural products

Polyene macrolide antibiotics[7]

Macrolides that incorporate a conjugated polyene ranging from three to seven double bonds in length are called as the polyene macrolides. The macrolide, a term introduced by Woodward to designate macrocyclic lactones, consists3 of a polyketide which may be linked to saccharide(s). The term polyketide was coined to refer to natural products containing multiple carbonyl and/or hydroxyl groups, each separated by a methylene or methine spacer unit, a characteristic functionalization pattern that betrays the biosynthetic origins. The polyene macrolide antibiotics can be further

divided into two groups: those having the polyene across the ring from the lactone carbonyl i.e. amphotericin B (**7**), rimocidin (**8**), nystatin A_1 (**9**) and filipin III (**10**) (Figure 4) whereas those having the polyene in conjugation with the lactone, generally described as the oxo polyene macrolides i.e., dermostatins (**11a**, **11b**), RK-397 (**12**), mycoticins (**13a**, **13b**) roxaticin (**14**) (Figure 5).[8]

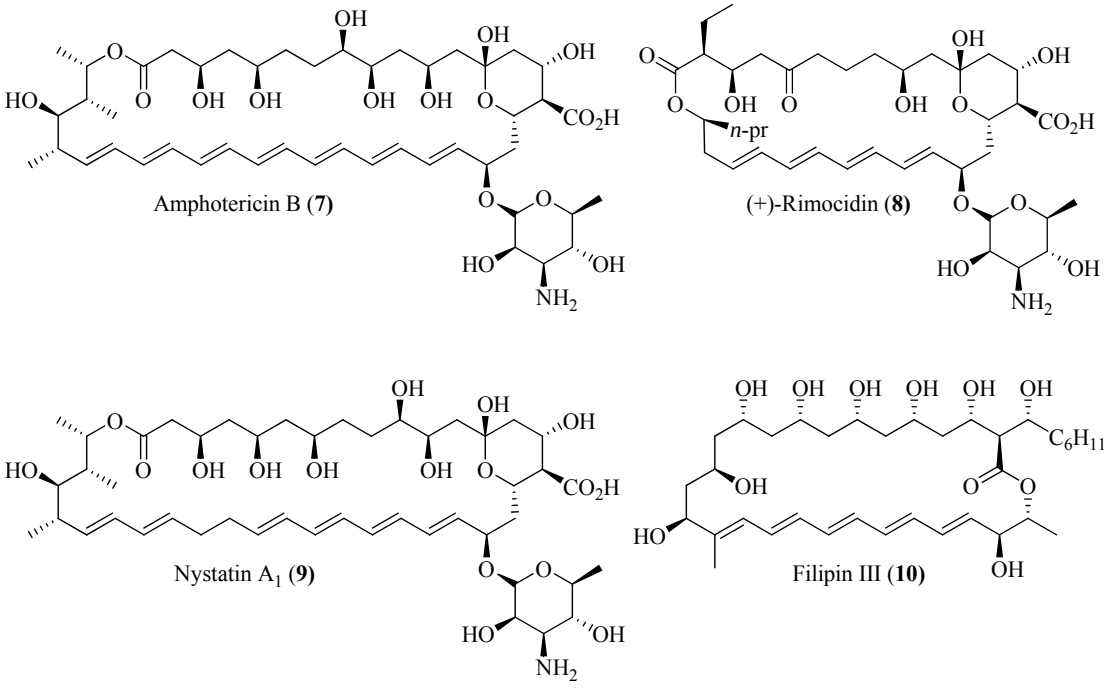


Figure 4. Structures of some antifungal polyene macrolides

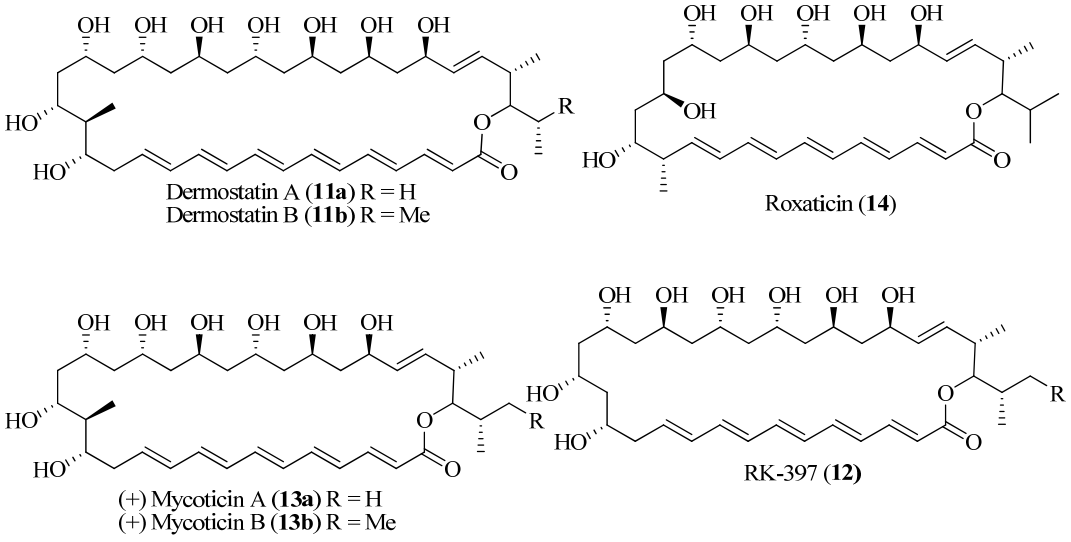


Figure 5. Structures of some representative Oxo Polyene Macrolide Antibiotics

Nature has evolved a flexible and iterative approach for the synthesis of 1,3-polyols and aldol compounds possessing a broad structural diversity. Polyketide-derived natural products, many of which contain a *syn*- or *anti*-1,3-diol unit, have attracted much attention, particularly since they belong to the most potent class of biological compounds known. The polyketide maitotoxin, for example, is the most toxic non-proteinogenic compound isolated as a natural product. The combination of highly specific biological activity and broad structural diversity is challenging for synthetic chemists, yet nature uses only a few building blocks like acetate, malonate, propionate or butyrate for construction of a broad structural diversity. Since humankind has not been able to replicate nature's general approach for the flexible synthesis of long-chain polyols and other polyketide-derived structural units, a plethora of methods for the stereoselective synthesis of 1,3-diols has instead been developed: asymmetric homogeneous and heterogeneous hydrogenation and diastereoselective reduction, chain elongation *via* radical mechanisms, enzymatic and non-enzymatic desymmetrization, and dynamic kinetic resolution, to mention just a few. It is pointed out that the development of different methodologies to synthesize 1,3-diols stereoselectively is important, as often small changes in a molecule result in low yields or low stereoselectivity with a known synthetic method. Here we intend to present a comprehensive review dealing with the aspects of stereoselective 1,3-diol synthesis.

Selected approaches for stereoselective construction of 1,3-Polyols[9,10]

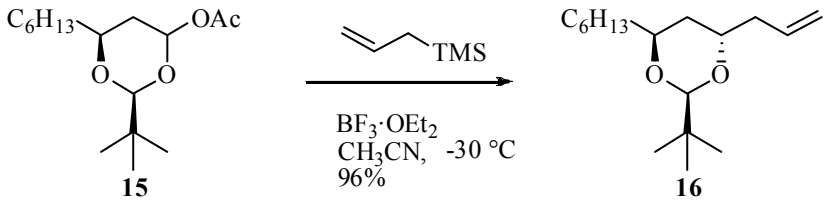
1. Carbon–Carbon Bond-Forming Reactions

Depending on the substrates, reagents, and conditions, *syn*- or *anti*-1,3-diols can be synthesized by carbon–carbon bond-forming reactions.

1.1. Alkylation

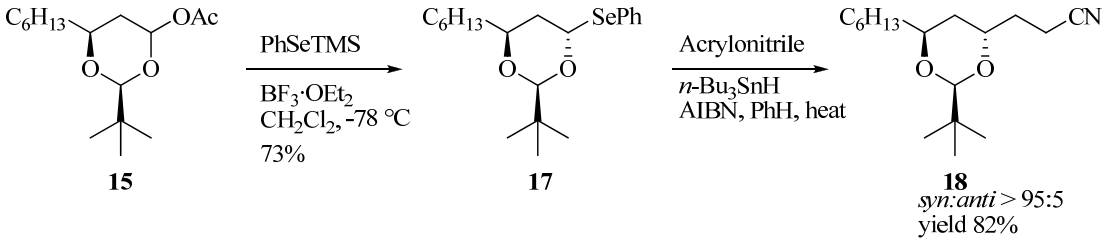
Rychnovsky explored carbon–carbon bond-forming strategies using cationic and radical intermediates. The cationic coupling of 4-acetoxy-1,3-dioxanes like **15** with allyltrimethylsilane and $BF_3 \cdot OEt_2$ resulted in *anti*-1,3- diols like **16** (Scheme 1). On treatment with Lewis acids, oxonium ions were produced that coupled with a variety of carbon- based nucleophiles.[11]

Almost quantitative yield for a 1:1 mixture of diastereoisomers was obtained since epimerization of the acetal center occurred after the coupling event. Reduction of the double bond and removal of the acetal protecting group gave the *anti*-1,3-diol as a single isomer.

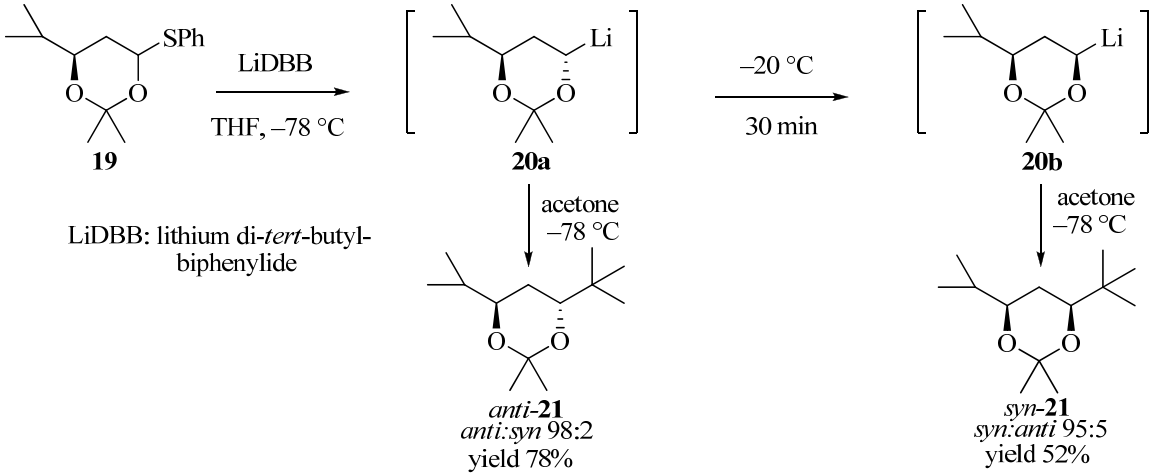


Scheme 1. Cationic carbon–carbon bond-forming reaction[11]

Phenylselenoacetals like **17** were used as intermediates for *anti*-selective carbon–carbon bond formation *via* a radical mechanism to produce **18** (Scheme 2).[12]



Scheme 2. Radical mediated carbon–carbon bond-forming reaction[12]

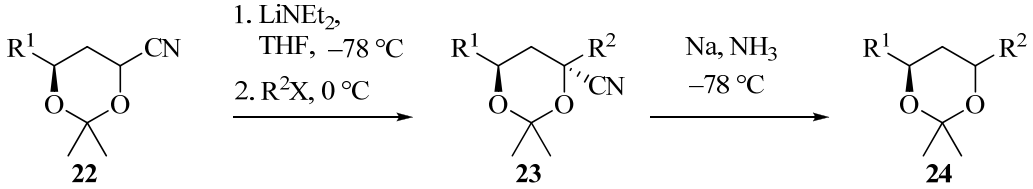


Scheme 3. Phenylthioacetals as precursors for stereochemically defined alkyllithium reagents[13]

Reductive lithiation of thioacetals like **19** resulted in 4-lithio-1,3-dioxanes **20**, representing synthons for *syn*- and *anti*-1,3-diols. The kinetically preferred axial alkyllithium reagent **20a** could be equilibrated to the equatorial one **20b** (Scheme 3).[13]

The quality of equilibration depended on the kind of acetal substrate: equilibration worked very well for unhindered acetals, but was not effective in hindered systems. The axial isomer **20a** underwent selective kinetic alkylation giving *anti*-diol acetonides like *anti*-**21** in 75–83% yield. Only a limited range of electrophiles like aldehydes, ketones, some epoxides, dimethyl sulfate, and carbon dioxide, reacted efficiently, whereas simple alkyl halides reacted poorly and with low stereoselectivity. Copper and zinc additives extended the range of electrophiles that could be alkylated with configurationally defined anions. α-Alkoxycopper and α-alkoxycuprate reagents reacted with a wider range of electrophiles, although configurations were not always retained.[14]

The stereoselective reductive decyanation of the corresponding cyanohydrine acetonides **23** (prepared from **22**) resulted in diastereomerically pure protected *syn*-1,3-diols **24** (Scheme 4).[14]

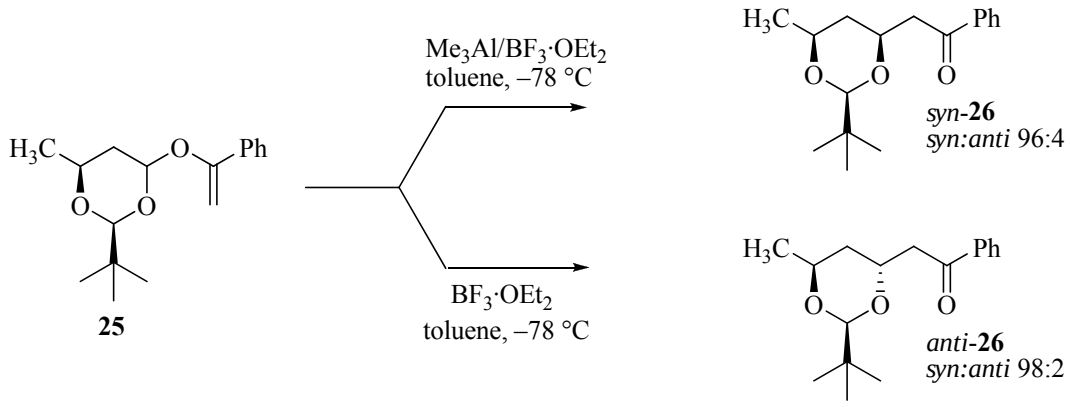


Scheme 4. Cyanohydrine acetonide as precursor for convergent coupling reaction[14]

Based on this approach, Rychnovsky and Griesgraber developed an iterative and convergent synthesis of alternating 1,3-polyol chains.[16] Here, cyanohydrine acetonide **22** was the precursor for both the nucleophilic and electrophilic components of a convergent coupling.

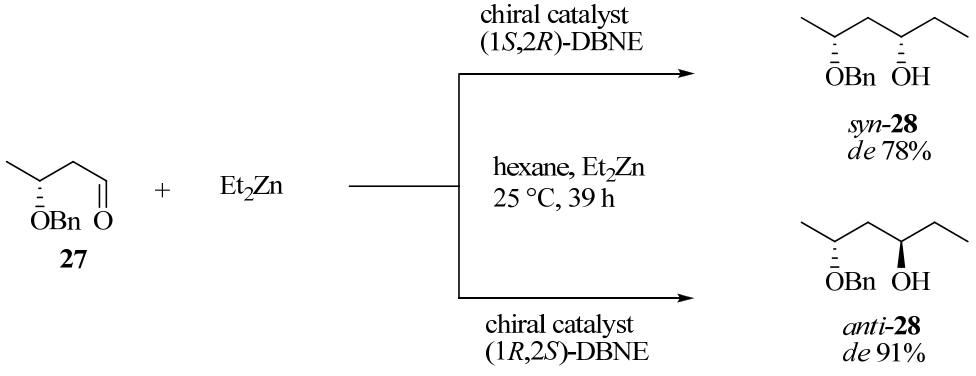
Lewis acid mediated rearrangement of dioxanyl-derived vinyl acetals was developed by Rovis and co-workers for the stereocontrolled synthesis of *syn*- and *anti*-3,5-dihydroxyketone units. Starting from 4-acyloxy-1,3-dioxanes (e.g. **15**), available from β-hydroxyacids in a three-step process, vinyl acetals like **25** were obtained in 53–75% yield (overall yield 20–70%). If $BF_3 \cdot OEt_2$ (1.2 equiv) was applied as Lewis acid in the rearrangement, the *anti*-1,3-diol (*anti*-**26**) was the major

product, while trimethylaluminium/ $BF_3 \cdot OEt_2$ (4.0 equiv/1.2 equiv) provided the *syn*-1,3-diol (*syn*-**26**) (Scheme 5).[15]



Scheme 5. Stereoselective rearrangement of vinyl acetals[15]

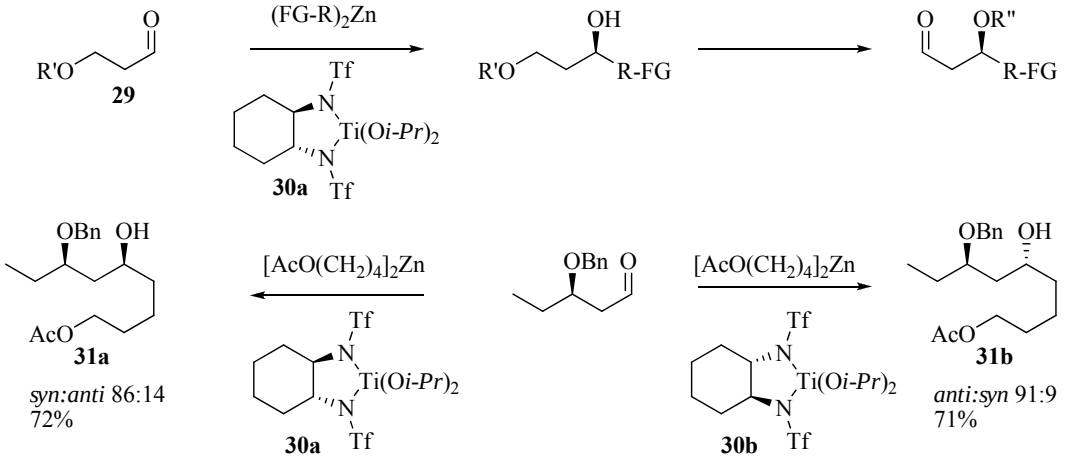
Functionalized organozinc reagents have been used for the stereoselective synthesis of optically active *syn*- and *anti*-1,3-diols *via* catalytic alkylation of a β-alkoxyaldehyde.[16] When (*R*)-3-benzyloxybutanal (**27**) was treated with diethylzinc using (1*S*,2*R*)-(–)-*N*,*N*-dibutylnorephedrine (DBNE) as a chiral catalyst, *syn*-**28** was obtained in 43% yield with 78% diastereoisomeric excess. On the other hand, when (1*R*,2*S*)-(+)-DBNE was used as a catalyst, *anti*-**28** was obtained in 45% yield with 91% *de* (Scheme 6).



Scheme 6. Catalytic alkylation of β-alkoxy aldehyde[16]

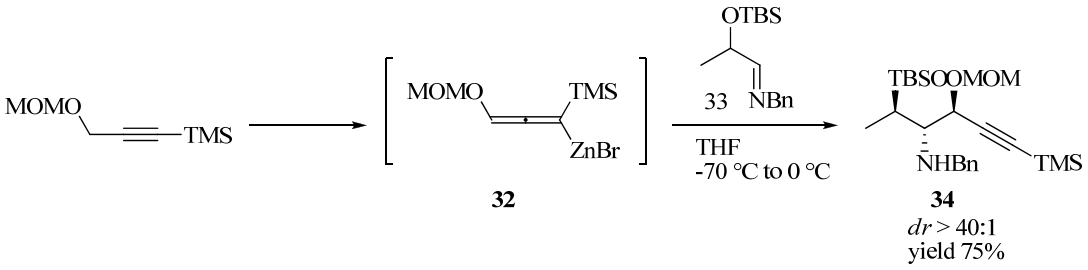
The catalytic stereoselective addition of functionalized dialkylzincs like bis(4-acetoxybutyl)zinc to β-alkoxyaldehydes **29**, developed by Knochel et al., has been

applied to the stereoselective synthesis of both *syn*- and *anti*-1,3-diols **31a** and **31b**. Since both enantiomeric forms of the catalyst **30a/30b** are readily available and the reaction is mainly under catalyst control, this method allows, in principal, the preparation of all four stereoisomeric 1,3-diols; nevertheless, the diastereoselectivity is only moderate (Scheme 7).[17]



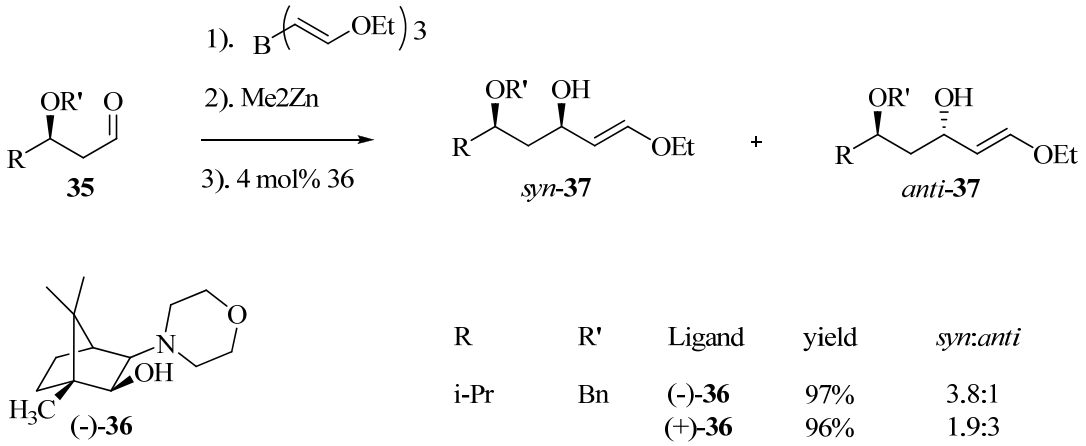
Scheme 7. Catalytic asymmetric addition of functionalized dialkylzincs to β-alkoxyaldehydes[17]

Normant and Poisson showed that the reaction of allenylzinc reagents **32** with benzyl imines **33** possessing a silyloxy group in the α-position proceeded in a highly diastereoselective manner, leading to 2-amino-1,3-diols **34** with a 1,2-*anti*-2,3-*anti* pattern (1,3-*syn*-diol) in 60–80% chemical yield (Scheme 8). However, for the same reaction with an aldehyde instead of an imine, low diastereoselectivity was observed.[18]



Scheme 8. Reaction of allenylzinc reagent with benzyl imine[18]

The diastereoselective alkenylzinc (vinyl ether) derivative addition to chiral β-hydroxyaldehydes **35** was developed by Walsh and co-workers.[19] Depending on the configuration of the amino alcohol ligand **36** used, either the *syn* (41–58% *de*) or *anti* (~ 80% *de*) mono-protected 1,3-diol **37** was obtained as the major product (Scheme 9).



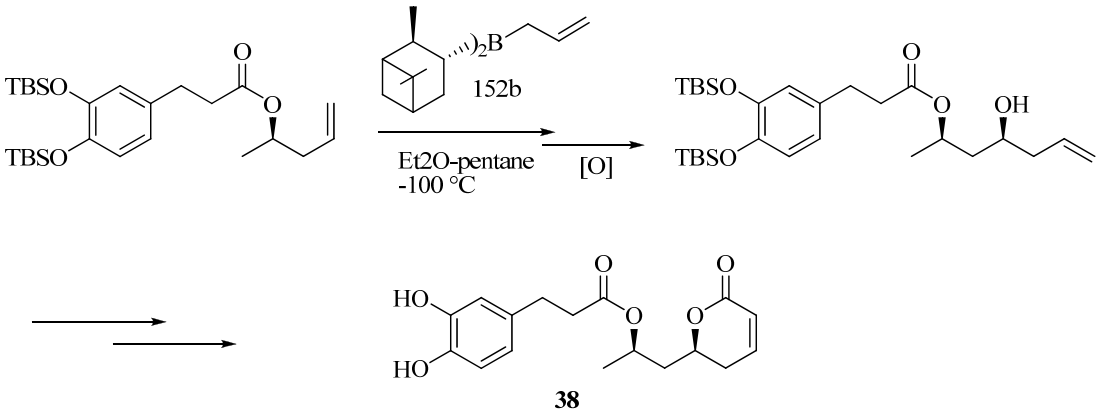
R	R'	Ligand	yield	*syn*:*anti*
i-Pr	Bn	(-)-**36**	97%	3.8:1
		(+)-**36**	96%	1.9:3

Scheme 9. Hydroboration of ethoxy acetylene, transmetallation to zinc, and addition to aldehydes in the presence of a chiral amino alcohol ligand[19]

The resulting β-hydroxy enol ethers could, in principle, be protected and hydrolyzed to prepare 1,3-polyols. The alkenylzinc reagent was prepared by hydroboration of ethoxy acetylene, followed by transmetallation to zinc using diethyl or dimethyl zinc.

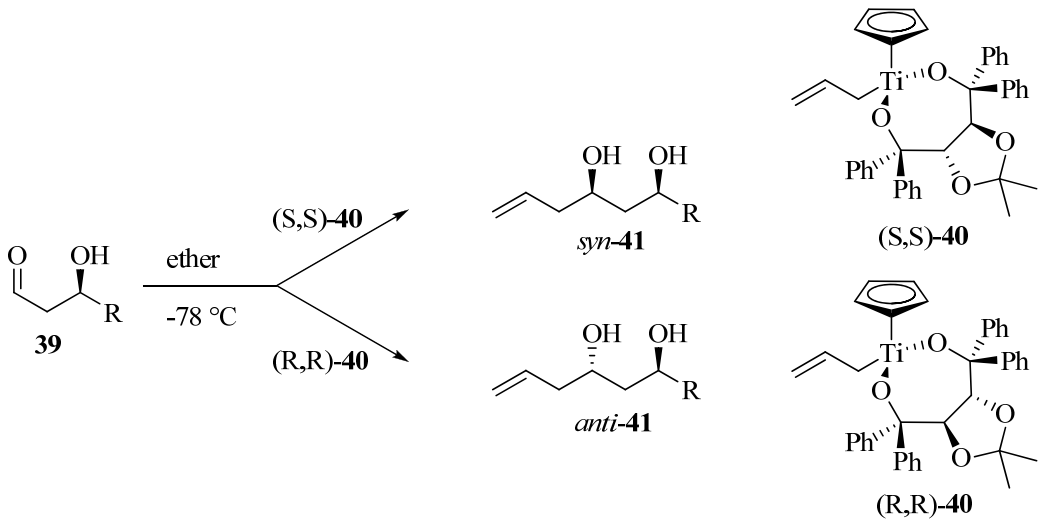
1.2. Allylation

The known allylation of β-alkoxyaldehydes under chelation control is a versatile method for the diastereoselective generation of 1,3-diols.[20a] Advantageously, allylation can be carried out iteratively: ozonolysis of the double bond yields β-alkoxyaldehydes, themselves substrates for allylation. Brown's auxiliary-induced methodology of allylboration[20b] was applied by Ramachandran and coworkers in the asymmetric synthesis of tarchonanthuslactone (**38**) (Scheme 10).[20c]



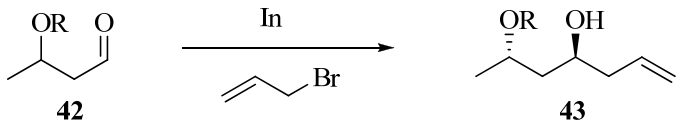
Scheme 10. Asymmetric synthesis of Tarchonanthuslactone using Brown's allylboration methodology[20c]

Unprotected β-hydroxyaldehydes were also transformed into *anti*-1,3-diols *via* allylboration, although with low to moderate diastereoselectivity.[21a] Both *syn*- and *anti*-forms of 1,3-diol **41** can be obtained with diastereomeric excesses of upto 93% in high chemical yield by allyltitanation of non-protected β-hydroxyaldehydes **39** using the Duthaler–Hafner[21b] cyclopentadienyldialkoxyallyltitanium complexes **40** (Scheme 11).[21c] This strategy was also applied to the desymmetrization of a *meso* dialdehyde.



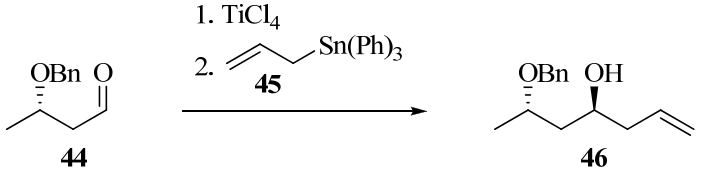
Scheme 11. Allyltitanation of non-protected β-hydroxyaldehyde[21b]

Paquette and Mitzel described a diastereoselective allylation, promoted by indium, that gave predominantly the *anti*-diol **43** (*anti*:*syn* 8.5:1) from aldehyde **42** (Scheme 12).[22a]



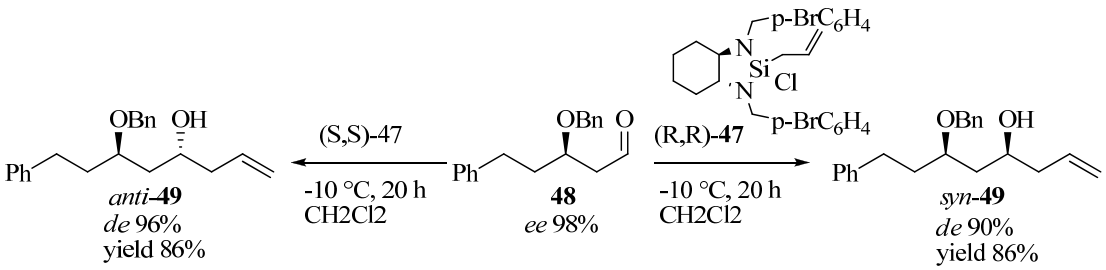
Scheme 12. Indium-promoted allylation of β-hydroxyaldehydes in aqueous media[22a]

Nevertheless, in a subsequent publication, Sugai, Paquette and co-workers mentioned that this method resulted in a 1:1 mixture of diastereomers.[22b] This observation is noteworthy, since several other examples demonstrate that the stereoselective formation of 1,3-diols can be very susceptible even to slight changes in substrate geometry or reaction conditions. Keck and Murry applied the known titanium tetrachloride promoted allylation of allylstannanes like **45** to an appropriately protected chiral aldehyde **44** to give the *anti*-homoallylic alcohol **46** in 75% yield (*anti:syn* 29:1) (Scheme 13).[23]



Scheme 13. Exposure of aldehyde **44** to $TiCl_4$ followed by addition of triphenylstannane **45** yielded *anti*-homoallylic alcohol **46**[23]

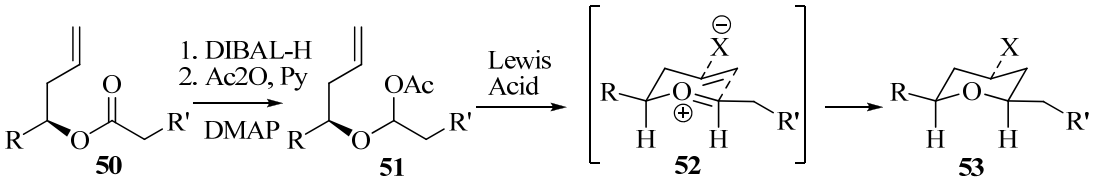
New allylation methodologies and modifications of known procedures applicable to the stereoselective synthesis of 1,3-diols emerge frequently. Leighton and Kubota, for example, developed strained chiral silacycles like **47** as reagents for the enantioselective allylation of aldehydes. Employing this method *syn* and *anti* diastereomers of 1,3-diols **49** were efficiently synthesized from aldehyde **48** (Scheme 14).[24]



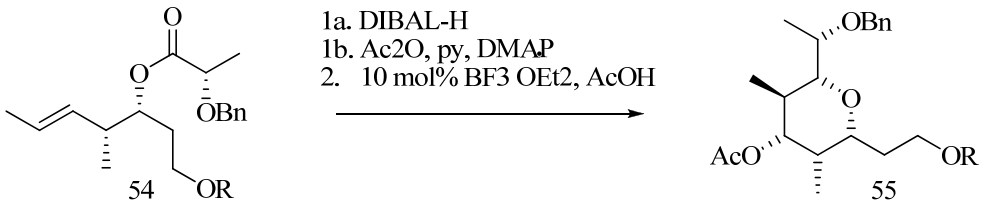
Scheme 14. Asymmetric allylation of chiral aldehydes[24]

1.3. Prins Reaction

The acid-catalyzed Prins cyclization was used to produce a *cis*-2,6-tetrahydropyran ring from an aldehyde and a homoallylic alcohol.[25a] Unfortunately, this condensation was not applicable to common aliphatic and aromatic aldehydes, which, in the presence of Lewis acid, give homoallylic alcohols following an 'ene' reaction pathway. Rychnovsky and co-workers introduced a reductive acetylation of esters **50** to α-acetoxy ethers **51**, providing an entry into the oxocarbonium ion intermediates **52** in Prins cyclizations that resulted in the formation of *cis*-2,6-dialkyltetrahydropyrans **53** with an equatorial acetate (or halide) at the 4-position (Scheme 15).[25b]



Scheme 15. Segment-coupling Prins cyclization[25b]

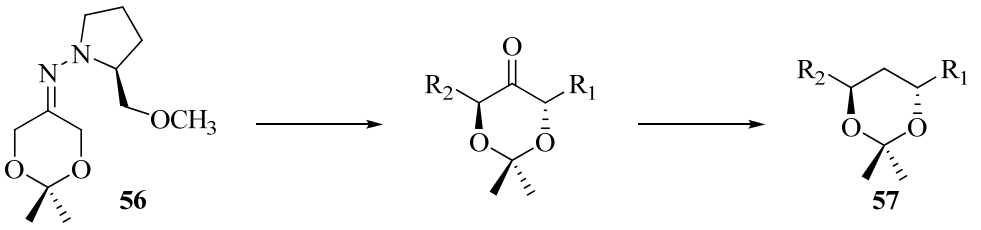


Scheme 16. Application of a Lewis acid catalyzed Prins cyclization[25c]

The Lewis acid ($BF_3 \cdot OEt_2$) catalyzed Prins cyclization has also been applied to, among others, the synthesis of the tetrahydropyran segment of phorboxazole **55** from ester **54** (Scheme 16),[25c] and the desymmetrization of C_2-symmetric 1,3-diols.

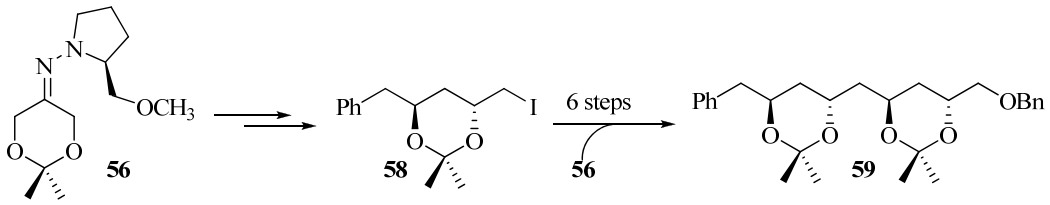
1.4. *anti*-1,3-Diols and Polyols *via* SAMP/RAMP Hydrazones

Enders and co-workers developed an efficient asymmetric synthesis of acetonide-protected *anti*-1,3-diols *via* diastereoselective and enantioselective α,α'-bisalkylation of 2,2-dimethyl-1,3-dioxan-5-one SAMP hydrazone **56** (Scheme 17). Subsequent removal of the auxiliary with oxalic acid, reduction of the carbonyl group ($NaBH_4$) and deoxygenation afforded 1,3-diols **57** with a broad range of substituents in good overall yield and selectivity (31–69% yield, >98% *de*, 92–98% *ee*).[26]



Scheme 17. *anti*-1,3-Diol synthesis employing the SAMP-hydrazone method[26a]

This method was extended for the iterative asymmetric synthesis of *anti*-1,3-polyol chains like **59** *via* **58** (Scheme 18), for the synthesis of trialkylated derivatives, and for the stereoselective synthesis of 2-alkyl-substituted acetonide-protected 1,3-diols.[26]



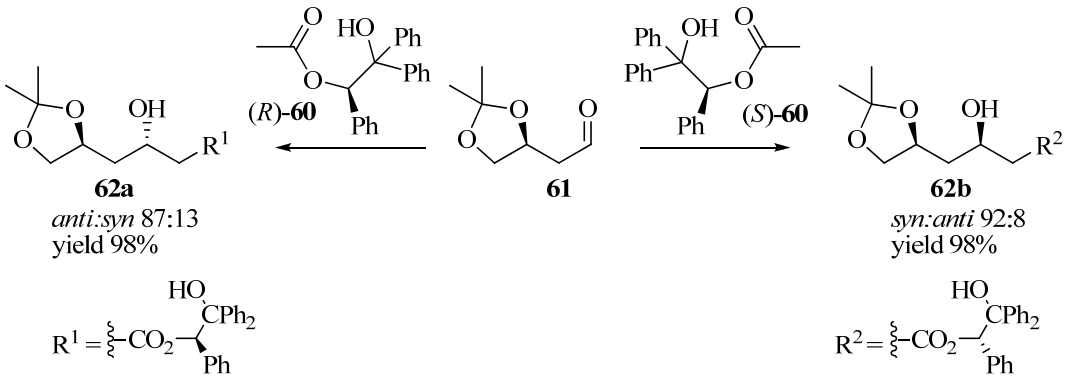
Scheme 18. Iterative asymmetric synthesis of *anti*-1,3-polyol chains[26]

2. Aldol Reaction

2.1. Aldol Reaction with 1,3-Induction

The asymmetric aldol reaction (in an iterative manner) mimics the stereocontrolled chain growth found in the biosynthesis of natural polyketides. For

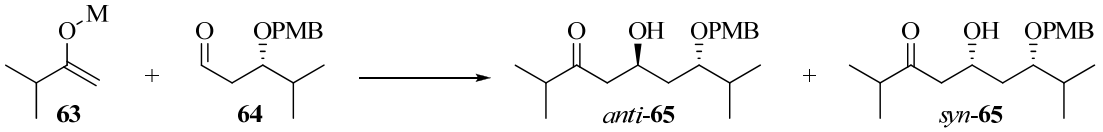
this, a reagent control of the stereoselective chain elongation would be highly desirable. Very often, however, chelation controls, *via* 1,3-induction, the newly formed stereocenter (substrate control).[22] In 1988, Braun and co-workers described a reagent-controlled addition of (*R*)- or (*S*)-2-hydroxy-1,2,2-triphenylethyl acetate (**60**) to chiral α- and β-alkoxy-substituted aldehydes **61** to furnish **62** (Scheme 19).[27] The success of this method depended on a low inherent selectivity of such aldehydes towards lithium and magnesium enolates. The products were obtained in high to almost quantitative chemical yields.



Scheme 19. Reagent-controlled aldol reaction of 2-hydroxy-1,2,2- triphenylethyl acetate with chiral aldehydes[27]

Evans and co-workers systematically investigated the direction and degree of stereoselectivity in aldol addition reactions.[28a] The $BF_3{\cdot}OEt_2$-mediated Mukaiyama aldol reaction of enolate **63** and α-unsubstituted, β-alkoxyaldehydes **64** afforded **65** with good levels of 1,3-*anti*-induction in the absence of internal aldol chelation (Scheme 20). A revised model for 1,3-induction was presented to explain these results, based primarily on minimization of internal electrostatic and steric repulsion between the aldehyde carbonyl moiety and the β-substituents. In accordance with this integrated model, uniformly high levels of Felkin 1,3-*anti*-diastereofacial selectivity were observed in Mukaiyama aldol reactions with *anti* substituted α-methyl-β-alkoxy aldehydes. In contrast, variable levels of aldehyde facial induction were observed in the corresponding reactions with *syn*-substituted aldehyde substrates, which contain stereocontrol elements in a non-reinforcing relationship. Dominant 1,3-stereoinduction arises from a synclinal transition state, preferred for less bulky enolsilane substituents. In accordance with this prediction, the trityl perchlorate

mediated enolsilane addition resulted in a dramatic reversal of facial selectivity relative to the $BF_3{\cdot}OEt_2$-mediated reaction.

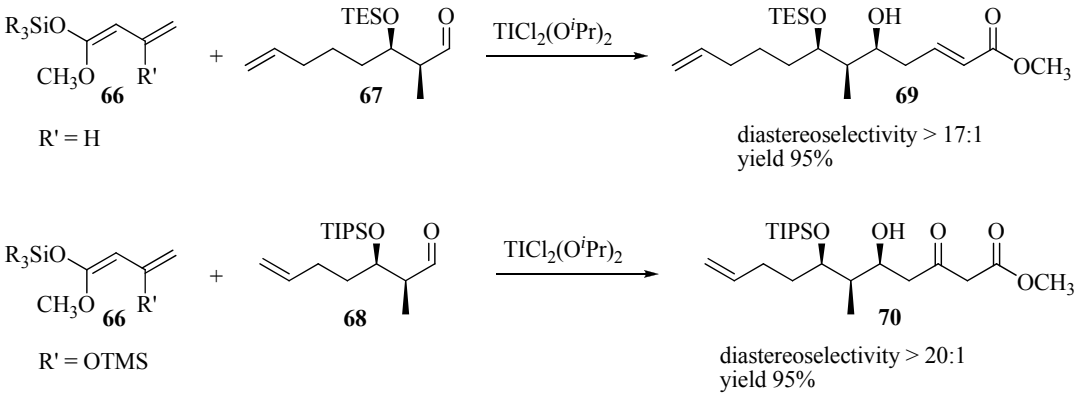


metal (M)	*anti*:*syn*	yield
Li	71:29	100%
$TiCl_n$	60:40	98%
B(9-BBN)	42:58	82%
TMS/$BF_3{\cdot}OEt_2$	92:8	91%

Scheme 20. Mukayaima aldol addition with β-oxy-substituted aldehyde according to Evans[28a,28b]

2.2. Vinylogous Aldol Reaction

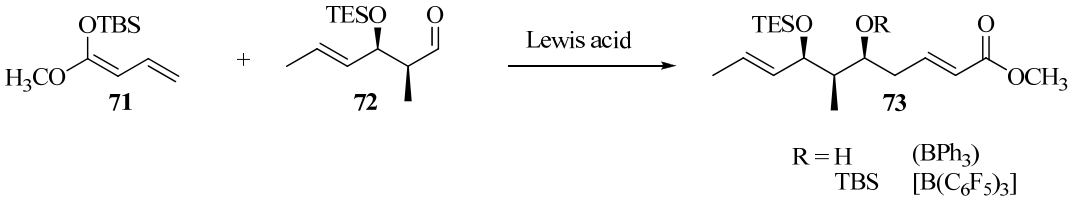
The vinylogous Mukaiyama aldol reaction has only recently been used for stereoselective addition reactions to chiral aldehydes.[29a] In their total synthesis of (+)-lepicidin A, Evans and Black employed the highly diastereoselective vinylogous addition of silylketene acetal **66** to β-silyloxy aldehydes **67** and **68** affording the *syn*-1,3-diol moiety **69** and **70** respectively in 81–95% yield (Scheme 21).[29b]



Scheme 21. $TiCl_2(O^iPr)_2$-promoted reaction of an aldehyde with dienoxy silane **66**[29b]

Kalesse[30] showed that the vinylogous Mukaiyama aldol reaction of aldehyde **72** and silyl ketene acetal **71** provided the aldol adduct **73** in 92% yield as a 3:1

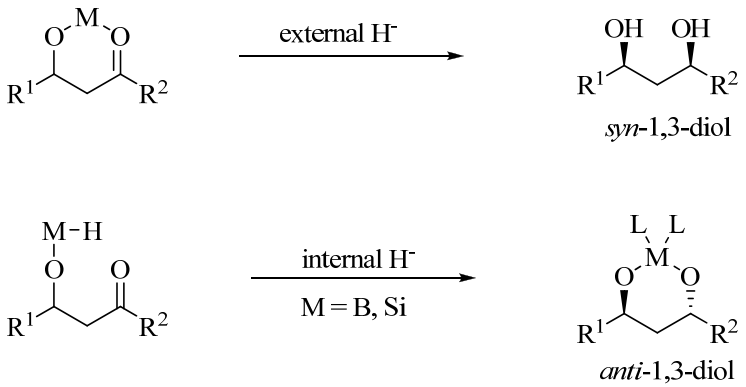
mixture in favor of the desired *syn*-1,3-diol if $BF_3{\cdot}OEt_2$ was used as a Lewis acid. When the reaction was performed with tris(pentafluorophenyl)borane under otherwise the same conditions as before, diastereoselective addition (*de* > 90%) was observed, accompanied by a transfer of the *tert*-butyldimethylsilyl group from the ketene acetal to the newly formed hydroxy group (Scheme 22). The use of the commercially less expensive triphenylborane gave the same selectivity, but without transfer of the *tert*-butyldimethylsilyl group. The use of other Lewis acids in this reaction resulted in either no reaction or decomposition.



Scheme 22. Vinylogous Mukaiyama aldol reaction with different Lewis acids[30]

3. Stereoselective Reduction

3.1. Substrate-Induced Diastereoselective Reduction of β-Hydroxyketones



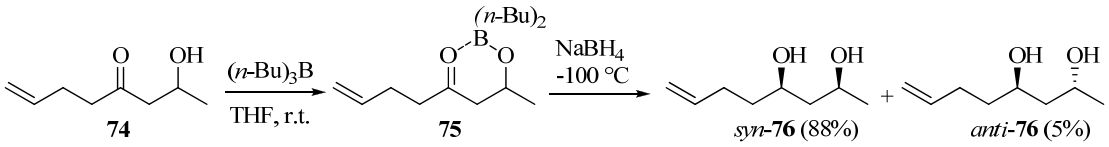
Scheme 23. Chelate-controlled addition of hydride reagents shows a preference for *syn* diastereoselectivity in the reduction of hydroxyketones; intramolecular delivery of hydride directed by the β-hydroxy group leads to *anti* diastereoselective reduction[30]

The stereoselective reduction of acyclic β-hydroxyketones *via* 1,3-induction is attractive, since both *syn*- and *anti*-1,3-diols can easily be synthesized from the same starting material simply by changing the reagents and reaction conditions. When the

reducing agent possesses the capacity to bind to the hydroxyl function with intramolecular transfer of hydride, the *anti*-1,3-diol is formed preferentially (Scheme 23). In contrast, when an additive is employed to preorganize the substrate prior to intermolecular hydride addition, the *syn* isomer becomes the major product. Bartoli et al. recently summarized the diastereoselective Lewis acid mediated reductions of α-alkyl-β-functionalized carbonyl compounds. Based on the Lewis acid ($CeCl_3$ or $TiCl_4$) in combination with the reducing agent used, the stereochemical outcome was controlled.

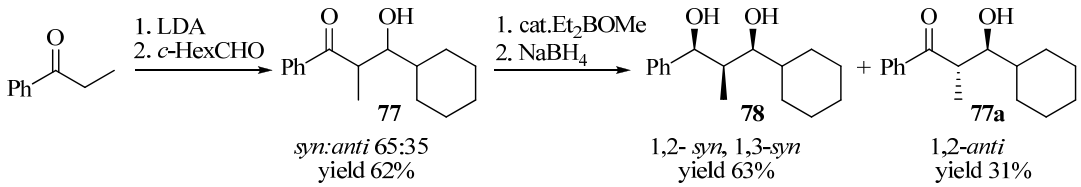
3.1a. Stereoselective Reduction of Hydroxyketones to *syn*-1,3-Diols

The reduction of β-hydroxyketones to *syn*-1,3-diols is usually carried out *via* an intermolecular hydride shift using stoichiometric reducing agents.[31a] The most widely applied method for the *syn*-selective reduction of β-hydroxyketones is based on the boron-chelate method developed by Narasaka and Pai[31b] and Prasad and co-workers.[31c] For example, treatment of **74** with trialkylborane to form the cyclic intermediate **75** and the successive reduction with sodium borohydride, *syn*-1,3-diols like **76** were predominantly obtained (Scheme 24).



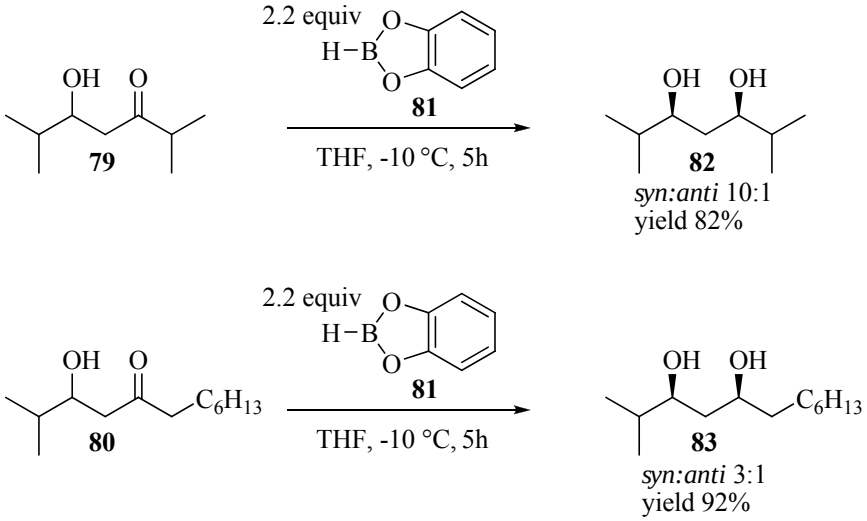
Scheme 24. Reduction of β-hydroxyketones after treatment with tributylborane[31b]

Several improvements of this method have been introduced. Application of preformed alkoxydialkylboranes as complexing agents resulted in the selective formation of the *syn*-1,3-diol (*de* > 96%). Alkoxydialkylboranes can be generated *in situ* by mixing triethylborane with methanol in tetrahydrofuran, and can be used in substoichiometric or even in catalytic amounts, e.g. for kinetic separation of the diastereomeric aldols **77a** and **78** from **77** (Scheme 35).[31d]



Scheme 25. Kinetic separation of diastereomeric aldols by *syn*-selective reduction with 10 mol% Et_2BOMe and $NaBH_4$ (–78 °C in THF–MeOH)[31d]

An operationally convenient method for the *syn*-selective reduction of β-hydroxyketones **79** and **80** using the mild reducing agent catecholborane in excess to provide **82** and **83**, was described by Evans and Hoveyda.[32] There, catecholborane (**81**) served both to provide substrate organization and to function as the hydride donor. However, subtle steric effects were found to have a dramatic effect on the level of stereocontrol (Scheme 26).

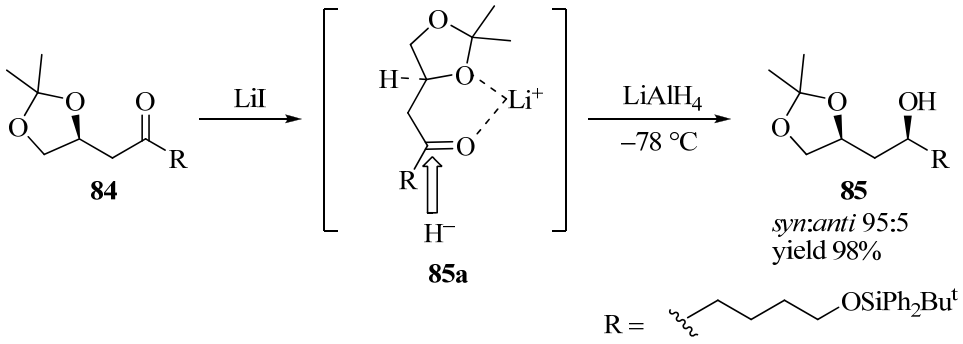


Scheme 26. Reduction of β-hydroxyketones by catecholborane[32]

In certain cases, the levels of diastereoselection could be improved by catalytic amounts of $Rh(PPh_3)_3Cl$. Despite the success of these selective and broadly applicable methods, the use of boron reagents proved to be problematic on an industrial scale due to economic and environmental concerns. This and the requirement for general methods providing *syn*-1,3-diols from β-hydroxy-, β-alkoxy- and β-silyloxyketones resulted in the development of numerous alternative methods. For example, reduction

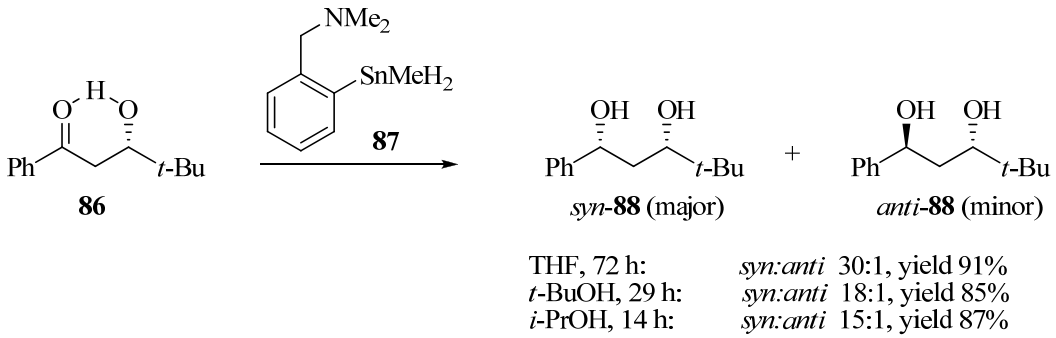
of β-hydroxyketones with diisobutylaluminum hydride also resulted in 1,3-*syn* selectivity.[81] The diastereoselective reduction of acyclic β-alkoxyketones with lithium aluminum hydride or lithium tri-*tert*-butoxyaluminum hydride in the presence of lithium iodide provided *syn*-1,3-diols with moderate to high diastereoselection. [33]

The lithium aluminum hydride reduction of β,γ-dihydroxy ketones **84** in the presence of lithium iodide affords the corresponding *syn*-l,3-diol **85** with high stereoselectivity. The high selectivity using lithium aluminum hydride/ lithium iodide may be attributed to the fact that the upper side of the carbonyl group in **85a** is highly hindered by the *gem*-dimethyl group of the acetonide thus hydride attack takes place from the lower side (Scheme 27).



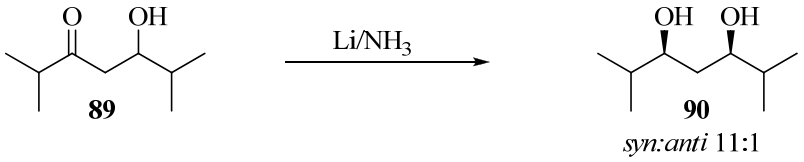
Scheme 27. Synthesis of *syn*-1,3-diol

DiMare and co-workers used a chelation strategy with protected β-hydroxyketones in which a discrete Lewis acid complex was first established with titanium tetrachloride or boron trichloride, followed by introduction of a hydride reducing agent such as borane–dimethyl sulfide complex for the *syn*-selective reduction of several β-hydroxyketones. The reagent {*o*-[(dimethylamino)methyl]phenyl}tin hydride (**87**) did not reduce simple ketones in aprotic solvents, but β-hydroxyketones like **86** were activated internally by the hydroxyl group, and were reduced in tetrahydrofuran to give 1,3-diol **88** with good control of stereochemistry (Scheme 28).[34] A catalytic version (10 mol%), which worked well for simple ketones, could not be applied to β-hydroxyketones. Additionally, the reduction of a 5-hydroxy-3-oxohexanoate gave a diastereomeric excess of only 50% of the desired *syn*-diol.



Scheme 28. Reduction of β-hydroxyketone with tin hydride **87**[34]

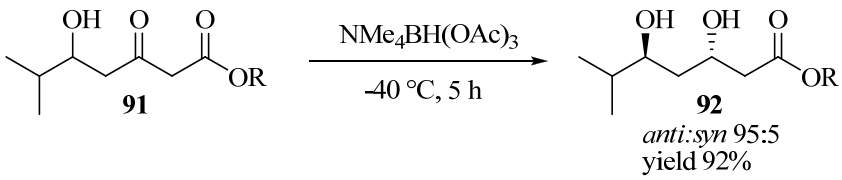
Poss et al. pointed out that dissolving-metal reduction of β-hydroxyketones **89** could produce *syn*-diols **90** (*de* ≥ 83%) (Scheme 29).[35] This method was applied in the synthesis of (+)-mycoticin.



Scheme 29. Diastereoselective dissolving-metal reduction of a β-hydroxyketone[35]

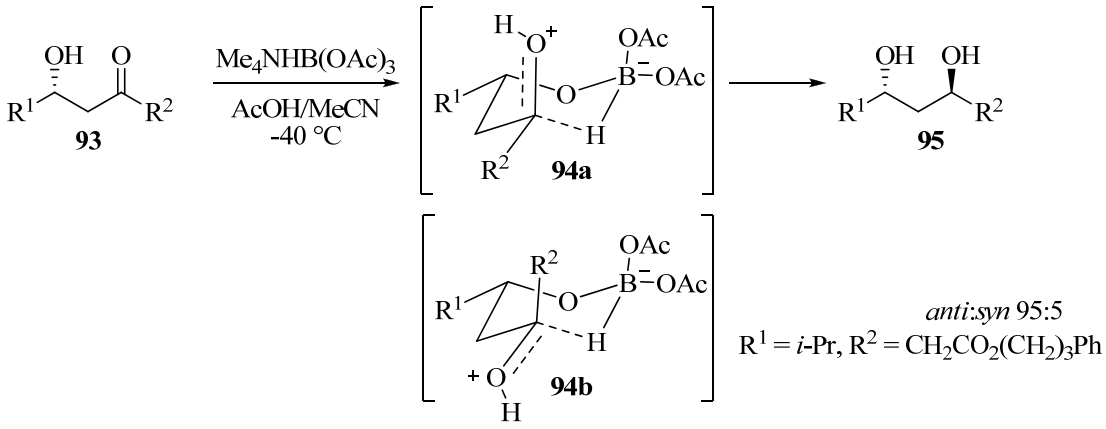
3.1b. Stereoselective Reduction of Hydroxyketones to *anti*-1,3-Diols

Anti-1,3-Diol units are most commonly accessed *via* the reduction of β-hydroxyketones with the mild reducing agent tetramethylammonium triacetoxyborohydride. In all cases examined, good to excellent yields of diastereomerically homogeneous diols were obtained e.g. reduction of **91** to the corresponding *anti*-diol **92** (Scheme 30).[36]



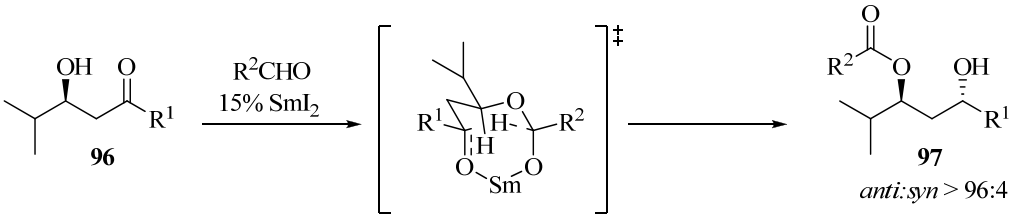
Scheme 30. Diastereoselective β-hydroxyketone reduction with $NMe_4BH(OAc)_3$[36]

The mechanism of these reductions involves an acid-promoted ligand exchange of acetate for substrate alcohol **93** by the triacetoxyborohydride anion. The resultant hydride intermediate **94**, presumably an alkoxydiacetoxyborohydride, reduces proximal ketones by intramolecular hydride delivery to *anti*-diol **95** (Scheme 31).



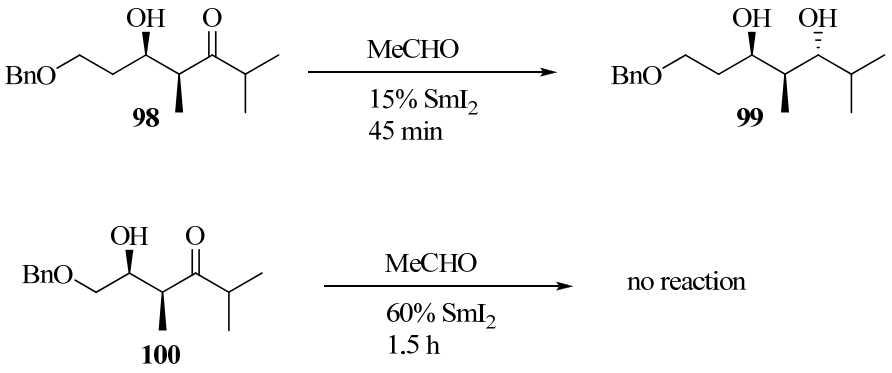
Scheme 31. Diastereoselective β-hydroxyketone reduction with $NMe_4BH(OAc)_3$[36]

The samarium diiodide catalyzed intramolecular Tishchenko reduction of β-hydroxyketones **96** afforded the corresponding *anti*-diol monoesters **97** in high yield and with excellent levels of stereochemical control (Scheme 32).[37] Hydride transfer occurred *via* an intramolecular process in a Meerwein–Ponndorf–Verley sense. Treatment of β-hydroxyketones with 4–8 equivalents of aldehyde and 15 mol% samarium diiodide resulted in the rapid formation of the *anti*-1,3-diol monoesters. A variety of aldehydes, such as acetaldehyde, isobutyraldehyde, and benzaldehyde, were effective hydride donors. In addition, these reactions showed little propensity for subsequent acyl migration (< 5%).



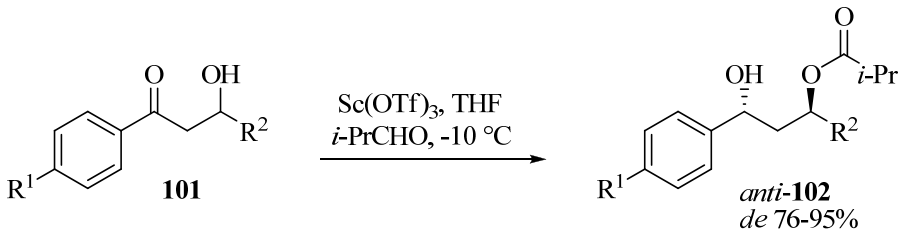
Scheme 32. Intramolecular Tishchenko reduction of β-hydroxyketones with SmI_2[37]

The samarium-catalyzed Tishchenko reduction was found to be sensitive to subtle structural variations (see below). The δ-benzyloxy-β-hydroxyketone **98** was reduced smoothly to the corresponding *anti*-diol **99** within 45 minutes, whereas γ-benzyloxy-β-hydroxyketone **100** was recovered unchanged even when higher amounts of samarium diiodide were employed (Scheme 33).



Scheme 33. Reduction of hydroxyketones with SmI_2

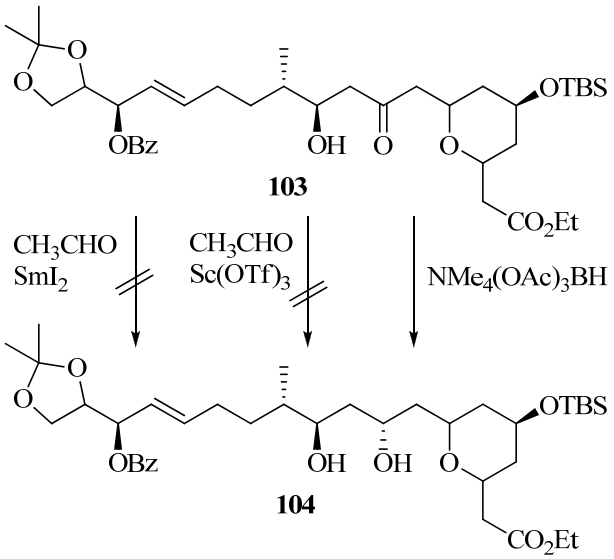
The Tishchenko-type reaction was also achieved in the presence of a catalytic amount of bidentate aluminum alkoxides or Cp_2ZrH_2 to form the corresponding diol monoesters with high levels of stereoselectivity under mild conditions. Scott and co-workers reported the use of a catalytic amount of scandium triflate for stereoselective Tishchenko reduction of β-hydroxyketones **101** to *anti*-diol **102** (Scheme 34).[38]



Scheme 34. Reduction of aromatic hydroxyketones with isobutyraldehyde in the presence of 10 mol% $Sc(OTf)_3$[38]

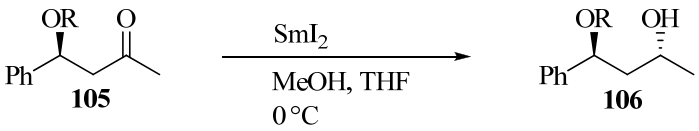
Carreira and Fettes observed that ketone **103** was resistant to reduction using acetaldehyde and samarium diiodide, and scandium triflate did not lead to any

improvement. As an alternative, reduction using tetramethylammonium triacetoxyborohydride afforded the diol **104** in good yield and diastereoselectivity (*anti*:*syn* > 95:5) (Scheme 35).[39]



Scheme 35. Reduction of ketone **103**[39]

Keck et al. described a method for the stereoselective reduction of β-hydroxyketones to afford *anti*-1,3-diols *via* a mechanism involving sequential one-electron reductions using samarium diiodide as the reducing agent.[40a] They noted that the free hydroxyl group was important not only in directing the stereochemical outcome of these reactions, but also in accelerating the rate of reduction relative to either the benzyl or TBS ethers of the same substrates. The results of reduction of β-alkoxyketone **105** to the corresponding *anti*-diol **106** are summerized below (Scheme 36).

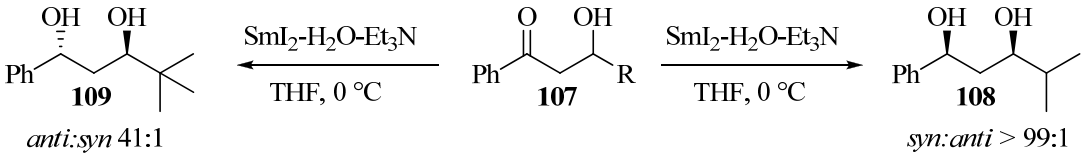


R	time (h)	yield (%)	*anti:syn*
H	1	95	99:1
Me	1	99	99:1
Et	18	30	87:13
Bn	12	no reaction	-

Scheme 36. Reduction of β-alkoxyketones using SmI_2–MeOH[40b]

The same group later demonstrated that some β-alkoxy derivatives, like methyl- or methylthiomethyl ethers, could act as directing and activating groups, resulting in monoprotected *anti*-1,3-diols.[40b] Ten equivalents of methanol in tetrahydrofuran proved to be optimal for activation and stereoselection.

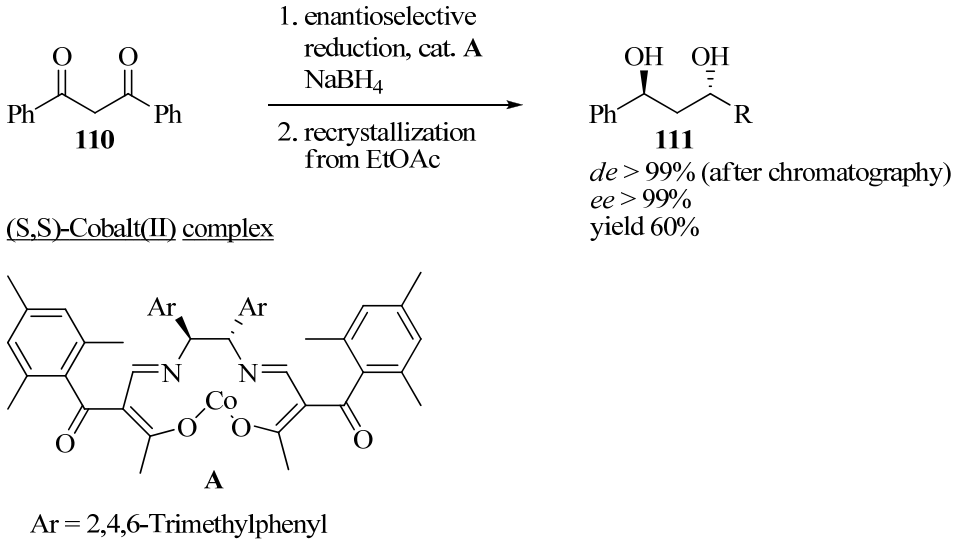
Flowers and co-workers showed that other solvent systems could be applied as well. Reductions in tetrahydrofuran, dimethoxyethane or tetrahydrofuran–water–triethylamine led predominantly to the *syn* diastereomer, while acetonitrile as solvent resulted in formation of the *anti* diol as the major product, however with rather low diastereoselectivity. Reductions in the solvent system tetrahydrofuran–water–triethylamine gave pure diol product in quantitative yield.[40c] It must be mentioned, however, that changes in substrate structure can have a dramatic influence on the stereoselectivity. For example the reduction of hydroxyketone **107** with β-isopropyl sustituent gave *syn*-diol **108** whereas with *tert*-butyl substiuent produced the *anti*-diol **109** (Scheme 37).



Scheme 37. Reduction of β-hydroxyketones by SmI_2 in the solvent system THF–H_2O–Et_3N[40c]

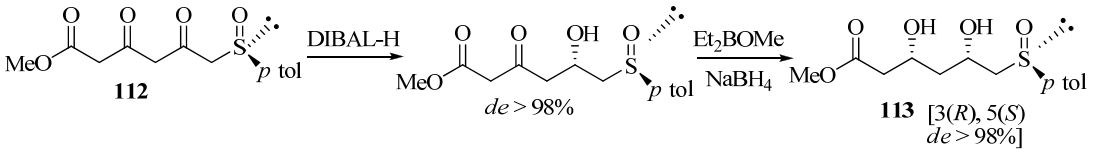
3.2. Stereoselective Reduction of 1,3-Diketones

Besides enzymatic and non-enzymatic catalytic (asymmetric) methods, 1,3-diketones can be reduced stereoselectively by hydride reagents into *syn*- and *anti*-1,3-diols. Ohtsuka et al., for instance, described the enantio- and diastereoselective sodium borohydride reduction of 1,3-diketones such as **110** in the presence of a catalytic amount (5 mol%) of β-ketoiminatocobalt(II) complex **A**.[41] Highly enantioenriched *anti*-1,3-diaryl-1,3-propanediols like **111** were obtained in high yield as the major product with *de* values ranging from 52–80% (Scheme 38).

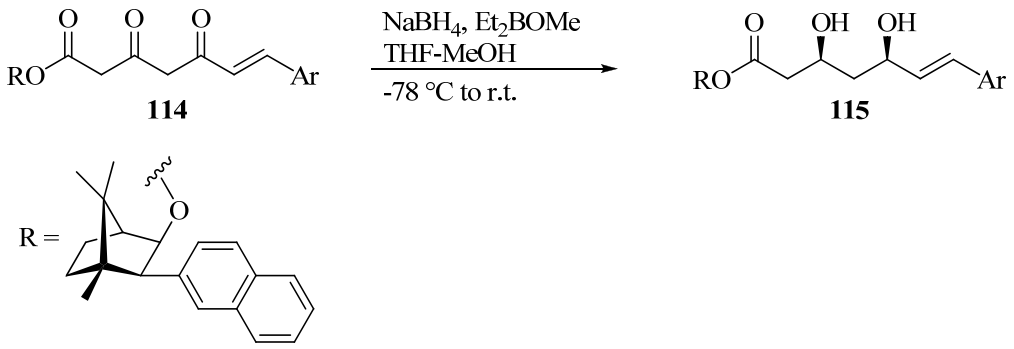


Scheme 38. Enantioselective reduction of dibenzoylmethane with a catalytic amount of cobalt(II) complex **A**[41]

The borohydride reduction of 1,3-diketones usually proceeds through a β-hydroxyketone intermediate. Accordingly, the methods described in the previous section were advantageously applied for the diastereoselective two-step reduction of 1,3-diketones. Several attempts to use auxiliary-induced diastereoselective reductions of 1,3- diketones in combination with the aforementioned substrate-induced diastereoselective reduction of the resulting hydroxyketones have been published. Chiral β,δ-diketoesters like **112**, **114** for example, were reduced either in one or two steps to give *syn*-β,δ-dihydroxyesters **113** and **115** respectively, with high diastereoselectivity (Scheme 39 and Scheme 40). The two-step reduction proved to be atleast as well suited as the attempted one-step reduction of the 1,3-diketone with regard to diastereo- and enantioselectivity.[42]



Scheme 39. Diastereoselective reduction of a chiral sulfoxide with Et_2BOMe and $NaBH_4$[42b]



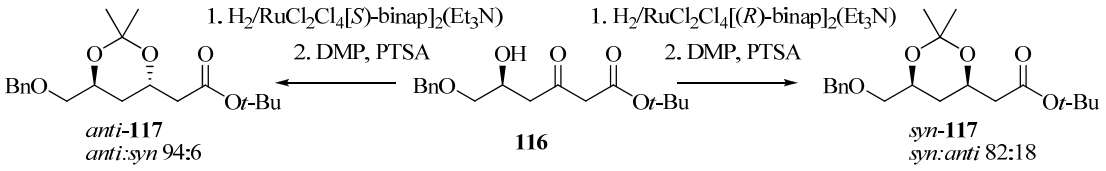
Scheme 40. Chiral β,δ-diketoesters derived from Taber's chiral alcohol[106]

4. Hydrogenation

As mentioned above, it is of great interest to develop efficient catalytic approaches for the *syn*- and *anti*-diastereoselective reduction of chiral β-hydroxyketones under environmentally friendly conditions, thus avoiding stoichiometric amounts of expensive borane reagents and low temperatures like –60 °C. Therefore, early on, catalytic asymmetric hydrogenations and transfer hydrogenations of β-hydroxyketones (and the parent 1,3-diketones) were elucidated.

4.1. Hydrogenation of 1,3-Hydroxyketones to *syn*- and *anti*-1,3-Diols

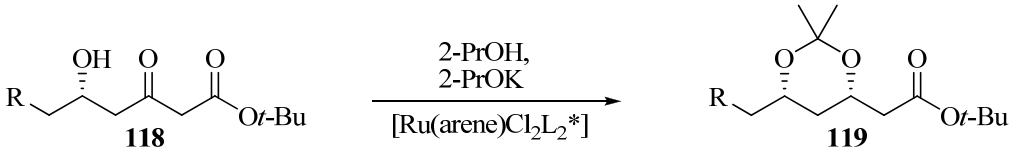
Reduction of 5-hydroxy-3-ketoester **116** with ruthenium catalysts followed by acetalization provided the *syn* and *anti* products **117** with diastereoselectivity of 64% in favor of the *syn* diastereomer (Scheme 41).[43] The reduction of **116** with the catalyst of the opposite configuration produced the *anti* diastereoisomer with 88% *de*.



Scheme 41. Asymmetric hydrogenation of 5-hydroxy-3-oxohexanoate catalyzed by Ru–binap complex[43]

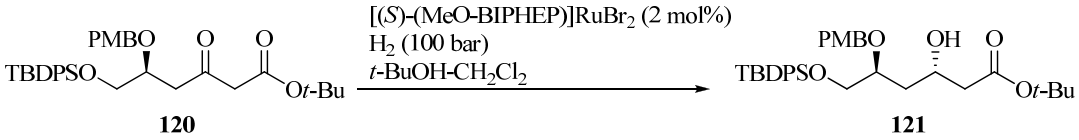
The asymmetric transfer hydrogenation of chiral 5-hydroxy-3-ketoesters **118** in 2-propanol using *in situ* catalyst combinations of chlororuthenium(II) arene and β-

aminoalcohol provided *syn*-3,5-dihydroxyesters **119** in high yields and in diastereoselectivities ranging from 12–80% *de* (Scheme 42).[44]



Scheme 42. Ruthenium-catalyzed asymmetric transfer hydrogenation of 5-hydroxy-3-ketoesters in 2-propanol[44]

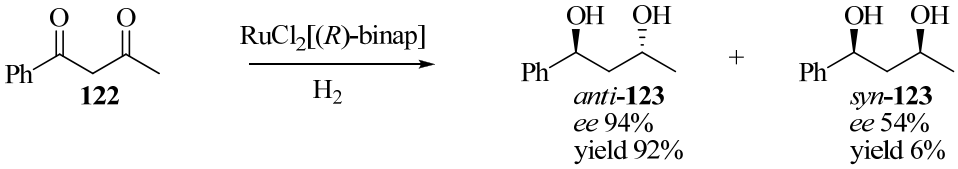
The ligand-controlled asymmetric hydrogenation of protected 5-hydroxy-3-ketoester **120** with (*S*)-(MeO–biphep) $RuBr_2$ as catalyst provided β-hydroxyester **121** in 80% yield and high diastereoselectivity (*anti*:*syn* 98:2). However, both high hydrogen pressure and a long reaction time were required (Scheme 43).[45]



Scheme 43. Ligand-controlled asymmetric reduction of **120**[45]

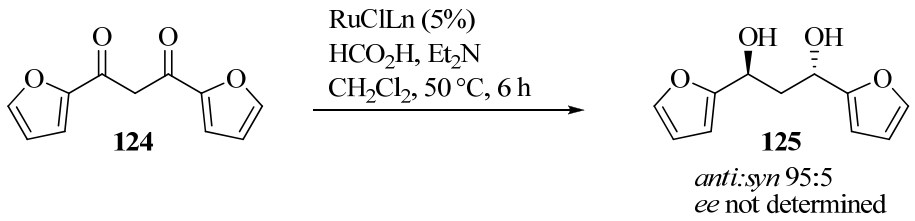
4.2. Hydrogenation of 1,3-Diketones

Hydrogenation of unsymmetrical 1,3-diketone **122** catalyzed by $RuCl_2$[(*R*)-binap] afforded the 1*S*,3*R* diol, *anti*-**123** (92% yield, 94% *ee*), together with a small amount of the 1*S*,3*S* diol, *syn*-**123** (Scheme 44).[46]



Scheme 44. Homogenous asymmetric hydrogenation of ketones with Ru(II)–binap complexes[46]

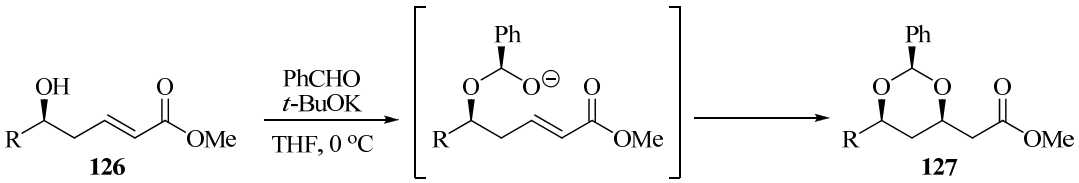
Cossy et al. introduced a transfer hydrogenation of 1,3- diketones by using a catalytic amount of RuCl[(*N*-arylsulfonyl)- 1,2-diamine (*p*-cymene)] complexes in the presence of formic acid and triethylamine (Scheme 45).[47] The reduction of symmetrical 1,3-diaryl-1,3-diketones **124** afforded predominantly *anti*-1,3-diols **125** of reasonably high *de* and *ee* (up to 90%), whereas hydrogenation of unsymmetrically substituted 1,3-diketones resulted in low stereoselectivity.



Scheme 45. Ruthenium-catalyzed asymmetric reduction of 1,3-diketones using transfer hydrogenation[47]

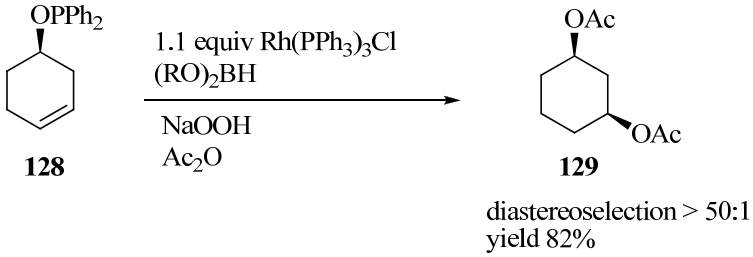
5. 1,3-Diols *via* Addition of Alkoxide Nucleophiles

Reaction of unsaturated hydroxyl esters **126** (or amides) with benzaldehyde and potassium *tert*-butoxide in tetrahydrofuran furnished the benzylidene acetals of *syn*-1,3- diols **127** in good yields (70–80%). For most examples, diastereoselectivity was greater than 95% favoring the more stable *syn*-diol diastereomer (Scheme 46). The use of other bases such as potassium hexamethyldisilazide afforded similar yields and selectivities.[48] When aliphatic aldehydes were employed instead of benzaldehyde, *syn*- and *anti*-1,3-diol acetals were formed in a 1:1 ratio.



Scheme 46. 1,3-*syn*-Diol acetals by base-catalyzed intramolecular addition of a hemiacetal alkoxide[48]

$Rh(PPh_3)_3Cl$-catalyzed hydroboration of the homoallylic phosphinite **128** afforded the *cis*-1,3-diol **129** with high regio- and stereocontrol (Scheme 47), whereas reaction of the corresponding silyl ether resulted in a mixture of 1,3- and 1,4-diols.[49]



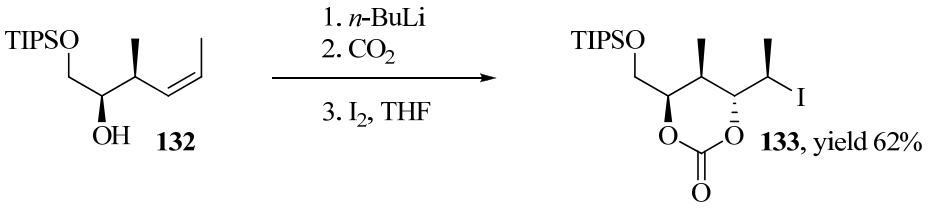
Scheme 47. Metal-catalyzed hydroboration reaction where phosphinite **128** serves as directing group[49]

6. Iodocarbonation

The known iodocarbonation of homoallylic carbonates like **130** was optimized by Smith and Duan using iodobromine in toluene at low temperature (–85 °C), resulting in *syn*-1,3-diols carbonates **131** (60–95% *de*) (Scheme 48).[50a]

Scheme 48. *syn*-1,3-diol by IBr-induced cyclization of homoallylic carbonate[50a]

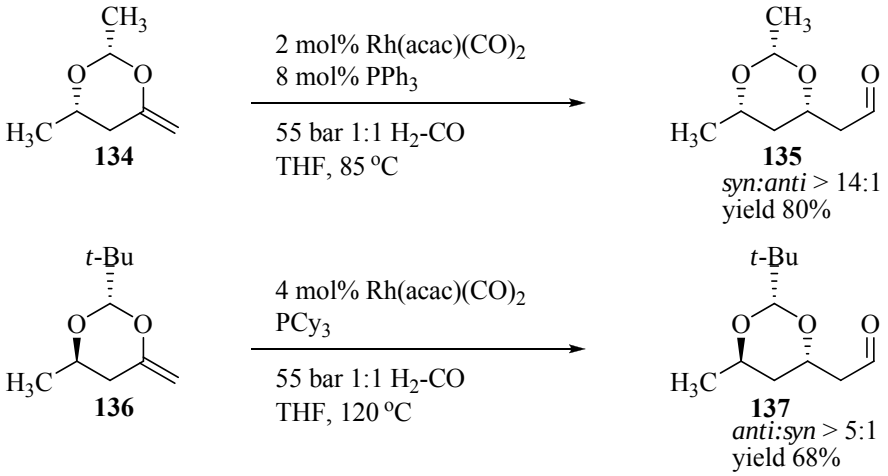
When homoallylic alcohols like **132**, that bore a methyl group at C_3 in 1,2-*syn*-geometry and with a *Z* double bond were used as substrates, a complete 1,3-*anti*-selectivity (>20:1 *anti*:*syn*) was observed providing **133** (Scheme 49).[50b]



Scheme 49. Iodocarbonation of 1,2-*syn*-homoallylic alcohol yields an *anti*-1,3-diol[50b]

7. 1,3-Diols *via* Olefin Carbonylation

Leighton and co-workers reported several elegant approaches to *syn*- and *anti*-1,3-diols, and extended these methodologies for the iterative stereoselective synthesis of polyols. They developed methods to control the regiochemistry of olefin carbonylation.

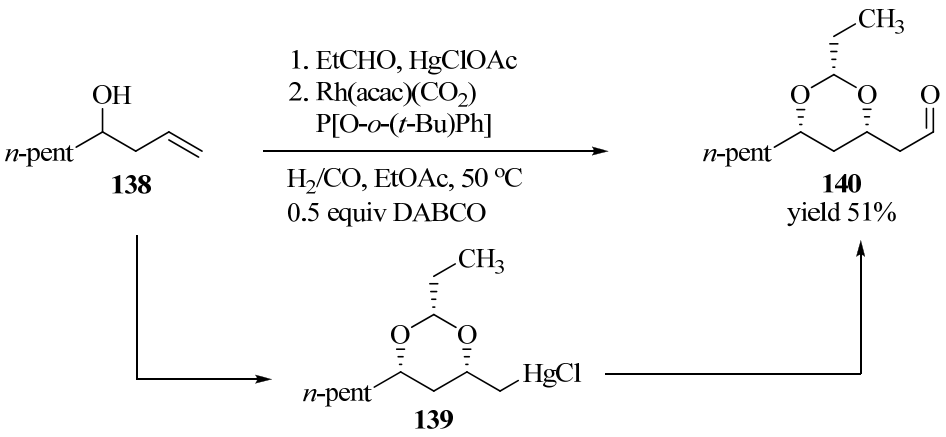


Scheme 50. Rhodium-catalyzed hydroformylation of enol acetals[51]

The highly diastereoselective rhodium-catalyzed hydroformylation of enol acetals like **134**, giving access to protected *syn*-3,5-dihydroxy aldehydes **135** was among these. The corresponding *anti* isomer **137** was obtained as the major product when an appropriately substituted 4-methylene-1,3-dioxane, like **136**, was used (Scheme 50).[51] However, the yields varied upon subtle changes in substrate structure, and diastereoselectivity was low to moderate.

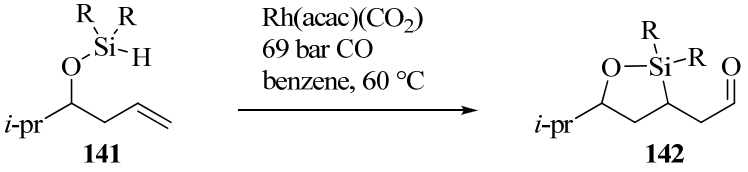
The rhodium-catalyzed hydroformylation was limited by the difficulty in synthesizing large quantities of the enol acetals. As an alternative, the rhodium-catalyzed formylation of organomercurials like **139** was introduced.

Oxymercuration of homoallylic alcohol derived hemiacetals and hemiketals was used for the diastereoselective synthesis of organomercurials containing the protected *syn*-1,3-diol moiety. In a two-step transformation, without purification of the organomercurial **139**, aldehyde **140** was obtained from homoallylic alcohol **138** in 51% yield (Scheme 51).[51]



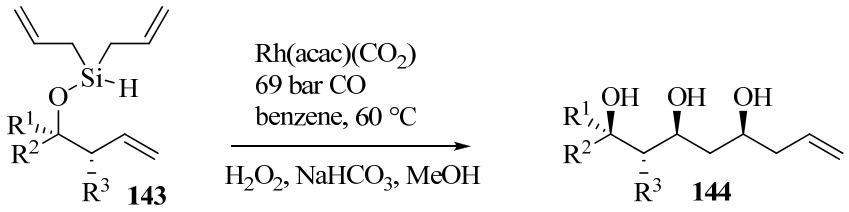
Scheme 51. Oxymercuration of a homoallylic alcohol followed by rhodium-catalyzed formylation[51]

This strategy was also used in an iterative manner: Brown allylation afforded a homoallylic alcohol, which was used again in the oxymercuration reaction.
Rhodium-catalyzed intramolecular silylformylation of alkenes provides an alternative entry into polyol synthesis using silyl protected homoallylic alcohols **141** as substrates (Scheme 52).[52] The use of 1-oxa-2-silacyclopentanes **142** as an intermediate in 1,3-diol synthesis is described below.

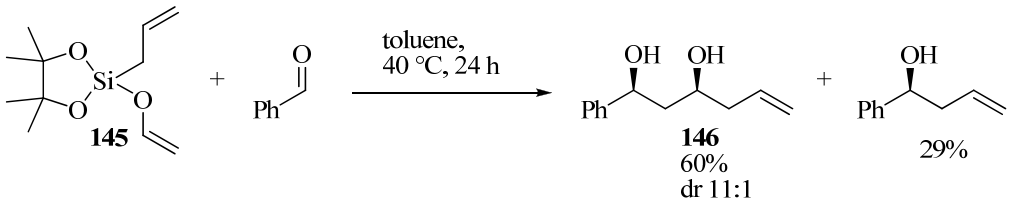


Scheme 52. Rhodium-catalyzed intramolecular regioselective silylformylation of alkenes[52]

When the silylformylation was performed with a diallylsilane like **143**, a tandem intramolecular silylformylation–allylsilylation took place, leading–after oxidative desilylation – to *syn*,*syn*-triols **144** in good yield (45–65%, with 42–86% *de*).[53]



Scheme 53. Rh(I)-catalyzed tandem silylformylation–allylsilylation[53]



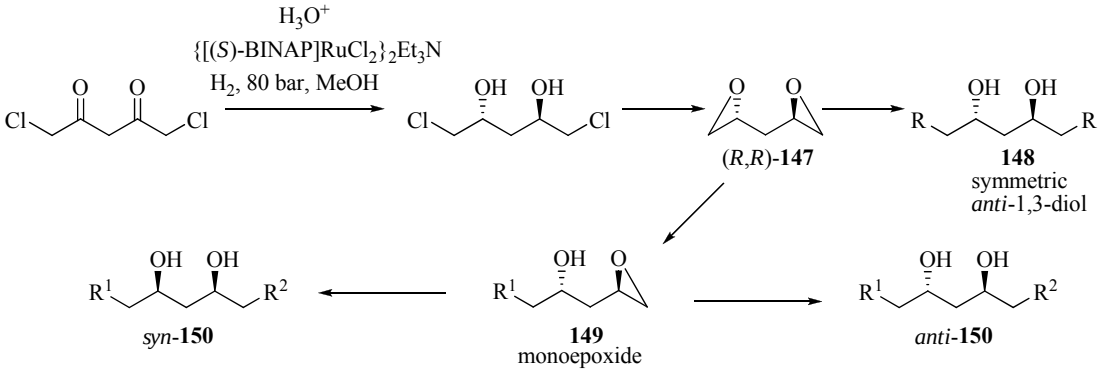
Scheme 54. Tandem aldol-allylation reaction of allylenolsilanes[54]

Both tandem reactions (Scheme 52 and 53) nicely demonstrate how homoallylic alcohols can be converted into new two-polyol-unit-extended homoallylic alcohols in three simple steps. Moreover, Leighton and co-workers introduced a tandem aldol–allylation reaction of allylenolsilane **145** and simple aldehydes resulting in *syn*-1,3-diols like **146** in 60–80% yield (Scheme 54).[54]

8. Desymmetrization

8.1. Desymmetrization *via* Chain Elongation

The idea of two-directional chain synthesis and terminus differentiation has been extensively studied by Schreiber and others.[55a] Different transformations have been applied using this strategy for the stereoselective synthesis of polyol chains possessing 1,3-diol functionalities. Based on the work of the Schreiber group, and using Noyori's asymmetric hydrogenation of 1,3-diketones, Rychnovsky et al. developed a three-step synthesis towards enantiopure diepoxide **147** (ee > 97%).[55b] This diepoxide can be regarded as an efficient precursor to a broad variety of enantiopure *syn*- and *anti*-1,3-diols (Scheme 55).[182] Reaction with excess nucleophile gave symmetric *anti*-1,3-diols **148** in good yield (61–94%), and only *tert*-butyllithium gave significantly lower yields (18%).

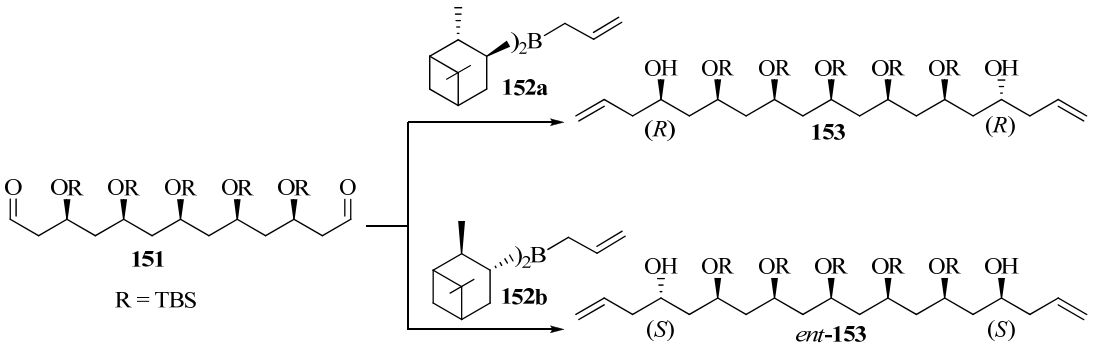


Scheme 55. Diepoxide **147** as precursor to a variety of enantiopure *syn*- and *anti*-1,3-diols[55b]

Thus, this method represents a valuable alternative to the asymmetric reduction of the corresponding 1,3-diketone. Reaction of diepoxide **147** with only a slight excess of alkyllithium gave the monoepoxide **149**, which in turn was used for the synthesis of the unsymmetrically substituted *anti*-1,3-diols, *anti*-**150**, in 50–68% overall yield. Chiral *syn*-1,3-diols, *syn*-**150**, were accessible *via* Mitsunobu inversion of monoepoxide **149**, followed by addition of a second nucleophile (overall yield 37%, one example given, R^1 = Bn, R^2 = vinyl).[55c]

8.2. Desymmetrization *via* Allylboration

Enantioselective desymmetrization of *meso* compounds into chiral products often relies on enzymatic and nonenzymatic diastereofacial-selective reactions controlled by both substrate and reagent.

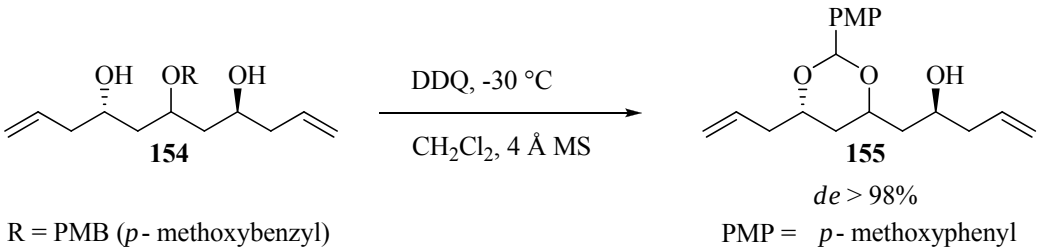


Scheme 56. Reaction with the Brown reagents, (+)- or (–)-diisopinocamphenyl allyl borane **152**, converts the σ-symmetric reactant into either antipode of the elongated product[56]

Wang and Deschênes developed a desymmetrization of *meso*-dialdehydes **151** *via* exclusively reagent-controlled diastereofacial-selective allylation at both termini to procure **153** using the Brown reagent **152** (Scheme 56).[56]

8.3. Miscellaneous

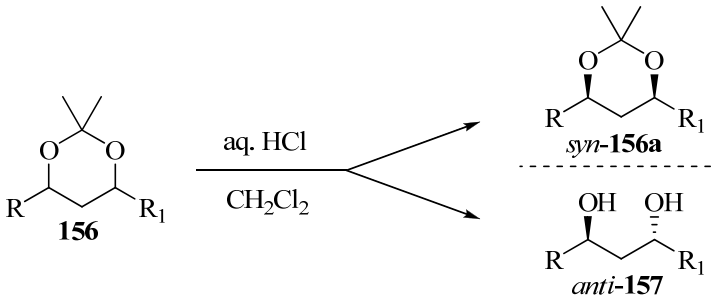
The known diastereoselective acetalization of *syn*-1,3-diols in the presence of an *anti*-1,3-diol could also be accomplished by way of an oxidative acetalization of *p*-methoxybenzyl ethers of pseudo-*C*2-symmetric 1,3,5-triols like **154** to obtain the *syn*-acetal **155** (Scheme 57).[57]



Scheme 57. Oxidative diastereoselective acetalization of pseudo- C2-symmetric 1,3,5-triols[57]

8.4. Diastereo-Differentiating Hydrolysis of 1,3-Diol Acetonides

The separation of 1,3-diol diastereomers can be a difficult task, especially for non-crystallizing 1,3-diols, and when the separation has to be conducted on a large scale, which prohibits difficult chromatographic separation.



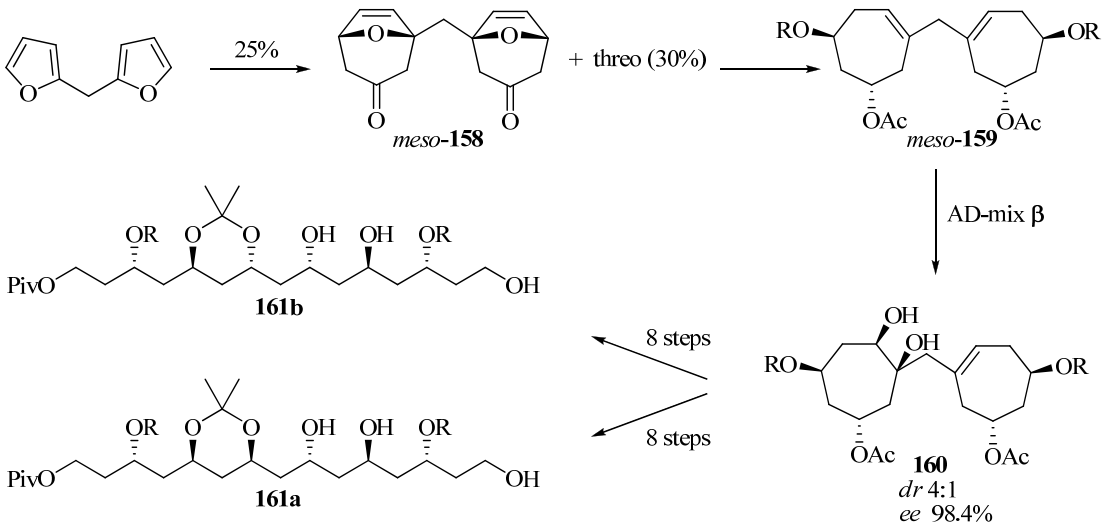
Scheme 58. Diastereomer-differentiating hydrolysis of 1,3-diol acetonides[58]

On deprotecting a *syn/anti* mixture of acetonide **156** with a catalytic amount of dilute aqueous hydrochloric acid in dichloromethane, the *anti* diastereomer hydrolyzed much more rapidly than the *syn* diastereomer. This led to the selective cleavage of the *anti* diastereomer (Scheme 58). Because of the great differences in polarity, the resulting *anti*-1,3-diol, *anti*-**157**, was easily separated from the unchanged *syn*-1,3-diol-acetonide, *syn*-**156**, by filtration through a short silica gel column.[58]

This general and simple method of efficiently separating diastereomeric 1,3-diols represents a new approach to *syn*- and *anti*-1,3-diols under mild reaction conditions.

8.5. Desymmetrization of 8-Oxabicyclo[3.2.1]oct-6-en-3-one and Derivatives

Vögel and co-workers developed non-iterative approaches for the asymmetric synthesis of octahydroxypentadecanols.[59a] The dimeric *meso* derivative **159**, accessible *via* a five-step synthesis starting from the oxabicyclic dimer *meso*-**158**, was desymmetrized using Sharpless asymmetric dihydroxylation to afford **160** (Scheme 59). Subsequent ring-opening of the carbacycles, diastereoselective reductions, and further transformations yielded stereomeric pentadeca-1,3,5,7,9,11,13,15-octol derivatives like **161a** and **161b**.[59b]

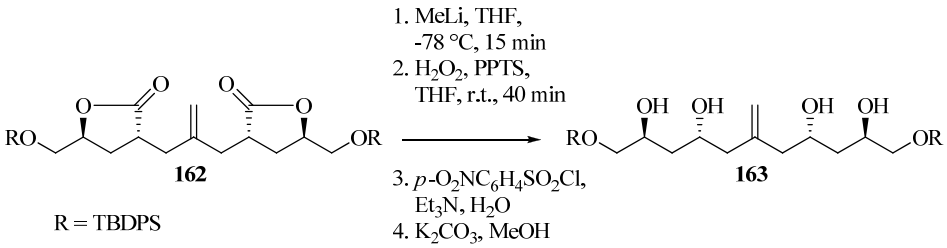


Scheme 59. Non-iterative asymmetric synthesis of long-chain 1,3- polyols[59b]

Although the strategy was somewhat lengthy, its superiority is obvious in the case where all or many of the possible stereoisomers are synthetic targets.

9. Butyrolactone Strategy

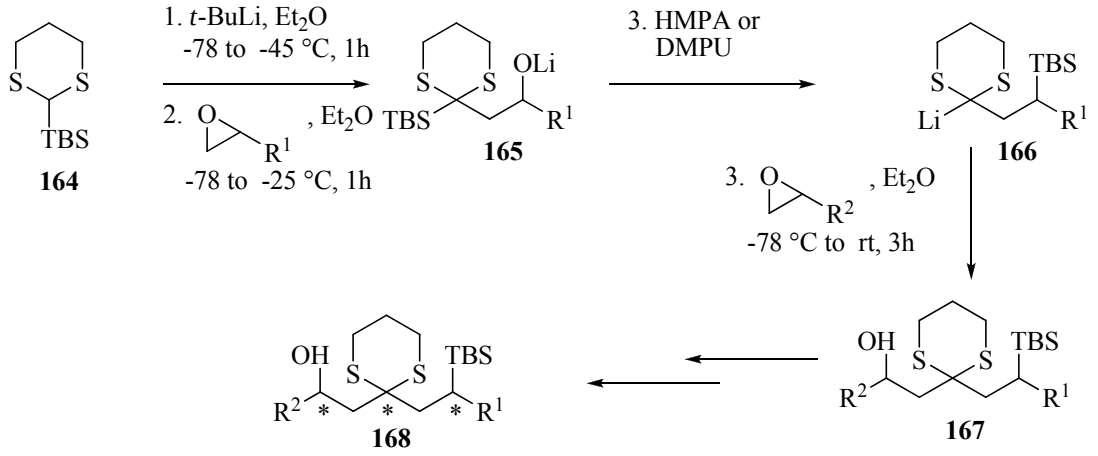
Brückner and Menges developed a method for the conversion of *cis*(*trans*)-butyrolactones into *syn*(*anti*)-1,3-diols,[60a] based on work by Ziegler and Schreiber. Using a four-step oxidative degradation *via* a Criegee rearrangement, which occurs with retention of configuration, 1,3-diols were accessed in good yield. In contrast to Ziegler, who used peroxoacetates, Brückner transformed the ketal hydroperoxide intermediates into peroxosulfonates. The stereostructure of the starting lactone was completely transferred to the diol. Hence, the bis(γ-butyrolactone) **162** was transformed into tetrol **163** in 74% chemical yield, corresponding to an average yield of 97% for each individual reaction (Scheme 60).[60b]



Scheme 60. Oxidative degradation of bis(γ-butyrolactone) **162** to tetrol **163**[60b]

10. Linchpin approach for polyol syntheses

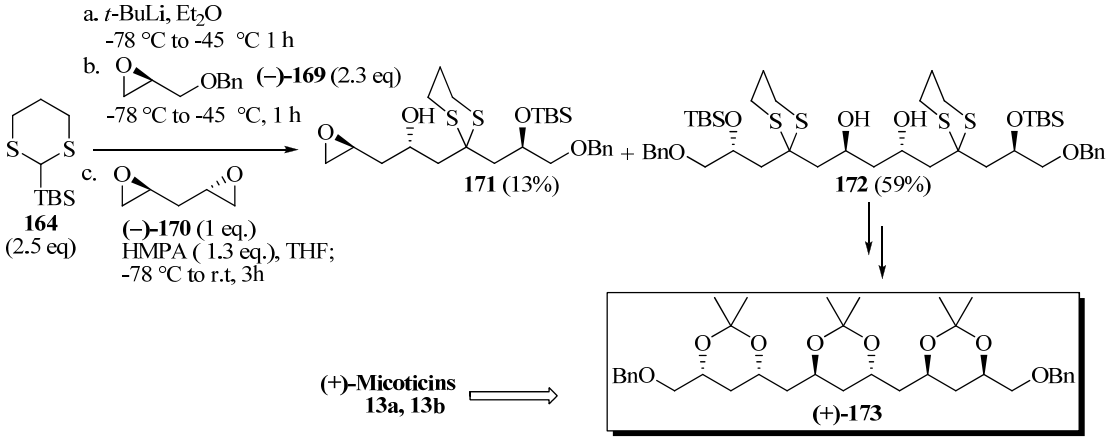
Smith et al. described a one-flask, multicomponent linchpin coupling of silyl dithianes with epoxides, exploiting a solvent-controlled Brook rearrangement (Scheme 61).[61a] The protocol involves lithiation of 2-*tert*-(butyldimethylsilyl)-1,3-dithiane (**164**), followed in turn by addition of an epoxide to generate alkoxy dithiane **165**, Brook rearrangement triggered by HMPA or DMPU to afford anion **166**, and alkylation with a second epoxide to provide the unsymmetrical adduct **167**.



Scheme 61. Multi component linchpin strategy[61a]

Ether rather than THF is required as solvent for the *initial* alkylation to suppress premature silyl migration leading to the formation of symmetric adducts. Altering the absolute configuration of the epoxides followed by removal of the dithiane and stereocontrolled reduction of the derived ketone provides access to all possible diastereomers of the 1,3-polyol fragment (**168**).

From the synthetic perspective, this tactic efficiently furnishes the polyol chain with both full stereochemical control and differentiation between hydroxyl groups. This strategy was exploited to good advantage in syntheses of the spiroketal segments of the spongistatin antitumor agents and in total syntheses of various polyketide natural products. For example synthesis of (+)-**173**, the Schreiber C(16-28) subtarget for mycoticins A and B, has been achieved by exploiting a one-flask, five component, linchpin coupling tactic between TBS-dithiane **164** and epoxides **169** and **170**. This tactic resulted in **172** as the major product along with **171**. The subsequent dithiane deprotection of **172** followed by diastereoselective reduction and some refunctionalizations completed the synthesis of (+)-**173**. Importantly, fragment (+)-**173** also holds promise as an effective building block for the synthesis of roxaticin (**14**) and the dermostatins (**11**) (Scheme 62).[61b]



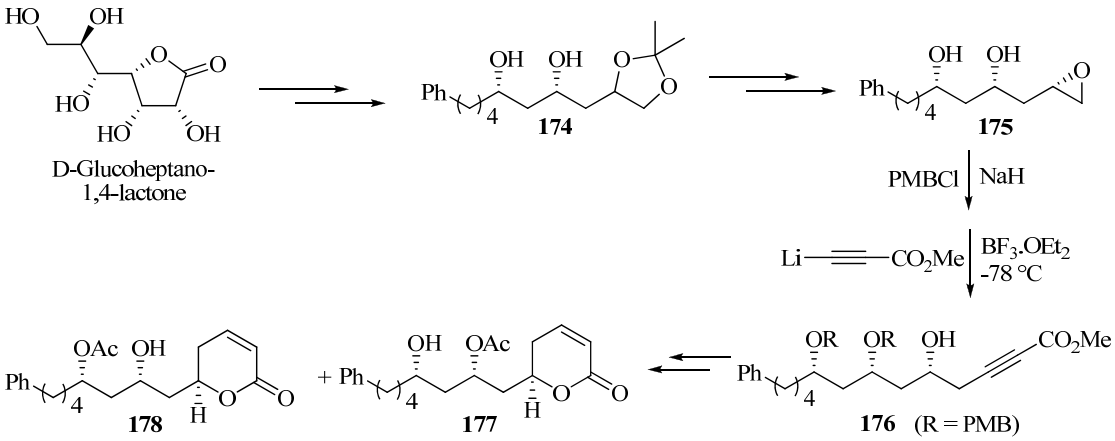
Scheme 62. A linchpin approach in polyene macrolide synthesis[61b]

11. Chiron approach[62]

For practical and aesthetic reasons, it is now common practice to plan syntheses in such a way so as to produce an enantiomerically pure (or enriched) target molecule. This has become a virtual necessity in pharmaceutical research laboratories since stereochemistry is the common denominator between chemistry and biology.

In the chiron approach, it is the type of chiral substructure present in the molecule that will dictate the strategy in as much as it can be related to an appropriately functionalized intermediate (chiron). Various types of chiral precursors have been used for the stereoselective synthesis of chiral 1,3-polyol natural products: (a) carbohydrates, mainly monosaccharides, (b) chiral hydroxy acids, (c) chiral epoxides, and (d) other chirons, including those prepared with the aid of microorganisms or enzymes. By relating a target structure to chiral starting materials at the outset, the scenario for a synthesis plan is established. The main issue now deals with proceeding in the forward direction using the inherent or newly-created chirality and building from there. Two of such approaches are discussed below.

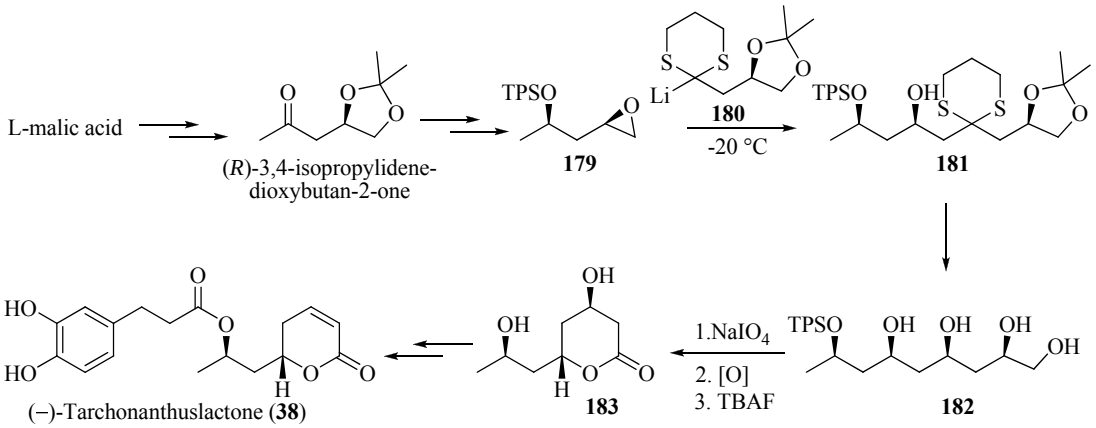
The inexpensive, commercially available, D-glucoheptono-1,4-lactone, served as the chiral starting material for the synthesis of the two antifungal pyrones **177** and **178** isolated from *Ravensara anisata*, a plant species found in Madagascar (Scheme 63).



Scheme 63. Synthesis of the antifungal pyrones **177**/**178** from D-glucoheptono-1,4-lactone[63]

A sequence of straightforward functional transformations, including an alcohol inversion involving the Mitsunobu reaction, converted the sugar precursor into acetonide **174** and then into epoxide **175**, retaining three out of the five stereogenic carbons of the starting chiron, albeit with an inverted configuration in one of them. Hydroxyl protection and epoxide ring opening with methyl 3-lithiopropiolate furnished the conjugated α,β-ynoate **176**, which was subsequently converted into the corresponding pyrone by means of Lindlar semihydrogenation of the C≡C bond and lactone ring closure. Cleavage of the protecting groups and partial acetylation unselectively provided a mixture of the natural lactones **177** and **178**.[63]

Tarchonanthuslactone has been obtained by Mori et al. from (*R*)-3,4-isopropylidenedioxybutan-2-one, which was, in turn, prepared from L-malic acid. Chelation-controlled reduction of the ketone, protection of the hydroxyl group, and standard functional manipulation afforded the epoxide **179**, which was then subjected to nucleophilic opening with the lithiated dithiane **180** prepared from the same chiral source. This gave compound **181**, which was then straightforwardly converted into the monoprotected pentaol **182**. Vicinal diol periodate cleavage, oxidation of the resulting lactol to lactone, and desilylation furnished dihydroxy lactone **183** which was later converted to the desired lactone **38** over few steps (Scheme 64).[64]



Scheme 64. Synthesis of (–)-tarchonanthus lactone from L-malic acid[64]

Introduction to δ-Lactones[65]

Lactone rings are a structural feature of many natural products.[66] Of the naturally occurring lactones, which all display a wide range of pharmacological activities, those bearing a 5,6-dihydropyran-2-one moiety are relatively common in various types of natural sources.[67] Because of their manifold biological properties, these compounds are of marked interest not only from a chemical, but also from a pharmacological perspective. As a matter of fact, 5,6-dihydropyran-2-ones of both natural and non-natural origin have been found to be cytotoxic. In addition, they inhibit HIV protease, induce apoptosis, and have even proven to be antileukemic, along with having many other relevant pharmacological properties. At least some of these pharmacological effects may be related to the presence of the conjugated double bond, which acts as a Michael acceptor.[68].

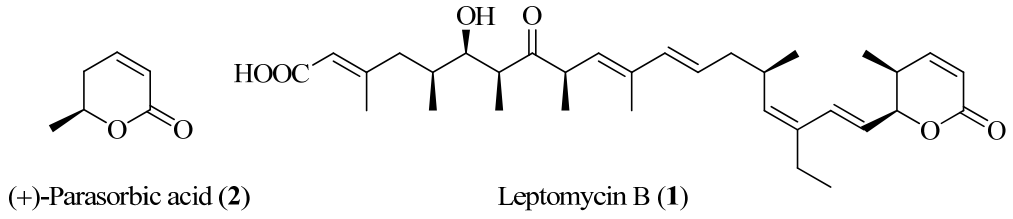


Figure 6. Representatives for naturally occurring 5,6-dihydropyran-2-ones

The structural features of this class of compounds vary widely. Indeed, molecules such as (+)-parasorbic acid (**2**), shown in Figure 6, barely display anything

other than the dihydropyranone ring. In contrast, this moiety goes almost unnoticed within the complex molecular architecture of leptomycin B (**1**). For this reason, syntheses of naturally occurring dihydropyranones cannot be classified according to a general, unified criterion

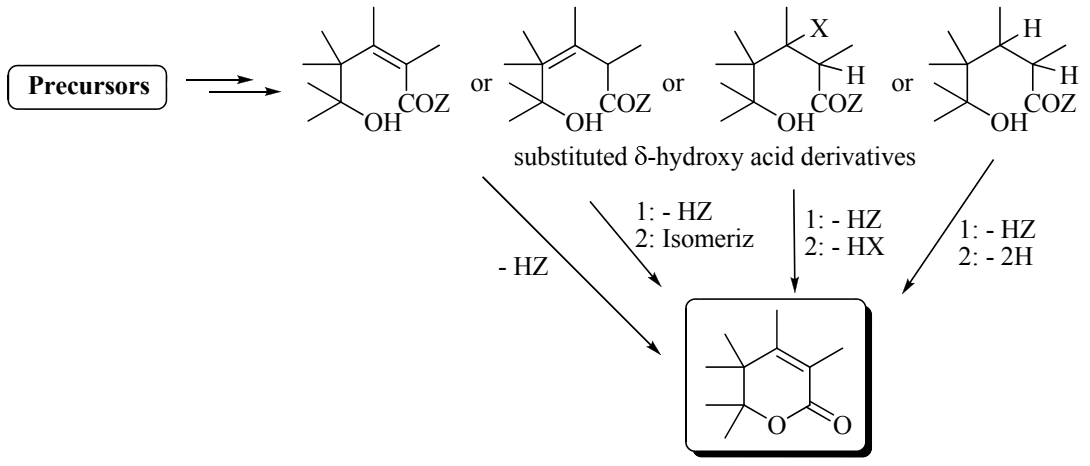
Synthetic methods for the construction of 5,6-dihydropyran-2-one

Many different synthetic methods for the creation of 5,6-dihydropyran-2-one rings have been reported. Emphasis has been placed almost exclusively on methods that have actually been employed for the synthesis of naturally occurring pyrones. These methods have been divided into four groups as follows:

- ❖ Lactonization of substituted δ-hydroxy acid derivatives
- ❖ Oxidation of substituted dihydropyran derivatives
- ❖ Ring closing metathesis
- ❖ Miscellaneous methods

(1) Lactonization of substituted δ-hydroxy acid derivatives

Methods that fall into this category include any reaction, which generates a δ-hydroxy acid or derivative thereof which later cyclizes to a δ-lactone, spontaneously in many cases. When the δ-hydroxy acid already carries a conjugated *Z* double bond, the final product will be the desired 5,6-dihydropyran-2-one. If the double bond is not present, but a suitable leaving group X is attached to the β-carbon (or, less often, the α-carbon), elimination of HX from the intermediate lactone can take place under mild conditions to yield the double bond.

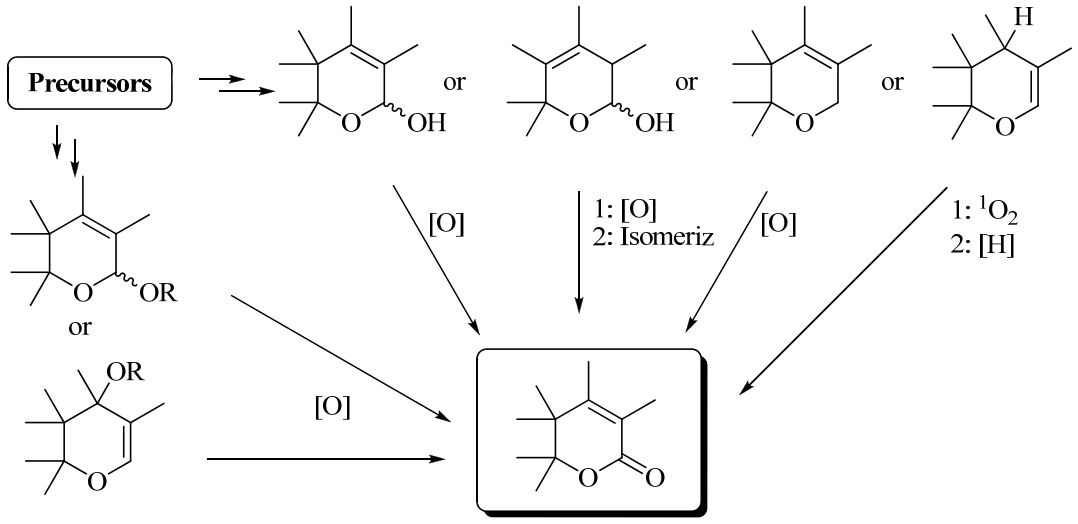


Scheme 65. Formation of 5,6-dihydropyran-2-ones *via* lactonization of a δ-hydroxy acid derivative

Often, these conditions may also cause double-bond migration from the β,γ-position to the conjugated α,β-position. In the absence of both the double bond and the leaving group, an additional dehydrogenation protocol is necessary (Scheme 65). This methodology for generating a 5,6-dihydropyran-2-one ring is widely represented in the literature.[69]

(2) Oxidation of substituted dihydropyran derivatives

Various synthetic methods begin by first generating a dihydropyran derivative. If this is a 2-hydroxy-5,6-dihydro-2H-pyran (a cyclic hemiacetal), a simple alcohol oxidation can be used to transform it into a 5,6-dihydropyran-2-one (Scheme 66). If the hydroxyl group is located at another position or is not present, the oxidation of a C–H bond contiguous to the oxygen atom is required. According to the position of the endocyclic C=C bond, this can be carried out either *via* direct C–H bond oxygenation or through a photochemical oxygenation with singlet oxygen, $^1O_2$. Other methods involve the treatment of pyranoid glycals or glycosides with specific oxidants.[70]

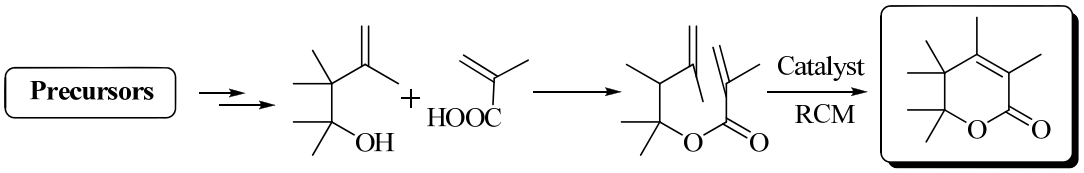


Scheme 66. Formation of 5,6-dihydropyran-2-ones *via* oxidation of dihydropyran intermediates

(3) Ring closing metathesis

The transition-metal-catalyzed olefin metathesis is a very recent development, which has become an extremely useful synthetic tool in the last 15 years. The ring-closing variant of this reaction (RCM) has proven to be particularly useful in the preparation of carbo- and heterocycles of any ring size, except for those that are very

strained. In the case of 5,6-dihydropyran-2-ones, RCM has been used for the direct creation of this heterocyclic system many times (Scheme 67).[71]



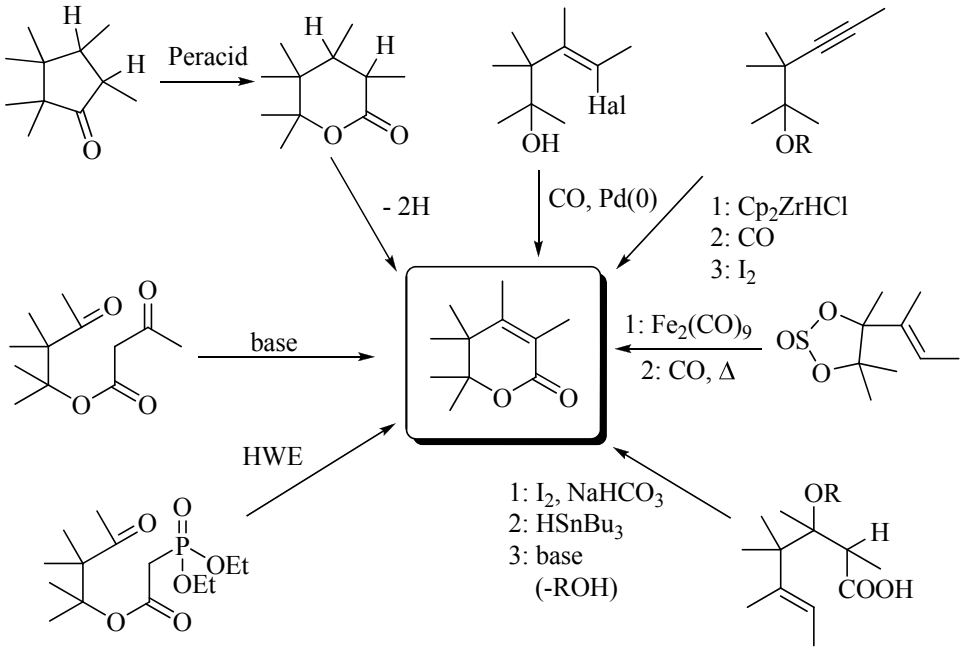
Scheme 67. Formation of 5,6-dihydropyran-2-ones *via* ring-closing metathesis

(4) Miscellaneous methods

In this last category, all those methods are grouped together, while not being intrinsically less valuable than those previously discussed, have been used in only a limited number of cases for the preparation of either tetrahydropyran-2-ones or 5,6-dihydropyran-2-ones. Scheme 68 illustrates these particular reactions:

- Intramolecular HWE olefinations
- Baeyer-Villiger reactions
- Metal-mediated/catalyzed cyclocarbonylations
- Halo- and selenolactonizations
- Cycloadditions
- Intramolecular aldolizations

As it can be seen in Scheme 68, these methods require precursors of different structural types and afford different products. Thus, intramolecular HWE olefinations and metal-mediated carbonylations usually yield 5,6-dihydropyran-2-ones directly. The Baeyer-Villiger reaction, however, provides tetrahydropyran-2-ones, which must subsequently be dehydrogenated. The halolactonization method gives a halogenated lactone, which must then be subjected to both reductive dehalogenation and base-catalyzed elimination of ROH or a similar fragment. Similar considerations apply to the selenolactonization reaction.



Scheme 68. Miscellaneous methods for the preparation of 5,6-dihydropyran-2-ones

Assignment of Relative Configuration of 1,3-polyols

R. W. Hoffmann and Weidmann proposed the use of ^{13}C NMR spectroscopy to assign the relative configuration of 1,3-diols and γ-alkoxyalcohols. Since these compounds exist predominantly in a hydrogen-bonded conformation, *threo* and *erythro* diastereomers show distinct differences in their ^{13}C NMR spectra. The authors suggested the comparison of the sum of the chemical shifts of the two oxygen-bearing carbon atoms. This sum should be numerically smaller for the *threo*-1,3-diols than for their *erythro* counterparts. However, this 'rule' is restricted to simple 1,3-diols or γ-alkoxyalcohols and, for example, cannot be applied to γ-silyloxyketones.[72]

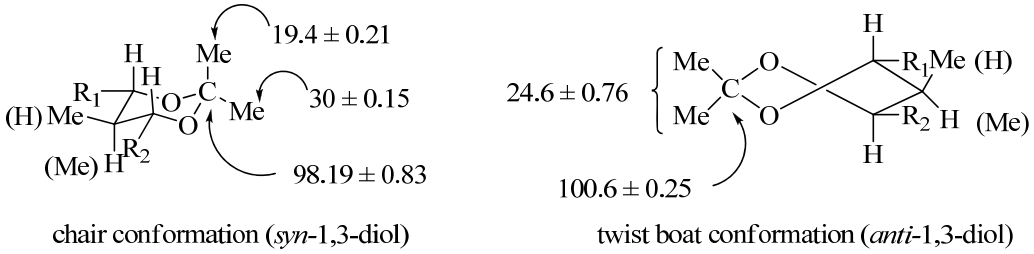


Figure 7. Average values for ^{13}C NMR resonances of *syn* and *anti* polypropionate polyols

Rychnovsky and co-workers developed the '^{13}C-acetonide method' to assign relative configuration of 1,3-diol acetonides.[73] *syn*-1,3-Diol acetonides prefer chair conformations, where one of the acetal methyl groups is axial and the other methyl group is equatorial. The axial methyl group has a ^{13}C chemical shift of ca. δ = 20 ppm, while the equatorial methyl has a chemical shift of ca. δ = 30 ppm. *anti*-1,3-Diol acetonides adopt twist-boat conformations, where the two methyl groups are in nearly identical environments, and thus both have ^{13}C chemical shifts of ca. δ = 25 ppm. The acetonide method has been applied to the configurational assignment of polyene macrolides and many more diols and polyols (Figure 7).[74]

Conclusion

Although many different highly selective and high-yielding methods have been developed, no generally applicable approach exists for the flexible synthesis of polyols and other polyketide-derived structural units. Small structural changes in a molecule may result in low yields or low stereoselectivity with a known method, thus a multitude of methods for the stereoselective synthesis of 1,3-diols has been developed, some of which were presented above. The development of new methods to synthesize 1,3- diols stereoselectively remains important, in order to cope with the structural diversity that nature provides in the form of polyketide-derived natural products.

Going through all the above approaches, it is clear that "living through" a total or partial synthesis can be an exciting, rewarding and very fulfilling endeavor. Again, with an acute sense of awareness of advances on the biological front, the synthetic organic chemist is in an ideal position to use his or her analytical, creative, and deductive skills in an effort to find relevant target molecules for synthesis, or to provide chemical insights into complex biological phenomena through the aegis of synthesis.

Nature generates the problems
Chemistry finds solutions
Biology has the last word ...

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REFERENCES

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CHAPTER-II

Section A: A carbohydrate-based approach to the total synthesis of strictifolione

INTRODUCTION

Over the course of the past half century, the structural elucidation of natural products has undergone a tremendous revolution. Before World War II, a chemist would have relied almost exclusively on the art of chemical synthesis, primarily in the form of degradation and derivatization reactions, to develop and test structural hypotheses in a process that often took years to complete when grams of material were available. Today, a battery of advanced spectroscopic methods, such as UV, IR, multidimensional NMR spectroscopy, circular dichroism (CD), high-resolution mass spectrometry (MS) and of course X-ray crystallography, exist for the expeditious assignment of structures to highly complex molecules isolated from nature in milligram or sub-milligram quantities. In fact, it could be argued that the characterization of natural products has become a routine task, one which no longer even requires a reaction flask! This current advancement in chemical techniques is nicely remarked in the following statement.

If penicillin were discovered today … the scientific problems of studying a pure crystalline compound with a molecular weight of about 350 would not have been nearly so difficult. The conclusion is that a good graduate student would probably work out the structure of penicillin in a day or so. Just a generation ago, that same scientific feat took the best of us years of intensive work.

John C. Sheehan (1982)[1]

Despite our present advantages, the mistakes are still very frequent and a common occurrence in the business of structure elucidation of the natural products. To understand this it would be relevant to cite an interesting observation by K. C. Nicolaou and S. A. Snyder.[2] While searching the scientific databases for the structural revisions, limiting their search to literature published from January 1990 to April 2004, they could find well over 300 examples of such revisions. Many of these included major and sometimes complete constitutional changes apart from simple stereochemical problems. Amazingly, the examples covered virtually every compound class, including steroids, terpenes, indole alkaloids and peptides, and included molecules of all sizes and levels of stereochemical complexity. The detail study of 50 examples out of these, taken in no particular order, revealed that the chemical synthesis was required in 27 cases to reach the revised structure. In 22 cases

out of 50, it was total synthesis, which indicated that there was a problem in originally proposed structure. This, in one sense, can be viewed as the victory of the nature on human progress. But man is more than familiar with this kind of circumstances and all the human progress has made its way through such obstacles and resistances. As is the case with all other walks of life, a difficulty or inability for particular branch is taken as a challenge or opportunity by the other one. The role of synthetic chemists becomes imperative in this kind of situations. The missing links are put in place by the synthetic chemists, by synthesizing various possible structures and comparing the data for each one of them with the natural product. There are abundant instances of this type where the challenge of nature was successfully faced by the harmonious efforts of '*synthetic'* and '*natural product isolation'* chemists.

The structural elucidation of strictifolione is one such case whose proposed structure was found to be wrong after carrying out the total synthesis leading to reassignment of the structure.

Strictifolione was isolated by Aimi et al.[4] from the plant *Cryptocarya strictifolia* which belongs to the family *Lauraceae* and grows in the Indonesian tropical rainforests. Plants of this genus are known to contain 6-substituted-5,6-dihydro-2-pyrones[3] in addition to other types of compounds, such as flavonoids, alkaloids and terpenoids. *C. strictifolia* is a large tree (25 m tall and 35 cm in diameter) which grows in the forests of West Kalimantan, at ca. 100 m altitude, and which has hitherto not been chemically studied.

185a **185b**

Figure 1. Acetonide derivatives of Strictifolione

The structure of strictifolione was proposed based on the spectroscopic analysis, as follows. A positive Cotton effect due to the carbonyl $n \rightarrow \pi^*$ transition of an α,β-unsaturated-δ-lactone was observed at λ_{max} 257 nm ($\Delta\varepsilon$ + 2.63) in the CD spectrum of natural strictifolione indicating the (*R*) absolute configuration at C-6. The *anti* relative stereochemistry of the 1,3-diol function at C4' and C6' was elucidated

from the ^{13}C NMR spectrum of the acetonide derivative **185a**/**185b** based on Rychnovsky's anology (Figure 1). At this point the structure of strictifolione can be assumed to be either as **184a** or **184b** (Figure 2).

Further, the absolute configurations of both hydroxyl-bearing carbons C-4' and C-6' were determined to be (*R*) and (*R*) respectively by the modified Mosher's method using the (*S*) and (*R*)-MTPA esters of strictifolione. Based on these observations the structure of strictifolione was confirmed to be **184b** and named as 6*R*-(4'*R*, 6'*R*-dihydroxy-8'-phenyloct-1'-enyl)-5,6-dihydro-2-pyrone ruling out the other possible isomer of strictifolione, **184a** (Figure 2).

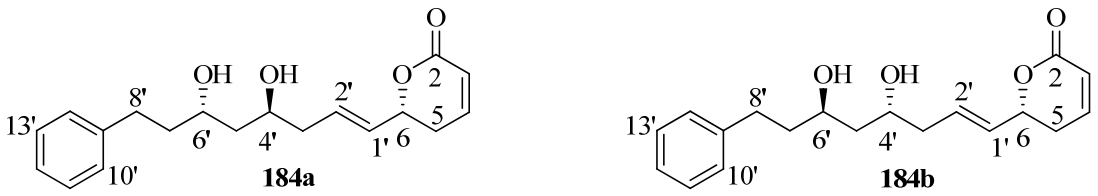


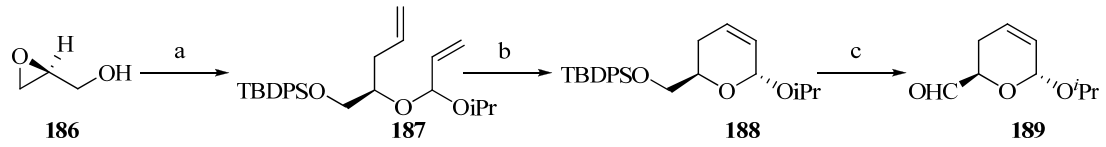
Figure 2. Possible structures for strictifolione

To confirm the structure inferred by the spectroscopic analysis Aimi et al. further attempted a chiral total synthesis of strictifolione using (*S*)- and (*R*)-malic acid to evaluate the stereogenic centers at C4' and C6'. (*S*)-glycidol was the other chiral synthon for the construction of the lactone ring. As the spectral parameters of the synthetic sample that was prepared from L-malic acid and (*S*)-glycidol were found to be matching exactly with the natural strictifolione, ultimately Aimi et al. concluded that the structure of strictifolione was wrongly assigned and revised the absolute configuration of strictifolione as 6*R*, 4'*S* and 6'*S* (**184a**).

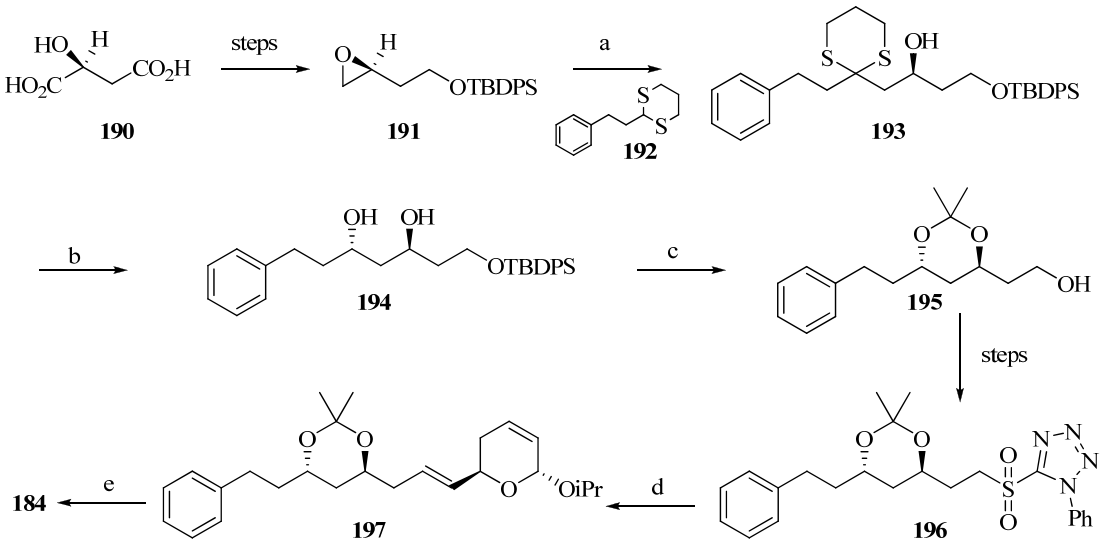
First total synthesis and determination of the absolute configuration of strictifolione (1)[5]

This approach features a late stage coupling of two fragments prepared from the chiral synthons *R*- and *S*-malic acid and (*S*)-glycidol.

The masked pyranone aldehyde **189** was synthesized from (*S*)-glycidol (**186**) according to the procedure of Crimmins et al., with slight modification and applying the RCM reaction as shown in Scheme 1.



Scheme 1. *Reagents and conditions*: (a) (i) TBDPSCl, imidazole, CH_2Cl_2, r.t., 3 h, 67%; (ii) vinylmagnesium bromide, CuI, THF, −25°C, 1 h, 88%; (iii) acrolein diisopropylacetal, PPTS, 40 → 60 °C, 32 h, 74% (diastereomeric mixture 1:1); (b) $RuCl_2(CHPh)(PCy_3)_2$, CH_2Cl_2, reflux, 2 h, quant. (*trans:cis* 1:1, isolated *trans*-isomer 44%); (c) (i) TBAF, THF, r.t., 1 h, 87%; (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C, 10 min, 90%.

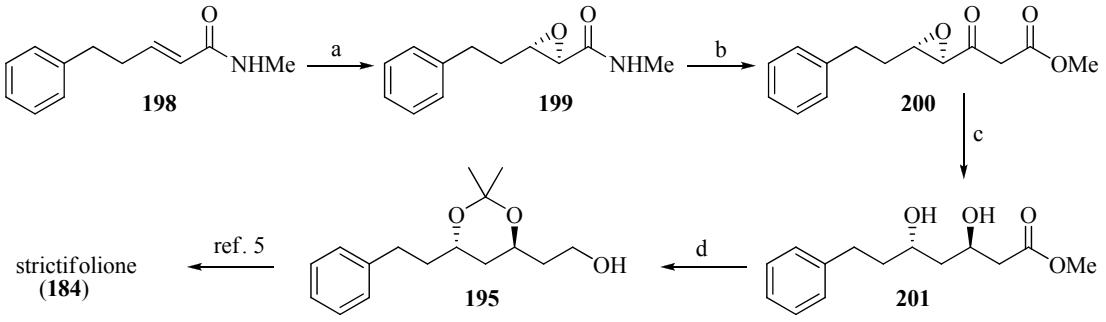


Scheme 2. *Reagents and conditions*: (a) **192**, *n*-BuLi, THF, r.t., 98%; (b) (i) $NaHCO_3$, I_2, aq. acetone, 0 °C, 77%; (ii) $Me_4NHB(OAc)_3$, MeCN–AcOH (1:1), −20 °C, 25 h, 95%; (c) (i) 2,2-dimethoxypropane, *p*-TsOH, CH_2Cl_2, r.t., 3 h, 82%; (ii) TBAF, 4 Å MS, THF, r.t., 2 h, 100%; (d) **189**, NaHMDS, THF,−60 °C, 1.5 h, 34% (*E*-, *Z*-isomer 4:1); (e) (i) PPTS, acetone–H_2O (6:1), r.t., 1.5 h, 80%; (ii) MnO_2, pyridine, CH_2Cl_2, 24 h, 50%.

A known chiral epoxide **191** was prepared from malic acid (**190**) in good yield by a newly developed process. The epoxide thus obtained was coupled with the lithiated anion of dithiane **192** to give secondary alcohol **193**. Deprotection of dithioacetal group followed by *anti*-selective reduction of the resulting β-hydroxy ketone accomplished the 1,3-diol **194**, which was further transformed into the corresponding acetonide derivative **195**. In the ^{13}C NMR of **195**, the two methyl groups of the acetonide resonated at δ 24.9 and 24.8 ppm, indicating that the two alcohol groups are in a 1,3-*anti* orientation. The alcohol group was converted to the sulfone **196** which was condensed with aldehyde **189** by employing the Kociensky-modified Julia olefination to furnish the olefin **197**. Acid hydrolysis of acetals followed by MnO_2 oxidation completed the total synthesis of strictifolione (**184**).

Shibasaki's approach[6a]

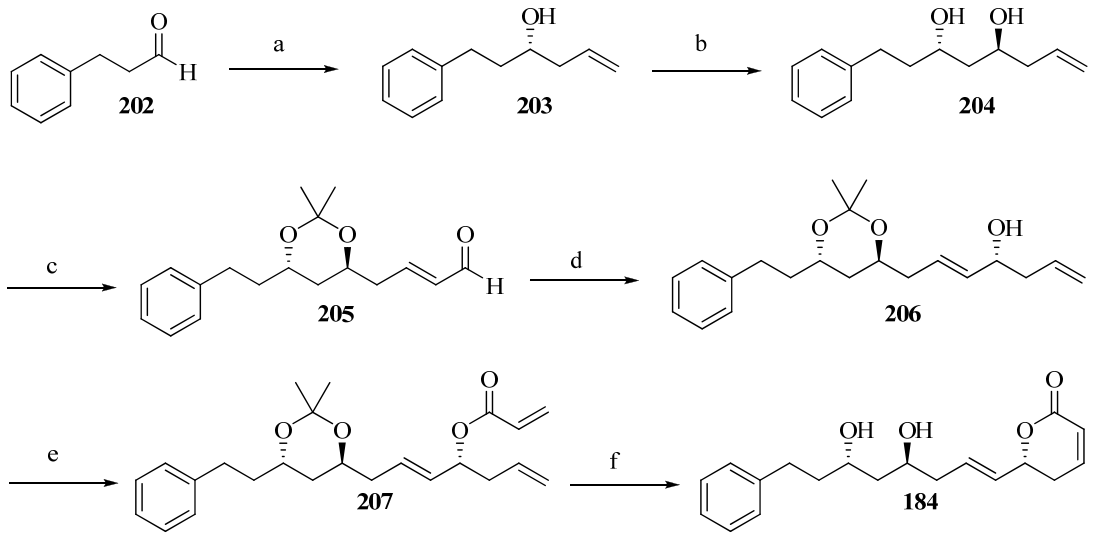
As depicted in the Scheme below, the method relies upon the catalytic asymmetric epoxidation of α,β-unsaturated amide **198**, using Sm-BINOL complexes to give the epoxy amide **199** which was converted to the methyl ester **200**. Regioselective epoxide opening, diastereoselective keto reduction gave the *anti*-3,5-dihydroxy ester **201** which was easily converted into the Aimi's intermediate **195**. This can be utilized further for catalytic asymmetric synthesis of **184**.



Scheme 3. *Reagents and conditions*: (a) 5 mol % of (*S*)-Sm-BINOL-Ph_3As=O (1:1:1) complex; b) (i) Martin sulfuran (3 equiv), THF, r.t., 3 h, then NaOMe (3 equiv); (ii) ethyl acetate, LHMDS, THF, –78 to –20 °C, 87%; (c) (i) PhSeSePh, $NaBH_4$, EtOH, r.t., 85%; (ii) $NMe_4BH(OAc)_3$, CH_3CN-AcOH, 0 °C, 80%; (d) (i) 2, 2'-dimethoxypropane, cat. TsOH, r.t.; (ii) LAH, THF, 0 °C, 92% for 2 steps.

Janine Cossy et al.[6b]

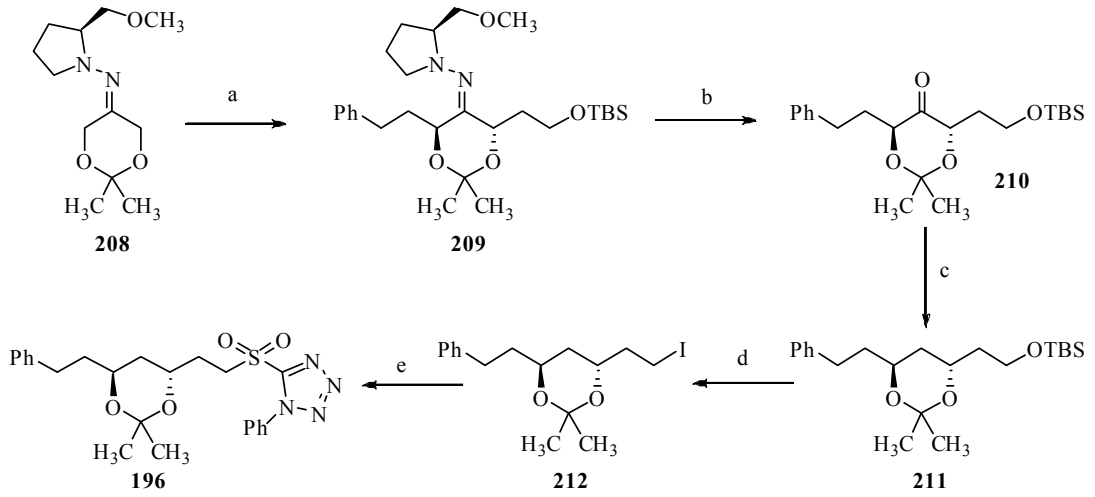
The synthesis of (+)-strictifolione was achieved from 3-phenylproprionaldehyde (**202**) by using enantioselective allyltitanations to control the stereogenic centers at C6, C4', and C6', cross-metathesis to control the configuration of the double bond at C1'–C2', and finally an RCM reaction for the construction of pyrone ring.



Scheme 4. *Reagents and conditions*: (a) (*S*,*S*)-**40**, ether, –78 °C, 4 h, 83%. (b) (1) OsO_4, NMO, acetone–H_2O, $NaIO_4$, 25 °C; (2) (*R*,*R*)-**40**, ether, –78 °C, 4 h, 76% for the two steps. (c) (1) DMP–acetone, CSA, 25 °C, 95%. (2) acrolein, Hoveyda's catalyst (5 mol%), CH_2Cl_2, 25 °C, 70%. (d) (*S*,*S*)-**40**, ether, –78 °C, 4 h, 84%. (e) acryloyl chloride, $^iPr_2NEt$, CH_2Cl_2, –78 °C, 92%. (f) (1) Grubb's I (5 mol%), CH_2Cl_2, reflux, 82%. (2) 1 N HCl, MeOH, 40 °C, 87%.

Enders et al.[6c]

Enders group has published both the asymmetric total synthesis and a formal synthesis of (+)-strictifolione. Both the approaches involve the Julia-Kociensky olefination as the key reaction in the latter stage of synthesis between the sulfone **196** and aldehydes **189**, **218** (Scheme 8).

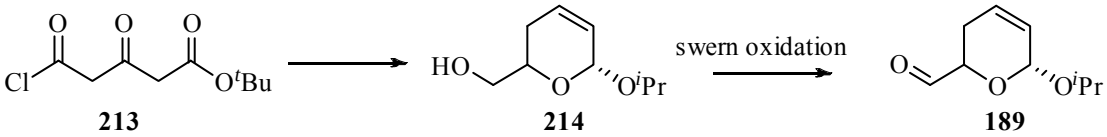


Scheme 5. *Reagents and conditions*: (a) (1) *t*-BuLi, THF, –78 °C; $Br(CH_2)_2OTBS$, –100 °C → r.t.; (2) *t*-BuLi, THF, –78 °C; $Ph(CH_2)_2I$, –100 °C → r.t., 71% over two steps; (b) sat. aq oxalic acid, Et_2O, r.t., 96%; (c) (1) $NaBH_4$, MeOH, 0 °C; (2) NaH, THF, 0 °C; CS_2; MeI, 0 °C → r.t., 99% over two steps; (3) Bu_3SnH, AIBN (cat.), toluene, reflux; (d) (1) TBAF, THF, r.t., 93% over two steps; (2) Ph_3P,

imidazole, I_2, Et_2O–CH_3CN, 0 °C, 84%; (e) (1) 1-Phenyl-1*H*-tetrazole-5-thiol, NaH, THF–DMF, 0 °C; **212**, 0 °C → r.t., 99%; (2) *m*CPBA, $NaHCO_3$, CH_2Cl_2, r.t., 87%.

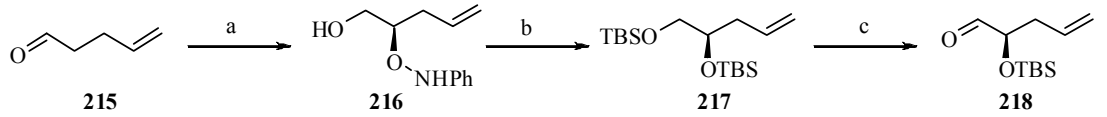
The *anti*-1,3-diol moiety in sulfone **196** was synthesized by employing a SAMP-hydrazone α, α'-bisalkylation/deoxygenation protocol (Scheme 5).

The stereogenic center of **189** and **218** which corresponds the lactone ring of strictifolione was established in two different ways, one based on the enzymatic reduction of **213** with baker's yeast (Scheme 6) and the other was by a (*S*)-proline catalyzed α-oxyamination of pent-4-enal **215** (Scheme 7).



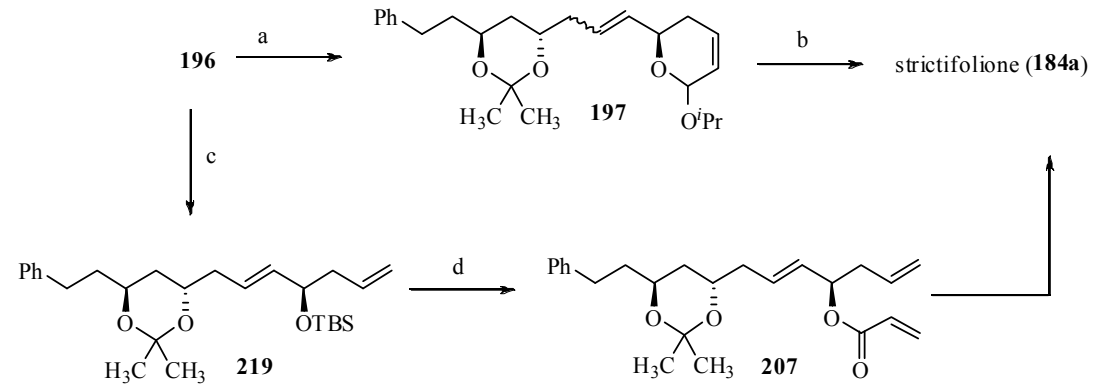
213 **214** **189**

Scheme 6.



215 **216** **217** **218**

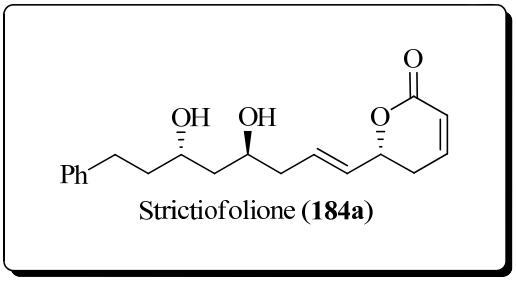
Scheme 7. *Reagents and conditions*: (a) (1) (*S*)-proline (10 mol%), PhNO, $CHCl_3$, 0 °C; (2) $NaBH_4$, MeOH, 0 °C, 92% over two steps; (b) (1) SmI_2, THF, r.t.; (2) TBSCl, imidazole, DMF, r.t., 50% over two steps; (c) (1) HF·pyridine, pyridine, THF, r.t., 57%; (2) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C; Et_3N, 0 °C, 98%.



Scheme 8. *Reagents and conditions*: (a) **189**, DME, –(65–60) °C, base, –(65–60) °C → r.t.; (b) (1) PPTS, acetone–H_2O, r.t.; (2) MnO_2, CH_2Cl_2, r.t., 69% over two steps; (c) **218**, DME, –(65–60) °C; KHMDS, –(65–60) °C → r.t., 69%; (d) (1) TBAF, THF, r.t.; (2) acryloyl chloride, $^iPr_2NEt$, CH_2Cl_2, –78 °C, 91% over two steps.

PRESENT WORK

Strictifolione **184a** belongs to the family of 5,6-dihydro-δ-pyrone derivatives having an alkyl side chain at the C-6 position.[7] The broad range of biological activities reported for this class of compounds has been ascribed to their inherent tendency to act as good Michael acceptors. Strictifolione was isolated by Aimi and co-workers from the stem bark of *Cryptocarya strictifolia* that grows in the Indonesian tropical rainforests.[4] The relative and the absolute configuration of strictifolione were revised by the same group after accomplishing its first total synthesis.[5] Later, asymmetric syntheses, primarily with RCM as one of the key reactions, have been reported.[6] As a part of our longstanding interest in the synthesis of bioactive natural products using the chiron approach,[8] we have taken up the total synthesis of strictifolione **184a**.



Strictiofolione (**184a**)

Figure 3.

Retrosynthetic Analysis

Our basic approach to the synthesis of strictifolione features dissecting the molecule at two junctions as shown in Figure 4. One of the final key reaction will be the *Z*-selective Wittig olefination and intramolecular lactonization leading to the α,β-unsaturated-δ-valerolactone of strictifoline. This led to the identification of **241** as a key intermediate in our total synthesis. This **241**, inturn can be prepared by nucleophilic opening of a suitably protected epoxide (**232**) with lithium acetylide derivative of (**240**) using Yamaguchi protocol. In this context, a chiral pool approach starting from easily available D-glucose for the synthesis of **232** and a catalytic

asymmetric epoxidation protocol for the synthesis of the alkyne fragment **240** were planned to execute the synthesis of key intermediate **241**.

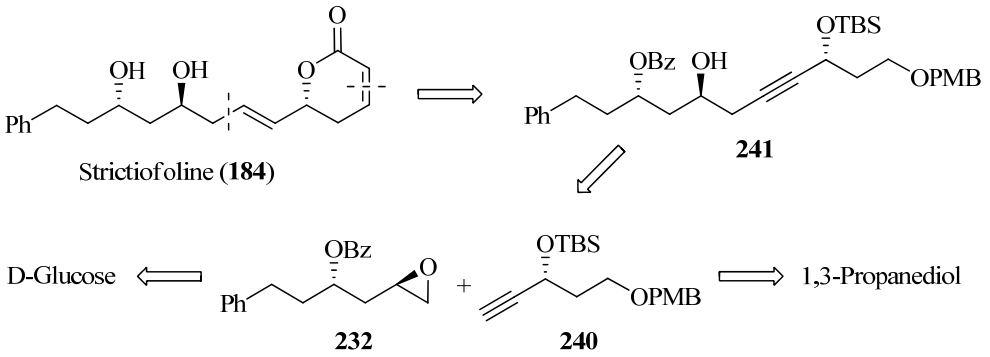
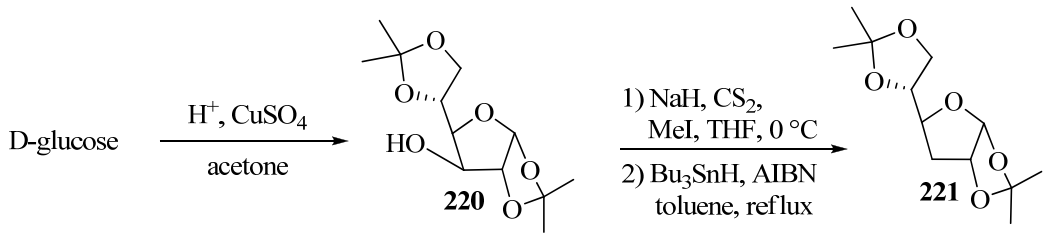


Figure 4.

Synthesis of epoxide 232

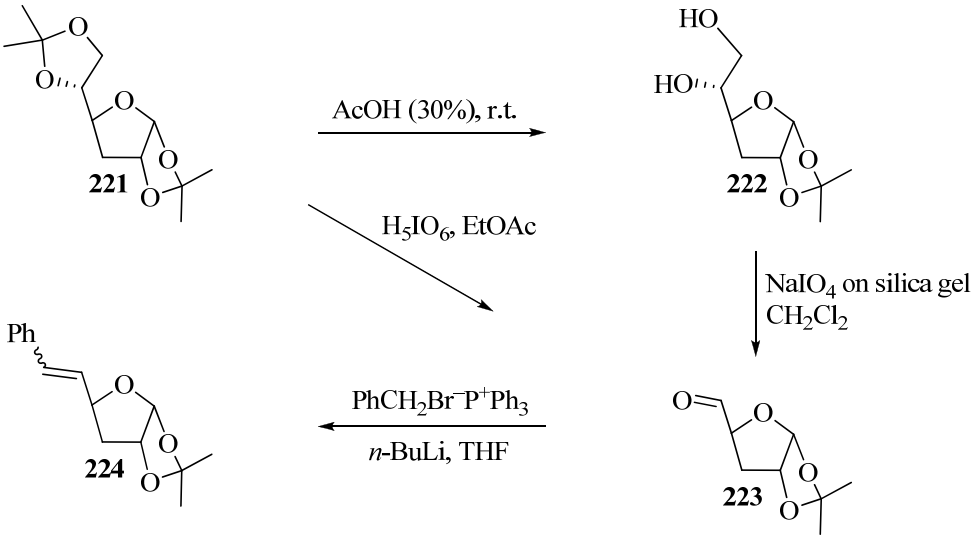
As intended, the synthesis of fragment **232** was initiated from D-glucose, following the literature procedures. D-glucose was first converted to its diacetonide derivative **220** by treating with conc. H_2SO_4, $CuSO_4$, in acetone. Compound **220** was then converted to the corresponding 3-deoxy derivative **221** *via* a xanthate ester formation followed by the Barton MacCombie protocol (Scheme 9).[9]



Scheme 9.

Selective deprotection of the 5,6-isopropylidene group was carried out using 30% AcOH at rt to obtain the diol **222**, which was subjected to periodate mediated oxidative cleavage to give the furanaldehyde **223**.[10] In another way aldehyde **223** was directly obtained by treating **221** with periodicacid in ethyl acetate. However, the yield in this case was not satisfactory compared with that of the earlier one. Wittig olefination of aldehyde **223** with benzyl triphenylphosphorane (generated from the

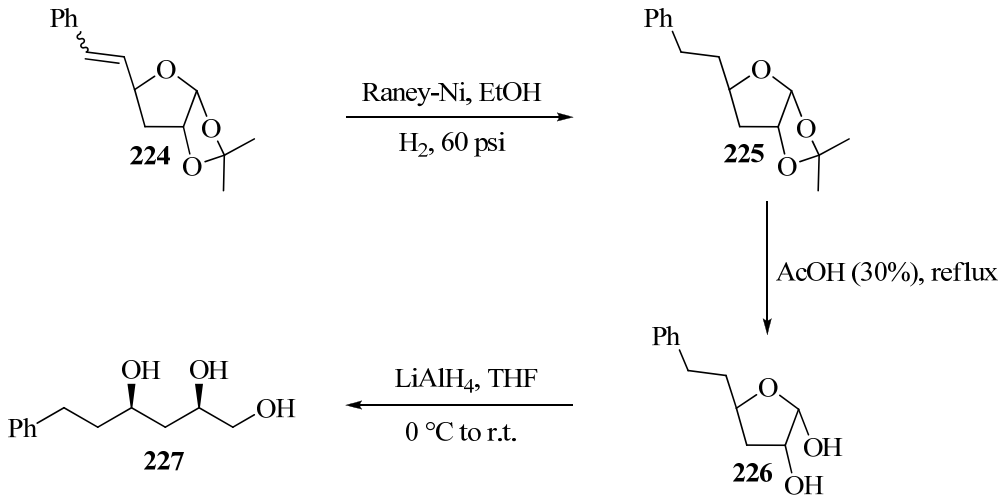
corresponding phosphonium bromide by the action of *n*-BuLi in THF) furnished mixture of styrene derivatives **224** (Scheme 10).[11]



Scheme 10.

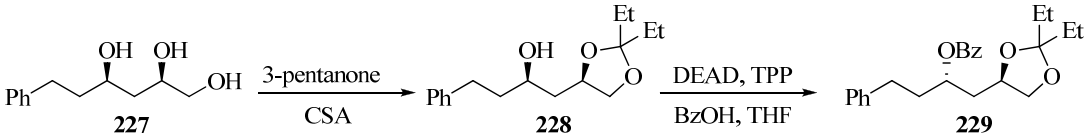
Hydrogenation of the styrene **224** using Raney-Ni in ethanol at 60 psi hydrogen atmosphere gave the saturated compound **225** in quantitative yield. The ^{1}H and ^{13}C NMR spectra of **225** revealed the absence of the olefinic protons and the presence of the peaks for the proposed structure **225**. The benzylic protons appeared as ddd at δ 2.79 and 2.69 each integrating for one proton in the ^{1}H NMR whereas a signal appeared at δ 38.8 as triplet in the ^{13}C NMR indicating the presence of the methylene group. The anomeric proton resonated at δ 5.83 as a doublet with J = 3.7 Hz whereas the C-1 resonated at δ 105.2 as doublet in the ^{13}C NMR. Two singlets at δ 1.49 and 1.32 in the ^{1}H NMR spectrum integrating for three protons each were assigned to methyl groups of 1,2-isopropylidene protection, which was further supported by presence of a peak for quarternary carbon at 110.7 ppm in the ^{13}C NMR spectrum. Results from mass spectrum (*m/z* 271.1 $[M+Na]^+$), IR, elemental analysis were in accordance with the structure **225**. Cleavage of the 1,2-*O*-isopropylidene group of **225** in refluxing 30% AcOH provided lactol **226** which upon reduction with $LiAlH_4$ in THF yielded triol **227** (Scheme 11).[12] The absence of the signals corresponding to the sugar moiety in ^{1}H and ^{13}C NMR spectrums clearly indicated the lactol reduction to the triol **227**. The proton NMR spectrum recorded in acetone-d_6

showed three multiplets in the region [4.26-4.27 (br m, 2H), 3.85-3.86 (br m, 3H), 3.41-3.41 (m, 2H)] indicating the presence of a triol moiety. Further in proof of structure **227** the ^{13}C NMR spectrum revealed the presence of a CH_2OH (δ 67.0 (t)) and two CHOH groups [δ 70.6 (d), and 72.5 (d)].



Scheme 11.

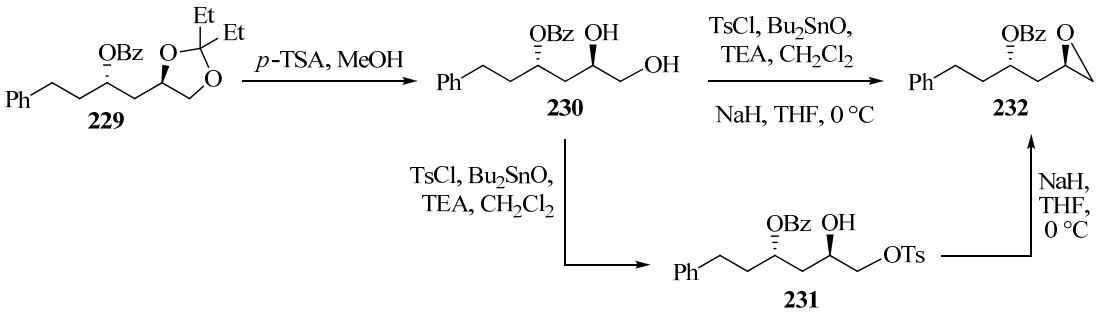
Our next target was to invert the center at C-4 for which the selective 1,2-glycol protection of **227** was carried out using 3-pentanone and catalytic CSA.[13] The required five membered dioxalane derivative **228** was obtained exclusively leaving the 4-hydroxy intact. In the ^1H NMR spectrum, two methyl groups of the dioxalane group resonated as triplets at 0.91 ppm and 0.89 ppm, whereas the four methylene protons resonated in the region 1.57–1.88 ppm as multiplets. In the ^{13}C NMR, spectrum, the signal due to quaternary dioxalane carbon appeared as a singlet at 113.8 ppm indicating the presence of only five membered dioxalane derivative rather than the six membered.



Scheme 12.

To install 4,6-*anti* hydroxyl groups in the target molecule, C(4)-hydroxyl of compound **228** was inverted under Mitsunobu conditions[14] by treating it with diethylazodicarboxylate in the presence of TPP and benzoic acid. Thus, the Mitsunobu reaction of **228** resulted in benzoate **229** with complete inversion. In the ^{1}H NMR spectrum the signals corresponding to the benzoate group appeared in the downfield region whereas in ^{13}C NMR a signal due to the ester carbonyl at 166 ppm (singlet) indicated the presence of benzoate group (Scheme 12).

Hydrolysis of dioxolane ketal **229** in *p*-TSA, MeOH gave benzoyl diol **230**. Selective 1°-OH tosylation[15] of **230** using TsCl, Bu_2SnO, triethyl amine in dichloromethane and subsequent treatment of the resulting tosylate **231** with NaH in THF afforded the desired fragment **232**. In the ^{1}H NMR spectrum of **232** the three signals in the upfield region (3.03-3.0 ppm, as multiplet integrating for one proton, at δ 2.7, (br d, J = 5.0, 4.0 Hz, 1H), and at 2.46 ppm (dd, J = 5.0, 2.7 Hz, 1H)) were ascribed to the characteristic terminal epoxide protons. The appearance of two peaks in the ^{13}C NMR spectrum, one at 46.8 ppm as triplet and the other at 49.1 ppm as doublet further confirmed that the structure assigned for fragment **232** was beyond any doubt (Scheme 13).

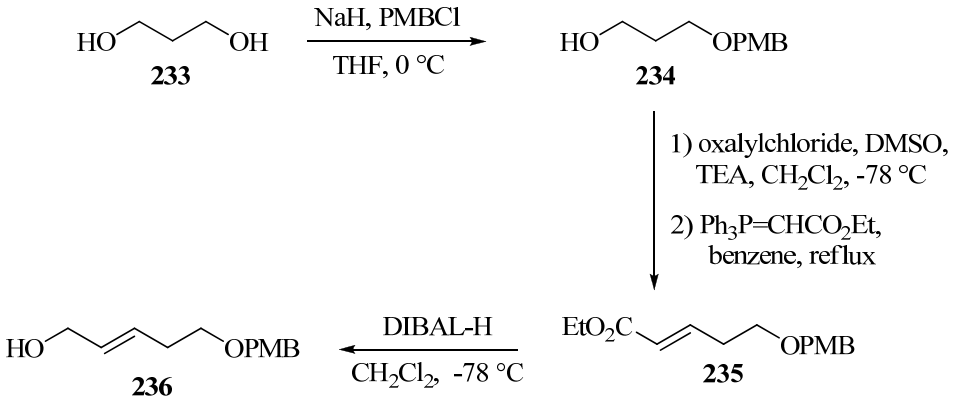


Scheme 13.

Synthesis of alkyne 240

Propane diol **233** was chosen as starting material for the synthesis of alkyne **241**. One of the two hydroxyls of propane diol was selectively protected as PMB ether by reacting with NaH, PMBCl in DMF to get the compound **234**. Oxidation of **234** under Swern conditions gave corresponding aldehyde, which on treatment with ethoxy carbonyl methylene triphenyl phosphorane in benzene under reflux gave

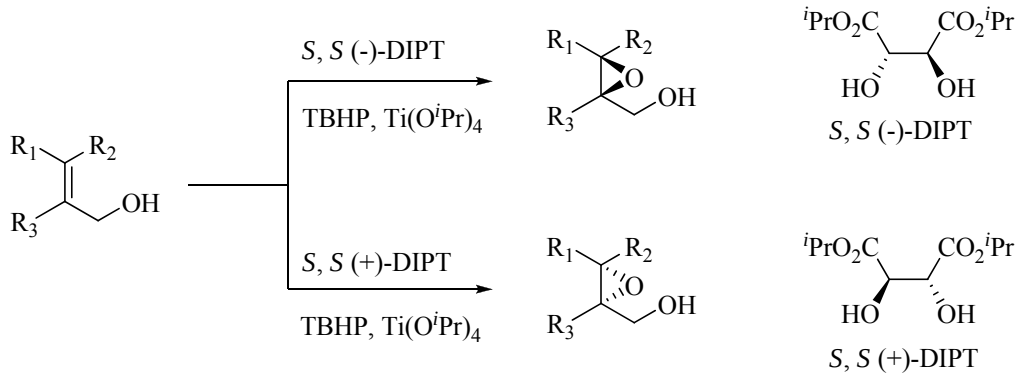
exclusively the *E*-isomer **235**. In the ^{1}H NMR spectrum of **235** the two olefinic protons appeared at δ 6.97 and 5.87 as doublet of triplets with a coupling constant of 15.8 Hz indicating the presence of an internal *trans* double bond. The downfield shift of one of the olefinic protons is an indicative of an ester group attached to the double bond. This was further confirmed by analysing its ^{13}C NMR where the olefinic carbons resonated as doublets at δ 122.7 and 129.1 whereas the ester carbonyl resonated as singlet at δ 166.1. Other analytical data such as IR (1714 cm^{-1}), mass (*m/z* 264.1 [M+Na]), microanalysis were in great support of the structure assigned for compound **235**. Selective carboxylate reduction of **235** using DIBAL-H in DCM at – 78 °C provided the required allyl alcohol **236** in good yield (Scheme 14).



Scheme 14.

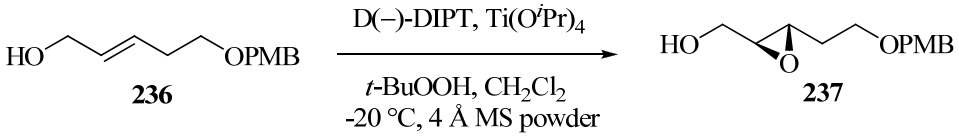
Sharpless asymmetric epoxidation (SAE)

Sharpless asymmetric epoxidation (SAE) is one of the most popular reactions used for the enantioselective epoxidation of achiral allylic alcohols in organic synthesis. When a prochiral Z- or E-allylic alcohol is treated with dialkyl tartrate (generally Et or ^{i}Pr), titanium tetraisopropoxide and tert-butylhydroperoxide, produces the corresponding chiral epoxyalcohol with high ee. Easy availability of reagents involved, and high enantiomeric (or diastereomeric) excess obtained in the reaction made the Sharpless asymmetric epoxidation to find widespread application for the introduction of chirality in the complex target molecules. The easy and accurate prediction of stereochemical outcome irrespective of substitution on the allylic alcohol further asserted the reaction application (Scheme 15).



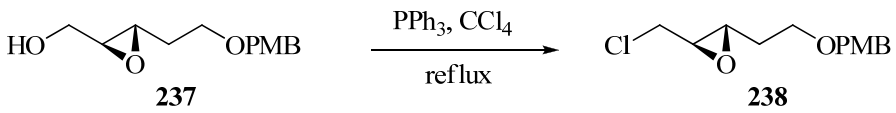
Scheme 15.

Sharpless asymmetric epoxidation[16] of **236** was carried out using D(–)-diisopropyl tartrate and titanium tetraisopropoxide in the presence of *tert*-butylhydroperoxide in dry dichloromethane and the epoxide **237** was obtained in good yield. The specific rotation {$[\alpha]_D^{25}$ = +18.0 (*c* 1.0 $CHCl_3$)}confirmed the high enantiomeric excess of compound **237**. The presence of an internal epoxide group was indicated by the ^{1}H-NMR signals at δ 3.09 (ddd, *J* = 2.5 Hz, 1H) and 2.97 (m, *J* = 2.5 Hz, 1H) and confirmed by resonances at δ 53.6 (d) and 58.4 (d) in the ^{13}C-NMR spectrum (Scheme 16).



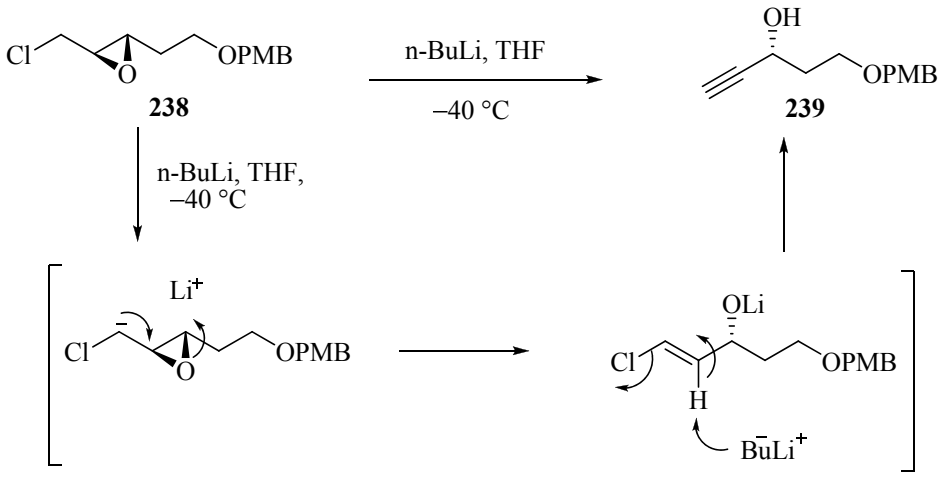
Scheme 16.

Chlorination[17] of **237** by refluxing in CCl_4 in the presence of triphenyl phosphine gave the chlorooxirane **238** in good yield (Scheme 17).



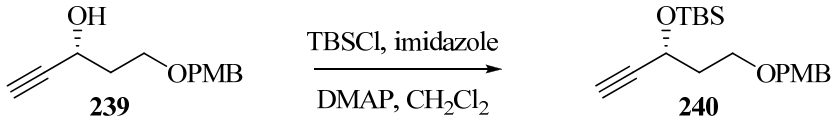
Scheme 17.

Treatment of **238** with excess *n*-BuLi in THF at –40 °C provided the α-hydroxy alkyne **239** *via* a double elimination reaction as shown in the Scheme 18.[18]



Scheme 18.

Finally, protection of **239** as its TBS-ether using TBSCl and imidazole in CH_2Cl_2 furnished the desired alkyne fragment **240** (Scheme 19). ^1H and ^{13}C NMR and other analytical data were in accordance with the proposed structure of **240**. For example, in ^1H NMR the characteristic peaks for TBS-group appeared in upfield region (δ 0.11 (s, 3H), 0.14 (s, 3H), and 0.9 (s, 9H)) and for PMB-group in downfield region [δ 7.25 (br dt, J = 2.3, 8.6 Hz, 2H), 6.87 (br dt, J = 2.3, 8.6 Hz, 2H)]. The presence of the terminal alkyne group was confirmed as the ^1H NMR showed the peak at δ 2.37 as a doublet with J = 2.3 Hz, and it was further supported by the signals at δ 72.1 (d) and 85.4 (s) in ^{13}C NMR spectrum.

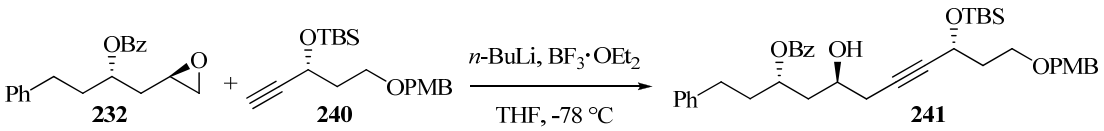


Scheme 19.

Coupling of Two Fragments

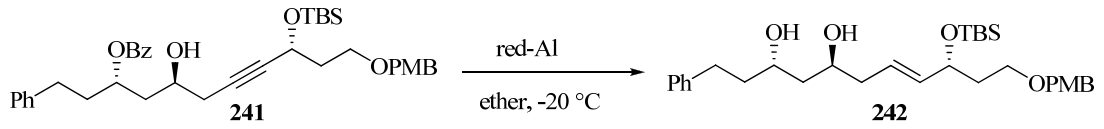
Having now access to both the fragments **232** and **240**, the Yamaguchi protocol[19] for C–C bond formation was investigated in the presence of *n*-BuLi, $BF_3.Et_2O$ in THF at –78 ^oC. This protocol resulted in the formation of the advanced

intermediate β-hydroxy alkyne **241** (Scheme 20). The spectral and analytical profiles of **241** were in agreement with the assigned structure. The presence of peaks corresponding to the benzoate ester, TBS ether and PMB ether in the ^{1}H and ^{13}C NMR spectrums supported a successful Yamaguchi coupling reaction. In the ^{1}H NMR spectrum the newly formed propargylic methylene group resonated as two multiplets, each integrating for one proton in the region 2.40-2.46 ppm and 2.32-2.36 ppm. Infact, the success of the coupling reaction was further confirmed by the appearance of two signals due to the internal alkyne carbons at 80.5 ppm and 85.1 ppm as singlets along with the signal due to the propargylic methylene at 41.9 ppm (triplet) in the ^{13}C NMR spectrum.



Scheme 20.

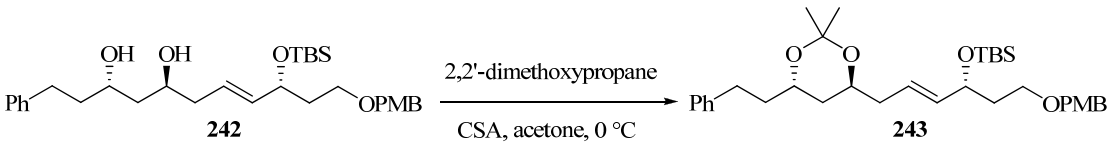
The next objective was to reduce the alkyne to *E*-olefin. The reduction of C≡C to the corresponding *E*-olefin with concomitant de-benzoylation occurred when **241** was treated with red-Al in ether at –20 °C to produce **242** (Scheme 21).[20]



Scheme 21.

Protection of **242** as its acetonide derivative was accomplished by treating with 2,2'-dimethoxypropane in the presense of catalytic amount of CSA in DCM and the resulting acetonide **243** (Scheme 22) was subjected for extensive NMR studies to confirm its relative stereochemistry: especially the 1,3-*anti* disposition of **243**. In the ^{1}H NMR spectrum a peak at δ 5.52 as doublet of triplet and at δ 5.48 as a doublet of doublet with a coupling constant of 15.5 Hz are due to the *trans* double bond. Two

singlets at δ 1.34 and 1.32 integrating for three protons each were assigned to methyl groups of 1,3-isopropylidene protection.



Scheme 22.

It has been already well established that in the ^{13}C NMR spectrum of acetonide of a 1,3-*anti* diol, the methyl groups will resonate with almost the same δ value, whereas in the case of a 1,3-*syn* diol, they will be separated by at least 8–12 ppm.[21] In the ^{13}C NMR spectrum of **243**, the acetonide methyl groups resonated together at 24.9 ppm indicating a 1,3-*anti*-relationship. This was further substantiated by the appearance of the quaternary carbon in the downfield region (100.3 ppm) (Figure 5).

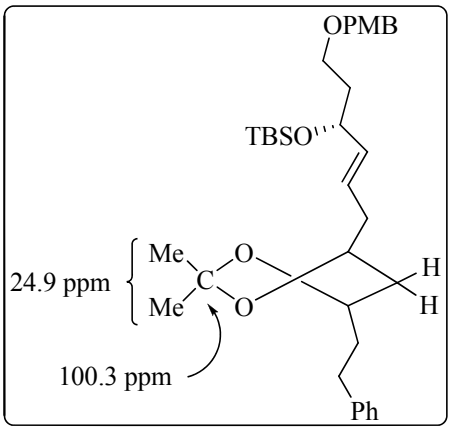
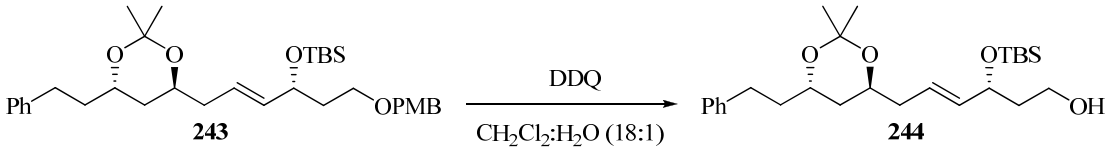


Figure 5. Twist boat conformation of **243** (*anti*-1,3-diol)

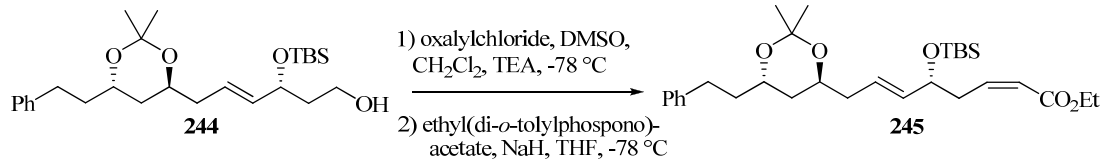
Completion of total synthesis

Our next concern was to install the dihydropyran ring. Cleavage of PMB ether **243** was effected with DDQ in 18:1 mixture of DCM and water to afford the alcohol **244** (Scheme 23).[22] In the ^{1}H and ^{13}C NMR spectrums the peaks due to the PMB-ether disappeared and the mass spectrum with the highest mass peak at m/z 471.3 $[M+Na]^{+}$ further supported the proposed structure of **244**.



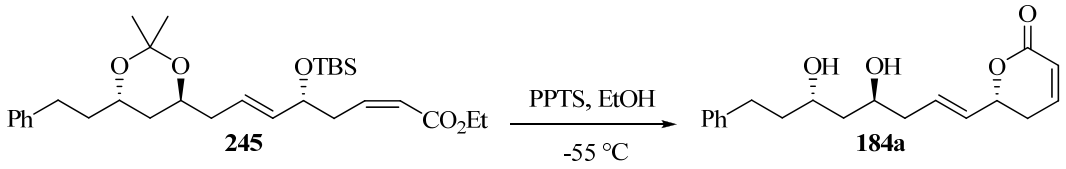
Scheme 23.

The free hydroxyl group of **244** was successively subjected to Swern oxidation to produce the corresponding aldehyde and HWE reaction with ethyl (di-*o*-tolylphosphono)acetate and NaH, in THF at –78 ^{o}C to obtain the *Z*-unsaturated ester **245** exclusively (Scheme 24).[23] In the ^{1}H NMR spectrum of **245** two olefinic protons newly appeared along with the already existing *trans* olefinic protons (5.58 ppm and 5.48 ppm). One proton appeared at δ 5.80 ppm (dt, *J* = 11.5, 7.2 Hz) and the other in the downfield region at δ 6.28 ppm (dt, *J* = 11.5, 1.3 Hz) indicating the presence of an α,β-unsaturated ester group. The geometry of the newly formed double bond was *cis* as it was evident by the coupling constant 11.5 Hz of the olefinic protons. Two signals at δ 120.8 and δ 146.3 as doublets and the ester carbonyl peak at δ 166.4 in the ^{13}C NMR spectrum were assigned to the newly formed α,β-unsaturated ester group. The structure was further supported by the IR spectrum which revealed ester carbonyl at 1712 cm^{-1}. The highest mass peak m/z 423.4 $[M+Na]^{+}$ and elemental analysis served as supporting evidences for structure **245**.



Scheme 24.

Among a few reagents examined PPTS in ethanol at 55 ^{o}C effectively deprotected both the TBS and acetonide groups.[24] Moreover, the lactonization also took place to furnish strictifolione (**184a**) and thus completed our total synthesis endeavour (Scheme 25).



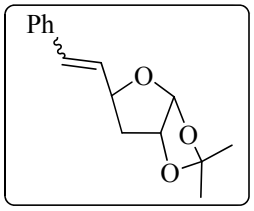
Scheme 25.

In the ^{1}H NMR spectrum the oxymethine proton (H-6) of lactone ring appeared as doublet of triplet at δ 4.89. A peak at 164.0 ppm in the ^{13}C NMR spectrum confirmed the lactone ring formation. In addition to this all the physical and spectroscopic data of the synthetic sample **184a** were in good agreement with the reported data of the natural strictifolione {$[\alpha]_D^{25}$ +61 (*c* 0.6, $CHCl_3$); lit.[4] $[\alpha]_D^{25}$ +81.5 (*c* 0.52, $CHCl_3$); lit.[6c] $[\alpha]_D^{25}$ +54.1 (*c* 0.33, $CHCl_3$)}.

In summary the total synthesis of strictifolione using a combination of chiral pool approach and an asymmetric epoxidation has been accomplished. The Yamaguchi protocol for C−C bond formation and a *Z*-selective HWE reaction for the lactone construction were the key reactions employed.

EXPERIMENTAL

2,2-Dimethyl-5-styryl-tetrahydrofuro[2,3-*d*][1,3]dioxole (224)



To a stirred solution of aldehyde **223** (10 g, 58.1 mmol) in THF (50 mL) at 0 °C, was added a solution of Ph_3P=CHPh [freshly generated from benzyl triphenylphosphonium bromide [(75.3 g, 174.3 mmol) and *n*-BuLi (71 mL, 165.6 mmol, 2.34 M in hexane) at 0 °C] in THF (250 mL). The reaction mixture was stirred at rt for 8 h and then quenched by adding a saturated solution of NH_4Cl. The contents were filtered through a celite pad while washing thoroughly with ether. The combined filtrate fractions were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (10% ethyl acetate in petroleum ether) to obtain an *E*/*Z* mixture (≈1:1) of **224** (9.3 g, 65% yield) as white crystalline solid.

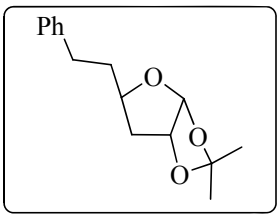
Mol. Formula	: $C_{15}H_{18}O_3$
$[\alpha]_D$	: +7.8 (*c* 1.6, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$	: 3019, 2401, 1600, 1644, 1495, 1216, 1016, 755, 667 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 7.41–7.23 (m, 5H), 6.72–6.64 (m, 1H), 6.16 (dd, *J* = 7.0, 15.9 Hz, 0.5H), 5.90–5.87 (m, 1H), 5.64 (dd, *J* = 9.0, 11.50 Hz, 0.5H), 5.08 (ddd, *J* = 4.2, 10.2, 14.0 Hz, 0.5H), 4.84 (ddd, *J* = 4.3, 7.0, 12.0 Hz, 0.5H), 4.79–4.75 (m, 1H), 2.24 (dt, *J* = 4.0, 13.4 Hz, 1H), 1.78–1.64 (m, 1H), 1.56 (s, 1.5H), 1.45 (s, 1.5H), 1.35 (s, 1.5H), 1.32 (s, 1.5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 26.0, 26.2 (2q, 1C), 26.5, 26.6 (2q, 1C), 39.6, 39.8 (2t, 1C), 73.6 (d), 78.3 (d), 80.4, 80.7 (2d, 1C), 105.2, 105.2 (2d, 1C), 110.9, 110.9 (2s, 1C), 126.4, 127.3, 127.4, 127.7, 128.1, 128.4, 128.6, 129.3, 132.3, 133.7 (10d, 6C), 136.1, 136.3 (2s, 1C) ppm.

ESI-MS (*m/z*) : 269.1 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 73.15; H, 7.37.

Found: C, 73.08; H, 7.42.

2,2-Dimethyl-5-phenethyl-tetrahydrofuro[2,3-*d*][1,3]dioxole (225)



A suspension of compound **224** (9 g, 36.5 mmol) and Raney-Ni (2 g) in ethanol (100 mL) in a 250 mL pyrex glass container was Hydrogenated for 3 h in a parr-shaker instrument keeping the hydrogen gas pressure at 60 psi. The reaction mixture was filtered through a celite pad. The filtrate was evaporated and purified by column chromatography (10% ethyl acetate in petroleum ether) to afford **225** (8.9 g, 98% yield) as colorless needles.

Mol. Formula : $C_{15}H_{20}O_3$

M. P. : 71–72 ^oC.

$[\alpha]_D$: –7.7 (*c* 1.1, $CHCl_3$)

IR ($CHCl_3$) $\tilde{\nu}$: 3436, 2934, 1603, 1216, 1020, 756, 699 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) : δ 7.30–7.19 (m, 5H), 5.83 (d, *J* = 3.7 Hz, 1H), 4.72 (br dd, *J* = 3.7 5.0 Hz, 1H), 4.26–4.17 (m, 1H), 2.79 (ddd, *J* = 5.8, 10.3, 13.8 Hz, 1H), 2.69 (ddd, *J* = 6.7, 9.7, 13.8 Hz, 1H), 2.09 (dd, *J* = 4.1, 13.2 Hz, 1H), 2.01–1.77 (m, 2H), 1.50–1.43 (m, 1H), 1.49 (s, 3H), 1.32 (s, 3H) ppm.

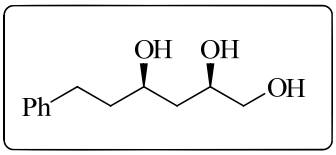
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 26.0 (q), 26.5 (q), 32.3 (t), 35.9 (t), 38.8 (t), 77.1 (d), 80.4 (d), 105.1 (d), 110.7 (s), 125.8 (d), 128.3 (d, 4C), 141.6 (s) ppm.

ESI-MS (*m/z*) : 271.1 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 72.55; H, 8.12.

Found: C, 72.53; H, 8.15.

(2*R*,4*R*)-6-Phenylhexane-1,2,4-triol (227)

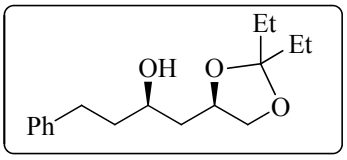


A solution of **225** (8.5 g, 34.3 mmol) in 35% aqueous aceticacid in water (60 mL) was refluxed for 2 h. The reaction mixture was neutralized by adding solid $NaHCO_3$ at 0 ^oC. The mixture was extracted with ethyl acetate several times. The combined organic extracts were washed with brine, filtered through Na_2SO_4, and concentrated to dryness. The residue was filtered through silica gel column using 40% ethyl acetate in petroleum ether to obtain the mixture of α/β lactols **226** (5.2 g, 72% yield) as pale yellow solid.

To a solution of lactol **226** (5 g, 24.0 mmol) in THF at 0 ^oC was added LAH (1.4 g, 36.0 mmol) in portions, stirring continued for overnight at rt. The reaction mixture was quenched with saturated solution of Na_2SO_4 and the inorganic solids were filtered off. The filtrate was concentrated and the crude was purified by column chromatography (80% ethyl acetate in petroleum ether) to afford **227** (4.64 g, 92% yield) as a colorless oil.

Mol. Formula	: $C_{12}H_{18}O_3$
$[\alpha]_D$	: + 24.6 (*c* 1, MeOH).
IR ($CHCl_3$) $\tilde{\nu}$	: 3369, 2940, 1713, 1603,1454, 1055, 749, 699 cm^{-1}
^{1}H NMR (Acetone-d_6, 400 MHz)	: δ 7.27–7.21 (m, 4H), 7.16–7.13 (m, 1H), 4.26 (br s, 2H), 3.86–3.84 (m, 3H), 3.49–3.41 (m, 2H), 2.78 (ddd, *J* = 6.5, 9.0, 15.8 Hz, 1H), 2.66 (ddd, *J* = 7.0, 9.5, 16.6 Hz, 1H), 1.77–1.68 (m, 3H), 1.52 (dt, *J* = 9.0, 14.0 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ 32.2 (t), 40.5 (t), 40.6 (t), 67.0 (t), 70.6 (d), 72.5 (d), 126.1 (d), 128.8 (d, 2C), 128.9 (d, 2C), 143.3 (s) ppm.
ESI-MS (*m/z*)	: 223.1 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 68.54; H, 8.63. Found: C, 68.49; H, 8.65.

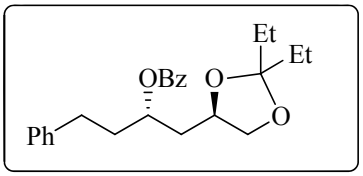
(*R*)-1-((*R*)-2,2-Diethyl-1,3-dioxolan-4-yl)-4-phenylbutan-2-ol (228)



To a stirred solution of triol **227** (4.5 g, 21.4 mmol) in 3-pentanone (50 mL) was added camphor-10-sulfonic acid (0.5 g, 2.1 mmol) at 0 ^{o}C and the reaction mixture was allowed to stir for 4 h at rt. The mixture was neutralized with a few drops of TEA and concentrated under reduced pressure. The residue was purified by column chromatography (15% ethyl acetate in petroleum ether) to procure **228** (5.06 g, 85% yield) as a colorless oil.

Mol. Formula	: $C_{17}H_{26}O_3$
$[\alpha]_D$	: +12.3 (*c* 1.9, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3393, 3018, 2940, 1603, 1454, 1216, 1054, 756, 667 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 7.33–7.18 (m, 5H), 4.32–4.19 (m, 1H), 4.11 (dd, *J* = 6.0, 7.7 Hz, 1H), 3.87 (br ttt, *J* = 4.0, 8.0 Hz, 1H), 3.50 (br t, *J* = 7.8 Hz, 1H), 3.34 (br s, 1H), 2.89–2.62 (m, 2H), 1.88–1.57 (m, 8H), 0.91 (br t, *J* = 7.4 Hz, 3H), 0.89 (br t, *J* = 7.5 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 7.9 (q), 8.1 (q), 29.4 (t), 29.8 (t), 31.7 (t), 39.1 (t), 40.1 (t), 70.2 (t), 70.3 (d), 76.1 (d), 113.4 (s), 125.7 (d), 128.3 (d, 2C), 128.4 (d, 2C), 142.0 (s) ppm.
ESI-MS (*m/z*)	: 301.2 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 73.34; H, 9.41.
	Found: C, 73.40; H, 9.50.

(*S*)-1-((*R*)-2,2-Diethyl-1,3-dioxolan-4-yl)-4-phenylbutan-2-yl benzoate (229)

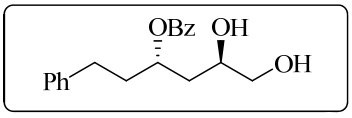


At 0 ^{o}C, a solution of alcohol **228** (5 g, 17.97 mmol) in THF (60 mL) was treated with benzoic acid (2.78 g, 21.56 mmol) and triphenylphosphine (5.65 g, 21.56 mmol)

followed by DEAD (3.4 mL, 21.56 mmol). Stirring was continued for 1 h at 0 ^{o}C and then 5 h at rt. The reaction mixture was concentrated under reduced pressure. The crude obtained was purified by column chromatography (5% ethyl acetate in petroleum ether) to furnish **229** (6.25 g, 91% yield) as a pale yellow oil.

Mol. Formula	: $C_{24}H_{30}O_4$
$[\alpha]_D$	: + 4.6 (*c* 1.5, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3416, 3026, 2970, 1718, 1602, 1273, 1113, 838, 756 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 8.04–8.02 (m, 2H), 7.57 (tt, *J* = 1.4, 7.4, 14.8 Hz, 1H), 7.47–7.43 (m, 2H), 7.28–7.24 (m, 2H), 7.19–7.17 (m, 3H), 5.37–5.30 (m, 1H), 4.20–4.11 (m, 1H), 4.00 (dd, *J* = 6.0, 7.8 Hz, 1H), 3.50 (dd, *J* = 7.8, 8.0 Hz, 1H), 2.79–2.66 (m, 2H), 2.12-2.04 (m, 3H), 1.97 (ddd, *J* = 5.5, 8.3, 14.0 Hz, 1H), 1.65–1.54 (m, 4H), 0.89 (t, *J* = 7.5 Hz, 3H), 0.84 (t, *J* = 7.5 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 7.9 (q), 8.1 (q), 29.6 (t), 29.8 (t), 31.5 (t), 36.5 (t), 38.2 (t), 70.4 (t), 72.2 (d), 73.5 (d), 112.5 (s), 125.9 (d), 128.2 (d, 2C), 128.3 (d), 128.4 (d, 3C), 129.5 (d, 2C), 130.2 (s), 132.9 (d), 141.3 (s), 166.0 (s) ppm.
ESI-MS (*m/z*)	: 405.4 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 75.36; H, 7.91.
	Found: C, 75.31; H, 7.95.

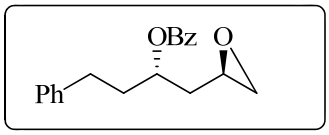
(3*S*,5*R*)-5,6-Dihydroxy-1-phenylhexan-3-yl benzoate (230)



To a stirred solution of benzoate **229** (6 g, 15.7 mmol) in methanol was added *p*-TSA (0.9 g, 5.25 mmol) and the reaction was allowed to stir overnight at rt. After the reaction is complete, excess *p*-TSA was quenched by adding few drops of TEA and the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (40% ethyl acetate in petroleum ether) to afford diol **230** (3.65 g, 74% yield) as pale yellow oil.

Mol. Formula	: $C_{19}H_{22}O_4$
$[\alpha]_D$	: –8.0 (*c* 1.1 $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3419, 2962, 1714, 1602, 1452, 1276, 713, 700 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 8.05–8.03 (m, 2H), 7.57 (br tt, *J* = 1.5, 7.5 Hz, 1H), 7.46 (dd, *J* = 7.5, 7.8 Hz, 2H), 7.28–7.24 (m, 2H), 7.19–7.14 (m, 3H), 5.36 (ddd, *J* = 4.0, 8.5, 12.8 Hz, 1H), 3.67–3.59 (m, 2H), 3.48 (br dd, *J* = 7.0, 10.3 Hz, 1H), 2.81–2.66 (m, 2H), 2.19–2.10 (m, 1H), 2.05–1.96 (m, 1H), 1.77–1.73 (m, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 31.9 (t), 36.8 (t), 38.8 (t), 66.4 (t), 68.0 (d), 71.7 (d), 126.0 (d), 128.3 (d, 2C), 128.5 (d, 4C), 129.6 (s), 129.7 (d, 2C), 133.4 (d), 141.1 (s), 167.8 (s) ppm.
ESI-MS (*m/z*)	: 337.1 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 72.59; H, 7.05.
	Found: C, 72.52; H, 7.10.

(*S*)-1-((*R*)-Oxiran-2-yl)-4-phenylbutan-2-yl benzoate (232)



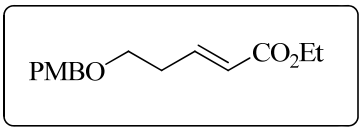
To a solution of diol **230** (3.5 g, 11.1 mmol) and TEA (4.6 mL, 33.3 mmol) in CH_2Cl_2 at 0 ^oC was added Bu_2SnO (55 mg, 0.22 mmol). After 10 min, tosylchloride (2.1 g, 11.1 mmol) was added to the reaction mixture and the progress of the reaction was monitored by TLC. After the completion of reaction (1 h), the mixture was concentrated under vacuum and the residue was purified by column chromatography (20% ethyl acetate in petroleum ether) to obtain tosylate **231** (4.62 g, 89% yield) as a pale yellow oil.

Tosylate **231** (4.5 g, 9.6 mmol) was taken in THF (50 mL) and NaH (0.23 g, 9.6 mmol) was added to it at 0 ^oC. Stirring continued for 1 h after which the TLC showed the complete conversion of the starting material. Ice water was added to the reaction mixture and extracted twice with ethyl acetate. Combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column

chromatography (10% ethyl acetate in petroleum ether) to give the epoxide **232** (3.45 g, 94% yield) as colorless oil.

Mol. Formula	: $C_{19}H_{20}O_3$
$[\alpha]_D$	: –12.7 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3019, 1714, 1602, 1275, 1216, 1113, 756, 712 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz)	: δ 8.04 (br dd, *J* = 1.4, 7.8 Hz, 2H), 7.57 (br tt, *J* = 1.4, 7.4 Hz, 1H), 7.46 (br d, *J* = 7.8 Hz, 1H), 7.45 (br d, *J* = 7.8 Hz, 1H), 7.27–7.24 (m, 2H), 7.18–7.15 (m, 3H), 5.37 (tt, *J* = 4.8, 7.7 Hz, 1H), 3.03–3.00 (m, 1H), 2.77 (ddd, *J* = 5.8, 10.0, 13.8 Hz, 1H), 2.72 (br dd, *J* = 4.0, 5.0 Hz, 1H), 2.70 (ddd, *J* = 6.7, 9.9, 13.7 Hz, 1H), 2.46 (dd, *J* = 2.7, 5.0 Hz, 1H), 2.16–2.03 (m, 2H), 1.98–1.88 (m, 2H) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz)	: δ 31.7 (t), 36.2 (t), 37.8 (t), 46.8 (t), 49.1 (d), 72.0 (d), 126.0 (d), 128.3 (d, 2C), 128.4 (d, 4C), 129.5 (d, 2C), 130.2 (s), 132.9 (d), 141.1 (s), 165.9 (s) ppm.
ESI-MS (*m/z*)	: 327.1 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 77.00; H, 6.80.
	Found: C, 76.93; H, 7.84.

(*E*)-Ethyl-5-(4-methoxybenzyloxy)-pent-2-enoate (235)

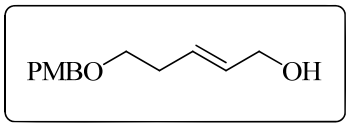


A solution of aldehyde (prepared from **234**, 8 g, 41.2 mmol) and $Ph_3P{=}CHCO_2Et$ (13.6 g, 49.5 mmol) in toluene was refluxed for 3 h. The reaction mixture was concentrated and the residue was purified by column chromatography (12% ethyl acetate in petroleum ether) to afford *E*-**235** (8.92 g, 82% yield) as pale yellow oil.

Mol. Formula	: $C_{15}H_{20}O_4$
IR ($CHCl_3$) $\tilde{\nu}$	: 3417, 2860, 2937, 1718, 1655, 1513, 1248, 771 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 7.24 (br dt, *J* = 2.5, 8.3 Hz, 2H), 6.97 (dt, *J* = 6.8, 15.8 Hz, 1H), 6.87 (br dt, *J* = 2.2, 8.7 Hz, 2H), 5.87 (dt, *J* = 1.6,

	15.7 Hz, 1H), 4.44 (br s, 2H), 4.18 (q, *J* = 7.2, 14.3 Hz, 2H), 3.8 (br s, 3H), 3.54 (t, *J* = 6.4 Hz, 2H), 2.52 (dd, *J* = 1.5, 6.6 Hz, 1H), 2.46 (br dd, *J* = 1.5, 6.7 Hz, 1H), 1.29 (t, *J* = 7.1, Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 14.1 (q), 32.5 (t), 54.9 (q), 59.9 (t), 67.7 (t), 72.5 (t), 113.6 (d, 2C), 122.7 (d), 129.1 (d, 2C), 130.0 (s), 145.4 (d), 159.1 (s), 166.1 (s) ppm.
ESI-MS (*m/z*)	: 287.1 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 68.16; H, 7.63. Found: C, 68.19; H, 7.69.

(*E*)-5-(4-Methoxybenzyloxy)pent-2-en-1-ol (236)

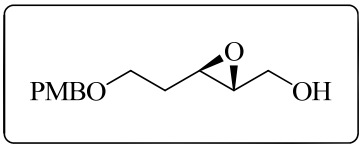


At –78 °C, a solution of ester **235** (8.8 g, 33.3 mmol) in CH_2Cl_2 was treated with DIBAL-H (18.5 mL, 1.8 M in toluene) and the reaction mixture was stirred for 5 h at –78 °C. A saturated solution of potassium sodium tartrate was added slowly to the reaction mixture at –78 °C. The solid was filtered off and the filtrate was concentrated. The crude residue obtained was purified by column chromatography (40% ethyl acetate in petroleum ether) to afford **236** (5.55 g, 75% yield) as colorless oil.

Mol. Formula	: $C_{13}H_{18}O_3$
IR ($CHCl_3$) $\tilde{\nu}$	: 3304, 3019, 2991, 2936, 1655, 1513, 1248, 771 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 7.24 (br dt, *J* = 2.5, 10.5 Hz, 2H), 6.86 (br dt, *J* = 2.5, 9.5 Hz, 2H), 5.73–5.68 (m, 2H), 4.43 (br s, 2H), 4.09–4.06 (m, 2H), 3.80 (br s, 3H), 3.48 (t, *J* = 6.7 Hz, 2H), 2.40–2.30 (m, 2H), 1.55 (br s, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 32.4 (t), 55.0 (q), 63.0 (t), 69.1 (t), 72.3 (t), 113.6 (d, 2C), 128.6 (d), 129.1 (d, 2C), 130.1 (s), 131.0 (d), 159.0 (s) ppm.
ESI-MS (*m/z*)	: 245.2 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 70.24; H, 8.16.
Found: C, 70.18; H, 8.17

((2*R*,3*R*)-3-(2-(4-Methoxybenzyloxy)ethyl)oxiran-2-yl)methanol (237)



In a dry two neck round bottom flask, 4Å molecular sieves powder (4 g) was placed and evacuated with flame under argon. 100 mL of CH_2Cl_2 was injected into the rb. The solution was allowed to cool to –20 °C. Then $Ti(O^iPr)_4$ (7.9 mL, 26.7 mmol) and D(-)-DIPT (5.6 mL, 27.2 mmol) were added sequentially. After stirring for 5 min, TBHP (13.5 mL, 48.6 mmol, 3.6 M in toluene) was added dropwise for 15 min. After stirring for 30 min at –20 °C, a solution of allylic alcohol **236** (5.4 g, 24.3 mmol) in CH_2Cl_2 was added to the reaction mixture and stirred overnight at the same temperature. Reaction was quenched by adding water (160 mL) and stirred vigorously while warming the reaction mixture slowly to rt. The reaction mixture was filtered through celite pad and the filtrate containing aqueous and organic layers was extracted with CH_2Cl_2. Combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (50% ethyl acetate in petroleum ether to obtain the pure epoxy alcohol **237** (4.9 g, 82% yield) as colorless oil.

Mol. Formula : $C_{13}H_{18}O_3$

$[\alpha]_D$: +26.5 (*c* 1.5, $CHCl_3$)

IR ($CHCl_3$) $\tilde{\nu}$: 3016, 1270, 840 cm^{-1}.

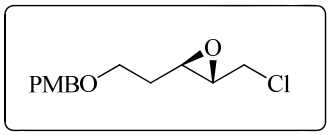
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 7.26 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.45 (s, 2H), 3.92–3.85 (m, 1H), 3.80 (s, 3H), 3.65–3.55 (m, 3H), 3.09 (ddd, *J* = 2.4, 4.9, 7.2 Hz, 1H), 2.97 (dt, *J* = 2.5, 4.4 Hz, 1H), 2.02–1.74 (m, 3H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 31.7 (t), 53.4 (d), 54.8 (q), 58.3 (d), 61.5 (t), 66.2 (t), 72.3 (t), 113.5 (d, 2C), 128.9 (d, 2C), 129.9 (s), 158.9 (s) ppm.

ESI-MS (*m/z*) : 261.2 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 70.24; H, 8.16.
Found: C, 70.22; H, 8.19

(2*S*,3*R*)-2-(Chloromethyl)-3-(2-(4-methoxybenzyloxy)ethyl)oxirane (238)



To a solution of epoxy alcohol **237** (4.9 g, 21.1 mmol) in CCl_4 (150 mL), was added TPP (6.6 g, 25.3 mmol) and the reaction mixture was refluxed for 8 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (12% ethyl acetate in petroleum ether) to give the chloro oxirane **238** (4.6 g, 87% yield) as a colorless oil.

Mol. Formula : $C_{13}H_{17}ClO_3$

$[\alpha]_D$: +14.0 (*c* 1, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 2954, 1514, 1301, 1247, 1098, 1034, 771, 733 cm^{-1}.

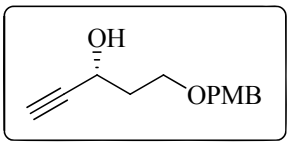
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 7.30–7.23 (m, 2H), 6.92–6.85 (m, 2H), 4.46 (br s, 2H), 3.82 (s, 3H), 3.61–3.53 (m, 4H), 3.08–3.01 (m, 2H), 2.02–1.73 (m, 2H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 31.9 (t), 44.5 (t), 55.0 (q), 56.5 (d), 57.0 (d), 66.2 (t), 72.6 (t), 113.7 (d, 2C), 129.1 (d, 2C), 130.1 (s), 159.1 (s) ppm.

ESI-MS (*m/z*) : 279.2 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 60.82; H, 6.67.
Found: C, 60.75; H, 6.71.

(*R*)-5-(4-Methoxybenzyloxy)pent-1-yn-3-ol (239)

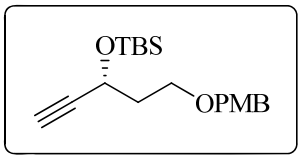


To a solution of **238** (4.5 g, 17.6 mmol) in dry THF was added excess *n*-BuLi (22 mL, 52.7 mmol, 2.34 M in hexane) at –40 °C and the reaction mixture was stirred for 1 h

at the same temperature. The reaction mixture was quenched by adding a saturated solution of NH_4Cl and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (20% ethyl acetate in petroleum ether) to afford the hydroxy alkyne **239** (3.05 g, 79% yield) as pale yellow oil.

Mol. Formula	: $C_{13}H_{16}O_3$
$[\alpha]_D$	: +22.3 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3410, 3289, 2933, 2113, 1513, 1248, 1032, 819 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 7.28–2.21 (m, 2H), 6.90–6.83 (m, 2H), 4.60–4.55 (m, 1H), 4.46 (br s, 2H), 3.91–3.82 (m, 1H), 3.80 (br s, 3H), 3.65 (ddd, *J* = 4.5, 5.8, 10.2 Hz, 1H), 2.44 (br d, *J* = 2.1 Hz, 1H), 2.17-1.85 (m, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 36.5 (t), 55.1 (q), 60.9 (d), 67.0 (t), 72.8 (d), 72.9 (t), 84.3 (s), 113.7 (d, 2C), 129.3 (d, 2C), 129.8 (s), 159.2 (s) ppm.
ESI-MS (*m/z*)	: 243.2 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 70.89; H, 7.32.
	Found: C, 70.90; H, 7.36.

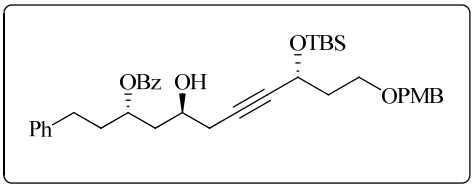
(*R*)-*tert*-Butyl(5-(4-methoxybenzyloxy)pent-1-yn-3-yloxy)dimethylsilane (240)



A solution of **239** (3.05 g, 1.4 mmol) and imidazole (143 mg, 2.1 mmol) in CH_2Cl_2 was treated with TBSCl (251 mg, 1.7 mmol) at 0 °C. The reaction mixture was stirred for 4 h at rt. Water was added to the reaction mixture and aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue obtained was purified by column chromatography (7% ethyl acetate in petroleum ether) to afford **240** (3.75 g, 81% yield) as colorless oil.

Mol. Formula	: $C_{19}H_{30}O_3Si$
$[\alpha]_D$	: +35.7 (*c* 1.8, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3308, 2930, 1613,1513, 1250, 1098, 838, 758 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 7.25 (br dt, *J* = 2.3, 8.6 Hz, 2H), 6.87 (br dt, *J* = 2.3, 8.8 Hz, 2H), 4.57 (dt, *J* = 5.3, 15.1 Hz, 1H), 4.42 (q, *J* = 11.3, 15.1 Hz, 2H), 3.80 (s, 3H), 3.61–3.55 (m, 2H), 2.37 (d, *J* = 2.3 Hz, 1H), 1.97 (q, *J* = 6.3, 12.5 Hz, 2H), 0.90 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ –5.1 (q), –4.6 (q), 18.2 (s), 25.8 (q, 3C), 38.7 (t), 55.1 (q), 59.7 (d), 65.8 (t), 72.1 (d), 72.7 (t), 85.4 (s), 113.7 (d, 2C), 129.2 (d, 2C), 130.4 (s), 159.1 (s) ppm.
ESI-MS (*m/z*)	: 357.4 $[M+Na]^+$.
Elemental Analysis	Calcd: C, 68.22; H, 9.04.
	Found: C, 68.14; H, 9.08.

(3*S*,5*S*,9*R*)-9-(*tert*-Butyldimethylsilyloxy)-5-hydroxy-11-(4-methoxybenzyloxy)-1-phenylundec-7-yn-3-yl benzoate (241)

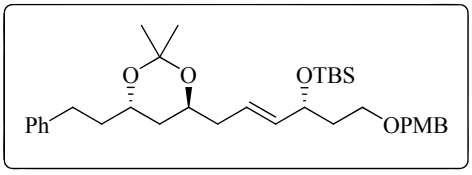


To a solution of alkyne **240** (2.25 g, 6.7 mmol) in anhydrous THF in a flame dried two neck round bottom flask under argon was added *n*-BuLi (4.2 mL, 6.7 mmol, 1.6 M in hexane) dropwise at –78 ^oC. After 15 min, $BF_3.Et_2O$ (0.84 mL, 6.7 mmol) was added slowly dropwise. Reaction mixture was allowed to stir for another 15 min at the same temperature after which a solution of epoxide **232** (1 g, 3.3 mmol) in THF was added. Reaction was quenched by adding a solution of THF–H_2O (1:1) when the TLC showed the complete consumption of the epoxide. The mixture was slowly warmed to rt and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified on flash

silica-gel (25% ethyl acetate in petroleum ether) to furnish the title compound **241** (1.76 g, 85% yield) as colorless oil.

Mol. Formula	: $C_{38}H_{50}O_6Si$
$[\alpha]_D$	: –4.0 (*c* 2.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3470, 2932, 1715, 1612, 1513, 1274, 1032, 648 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz)	: δ 8.06-8.05 (m, 2H), 7.61-7.57 (m, 1H), 7.46 (br t, *J* = 7.3 Hz, 2H), 7.28–7.23 (m, 4H), 7.19–7.16 (m, 3H), 6.88-6.86 (m, 2H), 5.41–5.36 (m, 1H), 4.57–4.51 (m, 1H), 4.43– 4.37 (m, 2H), 3.80 (s, 3H), 3.73–3.68 (m, 1H), 3.58–3.53 (m, 2H), 2.79–2.67 (m, 2H), 2.47–2.41 (m, 1H), 2.36–2.32 (m, 1H), 2.17–2.09 (m, 1H), 2.04–1.99 (m, 2H), 1.95–1.91 (m, 2H), 1.77–1.72 (m, 1H), 0.89 (br s, 9H), 0.09 (s, 3H), 0.08 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz)	: δ –5.1 (q), –4.6 (q), 18.2 (s), 25.8 (q, 3C), 27.2 (t), 31.9 (t), 36.8 (t), 38.9 (t), 41.9 (t), 55.2 (q), 60.1 (d), 66.0 (t), 66.1 (d), 71.7 (d), 72.6 (t), 80.5 (s), 84.1 (s), 113.7 (d, 2C), 126.0 (d), 128.3 (d, 2C), 128.4 (d, 2C), 128.5 (d, 3C), 129.2 (d), 129.2 (s), 129.7 (d, 2C), 130.5 (s), 133.2 (d), 141.2 (s), 159.1 (s), 167.4 (s) ppm.
ESI-MS (*m/z*)	: 653.5 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 72.34; H, 7.99. Found: C, 72.40; H, 7.96.

tert-Butyl((*R*,*E*)-6-((4*S*,6*S*)-2,2-dimethyl-6-phenethyl-1,3-dioxan-4-yl)-1-(4-methoxybenzyloxy)hex-4-en-3-yloxy)dimethylsilane (243)



To a solution of homopropargylic alcohol **241** (1.5 g 2.4 mmol) in ether (30 mL), was added Red-Al (65 wt % in toluene, 7.3 mL, 4.7 mmol) dropwise at –20 ^oC. The mixture was stirred at –20 ^oC for 8 h and quenched with saturated solution of potassium

sodium tartrate. After the mixture was stirred for 1 h, the layers were separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (35% ethyl acetate in petroleum ether) to accomplish **242** (0.9 g, 73% yield) as pale yellow oil.

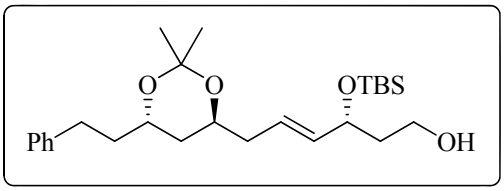
A solution of diol (500 mg, 0.9 mmol) and dimethoxypropane (1.7 mL, 1.4 mmol) in dry acetone was exposed to a catalytic amount of camphor-10-sulfonicacid (CSA) (22 mg, 0.09 mmol) at 0 ^oC and stirred for 30 min. The reaction mixture was neutralized with TEA (two drops) and concentrated under reduced pressure. The residual compound was purified by column chromatography (10% ethyl acetate in petroleum ether) to obtain **243** (500 mg, 95% yield) as a colorless oil.

Mol. Formula	: $C_{34}H_{52}O_5Si$
$[\alpha]_D$	: +10.3 (*c* 1.1, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3396, 3027, 2934, 1613, 1586, 1248, 1092, 836 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz)	: δ 7.25–7.23 (m, 4H), 7.19–7.14 (m, 3H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.52 (dt, *J* = 6.8, 15.4 Hz, 1H), 5.45 (dd, *J* = 6.2, 15.4 Hz, 1H), 4.42 (d, *J* = 11.5 Hz, 1H), 4.36 (d, *J* = 11.5 Hz, 1H), 4.24 (br q, *J* = 6.2 Hz, 1H), 3.83–3.78 (m, 1H), 3.79 (s, 3H), 3.76–3.70 (m, 1H), 3.53 (tt, *J* = 6.8, 9.2 Hz, 1H), 3.44 (dt, *J* = 6.2, 9.2 Hz, 1H), 2.75 (ddd, *J* = 5.3, 9.3, 13.7 Hz, 1H), 2.60 (ddd, *J* = 7.2, 8.9, 13.7 Hz, 1H), 2.20 (dt, *J* = 6.5, 13.7 Hz, 1H), 2.12 (dt, *J* = 6.5, 13.7 Hz, 1H), 1.86–1.78 (m, 1H), 1.76–1.69 (m, 3H), 1.58–1.55 (m, 2H), 1.34 (s, 3H), 1.32 (s, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ –4.8 (q), –4.2 (q), 18.2 (s), 24.9 (q, 2C), 25.9 (q, 3C), 31.7 (t), 37.5 (t), 38.2 (t), 38.4 (t), 38.6 (t), 55.1 (q), 65.7 (d), 66.3 (d), 66.4 (t), 70.4 (d), 72.6 (t), 100.3 (s), 113.7 (d, 2C), 125.7 (d, 2C), 128.3 (d, 2C), 128.4 (d, 2C), 129.2 (d, 2C), 130.6 (s), 135.9 (d), 141.9 (s), 159.1 (s) ppm.
ESI-MS (*m/z*)	: 591.5 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 71.79; H, 9.21.

Found: C, 71.56; H, 9.42.

(*R*,*E*)-3-(*t*-Butyldimethylsilyloxy)-6-((4*S*,6*S*)-2,2-dimethyl-6-phenethyl-1,3-dioxan-4-yl)hex-4-en-1-ol (244)



To a solution of **243** (0.5 g, 0.9 mmol) in CH_2Cl_2:H_2O (18:1, 10 mL), DDQ (0.24 g, 1.0 mmol) was added at 0 °C and the mixture was vigorously stirred for 30 min. The reaction was quenched with saturated $NaHCO_3$ solution and stirred for another 10 min. The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The crude was purified by column chromatography (20% ethyl acetate in petroleum ether to afford **244** (0.34 g, 86% yield) as pale yellow oil.

Mol. Formula : $C_{26}H_{44}O_4Si$

$[\alpha]_D$: +24.5 (*c* 1.5, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3369, 2930, 1471, 1253, 1063, 836, 776 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz) : δ 7.29–7.26 (m, 2H), 7.20–7.17 (m, 3H), 5.61 (dt, *J* = 6.6, 15.4 Hz, 1H), 5.54 (dd, *J* = 6.0, 15.4 Hz, 1H), 4.37 (dd, *J* = 6.0, 11.5 Hz, 1H), 3.85 (dt, *J* = 7.3, 14.0 Hz, 1H), 3.81–3.75 (m, 2H), 3.69 (ddd, *J* = 4.2, 6.1, 10.7 Hz, 1H), 2.77 (ddd, *J* = 5.2, 9.3, 14.2 Hz, 1H), 2.62 (ddd, *J* = 7.4, 8.8, 14.0 Hz, 1H), 2.26–2.15 (m, 2H), 1.88–1.78 (m, 2H), 1.76–1.68 (m, 2H), 1.63–1.57 (m, 1H), 1.41–1.38 (m, 1H), 1.37 (s, 3H), 1.34 (s, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H) ppm.

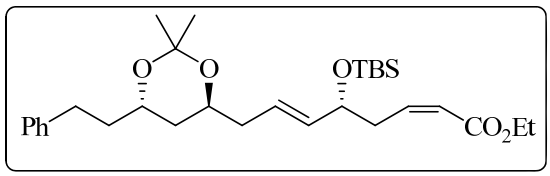
^{13}C NMR ($CDCl_3$, 125 MHz) : δ –5.0 (q), –4.3 (q), 18.0 (s), 24.8 (q, 2C), 25.8 (q, 3C), 31.6 (t), 37.4 (t), 38.2 (t), 38.5 (t), 39.6 (t), 60.1 (t), 65.7 (d), 66.2 (d), 73.0 (d), 100.4 (s), 125.7 (d), 126.4 (d), 128.3 (d, 2C), 128.4 (d, 2C), 135.0 (d), 141.9 (s) ppm.

ESI-MS (*m/z*) : 372.1 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 69.59; H, 9.88.

Found: C, 69.63; H, 9.86.

(*R*,2*Z*,6*E*)-Ethyl 5-(*tert*-butyldimethylsilyloxy)-8-((4*S*,6*S*)-2,2-dimethyl-6-phenethyl-1,3-dioxan-4-yl)octa-2,6-dienoate (245)



Oxalylchloride (38 µl, 0.44 mmol) in DCM (2 mL) was cooled to –78 °C. DMSO (62 µL, 0.88 mmol) was added dropwise. The reaction mixture was stirred at –78 °C until no gas evolution occurs anymore (30 min). Then alcohol **243** (0.1 g, 0.22 mmol) in DCM (3 mL) was added dropwise *via* a syringe. After stirring for 1 h at –78 °C, triethylamine (170 µL, 1.32 mmol) was added dropwise. The reaction mixture was slowly warmed to 0 °C over 30 min and quenched with water (10 mL). The layers were separated, and the water layer was extracted with DCM (2 x 10 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The crude product was directly used for the next reaction without any further purification.

To a solution of ethyl (di-*o*-tolylphosphono)acetate (155 mg, 0.44 mmol) in THF (12 mL) at 0 ^oC was added NaH (18 mg, 60% w/w in paraffin oil, 0.46 mmol). 30 min later, the reaction mixture was cooled to –78 ^oC and the solution of aldehyde **244** in THF (3 mL) was added dropwise. The resulting reaction mixture was stirred for 45 min at the same temperature. Reaction was quenched by adding ice water and slowly warmed to ambient temperature. The mixture was extracted with EtOAc, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (10% EtOAc in petroleum ether) to give the unsaturated ester **245** (93 mg, 81% over two steps) as pale yellow oil.

Mol. Formula : $C_{30}H_{48}O_5Si$

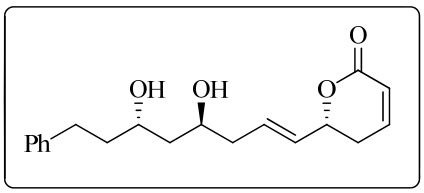
$[\alpha]_D$: +16 (*c* 2, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3401, 3020, 1712, 1596, 1530, 1351, 1215, 874, 756 cm^{-1}.

^{1}H NMR : δ 7.28–7.25 (m, 2H), 7.19–7.15 (m, 3H), 6.28 (dt, *J* = 7.2,

($CDCl_3$, 500 MHz)	11.5 Hz, 1H), 5.80 (dt, *J* = 1.3, 11.5 Hz, 1H), 5.58 (dt, *J* = 6.8, 15.4 Hz, 1H), 5.48 (dd, *J* = 6.2, 15.4 Hz, 1H), 4.23 (br q, *J* = 5.9 Hz, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.8 (br tt, *J* = 6.8, 8.2 Hz, 1H), 3.76–3.71 (m, 1H), 2.85–2.82 (m, 2H), 2.75 (ddd, *J* = 5.3, 9.3, 13.8 Hz, 1H), 2.61 (ddd, *J* = 7.2, 9.1, 13.8 Hz, 1H), 2.22 (dt, *J* = 6.8, 13.7 Hz, 1H), 2.12 (dt, *J* = 6.6, 13.7 Hz, 1H), 1.86–1.79 (m, 1H), 1.74–1.67 (m, 1H), 1.59–1.55 (m, 2H), 1.35 (s, 3H), 1.32 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz)	: δ –4.8 (q), –4.4 (q), 14.3 (q), 18.2 (s), 24.8 (q), 24.9 (q), 25.8 (q, 3C), 31.6 (t), 37.4 (t), 37.5 (t), 38.1 (t), 38.5 (t), 59.8 (t), 65.8 (d), 66.3 (d), 72.3 (d), 100.3 (s), 120.8 (d), 125.7 (d), 126.2 (d), 128.3 (d, 2C), 128.4 (d, 2C), 135.1 (d), 142.0 (s), 146.3 (d), 166.4 (s) ppm.
ESI-MS (*m/z*)	: 539.4 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 69.72; H, 9.36. Found: C, 69.77; H, 9.41.

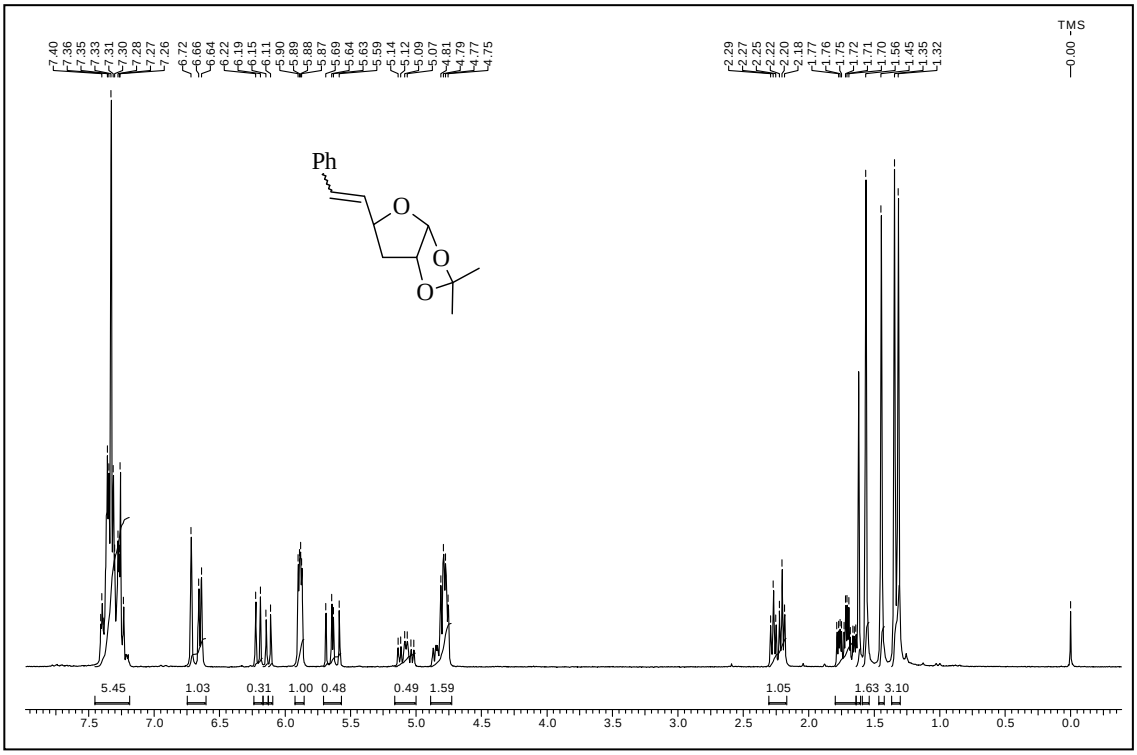
Strictifolione (184a)



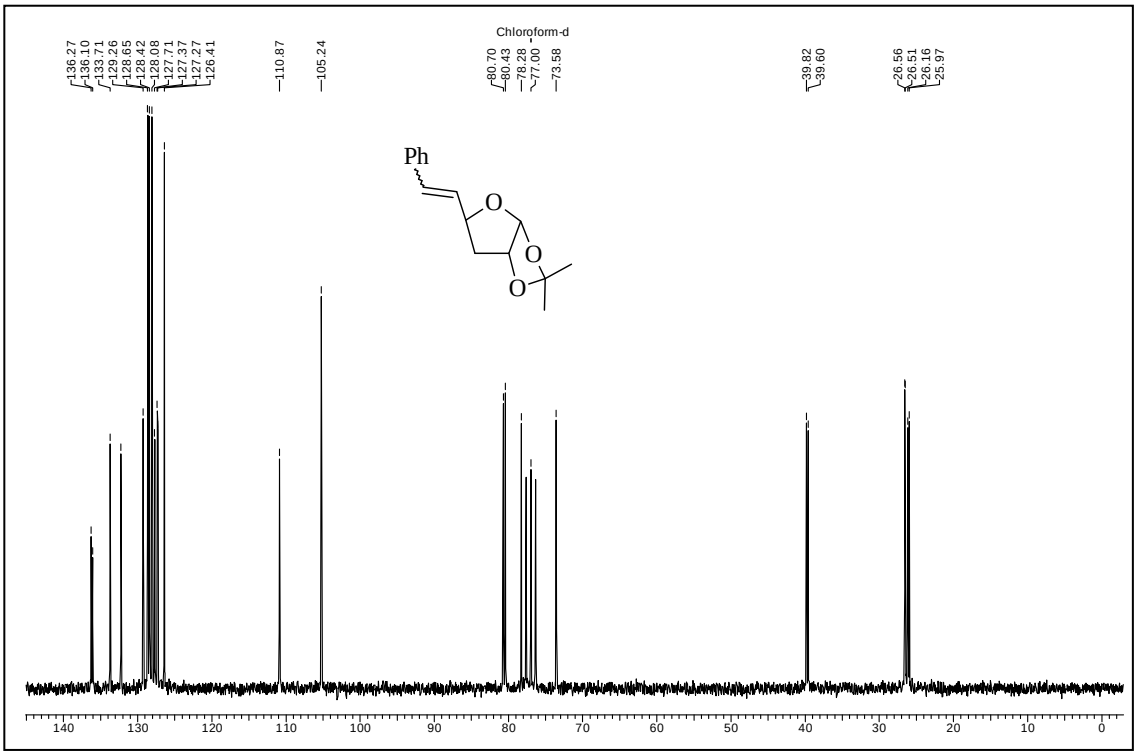
To a solution of **245** (50 mg, 0.096 mmol) in ethanol was added PPTS (13 mg, 0.05 mmol) and the reaction mixture was heated at 55 °C for 6 h. Reaction was neutralized with triethylamine and concentrated under reduced pressure. The crude product was purified by column chromatography using 60% ethyl acetate in petroleum ether to afford strictifolione (**184a**) (10 mg, 67% yield) as white crystalline solid.

Mol. Formula	: $C_{19}H_{24}O_4$
M.P.	: 118–119 °C
$[\alpha]_D$	: +61 (*c* 0.6, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$	: 3325, 2932, 1723, 1438, 1381, 1240, 1048 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz)	: δ 7.29–7.26 (m, 2H), 7.20–7.17 (m, 3H), 6.87 (ddd, *J* = 3.4, 4.9, 9.8 Hz, 1H), 6.04 (ddd, *J* = 1.5, 2.0, 9.8 Hz, 1H), 5.88–5.83 (m, 1H), 5.68 (ddd, *J* = 1.2, 6.4, 15.4 Hz, 1H), 4.89 (dt, *J* = 6.4, 8.8 Hz, 1H), 4.05–4.0 (m, 1H), 3.99–3.94 (m, 1H), 2.78 (ddd, *J* = 5.9, 9.8, 15.0 Hz, 1H), 2.67 (ddd, *J* = 6.7, 9.3, 15.6 Hz, 1H), 2.45–2.41 (m, 2H), 2.27 (t, *J* = 6.8 Hz, 2H), 1.90–1.83 (m, 1H), 1.81–1.75 (m, 1H), 1.65 (m, 2H) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz)	: δ 29.7 (t), 32.2 (t), 39.0 (t), 40.3 (t), 42.1 (t), 68.3 (d), 68.8 (d), 77.7 (d), 121.5 (d), 125.9 (d), 128.4 (d, 2C), 128.5 (d, 2C), 130.0 (d), 131.1 (d), 141.8 (s), 144.7 (d), 164.0 (s) ppm.
ESI-MS (*m/z*)	: 339.2 $[M+Na]^+$
Elemental Analysis	Calcd.: C, 72.13; H, 7.65. Found: C, 72.09; H, 7.67.

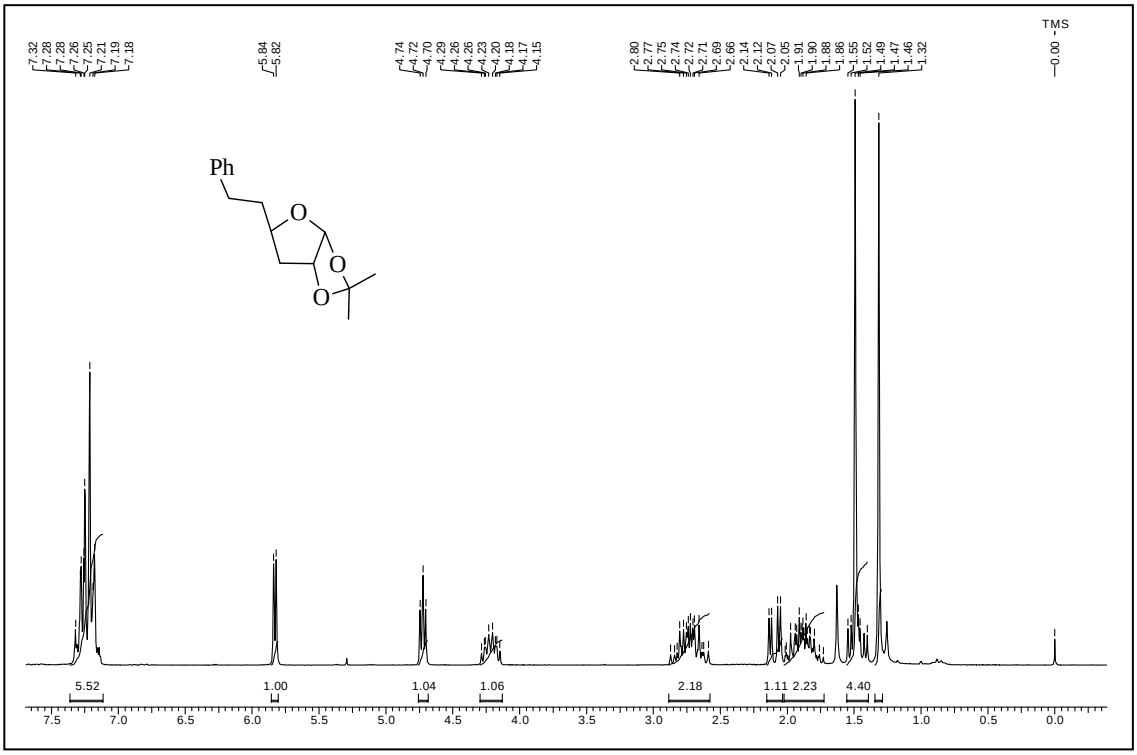
SPECTRA



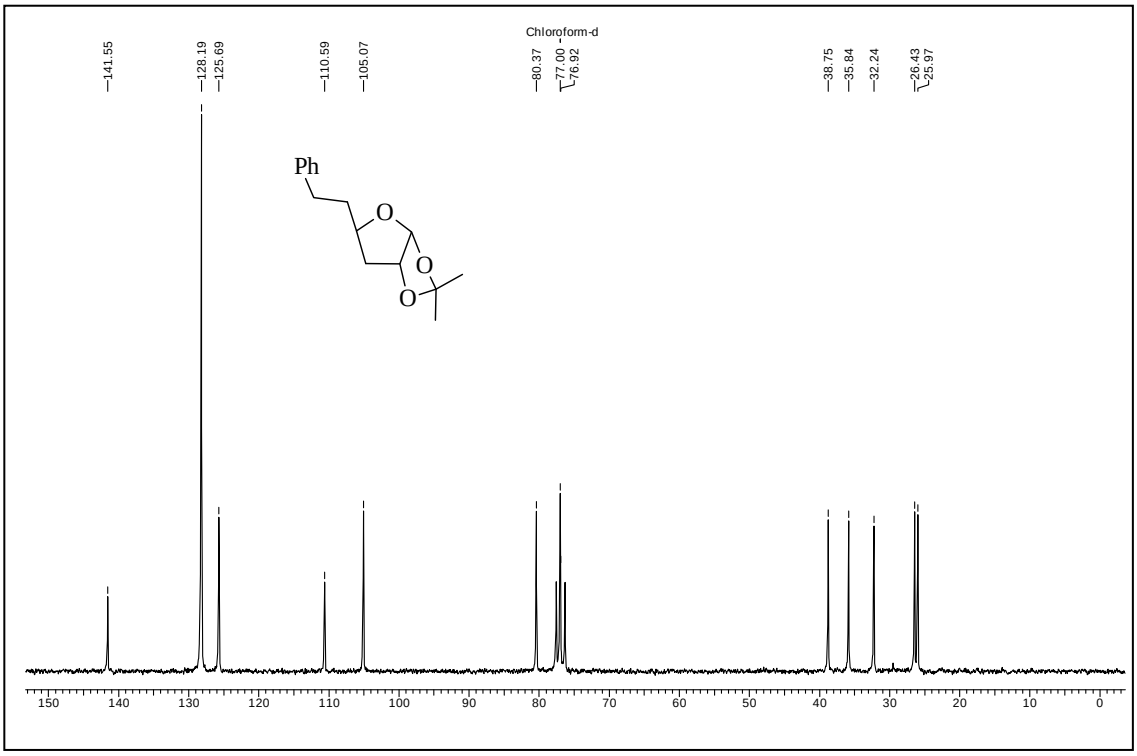
^{1}H NMR Spectrum of 224 in $CDCl_3$



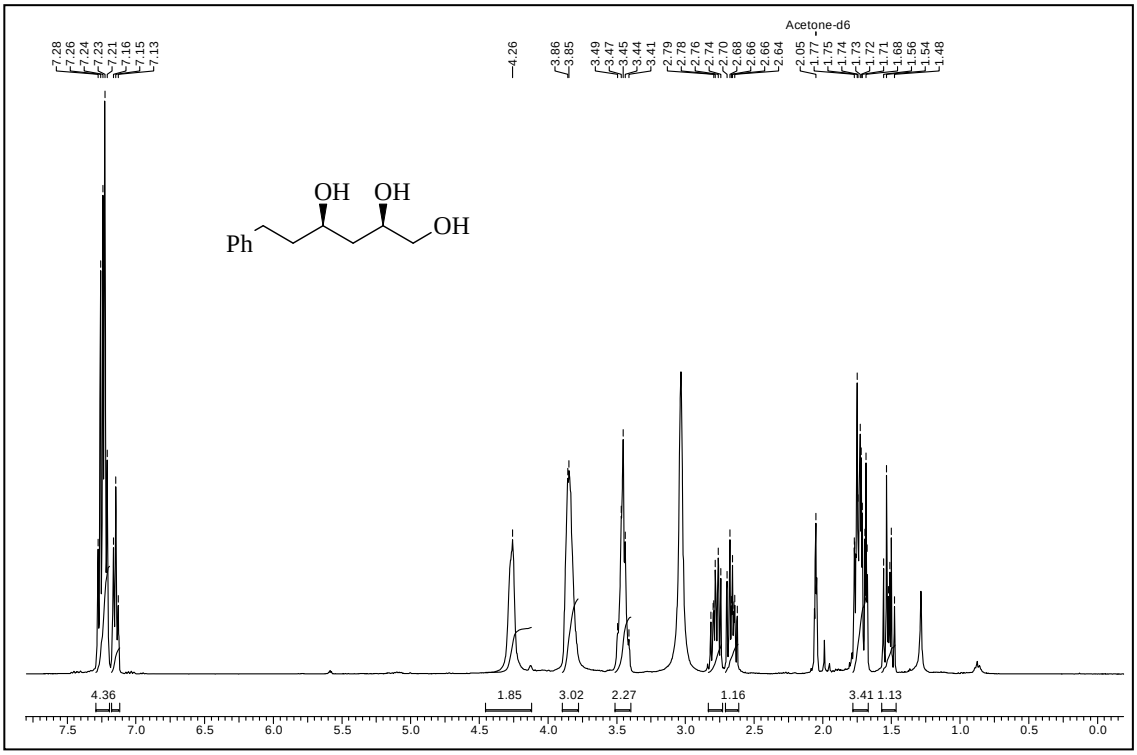
^{13}C NMR Spectrum of 224 in $CDCl_3$



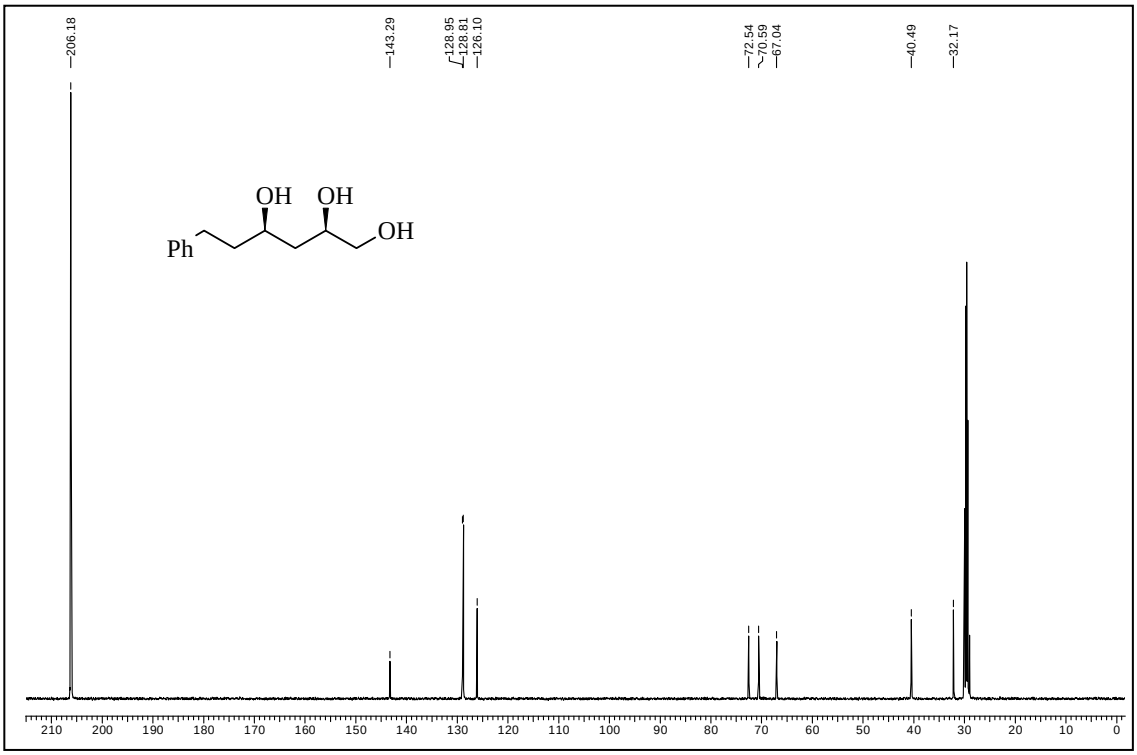
^{1}H NMR Spectrum of 225 in $CDCl_3$



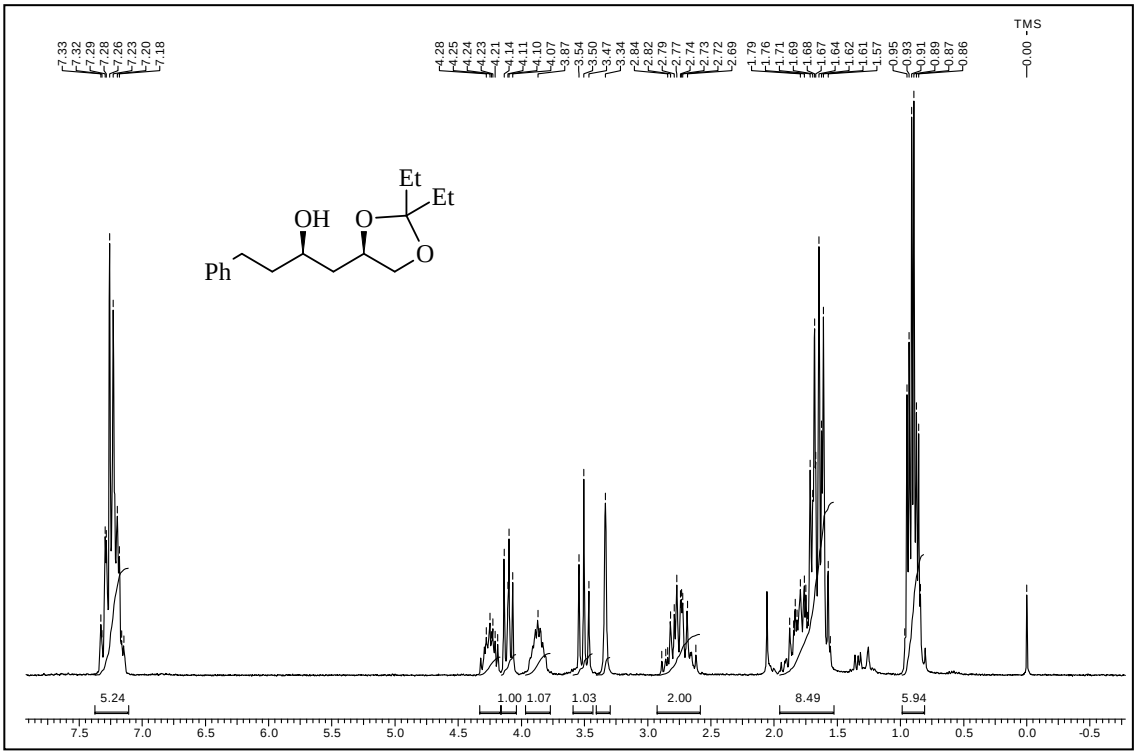
^{13}C NMR Spectrum of 225 in $CDCl_3$



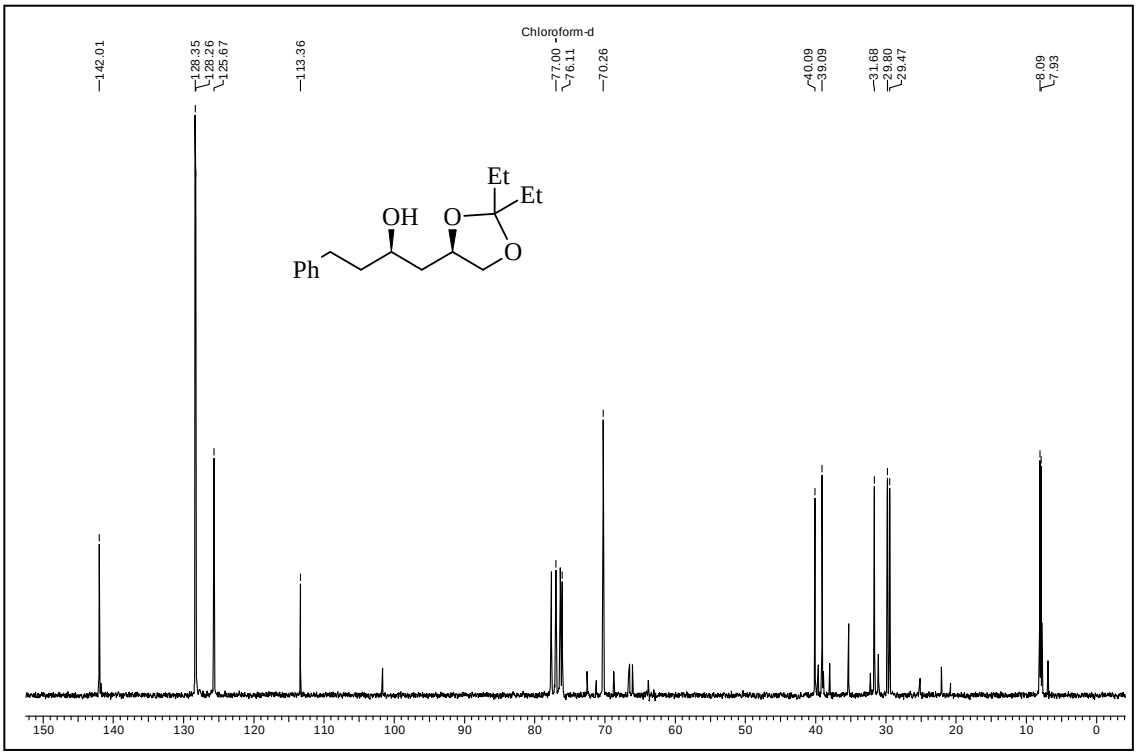
^{1}H NMR Spectrum of 227 in Acetone-d6



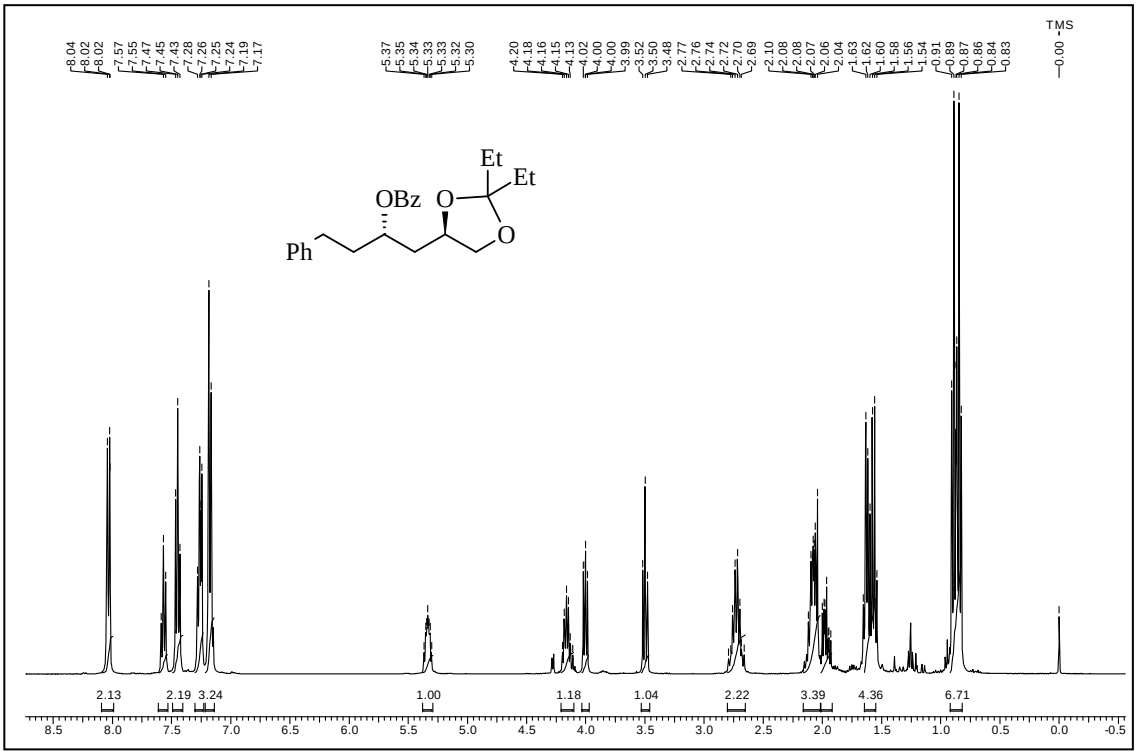
^{13}C NMR Spectrum of 227 in Acetone-d6



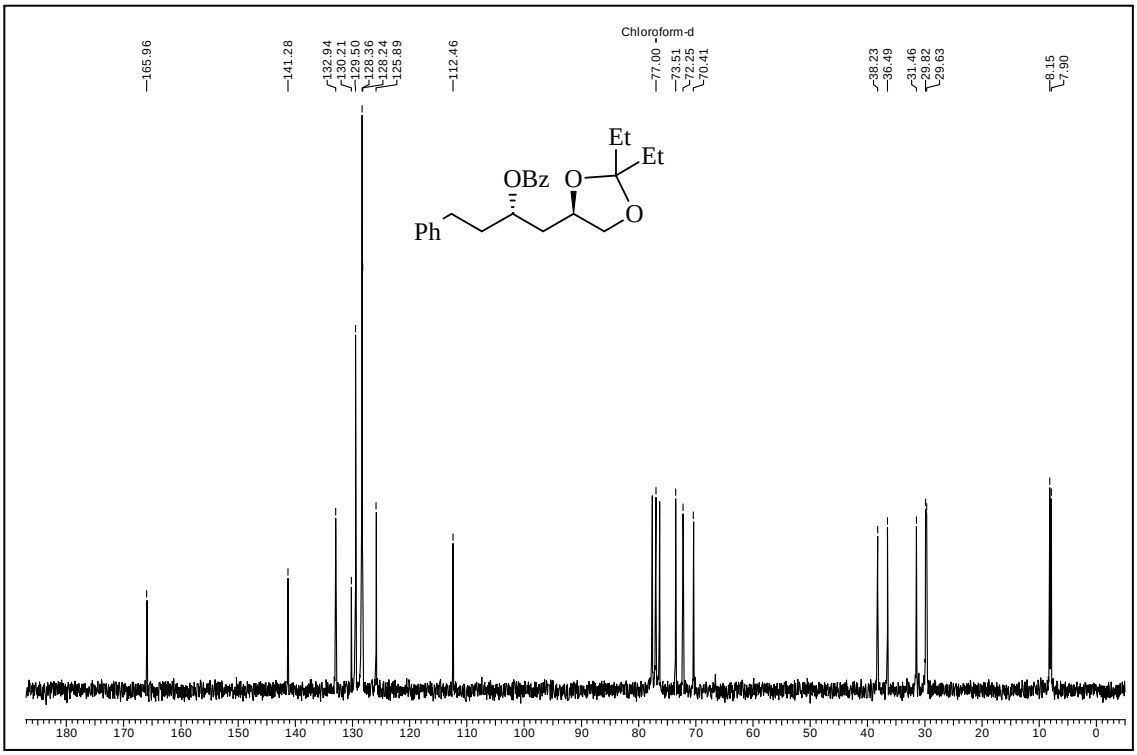
^{1}H NMR Spectrum of 228 in $CDCl_3$



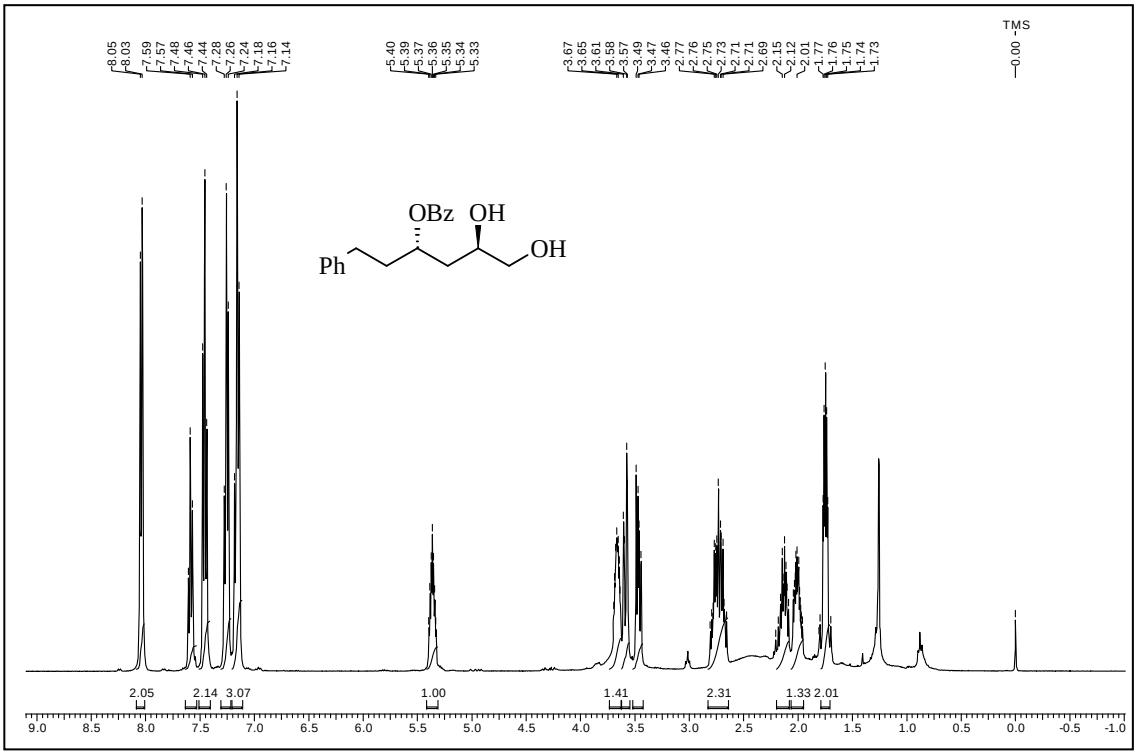
^{13}C NMR Spectrum of 228 in $CDCl_3$



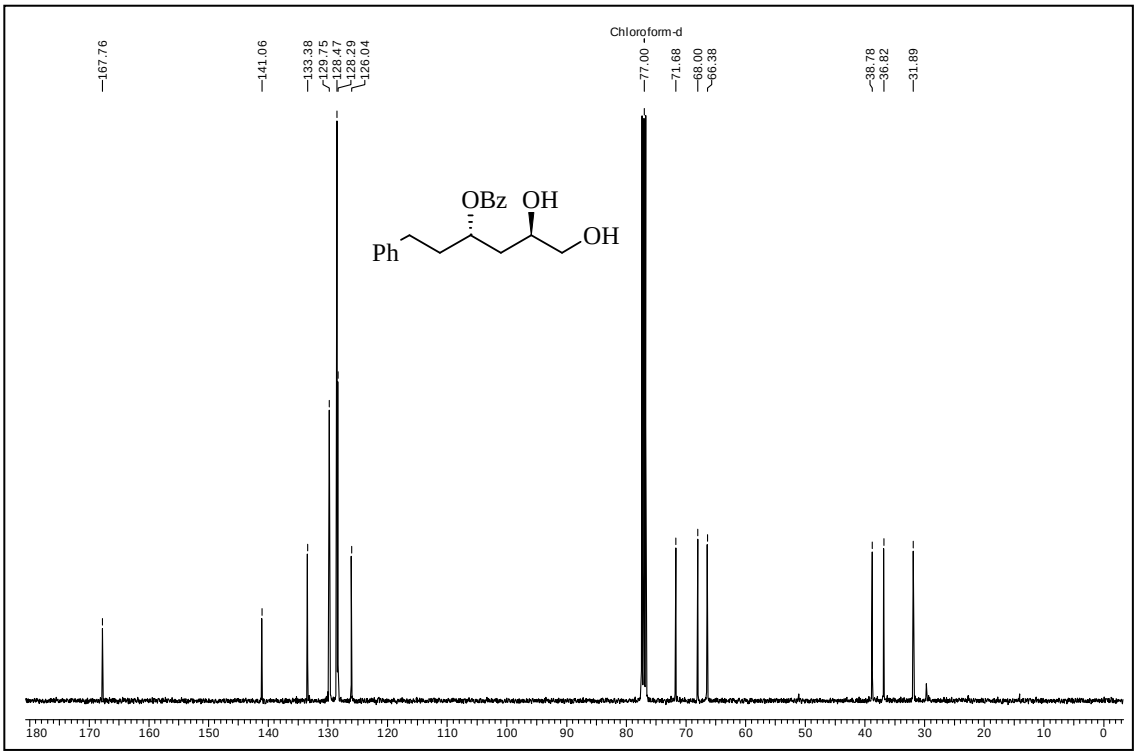
^{1}H NMR Spectrum of 229 in $CDCl_3$



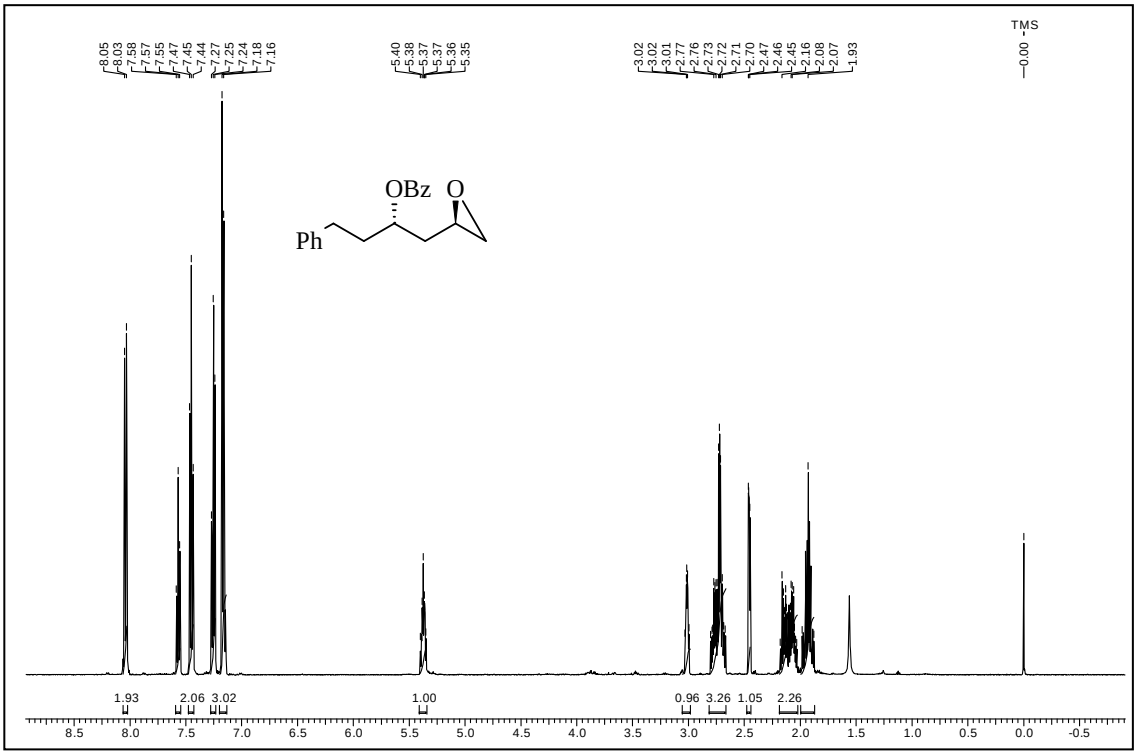
^{13}C NMR Spectrum of 229 in $CDCl_3$



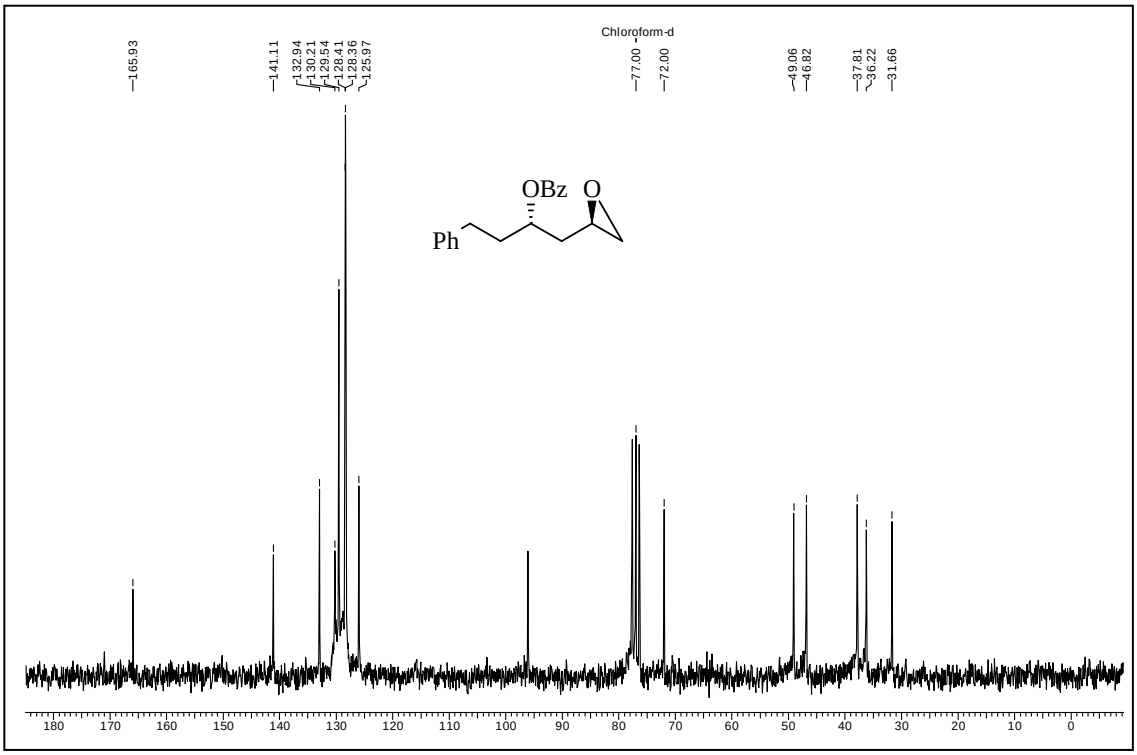
^{1}H NMR Spectrum of 230 in $CDCl_3$



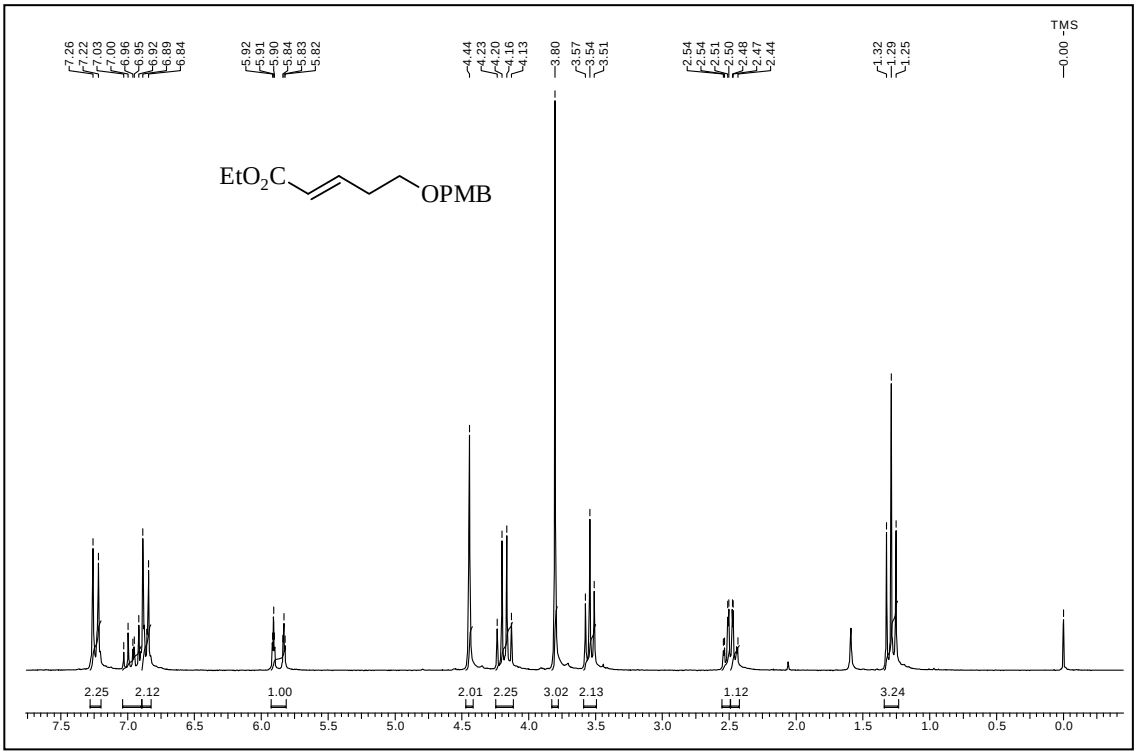
^{13}C NMR Spectrum of 230 in $CDCl_3$



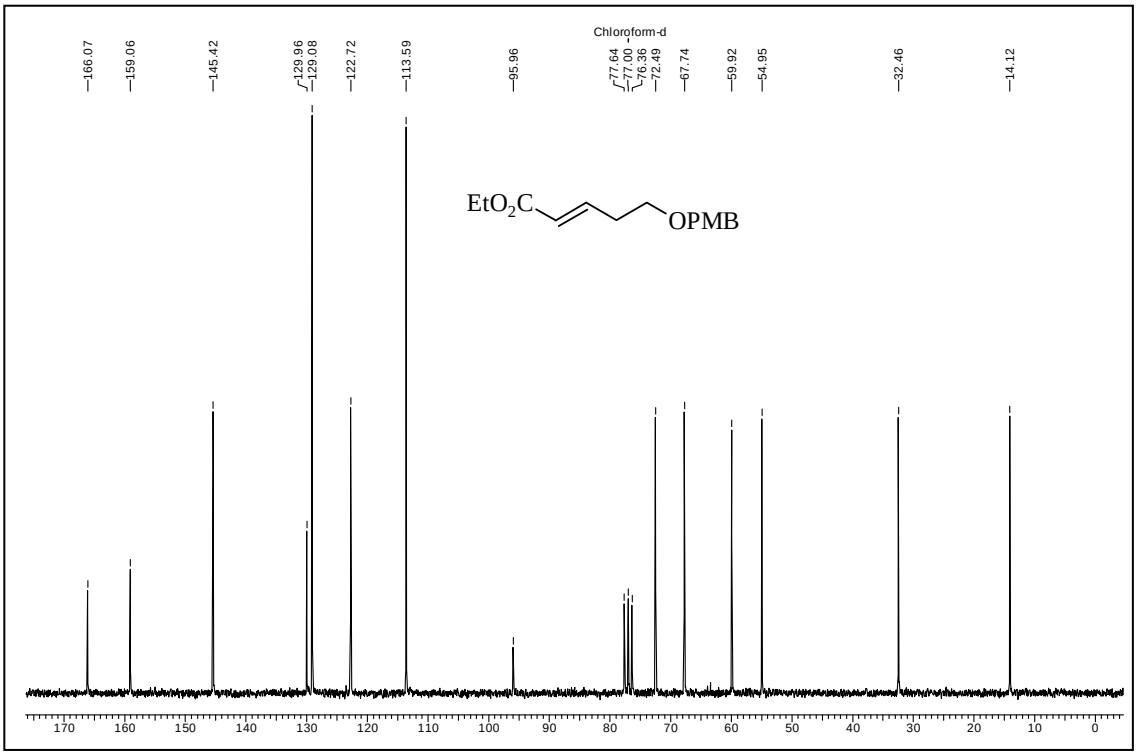
^{1}H NMR Spectrum of 232 in $CDCl_3$



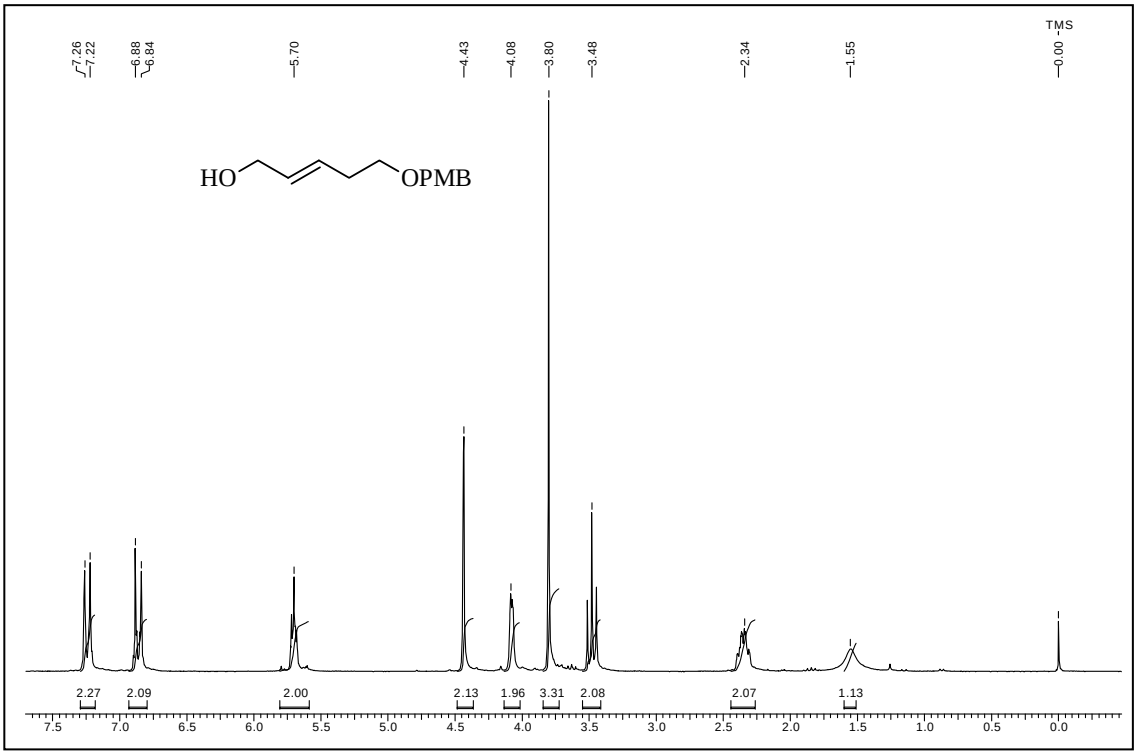
^{13}C NMR Spectrum of 232 in $CDCl_3$



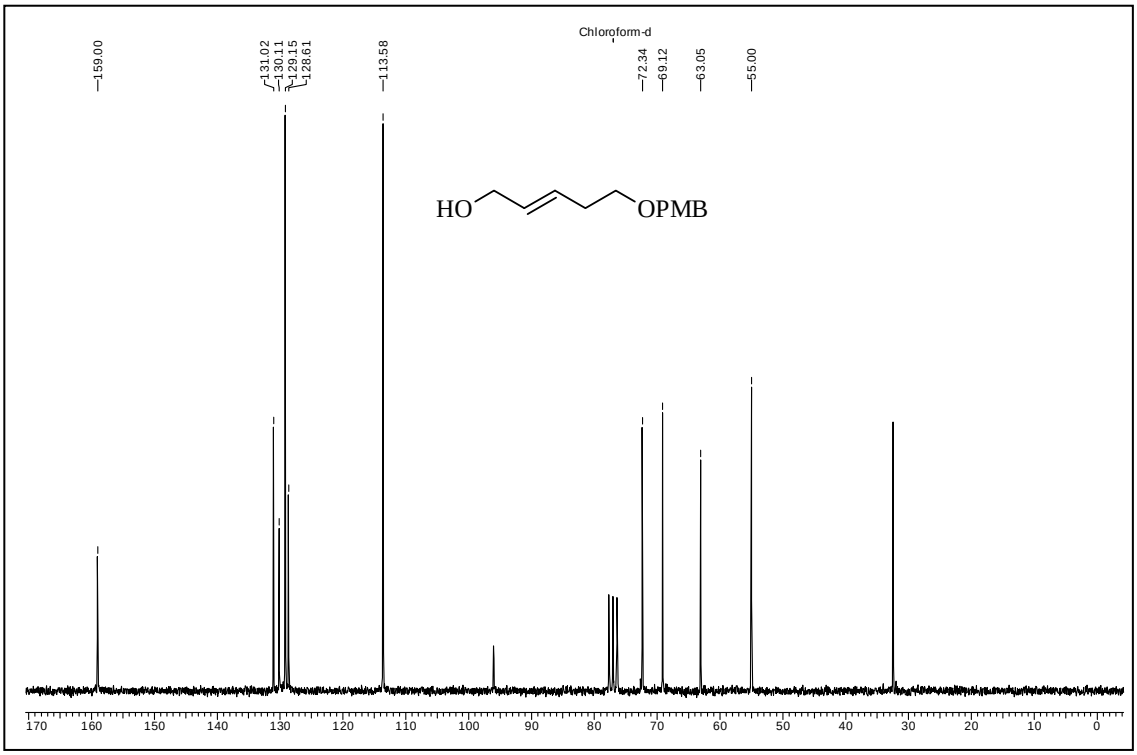
^{1}H NMR Spectrum of 235 in $CDCl_3$



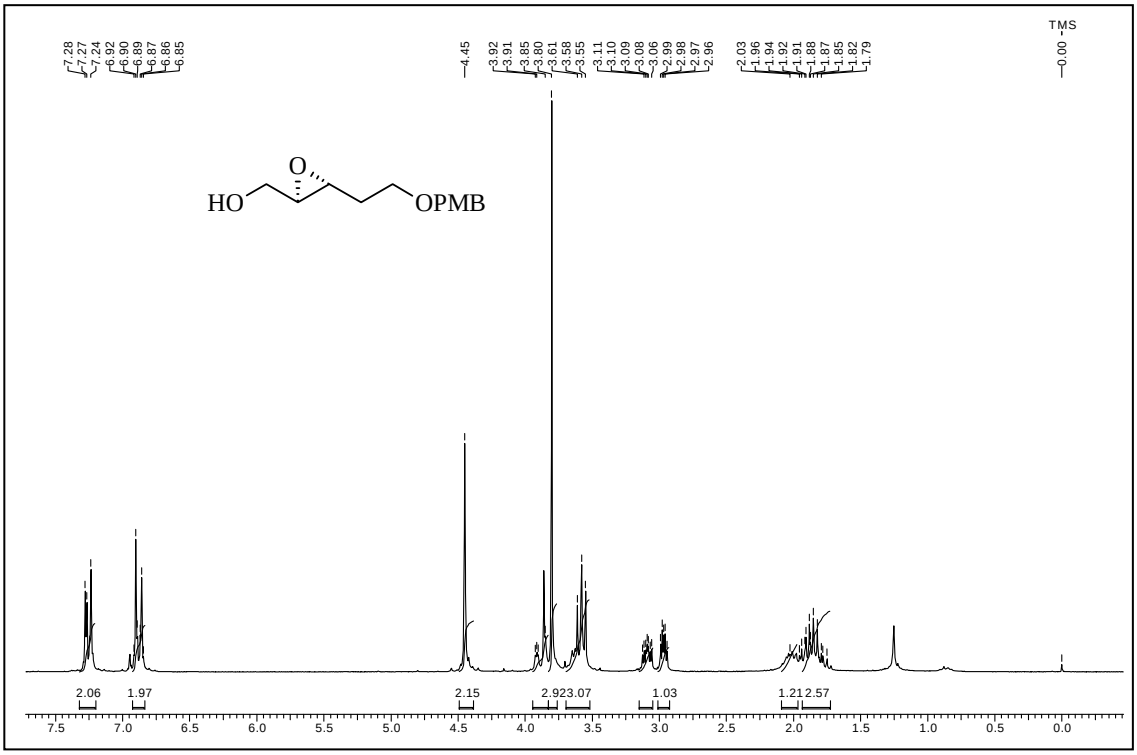
^{13}C NMR Spectrum of 235 in $CDCl_3$



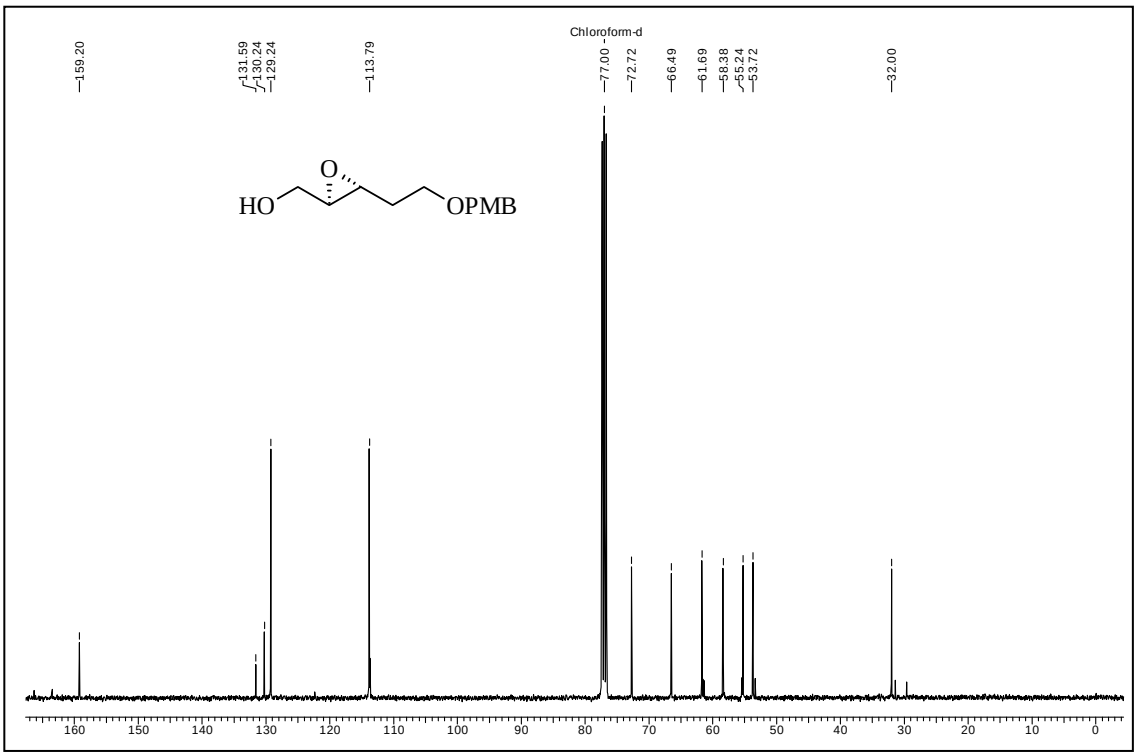
^{1}H NMR Spectrum of 236 in $CDCl_3$



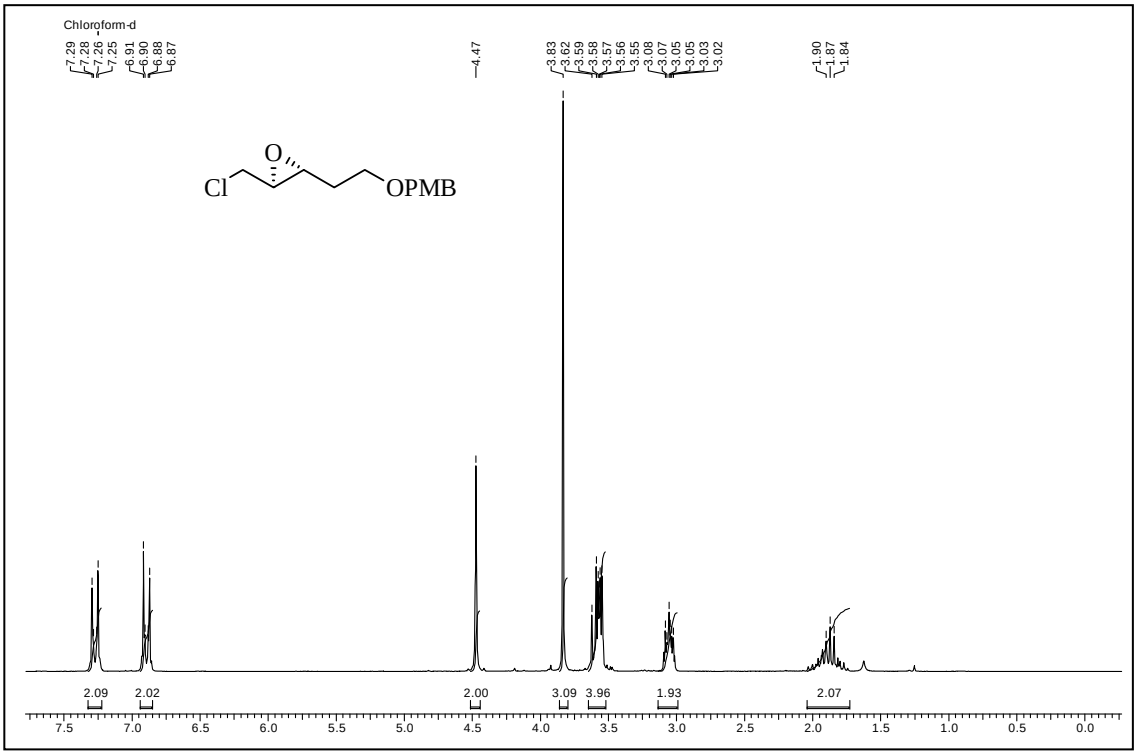
^{13}C NMR Spectrum of 236 in $CDCl_3$



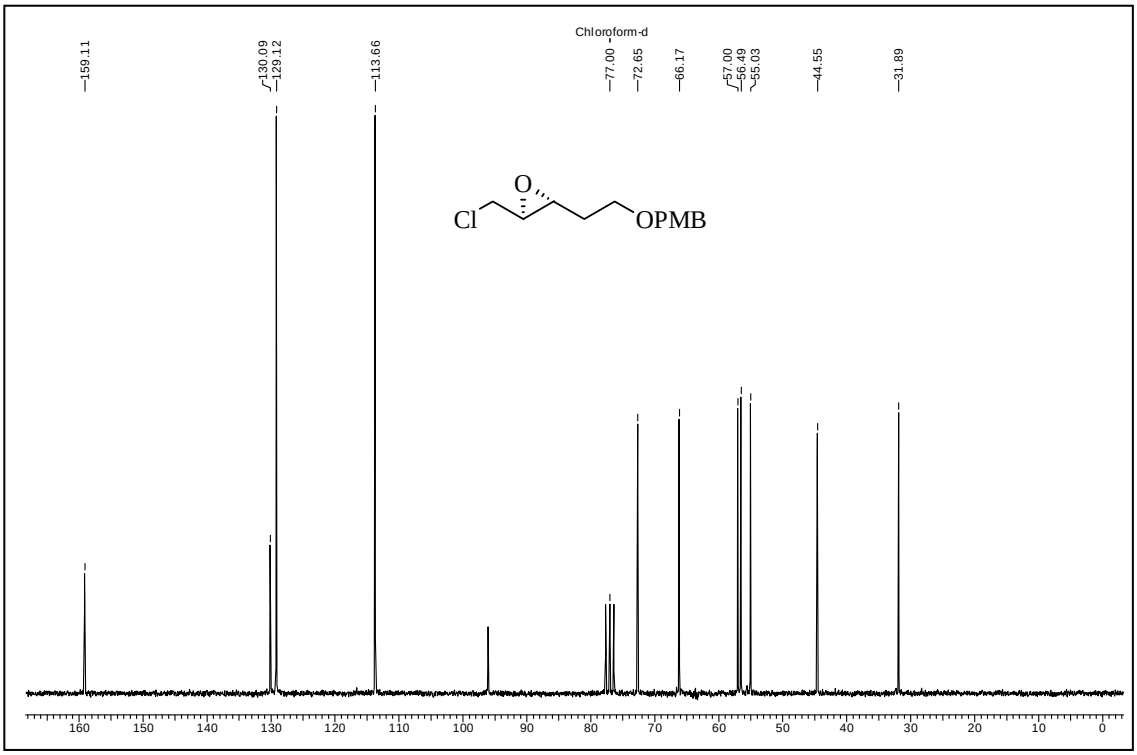
^{1}H NMR Spectrum of 237 in $CDCl_3$



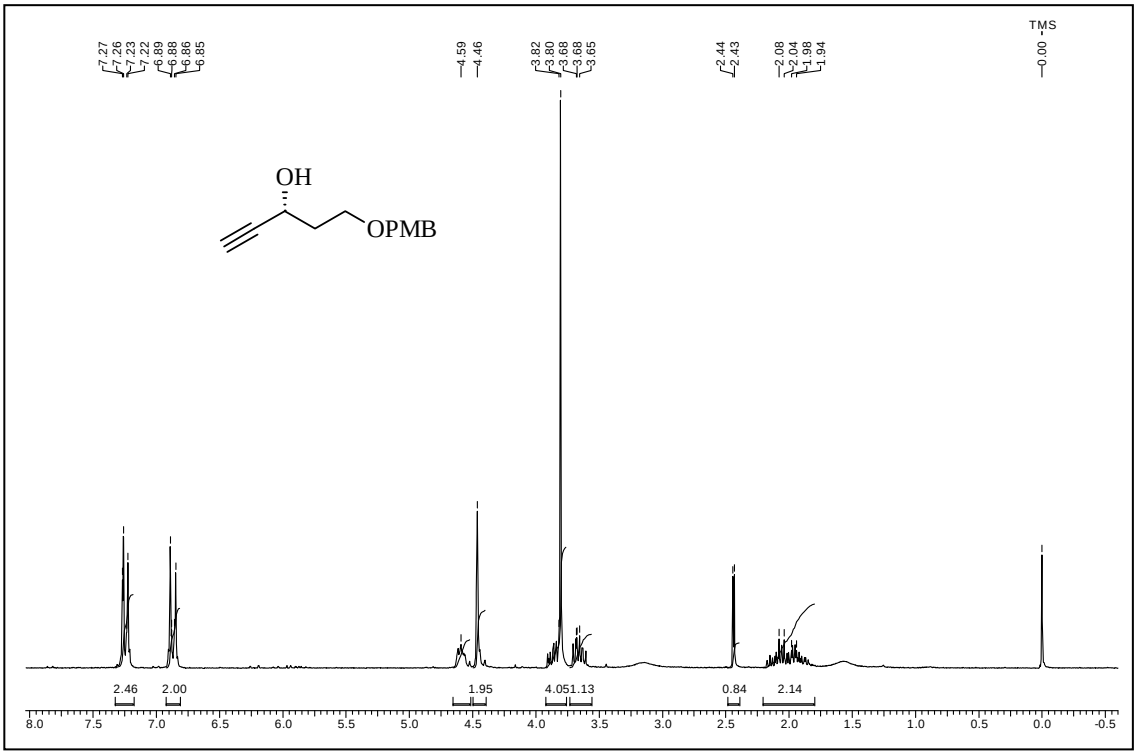
^{13}C NMR Spectrum of 237 in $CDCl_3$



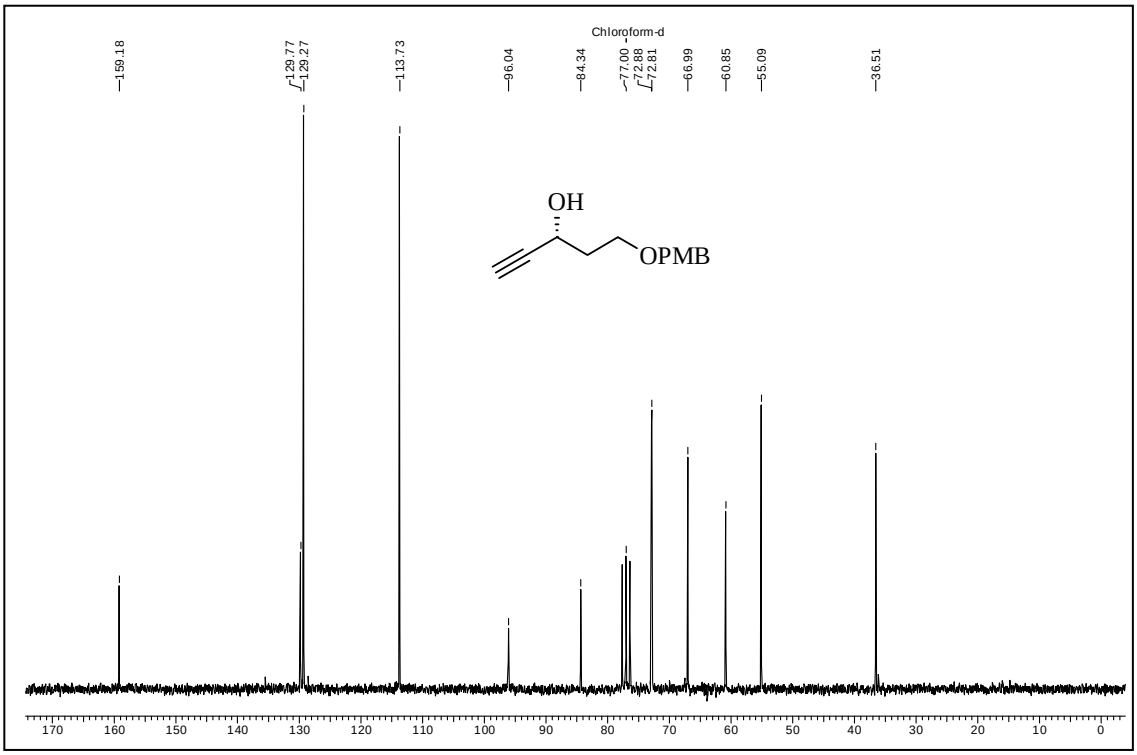
^{1}H NMR Spectrum of 238 in $CDCl_3$



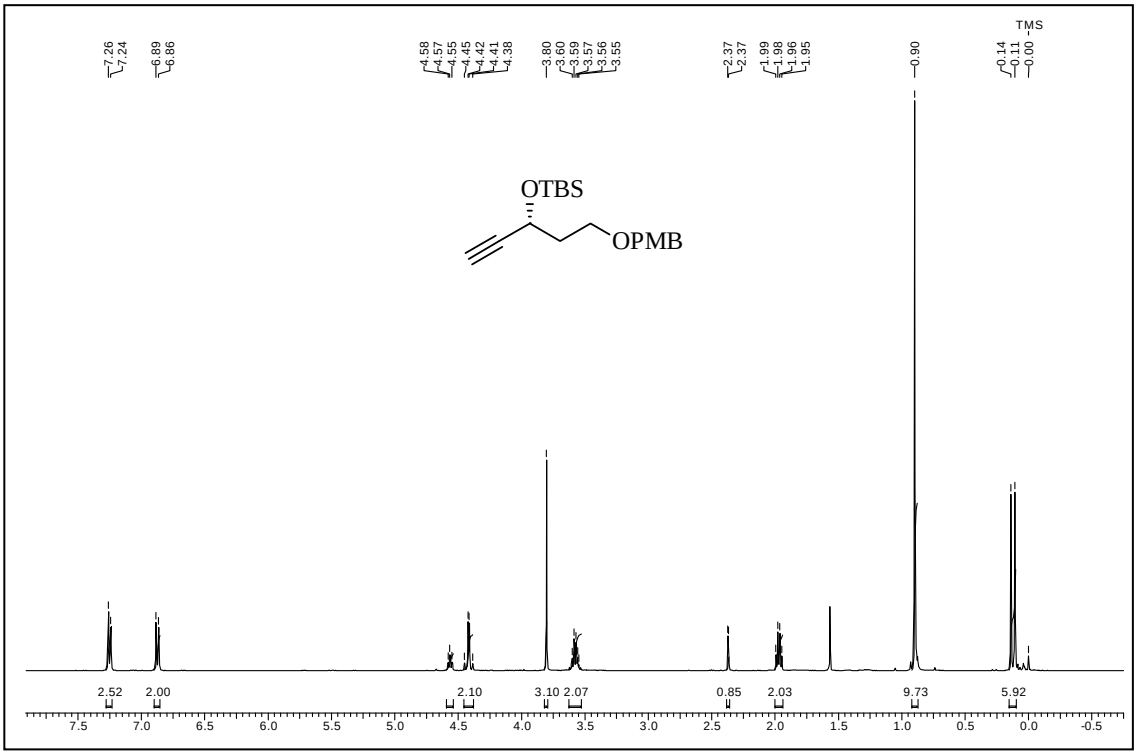
^{13}C NMR Spectrum of 238 in $CDCl_3$



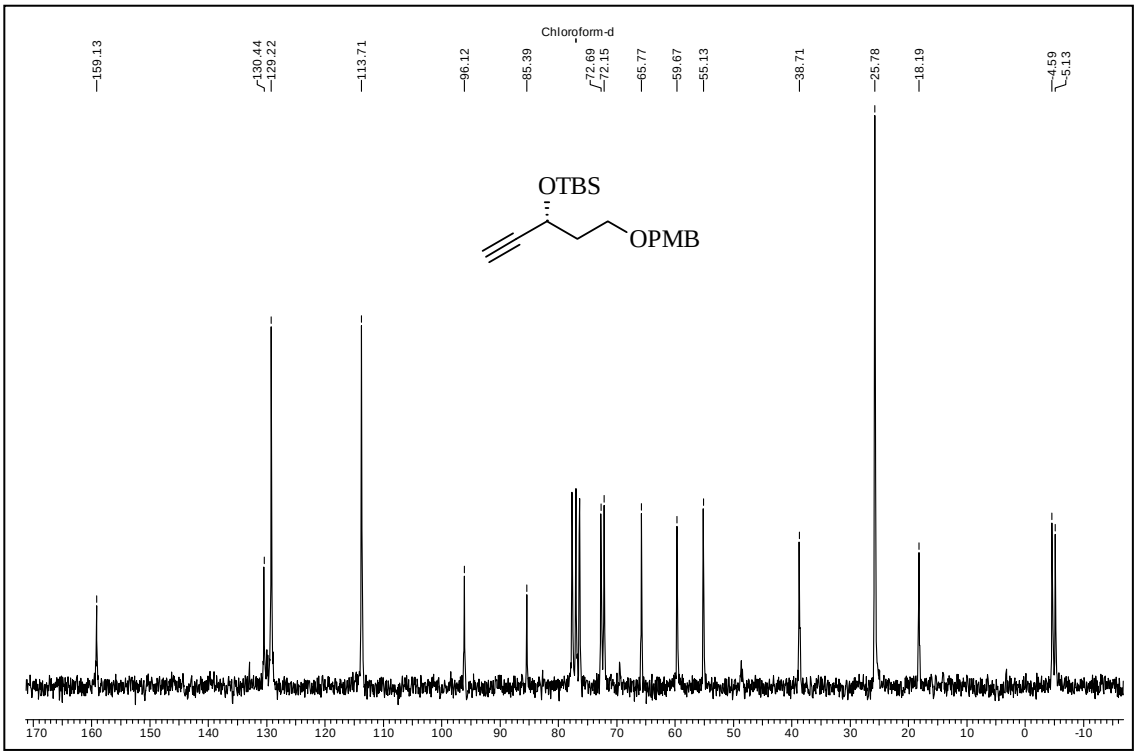
^{1}H NMR Spectrum of 239 in $CDCl_3$



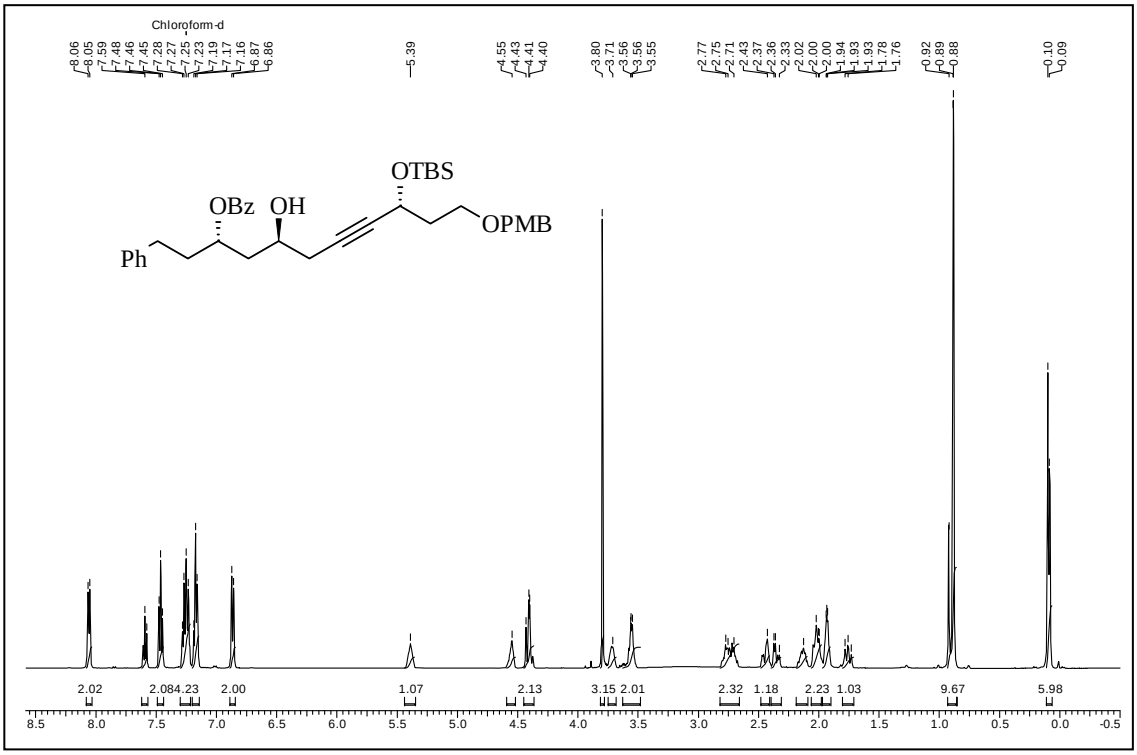
^{13}C NMR Spectrum of 239 in $CDCl_3$



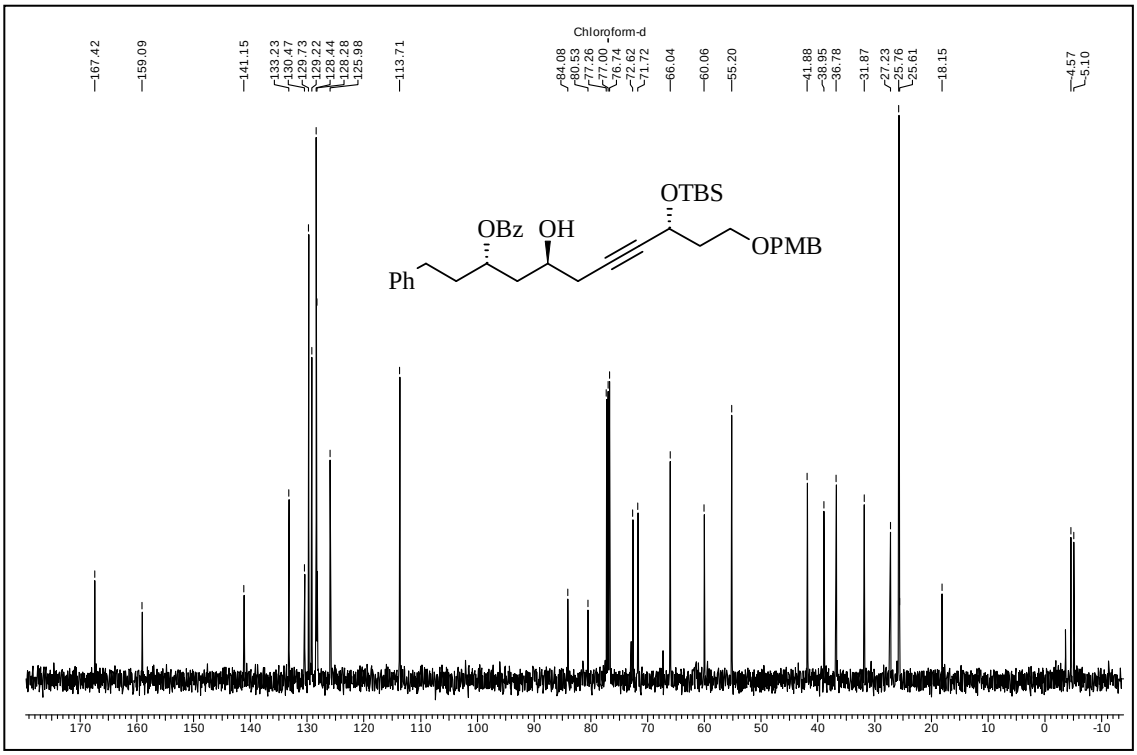
^{1}H NMR Spectrum of 240 in $CDCl_3$



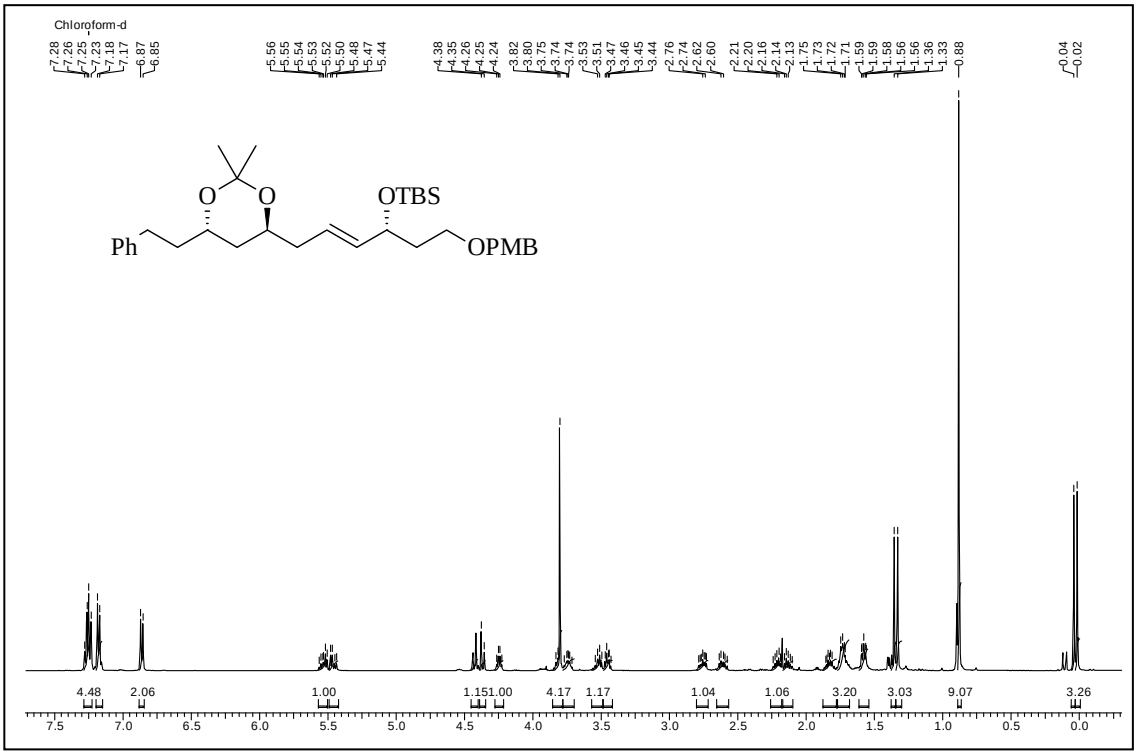
^{13}C NMR Spectrum of 240 in $CDCl_3$



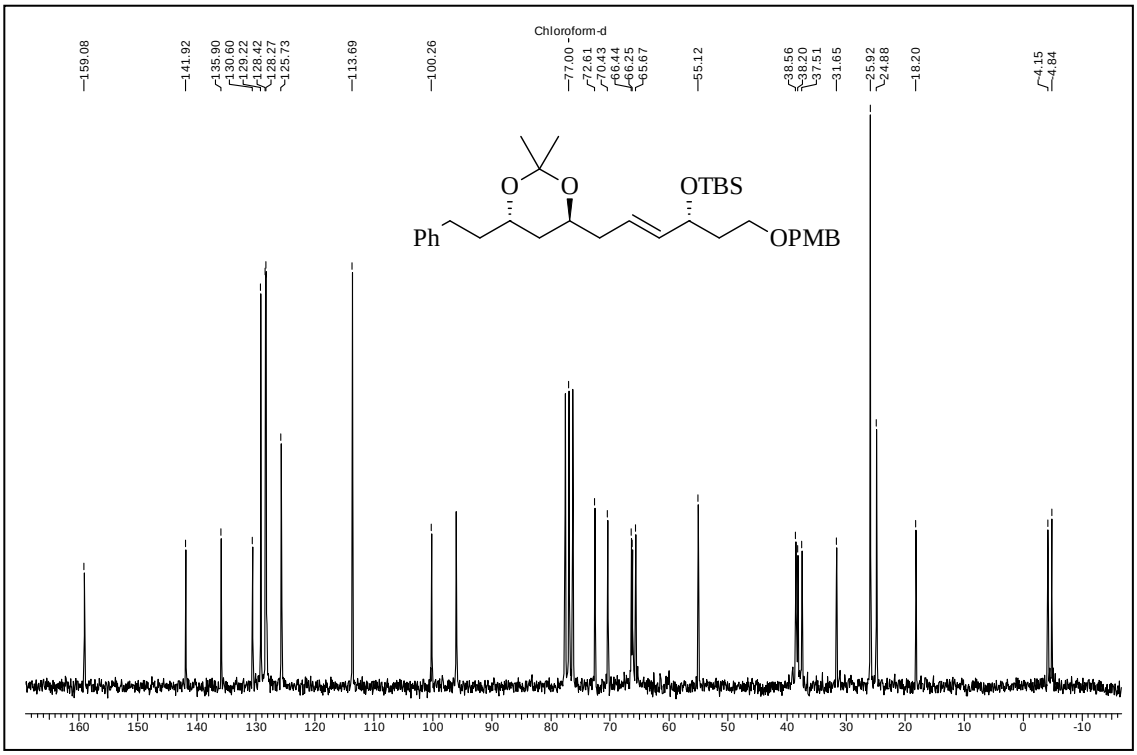
^{1}H NMR Spectrum of 241 in $CDCl_3$



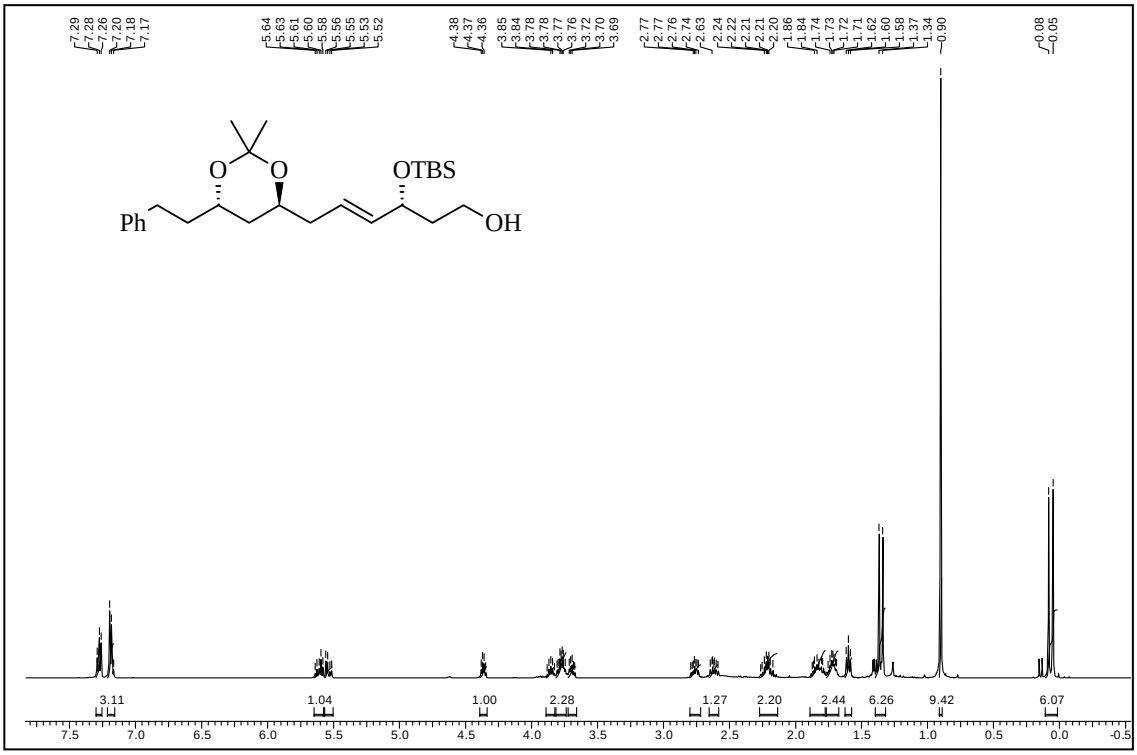
^{13}C NMR Spectrum of 241 in $CDCl_3$



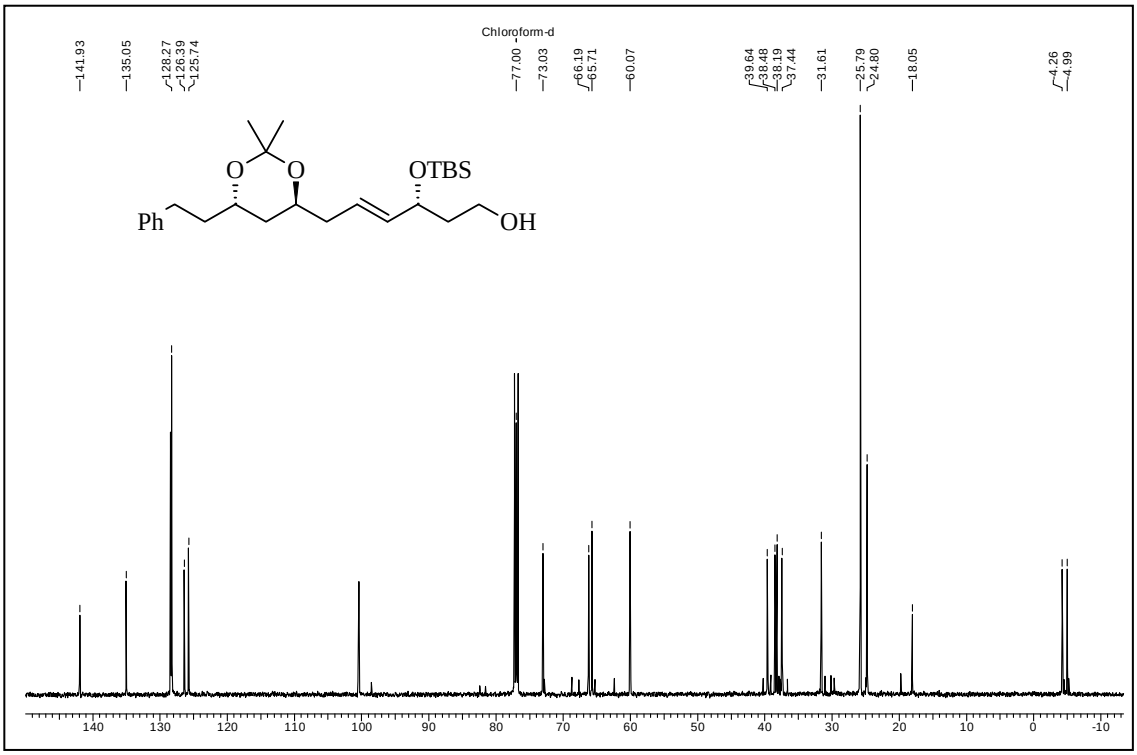
^{1}H NMR Spectrum of 243 in $CDCl_3$



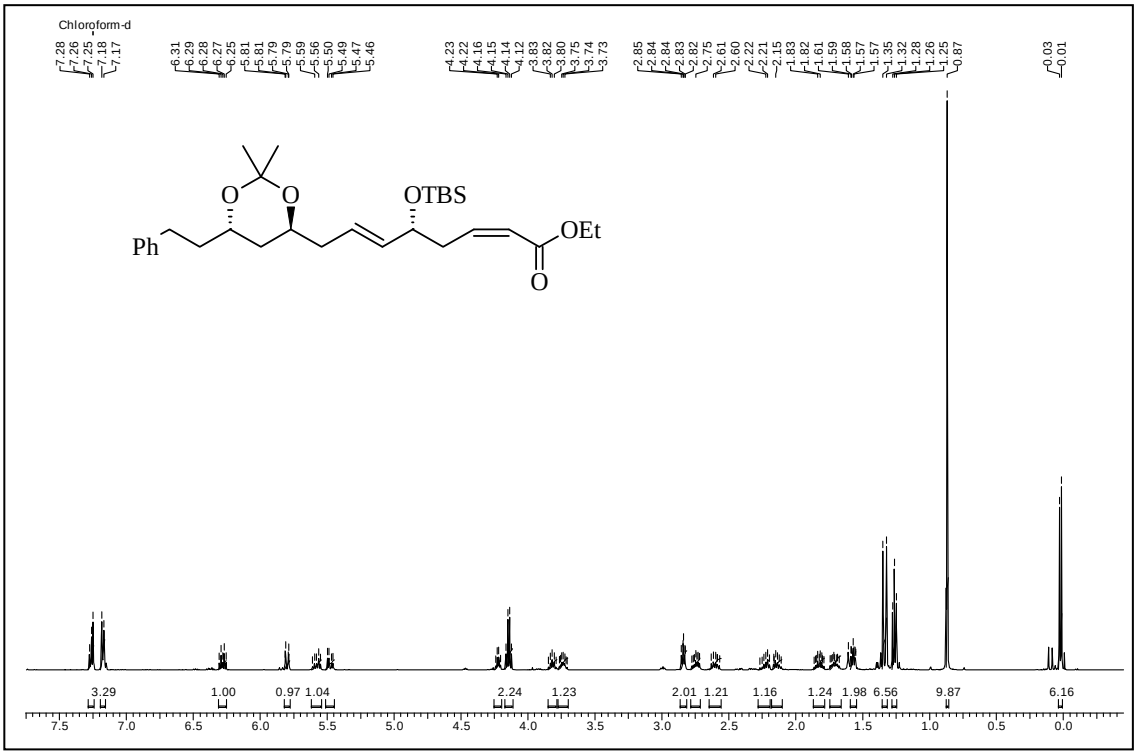
^{13}C NMR Spectrum of 243 in $CDCl_3$



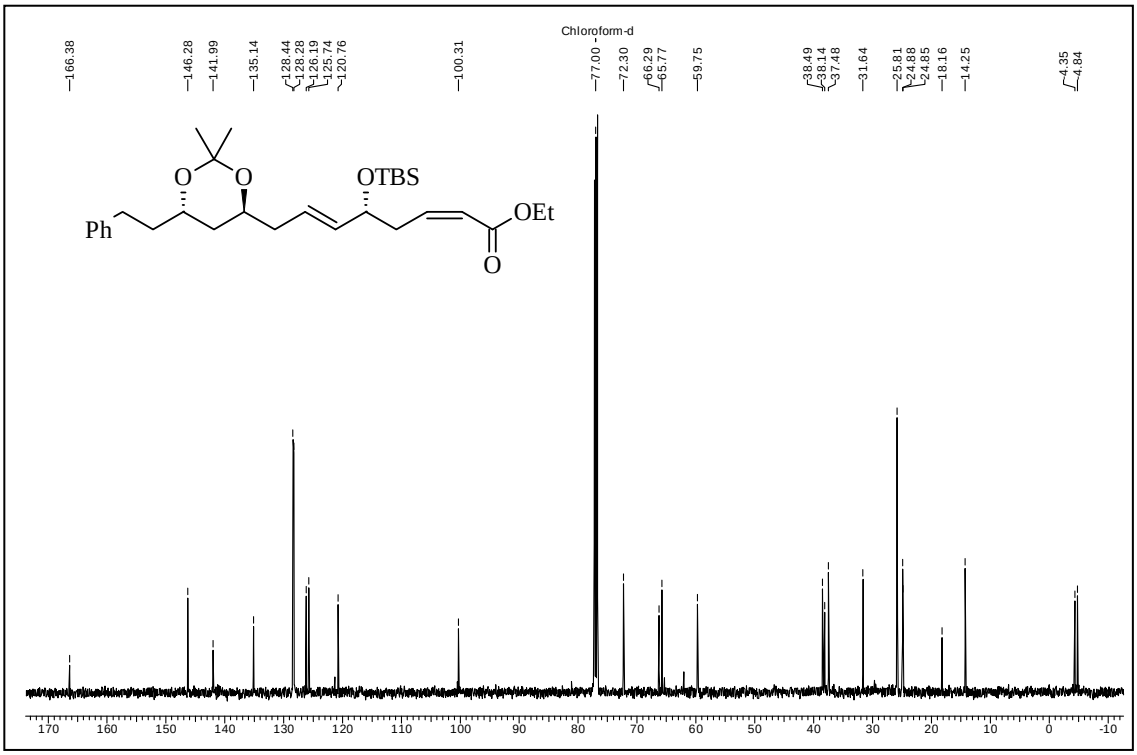
^{1}H NMR Spectrum of 244 in $CDCl_3$



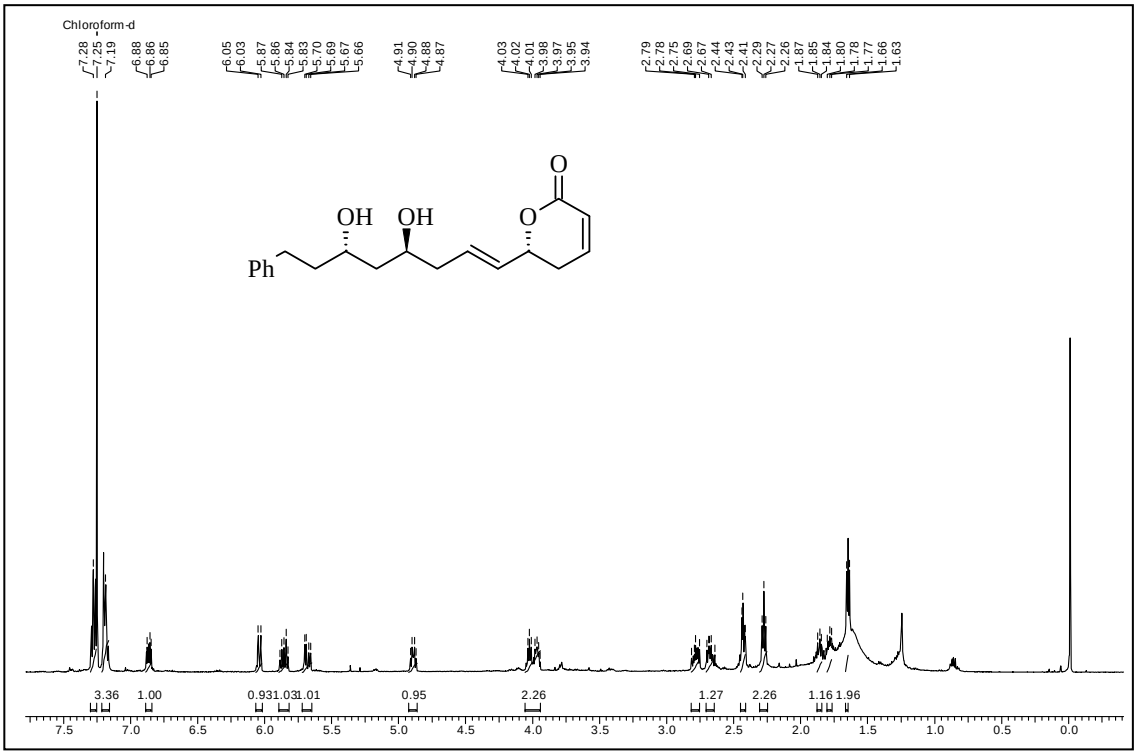
^{13}C NMR Spectrum of 244 in $CDCl_3$



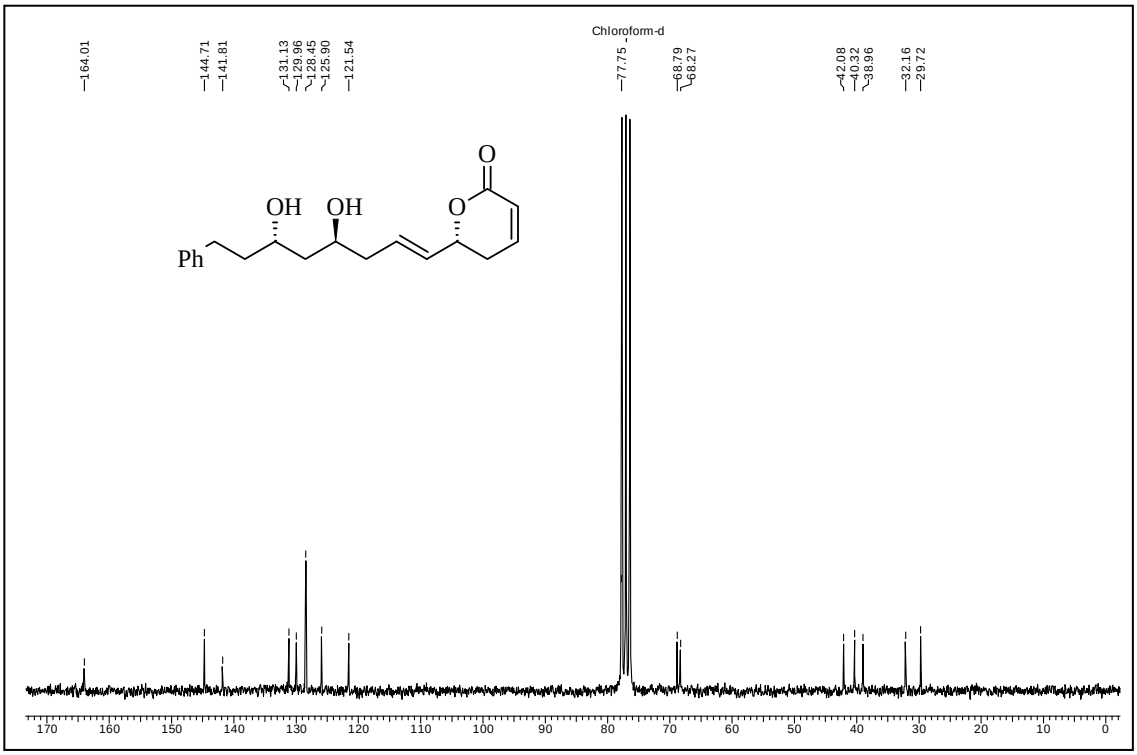
^{1}H NMR Spectrum of 245 in $CDCl_3$



^{13}C NMR Spectrum of 245 in $CDCl_3$



^{1}H NMR Spectrum of 184a in $CDCl_3$



^{13}C NMR Spectrum of 184a in $CDCl_3$

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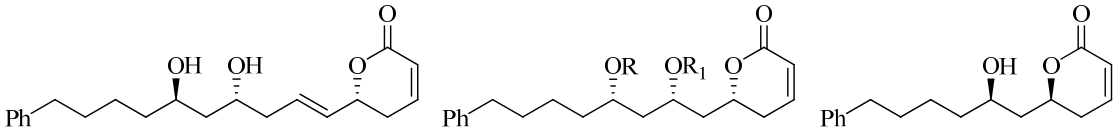
CHAPTER-II

Section B: A carbohydrate-based approach towards the synthesis of (6R)-6-[(4R,6R)-4,6-dihydroxy-10-phenyldec-1-enyl]-5,6-dihydro-2H-pyran-2-one

INTRODUCTION

Ravensara crassifolia is a tree up to 18–20 m growing in the eastern region of Madagascar. The genus *Ravensara* is considered as endemic to Madagascar. In a series of preliminary screenings by Hostettmann et al., the stem bark CH_2Cl_2 extract of *R. crassifolia* displayed antifungal activity against the phytopathogenic fungus *Cladosporium cucumerinum* in a bioautographic TLC assay.[1] Although no ethnomedical use is reported for *R. crassifolia*, other *Ravensara* species are used in traditional medicine and some of their essential oils have shown antimicrobial activity.[2] Activity-guided fractionation of the CH_2Cl_2 extract yielded two new 6-alkylated-α-pyrones **246** and **248**. These results support the fact that plants from the *Lauraceae* family represent an excellent source of this chemical class.[3] Some natural products isolated from *Ravensara* species for which no trivial names are known, are depicted below in Figure 1.

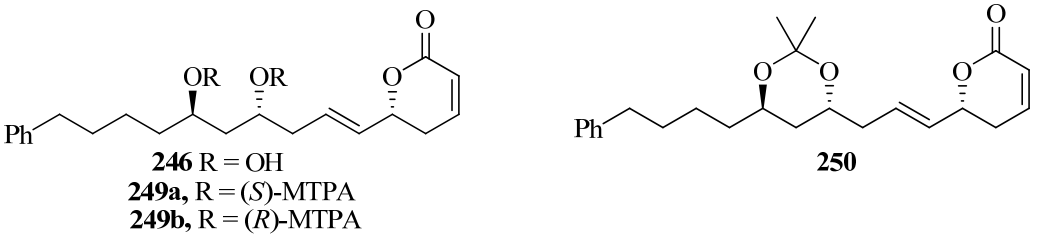


246 **247a** R = OAc, R_1 = H; **247b** R = H, R_1 = OAc **248**

Figure 1. Some natural products isolated from *Ravensara* species

Compound **246** showed a molecular ion M^+ at *m/z* 344 and the ammonium adduct $[M+NH_4]^+$ at *m/z* 362 in the D/CI-MS. This was supported by the presence of the molecular ion peak at *m/z* 344 in the EI-MS corresponding to the molecular formula $C_{21}H_{28}O_4$. The IR spectrum of **246** indicated the presence of an α,β-unsaturated lactone ring, a monosubstituted benzene ring and an OH group.[4] The structure of **246** was suggested by its ^1H and ^{13}C NMR analyses and confirmed by 2D-NMR spectroscopy including HSQC, HMBC and COSY experiments. The relative configuration of the proposed 1,3-diol moiety in **246** was deduced from the ^{13}C-NMR analysis of the acetonide derivative **250**. The observed chemical shifts of the two Me groups (δ 24.9 and 24.7) at the ketal C-atom (δ 100.2) were attributed to an "*anti*" 1,3-diol conformation in **250**.[5] Mosher esterification[6] at the stereogenic atoms C(4') and C(6') of **246** yielding the esters **249a** and **249b** established the

absolute configuration as (*R*) for both chiral centers (Figure 2), while an (*R*) absolute configuration was assigned to C(6) of **246** on the basis of the positive Cotton effect measured both in MeOH and in hexane at 254 and 265 nm, respectively.[7]



246 R = OH
249a, R = (*S*)-MTPA
249b, R = (*R*)-MTPA

250

Figure 2.

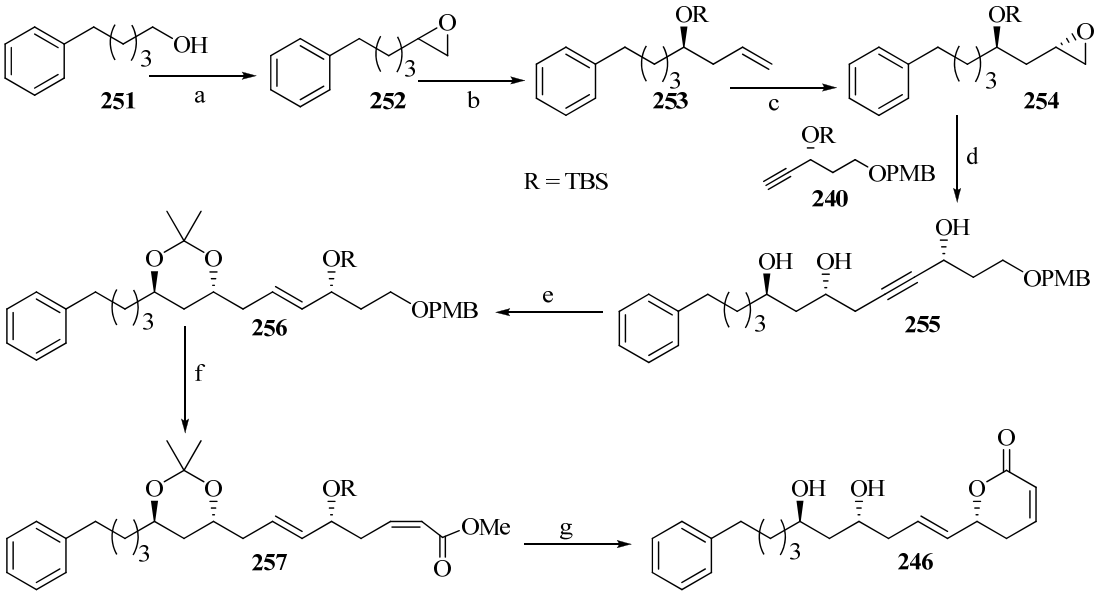
The proton assignments were done by analyzing the ^{1}H-NMR spectrum of **246**. In fact, signals at δ 7.11–7.27 (m, 5H) corresponding to the aromatic protons of the monosubstituted benzene ring were observed, together with signals at δ 6.03 (dd, *J* = 1.9, 9.8 Hz) and 6.85 (m), which were attributed to the olefinic protons H-C(3) and H-C(4) of the α,β-unsaturated lactone ring. The presence of an additional double bond carrying H-C(1') (δ 5.68) and H-C(2') (δ 5.85) was detected with a coupling constant *J*(1',2') = 15.5 Hz indicating a *trans*-configuration at C(1')-C(2'). The protons at δ 4.89, 4.00, and 3.91 were assigned to H-C(6) of the lactone ring, H-C(6'), and H-C(4'), respectively. A peak at *m/z* 308 [M-2H_2O] in the EI-MS suggested the presence of two OH groups in **246**; this was confirmed by the acetonide derivative **250** implicating 1,3-diol functionalities and by the Mosher esters with the appearance of two OMe groups in the ^{1}H-NMR spectrum of **249a** (both at δ 3.50 ppm) and **249b** (δ 3.54 ppm and 3.57 ppm).

Thus compound **246** was established as (6*R*)-[(4*R*,6*R*)-4,6-dihydroxy-10-phenyldec-1-enyl]- 5,6-dihydro-2H-pyran-2-one.

First total synthesis by Radhakrishna et al.[8]

This approach features in a nucleophilic ring-opening of the epoxide **254** (prepared from **251** utilizing an iterative Jacobsen's HKR method and vinylgrignard reaction sequence) with an anion of the known alkyne **240** which was reported by us (discussed in the previous section)[10] to furnish **255**. Reduction of the triple bond to the

corresponding *trans* double bond, and a preferential *cis*-Wittig olefination followed by lactonization completed the total synthesis (Scheme 1).



Scheme 1. *Reagents and conditions*: (a) i. $(COCl)_2$, DMSO, Et_3N, –78 °C, 92%; ii. $CH_3P^+Ph_3Br^-$, *n*-BuLi, 0 °C, 55%; iii. *m*-CPBA, CH_2Cl_2, rt, 95%; (b) i. (*R*,*R*)-(salen)Co^{III}(OAc), 0.55 equiv H_2O, 42%; ii. vinylmagnesium bromide, CuI, THF, rt, 71%; iii. TBSCl, imidazole, CH_2Cl_2, rt, 92%; (c) i. *m*-CPBA, CH_2Cl_2, rt, 96%; ii. (*S*,*S*)-(salen)Co^{III}(OAc), 0.55 equiv H_2O, 41%; (d) i. **240**, *n*-BuLi, $BF_3{\cdot}Et_2O$, THF, –78 °C 72%; ii. TBAF, THF, rt, 87%; (e) i. 2,2'-DMP, CH_2Cl_2, *p*-TSA (cat), rt, 95%; ii. LAH, THF, rt, 85%; iii. TBSCl, imidazole, CH_2Cl_2, rt, 98%; (f) i. DDQ, CH_2Cl_2:H_2O, rt, 79%; ii. IBX, DMSO, rt; iii. $(F_3CCH_2O)_2POCH_2COOMe$, KHMDS, 18-crown-6, THF, 76% (over two steps); (g) *p*-TSA, C_6H_6, rt, 65%.

PRESENT WORK

Several 6-substituted 5,6-dihydro-2H-pyran-2-one having chiral hydroxyl groups on the side chain have been isolated from natural sources. They possess 1,3-diol (*syn*/*anti*) moiety and thus are presumed to be belonging to a group of polyketides biogenetically (Figure 3). The α,β-unsaturated-δ-lactone/α-pyrone functionality is presumed to be responsible for biological activities, such as plant growth inhibition, antifeedent, antifungal, antibacterial, and antitumoral properties. This is mainly due to its ability to act as a Michael acceptor, enabling it to covalently link to a target enzyme. The (6*R*)-6- [(4*R*,6*R*)-4,6-dihydroxy-10-phenyldec-1-enyl]-5,6-dihydro-2H-pyran-2-one (**246**)[9] is one such natural product which was isolated from *Ravensara crassifolia* along with a structurally similar compound **248** (Figure 3). Fascinated by its broad range of biological activity, structural diversity and also having completed the total synthesis of strictifolione[10] (a similar kind of polyketide, Section-A) successfully, we next aimed at the synthesis of (6*R*)-6-[(4*R*,6*R*)-4,6-dihydroxy-10-phenyldec-1-enyl]-5,6-dihydro-2H-pyran-2-one (**246**) using the same strategy as discussed in the previous section.

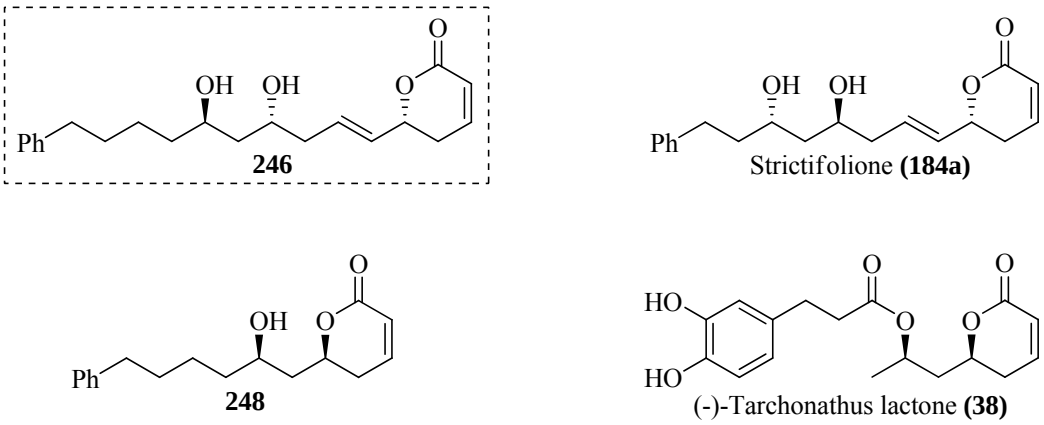


Figure 3.

Retrosynthetic strategy

Our strategy is illustrated in Figure 4. Retrosynthetically we sought to address the synthesis of **272** by employing Yamaguchi protocol for nucleophilic ring opening of epoxide **267** with lithium acetylide derivative of **240**, which was used in our

synthesis of strictifolione (Section A) followed by a *trans*-selective reduction of the resulting alkyne. The requisite epoxide fragment **267** inturn would be prepared from the furanaldehyde **223** which can be easily accessed from the commercially cheap D-glucose.

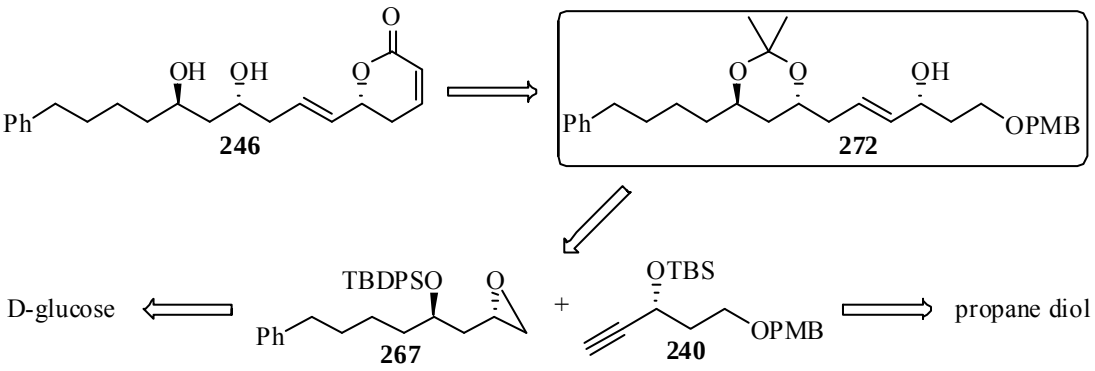
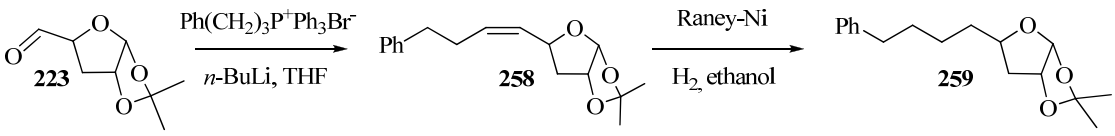


Figure 4.

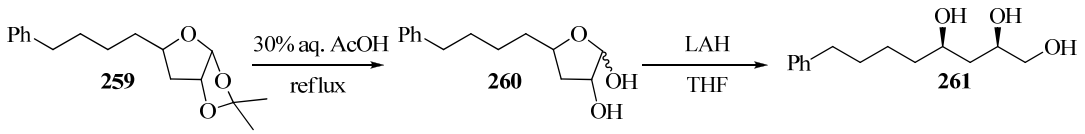
Our projected synthetic program commenced from the known aldehyde **223** prepared from D-glucose (3 steps, Section-A), which was treated with an ylide generated from $C_6H_5CH_2CH_2CH_2I^-P^+Ph_3$ using *n*-BuLi in THF to furnish the olefin **258**.[11] The control over the geometry of the newly formed olefin was not the matter of concern here as it would be reduced in the next step. However the ^{1}H NMR of **258** suggested the presence of only *Z*-isomer. In the ^{1}H NMR spectrum of **258** two signals as ddt at δ 5.60 and 5.37, each integrating for one proton with a coupling constant of 11.0 Hz were attributed to the *cis* olefinic protons. The aromatic protons appeared in the downfield region (δ 7.33–7.16, 5H). A signal at δ 5.81 as doublet (J = 3.7 Hz) integrating for one proton is due to the characteristic anomeric proton of the furan ring. Two singlets at δ 1.53 and 1.31 integrating each for 3 protons were assigned to the methyl groups of the 1,2-acetonide. In the ^{13}C NMR spectrum two signals, one at 105.2 (d) ppm of anomeric carbon and the other at 110.7 (s) ppm due to the quaternary carbon of the 1,2-acetonide group further confirmed the structure assigned for **258**. Results from mass spectrum (*m/z* 399.3 $[M+Na]^+$), IR, elemental analysis were in good agreement with the structure **258**.



Scheme 2.

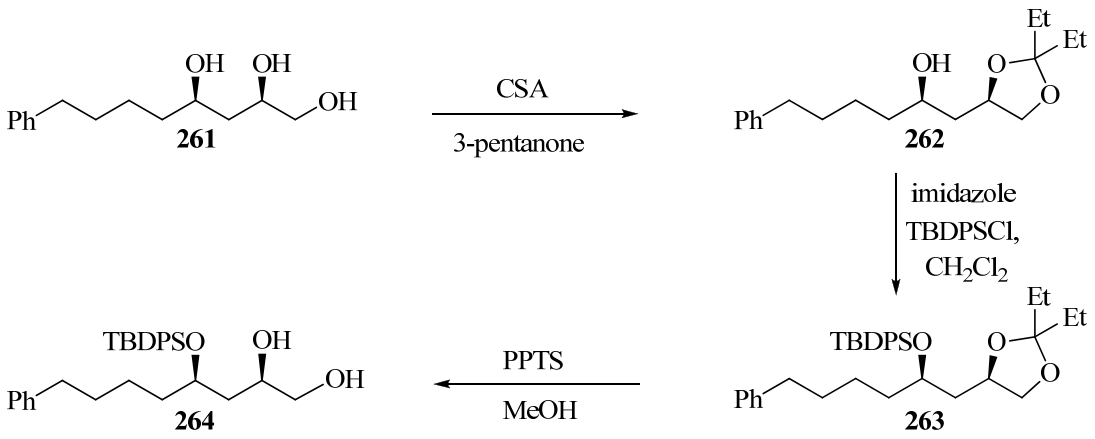
The double bond of **258** was reduced using Raney-Ni under H_2 gas (60 psi) to afford **259**. ^{1}H and ^{13}C NMR of **259** showed the absence of the olefinic protons. Instead, additional methylene protons appeared in upfield region of ^{1}H NMR indicating the conversion of **258** to **259** (Scheme 2).

The cleavage of 1,2-acetonide was achieved by refluxing **259** in 30% aqueous AcOH to accomplish the anomeric mixture (α/β) of lactol **260**. The reductive opening of the furan ring of **260** with LAH in THF resulted in triol **261** (Scheme 3).[12]



Scheme 3.

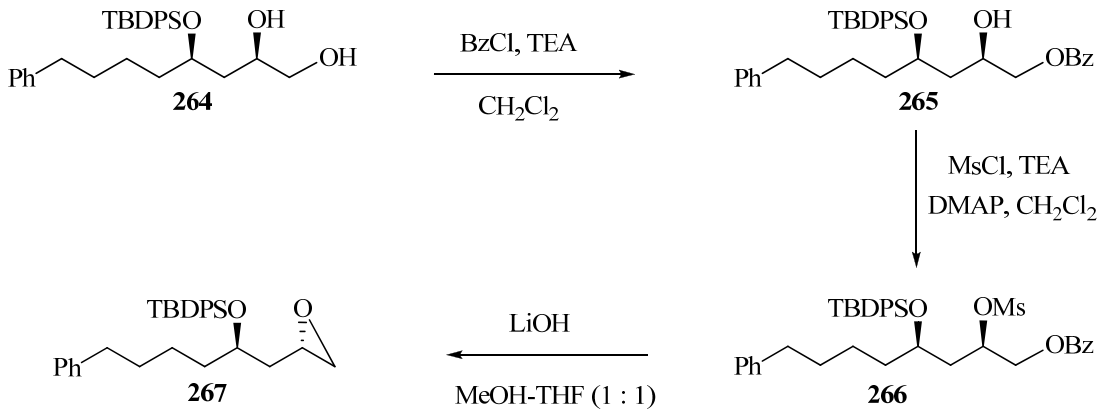
In order to get the 1,3-*anti* diol moiety in the target molecule, the inversion of the C(2)-OH was planned by an inverted epoxide formation in an SN^2 manner. Keeping this in view, first the 1,2 diol of **261** was selectively protected using 3-pentanone in the presence of CSA and the required five membered dioxalane derivative **262** was formed exclusively leaving the C(4)-OH free.[13] In the ^{1}H NMR spectrum, two signals at δ 0.90 and 0.89 as triplets with J = 7.5 Hz, each integrating for three protons were assigned to the methyl protons of isopentylidene group whilst the same methyl groups appeared as quartets at 8.0 and 8.2 ppm in the ^{13}C NMR spectrum. The methylene protons of isopentylidene group resonated together as a multiplet between δ 1.55–1.37 integrating for 4 protons. The presence of the 1,2-isopentylidene group was further confirmed by a signal due to the quaternary carbon at 113.4 ppm as singlet in ^{13}C NMR spectrum.



Scheme 4.

The C(4)-OH of **262** was then converted to its TBDPS ether **263** upon treatment with TBDPSCl, imidazole and catalytic DMAP using CH_2Cl_2 as solvent. In ^{1}H NMR spectrum the signals corresponding to the TBDPS group were visualized (10 additional aromatic protons in downfield region and 9 protons in upfield region). ^{13}C NMR spectrum showed the peaks due to the TBDPS group in the respected region. Hydrolysis of the dioxalane ketal **263** was achieved by the action of PPTS in MeOH to produce the diol **264**. ^{1}H and ^{13}C NMR spectra indicated the absence of the isopentylidene group (Scheme 4).

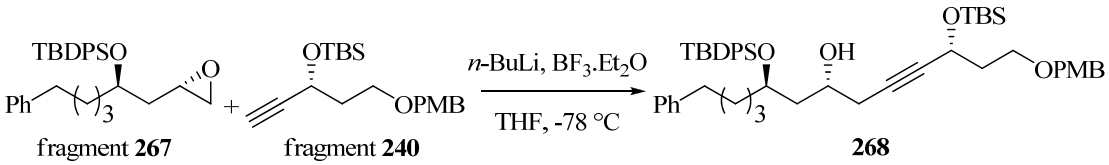
Now the objective was to convert diol **264** to the corresponding inverted epoxide. In this context, the 1^o-OH of **264** was selectively protected as benzoate **265** with ($BzCl/Et_3N/CH_2Cl_2$/rt) followed by mesylation of the secondary hydroxyl with ($MsCl/Et_3N/CH_2Cl_2$/DMAP/rt) to give the diprotected compound **266**. Base induced deprotection of the benzoate generated an alkoxide, which prompted simultaneous elimination of the mesylate and ring closure in an SN^2 mode to afford the desired epoxide **267**.[14] The presence of the terminal epoxide group was indicated by the ^{1}H NMR signals at δ 2.95–2.92 (m, 1H), 2.68 (t, J = 4.5 Hz, 1H), and 2.32 (dd, J = 2.8, 5.0 Hz, 1H). Whereas the ^{13}C NMR spectrum exhibited two signals at 49.7 (d) and 47.4 (t) ppm supporting the assigned structure **267**, observations from IR, mass (*m/z* 481.3 $[M+Na]^+$), microanalysis were also in support of the structure **267** (Scheme 5).



Scheme 5.

Coupling of two fragments

Having successfully prepared the fragments **267** and **240** (Section A) the next target was set to couple the two fragments by employing the Yamaguchi protocol.[15] Reaction of **267** with the lithiated anion of **240** generated by the sequential treatment with *n*-BuLi, $BF_3.Et_2O$ in THF at –78 ^oC afforded the advanced intermediate **268** (Scheme 6).

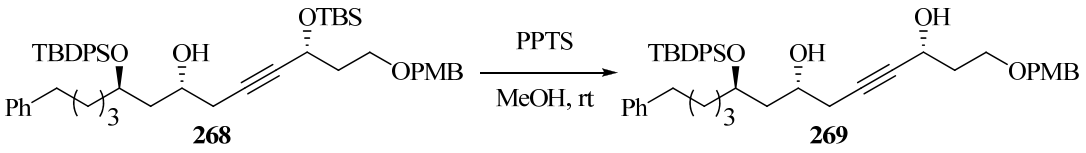


Scheme 6.

The peaks corresponding to the TBDPS, TBS and PMB ethers appeared in the expected region in the ^1H and ^{13}C NMR spectrums. In the ^1H NMR spectrum the propargylic methylene protons resulting from the newly formed C-C bond of **268** resonated in the upfield region [2.39-2.33 (m, 1H), 2.29-2.23 (m, 1H) ppm]. The structure of **268** was further confirmed by the appearance of two singlets at 80.8 and 83.9 ppm in the ^{13}C spectrum, which were assigned to the quaternary carbons of internal alkyne group. Other physical and analytical data such as IR, mass (*m/z* 701.5 $[M+Na]^+$), microanalysis were in accordance with the structure **268** (Scheme 6).

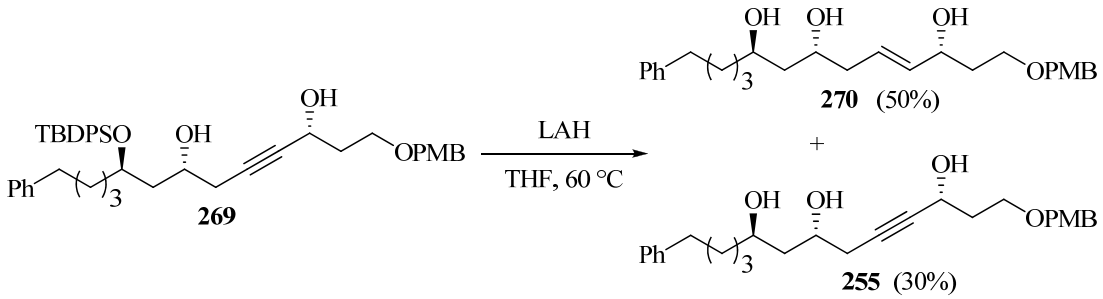
The next program of our synthesis was to reduce the alkyne to the corresponding *E*-olefin taking the advantage of the free homopropargylic alcohol.

Unfortunately all our efforts to bring out this transformation using Red-Al[16, 10] and LAH[17] in different solvents and reaction conditions[18] were unsuccessful. Of the available options for making this reduction successful, we speculated that unmasking the propargyl-OH group would facilitate the reaction. In this regard the TBS group was selectively deprotected by treating **268** with PPTS in methanol at rt to furnish the diol **269** (Scheme 7).



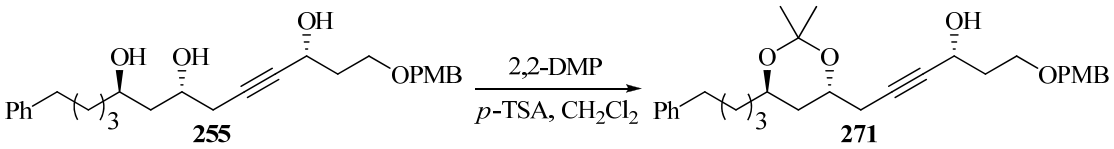
Scheme 7.

Now the aimed reduction of the alkyne proceeded smoothly when **269** was treated with LAH in THF at 60 °C[18] producing two easily separable triols **270** and **255**. The ^{1}H NMR spectra revealed **270** to be the olefinic triol and **255** to be the triol obtained from **269** by simple TBDPS deprotection. The configuration of the newly introduced olefin in **270** was confirmed as *E* considering the large *J* values (15.6 Hz) observed for the olefinic protons (Scheme 8).



Scheme 8.

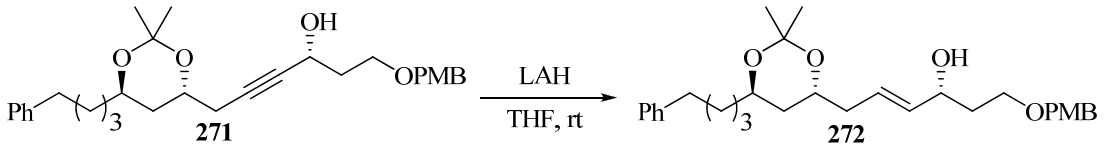
Triol **255** was then converted to its 1,3-isopropylidene derivative using 2,2-DMP in CH_2Cl_2 catalyzed by *p*-TSA to afford **271** (Scheme 9). In ^{1}H NMR spectrum methyl groups of the isopropylidene group resonated as singlets at δ 1.35 and 1.33 each integrating to three protons.



Scheme 9.

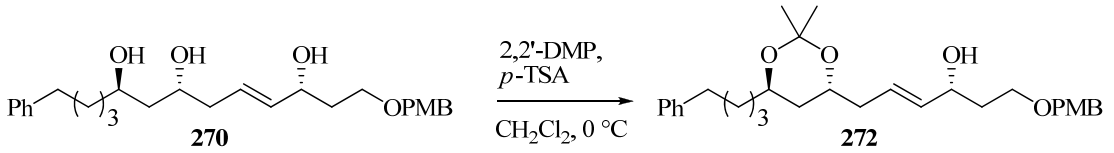
The stereochemical assignment of the hydroxyl groups was made based on Rychnovsky's analogy[5] wherein the ^{13}C NMR spectra of **271** exhibited both the acetonide methyl carbons at 24.9 and 24.7 ppm and the quaternary carbon at 100.4 ppm, confirming the twist boat conformation of the acetonide, an adoption which is a characteristic of the *anti*-1,3-diol moiety.

Selective reduction of the propargylic alcohol **271** proceeded smoothly with LAH in THF at rt to generate allylic alcohol **272** (Scheme 10).[8]



Scheme 10.

Finally the other triol **270** was treated with 2,2-DMP, *p*-TSA in CH_2Cl_2 to afford the known isopropylidene derivative **272** and thus completing the formal total synthesis of **246** (Scheme 11). The ^1H-NMR spectrum of **272** exhibited signals at δ 5.65 (dt, 1H) and δ 5.55 (ddd, 1H) due to the internal olefinic protons. The coupling constant 15.4 Hz was indicative of an *E*-geometry of the double bond.



Scheme 11.

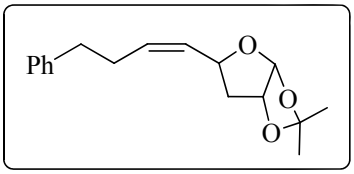
All that remained in this synthetic sequence was the final refunctionalizations such as deprotection of PMB group, oxidation followed by Horner-Wordsworth-Emmons homologation and lactonization to complete the total synthesis of **246**, like

we executed in the total synthesis of strictifolione and that was, however, reported exactly by Radhakrishna et al.

In summary a formal total synthesis of **246** was achieved starting from D-glucose. Notable features of this approach include a Yamaguchi's coupling of epoxide **267** with alkyne **240** to give the advanced intermediate **268** with all the requisite stereocenters followed by reduction to establish the (*E*) double bond at $C_{1'}$–$C_{2'}$ of target molecule **246**.

EXPERIMENTAL

2,2-Dimethyl-5-(4-phenylbut-1-enyl) tetrahydrofuro[2,3-d][1,3]dioxole (258)



To a vigorously stirred suspension of 3-phenylpropyl triphenylphosphonium iodide (44.3 g, 87.1 mmol) in THF (200 mL) was added *n*-BuLi (36.6 mL, 85.7 mmol, 2.34 M in hexane) at 0 °C over 10 min and stirred for 30 min at the same temperature. To this reddish orange colored ylide ($Ph_3P{=}CHCH_2CH_2Ph$), aldehyde **223** (5 g, 29.0 mmol) in THF (20 mL) was introduced at 0 °C. The reaction mixture was stirred at rt for 8 h and then quenched by adding a saturated solution of NH_4Cl. The contents were filtered through a celite pad while washing thoroughly with ether. The combined filtrate fractions were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (10% ethyl acetate in petroleum ether) to afford the *cis*-olefin **258** (4.86 g, 61%) as a pale yellow oil.

Mol. Formula : $C_{17}H_{22}O_3$

$[\alpha]_D$: +3.0 (*c* 1.1, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3392, 3019, 2400, 1599, 1376, 1216, 1018, 758, 669 cm^{-1}.

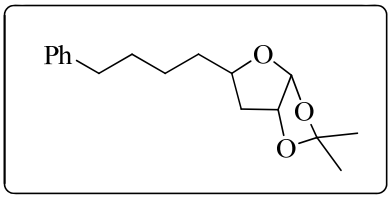
^{1}H NMR ($CDCl_3$, 400 MHz) : δ 7.33–7.16 (m, 5H), 5.81 (d, *J* = 3.7 Hz, 1H), 5.60 (ddt, *J* = 0.9, 7.9, 11.0 Hz, 1H), 5.37 (ddt, *J* = 1.4, 8.3, 11.0 Hz, 1H), 4.86 (ddd, *J* = 4.3, 8.3, 11.5 Hz, 1H), 4.70 (dd, *J* = 4.2, 4.3 Hz, 1H), 2.79–2.57 (m, 2H), 2.51–2.37 (m, 2H), 1.91 (dd, *J* = 4.3, 13.4 Hz, 1H), 1.53 (s, 3H), 1.48–1.39 (m, 1H), 1.31 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 26.0 (q), 26.6 (q), 29.6 (t), 35.6 (t), 39.4 (t), 73.3 (d), 80.5 (d), 105.2 (d), 110.7 (s), 125.8 (d), 128.2 (d, 2C), 128.4 (d, 2C), 128.6 (d), 132.7 (d), 141.3 (s) ppm.

ESI-MS (*m/z*) : 397.6 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 74.42; H, 8.08.
Found: C, 74.45; H, 8.17.

2,2-Dimethyl-5-(4-phenylbutyl)-tetrahydrofuro[2,3-d][1,3]dioxole (259)



A suspension of olefin **258** (4.8 g, 17.35 mmol) and Raney-Ni (1 g) in ethanol (50 mL) was hydrogenated for 3 h in a parr-shaker maintaining the hydrogen gas pressure at 60 psi. The reaction mixture was filtered through celite pad and the filtrate was concentrated. The residue obtained was purified by column chromatography (10% ethyl acetate in petroleum ether) to provide **259** (4.5 g, 93%) as colorless oil.

Mol. Formula : $C_{17}H_{24}O_3$

$[\alpha]_D$: –9.5 (*c* 1.1, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3436, 2934, 1603, 1216, 1020, 756, 699 cm^{-1}.

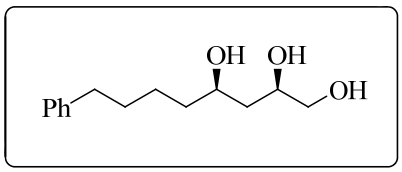
^{1}H NMR ($CDCl_3$, 400 MHz) : δ 7.29–7.25 (m, 2H), 7.18–7.15 (m, 3H), 5.80 (d, *J* = 4.0 Hz, 1H), 4.70 (dd, *J* = 4.3, 4.5 Hz, 1H), 4.20–4.13 (m, 1H), 2.61 (br t, *J* = 7.6 Hz, 2H), 2.08 (dd, *J* = 4.3, 13.3 Hz, 1H), 1.73–1.53 (m, 4H), 1.50 (s, 3H), 1.48–1.38 (m, 3H), 1.31 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz) : δ 25.7 (q), 26.0 (q), 26.5 (t), 31.4 (t), 34.1 (t), 35.7 (t), 38.9 (t), 77.8 (d), 80.4 (d), 105.2 (d), 110.6 (s), 125.6 (d), 128.2 (d, 2C), 128.3 (d, 2C), 142.4 (s) ppm.

ESI-MS (*m/z*) : 399.3 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 73.88; H, 8.75.
Found: C, 73.79; H, 8.80.

(2*R*,4*R*)-8-Phenyloctane-1,2,4-triol (261)

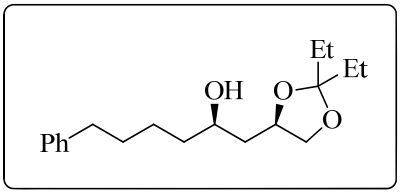


A solution of **259** (4.5 g, 16.28 mmol) in 35% aqueous acetic acid (40 mL) was refluxed for 2 h. The reaction mixture was neutralized by adding solid $NaHCO_3$ at 0 ^oC. The mixture was extracted with ethyl acetate several times. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. The residue was filtered through a short bed of silica gel column using 35% ethyl acetate in petroleum ether to obtain the mixture of α/β lactols **260** (3.85 g, 67% yield) as a pale yellow oil.

The above lactol **260** (3.85 g, 16.3 mmol) was dissolved in THF and treated with LAH (0.93 g, 24.5 mmol) in portions at 0 ^oC and stirred overnight at rt. The reaction mixture was quenched with saturated solution of Na_2SO_4 and the inorganic solids were filtered off. The filtrate was concentrated and the crude was purified by column chromatography (70% ethyl acetate in petroleum ether) to afford **261** (3.25 g, 84% yield) as a colorless oil.

Mol. Formula	: $C_{14}H_{22}O_3$
$[\alpha]_D$	: – 2.0 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3369, 2940, 1713, 1603, 1454, 1055, 749, 699 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 7.27–7.13 (m, 5H), 4.20 (d, *J* = 2.8 Hz, 1H), 4.12 (d, *J* = 3.0 Hz, 1H), 3.87–3.77 (m, 2H), 3.73–3.71 (m, 1H), 3.47–3.39 (m, 2H), 2.61 (t, *J* = 7.6 Hz, 2H), 1.67–1.58 (m, 4H), 1.48–1.39 (m, 4H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ 25.0 (t), 31.6 (t), 35.7 (t), 37.8 (t), 40.0 (t), 66.5 (t), 70.6 (d), 72.1 (d), 125.5 (d), 128.2 (d, 2C), 128.3 (d, 2C), 142.7 (s) ppm.
ESI-MS (*m/z*)	: 261.2 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 70.56; H, 9.30.
	Found: C, 70.49; H, 9.36.

(2*R*,4*R*)-1,2-Isopentylidene-8-phenyloctane-4-ol (262)

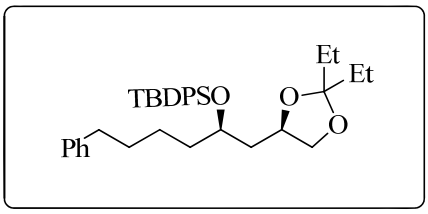


To a stirred solution of triol **261** (3.2 g, 13.4 mmol) in 3-pentanone (20 mL) was added camphor-10-sulfonic acid (0.35 g, 1.5 mmol) at 0 °C and the reaction

mixture was allowed to stir for 4 h at rt. The mixture was neutralized with TEA (few drops) and concentrated under reduced pressure. The residue was purified by column chromatography (15% ethyl acetate in petroleum ether) to afford **262** (3.3 g, 81% yield) as a colorless oil.

Mol. Formula	: $C_{19}H_{30}O_3$
$[\alpha]_D$	: +3.5 (*c* 1.8, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3469, 2936, 1603, 1462, 1077, 920, 752, 699 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 7.29–7.25 (m, 2H), 7.17 (m, 3H), 4.28–4.21 (m, 1H), 4.10 (dd, *J* = 6.3, 8.0 Hz, 1H), 3.85–3.80 (m, 1H), 3.49 (t, *J* = 8.0 Hz, 1H), 3.21 (br s, 1H), 2.64 (br t, *J* = 8.0 Hz, 2H), 1.68–1.57 (m, 8H), 1.55–1.37 (m, 4H), 0.90 (t, *J* = 7.5 Hz, 3H), 0.89 (t, *J* = 7.5 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ 8.0 (q), 8.2 (q), 25.2 (t), 29.6 (t), 29.9 (t), 31.5 (t), 35.9 (t), 37.3 (t), 40.1 (t), 70.4 (t), 71.2 (d), 76.4 (d), 113.4 (s), 125.6 (d), 128.2 (d, 2C), 128.4 (d, 2C), 142.6 (s) ppm.
ESI-MS (*m/z*)	: 329.4 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 74.47; H, 9.87.
	Found: C, 74.53; H, 9.92.

(2*R*,4*R*)-4-(*tert*-Butyldiphenylsilyloxy)-1,2-isopentylidene-8-phenyloctane (263)

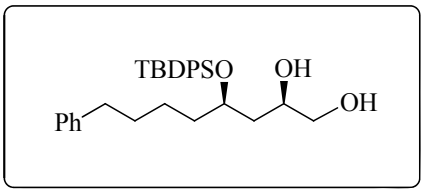


At 0 °C, a solution of **262** (3.2 g, 10.44 mmol) and imidazole (0.86 g, 12.5 mmol) in CH_2Cl_2 (40 mL) was treated with TBDPSCl (3.5 g, 12.5 mmol) and DMAP (0.13 g, 1.04 mmol). After 5 h stirring at rt, the reaction mixture was partitioned between CH_2Cl_2 and water. The organic layer separated was washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography using (7% ethyl acetate in petroleum ether) to obtain **263** (4.5 g, 79%) as a colorless oil.

Mol. Formula	: $C_{35}H_{48}O_3Si$
$[\alpha]_D$	: –15.2 (*c* 3.2, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3543, 2930, 1532, 1351, 1100, 838, 758, 673 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 7.67 (d, *J* = 7.8 Hz, 4H), 7.44–7.36 (m, 6H), 7.27 (t, *J* = 7.3 Hz, 2H), 7.18 (t, *J* = 7.3 Hz, 1H), 7.11 (d, *J* = 7.5 Hz, 2H), 4.17 (dt, *J* = 6.3, 14.0 Hz, 1H), 3.84 (t, *J* = 5.8 Hz, 1H), 3.80 (dd, *J* = 6.0, 7.5 Hz, 1H), 3.28 (t, *J* = 8.0 Hz, 1H), 2.50 (t, *J* = 7.5 Hz, 1H), 1.90 (dt, *J* = 6.0, 13.8 Hz, 1H 9H), 1.63–1.43 (m, 10H), 1.37–1.34 (m, 1H), 1.07 (s, 9H) 0.87 (t, *J* = 7.3 Hz, 3H), 0.83 (t, *J* = 7.3 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 7.9 (q), 8.2 (q), 19.3 (s), 24.4 (t), 27.0 (q, 3C), 29.8 (t), 30.0 (t), 31.3 (t), 35.7 (t), 36.3 (t), 39.5 (t), 70.4 (t), 70.7 (d), 73.1 (d), 112.1 (s), 125.6 (d), 127.5 (d, 2C), 127.6 (d, 2C), 128.2 (d, 2C), 128.3 (d, 2C), 129.5 (d), 129.6 (d), 134.1 (s), 134.3 (s), 135.8 (d, 2C), 135.9 (d, 2C), 142.5 (s) ppm.
ESI-MS (*m/z*)	: 567.4 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 77.16; H, 8.88.
	Found: C, 77.12; H, 9.91

(2*R*,4*R*)-4-(*tert*-Butyldiphenylsilyloxy)-8-phenyloctane-1,2-diol (264)



A solution of **263** (4.4 g, 8.07 mmol) and PPTS (0.5 g, 2.0 mmol) in methanol (50 mL) was stirred at rt for 8 h. After completion of reaction as indicated by TLC, mixture was neutralized by adding few drops of TEA and subsequently concentrated under reduced pressure. The residue was purified by column chromatography (30% ethyl acetate in petroleum ether) to afford diol **264** (2.64 g, 71%) as a pale yellow oil.

Mol. Formula	: $C_{30}H_{40}O_3Si$
$[\alpha]_D$	: –34.7(*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3432, 2931, 1603, 1427, 1216, 1110, 757, 668 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 7.72–7.67 (m, 4H), 7.48–7.33 (m, 6H), 7.29–7.15 (m, 3H), 7.04 (dd, *J* = 1.8, 8.1 Hz, 2H), 4.03–3.82 (m, 2H), 3.53 (dd, *J* = 3.5, 11.2 Hz, 1H), 3.37 (dd, *J* = 6.4, 11.2 Hz, 1H), 2.38 (t, *J* = 7.1 Hz, 2H), 1.80–1.58 (m, 4H), 1.46–

1.11 (m, 6H), 1.04 (s, 9H) ppm.

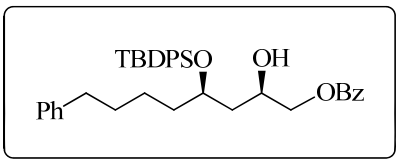
^{13}C NMR ($CDCl_3$, 100 MHz) : δ 19.2 (s), 24.3 (t), 26.9 (q, 3C), 31.0 (t), 35.5 (t), 36.8 (t), 39.0 (t), 66.7 (t), 70.5 (d), 73.0 (d), 125.5 (d), 127.5 (d, 2C), 127.6 (d, 2C), 128.1 (d, 2C), 128.2 (d, 2C), 129.6 (d), 129.8 (d), 133.4 (s), 134.1 (s), 135.8 (d, 4C), 142.3 (s) ppm.

ESI-MS (*m/z*) : 485.3 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 75.28; H, 8.28.

Found: C, 75.16; H, 8.34.

(2*R*,4*R*)-4-(*tert*-Butyldiphenylsilyloxy)-2-hydroxy-8-phenyloctyl benzoate (265)



At 0 °C, a solution of TBDPS-diol **264** (2.5 g, 5.4 mmol) in DCM (30 mL) was treated with TEA (2.3 mL, 16.3 mmol) followed by benzoyl chloride (0.64 mL, 5.5 mmol). After the completion of reaction (3 h), the mixture was concentrated under vacuum and the residue was purified by column chromatography (15% ethyl acetate in petroleum ether) to furnish **265** (2.5 g, 80% yield) as a colorless oil.

Mol. Formula : $C_{37}H_{44}O_4Si$

$[\alpha]_D$: −14.2 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3444, 2931, 1721, 1427, 1110, 1027, 702, 505 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz) : δ 8.02 (dd, *J* = 1.6, 8.4 Hz, 2H), 7.71–7.68 (m, 4H), 7.58–7.55 (m, 1H), 7.45–7.41 (m, 4H), 7.39–7.34 (m, 4H), 7.23 (br t, *J* = 7.7 Hz, 2H), 7.14 (tt, *J* = 1.7, 7.3 Hz, 1H), 7.05 (br d, *J* = 7.3 Hz, 2H), 4.24 (dd, *J* = 3.0, 11.0 Hz, 1H), 4.16–4.09 (m, 2H), 4.02–3.97 (m, 1H), 2.75 (br s, 1H), 2.42-2.39 (m, 2H), 1.74–1.71 (m, 2H), 1.48-1.43 (m, 2H), 1.37–1.31 (m, 2H), 1.28–1.22 (m, 1H), 1.17–1.11 (m, 1H), 1.05 (s, 9H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz) : δ 19.3 (s), 24.4 (t), 27.0 (q, 3C), 31.1 (t), 35.6 (t), 36.8 (t), 39.6 (t), 68.3 (d), 68.9 (t), 72.5 (d), 125.6 (d), 127.5 (d, 2C), 127.7 (d, 2C), 128.2 (d, 2C), 128.3 (d, 2C), 128.4 (d,

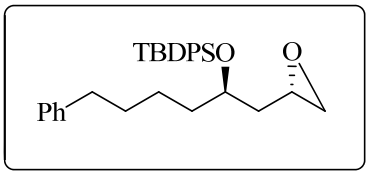
2C), 129.6 (d, 2C), 129.7 (d), 129.8 (d), 129.9 (s), 133.1 (d), 133.6 (s), 134.1 (s), 135.8 (d, 2C), 135.9 (d, 2C), 142.4 (s), 166.6 (s) ppm.

ESI-MS (*m/z*) : 603.3 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 76.51; H, 7.64.

Found: C, 76.47; H, 7.73.

tert-Butyl((*R*)-1-((*S*)-oxiran-2-yl)-6-phenylhexan-2-yloxy)diphenylsilane (267)



To a stirred solution of benzoate **265** (2.5 g, 4.3 mmol) and triethylamine (1.8 mL, 13 mmol) in CH_2Cl_2 (30 mL) was added mesylchloride (0.5 mL, 6.5 mmol) drop wise at 0 °C. To this DMAP (53 mg, 0.43 mmol) was added and stirring continued for 5 h at rt. The reaction mixture was diluted with water and two layers were separated. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The crude mesylate **266** was then dissolved in a mixture of THF–MeOH (1:1) (30 mL) and treated with $LiOH.H_2O$ (220 mg, 5.2 mmol) at 0 °C. The stirring was continued for 1 h after which the TLC showed the complete consumption of the starting material. The solvents were evaporated under reduced pressure and the residue was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue obtained was purified by column chromatography (10% ethyl acetate in petroleum ether) to give epoxide **267** (1.4 g, 71% yield over two steps) as a colorless oil.

Mol. Formula : $C_{30}H_{38}O_2Si$

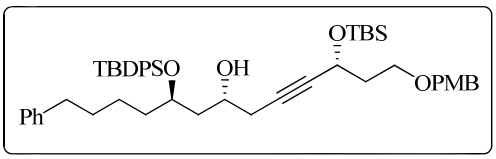
$[\alpha]_D$: –19.2 (*c* 1.2, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 2931, 1603, 1427, 1218, 1110, 1069, 822, 758 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz) : δ 7.69–7.66 (m, 4H), 7.44–7.34 (m, 6H), 7.26–7.23 (m, 2H), 7.17–7.14 (tt, *J* = 1.4, 7.4 Hz, 1H), 7.08 (d, *J* = 7.0 Hz, 2H), 3.97–3.91 (m, 1H), 2.95–2.92 (m, 1H), 2.68 (t, *J* = 4.5 Hz, 1H), 2.46 (dd, *J* = 6.5, 8.3 Hz, 2H), 2.32 (dd, *J* = 2.8, 5.0 Hz, 1H) 1.69–1.59 (m, 2H), 1.51–1.45 (m, 2H), 1.43–1.38 (m, 2H) 1.28–1.20 (m, 2H), 1.04 (s, 9H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 19.3 (s), 24.3 (t), 27.0 (q, 3C), 31.2 (t), 35.7 (t), 36.9 (t), 39.7 (t), 47.4 (t), 49.7 (d), 71.4 (d), 125.5 (d), 127.4 (d), 127.5 (d), 128.1 (d), 128.3 (d, 3C), 129.5 (d), 129.6 (d, 2C), 132.8 (d), 134.0 (s), 134.3 (s), 135.8 (d, 4C), 142.4 (s) ppm.
ESI-MS (*m/z*)	: 481.3 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 78.55; H, 8.35.
	Found: C, 78.46; H, 8.44.

3-(*tert*-Butyl-dimethyl-silanyloxy)-9-(*tert*-butyl-diphenyl-silanyloxy)-1-(4-methoxy-benzyloxy)-13-phenyl-tridec-4-yn-7-ol (268)



To a solution of alkyne **240** (1.46 g, 4.4 mmol) in anhydrous THF (15 mL) in a flame dried two neck round bottom flask under argon was added *n*-BuLi (2.8 mL, 4.5 mmol, 1.6 M in hexane) dropwise at –78 ^oC. After 15 min, $BF_3.Et_2O$ (0.54 mL, 4.4 mmol) was added slowly dropwise. Reaction mixture was allowed to stir for another 15 min at the same temperature after which a solution of epoxide **267** (1 g, 2.2 mmol) in THF (5 mL) was added. Reaction was quenched by adding a solution of THF:H_2O (1:1) when the TLC showed the complete consumption of the epoxide (45 min). The mixture was slowly warmed to rt and extracted with EtOAc. The combined organic extract was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was further purified by flash column chromatography (20% ethyl acetate in petroleum ether) to furnish the title compound **268** (1.2 g, 69% yield) as a colorless oil.

Mol. Formula	: $C_{49}H_{68}O_5Si_2$
$[\alpha]_D$	: –6.1 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3460, 3017, 2858, 2401, 1612, 1427, 1216, 758, 668 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 7.68–7.65 (m, 4H), 7.41–7.34 (m, 6H), 7.23–7.20 (m, 4H), 7.15–7.11 (m, 1H), 7.02 (d, *J* = 7.3 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 4.52 (t, *J* = 6.4 Hz, 1H), 4.38 (t, *J* = 11.4, 15.0 Hz, 2H), 4.01–3.95 (m, 2H), 3.76 (s, 3H), 3.58–3.49

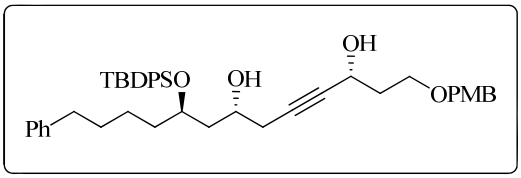
(m, 2H), 3.15 (br s, 1H), 2.39–2.33 (m, 3H), 2.29–2.23 (m, 1H), 1.91 (q, *J* = 6.3, 12.5 Hz, 2H) 1.75–1.62 (m, 3H), 1.55–1.40 (m, 2H), 1.36–1.29 (m, 2H), 1.19–1.08 (m, 1H), 1.04 (s, 9H), 0.87 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz): δ –5.1 (q), –4.5 (q), 18.2 (s), 19.2 (s), 24.8 (t), 25.8 (q, 3C), 27.0 (q, 3C), 27.8 (t), 31.1 (t), 35.5 (t), 35.9 (t), 39.1 (t), 40.6 (t), 55.2 (q), 60.0 (d), 66.1 (t), 67.2 (d), 72.2 (d), 72.6 (t), 80.8 (s), 83.9 (s), 113.7 (d, 2C), 125.6 (d), 127.6 (d, 2C), 127.7 (d, 2C), 128.7 (d, 2C), 128.3 (d, 2C), 129.2 (d, 2C), 129.7 (d), 129.8 (d), 130.5 (s), 133.4 (s), 133.9 (s), 135.9 (d, 4C), 142.4 (s), 159.1 (s) ppm

ESI-MS (*m/z*): 815.6 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 74.19; H, 8.64.
Found: C, 74.11; H, 8.73.

(3*R*,7*R*,9*R*)-9-(*tert*-Butyldiphenylsilyloxy)-1-(4-methoxybenzyloxy)-13-phenyltridec-4-yne-3,7-diol (269)



A solution of **268** (100 mg, 0.13 mmol) and PPTS (5 mg, 0.02 mmol) in methanol (5 ml) was stirred for 6 h at rt. Reaction mixture was neutralized with TEA and concentrated. The crude was purified by column chromatography (40% ethyl acetate in petroleum ether) to procure **269** (50 mg, 75% yield) as a pale yellow oil.

Mol. Formula: $C_{43}H_{54}O_5Si$

$[\alpha]_D$: – 8.6 (*c* 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.69–7.66 (m, 4H), 7.45–7.41 (m, 2H), 7.39–7.36 (m, 4H), 7.25–7.21 (m, 4H), 7.15 (tt, *J* = 1.5, 7.5 Hz, 1H), 7.03 (d, *J* = 6.8 Hz, 2H), 6.86 (dt, *J* = 2.5, 8.6 Hz, 2H), 4.56 (m, 1H), 4.44 (q, *J* = 11.5, 14.7 Hz, 2H), 4.07–4.02 (m, 1H), 3.98 (ddd, *J* = 4.4, 8.8,12.7 Hz, 1H), 3.80–3.76 (m, 1H), 3.78 (s, 3H), 3.61 (ddd, *J* = 4.6, 6.1, 10.8 Hz, 1H), 3.41 (br s, 1H), 3.06 (br s, 1H), 2.40–2.36 (m, 3H), 2.30 (ddd, *J* = 1.7, 6.3, 16.4 Hz, 1H), 2.04–1.98 (m, 1H), 1.93–1.86 (m,

1H), 1.75–1.68 (m, 3H), 1.63–1.55 (m, 1H), 1.50–1.43 (m, 1H), 1.37–1.31 (m, 2H), 1.18–1.08 (m, 1H), 1.05 (s, 9H) ppm.

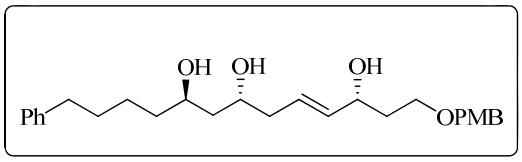
^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.2 (s), 24.8 (t), 27.0 (q, 3C), 27.7 (t), 31.0 (t), 35.5 (t), 35.6 (t), 37.0 (t), 40.2 (t), 55.2 (q), 61.5 (d), 67.1 (d), 67.4 (t), 72.3 (d), 72.9 (t), 81.8 (s), 82.7 (s), 113.8 (d, 2C), 125.6 (d), 127.6 (d, 2C), 127.7 (d, 2C), 128.2 (d, 2C), 128.3 (d, 2C), 129.3 (d, 2C), 129.8 (d), 129.8 (d), 129.9 (s), 133.3 (s), 133.7 (s), 135.9 (d, 4C), 142.3 (s), 159.2 (s) ppm..

ESI-MS (*m/z*): 701.5 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 76.07; H, 8.02

Found: C, 76.02; H, 8.14

(3*R*,7*R*,9*R*,*E*)-1-(4-Methoxybenzyloxy)-13-phenyltridec-4-ene-3,7,9-triol (270)



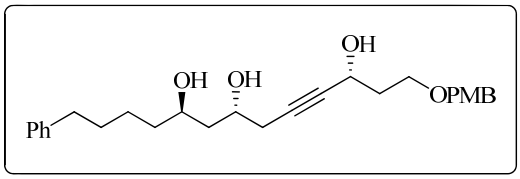
To an ice cooled solution of **269** (50 mg, 0.1 mmol) in THF (5 mL) was added LAH (6 mg, 0.15 mmol) under Argon. After the gas evolution was ceased (15 min), the reaction mixture was heated at 50 °C for 6 h. The excess LAH was quenched with EtOAc and ice at 0 °C. The resulting slurry was filtered through a pad of celite. The filtrate was concentrated and the residue was purified by flash column chromatography to produce the triols **255** (45% ethyl acetate in petroleum ether, 10 mg, 30% yield) and **270** (50% ethyl acetate in petroleum ether, 18 mg, 56% yield) as colorless oils.

Mol. Formula: $C_{27}H_{38}O_5$

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.29–7.24 (m, 5H), 7.17 (d, *J* = 7.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.66 (dt, *J* = 6.5, 15.6 Hz, 1H), 5.59 (dd, *J* = 5.8, 15.6 Hz, 1H), 4.44 (br s, 2H), 4.31 (dd, *J* = 5.8, 11.3 Hz, 1H), 3.98–3.88 (m, 2H), 3.80 (s, 3H), 3.69–3.57 (m, 2H), 2.62 (t, *J* = 7.7 Hz, 2H), 2.22 (t, *J* = 6.4 Hz, 2H), 1.81 (dd, *J* = 5.8, 11.3 Hz, 2H), 1.58–1.46 (m, 8H) ppm.

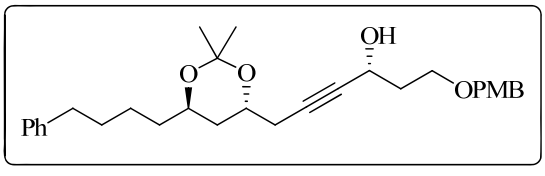
ESI-MS (*m/z*)	: 465.3 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 73.27; H, 8.65.
	Found: C, 73.08; H, 8.79.

(3*R*,7*R*,9*R*)-1-(4-Methoxybenzyloxy)-13-phenyltridec-4-yne-3,7,9-triol (255)



Mol. Formula	: $C_{27}H_{36}O_5$
$[\alpha]_D$	: –3.0 (*c* 1.0, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 7.28–7.23 (m, 4H), 7.18–7.15 (m, 3H), 6.86 (d, *J* = 8.5 Hz, 2H), 4.55 (br dd, *J* = 4.8, 6.8 Hz, 1H), 4.44 (s, 2H), 4.04 (br ddd, *J* = 6.3, 9.3, 14.6 Hz, 1H), 3.88 (ddd, *J* = 4.0, 7.7, 11.7 Hz, 1H), 3.78 (s, 3H), 3.76–3.71 (m, 1H), 3.61 (ddd, *J* = 5.0, 6.0, 11.0 Hz, 2H), 2.60 (t, *J* = 7.7 Hz, 2H), 2.38 (br dd, *J* = 1.7, 6.0 Hz, 2H), 2.05–1.89 (m, 2H), 1.69-1.59 (m, 4H), 1.55–1.43 (m, 2H), 1.38–1.30 (m, 1H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ 25.4 (t), 27.7 (t), 31.4 (t), 35.8 (t), 37.1 (t), 37.3 (t), 41.8 (t), 55.2 (q), 61.2 (d), 67.2 (t), 67.5 (d), 68.8 (d), 72.9 (t), 81.8 (s), 83.1 (s), 113.8 (d, 2C), 125.6 (d), 128.2 (d, 2C), 128.3 (d, 2C), 129.3 (d, 2C), 129.9 (s), 142.5 (s), 159.2 (s) ppm.
ESI-MS (*m/z*)	: 463.3 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 73.61; H, 8.24
	Found: C, 73.45; H, 8.29

(*R*)-6-((4*R*,6*R*)-2,2-Dimethyl-6-(4-phenylbutyl)-1,3-dioxan-4-yl)-1-(4-methoxybenzyloxy)hex-4-yn-3-ol (271)

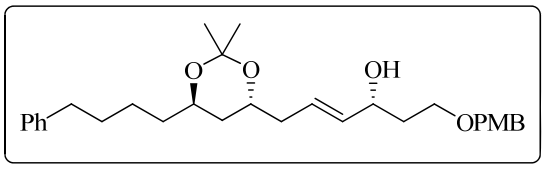


A solution of triol **255** (10 mg, 0.02 mmol) and 2,2-dimethoxypropane (5 μL, 0.04 mmol) in CH_2Cl_2 was treated with catalytic *p*-TSA (1 mg, 0.006 mmol) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and subsequently neutralized with

TEA (1 drop). The volatiles were evaporated under reduced pressure and the residue was purified by column chromatography (20% ethyl acetate in petroleum ether) to obtain **271** (10 mg, 96%) as a pale yellow oil.

Mol. Formula	: $C_{30}H_{40}O_5$
$[\alpha]_D$	: –14.6 (*c* 1.5, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 7.29–7.24 (m, 4H), 7.19–7.15 (m, 3H), 6.87 (d, *J* = 8.5 Hz, 2H), 4.58 (br m, 1H), 4.45 (s, 2H), 3.91 (dt, *J* = 7.3, 14.0 Hz, 1H), 3.84–3.73 (m, 5H), 3.63 (ddd, *J* = 4.8, 6.0, 11.0 Hz, 1H), 3.01 (br s, 1H), 2.60 (t, *J* = 7.6 Hz, 2H), 2.46 (ddd, *J* = 2.0, 7.9, 16.5 Hz, 1H), 2.35 (ddd, *J* = 1.7, 7.3, 16.5 Hz, 1H), 2.08–2.00 (m, 1H), 1.95–1.87 (m, 1H), 1.69–1.54 (m, 6H), 1.46–1.41 (m, 2H), 1.35 (s, 3H), 1.33 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ 24.7 (q), 25.0 (q), 25.1 (t), 25.9 (t), 31.4 (t), 35.7 (t), 35.9 (t), 37.0 (t), 37.7 (t), 55.2 (q), 61.7 (d), 65.5 (d), 66.5 (d), 67.5 (t), 73.0 (t), 81.4 (s), 82.1 (s), 100.4 (s), 113.8 (d, 2C), 125.6 (d), 128.2 (d, 2C), 128.3 (d, 2C), 129.3 (d, 2C), 129.9 (s), 142.6 (s), 159.3 (s) ppm.
ESI-MS (*m/z*)	: 503.4 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 74.97; H, 8.39. Found: C, 74.89; H, 8.45.

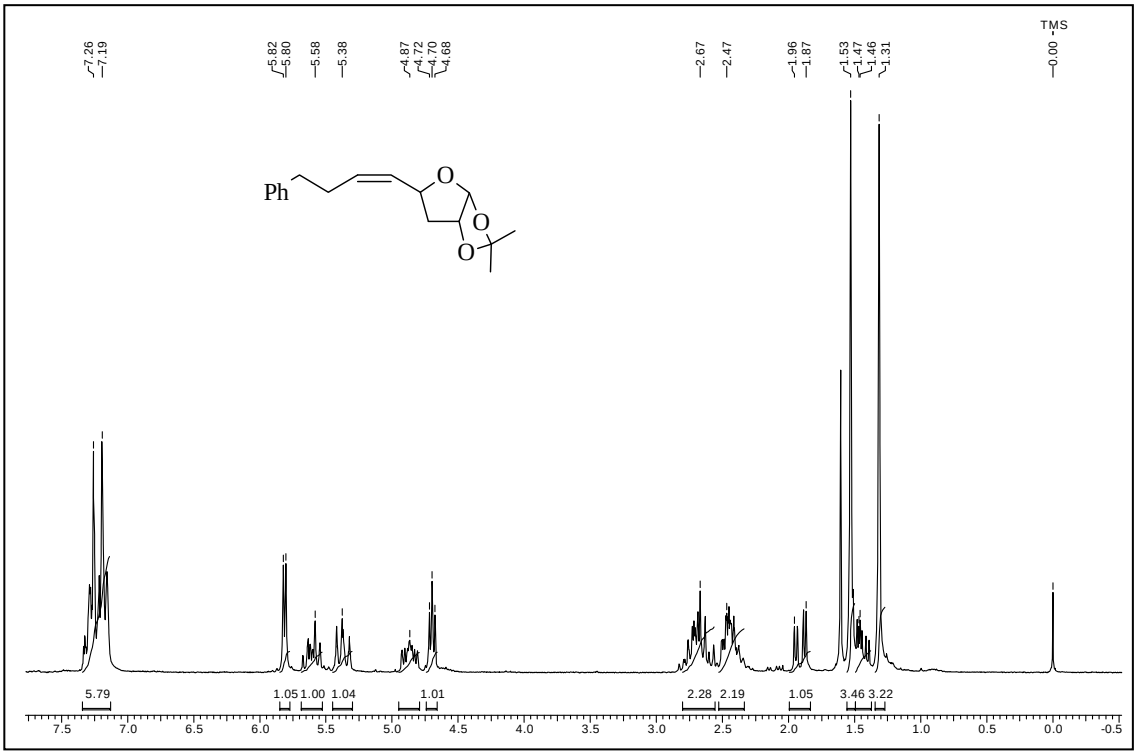
(*R*,*E*)-6-((4*R*,6*R*)-2,2-Dimethyl-6-(4-phenylbutyl)-1,3-dioxan-4-yl)-1-(4-methoxybenzyloxy)hex-4-en-3-ol (272)



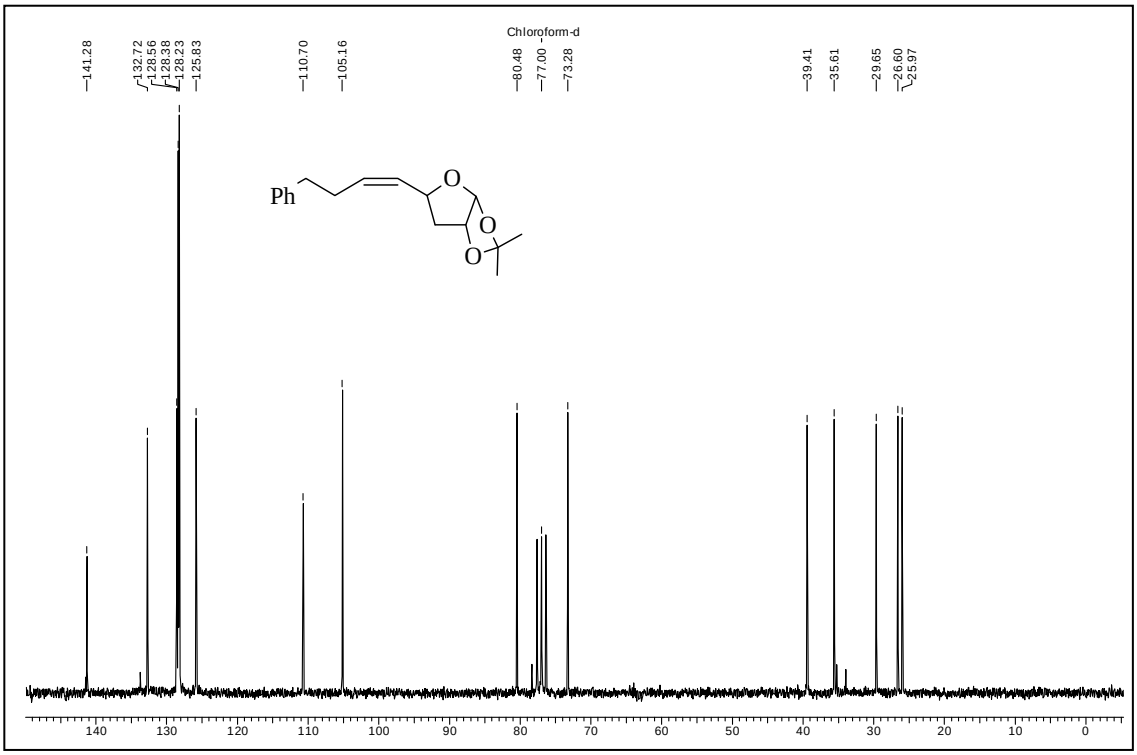
At 0 °C, a solution of triol **270** (18 mg, 0.04 mmol) and 2,2-dimethoxypropane (15 μL, 0.12 mmol) in CH_2Cl_2 was exposed to a catalytic *p*-TSA (2 mg, 0.01 mmol) for 30 min. The reaction mixture was neutralized with TEA (1 drop) and subsequently concentrated under reduced pressure. The residue obtained was purified by column chromatography (25% ethyl acetate in petroleum ether) to furnish **272** (17 mg, 92%) as a colorless oil.

Mol. Formula	: $C_{30}H_{42}O_5$
$[\alpha]_D$	: −6.0 (*c* 0.5, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 500 MHz)	: δ 7.29–7.24 (m, 5H), 7.19–7.16 (m, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.65 (dt, *J* = 6.3, 15.4 Hz, 1H), 5.55 (dd, *J* = 6.3, 15.4 Hz, 1H), 4.45 (s, 2H), 4.31–4.26 (m, 1H), 3.83–3.72 (m, 5H), 3.69–3.65 (m, 1H), 3.61–3.57 (m, 1H), 2.80 (br s, 1H), 2.60 (t, *J* = 7.8 Hz, 2H), 2.28 (dt, *J* = 6.3, 14.3 Hz, 1H), 2.15 (dt, *J* = 6.3, 14.3 Hz, 1H), 1.84–1.79 (m, 2H), 1.64–1.42 (m, 8H), 1.33 (2s, 6H) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz)	: δ 24.8 (q), 24.9 (q), 25.1 (t), 31.4 (t), 35.7 (t), 35.9 (t), 36.7 (t), 38.2 (t), 38.6 (t), 55.3 (q), 66.3 (d), 66.5 (d), 68.1 (t), 71.7 (d), 73.0 (t), 100.2 (s), 113.9 (d, 2C), 125.6 (d), 126.7 (d), 128.2 (d, 2C), 128.4 (d, 2C), 129.3 (d, 2C), 130.0 (s), 134.8 (d), 142.7 (s), 159.3 (s) ppm.
ESI-MS (*m/z*)	: 505.5 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 74.65; H, 8.77. Found: C, 74.51; H, 8.84.

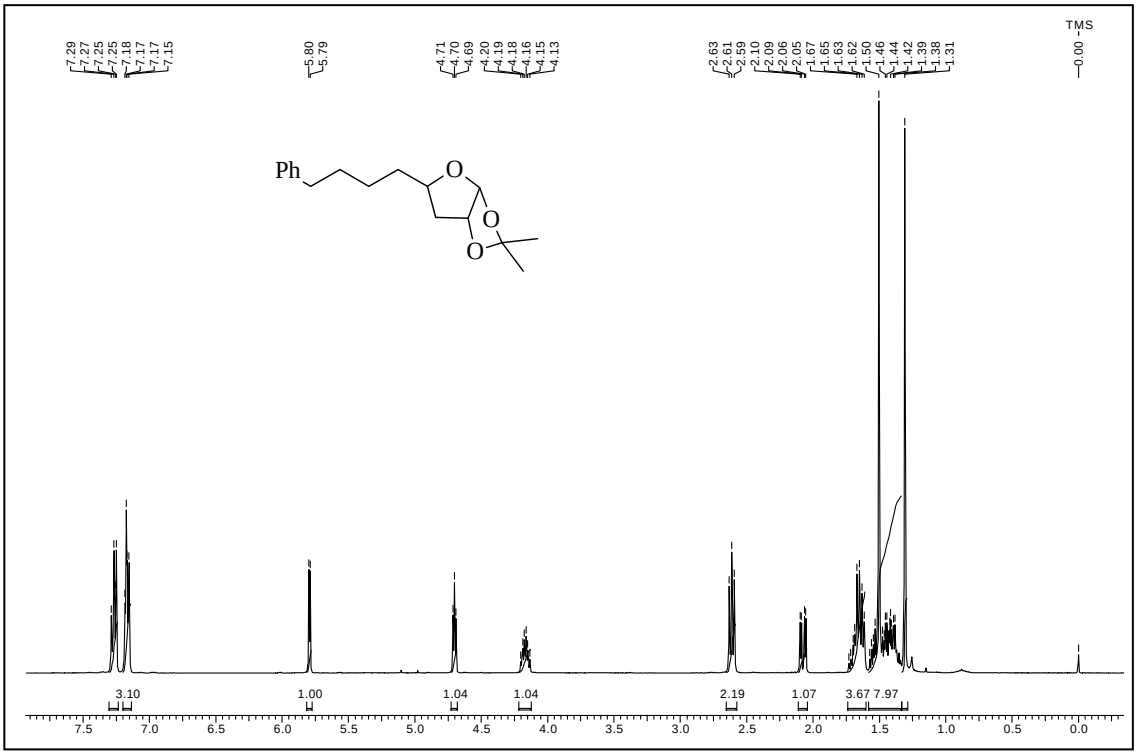
SPECTRA



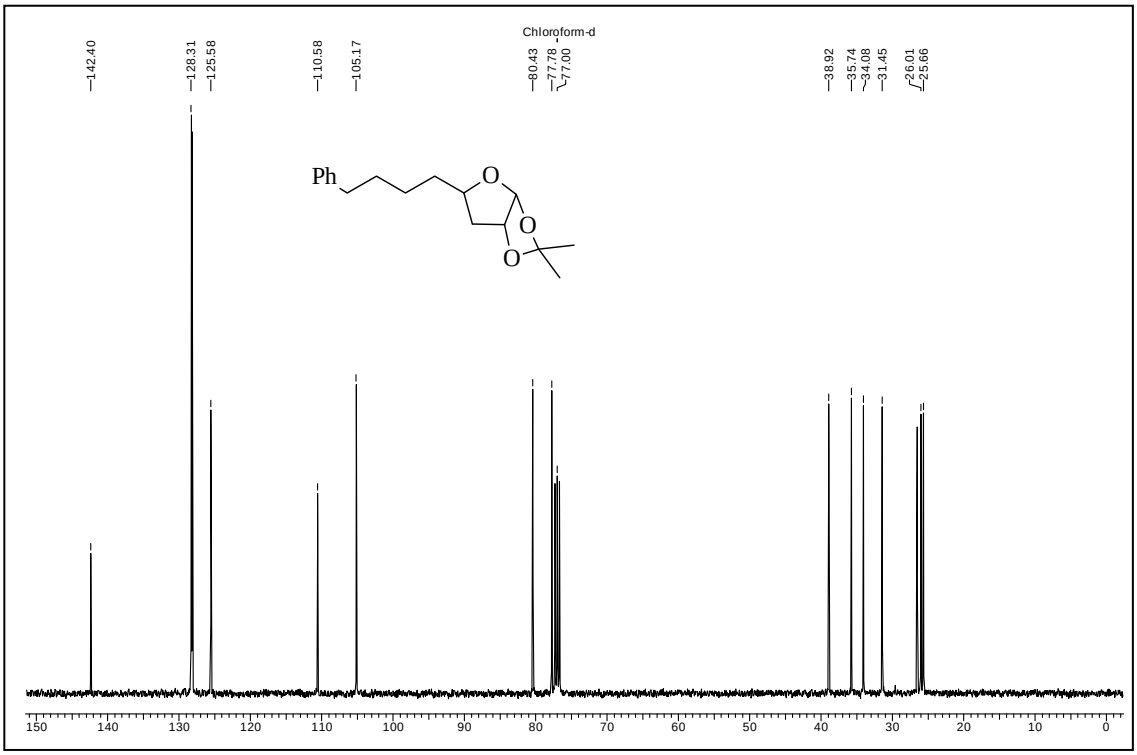
^{1}H NMR Spectrum of 258 in $CDCl_3$



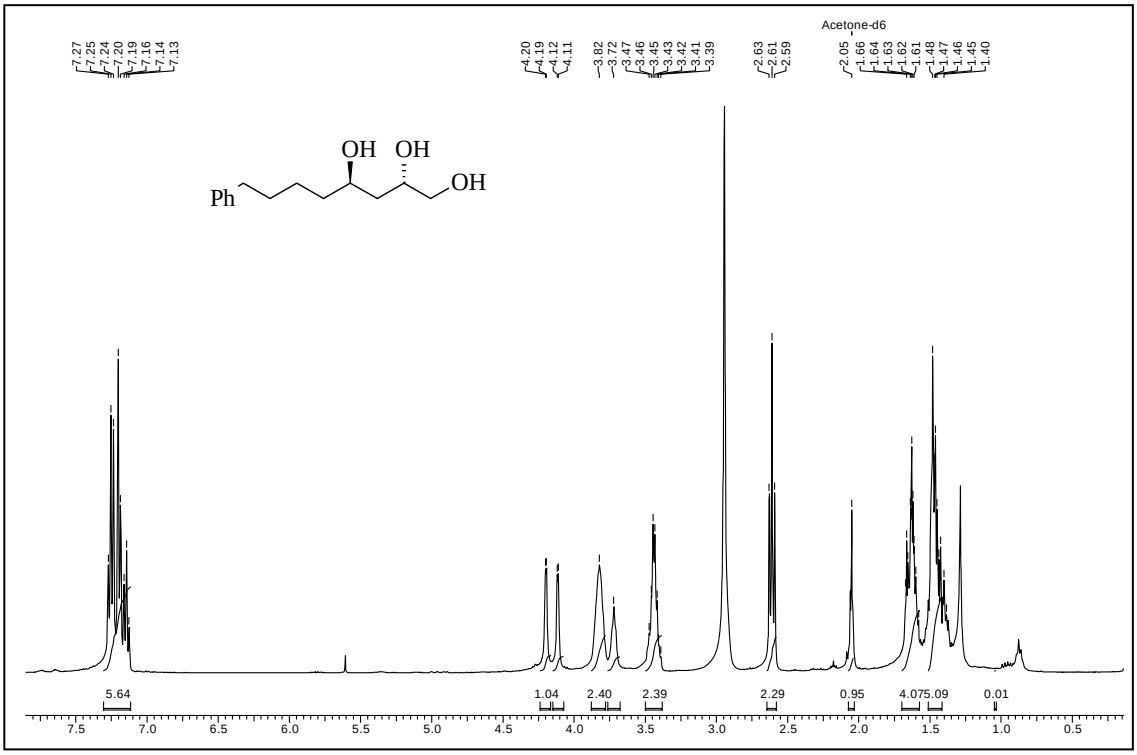
^{13}C NMR Spectrum of 258 in $CDCl_3$



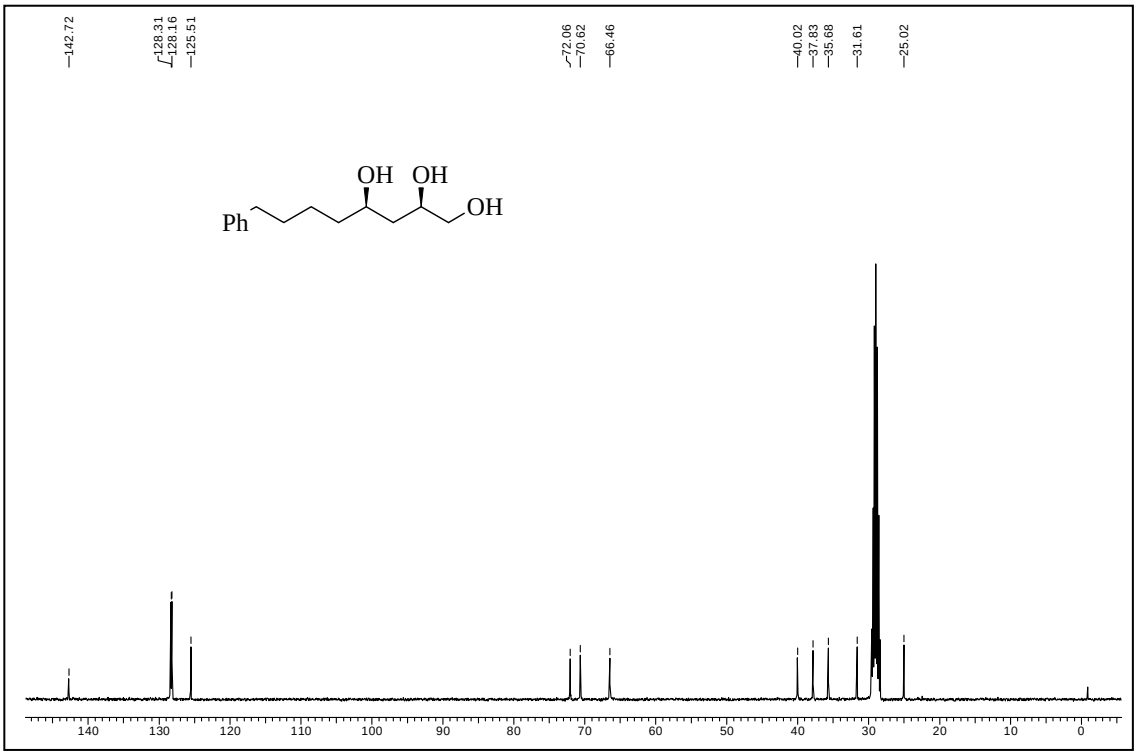
^{1}H NMR Spectrum of 259 in $CDCl_3$



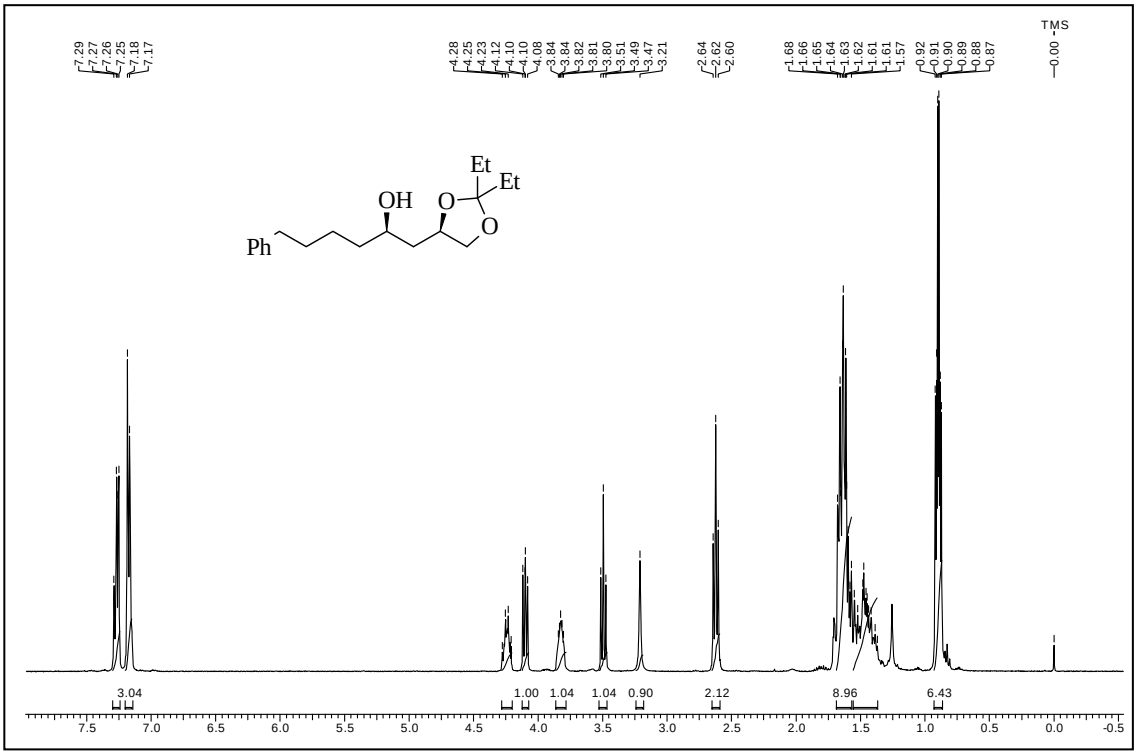
^{13}C NMR Spectrum of 259 in $CDCl_3$



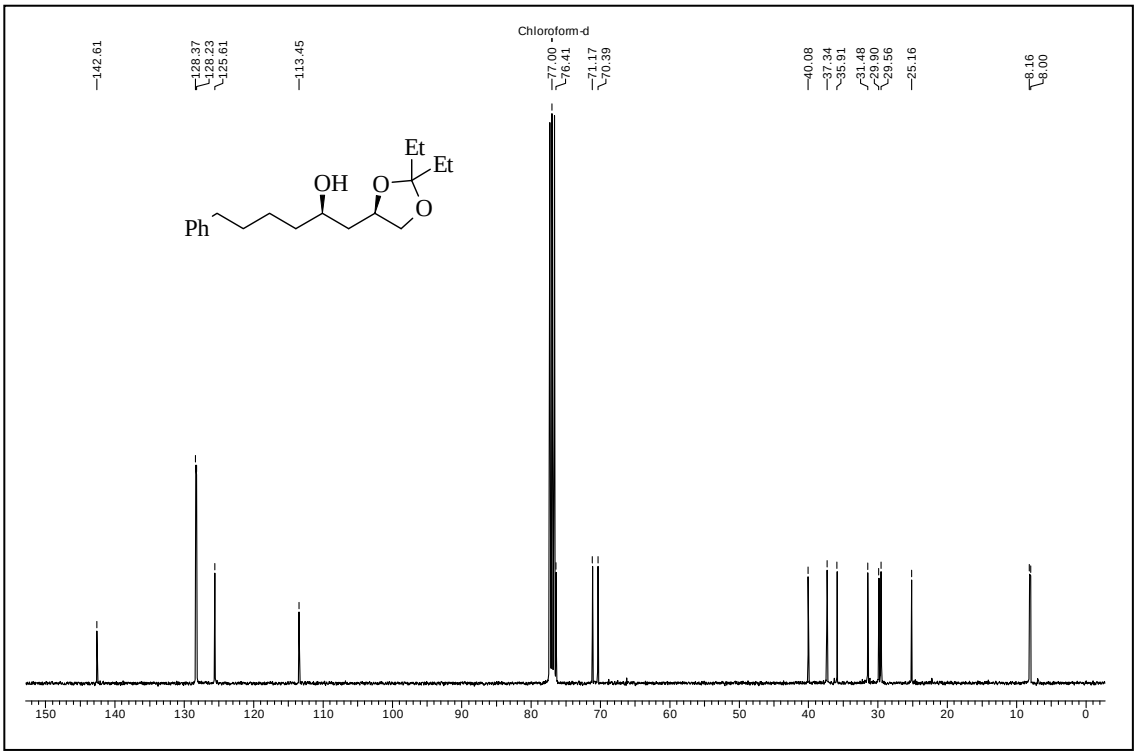
^{1}H NMR Spectrum of 261 in Acetone-d6



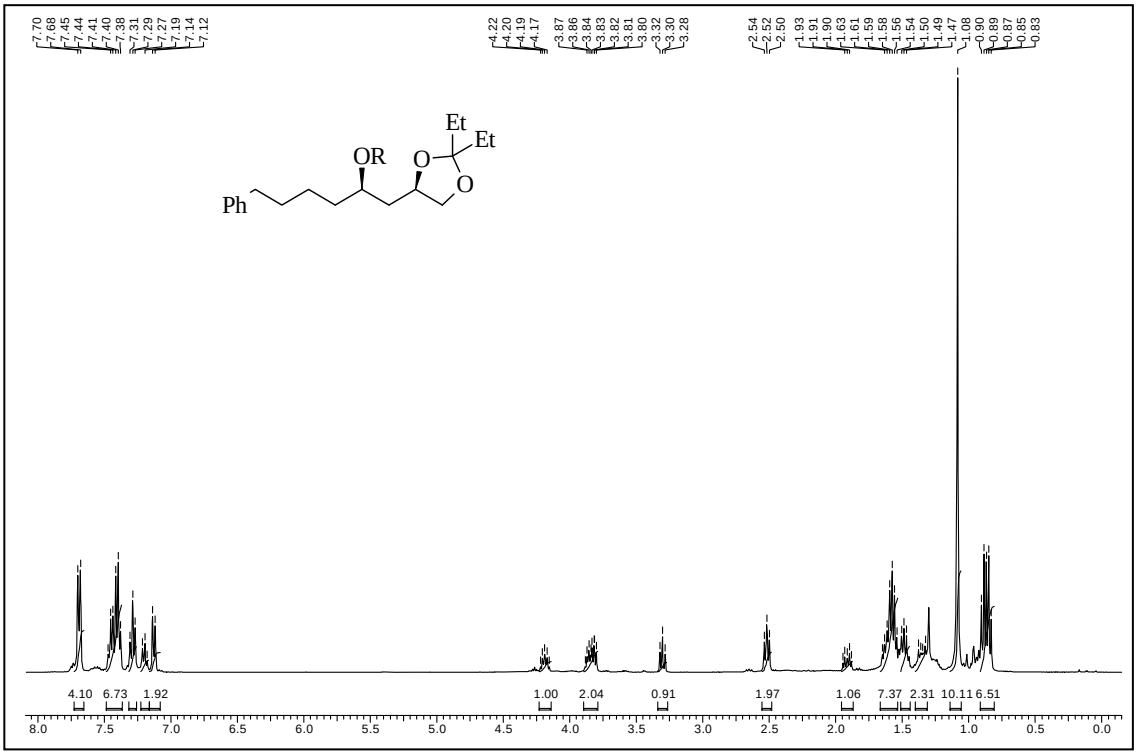
^{13}C NMR Spectrum of 261 in Acetone-d6



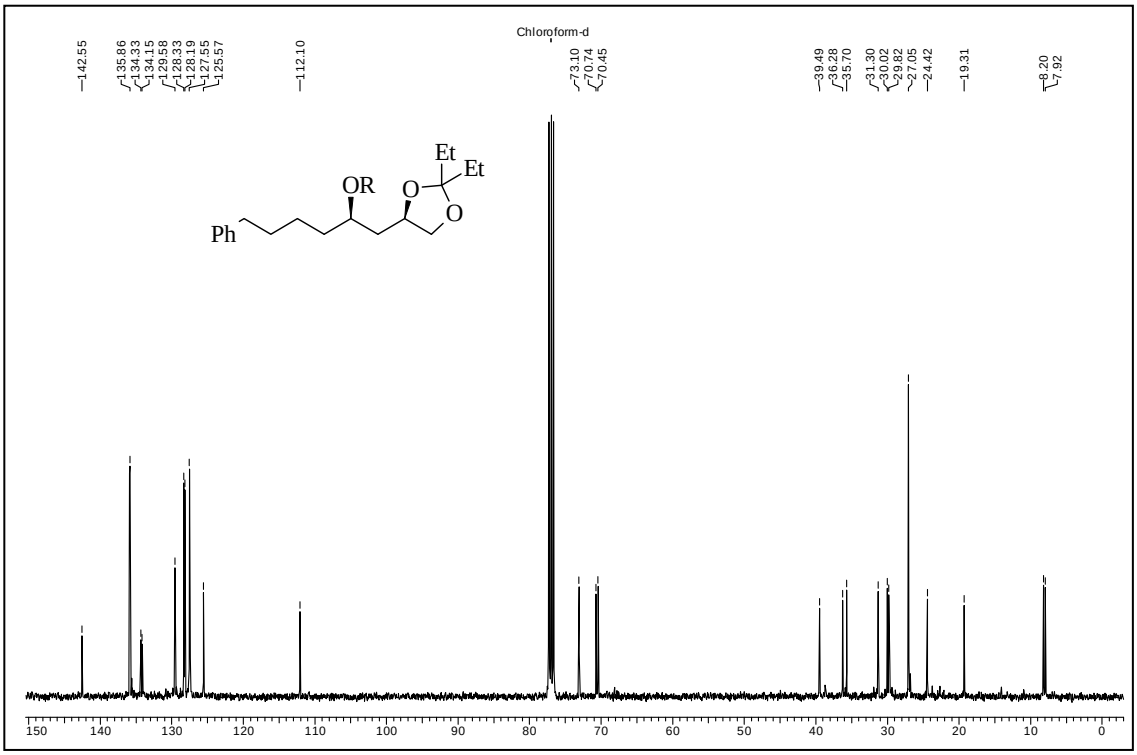
^{1}H NMR Spectrum of 262 in $CDCl_3$



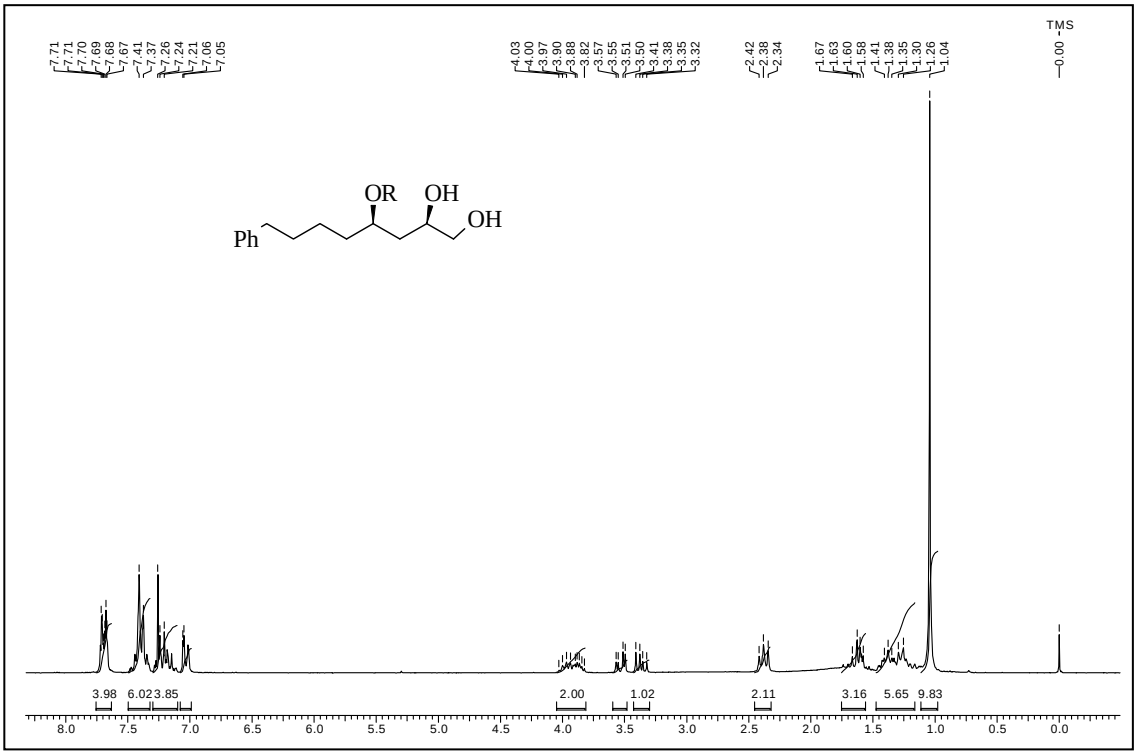
^{13}C NMR Spectrum of 262 in $CDCl_3$



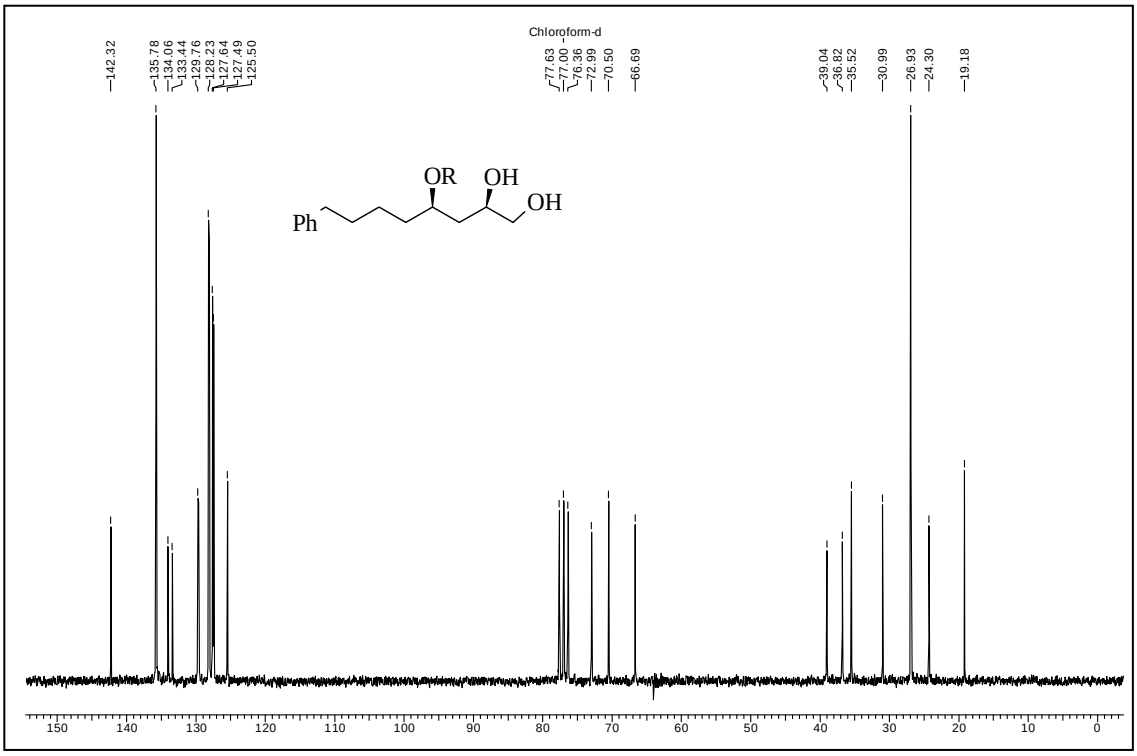
^{1}H NMR Spectrum of 263 in $CDCl_3$ (R = TBDPS)



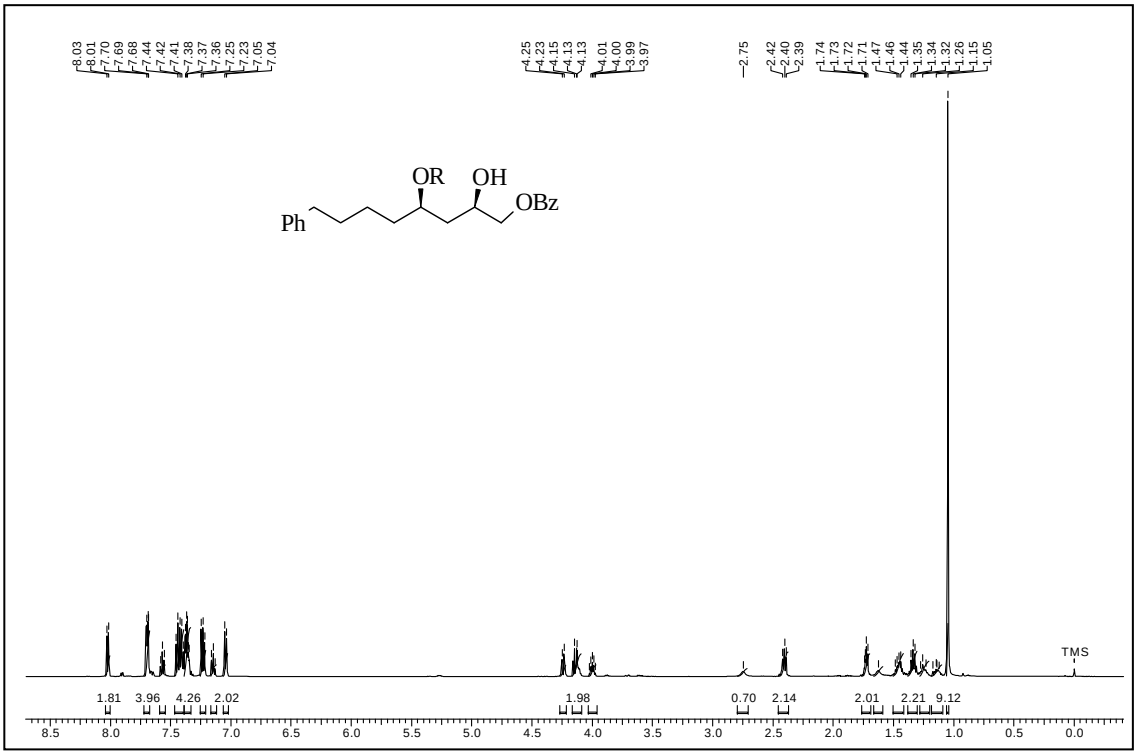
^{13}C NMR Spectrum of 263 in $CDCl_3$ (R = TBDPS)



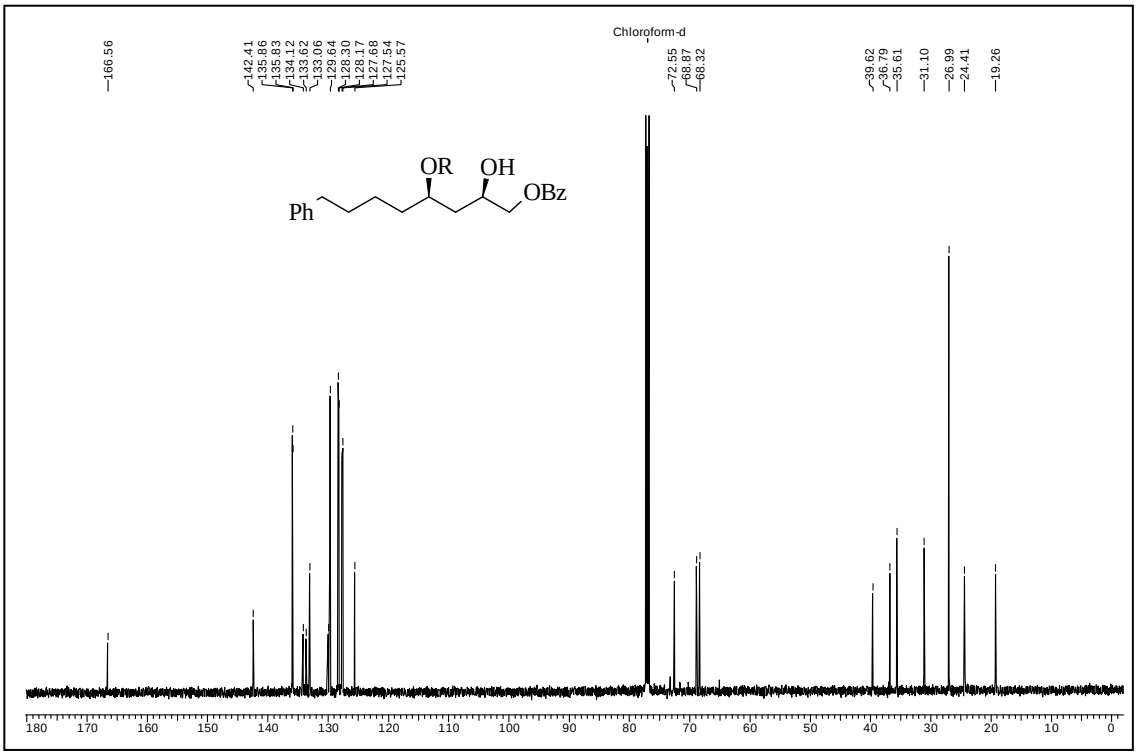
^{1}H NMR Spectrum of 264 in $CDCl_3$ (R = TBDPS)



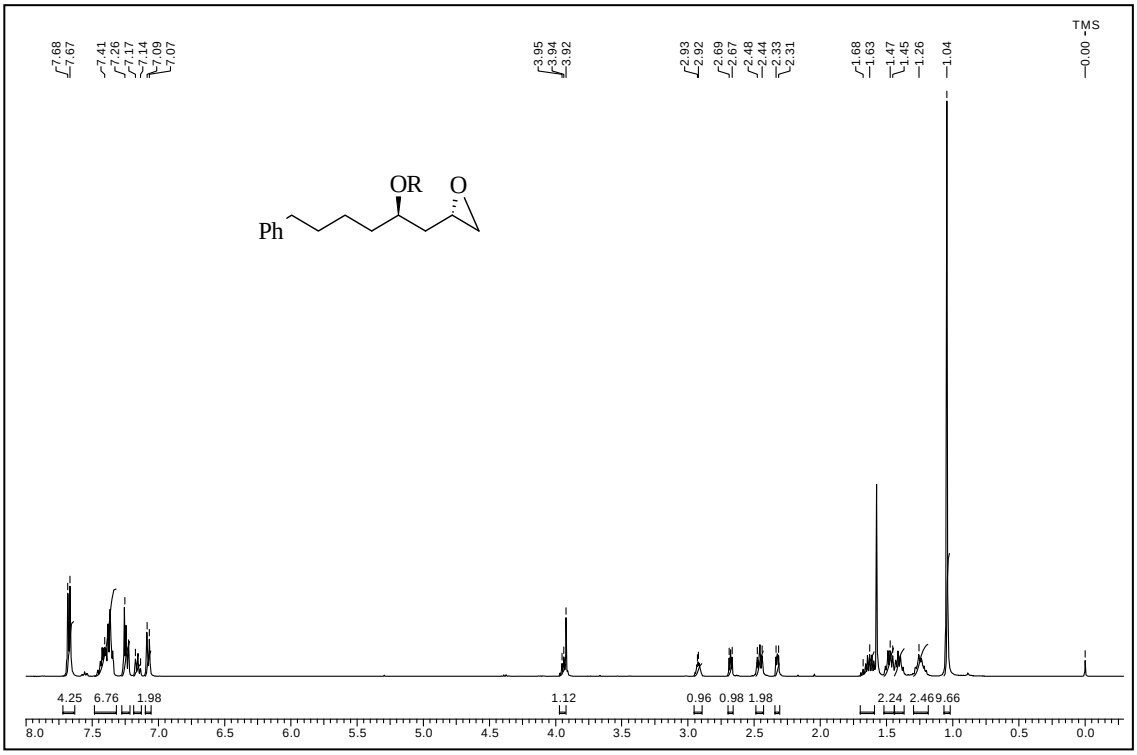
^{13}C NMR Spectrum of 264 in $CDCl_3$ (R = TBDPS)



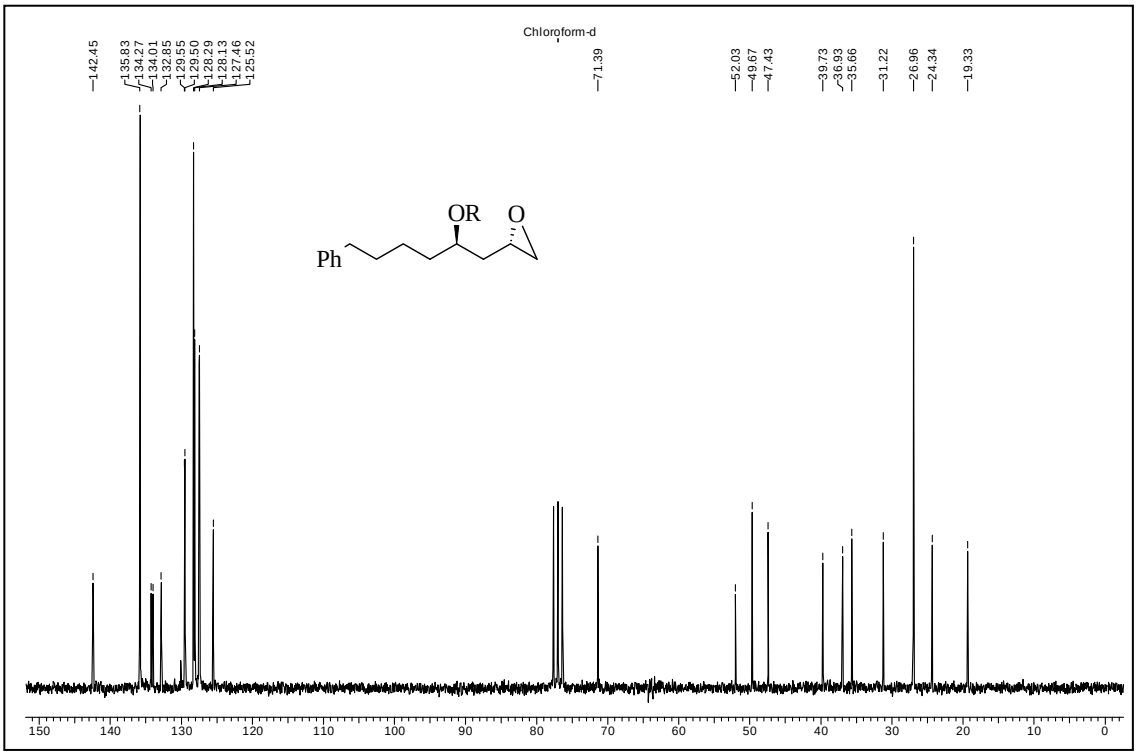
^{1}H NMR Spectrum of 265 in $CDCl_3$ (R = TBDPS)



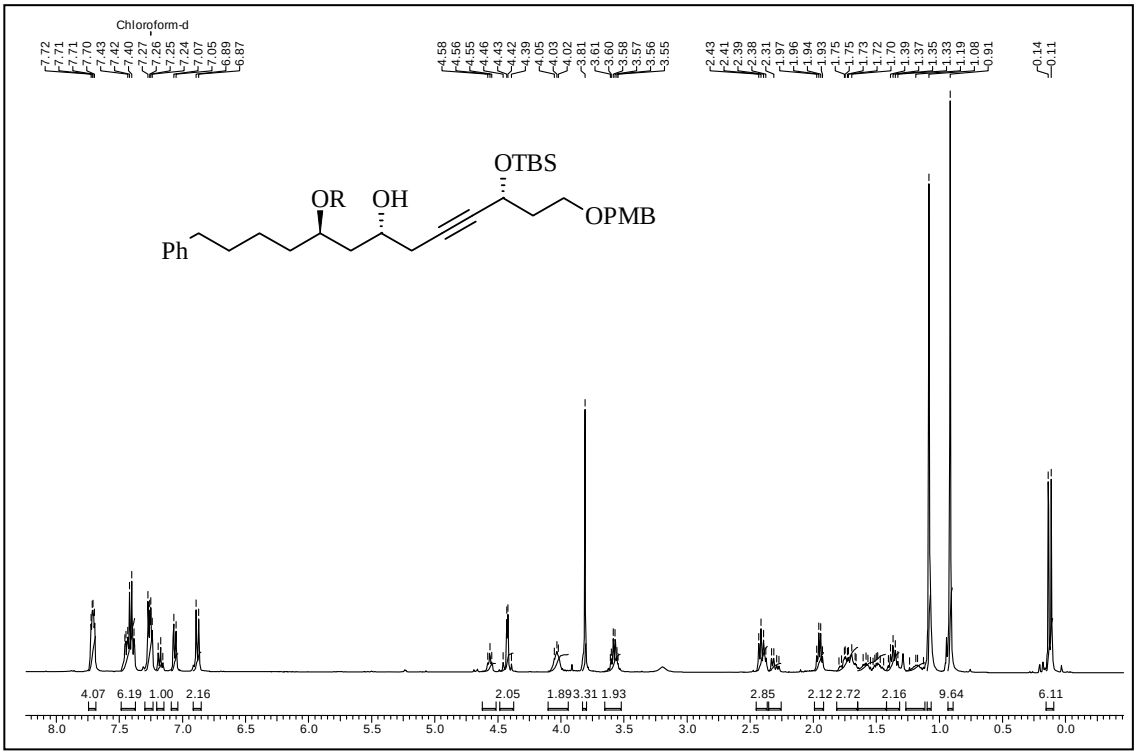
^{13}C NMR Spectrum of 265 in $CDCl_3$ (R = TBDPS)



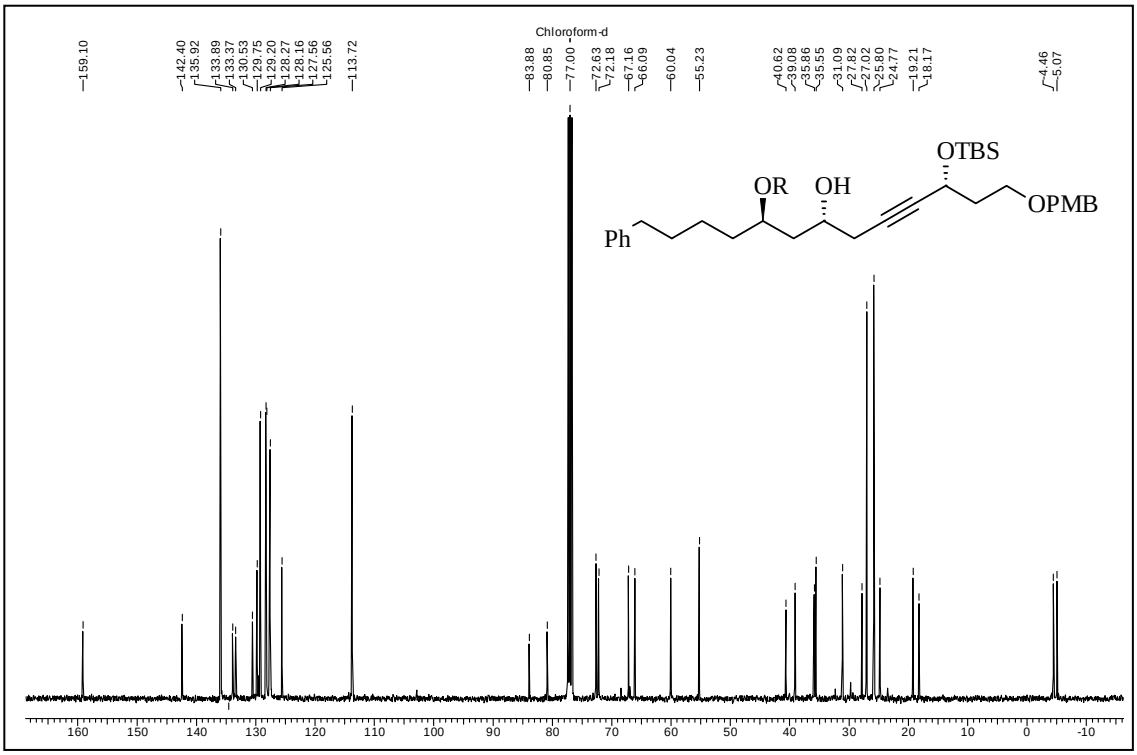
^{1}H NMR Spectrum of 267 in $CDCl_3$ (R = TBDPS)



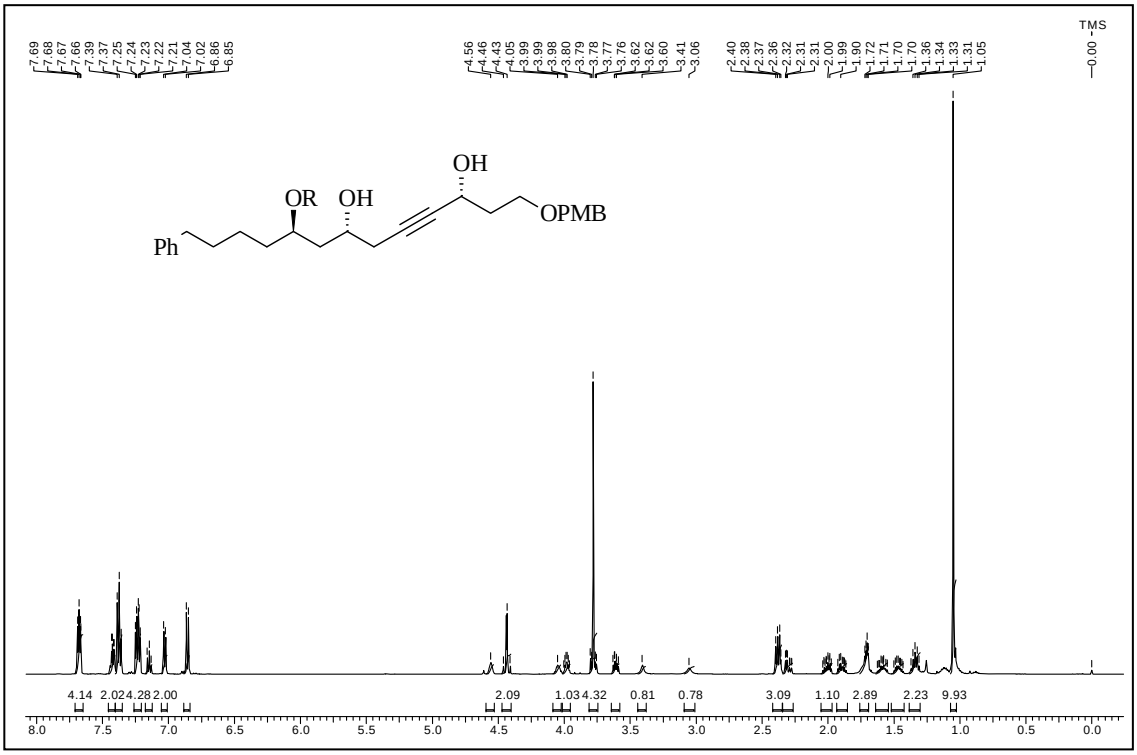
^{13}C NMR Spectrum of 267 in $CDCl_3$ (R = TBDPS)



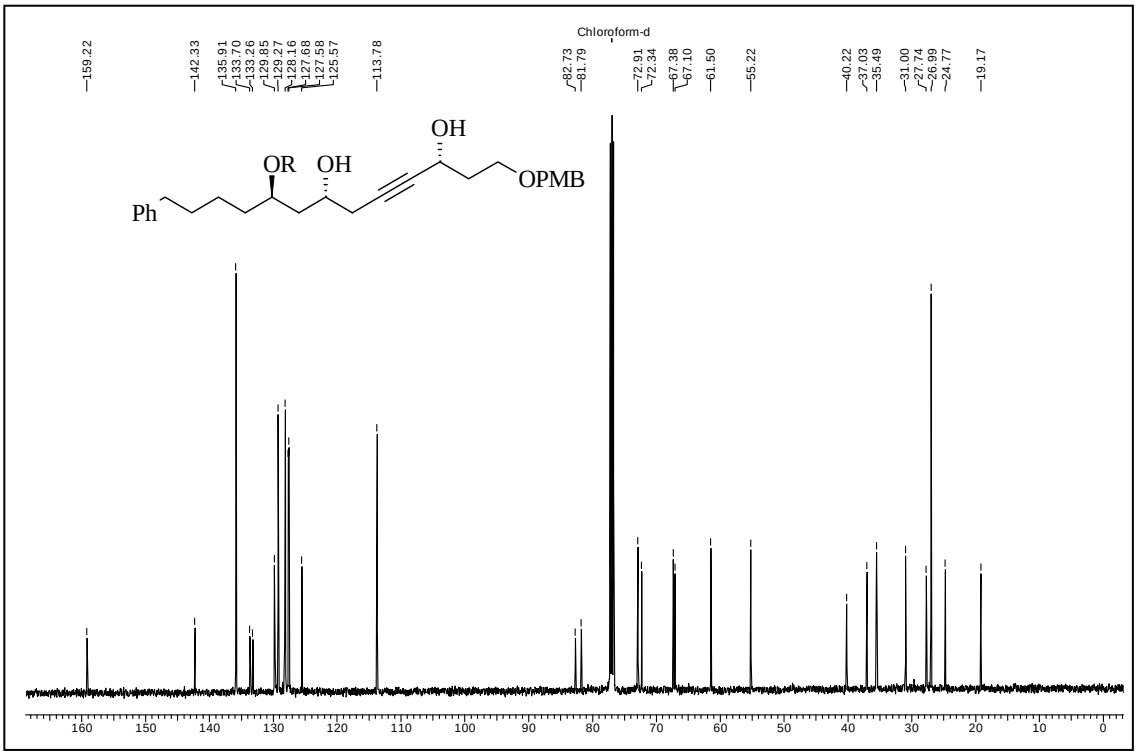
^{1}H NMR Spectrum of 268 in $CDCl_3$ (R = TBDPS)



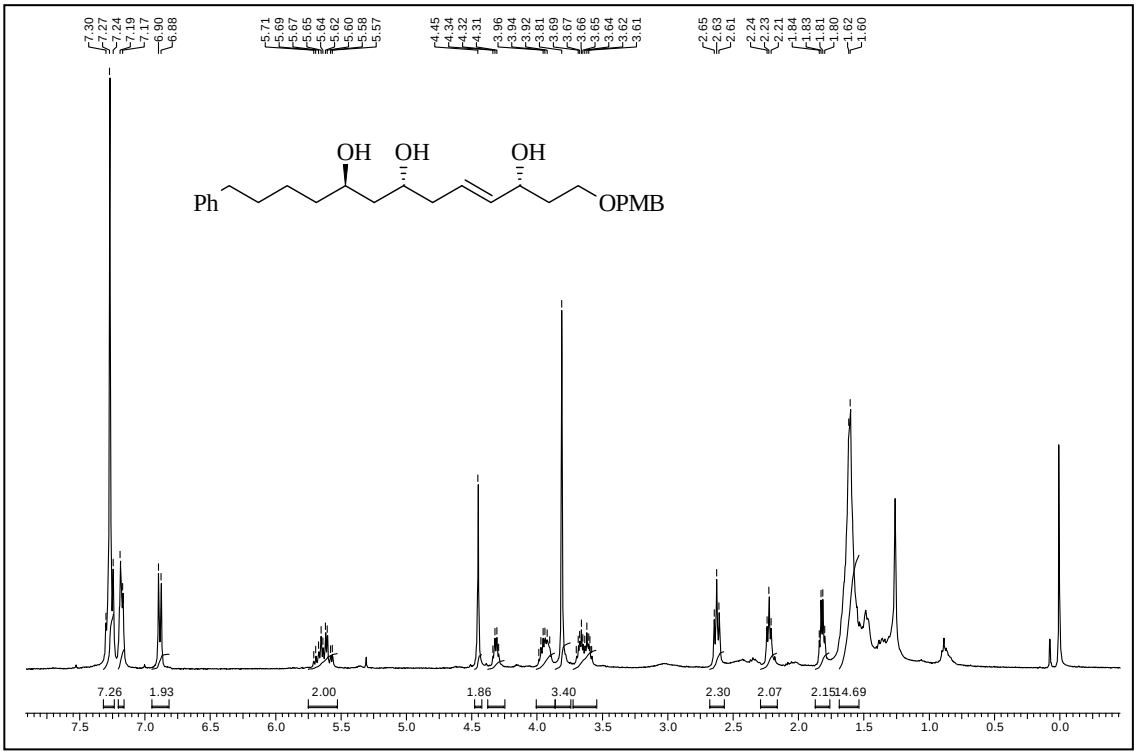
^{13}C NMR Spectrum of 268 in $CDCl_3$ (R = TBDPS)



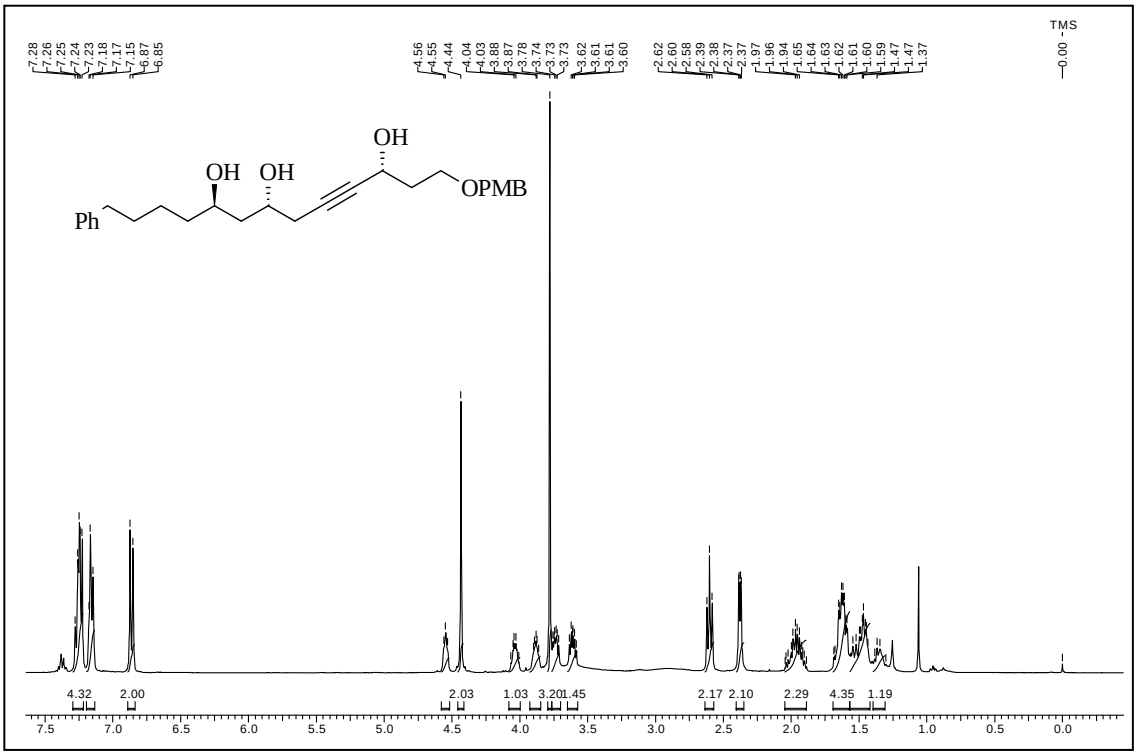
^{1}H NMR Spectrum of 269 in $CDCl_3$ (R = TBDPS)



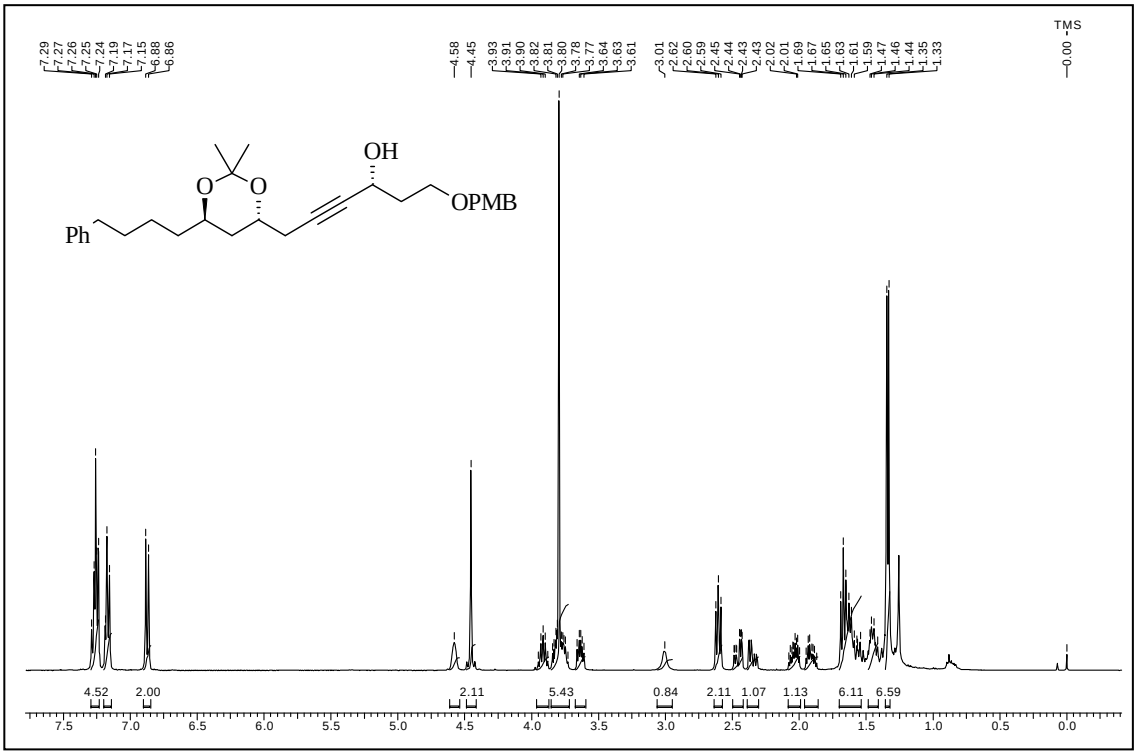
^{13}C NMR Spectrum of 269 in $CDCl_3$ (R = TBDPS)



^{1}H NMR Spectrum of 270 in $CDCl_3$



^{1}H NMR Spectrum of 255 in $CDCl_3$



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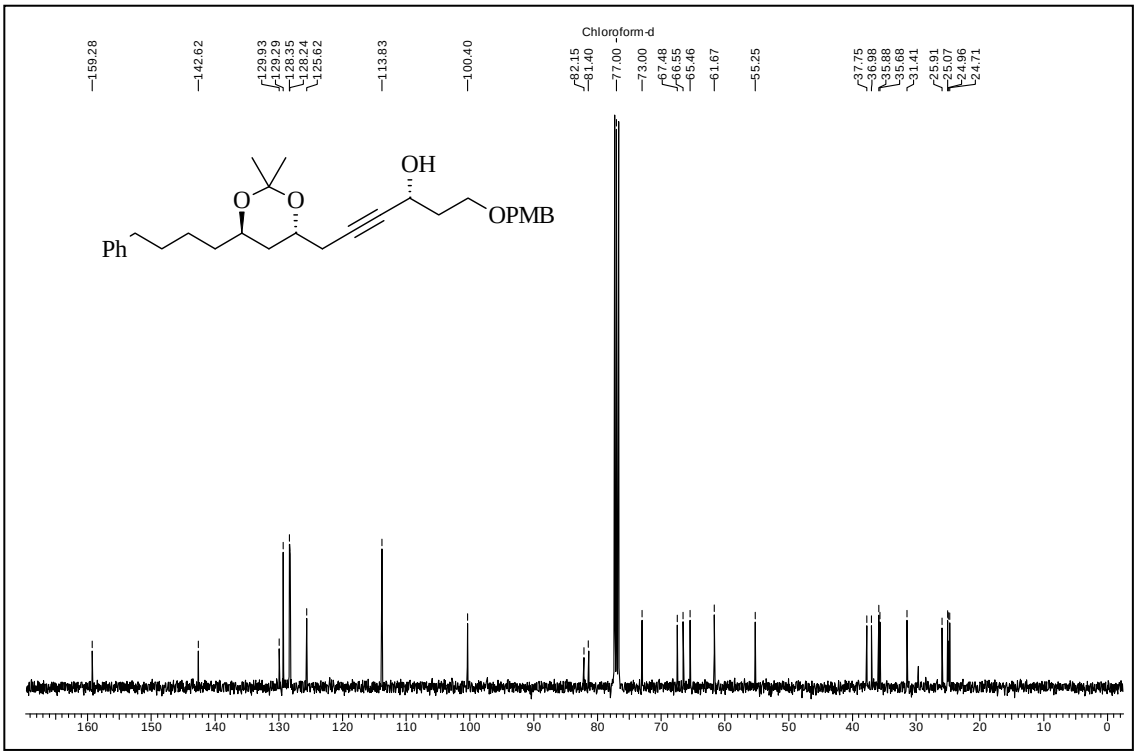

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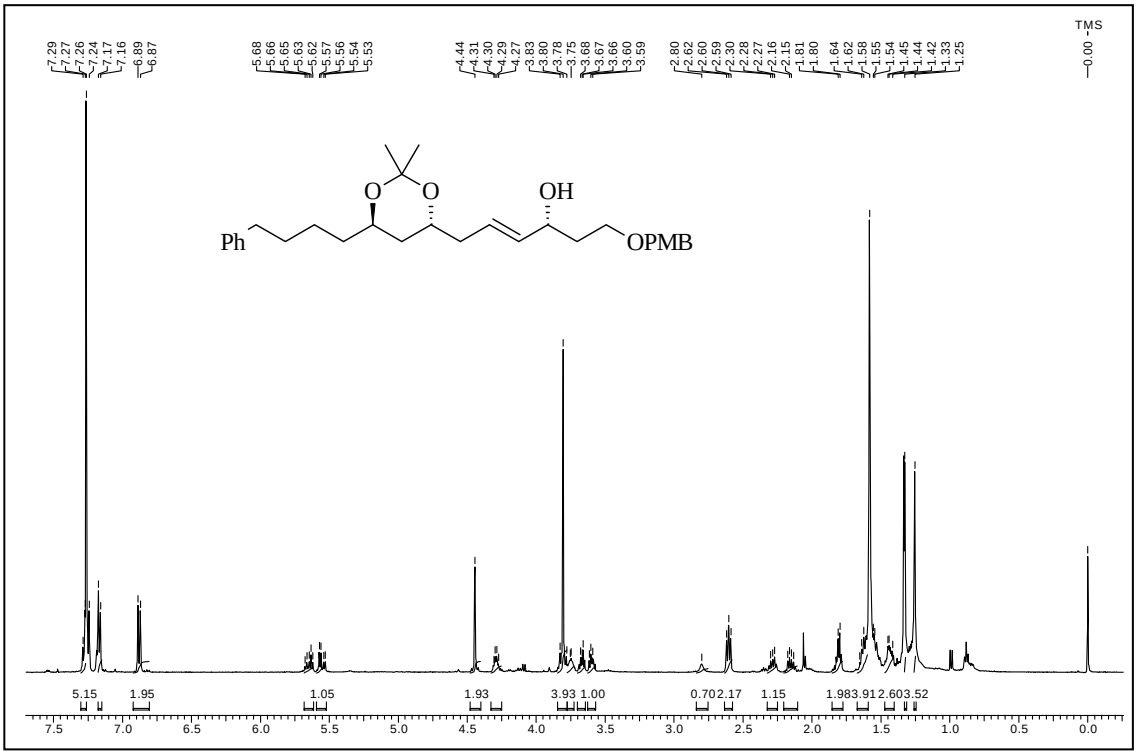

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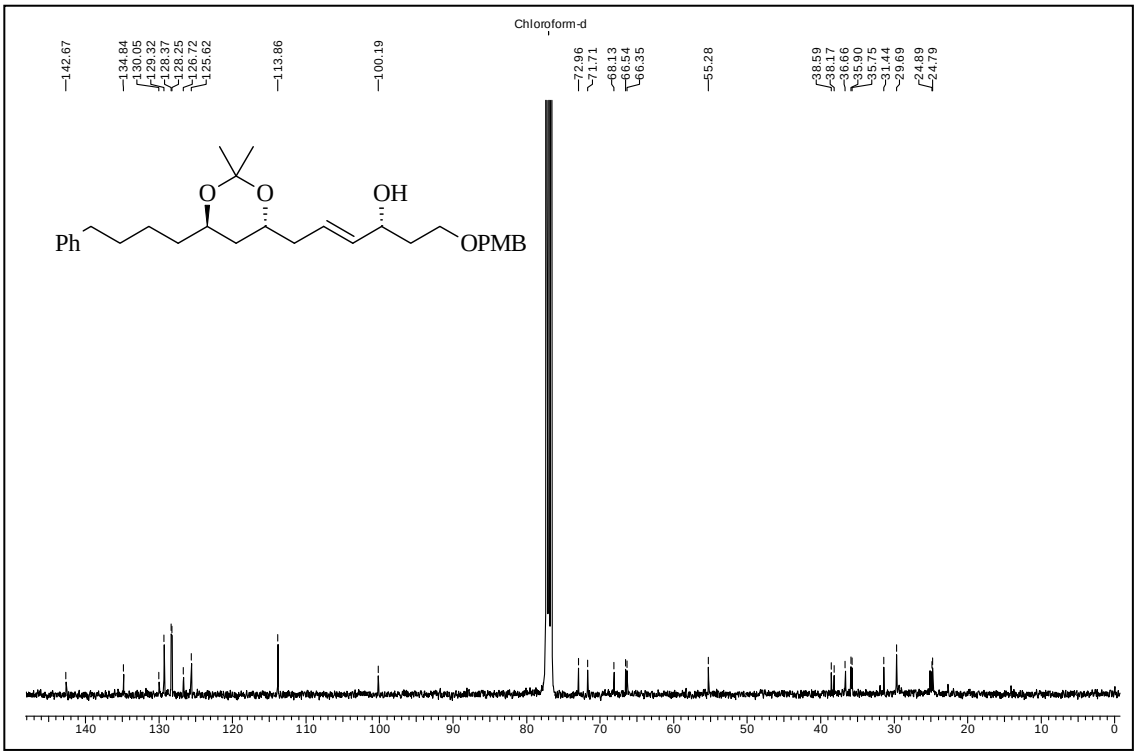

^{13}C NMR Spectrum of 272 in $CDCl_3$

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REFERENCES

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CHAPTER-III

Section A: Synthetic Studies toward the key polyol unit of marinomycin A

INTRODUCTION

INTRODUCTION

Natural products are both a fundamental source of new chemical diversity and integral component of today's pharmaceutical compendium. Among the potential sources of natural products, bacteria have proven to be a particularly prolific resource with a surprisingly small group of taxa accounting for the vast majority of compounds discovered. For example, of the 53 known bacterial phyla, only five are reported to produce anti-infective agents. And among these five, the Class Actinobacteria, and more specifically, bacteria belonging to the Order Actinomycetales (commonly called actinomycetes) account for approximately 7000 of the compounds reported in the Dictionary of Natural Products.[1] Looking individually at the more than 140 currently described actinomycete genera, it becomes clear that even within this Order it is a few well-known soil genera that account for the vast majority of microbial natural products discovered. In fact, the genus *Streptomyces* alone accounts for a remarkable 80% of the actinomycete natural products reported to date, a biosynthetic capacity that remains without rival in the microbial world. Yet interest in natural product drug discovery has waned, in part owing to diminishing returns from traditional resources such as soil bacteria. This inturn is a response to the realization that bacterial diversity has not been efficiently explored and, perhaps major environmental habitats have yet to be sampled with natural-product discovery in mind.[2]

Given the vast area of the world's oceans which cover 70% of the Earth's surface and harbor most of the planet's biodiversity, it is at first though surprising that the extensive drug discovery efforts involving soil bacteria have not been extended to this ecosystems resulting in a disregard for the drug discovery from microorganisms inhabiting the world's oceans. However the recent discovery of novel secondary metabolites from taxonomically unique populations of marine actinomycetes[3] suggests that these bacteria add an important new dimension to microbial natural product research. For example, the members of the genus *Salinispora* have proven to be a particularly rich source of new chemical structures, including the potent proteasome inhibitor salinosporamide A,[4] and other distinct groups such as

Marinispora (tentatively called MAR2), *Streptomyces* (MAR4) are yielding new classes of terpenoids, amino acid–derived metabolites and polyene macrolides.

The MAR2 or "*Marinispora*" clade has considerable phylogenetic diversity, which suggests that it is comprised of multiple new species. Interestingly, chemical studies of MAR2 strains consistently yield new polyketide-derived polyenes. The first example was the isolation of the Marinomycins A–C (**273**–**275**), exemplified by Marinomycin A (**273**, Figure 1).[5] Other members of the *Marinispora* group produce related polyketide-derived macrolides.[2b] Marinisporolide A (**276**) and Marinisporolide B (**277**) are polyene-polyols related to the roflamycoin (flavomycoin) class.[6]

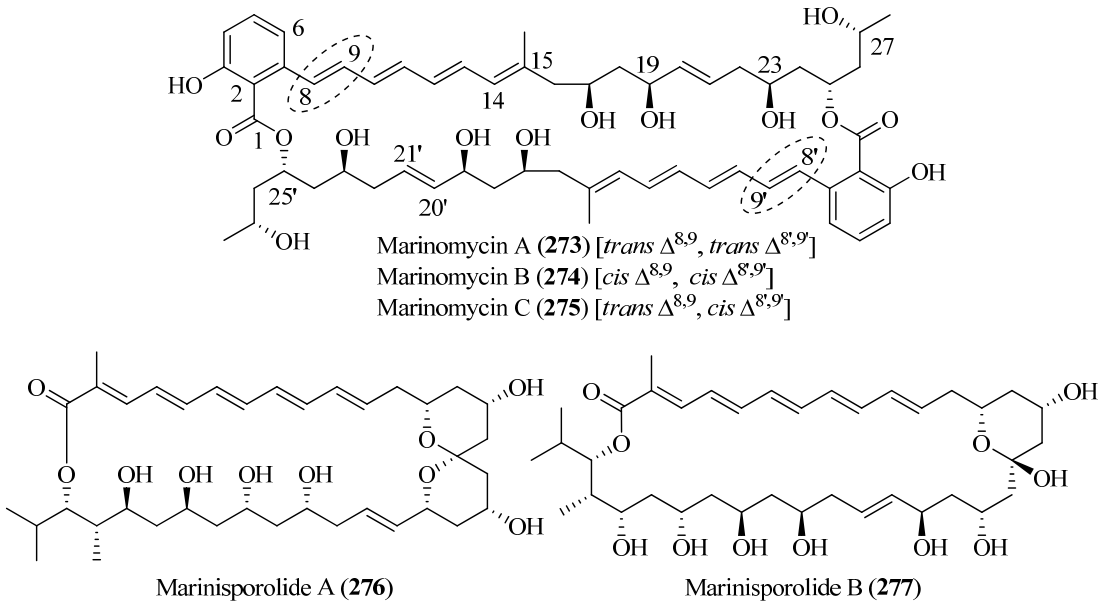


Figure 1. Some representative natural products isolated from *Marinispora*

Polyene macrolides from terrestrial actinomycetes are an important class of antifungal agents that include amphotericin B and nystatin. These compounds interact with cell membrane sterols (egosterol in fungi) to form permeable membrane channels that result in cell death. Though the polyene-polyols from the *Marinispora* group are structurally related to these polyenes, they rarely show antifungal activities. Marinomycin A (**273**), for example, shows an MIC_{90} of 7.8 μM against amphotericin-resistant *Candida albicans*, a value beyond consideration for clinical development. The Marinomycins are potent antitumor antibiotics with substantial activities against selected human tumors and drug-resistant bacterial pathogens. Testing performed at

the US National Cancer Institute has shown that marinomycin A has highly enhanced *in vitro* activity against six of eight melanoma cell lines, with SK-MEL-5 showing the highest sensitivity (concentration lethal to 50% of animals tested (LC_{50}) = 5.0 nM). Marinomycin A also inhibits the growth of human pathogenic bacteria with a minimum inhibitory concentration (MIC) value of 0.1 μM against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faceium* (VREF).[5]

Given the urgent need for new antibiotics to stem the tide of drug-resistant pathogens, this new source of chemical diversity could not have come at a better time. Continued efforts to characterize marine actinomycete diversity and how adaptations to the marine environment affect secondary metabolite production will create a better understanding of the potential utility of these bacteria as a source of useful products for biotechnology.

Recently many groups have shifted their efforts from terrestrial actinomycetes toward those of the ocean, which have, until now, been largely overlooked.[3] The Fenical group particularly has been successful in cultivating new colonies of actinomycetes from marine deep sea sediment samples, efforts that resulted in the isolation of several biologically active natural products[7] including marinomycins A-C (**273**–**275**, Figure 1) from a novel marine actinomycete, *Marinispora* strain CNQ-140, collected offshore of La Jolla, California.[5]

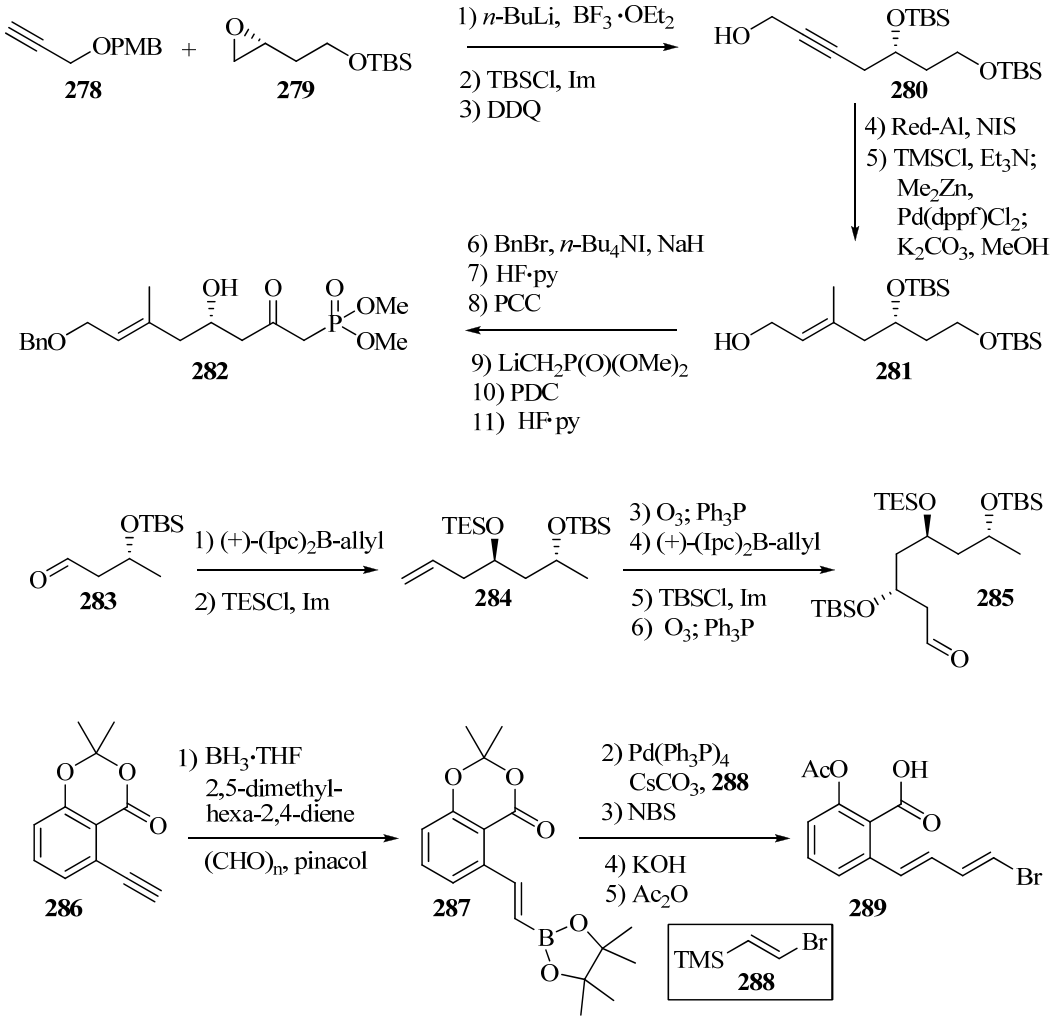
The extensive NMR studies and the supportive information collected from all other physical and analytical data revealed that marinomycin A (**273**) is a 44-membered *C*2-symmetrical dimeric macrodiolide constituted by a tetraene moiety conjugated with an aromatic unit derived from 2-hydroxybenzoic acid and connected to a pentahydroxylated polyketide chain.

The relative stereochemistry of marinomycin A (**273**) was assigned based on the spectral analysis and chemical modification by applying Kishi's universal NMR database[8] and Rychnovsky's ^{13}C NMR analogy[9] while the absolute stereochemistry was determined by application of the modified Mosher ester NMR method. These results supported the assignment of the absolute stereochemistry at C-17, C-17', C-19, C-19', C-23, C-23', C-25, and C-25' as *S*, while C-27 and C-27' were assigned as *R*.

Among all, only marinomycin A (**273**) is presumed to be the true natural product as it undergoes photoisomerization to its geometrical isomers marinomycins B (**274**) and C (**275**) upon exposure to light.[5] Keeping this fact in view Nicolaou et al.

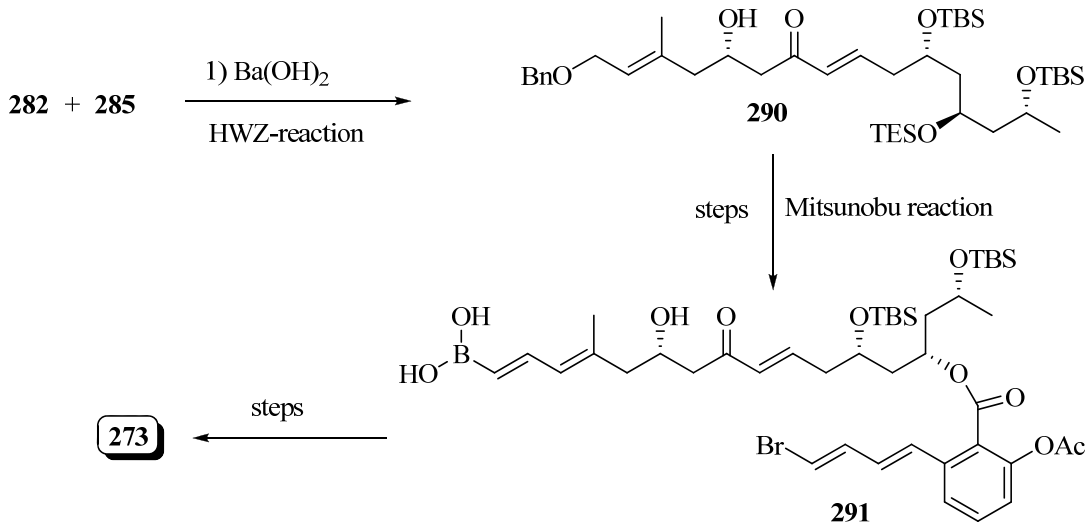
attempted the total synthesis of marinomycin A which apparently constituted the total synthesis of the others.

First total synthesis by K. C. Nicolaou et al.[10]



Scheme 1.

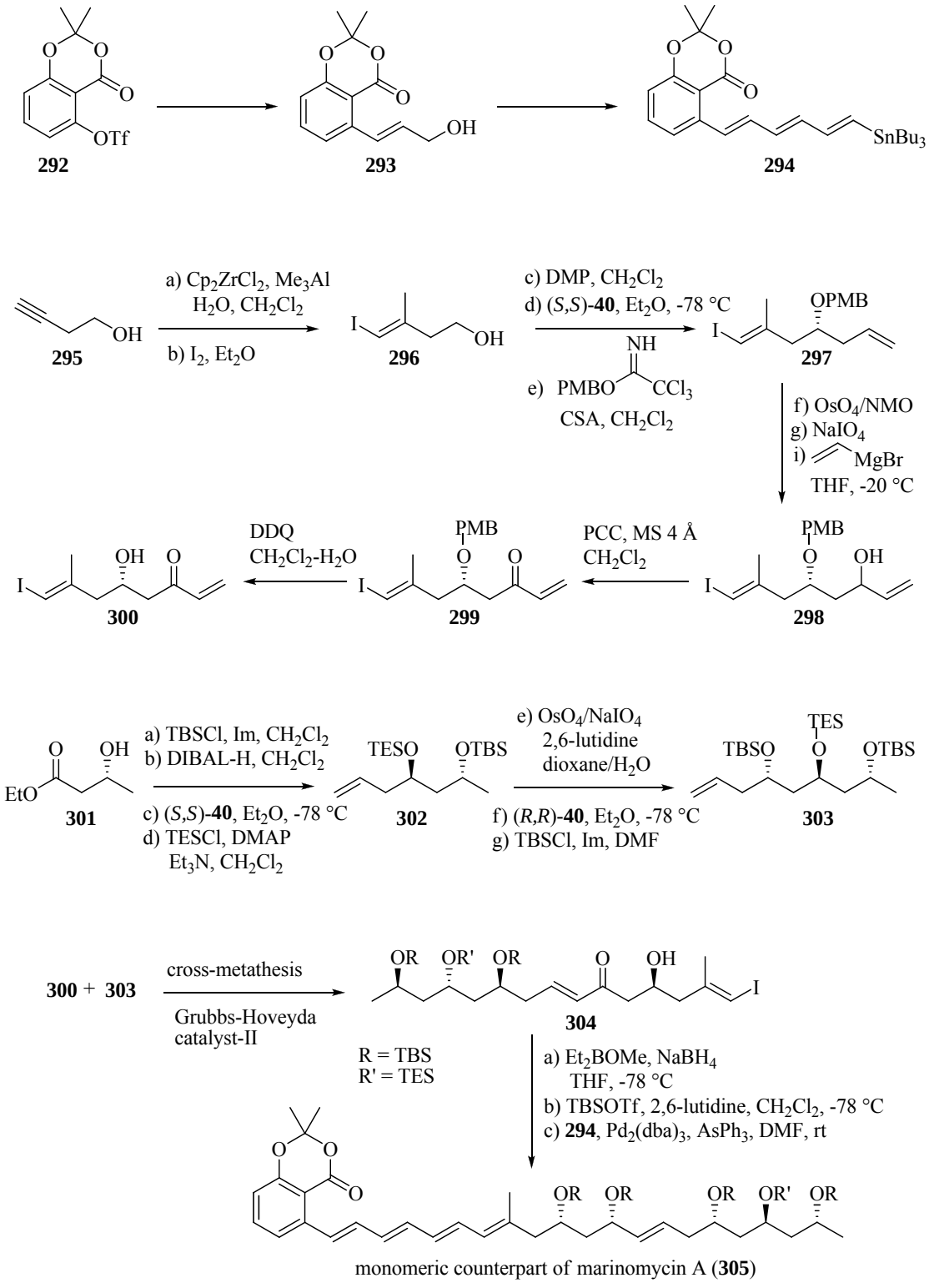
This strategy emphasized the Suzuki dimerization of boronic acid vinyl bromide **291** at the final stages of synthesis (Scheme 2). Assuming **291** to be the precursor monomeric unit, an intermediate whose origin was envisioned by assembling the building blocks ketophosphonate **282**, aldehyde **285**, and carboxylic acid **289** through the Horner-Wadsworth-Emmons (HWE) and Mitsunobu reactions. The required enantiomerically pure building blocks **282**, **285** and **289** were synthesized as summarized in Scheme 1.



Scheme 2.

Janine Cossy et al.[11]

The monomeric counterpart of marinomycin A, was synthesized efficiently in a highly convergent manner. The strategy was highlighted by a crucial regio- and stereoselective cross-metathesis between the olefins **300** and **303** to form the C20-C21 double bond, enantioselective allyltitanations to control the configuration of the C17, C23, and C25 stereogenic centers, and a stereocontrolled construction of the tetraene moiety based on an original Horner-Wadsworth-Emmons olefination followed by a Pd-catalyzed cross-coupling to complete the synthesis of **305**. The complete synthetic approach is presented in Scheme 3.


292
293
294
295
a) Cp_2ZrCl_2, Me_3Al
H_2O, CH_2Cl_2
b) I_2, Et_2O
296
c) DMP, CH_2Cl_2
d) (S,S)-40, Et_2O, -78 °C
e) PMBO CCl_3
CSA, CH_2Cl_2
297
f) OsO_4/NMO
g) $NaIO_4$
i) MgBr
THF, -20 °C
298
PCC, MS 4 Å
CH_2Cl_2
299
DDQ
CH_2Cl_2-H_2O
300
a) TBSCl, Im, CH_2Cl_2
b) DIBAL-H, CH_2Cl_2
301
c) (S,S)-40, Et_2O, -78 °C
d) TESCl, DMAP
Et_3N, CH_2Cl_2
302
e) OsO_4/$NaIO_4$
2,6-lutidine
dioxane/H_2O
f) (R,R)-40, Et_2O, -78 °C
g) TBSCl, Im, DMF
303
300 + 303
cross-metathesis
Grubbs-Hoveyda
catalyst-II
304
R = TBS
R' = TES
a) Et_2BOMe, $NaBH_4$
THF, -78 °C
b) TBSOTf, 2,6-lutidine, CH_2Cl_2, -78 °C
c) 294, $Pd_2(dba)_3$, $AsPh_3$, DMF, rt
monomeric counterpart of marinomycin A (305)

Scheme 3.

PRESENT WORK

Marinomycin A (**273**) is a polyene macrodiolide which has been recently isolated by Fenical et al. from the saline culture of a new group of marine actinomycetes, named *Marinispora* strain CNQ-140, cultured from a sediment collected from the bottom of the ocean offshore of La Jolla, California (USA). Marinomycin A (**273**) is a 44-membered *C*2-symmetrical dimeric macrodiolide constituted by a tetraene moiety conjugated with an aromatic unit derived from 2-hydroxybenzoic acid and connected to a pentahydroxylated polyketide chain (Figure 2).[3,5]

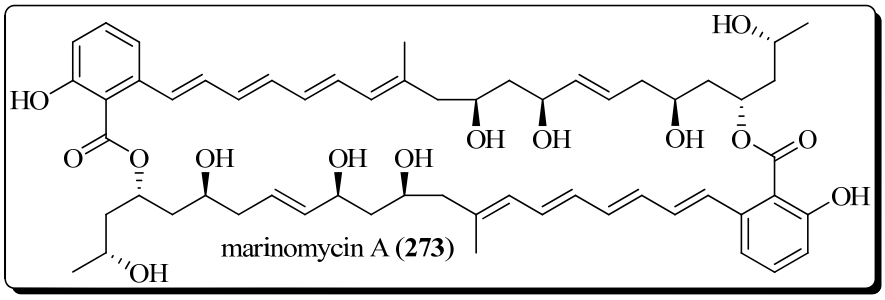


Figure 2.

This novel macrodiolide exhibits significant antibiotic activity against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*. Along with these unusual biological properties, it also demonstrated impressive and selective cancer cell cytotoxicities against 6 of the 8 melanoma cell lines of the National Cancer Institutes's 60 cancer cell line panel.[5]

The total synthesis of marinomycin A (**273**) has been reported recently by Nicolaou et al.[10] followed by a synthesis of monomeric counter part (**305**) of marinomycin A by Cossy et al.[11] The challenging molecular architecture and impressive biological properties of this marine natural product coupled with our longstanding interest in synthesis of polyketide natural products[12,15] impelled us to take on the synthesis of marinomycin A.

Retrosynthetic Analysis

The retrosynthetic analysis of marinomycin A (**273**) is depicted in Figure 3 and 4. It relied on the synthesis of polyol unit of marinomycin A, which led us to disconnect the molecule at the macrolactone linkage considering the Mitsunobu lactonization to visualize the monomeric counter part **306**. The construction of monomeric counter part was envisaged from Horner-Wadsworth-Emmons olefination on the trienic phosponate **308** which resulted in the identification of its counter part as the intriguing polyol unit **307**.

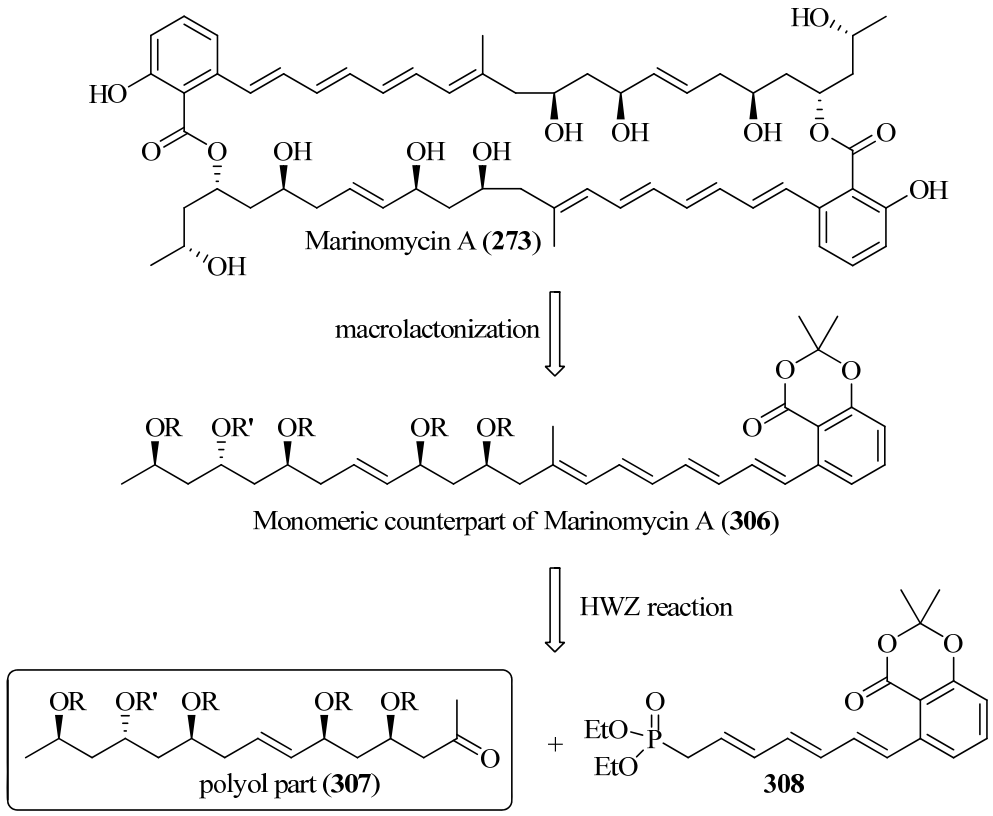


Figure 3.

Retrosynthetically the polyol **307** was traced back to **309** and the terminal olefin in **309** was to act as the surrogate to the ketone in **307** by means of the selective Wacker oxidation transform. The olefinic part could be obtained by performing a diastereoselective allylation on the advanced intermediates **320**, **328** and **329**. Considering the multiple options for the access to the target polyol, and to allow the modifications whenever required in an event of problems created by the protecting

groups in the synthetic sequences, the Yamaguchi protocol for the opening of epoxide **313** was planned with suitably protected alkynes **314**, **318**, and **319**. The requisite epoxide fragment **313** could be easily prepared by employing a multicomponent linchpin protocol of dithiane **310** with the commercially available epoxides **311** and **312**. The alkyne **314** would be accessed from D-glucose whereas alkynes **318** and **319** inturn could be synthesized from propane diol (discussed in Chapter 2).

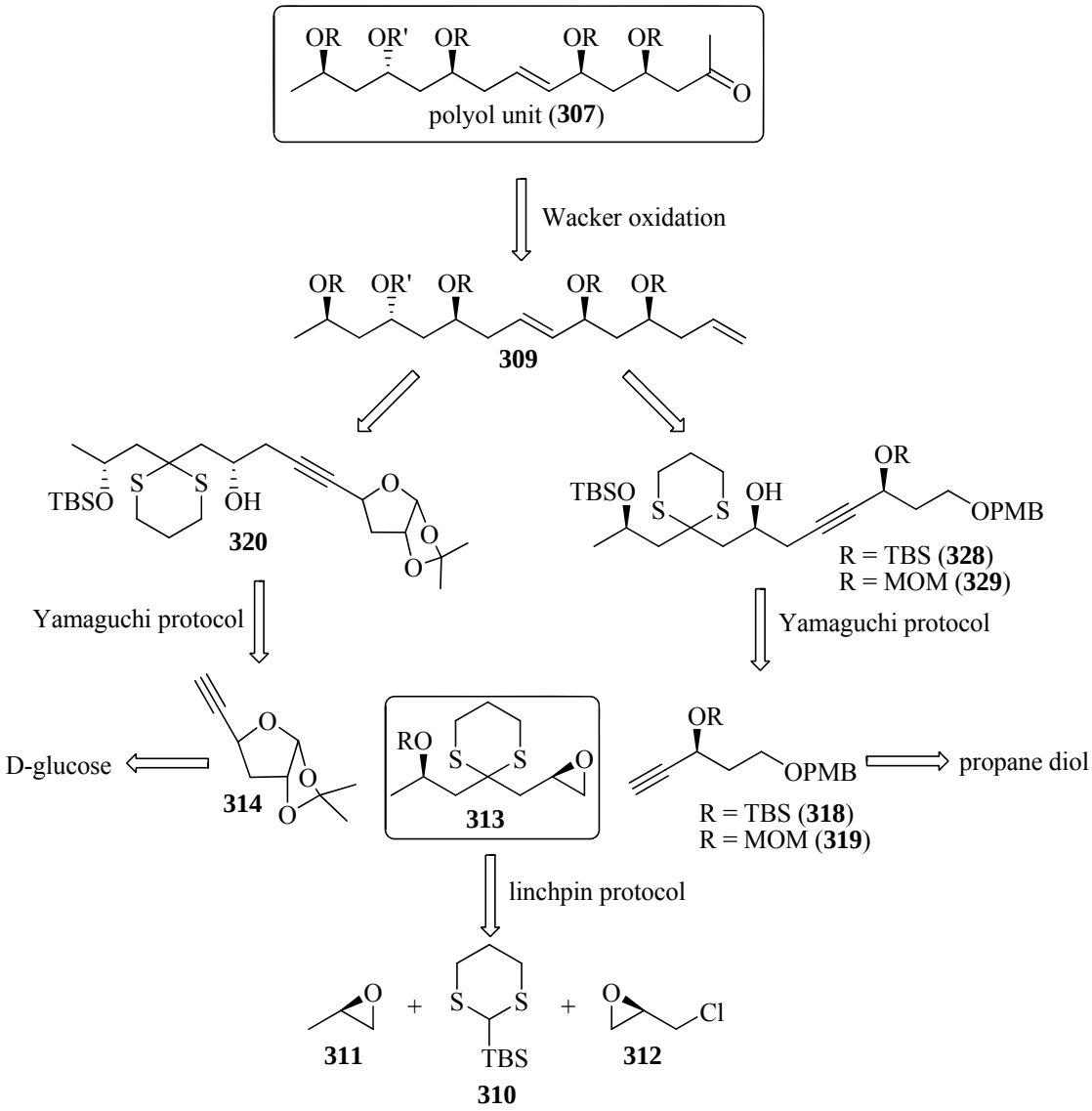
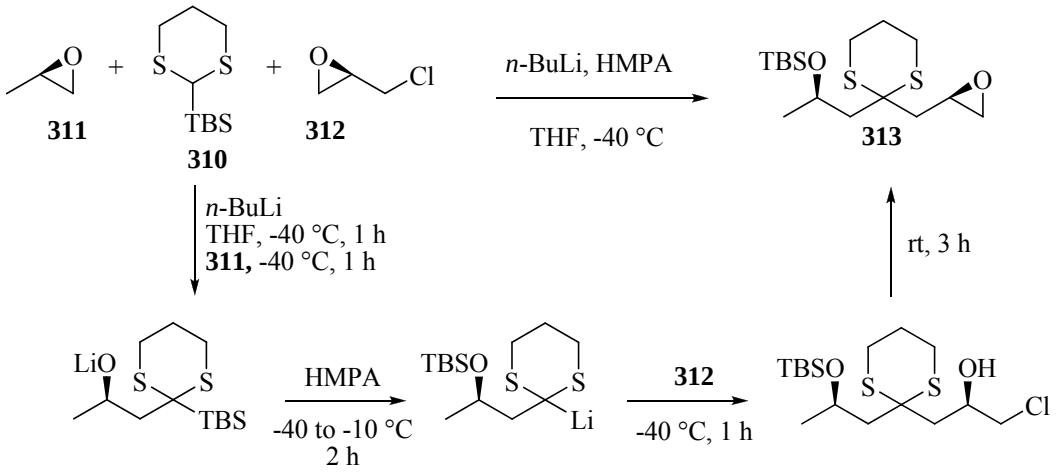


Figure 4.

Synthesis of epoxide 313

The synthetic studies toward marinomycin A (**273**) were instigated by the preparation of epoxide **313**. In this regard the projected linchpin bisalkylation[13] was

conducted with lithiated TBS-dithiane **310** using (*R*)-propyleneoxide (**311**) as first alkylating agent, HMPA for triggering the Brook rearrangement and (*R*)-epichlorohydrine (**312**) as the second alkylating agent. The tactic produced the required epoxide fragment **313** with the desired stereogenic centers (Scheme 4).

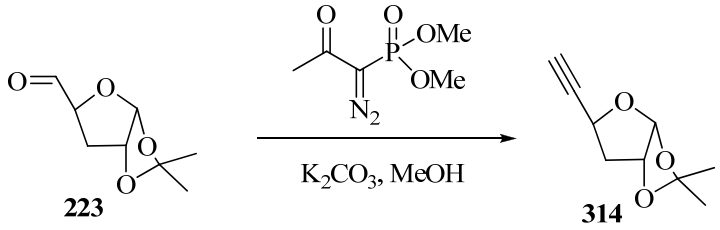


Scheme 4.

The ^{1}H and ^{13}C NMR spectra of **313** revealed the presence of all constituents of the three counterparts that were used for the linchpin reaction. For example signals corresponding to the TBS group appeared in the expected region in ^{1}H and ^{13}C NMR spectra. A doublet at δ 1.23 ppm with a coupling constant 6.1 Hz in the ^{1}H NMR spectrum integrating for three protons indicated the presence of a methyl group attached to a methine group and this was further substantiated by the appearance of a peak at 25.9 ppm (quartet) in the ^{13}C NMR spectrum. A peak at δ 51.3 ppm for a quarternary carbon in ^{13}C NMR spectrum further confirmed the presence of a dithioketal group. Three signals at δ 3.23–3.15 (m, 1H), 2.73–2.72 (m, 1H) and 2.50 (dd, J = 2.6, 5.0 Hz, 1H) in the ^{1}H NMR spectrum were attributed to the terminal epoxide which was further ascertained by the appearance of corresponding signals at δ 46.5 (triplet), and δ 48.9 (doublet) in the ^{13}C NMR spectrum. Results from mass spectrometry, IR, and elemental analysis were in good agreement with the assigned structure for **313**.

Synthesis of alkyne 314

Treatment of aldehyde **223**[15] with Ohira-Bestmann reagent in the presence of K_2CO_3 in methanol furnished furano alkyne **314** (Scheme 5).[14]

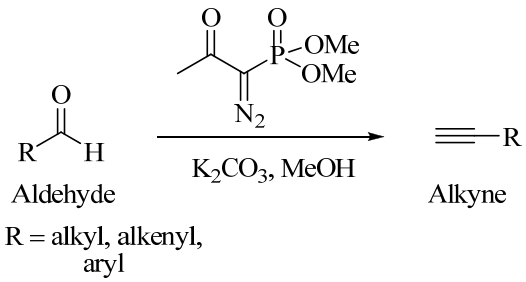


223 **314**

Scheme 5.

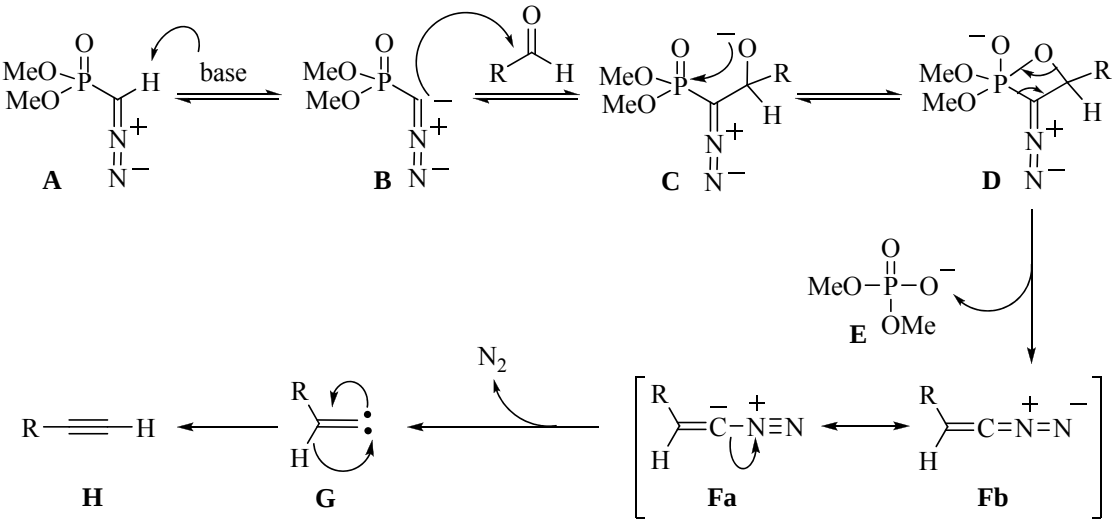
The ^{1}H and ^{13}C NMR spectra revealed the presence of the peaks for proposed structure **314**. The anomeric proton resonated at δ 5.85 as a doublet with J = 3.7 Hz in the ^{1}H NMR spectrum whereas the C-1 resonated at δ 105.1 as doublet in the ^{13}C NMR spectrum. Two singlets at δ 1.48 and 1.29 in the ^{1}H NMR spectrum integrating for three protons each were assigned to methyl groups of 1,2-isopropylidene protection, which was further supported by presence of a peak for quarternary carbon at 111.2 ppm in the ^{13}C NMR spectrum. The presence of terminal alkyne group was ascertained by appearance of a doublet with J = 2.1 Hz integrating for one proton in ^{1}H NMR spectrum which was further substantiated by the appearance of a doublet at δ 66.5 and a singlet at 80.6 ppm in ^{13}C NMR spectrum. Results from mass spectrum (*m/z* 271.1 $[M+Na]^+$), IR, elemental analysis were in accordance with the structure **314**.

Ohira-Bestmann homologation of aldehydes



Scheme 6.

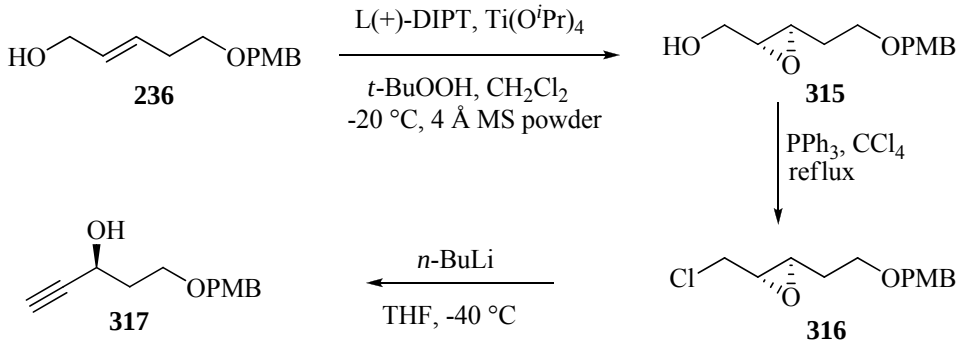
*An extremely mild and efficient method, utilizing dimethyldiazomethylphosphonate as a reagent for the homologation of aldehydes into alkynes. This is a widely used alternative to the longer known Corey-Fuchs method. The phosphonate is some times referred to as the Seyferth-Gilbert reagent though the corresponding diethyl ester was first synthesized by Regitz et al. and the reagent was first used for the synthesis of alkynes by Colvin et al. The modified Bestmann reagent, dimethyl-1-diazo-2-oxopropylphosphonate makes the method more convenient for the synthesis of terminal alkynes. The procedure utilizes in situ preparation of dimethyldiazomethylphophonate (Seyferth-Gilbert reagent). The easy one-pot procedure avoids the use of strong bases, low temperatures and inert gas techniques. The use of the milder potassium carbonate makes this procedure much more compatible with a wide variety of functional groups. The proposed mechanism (Scheme 7) of the transformation includes a Horner-Wadsworth-Emmons-type reaction, followed by loss of nitrogen and rearrangement of the resulting alkenylidenecarbene into the alkyne. Deprotonation of the Seyferth-Gilbert reagent **A** gives an anion **B** which reacts with the aldehyde to form the oxaphosphatane **D**. Elimination of dimethylphosphate **E** gives the vinyl diazo-intermediate **Fa** and **Fb**. The generation of nitrogen gas gives a vinyl carbine **G** which via a 1,2-migration forms the desired alkyne **H**.*



Scheme 7. *Mechanism of alkynylation*

Synthesis of alkyne fragments 318, 319[15]

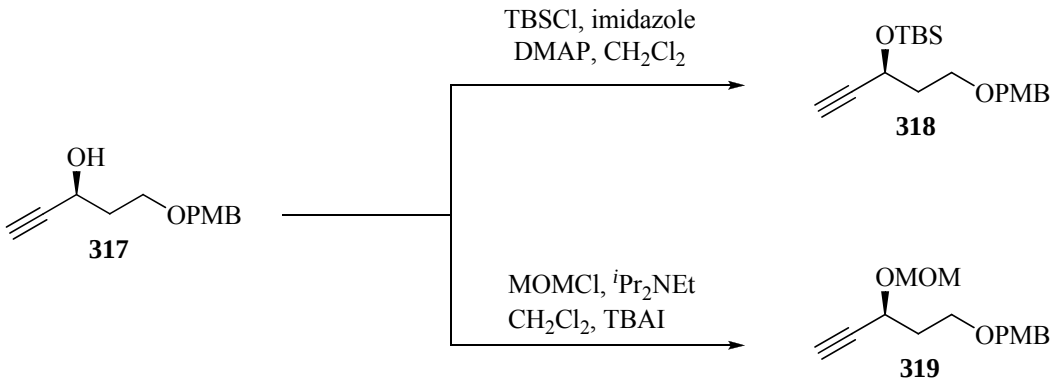
The alkyne fragments **318** and **319** were prepared by conducting a Sharpless asymmetric epoxidation on the known allylic alcohol derived from propane diol and following the same synthetic sequence which was discussed in previous chapter for synthesis of the antipode of current alkyne fragment **318**.



Scheme 8.

Thus the Sharpless asymmetric epoxidation[16] of **236** was carried out using L(+)-diisopropyl tartrate and titanium tetraisopropoxide in the presence of *t*-butylhydroperoxide in dry dichloromethane and the epoxide **315** was obtained in good yield. The specific rotation $\{[\alpha]_D^{25} = -19.6$ (*c* 1.0, $CHCl_3)\}$ confirmed the high enantiomeric excess of compound **315**. The presence of an internal epoxide group was indicated by the ^{1}H-NMR signals at δ 3.09 (ddd, *J* = 2.5 Hz, 1H) and 2.97 (dt, *J* = 2.5 Hz, 1H) and confirmed by resonances at δ 53.6 (d) and 58.4 (d) in the ^{13}C-NMR spectrum (Scheme 14). Chlorination of **315** by refluxing CCl_4 in the presence of triphenyl phosphine gave the chlorooxirane **316** which on treatment with excess *n*-BuLi in THF at –40 °C provided the α-hydroxy alkyne **317** (Scheme 8).

Finally, protection of half the portion of **317** as its TBS-ether using TBS-Cl and imidazole in dichloromethane furnished the desired alkyne fragment **318** (Scheme 15). The other half portion of the hydroxyl alkyne **317** was converted to its MOM ether by treating with MOMCl and Hunig's base in CH_2Cl_2 to produce **319** (Scheme 9).



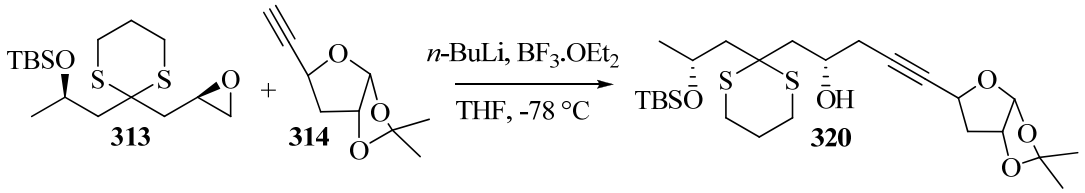
Scheme 9.

^{1}H and ^{13}C NMR and other analytical data were in accordance with the proposed structures of **318** and **319**. For example, in ^{1}H NMR of **318** the characteristic peaks for TBS-group appeared in upfield region [δ 0.11 (s, 3H), 0.14 (s, 3H), and 0.9 (s, 9H)] and for PMB-group in downfield region [δ 7.25 (br dt, J = 2.3, 8.6 Hz, 2H), 6.87 (br dt, J = 2.3, 8.6 Hz, 2H)]. The presence of the terminal alkyne group was confirmed as the ^{1}H NMR showed the peak at δ 2.37 as a doublet with J = 2.3 Hz, and it was further supported by the signals at δ 72.1 (d) and 85.4 (s) in ^{13}C NMR spectrum. Likewise in the ^{1}H NMR spectrum of **319** the peaks corresponding to MOM group resonated at δ 4.57 [m, 2H (OCH_2)] and 3.80 [s, 3H (OCH_3)]. Signals due to PMB-group appeared at the respective region in ^{1}H and ^{13}C NMR spectra. Acetylenic proton was found as a doublet with J = 2.0 Hz in the ^{1}H NMR spectrum. In ^{13}C NMR spectrum the signals at δ 73.6 (d) and 82.2 (s) were attributed to the terminal alkyne group.

Approach with sugar alkyne 314

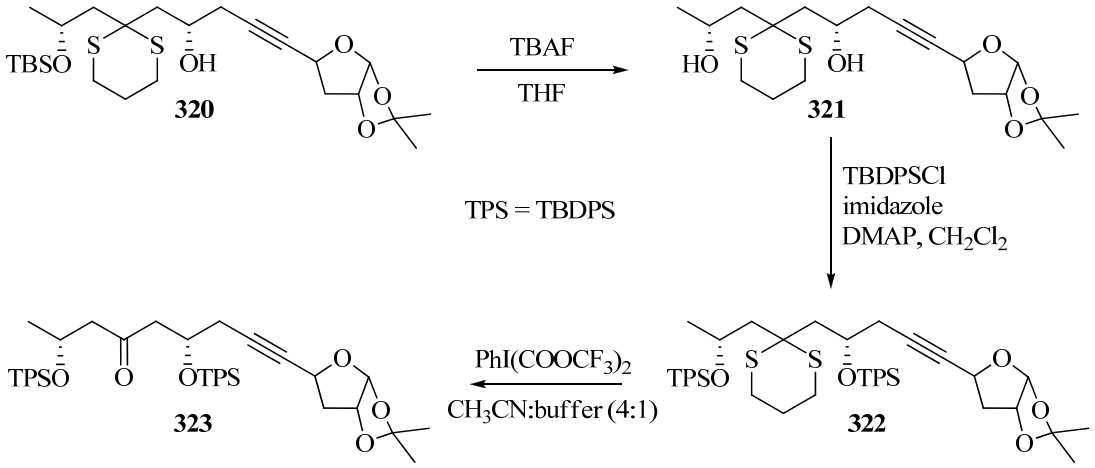
With all the key alkyne fragments and the epoxide in hand, preparations to investigate the Yamaguchi protocol[16] began in earnest. In this direction the regioselective ring opening of enantiomerically pure epoxide **313** with lithium species derived from easily accessed alkyne **314** and *n*-BuLi in the presence of $BF_3{\cdot}OEt_2$ was executed as the first stride of couplings which provided homopropargylic alcohol **320** (Scheme 10). The presence of all the constituents of two coupling partners (TBS, dithiane groups of epoxide and the characteristic sugar moiety of alkyne) were visualized in the ^{1}H and ^{13}C NMR spectra of **320**. In ^{13}C NMR, signals attributed to the resulting internal alkyne group were seen at δ 79.3 and 83.2 as singlets confirming the assigned

structure **320**. Additional data from mass spectrum (*m/z* 539.3 $[M+Na]^+$), IR, elemental analysis were in great support of structure **320**.



Scheme 10.

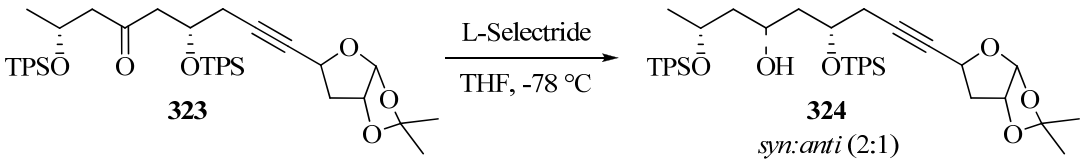
The next target was to functionalize the masked keto group to the corresponding *syn*-alcohol by means of a diastereoselective reduction for which the TBS group was cleaved by treating **320** with TBAF in THF. Considering the highly acidic conditions that would be used further for the cleavage of the isopropylidene group the resulting diol **321** was subsequently converted to the di-TPS ether **322** by reacting with (TBDPSCl/imidazole/DMAP/CH_2Cl_2). Hydrolysis of the dithioketal group was achieved by the action of $PhI(CF_3COO)_2$ in CH_3CN-buffer (pH 7, 4:1) to secure the required ketone **323** (Scheme 11).[17]



Scheme 11.

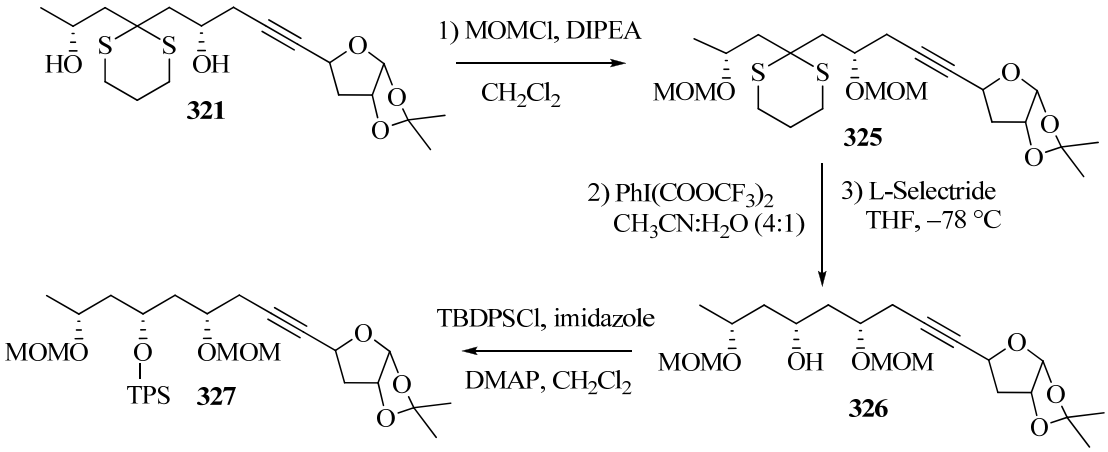
Now the anticipated diastereoselective reduction of the β,β'-disilyloxy ketone **323** was performed successfully using L-Selectride[18] in THF, at –78 °C which resulted in alcohols **324** in good yield (Scheme 12) but to our adversity with a poor

selectivity: *syn: anti* isomers in 2:1 ratio as an inseparable mixture, indicated by NMR analysis.



Scheme 12.

A speculation that the presence of the bulky TBDPS groups may be the reason for the poor stereochemical outcome in the previous reduction led us to consider the MOM group as the other suitable protecting group. To this end the diol **321** was converted to its di-MOM derivative **325** by treating with MOMCl and Hunig's base in CH_2Cl_2. In the ^{1}H NMR spectrum oxymethylene protons of MOM group resonated at δ 4.80-4.69 as multiplet integrating for four protons. A singlet at δ 3.37 ppm integrating for six protons was assigned to methoxy groups of two MOM groups. In ^{13}C NMR spectrum the two oxymethylene carbons appeared as triplets at δ 95.7 and 96.6 ppm. Whilst the signals due to the methoxy groups were found at δ 55.5 (q) and 55.7 (q) confirming the presence of two MOM groups and thus validating the structure **325**. The hydrolysis of the dithioketal with $PhI(CF_3COO)_2$ produced the corresponding ketone which upon the projected reduction with L-Selectride in THF at –78 °C furnished the desired *syn* alcohol **326** exclusively as confirmed by NMR analysis of its TPS derivative **327**. In the ^{1}H NMR spectrum the newly created oxymethine proton resonated at δ 3.90 as a doublet of triplet with J = 6.0, 12.0 Hz whereas the signal due to the corresponding carbon was found at δ 68.2 in ^{13}C NMR spectrum. The highest mass peak *m/z* 663.4 $[M+Na]^+$ and elemental analysis supported the assigned structure **327** (Scheme 13).



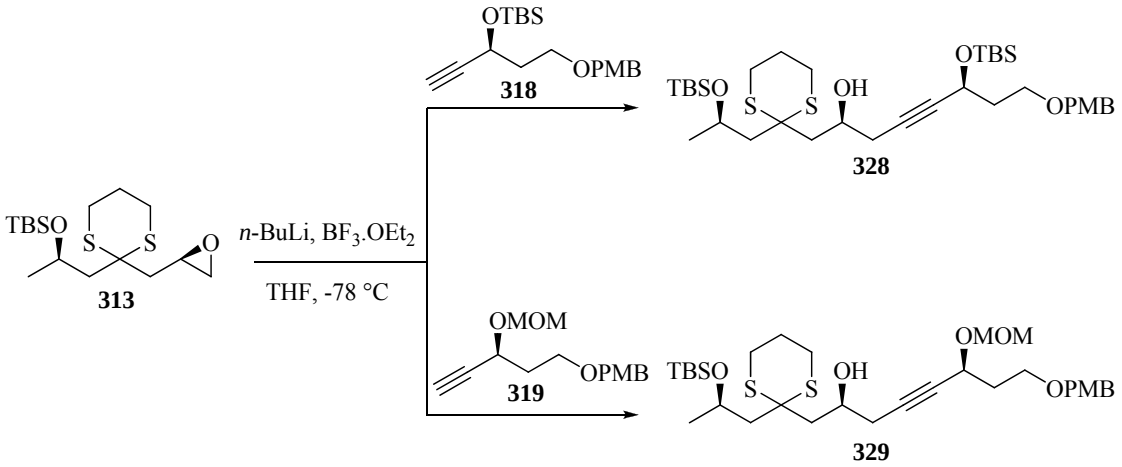
Scheme 13.

This was the state where we were having an advanced intermediate **327** with all the required stereochemical features of the target polyol with some further refunctionalizations needed and among which the hydrolysis of the 1,2 isopropylidene group of **327** being the foremost. However to our misfortune all the attempts for the cleavage of 1,2 acetonide group using Amberlite resin, 40% aq. AcOH and TFA at 50-60 °C were unsuccessful. Increased acid concentrations and temperature made the situation still worse resulting in a complex polar mixtures which were unidentified.

A parallel approach with alkynes 318 & 319

Being unsuccessful in reaching the target from the sugar alkyne approach the attention now turned towards the other available options that are still alive in the form of alkynes **318** and **319** which were coupled separately with the epoxide **313** employing the same Yamaguchi conditions (Scheme 14). The protocol proceeded smoothly providing the homopropargyl alcohols **328** and **329**. The spectral and analytical profiles of **328** and **329** were in agreement with the assigned structures. In the ^{1}H and ^{13}C NMR spectra the peaks corresponding to the two TBS groups, PMB and dithioketal groups of **328** and signals due to TBS, MOM, PMB and dithio groups of **329** appeared in the expected regions supporting a successful Yamaguchi coupling reaction. In the ^{1}H NMR spectrum of **328** the newly formed propargylic methylene group resonated as two multiplets, each integrating for one proton in the region δ 2.37-2.33 ppm and 2.20-2.17 ppm. In ^{13}C NMR spectrum signals due to the internal alkyne carbons emerged at 80.6 ppm and 84.0 ppm as singlets. Similarly in the ^{1}H NMR spectrum of **329** propargylic methylene group resonated as multiplets at δ 2.37–

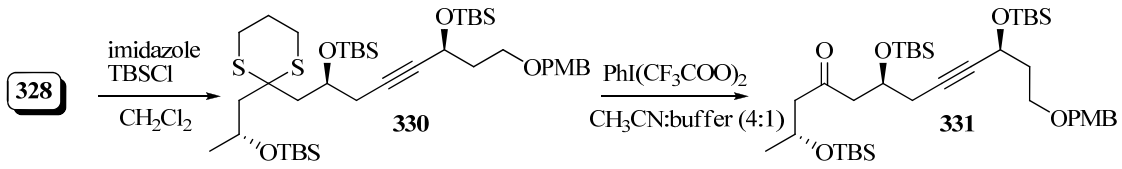
2.33 (m, 1H) and 2.15–2.12 (m, 1H). Whilst in ^{13}C NMR spectrum signals due to the internal alkyne carbons were visualized at 80.6 ppm and 82.6 ppm as singlets.



Scheme 14.

Functionalization of the masked keto group

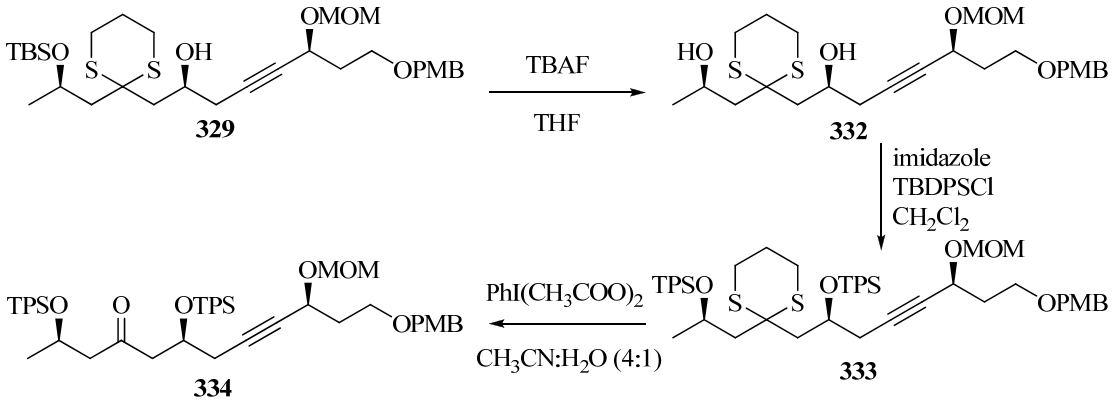
Conversion of homopropargylic alcohol **328** to the corresponding TBS ether **330** with TBSCl/imidazole/DMAP/CH_2Cl_2 followed by the dithio group cleavage with $PhI(CF_3COO)_2$ produced the ketone **331** (Scheme 15).



Scheme 15.

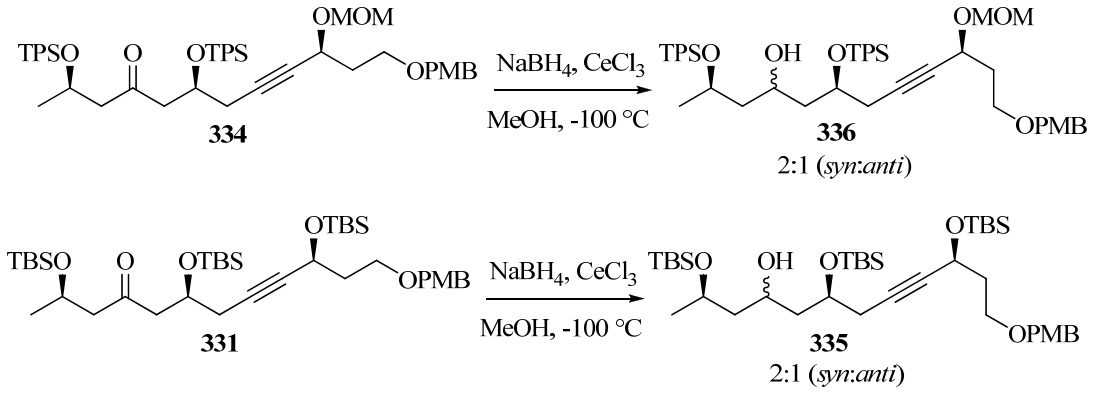
In a similar fashion the conversion of homopropargylic alcohol **329** to the corresponding ketone with suitable protecting groups was required at this stage. We needed a protecting group that can sustain the acidic conditions such as PPTS and *p*TSA which would be used for the cleavage of MOM group to facilitate the alkyne reduction to the *trans* olefin at the final stage of the aimed program. After observing various groups we turned the attention towards the TBDPS group. Thus the removal of TBS group of **329** using TBAF in THF and the conversion of the resulting diol **332**

to the di-TPS derivative **333** with TBDPSCl/imidazole/DMAP/CH_2Cl_2 followed by the cleavage of dithiane group accomplished the ketone **334** (Scheme 16).



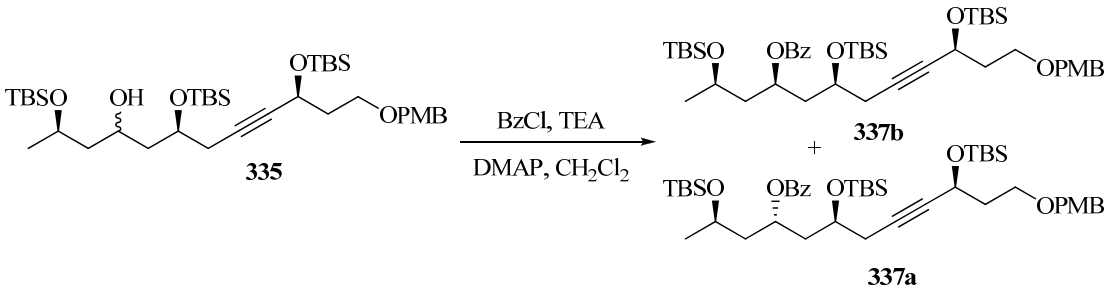
Scheme 16.

Now the aim is to reduce the ketones **331** and **334** to the corresponding either *syn* or *anti* alcohols by the use of various metal chelating agents in concert with the borohydride reagents on ketones and also taking advantage of the β-silyloxy groups. To our disappointment the intitial investigation with L-Selectride and K-Selectride[19] turned out to be a failure resulting in the starting material recovery. Turning to the Luche's reduction conditions[20] using $NaBH_4$ and $CeCl_3$ as the chelating agent in methanol at –100 °C we observed good progress in the reaction proceedings but a modest stereoselectivity: producing a 2:1 inseparable mixture of s*yn*/*anti* alcohols **335** and **336** from the ketones **331** and **334** respectively (Scheme 17).



Scheme 17.

In an attempt to separate the two diastereomers first, the mixture of **335** was exposed to benzoylchloride, triethylamine and catalytic DMAP in CH_2Cl_2. Despite a very sluggish reaction and with modest yield (62%) the attempt successfully produced the separable benzoates **337a** and **337b** (Scheme 18).



Scheme 18.

The structures and relative configuration of benzoates **337a** and **337b** were assumed by comparing their ^{13}C NMR chemical shifts with that of the natural product reported by Fenical et al.[5] and also Kishi's NMR database[8] for 1,3,5-triols and 1,3-diols (Figure 5).

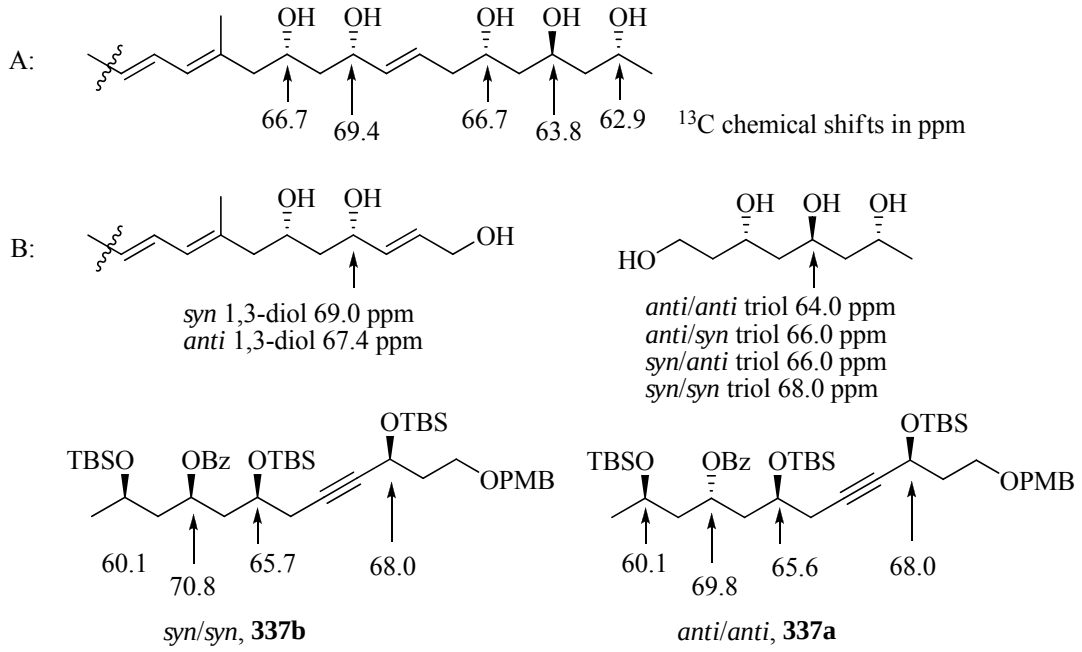
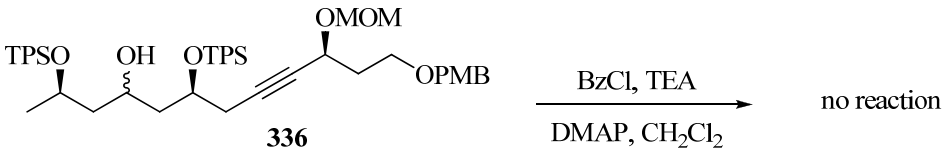


Figure 5. ^{13}C NMR chemical shift comparisons of the carbinol carbons in Fenical's data of marinomycin-A (A), Kishi's model compounds (B), synthetic benzoates **337a** and **337b**

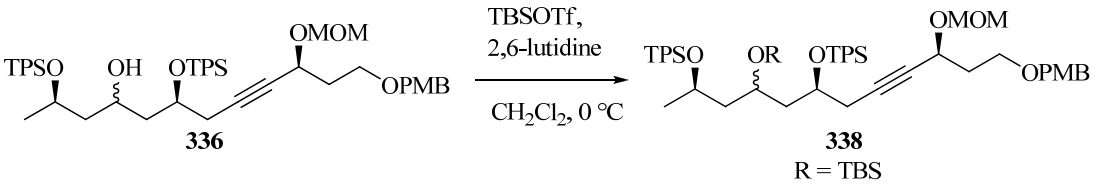
The ^{13}C NMR chemical shifts of **337a** and **337b** are almost the same for all the carbinol carbons except for the newly generated benzoate carbinol. As the corresponding carbinol carbon of the major product we obtained (**337b**) appeared downfield compared to that of **337a** and also considering the fact that the Luche reduction is a *syn*-selective, we concluded that the relative configuration of the 1,3,5-triol unit in **337b** as *syn*/*syn* and that of in **337a** as *anti*/*anti*.

In a similar fashion, benzoylatin of **336** was attempted with a hope to separate the corresponding benzoates. However, the initial benzoylation itself was found to be a futile exercise.



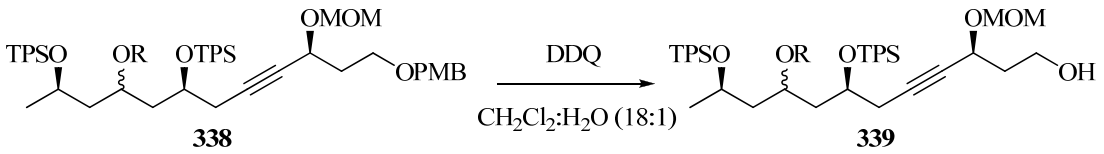
Scheme 19.

Being partly successful in the reduction of different ketones and having been left with few options, our further attempts were focused on advancing with the mixture of **336** to complete the synthesis of the target polyol. Treatment of **336** with TBSOTf and 2,6-lutidine in DCM at 0 °C secured the silyl ether **338**.



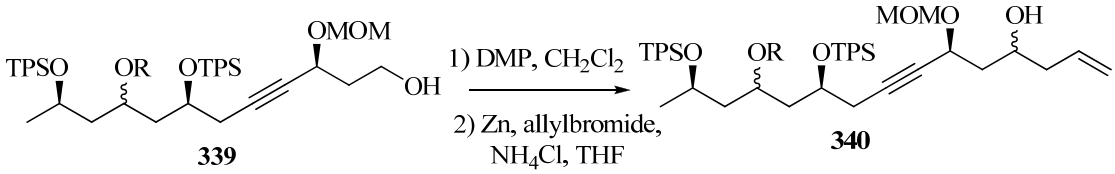
Scheme 20.

Cleavage of PMB ether was effected with DDQ in 18:1 mixture of DCM and water to afford the alcohol **339** (Scheme 23).[21] In the ^{1}H and ^{13}C NMR spectrums the peaks due to the PMB-ether disappeared and the mass spectrum with the highest mass peak at m/z 903.5 $[M+Na]^+$ further supported the proposed structure of **339**.



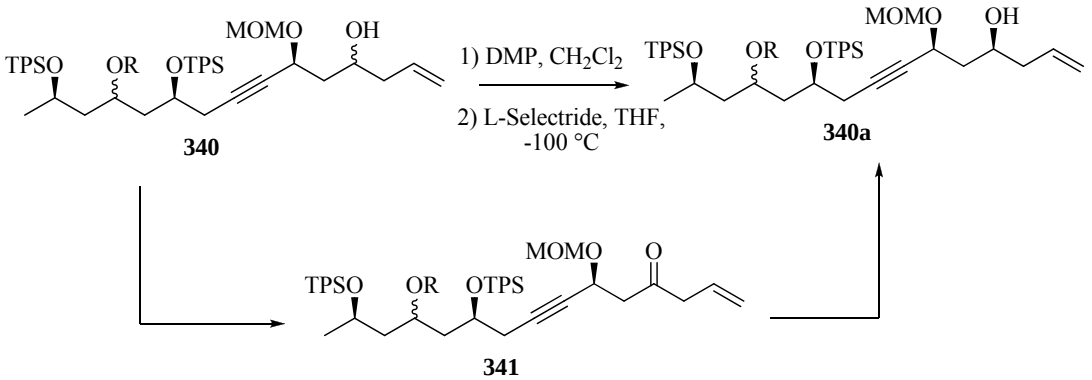
Scheme 21.

The free hydroxyl group of **339** was successively subjected to DMP oxidation to produce the corresponding aldehyde and allylation in Barbier conditions using Zn, allylbromide and NH_4Cl in THF furnished the homoallylic alcohols **340** (Scheme 22) as an inseparable epimeric mixture.[22]



Scheme 22.

To improve the stereoselectivity for the desired *syn*-**340** we then decided to explore the oxidation/reduction sequence on the mixture of isomers of *syn*/*anti* **340**. Treatment of **340** with Dess-Martin reagent[23] gave a clean conversion to the ketone **341** which was further subjected to the diastereoselective reduction using L-Selectride to accomplish the major *syn* isomer **340a** (Scheme 23).

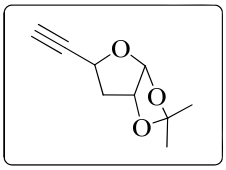


Scheme 23.

Overall a substantial synthetic work has been done for constructing the key polyol unit of marinomycin A. Linchpin approach for epoxide preparation, Yamaguchi protocol for regioselective ring opening of epoxide with different lithiated alkynes and diastereoselective keto reductions are the other notable reactions in our synthetic sequence. Attempts towards the total synthesis of marinomycin A is currently being pursued in our group.

EXPERIMENTAL

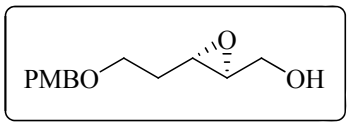
5-Ethynyl-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole (314)



At 0 ^{o}C, a solution of aldehyde **223** (5.0 g, 29.0 mmol) and dimethyl-1-diazo-2-oxopropyl phosphonate (7.2 g, 37.7 mmol) in dry methanol (100 mL) was treated with K_2CO_3 (8.0 g, 58.0 mmol). After 6 h stirring at rt, methanol was evaporated under reduced pressure, partitioned between ethyl acetate and water. Organic layer was separated and the aqueous layer was extracted with ethyl acetate. Combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (10% ethyl acetate in petroleum ether) to afford alkyne **314** (2.8 g, 58% yield) as a colorless oil.

Mol. Formula	: $C_9H_{12}O_3$
$[\alpha]_D$	: –25.2 (*c* 1.3, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3307, 2991, 1619, 1384, 1217, 1053, 769 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 5.85 (d, *J* = 3.7 Hz, 1H), 4.79–4.70 (m, 2H), 2.50 (d, *J* = 2.1 Hz, 1H), 2.35 (dd, *J* = 4.5, 13.4 Hz, 1H), 1.93 (ddd, *J* = 4.5, 11.0, 13.4 Hz, 1H), 1.48 (s, 3H), 1.29 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 25.8 (q), 26.5 (q), 40.0 (t), 66.5 (d), 74.2 (d), 79.9 (d), 80.6 (s), 105.1 (d), 111.2 (s) ppm.
ESI-MS (*m/z*)	: 191.2 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 64.27; H, 7.19.
	Found: C, 64.19; H, 7.22.

((2*S*,3*S*)-3-(2-(4-Methoxybenzyloxy)ethyl)oxiran-2-yl)methanol (315)

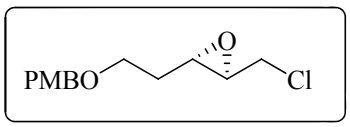


In a dry two neck round bottom flask, 4Å molecular sieves powder (5 g) was placed and evacuated with flame under argon. 250 mL of CH_2Cl_2 was injected into the rb. The solution was allowed to cool to –20 °C. Then $Ti(O^iPr)_4$ (14.0 g, 49.5

mmol) and L(+)-DIPT (12.6 g, 54.0 mmol) were added sequentially. After stirring for 5 min, TBHP (25 mL, 90.0 mmol, 3.6 M in toluene) was added dropwise for 15 min. After another 30 min stirring at –20 °C, a solution of allylic alcohol **236** (10 g, 45.0 mmol) in CH_2Cl_2 (50 mL) was added to the reaction mixture and stirred overnight at the same temperature. Reaction was quenched with water (280 mL) and stirred vigorously while warming the reaction mixture slowly to rt. The reaction mixture was filtered through celite pad and the filtrate containing aqueous and organic layers was extracted with CH_2Cl_2. Combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (50% ethyl acetate in petroleum ether) to obtain the pure epoxy alcohol **315** (9.0 g, 84% yield) as colorless oil.

Mol. Formula	: $C_{13}H_{18}O_3$
$[\alpha]_D$	: –24.0 (*c* 1.5, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$	: 3016, 1270, 840 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 7.26 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.45 (s, 2H), 3.92–3.85 (m, 1H), 3.80 (s, 3H), 3.65–3.55 (m, 3H), 3.09 (ddd, *J* = 2.4, 4.9, 7.2 Hz, 1H), 2.97 (dt, *J* = 2.5, 4.4 Hz, 1H), 2.02–1.74 (m, 3H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 31.7 (t), 53.4 (d), 54.8 (q), 58.3 (d), 61.5 (t), 66.2 (t), 72.3 (t), 113.5 (d, 2C), 128.9 (d, 2C), 129.9 (s), 158.9 (s) ppm.
ESI-MS (*m/z*)	: 261.2 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 70.24; H, 8.16. Found: C, 70.22; H, 8.19.

(2*R*,3*S*)-2-(Chloromethyl)-3-(2-(4-methoxybenzyloxy)ethyl)oxirane (316)

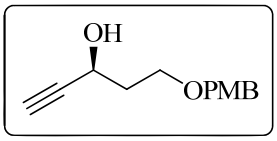


To a solution of epoxy alcohol **315** (9.0 g, 37.8 mmol) in CCl_4 (250 mL), was added TPP (11.9 g, 45.3 mmol) and the reaction mixture was refluxed for 8 h. The solvent was removed under reduced pressure and the residue was purified by column

chromatography (12% ethyl acetate in petroleum ether) to give the chloro oxirane **316** (8.2 g, 85% yield) as a colorless oil.

Mol. Formula	: $C_{13}H_{17}ClO_3$
$[\alpha]_D$	: –16.0 (*c* 1, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 2954, 1514, 1301, 1247, 1098, 1034, 771, 733 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 7.30–7.23 (m, 2H), 6.92–6.85 (m, 2H), 4.46 (br s, 2H), 3.82 (s, 3H), 3.61–3.53 (m, 4H), 3.08–3.01 (m, 2H), 2.02–1.73 (m, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 31.9 (t), 44.5 (t), 55.0 (q), 56.5 (d), 57.0 (d), 66.2 (t), 72.6 (t), 113.7 (d, 2C), 129.1 (d, 2C), 130.1 (s), 159.1 (s) ppm.
ESI-MS (*m/z*)	: 279.2 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 60.82; H, 6.67. Found: C, 60.75; H, 6.66.

(*S*)-5-(4-Methoxybenzyloxy)pent-1-yn-3-ol (317)

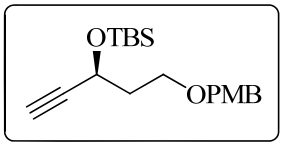


To a solution of **316** (8.0 g, 32.0 mmol) in dry THF was added excess *n*-BuLi (34 mL, 80.0 mmol, 2.34 M in hexane) at –40 °C and the reaction mixture was stirred for 1 h at the same temperature. The reaction mixture was quenched with a satd. solution of NH_4Cl and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (20% ethyl acetate in petroleum ether) to afford the hydroxy alkyne **317** (5.7 g, 81% yield) as pale yellow oil.

Mol. Formula	: $C_{13}H_{16}O_3$
$[\alpha]_D$	: –21.5 (*c* 1.2, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3410, 3289, 2933, 2113, 1513, 1248, 1032, 819 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 7.28–2.21 (m, 2H), 6.90–6.83 (m, 2H), 4.60–4.55 (m, 1H), 4.46 (br s, 2H), 3.91–3.82 (m, 1H), 3.80 (br s, 3H), 3.65 (ddd, *J* = 4.5, 5.8, 10.2 Hz, 1H), 2.44 (br d, *J* = 2.1 Hz, 1H), 2.17-1.85 (m, 2H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 36.5 (t), 55.1 (q), 60.9 (d), 67.0 (t), 72.8 (d), 72.9 (t), 84.3 (s), 113.7 (d, 2C), 129.3 (d, 2C), 129.8 (s), 159.2 (s) ppm.
ESI-MS (*m/z*)	: 243.2 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 70.89; H, 7.32.
	Found: C, 70.96; H, 7.40.

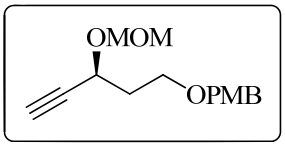
(3*S*)-1-(4-Methoxybenzyloxy-3-*tert*-butyldimethylsilyloxy-pent-4-yne (318)



A solution of **317** (2.5 g, 11.35 mmol) and imidazole (1.1 g, 17.0 mmol) in CH_2Cl_2 (30 mL) was treated with TBSCl (3.1 g, 20.4 mmol) at 0 °C. The reaction mixture was stirred for 4 h at rt. Water was added to the reaction mixture and aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue obtained was purified by column chromatography (7% ethyl acetate in petroleum ether) to afford **318** (2.9 g, 78% yield) as a colorless oil.

Mol. Formula	: $C_{19}H_{30}O_3Si$
$[\alpha]_D$	: –29.5 (*c* 1.8, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3308, 2930, 1613,1513, 1250, 1098, 838, 758 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 7.25 (br dt, *J* = 2.3, 8.6 Hz, 2H), 6.87 (br dt, *J* = 2.3, 8.8 Hz, 2H), 4.57 (dt, *J* = 5.3, 15.1 Hz, 1H), 4.42 (q, *J* = 11.3, 15.1 Hz, 2H), 3.80 (s, 3H), 3.61–3.55 (m, 2H), 2.37 (d, *J* = 2.3 Hz, 1H), 1.97 (q, *J* = 6.3, 12.5 Hz, 2H), 0.90 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ –5.1 (q), –4.6 (q), 18.2 (s), 25.8 (q, 3C), 38.7 (t), 55.1 (q), 59.7 (d), 65.8 (t), 72.1 (d), 72.7 (t), 85.4 (s), 113.7 (d, 2C), 129.2 (d, 2C), 130.4 (s), 159.1 (s) ppm.
ESI-MS (*m/z*)	: 357.4 $[M+Na]^+$.
Elemental Analysis	Calcd: C, 68.22; H, 9.04.
	Found: C, 68.17; H, 9.07.

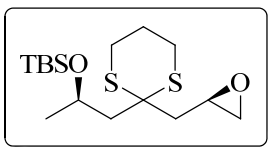
(3*S*)-1-(4-Methoxybenzyloxy)-3-methoxymethoxy-pentane-4-yne (319)



To an ice cooled solution of **317** (3.0 g, 13.6 mmol) and $^{i}Pr_2NEt$ (7.1 mL, 40.8 mmol) in CH_2Cl_2 was added MOMCl (1.5 mL, 20.4 mmol) and a catalytic TBAI. The reaction mixture was allowed to attain rt and stirred further for 4 h. Water was added to the reaction mixture and aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue obtained was purified by column chromatography (7% ethyl acetate in petroleum ether) to afford **319** (3.0 g, 86% yield) as a pale yellow oil.

Mol. Formula	: $C_{15}H_{20}O_4$
$[\alpha]_D$	: –55.3 (*c* 1.5, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3308, 2930, 1613,1513, 1250, 1098, 838, 758 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.92 (d, *J* = 6.7 Hz, 1H), 4.59 (d, *J* = 6.7 Hz, 1H), 4.56–4.49 (m, 1H), 4.43 (s, 2H), 3.80 (s, 3H), 3.61 (t, *J* = 5.9 Hz, 2H), 3.36 (s, 3H), 2.40 (d, *J* = 2.0 Hz, 1H), 2.09–1.98 (m, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 35.8 (t), 55.1 (q), 55.5 (q), 62.5 (d), 65.7 (t), 72.6 (t), 73.6 (d), 82.2 (s), 94.0 (t), 113.6 (d, 2C), 129.1 (d, 2C), 130.2 (s), 159.0 (s) ppm.
ESI-MS (*m/z*)	: 287.2 $[M+Na]^+$.
Elemental Analysis	Calcd: C, 68.16; H, 7.63.
	Found: C, 68.11; H, 7.66.

***tert*-Butyldimethyl((*R*)-1-(2-((*R*)-oxiran-2-ylmethyl)-1,3-dithian-2-yl)propan-2-yloxy)silane (313)**

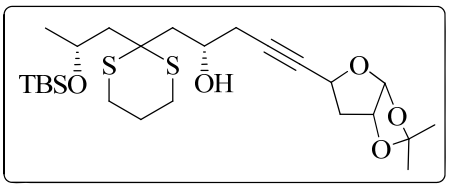


n-Butyllithium (5.4 mL, 2.34 M in hexanes, 8.5 mmol) was added under argon, to a solution of TBS-dithiane **310** (2 g, 8.5 mmol) in THF (20 mL) at –10 ^{o}C and allowed to stir for 2 h. The mixture was cooled to –78 ^{o}C and added (*S*)-propyleneoxide **311** (580 μL, 8.3 mmol) in THF (1 mL). The first alkylation was complete in 1 h while warming the reaction mixture slowly to –40 ^{o}C. The mixture

was cooled to –78 ^{o}C and HMPA (870 μL, 5 mmol) was added. Warming the mixture to –40 ^{o}C and stirring for 1 h at the same temperature resulted in complete Brook's rearrangement of the silyl group. Then the mixture was recooled to –40 ^{o}C and the second epoxide **312** (550 μL, 7 mmol) in THF (1 mL) was added. After 1 h stirring at –10 ^{o}C, the reaction was slowly warmed to attain rt and stirred for additional 3 h. The reaction mixture was quenched with satd. NH_4Cl solution and extracted with ether (2 x 20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (7% ethyl acetate in petroleum ether) to furnish **313** (1.8 g, 61% yield) as a pale yellow oil.

Mol. Formula	: $C_{16}H_{32}O_2S_2Si$
$[\alpha]_D$	: –9.1 (*c* 1.2, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3401, 2019, 1215, 1425, 1256, 1133, 1088, 836, 758 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 4.21 (ddd, *J* = 2.6, 6.3, 12.5 Hz, 1H), 3.23–3.15 (m, 1H), 2.85–2.73 (m, 5H), 2.50 (dd, *J* = 2.6, 5.0 Hz, 1H), 2.35–2.03 (m, 4H), 2.00–1.89 (m, 2H), 1.23 (d, *J* = 6.1 Hz, 3H), 0.86 (s, 9H), 0.07 (s, 6H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ –4.1 (q), –3.9 (q), 17.9 (s), 25.0 (t), 26.0 (q, 3C), 25.9 (q), 26.1 (t), 26.2 (t), 41.91 (t), 46.5 (t), 48.4 (t), 48.9 (d), 51.3 (s), 66.1 (d) ppm.
ESI-MS (*m/z*)	: 371.2 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 55.12; H, 9.25. Found: C, 55.08; H, 9.31.

(2*S*)-1-(2-((*R*)-2-(*tert*-Butyldimethylsilyloxy)propyl)-1,3-dithian-2-yl)-5-(2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)pent-4-yn-2-ol (320)

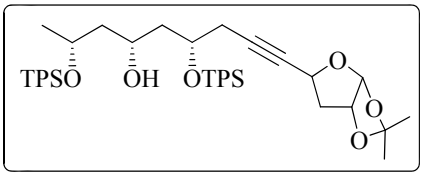


To a solution of alkyne **314** (1.2 g, 7.2 mmol) in anhydrous THF in a flame dried two neck round bottom flask under argon was added *n*-BuLi (4.7 mL, 7.5 mmol, 1.6 M in hexane) dropwise at –78 ^{o}C. After 15 min, $BF_3.Et_2O$ (0.89 mL, 7.2 mmol) was added slowly dropwise. Reaction mixture was allowed to stir for another 15 min at the same temperature after which a solution of epoxide **313** (1 g, 2.9 mmol) in THF

was added. Reaction was quenched by adding a solution of THF-H_2O (1:1) when the TLC showed the complete consumption of the epoxide (1 h). The mixture was slowly warmed to rt and extracted into EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified on flash silica-gel (25% ethyl acetate in petroleum ether) to furnish the title compound **320** (1.2 g, 81% yield) as a pale yellow oil.

Mol. Formula	: $C_{25}H_{44}O_5S_2Si$
$[\alpha]_D$	: –7.0 (*c* 0.8, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 5.84 (d, *J* = 3.7 Hz, 1H), 4.79 (ddt, *J* = 2.2, 4.4, 11.0 Hz, 1H), 4.73 (t, *J* = 4.4 Hz, 1H), 4.25 (dd, *J* = 4.9, 5.9 Hz, 1H), 4.23–4.19 (m, 1H), 3.48 (br s, 1H), 2.96 (ddd, *J* = 2.9, 9.0, 14.2 Hz, 1H), 2.90 (ddd, *J* = 2.9, 9.0, 14.2 Hz, 1H), 2.81 (ddd, *J* = 3.2, 7.3, 14.4 Hz, 1H), 2.77 (ddd, *J* = 3.2, 7.1, 14.4 Hz, 1H), 2.46–2.43 (m, 2H), 2.37 (dd, *J* = 9.2, 15.3 Hz, 1H), 2.31 (dd, *J* = 4.4, 13.2 Hz, 1H), 2.18–2.13 (m, 3H), 2.03–1.95 (m, 1H), 1.93–1.87 (m, 2H), 1.49 (s, 3H), 1.30 (s, 3H), 1.25 (d, *J* = 6.1 Hz, 3H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ –4.1 (q), –4.0 (q), 18.0 (s), 24.7 (q), 26.0 (q, 3C), 26.0 (q), 26.1 (q), 26.6 (t), 26.6 (t), 26.6 (t), 27.9 (t), 40.5 (t), 44.6 (t), 49.4 (t), 51.1 (s), 66.1 (d), 67.2 (d), 67.3 (d), 79.3 (s), 80.1 (d), 83.2 (s), 105.2 (d), 111.2 (s) ppm.
ESI-MS (*m/z*)	: 539.3 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 58.10; H, 8.58; S, 12.41; Si, 5.43. Found: C, 58.06; H, 8.64; S, 12.44; Si, 5.47.

(5*S*,7*R*,9*R*)-5-(3-(2,2-Dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)prop-2-ynyl)-2,2,9,12,12-pentamethyl-3,3,11,11-tetraphenyl-4,10-dioxa-3,11-disilatridecan-7-ol (324)

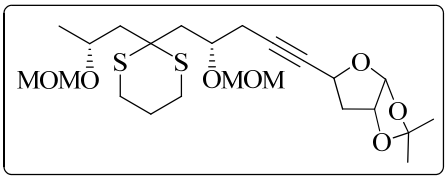


To a solution of **323** (250 mg, 0.31 mmol) in 5 mL of THF at –78 °C, L-Selectride (0.65 mL of 1 M solution in THF, 0.65 mmol) was added dropwise over 5 min, under an argon atmosphere. The reaction mixture was stirred for 3 h, quenched

with water (5 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4. The residue obtained after evaporation of solvent was purified by column chromatography (20% ethyl acetate in petroleum ether) to provide **324** (200 mg, 80% yield) as a colorless oil.

Mol. Formula	: $C_{48}H_{62}O_6Si_2$
$[\alpha]_D$	: +6.5 (*c* 1.5, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 7.70–7.64 (m, 8H), 7.40–7.31 (m, 12H), 5.81 (dd, *J* = 3.2, 3.4 Hz, 1H), 4.72–4.66 (m, 2H), 4.17–4.12 (m, 1H), 3.97–3.92 (m, 2H), 3.38–3.29 (m, 1H), 2.34–2.17 (m, 3H), 1.88–1.72 (m, 2H), 1.67–1.60 (m, 3H), 1.49 (s, 3H), 1.30 (s, 3H), 1.06, 1.05, 1.01 (3s, 18H) 0.90 (d, *J* = 6.1 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ 19.1, 19.27, 19.33 (3s, 2C), 22.8, 23.9 (2q, 1C), 26.0 (q), 26.6 (q), 26.9 (q, 3C), 26.95 (q, 3C), 27.1 27.4 (2t, 1C), 40.3 (t), 43.3, 43.6 (2t, 1C), 45.4, 46.1 (2t, 1C), 67.2 (d), 68.1, 68.4 (2d, 1C), 69.4, 69.9 (2d, 1C), 70.2 (d), 79.1 (s), 80.1 (d), 83.46, 83.53 (2s, 1C), 105.1 (d), 111.1 (d), 127.4, 127.5 (2d, 4C), 127.6, 127.7 (2d, 4C), 129.54, 129.6, 129.70, 129.8 (4d, 4C), 133.3, 133.4 (2s, 1C), 133.5, 133.6 (2s, 1C), 133.8, 133.9 (2s, 1C), 134.1, 134.3 (2s, 1C), 135.8 (d, 4C), 135.9 (d, 4C) ppm.
ESI-MS (*m/z*)	: 813.5 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 72.87; H, 7.90. Found: C, 72.83; H, 7.94.

5-((*S*)-4-(Methoxymethoxy)-5-(2-((*R*)-2-(methoxymethoxy)propyl)-1,3-dithian-2-yl)pent-1-ynyl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole (325)

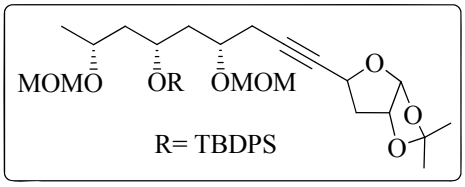


At 0 °C, a solution of diol **321** (300 mg, 0.74 mmol) in CH_2Cl_2 (10 mL) was treated with diisopropylethylamine (0.8 mL, 4.5 mmol) followed by MOM-Cl (170 μL, 2.2 mmol) and allowed to stir for 8 h at rt. Reaction mixture was worked up with CH_2Cl_2 and water. The organic fraction was dried over Na_2SO_4 and concentrated.

The crude was purified by flash chromatography (20% ethyl acetate in petroleum ether) to afford **325** (215 mg, 60 % yield) as a pale yellow oil.

Mol. Formula	: $C_{23}H_{38}O_7S_2$
$[\alpha]_D$	: –6.2 (*c* 1.3, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3431, 2931, 2245, 1726, 1441, 1215, 875, 756 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 5.81 (d, *J* = 3.8 Hz, 1H), 4.80–4.69 (m, 4H), 4.63 (dd, *J* = 1.1, 6.9 Hz, 2H), 4.08–3.94 (m, 2H), 3.37 (s, 6H), 2.96–2.68 (m, 4H), 2.60–2.57 (m, 2H), 2.48–2.16 (m, 4H), 2.03–1.80 (m, 4H), 1.48 (s, 3H), 1.29 (s, 3H), 1.24 (d, *J* = 6.2 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ 22.5 (q), 24.8 (t), 25.8 (q), 25.9 (t), 26.2 (t, 2C), 26.4 (q), 40.2 (t), 43.3 (t), 47.1 (t), 51.4 (s), 55.5 (q), 55.7 (q), 67.0 (d), 71.5 (d), 74.8 (d), 78.9 (s), 79.9 (d), 83.2 (s), 95.7 (t), 96.6 (t), 104.9 (d), 110.9 (s) ppm.
ESI-MS (*m/z*)	: 513.3 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 56.30; H, 7.81.
	Found: C, 56.28; H, 7.84.

(5*R*,7*R*)-7-((2*S*)-5-(2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-2-(methoxymethoxy)pent-4-ynyl)-5,10,10-trimethyl-9,9-diphenyl-2,4,8-trioxa-9-silaundecane (327)



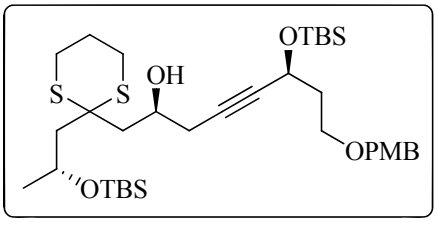
The dithio group of **325** was deprotected using PIFA and following the same procedure described for compound **334**. To a solution of the resulting ketone (150 mg, 0.37 mmol) in THF (5 mL) at –78 °C, L-Selectride (0.75 mL of 1 M solution in THF, 0.75 mmol) was added dropwise over 5 min, under an argon atmosphere. The reaction mixture was stirred for 3 h, quenched with water (5 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4. The residue obtained after evaporation of solvent was purified by column chromatography (30% ethyl acetate in petroleum ether) to furnish **326** (125 mg, 84% yield) as a colorless oil.

At 0 ^oC, a solution of alcohol **326** (125 mg, 0.31 mmol) and imidazole (35 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) was treated with TBDPSCl (103 mg, 0.37 mmol) and

DMAP (5 mg, 0.04 mmol). After 6 h stirring at rt, the reaction mixture was partitioned between water and CH_2Cl_2. The layers were separated and the organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (15% ethyl acetate in petroleum ether) to produce **327** (150 mg, 75% yield) as a colorless oil.

Mol. Formula	: $C_{36}H_{52}O_8Si$
$[\alpha]_D$	: +6.4 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3449, 3018, 1734, 1490, 1376, 1216, 875, 755, 667 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 7.69–7.63 (m, 4H), 7.41–7.34 (m, 6H), 5.81 (d, *J* = 3.8 Hz, 1H), 4.74–4.67 (m, 2H), 4.56 (dd, *J* = 3.8, 6.9 Hz, 2H), 4.48 (dd, *J* = 1.0, 6.9 Hz, 2H), 3.90 (dt, *J* = 6.0, 12.0 Hz, 1H), 3.76 (ddd, *J* = 6.0, 12.3, 18.8 Hz, 2H), 3.24 (s, 3H), 3.22 (s, 3H), 2.34 (ddd, *J* = 1.7, 5.5, 16.8 Hz, 1H), 2.24–2.16 (m, 2H), 1.88–1.76 (m, 4H), 1.57–1.54 (m, 1H), 1.48 (s, 3H), 1.29 (s, 3H), 1.04 (s, 9H), 0.94 (d, *J* = 6.1 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ 19.3 (s), 20.5 (q), 25.0 (t), 26.0 (q), 26.6 (q), 27.1 (q, 3C), 40.4 (t), 41.4 (t), 44.0 (t), 55.2 (q), 55.6 (q), 67.2 (d), 68.2 (d), 70.7 (d), 72.9 (d), 78.8 (s), 80.1 (d), 83.2 (s), 95.0 (t), 95.7 (t), 105.1 (d), 111.2 (s), 127.5 (d, 4C), 129.6 (d, 2C), 134.0 (s), 134.1 (s), 136.0 (d, 4C) ppm.
ESI-MS (*m/z*)	: 663.4 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 67.47; H, 8.18. Found: C, 67.43; H, 8.23.

(2*S*,6*S*)-6-(*tert*-Butyldimethylsilyloxy)-1-(2-((*R*)-2-(*tert*-butyldimethylsilyloxy)propyl)-1,3-dithian-2-yl)-8-(4-methoxybenzyloxy)oct-4-yn-2-ol (319)

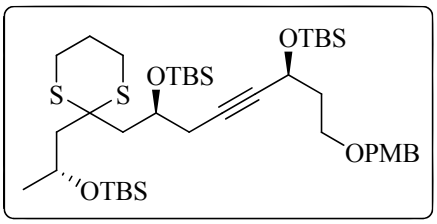


To a solution of alkyne **318** (1.2 g, 3.6 mmol) in anhydrous THF in a flame dried two neck round bottom flask under argon was added *n*-BuLi (2.4 mL, 3.8 mmol, 1.6 M in hexane) dropwise at –78 ^oC. After 15 min, $BF_3.Et_2O$ (0.45 mL, 3.6 mmol) was added slowly dropwise. Reaction mixture was allowed to stir for another 15 min

at the same temperature after which a solution of epoxide **313** (1 g, 3.3 mmol) in THF was added. Reaction was quenched by adding a solution of THF-H_2O (1:1) when the TLC showed the complete consumption of the epoxide. The mixture was slowly warmed to rt and extracted into EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (25% ethyl acetate in petroleum ether) to furnish the title compound **319** (0.83 g, 85% yield) as a colorless oil.

Mol. Formula	: $C_{35}H_{62}O_5S_2Si_2$
$[\alpha]_D$	: –4.8 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3438, 2930, 1731, 1513, 1250, 1096, 837, 667 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 7.25 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 4.56 (t, *J* = 6.5 Hz, 1H), 4.45–4.39 (m, 2H), 4.24 (dt, *J* = 6.0, 10.8 Hz, 1H), 4.19–4.13 (m, 1H), 3.80 (s, 3H), 3.60–3.55 (m, 2H), 3.37 (d, *J* = 2.5 Hz, 1H), 2.98–2.86 (m, 2H), 2.83–2.73 (m, 2H), 2.42–2.33 (m, 3H), 2.20–2.12 (m, 3H), 1.97–1.92 (m, 4H), 1.24 (d, *J* = 6.0 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.14 (s, 3H), 0.10 (s, 6H), 0.09 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ –5.1 (q), –4.4 (q), –4.1 (q), –4.0 (q), 17.9 (s), 18.1 (s), 24.7 (t), 25.8 (q, 3C), 25.9 (q, 3C), 26.0 (q), 26.1 (t), 26.5 (t), 27.9 (t), 39.0 (t), 44.6 (t), 49.2 (t), 51.1 (s), 55.2 (q), 60.0 (d), 66.0 (d), 66.0 (t), 67.3 (d), 72.6 (t), 80.6 (s), 84.0 (s), 113.6 (d, 2C), 129.2 (d, 2C), 130.5 (s), 159.0 (s) ppm.
ESI-MS (*m/z*)	: 705.4 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 61.53; H, 9.15. Found: C, 61.49; H, 9.19.

(5*S*,9*S*)-9-((2-((*R*)-2-(*tert*-Butyldimethylsilyloxy)propyl)-1,3-dithian-2-yl)methyl)-5-(2-(4-methoxybenzyloxy)ethyl)-2,2,3,3,11,11,12,12-octamethyl-4,10-dioxa-3,11-disilatridec-6-yne (330)

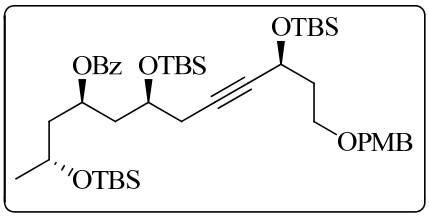


To a stirred solution of **328** (620 mg, 1.3 mmol), imidazole (180 mg, 2.6 mmol) in CH_2Cl_2 (5 mL) was added TBSCl (232 mg, 1.6 mmol) and a catalytic DMAP (30 mg, 0.26). The resulting mixture was stirred for 6 h at rt and subsequently

diluted with water. The mixture was extracted with CH_2Cl_2, dried over Na_2SO_4 and concentrated. The residue obtained was purified by column chromatography (5% ethyl acetate in petroleum ether) to provide **330** (830 mg, 80% yield) as a clear oil.

Mol. Formula	: $C_{41}H_{76}O_5S_2Si_3$
$[\alpha]_D$	: –3.1 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3436, 2929, 2856, 1613, 1250, 1094, 809, 776, 666 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 7.24 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.54 (t, *J* = 6.5 Hz, 1H), 4.40 (s, 2H), 4.22 (dd, *J* = 5.5, 10.7 Hz, 1H), 4.16–4.09 (m, 1H), 3.79 (s, 3H), 3.60–3.54 (m, 2H), 2.95–2.60 (m, 4H), 2.57–2.40 (m, 3H), 2.25–1.88 (m, 7H), 1.22 (d, *J* = 6.1 Hz, 3H), 0.88 (2s, 18H), 0.89 (s, 9H), 0.13 (s, 6H), 0.11 (s, 3H), 0.09 (s, 6H), 0.07 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ –5.1 (q), –4.4 (q), –4.2 (q), –4.1 (q), –4.0 (q), –3.8 (q), 17.9 (s), 18.0 (s), 18.2 (s), 25.0 (t), 25.8 (q, 3C), 26.0 (q, 6C), 26.1 (t), 26.3 (q), 26.5 (t), 29.2 (t), 39.1 (t), 45.7 (t), 50.0 (t), 51.9 (s), 55.2 (q), 60.1 (d), 66.1 (d), 66.2 (t), 68.9 (d), 72.6 (t), 81.3 (s), 83.8 (s), 113.7 (d, 2C), 129.2 (d, 2C), 130.6 (s), 159.1 (s) ppm.
ESI-MS (*m/z*)	: 819.5 $(M+Na)^+$.
Elemental Analysis	Calcd.: C, 61.75; H, 9.61. Found: C, 61.69; H, 9.66.

(5*R*,7*R*,9*S*,13*S*)-9-(*tert*-Butyldimethylsilyloxy)-13-(2-(4-methoxybenzyloxy)ethyl)-2,2,3,3,5,15,15,16,16-nonamethyl-4,14-dioxa-3,15-disilaheptadec-11-yn-7-yl benzoate (337b)



At 0 ^oC, a solution of dithioketal **330** (300 mg, 0.38 mmol) in CH_3CN-buffer (4:1, 10 mL) was treated with $PhI(CF_3COO)_2$ (243 mg, 0.6 mmol) and stirred for 15 min. A satd. solution of $NaHCO_3$ was added to the reaction mixture and extracted with ethyl acetate (2 x 10 mL). Combined organic fractions were washed with brine, dried over Na_2SO_4 and concentrated. The crude was purified by column

chromatography (10% ethyl acetate in petroleum ether) to furnish ketone **331** (236 mg, 88% yield) as pale yellow oil.

A solution of ketone **331** (230 mg, 0.32 mmol) in MeOH was cooled to –100 ^{o}C and treated with $CeCl_3.7H_2O$ (60 mg, 0.16 mmol) under argon. After 10 min, $NaBH_4$ (25 mg, 0.65 mmol) was added and the reaction mixture was stirred for 3 h at the same temperature. The reaction was quenched with satd. NH_4Cl solution and the mixture was allowed to slowly attain ambient temperature. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The residue obtained was subsequently purified by flash chromatography (15% EtOAc in petroleum ether) to afford **335** (175 mg, 77% yield) as a colorless oil.

To a flask containing a solution of **335** (160 mg, 0.22 mmol) in CH_2Cl_2 (5 mL) were added Et_3N (100 μL, 0.67 mmol), benzoylchloride (40 μL, 0.33 mmol) and catalytic DMAP sequentially at 0 °C. The mixture was allowed to stir for 12 h at rt, and consequently diluted with water and extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried over Na_2SO_4. The residue obtained after evaporation of solvent was purified by flash column chromatography (5% ethyl acetate in petroleum ether) to provide **337a** (38 mg, 22% yield) and **337b** (82 mg, 45% yield) as colorless oils.

Mol. Formula : $C_{45}H_{76}O_7Si_3$

$[\alpha]_D$: –16.0 (*c* 1.8, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) : δ 8.02–8.00 (m, 2H), 7.52 (tt, *J* = 1.2, 7.8 Hz, 1H), 7.42–7.38 (m, 2H), 7.24 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 5.22–5.16 (m, 1H), 4.54 (br t, *J* = 6.5 Hz, 1H), 4.39 (s, 2H), 3.97–3.89 (m, 2H), 3.79 (s, 3H), 3.60–3.51 (m, 2H), 2.40 (ddd, *J* = 2.0, 4.3, 16.6 Hz, 1H), 2.32 (ddd, *J* = 1.8, 7.8, 16.6 Hz, 1H), 2.11 (ddd, *J* = 2.8, 9.0, 14.3 Hz, 1H), 1.94 (d, *J* = 6.3 Hz, 1H), 1.91 (d, *J* = 6.5 Hz, 1H), 1.89–1.75 (m, 3H), 1.17 (d, *J* = 6.0 Hz, 3H), 0.88 (s, 9H), 0.86 (s, 9H), 0.85 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H), 0.01 (s, 6H), 0.00 (s, 3H), –0.01 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz) : δ –5.1 (q), –4.8 (q), –4.7 (q), –4.5 (q), –4.4 (q), –4.3 (q), 17.9 (s), 18.0 (s), 18.2 (s), 24.3 (q), 25.8 (q, 3C), 25.9 (q,

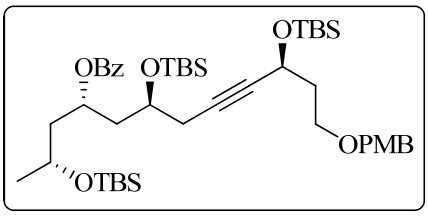
3C), 25.9 (q, 3C), 28.4 (t), 39.1 (t), 42.2 (t), 45.3 (t), 55.3 (q), 60.1 (d), 65.7 (d), 66.2 (t), 68.0 (d), 70.8 (d), 72.7 (t), 80.8 (s), 83.8 (s), 113.7 (d, 2C), 128.3 (d, 2C), 129.2 (d, 2C), 129.5 (d, 2C), 130.6 (s), 130.9 (s), 132.6 (d), 159.1 (s), 165.9 (s) ppm.

ESI-MS (*m/z*) : 835.5 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 66.45; H, 9.42.

Found: C, 66.41; H, 9.46.

(5*R*,7*S*,9*S*,13*S*)-9-(*tert*-Butyldimethylsilyloxy)-13-(2-(4-methoxybenzyloxy)ethyl)-2,2,3,3,5,15,15,16,16-nonamethyl-4,14-dioxa-3,15-disilaheptadec-11-yn-7-yl benzoate (337a)

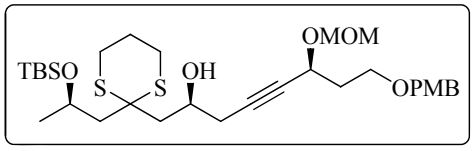


^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.04–8.00 (m, 2H), 7.52 (tt, *J* = 1.5, 7.2 Hz, 1H), 7.45–7.37 (m, 2H), 7.23 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.36–5.23 (m, 1H), 4.51 (br t, *J* = 6.5 Hz, 1H), 4.38 (s, 2H), 3.93–3.82 (m, 2H), 3.79 (s, 3H), 3.59–3.49 (m, 2H), 2.41 (d, *J* = 1.8 Hz, 1H), 2.38 (br d, *J* = 1.8 Hz, 1H), 2.02–1.85 (m, 4H), 1.89–1.69 (m, 2H), 1.19 (d, *J* = 6.1 Hz, 3H), 0.88 (s, 9H), 0.86 (s, 9H), 0.85 (s, 9H), 0.08 (s, 3H), 0.06 (2s, 6H), 0.04 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) : δ –5.1 (q), –4.8 (q), –4.7 (q), –4.5 (q), –4.4 (q), –4.3 (q), 18.0 (s), 18.1 (s), 18.2 (s), 23.3 (q), 25.9 (q, 6C), 25.9 (q, 3C), 27.6 (t), 39.0 (t), 41.9 (t), 44.8 (t), 55.2 (q), 60.1 (d), 65.6 (d), 66.2 (t), 68.0 (d), 69.8 (d), 72.6 (t), 80.8 (s), 83.8 (s), 113.7 (d, 2C), 128.3 (d, 2C), 129.2 (d, 2C), 129.5 (d, 2C), 130.4 (s), 130.6 (s), 132.8 (d), 159.1 (s), 165.8 (s) ppm.

$[\alpha]_D$: +4.0 (*c* 2.2, $CHCl_3$).

(2*S*,6*S*)-1-(2-((*R*)-2-(*tert*-Butyldimethylsilyloxy)propyl)-1,3-dithian-2-yl)-8-(4-methoxybenzyloxy)-6-(methoxymethoxy)oct-4-yn-2-ol (329)

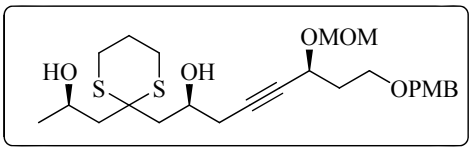


To a solution of alkyne **314** (1.5 g, 5.8 mmol) in anhydrous THF in a flame dried two neck round bottom flask under argon was added *n*-BuLi (3.75 mL, 6.0 mmol, 1.6 M in hexane) dropwise at –78 ^{o}C. After 15 min, $BF_3.Et_2O$ (0.730 mL, 5.9 mmol) was added slowly dropwise. Reaction mixture was allowed to stir for another 15 min at the same temperature after which a solution of epoxide **313** (1 g, 2.9 mmol) in THF was added. Reaction was quenched by adding a solution of THF-H_2O (1:1) when the TLC showed the complete consumption of the epoxide. The mixture was slowly warmed to rt and extracted into EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (25% ethyl acetate in petroleum ether) to furnish the title compound **329** (1.7 g, 95% yield) as a pale yellow oil.

Mol. Formula	: $C_{31}H_{52}O_6S_2Si$
$[\alpha]_D$	: –6.7 (*c* 1.2, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3426, 3017, 1613, 1514, 1216, 1034, 835, 758, 668 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 7.28–7.24 (m, 2H), 6.87 (br d, *J* = 8.7 Hz, 2H), 4.93 (d, *J* = 6.7 Hz, 1H), 4.58 (d, *J* = 6.7 Hz, 1H), 4.52 (d, *J* = 6.8 Hz, 1H), 4.44 (s, 2H), 4.28–4.13 (m, 2H), 3.8 (s, 3H), 3.62 (br t, *J* = 6.3 Hz, 2H), 3.49 (br s, 1H), 3.35 (s, 3H), 3.02-2.69 (m, 4H), 2.44–2.33 (m, 3H), 2.20–2.12 (m, 3H), 2.08–1.91 (m, 4H), 1.24 (d, *J* = 6.2 Hz, 3H), 0.88 (s, 9H), 0.1 (s, 3H), 0.09 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ –4.2 (q), –4.0 (q), 17.9 (s), 24.7 (t), 25.9 (q), 26.0 (q), 26.030 (t), 26.5 (t), 27.9 (t), 36.1 (t), 44.5 (t), 49.2 (t), 51.1 (s), 55.2 (d), 55.5 (d), 63.0 (d), 63.1 (d), 65.9 (d), 66.0 (t), 67.3 (d), 72.6 (t), 80.6 (s), 82.6 (s), 93.9 (t), 94.0 (s), 113.6 (d, 2C), 129.2 (d, 2C), 130.4 (s), 159.0 (s) ppm.
ESI-MS (*m/z*)	: 635.3 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 60.74; H, 8.55; S, 10.46.
Found: C, 60.71; H, 8.59; S, 10.48.

(2*S*,6*S*)-1-(2-((*R*)-2-(*tert*-Butyldimethylsilyloxy)propyl)-1,3-dithian-2-yl)-8-(4-methoxybenzyloxy)-6-(methoxymethoxy)oct-4-yn-2-ol (332)



TBAF (1 M solution in THF, 2 mL, 2 mmol) was added to a solution of **329** (1.0 g, 1.6 mmol) in THF (10 mL) at 0 °C and stirred for 3 h at rt. Reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (40% ethyl acetate in petroleum ether) to give diol **332** (730 mg, 90% yield) as a colorless oil.

Mol. Formula : $C_{25}H_{38}O_6S_2$

$[\alpha]_D$: –3.5 (*c* 1, $CHCl_3$).

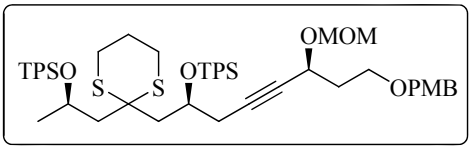
^{1}H NMR ($CDCl_3$, 400 MHz) : δ 7.24 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 4.91 (d, *J* = 6.8 Hz, 1H), 4.58 (dd, *J* = 3.8, 6.8 Hz, 1H), 4.53–4.49 (m, 1H), 4.42 (s, 2H), 4.25–4.20 (m, 1H), 4.16 (ddd, *J* = 3.8, 6.3, 13.0 Hz, 1H), 3.79 (s, 3H), 3.60 (t, *J* = 6.3 Hz, 2H), 3.34 (s, 3H), 3.16 (br s, 1H), 2.92–2.85 (m, 4H), 2.41 (dt, *J* = 6.3, 8.0 Hz, 2H), 2.28–2.21 (m, 3H), 2.07–1.93 (m, 5H), 1.18 (d, *J* = 6.3 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz) : δ 24.1 (q), 24.6 (t), 26.1 (t), 26.5 (t), 28.3 (t), 36.1 (t), 45.0 (t), 47.4 (t), 51.2 (s), 55.2 (q), 55.6 (q), 63.3 (d), 64.6 (d), 66.0 (t), 67.0 (d), 72.6 (t), 81.1 (s), 82.5 (s), 94.1 (t), 113.7 (d, 2C), 129.3 (d, 2C), 130.4 (s), 159.1 (s) ppm.

ESI-MS (*m/z*) : 521.3 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 60.21; H, 7.68; S, 12.86.
Found: C, 60.18; H, 7.74; S, 12.91.

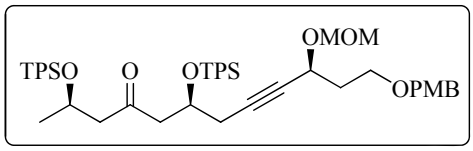
(5*S*,9*S*)-9-((2-((*R*)-2-(*tert*-Butyldiphenylsilyloxy)propyl)-1,3-dithian-2-yl)methyl)-5-(2-(4-methoxybenzyloxy)ethyl)-12,12-dimethyl-11,11-diphenyl-2,4,10-trioxa-11-silatridec-6-yne (333)



At 0 ^{o}C, A solution of diol **332** (700 mg, 1.4 mmol) and imidazole (290 mg, 4.2 mmol) in CH_2Cl_2 (15 mL) was treated with TBDPSCl (960 mg, 3.5 mmol) and DMAP (90 mg, 0.7 mmol). After 8 h stirring at rt, the reaction mixture was partitioned between water and CH_2Cl_2. The organic layer separated was washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography to procure **333** (990 mg, 73% yield) as pale yellow oil.

Mol. Formula	: $C_{57}H_{74}O_6S_2Si_2$
$[\alpha]_D$	: +8.9 (*c* 1.6, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 7.76–7.67 (m, 8H), 7.40–7.34 (m, 12H), 7.23 (d, *J* = 7.3 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 4.91 (dd, *J* = 2.3, 6.7 Hz, 1H), 4.55–4.46 (m, 2H), 4.40 (s, 2H), 4.25–4.16 (m, 2H), 3.79 (s, 3H), 3.60 (t, *J* = 6.3 Hz, 2H), 3.31 (s, 3H), 2.70–2.65 (m, 1H), 257–2.47 (m, 3H), 2.42–2.26 (m, 4H), 2.11–1.86 (m, 4H), 1.70–1.67 (m, 2H), 1.05 (s, 9H), 1.02 (s, 9H), 1.08 (d, *J* = 6.3 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ 19.2 (s), 19.3 (s), 24.7 (t), 25.8 (q), 26.1 (t), 26.3 (t), 27.0 (q, 6C), 28.4 (t), 36.3 (t), 46.4 (t), 50.2 (t), 50.7 (s), 55.3 (q), 55.6 (q), 63.0 (d), 66.3 (t), 67.7 (d), 69.3 (d), 72.7 (t), 80.8 (s), 83.2 (s), 93.9 (t), 113.7 (d, 2C), 127.3 (d, 2C), 127.4 (d, 2C), 127.5 (d, 2C), 127.6 (d, 2C), 129.2 (d, 2C), 129.3 (d), 129.4 (d), 129.6 (d), 129.7 (d), 130.5 (s), 133.6 (s), 134.3 (s), 134.8 (s), 135.0 (s), 135.9 (d, 2C), 136.0 (3d, 6C), 159.1 (s) ppm.
ESI-MS (*m/z*)	: 997.5 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 70.18; H, 7.65; S, 6.57. Found: C, 70.13; H, 7.69; S, 6.61.

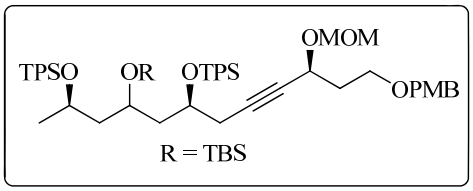
(5*S*,9*S*,13*R*)-9-(*tert*-Butyldiphenylsilyloxy)-5-(2-(4-methoxybenzyloxy)ethyl)-13,16,16-trimethyl-15,15-diphenyl-2,4,14-trioxa-15-silaheptadec-6-yn-11-one (334)



At 0 ^{o}C, a solution of dithioketal **333** (950 mg, 1.0 mmol) in CH_3CN-buffer (4:1, 20 mL) was treated with $PhI(CF_3COO)_2$ (520 mg, 1.2 mmol) and stirred for 15 min. A satd. solution of $NaHCO_3$ was added to the reaction mixture and extracted with ethyl acetate (2 x 10 mL). Combined organic fractions were washed with brine, dried over Na_2SO_4 and concentrated. The crude was purified by column chromatography (10% ethyl acetate in petroleum ether) to furnish ketone **334** (700 mg, 79% yield) as pale yellow oil.

Mol. Formula	: $C_{54}H_{68}O_7Si_2$
$[\alpha]_D$	: +7.5 (*c* 0.6, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3449, 3018, 1734, 1490, 1376, 1216, 875, 755, 667 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 7.68–7.60 (m, 8H), 7.42–7.31 (m, 12H), 7.24 (d, *J* = 7.5 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.89 (dd, *J* = 4.2, 6.7 Hz, 1H), 4.55–4.46 (m, 2H), 4.41 (s, 2H), 4.26–4.15 (m, 2H), 3.79 (s, 3H), 3.69–3.56 (m, 2H), 3.32 (s, 3H), 2.73–2.37 (m, 4H), 2.33–2.27 (m, 2H), 2.04–1.93 (m, 2H), 1.01 (s, 9H), 1.10 (s, 9H), 0.98 (d, *J* = 6.3 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ 19.1 (s), 19.2 (s), 23.5 (q), 26.8 (q, 3C), 26.9 (q, 3C), 26.9 (t), 36.3 (t), 49.7 (t), 53.2 (t), 55.2 (q), 55.5 (q), 63.0 (d), 66.0 (d), 66.1 (t), 67.5 (d), 72.7 (t), 80.9 (s), 82.2 (s), 93.9 (t), 113.7 (d, 2C), 127.5 (d, 2C), 127.6 (d, 4C), 127.7 (d, 2C), 129.2 (d, 2C), 129.5 (d), 129.6 (d), 129.7 (d), 129.8 (d), 130.4 (s), 133.3 (s), 133.7 (s), 133.8 (s), 134.3 (s), 135.7 (d, 8C), 159.1 (s), 206.8 (s) ppm.
ESI-MS (*m/z*)	: 907.5 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 73.26; H, 7.74. Found: C, 73.21; H, 7.78.

(5*S*,9*S*,13*R*)-11-(*tert*-Butyldimethylsilyloxy)-9-(*tert*-butyldiphenylsilyloxy)-5-(2-(4-methoxybenzyloxy)ethyl)-13,16,16-trimethyl-15,15-diphenyl-2,4,14-trioxa-15-silaheptadec-6-yne (338)



A solution of ketone **334** (300 mg, 0.34 mmol) in MeOH was cooled to –100 ^{o}C and was added $CeCl_3.7H_2O$ (76 mg, 0.20 mmol) under argon. After 5 min, $NaBH_4$ (26 mg, 0.68 mol) was added to the reaction mixture and stirred for 3 h at the same temperature. The reaction mixture was quenched with satd. NH_4Cl solution and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The residue obtained was subsequently purified by flash chromatography (15% EtOAc in petroleum ether) to afford **336** (215 mg, 71% yield, over two steps) as a clear oil.

At 0 °C, a solution of **336** (200 mg, 0.22 mmol) in CH_2Cl_2 was treated with TBSOTf (90 mg, 0.33 mmol) followed by 2,6-lutidine (80 μL, 0.7 mmol). After 1 h, satd. NH_4Cl solution was added to the reaction mixture and extracted with CH_2Cl_2. The combined organic fractions were successively washed with water, brine and dried over Na_2SO_4. The residue obtained after the evaporation of the solvent was purified by chromatography (7% ethyl acetate in petroleum ether) to afford **338** (190 mg, 86% yield) as a colorless oil.

Mol. Formula : $C_{60}H_{84}O_7Si_3$

$[\alpha]_D$: +14.5 (*c* 3.2, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) : δ 7.70–7.62 (m, 8H), 7.39–7.32 (m, 12H), 7.25 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 4.93–4.88 (m, 1H), 4.54–4.47 (m, 2H), 4.41 (s, 2H), 3.97–3.89 (m, 1H), 3.87–3.83 (m, 2H), 3.79 (s, 3H), 3.62–3.56 (m, 2H), 3.32 (s, 3H), 2.33–2.17 (m, 2H), 2.03–1.94 (m, 2H), 1.77 (dt, *J* = 6.0, 13.8 Hz, 1H), 1.67 (dt, *J* = 6.3, 13.3 Hz, 1H), 1.46–1.34 (m, 2H), 1.04–1.01 (m, 18H), 0.96, 0.93 (2d, *J* = 6.0 Hz, 3H), 0.77, 0.73 (2d, 9H), –0.04, –0.07 (2s, 3H), –0.08, –0.10 (2s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz) : –4.6, –4.2, –4.0 (3q, 2C), 17.8, 17.9 (2s, 1C), 19.1, 19.2 (2s, 1C), 19.2, 19.3 (2s, 1C), 23.2, 24.0 (2q, 1C), 25.8,

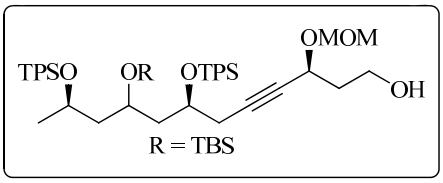
25.9 (2q, 3C), 26.99 (q, 3C), 27.0 (q, 3C), 27.37, 27.43 (2t, 1C), 36.3 (t), 44.4, 44.7 (2t, 1C), 47.0, 48.3 (2t, 1C), 55.2 (q), 55.5 (q), 63.01, 63.04 (2d, 1C), 66.29, 66.33 (2t, 1C), 66.97, 67.03 (2d, 1C), 67.3, 67.5 (2d, 1C), 68.9, 69.6 (2d, 1C), 72.7 (t), 80.5 (s), 82.9 (s), 93.9 (t), 113.7 (d, 2C), 127.37, 127.41, 127.49, 127.53, 127.60, 127.65 (6d, 8C), 129.2 (d, 2C), 129.3 (d), 129.4 (d), 129.5 (d), 129.6 (d), 129.7 (d), 130.6 (s), 133.7 (s), 134.1 (s) 134.4 (s), 134.8 (d), 134.9, 135.0 (2s, 1C), 135.78, 135.86, 135.89 (3d, 6C), 159.1 (s) ppm.

ESI-MS (*m/z*) : 1023.6 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 71.95; H, 8.45.

Found: C, 71.91; H, 8.49.

(3*S*,7*S*,11*R*)-9-(*tert*-Butyldimethylsilyloxy)-7,11-bis(*tert*-Butyldiphenylsilyloxy)-3-(methoxymethoxy)dodec-4-yn-1-ol (339)



To a solution of **338** (150 mg, 0.15 mmol) in CH_2Cl_2:H_2O (18:1, 10 mL), DDQ (45 mg, 0.2 mmol) was added at 0 °C and the mixture was vigorously stirred for 30 min. The reaction was quenched with satd. $NaHCO_3$ solution and stirred for another 10 min. The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The crude was purified by column chromatography (20% ethyl acetate in petroleum ether) to afford **339** (122 mg, 92% yield) as pale yellow oil.

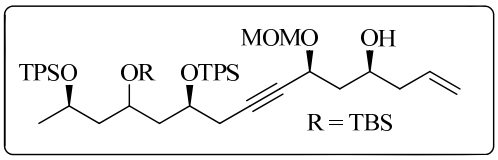
Mol. Formula : $C_{52}H_{76}O_6Si_3$

$[\alpha]_D$: +8.4 (*c* 3.5, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) : δ 7.66–7.62 (m, 8H), 7.40–7.33 (m, 12H), 4.93 (ddd, *J* = 1.9, 3.9, 6.6 Hz, 1H), 4.55–4.50 (m, 2H), 3.93–3.56 (m, 5H), 3.37 (s, 3H), 2.27–2.23 (m, 2H), 1.93–1.90 (m, 2H), 1.78–1.60 (m, 2H), 1.44–1.34 (m, 2H), 1.04, 1.03, 1.02, 1.01 (4s, 18H), 0.95 (d, *J* = 6.2 Hz, 3H), 0.77, 0.73 (2d, 9H), –0.04, –0.07 (2s, 3H), –0.08, –0.10 (2s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz)	: δ –4.6, –4.3, –4.1 (3q, 2C), 17.8, 17.9 (2s, 1C), 19.1, 19.2 (2s, 1C), 19.2, 19.3 (2s, 1C), 23.2, 23.9 (2q, 1C), 25.8, 25.8 (2q, 3C), 26.9 (q, 3C), 27.0 (q, 3C), 27.3, 27.4 (2t, 1C), 38.1 (t), 44.3, 44.7 (2t, 1C), 46.9, 48.3 (2t, 1C), 55.7 (q), 60.0 (t), 64.7 (d), 66.9, 67.0 (2d, 1C), 67.3, 67.5 (2d, 1C), 68.8, 69.5 (2d, 1C), 79.6, 79.8 (2s, 1C), 83.7, 83.7 (2s, 1C), 93.8 (t), 127.3 (d), 127.4 (d), 127.5 (d, 2C), 127.52 (d, 2C), 127.6 (d), 127.7 (d), 129.3, 129.4, 129.45, 129.5, 129.6, 129.7, 129.72 (7d, 8C), 133.6, 133.8, 134.1, 134.4, 134.8, 134.9 (6s, 4C), 135.8 (d), 135.9 (d, 3C) ppm.
ESI-MS (*m/z*)	: 903.5 $(M+Na)^+$.
Elemental Analysis	Calcd.: C, 70.86; H, 8.69.
	Found: C, 70.71; H, 8.86

(4*S*,6*S*,10*S*,14*R*)-12-(*tert*-Butyldimethylsilyloxy)-10,14-bis(*tert*-Butyldiphenylsilyloxy)-6-(methoxymethoxy)pentadec-1-en-7-yn-4-ol (340a)



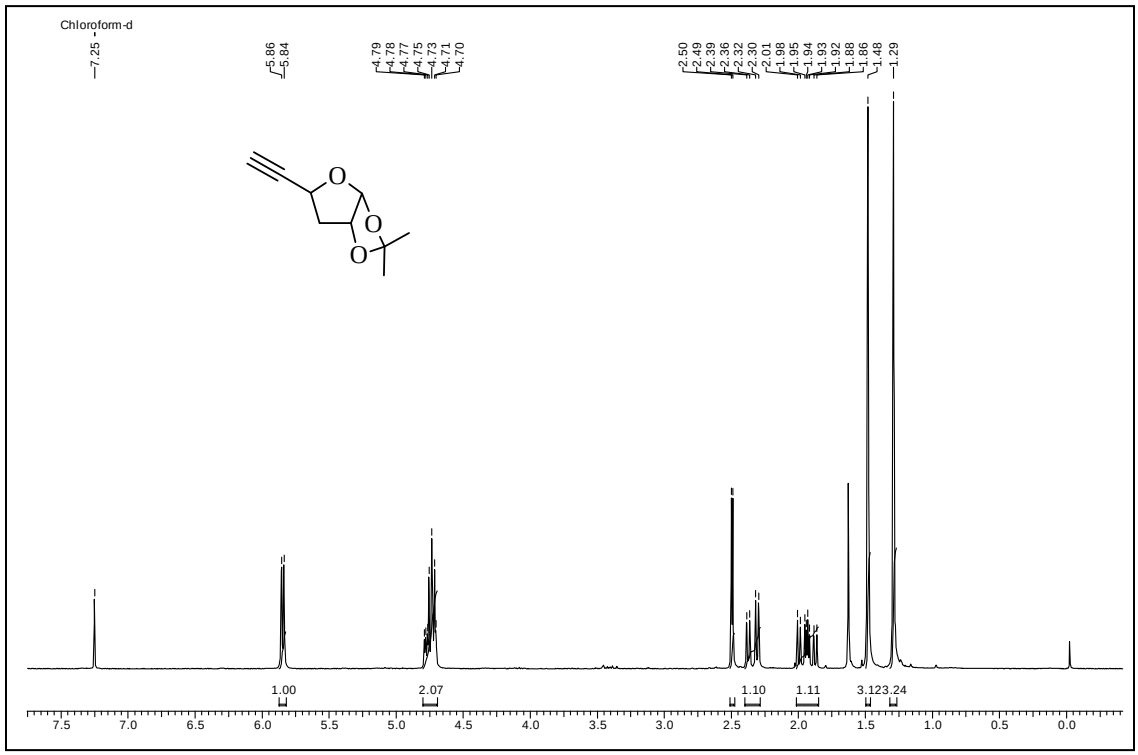
A solution of alcohol **339** (100 mg, 0.11 mmol) in CH_2Cl_2 was exposed to Dess-Martin reagent (DMP) (96 mg, 0.23 mmol) for 3 h. The reaction mixture was concentrated under reduced pressure and filtered through a short pad of silica gel column (5% ethyl acetate in petroleum ether) to give the aldehyde (93 mg, 96% yield) as pale yellow oil which was subsequently subjected to the allylation reaction.

To a stirred suspension of Zn (24 mg, 0.37 mmol) in THF (5 mL) was added allylbromide (27 μL, 0.31 mmol) at 0 °C under Argon. The reaction mixture was allowed to stir for 30 min at rt. A solution of aldehyde (90 mg, 0.105 mmol) in THF (2 mL) was then added to the reaction mixture at 0 °C. After 1 h stirring at rt, a satd. NH_4Cl solution (1 mL) was added dropwise to the reaction mixture and stirring continued for additional 3 h. The biphasic mixture was diluted with ethyl acetate and the organic layer separated was dried over $NaSO_4$ and concentrated. The residue was purified by column chromatography (7.5% ethyl acetate in petroleum ether) to secure **340** (80 mg, 83% yield) as a colorless oil.

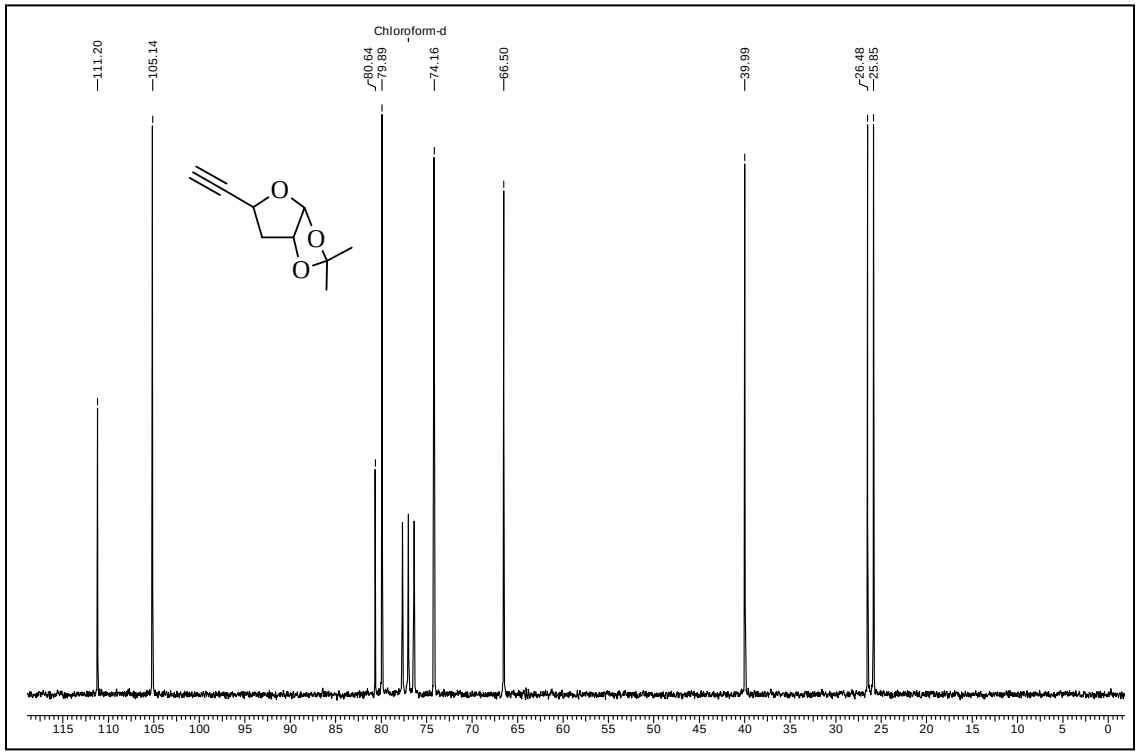
Oxidation of **340** using Dess-Martin reagent following the same procedure discussed above produced the corresponding aldehyde **341** in almost quantitative yield. To a solution of **341** in 5 mL of THF at –100 °C, L-Selectride (200 μL of 1 M solution in THF, 0.2 mmol) was added slowly dropwise, under an argon atmosphere. The reaction mixture was stirred for 3 h, quenched with water (5 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4. The residue obtained after evaporation of solvent was purified by flash column chromatography (20% ethyl acetate in petroleum ether) to provide the title compound **340a** (67 mg, 85% yield) as a colorless oil.

Mol. Formula	: $C_{55}H_{80}O_6Si_3$
$[\alpha]_D$	: +4.3 (*c* 1.6, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3460, 3078, 2929, 1641, 1472, 1255, 1090, 777 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 7.68–7.61 (m, 8H), 7.41–7.31 (m, 12H), 5.86–5.75 (m, 1H), 5.13–5.08 (m, 2H), 4.97–4.87 (m, 1H), 4.61–4.50 (m, 2H), 4.07–3.55 (m, 4H), 3.36 (s, 3H), 2.29–2.23 (m, 4H), 1.87–1.62 (m, 4H), 1.43–1.33 (m, 2H), 1.03, 1.02, 1.01, 1.00 (4s, 18H), 0.95 (d, *J* = 6.0 Hz, 3H), 0.76, 0.72 (2d, 9H), –0.06, –0.08 (2s, 3H), –0.10, –0.11 (2s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ –4.6, –4.3, –4.1 (3q, 2C), 17.8, 17.9 (2d, 1C), 19.1, 19.2 (2d, 1C), 19.24, 19.27 (2d, 1C), 24.0 (q), 25.77, 25.84 (29, 3C), 26.9, 27.0 (2q, 6C), 27.3, 27.4 (2t, 1C), 41.7, 41.9 (2t, 1C), 42.0, 42.3 (2t, 1C), 44.3, 44.7 (2t, 1C), 46.9, 48.3 (2t, 1C), 55.8 (q), 63.9 (d), 65.2 (d), 67.2 (d), 67.4 (d), 69.5 (d), 79.7 (s), 83.7 (s), 93.7 (t), 117.8 (t), 127.4, 127.4, 127.5, 127.6, 127.6 (d, 8C), 129.37, 129.43, 129.46, 129.53, 129.65, 129.72 (6d, 6C), 133.9, 134.1, 134.2, 134.4 (4s, 2C), 134.5 (d), 134.6, 134.7, 134.87, 134.94 (4s, 2C), 135.8 (d), 135.9 (d, 5C) ppm.
ESI-MS (*m/z*)	: 946.6 $(M+Na)^+$.
Elemental Analysis	Calcd.: C, 71.69; H, 8.75. Found: C, 71.66; H, 8.71.

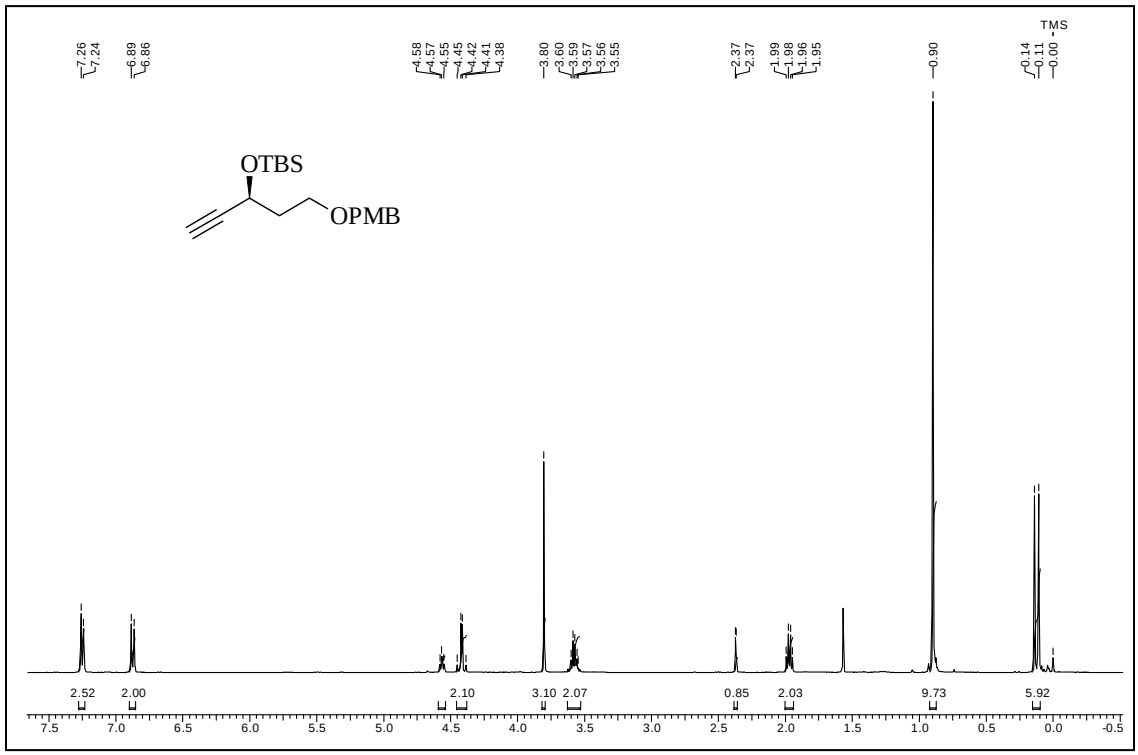
SPECTRA



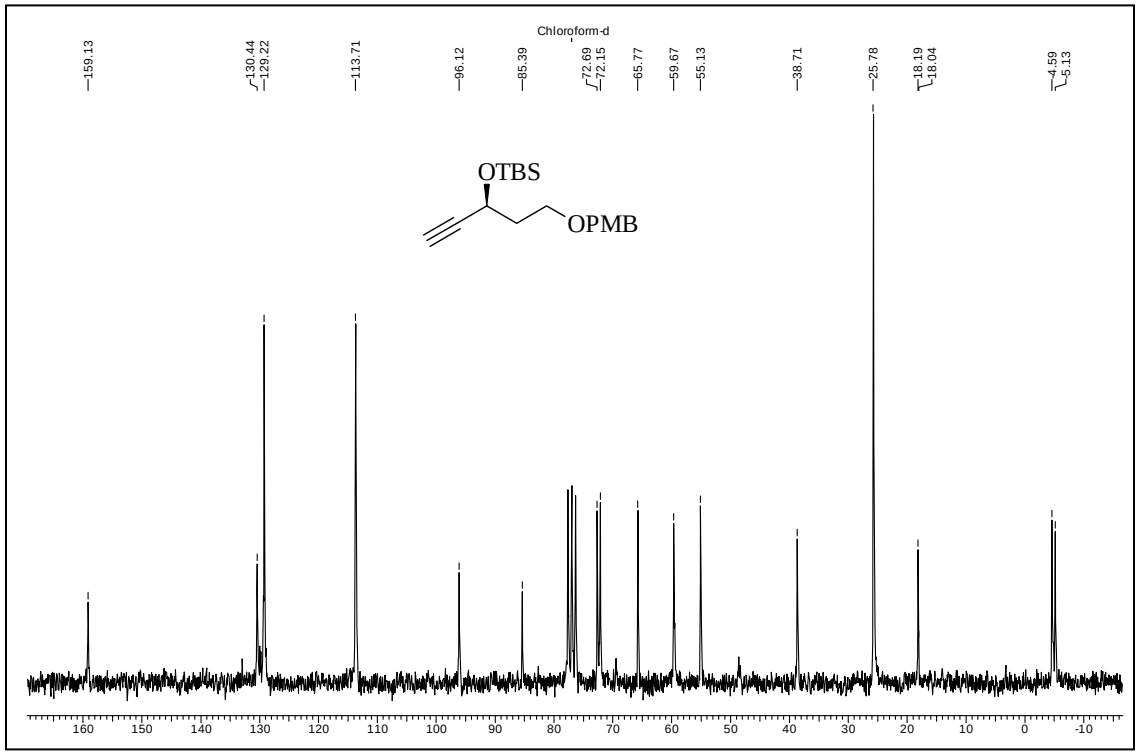
^{1}H NMR Spectrum of 314 in $CDCl_3$



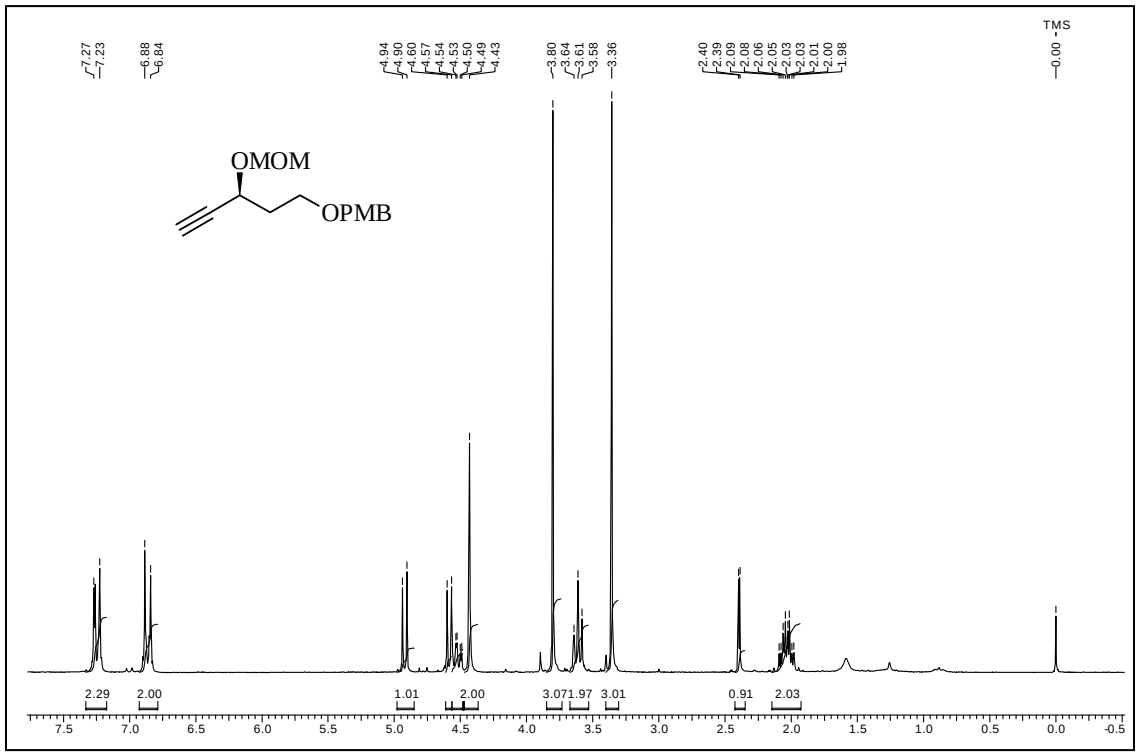
^{13}C NMR Spectrum of 314 in $CDCl_3$



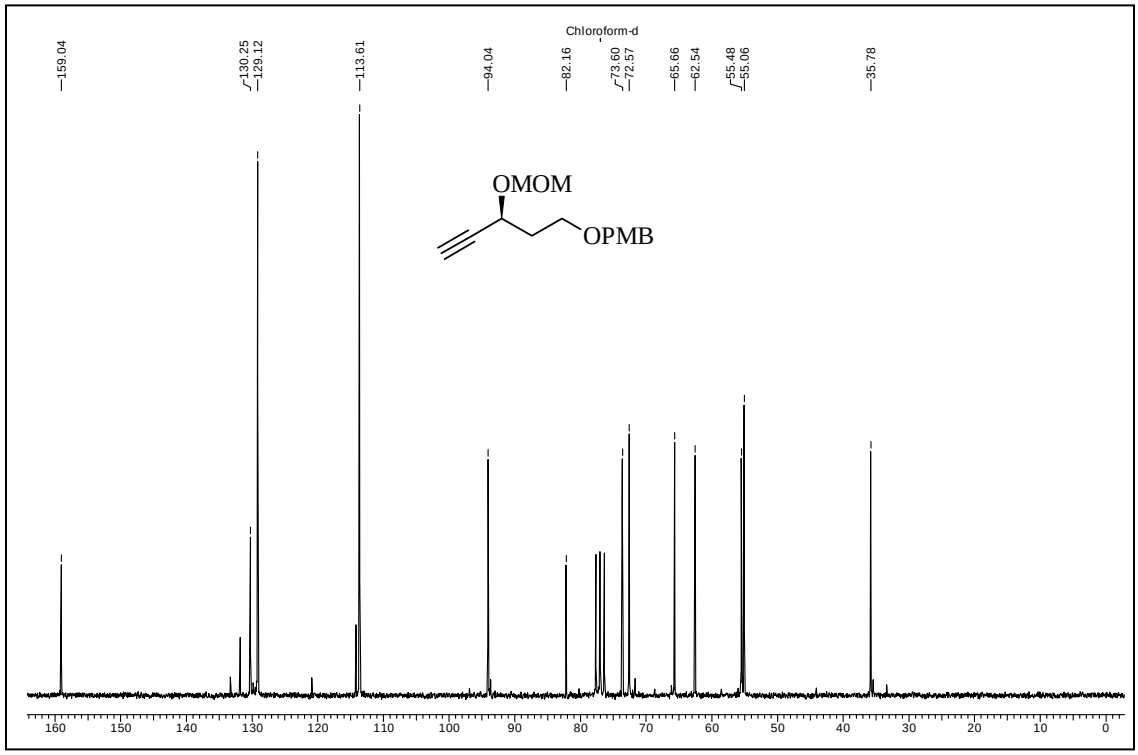
^{1}H NMR Spectrum of 318 in $CDCl_3$



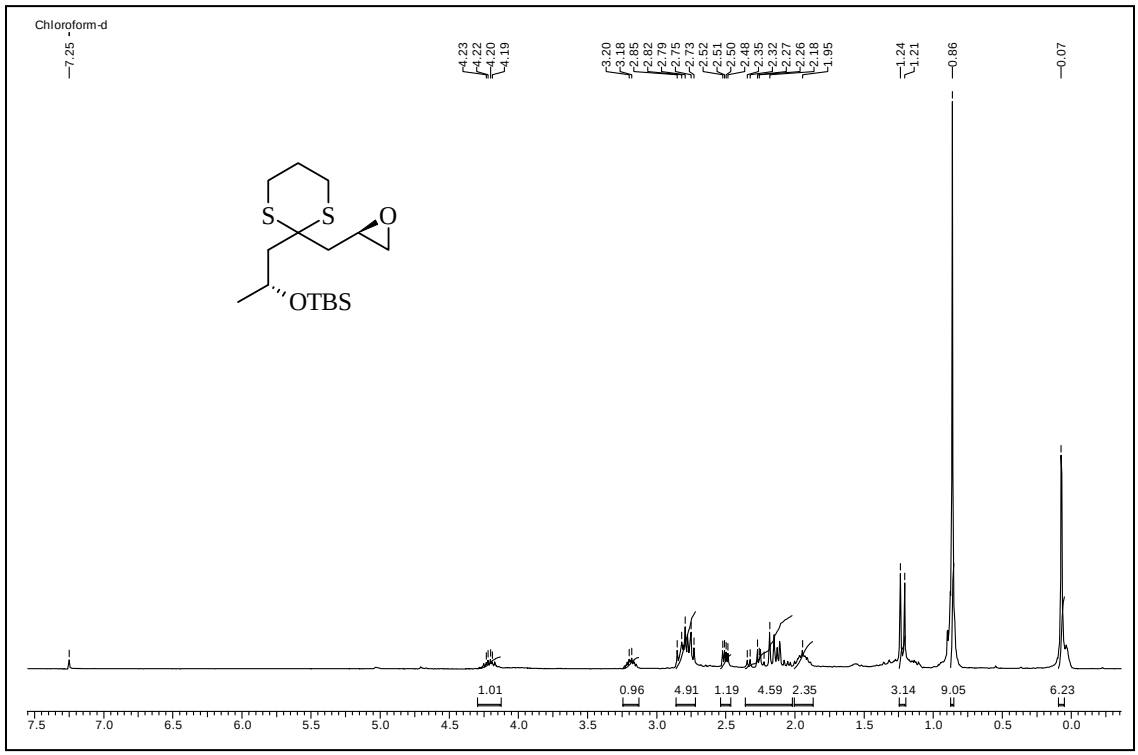
^{13}C NMR Spectrum of 318 in $CDCl_3$



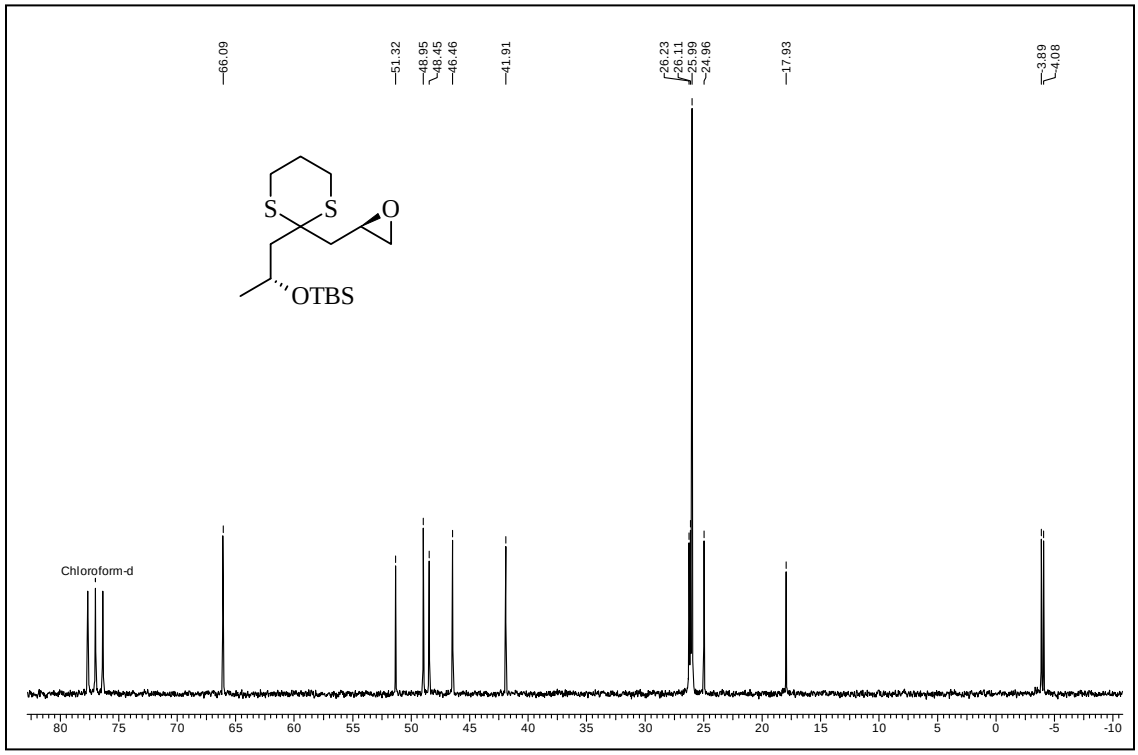
^{1}H NMR Spectrum of 319 in Acetone-d6



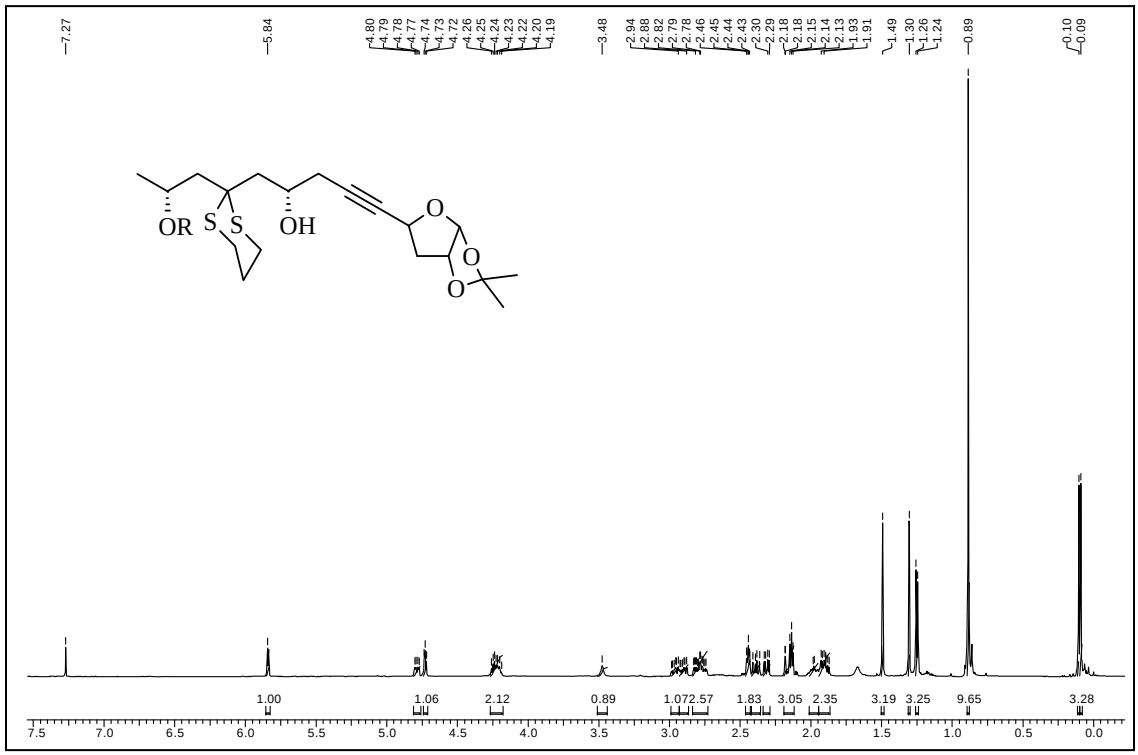
^{13}C NMR Spectrum of 319 in Acetone-d6



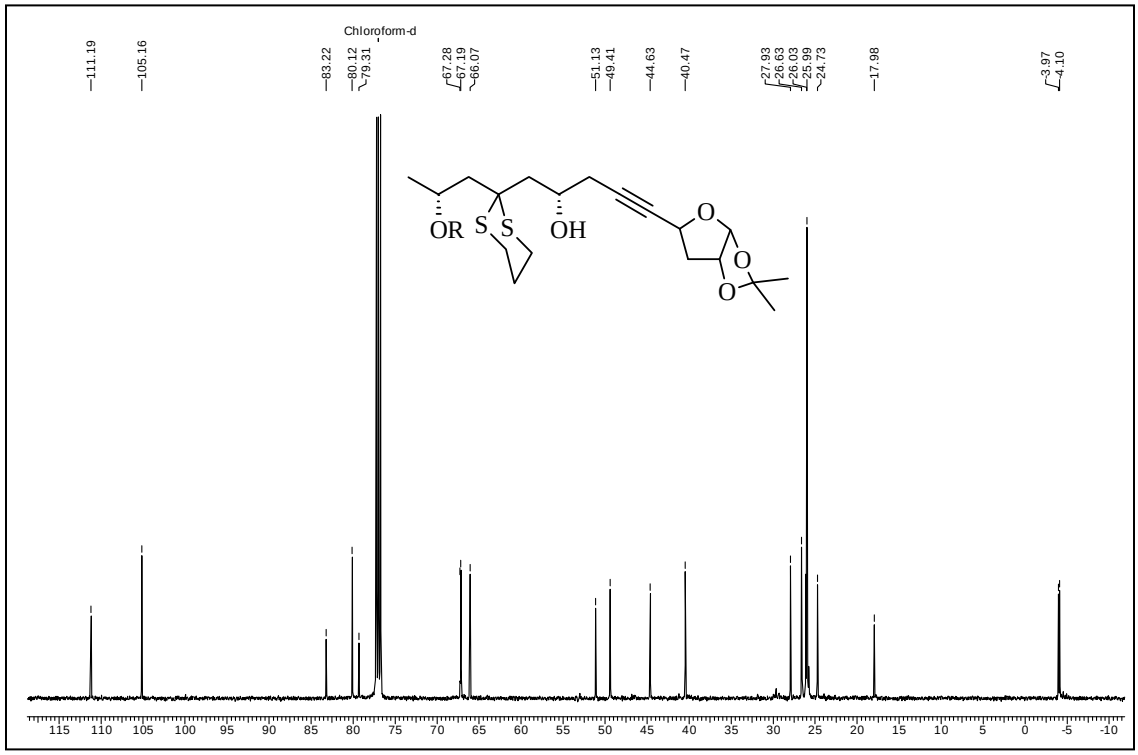
^{1}H NMR Spectrum of 313 in $CDCl_3$



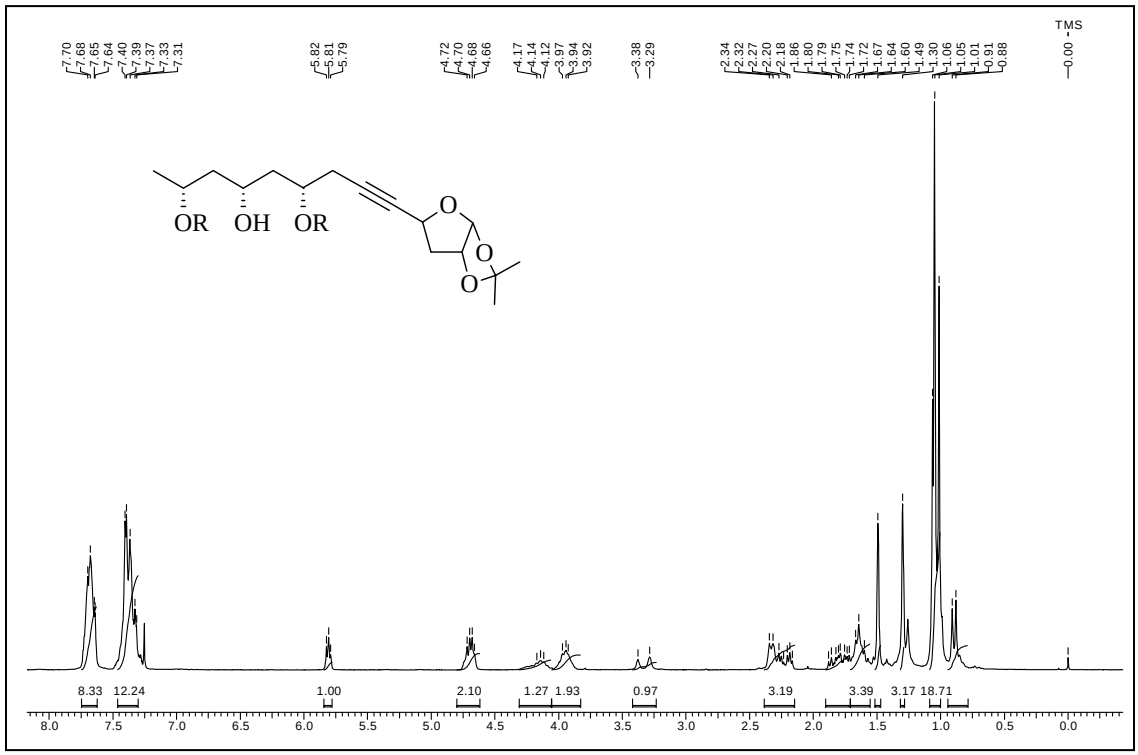
^{13}C NMR Spectrum of 313 in $CDCl_3$



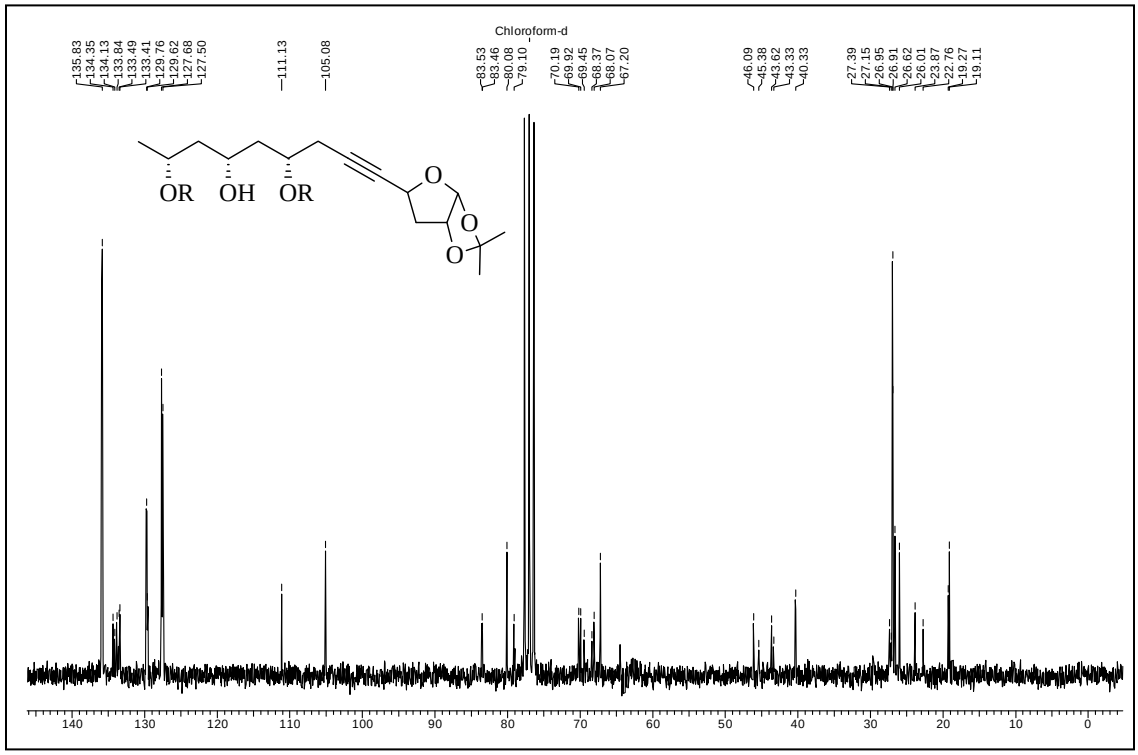
^{1}H NMR Spectrum of 320 in $CDCl_3$ (R = TBS)



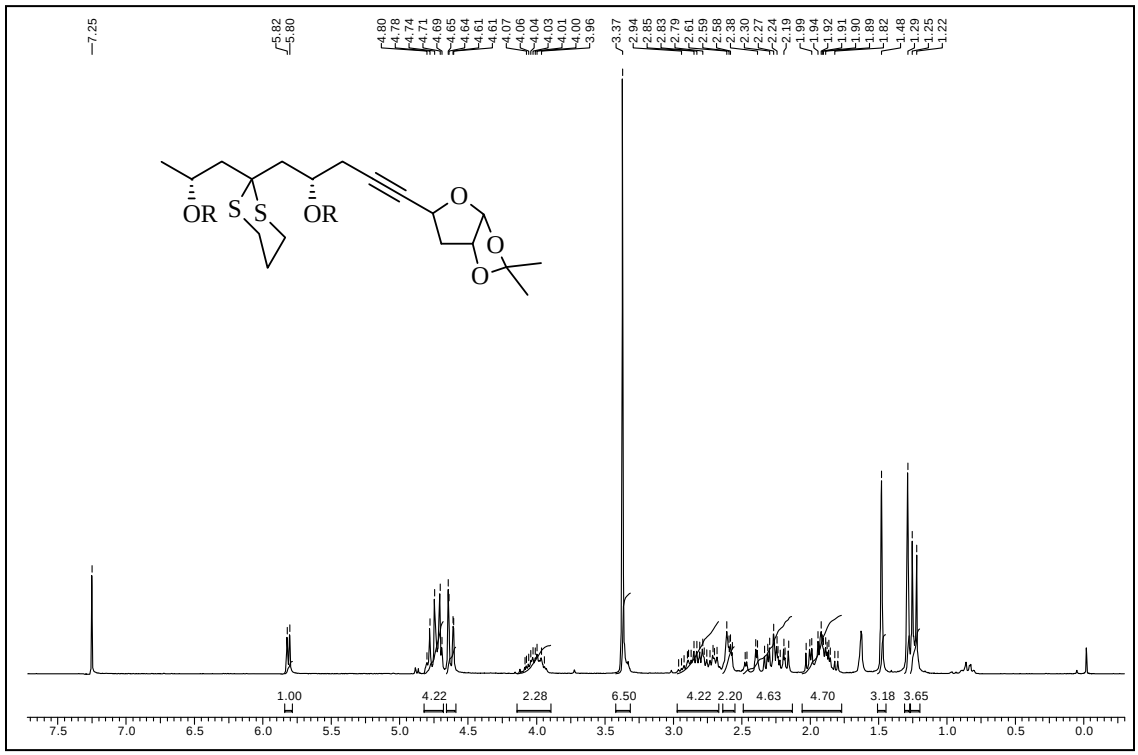
^{13}C NMR Spectrum of 320 in $CDCl_3$ (R = TBS)



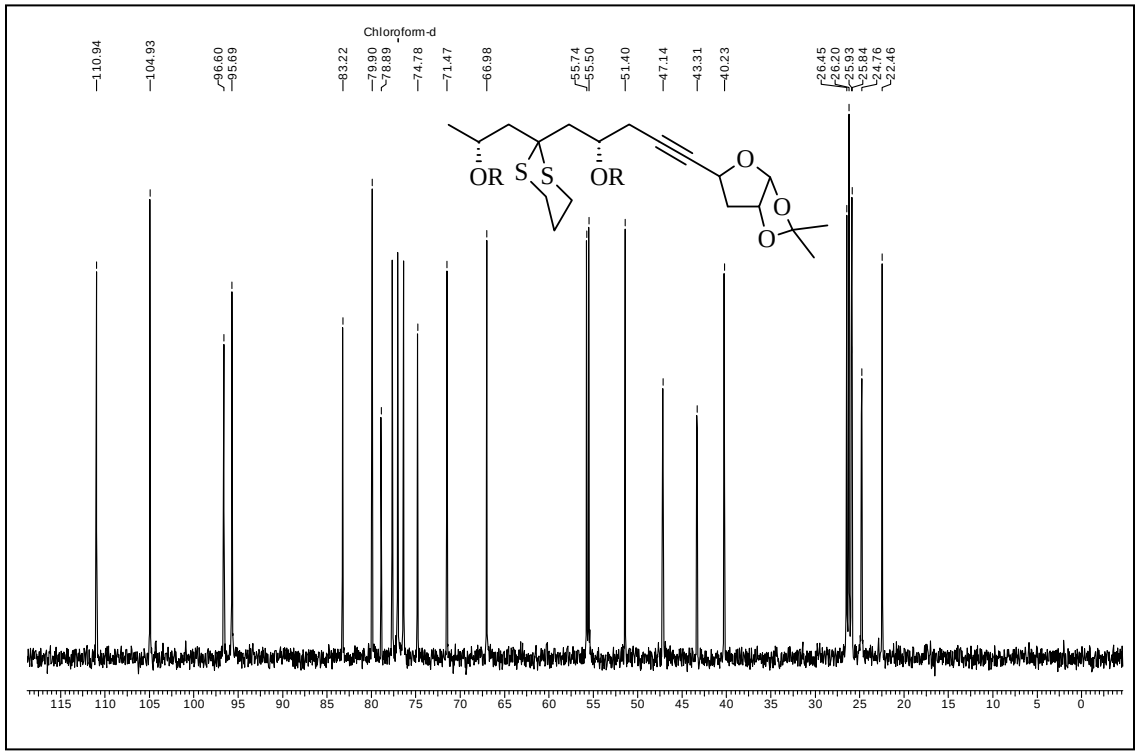
^{1}H NMR Spectrum of 324 in $CDCl_3$ (R = TBDPS)



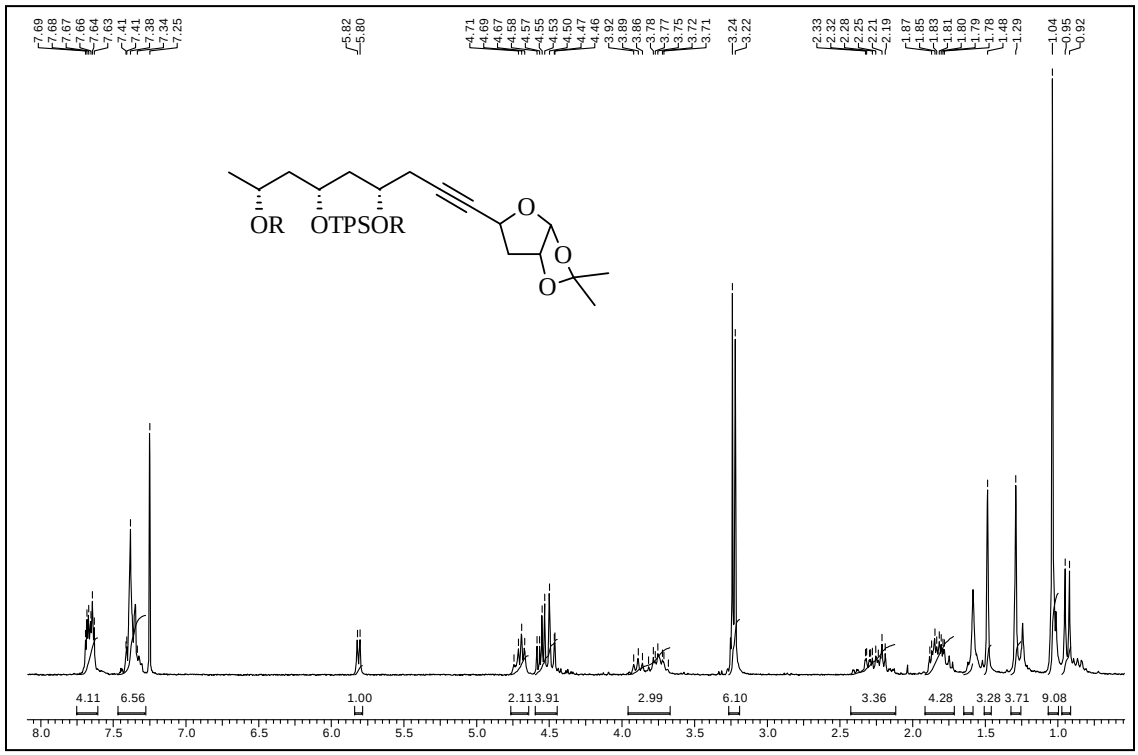
^{13}C NMR Spectrum of 324 in $CDCl_3$ (R = TBDPS)



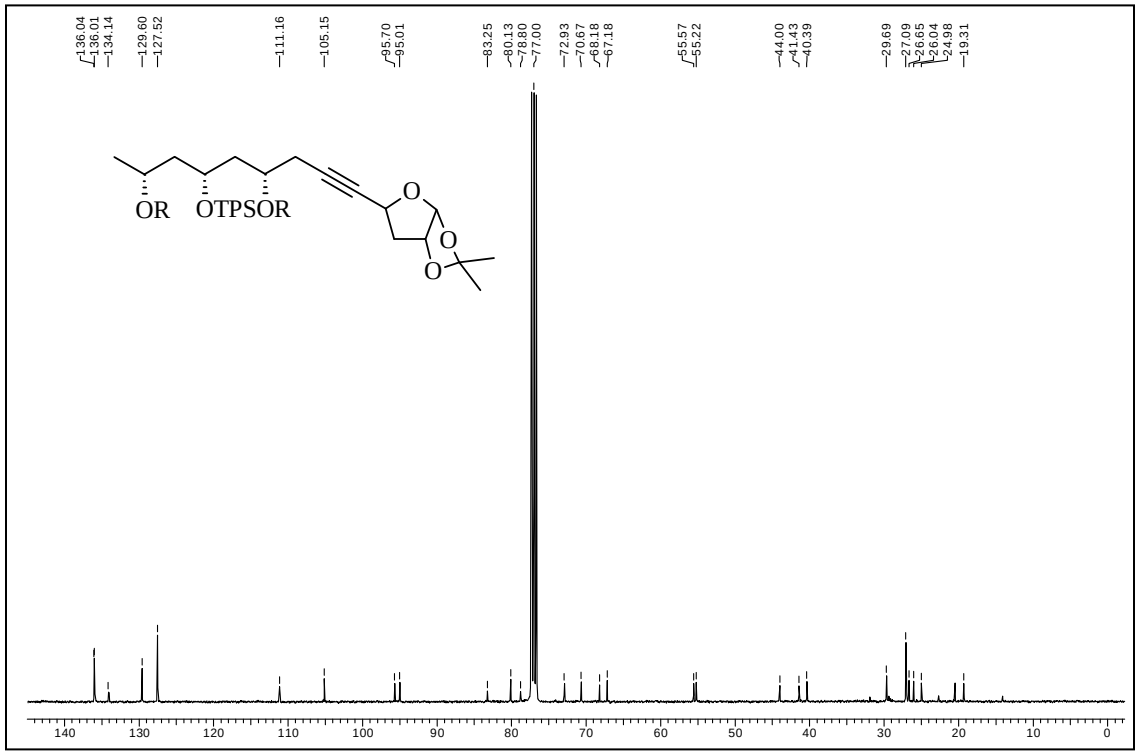
^{1}H NMR Spectrum of 325 in $CDCl_3$ (R = MOM)



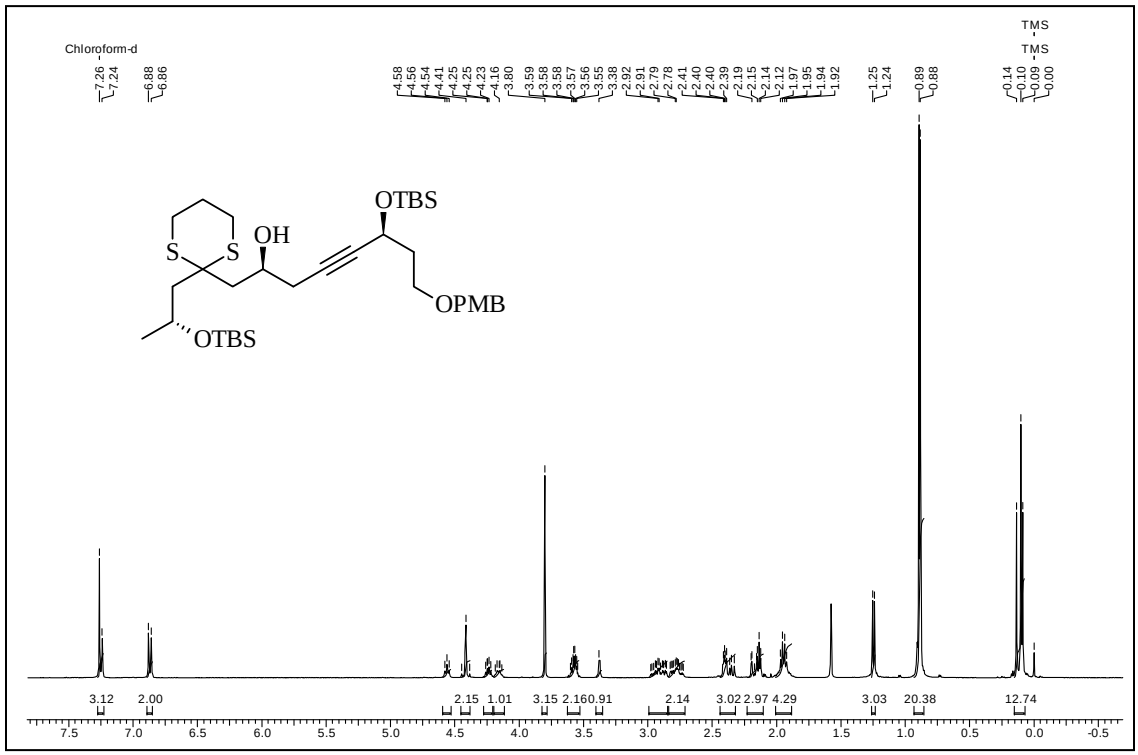
^{13}C NMR Spectrum of 325 in $CDCl_3$ (R = MOM)



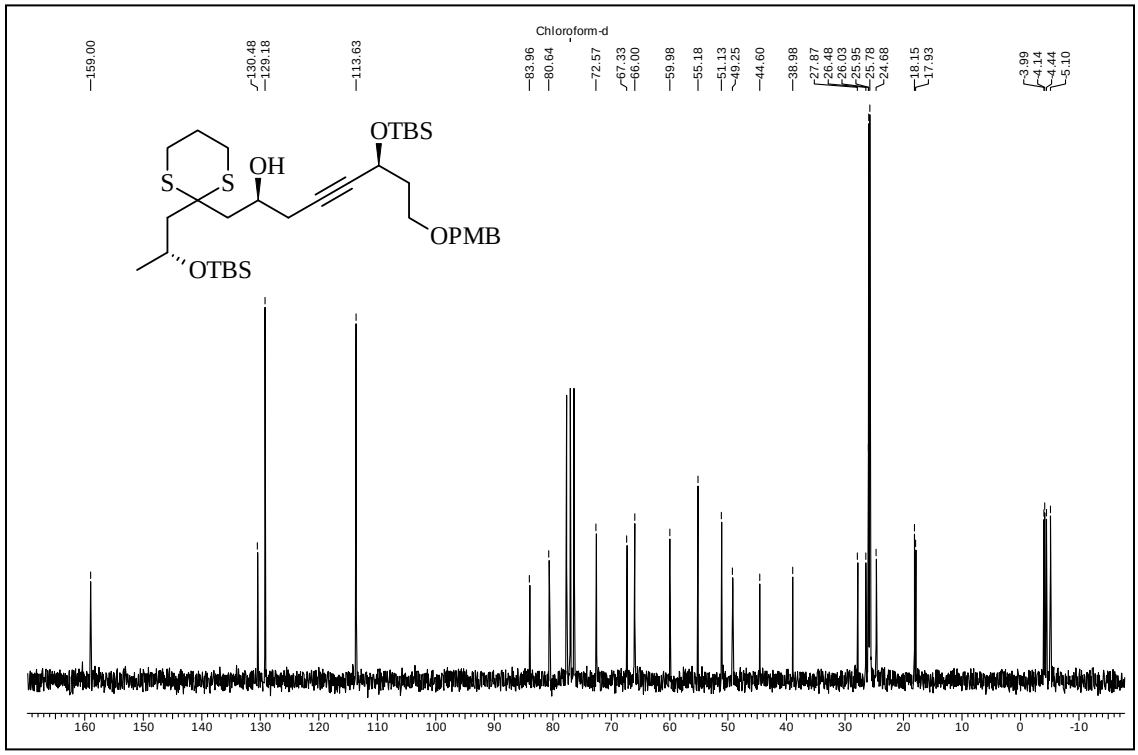
^{1}H NMR Spectrum of 327 in $CDCl_3$ (R = MOM)



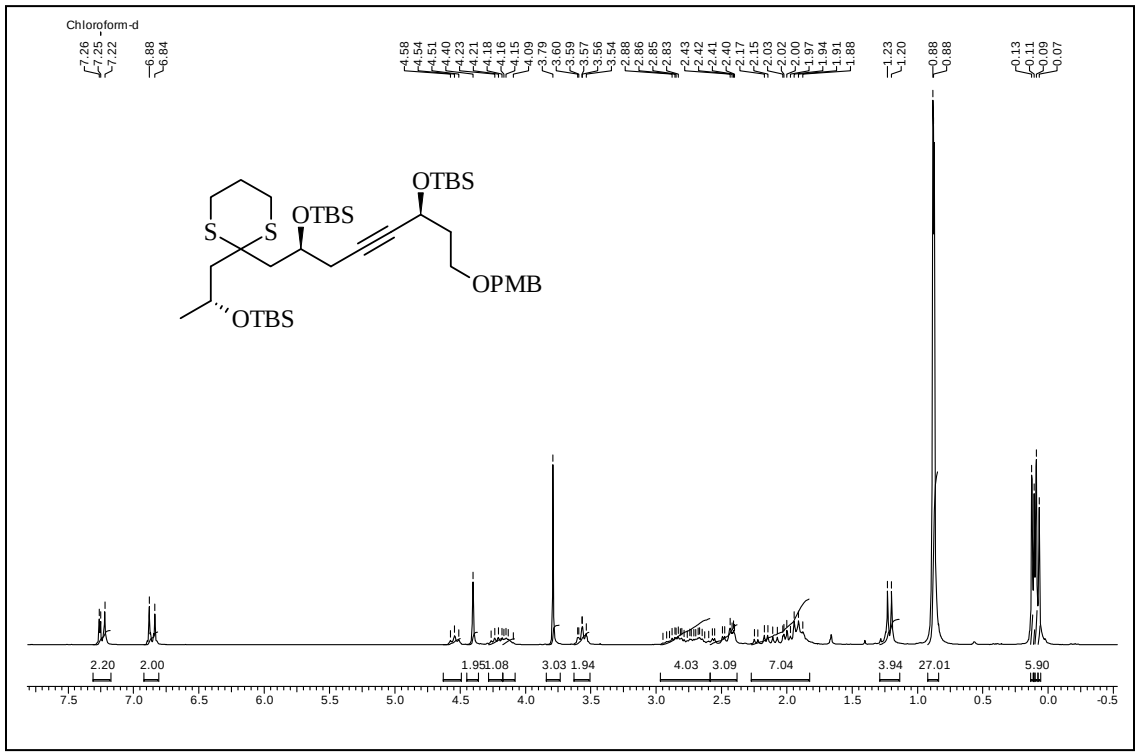
^{13}C NMR Spectrum of 327 in $CDCl_3$ (R = MOM)



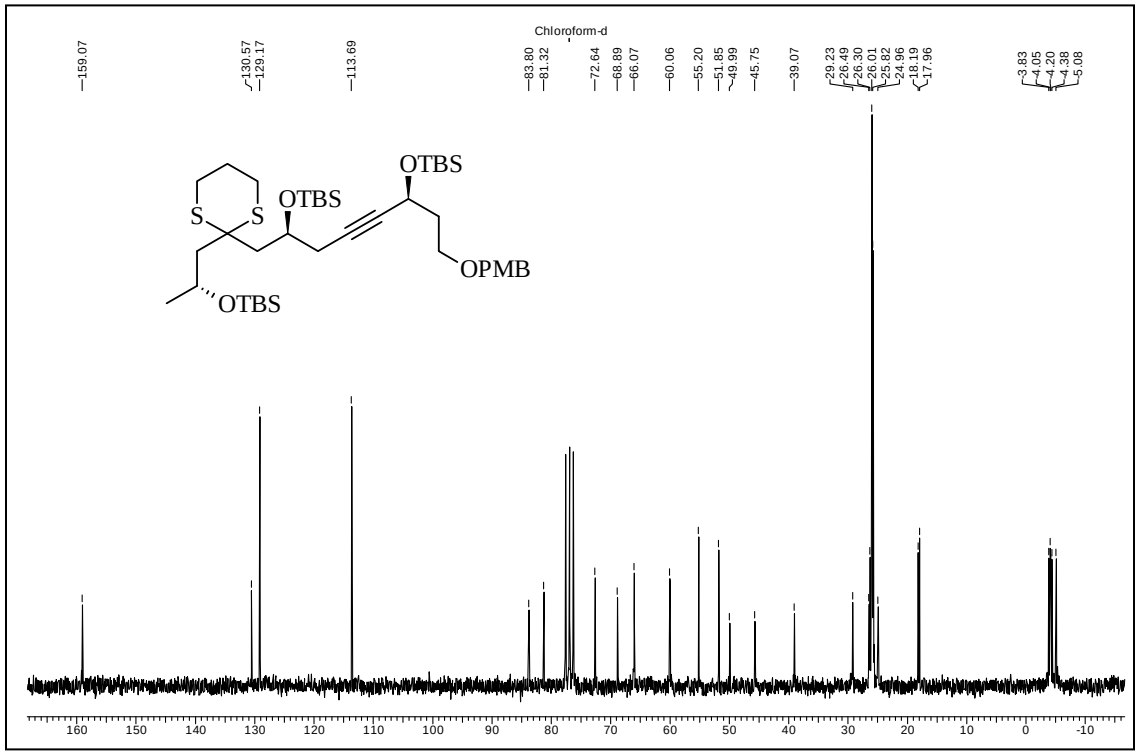
^{1}H NMR Spectrum of 328 in $CDCl_3$



^{13}C NMR Spectrum of 328 in $CDCl_3$



^{1}H NMR Spectrum of 330 in $CDCl_3$



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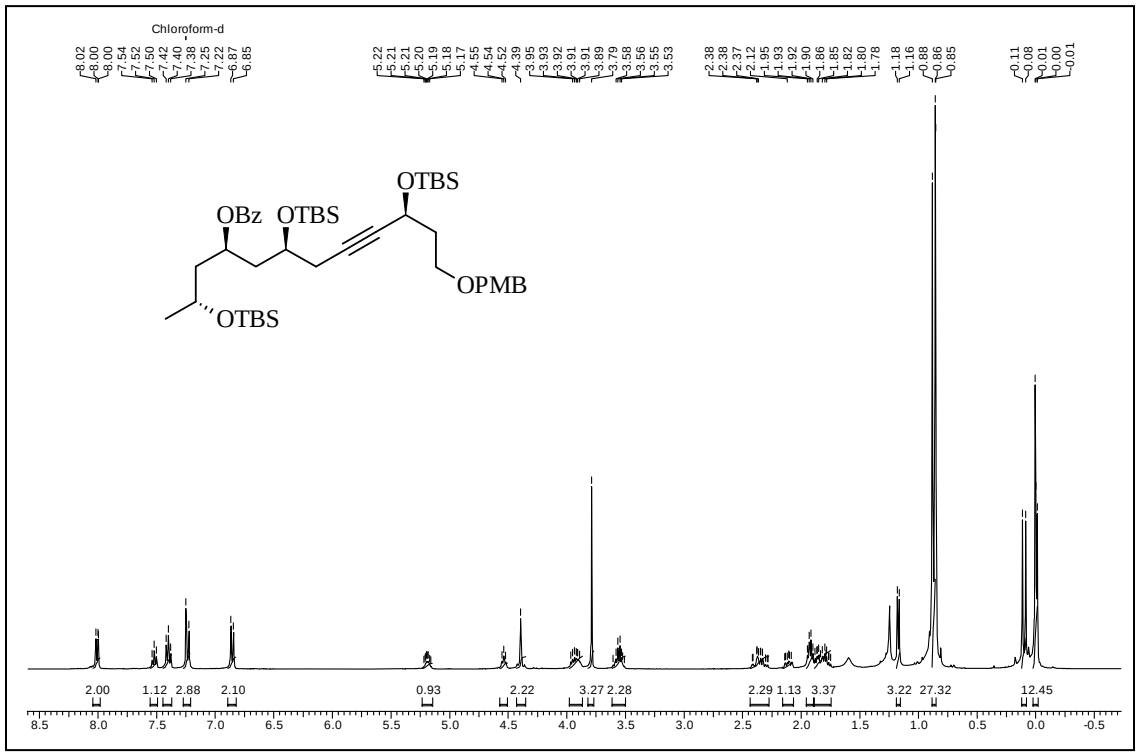
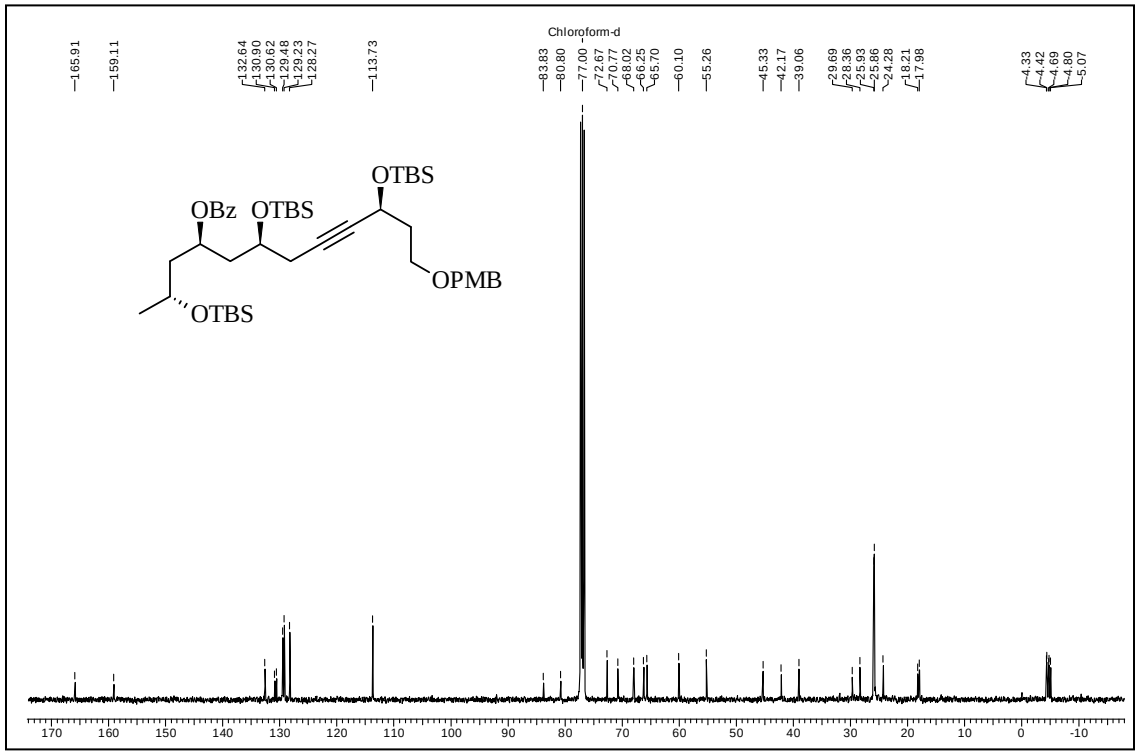
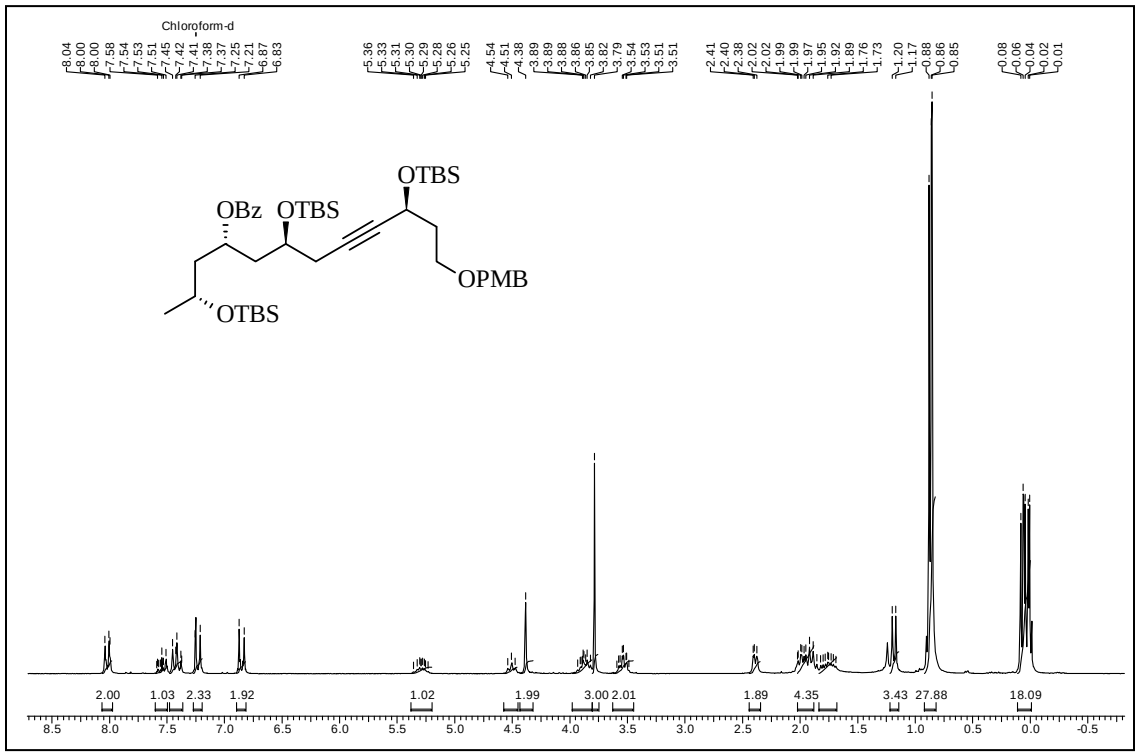


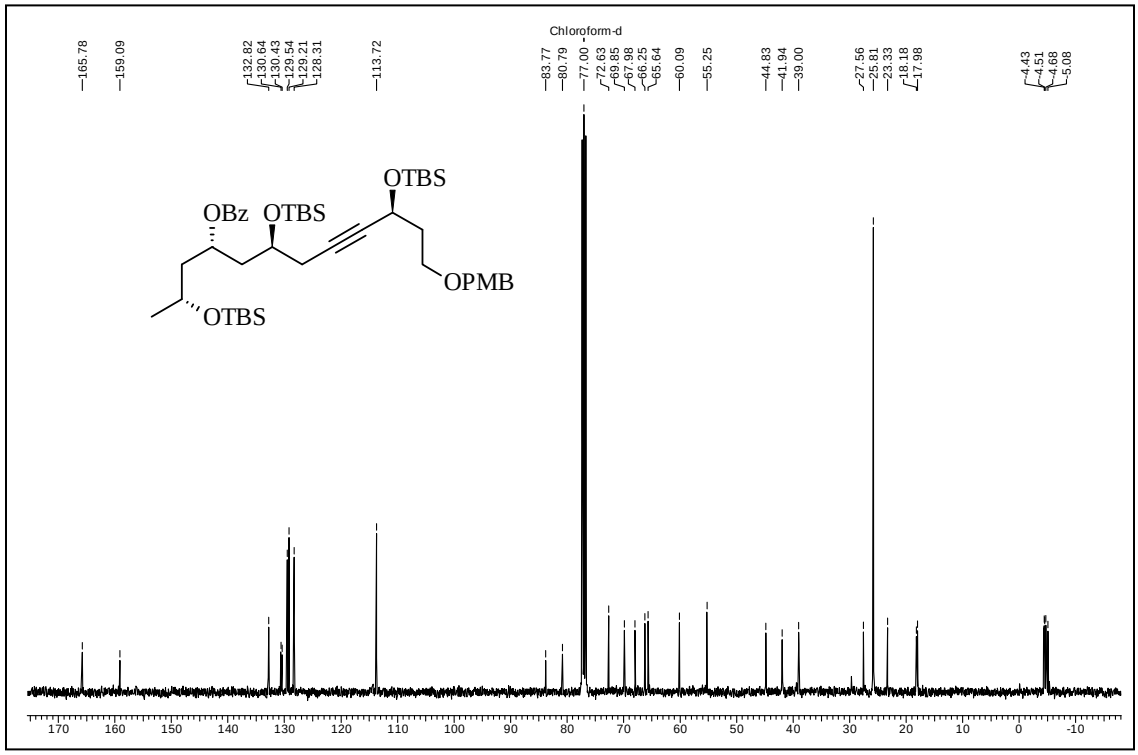
^{1}H NMR Spectrum of 337b in $CDCl_3$



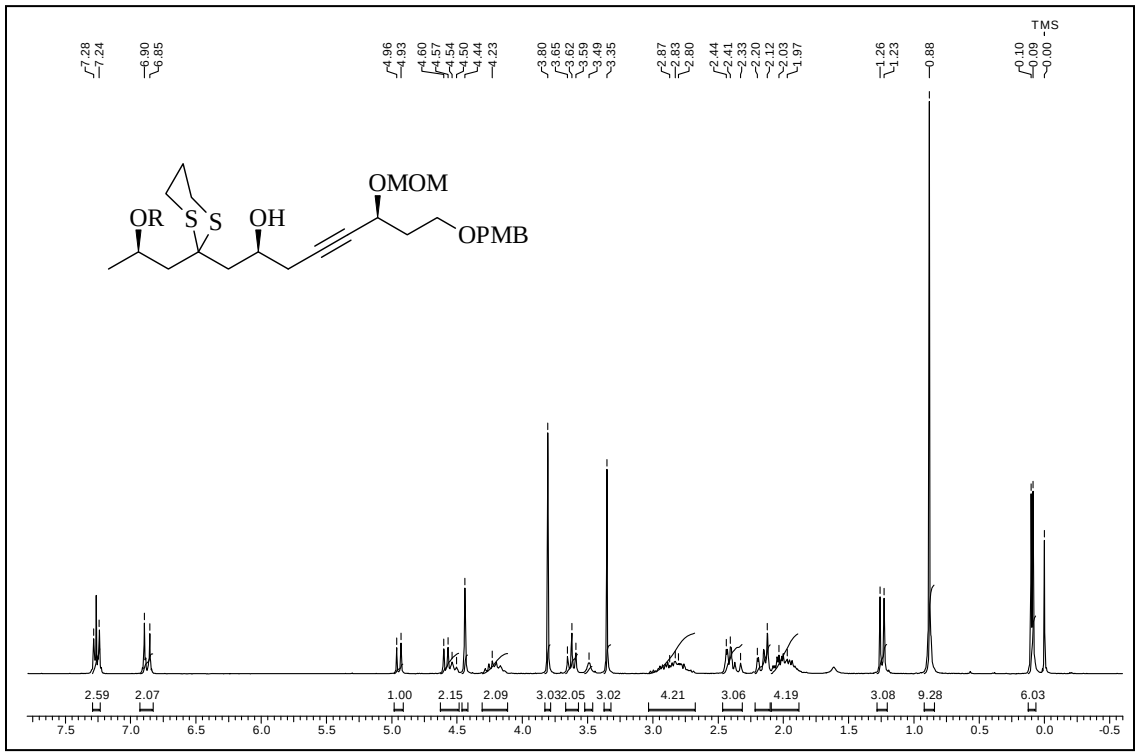
^{13}C NMR Spectrum of 337b in $CDCl_3$



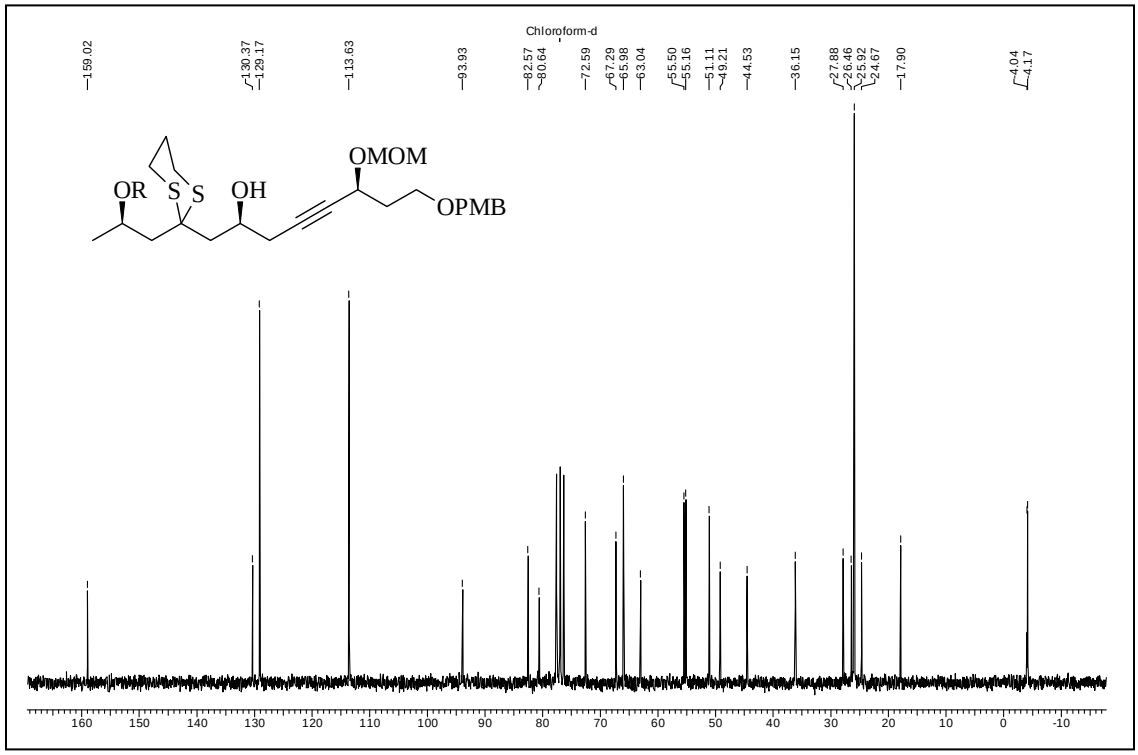
^{1}H NMR Spectrum of 337a in $CDCl_3$



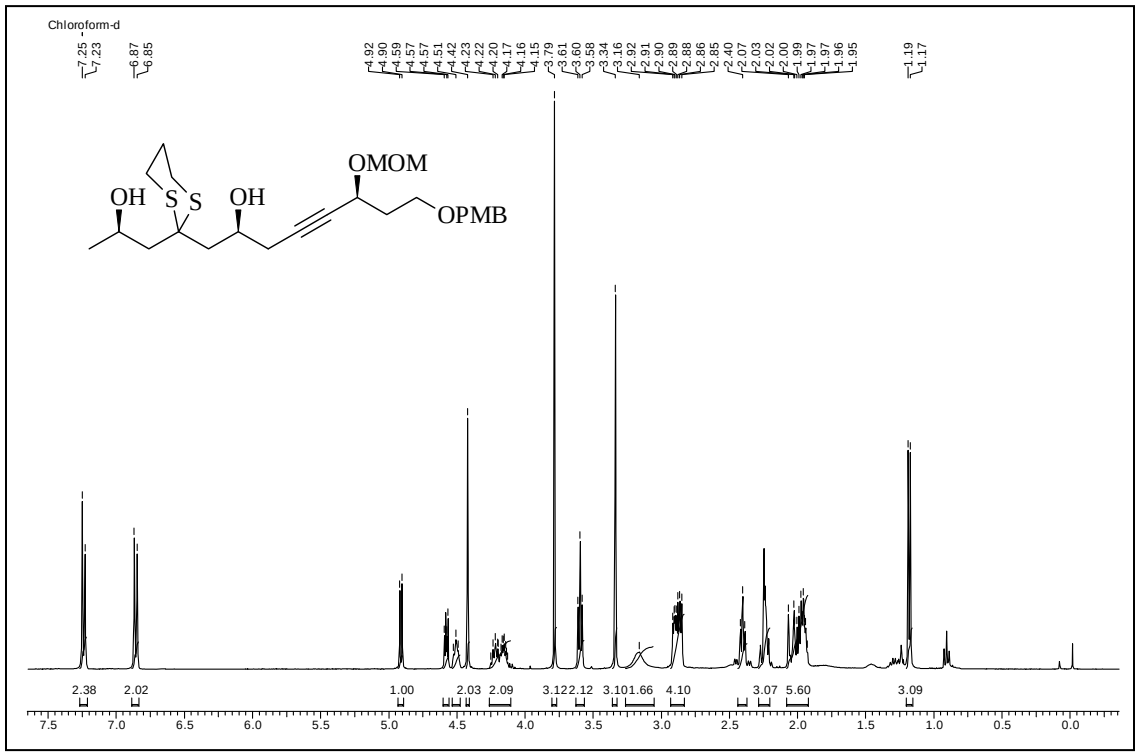
^{13}C NMR Spectrum of 337a in $CDCl_3$



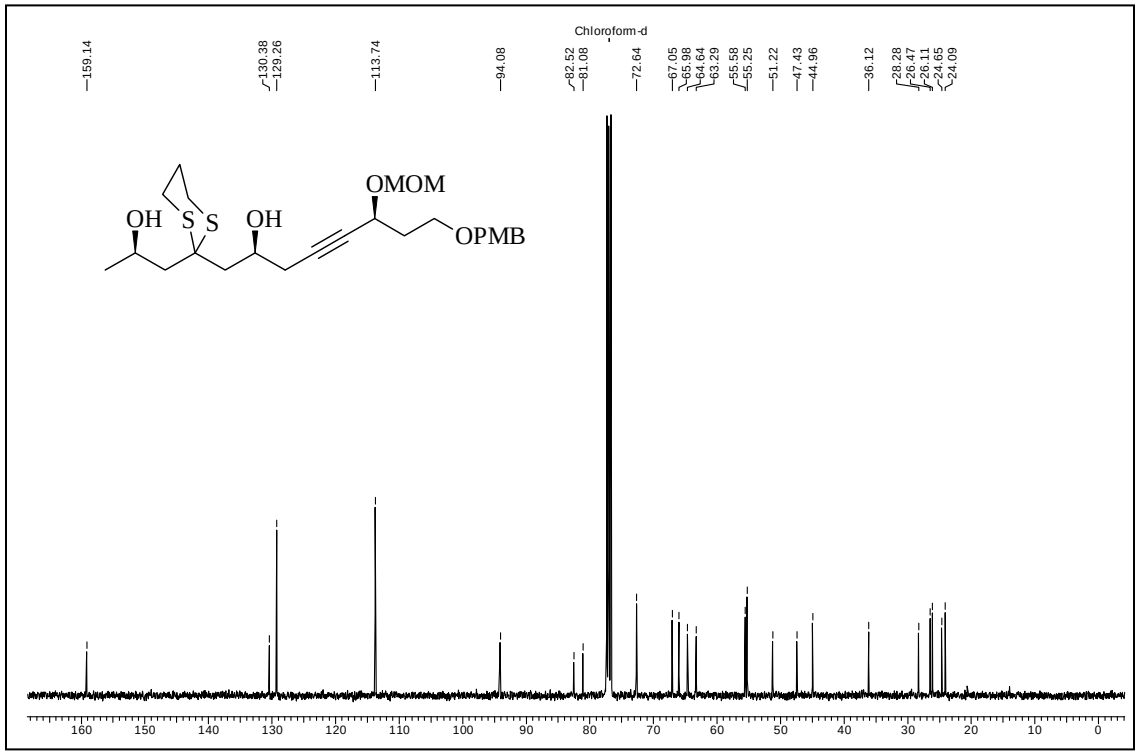
^{1}H NMR Spectrum of 329 in $CDCl_3$ (R = TBS)



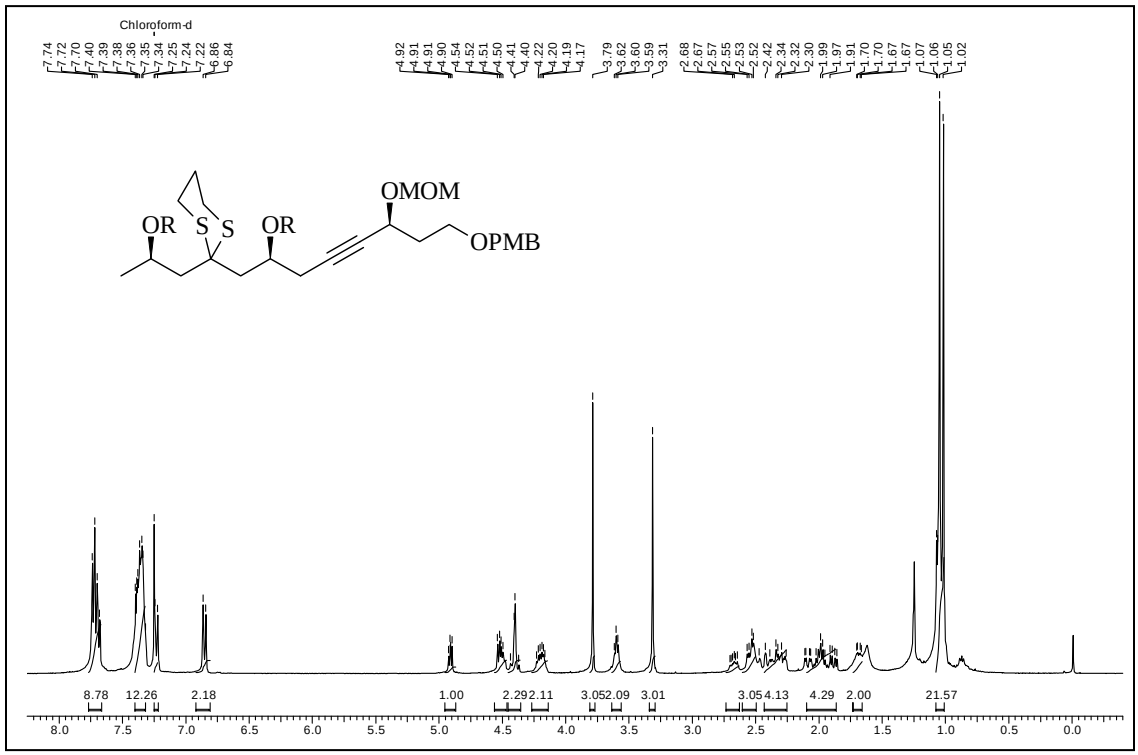
^{13}C NMR Spectrum of 329 in $CDCl_3$ (R = TBS)



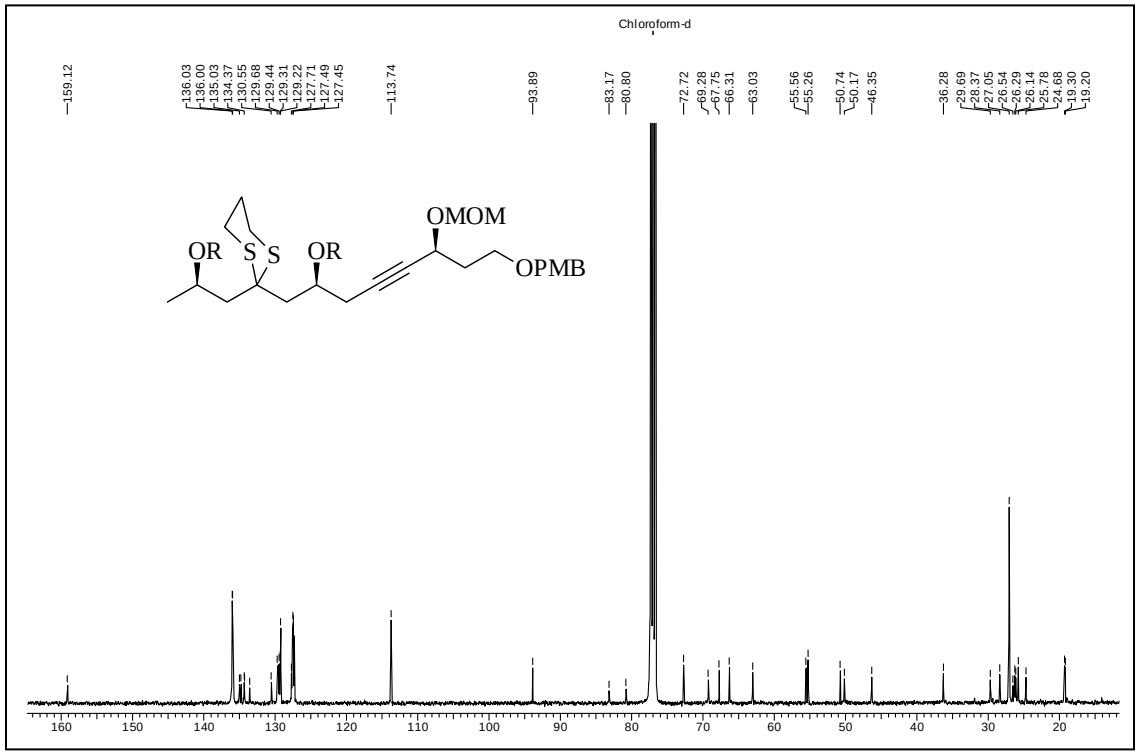
^{1}H NMR Spectrum of 332 in $CDCl_3$



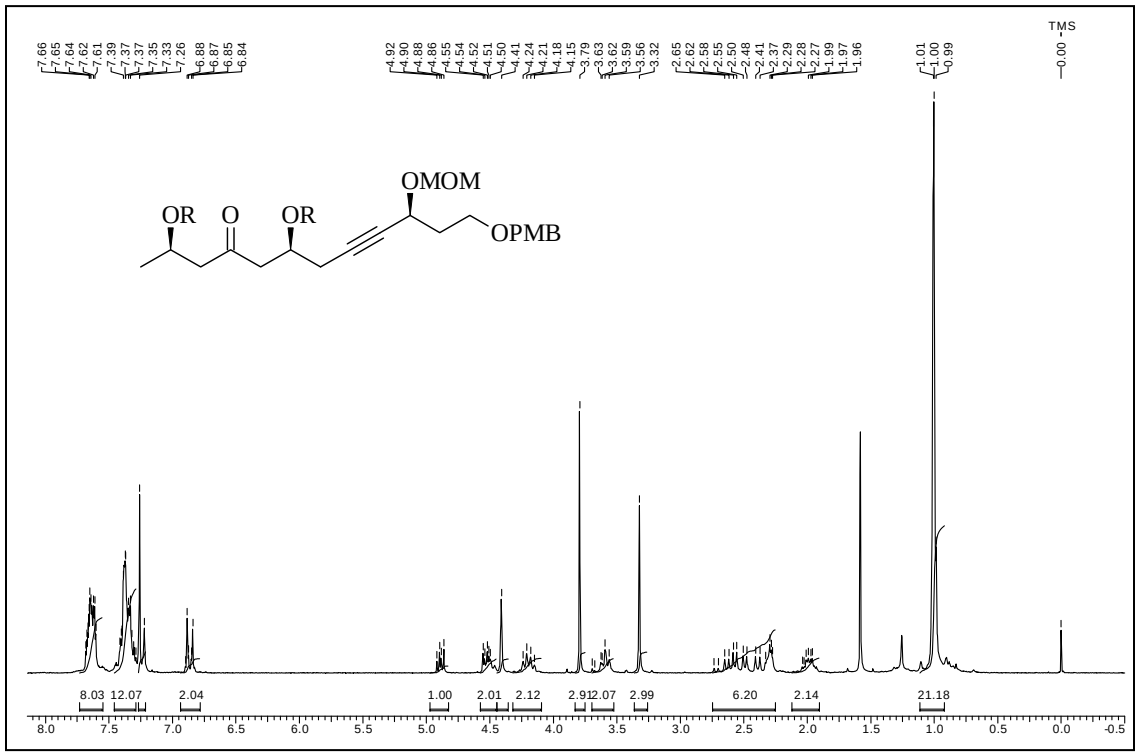
^{13}C NMR Spectrum of 332 in $CDCl_3$



^{1}H NMR Spectrum of 333 in $CDCl_3$ (R = TBDPS)



^{13}C NMR Spectrum of 333 in $CDCl_3$ (R = TBDPS)



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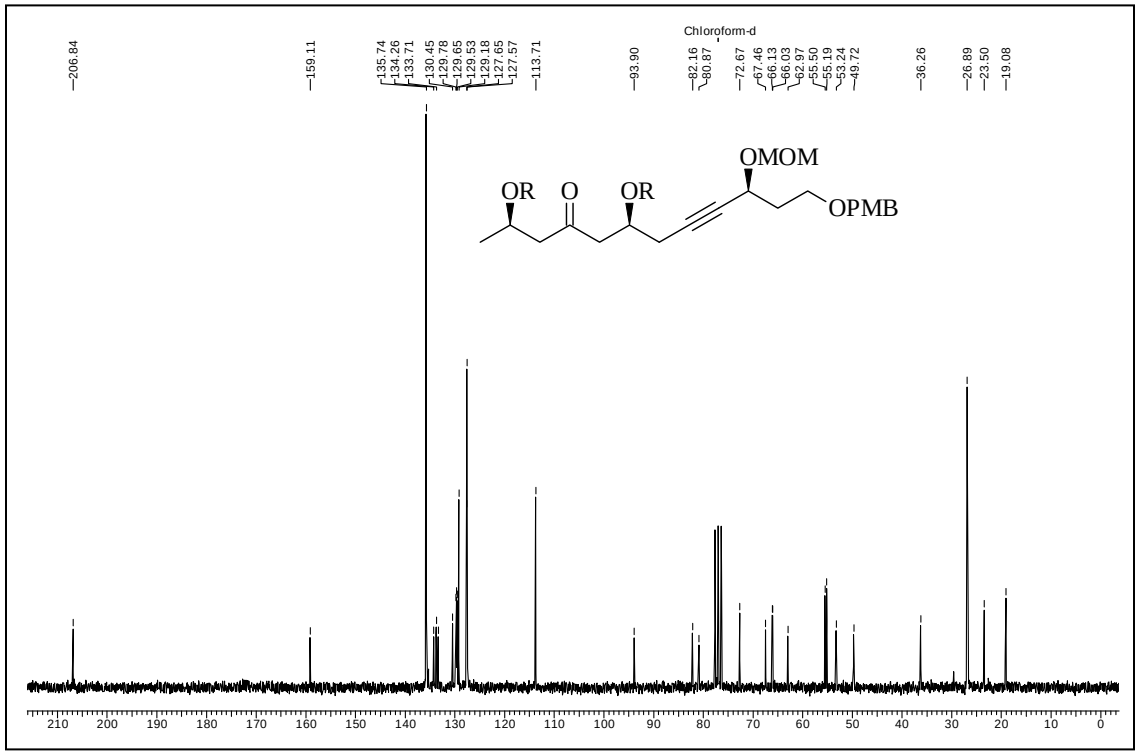

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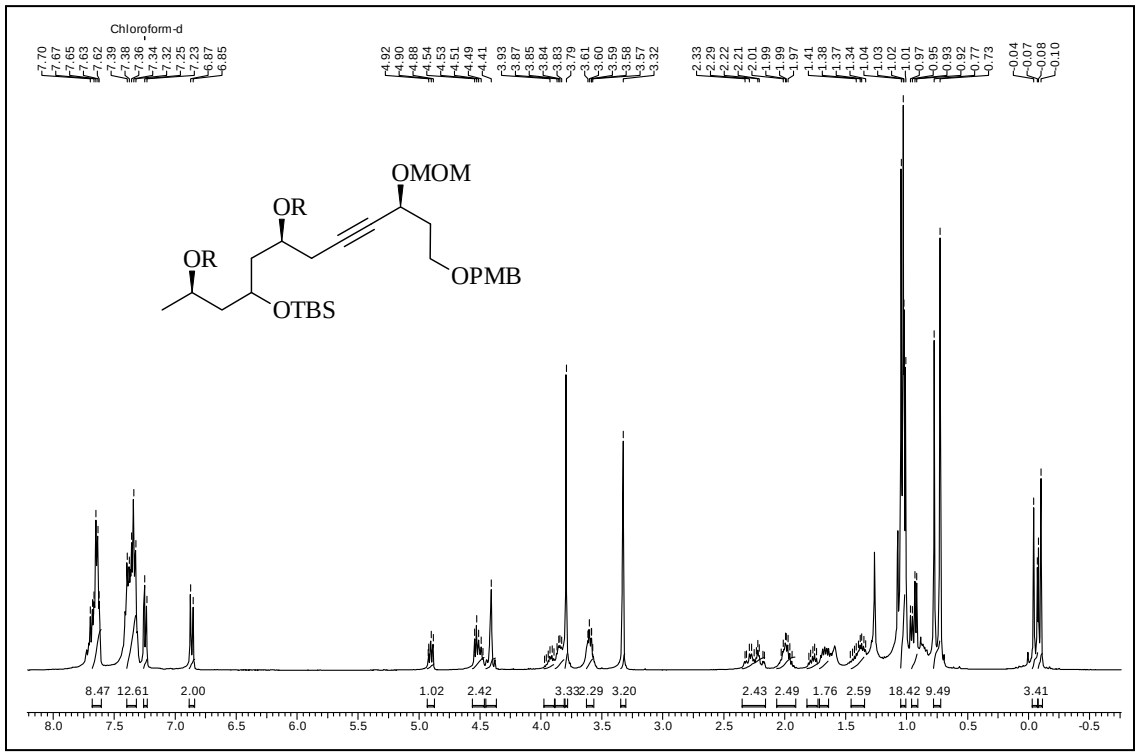
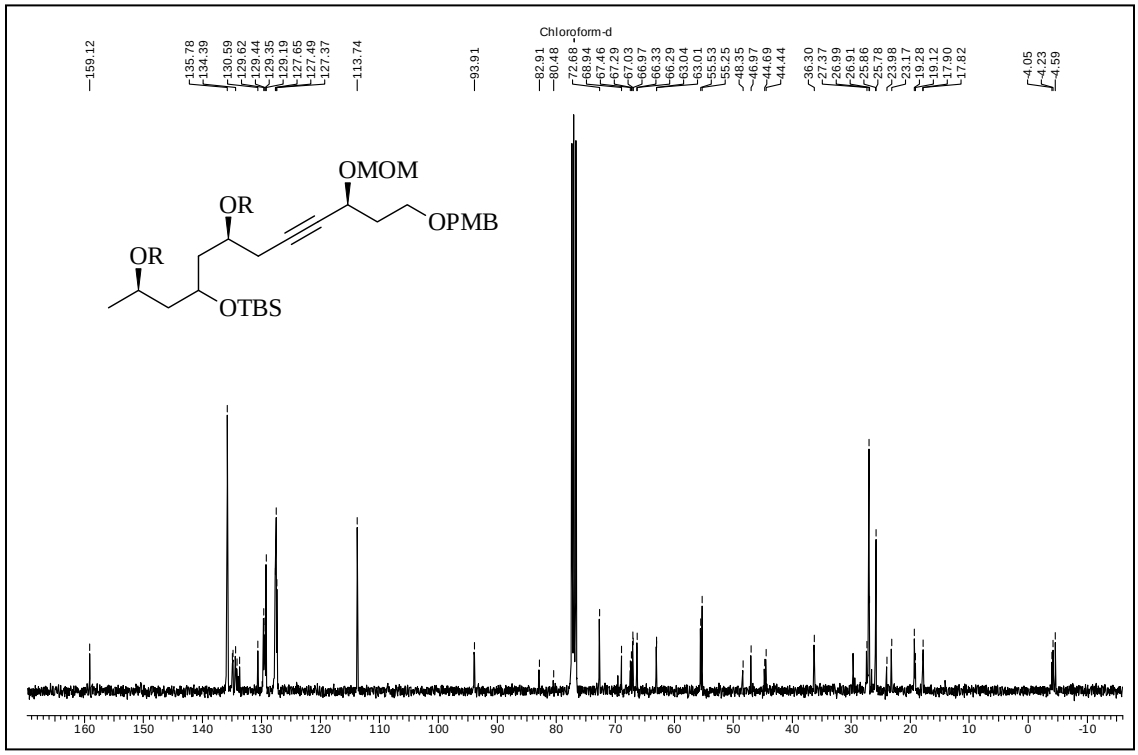
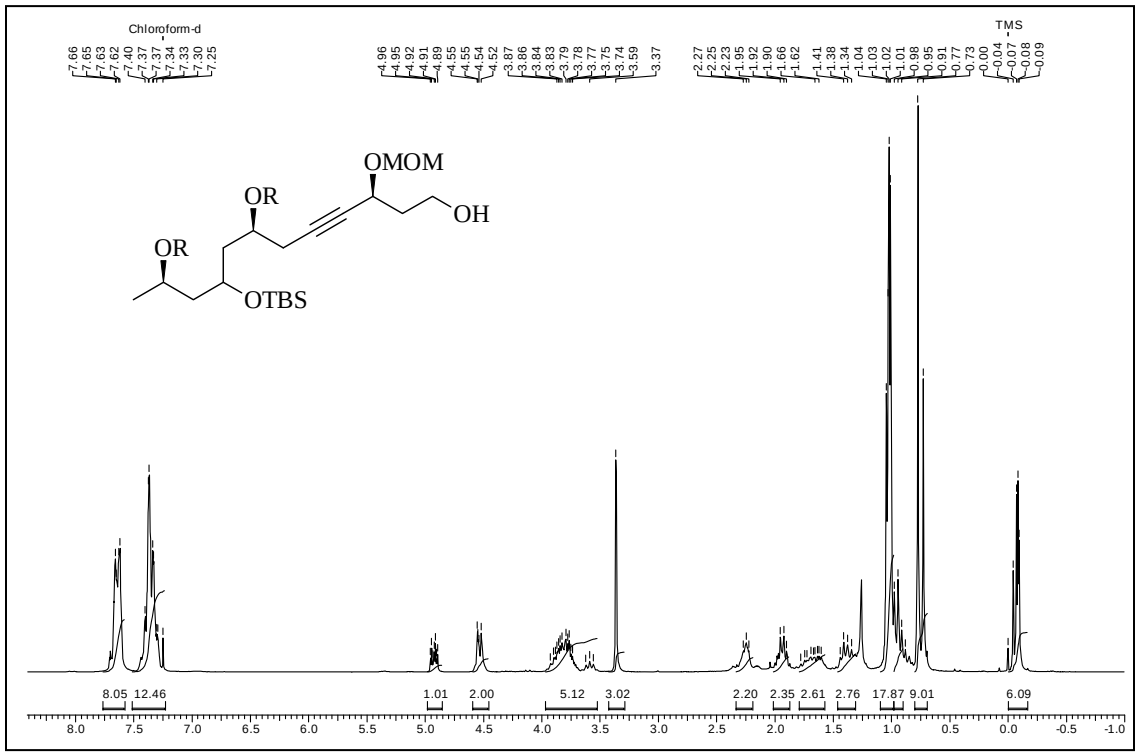


^{1}H NMR Spectrum of 338 in $CDCl_3$ (R = TBDPS)



^{13}C NMR Spectrum of 338 in $CDCl_3$ (R = TBDPS)



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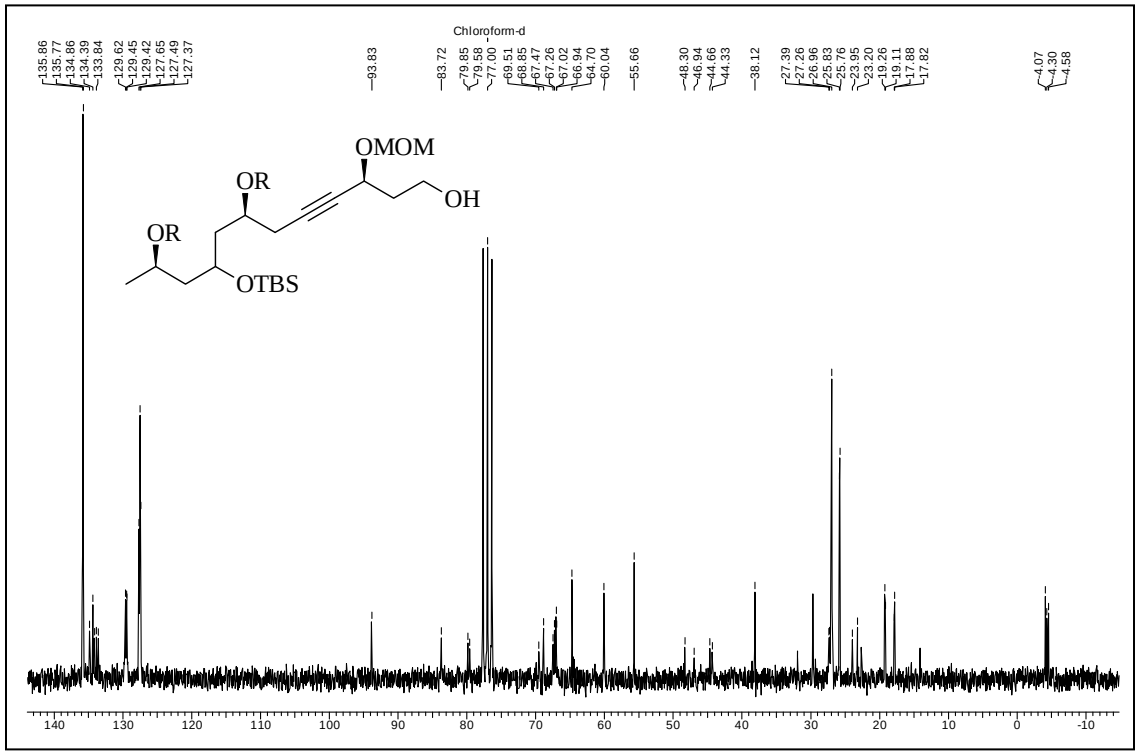
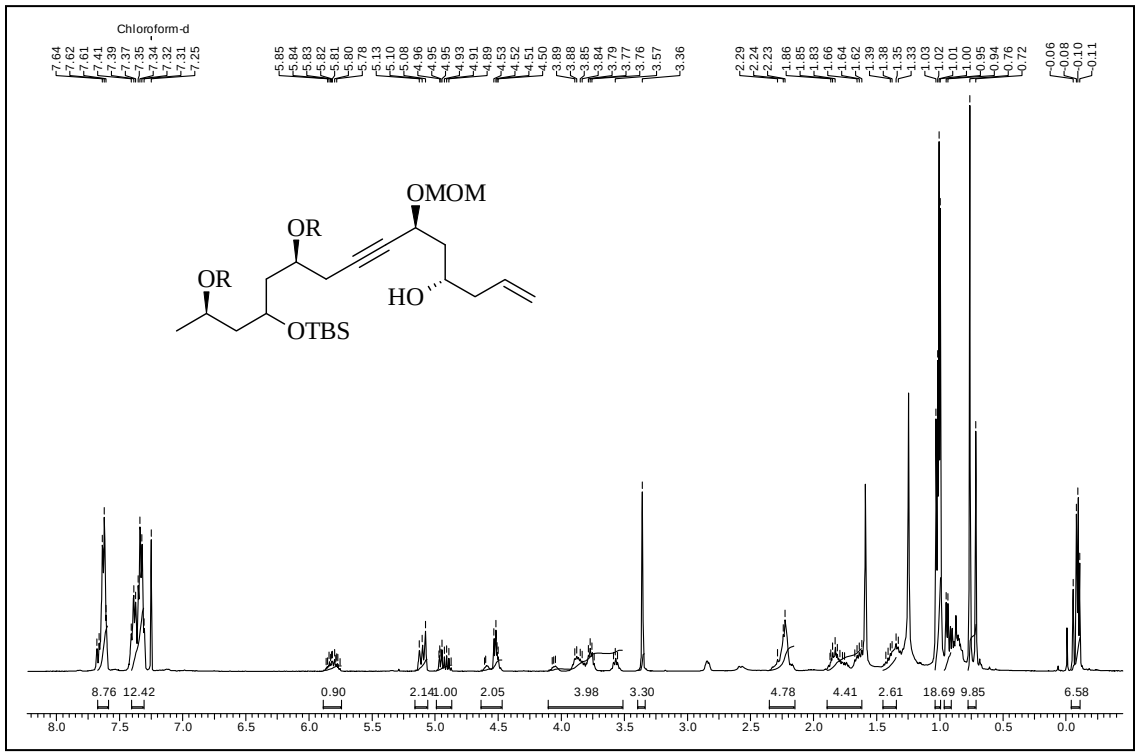
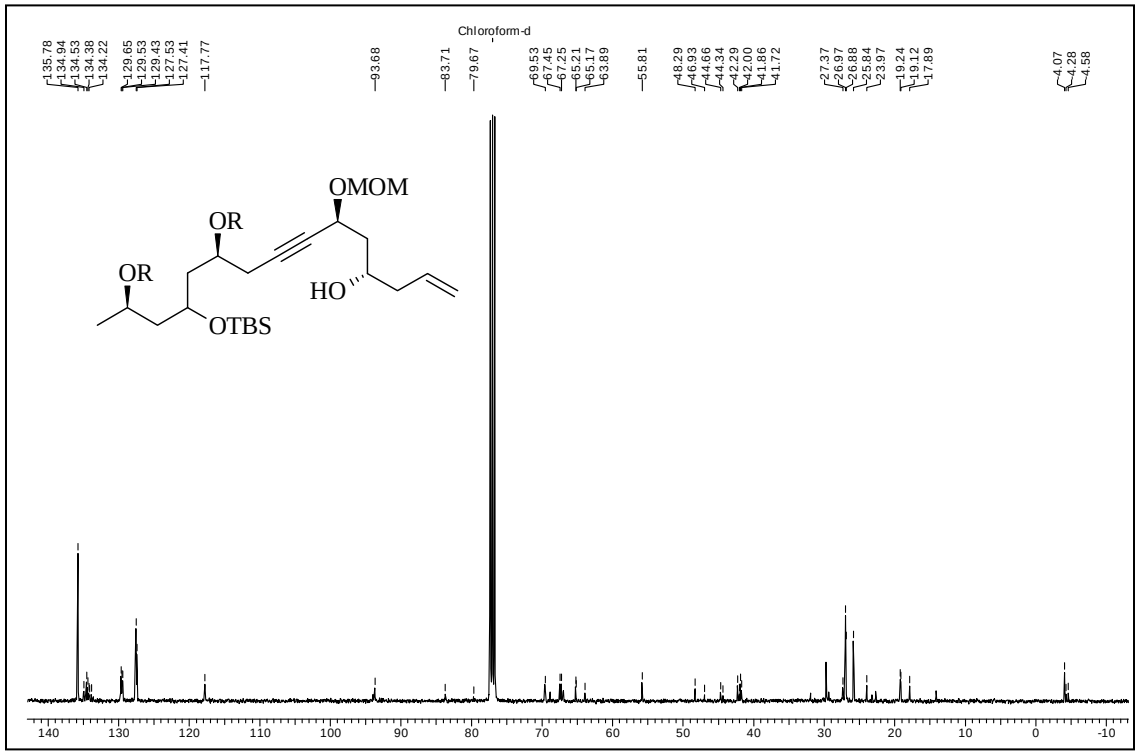


^{13}C NMR Spectrum of 339 in $CDCl_3$ (R = TBDPS)



^{1}H NMR Spectrum of 340a in $CDCl_3$ (R = TBDPS)



^{13}C NMR Spectrum of 340a in $CDCl_3$ (R = TBDPS)

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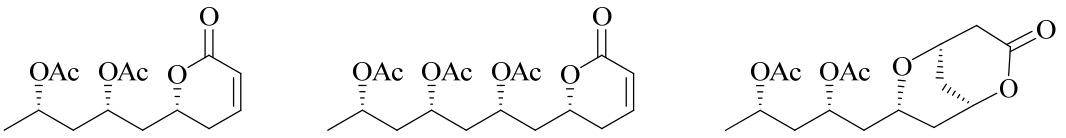
CHAPTER-III

Section B: A short total synthesis of (+)-cryptocarya diacetate

INTRODUCTION

Cryptocarya latifolia is a plant indigenous to Southern Africa belonging to Lauraceae family and also known as the broad-leafed laurel (umkhondweni in Zulu). It is a large tree (upto 20 m) and its distribution ranges along the entire Natal coastline. The bark of this species is used by the Zulu people to treat chest complaints but it is also used for mythical purposes. This is an important component of Zulu culture and ethnobotanists have recently observed a substitution of *Cryptocarya* bark for the much less accessible (through over exploitation) bark of *Ocotea bullata* (also belongs to the Lauraceae) among practicing herbalists.

Cryptocarya diacetate (**345**) is one of the several 6-substituted 5,6-dihydropyran-2-one natural products that were isolated by Horn et al. from the leaves and bark of *Cryptocarya latifolia*[1] along with cryptocarya triacetate (**346**), cryptocaryolone (**347**) etc. (Figure 1). These compounds have long been known for their promising biological activities ranging from the treatment of headaches, morning sickness to that of cancer, pulmonary diseases, and various bacterial and fungal infections.[2]



cryptocarya diacetate (**345**) cryptocarya triacetate (**346**) cryptocaryolone diacetate (**347**)

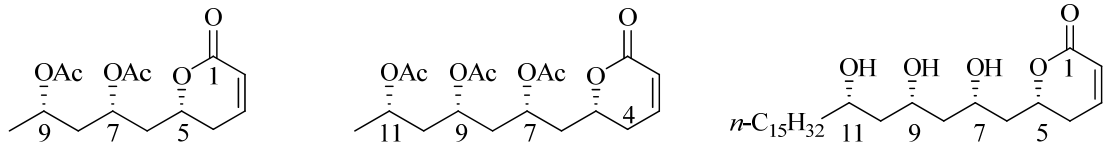
Figure 1.

The structure of cryptocarya diacetate was established by employing the NMR spectral techniques (COSY, HETCOR) at 200 MHz. Where any doubt existed with regard to specific features in the molecules, more advanced gradient techniques such as DQFCOSY, HSQC and HMBC at 500 MHz were applied in order to give an unambiguous result. It was possible to establish all relevant $^{1}H/^{1}H$ correlations and all relevant $^{13}C/^{1}H$ long-range (upto three bonds away) correlations for **345** using the techniques mentioned above. For example, the correlation between the two H-5 protons (δ 2.42, 2.29) to the carbonyl group at C-2 (163.7 ppm), which is four bonds

away, was clearly discernible. The critical H-6 proton (δ 4.47) exhibited a very clear connectivity to C-2 (163.7 ppm), C-4 (144.5 ppm), C-2^1 (67.7 ppm), C-1^1 (39.1 ppm) and C-5 (29.2 ppm). This proton, in turn, showed $^1H/^1H$ connectivities to H-5a (δ 2.42), H-5b (δ 2.29), H-1^1a (δ 2.14), and H-1^1b (δ 1.93).

The absolute stereochemistry of **346** was unequivocally determined to be 5*R*, 7*R*, 9*S*, 11*S* based on Mosher's method[3] using the ^1H NMR of the MTPA ester and Rychnovsky's method using the ^{13}C NMR of the acetonide.[4] Although the stereochemistry of the 5*R* and 7,9-*syn* configuration of **345** was also determined, the absolute stereochemistry at C7 and C9 remains unknown; however, because of the proven stereochemistry of **346**, it was reported that the δ-lactone **345** probably possesses a 7*S*, 9*S*-configuration.

It has been reported that the relative stereochemistry at C5 and C7 in these types of α,β-unsaturated δ-lactones can be determined by the ^1H NMR splitting pattern of the C4-methylene protons;[5] i.e., a separated pattern of the C4-methylene protons means a 5,7-*syn*-configuration and an overlapped pattern means a 5,7-*anti*-configuration. Since the reported ^1H NMR data of **345** showed a separated pattern at δ 2.29 and 2.42, the relative stereochemistry should be 5,7-*syn* i.e., the absolute stereochemistry of **345** is 5*R*, 7*S*, 9*S*.



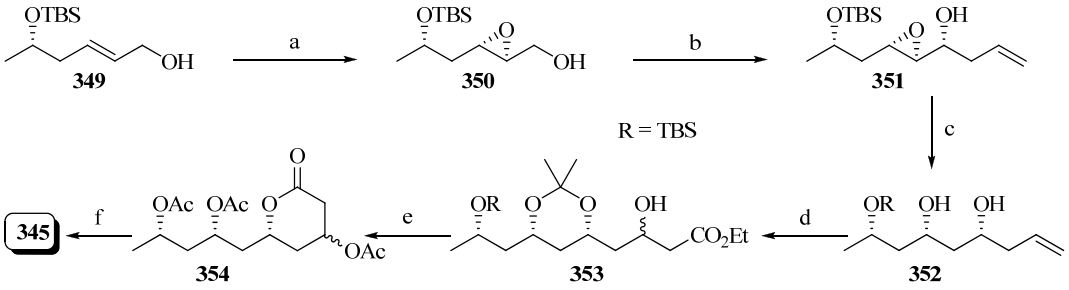
cryptocarya diacetate (**345**) cryptocarya triacetate (**346**) **348**

Figure 2.

Interestingly, in contrast to the above conclusions the same type of α,β-unsaturated δ-lactone **348** (Figure 2), isolated from *Eupatorium pilosum*,[6] has the opposite absolute stereochemistry of the 5,7,9,11-all-*syn*-hydroxyl groups, which was determined through synthesis by the same group. This prompted Nakata et al. to determine the absolute stereochemistry of **345** by completing its first total synthesis. There have been around 7 stereoselective total syntheses reported till date ever since its isolation, which are discussed below briefly.

Nakata et al.[7]

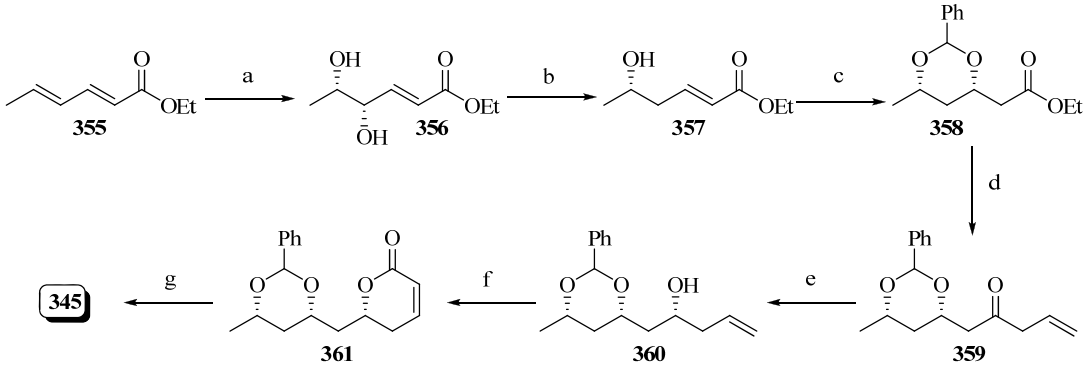
The synthesis started by conducting a Sharpless asymmetric epoxidation of the allylic alcohol **349** to produce the epoxy alcohol **350**. The stereoselective allyl addition of the corresponding epoxy aldehyde of **350** furnished **351**. The regioselective reductive ring opening of **351** resulted in *syn*-diol **352**. Oxidative cleavage of the suitably protected diol **352** followed by an aldol reaction led to the formation of **353**. Finally, lactonization-acetylation, and DBU treatment furnished α,β-unsaturated δ-lactone **345** (Scheme 1).



Scheme 1. *Reagents and conditions:* (a) *t*-BuOOH, (+)-DET, Ti(O*i*-Pr)$_4$, 4Å-MS, CH_2C1_2, –21 °C (80%); (b) (i) $(COC1)_2$, DMSO, CH_2Cl_2, –78 °C; Et_3N, –78 °C– r.t.; (ii) allylSnBu_3, 5 M $LiC1O_4$, ether, r.t., ;(c) Cp_2TiC1, *t*-BuSH, THF, r.t., (78%); (d) (i) $Me_2C(OMe)_2$, CSA, acetone, r.t., (97%); (ii) OsO_4–*t*-BuOH, NMO, acetone–H_2O, r.t; $NaIO_4$, THF–H_2O, r.t., (92%); (iii) LDA, EtOAc, THF, –78 °C (90%); (e) (i) Dowex ® 50W-X2, MeOH–H_2O, r.t.; (ii) LiOH, THF–H_2O, r.t.; (iii) Dowex ® 50W-X_2; (iv) Ac_2O, DMAP, pyridine, r.t.; (f) DBU, toluene, r.t., (59% from **353**).

Doherty et al.[8]

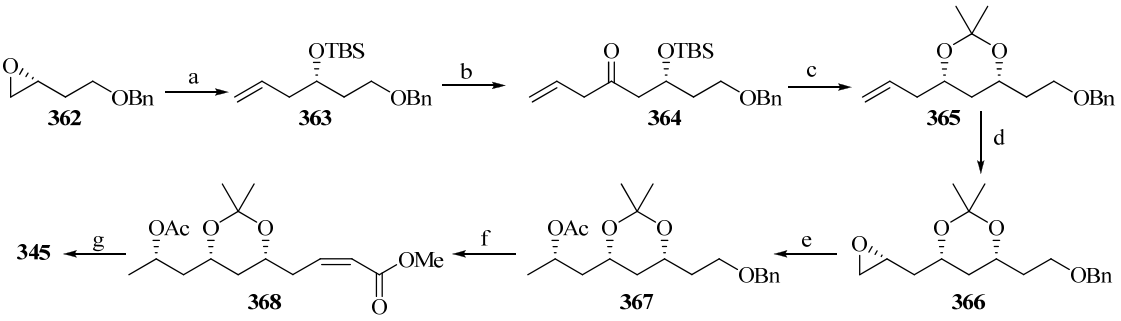
This approach relies upon an enantio and regioselective Sharpless dihydroxylation of ethyl sorbate **355** to afford the diol **356**. A palladium-catalyzed reduction of **356** to form δ-hydroxy-1-enoate **357**, which was subsequently converted into a benzylidene-protected 3,5-dihydroxy carboxylic ester **358**. This ester was successfully transformed into cryptocarya diacetate **1** *via* allylation, stereoselective keto-reduction and RCM-reaction sequence (Scheme 2).



Scheme 2. *Reagents and conditions:* (a) 1% OsO_4, 1.1% $(DHQ)_2PHAL$, K_3FeCN_6, $MeSO_2NH_2$, *t*-BuOH/H_2O, 0 °C, 71%; (b) 1) $(Cl_3CO)_2CO$, Py/CH_2Cl_2, 87%; 2) HCO_2H, TEA, 2.5% $Pd_2(dba)_3.CHCl_3$, 6.3% PPh_3, THF, 66 °C, 66%; (c) 3.3 equiv PhCHO, 30% *t*-BuOK, 64%; (d) 1) DIBAL-H, THF, –78 °C, AllyMgCl, 91%; 2) Dess-Martin reagent, r.t., (90%); e) L-Selectride, THF, –90 °C, 87%; (f) 1) Acrylicacid, DCC, DMAP, CH_2Cl_2, r.t., 83%; 2) $(Cy_3P)_2Cl_2Ru$=CHPh, CH_2Cl_2, reflux, 88%; (g) AcOH-H_2O (4:1) 60 °C, 3 h then Ac_2O, pyridine, DMAP, r.t., 78%.

Radhakrishna et al.[9a]

This synthetic sequence involves a combination of Jacobsen hydrolytic kinetic resolution (HKR) and diastereoselective ketone reduction to garner the required chiral centres.



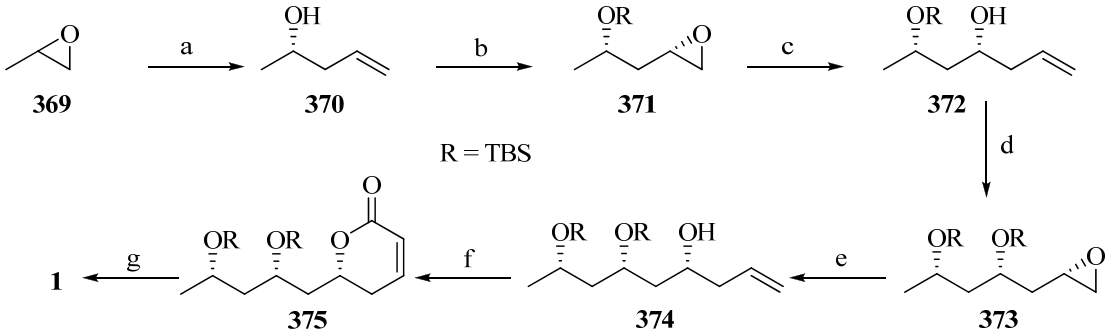
Scheme 3. *Reagents and conditions:* (a) (i) vinylmagnesium bromide, THF, CuI, r.t., 74%, (ii) TBSCl, imidazole, r.t., 82%; (b) (i) O_3, CH_2Cl_2, –78 °C, 0.5 h, then Me_2S, r.t., 0.5 h; (ii) allyl bromide, Zn, NH_4Cl, THF, r.t., 82%; (iii) PCC, NaOAc, CH_2Cl_2, r.t., 72%; (c) (i) HF–pyridine, THF, r.t., 63%; (ii) $B(Et)_2OMe$, $NaBH_4$, THF, 75%; (iii) 2,2'-dimethoxypropane, *p*-TSA, DMSO, 94%; (d) (i) oxone, acetone, $NaHCO_3$, EDTA (cat.) 73%; (ii) (*R*,*R*)-(salen)Co^{III}(OAc), 0.55 equiv H_2O, 43%; (e) (i) LAH, THF, r.t., 89%; (ii) Ac_2O, pyridine, DMAP (cat.), CH_2Cl_2, r.t., 94%; (f) (i) Pd/C, H_2, EtOAc, r.t., 95%; (ii) IBX, DMSO, r.t.; (iii) $(F_3CCH_2O)_2POCH_2COOMe$, KHMDS, 18-crown-6, THF, –78 °C, 79% over two steps; (g) (i) 80% aq AcOH; (ii) *p*-TSA, C_6H_6; (iii) Ac_2O, pyridine, CH_2Cl_2, DMAP (cat.), r.t., 86% over three steps.

A known epoxide **362** which was prepared by HKR of the corresponding homoallylic alcohol derivative, on exposure to vinylmagnesiumbromide in THF followed by TBS protection afforded **363**. This was converted to olefin **365** by a sequence of reactions such as oxidative cleavage of olefin in **363**, allylation, oxidation, *syn*-selective keto reduction and acetonide protection. The racemic epoxide derivative of **365** was transformed into chiral epoxide **366** by applying HKR protocol. The regioselective epoxide opening followed by acetyl protection furnished **367**. Finally a *Z*-selective HWE olefination, lactonization-acetalization accomplished **345**.

Pradeep kumar et al.[9b]

The sequence involves a repeated iterative Jacobsen's hydrolytic kinetic resolution (HKR), followed by a vinyl grignard opening of the epoxides to convert the

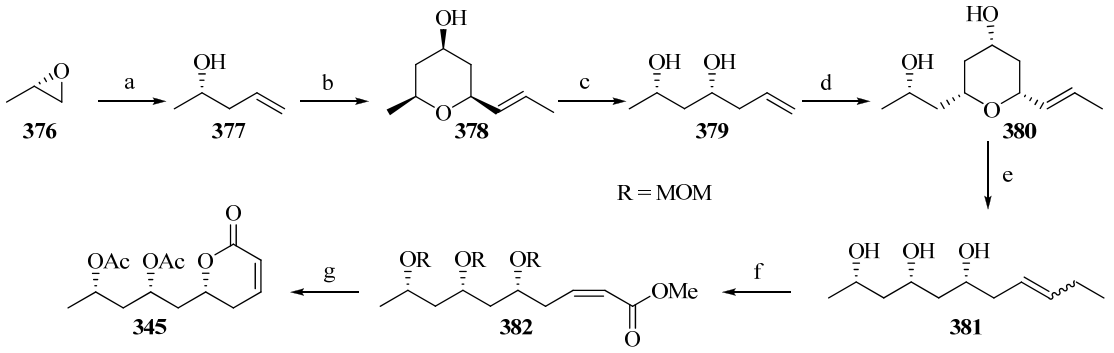
racemic propylene oxide **369** to chiral homoallylic alcohol **372**. The diastereoselective iodine-induced electrophilic cyclization of *O*-BOC derivative of **372** followed by base treatment led to the *syn*-epoxide **373**. Finally ring-closing metathesis (RCM) for the construction of pyrone ring followed by a simple deprotection, protection sequence of reactions completed the total synthesis of **345** as depicted in Scheme 4.



Scheme 4. *Reagents and conditions:* a) (1) *S,S*-Salen-Co-(OAc) (0.5 mol%), dist. H_2O (0.55 equiv), 0 ^oC, 14 h; (2) Vinylmagnesium bromide, CuI, THF, –20 ^oC, 12 h, 87%; b) (1) *m*CPBA, CH_2Cl_2, 0 ^oC to r.t., 10 h, 96%; (2) TBS-Cl, imidazole, CH_2Cl_2, 0 ^oC to r.t., 4 h, 95%; (3) Jacobsen's HKR; c) Vinylmagnesium bromide, THF, CuI, –20 ^oC, 1 h, 82%; d) (1) Boc_2O, DMAP, CH_3CN, r.t., 5 h, 90%; (2) IBr, PhMe, –85 ^oC, 1 h; (3) K_2CO_3, MeOH, r.t., 2 h, 81% from both the steps; (4) TBS-Cl, imidazole, DMF, 0 ^oC to r.t., 22 h, 89%; e) Vinylmagnesium bromide, THF, CuI, –20 ^oC, 1 h, 80%; f) (1) Acryloyl chloride, Et_3N, CH_2Cl_2, 0 ^oC to r.t., 5 h, 82%; (2) $(PCy_3)_2Ru(Cl)_2$=CHPh (20 mol%), CH_2Cl_2, $Ti(^iPrO)_4$ (0.03 equiv), reflux, 6 h, 84%; g) (1) TBAF, THF, r.t., overnight; (2) Ac_2O, pyridine, 2 h, 75% from both the steps.

Yadav et al.[9c]

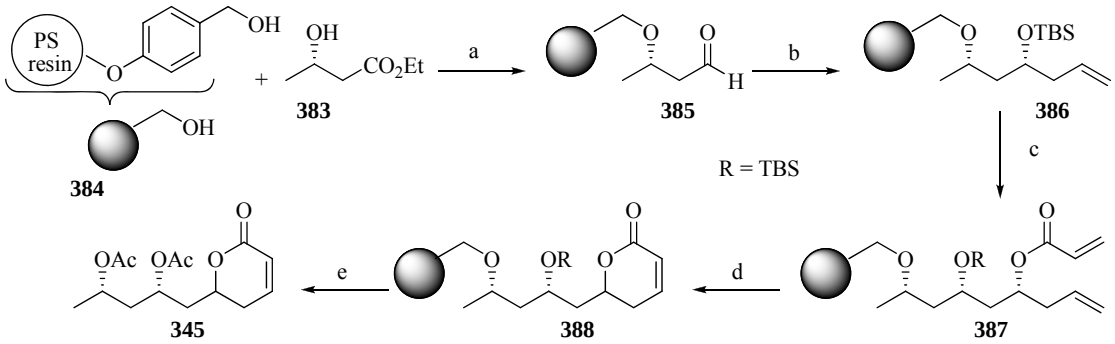
The strategy mainly relies on iterative Prince cyclization followed by susbsequent reductive cleavage of the allylic ethers to construct the well furnished **381**, containing all the required stereocenters. Ozonolysis of suitably protected **381**, *cis*–Wittig olefination afforded the ester **382**, which upon treatment with acid followed by acetylation completed the synthesis of **345** (Scheme 5).



Scheme 5. *Reagents and conditions:* (a) vinylmagnesium bromide, CuCN, THF, –78 °C to –40 °C, 4 h, 92%; (b) crotonaldehyde, TFA, CH_2Cl_2 then K_2CO_3, MeOH, r.t., 4 h, 70%; (c) (i) Na, liq NH_3, THF, –33 °C, 45 min, 90%; (ii) O_3, TPP, CH_2Cl_2, –78 °C, then $CH_3P(Ph_3)_3I$, KO^{t}Bu, THF, 0 °C, 2 h, 60%; (d) crotonaldehyde, TFA, CH_2Cl_2 then K_2CO_3, MeOH, r.t., 4 h, 55%; (e) (i) MOMCl, DIPEA, DMAP, CH_2Cl_2, 0 °C–r.t., 4 h, 92%; (ii) Na, liq NH_3, THF, –33 °C, 45 min, 86%; (iii) DEAD, TPP, *p*-$C_6H_4(NO_2)COOH$, THF, 30 min, 0 °C–r.t., then K_2CO_3, MeOH, r.t., 1 h, 78%; (iv) MOMCl, DIPEA, DMAP, CH_2Cl_2, 0 °C– r.t., 4 h, 90%; (f) O_3, TPP, CH_2Cl_2, –78 °C then $(F_3CCH_2O)_2POCH_2COOMe$, NaH, 0 °C, 2 h, 70%; (g) (i) conc HCl, MeOH, r.t., 6 h then *p*-TSA, benzene, r.t., 4 h; (ii) Ac_2O, py, DMAP, CH_2Cl_2, r.t., 3 h, 70% (three steps).

Waldmann et al.[10]

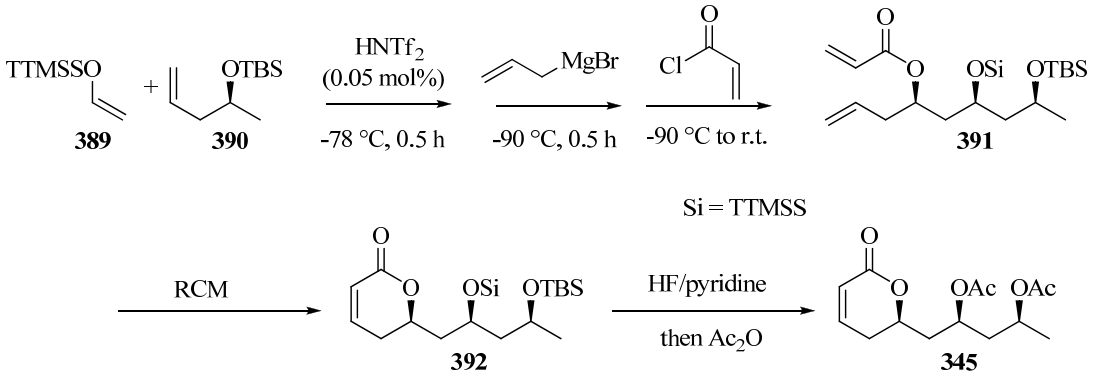
For the synthesis of cryptocarya diacetate, (*S*)-3-hydroxybutyric acid ester **383** was immobilized on Wang resin **384**, activated as the trichloroacetimidate and converted into polymer-bound aldehyde **385** in two steps. Allylation with *l*-Ipc$_2$BAll, and protection of the secondary alcohol as a silyl ether yielded resin **386**. A careful ozonolysis of the double bond followed by second allylation with *l*-Ipc$_2$BAll and the formed secondary alcohol was converted to acrylic ester **387**. Ring closing metathesis employing the Grubbs II catalyst induced formation of the α,β-unsaturated lactone **388**. Release from the solid support, with consecutive cleavage of the silyl group and subsequent acetylation, yielded a mixture of four stereoisomers, from which the all-*syn* isomers of cryptocarya diacetate **345** was isolated by means of simple flash chromatography (Scheme 6).



Scheme 6. *Reagents and conditions:* (a) (i) **384** (1.2 mmol g^{-1}), trichloroacetonitrile, DBU, CH_2Cl_2, then **383**, $BF_3.OEt_2$, cyclohexane/CH_2Cl_2; (ii) DIBAL–H, THF, –78 °C to r.t., 16 h; (iii) IBX, DMSO/THF, r.t., 16 h; (b) (i) 3 equiv. *l*-Ipc$_2$BAll, THF, –78 °C to r.t.; (ii) pH 7 buffer, H_2O_2 30%, DMF/MeOH (1:1), 0 °C, 2 h; (iii) TBS–Cl, imidazole, cat. DMAP, CH_2Cl_2, r.t., 16 h; (c) (i) O_3, CH_2Cl_2, –78 °C, then PPh_3, –78 °C to r.t; (ii) 3 equiv. *l*-Ipc$_2$BAll, THF, –78 °C to r.t.; (iii) acryloyl chloride, NEt_3, cat. DMAP, CH_2Cl_2, 0 °C to r.t., 16 h; (d) 2 X 20 mol% Grubbs II catalyst, CH_2Cl_2, reflux, 24 h; (e) (i) trifluoroacetic acid/CH_2Cl_2 (1:2), 20 min, r.t.; (ii) Ac_2O, NEt_3, cat. DMAP, CH_2Cl_2, 0 °C to r.t., 3 h.

Yamamoto et al.[11]

Yamamoto et al. achieved a three step synthesis by a newly developed onepot-multireaction protocol utilizing the *tris*(trimethylsilyl)silyl (TTMSS), also called "super silyl" for the stereoselective generation of the 1,3-*syn*-diol moiety. As presented in the Scheme 7, the aldol reaction was performed with $HNTf_2$; subsequent addition of 1.2 equiv of allyl magnesium bromide followed by acryloyl chloride provided dienyl compound **391**. Use of Grubbs second generation catalyst for ring-closing metathesis gave **392**, which was treated with HF/pyridine followed by addition of excess pyridine and acetic anhydride to give cryptocarya diacetate **345** (Scheme 7).



Scheme 7.

PRESENT WORK

Cryptocarya diacetate (**345**) (Figure 3) is one of the several 6-substituted 5,6-dihydropyran-2-one natural products that were isolated by Horn et al. from the leaves and bark of the South African plant *Cryptocarya latifolia.*[1] These compounds have long been known for their promising biological activities due to the fact that they are used as medicines in the treatment of various bacterial and fungal infections.[2] Simple structure and broad spectrum biological activities of **345** have stimulated substantial synthetic work, culminating in several total syntheses.[7-11]

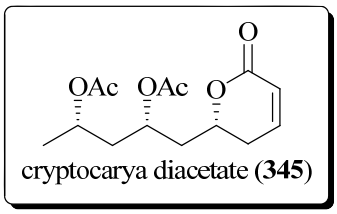


Figure 3.

Retrosynthesis

Herein we document a short total synthesis of **345** exploiting a one-flask three-component linchpin coupling reaction (Figure 4) for building the central carbon chain with requisite stereochemical features.

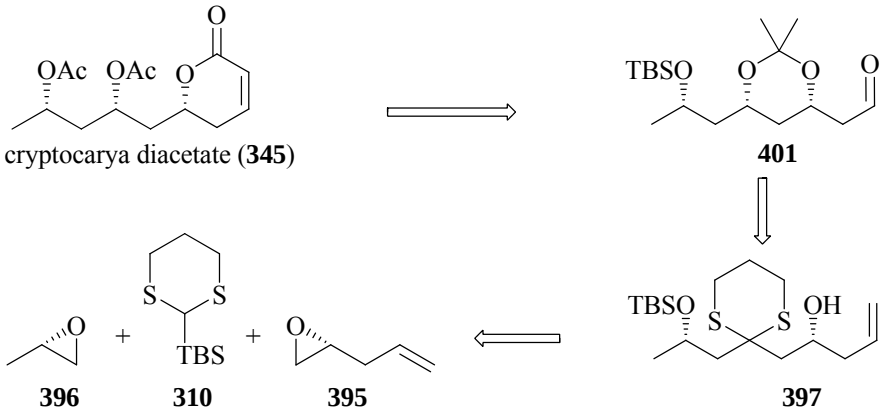
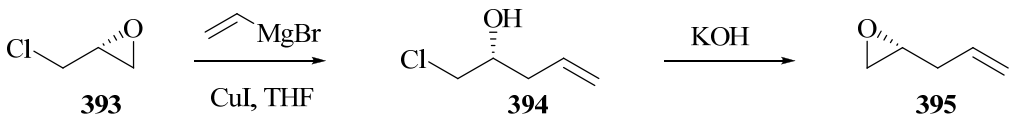


Figure 4.

A *Z*-selective Horner-Wadsworth-Emmons reaction (HWE reaction) of aldehyde **401** was opted for 5,6-dihydropyran-2-one construction. Considering an olefin group as surrogate for the requisite aldehyde, the advanced dithiane derivative **397** was identified as the key intermediate, which in turn can be obtained by linchpin coupling[5] of dithiane **310** with known epoxides **396** and **395**.

In this context a known chiral epoxide **395** was prepared following the literature procedure but with a slight modification, from (*R*)-epichlorohydrin (**393**) by treating it with vinylmagnesiumbromide in the presence of CuI, THF as solvent to give the chlorohydrin **394** which on subsequent treatment with KOH followed by distillation under reduced pressure afforded the epoxide **395** in an optically pure form. The spectral and analytical data of **395** were similar to that of the reported one (Scheme 8).[12]

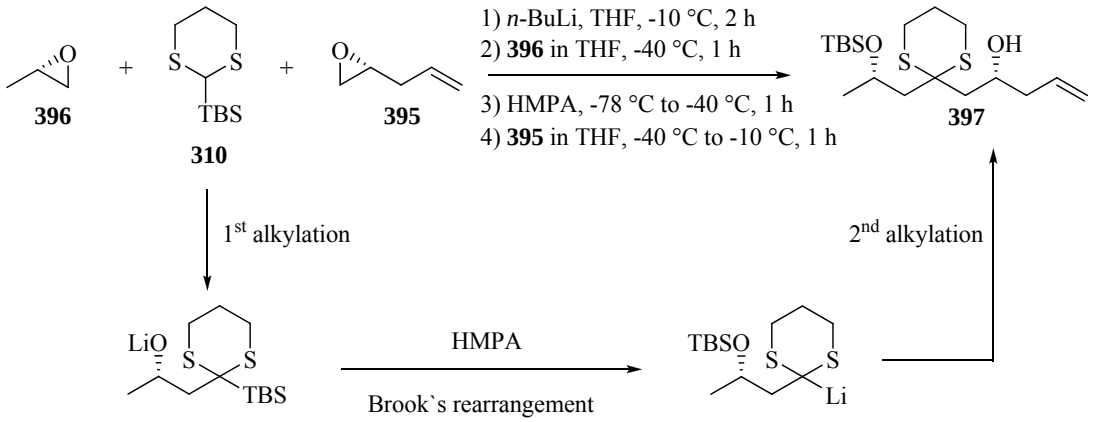


393 **394** **395**

Scheme 8.

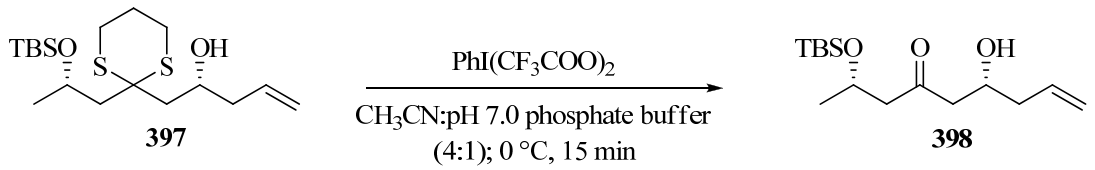
The synthesis of cryptocarya diacetate (**345**) was started by conducting the projected dialkylation of lithiated dithiane **310** using commercially available (*S*)-propyleneoxide (**396**) as first alkylating agent, HMPA for triggering the Brook rearrangement and the known epoxide **395** as the second alkylating agent.[13] This protocol resulted in the formation of the advanced intermediate **397**. The ^{1}H and ^{13}C NMR spectra of **397** revealed the presence of all constituents of the three counterparts that were used for the linchpin reaction. A doublet at δ 1.22 with a coupling constant 6.2 Hz in the ^{1}H NMR spectrum integrating for three protons indicated the presence of a methyl group attached to a methine group and this was further supported by the appearance of a peak at 26.0 ppm (quartet) in the ^{13}C NMR spectrum. In the ^{1}H NMR spectrum the six methylenic protons of the 1,3-dithiane group resonated in upfield region and a peak at 51.3 ppm for a quarternary carbon in ^{13}C NMR spectrum further confirmed the presence of a dithioketal group. Two multiplet signals for terminal olefinic protons, one between δ 5.76–5.96 (1H), the other between 5.06–5.16 (2H) appeared in ^{1}H NMR spectrum and in support of this the ^{13}C NMR spectrum exhibited

the signals of olefinic carbons at 117.4 (t) and 134.7 (d) ppm. Results from mass spectrometry, IR, and elemental analysis were in accordance with the assigned structure for **397** (Scheme 9).



Scheme 9.

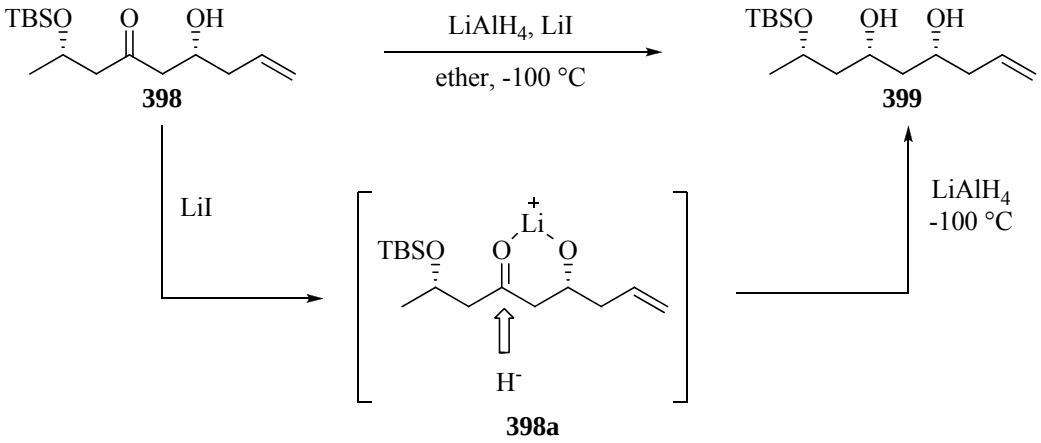
Being successful in constructing the key structural unit **397** in a single transformation, the next attention was turned towards deprotecting the dithioketal and functionalizing the so formed keto group. Amongst a few reagents examined, $PhI(CF_3COO)_2$, in CH_3CN-phosphate buffer (pH 7.0) (4:1) effectively deprotected dithioketal to give the corresponding hydroxyketone **398** in good yield (Scheme 10).[14]



Scheme 10.

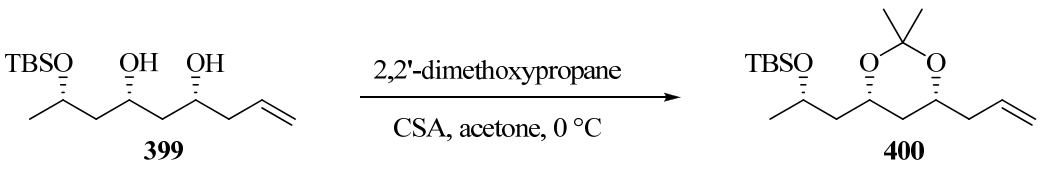
The signals corresponding to dithioketal group disappeared in the ^1H and ^{13}C NMR spectrums of **398**. The two methylene groups attached to the unmasked keto functionality shifted to downfield region in ^1H NMR spectrum and the carbonyl carbon resonated at 210.9 ppm in ^{13}C NMR spectrum. The presence of the keto functionality was also confirmed by the IR spectrum of **398** with C=O stretching at 1707 cm^{-1}.

The diastereoselective reduction of **398** with $LiAlH_4$ in the presence of LiI as a chelating agent in ether at –100 ^oC afforded diol **399** as the major product (*syn*/*anti* in 9:1 ratio).[15] The high selectivity using lithium aluminum hydride/ lithium iodide may be attributed to the fact that the upper side of the carbonyl group in **398a** is highly hindered due to the chelation with lithium cation thus hydride attack takes place from the lower side resulting in a *syn* isomer as the major product (Scheme 11). The stereochemical outcome of the keto reduction was further confirmed by converting the diol to the corresponding acetonide derivative.



Scheme 11.

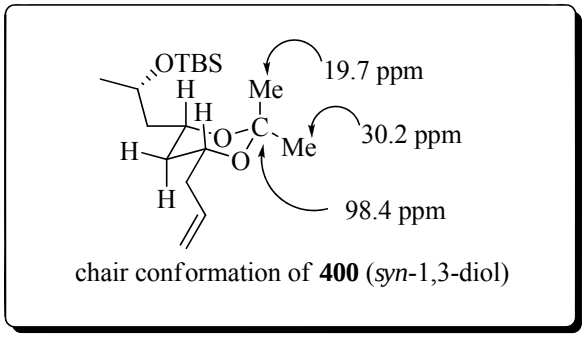
The diol **399** was subsequently transformed into the isopropylidene derivative **400** by treating with 2,2'-dimethoxypropane-catalytic CSA in acetone (Scheme 12).



Scheme 12.

The ^1H, ^{13}C NMR spectra of **400** revealed the presence of *syn* and *anti* isopropylidenes, approximately in 9:1 diastereomeric ratio. Two singlets at δ 1.36 and 1.41 in ^1H NMR spectrum, integrating for three protons each were assigned to the isopropylidene protection.

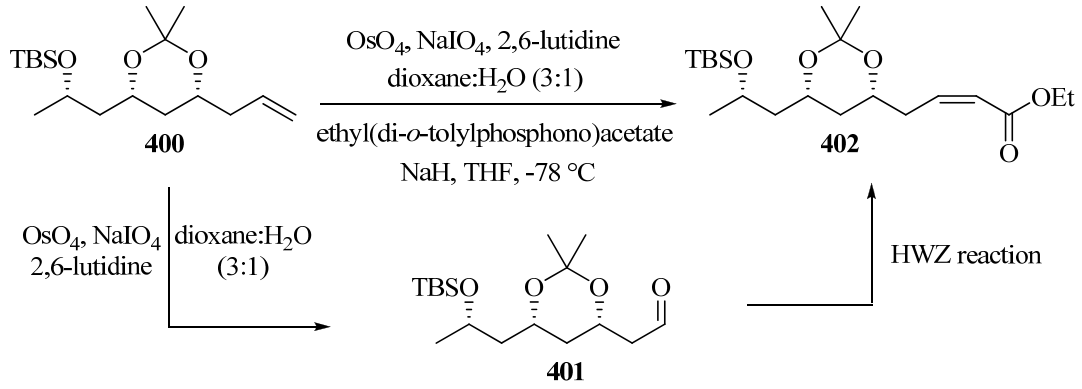
The 1,3-*syn* disposition of the diol moiety in **400** was established by analyzing its ^{13}C NMR spectrum. In the ^{13}C NMR of **400**, the acetonide methyl groups resonated at 19.7 and 30.2 ppm indicating a 1,3-*syn*-relationship and this was further substantiated by the appearance of the quaternary carbon in the downfield region 98.4 ppm (Figure 5).[4]



chair conformation of **400** (*syn*-1,3-diol)

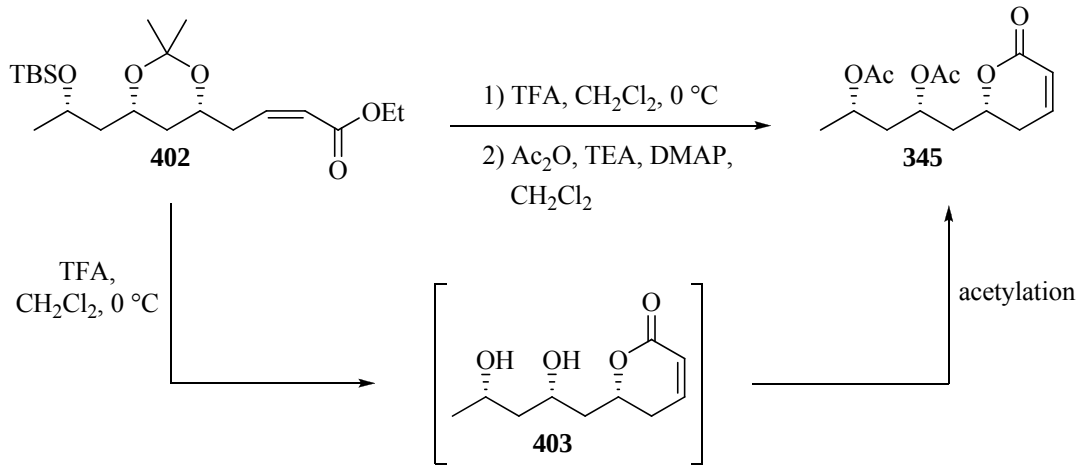
Figure 5.

Having established all the required stereocenters in compound **400**, the next target was set to install the dihydropyran ring. The oxidative cleavage of the terminal double bond of **400** using $OsO_4/NaIO_4$/2,6-lutidine[16] in dioxane-H_2O afforded the corresponding aldehyde **401** which was directly used for HWE reaction with ethyl(di-*o*-tolylphosphono)acetate[17] and NaH in THF to obtain *Z*-unsaturated ester **402** exclusively (Scheme 13). In the ^1H NMR spectrum of **402** two doublet of triplet signals each integrating for one proton appeared, one at δ 5.84 and the other in the downfield region at δ 6.32 indicating the presence of an α,β-unsaturated ester group. The geometry of the newly formed double bond was *cis* as it was evident by the coupling constant 11.5 Hz of the olefinic protons. Two signals corresponding to the internal olefin appeared at 121.1 and 145.7 ppm as doublets whereas the ester carbonyl group was visualized at 166.4 ppm in the ^{13}C NMR spectrum. The structure was further supported by the IR spectrum which revealed ester carbonyl at 1712 cm^{-1}. The highest mass peak *m/z* 423.4 $[M+Na]^+$ and elemental analysis supported the assigned structure **402**.



Scheme 13.

After some experimentation with various acids, TFA in CH_2Cl_2 at 0 ^oC was found to be apt for the deprotection of TBS and acetonide groups of **402** with concomitant lactonization to afford the dihydroxy lactone **403** which was acylated further by treating with acetic anhydride, triethylamine-DMAP in CH_2Cl_2 to complete the synthesis of cryptocarya diacetate (**345**) (Scheme 14).



Scheme 14.

The spectral and analytical data of the synthetic sample **345** were in good agreement with the reported data of natural cryptocarya diacetate.[1] In the ^1H NMR spectrum, proton of the δ-pyrone ring (H5) resonated as a multiplet at the range δ 5.12-5.06 which is a characteristic of the δ-pyranone ring systems. The signals due to the ring olefinic protons α (H1) and β (H2) to the lactone group were seen as ddd with

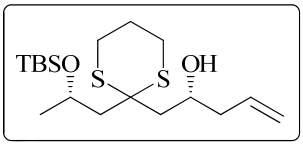
J = 9.5 Hz, at δ 6.0 and 6.85 respectively. The peaks corresponding to the two acetate protons appeared as singlets at δ 2.03 and 2.06. In the ^{13}C spectrum the peaks due to the two acetate groups were observed as singlets at 170.6 and 170.7 ppm, whereas the lactone carbonyl group appeared as a singlet at 163.8 ppm. The highest mass peak *m/z* 307.2 $[M+Na]^+$, elemental analysis and optical rotation [($[\alpha]_D^{22}$ +51.5, *c* 0.5, $CHCl_3$) {lit.[1a] $[\alpha]_D^{22}$ +55.8 (*c* 1.06, $CHCl_3$)}], not only serve as the supportive evidences in structure confirmation but also show the purity of the synthetic sample **345**.

Conclusion

A short synthesis of (+)-cryptocarya diacetate was achieved by employing three component linchpin coupling, diastereoselective reduction of β-hydroxyketone, and *Z*-selective HWE reaction as key transformations. The overall sequence involves about 6 linear steps and yielded the final natural product in 23% (overall). Considering simplicity of the strategy that was adopted and its potential for synthesis of related 1,3-polyol natural products, we believe that this work will be of interest to researchers working in this area.

EXPERIMENTAL

(2*S*,6*R*)-2-*O*-^{t}Butyldimethylsilyl)-4-(1,3-propanedithianyl)-2,6-hydroxy-non-8-ene (397)

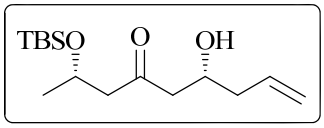


At –10 ^{o}C, a solution of TBS-dithiane **310** (500 mg, 2.13 mmol) in THF (10 mL) was treated with *n*-Butyllithium (0.92 mL, 2.34 M in hexanes, 2.15 mmol) under argon and allowed to stir for 2 h. The mixture was cooled to –78 ^{o}C and added (*S*)-propyleneoxide **396** (124 mg, 2.13 mmol) in THF (1 mL). The first alkylation was complete in 1 h while warming the reaction mixture slowly to –40 ^{o}C. The mixture was cooled to –78 ^{o}C and HMPA (1.15 g, 6.4 mmol) was added. Warming the mixture to –40 ^{o}C and stirring for 30 min at the same temperature resulted in complete Brook's rearrangement. Then the mixture was recooled to –78 ^{o}C and the second epoxide **395** (250 mg, 2.5 mmol) in THF (1 mL) was added. After 1 h stirring at –10 ^{o}C, the reaction was quenched with saturated NH_4Cl and extracted with ether (2 x 20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (15% ethyl acetate in petroleum ether) to furnish **397** (549 mg, 68% yield) as a colorless oil.

Mol. Formula	: $C_{18}H_{36}O_2S_2Si$
$[\alpha]_D$	: –2.5 (*c* 1, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3438, 2954, 1640, 1439, 1254, 1130, 836, 775 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 5.96–5.76 (m, 1H), 5.16–5.06 (m, 2H), 4.22–4.06 (m, 2H), 3.42 (br s, 1H), 2.95–2.76 (m, 4H), 2.39–1.88 (m, 8H), 1.22 (d, *J* = 6.19 Hz, 3H), 0.87 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ –4.2 (q), –3.9 (q), 17.9 (s), 24.7 (t), 25.9 (q, 3C), 26.0 (q), 26.1 (t), 26.5 (t), 42.2 (t), 45.0 (t), 49.2 (t), 51.3 (s), 65.9 (d), 67.9 (d), 117.4 (t), 134.7 (d) ppm
ESI-MS (*m/z*)	: 399.2 $[M+Na]^{+}$.

Elemental Analysis Calcd.: C, 57.39; H, 9.63; S, 17.02.
Found: C, 57.35; H, 9.67; S, 16.98.

(2*S*,6*R*)-2-*O*-^{t}Butyldimethylsilyl)-2,6-hydroxy-non-8-en-4-one (398)



To an ice cooled solution of dithiane **397** (500 mg, 1.32 mmol) in CH_3CN–phosphate buffer (pH 7, 4:1, 10 mL) was added $PhI(CF_3COO)_2$ (645 mg, 1.5 mmol). Reaction mixture was stirred at rt for 1 h after which the TLC indicated the disappearance of starting material. The mixture was diluted with ethyl acetate and two layers were separated. Organic layer was washed with satd. $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (20% ethyl acetate in petroleum ether) to give the hydroxy ketone **398** (295 mg, 78% yield) as a colorless oil.

Mol. Formula : $C_{15}H_{30}O_3Si$

$[\alpha]_D$: –7.1 (*c* 0.5, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3419, 2928, 2855, 1707, 1376, 1256, 1128, 1088, 836, 758 cm^{-1}.

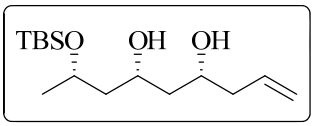
^{1}H NMR ($CDCl_3$, 400 MHz) : δ 5.84–5.76 (m, 1H), 5.14–5.12 (m, 1H), 5.10 (br t, *J* = 1.3 Hz, 1H) 4.34–4.26 (m, 1H), 4.11 (ddd, *J* = 2.4, 8.3, 14.8 Hz, 1H), 3.06 (br s, 1H), 2.69–2.62 (m, 2H), 2.54 (dd, *J* = 9, 17.8 Hz, 1H), 2.45 (dd, *J* = 5, 15 Hz, 1H), 2.31–2.20 (m, 2H), 1.17 (d, *J* = 6.2 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ –4.9 (q), –4.5 (q), 17.9 (s), 23.9 (q), 25.8 (q, 3C), 40.8 (t), 50.0 (t), 53.0 (t), 65.4 (d), 66.9 (d), 117.9 (t), 134.2 (d), 210.9 (s) ppm.

ESI-MS (*m/z*) : 309.2 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 62.89; H, 10.55.
Found: C, 62.93; H, 10.61.

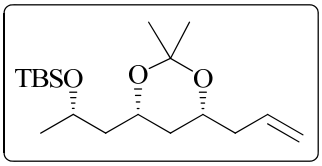
(2*S*,4*S*,6*R*)-2-*O*-^{t}Butyldimethylsilyl-nonene-2,4,6-triol (399)



To a solution of β-hydroxy ketone **398** (250 mg, 0.87 mmol) in dry ether (10 mL) at room temperature under argon was added LiI (584 mg, 4.36 mmol) and the mixture was stirred at –40 ^oC for 5 min. The resulting mixture was then cooled to –100 ^oC and $LiAlH_4$ (166 mg, 4.36 mmol) was added. The reaction mixture was stirred for 30 min at the same temperature. The reaction mixture was quenched with ice, diluted with ethyl acetate and subsequently filtered through a celite pad. The filtrate was concentrated and the residue was purified column chromatography (25% ethyl acetate in petroleum ether) to afford the title compound **399** (225 mg, 89% yield) as a colorless oil.

Mol. Formula	: $C_{15}H_{32}O_3Si$
$[\alpha]_D$	: +29.5 (*c* 0.8, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3460, 3019, 2932, 2400, 1597, 1428, 1215, 838, 758, 669 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 5.89–5.79 (m, 1H), 5.14–5.08 (m, 2H), 4.11–4.00 (m, 3H), 3.95–3.89 (m, 1H), 2.31–2.19 (m, 2H), 1.67–1.47 (m, 4H), 1.18 (d, *J* = 6 Hz, 3H), 0.90 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ –4.8 (q), –3.9 (q), 17.9 (s), 24.5 (q), 25.8 (q, 3C), 42.2 (t), 42.7 (t), 46.2 (t), 69.8 (d), 71.4 (d), 72.4 (d), 117.4 (t), 134.9 (d) ppm.
ESI-MS (*m/z*)	: 311.3 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 62.45; H, 11.18.
	Found: C, 62.41; H, 11.16.

(2*S*,4*S*,6*R*)-4,6-*O*-Isopropylidene-2-*O*-^{t}butyl-dimethylsilyl-nonene-2,4,6-triol (400)

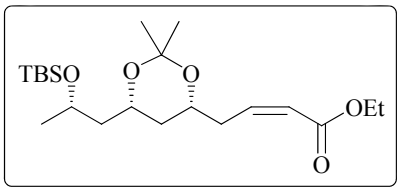


A solution of diol **399** (200 mg, 0.69 mmol), 2,2'-dimethoxypropane (0.17 mL, 1.4 mm) in dry acetone (5 mL) was exposed to CSA (16 mg, 0.07 mmol), at 0 ^oC and

the reaction mixture was allowed to stir for 30 min at room temperature. The mixture was neutralized by adding few drops of triethylamine and concentrated under vacuum. The crude was purified by column chromatography (10% ethyl acetate in petroleum ether) to afford the mixture of diastereomers of **400** (*syn*:*anti* 9:1) (227 mg, 91% yield) as a colorless oil.

Mol. Formula	: $C_{18}H_{36}O_3Si$
$[\alpha]_D$	: +13.3 (*c* 0.9, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3369, 3019, 2930, 2857, 1597, 1381, 1216, 1117, 836, 758, 668 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 5.83–5.73 (m, 1H), 5.10–5.03 (m, 2H), 3.98–3.90 (m, 2H), 3.88–3.81 (m, 1H), 2.33–2.27 (m, 1H), 2.13 (dt, *J* = 7.1, 14.2 Hz, 1H), 1.73 (dt, *J* = 6.5, 13.5 Hz, 1H), 1.54 (dt, *J* = 2.5, 12.9 Hz, 1H), 1.44–1.33 (m, 2H), 1.41 (s, 3H), 1.36 (s, 3H), 1.13 (d, *J* = 5.9 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H) 0.03 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ –4.8 (q), –4.2 (q), 18.1 (s), 19.7 (q), 23.7 (q), 25.8 (q, 3C), 30.2 (q), 36.5 (t), 40.9 (t), 46.1 (t), 65.0 (d), 66.2 (d), 68.6 (d), 98.4 (s), 117.1 (t), 134.2 (d) ppm
ESI-MS (*m/z*)	: 351.3 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 65.80; H, 11.04. Found: C, 65.78; H, 11.07.

(5*R*,7S,9S)-Ethyl-5,7-*O*-isopropylidene-9-*O*-^{t}butyldimethylsilyl-5,7,9-trihydroxy-dec-2-enoic acid (402)



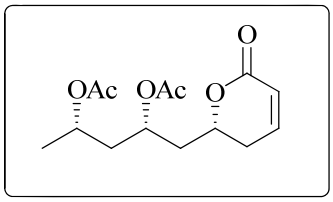
To a solution of olefin **400** (100 mg, 0.3 mmol) in dioxane:water (3:1, 4 mL) were added 2,6-lutidine (70 µl, 0.6 mmol), OsO_4 (0.1 mL, 0.1 M in toluene, 165 mg, 0.01 mmol), and $NaIO_4$ (257 mg, 1.2 mmol). The reaction was stirred at rt, and the progress of the reaction was monitored by TLC. After the reaction was complete (3 h), water (5 mL) and CH_2Cl_2 (10 mL) were added. The layers ware separated, and the water layer was extracted by CH_2Cl_2 (3 x 10 mL). The combined organic layers were

washed with brine, and dried over Na_2SO_4. The solvent was removed, and the crude aldehyde **401** was directly used for next reaction without any further purification.

To a solution of ethyl (di-*o*-tolylphosphono)acetate (210 mg, 0.6 mmol) in THF (12 mL) at 0 ^oC was added NaH (24 mg, 60% w/w in paraffin oil, 0.6 mmol). 30 min later the reaction mixture was cooled to –78 ^oC and a solution of aldehyde **401** in THF (3 mL) was added dropwise. The resulting reaction mixture was stirred for 45 min at the same temperature. Reaction was quenched with ice water and slowly warmed to ambient temperature. The mixture was extracted with ethyl acetate, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (10% ethyl acetate in petroleum ether) to produce the Z-unsaturated ester **402** exclusively (95 mg, 76% yield over two steps) as a pale yellow oil.

Mol. Formula	: $C_{21}H_{40}O_5Si$
$[\alpha]_D$	: +24.0 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3401, 3020, 2930, 2857, 1712, 1596, 1381, 1216, 1119, 1036, 938, 836, 757, 668, cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 6.32 (dt, *J* = 7.0, 11.5 Hz, 1H), 5.84 (dt, *J* = 1.8, 11.5 Hz, 1H), 4.15 (q, *J* = 7 Hz, 2H), 3.99–3.90 (m, 3H), 2.94–2.86 (m, 1H), 2.77–2.69 (m, 1H), 1.73 (dt, *J* = 6.8, 13.5 Hz, 1H), 1.52 (dt, *J* = 2.5, 13.0 Hz, 1H), 1.44–1.32 (m, 2H), 1.41 (s, 3H), 1.36 (s, 3H), 1.27 (t, *J* = 7.0 Hz, 3H), 1.13 (d, *J* = 6.0 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz)	:δ –4.8 (q), –4.3 (q), 14.3 (q), 18.0 (s), 19.7 (q), 23.6 (q), 25.8 (q, 3C), 30.1 (q), 35.6 (t), 36.7 (t), 46.1 (t), 59.8 (t), 65.0 (d), 66.2 (d), 68.4 (d), 98.5 (s), 121.1 (d), 145.7 (d), 166.4 (s) ppm.
ESI-MS (*m/z*)	: 423.4 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 62.96; H, 10.06. Found: C, 62.92; H, 10.10.

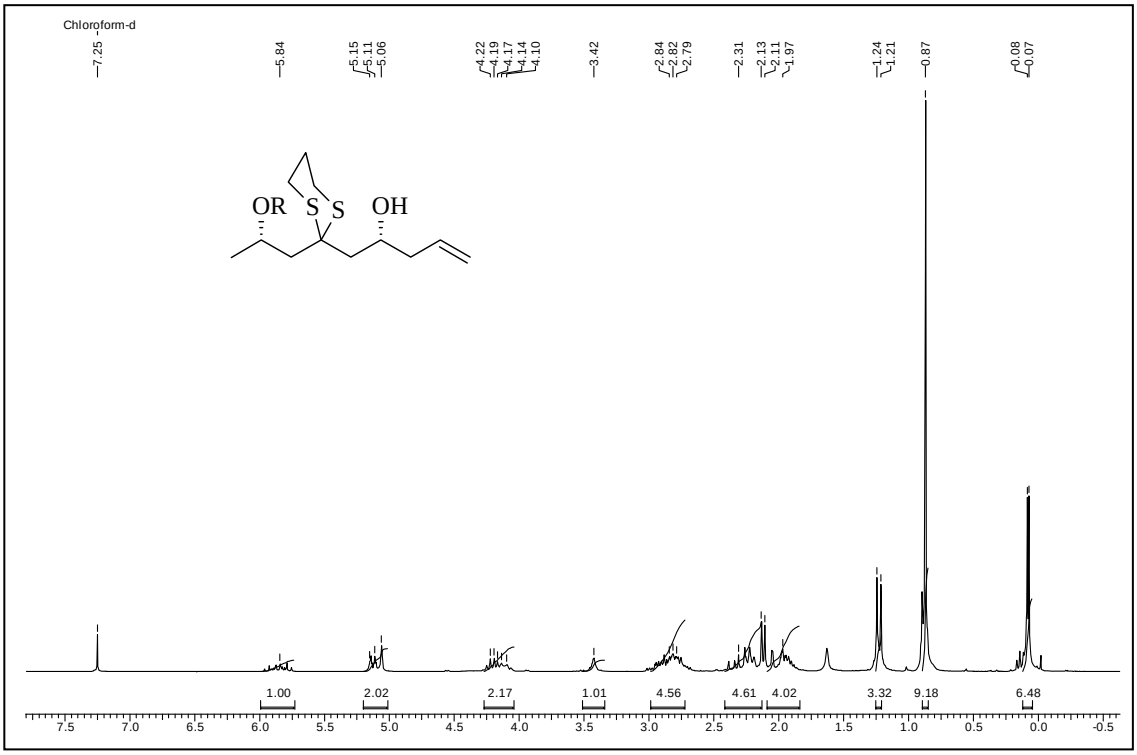
Cryptocarya diacetate (345)



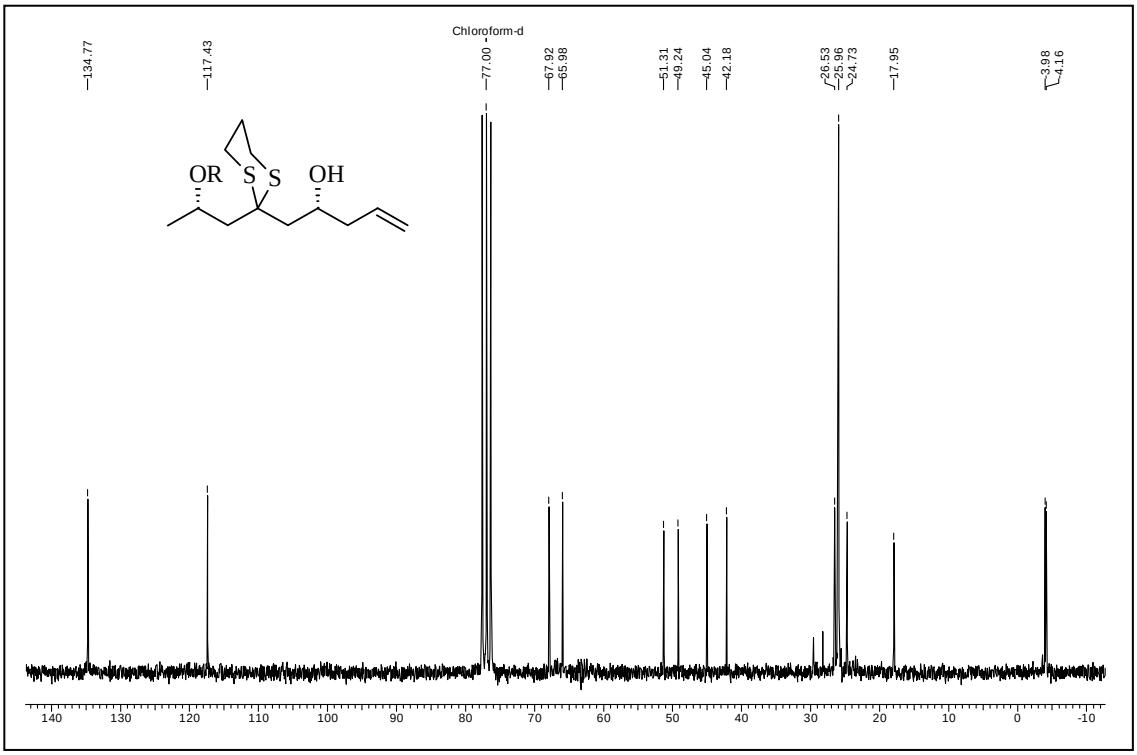
A solution of ester **402** (30 mg, 0.075 mmol) in CH_2Cl_2 was treated with TFA at 0 ^oC and allowed to stir for 1 h at the same temperature. Reaction mixture was concentrated and co-distilled twice with toluene under reduced pressure to remove TFA completely. The crude dihydroxylactone **403** was then dissolved in CH_2Cl_2, and was treated with triethylamine (0.1 mL, 0.75 mmol), Ac_2O (0.05 mL, 0.375 mmol) and catalytic amount of DMAP. The reaction mixture was stirred for 3 h at room temperature. The mixture was concentrated under reduced pressure and the residue was consequently purified by flash chromatography (40% EtOAc in petroleum ether) to afford cryptocarya diacetate (**345**) (15 mg, 70% yield, over two steps) as a colorless oil.

Mol. Formula	: $C_{14}H_{20}O_6$
$[\alpha]_D$	: +51.5 (*c* 0.5, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3449, 3018, 1734, 1490, 1376, 1216, 875, 755, 667 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 6.85 (ddd, *J* = 2.5, 6.0, 9.5 Hz, 1H), 6.00 (ddd, *J* = 0.9, 2.5, 9.5 Hz, 1H), 5.12–5.06 (m, 1H), 5.01–4.93 (m, 1H), 4.54–4.46 (m, 1H), 2.44 (dddd, *J* = 0.9, 3.9, 5.8, 18.4 Hz, 1H), 2.30 (ddt, *J* = 2.6, 11.5, 18.4 Hz, 1H), 2.15 (ddd, *J* = 6.5, 8.5, 14.6 Hz, 1H), 2.06 (s, 3H), 2.03 (s, 3H), 1.98 (dd, *J* = 7.2, 14.4 Hz, 1H), 1.93 (ddd, *J* = 3.9, 6.6, 14.6 Hz, 1H), 1.78 (dt, *J* = 5.8, 14.3 Hz, 1H), 1.25 (d, *J* = 6.3 Hz, 3H).
^{13}C NMR ($CDCl_3$, 100MHz)	: δ 20.2 (q), 21.2 (q), 21.3 (q), 29.2 (t), 39.2 (t), 40.5 (t), 67.7 (d), 67.8 (d), 74.9 (d), 121.4 (d), 144.7 (d), 163.8 (s), 170.6 (s), 170.7 (s) ppm.
ESI-MS (*m/z*)	: 307.2 $(M+Na)^+$.
Elemental Analysis	Calcd.: C, 59.14; H, 7.09. Found: C, 59.19; H, 7.11.

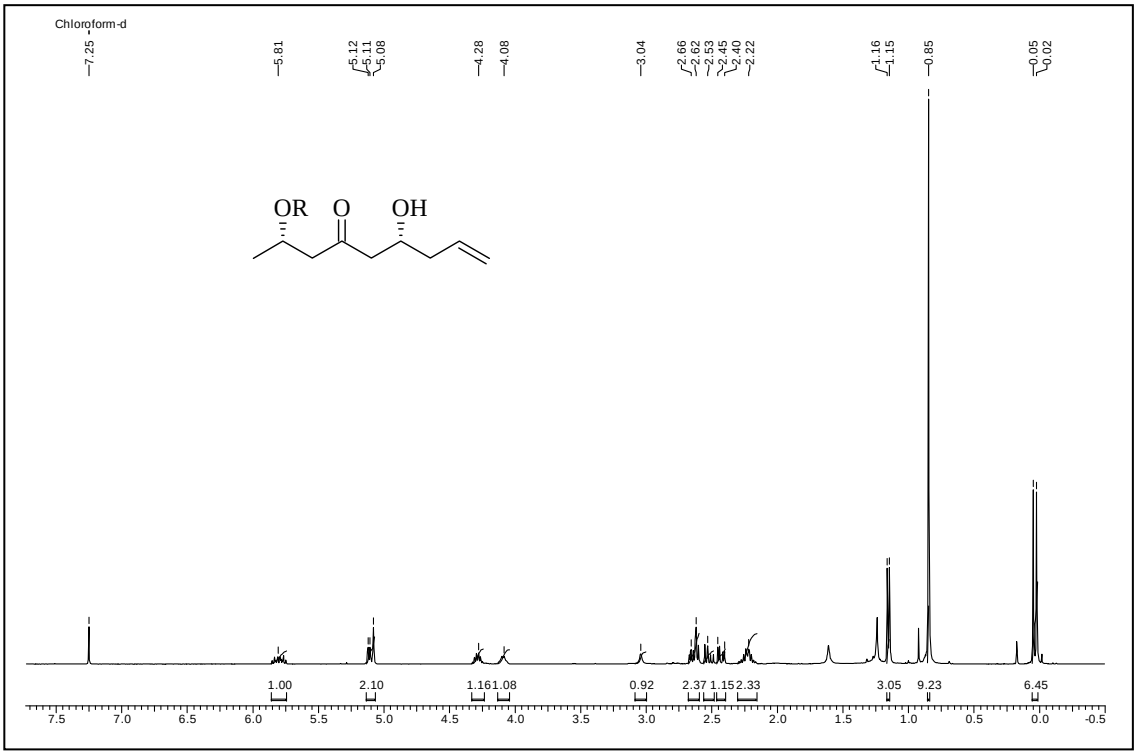
SPECTRA



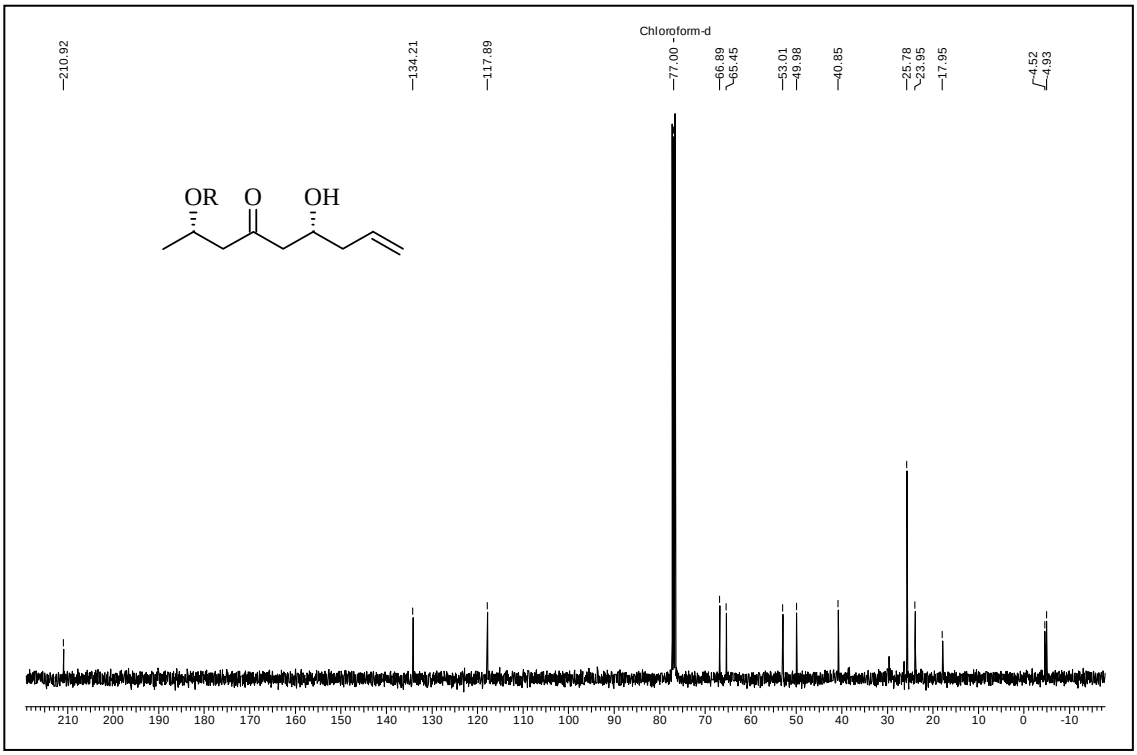
^{1}H NMR Spectrum of 397 in $CDCl_3$ (R = TBS)



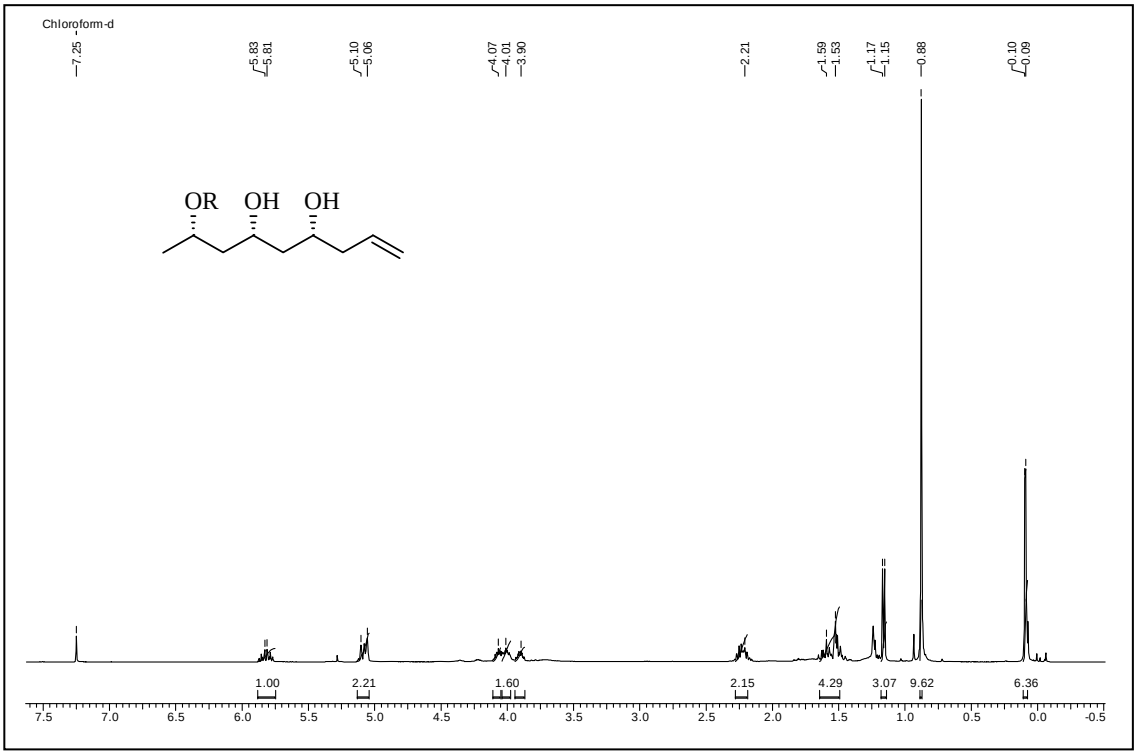
^{13}C NMR Spectrum of 397 in $CDCl_3$ (R = TBS)



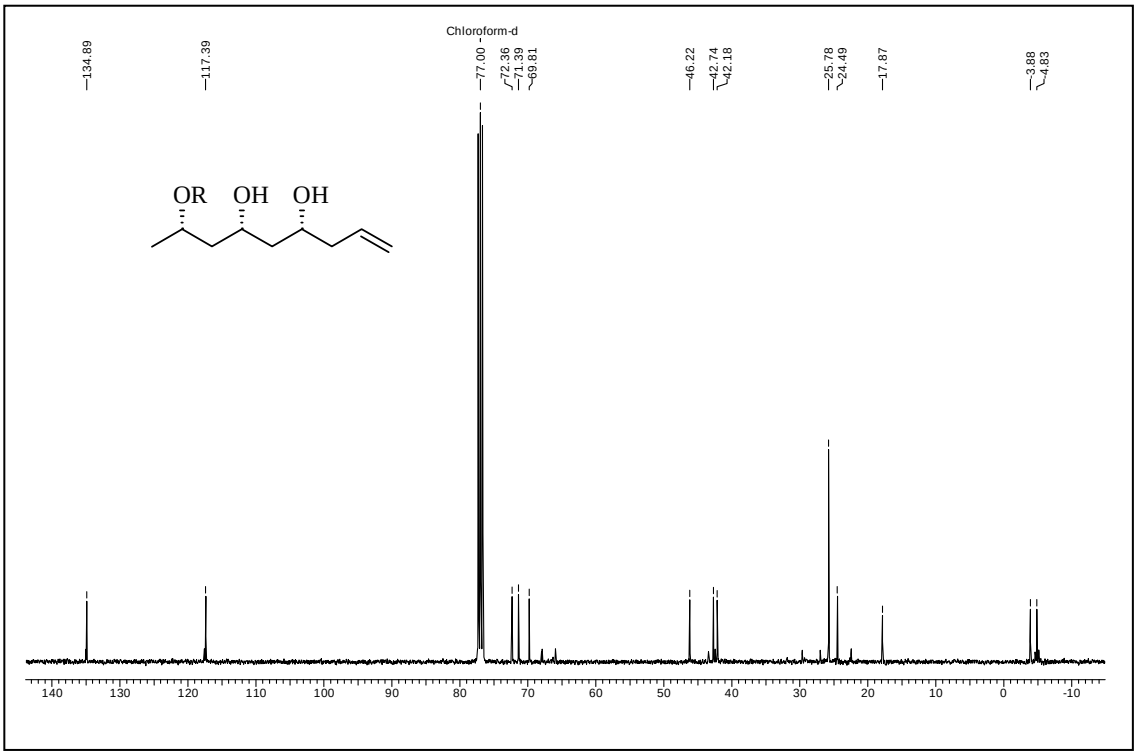
^{1}H NMR Spectrum of 398 in $CDCl_3$ (R = TBS)



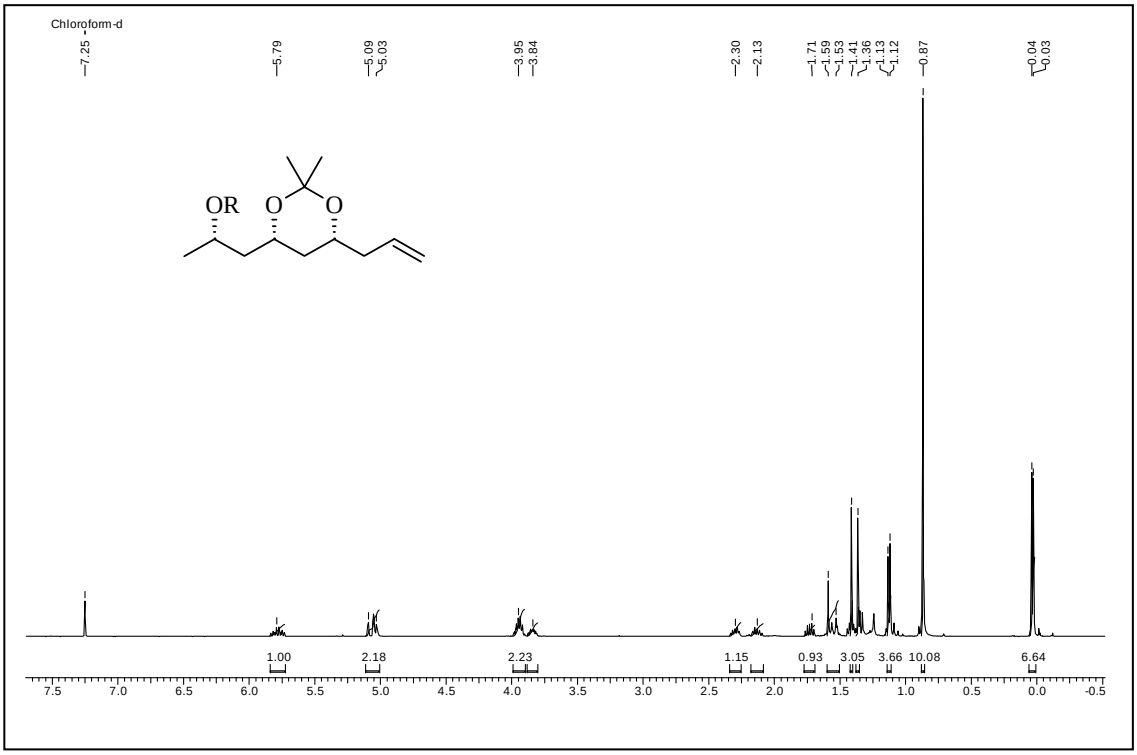
^{13}C NMR Spectrum of 398 in $CDCl_3$ (R = TBS)



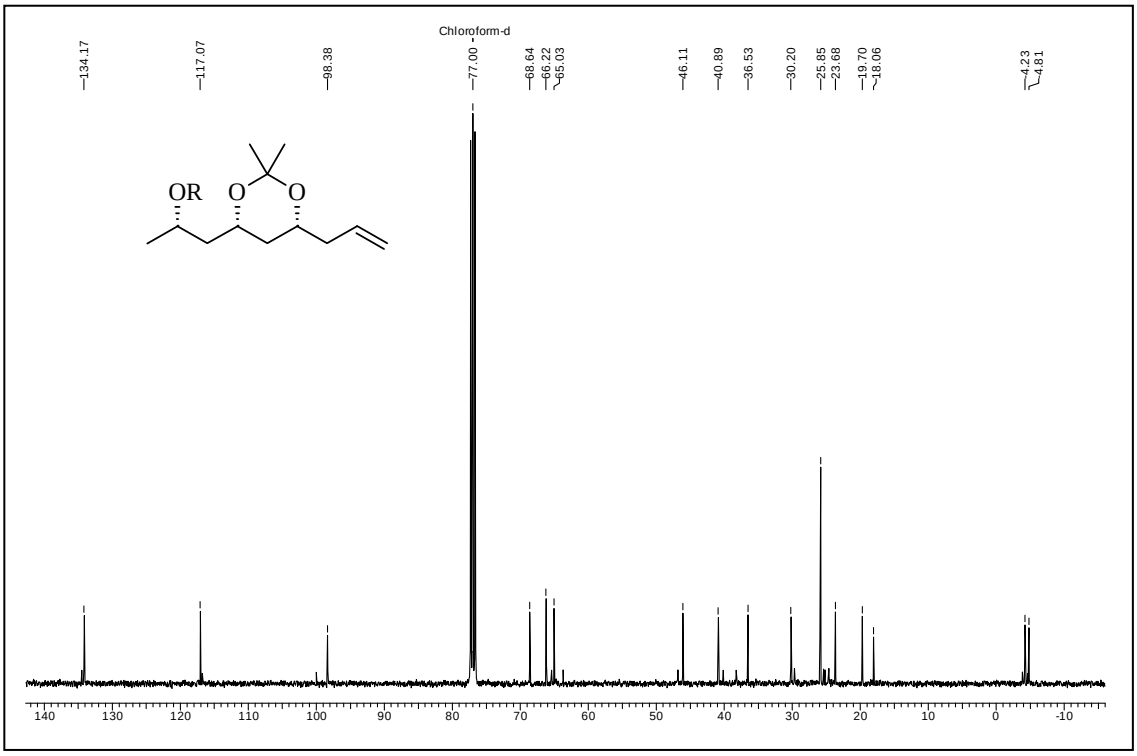
^{1}H NMR Spectrum of 399 in $CDCl_3$ (R = TBS)



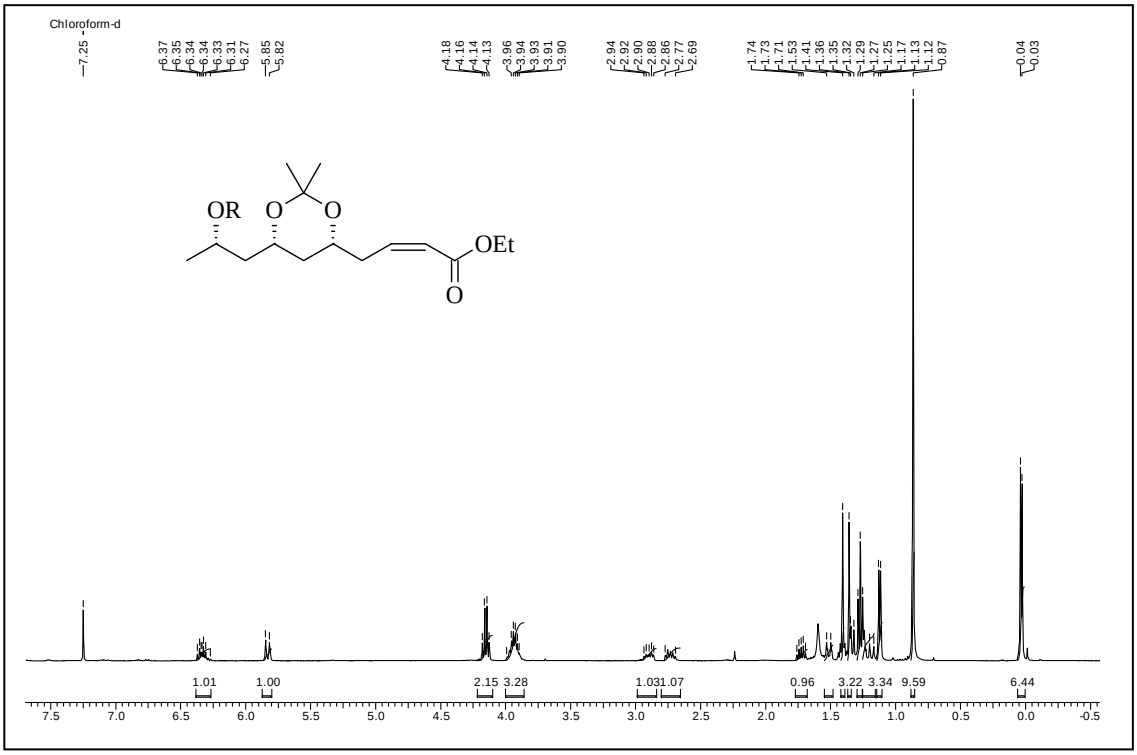
^{13}C NMR Spectrum of 399 in $CDCl_3$ (R = TBS)



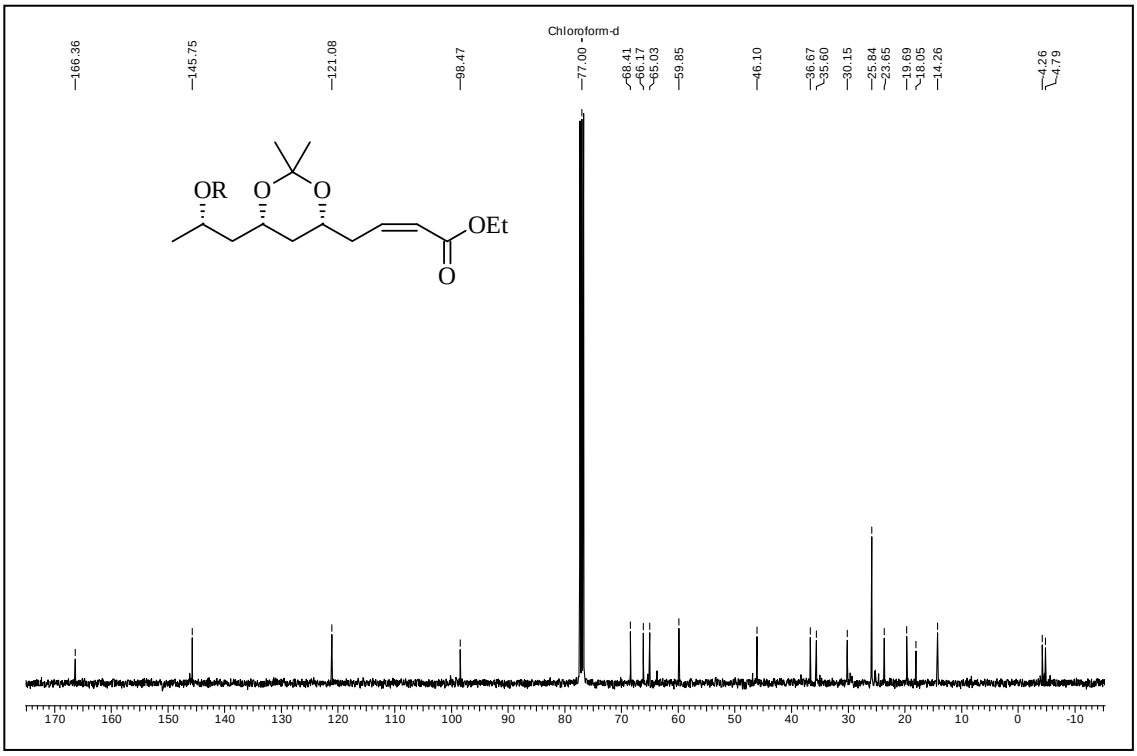
^{1}H NMR Spectrum of 400 in $CDCl_3$ (R = TBS)



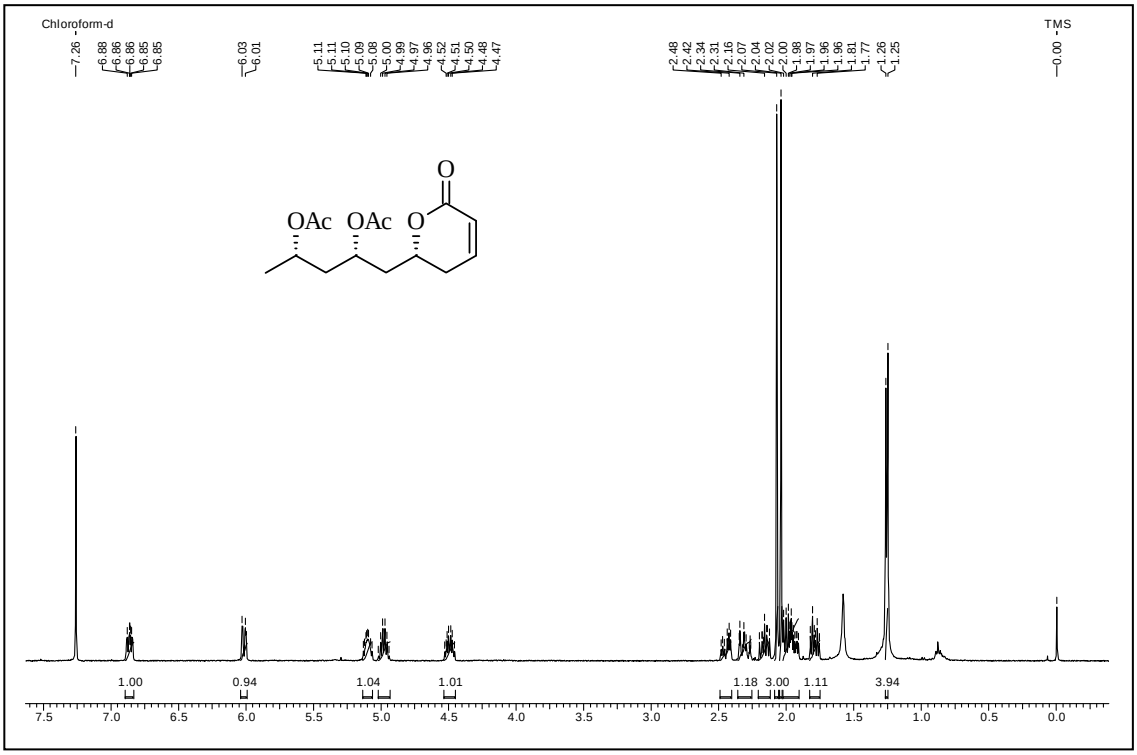
^{13}C NMR Spectrum of 400 in $CDCl_3$ (R = TBS)



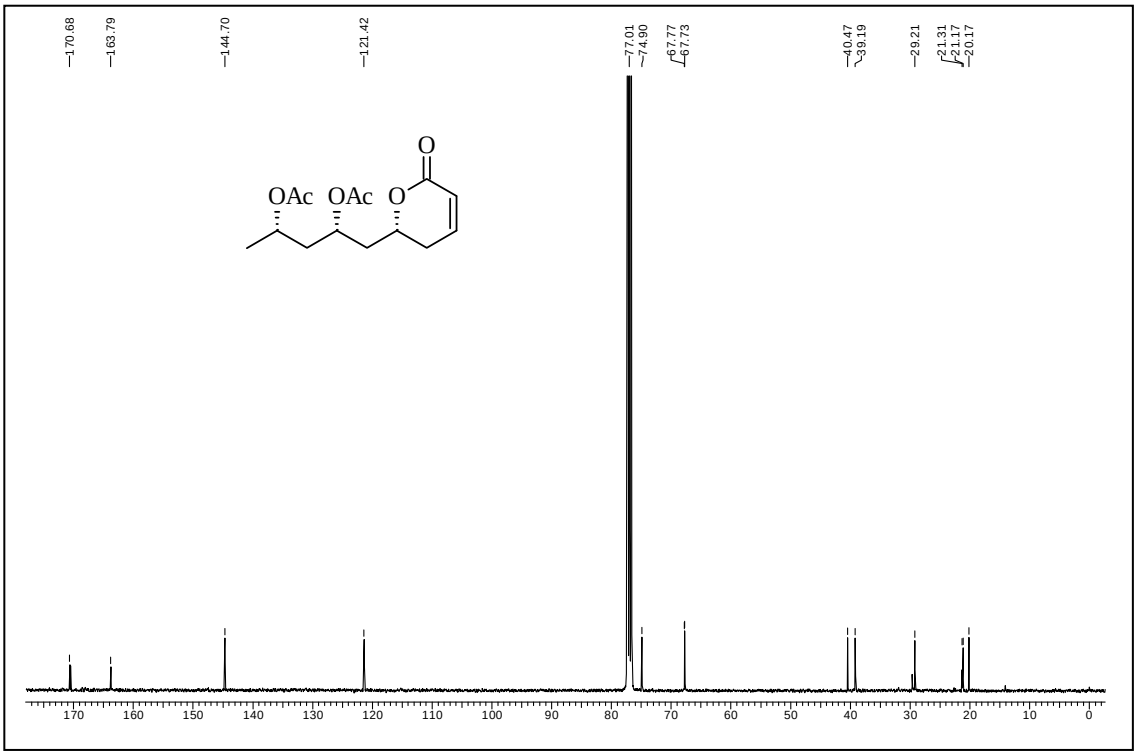
^{1}H NMR Spectrum of 402 in $CDCl_3$ (R = TBS)



^{13}C NMR Spectrum of 402 in $CDCl_3$ (R = TBS)



^{1}H NMR Spectrum of 345 in $CDCl_3$



^{13}C NMR Spectrum of 345 in $CDCl_3$

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LIST OF PUBLICATIONS

1. " A carbohydrate-based approach for the total synthesis of strictifolione" C. V. Ramana,* N. Raghupathi, Mukund K. Gurjar and Mukund S. Chorghade, *Tetrahedron Lett.* **2005,** *46*, 4073.

2. "A short total synthesis of (+)-cryptocarya diacetate**"** Mukund K. Gurjar,* N. Raghupathi and Mukund S. Chorghade, *communicated for publication.*

3. "Synthesis of the key polyol unit of marinomycin A" *manuscript under preparation.*