# Studies Directed Towards Enantioselective Total Synthesis of Some Naturally Occurring Lactones and Hydrolytic Kinetic Resolution (HKR) of Terminal Mono and Bis-Epoxides

A THESIS SUBMITTED TO THE

**UNIVERSITY OF PUNE**

FOR THE DEGREE OF

***DOCTOR OF PHILOSOPHY***

*IN*

**CHEMISTRY**

*BY*

**Partha Sarathi Chowdhury**

**(RESEARCH GUIDE)**

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## CERTIFICATE

This is to certify that the work presented in the thesis entitled "**Studies Directed Towards Enantioselective Total Synthesis of Some Naturally Occurring Lactones and Hydrolytic Kinetic Resolution (HKR) of Terminal Mono and Bis-Epoxides"** submitted by **Partha Sarathi Chowdhury** was carried out by the candidate at CSIR-National Chemical Laboratory, Pune under my supervision. Such materials as obtained from other sources have been duly acknowledged in the thesis.

**(Dr. Pradeep Kumar)**

**Research Guide** **September 2013**


# CANDIDATE'S DECLARATION

I hereby declare that the thesis entitled "**Studies Directed Towards Enantioselective Total Synthesis of Some Naturally Occurring Lactones and Hydrolytic Kinetic Resolution (HKR) of Terminal Mono and Bis-Epoxides**" submitted for the degree of Doctor of Philosophy in Chemistry to the University of Pune has not been submitted by me to any other university or Institution. This work was carried out at CSIR-National Chemical Laboratory, Pune, India.

**Partha Sarathi Chowdhury**

**Senior Research Fellow (CSIR)**

**Organic Chemistry Division** **September 2013**

**CSIR-National Chemical Laboratory**

**Pune-411008**

*Dedicated to*
*To*
*My Beloved*
*Family*

**We are responsible for what we are, and whatever we wish ourselves to be, we have the power to make urselves. If what we are now has been the result of our own past actions, it certainly follows that whatever we wish to be in the future can be produced by our present actions; so we have to know how to act.**

**Swami Vivekananda.**

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***Partha Sarathi Chowdhury***

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## Chapter 2

## Asymmetric Total Synthesis of Naturally Occurring 10-Membered Lactones



## Chapter 3

## Synthesis of 6-Substituted-5,6-Dihydro-2*H*-Pyran-2-Ones

# Abbreviations

| | | |
|---|---|---|
| Ac | - | Acetyl |
| AcOH | - | Acetic acid |
| $Ac_2O$ | - | Acetic anhydride |
| Bn | - | Benzyl |
| BnBr | - | Benzyl bromide |
| $BH_3 \cdot Me_2S$ | - | Boron dimethyl sulfide complex |
| Boc | - | *tert*-Butoxy carbonyl |
| $(Boc)_2O$ | - | Di-*tert*-butyl dicarbonate |
| BuLi | - | Butyl lithium |
| Cat. | - | Catalytic |
| $CDCl_3$ | - | Deuterated chloroform |
| DBU | - | 1,8-Diazabicyclo[5.4.0]undecene-7 |
| DCM | - | Dichloromethane |
| DDQ | - | 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone |
| DIBAL-H | - | Diisobutylaluminium hydride |
| DMP | - | 2,2-Dimethoxypropane |
| DMF | - | *N, N′*-Dimethylformamide |
| DMAP | - | *N,N′*-Dimethylaminopyridine |
| DMSO | - | Dimethyl sulfoxide |
| *ee* | - | Enantiomeric excess |
| equiv. | - | Equivalents |
| EtOH | - | Ethanol |
| Et | - | Ethyl |
| $Et_2O$ | - | Diethyl ether |
| EtOAc | - | Ethyl acetate |

| | | |
|---|---|---|
| $Et_3N$ | - | Triethylamine |
| Hz | - | Hertz |
| HPLC | - | High pressure liquid chromatography |
| IBX | - | Iodoxybenzoic Acid |
| Im | - | Imidazole |
| LiHMDS | - | Lithium hexamethyl disilazide |
| *m*-CPBA | - | *m*-Chloroperbenzoic acid |
| MeOH | - | Methanol |
| mg | - | Milligram |
| min | - | Minutes |
| mL | - | Millilitre |
| mmnol | - | Millimole |
| M. p. | - | Melting point |
| Ms | - | Methanesulfonyl |
| Me | - | Methyl |
| MeI | - | Methyl iodide |
| $NaBH_4$ | - | Sodiumborohydride |
| NaH | - | Sodium hydride |
| Ph | - | Phenyl |
| Py | - | Pyridine |
| PMB | - | *para*-Methoxy benzyl |
| *p*-TSA | - | *par*a-Toluenesulfonic acid |
| RCM | - | Ring closing metathesis |
| TEA | - | Triethylamine |
| TBAI | - | Tetra-*n*-butylammonium iodide |
| TBAF | - | Tetra-*n*-butylammonium fluoride |
| TBDMS | - | *tert*-Butyldimethyl silyl |
| TBSCl | - | *tert*-Butyldimethyl silyl chloride |

| | | |
|---|---|---|
| THF | - | Tetrahydrofuran |
| TPP | - | Triphenylphosphine |
| *p*-TSA | - | *p*-Toluenesulphonic acid |
| TsCl | - | *p*-Toluenesulphonyl chloride |

# General remarks

- $^{1}H$ NMR spectra were recorded on AC-200 MHz, MSL-300 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 AC-50 MHz, MSL-75 MHz, and DRX-125 MHz spectrometer.
- EI Mass spectra were recorded on Finnigan 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, $I_2$, ninhydrin and anisaldehyde in ethanol as development reagents.
- All solvents and reagents were purified and dried by according to procedures given in Vogel's Text Book of Practical Organic Chemistry. All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 40 °C.
- Silica gel (60–120) used for column chromatography was purchased from ACME Chemical Company, Mumbai, India.
- All melting points and boiling points are uncorrected and the temperatures are in centigrade scale.

- The compounds, scheme and reference numbers given in each section of chapter refers to that particular section of the chapter only.

# Abstract

The thesis entitled "**Studies Directed Towards Enantioselective Total Synthesis of Some Naturally Occurring Lactones and Hydrolytic Kinetic Resolution (HKR) of Terminal Mono and Bis-Epoxides"** has been divided into four chapters.

**Chapter 1:** Introduction to Jacobsen's hydrolytic kinetic resolution, proline-catalysed reactions and silicon tethered ring-closing metathesis reactions.

**Chapter 2:** Asymmetric total synthesis of naturally occurring 10-membered lactones and is divided into two sections.

**Chapter 3:** Synthesis of 6-Substituted-5,6-Dihydro-2*H*-Pyran-2-Ones and is divided into two sections.

**Chapter 4:** A desymmetrization approach to the enantiopure *syn/anti*-1,5-diols via hydrolytic kinetic resolution (HKR) of functionalized meso bis-epoxides: Further elaboration to *syn/syn*-1,3,5-triols and application to the formal synthesis of cryptocarya diacetate

## Chapter 1: Introduction to Jacobsen's hydrolytic kinetic resolution, proline catalysed reactions and silicon tethered ring-closing metathesis reactions

This chapter gives a brief introduction to the Jacobsen's hydrolytic kinetic resolution (HKR),[1] proline catalysed reactions[2] and silicon tethered ring-closing metathesis reactions.[3] Asymmetric synthesis of bioactive molecules is in the forefront of synthetic organic chemistry due to varied applications in drug and pharmaceutical industries. A large number of enantiomerically pure compounds have been obtained from nature, but quite a few of them are either not easily isolated or not available in useful amounts. However, an organic chemist can provide multi-gram biologically active compounds. The ultimate goal of an organic chemist is, how to assemble a given target molecule from readily available starting materials and reagents in highly efficient way. It is more elegant and economical to prepare just wanted isomer by asymmetric synthesis and through inexpensive catalytic processes.

The hydrolytic kinetic resolution (HKR) of terminal epoxides catalyzed by chiral (salen) Co(III)OAc complex affords both recovered epoxides and 1,2-diol products in

highly enantio-enriched form. In many cases there exist no practical alternatives for accessing these valuable chiral building blocks from inexpensive racemic materials.

The field of asymmetric organocatalysis is rapidly developing and attracts an increasing number of research groups around the world. In particular, organocatalytic asymmetric syntheses have provided several new methods for obtaining chiral compounds. In this connection, proline, an abundant, inexpensive amino acid available in both enantiomeric forms, has emerged as arguably the most practical and versatile organocatalyst. Proline has also been found to be an excellent asymmetric catalyst for α-functionalization of carbonyl compounds.

Temporary tethers were developed to transform an intermolecular reaction into the corresponding intramolecular variant through the sequential coupling of reacting partners. A silicon tether was initially utilized in the context of free radical addition in mid 1980s by the independent study of Nishiyama and Stork. As the field progressed, reactions such as cross-coupling reactions, hydrosilylation and [4+2] cycloadditions further expanded the scope of silicon-tether chemistry. More recently, the focus has been shifted toward the transition-metal-catalyzed cycloisomerization and ring-closing metathesis reactions.

In this chapter, we have described aforementioned reactions. During the course of our research work we have prepared epoxides, chiral diols and polyacylated-6-heptenyl-5,6-dihydro-2*H*-pyran-2-ones and successfully employed these synthetic intermediate towards the synthesis of decarestrictine J, aspinolide A, umuravumbolide, hyptolide and 1,3-polyols.

**Chapter 2: Asymmetric Total Synthesis of Naturally Occurring 10-Membered Lactones.**

The chapter 2 deals with the asymmetric synthesis of naturally occurring 10-membered lactones such as decarestrictine J **1a** and aspinolide A **1b**.

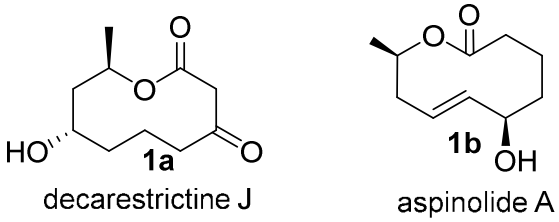



**Figure 1: Structures of decarestrictine J (1a) and aspinolide A (1b)**

**Section A: Total syntheis of decarestrictine J using ring-closing metathesis and Yamaguchi coupling**

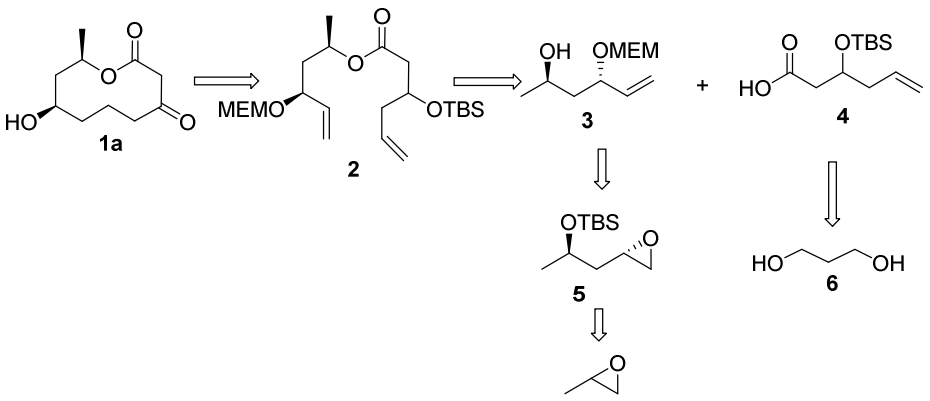
Decarestrictine J **1a**,[4] a ten membered lactone, has recently been isolated from a culture broth of *Penicillium simplicisium* and was shown to inhibit the biosynthesis of cholesterol.

The absolute stereochemistry of decarestrictine J **1a** itself has not been reported. However because decarestrictine J **1a** coexisted with decarestrictine B, whose absolute configuration had been determined by an X-ray analysis, it is presumed that natural (-)-decarestrictine J **1a** has (7*R*, 9*R*)-stereochemistry.

Only one synthesis of (-)-decarestrictine J **1a**[5] (Fig. 1) is reported. The asymmetric synthesis reported in the literature utilizes the Sharpless asymmetric epoxidation to generate the stereocentre.

The stereoselective synthesis of 1,3-polyol arrays is one of the most important topics in organic chemistry because of the ubiquity of 1,3-polyols in various biologically active natural products and drugs. Thus, numerous strategies for their synthesis have been developed with great success. With the development of an efficient approach to the synthesis of 1,3-polyols using iterative hydrolytic kinetic resolution, we became interested to apply this protocol for the synthesis of (-)-decarestrictine J **1a**.

Our retrosynthetic approach and strategy is delineated in Scheme 1. Retro-analysis revealed that macrolide **1a** could be synthesized from diene ester **2** by employing ring closing metathesis,[6] which in turn could be prepared by intermolecular Yamaguchi esterification[7] of two fragments alcohol **3** & acid **4**. The alcohol fragment **3** could be obtained from epoxide **5**. Epoxide **5** could be prepared via hydrolytic kinetic resolution which would be prepared from chiral propylene oxide, which in turn could be derived from racemic propylene oxide via hydrolytic kinetic resolution. The acid fragment **4** could be obtained from commercially available 1,3-propane diol.



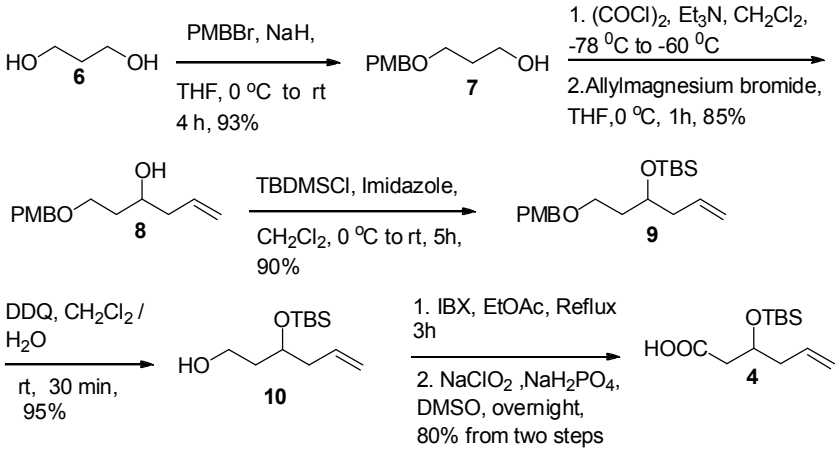

**Scheme 1: Retrosynthetic route to (-)-decarestrictine J (1a)**

**Results and discussions:**

Towards the total synthesis of **1a** we have employed hydrolytic kinetic resolution (HKR), intermolecular Yamaguchi esterification and ring-closing metathesis (RCM) as the key steps. The detailed synthesis of both the fragments and their coupling to arrive at target molecule is described below.

**Synthesis of acid fragment 4**

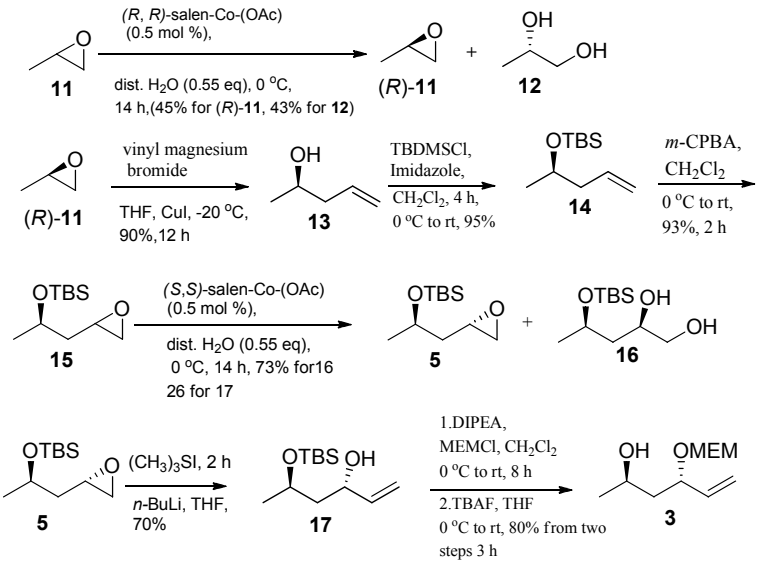
The synthesis of acid fragment **4** started from 1,3-propanediol **6**. It was monoprotected as *p*-methoxybenzyl ether **7**, which was subjected to Swern oxidation followed by reaction of aldehyde with allylmagnesium bromide to furnish homoallyllic alcohol **8**. Protection of hydroxy group of **8** as silyl ether followed by deprotection of PMB group by DDQ resulted primary alcohol **10**, which was further oxidized to give acid fragment **4**.




**Scheme 2: Synthesis of acid fragment 4**

**Synthesis of alcohol fragment 3**

The two stereocentres were generated by Jacobsen's hydrolytic kinetic resolution. Thus, commercially available propylene oxide **11** was subjected to Jacobsen's hydrolytic kinetic resolution by using (*R*,*R*)- Salen-Co-(OAc) catalyst to give epoxide **(*R*)-11** as a single isomer which was easily isolated from the diol **12** by distillation.[8] (*R*)-Propylene oxide was treated with vinylmagnesium bromide in the presence of cuprous iodide to give homoallylic alcohol **13**. Protection of hydroxy as TBDMS ether followed by epoxidation with *m*-CPBA afforded epoxide **15**. The HKR was performed on **15** with (*S, S*)-salen-Co-(OAc) complex (0.5mol %) and water (0.55eq) in THF (0.55 eq) to afford the diastereomerically pure epoxide **5** in >95% ee and 45% yield, and diol **16** in 43% yield. Epoxide **5** on reaction with dimethylsulfonium methylide[9] afforded one carbon homologated allylic alcohol **17** which was protected as MEM ether followed by TBS deprotection to furnish the alcohol frgment **3**.

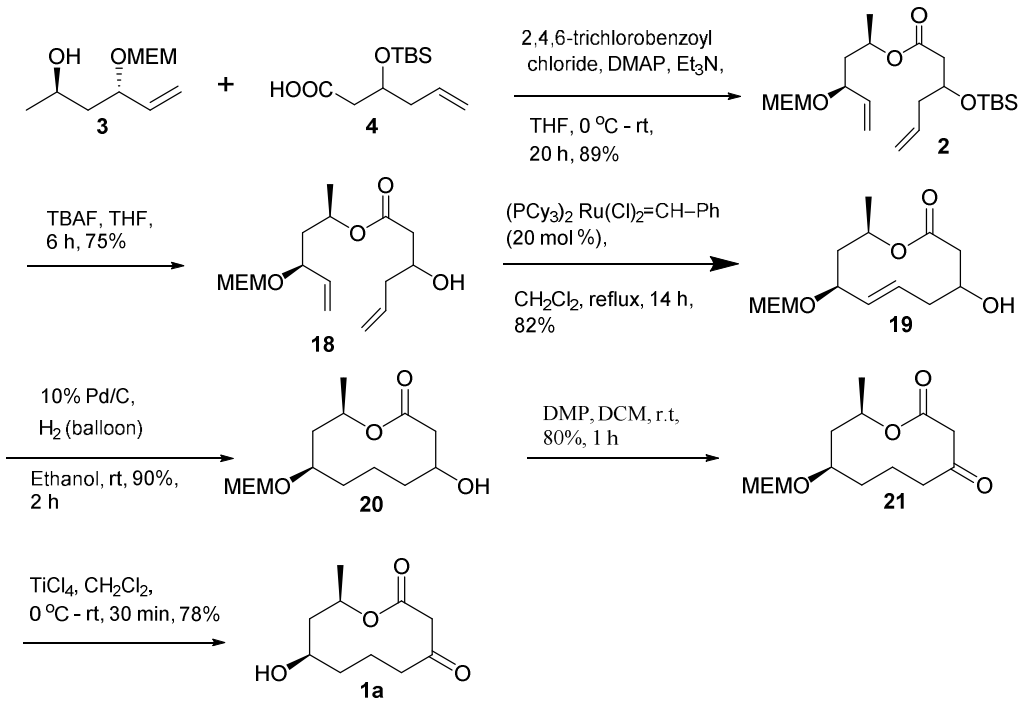



**Scheme 3: Synthesis of alcohol**

**Coupling of acid and alcohol fragments:**

Coupling of both the alcohol **3** & acid **4** was achieved by using intermolecular Yamaguchi esterification protocol followed by TBS deprotection to afford diene ester **2** which was subjected to ring-closing metathesis using Grubb's 1st generation catalyst to furnish cyclised product **19**. The internal double bond of **19** was reduced under hydrogenation condition to get compound **20**, the secondary hydroxy group of **20** was

oxidized by DMP to give **21**. Finally the deprotection of MEM ether of **21** afforded the target molecule **1a**.



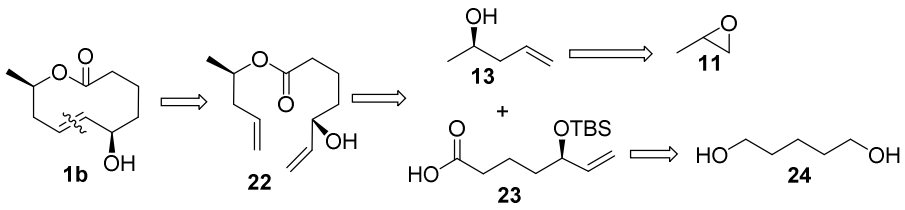

**Scheme 4: Coupling of acid and alcohol fragments**

## Section B: Total syntheis of aspinolide A using ring- closing metathesis and EDCI Esterification

Macrolides, particularly lactones with medium-sized rings (8-10 membered), have continued to attract the attention of both biologists and chemists during recent years, due to interesting biological properties and scarce availability of macrolides.

Aspinolide A **1b**,[10] is one such example, and has been isolated from *stagonospora circii*, a fungal pathogen isolated from *Cirsium arvense*. It shows antibacterial and antifungal activities.

The retrosynthetic analysis is outlined in Scheme 5. The target molecule **1b** could be synthesized from diene ester **22** by employing ring closing metathesis.[6] Compound **22** could be obtained by EDCI coupling of two fragments acid **23** alcohol **13**. The acid **23** could be prepared from 1,5-pentane diol **24** through Jacobsen's hydrolytic kinetic resolution by using (*S, S*)-Salen-Co-(OAc) while the alcohol **13** could be derived from propylene oxide **11**.




**Scheme 5: Retrosynthetic route to aspinolide A (1b)**

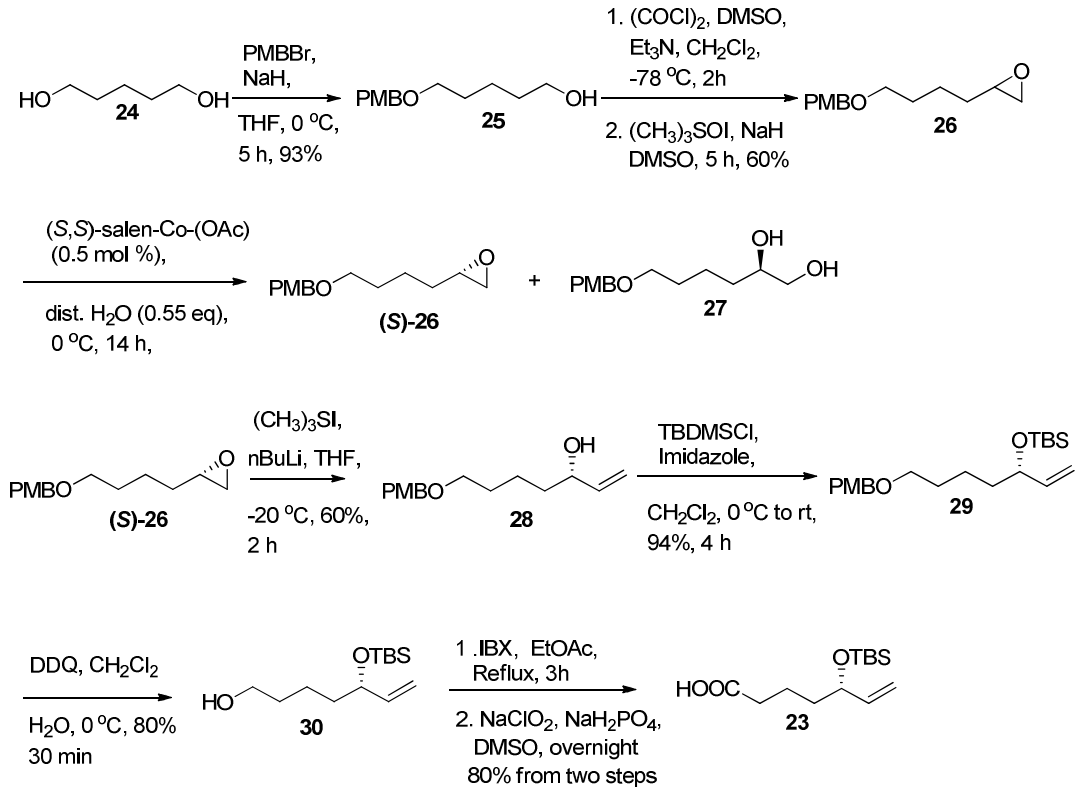
**Results and discussions:**

**Synthesis of alcohol fragment 13**

The synthesis of fragment **13** is already described in section A of chapter 2.

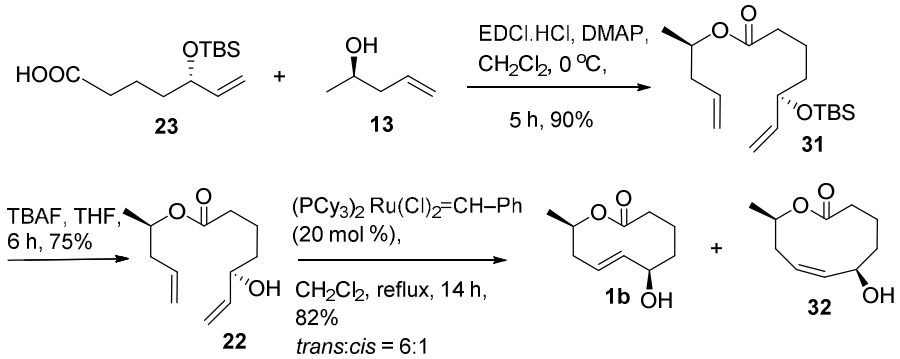
**Synthesis of acid fragment 23**

The synthesis of acid fragment **23** as outlined in Scheme 6 starts from 1,5-pentane diol **24**. It was monoprotected as *p*-methoxy benzyl (PMB) ether **25**, which was oxidized under Swern conditions to aldehyde & subsequently epoxidized using dimethylsulfoxonium methylide[11] to give epoxide **26**. Racemic epoxide **26** was subjected to Jacobsen's HKR by using (*S*, *S*)-salen-Co-OAc catalyst to provide chiral epoxide **(*S*)-26** along with diol **27**. Epoxide **(*S*)-26** on reaction with excess of dimethylsulfonium methylide[9] afforded one carbon homologated allylic alcohol **28** which was protected as silyl ether to give compound **29**. Deprotection of PMB group by DDQ furnished primary alcohol **30** which was oxidized to give acid fragment **23**.




**Scheme 6: Synthesis of acid fragment 23**

**Coupling of acid 23 and alcohol 13 fragments:**




**Scheme 7: Coupling of acid and alcohol fragments**

Coupling of both the fragment acid **23** & alcohol **13** was achieved by using EDCI followed by TBS deprotection to afford diene **22** which on ring-closing metathesis using Grubbs 1st generation catalyst afforded the target molecule **1b** along with the *cis*-compund **32** which was easily separated by column chromatography (Scheme 7).

## Chapter 3: Synthesis of 6-Substituted-5,6-Dihydro-2*H*-Pyran-2-Ones

This chapter deals with the asymmetric synthesis of 6-Substituted-5,6-Dihydro-2*H*-Pyran-2-Ones such as umuravumbolide **35b**, hyptolide **36** and hypurticin **37**.

### Section A: Total Synthesis of Umuravumbolide and Hyptolide *via* Silicon-Tethered Ring Closing Metathesis

The polyacylated-6-heptenyl-5,6-dihydro-2*H* -pyran-2-ones framework containing an *α, β*-unsaturated *δ*-lactone is known to bind protein thiol groups as a result of their ability to act as a Michael acceptor.

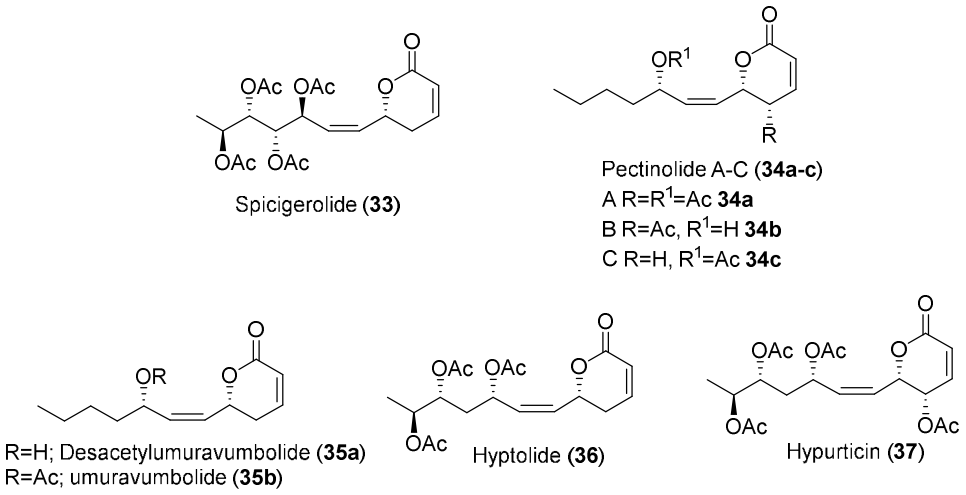



**Figure 2:** Structures of α, β-unsaturated δ-lactones

They show a wide range of pharmacological activities such as cytotoxicity against human tumor cells, antimicrobial and antifungal activity etc. We cite a few examples: spicigerolide (**33**)[12] exhibit cytotoxic activity whereas pectinolides A-C (**34a-c**)[13] exhibit significant antimicrobial and cytotoxic activity.

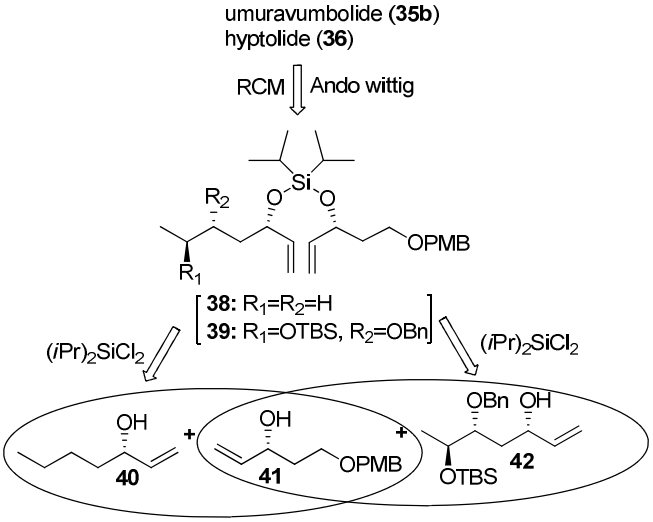
Desacetylumuravumbolide (**35a**)[14a] and umuravumbolide (**35b**)[14a] and structurally related hyptolide (**36**),[14b] isolated from species of *Tetradenia* and *Hyptis* are representative members of family Lamiaceae (Figure 2). They show a wide range of pharmacological activities such as cytotoxicity against human tumor cells, antimicrobial and antifungal activity etc. Besides, several compounds from Lamiaceae family have been shown to be an emetic to treat loss of appetite.

Synthetic studies toward the aforementioned molecules have been reported by Ramachandran,[15a] Marco,[15b] Chakraborty,[15c] Venkateswarlu[15d] and Sabitha[15e] *et al.* To the best of our knowledge, all attempts have been in linear fashion involving semi-

hydrogenation of the alkyne part using Lindlar's catalyst to generate the side chain olefin and ring-closing metathesis reaction for the construction of lactone ring.

As a part of our current interest in naturally occurring pharmacologically active *α, β*-unsaturated *δ*–lactones, we have accomplished the total synthesis of umuravumbolide (**35b**) and hyptolide (**36**) by a highly convergent strategy.

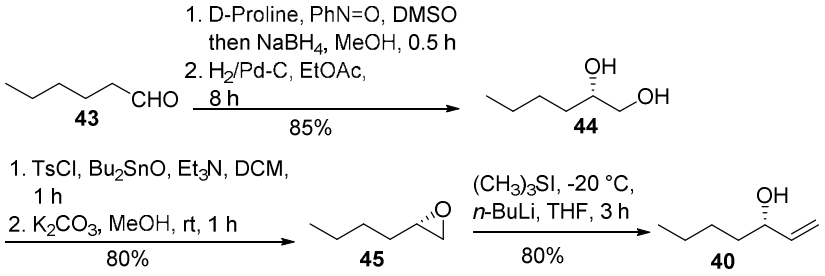
The general synthetic analysis is depicted in Scheme 8. We aimed to construct the side chain *Z*-olefin of both umuravumbolide **35b** and hyptolide **36** through ring-closing metathesis of bis-siloxane intermediate **38** and **39** respectively. The intermediates **38** and **39** would originate by the coupling of allylic alcohols **40**, **41** and **42** respectively.




**Scheme 8:** Retro-synthetic analysis of umuravumbolide (**35b**) and hyptolide (**36**).

**Synthesis of fragment 40**

Our synthesis started with the preparation of fragment **40**. The sequence developed to prepare fragment **40** is summarized in Scheme 9. Thus, the aldehyde **43** was exposed to sequential α-aminoxylation[16] catalyzed by D-proline, followed by in situ reduction using $NaBH_4$ to furnish *O*-amino-substituted diol, which was subjected to reductive hydrogenation conditions to afford the known diol **44**, which on selective monotosylation and base treatment furnished epoxide **45**.

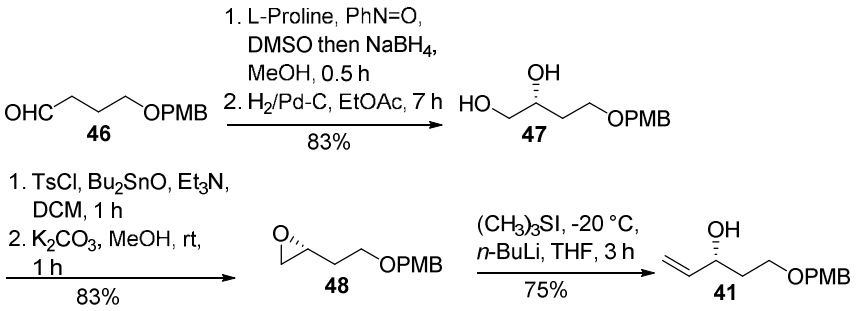



**Scheme 9.** Synthesis of fragment **40**

Finally, dimethylsulfonium methylide-mediated ring opening of epoxide **45** gave rise the fragment **40**.

**Synthesis of fragment 41**

The synthesis of fragment **41** commenced from 4-(4-methoxybenzyloxy)butanal **46** as illustrated in Scheme 10. The aldehyde **46** was subjected to α-aminoxylation catalyzed by L-proline, followed by similar set of reaction conditions, used in Scheme 9 to afford diol **47**, which on selective monotosylation and base treatment furnished epoxide **48**.



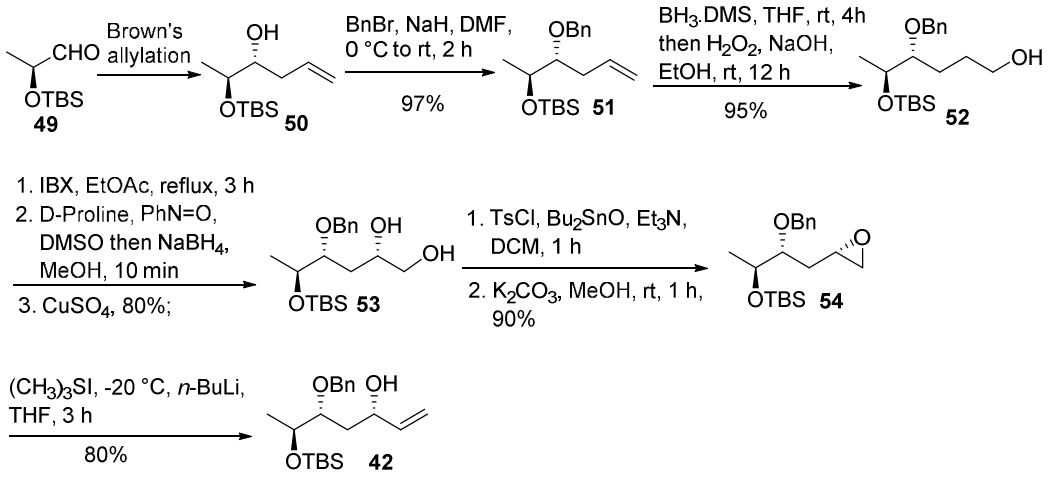

**Scheme 10.** Synthesis of fragment **41**.

This epoxide was opened with dimethylsulfonium methylide to afford the allylic alcohol fragment **41** in 75% yield.

**Synthesis of fragment 42**

The sequence developed to prepare fragment **42** is summarized in Scheme 11. As our point of departure, asymmetric allylation of TBS protected L-lactaldehyde **49** to known homoallylic alcohol **50** was performed with Brown's B-allyl diisopinocampheylborane,[15b] followed by treatment with benzyl bromide (BnBr) to afford **51**. Then we converted olefin **51** to alcohol **52** by the hydroboration oxidation technique. Thus compound **52** was oxidized by using IBX to furnish aldehyde, which was directly subjected to α-aminoxylation catalyzed by D-proline, followed by in situ

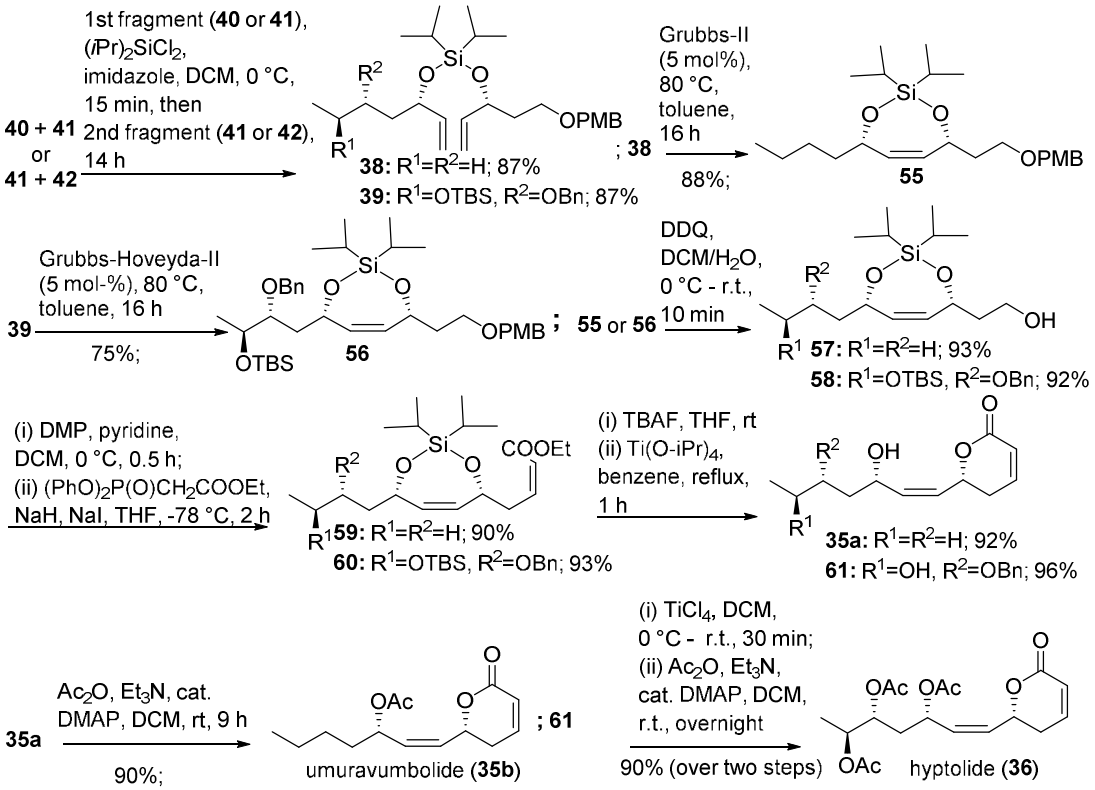
reduction using $NaBH_4$ to give the required *O*-amino substituted diol, which on treatment with catalytic amount of copper sulfate afforded the diol **53**. Diol **53** on selective monotosylation and base treatment furnished **54** in 90% yield. Finally, dimethylsulfonium methylide mediated (Corey–Chaykovsky's condition) ring opening of epoxide **54** gave rise the fragment **42**.




**Scheme 11:** Synthesis of fragment **42**.

**Coupling of fragments**

With the cross coupling partners in hand, the crucial silicon tethered coupling to construct the disiloxanes **38** & **39** were examined. The construction of the mixed *bis*-alkoxy silanes **38** & **39** was achieved from the allylic alcohols **40**, **41** and **42**. Next the ring closing metathesis reaction of disiloxane **38** using Grubbs second generation catalyst in toluene at 80 °C proceeded smoothly to get the required cyclic intermediate **55**. However cyclisation of **39** was achieved by using Grubbs-Hoveyda II to afford **56**. Then compounds **55** and **56** were subjected to the removal of PMB groups using DDQ producing the corresponding alcohols **57** and **58** respectively. Subsequent Dess Martin periodinane oxidation of alcoholic group led to the formation of corresponding aldehydes, which were directly subjected to two-carbon homologation under Ando conditions to give (*Z*)-unsaturated ester **59** and **60**.




**Scheme 12:** Synthesis of umuravumbolide **35b** and hyptolide **36**.

Then we first deprotected the silyl groups using TBAF in THF and the crude polyols thus obtained was eventually cyclized to give the six-membered lactones desacetylumuravumbolide (**35a**) and **61** upon treatment with catalytic amount of $Ti(OiPr)_4$ in refluxing benzene. The lactone desacetylumuravumbolide (**35a**) was futher acetylated to furnish umuravumbolide **35b**.

Towards the synthesis of target molecule **36**, compound **61** was subjected to debenzylation followed by acetylation of secondary hydroxyl group to furnish the target molecule hyptolide **36**.

## Section B: Attempted Synthesis of Hypurticin *via* Temporary Silicon Tethered-Ring Closing Metathesis

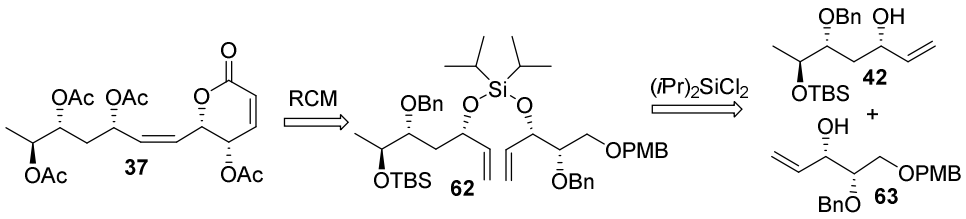
Hypurticin (**37**)[17] and structurally related hyptolide (**36)**, isolated from species of Hyptis and Syncolostemonand are representative members of family Lamiaceae (Figure 2).

To date there are no total synthesis of hypurticin **37** reported.

As a part of our current interest in naturally occurring, pharmacologically active *α, β*-unsaturated *δ*–lactone, we have attempted at the first total synthesis of hypurticin **37**

by a highly convergent strategy to confirm its structure, including the absolute stereochemistry.

The general synthetic analysis is depicted in Scheme 13. We aimed to construct the side chain *Z*-olefin through ring closing metathesis of bis-siloxane intermediate **62**. The intermediate **62** would originate by the coupling of two allylic alcohols **42** and **63.**



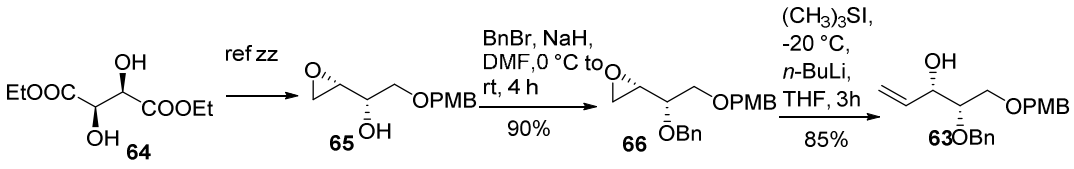

**Scheme 13.** Retro-synthetic analysis of hypurticin **37**

**Synthesis of fragment 42**

The synthesis of fragment **42** is already described in section A of chapter 3.

**Synthesis of fragment 63**

The preparation of other coupling partner i.e. the allylic alcohol **63** is summarized in scheme 14.



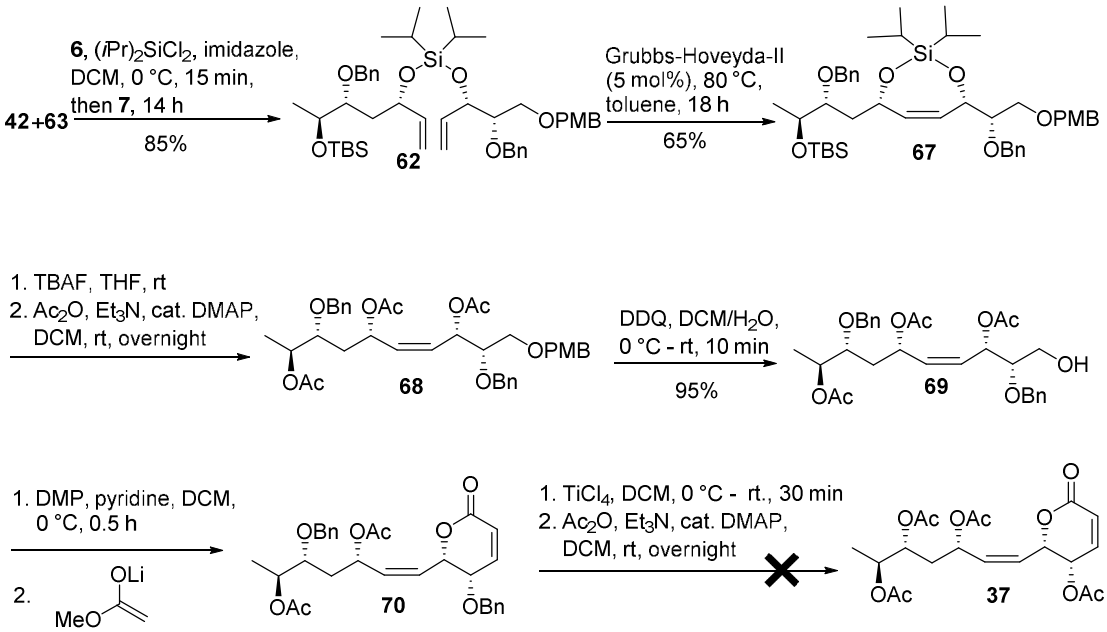

**Scheme 14**. Preparation of fragment **7**

The introduction of benzyl group on the secondary alcohol moiety of the known epoxy alcohol **65**,[18] derived from diethyl L-tartrate **64** according to Tatsuta's procedure afforded **66**, which was subsequently exposed to Corey–Chaykovsky's condition to produce fragment **63**.

**Coupling of fragments**

With substantial amount of both the fragments in hand the coupling of allylic alcohol **42** and **63** was achieved by using the modified condition for tethering, used for the synthesis of umuravumbolide, to afford the disiloxane intermediate **62**. The ring

closing metathesis reaction of disiloxane **62** using Grubbs-Hoveyda II catalyst in toluene at 80 °C proceeded smoothly producing the cyclic intermediate **67**.




**Scheme 15.** Synthetic strategy for hypurticin **1**.

Then we first deprotected the silyl groups using TBAF in THF and the crude triol thus obtained was eventually acetylated to give **68**, followed by removal of the PMB protecting group, gave the desired primary alcohol **69**. Dess Martin periodinane led to the formation of the aldehyde. Next lactone annulations[19] was effected by reaction of this material with the lithium enolate of methyl acetate to afford the desired lactone **70**. Unfortunately final debenzylation followed by the acetylation of secondary alcohols proved to be unsuccessful and could not give the target molecule hypurticin **37** (Scheme 15).

**Chapter 4: A desymmetrization approach to the enantiopure *syn/anti*-1,5-diols *via* hydrolytic kinetic resolution (HKR) of functionalized meso bis-epoxides: further elaboration to *syn*/*syn*-1,3,5-triols and application to the formal synthesis of cryptocarya diacetate.**

We have reported for the first time that the structurally diverse and complex terminal bis-epoxide can smoothly be resolved by using catalyst like (*R*,*R*)-salen-Co-OAc (***R,R*-A**) or (*S*,*S*)-salen-Co-OAc (***S,S*-A**) (Fig 3) under HKR condition and by desymmetrizing a meso precursor to generate both *syn/anti*-1,5-diols.[20]

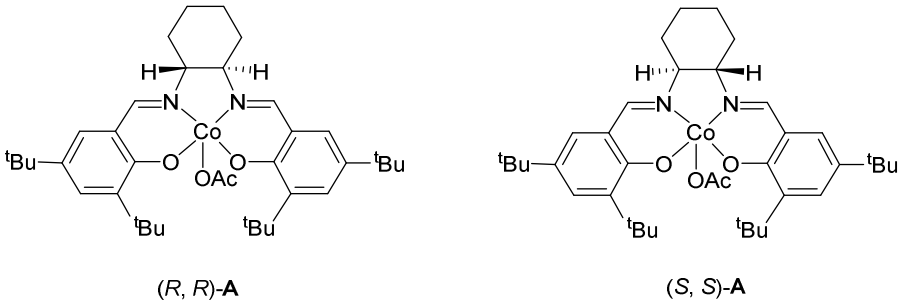
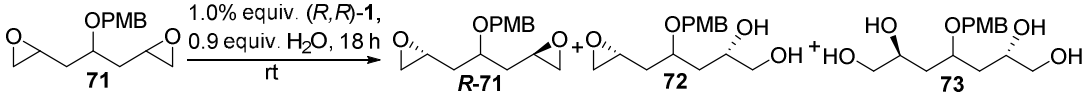



**Figure 3.** Structures of Co(III) salen complexes.

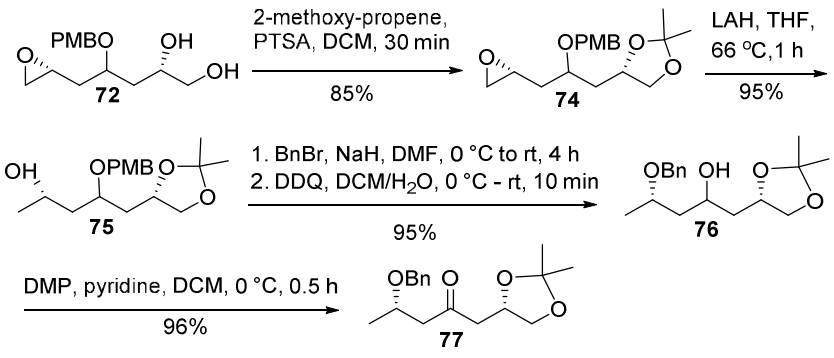
These synthetic precursors can be further manipulated to get 1,3,5-triols[21] simply by stereoselective reduction which can subsequently be utilized to the total synthesis of cryptocarya diacetate,[22] an *α,β*-unsaturated-*δ*-lactone containing 1,3-polyol.

Eventually we began with the resolution of compound **71** which was subjected to Jacobsen HKR conditions using 1.0% equiv. of (*R*,*R*)-salen-Co-OAc catalyst and 0.9 equiv. of $H_2O$. To our delight, the desired resolution occurred, giving a mixture of the expected bis-epoxide ***R*-71**, epoxy-diol **72** and tetrol **73** in 23%, 45% and 20% yields respectively (**Scheme 16**).

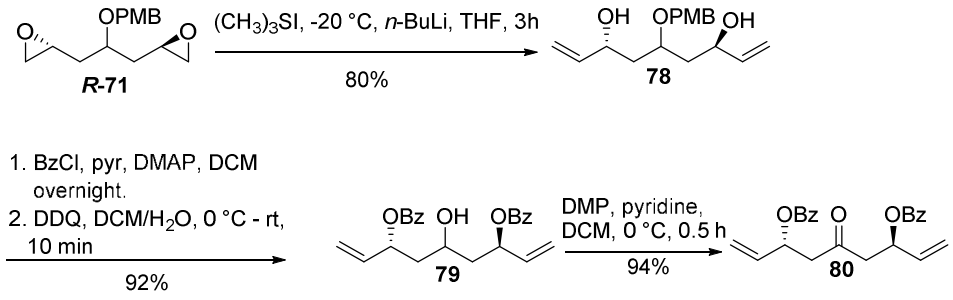



**Scheme 16:** Resolution of bis-epoxide **71.**

Our attempt to measure the enantioselectivity (*ee*) of the epoxy-diol **72** and resolved tetrol **73** proved to be a difficult task due to diastereomeric nature of these compounds. Therefore to minimize the number of diastereomers, epoxy-diol **72** and resolved bis-epoxide ***R*-71** were converted to their keto analogues **77** and **80** respectively (**Scheme 17** and **18**).




**Scheme 17:** Preparation of keto compound **77**.

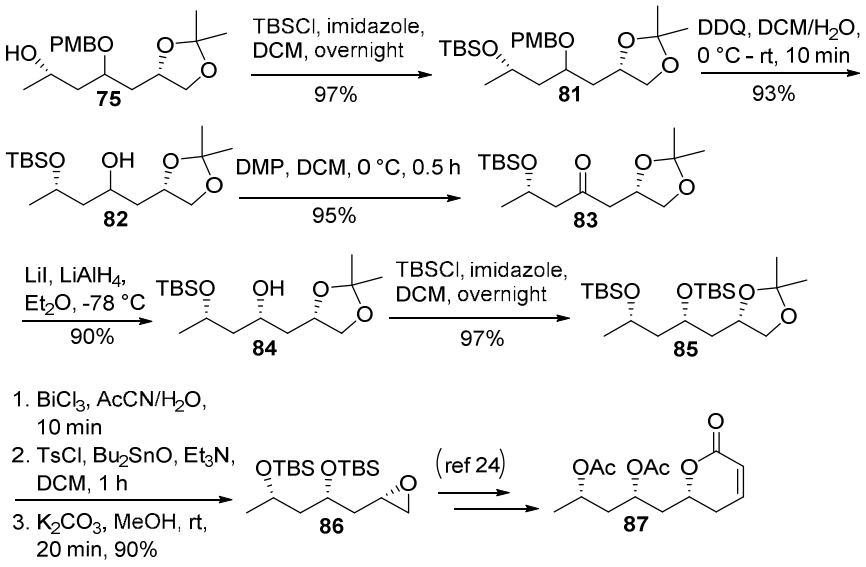



**Scheme 18:** Preparation of keto compound **80**.

To summarize the above findings, a concise strategy for the preparation of asymmetric 1,5-*syn*-diol **77** (**Scheme 17**) and $C_2$-symmetric 1,5-*anti*-diol **80** (**Scheme 18**) as hydroxy protected derivatives has been developed in high enantioselectivities, starting from meso bis-epoxide **71** and by utilizing desymmetrization technique which allows for further manipulations in terms of keto reduction to prepare various 1,3,5-triols.

After having established a novel approach for the stereoselective synthesis of 1,5-diol motif, we turned our attention towards extending this protocol to 1,3,5-triols and further apply to the formal synthesis of cryptocarya diacetate.

Towards the synthesis of target molecule **87** (**Scheme 19**), we began with the protection of the secondary alcohol **75** with TBSCl to furnish **81**. PMB group was then removed easily by DDQ to give the alcohol **82**. Oxidation of secondary alcohol was carried out by DMP to obtain **83** having the requisite keto group. Now the platform was set to create the desired *syn*-1,3,5-triols using *syn*-selective reduction conditions. The *syn*-selective reduction of such acyclic *β*-alkoxy ketones with $LiAlH_4$ in the presence of LiI as reported by Mori and co-workers[23] went smoothly affording **84** as a major diastereomer along with minor (10:1) which was determined from $^1H$ & $^{13}C$ NMR spectroscopy.




**Scheme 19:** Formal synthesis of cryptocarya diacetate **87**.

Towards the synthesis of target molecule, we then first carried out the protection of secondary hydroxyl group as TBS ether to produce **85**. To our delight at this stage the major diastereomer was separated from the minor one in chromatography and hence we proceeded further with single diastereomer. We then deprotected the acetonide group smoothly in the presence of TBS group on treatment with catalytic amount of bismuth trichloride affording the diol, which was directly converted to known di-TBS proteceted epoxide **86** through selective monotosylation and subsequent base promoted $S_N2$ displacement of tosyl group. Since transformation from **86** to the target molecule **87** is already reported,[24] this completes the formal synthesis of cryptocarya diacetate.

Thus starting from a meso precursor we have successfully synthesized both *syn/anti*-1,5-diols with further extension of this methodology to *syn*-1,3,5-triol and its application to cryptocarya diacetate.

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# CHAPTER-1

## Introduction to Jacobsen's hydrolytic kinetic resolution, proline-catalyzed reactions and silicon tethered ring-closing metathesis reactions

# 1.1 JACOBSEN'S HYDROLYTIC KINETIC RESOLUTION

## 1.1.1. Introduction

The search for new and efficient methods for the synthesis of optically pure compounds has been an active area of research in organic synthesis. Amongst various syntheses, the enantioselective syntheses of complex natural products containing multiple stereocentres are often the most challenging. Asymmetric catalysis provides a practical, cost-effective and efficient approach to the synthesis of such molecules. The use of catalytic methods not only provides an easy access to an enantiomerically pure product but also permits maximum variability in product structure with regard to stereochemical diversity, which is particularly important for making various synthetic analogues required for biological activity studies. While tremendous advances have been made in asymmetric synthesis, substrate-driven or catalytically induced resolution of racemates is still the most important industrial approach to the synthesis of enantiomerically pure compounds. In a kinetic resolution process, one of the enantiomers of the racemic mixture is transformed to the desired product while the other is recovered unchanged.

Epoxides are very important unit in a number of interesting natural products, moreover these are versatile building blocks that have been extensively used in the synthesis of complex organic compounds. Their utility as valuable intermediates has further expanded with the advent of asymmetric catalytic methods for their synthesis.[1]

As a consequence, the preparation of enantio-enriched epoxides has long stood as a most significant target for asymmetric synthesis. In particular, the identification of catalytic asymmetric olefin oxidation methods has been an area of active research for several decades, and the advances made in this field have increased greatly the number of enantiomerically enriched epoxides available for use in organic synthesis.

Among available methods for the preparation of enantio-enriched epoxides, the Sharpless epoxidation reaction has arguably had the most profound impact of any asymmetric catalytic reaction discovered thus far, providing general access to highly

enantio-enriched epoxy alcohols.[2] More recently, the epoxidation of unfunctionalized conjugated olefins by chiral (salen)Mn(III) complexes has enabled the practical synthesis of certain classes of enantiomerically enriched epoxides.[3] A highly complementary strategy for epoxidation of simple olefins involving chiral dioxirane intermediates has expanded the range of chiral epoxides now accessible in enantio-enriched form to a significant extent.[4] Indirect routes to enantiopure epoxides involving asymmetric catalytic dihydroxylation or reduction reactions have also proven highly valuable in specific contexts.[5] Despite these considerable advances in asymmetric catalytic synthesis of epoxides, no general methods have been identified for the direct preparation of highly enantio-enriched 1-oxiranes, arguably the most valuable class of epoxides for organic synthesis.[6] The utility of terminal epoxides as chiral building blocks is perhaps best illustrated by the fact that the few examples for which effective catalytic approaches exist have found extensive use in asymmetric synthesis. In particular, glycidol and a number of its derivatives are available in enantiomerically enriched form using the Sharpless epoxidation technology[7] or by enzymatic kinetic resolution methods,[8] and these compounds have become widely used starting materials for target-oriented synthesis.[9] Epichlorohydrin has been rendered commercially available in bulk by microbial resolution of ((±)-2, 3-dichloro-1-propanol, and it, too, has found widespread application.

Recently Jacobsen had discovered the (salen) Co complex **1** (**Figure 1**) catalyzed efficient hydrolytic kinetic resolution (HKR) of a variety of terminal epoxides (**Scheme 1**).[10, 11, 12] This new method appeared to hold considerable promise with regard to meeting all of the criteria outlined above for kinetic resolution to be practical. Racemic 1,2-epoxides are generally available directly from commercial suppliers at low cost or are obtainable in one step from inexpensive olefins or aldehydes. In fact, certain racemic epoxides, such as propylene oxide, epichlorohydrin, styrene oxide, and butadiene monoepoxide, are commodity chemicals and are no more expensive than common organic solvents. Second, the ligands for catalyst **1** had previously been commercialized and manufactured on a ton scale in the context of (salen)Mn epoxidation catalysts.[13] The cobalt analogues (*R*,*R*)-**1** and (*S*,*S*)-**1** proved equally accessible, and these are also now available in bulk.[14] Third, water is perhaps the ideal reagent for effecting the resolution reaction: it is inexpensive and safe, and the rate of the ring-opening reaction can be controlled

simply by modulating the rate of addition of water to the epoxide-catalyst mixture.[15] Fourth, for those examples that were described in the preliminary report, highly enantio-enriched epoxides were recovered from the HKR. Finally, the HKR provided useful enantio-enriched 1,2-diols, including many that are otherwise not readily accessible using existing asymmetric dihydroxylation methods.[16, 17]

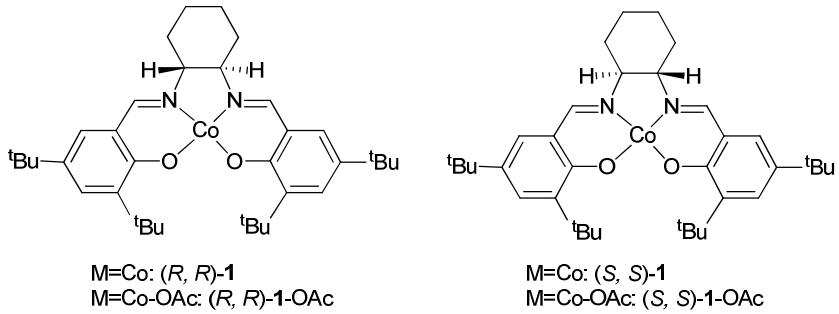
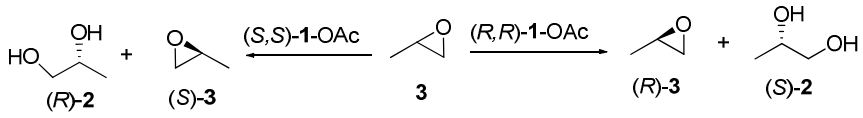



**Figure 1:** (Salen) Co complexes

The HKR has seen rapid adoption as the method of choice for the preparation of a variety of terminal epoxides in enantio-enriched form, and a number of applications in target oriented synthesis have been reported already.[18] In addition, the commercial manufacture of enantio-enriched propylene oxide, epichlorohydrin, and styrene oxide using HKR methodology has been implemented, thereby reducing the cost of these useful chiral building blocks.[13] Jacobsen has discovered that the HKR is an extraordinarily general reaction, allowing efficient kinetic resolution of virtually any type of terminal epoxide.

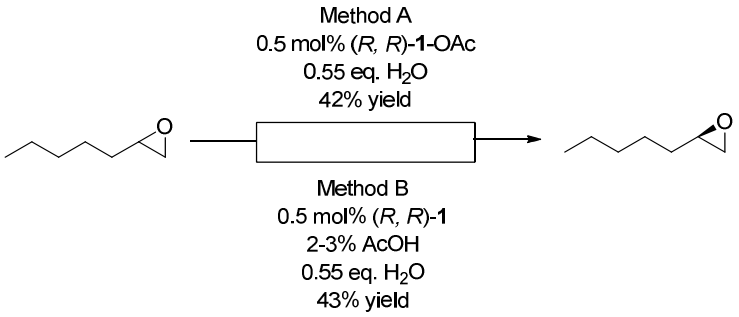



**Scheme 1**

## 1.1.2. Preparation of Catalyst and General Experimental Considerations

Both enantiomers of the (salen)CoII complex **1** are available commercially for research purpose or commercial scale, or they can be prepared from the commercially available ligands using $Co(OAc)_2$.[13] The Co(II) complex **1** is catalytically inactive, however, and it must be subjected to one-electron oxidation to produce a (salen)CoIII

X complex (X) anionic ligand) prior to the HKR. This may be done conveniently by aerobic oxidation in the presence of a mild Brönsted acid. Water alone was found not to mediate the oxidation reaction, but a screen of additives revealed that acetic acid was effective and that the corresponding Co(III) precatalyst **1**.OAc is convenient for use in HKR reactions both in terms of its preparation and reactivity. Two useful methods for the generation of complex **1**.OAc have been developed. Method A involves isolation of **1**.OAc as a crude solid prior to the HKR. The Co(II) complex **1** is dissolved in toluene to generate *ca*. 1 M solution, and acetic acid (2 equiv) is added. The resulting solution is stirred open to air at room temperature for 30 min, during which time the color of the mixture changes from orange to dark brown. All volatile materials are removed in vacuo, affording **1**.OAc as a brown solid residue that can be used without further purification. Method B involves in situ generation of **1**.OAc under HKR conditions by suspension of the Co(II) complex **1** in epoxide or epoxide/solvent and addition of HOAc under an aerobic atmosphere. Catalyst obtained by both methods was examined for each of the epoxides described in this study. For certain substrates such as 1-hexene oxide, catalyst prepared by either method leads to essentially identical results. In these situations, *in situ* catalyst generation (method B) is preferable since the procedure avoids an extra solvent removal step. On the other hand, catalyst prepared by method A was found to be more effective with less reactive substrates (vide infra) and was applicable to all substrates examined. Therefore, if HKR did not afford epoxide in >99% *ee* with catalyst prepared by method B after optimization of solvent and catalyst loading, then catalyst prepared by method A was employed. Aside from the method of generation of **1**.OAc, the only reaction parameters in the HKR that required optimization for individual substrates were catalyst loading and choice of solvent. With few exceptions, epoxide of >99% ee could be obtained using 0.55 equiv of water relative to racemate. Relatively small epoxides with some degree of water solubility could be resolved effectively without added solvent. However, the HKR of more lipophilic substrates did benefit from inclusion of a water miscible organic solvent such as tetrahydrofuran (THF), 2-propanol, or 1,2-hexanediol.




**Scheme 2**: General Reaction

In general, one volume of solvent relative to racemic epoxides was sufficient to allow efficient HKR. Catalyst loadings of 0.5 mol% or lower relative to racemic epoxide were effective for many substrates, but epoxides bearing sterically hindered or unsaturated substituents often required more catalyst (up to 2 mol%) to attain complete resolution. Reactions were initiated at 0 °C and then allowed to warm to room temperature with continued stirring for 12-18 h.

## 1.1.3. Attractive features of HKR

1. The reaction is applicable to a wide range of racemic terminal epoxide, most of them are quite inexpensive.
2. Access to highly enantio-enriched (99% ee) products in close to theoretical yields.
3. A practical and scaleable protocol.
4. The low loading (0.2 to 2 mol%) and recyclability of commercially available catalyst at low cost.
5. Use of water as nucleophile for epoxide ring opening.
6. The ease of product separation from the epoxide due to the large boiling point and polarity differences.
7. Both epoxide and diol are obtained in high yield and high optical purity.
8. Absence of useful alternative approaches to the preparation of enantio-pure terminal epoxides.

# 1.2 PROLINE-CATALYZED REACTIONS

## 1.2.1. Introduction to organocatalysis

The broad utility of synthetic chiral molecules as single-enantiomer pharmaceuticals, in electronic and optical devices, as components in polymers with novel properties, and as probes of biological function, has made asymmetric catalysis a prominent area of investigation. Organocatalysis, or the use of small organic molecules to catalyse organic transformations, is a relatively new and popular field within the domain of chiral molecule (or enantioselective) synthesis. Although chemical transformations that use organic catalysts, or organocatalysts, have been documented sporadically over the past century, it was not until the late 1990s that the field of organocatalysis was 'born'.[19] It is now widely accepted that organocatalysis is one of the main branches of enantioselective synthesis (the other, previously accepted, branches being enzymatic catalysis and organometallic catalysis), and those who are involved in the synthesis of chiral molecules consider organocatalysis to be a fundamental tool in their catalysis toolbox.

This rediscovery has initiated an explosive growth of research activities in organocatalysis both in industry and in academia. The 1970s brought a milestone in the area of asymmetric organocatalysis, when two industrial groups led by Hajos and Wiechert published the first and highly enantioselective catalytic aldol reactions using simple amino acid proline as the catalyst. Organocatalysis is the catalysis of chemical transformations using a purely organic molecule, which is composed of mainly carbon, hydrogen, nitrogen, sulfur and phosphorus, and does not contain any metals. The advent of organocatalysis brought the prospect of a complementary mode of catalysis, with the potential for savings in cost, time and energy, an easier experimental procedure, and reductions in chemical waste, which confers a huge direct benefit in the production of pharmaceutical intermediates when compared with transition metal catalysts. Organic molecules not only have ease of manipulation and a green advantage but also can be very efficient catalysts. Several aspects of organocatalysis will undoubtedly attract researcher's attention. Tremendous efforts

will continue to be directed towards the discovery and design of catalysts with better efficiency, new reactivities and greater turnover numbers. And in near future asymmetric organocatalysis may begin to catch up with the spectacular advancements of enantioselective transition metal catalysis.

Recently, List[20] introduced a system of classification based on the mechanism of catalysis (**Figure 2**). The four categories are Lewis base, Lewis acid, Bronsted base and Brönsted acid catalysis. Accordingly, Lewis base catalysts (B:) initiate the catalytic cycle via nucleophilic addition to the substrate (S). The resulting complex undergoes a reaction and then releases the product (P) and the catalyst for further turnover. Lewis acid catalysts (A) activate nucleophilic substrates (S:) in a similar manner. Bronsted base and acid catalytic cycles are initiated via a (partial) deprotonation or protonation, respectively.

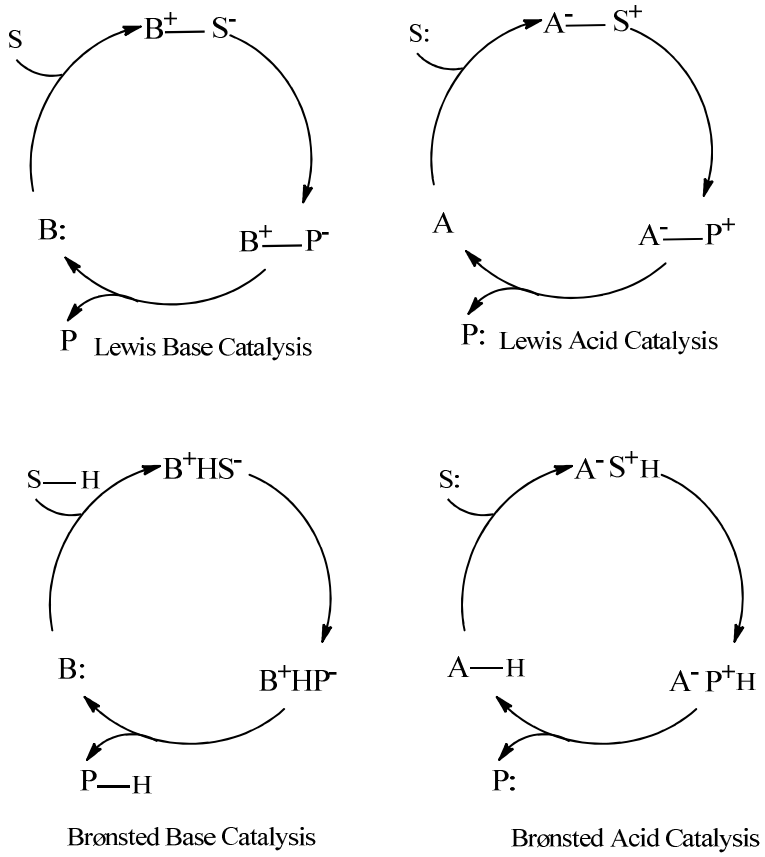



**Figure 2**: Organocatalytic cycles

## 1.2.2. Proline a "Universal catalyst"

Proline (**4**) has been defined as a "universal catalyst" because of its high utility in variety of asymmetric organic transformations. Proline is the only natural amino acid with a secondary amine functionality, which raises the pKa value and better nucleophilicity as compared to other amino acids. It can act as a nucleophile to carbonyl groups (iminium intermediate) or Michael acceptors (enamines).

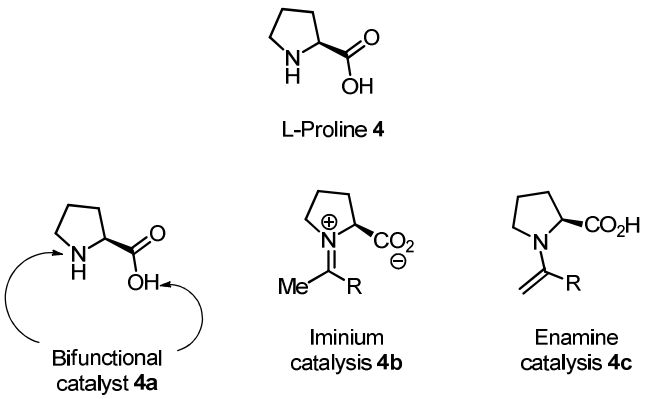


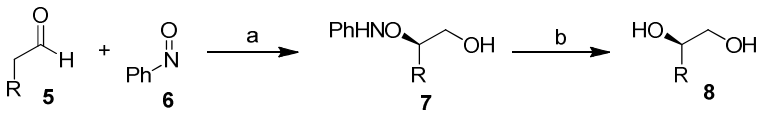

**Figure 3:** Modes of proline catalysis

It can be regarded as a bifunctional catalyst as the secondary amine acts as Lewis base and the acid group acts as Brönsted acid (**Figure 3**). The high stereoselectivity in the proline-catalyzed reactions is possibly due to its formation of organized transition states with many hydrogen bonding frameworks. Proline is not the only molecule to promote catalysis, but it still seems to be one of the best in the diversity of transformations. It is known to catalyze aldol,[21] Diels-Alder,[22] Michael addition[23] and α-functionalization[24] among many other organic transformations.[25] Particularly proline-catalyzed α-aminoxylation[26] and α-amination[27] of carbonyl compounds have emerged as powerful methods because chiral building materials can be synthesized in effective manner starting from easily available materials.

## 1.2.3. Proline-catalyzed α-aminoxylation

Optically active α-hydroxyaldehydes and ketones are important intermediates in organic synthesis as they are direct precursors to 1, 2-diols. Because of this utility many methods have been developed for their preparation. The more prominent, well-

established methods of enantioselective α-oxygenations include the use of Davis oxaziridine,[28a] Sharpless dihydroxylation of enol ethers,[28b] manganese–salen epoxidation of enol ethers,[28c] and Shi epoxidation of enol ethers.[28c] It is only rather recently that direct catalytic, asymmetric variants have been reported.[29] Most of these methods, however, require multiple manipulations and there is no direct method, nor catalytic asymmetric method for their synthesis from the corresponding aldehyde. Recently, proline has been found to be an excellent asymmetric catalyst for α-aminoxylation[20] of carbonyl compounds. When an aldehyde **5** without substitution at α-position was reacted with nitrosobenzene **6** in presence of L-proline in DMSO at ambient temperature, aminoxylation of the aldehyde takes place at the α-position. Aldehyde can be reduced *in situ* with sodium borohydride and the aminoxyl moiety undergoes hydrogenolysis with Pd/C, $H_2$ or $CuSO_4$ to give the corresponding diols **8** in very high enantioselectivities (Scheme 3).




**Scheme 3**. *Reaction and reagents*: (a) (i) S-proline (20 mol%), DMSO, 25 °C; (ii) $NaBH_4$ MeOH; (b) Pd/C, $H_2$ or 30 mol% $CuSO_4$. R = Ph, *i*-Pr, *n*-Bu, $CH_2Ph$ etc. > 99% ee

The mechanism of the α-aminoxylation reaction is shown in (**Figure 4**). The observed enantioselectivitiy of the catalytic α-aminoxylation of aldehydes can be rationalized

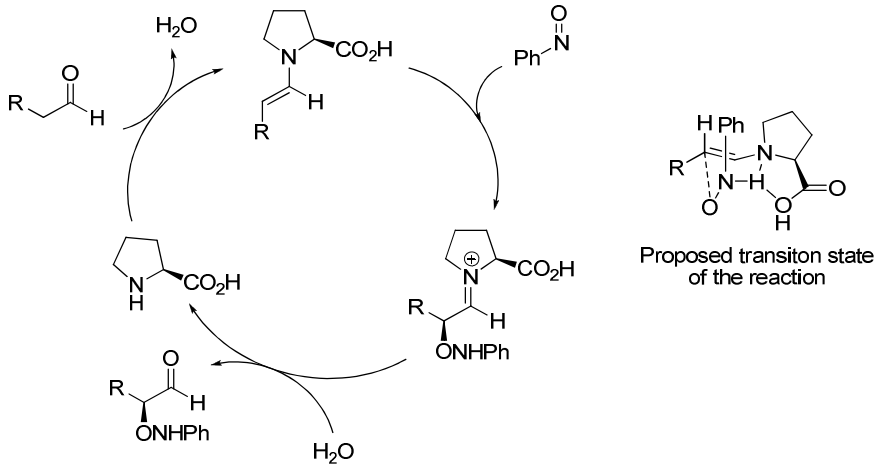


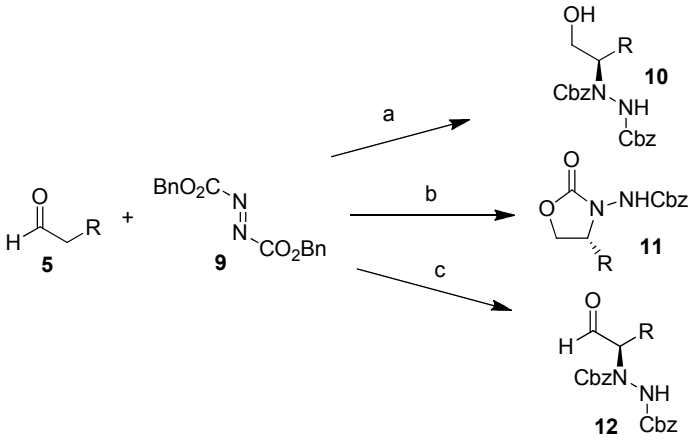

**Figure 4**: Proposed mechanism of the α-aminoxylation reaction

by invoking an enamine mechanism operating through a chair transition state where the *Si* face of an α-enamine formed from the aldehyde and L-proline approaches the less hindered oxygen atom of nitrosobenzene to provide a chiral α-aminoxyaldehyde with *R* configuration. Since proline is commercially available in both enantiopure forms, a one pot sequential catalytic α-aminoxylation of aldehydes followed by *in situ* reduction with $NaBH_4$ affords *R*- or *S*- configured 1, 2-diol units (the secondary alcohol "protected" by an *O*-amino group) with excellent enantioselectivities and in good yields.

## 1.2.4. Proline-catalyzed α-amination

The importance of optically active α-amino acids, α-amino aldehydes, and α-amino alcohols, formed by asymmetric catalysis, has stimulated an enormous development in synthetic strategies, and two different catalytic, enantioselective approaches are attractive: the *C-C* and the *C-N* bond-forming reactions.

Asymmetric α-amination[21] of aldehydes using proline-catalyzed reactions represents a direct approach synthesizing chiral building blocks such as α-amino acids, α-amino aldehydes, and α-amino alcohols. The use of organocatalysis, in particular proline represents a drastic change in approach to asymmetric α-amination. Recently, both List[27a] and Jørgensen[27b] disclosed the asymmetric α-amination of aldehydes (Scheme 4) using catalytic quantities of proline. While these approaches parallel each other in many ways, minor variations in reaction conditions result in different products, as well as differences in yields and enantiomeric ratios.



**Scheme 4**: *Reactions and conditions*: (a) L-proline (10 mol%), $CH_3CN$, 0 °C, 3 h; $NaBH_4$, EtOH; (b) L-proline (10 mol%), $CH_2Cl_2$, 25 °C; $NaBH_4$, MeOH; 0.5 N NaOH; (c) L-proline (10 mol%), $CH_2Cl_2$, 25 °C; $H_2O$.

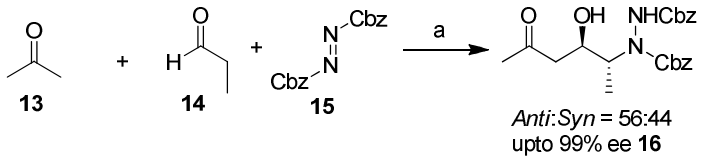
While both transition structures lead to identical products directed by the hydrogen bond from the carboxylic acid of proline, they presumably possess unique energies, so one transition state should be favored. However, the operative transition state has yet to be established.

## 1.2.5. Proline-catalyzed sequential transformations

Proline-catalyzed sequential transformations,[30] is a emerging research field in organic synthesis as synthesis of complex organic molecules could be accessible in one-pot procedure. Recently a variety of such transformations has been developed by different research groups, some of them are described below.

### 1.2.5.1. Sequential amination-aldol[30a]

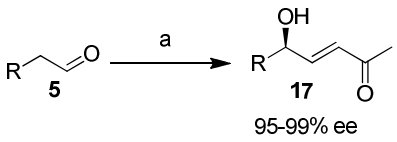
Barbas III *et al*. have developed a one-pot protocol for the synthesis of functionalized β- amino alcohols **16** from aldehydes, ketones and azodicarboxylates (Scheme 5).




**Scheme 5**: *Reactions and conditions*: (a) L-proline (20 mol%), $CH_3CN$, rt, 72 h, 80%.

### 1.2.5.2. Sequential aminoxylation-olefination[30b]

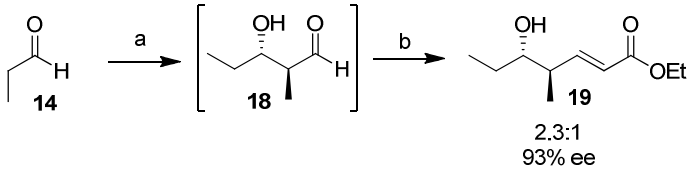
Zhong *et al*. have reported sequential asymmetric α-aminoxylation/Wadsworth-Emmons- Horner olefination of aldehydes for the synthesis of optically active *O*-amino-substituted allylic alcohols **17** in good enantioselectivities using cesium carbonate as base (Scheme 6).



**Scheme 6**. *Reactions and conditions*: (a) L-proline (20 mol%), nitrosobenzene (1.0 equiv.), DMSO, rt, 10-20 min then diethyl(2-oxopropyl)phosphonate, cesium carbonate (1.5 equiv.).

## 1.2.5.3. Sequential aldol-olefination[30c]

Cordova *et al*. have reported one-pot organocatalytic asymmetric tandem cross-aldol/Horner-Wittig-Emmons olefination for the synthesis of polyketide and carbohydrate derivatives (Scheme 7).

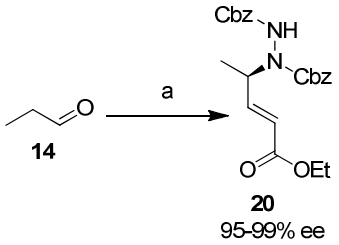



**Scheme 7**: *Reactions and conditions*: (a) L-proline (10 mol%), DMF; (b) Diethyl(2-oxopropyl)phosphonate, cesium carbonate (1.5 equiv.).

Apart from this transformation, Cordova *et al*. have also reported tandem Mannich olefination reaction.[30d]

## 1.2.5.4. Sequential α-amination-olefination[30e]

Sudalai *et al*. have reported sequential asymmetric α-amination/Wadsworth-Emmons-Horner olefination of aldehydes for the synthesis of optically active allylic amine in good enantioselectivities and yields (Scheme 8).




**Scheme 8**: *Reactions and conditions*: (a) L-proline (20 mol%), DBAD (1.0 equiv.), $CH_3CN$, rt, 10-20 min then diethyl(2-oxopropyl)phosphonate, cesium carbonate (1.5 equiv.).

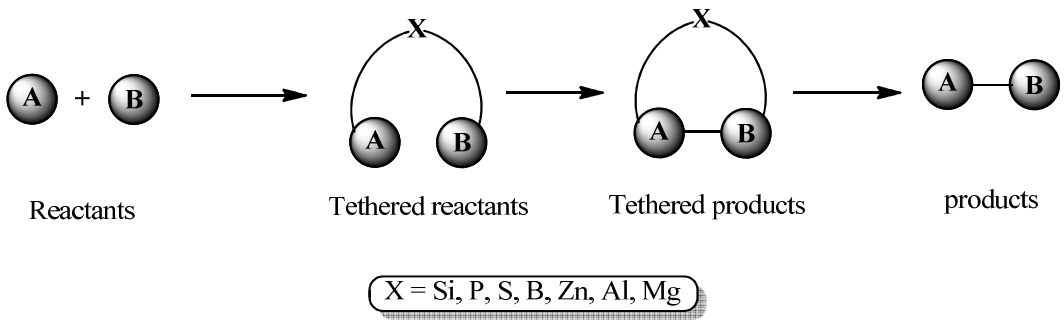
The high, and often exceptional, enantioselectivity of proline-mediated reactions can be rationalized by the capacity of the molecule to orchestrate highly organized

transition states by an extensive hydrogen-bonding network. In all proline-mediated reactions, proton-transfer from the amine or the carboxylic acid group of proline to the forming alkoxide or imide is essential for charge stabilization and to facilitate C-C bond formation in the transition state.[31] While most of the partial steps in aminocatalytic reactions are in equilibrium, the enhanced nucleophilicity of the catalyst can entail a number of equilibrated reactions with electrophiles present in the medium, resulting in a low turnover number. However, this drawback can be remedied by upsetting the equilibrium by higher catalyst loading, whilst the catalyst is of low cost.

# 1.3 SILICON TETHERED RING-CLOSING METATHESIS REACTIONS

## 1.3.1. Introduction to Silicon Tethered Reactions

Well-documented advantages of intramolecular transformations as opposed to intermolecular ones greatly contributed to the arrival of the concept of temporary tethers.[32] Temporary tethers were developed to transform an intermolecular reaction into the corresponding intramolecular variant through the sequential coupling of reacting partners. Tethered reactions are often compared in the literature to effective enzymatic transformations. Such comparison arises from the temporary intramolecular coupling of an enzyme and a specific substrate, leading to the formation of enzyme–substrate complex. As the reaction proceeds, the product promptly migrates from the active site liberating the substrate from enzyme, thus illustrating the temporary character of this process.[33] Careful selection of a tether that would satisfy the synthetic criteria in the multistep synthesis is an essential task. Optimal tethers allow for facile introduction of coupling partners, display a good stability toward the reaction conditions and are readily removed or functionalized to provide the products often not available from an intermolecular version of a particular reaction (Scheme 9).




**Scheme 9.** Application of temporary tethers in organic synthesis.

Furthermore, tethering reaction partners decrease the entropic demands of a reaction thus translating into the higher reaction rates and milder reaction conditions.

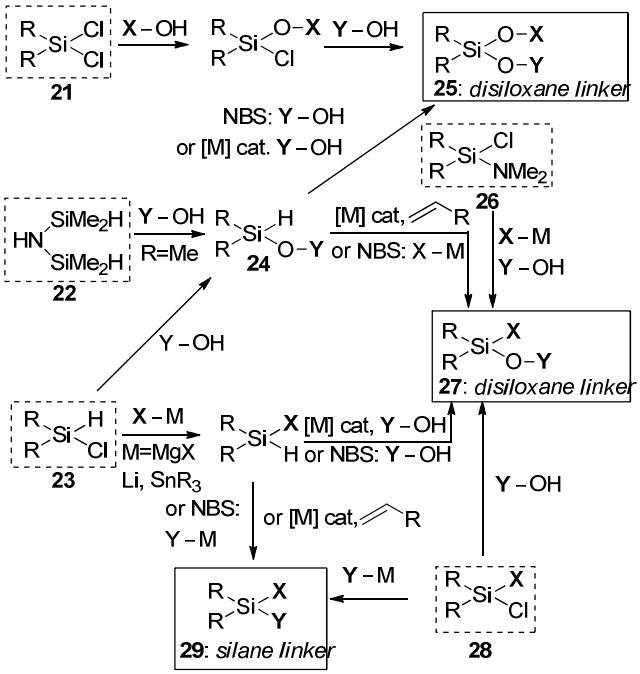
Transition states of tethered reactions retain fewer degrees of freedom, which results in improved regio- and stereoselectivity. From the variety of temporary tethers currently available, silicon is used the most frequently, because it is readily accessible, it is stable to a multitude of reaction conditions and it is easily and selectively cleaved towards the end of the reaction.[34] Additionally, silicon readily undergoes refunctionalization to give a series of synthetically useful intermediates through protodesilylation, oxidation, silane-group transfer, or transmetallation. Due to a significant versatility in postmetathesis functionalization, silicon frequently represents "the tether of choice" in many target directed synthesis. A silicon tether was initially utilized in the context of free radical addition in mid 1980s by the independent study of Nishiyama and Stork.[35] As the field progressed, reactions such as cross-coupling reactions,[36] hydrosilylation[37] and [4+2] cycloadditions[38] further expanded the scope of silicon-tether chemistry. More recently, the focus has been shifted toward the transition-metal-catalyzed cycloisomerization[39] and ring-closing metathesis reactions. Furthermore, the temporary silicon tether concept is well established in the synthetic community, particularly as it has been the subject of several comprehensive reviews.[40]

## 1.3.2. Common methods for tether incorporation

Due to the strength and ease of formation of silicon–oxygen bonds, the most common linkers employed in TST reactions are the disiloxane (**25**) or siloxane (**27**) functionalities, containing two and one Si–O bonds respectively (**Scheme 10**), with more limited use of the all-carbon silane linker **29**. As might be expected, there are a number of methods for tether construction; only the most commonly used of these will be examined here. The disiloxane motif **25** is often approached from the appropriate dichlorodialkylsilane **21** via sequential addition of two alcohol components to the silicon species. The use of excess dichlorosilane overcomes the obvious problem of double substitution, and usually allows the disiloxane product **25** to be accessed in good yield, although this tactic is limited to volatile dialkylsilanes which can be removed by simple evaporation prior to the addition of the second alcohol. In cases where better control over substitution is desired, a number of stepwise routes may be employed. For example, tetraalkyldisilazanes **22** or chlorosilanes **23** will silylate alcohols to give intermediate siloxanes **24**,[41,42] which can

be reactivated to a second nucleophilic displacement using halide electrophiles, or perhaps more appealingly can undergo metal-catalyzed Si–O bond formation.[43]

Siloxanes **27** are also readily accessed from the same intermediates **24**, again via a 'reactivation/displacement'sequence, or through metal-catalyzed C–Si bond formation (for example by hydrosilylation, **24**-**27**). The order of substituent addition can be reversed for the chlorosilanes **23**, proceeding through intermediate silane if the initial nucleophile is an organometallic reagent rather than an alcohol. Although these strategies eliminate the potential for the formation of disubstituted byproducts, the cost for this control is the need for an additional reaction step. However, a further group of reagents which exhibit this substitution selectivity but avoid the need for isolation of an intermediate are the chloroaminosilanes **26**, which can be converted to the siloxane 4 in a one-pot operation by addition of an alcohol nucleophile directly to the intermediate aminosilane (**26** - **27**).[44] In cases where the 'functional' carbon substituent is commercially available in the form of the chlorosilane **28**, a very straightforward alcohol silylation may be employed (**28** - **27**). Finally, silane linkers **5** can be directly accessed from either the chlorosilane **28** if it is readily available, or again from the intermediate silane, via the C–Si bond forming strategies discussed above.




**Scheme 10:** Common routes for TST construction.

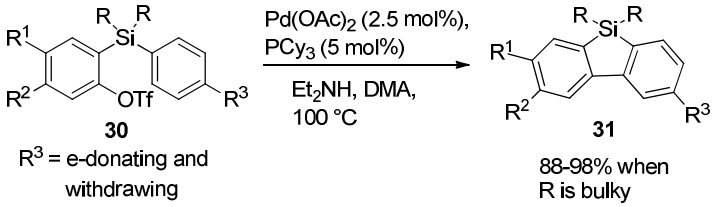
The inherent flexibility of these pathways allows a wide variety of silicon-tethered substrates to be easily synthesised, often in excellent yields. Given that many of these variations initiate with inexpensive, commercially available chlorosilanes, the effect of the spectator silicon alkyl substituents on reactivity and TST stability can be readily examined for any process. This latter point can be particularly important, as silicon tethers are not without drawbacks, such as their tolerance of harsher reaction conditions (particularly acidic environments where siloxanes exhibit the same lability as standard silyl ether protecting groups, and thermal conditions where they may be susceptible to nucleophilic attack). In these instances, increasing the steric bulk of the spectator substituents may protect the TST from unwanted degradation, but at the cost of increased steric hindrance—itself potentially leading to a reduction in reaction efficiency. Thus, the selection of an appropriate tether calls for a balance between tether stability and reacting group accessibility, for which solutions are often possible but not guaranteed.

### 1.3.3. Silicon-tethered reactions

The "temporary silicon connection" achieves the regiospecific, and often stereoselective, formation of carbon-carbon bonds by temporarily bringing together two reaction partners by means of an eventually removable silicon atom. During the last few years there have been tremendous upsurge of interest in different Silicon-tethered reactions.

#### 1.3.3.1. Palladium-catalyzed cross-coupling reactions

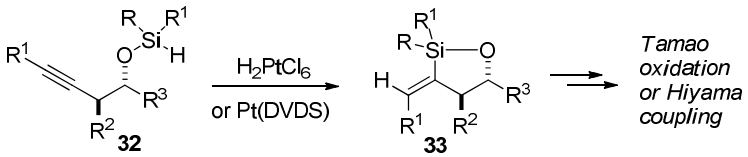
One of the most topical fields of modern organic chemistry is C–H activation, and it is no surprise that silicon-tethering methodology has recently found application in this arena. The Hiyama group first applied intramolecular palladium catalyzed C–H activation to the synthesis of dibenzosiloles **31** (Scheme 11). Upon treatment of tethered aryl triflates **30** with $Pd(OAc)_2/PCy_3$, a range of siloles **31** could be synthesised incorporating both electron-donating and electron-withdrawing groups about the two aromatic systems.




**Scheme 11:** Synthesis of silicon-bridged biaryls via C–H activation (Hiyama).

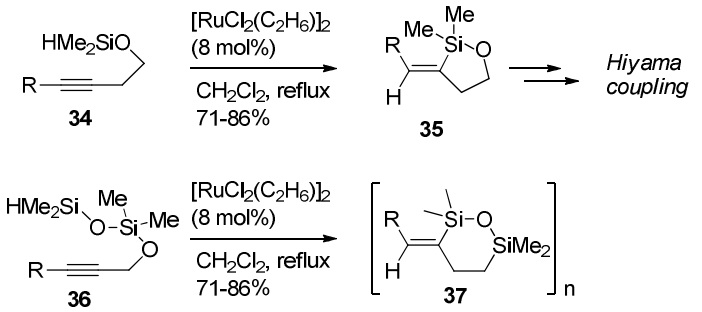
## 1.3.3.2 Hydrosilylation and carbosilylation

The metal-catalyzed addition of organosilanes across alkynes provides one of the most obvious and suitable opportunities for intramolecularisation, with the silicon tether now being intimately involved in the reaction itself. The challenge with intramolecular hydrosilylation lies in controlling both the regio- and stereoselectivity of the reaction. There have been considerable developments in the field of intramolecular alkyne hydrosilylation since the first report of this reaction by the Tamao group in 1988,[45] and methods to access all possible stereochemistries of H/Si addition to alkynes have now been achieved. A wide range of transition metal catalysts have been employed, with the cyclization selectivity being highly dependent on the precise nature of the metal species. Following Tamao's seminal work on platinum-catalyzed intramolecular *syn*, exo-hydrosilylations of homopropargylic alcohols, the Marshall and Denmark groups have greatly extended the substrate scope of this transformation (Scheme 12).[46] Under the influence of either Speier's catalyst ($H_2PtCl_6$) or Pt(1,1,3,3-tetramethyl-1,3-divinyldisiloxane) [(Pt(DVDS)], this cyclization proceeds with high selectivity for the *syn*, *exo*-addition of Si–H, yielding the corresponding E-vinyl siloxanes **33** from the silanes **32**. Marshall has used these products in the synthesis of aldol-type stereodiads and triads via Tamao oxidation of the cyclic siloxanes, while the efforts of the Denmark group have focused on the potential of the reaction products to undergo Hiyama cross-coupling. ***Marshall, Denmark: syn, exo***




[DVDS=1, 1, 3, 3-tetramethyl-1, 3-divinyldisiloxane]

***Denmark: anti, exo***

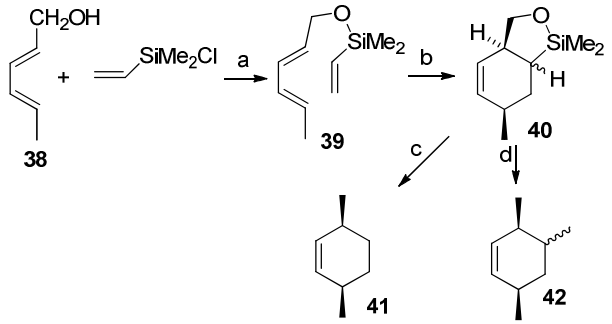



**Scheme 12:** Platinum-catalyzed (*syn*, exo) and ruthenium-catalyzed (*anti*, exo) hydrosilylation.

Later work presented by Denmark on the application of ruthenium arene catalysts to silicon-tethered hydrosilylation revealed an important switch in selectivity—an *anti*-selective *exo*-cyclization now being observed (Scheme 12).[46c, 47]

## 1.3.3.3. (4 + 2) Cycloadditions

Scheme 13 illustrates the process of a (4+2) cycloaddition reaction. In this prototypical case, the overall reaction **38** - **41**[48] is equivalent to the addition of ethylene, acting as a dienophile, to diene **38.**




**Scheme 13**: *Reactions and conditions*: (a) $Et_3N$-THF; (b) 160 $^oC$**,** 3.5 h, 70%; (c) 4 equiv of TBAF-DMF, 75 $^oC$, 4 h, 75%; (d) 1 equiv of TBAF-DMF, 10 equiv of 30% $H_20_2$, 55 $^oC$, 2 h, 85% (*cis*-1,2:*trans*-1,2 = 70:30)

No question of regiochemistry arises in this case when the silicon is simply removed from the adduct, but even in this simple case, the regiochemistry implicit in the process is brought forth when the silicon atom is replaced by a hydroxyl, as in **38 - 42**.

## 1.3.4. Modern Application of Silicon Tethers: Ring-Closing Metathesis Reaction

Olefin metathesis has transpired as the one of the most important carbon–carbon bond-forming reactions in a modern synthetic chemistry. The reaction utilizes metal-mediated exchange of metal–alkylidene species and tethered dienes and is used efficiently for the construction of functionally diverse carbo- and heterocycles.[49] The stunning success of the ring-closing metathesis reaction is largely attributed to the development of well-defined transition-metal catalysts that display a high activity, high thermal stability and excellent functional-group compatibility. (**Figure 5)** depicts four of the most prominent olefin metathesis catalysts developed to date.

One of the evident limitations in ring-closing metathesis has been an inability to control *E*/*Z* olefin geometry especially during the formation of medium and large rings. In these systems the cyclization often suffers from a large enthalpic and entropic cost of ring formation, as well as unfavorable transannular interactions that affect the control of olefin geometry.

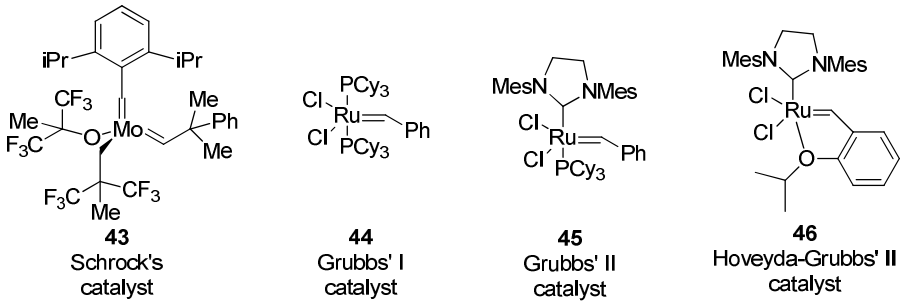


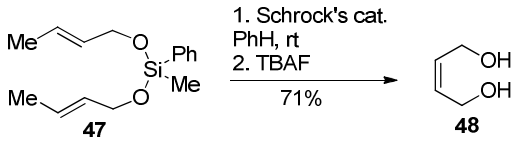

**Figure 5:** Some of the most heavily used metal-alkylidene metathesis catalysts.

The application of temporary silicon tethers in combination with a ring-closing metathesis surpasses this limitation by using a ring strain as a dominant factor; this affects the formation of (*Z*)-olefin in most medium rings. Furthermore, increasing the size of geminal alkyl substitution on silicon leads to bond angle distortion in which the angle between the substituents containing reactive alkenes decreases. This phenomenon, also known as the Thorpe–Ingold effect, greatly facilitates the cyclization of tethered alkenes. In addition, ruthenium-based metathesis catalysts occasionally display intolerance toward the strongly coordinating heteroatoms, as well as increased sensitivity toward the olefin substitution pattern. An ongoing search for a

new generation of catalysts has seen the advent of systems with a broader functional group tolerance and enhanced reactivity. Hence, temporary silicon-tethered ring-closing metathesis has become a powerful synthetic strategy utilized for the construction of biologically important, complex natural products.

### 1.3.4.1. Alkene RCM of Substrates Containing O-Si-O Linkage: Symmetrical Silaketals

The temporary silicon-tethered ring-closing metathesis (TST-RCM) sequence was initially described by Grubbs and Fu, as a methodology for the construction of achiral 1,4-diols.[50] The key feature of this approach was the tolerance of cyclization process to potentially sensitive bis-(alkoxy)silane functionality. However, due to sensitivity of cyclic silaketal during the purification, the crude material was treated with tetra-n-butylammonium fluoride (TBAF) prior to isolation (Scheme 14). One of the principal advantages of this strategy is the simplicity of preparation of symmetrical silaketals as opposed to the unsymmetrical silaketals. From the practical standpoint, the symmetrical silaketals are prepared by a simple silylation of the hydroxyl group with the appropriate tethering agent bearing the reactive dichlorosilane functionality.

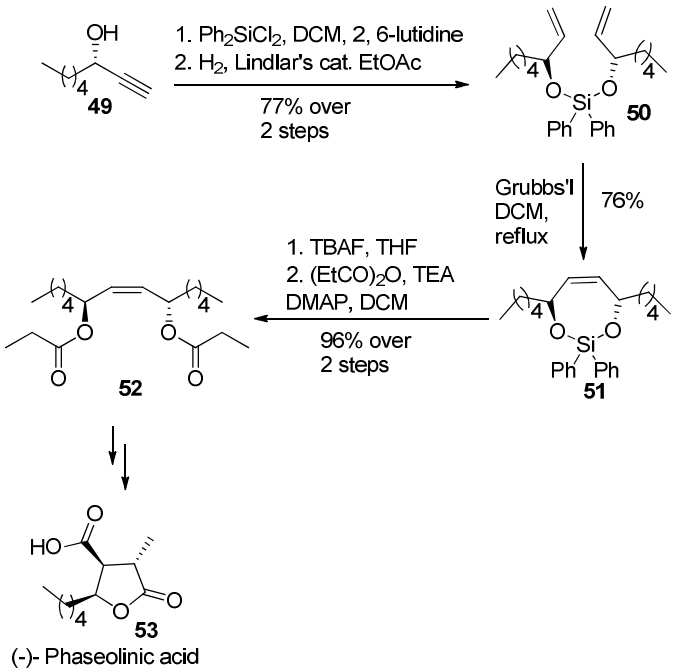



**Scheme 14:** Construction of achiral 1,4-diols.

The synthetic utility of $C_2$-symmetrical silaketals in the context of the TST-RCM reaction has been subsequently demonstrated with the synthesis of carbohydrate d-altritol[51] and the library of long-chain-linked disaccharides.[52] Furthermore, Hoye and Promo used the achiral silaketal intermediates for the construction of variety of medium ring-sized silacycles by means of a TST-RCM reaction with a satisfactory (*Z*)-olefin selectivities.[53]

Garcia and co-workers utilized the temporary silicon-tethered ring-closing metathesis as a key strategy in the synthesis of (−)-phaseolinic acid **53**.[54] This natural product belongs to the class of γ-butyrolactones that display notable antibacterial, antifungal,

and antitumor biological activities. Garcia and co-workers prepared the $C_2$-symmetrical 1,4-diol by the standard TST-RCM chemistry.




**Scheme 15:** Total synthesis of (−)-phaseolinic acid.

With the key intermediate in hand, the desired lactone framework was constructed by a stereospecific Ireland–Claisen rearrangement of the dipropanoate **52** followed by a subsequent treatment of the base and then acid.

## 1.3.4.2. Alkene RCM of Substrates Containing O-Si-O Linkage: Unsymmetrical Silaketals

The synthesis of unsymmetrical bis (alkoxy)silanes is frequently hampered by the formation of undesired, symmetrical bis (alkoxy)silanes. Usual protocol for the preparation of unsymmetrical bis (alkoxy)silanes includes a silylation of the first alcohol with large excess of dialkyldichlorosilane under dilute conditions. The subsequent step includes a removal of volatile dichlorosilane in vacuo and silylation with the second alcohol. However, this method suffers from the following disadvantages:

(1) the excess of dialkyldichlorosilane has to be evacuated from the monochlorosilane in vacuo,

(2) the preparation of heavier bis (alkoxy)silanes by using a higher boiling dialkyldichlorosilanes is highly impractical. Several elegant approaches have been reported to circumvent these shortcomings.[55, 56, 57]

Mioskowski and co-workers reported a comparative study in the preparation of various heterocycles through the ring-closing metathesis employing Schrock's alkoxy imidomolybdenum, Grubbs' first- and second-generation catalysts.[58]

Further Eustache and co-workers reported the TST-RCM approach toward the synthesis of spiro[5.5]ketal fragment of okadaic acid.[59] The TST-RCM strategy was utilized for the construction of (*Z*)-2-ene-1,5-diol moiety, which was synthetically transformed into the corresponding dihydroxyketone, an intermediate required for the acid-catalyzed spiroketalization. The robustness of this approach was demonstrated unambiguously as it was utilized for the total synthesis of the spiroketal-containing natural product, attenol A.[60]

Evans and co-workers further expanded the utility of the TST-RCM sequence in the total synthesis of the potent antitumor agent (−)-mucocin.[61]

### 1.3.4.3. Enyne RCM of Substrates Containing O-Si-O Linkage: Symmetrical and Unsymmetrical Silaketals

Enyne metathesis is an exceptional reaction because it provides a product containing the 1,3-diene functionality, clearly distinctive from the functionality of starting material.[62,63] Moreover, the enyne metathesis can be used as a part of tandem process in the combination with ring-closing metathesis or cross-metathesis to construct multiple carbon–carbon bonds in the acyclic or cyclic framework.[64] Unlike other metathesis reactions, however, enyne metathesis suffers from a lack of regio- and stereocontrol. In the last few years, the focus of research concerning this reaction has been directed toward the development of methodology that would provide solutions to these shortcomings and transform this reaction into a general method for the construction of stereodefined dienes.[65] Temporary silicon-assisted enyne metathesis offers new insights into the reactivity profile of tethered enyne intermediates through the stereoselective construction of silacyclic dienes.[68]

Temporary silicon-tethered ring-closing metathesis (TST-RCM) rapidly established as powerful cross-coupling reaction. Tremendous progress of this strategy is primarily due to advent of well-defined transition-metal catalysts that display a high reactivity and functional group tolerance. In TST-RCM chemistry, this catalyst has proven valuable in long-range asymmetric induction, thus providing the highest level of stereoselection. Its limitations are low thermal stability and sensitivity toward the strongly coordinating functional groups.

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# CHAPTER-2

## Asymmetric Total Synthesis of Naturally Occurring 10-Membered Lactones

**Section A:- Enantioselective Total Synthesis of Decarestrictine J**

**Section B:- First Asymmetric Total Synthesis of Aspinolide A**

# 2.1 Section A

# ENANTIOSELECTIVE TOTAL SYNTHESIS OF DECARESTRICTINE J

## 2.1.1. Introduction

Decanolides have attracted special attention over the last years[1,2,3] and an important class of compounds is the decarestrictine family. The decarestrictines are secondary metabolites that were isolated from various Penicillium strains and identified as bioactive compounds by chemical screening.[4,5,6] Among them, several members of the decarestrictine family of natural products have been shown to inhibit the biosynthesis of cholesterol.[4,6]

It is worthy of note that maintenance of cholesterol blood level is of considerable interest for the control of coronary diseases, which are responsible for about 40% of morbidity in developed countries. Efficient drugs are now in the market and most of these compounds, known as statines or mevinic acids, are more or less related to a family of lactonic compounds derived from the lead compounds pravastatin **1** and mevinolin **2** (Figure 1).[7] The structural difference between decarestrictines and these well-known cholesterol inhibitors suggests another mode of action to be operative. In addition, decarestrictines exhibit no other effects such as antibacterial or antifungal activities. Taking together their strong and selective biological profile, decarestrictines are attractive compounds for developing a new class of cholesterol-lowering drugs.

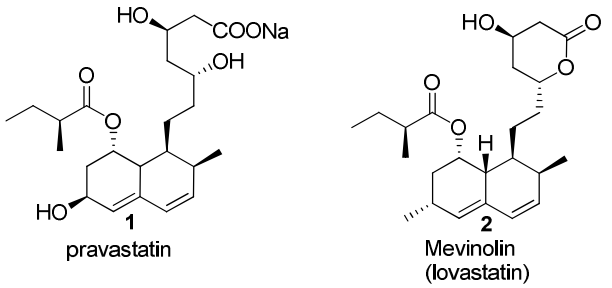



**Figure 1**: Commercial drugs used for lowering cholesterol level in the blood.

The absolute stereochemistry of decarestrictine J itself has not been reported. However, because it coexisted with decarestrictine B, whose absolute configuration had been determined by an X-ray analysis, Yamada and co-workers[8] suggested (7*R*, 9*R*)-stereochemistry for natural (-)-decarestrictine J.

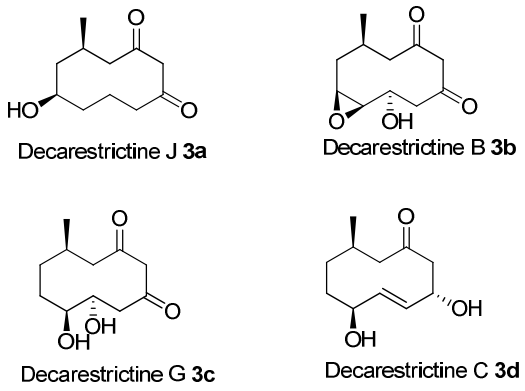


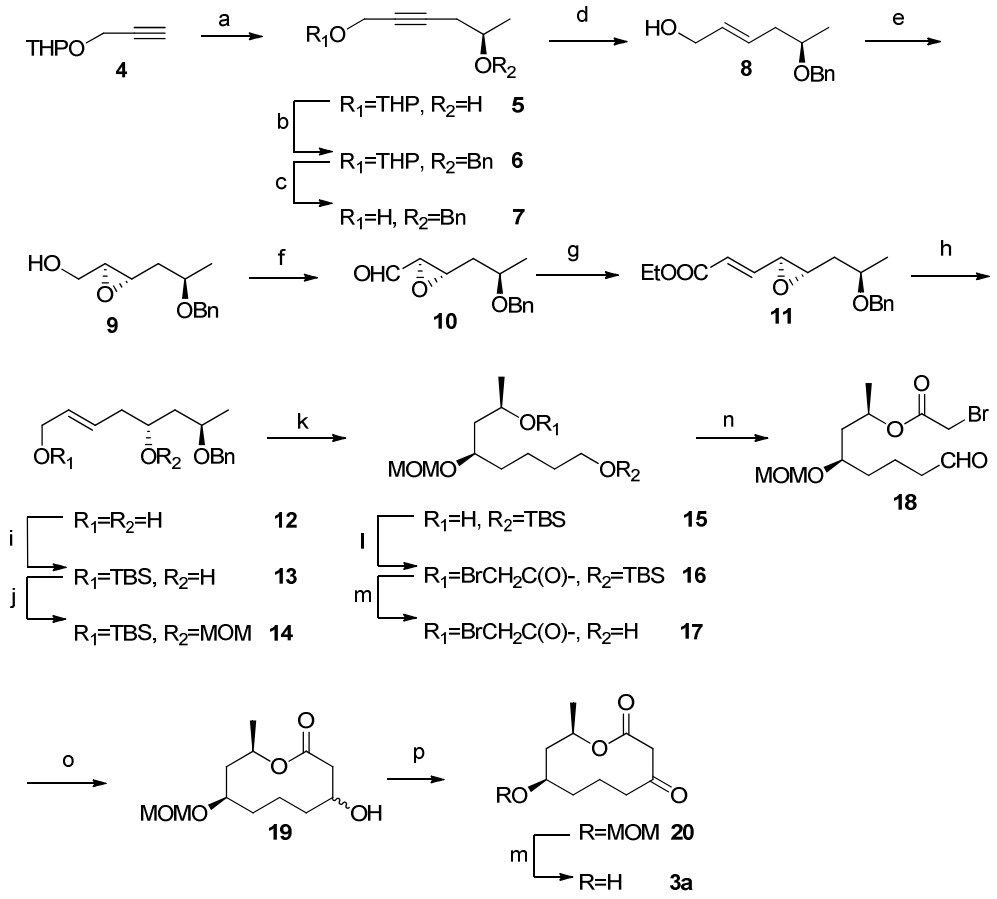

**Figure 2:** Examples of 10-membered lactones

## 2.1.2. Review of Literature: Decarestrictine J

Only one total synthesis of the proposed structure of (-)-decarestrictine J (**3a**) was reported by Yamada *et al*. when we completed our total synthesis. In the literature report Sharpless asymmetric epoxidation and samarium(II) iodide-promoted Reformatsky reaction were employed as the key steps.[8]

## Yamada *et al*. (1995)[8]

Yamada and co-workers synthesized (-)-decarestrictine J (**3a**) by utilizing the readily available starting material (*R*)-propylene oxide and tetrahydropyranyl propargyl ether **4**. Thus as shown in scheme 1, the base-promoted ring opening of propylene oxide with **4** afforded **5**. Compound **5** was transformed to trans-allylic alcohol **8** by selective triple bond reduction with LAH. The (–)-epoxy alcohol **9**, which was obtained by the Sharpless asymmetric epoxidation of trans-allylic alcohol **8**, was converted to bromoacetoxy aldehyde **18** through a nine-step sequence. The samarium (II) iodide-promoted intramolecular Reformatsky reaction of **18** and subsequent oxidation afforded keto lactone **19** which, on treatment with trimethylsilyl bromide, provided (–)-decarestrictine J (**3a**).




**Scheme 1**: *Reagents and conditions*: (a) $LiNH_2$, liq. $NH_3$, (*R*)-propylene oxide, 60%; (b) BnBr, NaH, TBAI; (c) TsOH, MeOH; (d) LAH, THF, 88%; (e) (+)-DET, $Ti(O^iPr)_4$, TBHP, MS-4Å; (f) Dess-Martin periodinane; (g) $(EtO)_2P(O)CH_2COOEt$, NaH, THF; (h) DIBAL, $CH_2Cl_2$, 70%; (i) TBSCl, $Et_3N$, DMAP, $CH_2Cl_2$; (j) MOMCl, DIPEA, $CH_2Cl_2$; (k) $H_2$/Pd-C, EtOH; (l) $BrCH_2C(O)Br$, $Me_2NPh$, $Et_2O$; (m) HF, $CH_3CN$; (n) PCC, $CH_2Cl_2$; (o) $SmI_2$, THF, 79%; (p) TMSBr, $CH_2Cl_2$.

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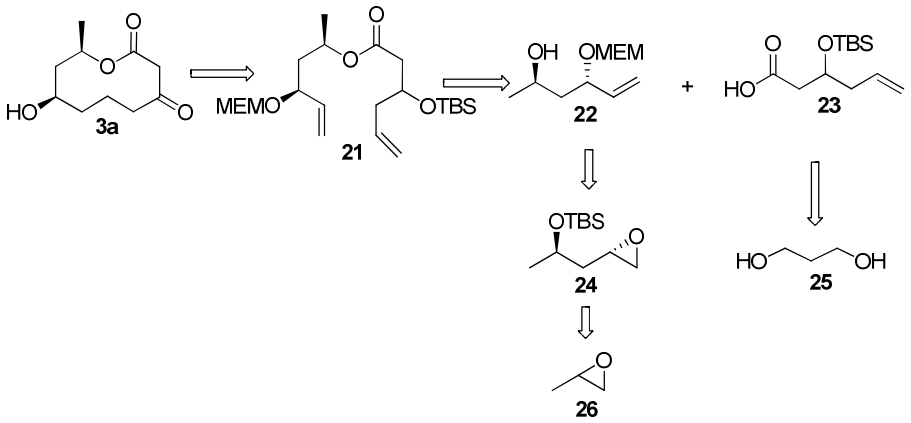
# 2.1.3 PRESENT WORK

## *Objective*

As a part of our research programme aimed at developing enantioselective synthesis of biologically active natural products based on hydrolytic kinetic resolution (HKR),[9] we considered devising a simple and concise route to decarestrictine J. Herein we describe our successful endeavours towards the total synthesis of **3a** employing HKR,[10] Yamaguchi esterification[11] and ring-closing metathesis (RCM)[12] as the key steps.

The HKR method involves the readily accessible cobalt based chiral salen complex as catalyst and water to resolve a racemic epoxide into an enantiomerically enriched epoxide and diol, which serve as useful precursor in the synthesis of various compounds of biological importance.[13]

Our retrosynthetic analysis for the synthesis of decarestrictine J **3a** is based on convergent approach as outlined in Scheme 2. We envisioned that the ring-closing could be affected by ring-closing metathesis of diene **21**. Diene **21** could be prepared



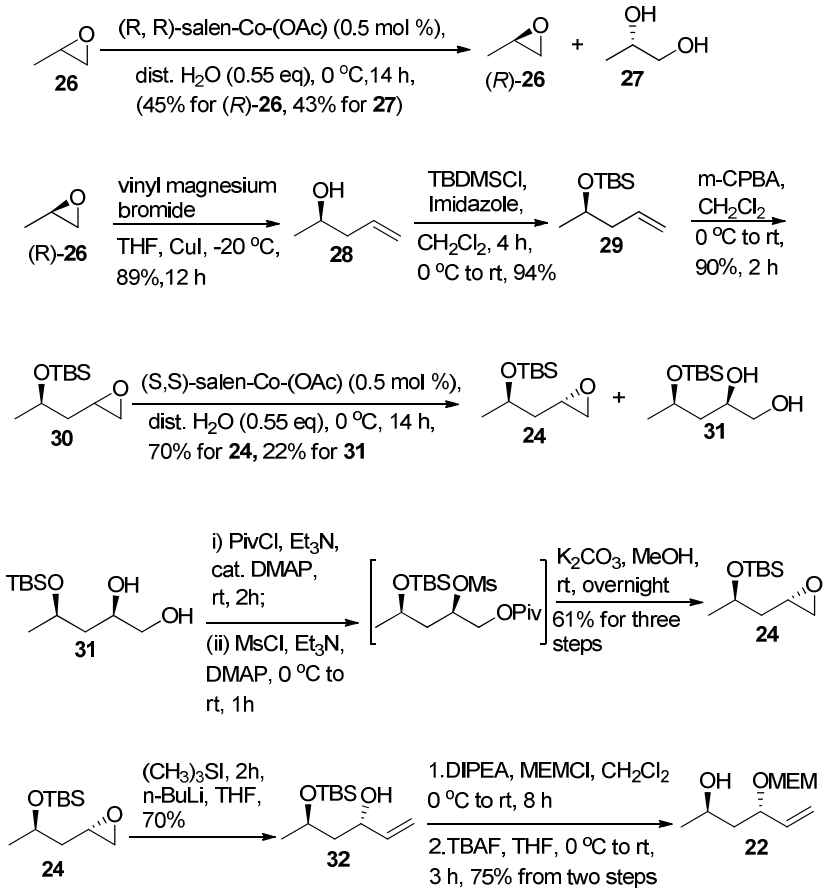

**Scheme 2:** Retrosynthetic analysis of decarestrictine J

by intermolecular Yamaguchi esterification of the alcohol **22** and acid **23**. Alcohol **22** could be obtained from *rac*-propylene epoxide **26** *via* iterative HKR, while acid fragment **23** could be prepared from 1,3-propane diol (**25**).

## 2.1.4. Results and Discussion

### Synthesis of alcohol fragment 22

As shown in Scheme 3, synthesis of alcohol fragment **22** started with a Jacobsen's hydrolytic kinetic resolution of *rac*-epoxide **26** using (*R*,*R*)-salen-Co-(OAc) catalyst to give epoxide (*R*)-**26** as a single isomer which was easily isolated from diol **27** by distillation.[10b]




**Scheme 3:** Synthesis of fragment **22**

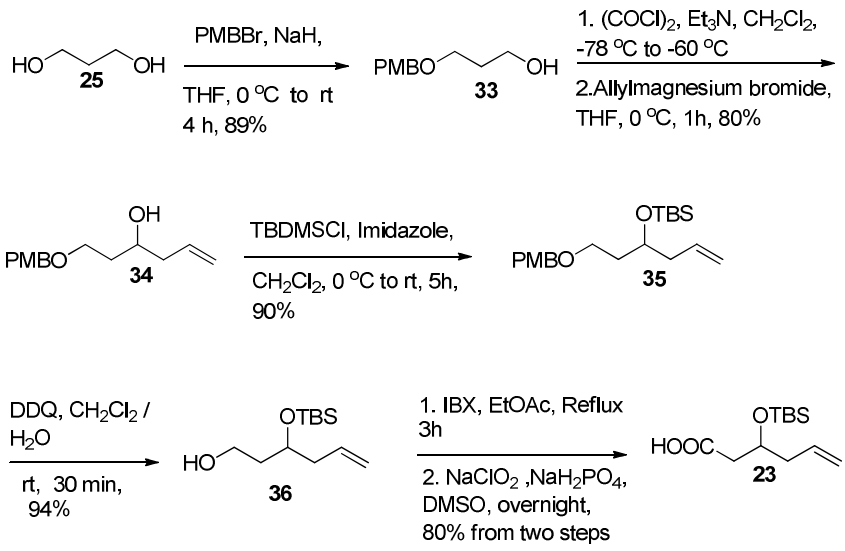
Epoxide (*R*)-**26** was treated with vinylmagnesium bromide in the presence of cuprous iodide to give homoallylic alcohol **28** in 89% yield.[9e] The IR spectrum of **28** gave broad hydroxyl absorption at 3400 $cm^{-1}$. The $^1H$ NMR spectrum of **28** gave olefin peaks at 5.85-5.77 (multiplet, one proton), 5.12 (doublet, one proton), 5.09 (doublet, one proton). We then further proceeded to explore the stereoselective outcome of the epoxidation reaction with hydroxyl group protection. Towards this end, the hydroxyl group of homoallylic alcohol **28** was first protected as the TBDMS ether, followed by

epoxidation with *m*-CPBA to afford epoxide **30**. The epoxide thus obtained was found to be a mixture of two diastereomers (*anti*:*syn*/3:1). The $^1$H NMR spectrum of **30** showed epoxide peaks at δ 3.13-3.01 (multiplet, one proton), 2.81-2.69 (multiplet, one proton), 2.52-2.43 (multiplet, one proton) in $^1$H NMR spectrum. In order to improve the diastereoselectivity, we attempted at the hydrolytic kinetic resolution method (HKR) as depicted in Scheme 3. Thus, the HKR was performed on epoxide **30** with (*S,S*)-salen-Co-(OAc) complex (0.5 mol %) and water (0.55eq) in THF (0.55 eq) to afford the diastereomerically pure epoxide **24** in 70% yield (>95% ee) and diol **31** in 22% yield. As the HKR method provided the desired epoxide **24** along with unwanted diol **31**, we thought it would be appropriate to convert diol **31** into the required epoxide **24** *via* internal nucleophilic substitution of a secondary mesylate.[14] Accordingly chemoselective pivalation of diol **31** with pivaloyl chloride followed by mesylation of the secondary hydroxyl and treatment of the crude mesylate with $K_2CO_3$ in methanol led to deprotection of the pivalate ester. Concomitant ring closure *via* intramolecular $S_N2$ displacement of the mesylate furnished the epoxide **24** in 61% overall yield. Epoxide **24** on reaction with dimethylsulfonium methylide[15] afforded one-carbon homologated allylic alcohol **32** in 70% yield. The IR spectrum of **32** gave broad hydroxyl absorption at 3430 cm$^{-1}$. The $^1$H NMR spectrum of **32** gave olefin peaks at δ 5.83-5.67 (multiplet, one proton) and 5.18-5.01 (multiplet, two protons). Alcohol **32** was protected as its MEM ether using MEMCl, DIPEA in anhydrous $CH_2Cl_2$ at ambient temperature followed by TBDMS removal to furnish the alcohol fragment **22** in 75% yield from both the steps. The IR spectra of **22** showed hydroxyl absorption at 3462 cm$^{-1}$. The $^1$H NMR spectra of **22** showed multiplet resonating at δ 4.81-4.73 ($OCH_2O$), δ 3.39 ($OCH_3$), and a multiplet at 3.62-3.53 ($OCH_2CH_2O$) corresponding with MEM group (Scheme 3). It may be noted that the alcohol fragment **22** could be synthesized in eight steps employing iterative HKR method, while our previous method involving Sharpless asymmetric dihydroxylation required three additional steps to prepare the same alcohol fragment.[9h]

## Synthesis of acid fragment 23

As shown in Scheme 4, synthesis of acid fragment **23** started from 1,3-propanediol **25**. Selective monoprotection of hydroxy group with *p*-methoxybenzyl bromide (PMBBr) in the presence of NaH afforded compound **33** in 89% yield. The $^1$H NMR

spectrum gave benzylic protons at δ 4.47 (singlet, two protons) and aromatic protons at δ 7.29-7.24 (multiplet) and 6.92-6.88 (multiplet). The IR spectrum gave hydroxyl absorption at 3410 $cm^{-1}$. The compound **33** was subjected to Swern oxidation[16] followed by reaction of the resulting aldehyde with allylmagnesium bromide to furnish the homoallyllic alcohol **34** in 80% yield**.** The appearance of terminal olefin at δ 5.96-5.75 and 5.18-5.07 in $^1$H NMR and broad hydroxyl absorption band at 3386 $cm^{-1}$ in IR spectrum confirmed the product.



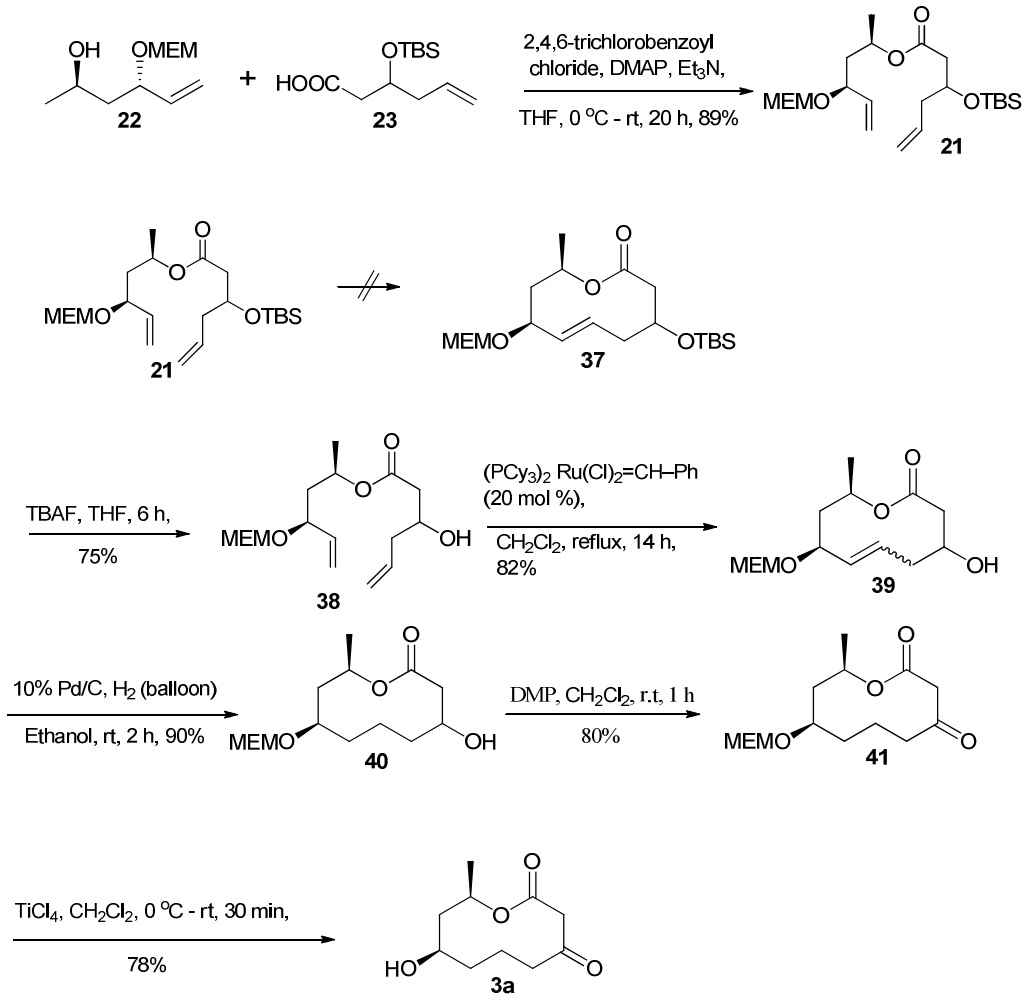

**Scheme 4**: Synthesis of fragment **23**

Protection of the hydroxy group of **34** as its TBDMS ether followed by removal of the PMB group[17] by DDQ resulted in the primary alcohol **36** with 94% yield. The IR spectra of **36** showed hydroxyl absorption at 3460 $cm^{-1}$. In the $^1$H NMR spectra, the peaks owing to PMB group disappeared. The alcohol **36** was oxidised to the aldehyde using 2-iodoxybenzoic acid (IBX) followed by subsequent oxidation using $NaClO_2$ to give the required acid fragment **23** in 80% yield. The IR spectra of **23** showed hydroxyl absorption at 3310 $cm^{-1}$ and acid carbonyl at 1714 $cm^{-1}$. The $^1$H NMR and $^{13}$C NMR spectra of **23** were compatible with the assigned structure.

## Coupling of Acid fragment 23 and Alcohol fragment 22 and completion of the Synthesis of Decarestrictine J

With substantial amount of both the fragments in hand the coupling of alcohol **22** and acid **23** was achieved by using the intermolecular Yamaguchi esterification

protocol to afford the diene ester **21** in 89% yield. The IR spectra of **21** showed ester carbonyl at 1735 $cm^{-1}$. In $^{13}C$ NMR, peak owing to carbonyl carbon was present at δ 171.4. Ring-closing metathesis of **21** under various conditions using Grubbs'1$^{st}$ and 2$^{nd}$ generation catalysts failed to provide the required ten-membered lactone **37**. In order to circumvent the problem, we thought it appropriate to first remove the TBDMS group and then use the ring-closing metathesis for macrocyclization.




**Scheme 5:** Coupling of acid fragment **23** and alcohol fragment **22**

Thus the TBDMS group of diene **21** was removed to give the alcohol **38** which on ring-closing metathesis by using Grubbs 1$^{st}$ generation catalyst furnished the cyclized product **39** as a mixture of *E*/*Z* isomers in 82% yield. The IR spectrum of **39** showed carbonyl group of lactone at 1720 $cm^{-1}$. The appearance of internal olefin at δ 5.73-5.54 in $^{1}H$ NMR confirmed the product. Compound **38** was subjected to hydrogenation using 10% Pd/C to give **40** in 90% yield. In the $^{1}H$ NMR spectrum of **40** peak owing to olefin was absent. Compound **40** was oxidized using Dess-Martin

periodinane (DMP) to afford keto compound **41** in 80% yield. The IR spectra of **41** showed the absence of hydroxyl absorption at 3459 $cm^{-1}$. In $^{13}C$ NMR, peak owing to carbonyl carbon was present at δ 202.3.Finally removal of the MEM group using $TiCl_4$ afforded the target compound **3a** in 78% yield. $[\alpha]_D^{25} = -152.4$ (*c* 0.1, MeOH) [lit[8] $[\alpha]_D^{23} = -154.0$ (*c* 0.1, MeOH)]. The physical and spectroscopic data of **3a** were in full agreement with the literature data.[8]

## 2.1.5. Conclusion

In conclusion, a convergent and efficient total synthesis of decarestrictine J, with high enantioselectivities has been accomplished in which stereocentres were generated by means of iterative Jacobsen's hydrolytic kinetic resolution and cyclization was achieved by ring closing metathesis. This approach could be used for the synthesis of other members of decarestrictine family for structure–activity relationship. Currently work is in progress in this direction.

## 2.1.6. Experimental Section

***General information:***

All reactions were carried out under argon or nitrogen in oven-dried glassware using standard gas-light syringes, cannulas and septa. Solvents and reagents were purified and dried by standard methods prior to use. Optical rotations were measured at room temperature. IR spectra were recorded on an FT-IR instrument. $^1H$ NMR spectra were recorded on 200 MHz, 300 MHz and 500 MHz and are reported in parts per million (δ) downfield relative to $CDCl_3$ as internal standard and $^{13}C$ NMR spectra were recorded at 50 MHz, 75 MHz and 125 MHz and assigned in parts per million (δ) relative to $CDCl_3$. Column chromatography was performed on silica gel (100-200 and 230-400 mesh) using a mixture of petroleum ether and ethyl acetate as the eluent. Enantiomeric excess was determined using chiral HPLC.

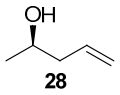
**(*R*)-Propylene oxide (*R*-26).**

(*R*)-**26**

The racemic propylene oxide **26** was resolved to chiral epoxide *R*-**26** in high enantiomeric excess (>99% *ee*) by the HKR method following a literature procedure.[10b]

$[\alpha]_D^{25}$: +11.5 (neat), lit.[10b] $[\alpha]_D^{25}$: –11.6 (neat) (for (*S*)-propylene oxide)

**(*R*)-Pent-4-en-2-ol (28)**




**28**

A round bottomed flask was charged with copper (I) iodide (1.64 g, 8.6 mmol), gently heated under vacuum, and slowly cooled with a flow of argon, and dry THF (20 mL) was added. This suspension was cooled to –20 $^oC$ and vigorously stirred, and vinylmagnesium bromide (1M in THF, 172 mL, 172.4 mmol) was injected to it. A solution of propylene oxide (*R*)-**90** (5 g, 86.09 mmol) in THF (10 mL) was added slowly to the above reagent, and the mixture was stirred at –20 $^oC$ for 12 h. The reaction mixture was quenched with a saturated aqueous solution of $NH_4Cl$. The organic layer was washed with brine, dried ($Na_2SO_4$) and concentrated to afford the crude homoallylic alcohol which on distillation provided alcohol **28** (6.6 g, 89%) as a colorless liquid (bp 115 $^oC$)

**Yield:** 6.6 g, 89%

**B.P.:** 115 $^oC$, lit.[9e] 115 $^oC$

**Mol. Formula**: $C_5H_{10}O$

$[\alpha]_D^{25}$: –10.86 (*c* 3.2 in $Et_2O$).

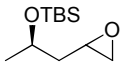
**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3400, 3078, 2931, 2975, 1562, 1457, 1432, 1243, 1071, 914.

**$^1$H NMR** (500 MHz, $CDCl_3$): δ 5.85-5.77 (m, 1H), 5.12 (d, *J* = 6.6 Hz, 1H), 5.09 (d, *J* = 2.4 Hz, 1H), 3.86-3.80 (m, 1H), 2.38-2.22 (m, 2H), 1.82 (s, 1H), 1.18 (d, *J* = 6.1, 3H).

**$^{13}$C NMR** (50 MHz, $CDCl_3$): δ 134.6, 116.6, 66.5, 43.2, 22.1.

**LC–MS**: m/z =109 $[M + Na]^+$.

***tert*-Butyldimethyl(((2*R*)-1-(oxiran-2-yl)propan-2-yl)oxy)silane (30)**




**30**

To a stirred soluion of alcohol **28** (3.0 g, 34.83 mmol) in $CH_2Cl_2$ (25 mL), imidazole (3.57, 52.24 mmol) was added. To this solution *t*-butylchlorodimethyl silane (5.77 g, 38.31 mmol) was added at 0 $^oC$ and reaction was stirred at room temperature for 4 h. The reaction mixture was quenched with a saturated aqueous solution of $NH_4Cl$ and extracted with $CH_2Cl_2$ (3 X 50 mL). The extract was washed with brine, dried ($Na_2SO_4$) and concentrated. Silica gel column chromatography of the crude product using pet ether/EtOAc (49:1) as eluent provided **29**.

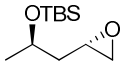
**Yield:** 6.56 g, 94%.

To a stirred solution of olefin **29** (6 g, 30.0 mmol) in $CH_2Cl_2$ (50 mL) at 0 $^oC$ was added *m*-CPBA (50%) (12.42 g, 36.0 mmol). The reaction mixture was stirred at room temperature for 2 h and quenched by saturated $NaHCO_3$ solution, extracted with $CH_2Cl_2$, washed with sat. $NaHCO_3$ and brine, dried ($Na_2SO_4$), concentrated and purified by silica gel column chromatography using pet ether/EtOAc (9:1) as eluent to yield the epoxide **30** as a colorless liquid in diastereomeric mixture (3:1).

**Yield:** 5.83 g, 90%.

**Mol. Formula**: $C_{11}H_{24}O_2Si$

***tert*-Butyldimethyl(((*R*)-1-((*S*)-oxiran-2-yl)propan-2-yl)oxy)silane (24)**




**24**

A solution of epoxide **30** (5 g, 23.1 mmol) and (*R,R*)-Salen-Co(III)-OAc (0.076 g, 0.11 mmol) in THF (0.23 mL) was stirred at 0 $^oC$ for 5 min, and then distilled water (230 µL, 12.6 mmol) was added. After stirring for 14 h, it was concentrated and purified by silica gel column chromatography using pet ether/EtOAc (9:1) to afford **24 (**3.5g, 70%) as a yellow color liquid. Continued chromatography with pet ether/EtOAc (3:2) provided the diol **31** as a brown color liquid as a single diastereomer.

**Yield:** 3.5g, 70%

**Mol. Formula**: $C_{11}H_{24}O_2Si$

$[\alpha]_D^{25}$: –11.4 (*c* 0.67, $CHCl_3$).

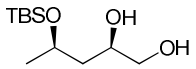
**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3018, 2958, 2930, 1858, 1472, 1463, 1377, 1256, 1216, 1101, 1005, 938, 878, 760.

**$^1$H NMR** (500 MHz, $CDCl_3$): δ 3.96-3.83 (m, 1H), 3.13-3.01 (m, 1H), 2.81-2.69 (m, 1H), 2.52-2.43 (m, 1H), 1.95-1.76 (m,1H), 1.69-1.60 (m, 1H), 1.18 (d, *J* = 6.53 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 6H).

**$^{13}$C NMR** (50 MHz, $CDCl_3$): δ 70.5, 50.1, 47.8, 47.0, 25.6, 19.6, 17.9, –4.4, –4.7

**LC–MS**: m/z =239 $[M + Na]^+$.

**(2*R*,4*R*)-4-((*tert*-Butyldimethylsilyl)oxy)pentane-1,2-diol (31)**




**31**

**Yield:** 1.19g, 22%

**Mol. Formula**: $C_{11}H_{26}O_3Si$

$[\alpha]_D^{25}$: + 32.6 (*c* 1.04, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3430, 3018, 2957, 2931, 2859, 1652, 1471, 1379, 1256, 1212, 1101, 1036, 971, 869, 758.

**$^1$H NMR** (200 MHz, $CDCl_3$): δ 4.5-4.41 (m, 1H), 3.99-3.96 (m, 1H), 3.56-3.47 (m, 2H), 1.73-1.54 (m, 4H), 1.08 (d, *J* = 6.57 Hz, 3H), 0.82-0.81 (m, 9H), 0.00-0.01 (m, 6H).

**$^{13}$C NMR** (50 MHz, $CDCl_3$): δ 72.4, 70.5, 70.4, 47.0, 25.8, 17.9, –4.4, –4.7.

**LC–MS**: m/z =257 $[M + Na]^+$.

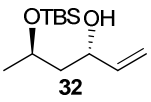
**Conversion of 31 into 24.**

Diol **31** (1 g, 4.25 mmol) was dissolved under argon in dry $CH_2Cl_2$ (10 mL) and treated with pivaloyl chloride (0.56 g, 4.7 mmol), $Et_3N$ (0.51 g, 5.1 mmol) and catalytic amount of DMAP. The mixture was stirred at room temperature for 2 h, then worked up (extraction with $CH_2Cl_2$). Removal of volatiles under reduced pressure gave an oily crude mono pivalate. The crude compound was then dissolved under argon in dry $CH_2Cl_2$ (15 mL) and treated with MsCl (0.49 g, 4.25 mmol), $Et_3N$ (0.516 g, 5.1 mmol) and catalytic amount of DMAP. The reaction mixture was stirred at room temperature for 1 h and then quenched with water. The water layer was extracted with $CH_2Cl_2$ (3 x 25 mL). The combined organic layer was washed with brine, dried ($Na_2SO_4$) and concentrated to give a crude product which was dissolved in MeOH (10 mL) and treated with $K_2CO_3$ (0.585 g, 4.25 mmol). The reaction mixture was then stirred overnight at room temperature and filtered through Celite. Removal of volatile under reduced pressure and column chromatography on silica gel using pet ether/EtOAc (9:1) as eluent gave the epoxide **24** as a yellow color liquid.

**Yield:** 0.565 g, overall yield 61%

$[\alpha]_D^{25}$: –11.4 (*c* 0.67, $CHCl_3$).

**(3*S*, 5*R*)-5-((*tert*-Butyldimethylsilyl)oxy)hex-1-en-3-ol (32)**




**32**

To a suspension of trimethylsulfonium iodide (5.76 g, 28.2 mmol) in dry THF (10 mL) at −20 °C was added *n*-BuLi (14.3 mL, 2.1 M solution in hexane, 30.0 mmol) dropwise over 20 min and stirred for 30 min. Then the epoxide **24** (1 g, 4.6 mmol) in dry THF (10 mL) was added to the above reaction mixture and stirred for 2 h. After consumption of the starting material the reaction mixture was quenched with $H_2O$ (15 mL) and extracted with EtOAc (4 × 15 mL). The combined extracts were washed with brine, dried over $Na_2SO_4$ and concentrated. The column chromatography of crude product using pet ether:ethyl acetate (85:15) gave **32**.

**Yield:** 0.74g, 70%

**Mol. Formula**: $C_{12}H_{26}O_2Si$

$[\alpha]_D^{25}$: –29.18 (*c* 1.04, $CHCl_3$).

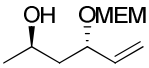
**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3430, 3018, 2957, 2931, 2859, 1652, 1471, 1379, 1256, 1212, 1101, 1036, 971, 869, 758.

**$^1$H NMR** (200 MHz, $CDCl_3$): δ 5.83-5.67 (m, 1H), 5.18-5.01 (m, 2H), 4.54-4.41 (m, 1H), 4.27-4.18 (m, 1H), 1.74-1.59 (m, 2H), 1.08 (d, *J* = 6.44 Hz, 3H), 0.82 (s, 9H), –0.01 (s, 6H).

**$^{13}$C NMR** (50 MHz, $CDCl_3$): δ 140.8, 114.2, 71.3, 70.6, 40.1, 25.8, 18.9, –4.6, –4.7.

**LC–MS**: m/z =253 $[M + Na]^+$.

**(2*R*, 4*S*)-4-((2-Methoxyethoxy)methoxy)hex-5-en-2-ol (22).**




**22**

A mixture of compound **32** (0.5 g, 2.17 mmol), diisopropylethylamine (0.84 g, 1.13 mL, 6.5 mmol), MEM-Cl (0.32 g, 0.30 mL, 2.60 mmol) in $CH_2Cl_2$ (20 mL) was stirred at room temperature for 8 h. The reaction mixture was quenched with water and extracted with $CH_2Cl_2$, washed with water, brine, dried ($Na_2SO_4$) and evaporated to afford crude product, which was used as such for the next step without purification.

To a solution of olefin (0.69 g, 2.17 mmol) in THF (10 mL) was added TBAF (3.25 mL, 3.25 mmol, 1.0 M solution in THF) at room temperature. The reaction mixture was stirred for 6 h and then diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried ($Na_2SO_4$) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (7:3) as eluent gave alcohol **22** as a colorless liquid.

**Yield:** 0.33 g, 75%

**Mol. Formula** : $C_{10}H_{20}O_4$

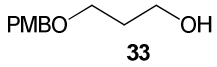
$[\alpha]_D^{25}$: –95.88 (*c* 1.22, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3462, 3016, 2968, 2893, 2448, 1645, 1456, 1422, 1367, 1241, 1216, 1133, 1098, 993.

**$^1$H NMR** (200 MHz, $CDCl_3$): δ 5.79-5.61 (m, 1H), 5.27-5.14 (m, 2H), 4.81-4.73 (m, 2H), 4.11- 4.01 (m, 1H), 3.73-3.68 (m, 1H), 3.62-3.53 (m, 4H), 3.39 (s, 3H). 2.36 (brs, 1H), 1.64-1.55 (m, 2H), 1.17 (d, *J* = 6.2 Hz, 3H).

**LC–MS**: m/z =227 $[M + Na]^+$.

**3-(4-Methoxybenzyloxy)propan-1-ol (33):**




**33**

To a solution of 1,3-propanediol **25** (5.0 g, 65.71 mmol) in dry DMF (200 mL) was added sodium hydride (60%, 2.90 g, 72.28 mmol) at 0 $^oC$. The reaction mixture was then stirred at room temperature for 30 min after which it was again cooled to 0 $^oC$. To this was added slowly *p*-methoxybenzyl chloride (11.32 g, 10.75 mL, 72.28 mmol) and *tetra n*-butylammonium iodide (2.6 g, 6.57 mmol) with further stirring for 4 h at the same temperature. The reaction mixture was quenched with addition of cold water at 0 $^oC$. The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with water (3 x 100 mL), brine, dried over $Na_2SO_4$ and concentrated. The residual oil was purified by silica gel column chromatography using petroleum ether/EtOAc (6:4) as eluent to furnish the mono-PMB protected alcohol **33** as colorless oil.

**Yield:** 11.87 g, 89%.

**Mol. Formula:** $C_{11}H_{16}O_3$

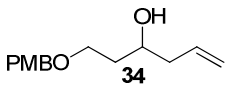
**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3410, 2940, 2863, 1612, 1513, 1249, 1175, 1098.

**$^1$H NMR (500 MHz, $CDCl_3$):** δ 7.29-7.24 (m, 2H), 6.92-6.88 (m, 2H), 4.47 (s, 2H), 3.82-3.72 (m, 5H), 3.67-3.62 (m, 2H), 2.57 (brs, 1H), 1.92-1.81 (m, 2H).

**$^{13}$C NMR (125 MHz, $CDCl_3$):** δ 159.1, 130.0, 129.2, 113.7, 72.7, 68.7, 61.4, 55.1, 31.9.

**LC–MS**: m/z =219 $(M+Na)^+$.

**1-((4-Methoxybenzyl)oxy)hex-5-en-3-ol (34):**




To a solution of oxalyl chloride (3.33 mL, 38.21 mmol) in dry $CH_2Cl_2$ (50 mL) at –78 $^oC$ was added dropwise dry DMSO (5.42 mL, 76.43 mmol) in $CH_2Cl_2$ (20 mL). After 30 min, alcohol **33** (5.0 g, 25.47 mmol) in $CH_2Cl_2$ (20 mL) was added over 10 min giving copious white precipitate. After stirring for 1 h at –78 $^oC$, the reaction mixture was brought to –60 $^oC$ and $Et_3N$ (15.62 mL, 112.24 mmol) was added slowly and stirred for 30 min allowing the reaction mixture to warm to room temperature. The reaction mixture was then diluted with water (100 mL) and $CH_2Cl_2$. The organic layer was separated and washed with water and brine, dried over $Na_2SO_4$ and passed through short pad of celite. The filtrate was concentrated to give the aldehyde as pale yellow oil, which was used as such for the next step without purification.

Allylmagnesium bromide (commercial 1 M solution in $Et_2O$, 38.24 mL, 38.24 mmol) was added dropwise under $N_2$ via syringe to a solution of the crude aldehyde (4.95 g, 25.00 mmol) in dry $Et_2O$ (50 mL) at 0 $^oC$ and stirred for 30 min allowing the reaction mixture to warm to room temperature. The reaction mixture was quenched with a saturated aqueous solution of $NH_4Cl$ and extracted with $Et_2O$. The extract was washed with brine, dried over $Na_2SO_4$, and concentrated. Purification of crude product by silica gel column chromatography using petroleum ether/EtOAc (70:30) as eluent afforded **34** as a colorless liquid.

**Yield:** 4.8 g, 80%.

**Mol. Formula:** $C_{14}H_{20}O_3$

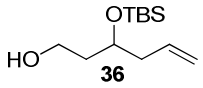
IR ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3386, 1640, 1603, 1493, 1453, 1243.

**$^1$H NMR (200 MHz, $CDCl_3$):** δ 7.29-7.24 ms, 2H), 6.93-6.87 (m, 2H), 5.96-5.75 (m, 1H), 5.18-5.07 (m, 2H), 4.47 (s, 2H), 3.94-3.85 (m, 1H), 3.82 (s, 3H), 3.77-3.58 (m,2H), 2.97 (brs, 1H), 2.29-2.23 (m, 2H), 1.81-1.72 (m, 2H).

**$^{13}$C NMR (50 MHz, $CDCl_3$):** δ 159.2. 134.8, 129.9, 129.2, 117.4, 113.7, 77.0, 72.8, 70.3, 68.5, 55.2, 41.8, 35.7

**LC–MS**: m/z =259 $(M+Na)^+$.

**3-((*tert*-Butyldimethylsilyl)oxy)hex-5-en-1-ol (36)**




**36**

To a stirred solution of alcohol **34** (2 g, 8.46 mmol) in $CH_2Cl_2$ was added imidazole (0.86 g, 12.7 mmol). To this solution *t*-butyl dimethylchlorosilane (1.53 g, 10.00 mmol) was added at 0 $^oC$ and the reaction was stirred at rt for 5 h. The reaction mixture was quenched with a saturated aqueous solution of $NH_4Cl$ and extracted with $CH_2Cl_2$. The extract was washed with brine, dried over $Na_2SO_4$, and concentrated. Purification of crude product by silica gel column chromatography using petroleum ether/EtOAc (95:5) as eluent afforded **35** as a colorless liquid.

**Yield:** 2.67 g, 90%.

**Mol. Formula:** $C_{20}H_{34}O_3Si$

To a stirring solution of PMB ether **35** (2 g, 5.68 mmol) in $CH_2Cl_2/H_2O$ (30:2) was added DDQ (1.55 g, 6.84 mmol). The resulting mixture was stirred for 30 min at 0 $^oC$. The mixture was poured into saturated aqueous $NaHCO_3$ and further diluted with $CH_2Cl_2$. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 15 mL). The combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated. The solvents were removed under reduced pressure to give the crude product mixture as yellow oil. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (95:5) as eluent gave **36** as a colorless liquid.

**Yield:** 1.23 g, 94%.

**Mol. Formula:** $C_{12}H_{26}O_2Si$

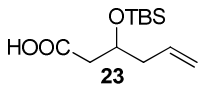
**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3460, 2959, 2857, 1640, 1448, 1376, 1255, 1078.

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 5.30-5.09 (m, 1H), 4.54-4.45 (m, 2H), 3.44-3.37 (m, 1H), 3.27-3.09 (m, 2H), 2.23 (brs, 1H), 1.76-1.70 (m, 2H), 1.32-0.98 (m, 2H), 0.34-0.31 (m, 9H), –0.47- –0.53 (m, 6H)

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 134.5, 114.2, 70.8, 59.8, 41.6, 37.8, 30.6, 25.7, 25.6, –4.5, –4.9.

**LC–MS**: m/z =253 $(M+Na)^+$.

**3-((*tert*-Butyldimethylsilyl)oxy)hex-5-enoic acid (23)**




**23**

To a solution of alcohol **36** (1.0 g, 4.34 mmol) in EtOAc (10 mL) was added IBX (3.64g, 13.01 mmol) in one portion and the reaction mixture was refluxed for 3 h. The reaction mixture was filtered through a pad of celite and filtrate was concentrated to give the crude aldehyde, which was used for the next step without purification.

A solution of 79% $NaClO_2$ (0.725 g, 6.5 mmol) in 2.5 mL of water was added dropwise to a stirred solution of above crude aldehyde (0.99 g, 4.33 mmol) in 2.5 mL of DMSO and $NaH_2PO_4$ (0.584 g, 4.9 mmol) in 2.5 mL of water in 5 min at room temperature. The mixture was left overnight at room temperature, and then 5% aqueous solution of $NaHCO_3$ was added. The aqueous phase was extracted 3 times with $CH_2Cl_2$ and washed with brine, dried ($Na_2SO_4$), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent gave the acid **23** as a syrupy liquid.

**Yield:** 0.84 g, 80%.

**Mol. Formula** : $C_{12}H_{24}O_3Si$

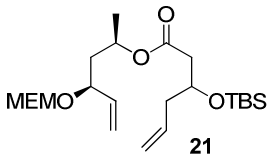
**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3310, 3078, 2856, 1714, 1642, 1515, 1361, 1091, 939, 837, 776.

**$^1$H NMR** ($CDCl_3$, 200 MHz): δ 5.82-5.73 (m, 1H), 5.09-5.06 (m, 2H), 4.20-4.16 (m, 1H), 2.53-2.43 (m, 2H), 2.30-2.28 (m, 2H), 0.87 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H);

**$^{13}$C NMR** ($CDCl_3$, 50 MHz): δ 177.2, 133.7, 118.1, 68.9, 41.9, 41.7, 25.7, 17.9, - 4.5, -4.9

**LC–MS**: m/z =267 $(M+Na)^+$.

**(2*R*,4*S*)-4-((2-Methoxyethoxy)methoxy)hex-5-en-2-yl 3-((tert-butyldimethylsilyl)oxy)hex-5-enoate (21)**




**21**

To a solution of acid **23** (500 mg, 2.04 mmol) in THF, was added triethyl amine (0.4 mL, 3.07 mmol) and 2, 4, 6-trichlorobenzoyl chloride (0.48 mL, 3.07 mmol) under nitrogen atmosphere at 0 $^{o}$C and the reaction mixture was allowed to stir under this condition for 1 h. To this, alcohol **22** (0.33 g, 1.6 mmol) in THF (5 mL) and catalytic amount of 4-dimethyl aminopyridine (DMAP) were added successively at 0 $^{o}$C. Stirring was continued for additional 20 h at rt. The reaction mixture was quenched with water and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were thoroughly washed with saturated sodium bicarbonate solution, brine, dried ($Na_2SO_4$), and concentrated to afford the crude product which was purified by silica gel column chromatography using petroleum ether/EtOAc (95:5) as eluent to afford the ester **21** as a colorless syrupy liquid.

**Yield:** 0.78 g, 89%

**Mol. Formula**: $C_{22}H_{42}O_6Si$

$[\alpha]_D^{25} = -36.17$ (*c* 3.19, $CHCl_3$).

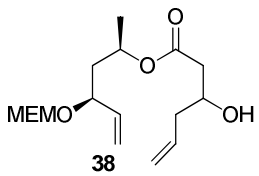
**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 2926, 2855, 1735, 1647, 1463, 1258, 1096, 837, 759.

**$^1$H NMR** ($CDCl_3$, 200 MHz): δ 5.89-5.55 (m, 2H), 5.28-5.05 (m, 4H), 5.02-4.91 (m, 1H), 4.80-4.71 (m, 1H), 4.63-4.56 (m, 1H), 4.24- 4.00 (m, 2H), 3.83-3.67 (m, 1H), 3.65-3.58 (m, 1H), 3.55- 3.46 (m, 2H), 3.35 (s, 3H), 2.48-2.38 (m, 2H), 2.02-1.83 (m, 2H), 1.79-1.69 (m, 2H), 1.18 (d, *J* = 6.32 Hz, 3H), 0.84 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 50 MHz): δ 171.4, 137.6, 134.2, 127.9, 117.6, 92.7, 74.2, 71.7, 68.7, 67.8, 58.9, 42.1, 41.9, 41.8, 25.7, 20.6, 17.9, -4.6, -4.8.

**LC–MS**: m/z =453 $(M+Na)^+$.

**(2*R*, 4*S*)-4-((2-Methoxyethoxy)methoxy)hex-5-en-2-yl 3-hydroxyhex-5-enoate (38)**




**38**

To a solution of ester **21** (0.6 g, 1.39 mmol) in THF (7 mL) was added TBAF (2.06 mL, 2.09 mmol, 1.0 M solution in THF) at room temperature. The reaction mixture was stirred for 6 h and then diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried ($Na_2SO_4$) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (80:20) as eluent gave alcohol **38** as a colorless liquid.

**Yield:** 0.33 g, 75%

**Mol. Formula** : $C_{16}H_{28}O_6$

$[\alpha]_D^{25}$: –55.12 (*c* 1.25, $CHCl_3$).

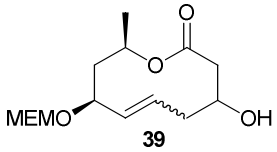
**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3462, 2930, 2868, 1740, 1647, 1455, 1304, 1110, 865, 745.

**$^1$H NMR** (200 MHz, $CDCl_3$): δ 5.94-5.57 (m, 2H), 5.27-5.08 (m, 5H), 4.77-4.73 (m, 1H), 4.63-4.59 (m, 1H), 4.17-4.02 (m, 2H), 3.84-3.71 (m, 1H), 3.63-3.49 (m, 3H), 3.37 (s, 3H), 2.50-2.41 (m, 2H), 2.33-2.24 (m, 2H), 1.82-1.73 (m, 2H), 1.24 (d, *J* = 6.4 Hz, 3H).

**$^{13}$C NMR** (50 MHz, $CDCl_3$): δ 172.4, 137.5, 134.0, 117.8, 117.5, 92.8, 73.8, 71.7, 71.6, 68.0, 67.3, 58.9, 41.8, 41.2, 41.0, 20.4.

**LC–MS**: m/z =339 $(M+Na)^+$.

**(8*S*, 10*R*)-4-Hydroxy-8-((2-methoxyethoxy)methoxy)-10-methyl-3,4,5,8,9,10-hexahydro-2H-oxecin-2-one (39)**




**39**

A mixture of **38** (0.15 g, 0.04 mmol) in anhydrous $CH_2Cl_2$ (100 mL) and Grubbs' First generation catalyst (80 mg, 20 mol%) was refluxed for 14 h. Solvent was removed

under reduced pressure to leave highly dark brown colored residue. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (3:2) as eluent afforded compound **39** as a colorless liquid.

**Yield:** 112 mg, 82%

**Mol. Formula** : $C_{14}H_{24}O_6$

$[\alpha]_D^{25}$: –42.89 (*c* 0.88, $CHCl_3$).

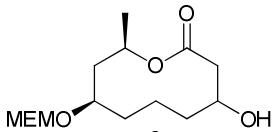
**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3450, 3019, 2944, 2880, 1720, 1680, 1647, 1110.

**$^1$H NMR** (200 MHz, $CDCl_3$): δ 5.73-5.54 (m, 2H), 5.25-5.07 (m, 2H), 4.75-4.71 (m, 1H), 4.62-4.57 (m, 1H), 4.21-4.04 (m, 2H), 3.81-3.68 (m, 1H), 3.59-3.48 (m, 2H), 3.36 (s, 3H), 2.79 (brs, 1H), 2.52-2.38 (m, 2H), 2.30-2.15 (m, 2H), 1.78-1.65 (m, 2H), 1.22 (d, *J* = 6.35 Hz, 3H).

**$^{13}$C NMR** (50 MHz, $CDCl_3$): δ 172.1, 137.5, 129.2, 92.8, 73.8, 71.7, 71.6, 68.1, 67.3, 58.9, 41.8, 41.4, 39.8, 20.4.

**LC–MS**: m/z =311 $(M+Na)^+$.

**(8*R*, 10*R*)-4-Hydroxy-8-((2-methoxyethoxy)methoxy)-10-methyloxecan-2-one (40)**




**40**

To compound **39** (0.1 g, 0.35 mmol) in Ethanol was added Pd-C (10%) under hydrogenation condition and the reaction mixture was allowed for 2 h. On completion of reaction, the mixture was filtered through a pad of celite and concentrated in vacuo. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (3:2) as eluent afforded compound **40** as a colorless liquid.

**Yield:** 0.09 g, 90%

**Mol. Formula** : $C_{14}H_{26}O_6$

$[\alpha]_D^{25}$ = –32.92 (*c* 0.40, $CHCl_3$).

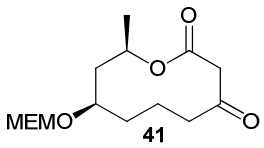
**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3459, 3015, 2932, 1729, 1462, 1378, 1253, 1179, 1042.

**$^1$H NMR** ($CDCl_3$, 200 MHz): δ 5.11-5.02 (m, 1H), 4.75-4.63 (m, 2H), 3.98 (brs, 1H), 3.71-3.66 (m, 2H), 3.53-3.51 (m, 2H), 3.36 (s, 3H), 2.44-2.31 (m, 3H), 1.56-1.43 (m, 8H), 1.24 (d, *J* = 6.19 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 50 MHz): δ 172.7, 94.7, 71.7, 68.4, 67.9, 67.3, 59.0, 42.1, 40.4, 36.4, 27.1, 20.6, 9.06.

**LC–MS**: m/z =313 $(M+Na)^+$.

**(8*R*, 10*R*)-8-((2-Methoxyethoxy)methoxy)-10-methyloxecane-2,4-dione (41)**



**41**

Dess–Martin periodinane (0.11 g, 0.26 mmol) was added to a solution of compound **40** (0.07 g, 0.24 mmol) in $CH_2Cl_2$ (0.7 ml) at 0 $^oC$. The reaction was stirred at rt for 30 min, before being quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. The organic layer was washed with satd NaCl solution and dried over $Na_2SO_4$ and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (7:3) as eluent gave alcohol **41** as a colorless liquid.

**Yield:** 0.06 g, 80%

**Mol. Formula** : $C_{14}H_{24}O_6$

$[\alpha]_D^{25}$: –29.88 (*c* 0.25, $CHCl_3$).

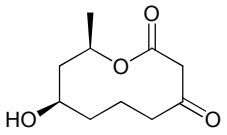
**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3016, 2968, 2893, 1745, 1701, 1452, 1265, 1076, 970.

**$^1$H NMR** (200 MHz, $CDCl_3$): δ 4.77-4.66 (m, 2H), 4.24-4.13 (m, 1H), 3.71-3.66 (m, 2H), 3.60-3.47 (m, 3H), 3.39-3.35 (m, 4H), 2.64-2.42 (m, 2H), 2.39-2.12 (m, 1H), 1.78-1.72 (m, 3H), 1.60 -1.50 (m, 3H), 1.27 (d, *J* = 6.4 Hz, 3H).

**$^{13}$C NMR** (50 MHz, $CDC_{l3}$): δ 202.3, 166.8, 94.7, 75.2, 71.7, 69.5, 67.3, 58.9, 49.5, 42.6, 40.5, 37.1, 22.6, 20.6.

**LC–MS**: m/z =311 $(M+Na)^+$.

**Decarestrictine J (3a)**



decarestrictine J (**3a**)

To a solution of **41** (0.05 g, 0.17 mmol) in anhydrous $CH_2Cl_2$ (1.5 mL) under nitrogen at 0 $^oC$ was added $TiCl_4$ (0.33 g, 0.19 mL, 1.73 mmol). After 30 min, excess of reagent was quenched with water, extracted with $CH_2Cl_2$, washed with water, dried ($Na_2SO_4$), evaporated. The reaction mixture was purified on silica gel by eluting with EtOAc to afford decarestrictine J **3a**.

**Yield:** 0.027 g, 78%

**M.P.:** 50–55 $^oC$, lit.[8] 54–55 $^oC$

**Mol. Formula**: $C_{10}H_{16}O_4$

$[\alpha]_D^{25}$: –152.4 (*c* 0.1, MeOH), [lit[8] $[\alpha]_D^{23}$ = –154.0 (*c* 0.1, MeOH)].

**IR** (neat, $cm^{-1}$): $\nu_{max}$ 3430, 2912, 2850, 1745, 1701, 1452, 1265, 1076, 970

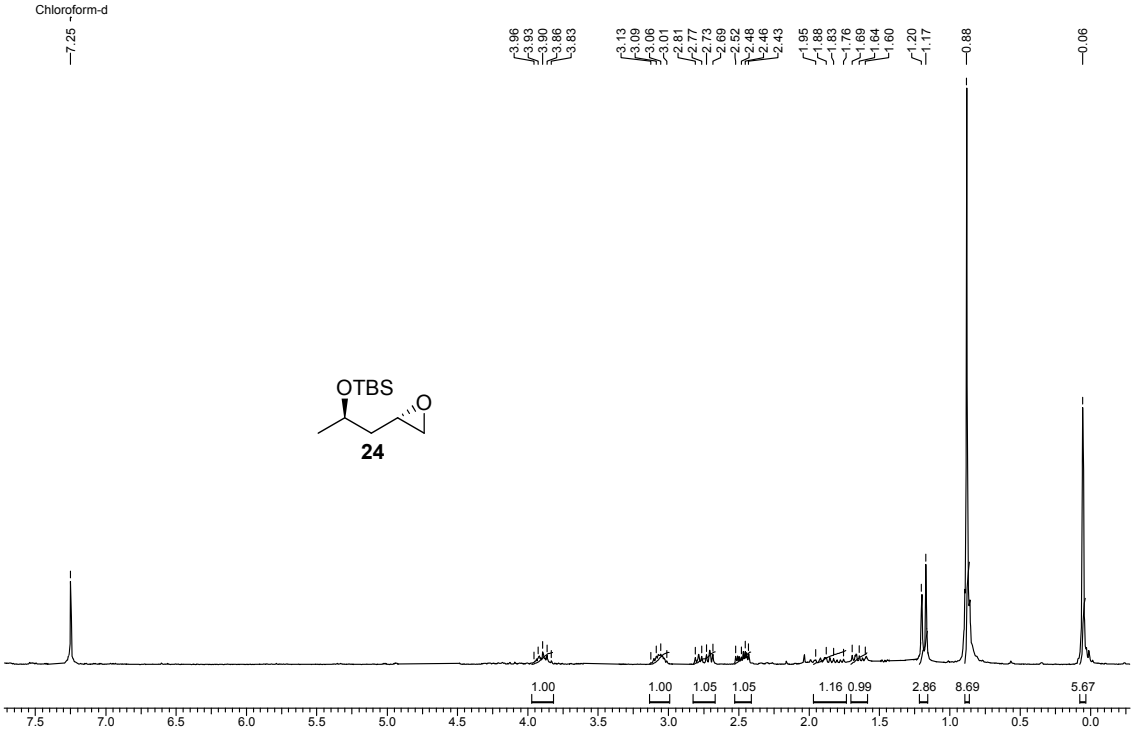
**$^1$H NMR** (200 MHz, $CDCl_3$): δ 5.12-5.06 (m, 1H), 3.69-3.67 (m, 1H), 3.39 (m, 2H), 2.55-2.53 (m, 1H), 2.37-2.13 (m, 1H), 2.07-1.97 (m, 1H), 1.92-1.79 (m, 2H), 1.59-1.56 (m, 3H), 1.27 (d, *J* = 6.19 Hz, 3H).

[lit[8] **$^1$H NMR** (300 MHz, $CDCl_3$): δ 5.22-5.15 (m, 1H), 3.72-3.65 (m, 1H), 3.38 (d, *J*=2.8 Hz, 2H), 2.76-2.66 (m, 1H), 2.34-2.25 (m, 1H), 2.08-2.00 (m, 1H), 1.92-1.83 (m, 2H), 1.74-1.51 (m, 3H), 1.30 (d, *J*=6.2 Hz, 3H)]

**LC–MS**: m/z =223 $(M+Na)^+$.

## 2.1.7. Spectra

| | |
|---|---|
| $^{1}$H and $^{13}$C spectra of compound | **24** |
| $^{1}$H and $^{13}$C spectra of compound | **31** |
| $^{1}$H and $^{13}$C spectra of compound | **32** |
| $^{1}$H spectra of compound | **22** |
| $^{1}$H and $^{13}$C spectra of compound | **33** |
| $^{1}$H and $^{13}$C spectra of compound | **34** |
| $^{1}$H and $^{13}$C spectra of compound | **36** |
| $^{1}$H and $^{13}$C spectra of compound | **23** |
| $^{1}$H and $^{13}$C spectra of compound | **21** |
| $^{1}$H and $^{13}$C spectra of compound | **38** |
| $^{1}$H and $^{13}$C spectra of compound | **39** |
| $^{1}$H and $^{13}$C spectra of compound | **40** |
| $^{1}$H and $^{13}$C spectra of compound | **41** |
| $^{1}$H spectra of compound | **3a** |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3.96
3.93
3.90
3.86
3.83
3.13
3.09
3.06
3.01
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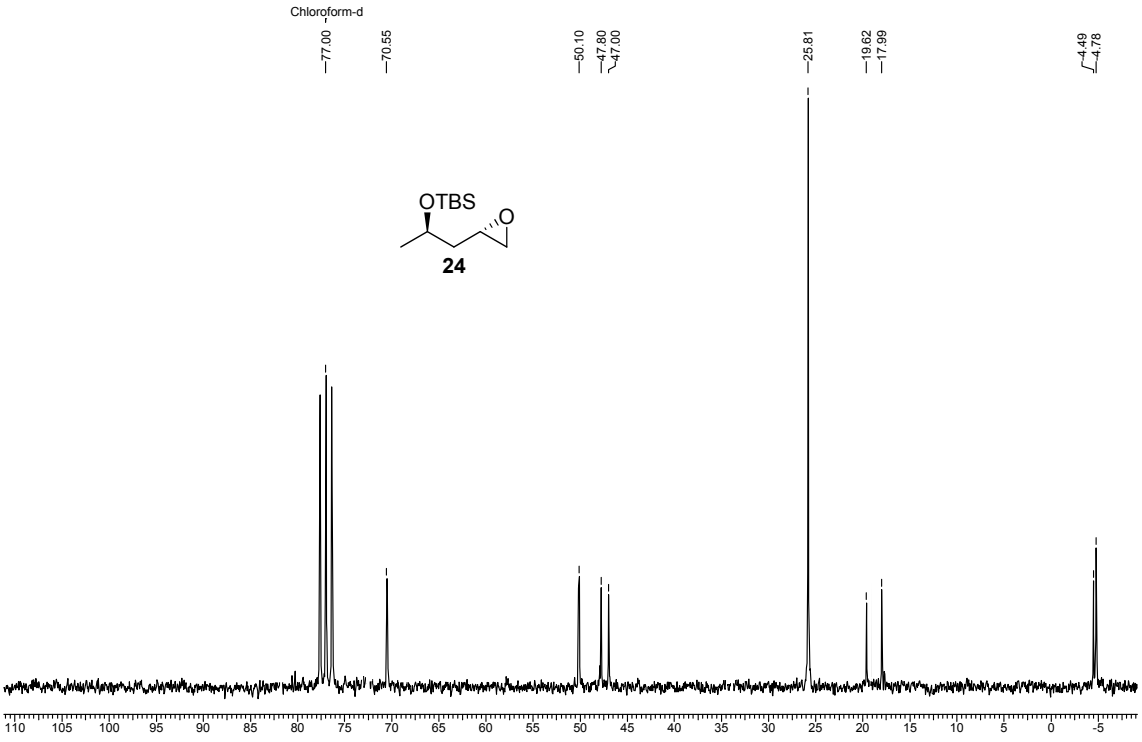
2.77
2.73
2.69
2.52
2.48
2.46
2.43
1.95
1.88
1.83
1.76
1.69
1.64
1.60
1.20
1.17
0.88
0.06
OTBS
O
24
1.00
1.00
1.05
1.05
1.16
0.99
2.86
8.69
5.67


Chloroform-d
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47.00
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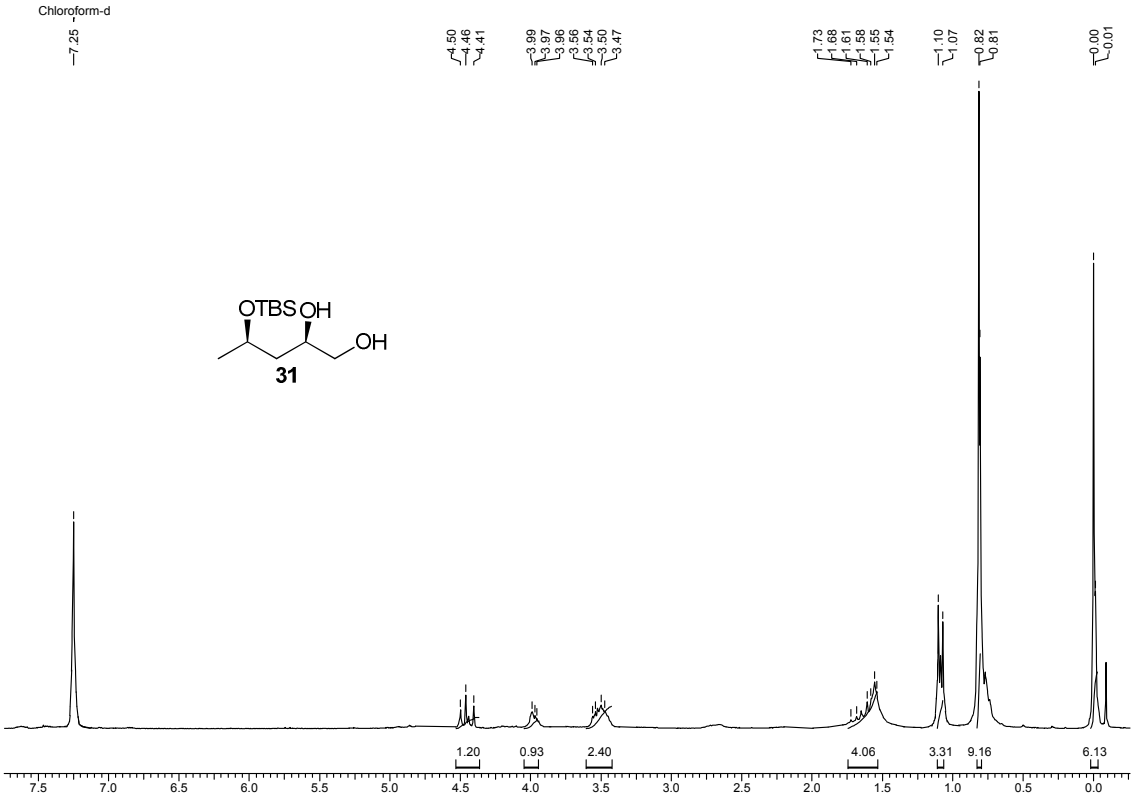
19.62
17.99
4.49
4.78
OTBS
O
24


Chloroform-d
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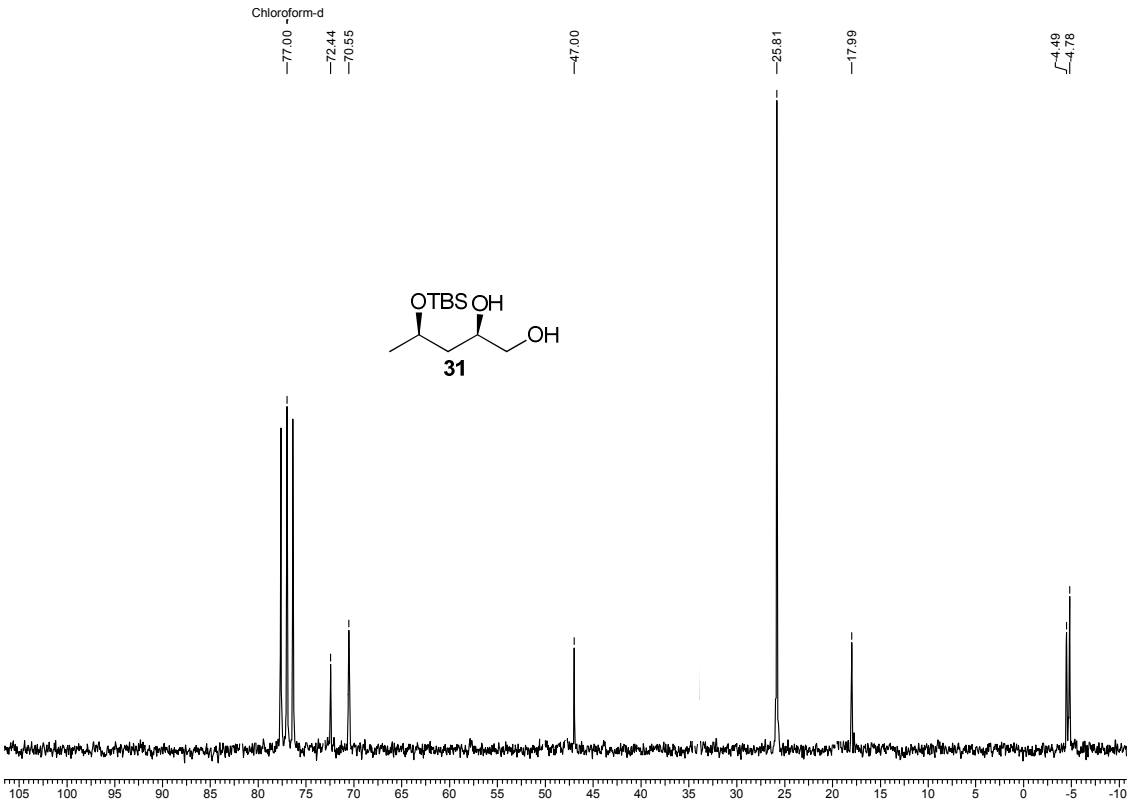
4.50
4.46
4.41
3.99
3.97
3.96
3.56
3.54
3.50
3.47
1.73
1.68
1.61
1.58
1.55
1.54
1.10
1.07
0.82
0.81
0.00
0.01
OTBS OH
OH
31
1.20
0.93
2.40
4.06
3.31
9.16
6.13


Chloroform-d
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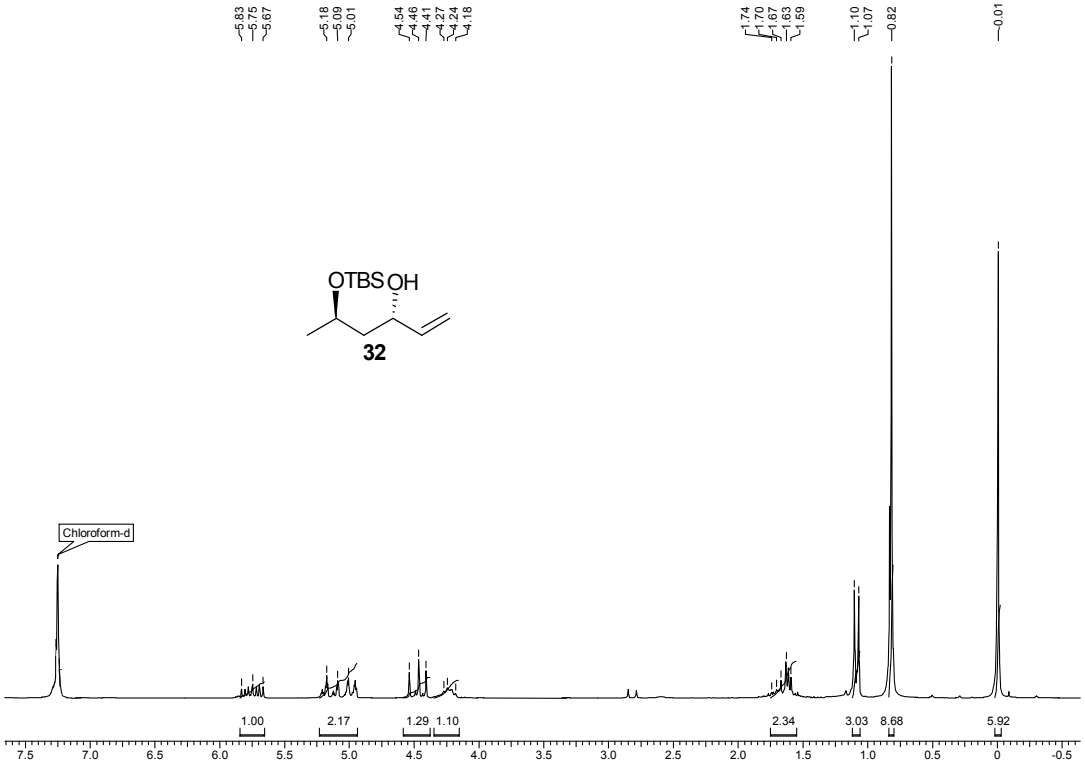
72.44
70.55
47.00
25.81
17.99
4.49
4.78
OTBS OH
OH
31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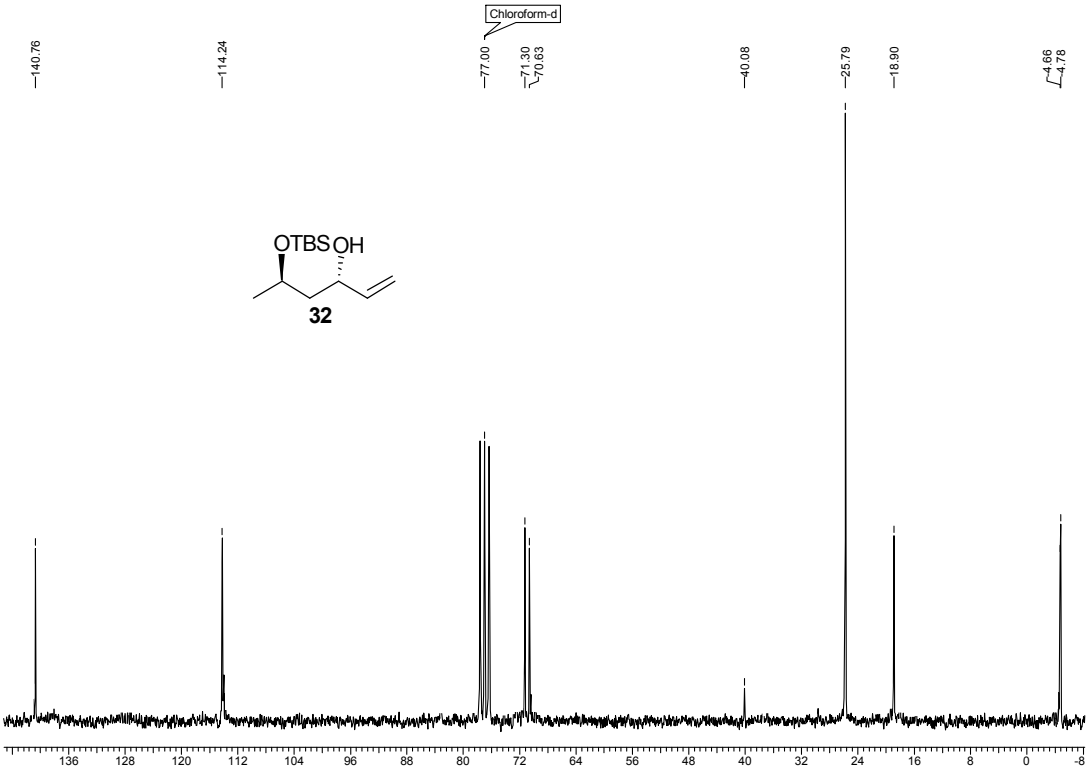
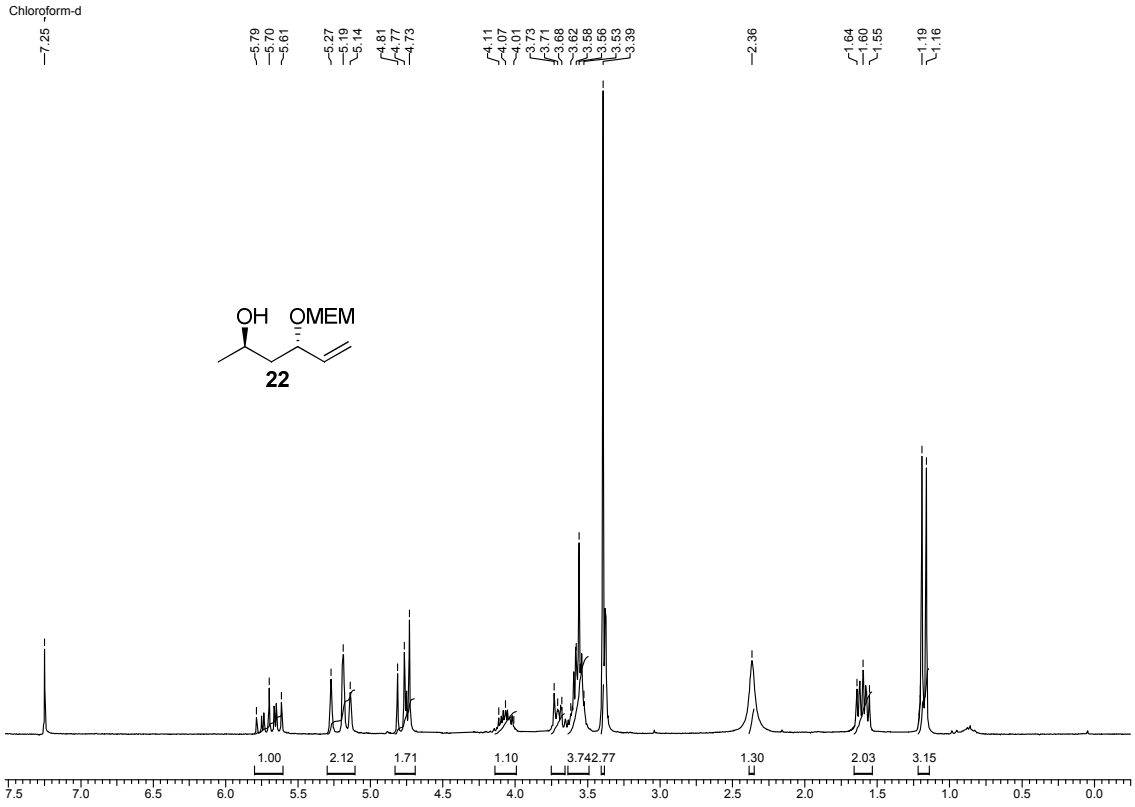
5.75
5.67
5.18
5.09
5.01
4.54
4.46
4.41
4.27
4.24
4.18
1.74
1.70
1.67
1.63
1.59
1.10
1.07
0.82
0.01
OTBS OH
32
Chloroform-d
1.00
2.17
1.29
1.10
2.34
3.03
8.68
5.92
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
-0.5


140.76
114.24
Chloroform-d
77.00
71.30
70.63
40.08
25.79
18.90
4.66
4.78
OTBS OH
32
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
-8


Chloroform-d
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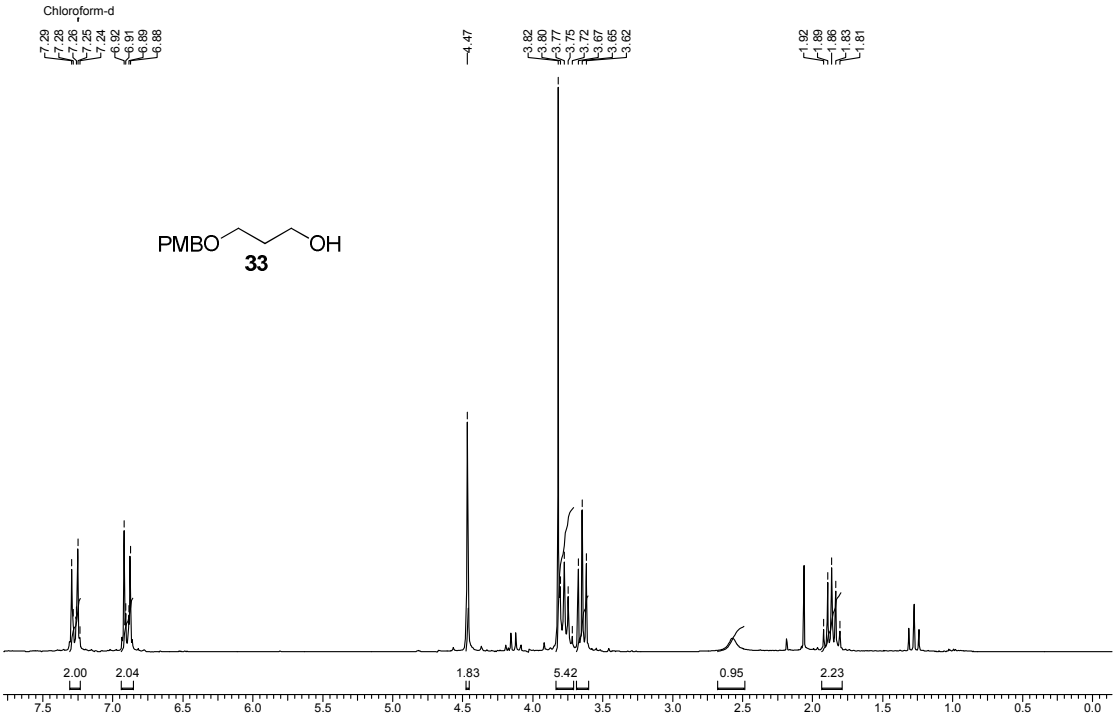
5.79
5.70
5.61
5.27
5.19
5.14
4.81
4.77
4.73
4.11
4.07
4.01
3.73
3.71
3.68
3.62
3.58
3.56
3.53
3.39
2.36
1.64
1.60
1.55
1.19
1.16
OH
OMEM
22
1.00
2.12
1.71
1.10
3.74
2.77
1.30
2.03
3.15
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


Chloroform-d
7.29
7.28
7.26
7.25
7.24
6.92
6.91
6.89
6.88
4.47
3.82
3.80
3.77
3.75
3.72
3.67
3.65
3.62
1.92
1.89
1.86
1.83
1.81
PMBO
OH
33
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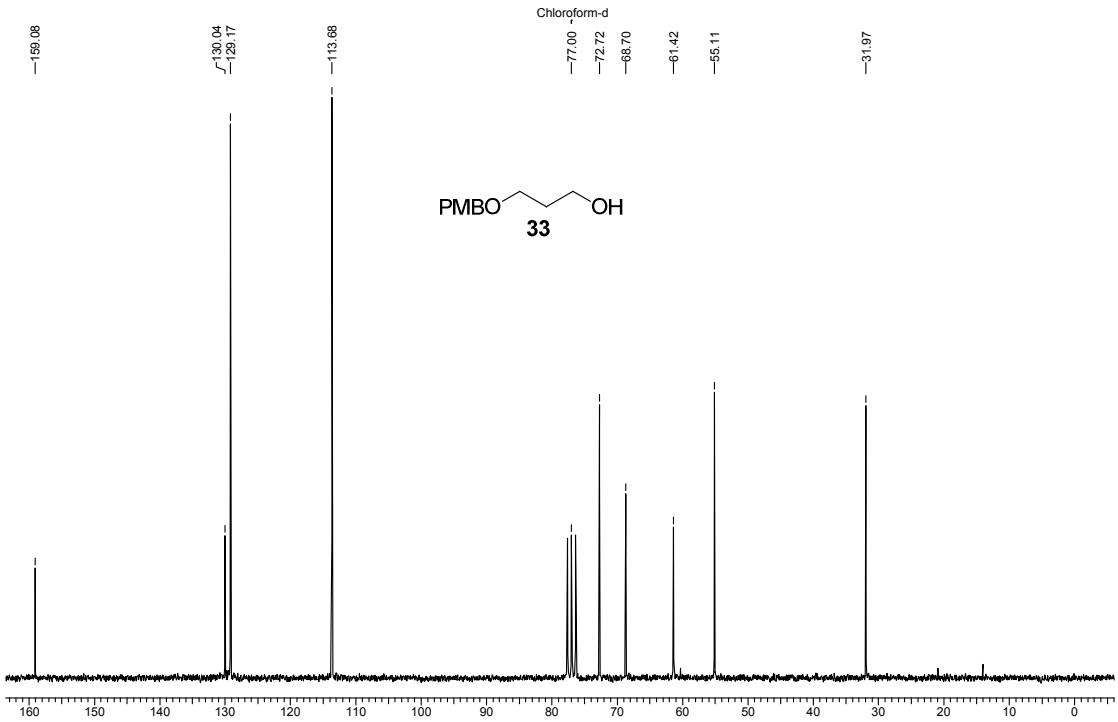
2.04
1.83
5.42
0.95
2.23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130.04
129.17
113.68
Chloroform-d
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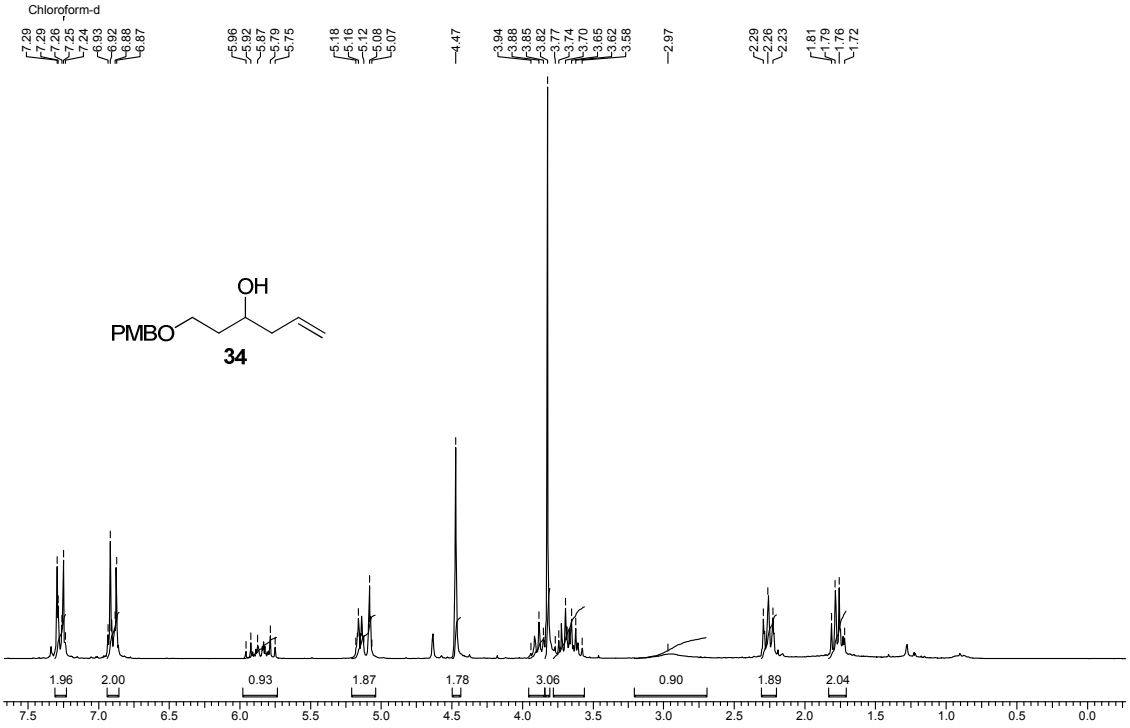
72.72
68.70
61.42
55.11
31.97
PMBO
OH
33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7.29
7.26
7.25
7.24
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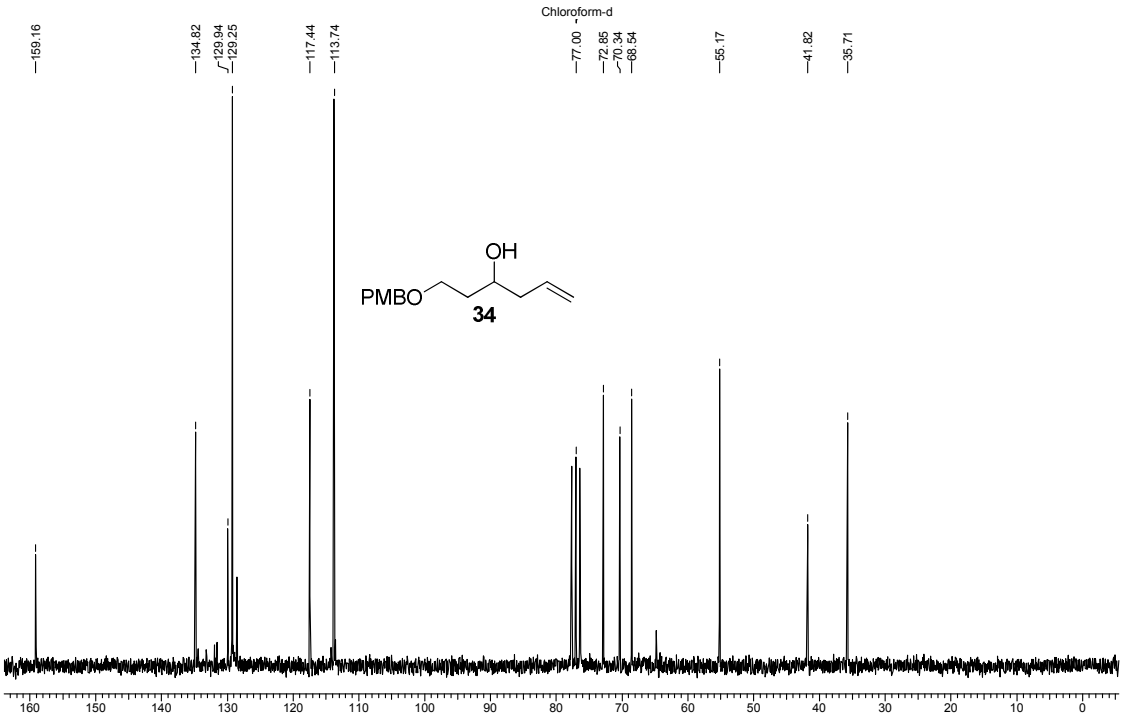
6.92
6.88
6.87
5.96
5.92
5.87
5.79
5.75
5.18
5.16
5.12
5.08
5.07
4.47
3.94
3.88
3.85
3.82
3.77
3.74
3.70
3.65
3.62
3.58
2.97
2.29
2.26
2.23
1.81
1.79
1.76
1.72
OH
PMBO
34
1.96
2.00
0.93
1.87
1.78
3.06
0.90
1.89
2.04
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0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129.94
129.25
117.44
113.74
77.00
72.85
70.34
68.54
55.17
41.82
35.71
OH
PMBO
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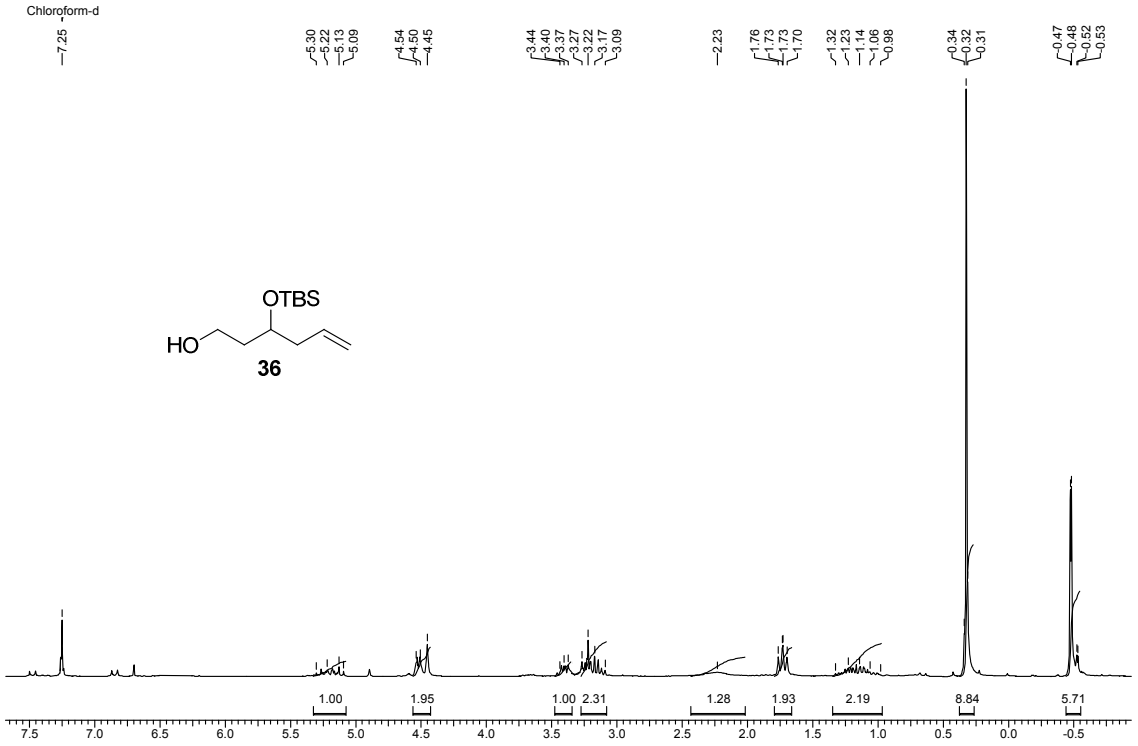
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


Chloroform-d
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5.30
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5.13
5.09
4.54
4.50
4.45
3.44
3.40
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3.22
3.17
3.09
2.23
1.76
1.73
1.73
1.70
1.32
1.23
1.14
1.06
0.98
0.34
0.32
0.31
0.47
0.48
0.52
0.53
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HO
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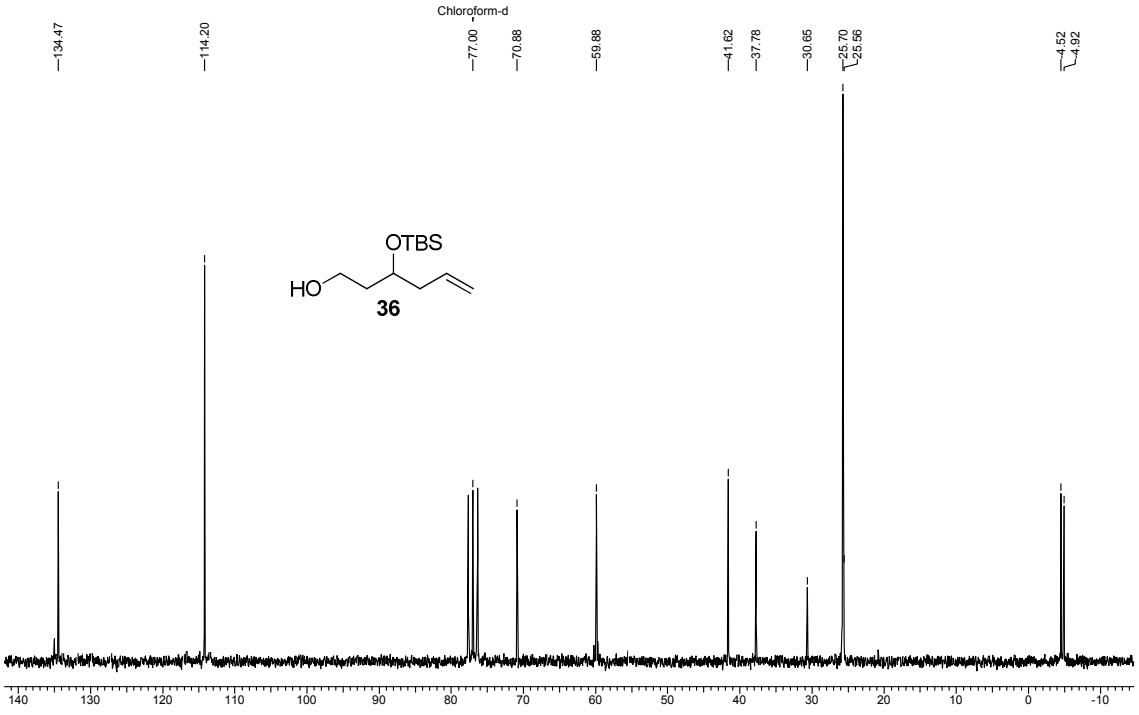
1.00
2.31
1.28
1.93
2.19
8.84
5.71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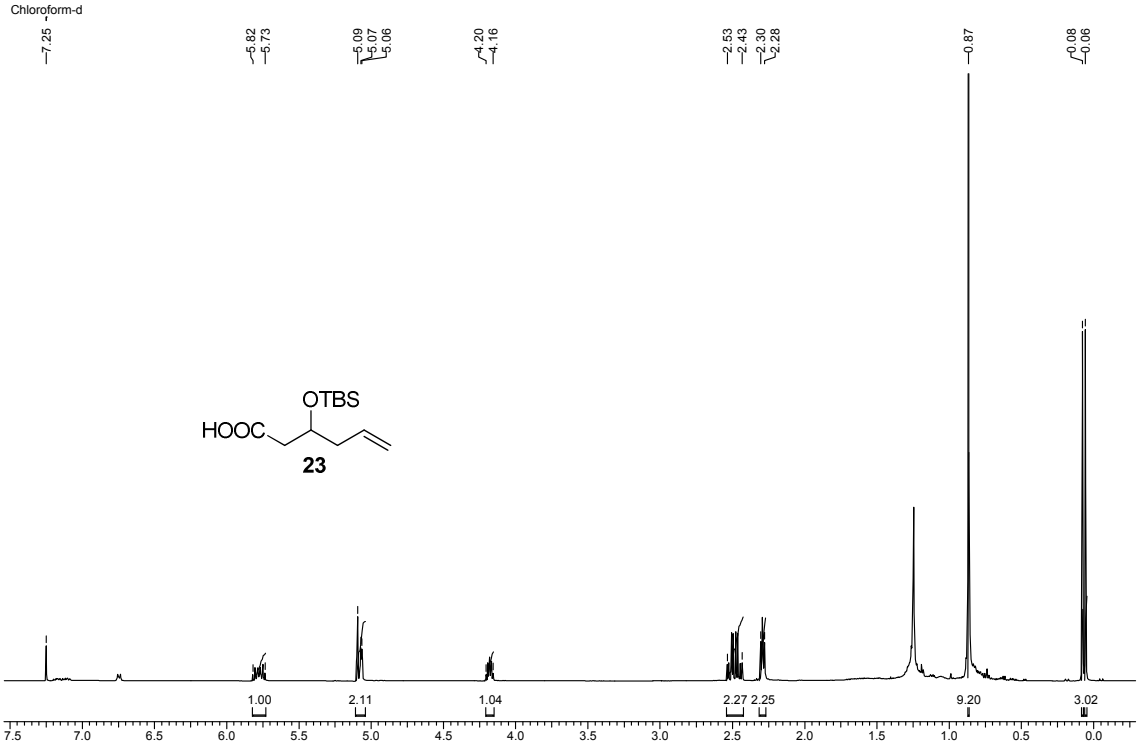
4.92
OTBS
HO
36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5.06
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2.28
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0.08
0.06
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HOOC
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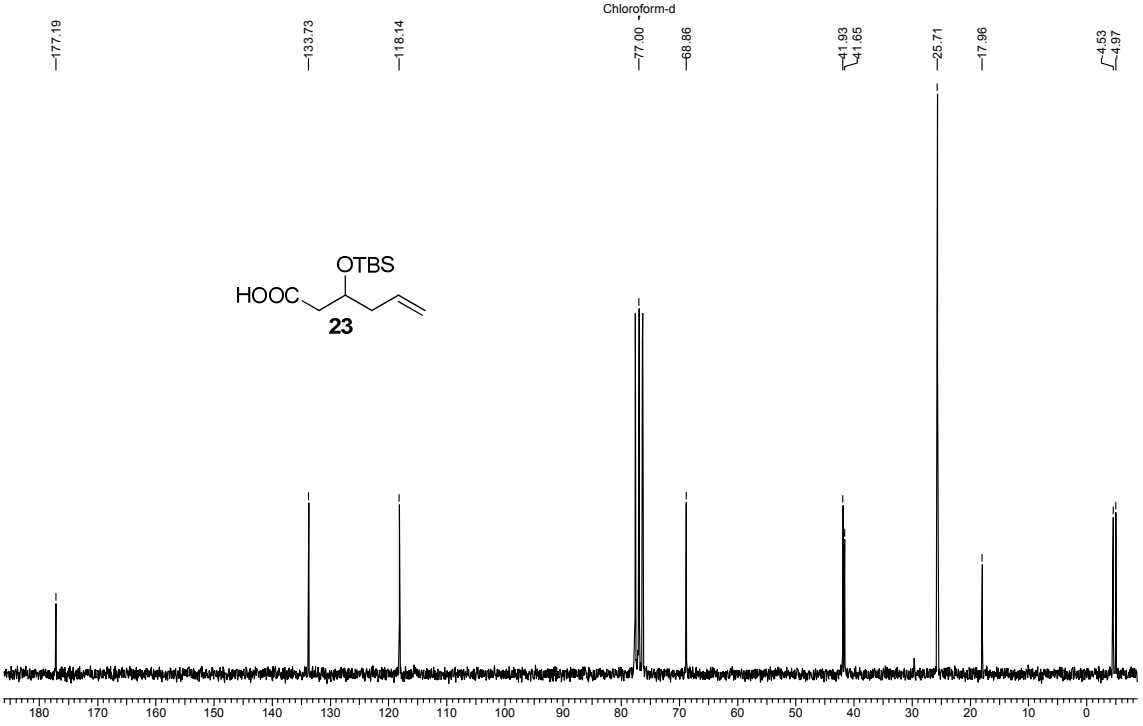
2.25
9.20
3.02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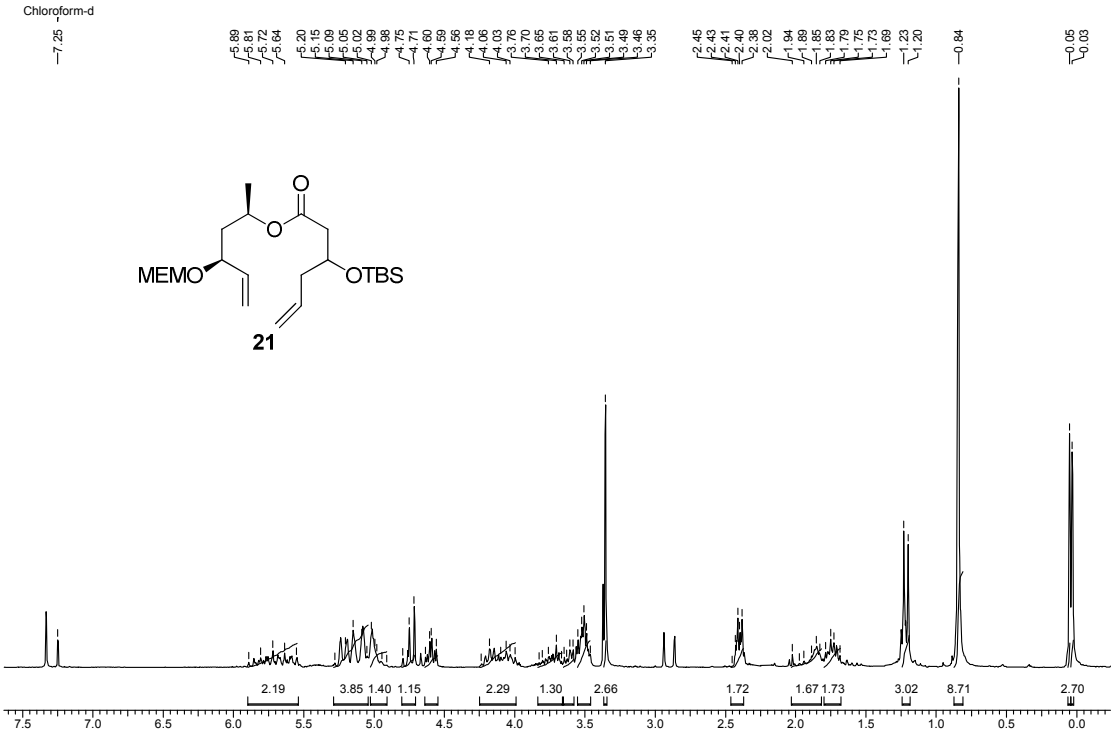
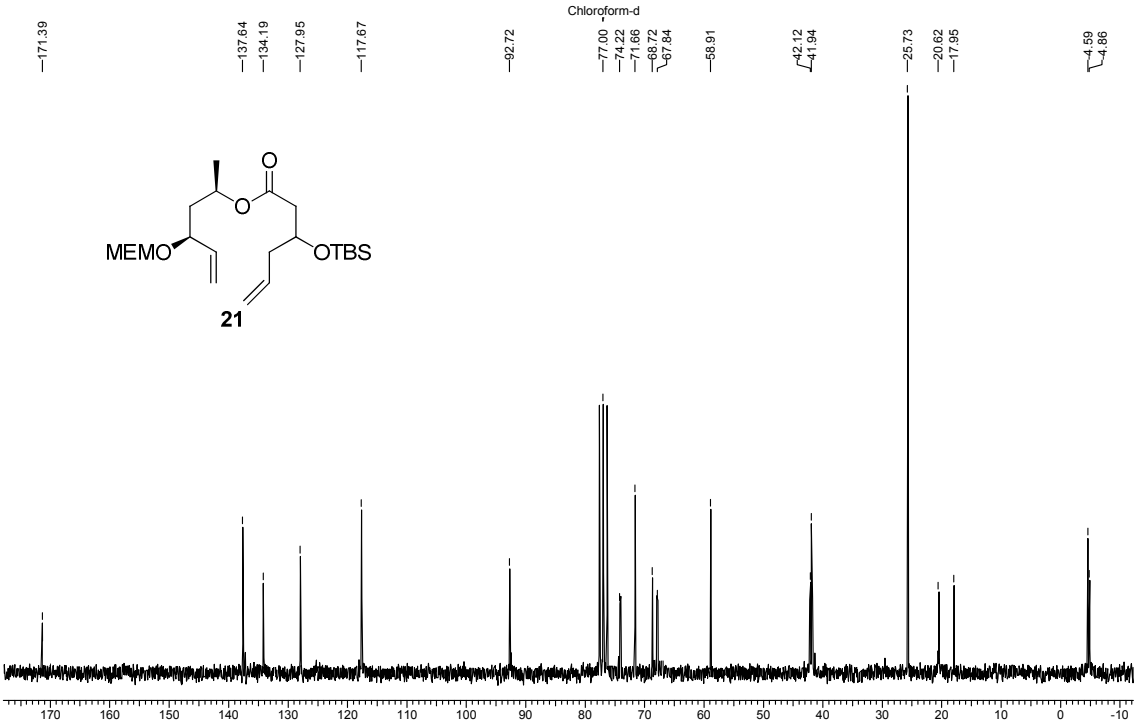
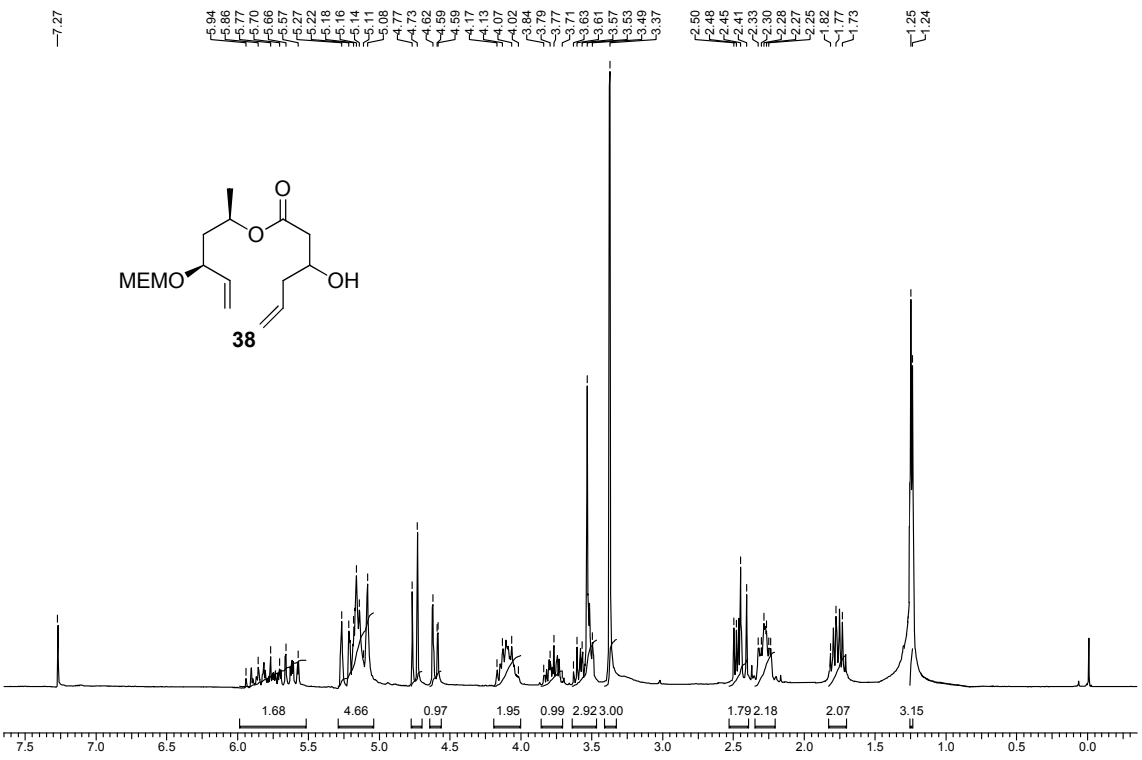
41.65
25.71
17.96
4.53
4.97
OTBS
HOOC
23


Chloroform-d
MEMO
OTBS
21


Chloroform-d
MEMO
OTBS
21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2.27
2.25
1.82
1.77
1.73
1.25
1.24
O
O
MEMO
OH
38
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4.66
0.97
1.95
0.99
2.92
3.00
1.79
2.18
2.07
3.15
7.5
7.0
6.5
6.0
5.5
5.0
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4.0
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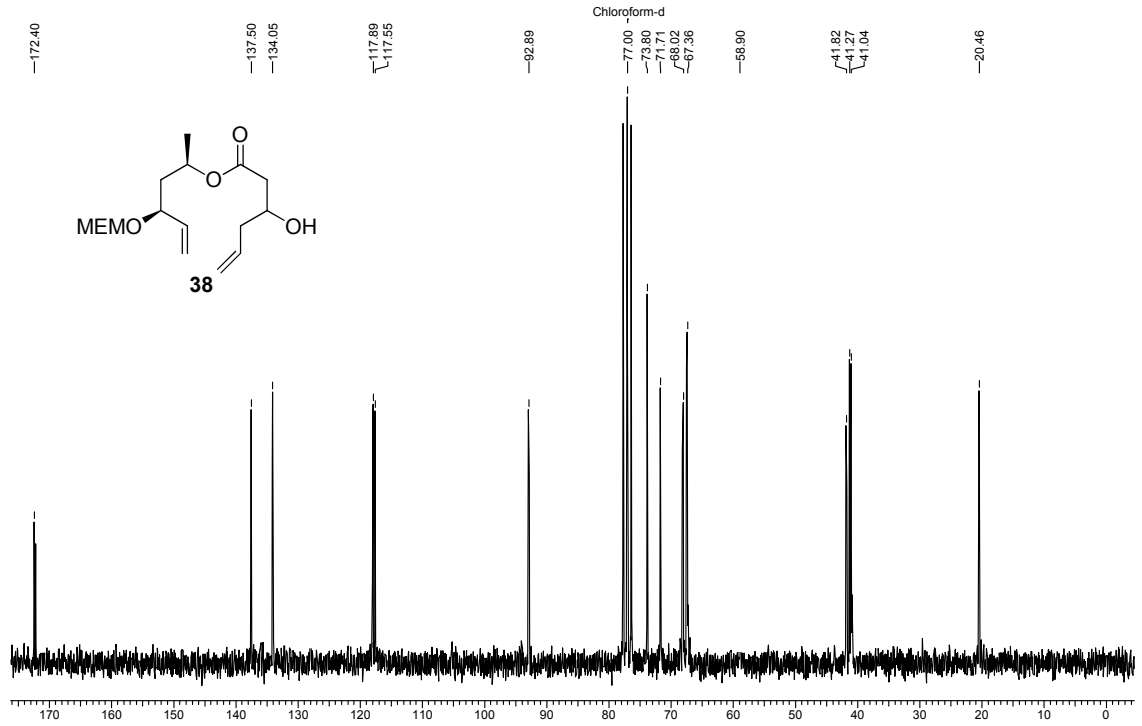
3.0
2.5
2.0
1.5
1.0
0.5
0.0


Chloroform-d
172.40
137.50
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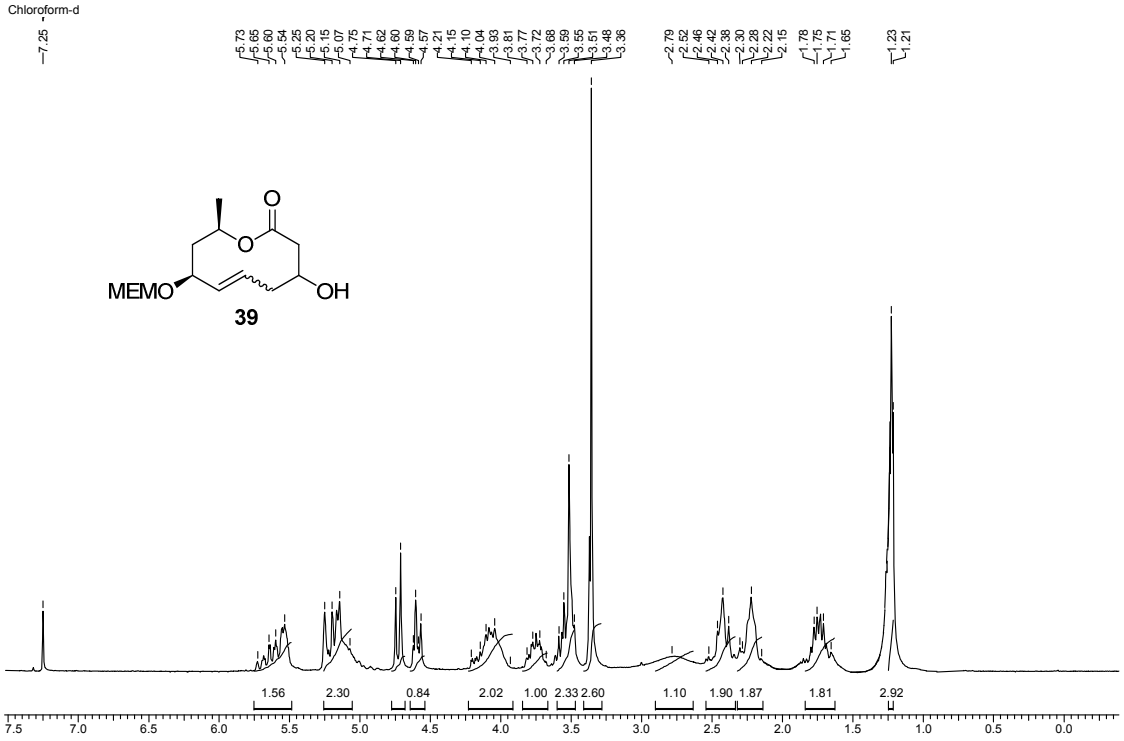
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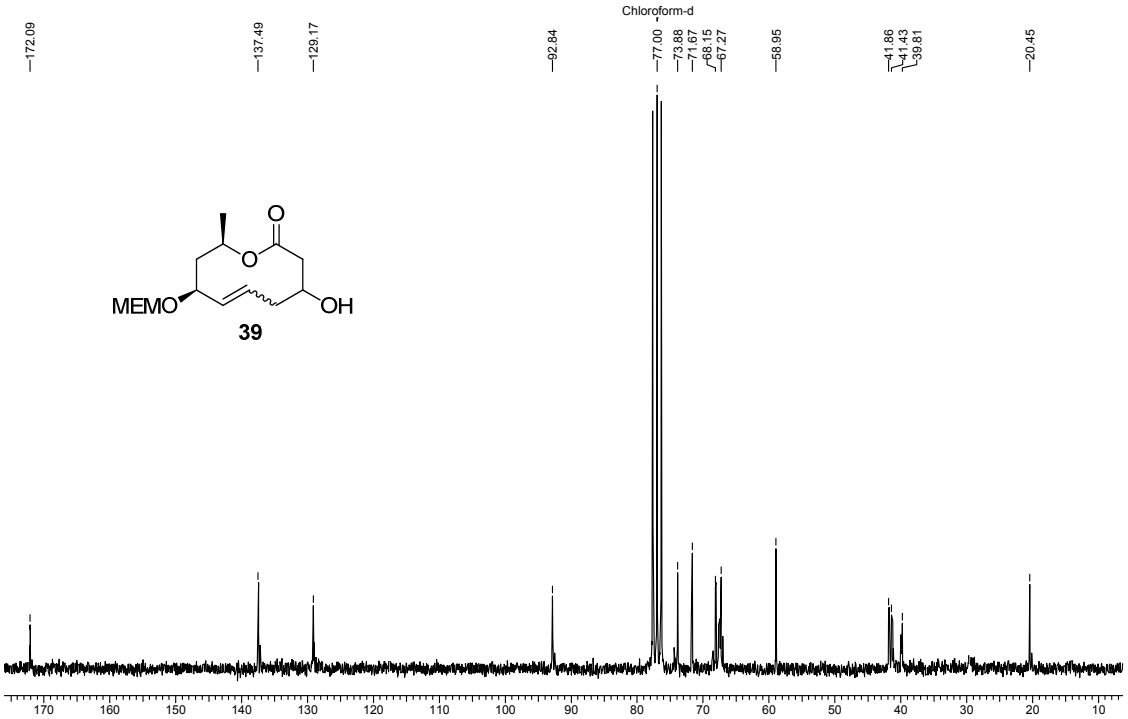
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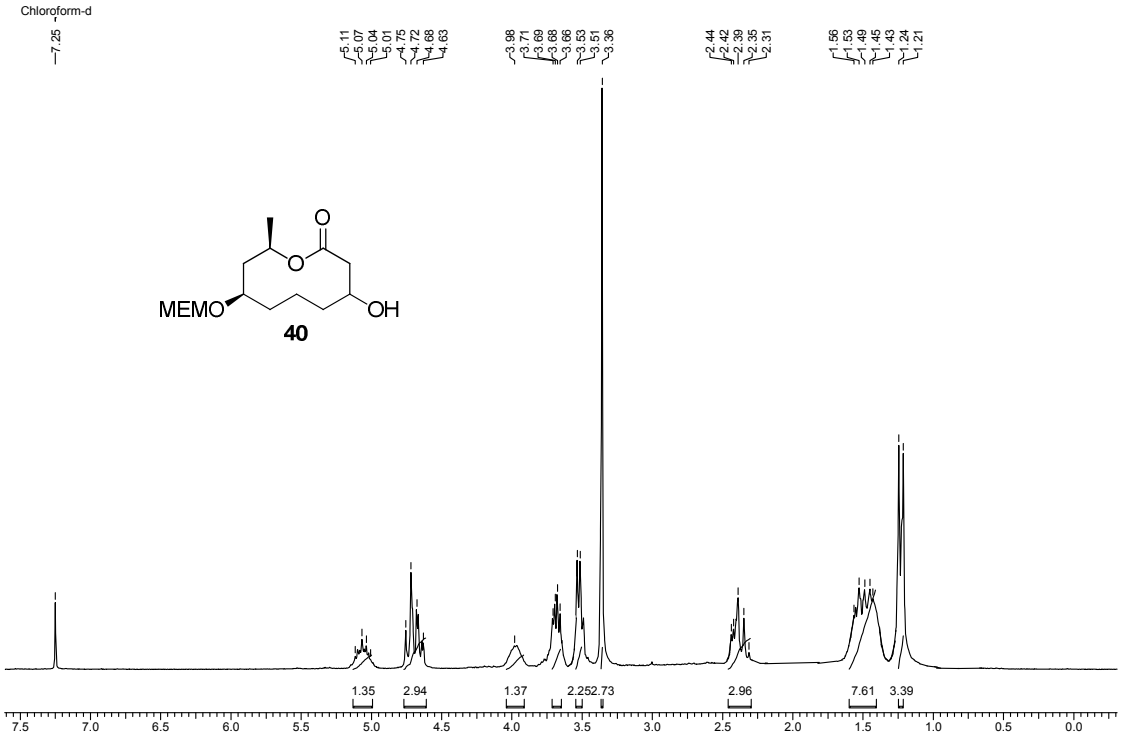
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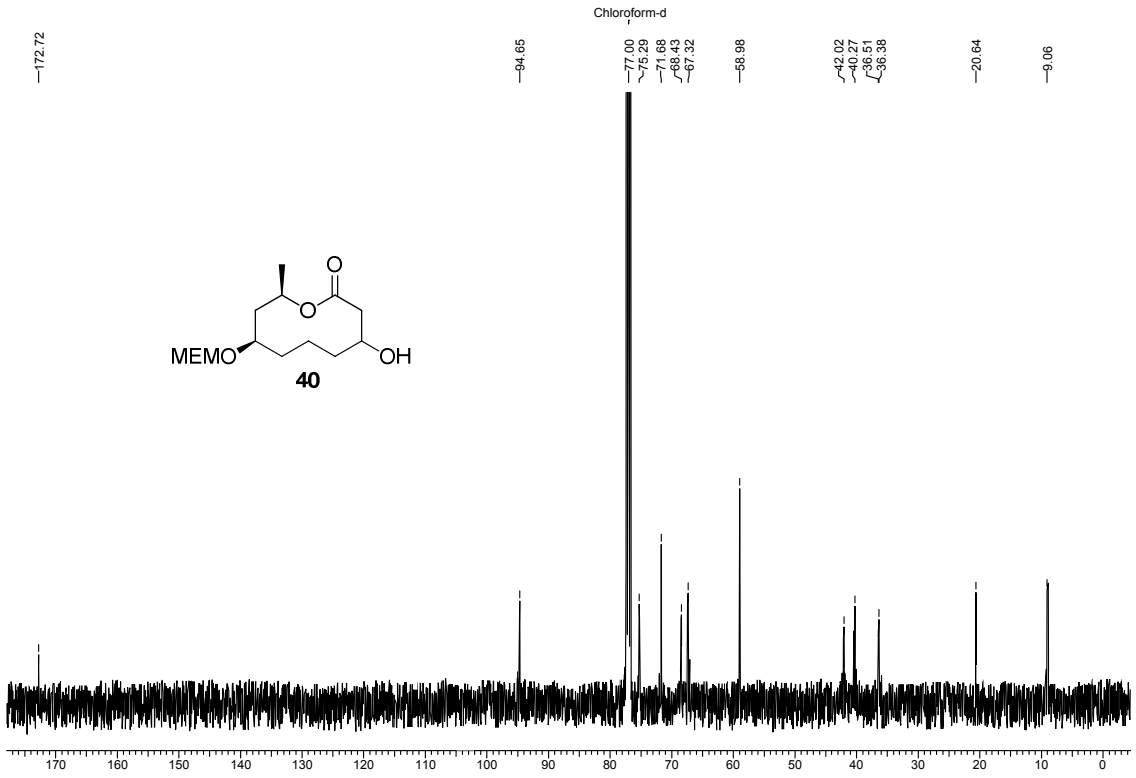
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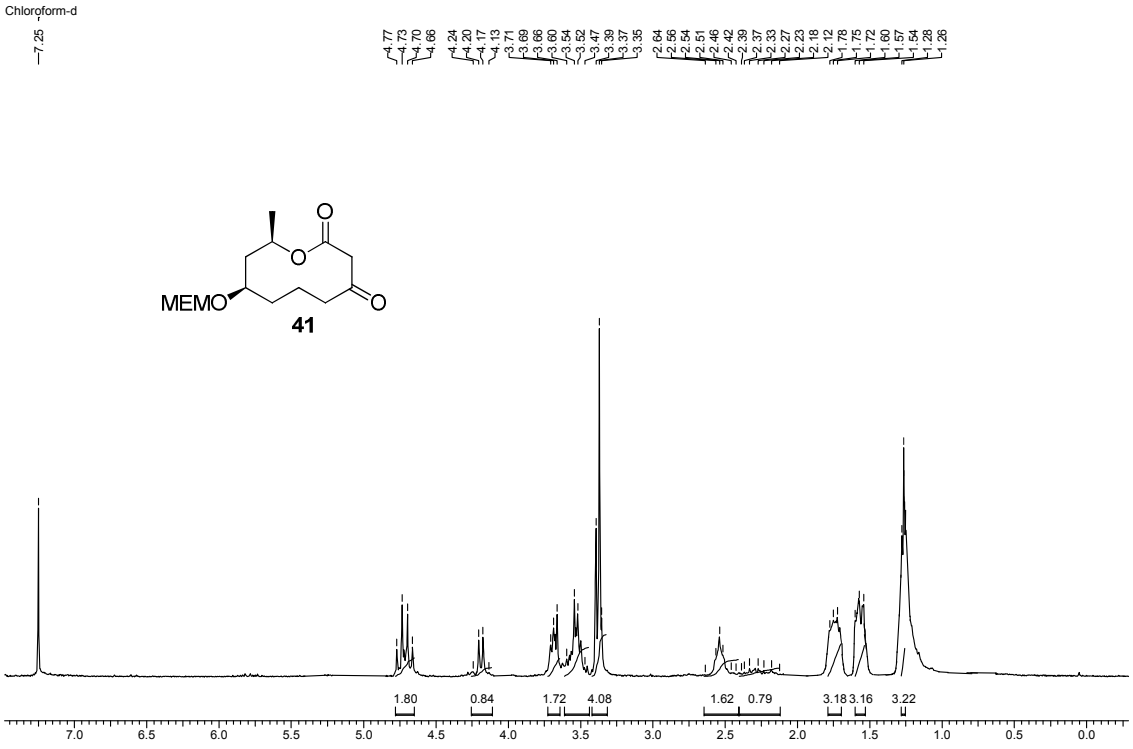
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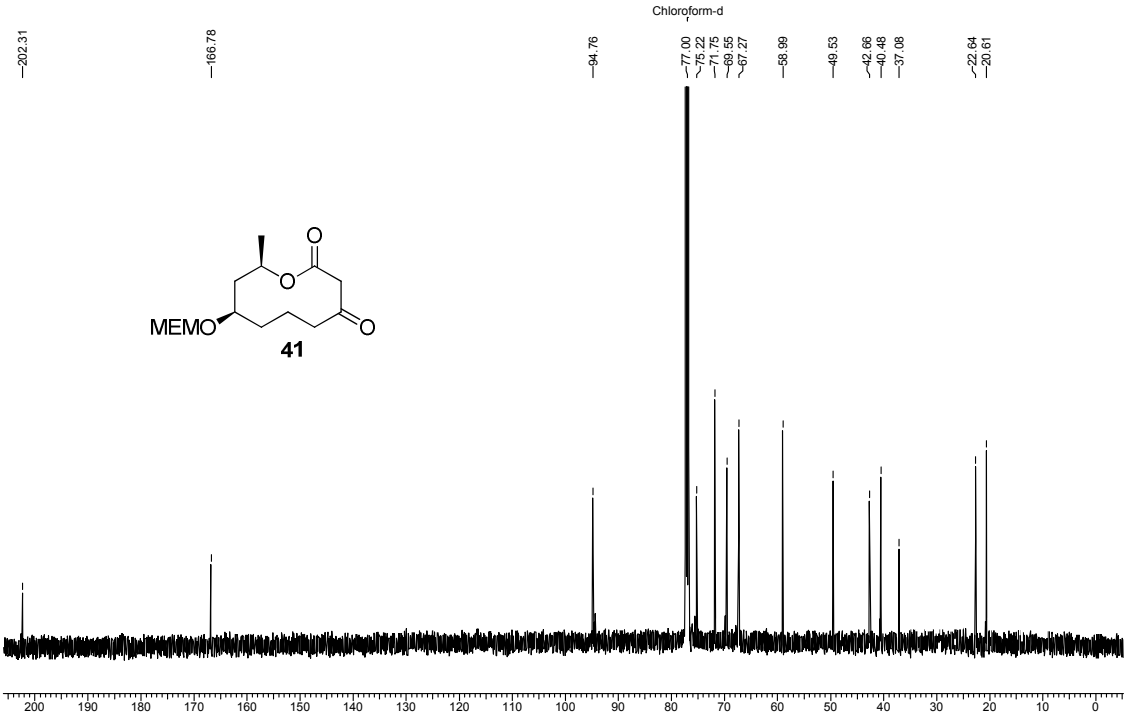
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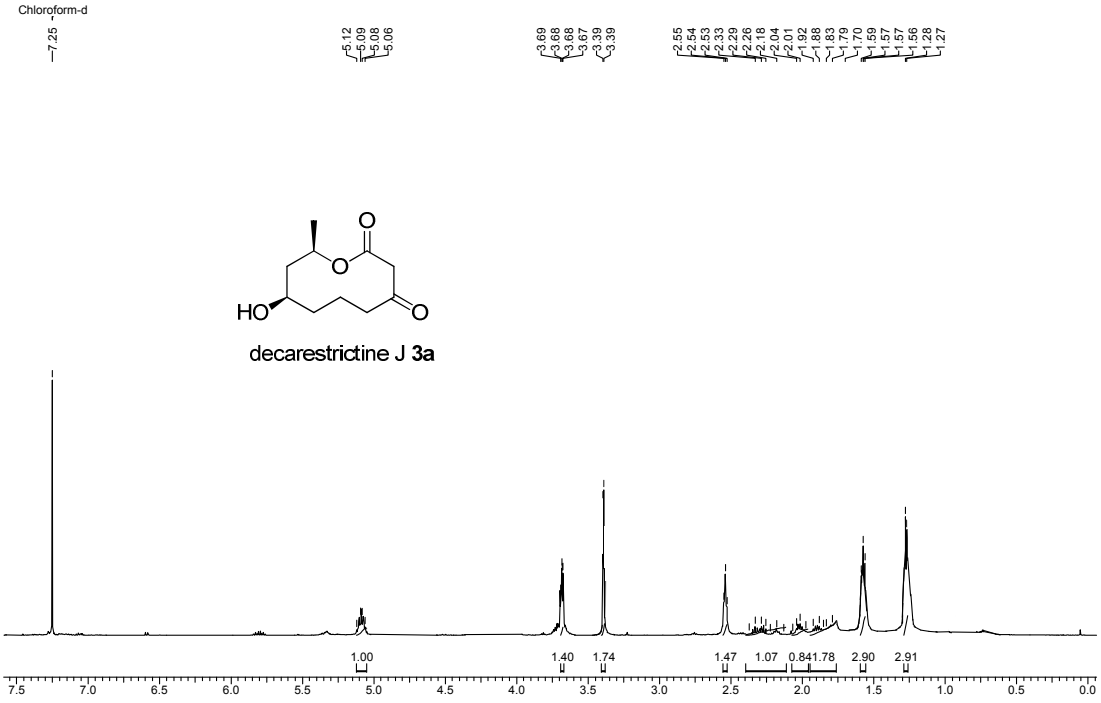


decarestrictine J **3a**

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# 2.2 Section B

# FIRST ASYMMETRIC TOTAL SYNTHESIS OF ASPINOLIDE A

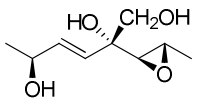
## 2.2.1. Introduction

Aspinonene (**1**) and aspyrone (**2**) are the main polyketide metabolites of *Aspergillus ochruceus* (DSM-7428).[1, 2] Evaluation of their biosynthesis revealed a close relationship: A carbon-skeleton rearrangement leads to a branched pentaketide,[3] and then the hypothetic aldehyde intermediate is either reduced or oxidised, yielding **1** and **2**, respectively, after finishing the biosynthetic cascade. Surprisingly, the pathways could be directed towards **2** by using increased dissolved oxygen concentrations during fermentation.[2] The analysis of the extracts of *Aspergillus ochruceus* grown under different culture conditions by chemical screening method[4,5] resulted in the isolation of seven new pentaketide metabolites, which are produced in varying amounts (Table 1).

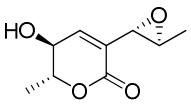
**Table 1.** Yields of the pentaketide metabolites of *Aspergillus oclzraceus,* resulting from altered fermentation conditions (isolated yields in mg/l, + = detectable on TLC plates)[a]

| Compound | 1 | 2 | 2a | 3 | 4 | 5 1bar | 5 2.5bar | 5 5bar |
|---|---|---|---|---|---|---|---|---|
| Aspinonene (**1**) | **8.5** | + | - | + | **10** | **14** | **12** | **3.0** |
| Aspyrone (**2**) | **2.0** | + | - | + | **2.8** | **7.0** | **64** | **94** |
| Aspinolide A (**3**) | - | **6.2** | **6.0** | + | **2.0** | + | + | + |
| Aspinolide B (**4**) | - | **5.5** | **6.9** | + | **5.7** | + | + | + |
| Aspinolide C (**5**) | - | - | **2.0** | - | - | - | - | - |

[a] 1. Static surface culture (1..5-1 P flask); 2. 300 ml Erlenmeyer flasks; 2a. addition of ancymidol; 3. 1 l stirring fermentor; 4. 50 l stirring fermentor; 5. 1- l airlift-loop fermentor.




**1**




**2**

The fermentation, purification and structure elucidation of these compounds have been discussed in the next section. The results are the base for a comprehensive discussion of the biosynthetic pathways of the strain and led to some further experiments to verify the assumptions.

**Fermentation and Isolation**

Fermentation of *Aspergillus ochruceus* was carried out in the optimised medium by using different culture vessels and aeration conditions (Table 1). The interesting metabolites of each fermentation were found in the culture filtrate only, which was separated from the mycelium by filtration and was successively extracted with chloroform and ethyl acetate to furnish two crude evaporation residues. Besides aspinonene (**1**) and aspyrone (**2**), the 10-membered lactones aspinolide A-C (**3**-**5**) were isolated by column chromatography. Their *R,* values and colour reactions on TLC plates with different staining reagents are given in Table 2.

**Aspinolides**

The colourless aspinolides A (**3**) and B (**4**) were produced in stirred or shaken cultures in amounts of 2-8 mg/l. They could not be detected in static cultures. Aspinolide C (**5**) was present in one culture only.

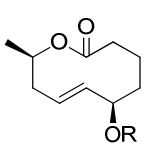
The molecular formula $C_{10}HI_6O_3$ of aspinolide A (**3**) was deduced from an HREI mass spectrum *(mls* = 184.1099 [$M^+$]). The elimination of $CO_2$ results in a characteristic peak at *id:* = 140 [M+ - 44]. The IR spectrum displays a CO-ester absorption band at 3 = 1730 cm-$^1$. The $^{13}$CNMR spectrum shows the expected 10 signals, which could be assigned to an unstrained lactone CO ($\delta_C$, = 175.5), two olefinic methine groups, two methine groups attached to oxygen, three methylene groups and a methyl group. In

the $^{1}$H-NMR spectrum ($CDC1_3$, 500 MHz) signals of 16 protons can be seen, which could be assigned to the C atoms by $^{1}$H-$^{13}$C shift correlations.

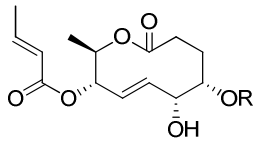
**Table 2.** $R_f$ values and colour reactions of the isolated pentaketide metabolites[a]

| Compound | **I** | **II** | **III** | **A** | **B** |
|---|---|---|---|---|---|
| **1** | 0.26 | 0.06 | 0.54 | brown | brown |
| **2** | 0.55 | 0.24 | 0.71 | brown | pink |
| **3** | 0.60 | 0.55 | 0.69 | Dark-pink | Blue |
| **4** | 0.46 | 0.30 | 0.62 | brown | brown |
| **5** | 0.77 | 0.64 | 0.65 | Dark-pink | Blue |

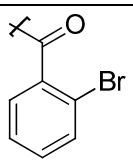
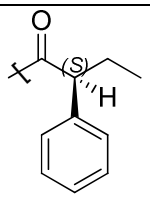
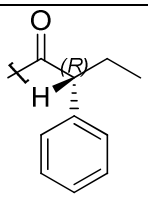
[a] Solvent systems: (I) $CHC1_3$/MeOH = 9: 1; (II) pentane/ethyl acetate = 1 : 1, (III) acetic acid/l-butanol/water (upper layer) = I :4:5. - Staining reagents: (**A**) vanillin/sulfuric acid, (**B**) anisaldehyde/sulfuric acid.




**3, 3a, 3b, 3c**



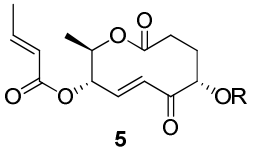

**4, 4a, 4b, 4c**

| | **3/4** | **3a/4a** | **3b/4b** | **3c/4c** |
|---|---|---|---|---|
| **R=** | **H** |  |  |  |










**5**

The connectivities between the proton-bearing groups were revealed by a $^{1}$H-$^{1}$H COSY experiment. Due to three double-bond equivalents a required cyclization leads

to a lactone. Its ring size was confirmed by characterising 5-*O*-(2-bromobenzoyl)aspinolide A (**3a**), the 5-H signal of which appears at $\delta_H$ = 5.32 and is shifted 1.34 ppm downfield compared with that of **3.** Thus, aspinolide A (**3**) is a 10-membered lactone with an *(E)* double bond and two centres of chirality. The *(R)* configuration of the secondary alcohol (C-5) was assigned by applying the Helmchen method[6]. The significant highfield shifts of the neighbouring protons in the 5-*O*-[(53-2-phenylbutyryl]- (**3b**) and the 5-*O*-[(R)-2-phenylbutyryl]aspinolide B (**3c**) are reported. The *(R)* configuration of C-9 is assumed by analogy with aspinolide B (**4**).

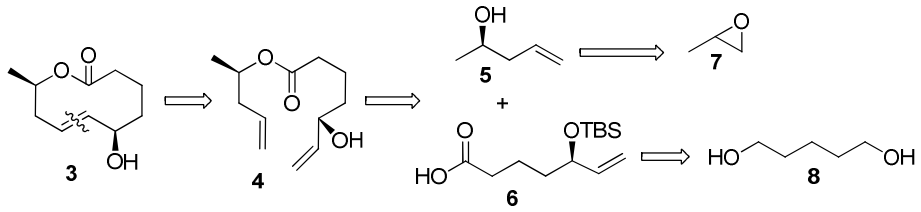
# 2.2.2. PRESENT WORK

## *Objective*

As a part of our research programme aimed at developing enantioselective synthesis of biologically active natural products[7] and having successfully completed the synthesis of decarestrictine J we considered attempting an yet another structurally related 10-membered lactone called, aspinolide A. Herein we describe our successful endeavour towards the first total synthesis of **3** employing HKR[8] and ring-closing metathesis (RCM)[9] as key steps.

The HKR method involves the readily accessible cobalt based chiral salen complex as catalyst and water to resolve a racemic epoxide into an enantiomerically enriched epoxide and diol, which serve as useful precursor in the synthesis of various compounds of biological importance.[10]

Our retrosynthetic analysis for synthesis of aspinolide A **3** is based on convergent approach as outlined in Scheme 1. We envisioned that the ring-closing could be effected by ring-closing metathesis of diene **4**. Diene **4** could be prepared by EDCI coupling of the alcohol **5** and acid **6**. Alcohol **5** could be obtained from rac-propylene oxide **7** *via* HKR, while acid fragment could be prepared from 1,5-pentane diol **8**.




**Scheme 1**. Retrosynthetic analysis of Aspinolide A **3**

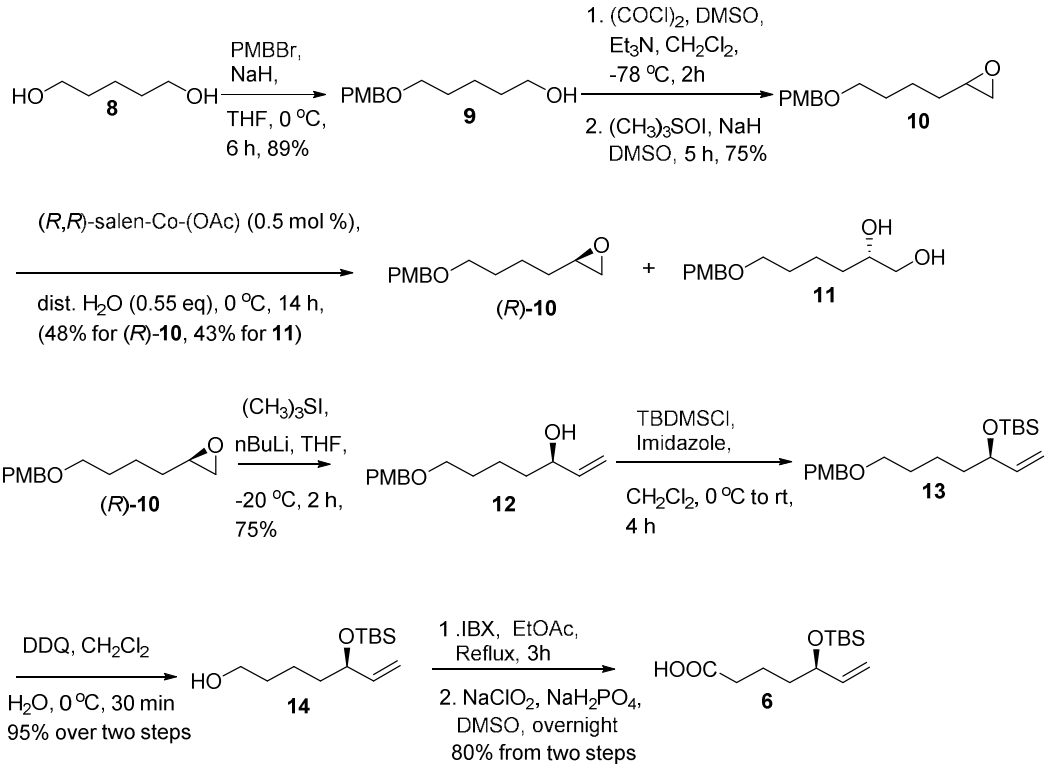
# 2.2.3. Results and Discussion

## Synthesis of fragment 5

The synthesis of fragment **5** is already been documented in section A of chapter 2 (**page no. 37**).

## Synthesis of fragment 6

The synthesis of acid fragment **6** started from commercially available 1,5-pentanediol **8** as illustrated in Scheme 2. Thus selective monoprotection of **8** with *p*-methoxybenzyl bromide gave PMB ether **9**. The $^1$H NMR spectrum gave benzylic protons at δ 4.44 (singlet, two protons) and aromatic protons at δ 7.29-7.25 (multiplet) and 6.91-6.87 (multiplet). The IR spectrum gave hydroxyl absorption at 3415 cm$^{-1}$. The compound **9** was subjected to Swern oxidation[11] followed by Corey Chaykovsky reaction[12] with dimethylsulfoxonium methylide to afford the racemic epoxide **10** in 75% yield. The epoxide peaks appeared at δ 2.89-2.84 (multiplet, one proton), 2.73-2.69 (multiplet, one proton) and 2.54-2.41 (multiplet, one proton) in $^1$H NMR spectrum. Compound **10** was subjected to Jacobsen's hydrolytic kinetic resolution using (*R*,*R*)-salen-Co-OAc catalyst to give (*R*)-epoxide **10** in >99% ee,[13] which was easily separated from the (*S*)-diol **11** by column chromatography. Epoxide (*R*)-**10** on reaction with dimethylsulfonium methylide[14] afforded the required allylic alcohol **12** in 75% yield. The IR spectrum of **12** gave broad hydroxyl absorption at 3386 cm$^{-1}$. The $^1$H NMR spectrum of **12** gave olefin peaks at δ 5.95-5.78 (multiplet, one protons) and 5.27-5.08 (multiplet, two proton).

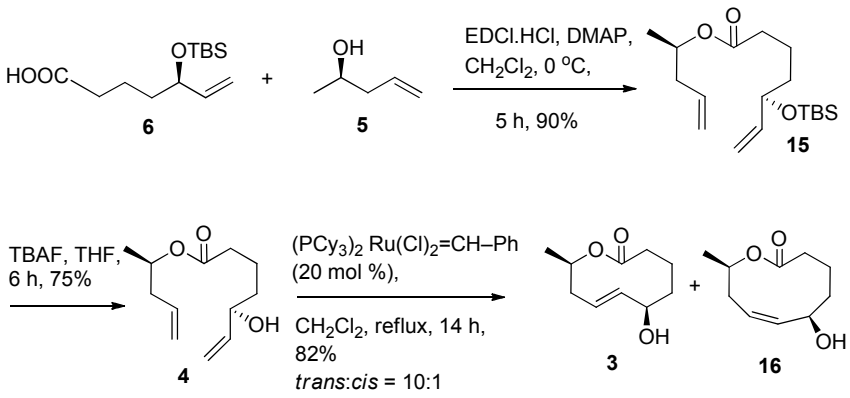



**Scheme 2**: Synthesis of acid fragment **6**.

Protection of hydroxy group of **12** as TBS ether followed by deprotection of PMB group[15] by DDQ gave the primary alcohol **14** in 95% yield. The IR spectra of **14** showed hydroxyl absorption at 3460 $cm^{-1}$. In the $^{1}H$ NMR spectra, the peaks owing to PMB group disappeared. The alcohol **14** was oxidised to aldehyde using IBX followed by subsequent oxidation using $NaClO_2$ to give the required acid fragment **6** in 80% yield. The IR spectra of **6** showed hydroxyl absorption at 3442 $cm^{-1}$ and acid carbonyl at 1713 $cm^{-1}$. The $^{1}H$ NMR and $^{13}C$ NMR spectra of **6** were compatible with the assigned structure.

## Coupling of Acid fragment 6 and Alcohol fragment 5 and The Synthesis of Aspinolide A

With substantial amount of both the fragments in hand the coupling of alcohol **5** and acid **6** was achieved by using EDCI to afford diene **15** in 90% yield. The IR spectra of **15** showed ester carbonyl at 1732 $cm^{-1}$. In $^{13}C$ NMR, peak owing to carbonyl carbon was present at δ 173.1. Ring-closing metathesis of **15** under various conditions using Grubbs'1$^{st}$ & 2$^{nd}$ generation catalyst failed to provide the required ten-membered lactone. In order to circumvent the problem, we thought it appropriate to first deprotect the TBS group and then use the ring-closing metathesis for macrocyclization. Thus the TBS group of diene **15** was deprotected to get the alcohol **4** which on ring-closing metathesis by using Grubb's first generation catalyst under high dilution conditions furnished a 10:1 (*E*:*Z*) mixture, which on chromatographic purification gave the target molecule **3** in 82% yield. The IR spectrum of **3** showed carbonyl group of lactone at 1729 $cm^{-1}$. The appearance of internal olefin at δ 5.46-5.41 and 4.93-4.87 in $^{1}H$ NMR confirmed the product. The olefinic carbons appeared at δ139.3 and 130.9 in $^{13}C$ NMR spectrum. The prepared synthetic aspinolide A is identical (IR, $^{1}H$ NMR, $^{13}C$ NMR) with the natural product and also has an optical rotation ($[\alpha]_D^{25}$ = –41.6 (*c* 0.25, MeOH)) which is in good agreement with the literature value [lit[2] $[\alpha]_D^{23}$ = –43.8 (*c* 0.3, MeOH)]. Thus, the absolute stereochemistry of aspinolide A **3** was established as 5*R* and 9*R*.




**Scheme 3**: Completion of synthesis of aspinolide A **3** by coupling of acid fragment **6** and alcohol fragment **5.**

## 2.2.4. Conclusion

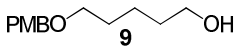
In conclusion, a convergent and efficient first total synthesis of aspinolide A, with high enantioselectivities has been accomplished and its absolute stereochemistry has been fixed. The stereocentres were generated by means of Jacobsen's hydrolytic kinetic resolution and cyclization was achieved by ring closing metathesis. This approach could be used for synthesis of other members of aspinolide family for structure–activity relationship. Currently work is in progress in this direction.

## 2.2.5. Experimental Section

***General information:***

All reactions were carried out under argon or nitrogen in oven-dried glassware using standard gas-light syringes, cannulas and septa. Solvents and reagents were purified and dried by standard methods prior to use. Optical rotations were measured at room temperature. IR spectra were recorded on an FT-IR instrument. $^{1}H$ NMR spectra were recorded on 200 MHz, 300 MHz and 500 MHz and are reported in parts per million (δ) downfield relative to $CDCl_3$ as internal standard and $^{13}C$ NMR spectra were recorded at 50 MHz, 75 MHz and 125 MHz and assigned in parts per million (δ) relative to $CDCl_3$. Column chromatography was performed on silica gel (100-200 and 230-400 mesh) using a mixture of petroleum ether and ethyl acetate as the eluent.

**5-((4-Methoxybenzyl)oxy)pentan-1-ol (9):**




**9**

To a solution of 1,3-pentanediol **8** (5.0 g, 48.07 mmol) in dry THF (200 mL) was added sodium hydride (60%, 2.53 g, 52.8 mmol) at 0 $^{o}$C. The reaction mixture was then stirred at room temperature for 30 min after which it was again cooled to 0 $^{o}$C. To this was added slowly *p*-methoxybenzyl bromide (10.61 g, 52.8 mmol) and catalytic amount *tetra n*-butylammonium iodide with further stirring for 6 h at the same temperature. The reaction mixture was quenched with addition of cold water at 0 $^{o}$C. The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with water (3 x 100 mL), brine, dried over $Na_2SO_4$ and concentrated. The residual oil was purified by silica gel column chromatography using petroleum ether/EtOAc (6:4) as eluent to furnish the mono-PMB protected alcohol **9** as colorless oil.

**Yield:** 9.58 g, 89%.

**Mol. Formula:** $C_{13}H_{20}O_3$

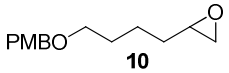
**IR (**$CHCl_3$, $cm^{-1}$**):** $\nu_{max}$ 3415, 2950, 2905, 1630, 1513, 1256, 1190, 1110.

**$^1$H NMR (500 MHz, $CDCl_3$):** δ 7.29-7.25 (m, 2H), 6.91-6.87 (m, 2H), 4.44 (s, 2H), 3.81 (s, 3H), 3.64 (t, *J*=6.19 Hz, 2H), 3.46 (t, *J*=6.32 Hz, 2H), 1.64-1.47 (m, 6H).

**$^{13}$C NMR (125 MHz, $CDCl_3$):** δ 158.9, 130.4, 129.1, 113.6, 72.3, 69.8, 69.8, 62.2, 55.0, 32.2, 29.2, 22.2.

**LC–MS**: m/z =247 $[M + Na]^+$.

**2-(4-((4-Methoxybenzyl)oxy)butyl)oxirane (10):**




**10**

**(i) Swern oxidation.** To a solution of oxalyl chloride (2.36 mL, 27.14 mmol) in dry $CH_2Cl_2$ (50 mL) at -78 $^{o}$C was added dropwise dry DMSO (3.84 mL, 54.3 mmol) in $CH_2Cl_2$ (20 mL). After 30 min, alcohol **9** (4.0 g, 18.1 mmol) in $CH_2Cl_2$ (20 mL) was added over 10 min giving copious white precipitate. After stirring for 2 h at -78 $^{o}$C,

the reaction mixture was brought to -60 $^{o}$C and $Et_3N$ (11.36 mL, 81.44 mmol) was added slowly and stirred for 30 min allowing the reaction mixture to warm to room temperature. The reaction mixture was then diluted with water (100 mL) and $CH_2Cl_2$. The organic layer was separated and washed with water and brine, dried over $Na_2SO_4$ and passed through short pad of celite. The filtrate was concentrated to give the aldehyde as pale yellow oil, which was used as such for the next step without purification.

**(ii)** To a solution of trimethylsulfoxonium iodide (4.32 g, 19.62 mmol) in dry DMSO was added NaH (0.78 g, 19.62 mmol). After 1 h, aldehyde (3.96 g, 17.8 mmol) dissolved in THF was added at 25 $^{o}$C. After stirring for 5 h ice was added to the reaction mixture and the reaction mixture was extracted with water, brine, dried over $Na_2SO_4$. Solvent was removed under pressure and the crude product was purified by silica gel column chromatography using pet ether/EtOAc (95:5) to get pure epoxide **10** as colorless liquid.

**Yield:** 3.16 g, 75%.

**Mol. Formula:** $C_{14}H_{20}O_3$

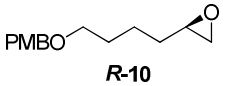
**IR (**$CHCl_3$**, cm$^{-1}$):** $\nu_{max}$ 3490, 2940, 2863, 1612, 1513, 1249, 1175, 1098.

**$^1$H NMR (200 MHz, $CDCl_3$):** δ 7.25-7.21 (m, 2H), 6.87-6.81 (m, 2H), 4.40 (s, 2H), 3.77 (s, 3H), 3.42 (t, *J*=6.32 Hz, 2H), 2.89-2.84 (m, 1H), 2.73-2.69 (m, 1H), 2.54-2.41 (m, 1H), 1.61-1.45 (m, 6H).

**$^{13}$C NMR (50 MHz, $CDCl_3$):** δ 159.1, 130.6, 129.2, 113.7, 72.5, 69.8, 55.0, 52.2, 47.1, 32.2, 29.5, 22.7.

**LC–MS**: m/z =259 $[M + Na]^+$.

**(*R*)-2-(4-((4-Methoxybenzyl)oxy)butyl)oxirane (*R*-10):**




***R*-10**

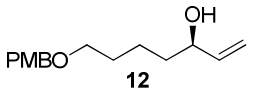
A solution of epoxide **10** (3.0 g, 12.7 mmol) and (*R,R*)-salen-Co(III)-OAc (42 mg, 0.063 mmol) in THF (125 µL) was stirred at 0 $^{o}$C for 5 min, and then distilled water (125 µL, 6.98 mmol) was added. After stirring for 14 h, it was concentrated and

purified by silica gel column chromatography using pet ether: EtOAc (19:1) to afford ***R*-10** as a pale yellow color liquid. Continued chromatography with pet ether/EtOAc (3:2) provided the diol **11** as a yellow liquid as a single enantiomer.

**Yield:** 1.4 g, 48%.

$[\alpha]_D^{25}$: 2.77 (*c* 1.05, $CHCl_3$).

**(*R*)-7-((4-Methoxybenzyl)oxy)hept-1-en-3-ol (12)**




**12**

To a suspension of trimethylsulfonium iodide (6.85 g, 5.43 mmol) in dry THF (20 mL) at −20 $^oC$ was added *n*-BuLi (22.34 mL, 1.6 M solution in hexane, 35.7 mmol) dropwise over 20 min and stirred for 30 min. Then the epoxide ***R*-10** (1.3 g, 5.5 mmol) in dry THF (10 mL) was added to the above reaction mixture and stirred for 2 h. After consumption of the starting material the reaction mixture was quenched with $H_2O$ (20 mL) and extracted with EtOAc (4 × 10 mL). The combined extracts were washed with brine, dried over $Na_2SO_4$ and concentrated. The column chromatography of crude product using pet ether:ethyl acetate (90:10) gave **12** as a colorless liquid.

**Yield:** 1.03 g, 75%.

**Mol. Formula:** $C_{15}H_{22}O_3$

$[\alpha]_D^{25}$: –5.45 (*c* 0.94, $CHCl_3$).

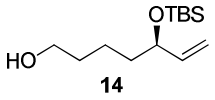
**IR (**$CHCl_3$**,** $cm^{-1}$): $\nu_{max}$ 3386, 1640, 1603, 1493, 1453, 1243.

**$^1$H NMR (200 MHz, $CDCl_3$):** δ 7.29-7.24 (m, 2H), 6.91-6.86 (m, 2H), 5.95-5.78 (m, 1H), 5.27-5.08 (m, 2H), 4.44 (s, 2H), 4.15-4.06 (m, 1H), 3.81 (s, 3H), 3.49-3.42 (m, 2H), 1.92 (brs, 1H), 1.68-1.42 (m, 6H).

**$^{13}$C NMR (50 MHz, $CDCl_3$):** δ 158.9, 141.2, 130.5, 129.1, 114.3, 113.6, 72.8, 72.4, 69.8, 55.1, 36.6, 29.4, 21.9.

**LC–MS**: m/z =273 $[M + Na]^+$.

**(*R*)-5-((*tert*-Butyldimethylsilyl)oxy)hept-6-en-1-ol (14)**




**14**

To a stirred solution of alcohol **12** (5 g, 21.86 mmol) in $CH_2Cl_2$ was added imidazole (0.53 g, 7.8 mmol). To this solution *t*-butyl dimethylchlorosilane (0.73 g, 4.79 mmol) was added at 0 $^oC$ and the reaction was stirred at rt for 4 h. The reaction mixture was quenched with a saturated aqueous solution of $NH_4Cl$ and extracted with $CH_2Cl_2$. The extract was washed with brine, dried over $Na_2SO_4$, and concentrated, which was used as such for the next step without purification.

To a stirring solution of PMB ether (1.44 g, 3.95 mmol) in $CH_2Cl_2/H_2O$ (18:1) was added DDQ (1.08 g, 4.74 mmol) at 0 $^oC$ . The resulting mixture was stirred for 10 min at r. t. The mixture was poured into saturated aqueous $NaHCO_3$ and further diluted with $CH_2Cl_2$. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 10 mL). The combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated. The solvents were removed under reduced pressure to give the crude product mixture as yellow oil. Silica gel column chromatography of the crude product using pet ether:ethyl acetate (96:4) as eluent gave **14**.

**Yield:** 0.92 g, 95%.

**Mol. Formula:** $C_{13}H_{28}O_2Si$

$[\alpha]_D^{25}$: – 6.67 (*c* 0.28, $CHCl_3$).

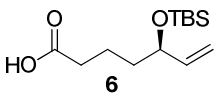
**IR (**$CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3460, 2959, 2857, 1640, 1448, 1376, 1255, 1078.

**$^1$H NMR (200 MHz, $CDCl_3$):** δ 5.86-5.69 (m, 1H), 5.17-4.98 (m, 2H), 4.09-4.03 (m, 1H), 3.65-3.59 (m, 2H), 1.59-1.37 (m, 6H), 0.88 (s, 9H), 0.03-0.02 (m, 6H).

**$^{13}$C NMR (50 MHz, $CDCl_3$):** δ 141.6, 113.6, 73.7, 62.8, 37.7, 32.7, 25.8, 21.2, 18.2, –4.4, –4.8.

**LC–MS**: m/z =263 $[M + Na]^+$.

**(*R*)-5-((*tert*-Butyldimethylsilyl)oxy)hept-6-enoic acid (6)**




**6**

To a solution of alcohol **14** (0.45 g, 8.19 mmol) in EtOAc (5 mL) was added IBX (1.72g, 24.5 mmol) in one portion and the reaction mixture was refluxed for 3 h. The reaction mixture was filtered through a pad of celite and filtrate was concentrated to give the crude aldehyde, which was used for the next step without purification.

A solution of 79% $NaClO_2$ (0.315 g, 2.78 mmol) in 1.0 mL of water was added dropwise to a stirred solution of above crude aldehyde (0.45 g, 1.85 mmol) in 1.0 mL of DMSO and $NaH_2PO_4$ (0.167 g, 1.39 mmol) in 1.0 mL of water in 5 min at room temperature. The mixture was left overnight at room temperature, and then 5% aqueous solution of $NaHCO_3$ was added. The aqueous phase was extracted 3 times with $CH_2Cl_2$ and washed with brine, dried ($Na_2SO_4$), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (4:1) as eluent gave the acid **6** (1.25 g, 80%) as a syrupy liquid.

**Yield:** 0.38 g, 80%.

**Mol. Formula:** $C_{13}H_{26}O_3Si$

$[\alpha]_D^{25}$: – 6.56 (*c* 1.15, $CHCl_3$).

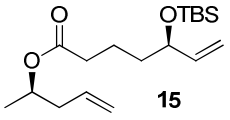
**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3442, 2930, 2858, 1713, 1463, 1254, 1087, 923

**$^1$H NMR (200 MHz, $CDCl_3$):** δ 5.86-5.69 (m, 1H), 5.18-5.00 (m, 2H), 4.15-4.09 (m, 1H), 2.39-2.32 (m, 2H), 1.76-1.49 (m, 5H), 0.88 (s, 9H), 0.04 (m, 6H).

**$^{13}$C NMR (50 MHz, $CDCl_3$):** δ 179.9, 141.3, 113.9, 73.4, 37.1, 34.0, 29.7, 25.8, 20.3, –4.4, –4.8.

**LC–MS**: m/z =281 $[M + Na]^+$.

**(*R*)-(*R*)-Pent-4-en-2-yl 5-((tert-butyldimethylsilyl)oxy)hept-6-enoate (15)**




**15**

To a solution of the carboxylic acid **6** (0.77 g, 2.99 mmol) in $CH_2Cl_2$ (10 ml) was added EDCI.HCI (0.835 g, 4.35 mmol), DMAP (35 mg, 0.29 mmol) and the hydroxy amide **5** (0.25 g, 2.90 mmol) at 0 °C, and the mixture was stirred at 0 $^oC$ for 5 h. The mixture was diluted with $Et_2O$ and successively washed with $H_2O$, saturated aqueous

$NaHCO_3$, and saturated brine, and then dried over $MgSO_4$ and concentrated in vacuo. Silica gel column chromatography of the crude product using petroleum ether: EtOAc (5:1) as eluent afforded compound **15** as pale yellow oil.

**Yield**: 0.876 g, 90%

**Mol. Formula:** $C_{18}H_{34}O_3Si$

$[\alpha]_D^{25}$: – 14.9 (*c* 0.50, $CHCl_3$).

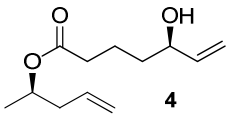
**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 2931, 2864, 1732, 1655, 1466, 1425, 1218, 1170, 781.

**$^1$H NMR (200 MHz, $CDCl_3$):** δ 5.81-5.68 (m, 2H), 5.15-5.00 (m, 4H), 4.98-4.91 (m, 1H), 4.10-4.06 (m, 1H), 2.35-2.21 (m, 4H), 1.64-1.58 (m, 5H), 1.52-1.44 (m, 2H), 1.20 (d, *J*=6.53 Hz, 3H), 0.88 (s, 9H), 0.04-0.01 (m, 6H).

**$^{13}$C NMR (50 MHz, $CDCl_3$):** δ 173.1, 141.4, 133.7, 117.6, 113.8, 73.5, 69.8, 40.3, 37.3, 34.6, 25.9, 20.8, 19.5, 18.2, –4.4, –4.8.

**LC–MS**: m/z =349 $[M + Na]^+$.

**(*R*)-(*R*)-Pent-4-en-2-yl 5-hydroxyhept-6-enoate (4)**




**4**

To a solution of olefin **15** (0.255 g, 0.78 mmol) in THF (3 mL) was added TBAF (1.17 mL, 1.17 mmol, 1.0 M solution in THF) at room temperature. The reaction mixture was stirred for 6 h and then diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried ($Na_2SO_4$) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (7:3) as eluent gave alcohol **4** as a colorless liquid.

**Yield:** 0.124 g, 75%

**Mol. Formula:** $C_{12}H_{20}O_3$

$[\alpha]_D^{25}$: – 10.2 (*c* 0.3, $CHCl_3$).

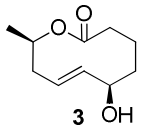
**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3438, 2933, 1731, 1645, 1424, 1380, 1245, 1061

**$^1$H NMR (200 MHz, $CDCl_3$):** δ 5.93-5.62 (m, 2H), 5.26-5.02 (m, 4H), 4.97-4.91 (m, 1H), 4.14-4.05 (m, 1H), 2.33-2.24 (m, 4H), 1.79 (brs, 1H), 1.71-1.52 (m, 4H), 1.20 (d, *J*=6.32 Hz, 3H).

**$^{13}$C NMR (50 MHz, $CDCl_3$):** δ 173.1, 140.9, 133.7, 117.7, 114.8, 72.6, 69.9, 40.3, 36.2, 34.3, 20.7, 19.5.

**LC–MS**: m/z =235 $[M + Na]^+$.

**Aspinolide A 3**




A mixture of **4** (50 mg, 0.23 mmol) in anhydrous $CH_2Cl_2$ (20 mL) and Grubbs' first generation catalyst (39 mg, 0.047 mmol) was degassed with argon for 15 min, and refluxed for 14 h. Solvent was removed under reduced pressure to leave highly dark brown colored residue. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent afforded aspinolide A (**3**) as a colorless oil.

**Yield:** 35 mg, 82%

**Mol. Formula:** $C_{10}H_{16}O_3$

$[\alpha]_D^{25}$: –41.6 (*c* 0.25, MeOH), [lit[2] $[\alpha]_D^{23}$ = –43.8 (*c* 0.3, MeOH)]

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3435, 2925, 2854, 1729, 1462, 1275, 1073, 971

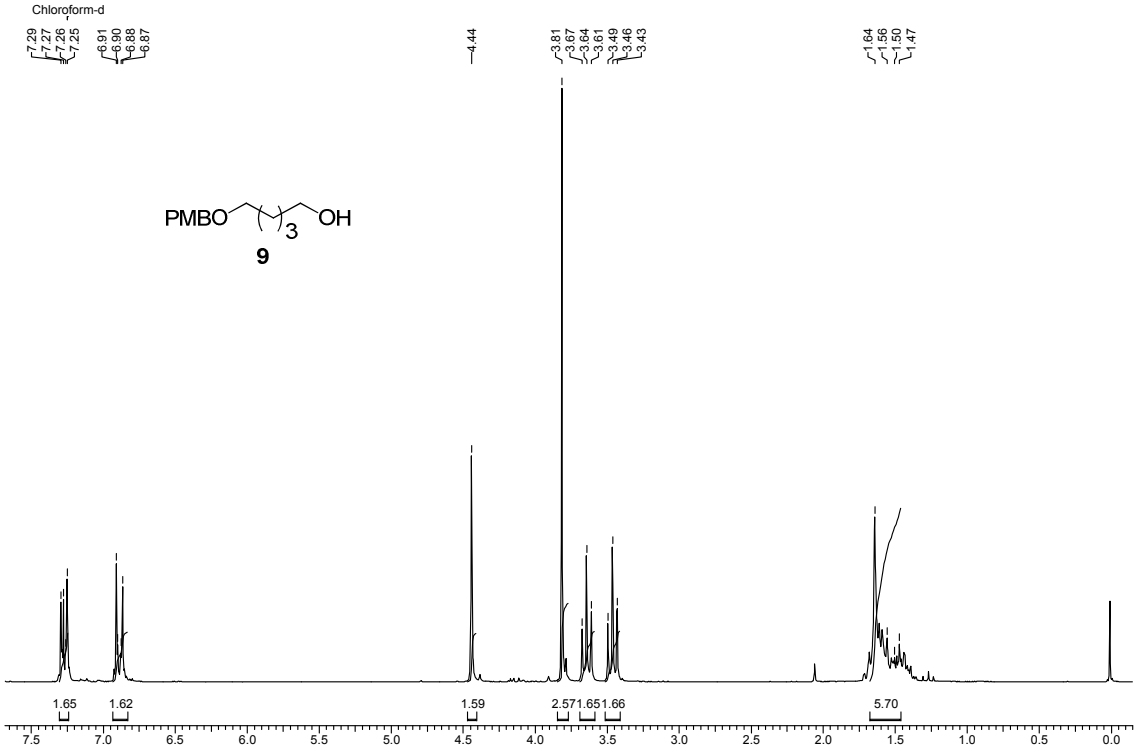
**$^1$H NMR (200 MHz, $CDCl_3$):** δ 5.46-5.41 (m, 1H), 4.93-4.87 (m, 1H), 3.71 (q, *J*=6.48 Hz, 1H), 2.49 (t, *J*=7.03 Hz, 2H), 2.30-2.26 (m, 2H), 1.88-1.84 (m, 2H), 1.60-1.55 (m, 2H), 1.18 (d, *J*=6.27 Hz, 3H).

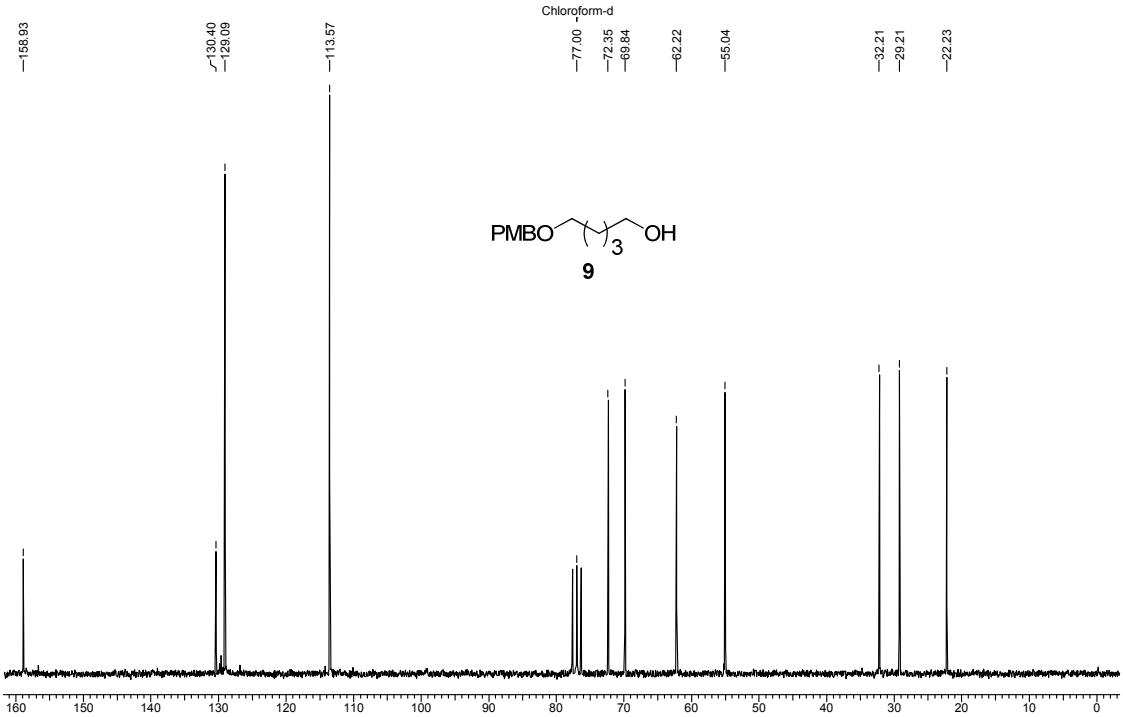
**$^{13}$C NMR (50 MHz, $CDCl_3$):** δ 172.7, 139.3, 130.9, 70.3, 68.5, 42.5, 38.9, 37.1, 22.6, 18.9.

**LC–MS**: m/z =207 $[M + Na]^+$.

## 2.2.6. Spectra

| | |
|---|---|
| $^{1}H$ and $^{13}C$ spectra of compound | **9** |
| $^{1}H$ and $^{13}C$ spectra of compound | **10** |
| $^{1}H$ and $^{13}C$ spectra of compound | **12** |
| $^{1}H$ and $^{13}C$ spectra of compound | **14** |
| $^{1}H$ and $^{13}C$ spectra of compound | **6** |
| $^{1}H$ and $^{13}C$ spectra of compound | **15** |
| $^{1}H$ and $^{13}C$ spectra of compound | **4** |
| $^{1}H$ and $^{13}C$ spectra of compound | **3** |
| $^{19}F$ spectra of compound | **12** |


Chloroform-d
7.29
7.27
7.26
7.25
6.91
6.90
6.88
6.87
4.44
3.81
3.67
3.64
3.61
3.49
3.46
3.43
1.64
1.56
1.50
1.47
PMBO
3
OH
9
1.65
1.62
1.59
2.57
1.65
1.66
5.70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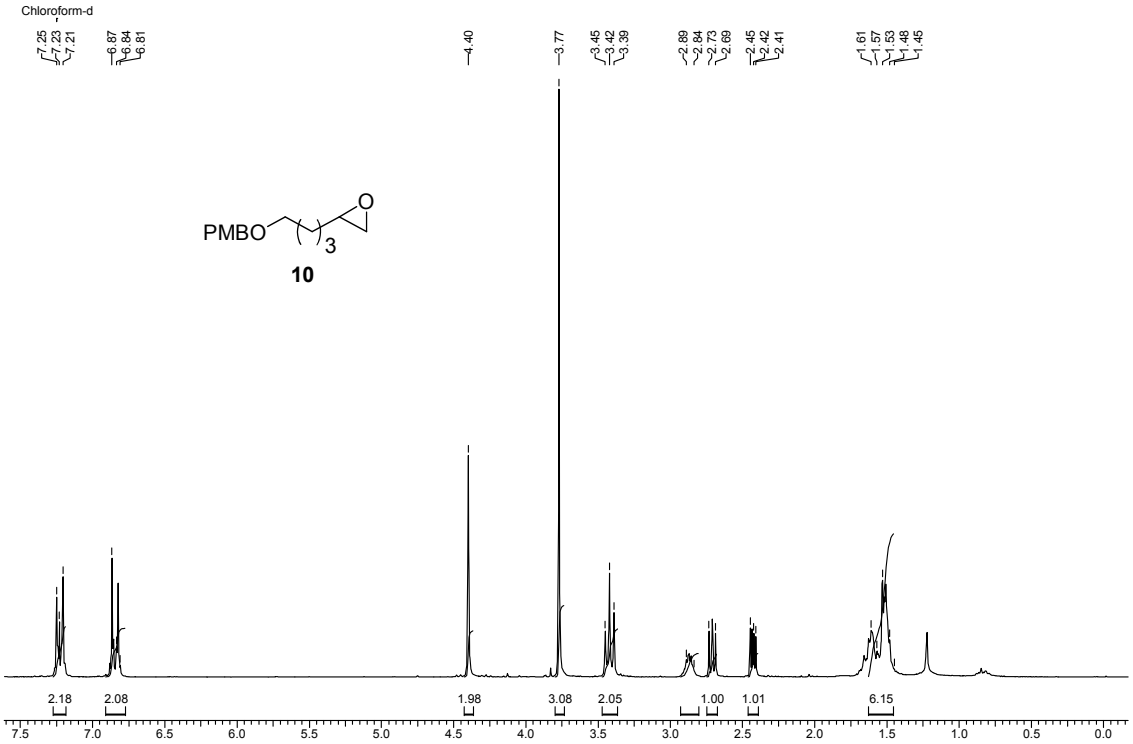
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2.73
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2.45
2.42
2.41
1.61
1.57
1.53
1.48
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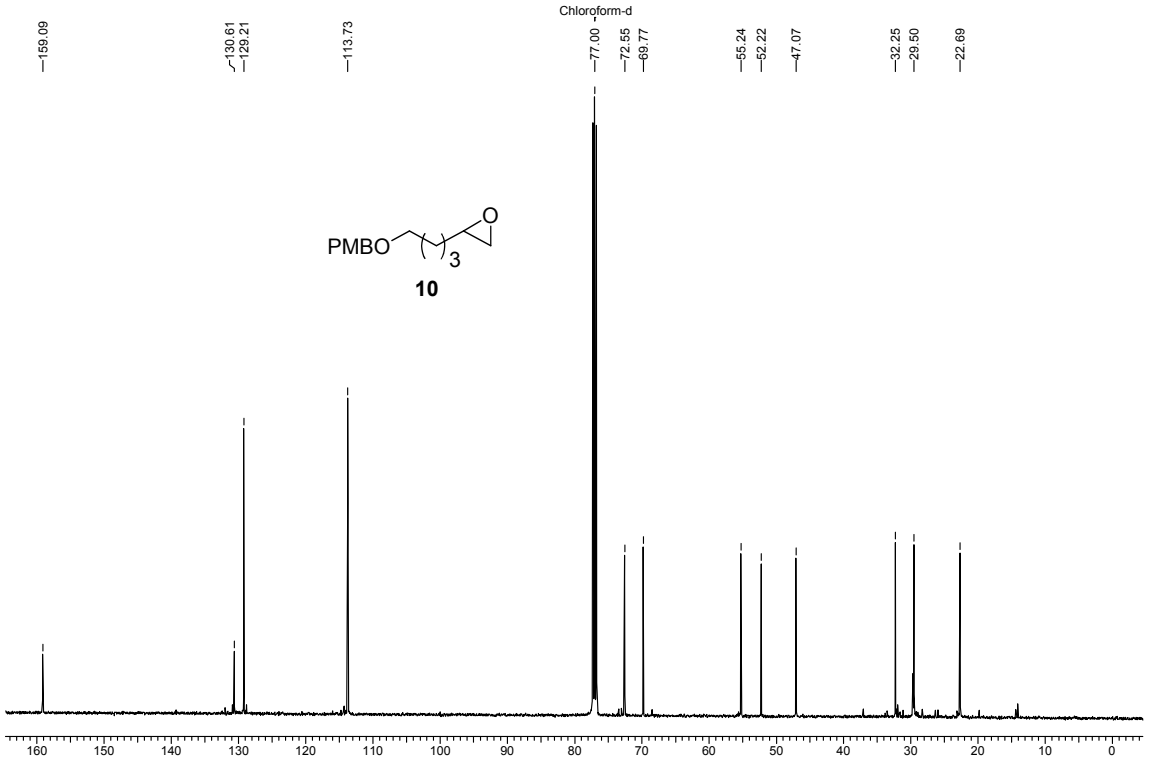
1.98
3.08
2.05
1.00
1.01
6.15

**10**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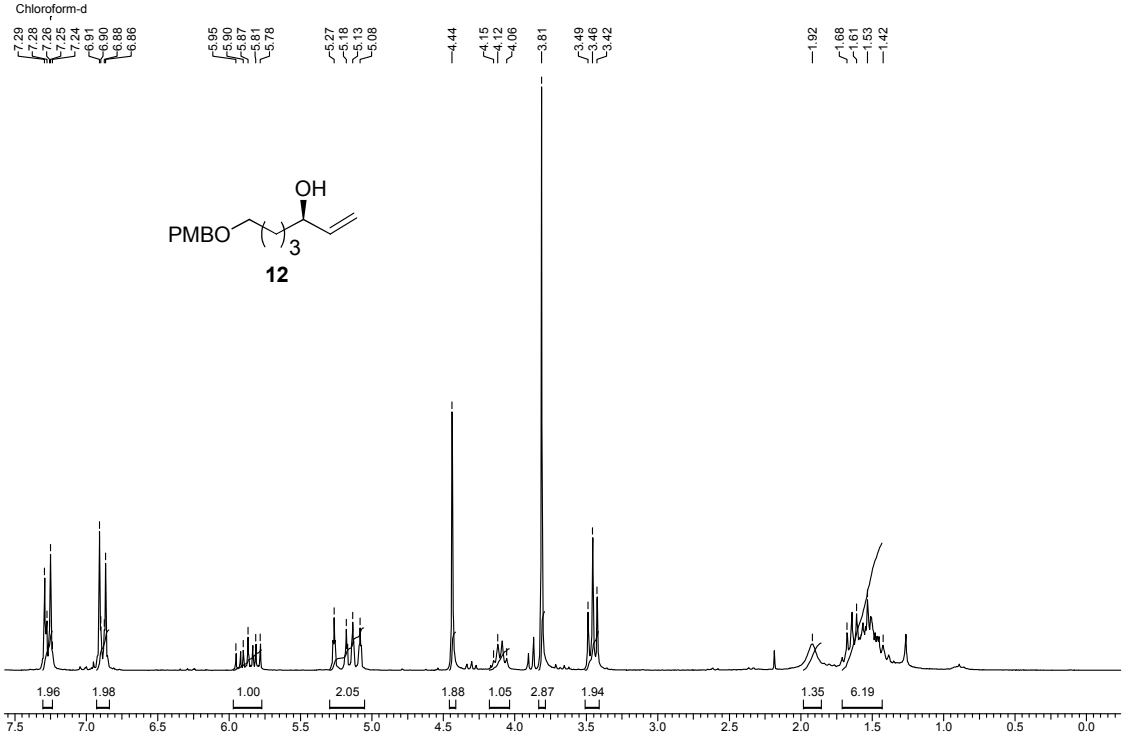
**10**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3.46
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1.61
1.53
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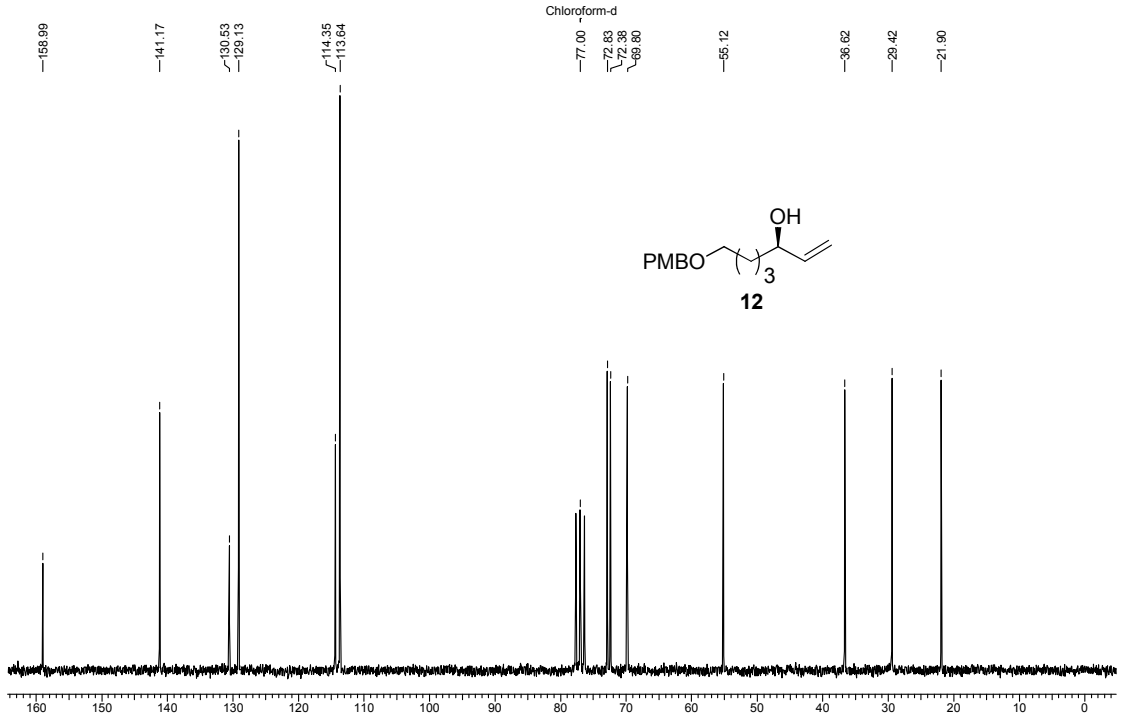
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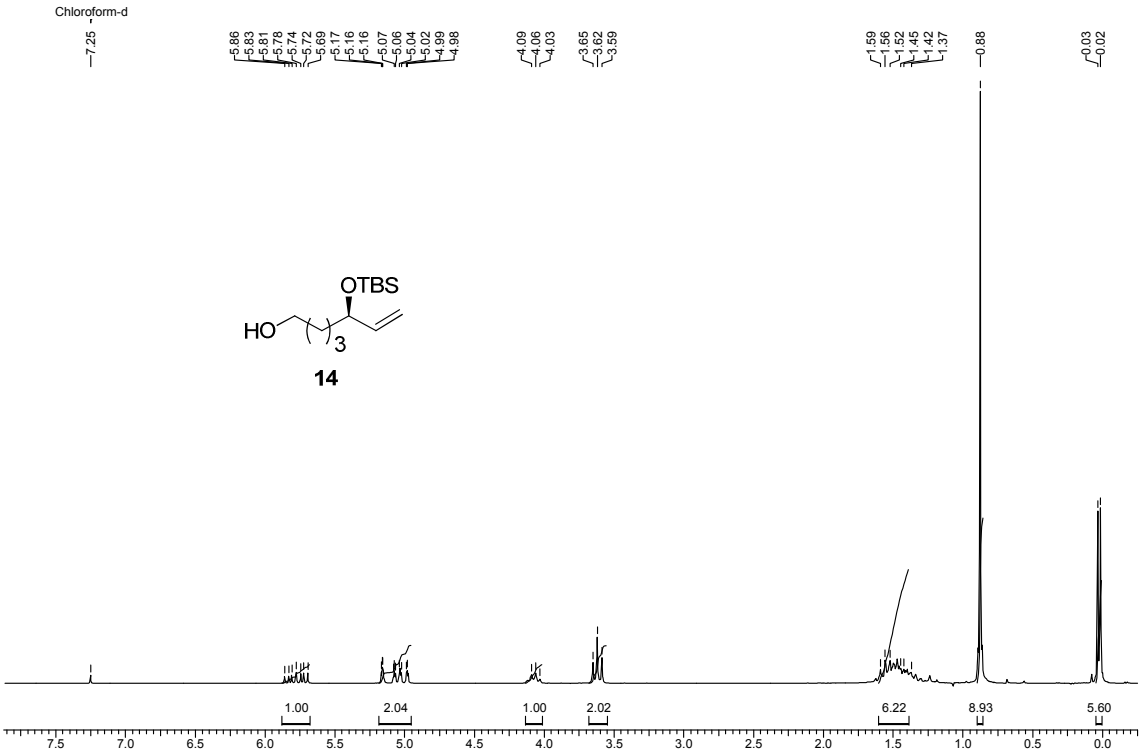
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0.03
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OTBS
HO
3
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8.93
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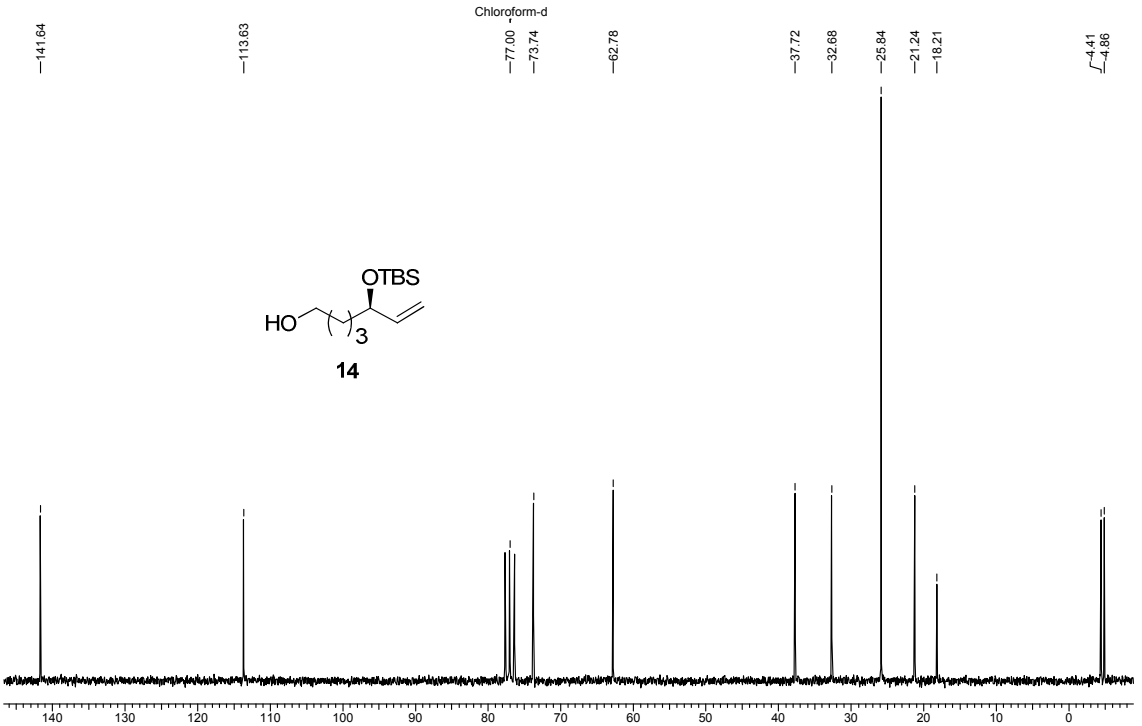
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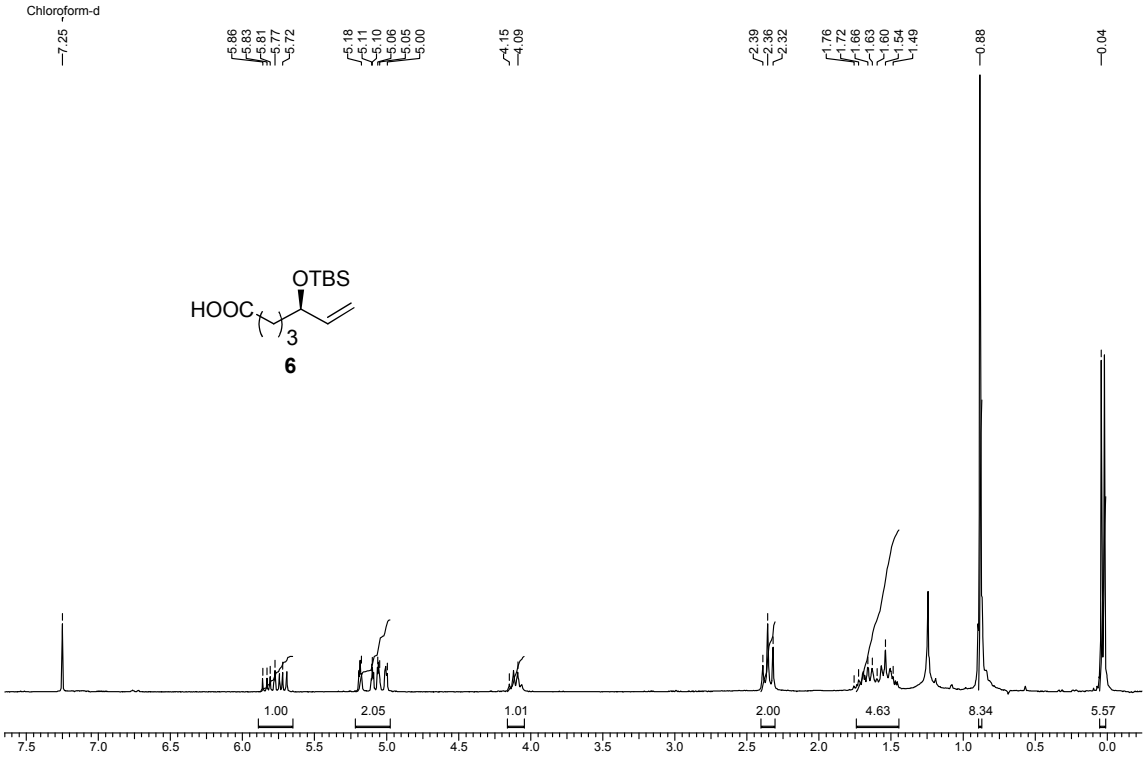
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4.15
4.09
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2.36
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1.76
1.72
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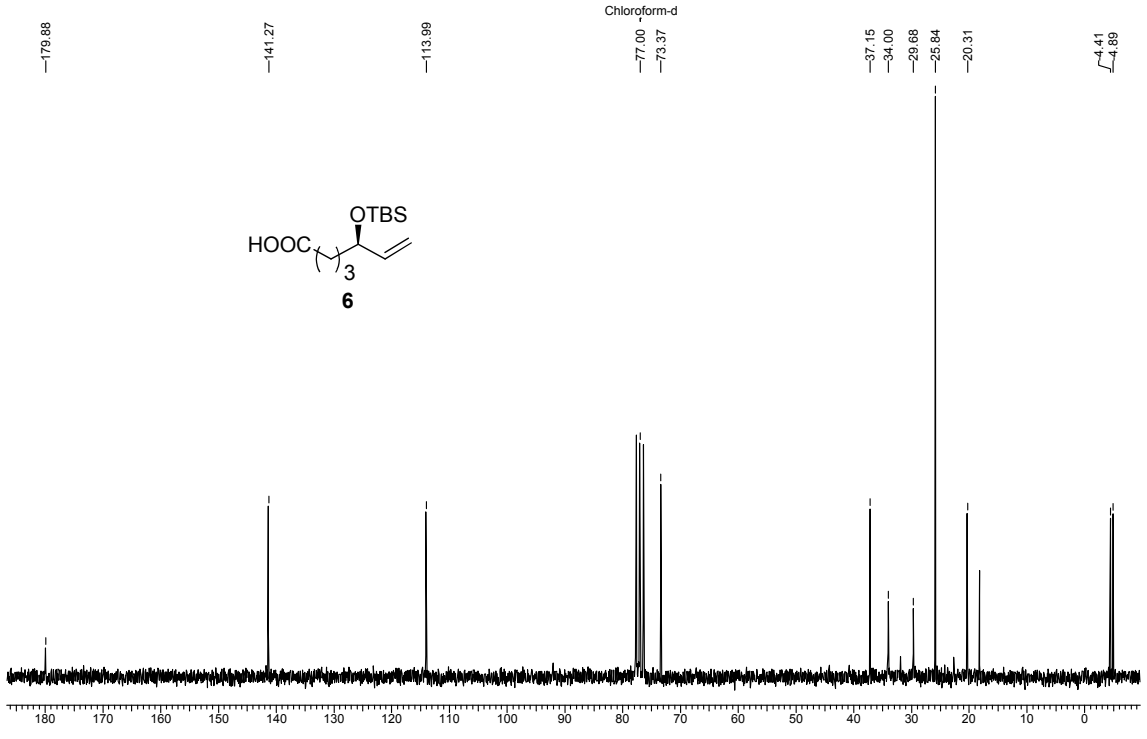
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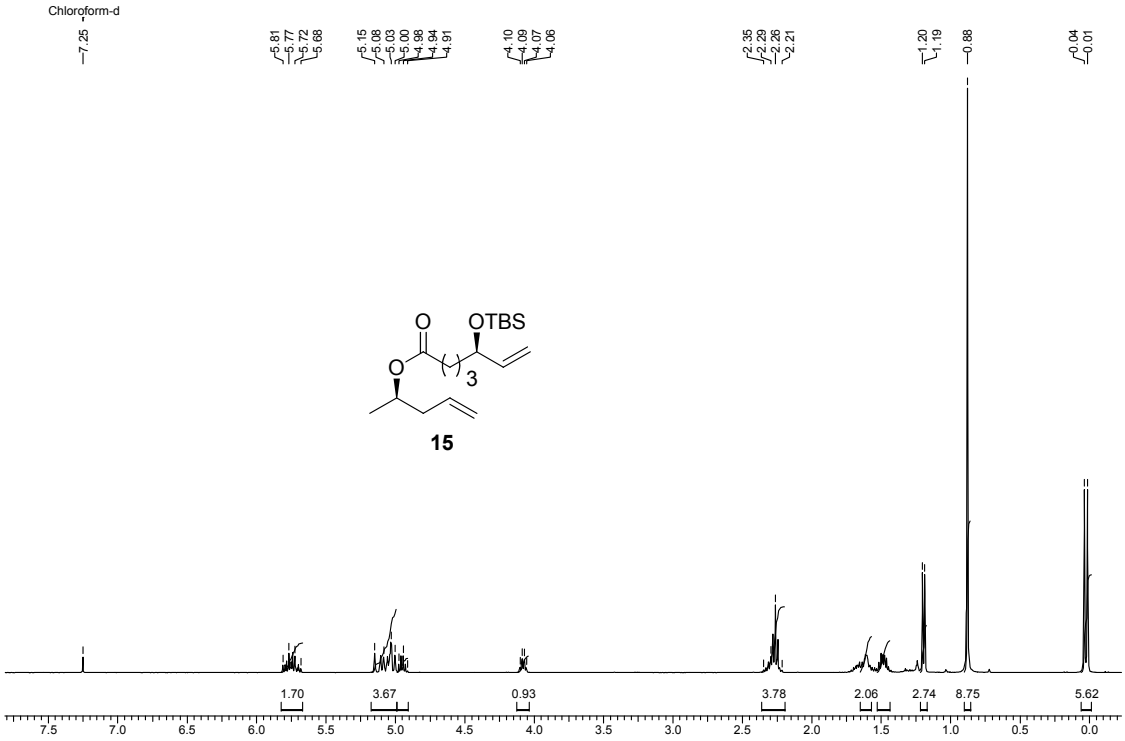
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4.06
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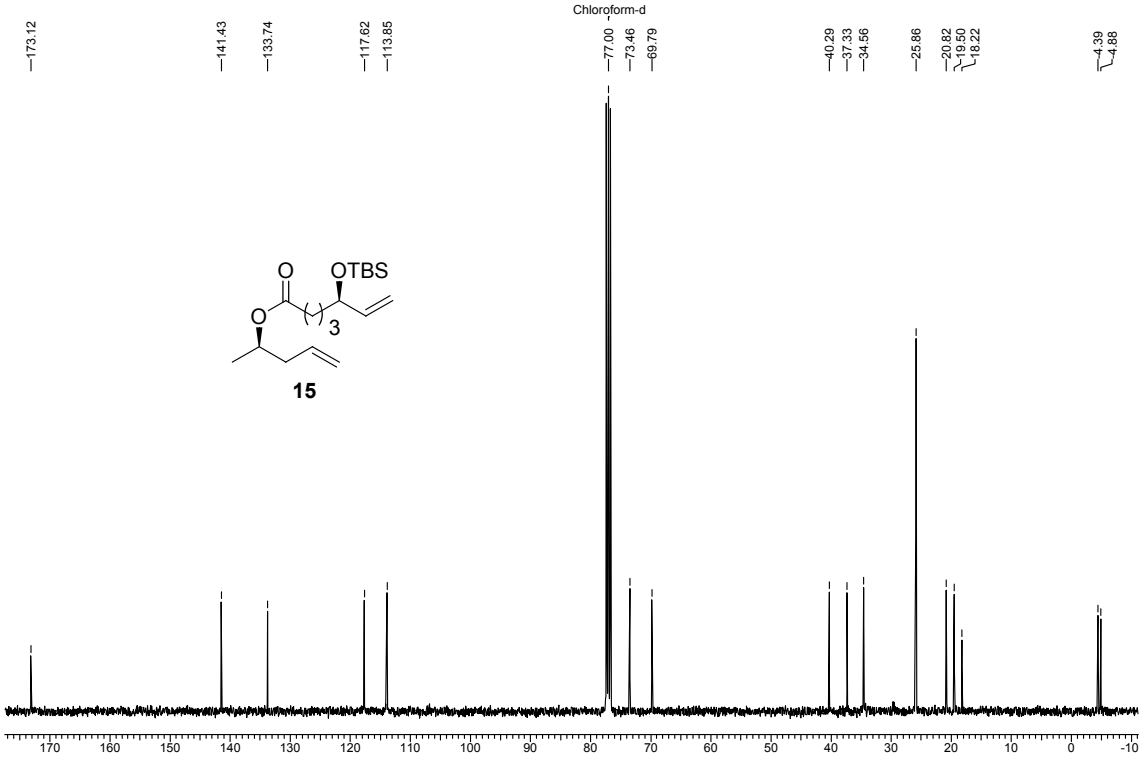
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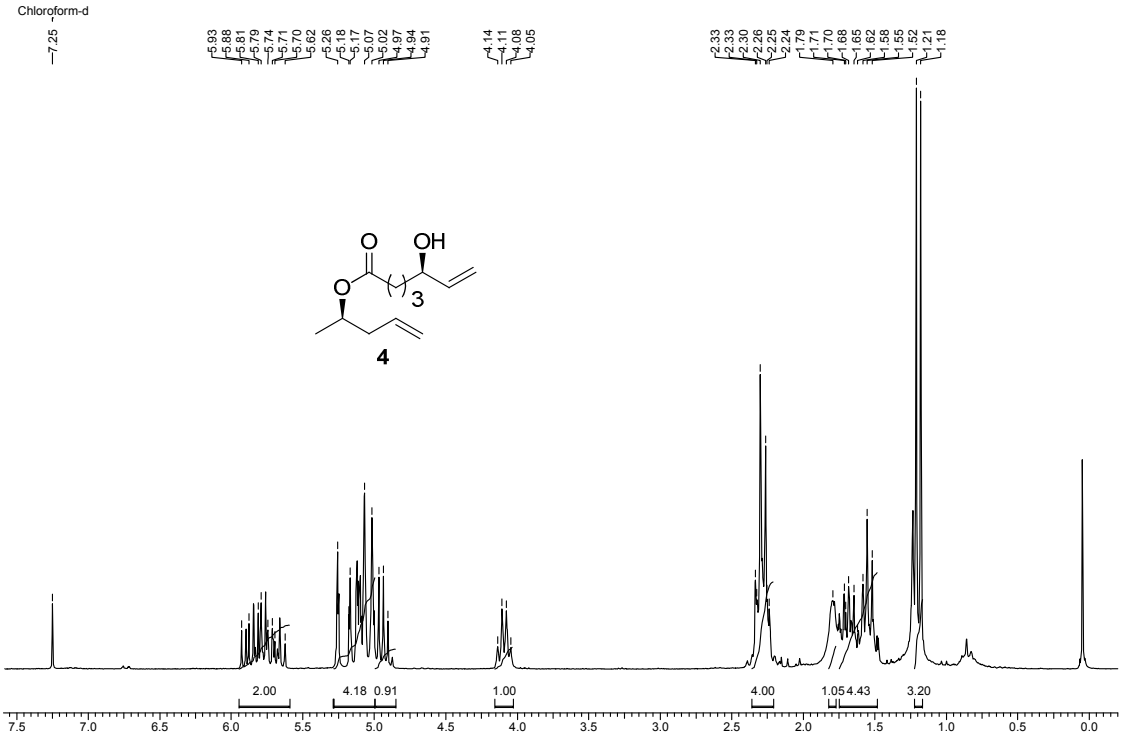
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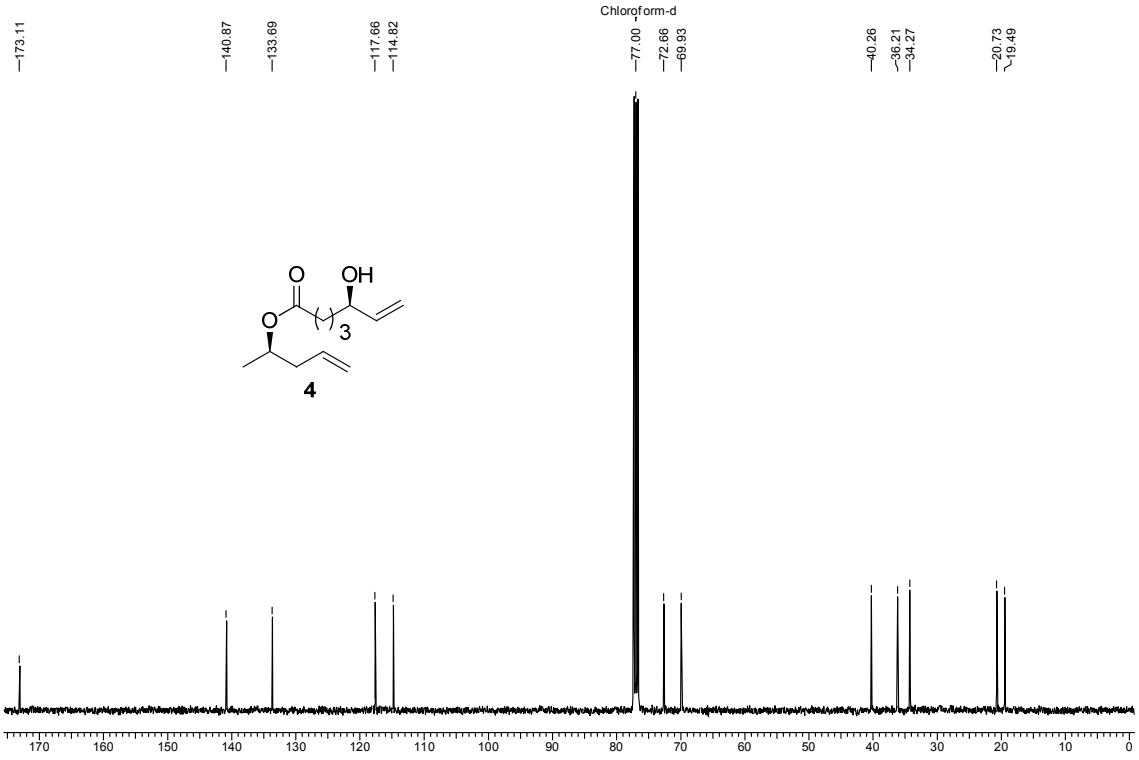
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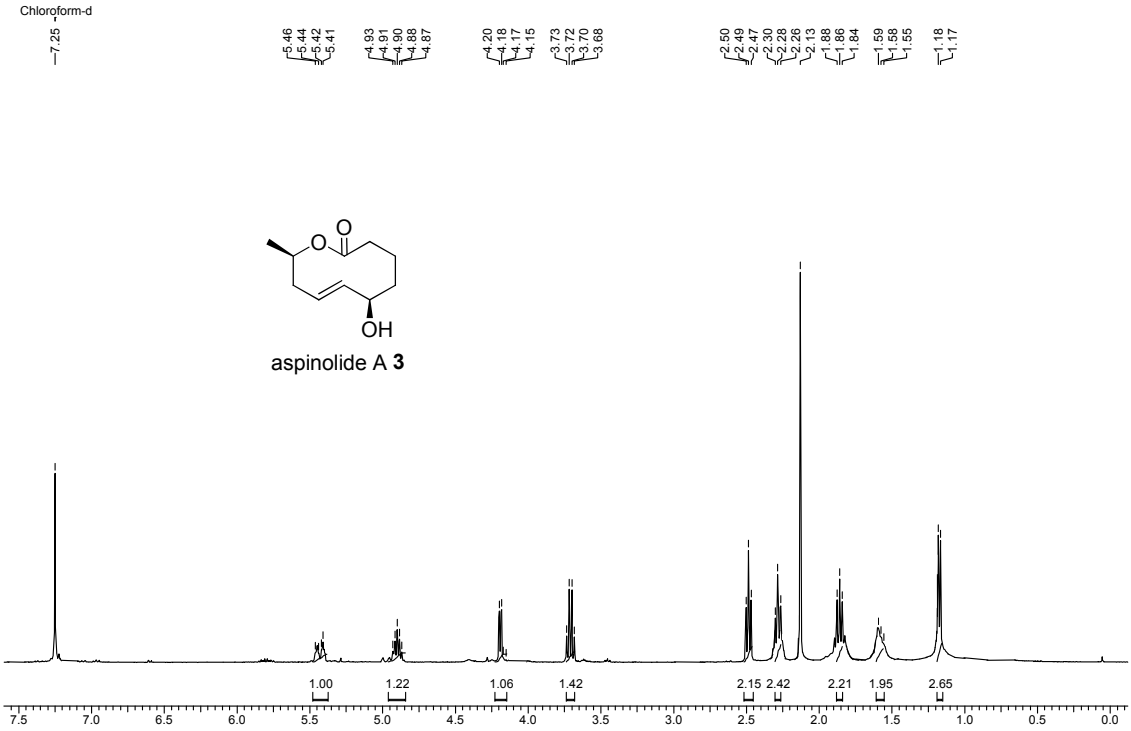
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4.18
4.17
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3.70
3.68
2.50
2.49
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2.28
2.26
2.13
1.88
1.86
1.84
1.59
1.58
1.55
1.18
1.17
O
O
OH
aspinolide A **3**
1.00
1.22
1.06
1.42
2.15
2.42
2.21
1.95
2.65
7.5
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6.5
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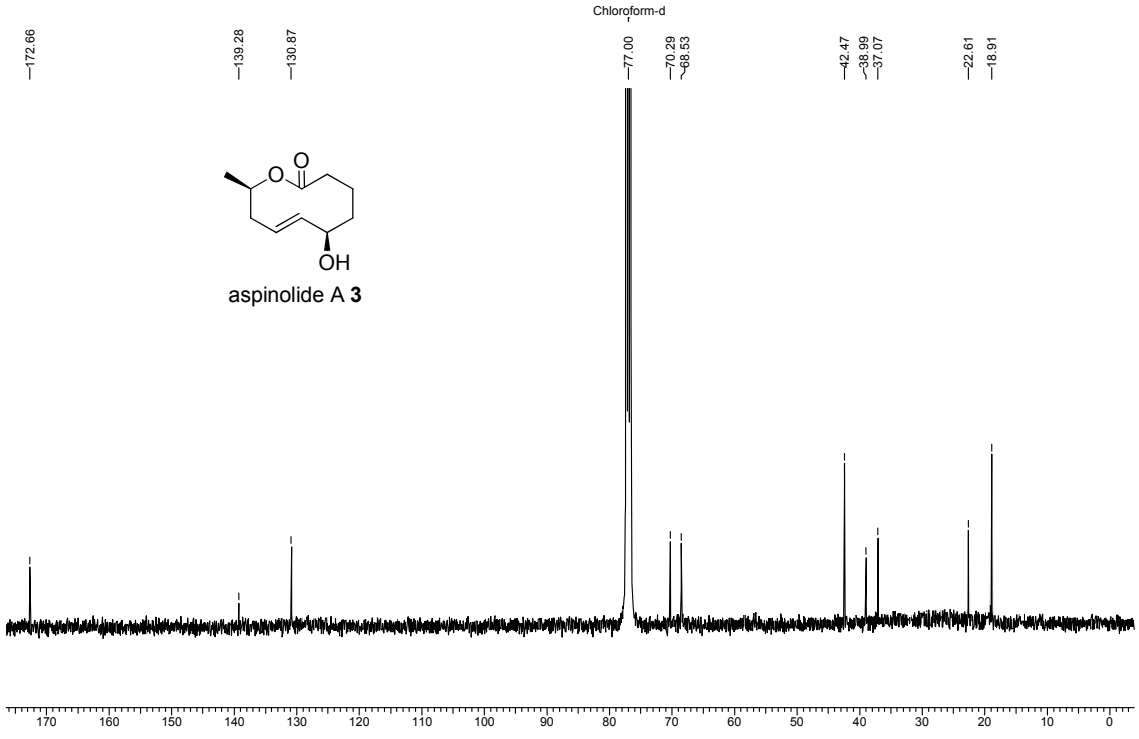
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O
O
OH
aspinolide A **3**
170
160
150
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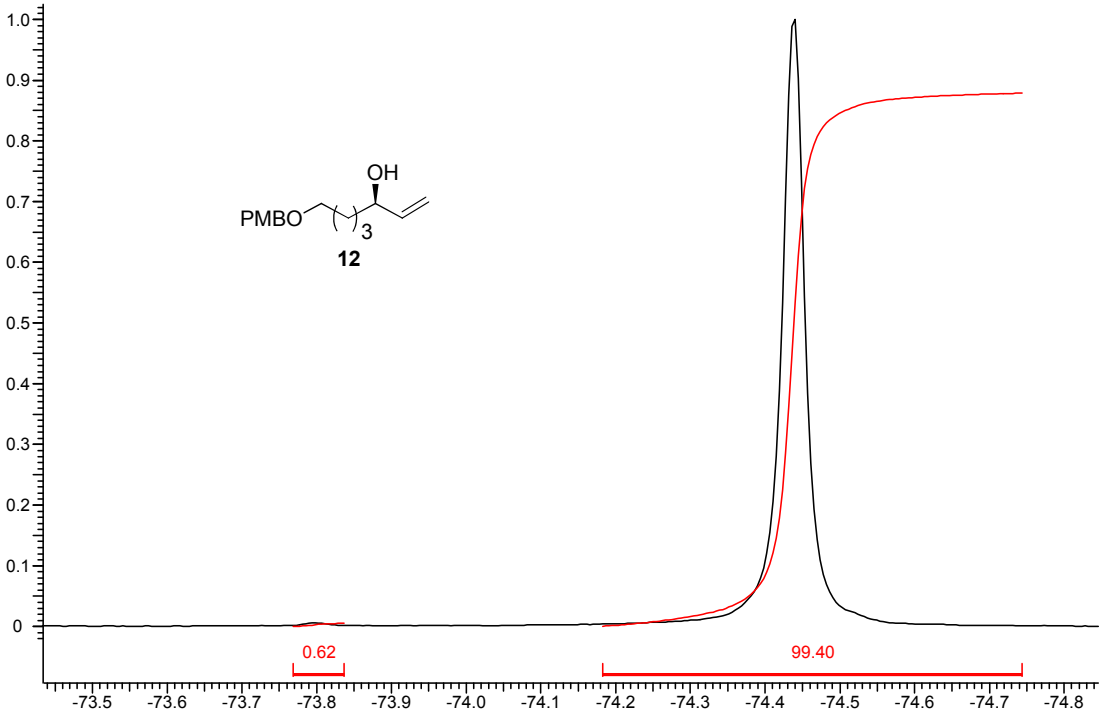
10
0

## $^{19}$F spectrum of Mösher ester of **12**



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# CHAPTER-3

## Synthesis of 6-Substituted-5,6-Dihydro-2*H*-Pyran-2-Ones

## Section A:- Total Synthesis of Umuravumbolide and Hyptolide *via* Silicon-Tethered Ring Closing Metathesis

## Section B:- Attempted Synthesis of Hypurticin *via* Temporary Silicon Tethered-Ring Closing Metathesis

# 3.1 Section A

# TOTAL SYNTHESIS OF UMURAVUMBOLIDE AND HYPTOLIDE *VIA* SILICON-TETHERED RING CLOSING METATHESIS

## 3.1.1. Introduction

Protozoal diseases, particularly malaria, leishmaniasis and Chagas disease, represent major causes of mortality in various tropical and subtropical regions. These diseases remain significant health problems in many developing countries, and this situation is compounded by increasing treatment failures using current drugs.

Malaria causes more than 300 million acute illnesses and at least one million deaths annually. Resistance of the malaria parasites, *Plasmodium spp*., to drugs such as chloroquine (and, more lately, quinine) occurs with increasing frequency.[1, 2] This resistance underlies the necessity of developing new agents for malaria chemotherapy, with new modes of action to replace current ineffective drugs.

Leishmaniasis is a major health problem that affects approximately 12 million people worldwide, with 2 million new cases diagnosed every year.[3] The causative agents of this disease are parasites of the genus *Leishmania*, which infect and replicate in macrophages of the vertebrate host. Recently, a dramatic increase in the number of cases of leishmaniasis has been observed in patients with compromised T-cell function, such as those infected with the human immunodeficiency virus.[4] The chemotherapy of leishmaniasis has been based on pentavalent antimonials, sodium stibogluconate (pentostam) and meglumine antimonite (glucantime). These drugs contain multiple uncharacterized molecular structures with variable efficacies and toxicities, they are associated with moderate and severe side effects,[5, 6, 7] prone to induce resistance[8, 9] and require parenteral administration over a long period.[10] Second-line drugs, such as amphotericin B and its lipid formulations, are either more toxic and expensive for routine use in developing countries.

*Trypanosoma cruzi* is a protozoa that causes Chagas disease (American trypanosomiasis); it is an obligate intracellular protozoan parasite that causes acute and chronic infection in several mammalian species including humans. This illness affects approximately 16 to 18 million people in tropical and sub-tropical Americas leading to the death of approximately 400.000 people per year.[11] Nifurtimox and benznidazole, the drugs currently in use against this disease, present several side effects and have limited efficacy.[12] Gentian violet, another compound for the prevention of Chagas disease by blood transfusion,[13] leads to purple colouring of the blood and staining of patients' tissues. The use of gentian violet is limited due to its toxicity and other side effects such as alteration of skin color, mucous membranes and urine.[14]

The development of new, effective, non-toxic and less expensive drugs is required to contribute to the world-wide control of these diseases. 6-Substituted 5,6-dihydro-$\alpha$-pyrones, so-called $\alpha,\beta$-unsaturated $\delta$-lactones (see Fig 1) of both natural and nonnatural origin have been found to exhibit relevant pharmacological activities.

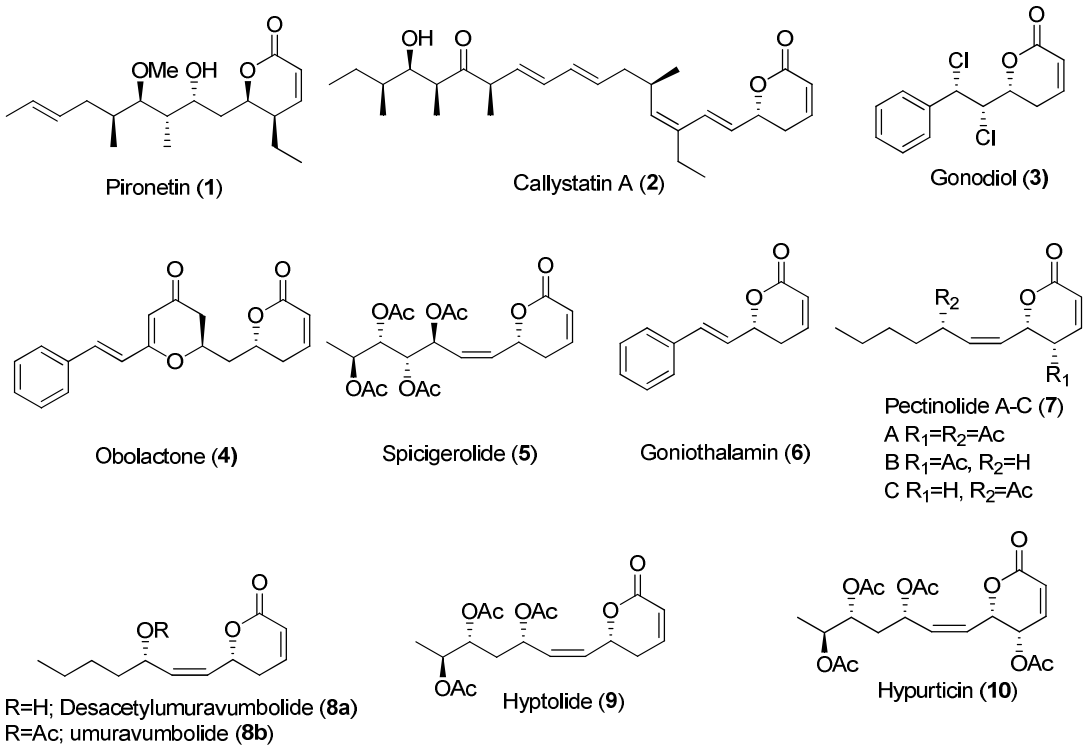



**Figure 1:** Structures of $\alpha,\beta$-unsaturated $\delta$-lactones

We cite a few examples: pironetin (**1**)[15] has been found to inhibit cell cycle progression in the M phase. Callystatin A (**2**),[16] gonodiol (**3**),[17] obolactone (**4**),[18] and spicigerolide (**5**)[19] exhibit cytotoxic activity. Goniothalamin (**6**)[20] induce the apoptotic process. Pectinolides A-C (**7**) exhibit significant antimicrobial and cytotoxic activity.[21] Umuravumbolide (**8b**), hyptolide (**9**) and hypurticin (**10**) also show a wide range of pharmacological activities. In an effort to discover new compounds for infectious diseases treatment, several *α,β*-unsaturated *δ*-lactones were evaluated and found to have high antiprotozoal activity.

Desacetylumuravumbolide (**8a**),[22a] umuravumbolide (**8b**),[22a] structurally related hyptolide (**9**)[22b] were isolated from species of *Tetradenia* and *Hyptis* respectively are representative members of family Lamiaceae (Figure 1).

These compounds have a common structural feature, the polyacylated-6-heptenyl-5,6-dihydro-2*H*-pyran-2-ones framework containing an *α,β*-unsaturated *δ*-lactone and are known to bind protein thiol groups as a result of their ability to act as a Michael acceptor. They show a wide range of pharmacological activities such as cytotoxicity against human tumor cells, antimicrobial and antifungal activity etc.

They inhibit HIV protease,[23] induce apoptosis,[24] and have even been shown to be antileukemic[25] and anticancer agents.[26] Further, they have shown a variety of biological activities, such as plant-growth inhibitors, pheromones, and antifeedant, antifungal, and antibacterial reagents.[27]

Although biological activities of umuravumbolide (**8b**) are not known so far, but several compounds from Lamiaceae family have been shown to be an emetic to treat loss of appetite.

The structures of (–)-deacetylumuravumbolide (**8a**) and (+)-umuravumbolide (**8b**) were revised by Davies-Coleman and Rivett, and they determined the absolute configuration on the basis of NMR and CD spectral studies and also reported the optical rotations of these compounds.[28]

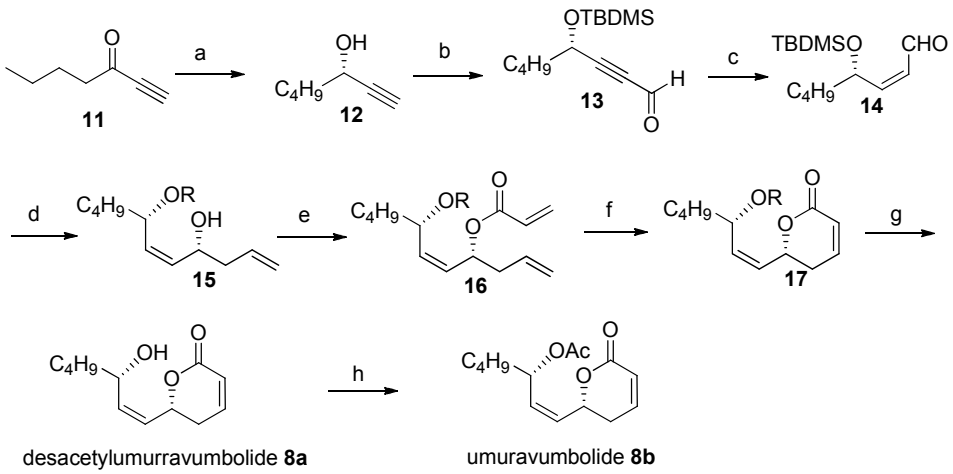
## 3.1.2. Review of Literature

Synthetic studies toward the aforementioned molecules (**8**, **9**) have been described. To the best of our knowledge, all attempts have been in linear fashion involving semi-hydrogenation of the alkyne part using Lindlar's catalyst to generate the side chain olefin and ring-closing metathesis reaction for the construction of lactone ring. A detailed report of these syntheses is described below.

### 3.1.2.1 Synthesis of Umuravumbolide

**Ramachandran *et al.*[29] (2001)**

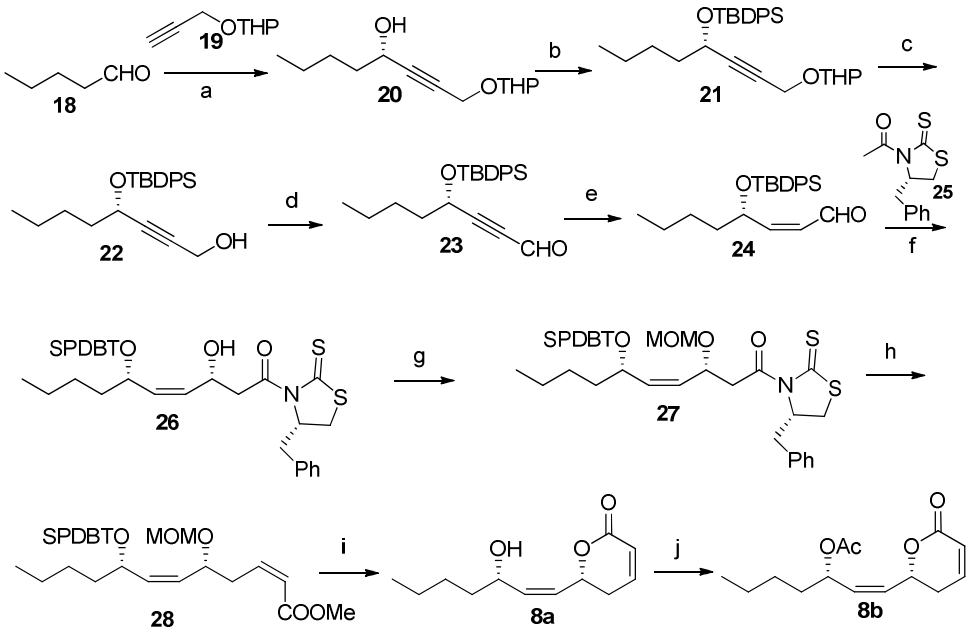
Ramachandran and co-workers first synthesized desacetylumuravumbolide and umuravumbolide via asymmetric reduction, allylboration, and ring-closing metathesis and confirmed their revised structures and configurations. They required optically pure (*S*)-1-heptyn-3-ol (**12**). Reduction of the corresponding acetylenic ketone **11** with (*S*)-*B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane (Alpine-Borane)[30] provided (*S*)-**12**.[31] After recrystallization the enantiomeric becomes ≥99% *ee* as determined by the HPLC.[32] TBDMS protection of **12**, followed by formylation, provided the acetylenic aldehyde **13**. This was converted to the required *Z*-olefinic aldehyde **6** by hydrogenation under Lindlar catalysis. Allylboration of **14** with *B*-allyldiiso-2-caranylborane[33] provided enantiomerically pure **15**.[34] Esterification with acryloyl chloride, followed by ring-closing metathesis using Grubbs ruthenium catalyst,[35] provided the lactenone **17**.[36] The deprotection of TBDMS was achieved by utilizing triethylamine trihydrofluoride.[37] Acetylation provided the target molecule **8b**.



**Scheme 1**: *Reagents and conditions*: (a) Alpine-Borane, 75%; (b) (i) TBDMS-Cl, imidazole, DMF; (ii) BuLi, $Me_2NCHO$, –78°C to 0°C, 50%; (c) $H_2$, Lindlar catalyst, 65%; (d) $AllylBIpc_2$ [from (+)-DIP-Cl], $Et_2O$, –78°C, 79%, (e) Acryloyl chloride, $NEt_3$, cat. DMAP, $CH_2Cl_2$, rt, 70%; (f) 10% $PhCH=RuCl_2(PCy_3)_2$, $CH_2Cl_2$, reflux, 65%; (g) triethylamine trihydrofluoride, AcCN; (h) $Ac_2O$, $Et_3N$, cat. DMAP, $CH_2Cl_2$, rt, 98%.

## Venkateswarlu *et al.*[38] (2011)

Venkateswarlu and co-workers reported the synthesis of desacetylumuravumbolide (**8a**) and umuravumbolide (**8b**), starting from commercially available valeraldehyde **18**. As outlined in Scheme 2, the first stereocenter was generated by the highly enantioselective addition of propargyl alcohol **19** and **18** to give compound **20**.[39] The secondary hydroxyl group in compound **20** was protected with *tert*-butyldiphenylsilyl (TBDPS) chloride as TBDPS ether **21**. The tetrahydropyranyl group in compound **21** was deprotected with pyridinium *p*-toluenesulfonate (PPTS)/MeOH to give compound **22**, which was oxidized with 2-iodoxybenzoic acid (IBX) to afford aldehyde **23** in 90% yield. Aldehyde **23** was converted into required (*Z*)-olefinic aldehyde **24** in 85% yield by hydrogenation using Lindlar's catalyst in dry DCM.



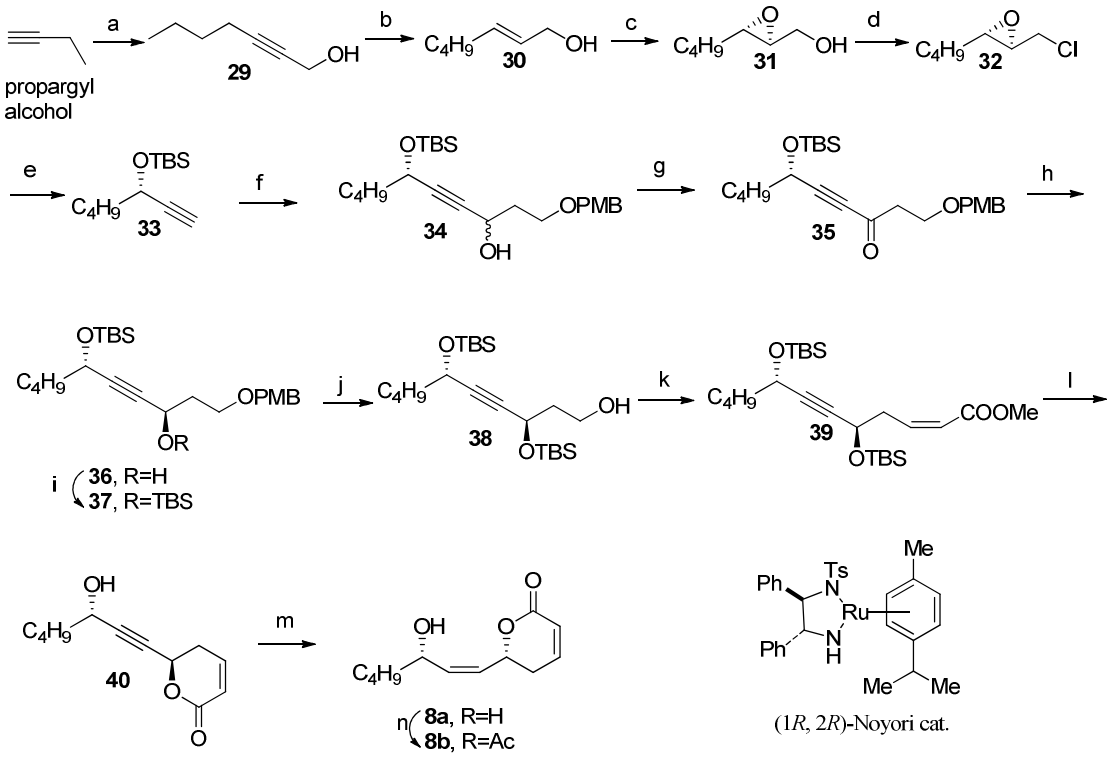

**Scheme 2**: *Reagents and conditions*: (a) **19**, $Et_2Zn$, (*R*)-BINOL, $Ti(O^iPr)_4$, PhOH, 95%, 93% *ee*; (b) TBDPSCl, imidazole, dry $CH_2Cl_2$, 6 h, r.t., 93%; (c) PPTS, MeOH,

r.t., 95%; (d) IBX /DMSO, $CH_2Cl_2$, 0 °C to r.t., 90%; (e) Lindlar's catalyst, $CH_2Cl_2$, $H_2$, 8 h, 85%. (f) **25**, $TiCl_4$, DIPEA, dry $CH_2Cl_2$, –78 °C, 77%; (g) MOMCl, DIPEA, 7 h, 0 °C to r.t., 95%; (h) (i) DIBAL-H, dry $CH_2Cl_2$, –78 °C, 5 min; (ii) NaH/THF, –78 °C, 30 min, then $(CF_3CH_2O)_2P(O)CH_2COOCH_3$, THF, 30–45 min, 82%; (i) 3 m HCl, THF (1:1), 3 h, r.t.; (j) $Ac_2O$, pyridine, $CH_2Cl_2$, 18 h, 97%.

Aldehyde **24** was subjected to an aldol reaction under the Crimmins protocol[40] to give a mixture of diastereomers. Amide **27** was treated with DIBAL-H to give the aldehyde, which was subjected to Horner–Wadsworth–Emmons olefination[41] to give *cis*-olefinic ester **28**. One-pot deprotection of the protecting groups with concomitant cyclization of the ester and alcohol functionalities with 3.0 m HCl/THF (1:1) at room temperature afforded **8a**. Further **8a** was acetylated by using acetic anhydride/pyridine to afford the target molecule **8b**.

**Sabitha *et al.*[42] (2011)**

Sabitha and co-workers reported the stereoselective synthesis of naturally occurring *α,β*-unsaturated *δ*-lactones desacetylumuravumbolide and umuravumbolide, starting from commercially available propargyl alcohol. As outlined in Scheme 3, the key steps of this synthesis were alkynylation, a Noyori asymmetric reduction and Still–Gennari olefination.

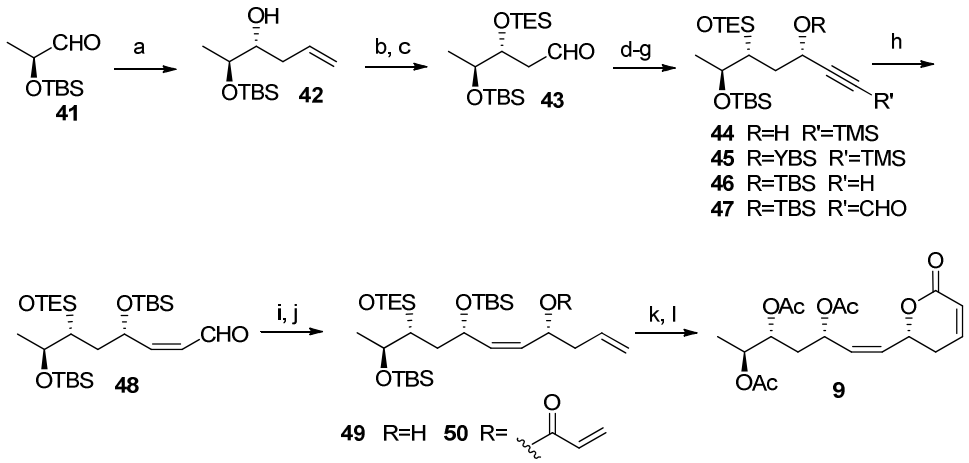



**Scheme 3** *Reagents and conditions*: a) Li, liq. $NH_3$, Fe $(NO_3)_3.9H_2O$, *n*-BuBr, THF, –33 $^oC$, 8 h, 70%. b) $LiAlH_4$, THF, 0 $^oC$–r.t, 6 h, 85%. c) (+)-DIPT, Ti(*i*PrO)$_4$, 5 M TBHP in $CH_2Cl_2$, 4Å molecular sieves powder, $CH_2Cl_2$, –30 $^oC$, 6 h, 85%. d) $CCl_4$, $PPh_3$, $NaHCO_3$, reflux, 6 h, 80%. e) (i) *n*-BuLi, THF, –78 $^oC$, 3 h, (ii) TBSCl, imidazole, $CH_2Cl_2$, 0 $^oC$, r.t, 2 h, (69% overall yield of two steps). f) *n*-BuLi, THF, -30 $^oC$ then add aldehyde 6 at –78 $^oC$, 4 h, 70%. g) IBX, DMSO, $CH_2Cl_2$, 0 $^oC$–r.t, overnight, 80%. h) (1*R*,2*R*)-Noyori catalyst, $HCO_2H$ (10 eq), $Et_3N$ (4eq), r.t, overnight, 89%. i) TBSCl, imidazole, $CH_2Cl_2$, 0 $^oC$–r.t, 3 h, 92%. j) DDQ, $CH_2Cl_2$, pH 7 (10 : 1), r.t, 4 h, 75%. k) (i) IBX, DMSO, $CH_2Cl_2$, 0 $^oC$–r.t, overnight, (ii) NaH, Still–Gennari reagent, 30 min at 0 $^oC$, then addition of 14 at –78 $^oC$, 2 h, (75% overall yield of two steps). l) PTSA, MeOH, 0 $^oC$–r.t, overnight, 80%. m) Pd/$CaCO_3$, $H_2$, quinoline (cat.), EtOAc, rt, 6 h, 92%. n) $Ac_2O$, $Et_3N$, DMAP (cat.), $CH_2Cl_2$, 0 $^oC$, r.t, 2 h, 85%.

## 3.1.2.2 Synthesis of Hyptolide

**Marco *et al.*[43] (2003)**

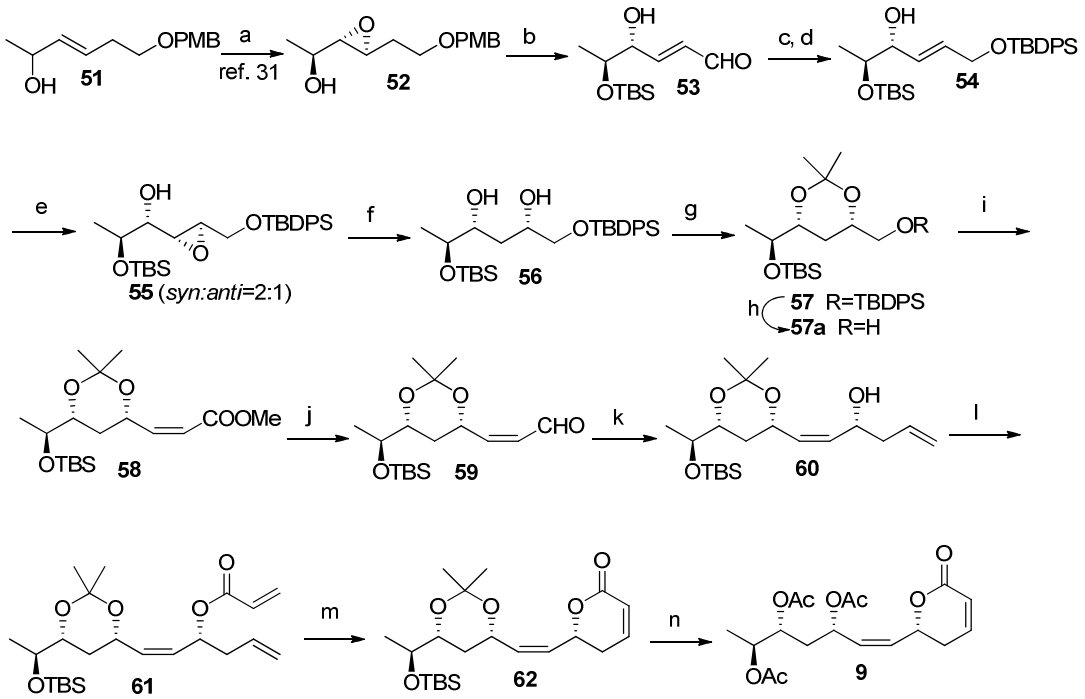
Marco and co-workers first synthesized hyptolide using a chiral pool starting material ethyl L-lactate (scheme 4). Asymmetric allylation of **41**[44] to homoallyl alcohol **42** was performed with Brown's B-allyl di*iso*pinocampheylborane.[45] Protection of the hydroxyl group as a TES derivative[46, 47] was followed by oxidative cleavage of the olefinic bond to yield *β*-silyloxy aldehyde **43**. Next by using Carreira's asymmetric protocol[48, 49, 50] propargyl alcohol **44** was obtained as a single diastereomer. Alcohol silylation followed by selective cleavage of the C-silyl group furnished the terminal acetylene **46**, which was C-formylated to **47** via the intermediate lithium derivative. Semihydrogenation of the C≡C bond in **47** was performed using Lindlar catalyst. *Z*-Enal **48** was subjected as above to Brown's asymmetric allylation, which provided alcohol **49**. Acylation of **49** with acryloyl chloride furnished acrylate **50**, which was then subjected to RCM to form δ-lactone. Finally, cleavage of all silyl groups and acetylation of the three hydroxyl functions was achieved to afford (+)-**9**.




**Scheme 4**: *Reagents and conditions*: (a) AllylBIpc$_2$ [prepared from allylmagnesium bromide and (+)-DIP-Cl], $Et_2O$, −78°C (82%, 92:8 diastereomeric mixture). (b) TESOTf, 2, 6-lutidine, $CH_2Cl_2$, rt, 87%. (c) $OsO_4$ (cat.), NMO, $^t$BuOH/THF/$H_2O$, then $NaIO_4$, aq. THF, 78%. (d) TMSC≡CH, $Zn(OTf)_2$, $Et_3N$, (−)-*N*-methylephedrine, tol, rt. (e) TBSOTf, 2, 6-lutidine, 0°C, $CH_2Cl_2$. (f) $K_2CO_3$/MeOH, rt, 58% overall. (g) BuLi, THF, 0°C, then DMF, 70%. (h) $H_2$, Lindlar catalyst, 84%. (i) AllylBIpc$_2$ [from (+)-DIP-Cl], $Et_2O$, −78°C, (79%, single diastereomer). (j) Acryloyl chloride, $NEt_3$, cat. DMAP, $CH_2Cl_2$, rt, 70%. (k) 10% PhCH=$RuCl_2(PCy_3)_2$, $CH_2Cl_2$, reflux, 82%. (l) PPTS, aq. MeOH, 70°C, then $Ac_2O$, $Et_3N$, cat. DMAP, $CH_2Cl_2$, rt, 83%.

**Chakraborty *et al.*[51] (2008)**

Chakraborty and co-workers synthesized hyptolide (scheme 5) starting from compound **52**, which was prepared from alcohol **51** according to the reported procedure[52] involving Sharpless asymmetric kinetic resolution,[53] followed by protective group manipulations. The chiral epoxy alcohol **52** was subjected to Swern oxidation[54] to afford exclusively the trans enal, (4*R*, 5*S*, *E*)-5-(*tert*-butyl-dimethylsilyloxy)-4-hydroxy-hex-2-en-1-al (**53**). Reduction of the aldehyde functionality with DIBAL-H followed by selective protection of the resultant primary alcohol as a TBDPS-ether furnished compound **54**. Stereoselective epoxidation of **54** with *m*CPBA afforded the epoxide **54**. Then compound **55** was treated with $Cp_2TiCl_2$[55, 56] to obtain diol **56**. Acetonide protection of the 1,3-diol of **56** gave **57**. Chemoselective deprotection of the TBDPS-ether afforded the primary alcohol **57a**, which was converted to alkene **58** first by oxidation of **57a** followed by selective *Z*-olefination following Still's protocol.[57]




**Scheme 5**: *Reagents and conditions* (a) Ref. 31; (b) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, −78°C, 1 h, 90%; (c) DIBAL-H, $CH_2Cl_2$, −78°C, 0.5 h; (d) TBDPSCl, $Et_3N$, DMAP (cat), $CH_2Cl_2$, 0°C to rt, 3 h, 81% over two steps; (e) *m*CPBA, $CH_2Cl_2$, 0°C, 12 h,

90% (2:1 in favor of the required isomer); (f) $Cp_2TiCl_2$, Zn, $ZnCl_2$, THF, −20°C to rt, 12 h, 85%; (g) 2, 2-dimethoxypropane, CSA (cat), $CH_2Cl_2$, rt, 1 h; (h) TBAF, THF, 0°C to rt, 1 h, 85%, over two steps; (i) (i) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, −78°C, 2 h; (ii) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, NaH, THF, −78°C to 0°C, 1.5 h, 80% (*Z:E* = 95:5) over two steps; (j) (i) step c; (ii) DMP, $CH_2Cl_2$, 0°C to rt, 0.5 h, 85% over two steps; (k) (+)-$Ipc_2B$(allyl), $Et_2O$, −78°C, 1 h, 70%; (l) acryloyl chloride, $Et_3N$, DMAP, $CH_2Cl_2$, 0°C; 15 min, 70%; (m) Grubbs'1st generation catalyst, $CH_2Cl_2$, reflux, 5 h, 85%; (n) (i) PPTS, MeOH, rt, 24 h; (ii) $Ac_2O$, $Et_3N$, DMAP (cat), $CH_2Cl_2$, 0°C to rt, 0.5 h, 80% over two steps.

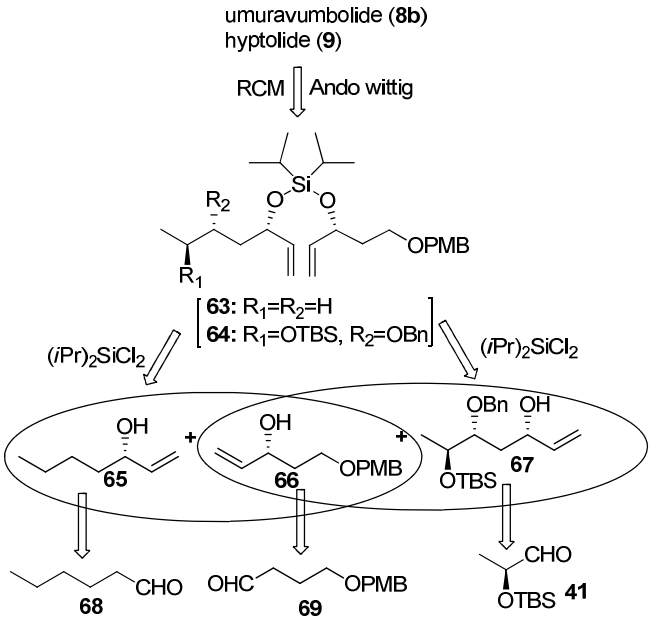
The *α,β*-unsaturated aldehyde **59** was obtained from **58** in two steps. Asymmetric allylation of **59** using Brown's protocol[58] afforded the secondary alcohol **60**. Acylation of **60** with acryloyl chloride furnished acrylate **61**, which was then subjected to RCM to form *δ*-lactone **62**. Finally, global deprotection followed by acetylation was achieved to afford (+)-**9**.

# 3.1.3. PRESENT WORK

## *Objective*

Numerous strategies has been developed for the synthesis of polyacylated-6-heptenyl-5,6-dihydro-2*H*-pyran-2-ones with great success. With the development of an efficient approach to the synthesis of various $\alpha,\beta$-unsaturated $\delta$–lactones,[59] we further considered attempting at the total synthesis of umuravumbolide (**8b**) and hyptolide (**9**).

Towards this end, we were interested in a concise and versatile approach exploiting temporary silicon-tethered ring-closing metathesis (TST-RCM)[60] and Ando's protocol[61] to construct the olefins. The strategy provides convergent synthetic access to all members of the Lamiaceae family. The general synthetic analysis is depicted in Scheme 6.




**Scheme 6**. Retro-synthetic analysis of umuravumbolide (**8b**) and hyptolide (**9**).

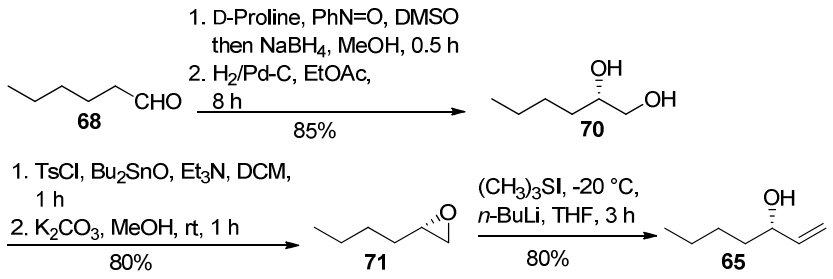
We aimed to construct the side chain *Z*-olefin of both umuravumbolide **8b** and hyptolide **9** through ring-closing metathesis of bis-siloxane intermediate **63** and **64** respectively. The intermediates **63** and **64** would originate by the coupling of allylic alcohols **65**, **66** and **66**, **67** respectively, whereas the requisite fragments **65**, **66** and **67**

could be prepared from hexanal **68**, 4-(4-methoxybenzyloxy)butanal **69**[62] and TBS protected L-lactaldehyde **41** respectively.

## 3.1.4. Results and Discussion

## Synthesis of fragment 65

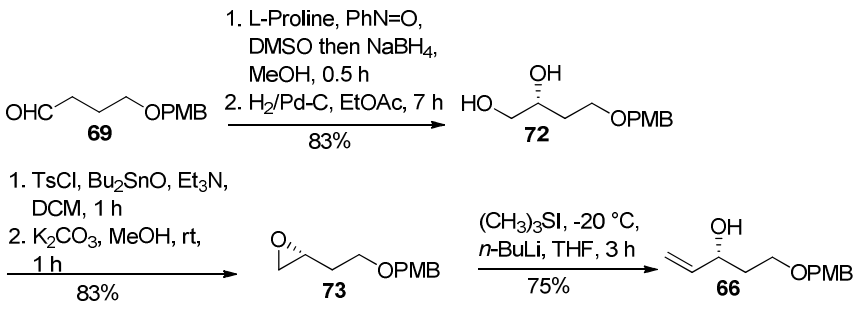
Our synthesis started with the preparation of fragment **65**. The sequence developed to prepare fragment **65** is summarized in Scheme 7. Thus, the aldehyde **68** was exposed to sequential α-aminoxylation[63] catalyzed by D-proline, followed by in situ reduction using $NaBH_4$ to furnish *O*-amino-substituted diol, which was subjected to reductive hydrogenation conditions to afford the known diol **70**[64] in 85% yield, which on selective monotosylation and base treatment furnished epoxide **71**[64] in 80% yield. Appearance of multiplet in the range of δ 2.71-2.67, 2.57-2.52, 2.28-2.25 in $^1$H NMR and disappearance of OH peak at 3372 $cm^{-1}$ in IR spectrum confirmed the formation of the epoxide **71**. Finally, dimethylsulfonium methylide-mediated[65] ring opening of epoxide **71** gave rise the fragment **65**[66] in 72% yield. The IR spectrum of **65** gave broad hydroxyl absorption at 3485 $cm^{-1}$. The $^1$H NMR spectrum of **65** gave olefin peaks at δ 5.88-5.71 (multiplet, one proton) and 5.19-4.99 (multiplet, two protons).




**Scheme 7.** Synthesis of fragment **65**.

## Synthesis of fragment 66

The synthesis of fragment **66** commenced from 4-(4-methoxybenzyloxy)butanal **69** as illustrated in Scheme 8.



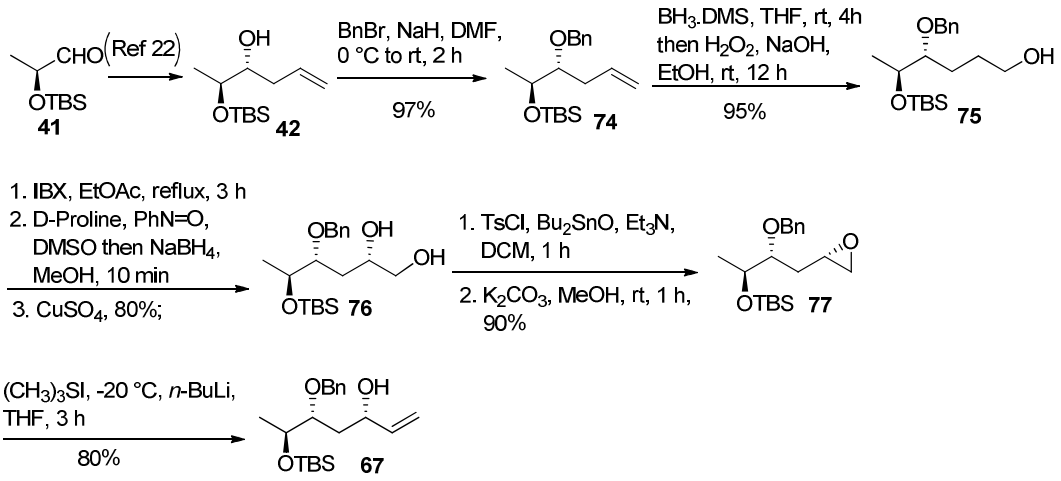

**Scheme 8.** Synthesis of fragment **66**.

The aldehyde **69** was subjected to *α*-aminoxylation catalyzed by L-proline, followed by similar set of reaction conditions, used in Scheme 7 to afford diol **72**[67] in 83% yield and in 97% *ee*,[68] which on selective monotosylation and base treatment furnished epoxide **73**[67] in 83% yield. Appearance of multiplet in the range of δ 3.11-3.02, 2.81-2.76, 2.54-2.50 in $^1$H NMR and disappearance of OH peak at 3384 cm$^{-1}$ in IR spectrum confirmed the formation of the epoxide **73**. This epoxide was also opened with dimethylsulfonium methylide to afford the allylic alcohol fragment **66**[69] in 75% yield and was confirmed by IR spectrum and $^1$H NMR. The IR spectrum of **66** gave broad hydroxyl absorption at 3414 cm$^{-1}$ and the $^1$H NMR spectrum of **66** gave olefin peaks at δ 5.97-5.80 (multiplet, one proton) and 5.33-5.08 (multiplet, two protons) which confirmed the structure.

## Synthesis of fragment 67

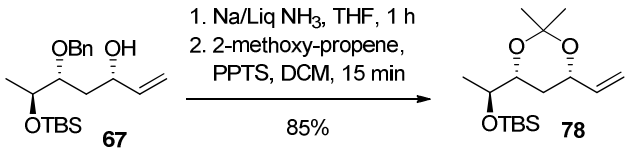
The sequence developed to prepare fragment **67** is summarized in Scheme 9. As our point of departure, asymmetric allylation of TBS protected L-lactaldehyde **41** to known homoallylic alcohol **42**[22] was performed with Brown's B-allyl diisopinocampheylborane, followed by treatment with benzyl bromide (BnBr) to afford **74** in 97% yield. We next examined proline-catalyzed *α*-aminoxylation reaction of aldehyde to generate the third stereogenic centre. Towards this we converted olefin **74** to alcohol **75** in 95% yield by the hydroboration oxidation technique. Thus compound **75** was oxidized by using IBX to furnish aldehyde, which was directly subjected to α-aminoxylation catalyzed by D-proline, followed by in situ reduction using $NaBH_4$ to give the required *O*-amino substituted diol, which on treatment with catalytic amount of copper sulfate afforded the diol **76** in 80% yield along with minor diastereomer (10%), which could be separated easily by chromatography. The

stereochemistry of the major diastereomer **76** was confirmed by $^{13}C$ NMR analysis. Diol **76** on selective monotosylation and base treatment furnished **77** in 90% yield. Appearance of multiplet in the range of δ 3.05-2.95, 2.73-2.61, 2.44-2.35 in $^{1}H$ NMR and disappearance of OH peak at 3412 $cm^{-1}$ in IR spectrum confirmed the formation of the epoxide **77**. Finally, dimethylsulfonium methylide mediated (Corey–Chaykovsky's condition)[65] ring opening of epoxide **77** gave rise the fragment **67** in 80% yield and was confirmed by IR spectrum and $^{1}H$ NMR. The IR spectrum of **67** gave broad hydroxyl absorption at 3290 $cm^{-1}$ and the $^{1}H$ NMR spectrum of **67** gave olefin peaks at δ 5.83-5.67 (multiplet, one proton) and 5.21-4.96 (multiplet, two protons) which confirmed the structure.




**Scheme 9.** Synthesis of fragment **67**.

The stereochemistry of compound **76** was confirmed from $^{13}C$ NMR spectra by converting compound **67** (derived from **76**, Scheme 9) into compound **78** through the following sequence of reaction. Compound **67** was subjected to Birch reaction condition followed by acetonide protection of 1,3-diol into the cyclic moiety **78**.



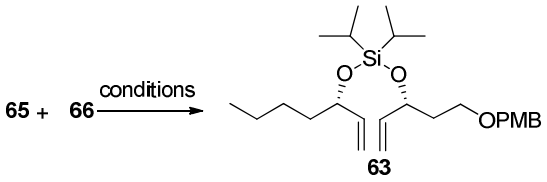

**Scheme 10.** Synthesis of cyclic acetonide.

The appearance of methyl resonance peaks at δ 19.8 and 30.0 ppm and acetal carbon resonating at δ 98.5 ppm confirmed the stereochemistry of syn-acetonide **78**.

## Coupling of Fragments 65, 66 and Fragments 66, 67 for The Synthesis of Umuravumbolide 8a and Hyptolide 9 Respectively

With the cross coupling partners in hand, the crucial silicon tethered coupling to construct the disiloxane **63** was examined (Table 1). Initial attempts using different silicon tethering reagents such as $Me_2SiCl_2$ and $Ph_2SiCl_2$ proved to be unsuccessful. Then we considered using $(i\text{Pr})_2SiCl_2$ as tethering reagent following the reaction conditions as reported by Evans and coworkers.[70] Accordingly, the addition of fragment **65** to $(i\text{Pr})_2SiCl_2$ followed by further addition of second fragment **66** after 24 h led to the exclusive formation of homodimer of **65** (Table 1; entry 1). We attributed this failure to the use of excess tethering reagent and prolonging the reaction mixture for long after the addition of first fragment **65**.

**Table 1.** Optimization of the coupling reaction of fragments **65** and **66**




| Entry | Fragment **65** (equiv) | $(i\text{Pr})_2SiCl_2$ (equiv) | Time[a] | yield of **63** (%) |
|---|---|---|---|---|
| 1 | 1 | 10 | 24 h | _[b] |
| 2 | 1 | 5 | 24 h | _[b] |
| 3 | 1 | 1.1 | 24 h | 5[c] |
| 4 | 1 | 1.1 | 5 h | 5[c] |
| 5 | 1 | 1.1 | 1 h | 30[c] |
| 6 | 1 | 1.1 | 15 min | 87[d] |

[a] time duration between the addition of first fragment and second fragment [b] only homodimer of **65** [c] along with homodimer of **65** [d] along with 5% homodimer of **65** and unreacted **66**.

Consequently we performed reaction with 5 equivalents of tethering reagent, but there was no product formation (entry 2). Nevertheless we could isolate 5% of coupled product **63** when the equivalent of tethering reagent was lowered to 1.1 (entry 3). The structure of **63** was proven by the $^{1}$H NMR and $^{13}$C NMR spectra. We then reduced the time duration between the addition of fragment **65** and fragment **66** from 24 h to 5 h, but we ended with no improvement in the yield of coupled product **63** (entry 4). Yields higher than 25% were obtained when the time gap was reduced to 1 h (entry 5). The best yield 87% could be achieved when we added fragment **66** just after 15 min of the addition of fragment **65** (entry 6).

Thus the coupled product **63** could be synthesized in excellent yield by reducing the equivalent of tethering reagent from previously used 10 to 1.1 as well as time duration between the addition of two fragments from 24 h to 15 min. Reduction in the amount of tethering reagent also takes care the cost effectiveness of the reaction. With disiloxane intermediates **63** and **64** in hand, we turned our attention to its further elaboration to umuravumbolide (**8b**) and hyptolide (**9**) by transforming the disiloxane moieties (**63** and **64**) to the corresponding cyclic intermediates **79** and **80** respectively and subsequent synthetic manipulations (Scheme 11). Eventually the ring closing metathesis reaction of disiloxane **63** using Grubbs second generation catalyst **A** in toluene at 110 °C proceeded smoothly to get the required cyclic intermediate **79** in 88% yield. The appearance of internal olefin at δ 5.86-5.39 and disappearance of four protons at δ 5.23-5.01 in $^{1}$H NMR confirmed the product.

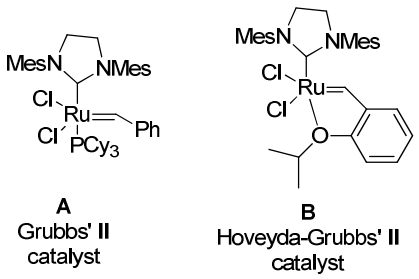



**Figure 2:** Metal-alkylidene metathesis catalysts.

However cyclization of **64** under similar conditions furnished the required cyclic intermediate **80** only in low yield. Hence we examined the ring closing metathesis (RCM) of disiloxane **64** using Grubbs catalyst under a variety of reaction conditions

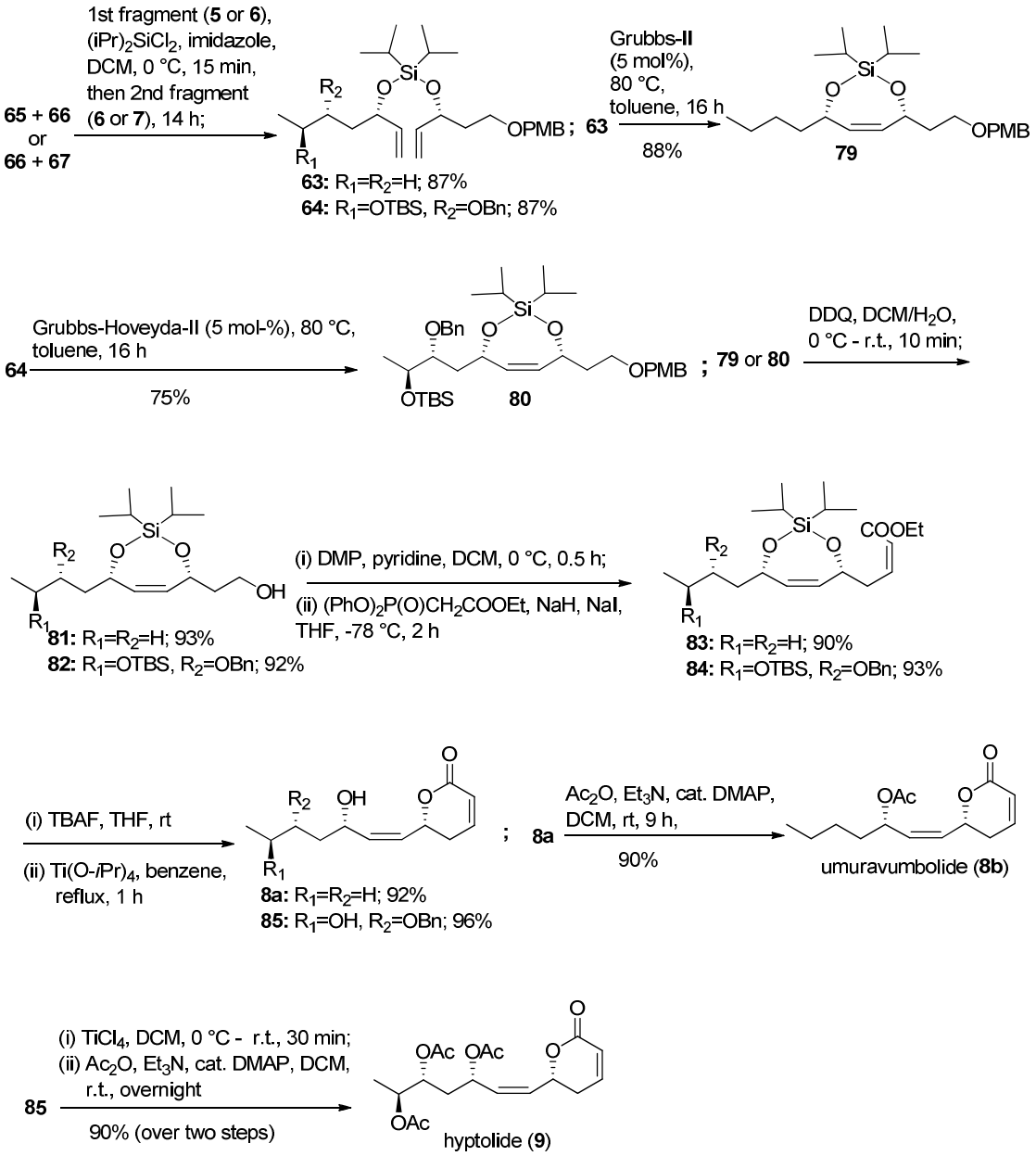
to get exclusively the cis-product in appreciable yield (Table 2). The best yield 75% could be achieved when we used Grubbs-Hoveyda second generation catalyst **B** in toluene at 110 °C (entry 4). The appearance of internal olefin at δ 5.60-4.63 and disappearance of four protons at δ 5.12-4.91 in $^{1}$H NMR confirmed the product. Our next objective towards the completion of the synthesis was to form the requisite lactone rings with unsaturation. Towards this end, compounds **79** and **80** were subjected to the removal of PMB groups using DDQ producing the corresponding alcohols **81** and **82** respectively in excellent yields. Subsequent Dess Martin periodinane oxidation of alcoholic group led to the formation of corresponding aldehydes, which were directly subjected to two-carbon homologation under Ando conditions[61] to give (*Z*)-unsaturated ester **83** and **84** in 70% yield with excellent stereoselectivity. The IR spectrum of **83** and **84** showed the ester carbonyl absorption at 1723, 1742 cm$^{-1}$ respectively and olefin C=C stretching at 1610, 1620 cm$^{-1}$ respectively.

Table 2. Optimization of RCM condition for disiloxane **64**

| entry | Catalyst | solvent | Temperature ($^{o}$C) | Yield (%) |
|---|---|---|---|---|
| 1 | Grubbs II **A** | DCM | 40 | 10 |
| 2 | Grubbs II **A** | DCE | 84 | 10 |
| 3 | Grubbs II **A** | Toluene | 110 | 20 |
| 4 | Grubbs-Hoveyda II **B** | Toluene | 110 | 75 |

With substantial amount of compound **83** and **84** in hand, the platform was then set to construct the lactone ring of the target molecules. At the begining we attempted the simultaneous deprotection of the silyl groups and cyclization in order to prepare the lactones **8a** and **85** using *p*TSA in MeOH. However the reaction led to the formation

of some unidentified products. Hence the obvious choice was two-step procedure; we first deprotected the silyl groups using TBAF in THF and the crude polyols thus obtained was eventually cyclized to give the six-membered lactones desacetylumuravumbolide (**8a**) and **85** in 70% yield upon treatment with catalytic amount of $Ti(OiPr)_4$ in refluxing benzene.




**Scheme 11.** Completion of the synthesis of umuravumbolide **8b** and hyptolide **9**.

The IR spectrum of **8a** and **85** showed characteristic carbonyl group absorption of *α,β*-unsaturated *δ*-lactone at 1644 and 1654 $cm^{-1}$ respectively. The lactone

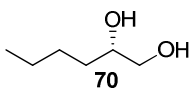
desacetylumuravumbolide (**8a**) was futher acetylated to furnish umuravumbolide **8b**. The spectroscopic and physical data of desacetylumuravumbolide (**8a**) and umuravumbolide (**8b**) were identical in all respects to those reported in the literature.[22a] Towards the synthesis of target molecule **9**, compound **85** was subjected to debenzylation followed by acetylation of secondary hydroxyl group to furnish the target molecule hyptolide **9** in excellent yield. The spectroscopic and physical data of compound **9** were identical in all respects to those reported in the literature.[22b]

## 3.1.5. Conclusion

In conclusion, an efficient synthesis for umuravumbolide (**8b**) and hyptolide (**9**) has been achieved via temporary silicon tetherd ring closing metathesis (TST-RCM) and Ando olefination reaction. The stereogenic centres were installed by using proline catalyzed $\alpha$-aminoxylation reactions and by Brown's asymmetric allyl boration. Further application of this methodology to the synthesis of other structurally related biologically active compounds for the studies of structure activity relationship is currently underway in our laboratory.

## 3.1.6. Experimental Section

General Methods: All reactions were carried out under argon or nitrogen in oven-dried glassware using standard gas-light syringes, cannulas and septa. Solvents and reagents were purified and dried by standard methods prior to use. Optical rotations were measured at room temperature. IR spectra were recorded on an FT-IR instrument. $^{1}$H NMR spectra were recorded on 200 MHz, 300 MHz and 500 MHz and are reported in parts per million (δ) downfield relative to $CDCl_3$ as internal standard and $^{13}$C NMR spectra were recorded at 50 MHz, 75 MHz and 125 MHz and assigned in parts per million (δ) relative to $CDCl_3$. Column chromatography was performed on silica gel (100-200 and 230-400 mesh) using a mixture of petroleum ether and ethyl acetate as the eluent.




**70**

**(*S*)-Hexane-1,2-diol (70):** To a stirred solution of aldehyde **68** (1.0 g, 9.98 mmol) and nitrosobenzene (1.06 g, 9.98 mmol) in DMSO (9 mL) was added D-proline (0.23 g, 1.9 mmol, 20 mol %) in one portion at 25 °C. After 1 h, the temperature was lowered to 0 $^{o}$C, followed by dilution with anhyd. MeOH (10 mL) and careful addition of excess $NaBH_4$ (1.32 g, 35 mmol). The reaction was quenched after 10 min by pouring the reaction mixture into a vigorously stirred biphasic solution of $Et_2O$ and aqueous HCl (1M). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phase was dried over anhyd $Na_2SO_4$, concentrated, and purified by column chromatography over silica gel using EtOAc/Pet. Ether (40:60) as eluent to give pure aminoxy alcohol, which was dissolved in EtOAc (10 mL) and to the solution was added 10% Pd/C (0.050 g) and the reaction mixture was stirred in a hydrogen atmosphere (1 atm, balloon pressure) for 12 h. After completion of the reaction (monitored by TLC) the reaction mixture was filtered through a celite pad, concentrated, and the crude product was then purified by silica gel chromatography using EtOAc/Pet. Ether (40:60) as eluent to give pure diol **70** as a colourless liquid.

**Yield:** 1.0 g, 85%

**Mol. Formula**: $C_6H_{14}O_2$

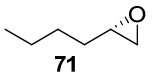
$[\alpha]_D^{25}$: −14.3 (*c* 1.0, MeOH). lit.[64] $[\alpha]_D^{25}$: −16.4 (*c* 1.0, MeOH).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3372, 2925.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 4.38-3.36 (m, 5H), 1.32-1.22 (m, 6H), 0.84-0.82 (m, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 71.9, 66.2, 33.1, 27.7, 22.6, 13.8.

**HRMS** ($ESI^+$) m/z calcd for $C_6H_{14}O_2$ $[M + Na]^+$ 141.0891, found 141.0893.



**71**

**(*S*)-2-Butyloxirane (71):** To a mixture of diol **70** (0.21 g, 1.77 mmol), in dry DCM (5 mL) was added dibutyltin oxide (0.008 mg, 0.035 mol) followed by the addition of *p*-

toluenesulfonyl chloride (0.337 g, 1.77 mmol) and triethylamine (0.25 mL, 1.77 mmol) and reaction was stirred at room temperature under nitrogen. The reaction was monitored by TLC, after completion of reaction the mixture was quenched by adding water. The solution was extracted with DCM (3 x 10 ml) and then combined organic phase was washed with water, dried ($Na_2SO_4$) and concentrated. To this crude mixture in MeOH at 0 °C was added $K_2CO_3$ (0.5 g, 3.61 mmol) and the resultant mixture was allowed to stir for 1 h at same temp. After completion of reaction as indicated by TLC the reaction was quenched by addition of ice pieces and methanol was evaporated. The concentrated reaction mixture was then extracted with ethyl acetate (3 x 20 mL), the combined organic layer was washed with brine, dried ($Na_2SO_4$) and concentrated. The column chromatography of crude product using pet ether:ethyl acetate (70:30) gave the epoxide **71** as a colorless liquid.

**Yield:** 0.14 g, 80%

**Mol. Formula**: $C_6H_{14}O_2$

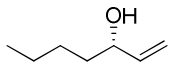
$[\alpha]_D^{25}$: −16.5 (*c* 1.0, pentane). lit.[64] $[\alpha]_D^{25}$: –18.7(*c* 0.93, pentane).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 2989, 2925, 2870.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 2.71-2.67 (m, 1H), 2.57-2.52 (m, 1H), 2.28-2.25 (m, 1H), 1.34-1.10 (m, 6H), 0.78-0.71 (t, *J*=6.13 Hz, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 51.9, 46.6, 31.9, 27.8, 22.2, 13.6.

**HRMS** ($ESI^+$) m/z calcd for $C_6H_{12}O$ $[M + Na]^+$ 123.0786, found 123.0784.




**65**

**(*S*)-Hept-1-en-3-ol (65):**To a suspension of trimethylsulfonium iodide (5.44 g, 26.5 mmol) in dry THF (10 mL) at −20 $^0$C was added *n*-BuLi (16.68 mL, 1.6 M solution in hexane, 26.5 mmol) dropwise over 20 min and stirred for 30 min. Then the epoxide **71** (0.5 g, 4.37 mmol) in dry THF (5 mL) was added to the above reaction mixture and slowly allowed to warm to 0 °C over 1 h. The reaction mixture was then stirred at ambient temperature for 2 h. After consumption of the starting material the reaction

mixture was quenched with $H_2O$ (10 mL) and extracted with EtOAc (4 × 10 mL). The combined extracts were washed with brine, dried over $Na_2SO_4$ and concentrated. The column chromatography of crude product using pet ether:ethyl acetate (70:30) gave **65** as a colorless liquid.

**Yield:** 0. 45 g, 80%

**Mol. Formula**: $C_7H_{14}O$

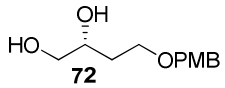
$[\alpha]_D^{25}$: +9.5 (*c* 1.4, pentane).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3485, 1613, 1586.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 5.88-5.71 (m, 1H), 5.19-4.99 (m, 2H), 4.08-3.96 (m, 1H), 2.34 (s, 1H), 1.48-1.22 (m, 6H), 0.88-0.81 (m, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 141.3, 114.2, 73.0, 36.6, 27.4, 22.5, 13.8.

**HRMS** ($ESI^+$) m/z calcd for $C_7H_{14}O$ $[M + Na]^+$ 137.0942, found 137.0945.




**72**

**(*R*)-4-(4-Methoxybenzyloxy)butane-1,2-diol (72):** Compound **72** was prepared from compound **69** using L-proline as catalyst following the procedure as described for **70** (colorless liquid).

**Yield:** 0. 9 g, 83%

**Mol. Formula**: $C_{12}H_{18}O_4$

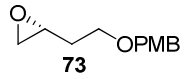
$[\alpha]_D^{25}$: −1.03 (*c* 1.0, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3384, 2934, 1613, 1514, 1249.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.27-7.20 (m, 2H), 6.90-6.84 (m, 2H), 4.44 (s, 2H), 3.93-3.82 (m, 1H), 3.79 (s, 3H), 3.69-342 (m, 4H), 1.89-1.62 (m, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 159.3, 129.8, 129.4, 113.8, 72.9, 71.3, 67.8, 66.5, 55.23, 32.7.

**HRMS** ($ESI^+$) m/z calcd for $C_{12}H_{18}O_4$ $[M + Na]^+$249.1103, found 249.1106.




**73**

**(*R*)-2-(2-(4-Methoxybenzyloxy)ethyl)oxirane (73):** Compound **73** was prepared following the procedure as described for **71** (colorless liquid).

**Yield:** 0. 16 g, 83%

**Mol. Formula**: $C_{12}H_{16}O_3$

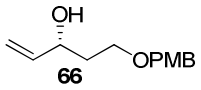
$[\alpha]_D^{25}$: +13.82 (*c* 1.0, $CHCl_3$), lit.[67] $[\alpha]_D^{25}$ +12.0 (*c* 1.0, $CHCl_3$)

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 2997, 2924, 2860, 1613, 1513.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.29-7.24 (m,2H), 6.91-6.85 (m, 2H), 4.47 (s, 2H), 3.81 (s, 3H), 3.63-3.57 (m, 2H), 3.11-3.02 (m, 1H), 2.81-2.76 (m, 1H), 2.54-2.50 (m, 1H), 1.99-1.71 (m, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 158.7, 128.8, 128.5, 112.3, 73.3, 67.5, 55.5, 50.1, 47.3, 33.8.

**HRMS** ($ESI^+$) m/z calcd for $C_{12}H_{16}O_3$ $[M + Na]^+$231.0997, found 231.0993.




**66**

**(*R*)-5-(4-Methoxybenzyloxy)pent-1-en-3-ol (66):** Compound **66** was prepared following the procedure as described for **65** (colorless liquid).

**Yield:** 0. 4 g, 75%

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

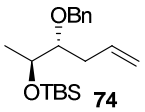
$[\alpha]_D^{25}$: – 10.0 (*c* 1.4, $CHCl_3$), lit.[69] $[\alpha]_D^{19}$: – 9.2 (*c* 1.0, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3414, 1613, 1586.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.31-7.24 (m, 2H), 6.93-6.86 (m, 2H), 5.97-5.80 (m, 1H), 5.33-5.08 (m, 2H), 4.46 (s, 2H), 3.82 (s, 3H), 3.76-3.57 (m, 2H), 2.99 (s. 1H), 1.94-1.79 (m, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 159.1, 140.5, 129.9, 129.2, 114.2, 113.7, 72.8, 71.7, 67.8, 55.1, 36.1.

**HRMS** ($ESI^+$) m/z calcd for $C_{13}H_{18}O_3$ $[M + Na]^+$245.1154, found 245.1158.



**74**

**(((2*S*, 3*R*)-3-(Benzyloxy)hex-5-en-2-yl)oxy)(*tert*-butyl)dimethylsilane (74):** To the known homoallylic alcohol **41** (2 g, 8.67 mmol) in DMF (7.5 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 0.38 g, 9.54 mmol). After 15 min, benzyl bromide (1.63 g, 1.13 mL, 9.54 mmol) was introduced and the reaction mixture further stirred for 2 h at room temperature. Water was carefully added to the reaction mixture, extracted with diethyl ether, washed with water and dried ($Na_2SO_4$). Silica gel column chromatography of the crude product using petroleum ether/EtOAc (95:5) as eluent afforded benzyl protected compound **74**.

**Yield:** 2.69 g, 97%

**Mol. Formula**: $C_{19}H_{32}O_2Si$

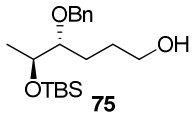
$[\alpha]_D^{25}$: +10.16 (*c* 0.9, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 2933, 2867, 1613, 1514, 1464, 1248, 1039, 920, 885.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.30-7.19 (m, 5H), 5.92-5.75 (m, 1H), 5.08-4.93 (m, 2H), 4.64-4.45 (m, 2H), 3.92-3.61 (m, 1H), 3.31-3.21 (m, 1H), 2.25 (t, *J*=6.53 Hz, 2H), 1.13 (d, *J*=6.42 Hz, 3H), 0.83-0.80 (m, 9H), -0.01-0.06 (m, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 138.9, 135.6, 128.2, 127.8, 127.3, 116.6, 83.6, 72.7, 70.4, 35.7, 33.7, 25.9, 19.3, -4.3, -4.7.

**HRMS** ($ESI^+$) m/z calcd for $C_{19}H_{33}O_2Si$ $[M + H]^+$ 321.2250, found 321.2254.




**75**

**(4*R*, 5*S*)-4-(Benzyloxy)-5-((*tert*-butyldimethylsilyl) oxy) hexan-1-ol (75):** A solution of olefin **74** (2.5 g, 7.8 mmol ) in dry THF (30 mL) was treated under $N_2$ with $BH_3$.DMS (0.75 mL, 7.8 mmol, d=0.8 g/ml ). The reaction mixture was stirred for 4 h at room temperature and then quenched by addition of MeOH (25 mL), 6 M aqueous NaOH (9 mL), and 30% $H_2O_2$ (15 mL) and stirred for additional 12 h. The resulting mixture was then stirred for 1 h and worked up (extraction with EtOAc). Column chromatography on silica gel (petroleum ether : EtOAc, 90 : 10) afforded **75** as a light yellow colored oil.

**Yield:** 2.5 g, 95%

**Mol. Formula**: $C_{19}H_{34}O_3Si$

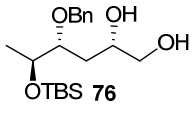
$[\alpha]_D^{25}$: +9.31 (*c* 0.9, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3377, 3019, 2400, 1501, 1427, 1230, 1070, 993, 857, 725.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.27-7.18 (m, 5H), 4.73-4.37 (m, 2H), 4.01-3.73 (m, 1H), 3.63-3.47 (m, 2H), 3.35-3.15 (m, 1H), 1.61-1.50 (m, 4H), 1.11 (d, *J*=6.19 Hz, 3H), 0.81-0.79 (m, 9H), -0.01-0.07 (m, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 138.7, 128.3, 127.9, 127.5, 83.8, 72.9, 70.8, 63.0, 29.6, 29.0, 27.4, 25.8, 19.2, -4.3, -4.7.

**HRMS** ($ESI^+$) m/z calcd for $C_{19}H_{35}O_3Si$ $[M + H]^+$ 339.2355, found 339.2354.




**76**

**(2*S*, 4*R*, 5*S*)-4-(Benzyloxy)-5-((*tert*-butyldimethylsilyl)oxy)hexane-1,2-diol (76):** To a solution of **75** (2 g, 5.9 mmol ) in 10 mL EtOAc was added IBX (4.6 g, 17.7 mmol ) and it was heated to 80 °C for 3 h. It was cooled to rt and filtered through a pad of Celite. The filtrate was concentrated and the crude aldehyde was used for the next step without purification. To a stirred solution of above aldehyde (1.5 g, 4.45

mmol) and nitrosobenzene (0.48 g, 4.45 mmol) in DMSO (4 mL) was added D-proline (0.1 g, 0.89 mmol, 20 mol %) in one portion at 25 °C. After 1 h, the temperature was lowered to 0 $^{o}$C, followed by dilution with anhyd. MeOH (5 mL) and careful addition of excess $NaBH_4$ (0.6 g, 15.6 mmol). The reaction was quenched after 10 min by sat. $NH_4Cl$. The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phase was dried over anhyd $Na_2SO_4$, concentrated, and purified by column chromatography over silica gel using EtOAc/Pet. Ether (40:60) as eluent to give pure aminoxy alcohol (1.5 g, 80%). The aminoxy alcohol (1.5 g, 3.5 mmol) was dissolved in MeOH (10 mL) and to the solution was added 3% copper sulfate and the reaction mixture was stirred for 12 h. After completion of the reaction (monitored by TLC) it was quenched with sat. $NH_4Cl$. The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phase was dried over anhyd $Na_2SO_4$, concentrated, and purified by silica gel chromatography using EtOAc/Pet. Ether (50:50) as eluent to give pure diol **76** as a colorless liquid.

**Yield:** 0.66 g, 80%

**Mol. Formula**: $C_{19}H_{34}O_4Si$

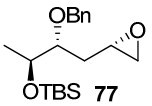
$[\alpha]_D^{25}$: +41.86 (*c* 0.2, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3412, 3020, 2978, 1652, 1534, 1248, 1237.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.31-7.19 (m, 5H), 4.77-4.41 (m, 2H), 3.99-3.78 (m, 3H), 3.56-3.47 (m, 2H), 3.41-3.29 (m, 1H), 1.58-1.54 (m, 2H), 1.10-1.07 (m, 3H), 0.82-0.81 (m, 9H), -0.01 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 138.0, 128.5, 127.9, 83.0, 72.4, 70.5, 70.1, 66.8, 33.0, 29.6, 25.8, 18.9, -4.8.

**HRMS** ($ESI^+$) m/z calcd for $C_{19}H_{35}O_4Si$ $[M + H]^+$ 355.2305, found 355.2301.



77

**(((2*S*, 3*R*)-3-(Benzyloxy)-4-((*S*)-oxiran-2-yl)butan-2-yl)oxy)(*tert*-butyl)dimethylsilane (77):** Compound **77** was prepared following the procedure as described for **71** (colorless liquid).

**Yield:** 0.18 g, 90%

**Mol. Formula**: $C_{19}H_{32}O_3Si$

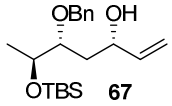
$[\alpha]_D^{25}$: +12.8 (*c* 0.5, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 2930, 2856, 1620, 1600, 1557, 1501, 1310.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.30-7.21 (m, 5H), 4.74-4.45 (m, 2H), 3.87-3.79 (m, 1H), 3.51-3.30 (m, 1H), 3.05-2.95 (m, 1H), 2.73-2.61 (m, 1H), 2.44-2.35 (m, 1H), 1.92-1.37 (m, 2H), 1.10 (t, *J*=6.22 Hz, 3H), 0.81-0.79 (m, 9H), -0.02-0.04 (m, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 138.8, 135.6, 128.3, 127.8, 127.5, 81.7, 73.1, 70.5, 50.1, 47.8, 34.5, 34.0, 25.8, 19.2, -4.4, -4.7.

**HRMS** ($ESI^+$) m/z calcd for $C_{19}H_{33}O_3Si$ [M + H] 337.2199, found 337.2196.



**67**

**(3*S*, 5*R*, 6*S*)-5-(Benzyloxy)-6-((*tert*-butyldimethylsilyl)oxy)hept-1-en-3-ol (67):** Compound **67** was prepared following the procedure as described for **65** (colorless liquid).

**Yield:** 0.41 g, 80%

**Mol. Formula**: $C_{20}H_{33}O_3Si$

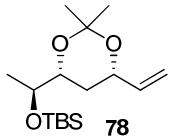
$[\alpha]_D^{25}$: +26.42 (*c* 1.1, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3290, 3032, 2430, 1652, 1561, 1504, 1215, 1012, 901, 876.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.27-7.16 (m, 5H), 5.83-5.67 (m, 1H), 5.21-4.96 (m, 2H), 4.77-4.41 (m, 2H), 4.25-4.18 (m, 1H), 3.93-3.77 (m, 1H), 3.56-3.46 (m, 1H), 1.74-1.59 (m, 2H), 1.09 (d, *J*=6.42 Hz, 3H), 0.83-0.82 (m, 9H), -0.01 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 140.8, 138.2, 128.4, 127.9, 127.7, 114.2, 83.2, 72.5, 71.3, 76.6, 40.1, 37.5, 25.7, 18.9, -4.6, -4.7.

**HRMS** ($ESI^+$) m/z calcd for $C_{20}H_{34}O_3Si$ $[M + H]^+$ 351.2355, found 351.2350.




78

***tert*-Butyl((*S*)-1-((4*R*, 6*S*)-2,2-dimethyl-6-vinyl-1,3-dioxan-4-yl)ethoxy)dimethylsilane (78):** To a dark blue solution of sodium-ammonia prepared from excess sodium and liquid ammonia (30 ml) was added a solution of **67** (0.05 g, 0.14 mmol) in THF (5 ml) at -78 °C. The solution was warmed to -50 °C and was stirred for 1 h. The reaction was quenched with ammonium chloride. The cooling bath was removed, and after all ammonia was evaporated, the mixture was diluted with water and the aqueous layer extracted with EtOAc. The extract was washed with water, and was concentrated under reduced pressure.

To a solution of this compound in DCM (5 mL) at 25 °C was added 2-methoxy-propene (40 μL, 0.42 mmol), followed by PPTS (2.5 mg, 10 μmol) portionwise. The reaction mixture was stirred at 25 °C for 15 min, then quenched with solid $NaHCO_3$ and stirred for 30 min. The reaction mixture was filtered through a pad of celite and concentrated. Silica gel column chromatography using petroleum ether:ethyl acetate (24:1) gave **78** as a colorless liquid.

**Yield:** 0.036 g, 85%

**Mol. Formula**: $C_{16}H_{32}O_3Si$

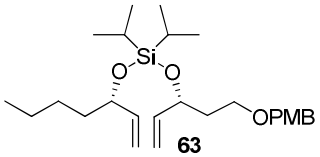
$[\alpha]_D^{25}$: +11.50 (*c* 0.5, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 2901, 2823, 1580, 1545, 1309, 745.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 5.92-5.79 (m, 1H), 5.27-5.18 (m, 1H), 5.13-5.04 (m, 1H), 4.39-4.18 (m, 1H), 3.98-3.70 (m, 1H), 3.64-3.55 (m, 1H), 1.92-1.64 (m, 2H), 1.57 (s, 6H), 1.15-1.11 (m, 3H), 0.88-0.86 (m, 9H), 0.05 (m, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 139.0, 115.3, 114.2, 98.5, 73.4, 71.3, 70.2, 32.7, 30.1, 29.7, 25.8, 19.9, -4.4, -4.6.

**HRMS** ($ESI^+$) m/z calcd for $C_{16}H_{33}O_3Si$ $[M + H]^+$ 301.2199, found 303.2197.




63

**((5*R*, 9*S*)-7, 7-Diisopropyl-1-(4-methoxyphenyl)-5,9-divinyl-2,6,8-trioxa-7-silatridecane (63):** Dichlorodiisopropylsilane (0.085 ml, 0.48 mmol) was added to imidazole (0.089 g, 1.31 mmol) in DCM (0.24 ml) at 0 ºC. The solution was stirred for 5 minutes, then the fragment **65** (0.05 g, 0.437 mmol) in DCM (0.18 ml) was added dropwise over 1 h period at 0 ºC. After the mixture was stirred for 15 minutes at 0 ºC, a solution of the fragment **66** (0.097 g, 0.437 mmol) in DCM (0.035 mL) was added at 0 ºC. The reaction mixture was warmed to the room temperature and stirred for 14 h. The reaction mixture was filtered and washed with hexane, then concentrated in vacuo to afford the crude oil, which was purified by flash chromatography on silica gel (pet ether:ethyl acetate = 95:5) to afford bis-alkoxysilane **63** as a colorless oil.

**Yield:** 0.196 g, 87%

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

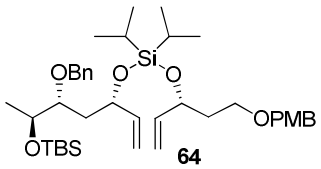
$[\alpha]_D^{25}$: – 1.98 (*c* 1.3, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 2933, 2867, 1613, 1514, 1464, 1248, 1089, 1039, 920, 885.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.31-7.24 (m, 2H), 6.92-6.85 (m, 2H), 5.95-5.74 (m, 2H), 5.23-5.01 (m, 4H), 4.55-4.24 (m, 4H), 3.82 (s, 3H), 3.63-3.44 (m, 2H), 2.02-1.76 (m, 2H), 1.35-1.23 (m, 7H), 1.05-1.04 (m, 12H), 0.97-0.93 (m, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 159.0, 141.4, 141.1, 129.4, 129.2, 113.9, 113.7, 113.7, 73.6, 72.6, 70.9, 66.4, 55.3, 38.0, 37.7, 22.8, 22.6, 17.4, 17.2, 14.3.

**HRMS** ($ESI^+$) m/z calcd for $C_{26}H_{44}O_4Si$ $[M + Na]^+$471.2907, found 471.2907.




64

**(5*R*, 9*S*, 11*R*, 12*S*)-11-(Benzyloxy)-7,7-diisopropyl-1-(4-methoxyphenyl)-12,14,14,15,15-pentamethyl-5,9-divinyl-2,6,8,13-tetraoxa-7,14-disilahexadecane (64):** Dichlorodiisopropylsilane (0.028 ml, 0.15 mmol) was added to imidazole (0.029 g, 1.31 mmol) in DCM (0.13 ml) at 0 ºC. The solution was stirred for 5 minutes, then the fragment **67** (0.05 g, 0.142 mmol) in DCM (0.1 ml) was added dropwise over 1 h period at 0 ºC. After the mixture was stirred for 15 minutes at 0 ºC, a solution of the fragment **66** (0.031 g, 0.142 mmol) in DCM (0.1 ml) was added at 0 ºC. The reaction mixture was warmed to the room temperature and stirred for 14 h. The reaction mixture was filtered and washed with hexane, then concentrated in vacuo to afford the crude oil, which was purified by flash chromatography on silica gel (pet ether:ethyl acetate = 95:5) to afford bis-alkoxysilane **64** as a colorless oil.

**Yield:** 0.084 g, 87%

**Mol. Formula**: $C_{39}H_{64}O_6Si_2$

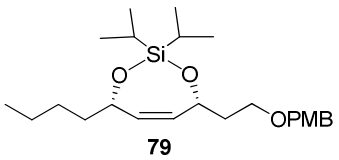
$[\alpha]_D^{25}$: +26.86 (*c* 0.2, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 2935, 2856, 1713, 1600, 1504, 1265, 1065, 1071, 920, 885.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.27-7.15 (m, 7H), 6.82-6.77 (m, 2H), 5.84-5.62 (m, 2H), 5.12-4.91 (m. 4H), 4.48-4.19 (m, 6H), 4.03-3.79 (m, 1H), 3.73 (s, 3H), 3.66-3.26 (m, 3H), 1.68-1.66 (m, 4H), 1.53-1.33 (m, 2H), 1.07 (d, *J*=6.31 Hz, 3H), 0.95-0.94 (m, 12H), 0.83 (s, 9H), -0.02 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 159.0, 140.9, 139.3, 139.1, 130.8, 129.1, 128.2, 127.6, 127.3, 127.2, 114.6, 113.7, 81.6, 72.9, 72.7, 71.6, 71.2, 70.6, 55.2, 39.9, 26.0, 25.8, 18.0, 17.4, 17.3, -4.6, -4.7.

**HRMS** ($ESI^+$) m/z calcd for $C_{39}H_{64}O_6Si_2$ $[M + Na]^+$707.4139, found 707.4139.




**79**

**(4*S*, 7*R*)-4-Butyl-2,2-diisopropyl-7-(2-(4-methoxybenzyloxy)ethyl)-4,7-dihydro-1,3,2-dioxasilepine (79):** A solution of 0.1 g (0.22 mmol) **63** in 50 mL toluene was degassed (for 5 minutes using argon), then 0.006 g (0.006 mmol) Grubbs-II catalyst **A** were added and the solution was degassed again. It was stirred at 80 $^{o}$C for 18 h, before the solvent was removed in vacuo and the residue was purified by flash chromatography (pet ether:ethyl acetate = 95:5) to give cyclized product **79**.

**Yield:** 0.082 g, 88%

**Mol. Formula**: $C_{24}H_{40}O_4Si$

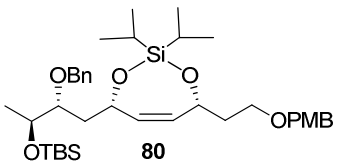
$[\alpha]_D^{25}$: + 3.00 (*c* 0.65, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 2929, 2865, 1612, 1513, 1465, 1248, 1092, 884.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.23-7.21 (m, 2H), 6.91-6.88 (m, 2H), 5.86-5.39 (m, 2H), 4.88-4.48 (m, 2H), 3.79 (s, 3H) 3.75-3.43 (m, 4H), 1.40-1.29 (m, 10H), 1.03 (s, 12 H), 0.89-0.87 (m, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 159.1, 135.5, 134.8, 133.9, 129.32, 113.7, 72.8, 71.0, 67.9, 66.7, 55.3, 38.6, 38.3, 22.6, 22.5, 17.6, 17.2, 14.1.

**HRMS** ($ESI^+$) m/z calcd for $C_{24}H_{41}O_4Si$ $[M + H]^+$421.2774, found 421.2775.




**80**

**(4*S*, 7*R*)-4-((2*R*, 3*S*)-2-(Benzyloxy)-3-((tert-butyldimethylsilyl)oxy)butyl)-2,2-diisopropyl-7-(2-((4-methoxybenzyl)oxy)ethyl)-4,7-dihydro-1,3,2-dioxasilepine (82):** A solution of 0.075 g (0.109 mmol) **64** in 18 mL toluene was degassed (for 5 minutes using argon), then 2 mg (3.28 μmol) Hoveyda–Grubbs second-generation catalyst **B** were added and the solution was degassed again. It was stirred at 80 $^{o}$C for

18 h, before the solvent was removed in vacuo and the residue was purified by flash chromatography (pet ether:ethyl acetate = 90:10) to give cyclized product **80**.

**Yield:** 0.054 g, 75%

**Mol. Formula**: $C_{37}H_{59}O_6Si_2$

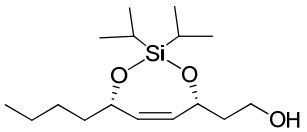
$[\alpha]_D^{25}$: 27.98 (*c* 0.8, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 2931, 2901, 2301, 1800, 1654, 1466, 885, 847, 770, 681.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.27-7.18 (m, 7H), 6.83-6.78 (m, 2H), 5.60-4.63 (m, 2H), 4.61-4.36 (m, 4H), 4.16-3.97 (m, 1H), 3.87-3.78 (m, 1H), 3.73 (s, 3H), 3.65-3.35 (m, 3H), 2.36-1.46 (m, 7H), 1.11 (d, *J*=6.19 Hz, 3H), 0.98-0.94 (m, 12H), 0.83 (s, 9H), -0.01 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 159.2, 138.7, 129.4, 128.2, 128.0, 127.8, 127.5, 113.7, 80.9, 72.9, 72.7, 71.0, 68.5, 67.9, 64.9, 55.2, 39.1, 39.0, 30.2, 25.8, 18.0, 17.2, 16.9, -4.5, -4.6.

**HRMS** ($ESI^+$) m/z calcd for $C_{37}H_{60}O_6Si_2$ $[M + H]^+$657.4007, found 657.4007.




**81**

**2-((4*R*, 7*S*)-7-Butyl-2,2-diisopropyl-4,7-dihydro-1,3,2-dioxasilepin-4-yl)ethanol (81):** To a stirring solution of PMB ether **79** (0.070 g, 0.164 mmol) in DCM/$H_2O$ (0.5:0.03) was added DDQ (0.046 g, 0.199 mmol). The resulting mixture was stirred for 10 min at r.t. The mixture was poured into saturated aqueous $NaHCO_3$ and further diluted with DCM. The layers were separated and the aqueous layer was extracted with DCM (2 x 10 mL). The combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated. The solvents were removed under reduced pressure to give the crude product mixture as yellow oil. Silica gel column chromatography of the crude product using pet ether:ethyl acetate (80:20) as eluent gave **81**.

**Yield:** 0.046 g, 93%

**Mol. Formula**: $C_{16}H_{32}O_3Si$

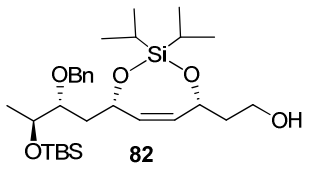
$[\alpha]_D^{25}$: – 6.18 (*c* 1.0, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3456, 2929, 2865, 1665, 1465, 1248, 1092, 884.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 5.68-5.45 (m, 2H), 3.89-3.83 (m, 2H), 3.66-3.62 (m, 2H), 1.35-1.29 (m, 10H), 0.92-0.80 (m, 15H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 135.2, 132.8, 71.8, 71.0, 61.3, 39.1, 37.7, 22.7, 22.6, 19.8, 17.2, 14.1.

**HRMS** ($ESI^+$) m/z calcd for $C_{16}H_{32}O_3Si$ $[M + Na]^+$323.2018, found 323.2018.




**82**

**2-((4*R*, 7*S*)-7-((2*R*, 3*S*)-2-(Benzyloxy)-3-((tert-butyldimethylsilyl)oxy)butyl)-2,2-diisopropyl-4,7-dihydro-1,3,2-dioxasilepin-4-yl)ethanol (82):** To a stirring solution of PMB ether **80** (0.050 g, 0.076 mmol) in DCM/$H_2O$ (0.2:0.012) was added DDQ (0.020 g, 0.091 mmol). The resulting mixture was stirred for 10 min at r.t. The mixture was poured into saturated aqueous $NaHCO_3$ and further diluted with DCM. The layers were separated and the aqueous layer was extracted with DCM (2 x 10 mL). The combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated. The solvents were removed under reduced pressure to give the crude product mixture as yellow oil. Silica gel column chromatography of the crude product using pet ether:ethyl acetate (80:20) as eluent gave **82**.

**Yield:** 0.037 g, 92%

**Mol. Formula**: $C_{29}H_{52}O_5Si_2$

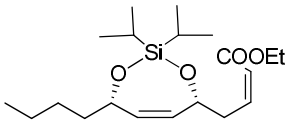
$[\alpha]_D^{25}$: 12.43 (*c* 0.8, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3440, 2967, 2861, 1609, 1582, 1513, 1445, 1348, 1092, 889.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.33-7.25 (m, 5H), 5.70-5.46 (m, 2H), 5.00-4.82 (m, 2H), 4.78-4.63 (m, 1H), 4.60-4.45 (m, 1H), 3.94-3.83 (m, 3H), 3.76-3.40 (m, 1H), 1.96-1.58 (m, 6H), 1.18-1.15 (m, 3H), 1.06-.0.99 (m, 12H), 0.89 (s, 9H), 0.06-0.01 (m, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 138.9, 135.7, 135.4, 134.9, 128.2, 127.8, 80.5, 73.3, 72.5, 69.3, 68.4, 61.3, 39.4, 39.2, 29.7, 25.8, 18.5, 17.4, 17.1, -4.5, -4.7.

**HRMS** ($ESI^+$) m/z calcd for $C_{29}H_{52}O_5Si_2$ $[M + Na]^+$559.3251, found 559.3252.




**83**

**(*Z*)-Ethyl 4-((4*R*, 7*S*)-7-butyl-2,2-diisopropyl-4,7-dihydro-1,3,2-dioxasilepin-4-yl)but-2-enoate (83):** Dess–Martin periodinane (0.046 g, 0.109 mmol) was added to a solution of compound **81** (0.030 g, 0.099 mmol) and pyridine ( 0.04 ml, 0.49 mmol) in DCM (0.8 ml) at 0 $^oC$. The reaction was stirred at rt for 30 min, before being quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. The organic layer was washed with satd NaCl solution and dried over $Na_2SO_4$ and concentrated to afford an aldehyde that was used immediately in the next step without further purification.

To a solution of $(PhO)_2P(O)CH_2COOEt$ (0.043 g, 0.108 mmol) in THF (0.6 mL) at 0°C was added NaI (0.012 g, 0.084 mmol). After 5 min NaH (60% dispersion, 0.002 g, 0.108 mmol) was added, and the resulting solution was cooled to −78 $^oC$. The aldehyde (0.026 g, 0.084 mmol) dissolved in 0.6 mL of THF was then added drop wise. After 2 h at −78 $^oC$, saturated $NH_4Cl$ (0.7 mL) was added and the reaction mixture was extracted with $Et_2O$ (3×5 mL). The combined organic extracts were dried ($Na_2SO_4$) and concentrated. The crude product was purified by flash chromatography using pet ether:ethyl acetate (85:15) as eluent to give **83**.

**Yield:** 0.033 g, 90%

**Mol. Formula**: $C_{20}H_{36}O_4Si$

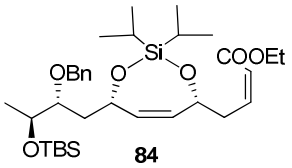
$[\alpha]_D^{25}$: – 7.60 (*c* 0.3, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 2930, 2861, 1723, 1650, 1610, 1512, 1460, 1241, 1092, 885.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 6.46-6.39 (m, 1H) 5.87-5.84 (m, 1H), 5.66-5.58 (m, 1H), 5.51-5.44 (m, 1H), 4.82-4.54 (m, 2H), 4.18-4.14 (m, 2H), 3.08-2.99 (m, 1H), 2.90-2.80 (m, 1H), 1.32-1.26 (m, 1H), 1.03-0.98 (m, 12H), 0.90-0.88 (m, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 166.5, 146.5, 135.1, 132.9, 120.9, 71.1, 70.2, 59.9, 38.3, 37.3, 22.7, 22.5, 17.6, 17.1, 14.3, 14.1.

**HRMS** ($ESI^+$) m/z calcd for $C_{20}H_{37}O_4Si$ $[M + H]^+$369.2461, found 369.2464.




**84**

**(*Z*)-Ethyl 4-((4*R*, 7*S*)-7-((2*R*, 3*S*)-2-(benzyloxy)-3-((tert-butyldimethylsilyl)oxy)butyl)-2,2-diisopropyl-4,7-dihydro-1,3,2-dioxasilepin-4-yl)but-2-enoate (84):** Dess–Martin periodinane (0.026 g, 0.061 mmol) was added to a solution of compound **82** (0.030 g, 0.055 mmol) and pyridine ( 22 µl, 0.3 mmol) in DCM (0.5 ml) at 0 $^oC$. The reaction was stirred at rt for 30 min, before being quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. The organic layer was washed with satd NaCl solution and dried over $Na_2SO_4$ and concentrated to afford an aldehyde that was used immediately in the next step without further purification.

To a solution of $(PhO)_2P(O)CH_2COOEt$ (0.026 g, 0.07 mmol) in THF (0.3 mL) at 0°C was added NaI (8 mg, 0.054 mmol). After 5 min NaH (60% dispersion, 0.003 g, 0.07 mmol) was added, and the resulting solution was cooled to −78 $^oC$. The aldehyde (0.029 g, 0.054 mmol) dissolved in 0.3 mL of THF was then added drop wise. After 2 h at −78 $^oC$, saturated $NH_4Cl$ (0.7 mL) was added and the reaction mixture was extracted with $Et_2O$ (3×5 mL). The combined organic extracts were dried ($Na_2SO_4$) and concentrated. The crude product was purified by flash chromatography using pet ether:ethyl acetate (85:15) as eluent to give **84**.

**Yield:** 0.030 g, 93%

**Mol. Formula**: $C_{20}H_{36}O_4Si$

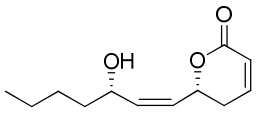
$[\alpha]_D^{25}$: 18.06 (*c* 0.6, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 2932, 2867, 1742, 1705, 1670, 1620, 1422, 1302, 1274, 1101, 965, 889, 773.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.33-7.25 (m, 5H), 6.46-6.36 (m, 1H), 5.86 (d, *J*=11.76 Hz, 1H), 5.67-5.48 (m, 2H), 4.92-4.46 (m, 5H), 4.16 (q, *J*=7.15 Hz, 2H), 3.94-3.83 (m, 1H), 1.79-1.57 (m, 4H), 1.27-1.24 (m, 5H), 1.18-1.15 (m, 3H), 1.02-.098 (m, 12H), 0.88 (s, 9H), 0.06 (m, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 166.4, 146.3, 139.0, 128.2, 127.8, 127.7, 127.4, 121.0, 80.5, 72.5, 70.2, 68.4, 59.8, 40.8, 37.5, 29.7, 25.8, 19.1, 17.4, 17.2, 14.3, -4.5, -4.7.

**HRMS** ($ESI^+$) m/z calcd for $C_{33}H_{56}O_6Si_2$ $[M + H]^+$605.3694, found 605.3696.




desacetylumuravumbolide (**8a**)

**Desacetylumuravumbolide (8a):** To a stirred solution of compound **83** (25 mg, 67.8 μmol) in THF (0.6 mL) was added TBAF (40 μL, 0.13 mmol) at room temperature and the yellow solution was stirred overnight at the same temperature. Water was added and the organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried with $Na_2SO_4$ and concentrated to give crude triol, which was used for the next step without purification.

The diol was dissolved in benzene (0.4 mL) and $Ti(OiPr)_4$ (2 μL, 6 μmol) was added. The yellow solution was refluxed for 1 h. The solution was cooled to RT and the solvent was removed in vacuo. The residue was purified by flash chromatography (100 g silica gel, DCM/MeOH, 98:2) to yield lactone **8a** as a colorless oil.

**Yield:** 16 mg, 92%

**Mol. Formula**: $C_{12}H_{18}O_3$

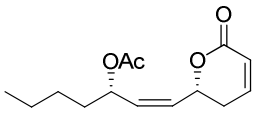
$[\alpha]_D^{25}$: $[\alpha]_D^{25} = -2.3$ (*c* 0.5, $CHCl_3$), lit.[29] $[\alpha]_D^{25} - 5.3$ (*c* 1.3, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3456, 1720, 1685, 1644, 1390, 1060.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 6.89-6.87 (m, 1H), 6.00-5.97 (m, 1H), 5.78-5.65 (m, 1H), 4.62-4.34 (m, 1H), 2.41-2.19 (m. 2H), 1.56-1.47 (m, 2H), 1.45-1.26 (m, 4H), 0.93 (m, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 164.1, 146.6, 135.8, 127.4, 123.1, 72.8, 67.2, 37.0, 29.9, 27.0, 23.1, 14.0.

**HRMS** ($ESI^+$) m/z calcd for $C_{12}H_{18}O_3$ $[M + Na]^+$ 233.1154, found 233.1155.




umuravumbolide (**8b**)

**Umuravumbolide (8b):** To a stirred solution of compound **8a** (15 mg, 0.071 mmol) in dry $CH_2Cl_2$ (1.5 mL) was added $Et_3N$ (0.023 mL, 0.171 mmol), acetic anhydride (0.008 mL, 0.085 mmol), DMAP (1.75 mg, 0.009 mmol) and the resulting mixture was stirred at room temperature for 1 h. After completion of the reaction, water was added, the organic layer was separated and the aqueous phase was extracted with $CH_2Cl_2$ (3x5 mL). The combined organic layers were washed with brine, dried over $Na_2SO_4$ and concentrated under reduced pressure. Purification by silica gel column chromatography (EtOAc/hexane, 2:8) afforded **8b** as a yellow oil.

**Yield:** 16.5 mg, 92%

**Mol. Formula**: $C_{14}H_{20}O_4$

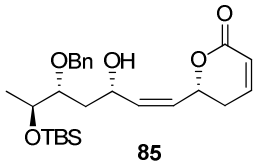
$[\alpha]_D^{25}$: + 15 (*c* 0.3, $CHCl_3$), lit.[29] $[\alpha]_D^{25}$ + 30 (*c* 2.1, $CDCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 1745, 1730, 1685, 1256.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 6.88-6.86 (m, 1H), 6.03-5.99 (m, 1H), 5.93-5.66 (m, 1H), 5.42-5.08 (m, 3H), 2.31-2.29 (m, 2H), 2.02 (s, 3H), 1.41-1.35 (m, 6H), 0.87 (m, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 169.7, 163.5, 146.4, 130.9, 130.5, 123.7, 72.8, 69.9, 34.5, 30.2, 28.9, 22.2, 21.9, 14.0.

**HRMS** ($ESI^+$) m/z calcd for $C_{14}H_{20}O_4$ $[M + Na]^+$ 275.1259, found 275.1258.




**85**

**(*R*)-6-((3*S*, 5*R*, 6*S*, *Z*)-5-(Benzyloxy)-3,6-dihydroxyhept-1-en-1-yl)-5,6-dihydro-2H-pyran-2-one (85):** To a stirred solution of compound **84** (25 mg, 40 μmol) in THF (0.6 mL) was added TBAF (85 μL, 0.293 mmol) at room temperature and the yellow solution was stirred overnight at the same temperature. Water was added and the organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried with $Na_2SO_4$ and concentrated to give crude triol, which was used for the next step without purification.

The diol was dissolved in benzene (0.2 mL) and $Ti(OiPr)_4$ (1.2 μL, 4 μmol) was added. The yellow solution was refluxed for 1 h. The solution was cooled to RT and the solvent was removed in vacuo. The residue was purified by flash chromatography (100 g silica gel, DCM/MeOH, 98:2) to yield lactone **85** as a colorless oil.

**Yield:** 12.6 mg, 96%

**Mol. Formula**: $C_{19}H_{24}O_5$

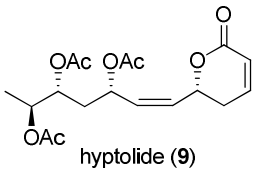
$[\alpha]_D^{25}$: – 1.7 (*c* 0.7, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3330, 2937, 1823, 1654, 1470, 1320, 1245, 1076, 872.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.30-7.23 (m, 5H), 6.40-6.31 (m, 1H), 5.80 (d, *J*=11.87 Hz, 1H), 5.62-5.43 (m, 2H), 4.87-4.54 (m, 3H), 3.88-3.79 (m, 1H), 1.74-1.52 (m, 4H), 1.13-1.10 (m, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 172.6, 144.2, 139.0, 130.7, 129.8, 128.5, 127.9, 127.7, 127.6, 126.7, 84.0, 70.3, 67.1, 66.6, 64.7, 41.6, 31.6, 22.4.

**HRMS** ($ESI^+$) m/z calcd for $C_{19}H_{24}O_5$ $[M + Na]^+$ 355.1521, found 355.1521.



hyptolide (**9**)

**Hyptolide (9):** To a solution of **85** (10 mg, 30 μmol) in anhydrous DCM (0.35 mL) under nitrogen at 0 °C was added $TiCl_4$ (28 mg, 16 μL, 0.15 mmol). After 20 min, excess of reagent was quenched with water, extracted with DCM, washed with water, dried ($Na_2SO_4$) and evaporated to afford the triol that was used immediately in the next step without further purification.

The triol was then dissolved in dry $CH_2Cl_2$ (0.12 mL) and treated with $Et_3N$ (33 μL, 0.24 mmol), acetic anhydride (20 μL, 0.2 mmol) and DMAP (1.4 mg, 12 μmol). After stirring overnight, the reaction mixture was worked up (extraction with DCM) and chromatographed on a silica gel column (pet ether:ethyl acetate = 70:30) to give hyptolide **9** as a colorless solid.

**Yield:** 7 mg, 90%

**Mol. Formula**: $C_{18}H_{24}O_8$

**MP** 83–86 °C, lit.[43] mp 87–88 °C

$[\alpha]_D^{25}$: +12.3 (*c* 0.7, $CHCl_3$), lit.[43] $[\alpha]_D^{25}$ +11.2 (*c* 0.6, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 1737, 1645, 1280.

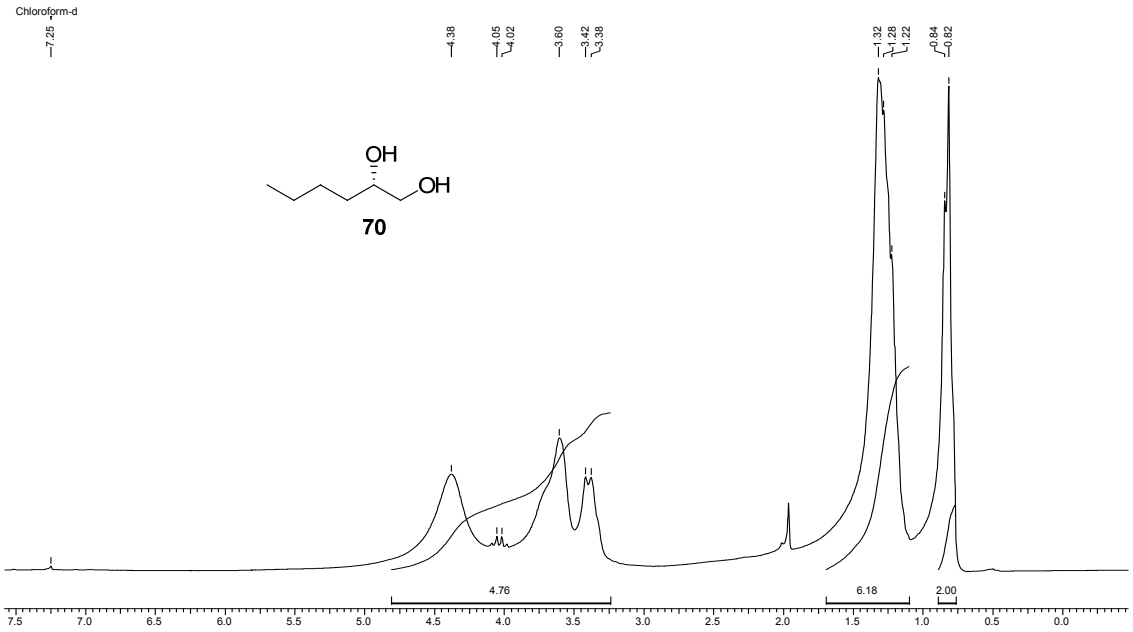
**$^1$H NMR** (400 MHz, $CDCl_3$): δ 6.86-6.84 (m, 1H), 6.09-6.03 (m, 1H), 5.73-5.71 (m, 1H), 5.52-5.50 (m, 2H), 5.11-5.07 (m, 1H), 5.03-4.80 (m, 2H), 2.36-2.33 (m, 2H), 2.04-2.02 (m, 10H), 1.81 (s, 1H), 1.15-1.11 (m, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 169.7, 169.0, 164.8, 139.2, 129.5, 126.5, 124.0, 72.8, 70.5, 69.9, 67.2, 61.5, 33.7, 22.6, 14.0.

**HRMS** ($ESI^+$) m/z calcd for $C_{18}H_{24}O_8$ $[M + Na]^+$ 511.2492, found 511.2495.

## 3.1.7. Spectra

| | | |
|---|---|---|
| 20 | $^{1}H$ and $^{13}C$ spectra of compound | **84** |
| 21 | $^{1}H$ and $^{13}C$ spectra of compound | **8a** |
| 22 | $^{1}H$ and $^{13}C$ spectra of compound | **85** |
| 23 | $^{1}H$ and $^{13}C$ spectra of compound | **8b** |
| 24 | $^{1}H$ and $^{13}C$ spectra of compound | **9** |
| 25 | $^{19}F$ spectra of compound | **66** |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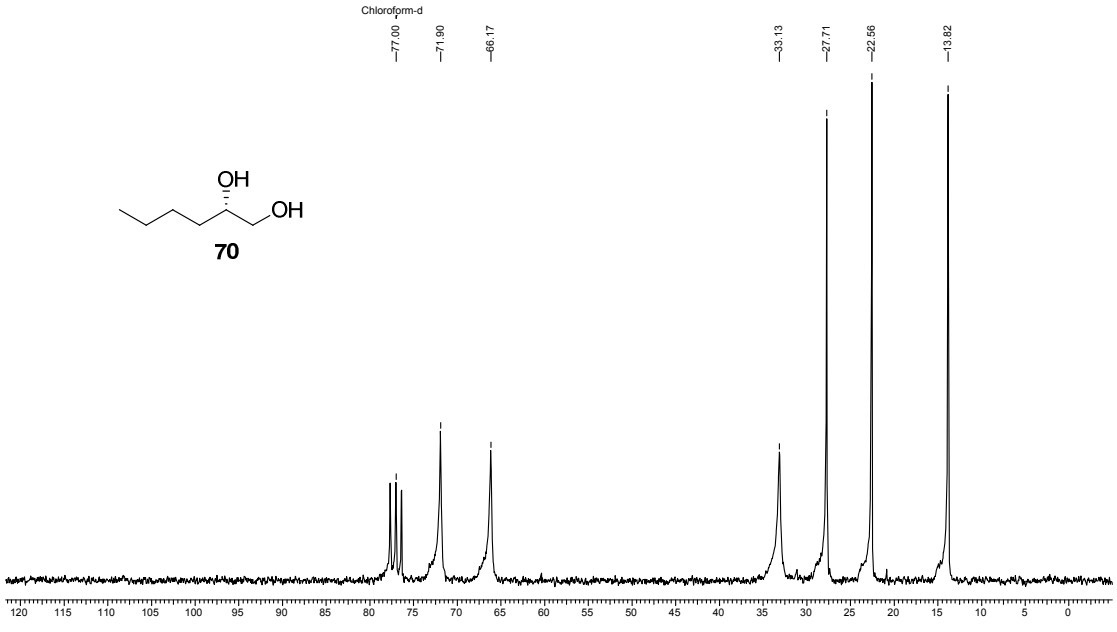
4.38
4.05
4.02
3.60
3.42
3.38
1.32
1.28
1.22
0.84
0.82
OH
OH
70
4.76
6.18
2.00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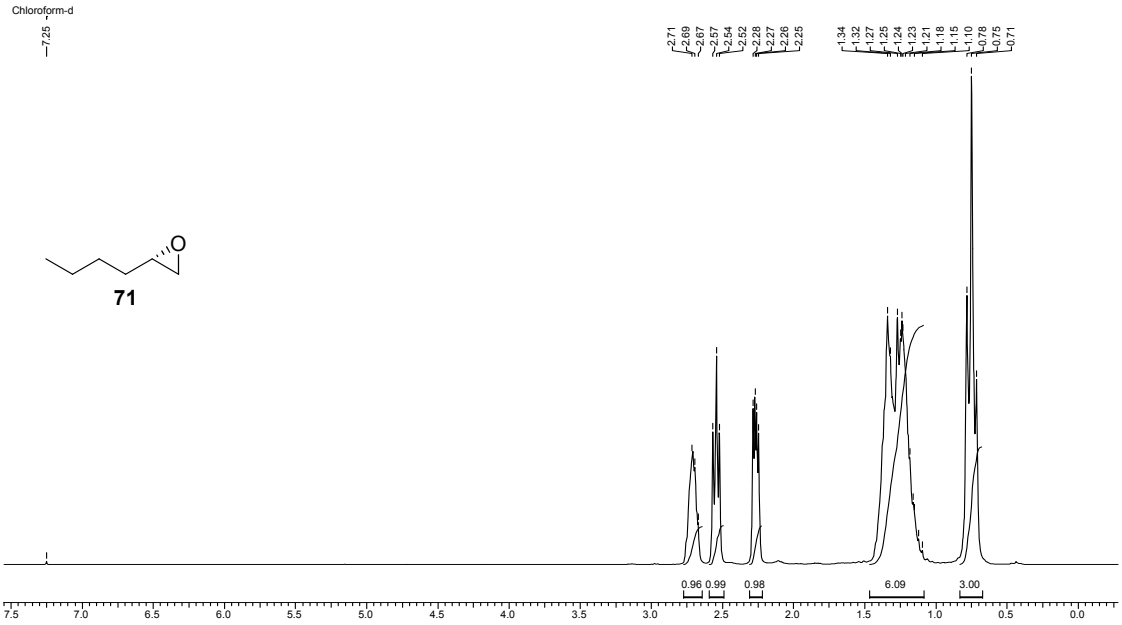
66.17
33.13
27.71
22.56
13.82
OH
OH
70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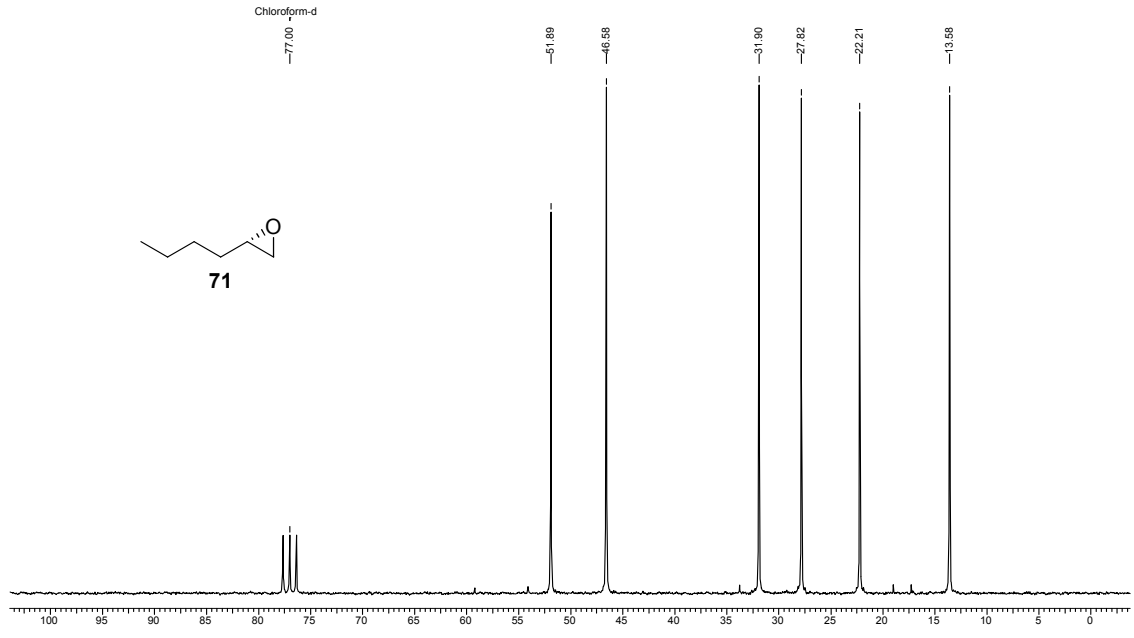
2.71
2.69
2.67
2.57
2.54
2.52
2.28
2.27
2.26
2.25
1.34
1.32
1.27
1.25
1.24
1.23
1.21
1.18
1.15
1.10
0.78
0.75
0.71
O
71
0.96
0.99
0.98
6.09
3.00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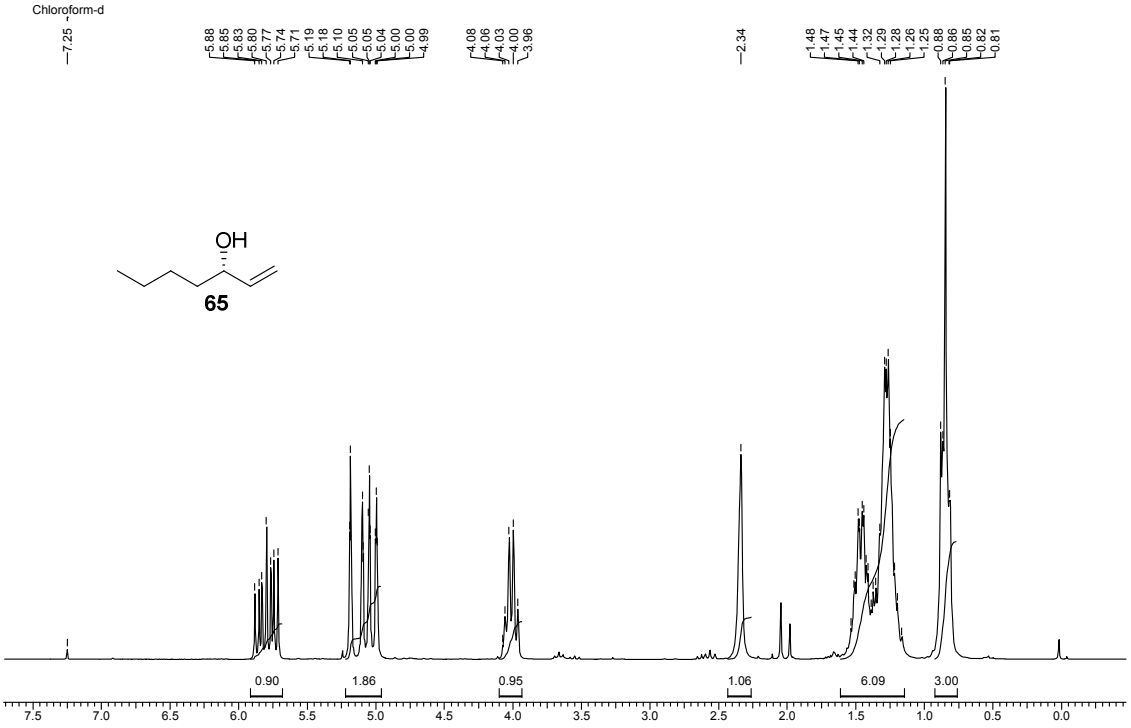
46.58
31.90
27.82
22.21
13.58
O
71


Chloroform-d
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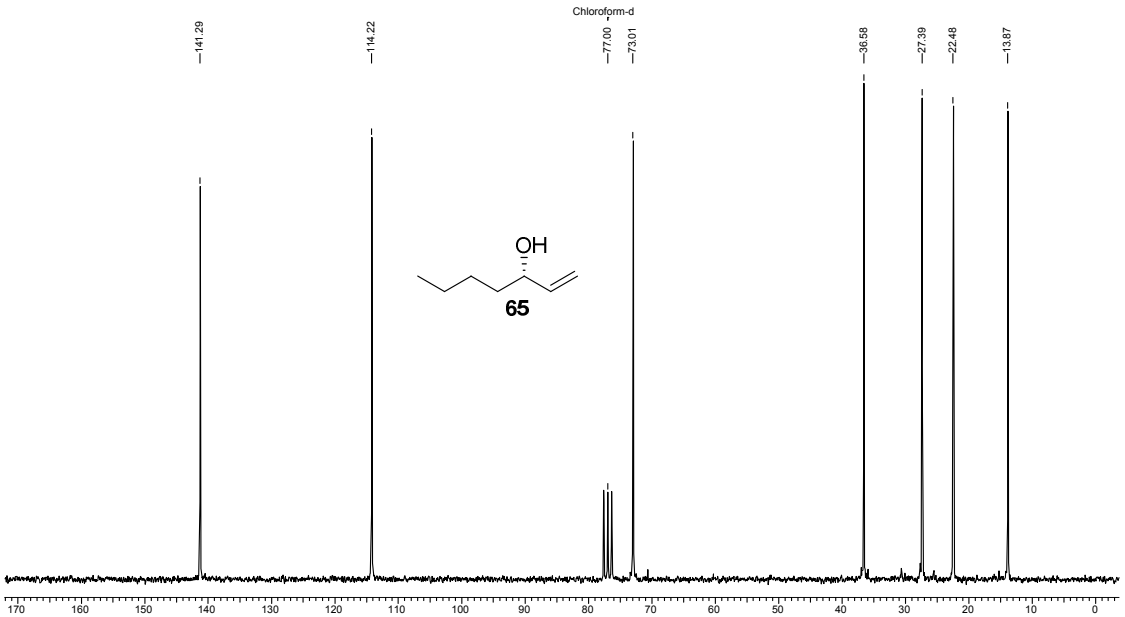
5.88
5.85
5.83
5.80
5.77
5.74
5.71
5.19
5.18
5.10
5.05
5.05
5.04
5.00
5.00
4.99
4.08
4.06
4.03
4.00
3.96
2.34
1.48
1.47
1.45
1.44
1.32
1.29
1.28
1.26
1.25
0.88
0.86
0.85
0.82
0.81
OH
65
0.90
1.86
0.95
1.06
6.09
3.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0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114.22
77.00
73.01
36.58
27.39
22.48
13.87
OH
65
170
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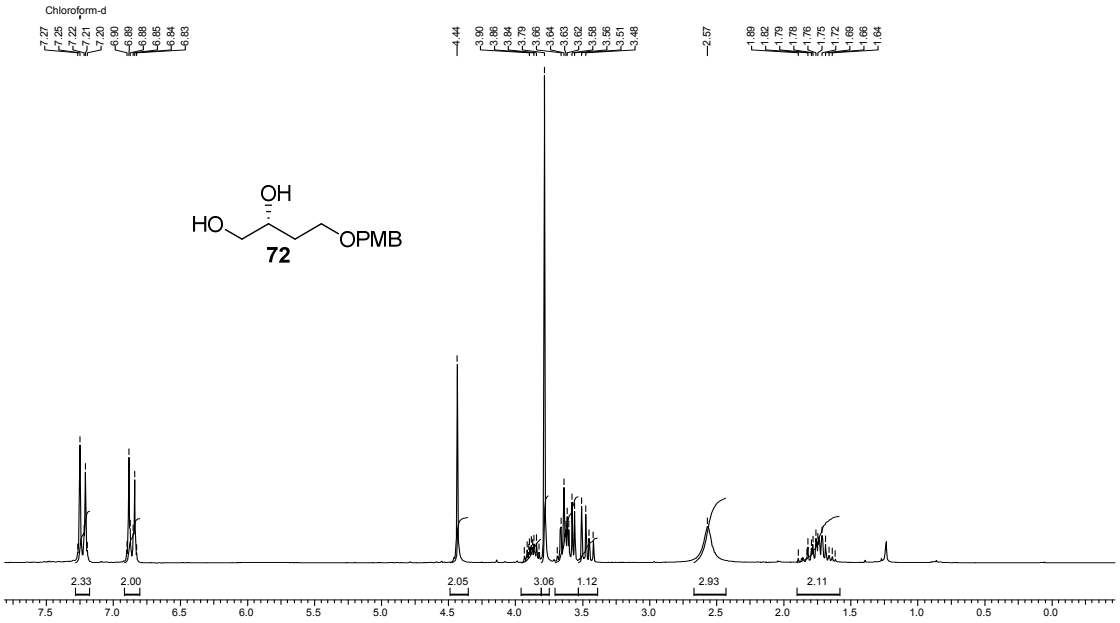
90
80
70
60
50
40
30
20
10
0


Chloroform-d
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7.25
7.22
7.21
7.20
6.90
6.89
6.88
6.85
6.84
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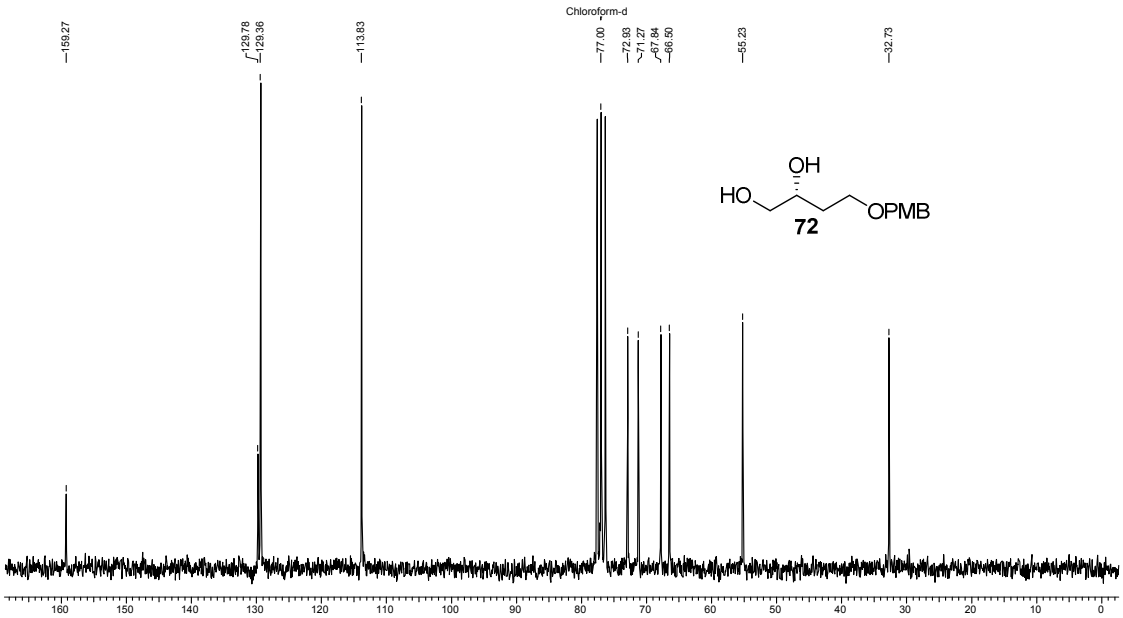
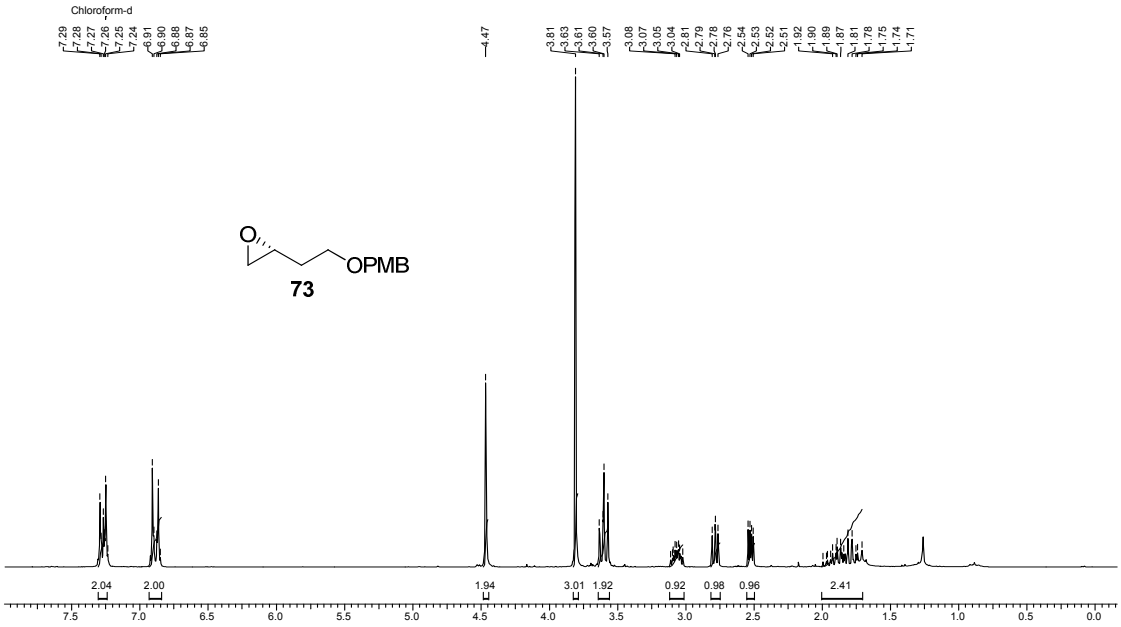
4.44
3.90
3.86
3.84
3.79
3.66
3.64
3.63
3.62
3.58
3.55
3.51
3.48
2.57
1.89
1.82
1.79
1.78
1.76
1.75
1.72
1.69
1.66
1.64
OH
HO
OPMB
72
2.33
2.00
2.05
3.06
1.12
2.93
2.11


159.27
129.78
129.36
113.83
Chloroform-d
77.00
72.93
71.27
67.84
66.50
55.23
32.73
OH
HO
OPMB
72


Chloroform-d
7.29
7.28
7.27
7.26
7.25
7.24
6.91
6.90
6.88
6.87
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3.81
3.63
3.61
3.60
3.57
3.08
3.07
3.05
3.04
2.81
2.79
2.78
2.76
2.54
2.53
2.52
2.51
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1.89
1.87
1.81
1.78
1.75
1.74
1.71
O
OPMB
73
2.04
2.00
1.94
3.01
1.92
0.92
0.98
0.96
2.41
7.5
7.0
6.5
6.0
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4.0
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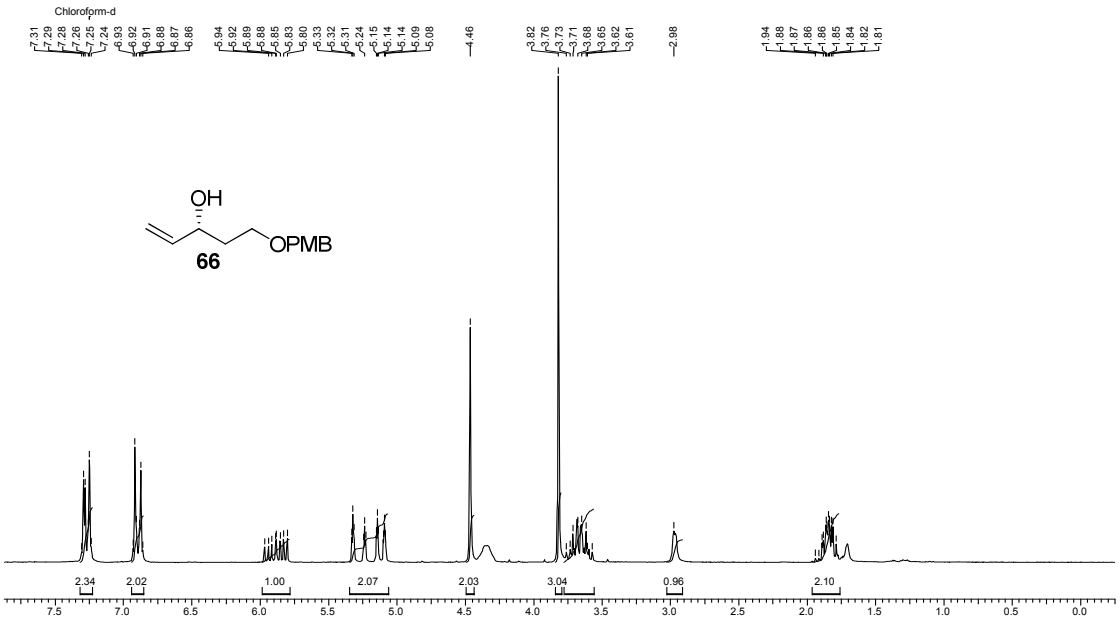
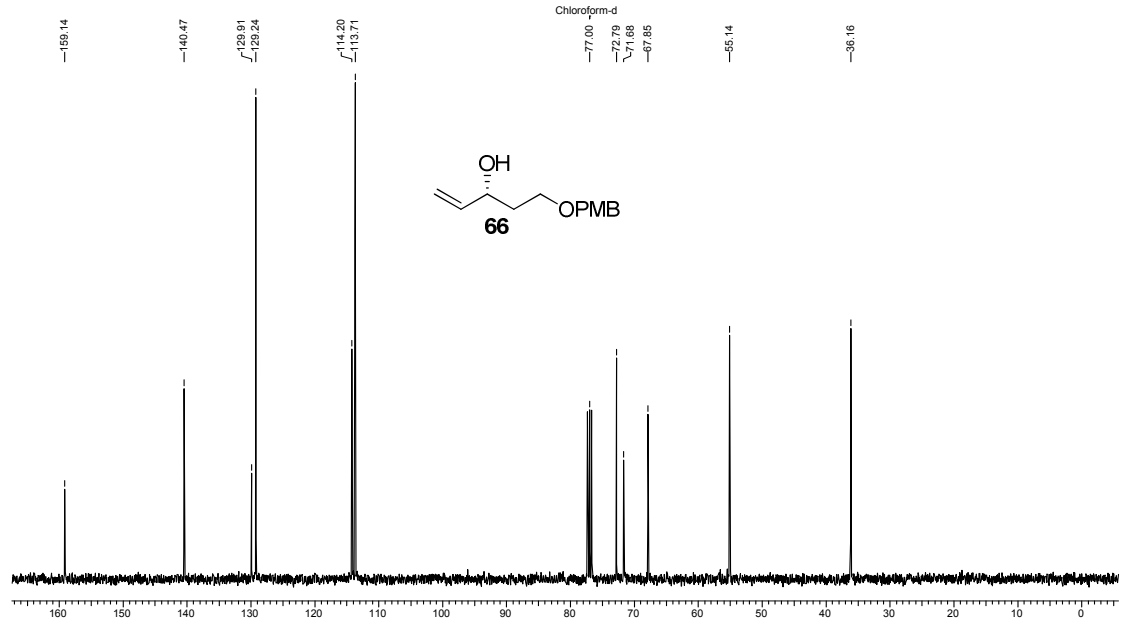
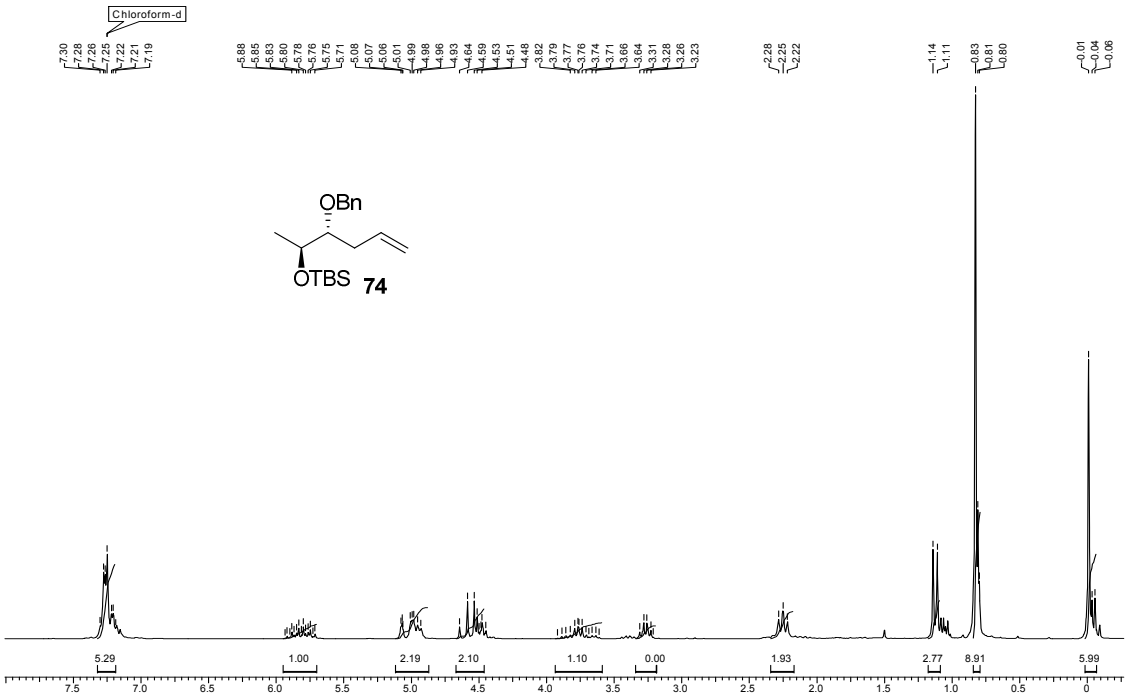
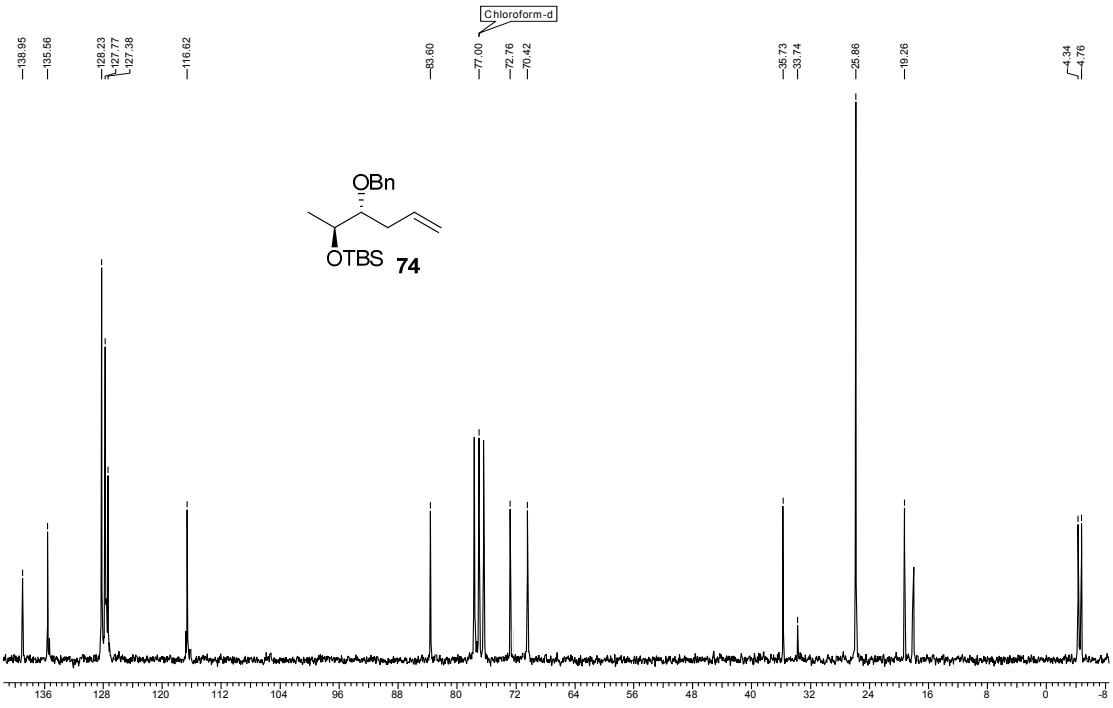
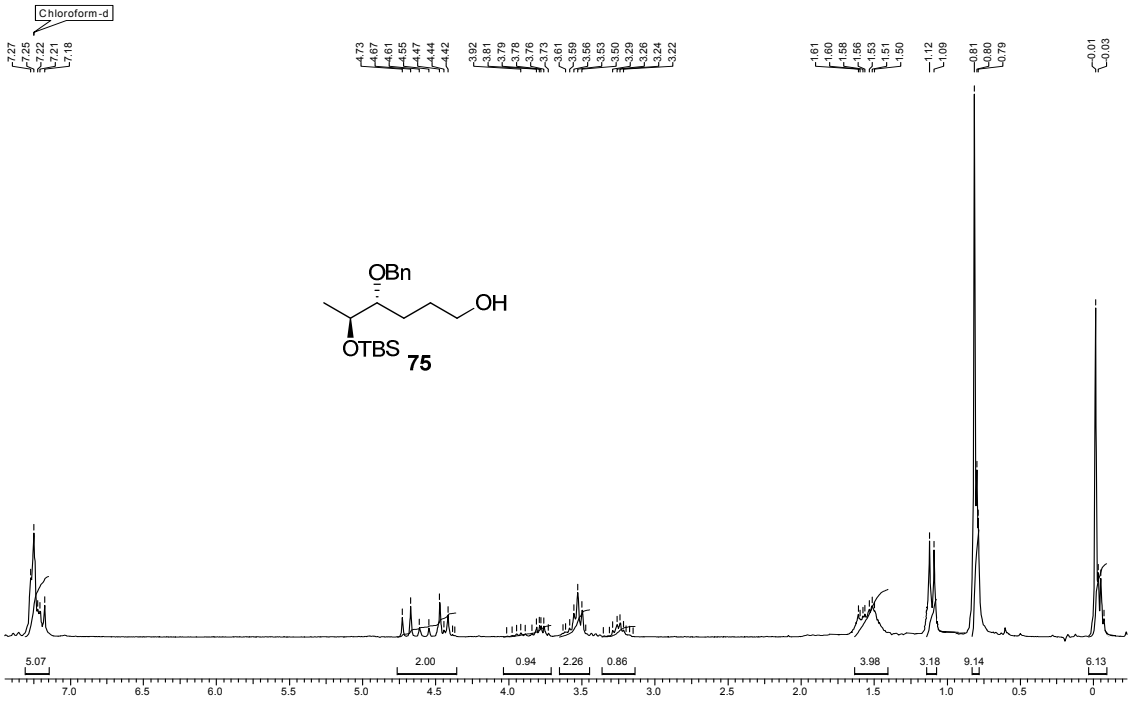
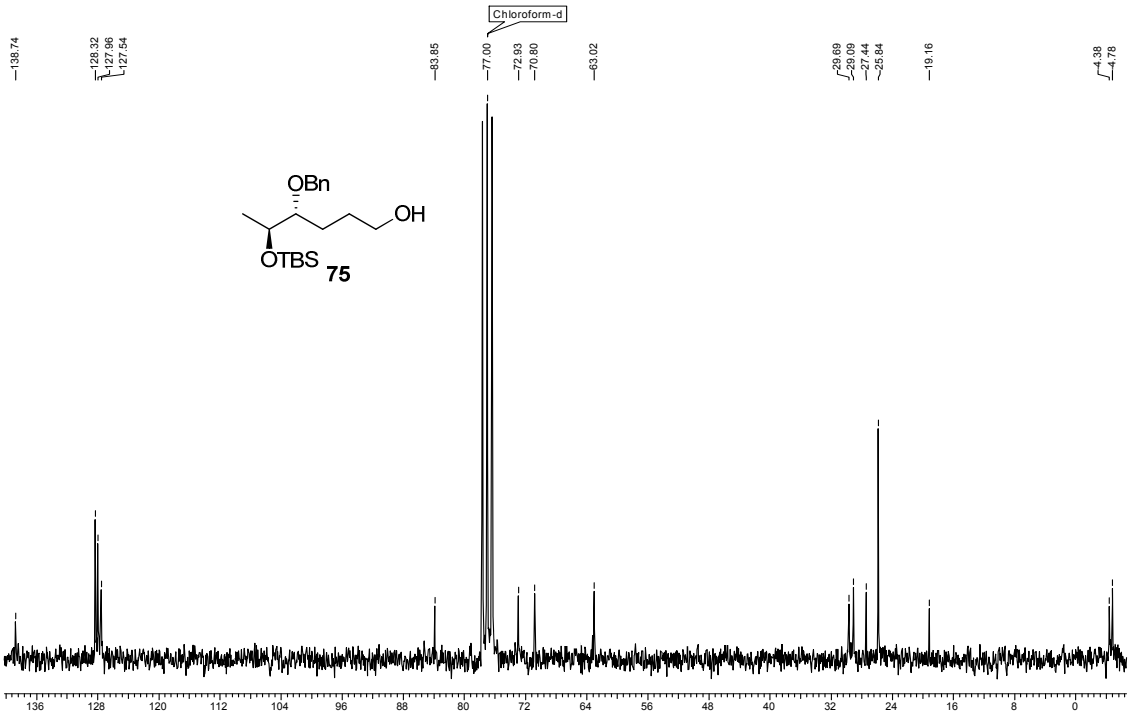

Chloroform-d
OH
OPMB
66

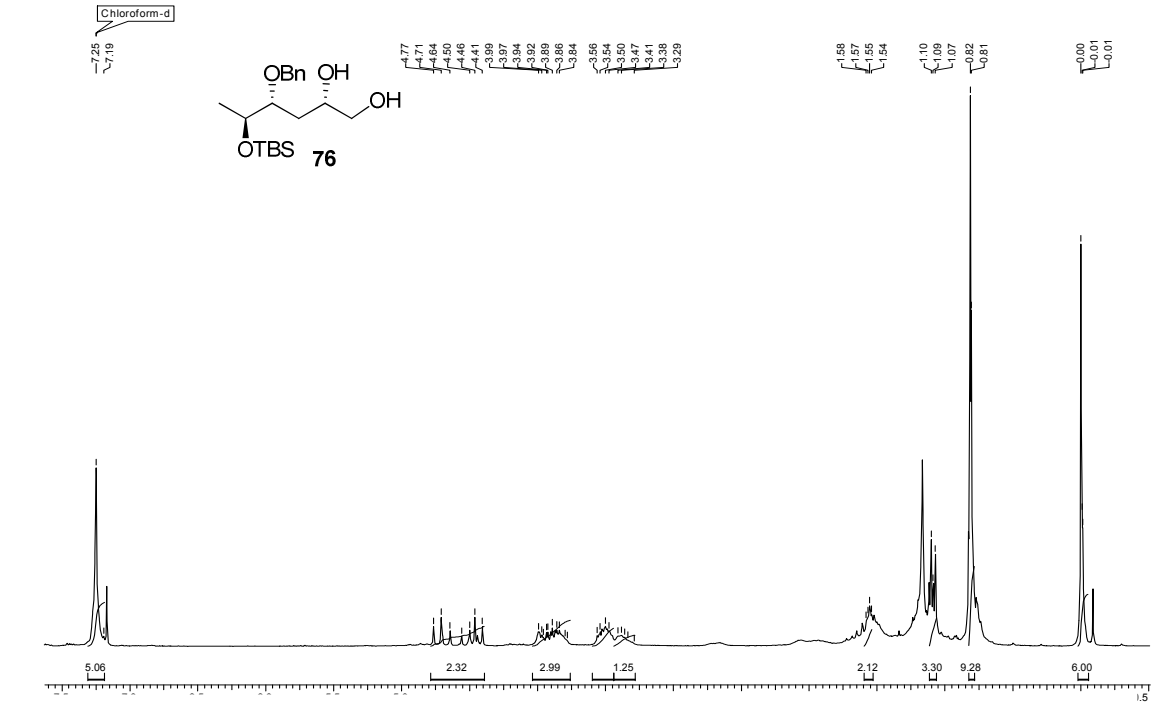

Chloroform-d
OH
OPMB
66

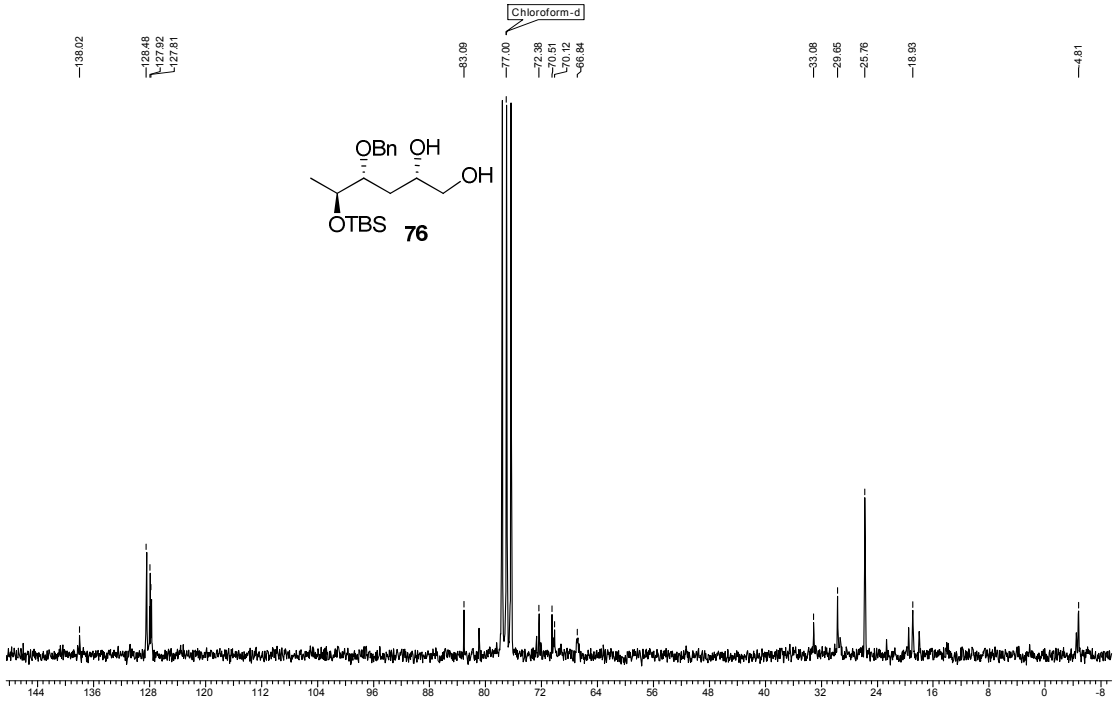

Chloroform-d
OBn
OTBS
74

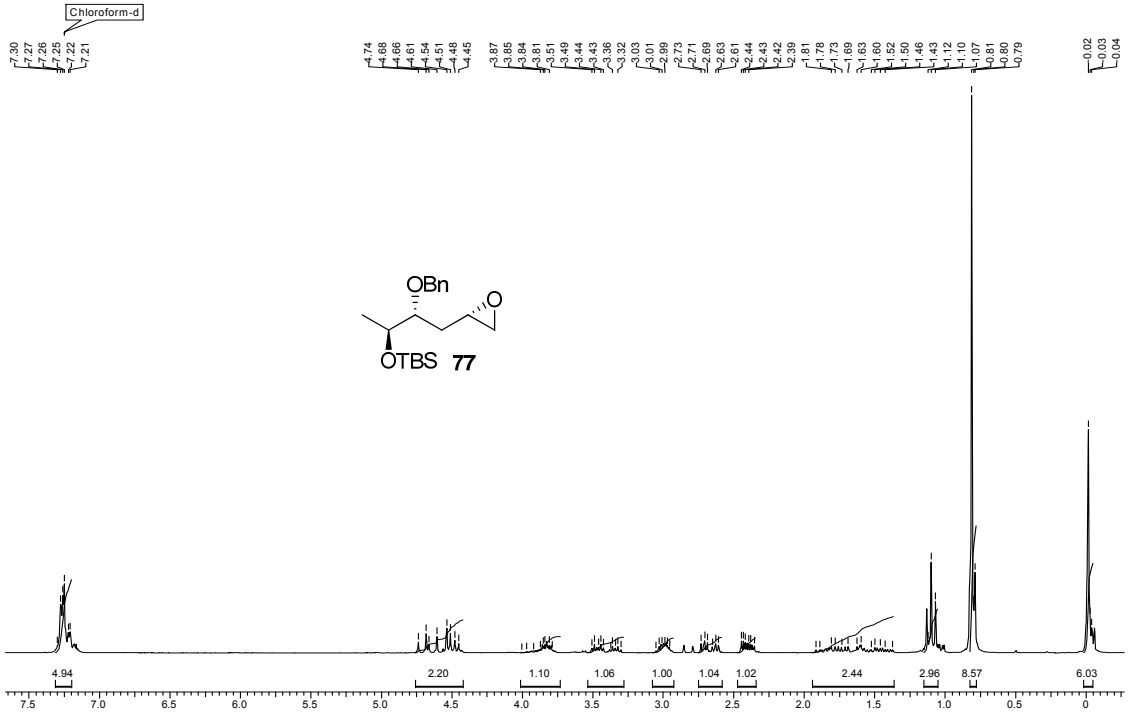

Chloroform-d
OBn
OTBS
74


Chloroform-d
OBn
OH
OTBS
75


Chloroform-d
OBn
OH
OTBS
75


Chloroform-d
OBn OH
OH
OTBS
76


Chloroform-d
OBn OH
OH
OTBS
76


Chloroform-d
OBn
OTBS
77
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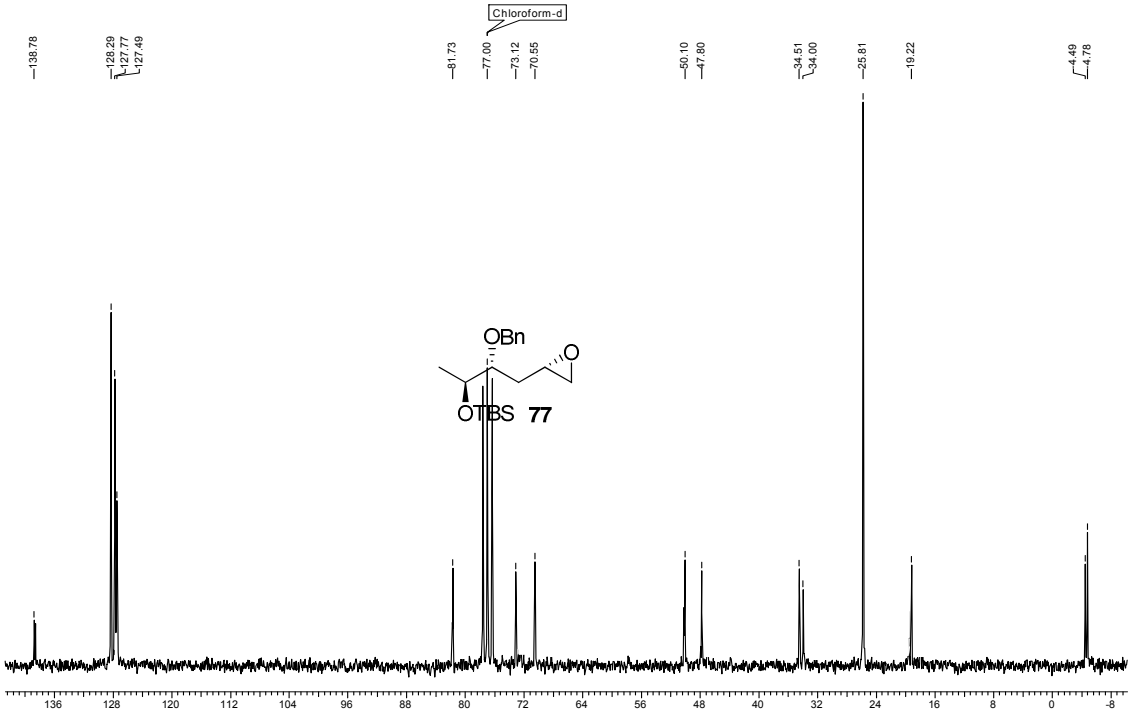
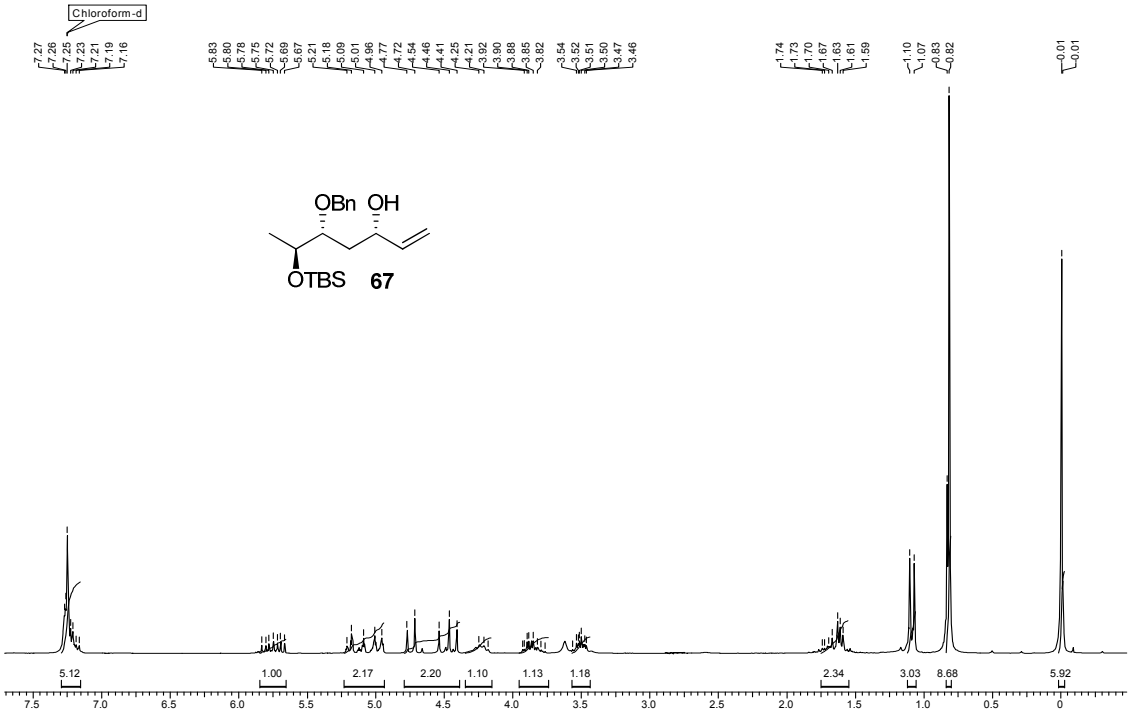
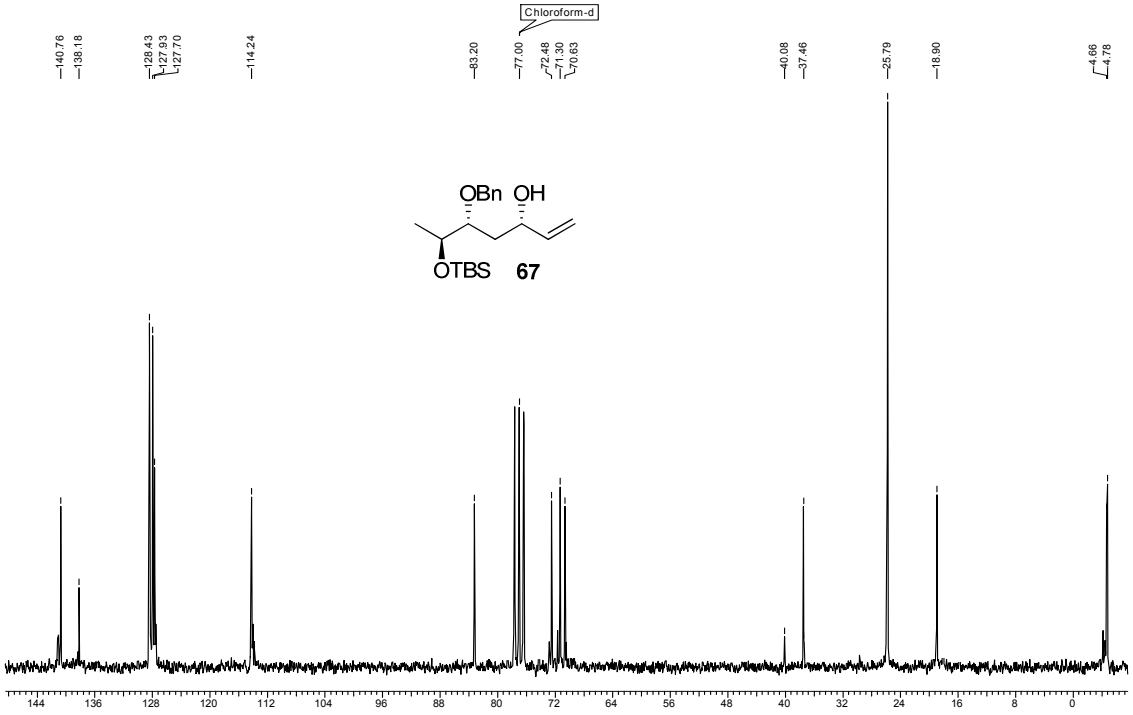
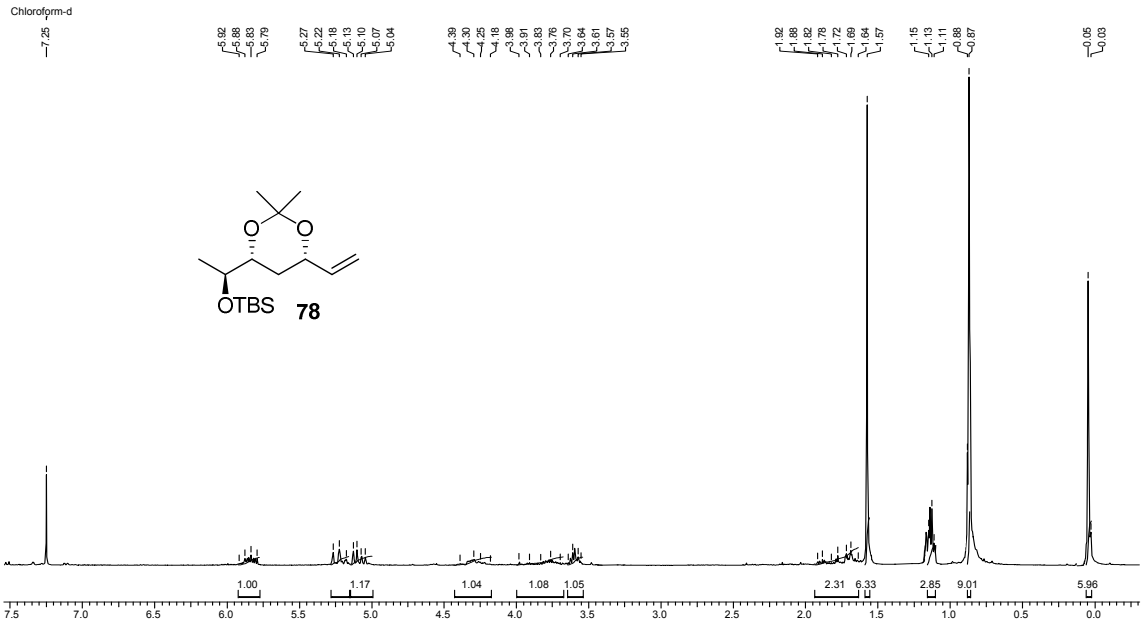
1.10
1.06
1.00
1.04
1.02
2.44
2.96
8.57
6.03


Chloroform-d
OBn
OTBS
77


Chloroform-d
OBn OH
OTBS 67


Chloroform-d
OBn OH
OTBS 67


Chloroform-d
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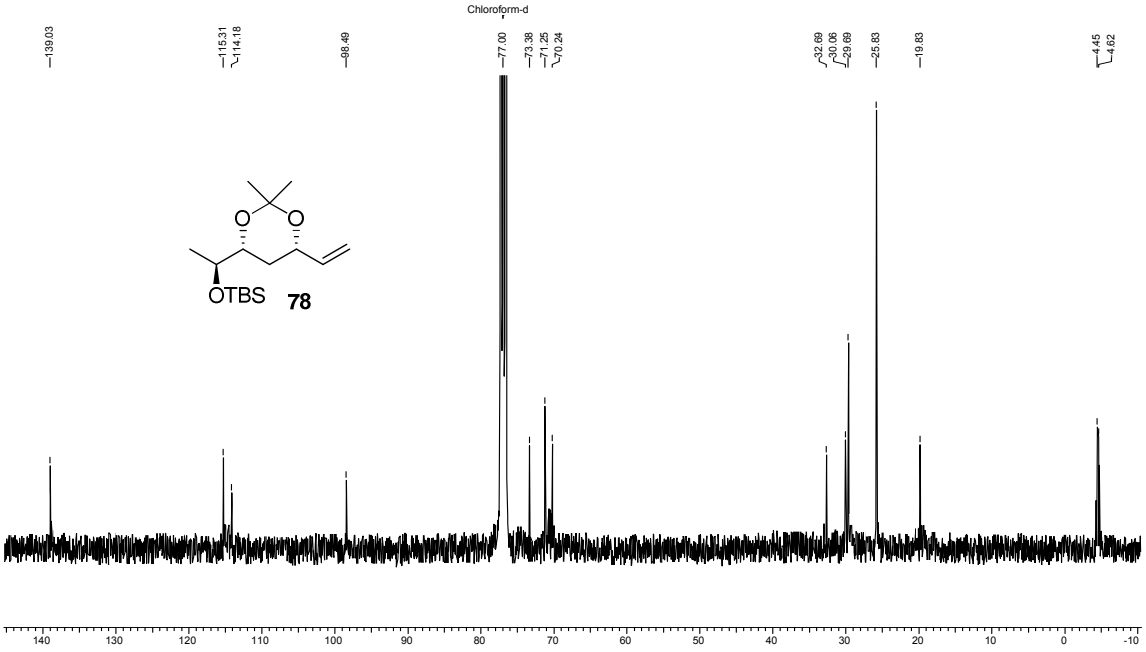
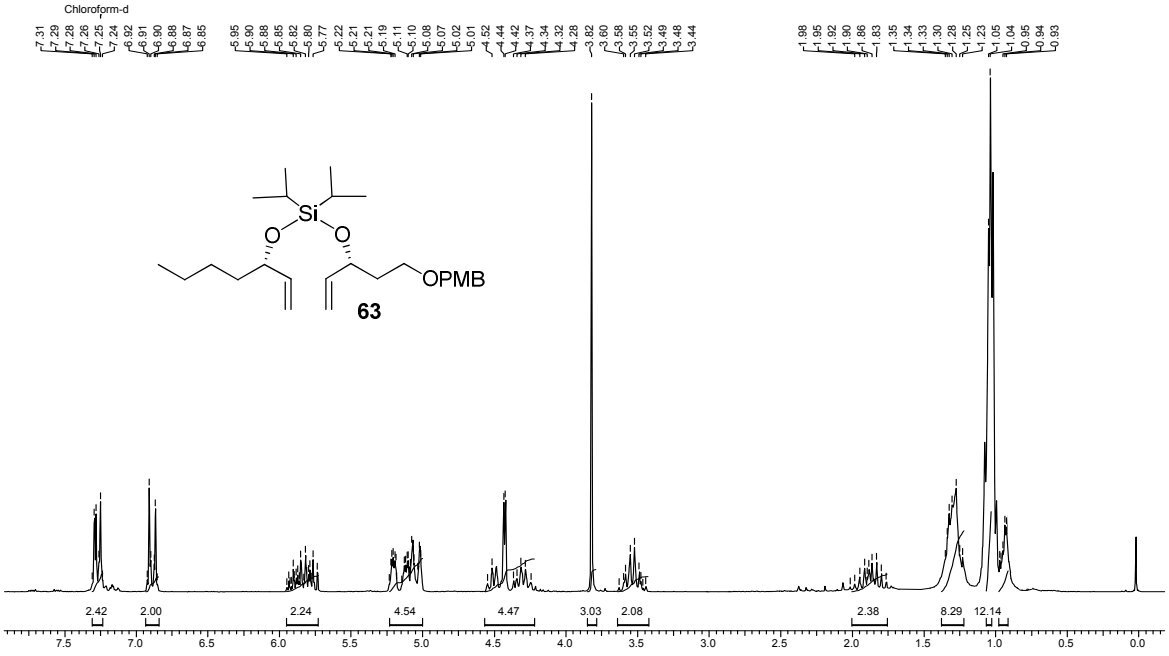
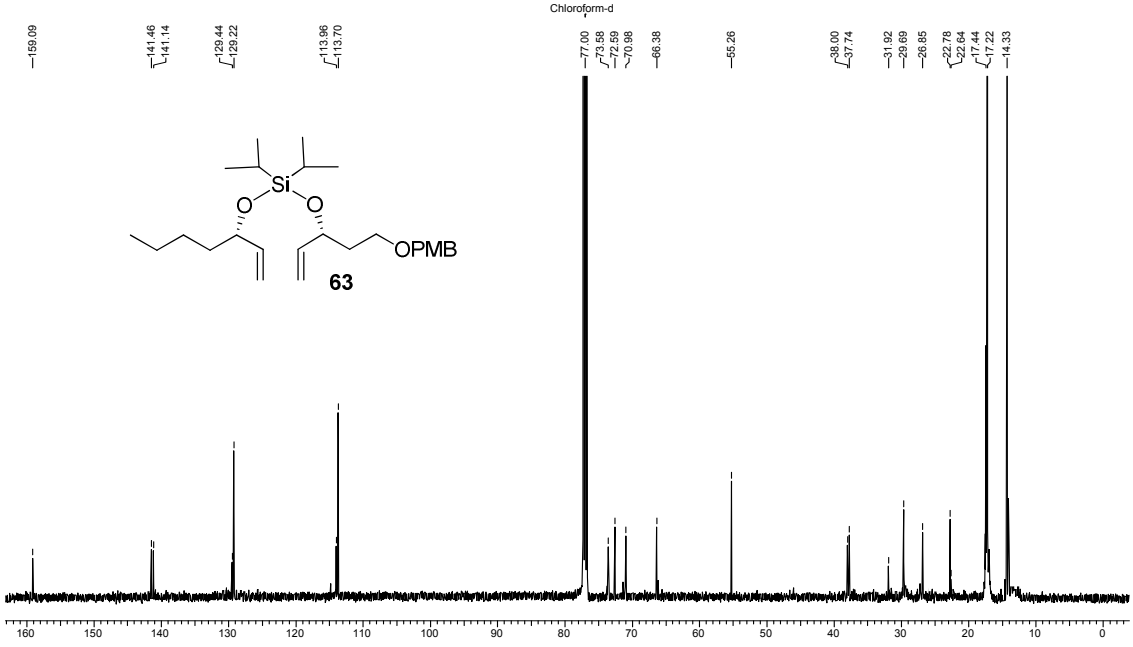
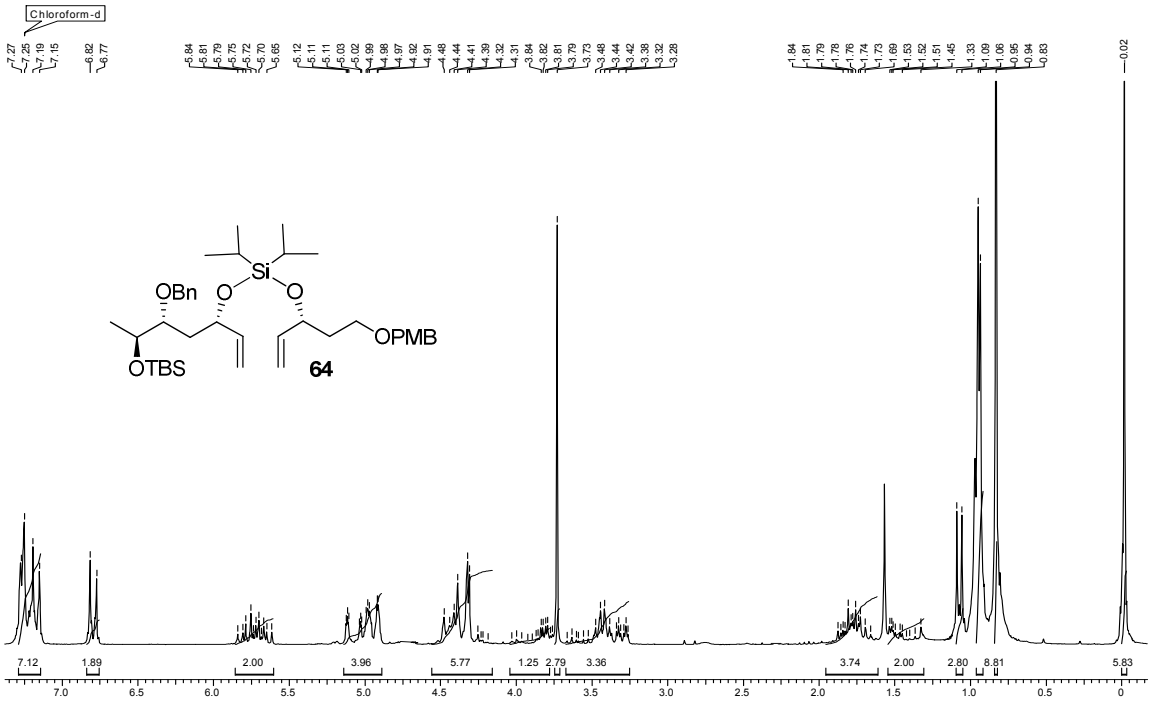
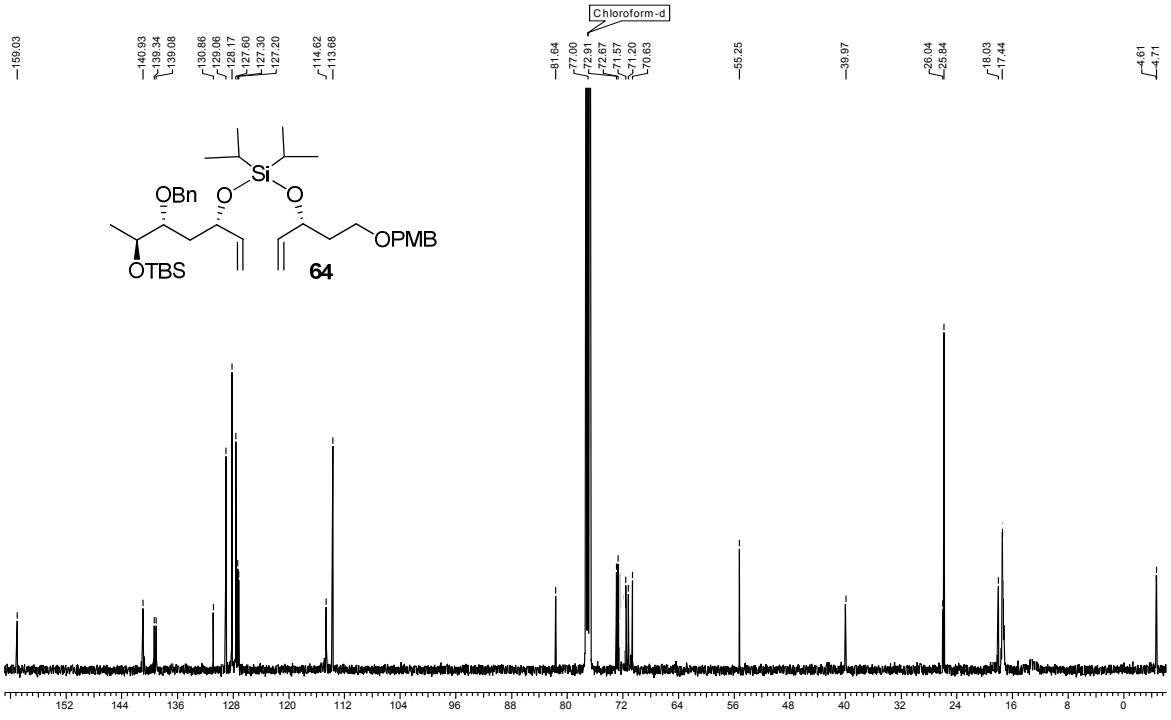
5.92
5.88
5.83
5.79
5.27
5.22
5.18
5.13
5.10
5.07
5.04
4.39
4.30
4.25
4.18
3.98
3.91
3.83
3.76
3.70
3.64
3.61
3.57
3.55
1.92
1.88
1.82
1.78
1.72
1.69
1.64
1.57
1.15
1.13
1.11
0.88
0.87
0.05
0.03
OTBS
78
1.00
1.17
1.04
1.08
1.05
2.31
6.33
2.85
9.01
5.96

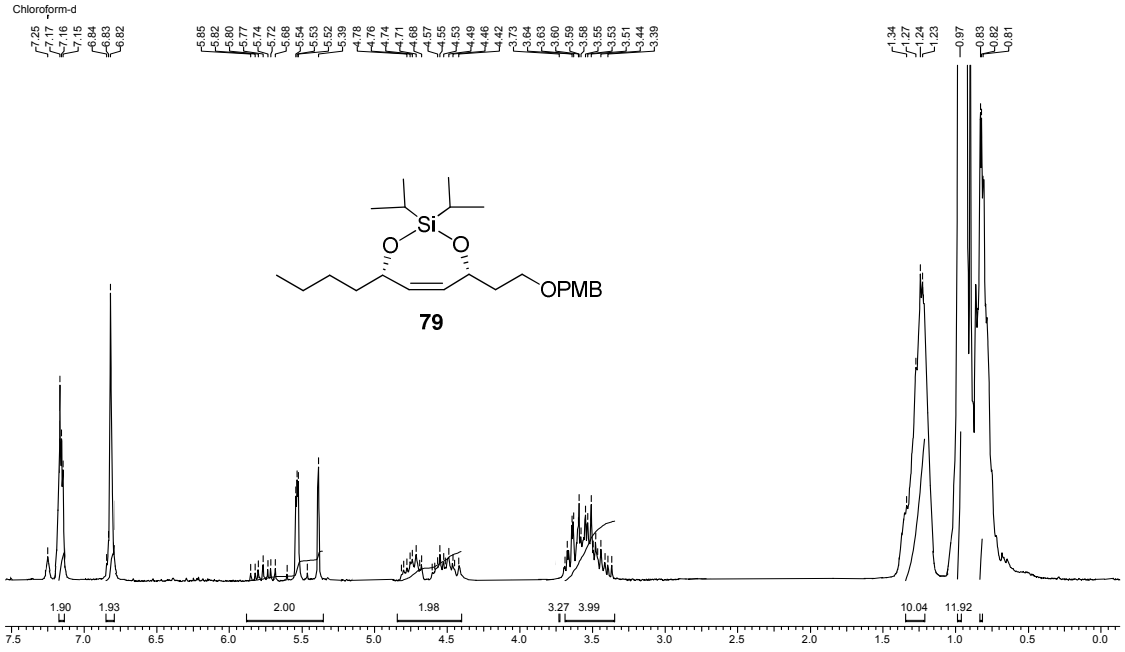

Chloroform-d
139.03
115.31
114.18
98.49
77.00
73.38
71.25
70.24
32.69
30.06
29.69
25.83
19.83
4.45
4.62
OTBS
78


Chloroform-d
7.31 7.29 7.28 7.26 7.25 7.24 6.92 6.91 6.90 6.88 6.87 6.85
5.95 5.90 5.88 5.85 5.82 5.80 5.77 5.22 5.21 5.21 5.19 5.11 5.10 5.08 5.07 5.02 5.01 4.52 4.44 4.42 4.37 4.34 4.32 4.28 3.82 3.60 3.58 3.55 3.52 3.49 3.48 3.44
1.98 1.95 1.92 1.90 1.86 1.83 1.35 1.34 1.33 1.30 1.28 1.25 1.23 1.05 1.04 0.95 0.94 0.93
Si
O
O
OPMB
63
2.42 2.00 2.24 4.54 4.47 3.03 2.08 2.38 8.29 12.14
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


159.09
141.46 141.14
129.44 129.22
113.96 113.70
Chloroform-d
77.00 73.58 72.59 70.98
66.38
55.26
38.00 37.74
31.92 29.69 26.85
22.78 22.64 17.44 17.22 14.33
Si
O
O
OPMB
63
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


Chloroform-d
OBn
OTBS
OPMB
64


Chloroform-d
OBn
OTBS
OPMB
64


Chloroform-d
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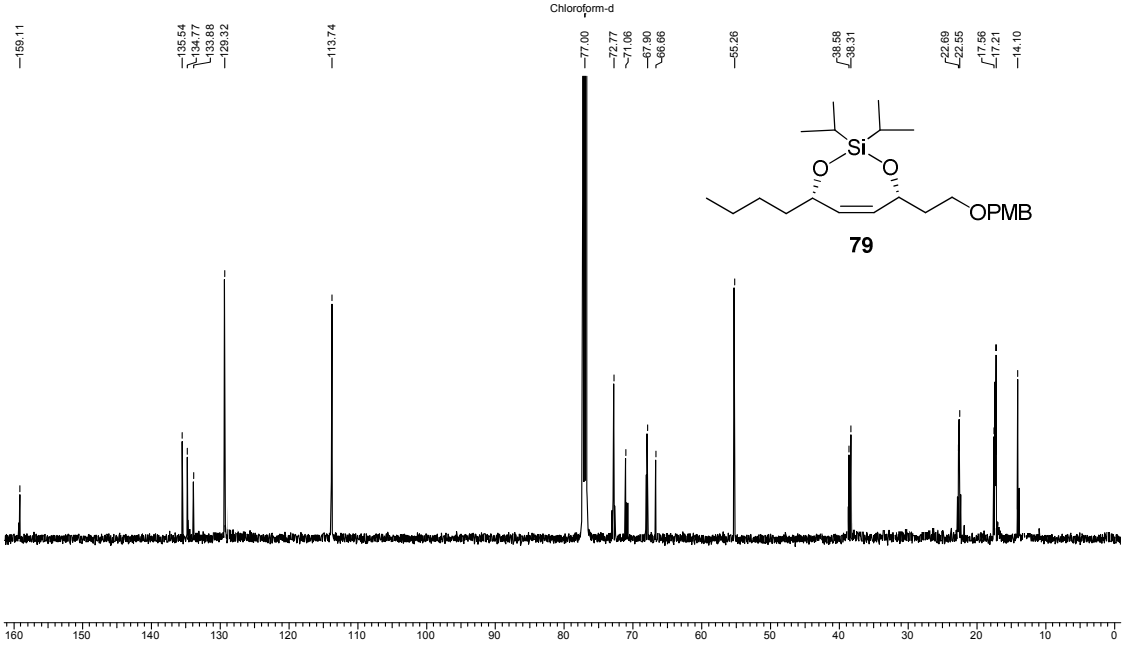
7.17
7.16
7.15
6.84
6.83
6.82
5.85
5.82
5.80
5.77
5.74
5.72
5.68
5.54
5.53
5.52
5.39
4.78
4.76
4.74
4.71
4.68
4.57
4.55
4.53
4.49
4.46
4.42
3.73
3.64
3.63
3.60
3.59
3.58
3.55
3.53
3.51
3.44
3.39
1.34
1.27
1.24
1.23
0.97
0.83
0.82
0.81
Si
O
O
OPMB
79
1.90
1.93
2.00
1.98
3.27
3.99
10.04
11.92
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


Chloroform-d
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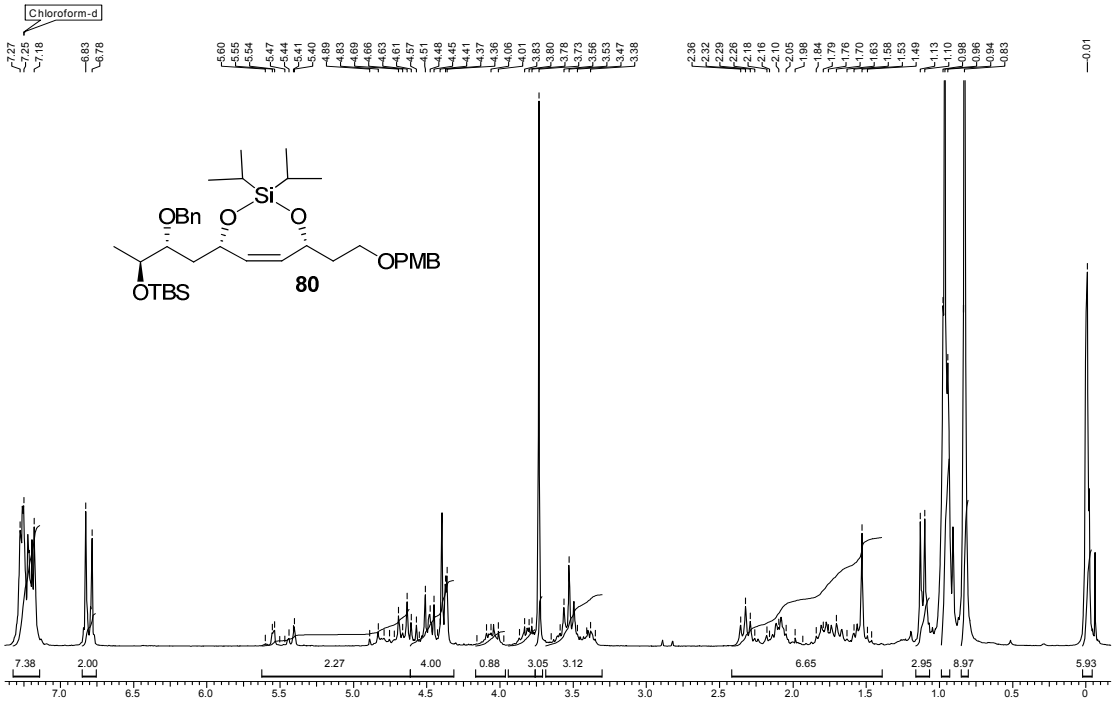
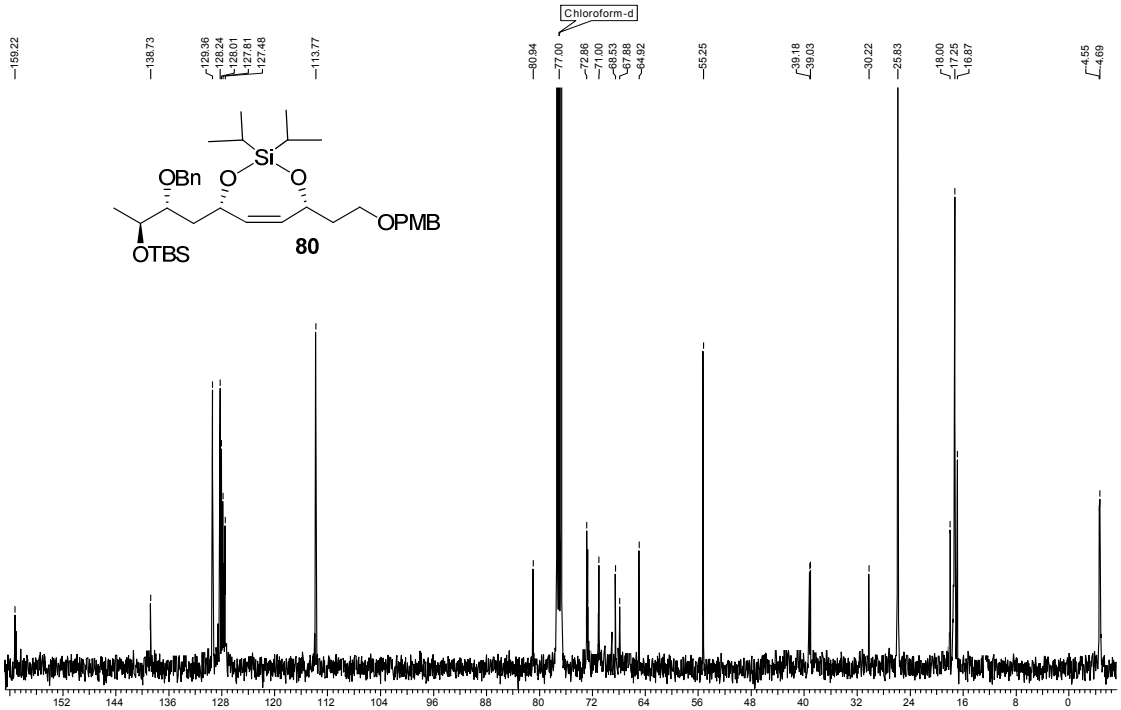
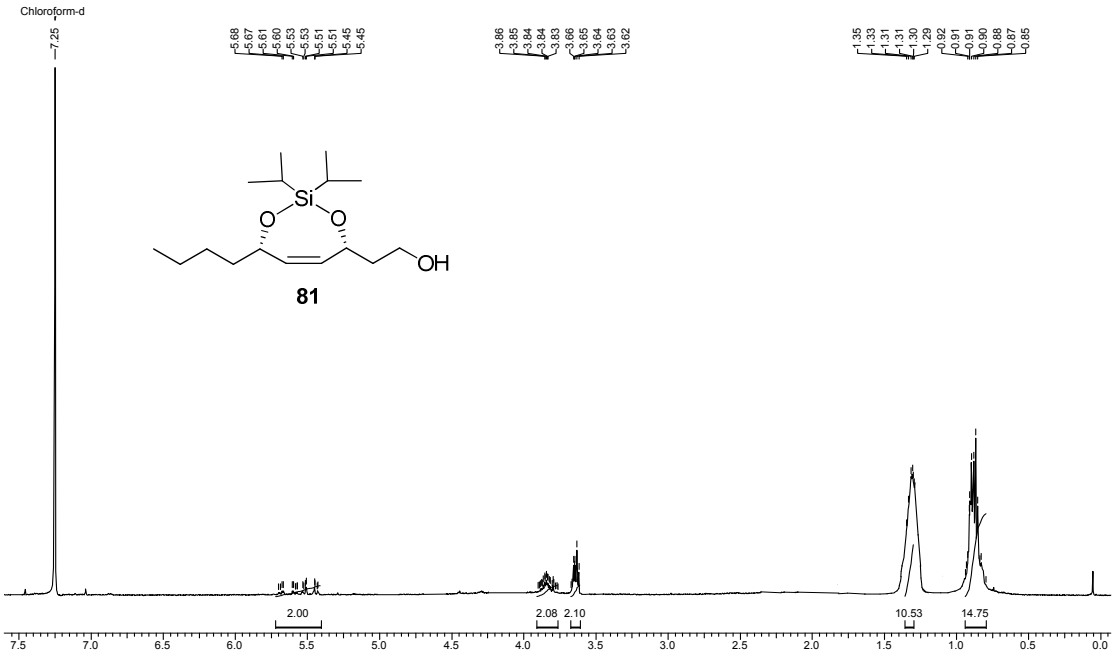
135.54
134.77
133.88
129.32
113.74
77.00
72.77
71.06
67.90
66.66
55.26
38.58
38.31
22.69
22.55
17.56
17.21
14.10
Si
O
O
OPMB
79
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


Chloroform-d
OBn
OTBS
OPMB
Si
O
O
80


Chloroform-d
OBn
OTBS
OPMB
Si
O
O
80


Chloroform-d
7.25
5.68
5.67
5.61
5.60
5.53
5.53
5.51
5.51
5.45
5.45
3.86
3.85
3.84
3.84
3.83
3.66
3.65
3.64
3.63
3.62
1.35
1.33
1.31
1.31
1.30
1.29
0.92
0.91
0.91
0.90
0.89
0.87
0.85
Si
O
O
OH
81
2.00
2.08
2.10
10.53
14.75
7.5
7.0
6.5
6.0
5.5
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4.0
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3.0
2.5
2.0
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1.0
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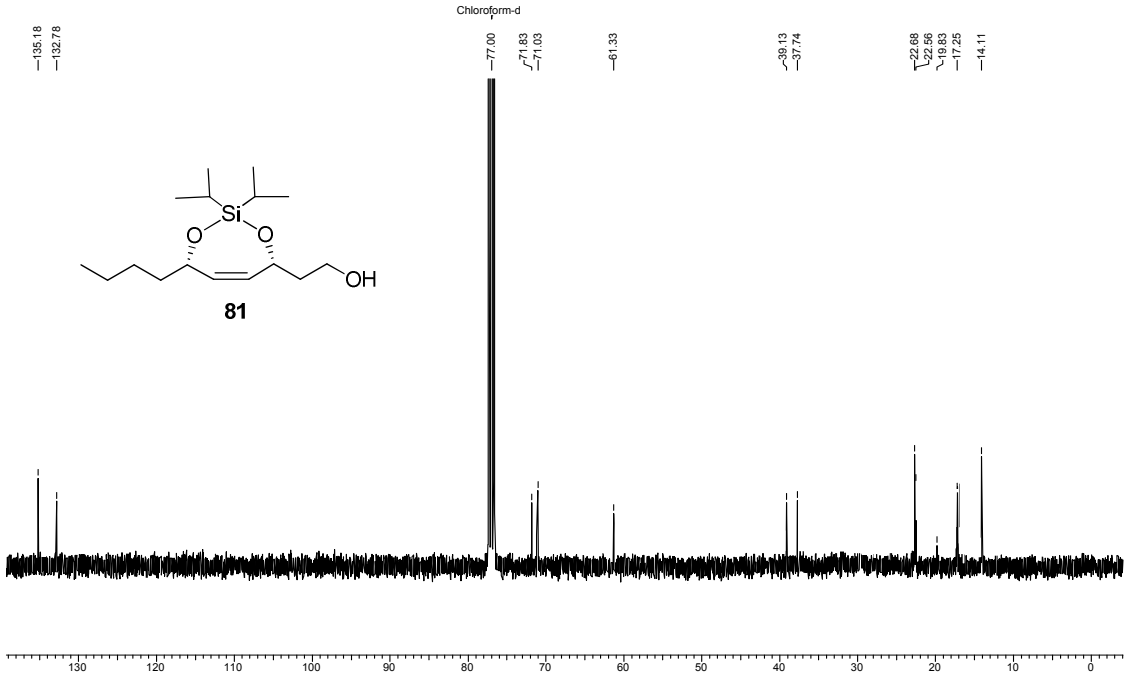
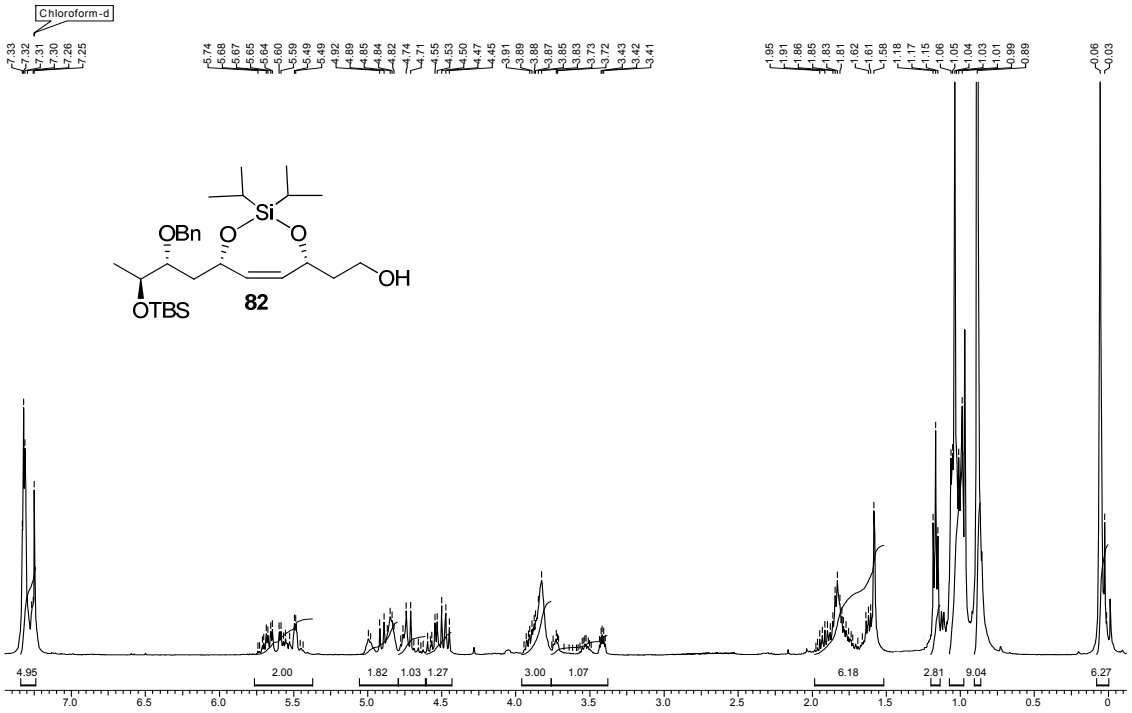
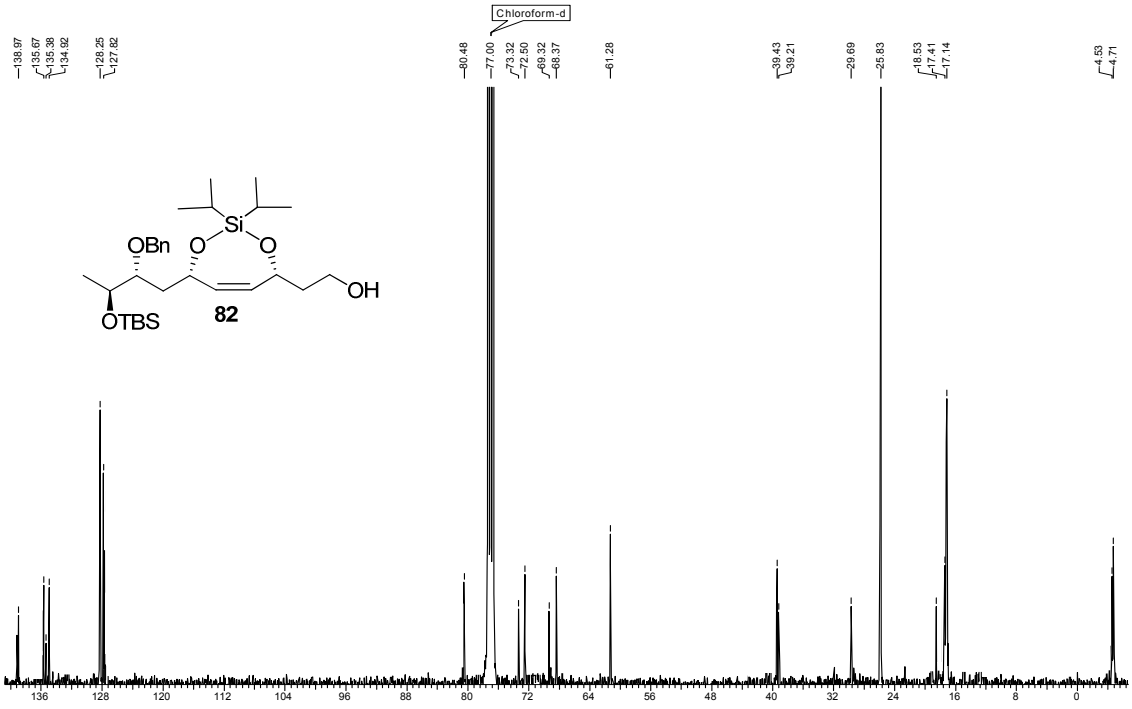
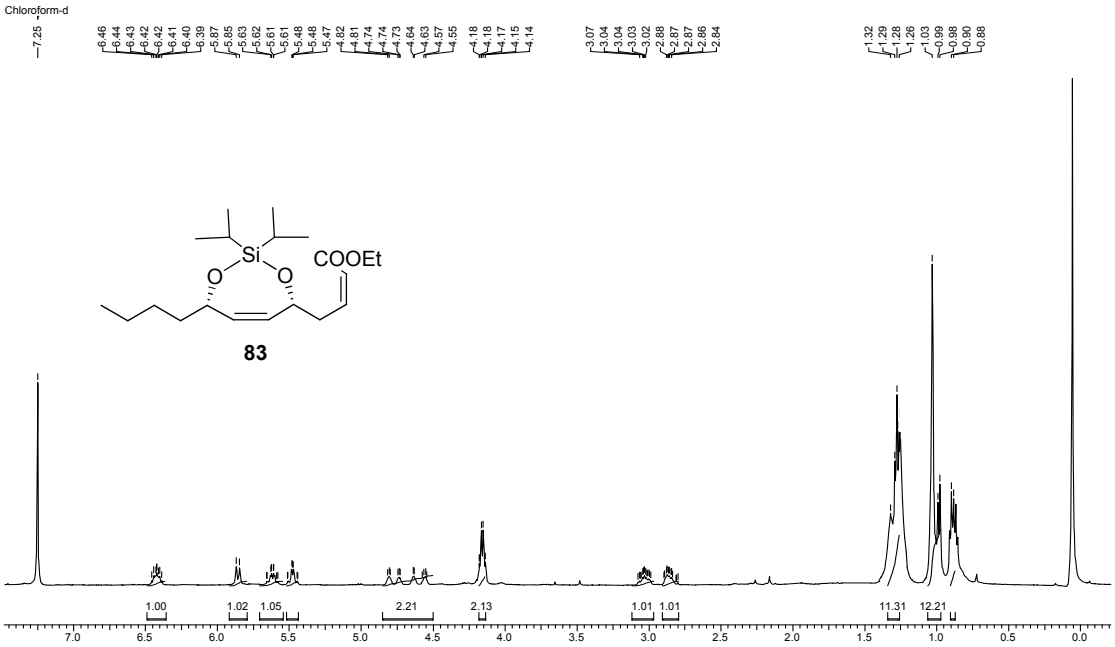
0.0


Chloroform-d
135.18
132.78
77.00
71.83
71.03
61.33
39.13
37.74
22.68
22.56
19.83
17.25
14.11
Si
O
O
OH
81
130
120
110
100
90
80
70
60
50
40
30
20
10
0


Chloroform-d
OBn
Si
O
O
OH
OTBS
82


Chloroform-d
OBn
Si
O
O
OH
OTBS
82


Chloroform-d
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6.46
6.44
6.43
6.42
6.42
6.41
6.40
6.39
5.67
5.65
5.63
5.62
5.61
5.61
5.48
5.48
5.47
4.82
4.81
4.74
4.74
4.73
4.64
4.63
4.57
4.55
4.18
4.18
4.17
4.15
4.14
3.07
3.04
3.04
3.03
3.02
2.88
2.87
2.87
2.86
2.84
1.32
1.29
1.28
1.26
1.03
0.99
0.98
0.90
0.88
Si
O
O
COOEt
1.00
1.02
1.05
2.21
2.13
1.01
1.01
11.31
12.21
7.0
6.5
6.0
5.5
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3.5
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2.5
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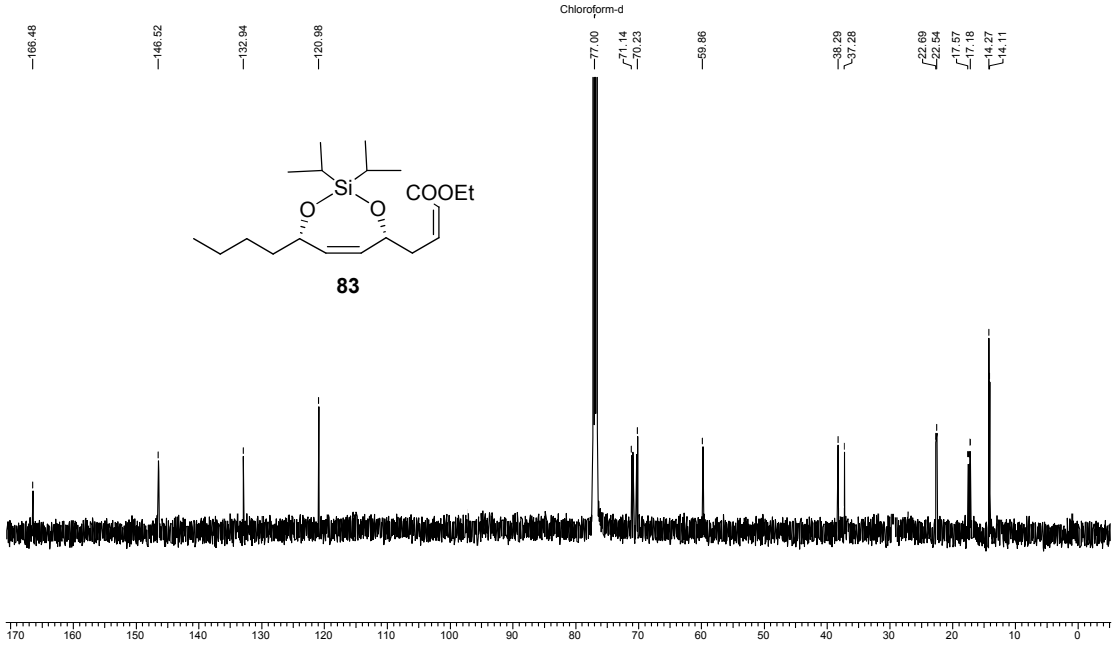
1.5
1.0
0.5
0.0

**83**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120.98
77.00
71.14
70.23
59.86
38.29
37.28
22.69
22.54
17.67
17.18
14.27
14.11
Si
O
O
COOEt
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160
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130
120
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100
90
80
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60
50
40
30
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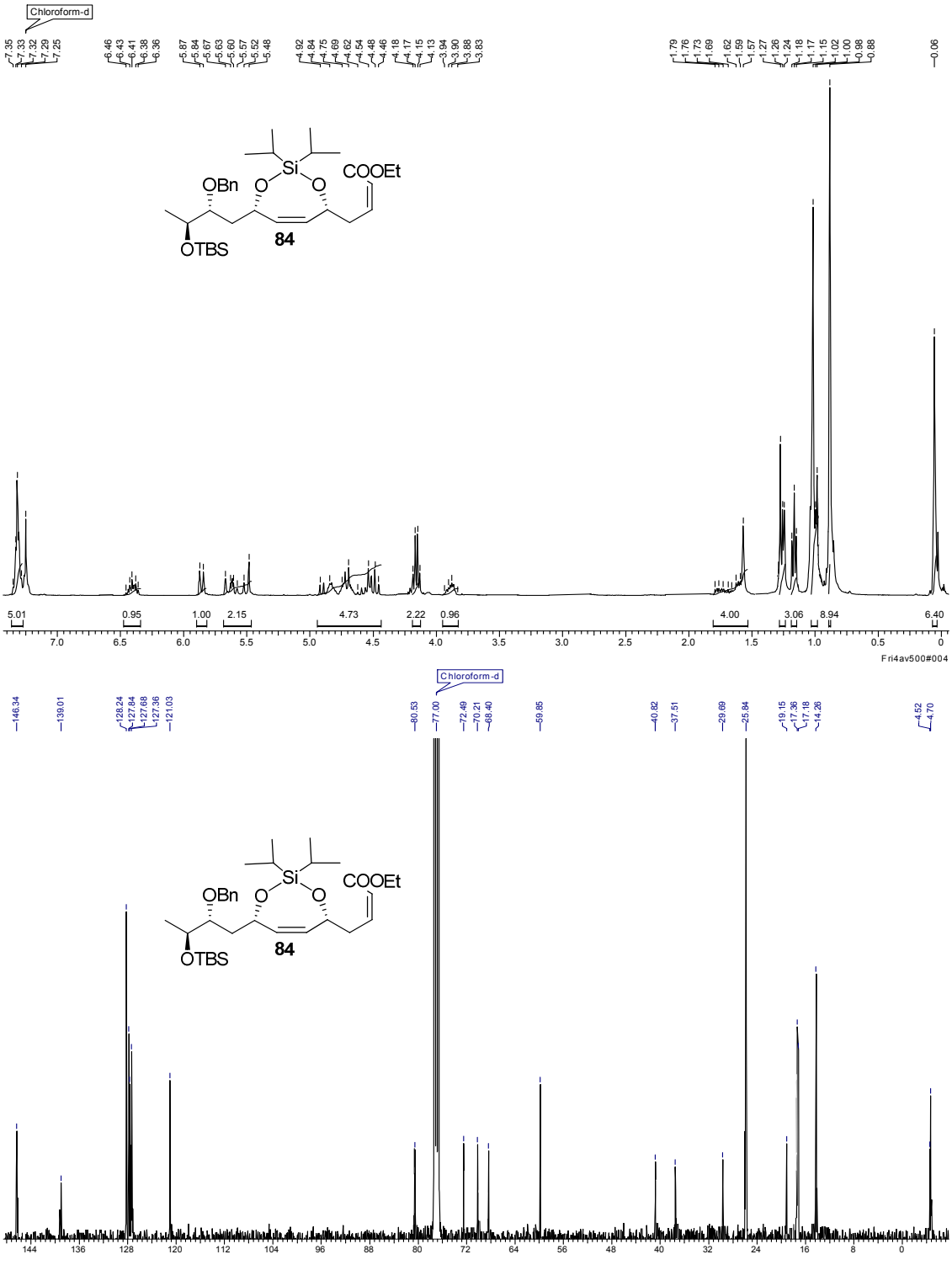
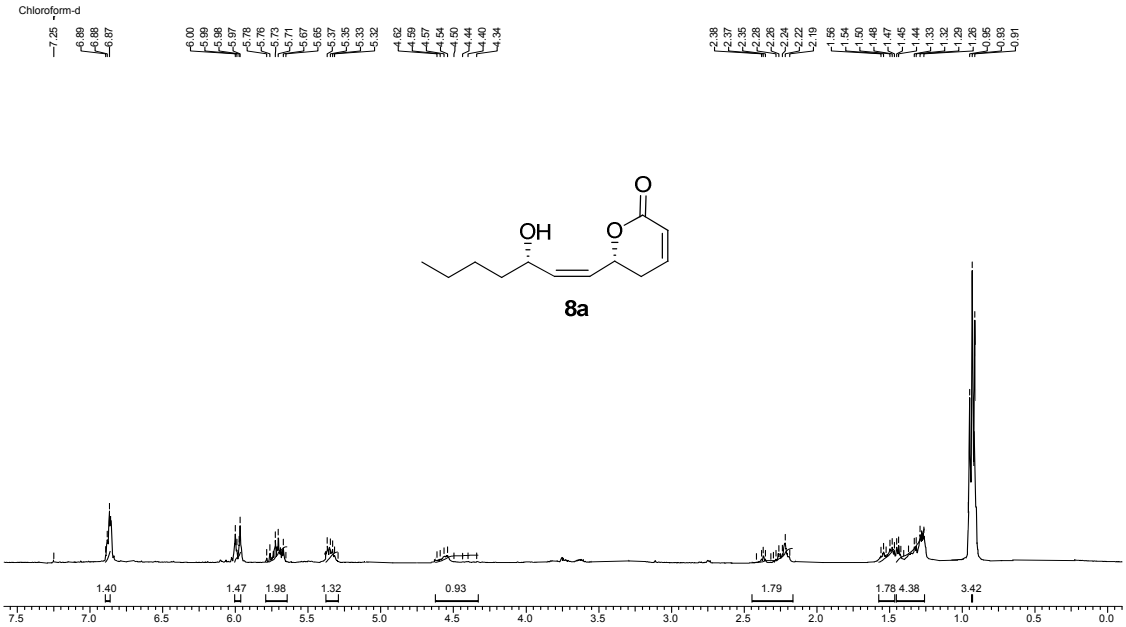
10
0

**83**


Chloroform-d
OBn
OTBS
COOEt
Si
O
84
Fri4av500#004
Chloroform-d
OBn
OTBS
COOEt
Si
O
84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6.88
6.87
6.00
5.99
5.98
5.97
5.78
5.76
5.73
5.71
5.67
5.65
5.37
5.35
5.33
5.32
4.62
4.59
4.57
4.54
4.50
4.44
4.40
4.34
2.38
2.37
2.35
2.28
2.26
2.24
2.22
2.19
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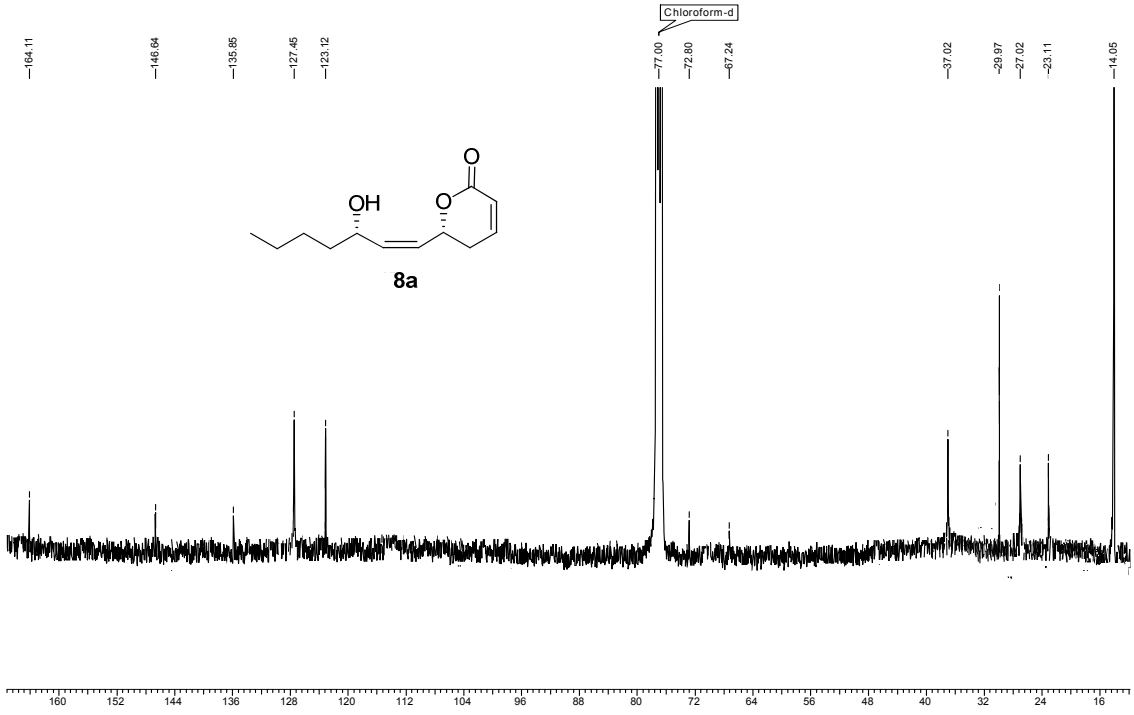
1.54
1.50
1.48
1.47
1.45
1.44
1.33
1.32
1.29
1.26
0.95
0.93
0.91
OH
O
O
8a
1.40
1.47
1.98
1.32
0.93
1.79
1.78
4.38
3.42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146.64
135.85
127.45
123.12
Chloroform-d
77.00
72.80
67.24
37.02
29.97
27.02
23.11
14.05
OH
O
O
8a


Chloroform-d
7.30
7.28
7.27
7.26
7.25
7.23
6.40
6.39
6.37
6.35
6.34
6.34
6.32
5.82
5.79
5.61
5.58
5.57
5.56
5.55
5.53
5.52
5.47
5.43
4.87
4.84
4.79
4.77
4.69
4.68
4.67
4.64
4.63
4.62
4.54
3.87
3.86
3.85
3.85
3.83
3.82
3.81
3.49
3.38
3.37
3.36
3.35
3.01
2.98
2.97
2.96
2.94
2.93
2.91
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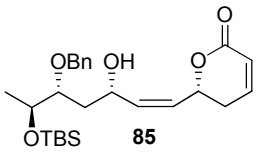
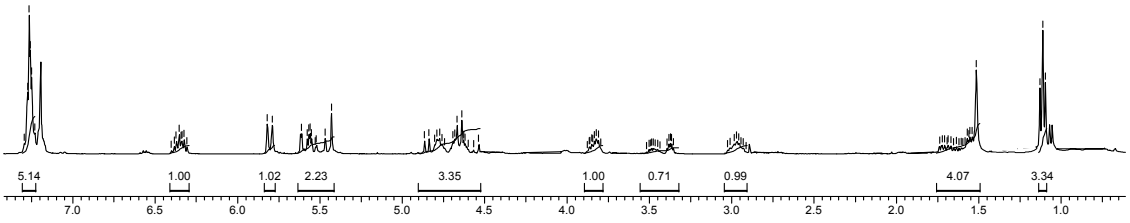
1.54
1.52
1.13
1.11
1.10


O
OBn
OH
O
OTBS

**85**


5.14
1.00
1.02
2.23
3.35
1.00
0.71
0.99
4.07
3.34
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
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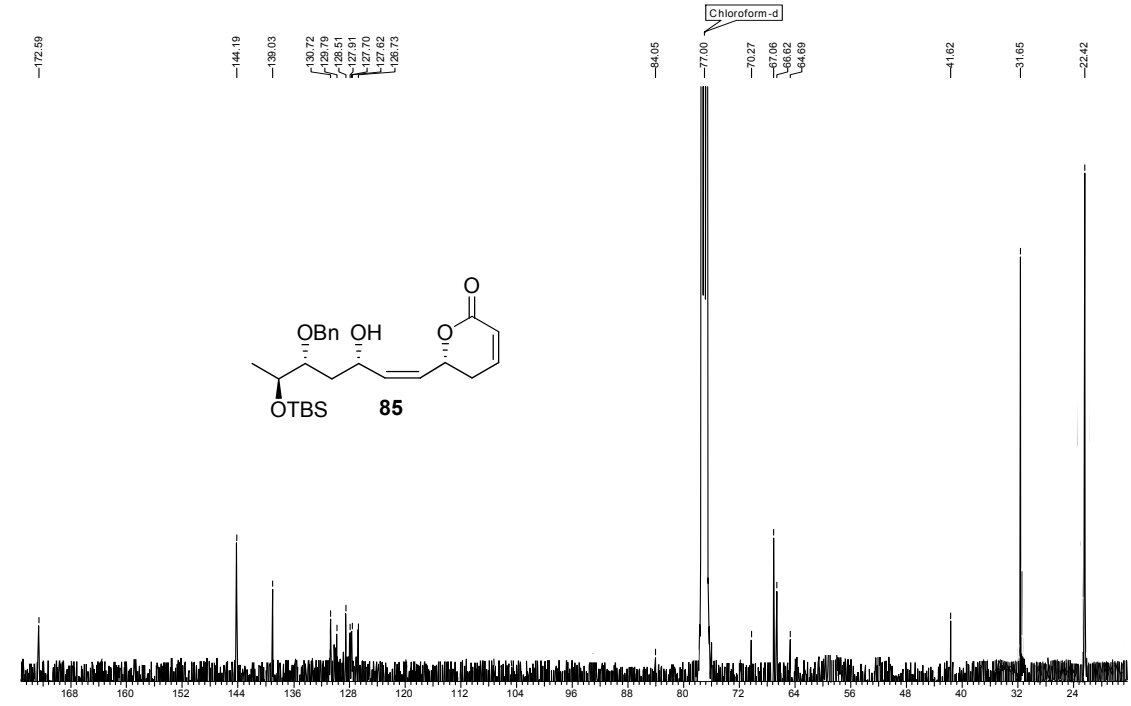
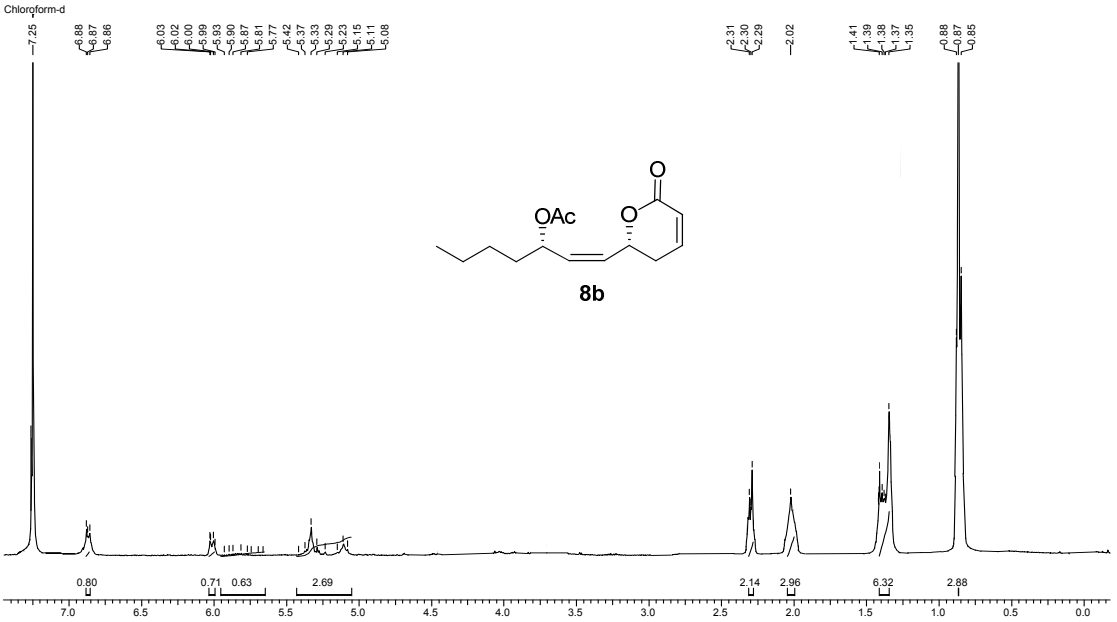
2.0
1.5
1.0


Chloroform-d
172.59
144.19
139.03
130.72
129.79
128.51
127.91
127.70
127.62
126.73
84.05
77.00
70.27
67.06
66.62
64.69
41.62
31.65
22.42
O
OBn
OH
O
OTBS
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24

**85**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5.77
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5.29
5.23
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5.11
5.08
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2.30
2.29
2.02
1.41
1.39
1.38
1.37
1.35
0.88
0.87
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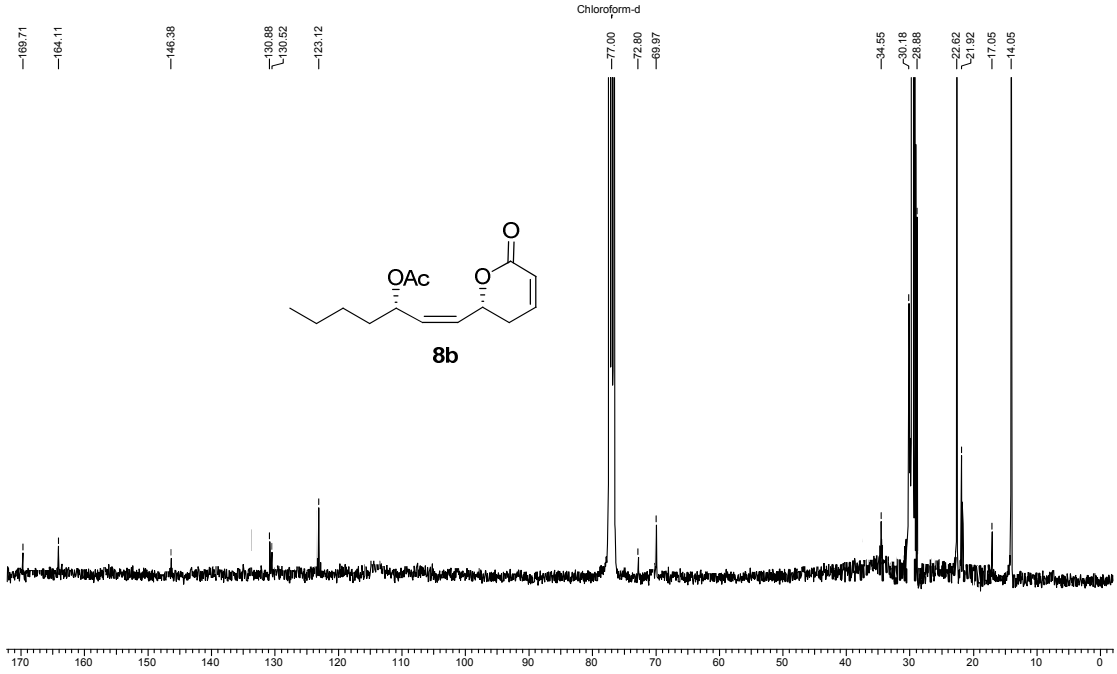
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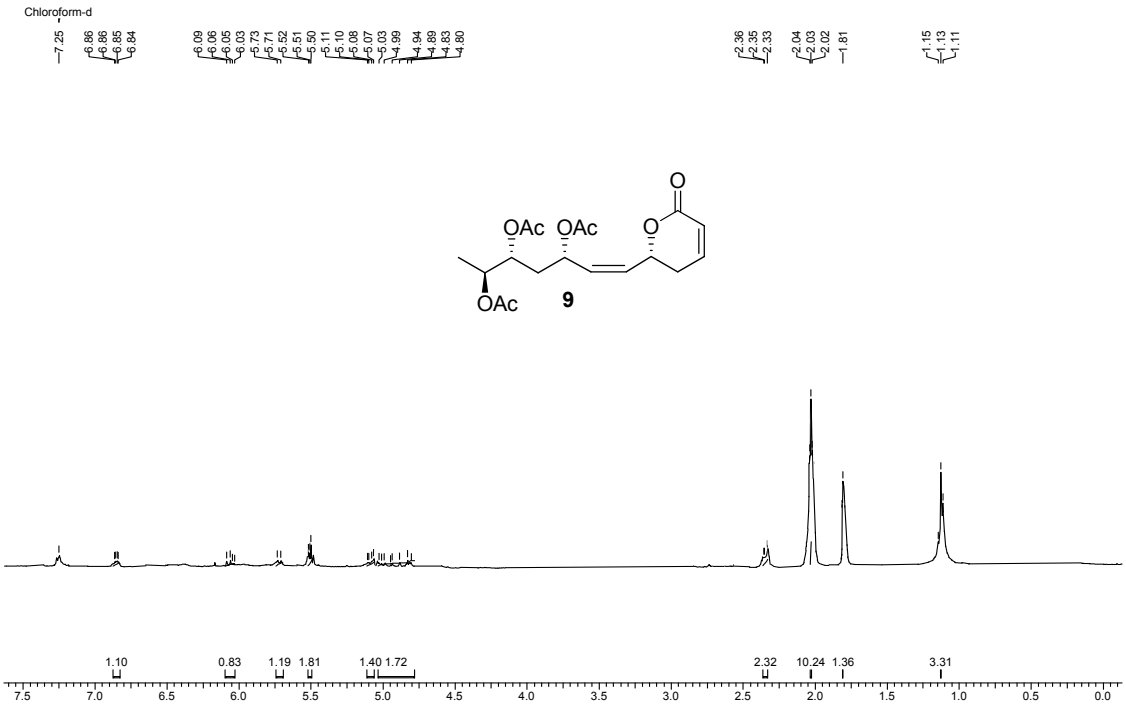
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5.51
5.50
5.11
5.10
5.08
5.07
5.03
4.99
4.94
4.89
4.83
4.80
2.36
2.35
2.33
2.04
2.03
2.02
1.81
1.15
1.13
1.11
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OAc
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O
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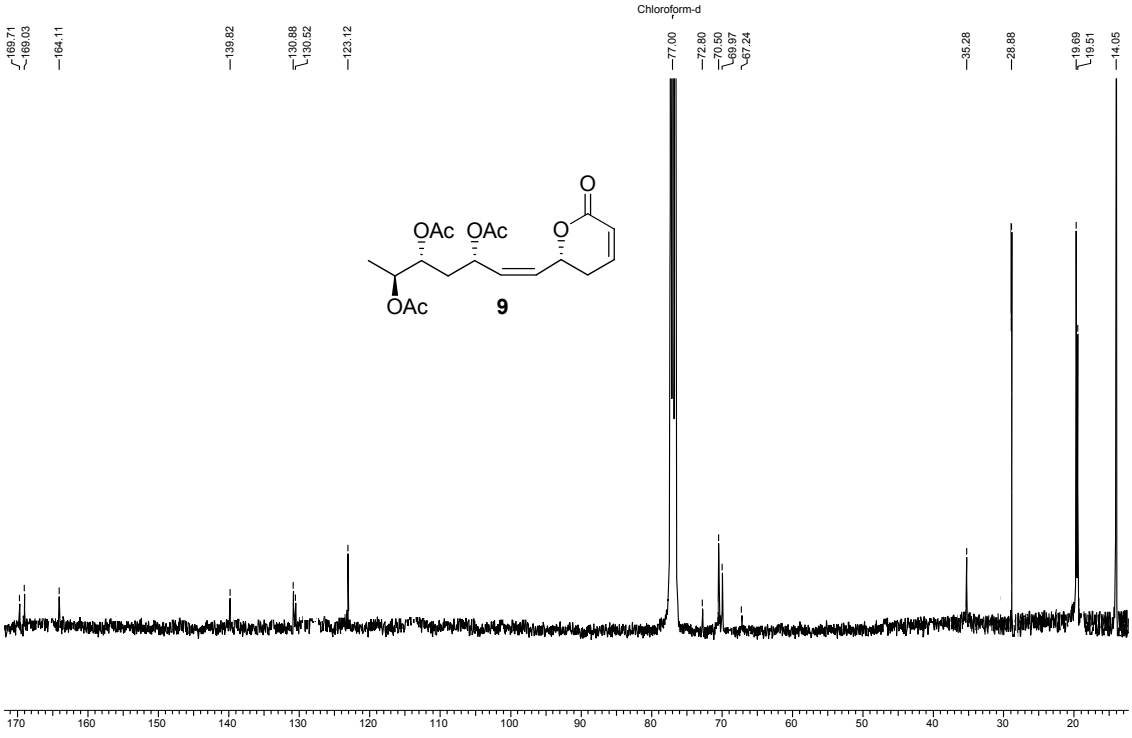
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67.24
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OAc
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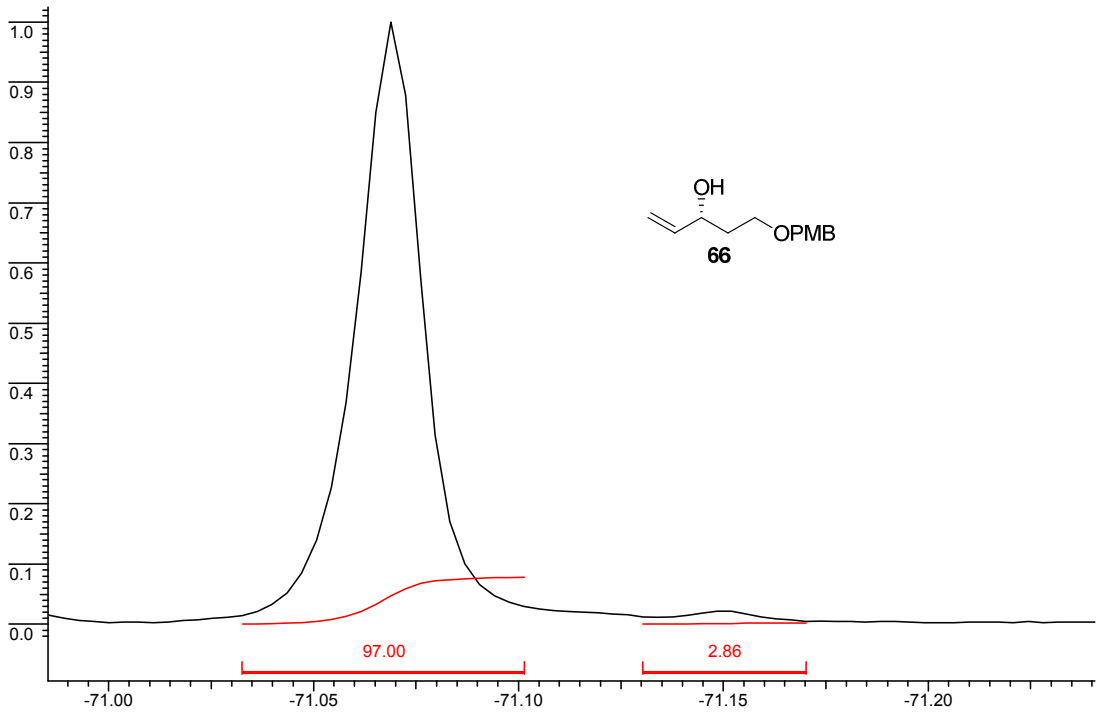
OAc
9

## $^{19}$F spectrum of Mösher ester of **58**



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# 3.2 Section B

# ATTEMPTED TOTAL SYNTHESIS OF HYPURTICIN *VIA* TEMPORARY SILICON TETHERED-RING CLOSING METATHESIS

## 3.2.1. Introduction

Currently, chemical and pharmacological research are largely directed toward the discovery of new cytotoxic agents from natural sources.[1] Configurational and conformational behaviour of bioactive principles requires an accurate description of their three-dimensional properties, thus permitting visualization and understanding of the possible interactions with target biomolecules.[2] For example, a relevant group of cytotoxic compounds, occurring in several members of the mint family (Lamiaceae), comprises polyacylated-6-heptenyl-5,6-dihydro-2*H*-pyran-2-ones[3] (e.g., **1**-**8**, Figure 1) containing an *α,β*-unsaturated *δ*-lactone known to bind protein thiol groups. This class of bioactive chemicals is structurally related to pironetin, an anticancer natural product, which selectively targets Lys-352 of R-tubulin.[4] Compounds such as hyptolide (**2**),[5] spicigerolide (**3**),[6] pectinolides A-C (**4**-**6**),[7] and 10-*epi*-olguine (**7**)[8] exhibit activity against specific tumor cell lines. However, the mechanism of action, the specific molecular target, the pharmacophore conformational requirements, and, in some cases, the absolute configuration of the stereogenic centers in the flexible side chain are not yet established, as in the case of the polyacylated chain of hypurticin (**1**), a natural 6-heptenyl-5,6-dihydro-2*H*-pyran-2-one. During the isolation of **1** from *Hyptis urticoides* by Romo de Vivar's group,[9] the C-6 absolute configuration was established as *S* by chiroptical measurements, the CD curve showing a positive Cotton effect similar to that of previously known 6-substituted-5,6-dihydro-*R*-pyrones,[10] such as hyptolide (**2**)[5] and olguine (**8**).[11] The C-5 stereogenic center was assigned the *S* configuration due to the $J_{5,6}$ coupling constant, which evidenced the *cis* relationship between these hydrogens.[9] However, the absolute configuration of the stereogenic centers located at the heptenyl side chain could not be determined. The variety of configurational possibilities and the high number of conformational arrangements

arising from the flexibility of this molecular moiety precluded its full structural determination at that time. However recently Pereda-Miranda and co-workers[12a] determined the configuration of polyacylated chain of hypurticin and the revised structure was found to correspond to that of pectinolide E, recently isolated from *Hyptis pectinata*.[12b]

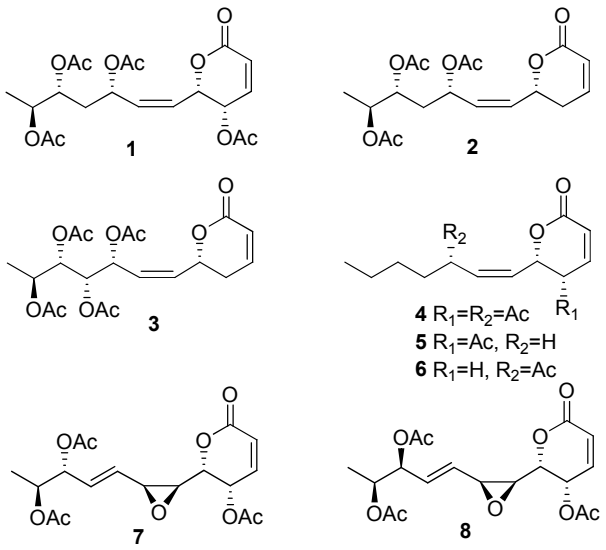


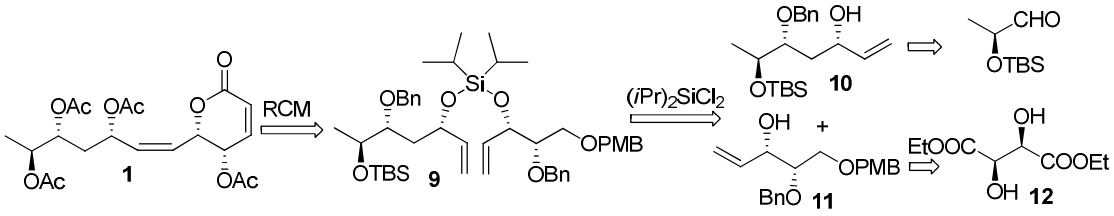

**Figure 1.** 6-Heptenyl-5,6-dihydro-2*H*-pyran-2-ones from Lamiaceae.

# 3.3.2. PRESENT WORK

## *Objective*

As discussed in foregoing section, with the development of an efficient approach to the synthesis of polyacylated-6-heptenyl-5,6-dihydro-2*H*-pyran-2-ones such as umuravumbolide, hyptolide through a silicon tethered ring-closing metathesis reaction sequence, our attention was further focused to extrapolate this protocol for the synthesis of hypurticin (**1**). Synthetic studies toward the aforementioned molecules (**2-6**) have been reported by Marco,[13] Chakraborty,[13b] and Yadav *et al.*[13c] To the best of our knowledge, all attempts have been in linear fashion involving semi-hydrogenation of the alkyne part using Lindlar's catalyst to generate the side chain olefin and ring closing metathesis reaction for the construction of lactone ring. However, no total synthesis of hypurticin **1** has yet been reported.

As a part of our current interest in naturally occurring, pharmacologically active *α, β*-unsaturated *δ*–lactone,[14] we have attempted at the first total synthesis of hypurticin **1** by a highly convergent strategy to confirm its structure, including the absolute stereochemistry. We note in advance that our approach is both concise and versatile exploiting temporary silicon tethered ring-closing metathesis (TST-RCM)[15] and reaction of *β*-acetoxy aldehydes with the lithium enolate of methyl acetate[16] to construct the olefins. The strategy provides convergent synthetic access to all members of the Lamiaceae family. The general synthetic analysis is depicted in Scheme 1.




**Scheme 1.** Retro-synthetic analysis of hypurticin **1**.

We aimed to construct the side chain *Z*-olefin through ring closing metathesis of bis-siloxane intermediate **9**. The intermediate **9** would originate by the coupling of two

allylic alcohols **10** and **11** which in turn could be derived from TBS protected L-lactaldehyde and diethyl L-tartrate **12** respectively.

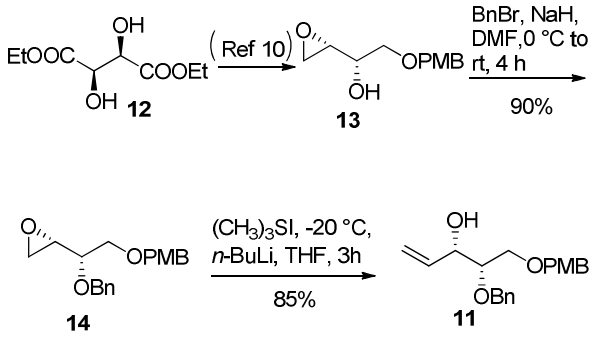
## 3.2.3. Results and Discussion

## Synthesis of fragment 10

The synthesis of fragment **10** is already mentioned in section B of chapter 3 (Scheme 9. Synthesis of fragment **67,** page no. **114**).

## Synthesis of fragment 11

The preparation of fragment **11** is summarized in scheme 2. The introduction of benzyl group on the secondary alcohol moiety of the known epoxy alcohol **13**,[17] derived from diethyl L-tartrate **12** according to Tatsuta's procedure afforded **14** in 90% yield. Appearance of multiplet in the range of δ 3.08-3.01, 2.72-2.68, 2.53-2.49 in $^1$H NMR and disappearance of OH peak in IR spectrum confirmed the formation of the product **14**. The epoxide **14** was subsequently exposed to Corey–Chaykovsky's[18] condition (dimethylsulfonium methylide mediated opening of epoxide) to produce the one carbon homologated allylic alcohol fragment **11** in 85% yield and was confirmed by IR spectrum and $^1$H NMR. The IR spectrum of **11** gave broad hydroxyl absorption at 3414 cm$^{-1}$ and the $^1$H NMR spectrum of **11** gave olefin peaks at δ 6.00-5.83 (multiplet, one proton) and 5.43-5.20 (multiplet, two protons) which confirmed the structure.



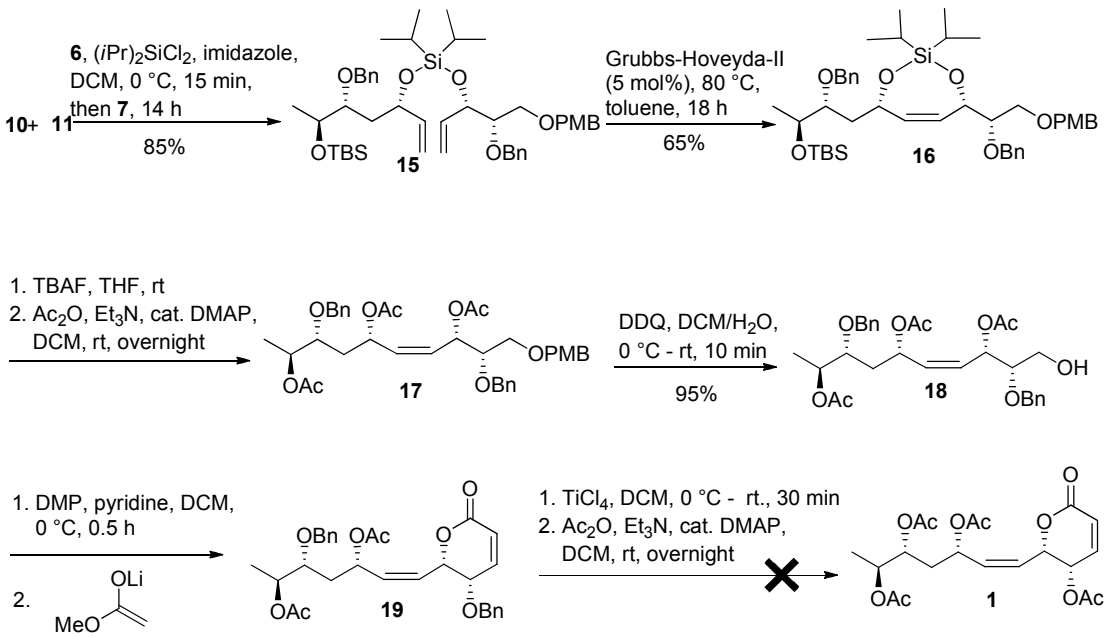

**Scheme 2**. Preparation of fragment **11**

## Coupling of Fragments 10 and 11: Synthesis of Hypurticin

With substantial amount of both the fragments in hand the coupling of allylic alcohol **10** and **11** was achieved by using the modified condition for tethering, used for the synthesis of umuravumbolide in the foregoing section, to afford the disiloxane intermediate 1**5** in 89% yield. The structure of **15** was proven by the $^{1}H$ NMR and $^{13}C$ NMR spectra. We next examined the ring closing metathesis (RCM) of disiloxane 1**5** using Grubbs catalyst (figure 2) under variety of reaction conditions to get exclusively the cis-product in appreciable yield (Table 1).

**Table 1.** Optimization of RCM condition for disiloxane 1**5**

| entry | Catalyst | solvent | Temperature ($^{o}C$) | Yield (%) |
|---|---|---|---|---|
| 1 | Grubbs II **A** | DCM | 40 | 10 |
| 2 | Grubbs II **A** | DCE | 84 | 10 |
| 3 | Grubbs II **A** | Toluene | 110 | 20 |
| 4 | Grubbs-Hoveyda II **B** | Toluene | 110 | 65 |




**Scheme 3.** Synthetic strategy for hypurticin **1**.

Initial few experiments using Grubbs second–generation catalyst **A** in different solvents such as DCM, DCE and toluene gave the required product albeit in low yield (Table 1; entry 1-3). However the best result was obtained when we employed Grubbs-Hoveyda second generation catalyst **B** in toluene at 110 °C providing the cyclized product **16** in 65% yield (Table 1; entry 4). The appearance of internal olefin at δ 5.98-5.70 and disappearance of four protons at δ 5.33-4.99 in $^1$H NMR confirmed the product.

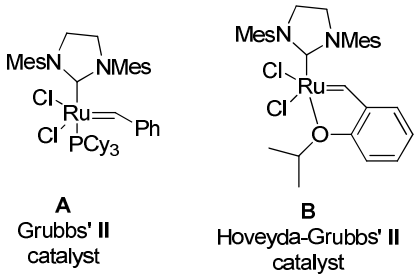


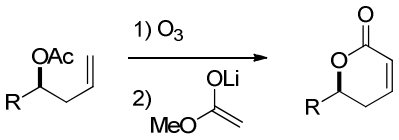

**Figure 2:** Metal-alkylidene metathesis catalysts.

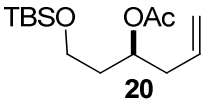
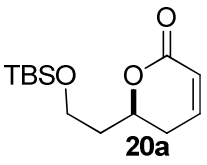
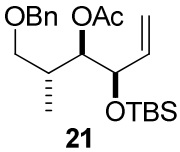
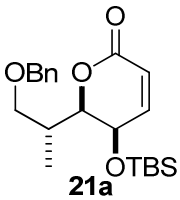
Our next objective toward the completion of the synthesis was to form the requisite lactone ring with unsaturation. Toward this end, we first deprotected the silyl groups using TBAF in THF and the crude triol thus obtained was eventually acetylated to give **17** in 92% yield. Appearance of singlet at δ 2.06, 2.02, 1.99 in $^1$H NMR and appearance of characteristic carbonyl group absorption of acetate at 1740 cm$^{-1}$ in IR spectrum confirmed the formation of the product **17**. This was followed by removal of the PMB protecting group, to give the desired primary alcohol **18** in 92% yield. The IR spectra of **18** showed hydroxyl absorption at 3449 cm$^{-1}$. In the $^1$H NMR spectra, the peaks owing to PMB group disappeared. Dess Martin periodinane oxidation led to the formation of aldehyde, now properly functionalized to effect incorporation of the lactone ring in a single step using the lactone annulation process. Lactone annulation was effected by reaction of this material with the lithium enolate of methyl acetate (initially at –78 °C for 15 min with warming to 0 °C and reaction at that temperature for 30 min). After quenching and normal workup, the desired lactone **19** was obtained in 74% yield. The IR spectrum of **19** showed characteristic carbonyl group absorption of $\alpha,\beta$-unsaturated $\delta$-lactone at 1650 cm$^{-1}$.

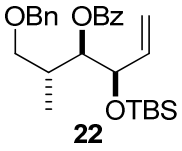
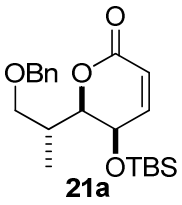
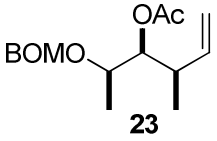
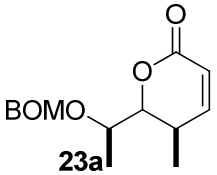
***Mechanism of the Cyclization Reaction***

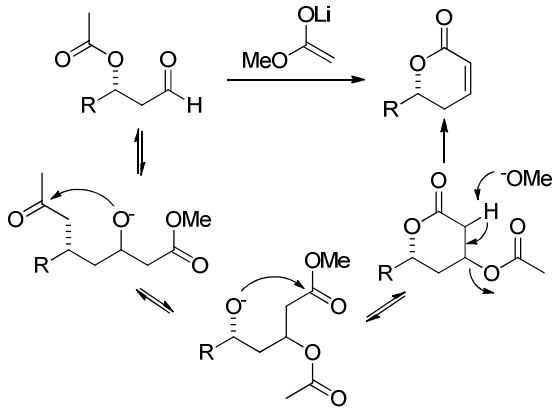
*It was proposed that these reactions proceed via initial addition of the lithium enolate to the aldehyde carbonyl, followed by acetate migration and subsequent lactonization and β-elimination (Scheme 4). An alternative possibility involving an intramolecular condensation of an acetate enolate generated by a proton transfer-equilibration process is considered extremely unlikely on the basis of the following evidence (Table 2). First of all, with substrate* ***24****, conversion to* ***21a*** *was found to occur (albeit in lower yield) when the benzoate derivative was used in place of the acetate (Table 1, entries 2 and 3). This is consistent with the suggested pathway, and also with the expectation that the benzoate would undergo the critical migration step less readily than the acetate. Second, when the propionate* ***24*** *rather than the acetate derivative of substrate* ***23*** *was employed in a reaction with the enolate of methyl acetate,* ***23a*** *was again obtained in essentially the same yield, demonstrating that the propionate group was lost in the reaction (Scheme 5). This result is compatible with the proposed overall pathway.*

**Table 2.** Preparation of Lactone Products

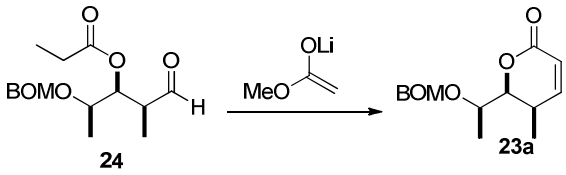



| Entry | Substrate | Product | %Yield |
|---|---|---|---|
| 1 |   **20** |   **20a** | 89 |
| 2 |   **21** |   **21a** | 73 |

| | | | |
|---|---|---|---|
| 3 |  **22** |  **21a** | 46 |
| 4 |  **23** |  **23a** | 62 |



***Scheme 4.*** *Proposed mechanism*



***Scheme 5.*** *Preparation of lactone*

Unfortunately final debenzylation followed by the acetylation of secondary alcohols proved to be unsuccessful and could not give the target molecule hypurticin **1** (Scheme 3).

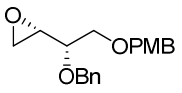
## 3.2.4. Conclusion

In conclusion, an attempt has been made to synthesize the polyacylated-6-heptenyl-5,6-dihydro-2*H*-pyran-2-one, hypurticin **1** by using temporary silicon tetherd ring closing metathesis (TST-RCM). The side chain *Z*-olefin and the *α,β*-unsaturated

lactone were synthesized successfully by the reaction of *β*-acetoxy aldehydes and the lithium enolate of methyl acetate as the key step.

## 3.2.5. Experimental Section

General Methods: All reactions were carried out under argon or nitrogen in oven-dried glassware using standard gas-light syringes, cannulas and septa. Solvents and reagents were purified and dried by standard methods prior to use. Optical rotations were measured at room temperature. IR spectra were recorded on an FT-IR instrument. $^{1}H$ NMR spectra were recorded on 200 MHz, 300 MHz and 500 MHz and are reported in parts per million (δ) downfield relative to $CDCl_3$ as internal standard and $^{13}C$ NMR spectra were recorded at 50 MHz, 75 MHz and 125 MHz and assigned in parts per million (δ) relative to $CDCl_3$. Column chromatography was performed on silica gel (100-200 and 230-400 mesh) using a mixture of petroleum ether and ethyl acetate as the eluent.




**14**

**(*S*)-2-((*S*)-1-(Benzyloxy)-2-((4-methoxybenzyl)oxy)ethyl)oxirane (14):** To the epoxy alcohol **13** (0.5 g, 2.23 mmol) in DMF (1.2 mL) at 0 °C was added NaH (60 % dispersion in mineral oil, 0.10 g, 2.45 mmol). After 15 min, benzyl bromide (0.42g, 0.3 mL, 2.45 mmol) was introduced and the reaction mixture further stirred for 4 h at room temperature. Water was carefully added to the reaction mixture, extracted with diethyl ether, washed with water and dried ($Na_2SO_4$). Silica gel column chromatography of the crude product using petroleum ether/EtOAc (90:10) as eluent afforded benzyl compound **14**.

**Yield:** 0.63 g, 90%

**Mol. Formula**: $C_{19}H_{22}O_4Na$

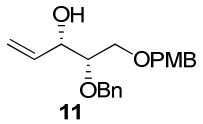
$[\alpha]_D^{25}$: – 9.02 (*c* 3, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 2970, 2858, 1457, 1460, 1370, 1256, 1110, 1001, 785.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.32-7.26 (m, 5H), 7.23-7.13 (m, 2H), 6.81-6.76 (m, 2H), 4.76-4.54 (m, 2H), 4.40 (s, 2H), 3.72 (s, 3H), 3.54-3.51 (m, 2H), 3.27-3.21 (m, 1H), 3.08-3.01 (m, 1H), 2.72-2.68 (m, 1H), 2.53-2.49 (m, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 159.2, 138.2, 129.2, 128.2, 127.9, 127.7, 127.5, 113.7, 79.1, 73.1, 71.9, 70.0, 55.2, 53.1, 43.3.

**HRMS** ($ESI^+$) m/z calcd for $C_{19}H_{22}O_4Na$ $[M + Na]^+$ 337.1416, found 337.1417.



**11**

**(3*S*, 4*S*)-4-(Benzyloxy)-5-((4-methoxybenzyl)oxy)pent-1-en-3-ol (11):** To a suspension of trimethylsulfonium iodide (1.18 g, 5.82 mmol) in dry THF (2.5 mL) at −20 $^oC$ was added *n*-BuLi (3.88 mL, 1.6 M solution in hexane, 6.2 mmol) dropwise over 20 min and stirred for 30 min. Then the epoxide **14** (0.3 g, 0.95 mmol) in dry THF (1.5 mL) was added to the above reaction mixture and stirred for 3 h. After consumption of the starting material the reaction mixture was quenched with $H_2O$ (10 mL) and extracted with EtOAc (4 × 10 mL). The combined extracts were washed with brine, dried over $Na_2SO_4$ and concentrated. The column chromatography of crude product using pet ether:ethyl acetate (85:15) gave **11** as a colorless liquid.

**Yield:** 0.26 g, 85%

**Mol. Formula**: $C_{20}H_{24}O_4Na$

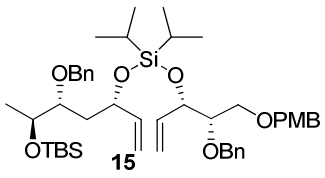
$[\alpha]_D^{25}$: +1.52 (*c* 3.4, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3414, 1613, 1586, 1248, 1089, 1039.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.40-7.35 (m, 5H), 7.29-7.24 (m, 2H), 6.92-6.88 (m, 2H), 6.00-5.83 (m, 1H), 5.43-5.20 (m, 2H), 4.79-4.48 (m, 5H), 4.29-4.24 (m, 1H), 3.82 (s, 3H), 3.73-3.55 (m, 3H), 2.42 (s, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 159.2, 138.0, 137.2, 129.9, 129.3, 128.3, 127.8, 127.7, 116.6, 113.7, 80.2, 73.1, 72.9, 72.5, 69.4, 55.2.

**HRMS** ($ESI^+$) m/z calcd for $C_{20}H_{24}O_4Na$ $[M + Na]^+$ 351.1572, found 351.1568.




**(4*S*, 5*S*, 9*S*, 11*R*, 12*S*)-4,11-Bis(benzyloxy)-7,7-diisopropyl-1-(4-methoxyphenyl)-12,14,14,15,15-pentamethyl-5,9-divinyl-2,6,8,13-tetraoxa-7,14-disilahexadecane (15):** Dichlorodiisopropylsilane (0.029 ml, 0.16 mmol) was added to imidazole (0.029 g, 0.43 mmol) in DCM (0.04 ml) at 0 ºC. The solution was stirred for 5 minutes, then the fragment **10** (0.05 g, 0.143 mmol) in DCM 0.035 ml) was added dropwise over a period of 1 h at 0 ºC. After the mixture was stirred for 15 minutes at 0 ºC, a solution of the fragment **11** (0.046 g, 0.143 mmol) in DCM (0.035 mL) was added at 0 ºC. The reaction mixture was warmed to the room temperature and stirred for 14 h. The reaction mixture was filtered and washed with hexane, then concentrated in vacuo to afford the crude oil, which was purified by flash chromatography on silica gel (pet ether:ethyl acetate = 98:2) to afford bis-alkoxysilane **15** as a colorless oil.

**Yield:** 0.094 g, 85%

**Mol. Formula**: $C_{46}H_{70}O_7Si_2Na$

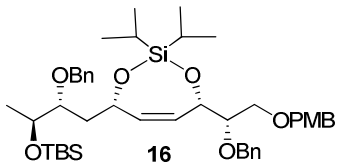
$[\alpha]_D^{25}$: – 1.86 (*c* 1.1, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 2935, 2856, 1713, 1600, 1504, 1265, 1065, 1071, 920, 885.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.40-7.25 (m, 12H), 6.88 (d, *J*=8.37 Hz, 2H), 6.00-5.72 (m, 2H), 5.33-4.99 (m, 4H), 4.91-4.77 (m, 2H), 4.72-4.43 (m, 6H), 3.94-3.87 (m, 1H), 3.83 (s, 3H), 3.77-3.72 (m, 2H), 3.53-3.37 (m, 2H), 1.18-1.14 (m, 3H), 1.10-1.08 (m, 4H), 1.04-1.02 (m, 12H), 0.92 (s, 9H), 0.10-0.05 (m, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 159.0, 140.9, 139.3, 139.1, 136.7, 134.8, 130.9, 129.1, 128.2, 127.6, 127.3, 127.2, 115.3, 114.6, 113.7, 81.6, 80.4, 72.9, 72.7, 72.4, 72.0, 71.6, 71.2, 70.63, 59.25, 39.9, 26.6, 26.0, 25.8, 18.7, 18.0, 17.4, 17.3, -4.6, -4.7.

**HRMS** ($ESI^+$) m/z calcd for $C_{46}H_{70}O_7Si_2Na$ $[M + Na]^+$ 813.4558, found 813.4552.




**(4*S*, 7*S*)-4-((*S*)-1-(Benzyloxy)-2-((4-methoxybenzyl)oxy)ethyl)-7-((2*R*, 3*S*)-2-(benzyloxy)-3-((*tert*-butyldimethylsilyl)oxy)butyl)-2,2-diisopropyl-4,7-dihydro-1,3,2-dioxasilepine (16):** A solution of 0.07 g (0.088 mmol) **15** in 16 mL toluene was degassed (for 5 minutes using argon), then 1 mg (0.003 mmol) Hoveyda–Grubbs second-generation catalyst **B** was added and the solution degassed again. It was stirred at 80 $^{o}$C for 18 h, before the solvent was removed in vacuo and the residue was purified by flash chromatography (pet ether:ethyl acetate = 98:2) to give cyclized product **16**.

**Yield:** 0.043 g , 65%

**Mol. Formula**: $C_{46}H_{70}O_7Si_2$

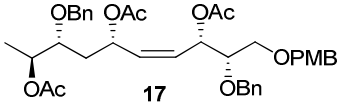
$[\alpha]_D^{25}$: – 1.73 (*c* 0.8, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 2931, 2901, 2301, 1800, 1654, 1466, 885, 847, 770, 681.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.38-7.26 (m, 12H), 6.86 (d, *J*=8.60 Hz, 2H), 5.98-5.70 (m, 2H), 4.90-4.75 (m, 2H), 4.56- 4.41 ( m, 6H), 3.92-3.86 (m, 1H), 3.81 ( s, 3H), 3.75-3.71(m,2H), 3.52-3.34 (m, 2H), 1.16-1.31 (m, 3H), 1.09-1.06 (m,4H), 1.02-1.00 (m, 12H), 0.90 (s,9H), 0.07-0.04 (m, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 159.1, 139.2, 130.9, 130.4, 129.2, 128.8, 128.2, 127.9, 127.7, 127.4, 113.7, 81.2, 81.0, 73.8, 73.5, 72.9, 71.0, 69.9, 65.6, 55.3, 39.5, 30.6, 30.2, 29.6, 25.8, 19.2, 18.9, 17.3, 17.0, -4.5, -4.7.

**HRMS** ($ESI^+$) m/z calcd for $C_{46}H_{71}O_7Si_2$ $[M + H]^+$ 763.4425, found 763.4423.



**(2*S*,3*R*,5*S*,8*S*,9*S*,*Z*)-3,9-Bis(benzyloxy)-10-((4-methoxybenzyl)oxy)dec-6-ene-2,5,8-triyl triacetate (17):** To a stirred solution of compound **16** (40 mg, 52 μmol) in THF (0.5 mL) was added TBAF (0.1 mL, 0.37 mmol) at room temperature and the yellow solution was stirred overnight at the same temperature. Water was added and the organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried with $Na_2SO_4$ and concentrated to give crude triol, which was used for the next step without purification.

The triol was then dissolved in dry $CH_2Cl_2$ (0.25 mL) and treated with $Et_3N$ (30 μL, 0.22 mmol), acetic anhydride (19 μL, 0.2 mmol) and DMAP (0.38 mg, 3 μmol). After stirring overnight, the reaction mixture was subjected to usual work up (extraction with $CH_2Cl_2$) and purification by silica gel column chromatography (pet ether:ethyl acetate = 80:20) to give triacetate **17**.

**Yield:** 0.03 mg, 98%

**Mol. Formula**: $C_{38}H_{46}O_{10}$

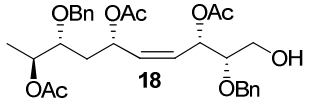
$[\alpha]_D^{25}$: – 20.45 (*c* 0.5, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 2900, 2301, 1800, 1740, 1654, 1513, 1445, 1348, 1092, 889.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.37-7.27 (m, 10H), 7.25-7.23(m, 2H), 6.89-6.87 (m, 2H), 5.78-5.67 (m, 2H), 5.53-5.45 (m, 1H), 5.42-5.35 (m, 1H), 5.16-5.09 (m, 1H), 4.72-4.60 (m, 3H), 4.45-4.34 (m, 3H), 3.82 (s, 3H), 3.69-3.64 (m, 1H), 3.55-3.43 (m, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 1.99 (s, 3H), 1.71-1.69 (m, 2H), 1.23 (d, J=6.66 Hz, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 170.4, 169.9, 159.2, 138.2, 138.1, 131.8, 130.9, 130.1, 129.2, 128.9, 128.4, 128.3, 127.8, 127.7, 113.7, 79.0, 78.9, 73.1, 73.0, 71.8, 71.6, 70.9, 69.1, 55.2, 35.1, 21.3, 21.2, 21.1, 15.1.

**HRMS** ($ESI^+$) m/z calcd for $C_{38}H_{47}O_{10}$ $[M + H]^+$ 663.3169, found 663.3169.



18

**(2*S*,3*R*,5*S*,8*S*,9*S*,*Z*)-3,9-Bis(benzyloxy)-10-hydroxydec-6-ene-2,5,8-triyl triacetate (18):** To a stirring solution of PMB ether **17** (0.03 g, 0.052 mmol) in DCM/$H_2O$ (0.15:0.008) was added DDQ (0.014 g, 0.063 mmol). The resulting mixture was stirred for 10 min at r.t. The mixture was poured into saturated aqueous $NaHCO_3$ and further diluted with DCM. The layers were separated and the aqueous layer was extracted with DCM (2 x 10 mL). The combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated. The solvents were removed under reduced pressure to give the crude product mixture as yellow oil. Silica gel column chromatography of the crude product using pet ether:ethyl acetate (70:30) as eluent gave **18**.

**Yield:** 0.026 g, 95%

**Mol. Formula**: $C_{30}H_{38}O_9$

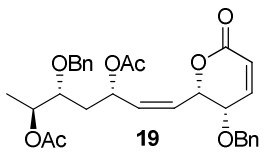
$[\alpha]_D^{25}$: – 17.61 (*c* 0.5, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3456, 2967, 2861, 2350, 1730, 1498, 1409, 1100, 905.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.37-7.29 (m, 10H), 5.71-5.59 (m, 2H), 5.44-5.42 (m, 1H), 5.36-5.32 (m, 1H), 5.10-5.09 (m, 1H), 4.70-4.45 (m, 4H), 3.56-3.42 (m, 5H), 2.04 (m, 6H), 1.98 (s, 3H), 1.74-1.69 (m, 2H), 1.21 (d, *J*=6.71Hz, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 170.4, 170.2, 170.1, 139.3, 137.9, 137.9, 132.3, 128.6, 128.5, 128.4, 127.9, 80.1, 73.4, 73.2, 71.8, 71.7, 70.0, 61.1, 35.1, 21.2, 21.1, 14.1.

**HRMS** ($ESI^+$) m/z calcd for $C_{30}H_{39}O_9$ $[M + H]^+$ 543.2594, found 543.2596.




**19**

**(2S,3R,5S,Z)-3-(benzyloxy)-7-((2S,3S)-3-(benzyloxy)-6-oxo-3,6-dihydro-2H-pyran-2-yl)hept-6-ene-2,5-diyl diacetate (19):** Dess–Martin periodinane (0.02 g, 0.05 mmol) was added to a solution of compound **18** (0.025 g, 0.046 mmol) in DCM (0.4 ml) at 0 $^oC$. The reaction was stirred at rt for 30 min, before being quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. The

organic layer was washed with satd NaCl solution and dried over $Na_2SO_4$ and concentrated to afford an aldehyde that was used immediately in the next step without further purification.

To a 0 °C solution of diisopropylamine (6.8 μL, 48 μmol) in THF (0.6 mL), was added *n*-BuLi (27 μL, 44 μmol). After 20 min at 0 °C the solution was cooled to –78 °C and methyl acetate (3.8 μL, 48 μmol) was added by syringe and stirring continued for 15 min. The aldehyde (24 mg, 44 μmol) in 0.2 mL THF was cooled to –78 °C and transferred to the enolate solution *via* cannula. Stirring was continued for 15 min at which time TLC analysis indicated the starting material was consumed. The reaction mixture was warmed to 0 °C, stirred an additional 30 min and finally warmed to rt for 15 min. The solution was transferred via cannula into an Erlenmeyer flask containing pH=7 buffer (3 mL) and $CH_2Cl_2$ (3 mL). The resulting solution was extracted with $CH_2Cl_2$ (2 × 5 mL) and ethyl acetate (1 × 5 mL). The combined organics were dried over $Na_2SO_4$, filtered through a pad of Celite, and concentrated by rotary evaporation. Silica gel column chromatography of the crude product using pet ether:ethyl acetate (80:20) as eluent gave **19** as a colorless oil.

**Yield:** 0.017 g, 75%

**Mol. Formula**: $C_{30}H_{34}O_8$

$[\alpha]_D^{25}$: – 3.1 (*c* 0.5, $CHCl_3$).

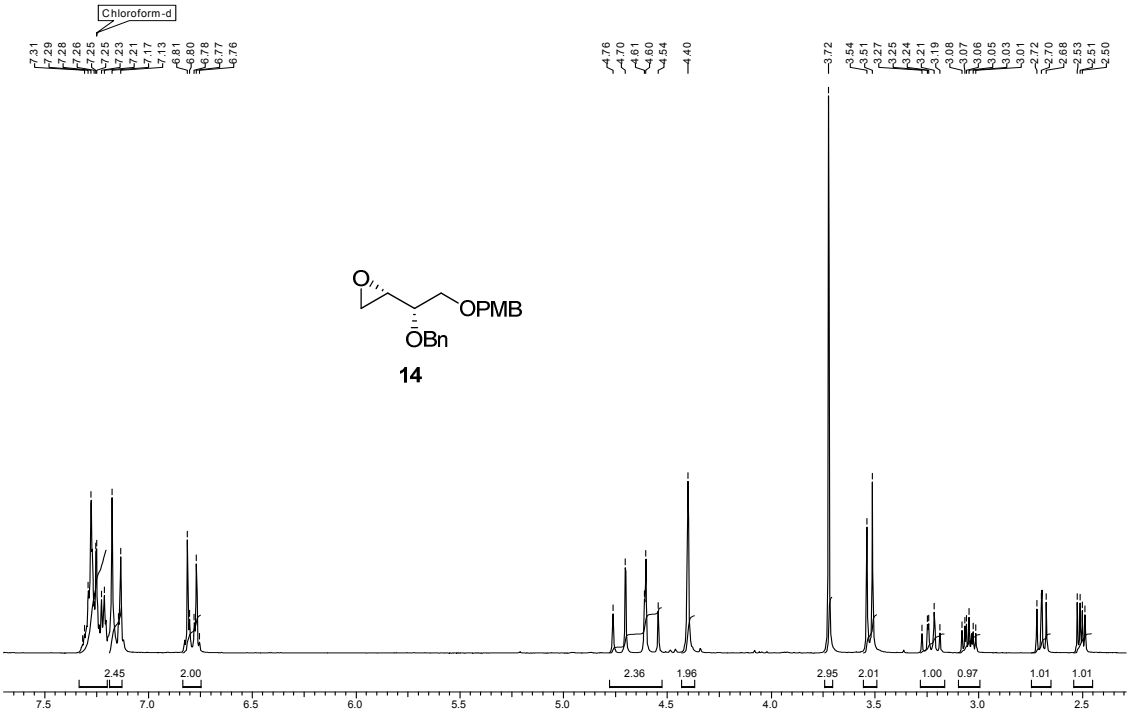
**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 1823, 1732, 1650, 1470, 1320, 1245, 1076, 872.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.20-7.17 (m, 10H), 6.98-6.94 (m, 1H), 6.67-6.63 (m, 1H), 6.03-5.99 (m, 1H), 5.85-5.80 (m, 1H), 5.13-5.06 (m, 1H), 4.40-4.31 (m, 4H), 3.95-3.90 (m, 1H), 3.68-3.52 (m, 3H), 2.10 (s, 3H), 1.97 (s, 3H), 1.72-1.56 (m, 2H), 1.15 (d, *J*= 6.67 Hz, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 174.4, 165.5, 146.5, 138.9, 133.4, 133.3, 130.4, 130.1, 129.7, 128.1, 127.6, 125.6, 74.3, 72.1, 70.6, 70.0, 69.2, 66.4, 65.5, 31.9, 22.7, 14.1.

**HRMS** ($ESI^+$) m/z calcd for $C_{30}H_{35}O_8$ $[M + H]^+$ 523.2332, found 523.2330.

## 3.2.6. Spectra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3.08
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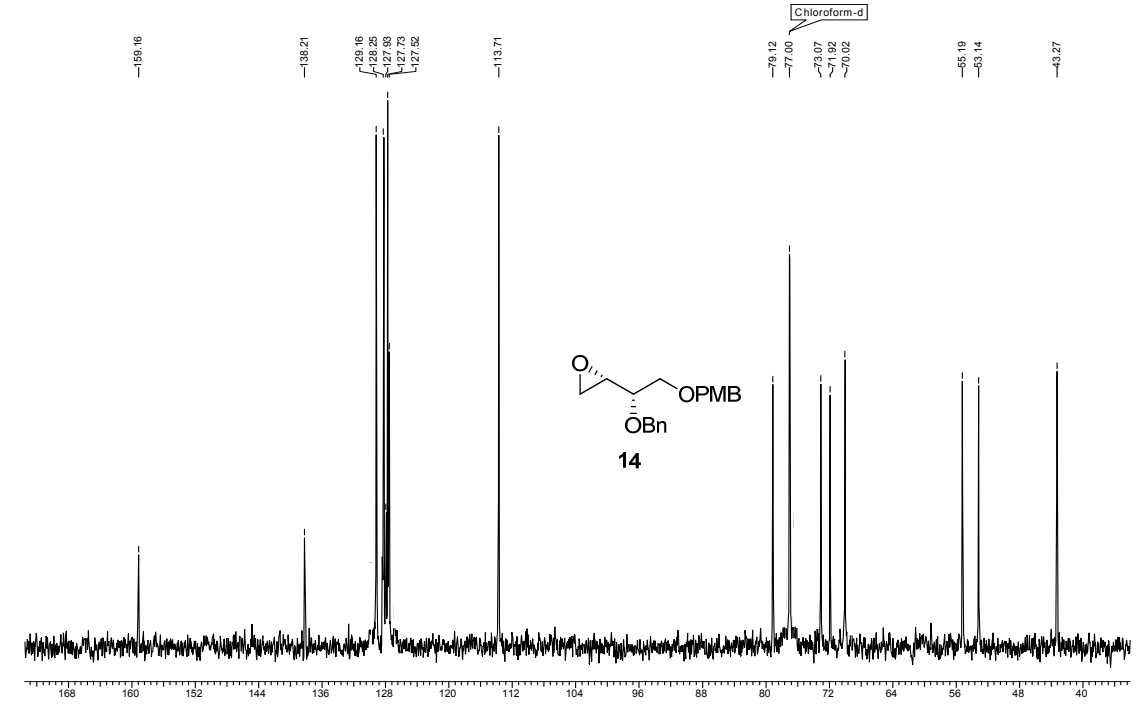
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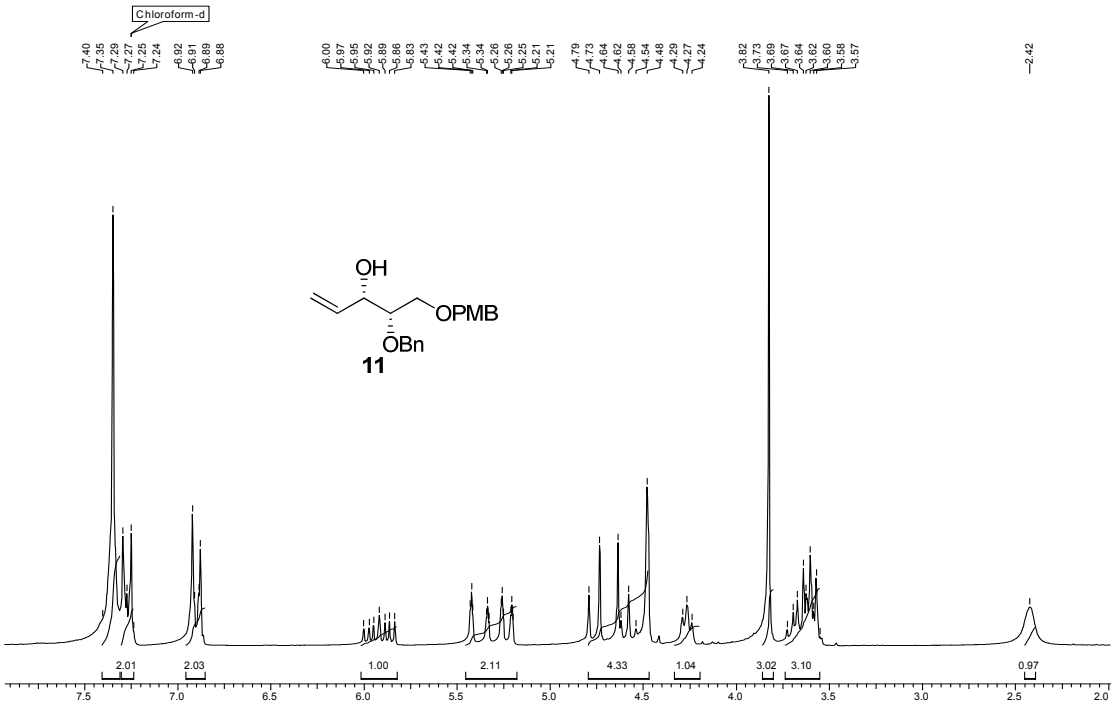
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5.42
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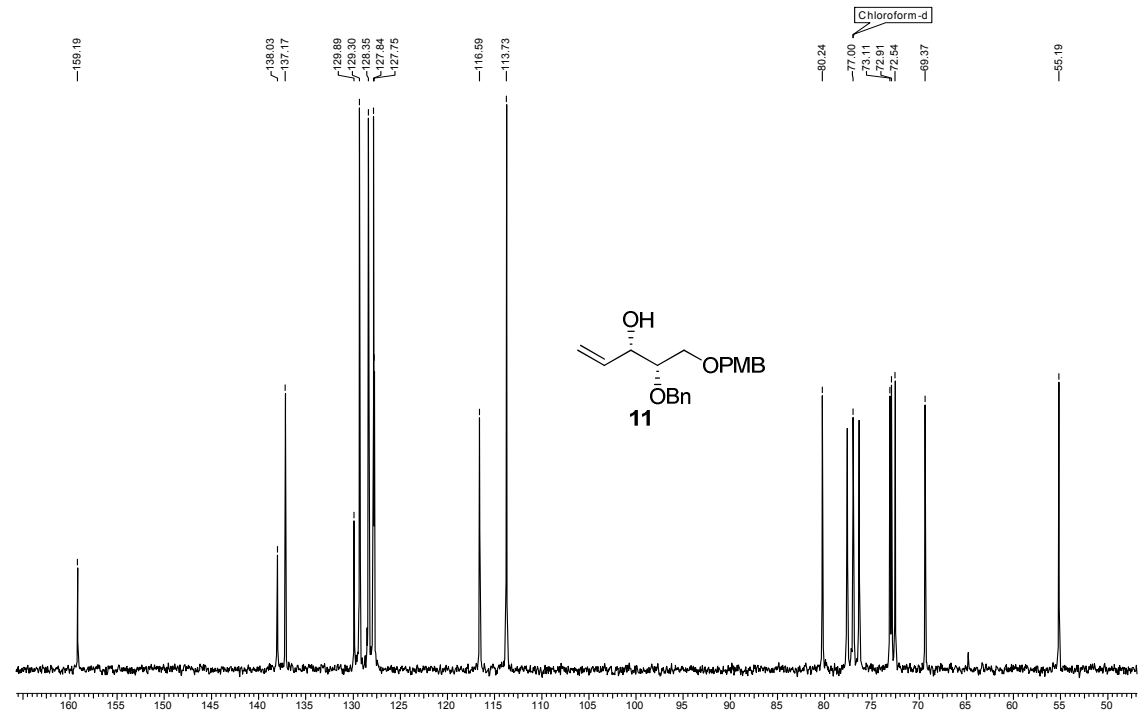
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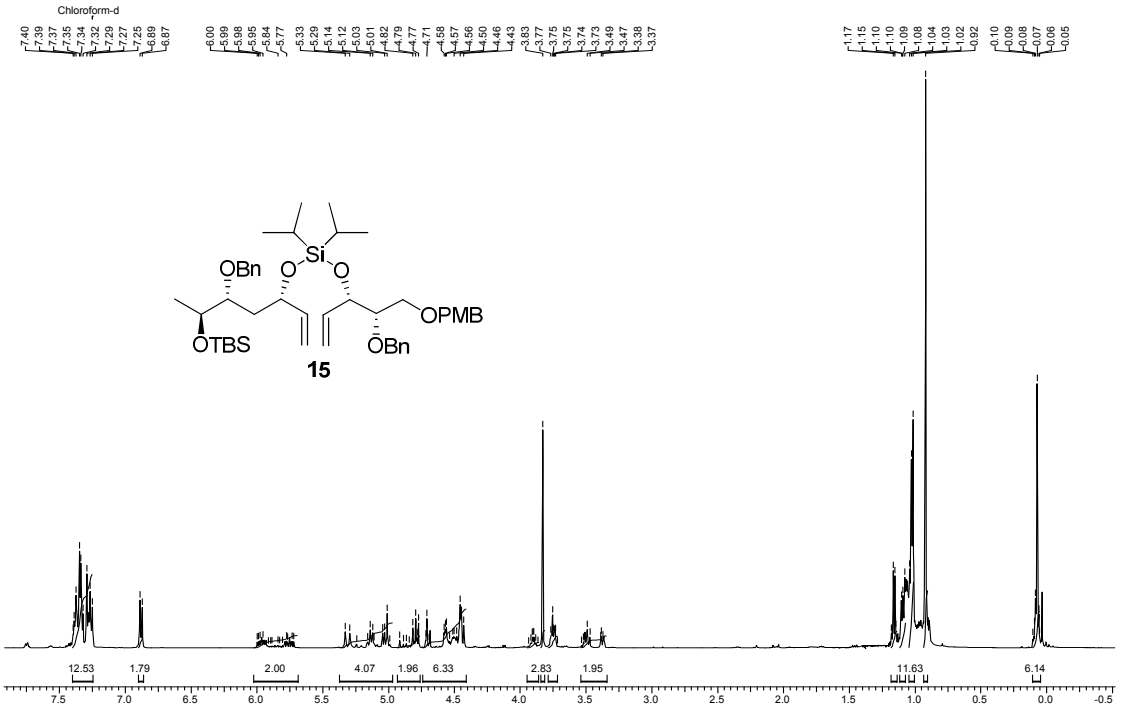
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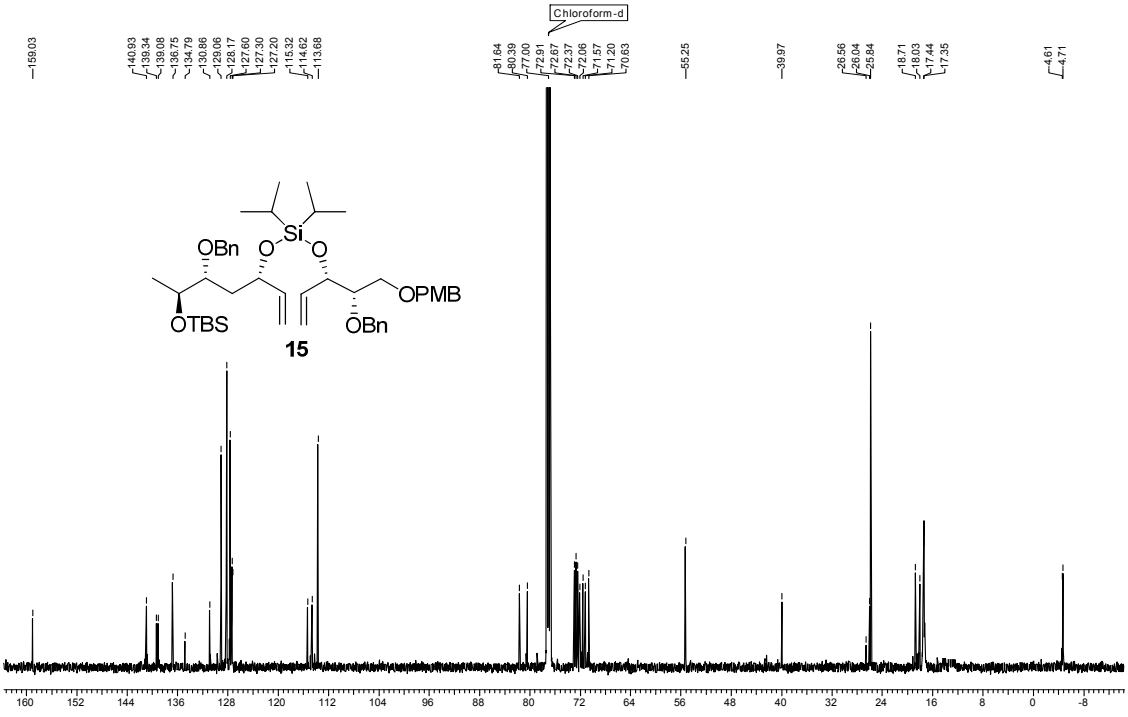
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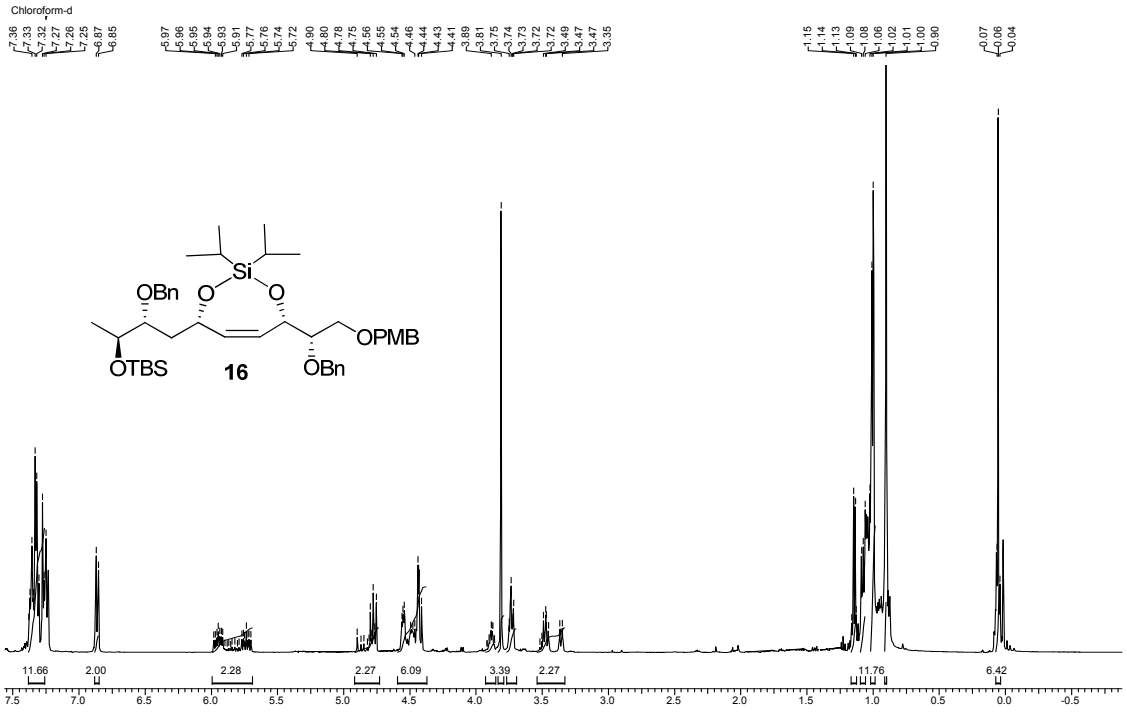
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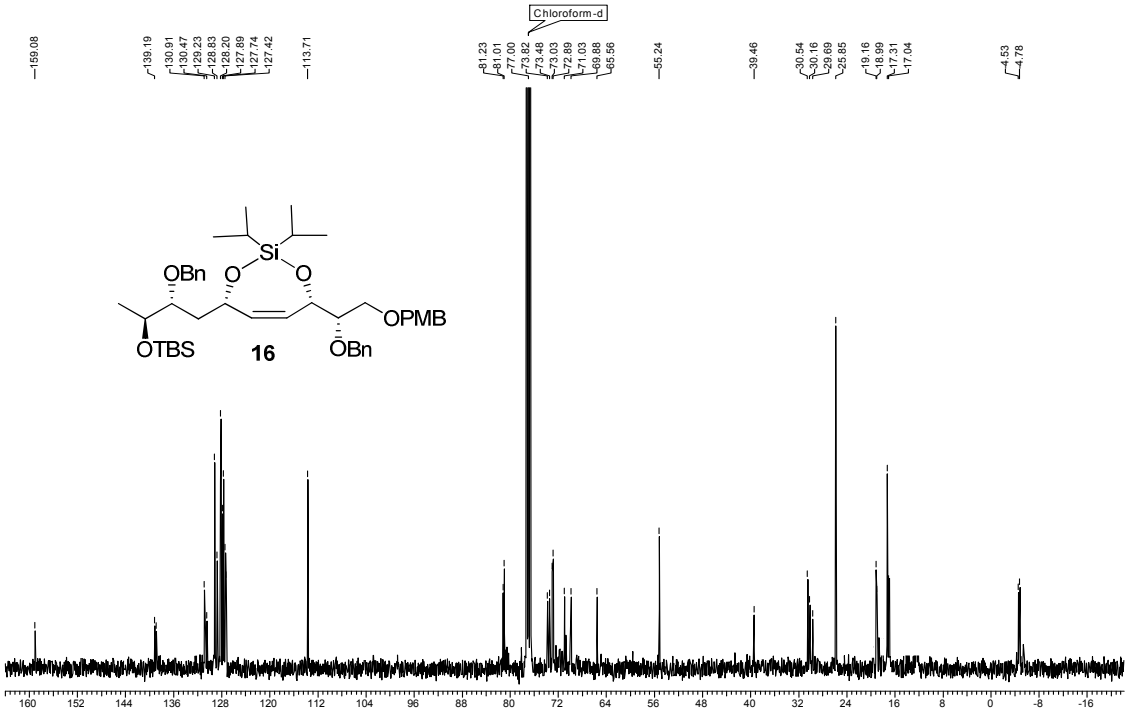
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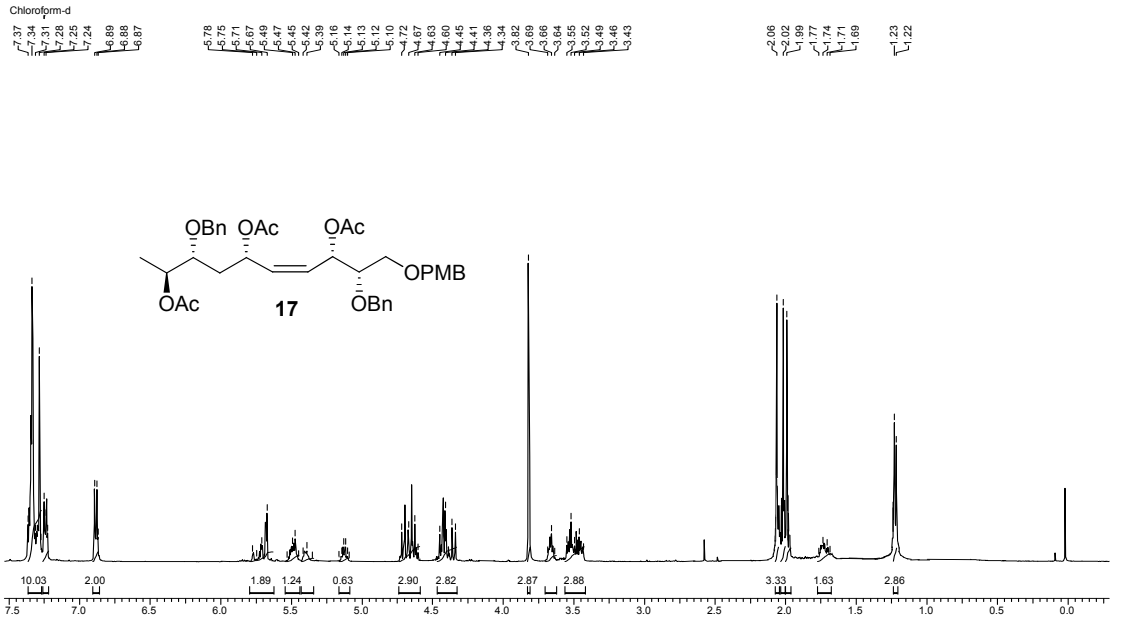
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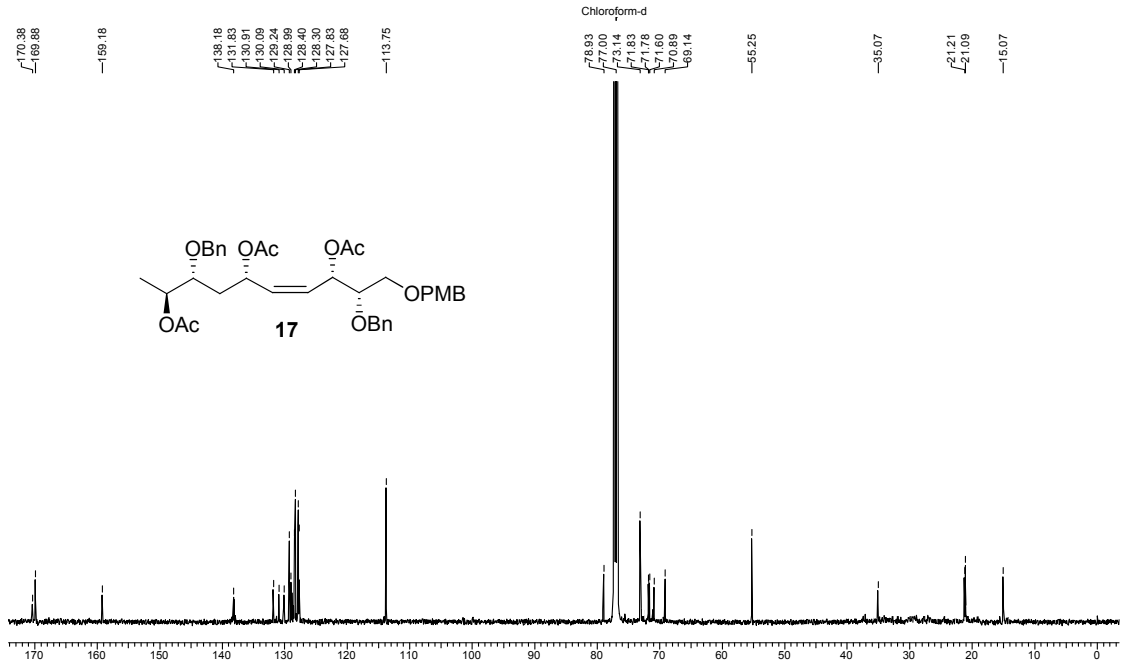
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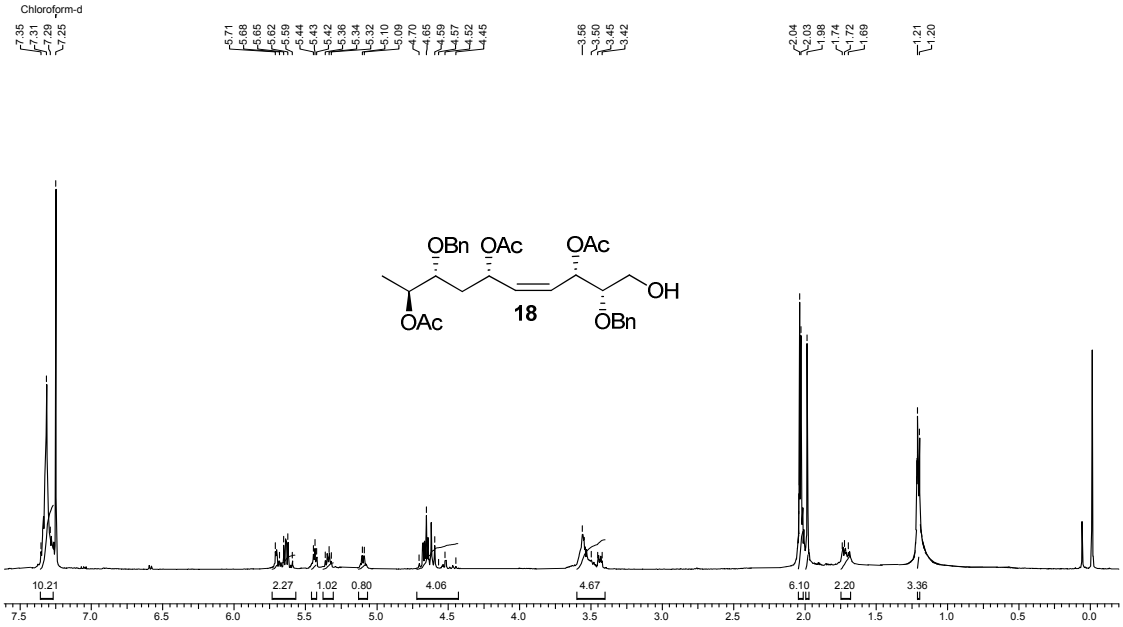
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3.56
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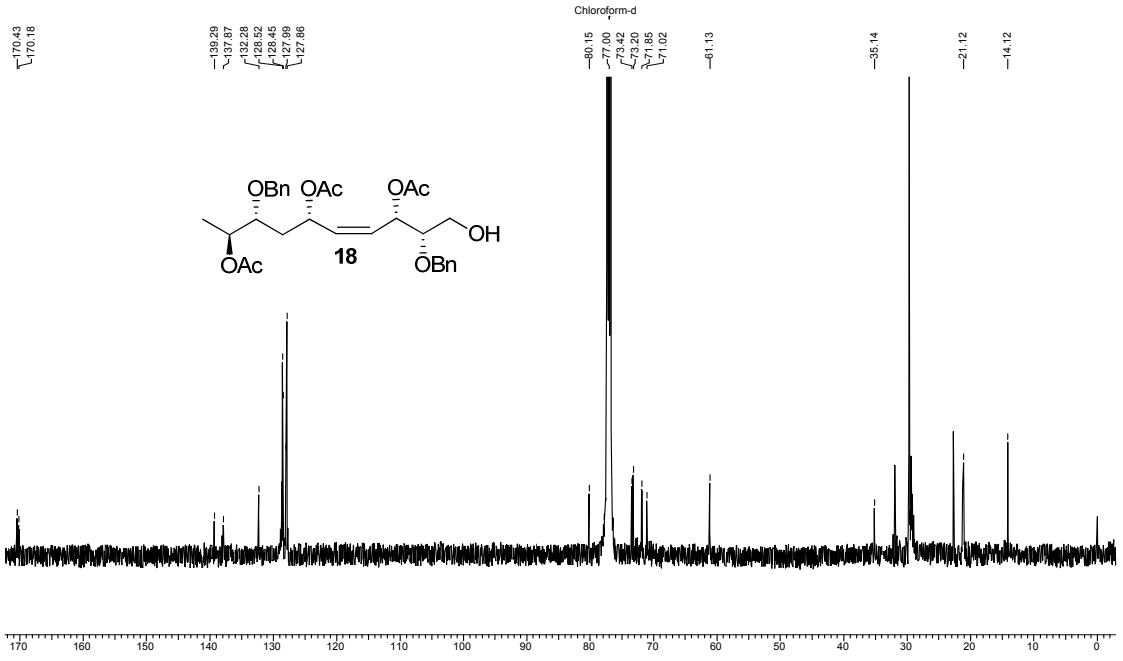
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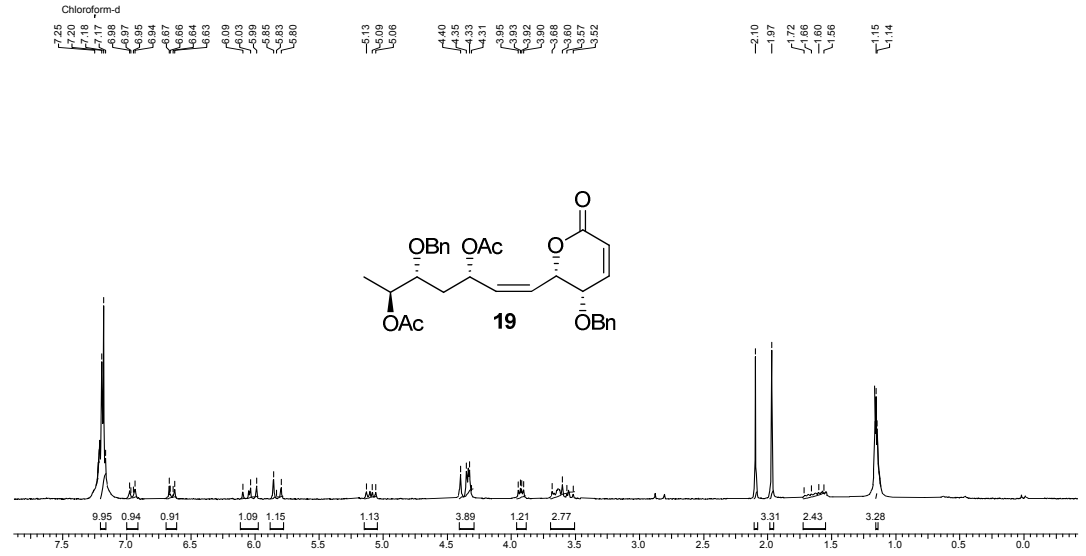
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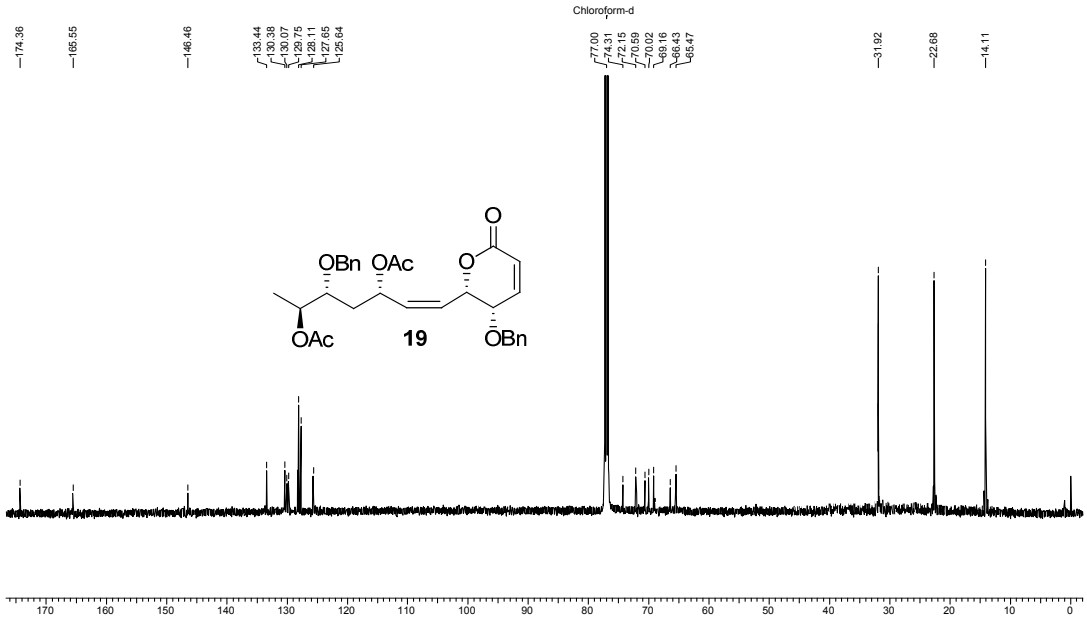
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O
OAc
19
OBn

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# CHAPTER-4

## A Desymmetrization Approach to the Enantiopure *syn/anti*-1,5-Diols *via* Hydrolytic Kinetic Resolution (HKR) of Functionalized Meso Bis-Epoxides: Further Elaboration to *syn*/*syn*-1,3,5-Triols and Application to the Formal Synthesis of Cryptocarya Diacetate

# 4

# A DESYMMETRIZATION APPROACH TO THE ENANTIOPURE *SYN/ANTI*-1,5-DIOLS *VIA* HYDROLYTIC KINETIC RESOLUTION (HKR) OF FUNCTIONALIZED MESO BIS-EPOXIDES: FURTHER ELABORATION TO *SYN/SYN*-1,3,5-TRIOLS AND APPLICATION TO THE FORMAL SYNTHESIS OF CRYPTOCARYA DIACETATE

## 4.1. Introduction

Last few decades have witnessed tremendous upsurge of interest in synthetic methods and strategies to generate 1,3,5...n-polyols,[1] which serve as an important scaffold in a variety of natural products with diverse bioactivity profiles (Figure 1).

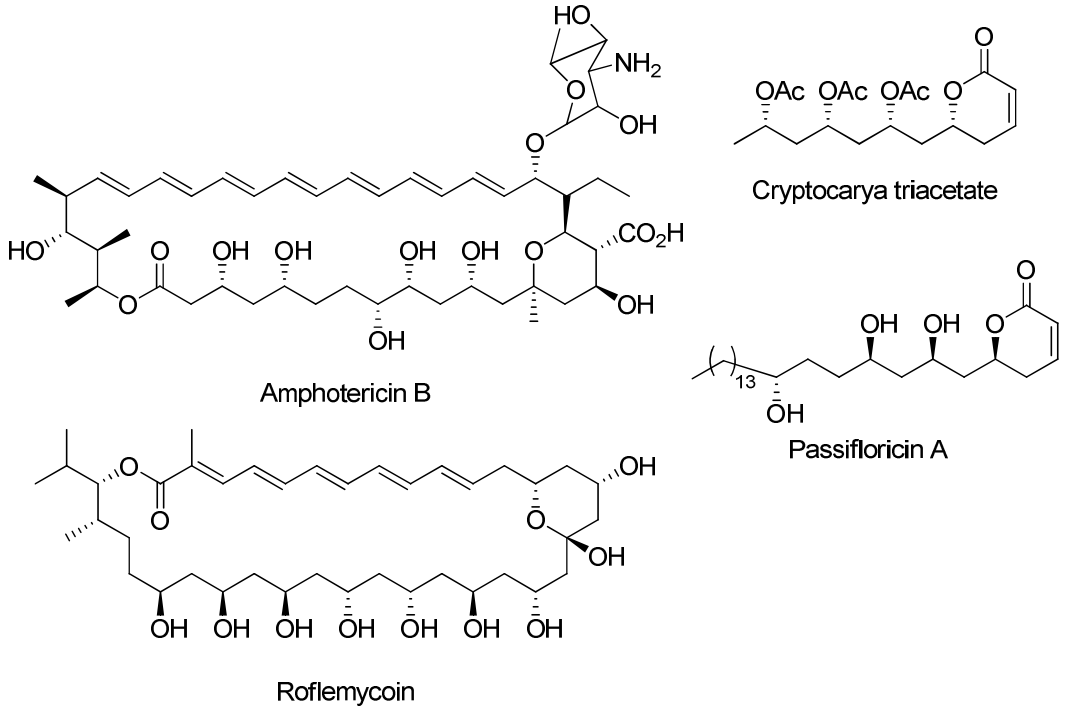



**Figure 1:** Representative examples of bioactive molecules containing 1,3-polyol moiety.

Despite the numerous strategies to synthesize polyols through substrate controlled asymmetric induction, the interest in the new methods of its synthesis continues unabated.[2]

In the last few years we have been actively involved in devising enantioselective methods to prepare 1,3-polyols. We have developed new routes to make both enantiomerically pure *syn/anti*-1,3-polyols by Jacobsen hydrolytic kinetic resolution of terminal epoxides in iterative fashion[3a] and also by proline-catalyzed *α*-aminoxylation of aldehydes.[3b] The utility of these methods was further demonstrated by synthesizing several natural products of biological importance.[4] However, in the first case the sequence of reaction suffers from a disadvantage due to the loss of 50% of starting compound as diol in each resolution step and in the second case it involves too many steps due to the iterative nature of the sequence.

Within the context of this work, the most widely used method to prepare 1,3-polyols in an iterative fashion are by allyl addition sequence utilizing stoichiometric amounts of chiral borons[5] and titanium.[6] Recently, Kirsch and coworkers have developed an efficient catalytic, iterative synthetic route to 1,3-polyols using Overmann esterification, [7a] while chromium-mediated asymmetric allylation has been reported by Kishi *et al*.[7b] However, the method involves a greater number of steps for each iteration[7a] (Kirsch *et al*.) or requires stringent reaction conditions[7b] (Kishi *et al*.) and uses an expensive catalyst.

All these multi-step processes are plagued by significant limitations in scope, selectivity and efficiency. In view of the above considerations, there is still need for a versatile synthetic method that addresses the following issues: mild reaction conditions, minimum steps for each iteration, cheap and readily available catalysts, and flexible construction of possible isomers.

*Syn/anti*-1,5-diols are important building blocks that are found in many polyketides such as tetrafribicin,[8] amphidinol[8b] and lienomycin[8c] etc (Figure 2).

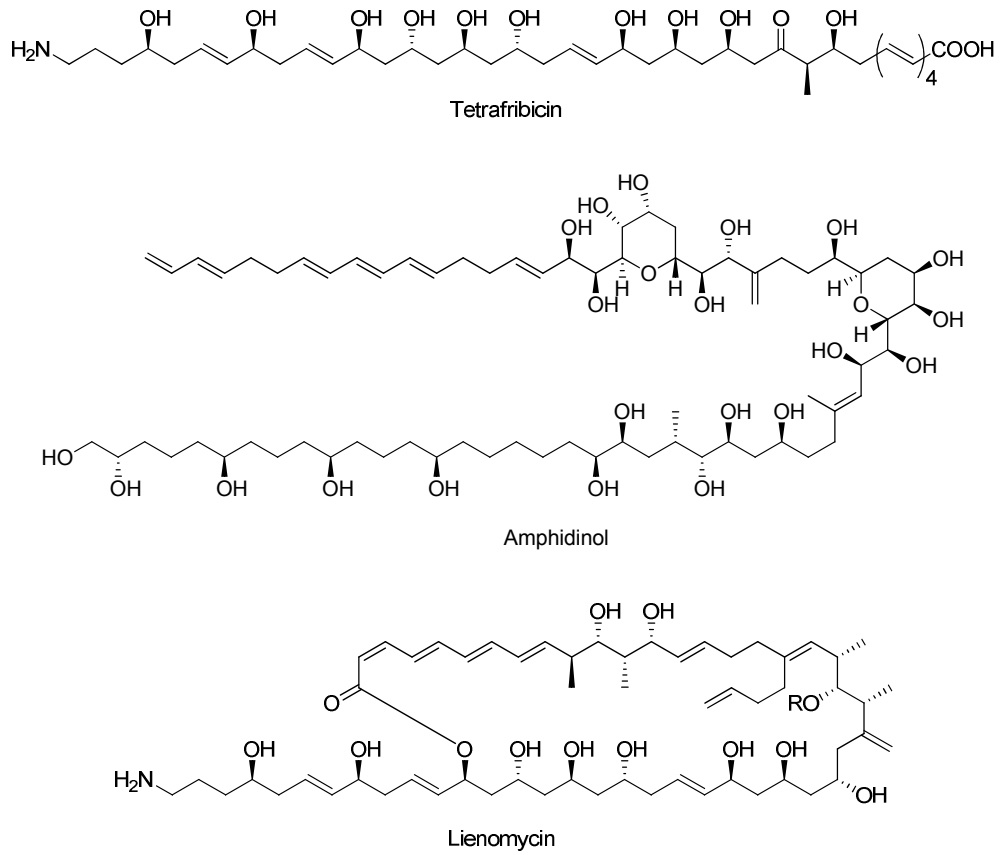



**Figure 2:** Representative examples of bioactive molecules containing 1,5-polyol moiety.

Though there are various synthetic strategies available for the preparation of 1,2-/ 1,3-diols but methods to prepare enantiomerically pure 1,5-diols[9] are rather scarce. Paterson[9a] and Evans[9b] have independently used boron-mediated aldol reactions of *β*-alkoxy methyl ketones for 1,5-stereoinduction. Roush and co-workers[9d] have also explored the boron chemistry for the synthesis of *syn/anti*-1,5-diols.

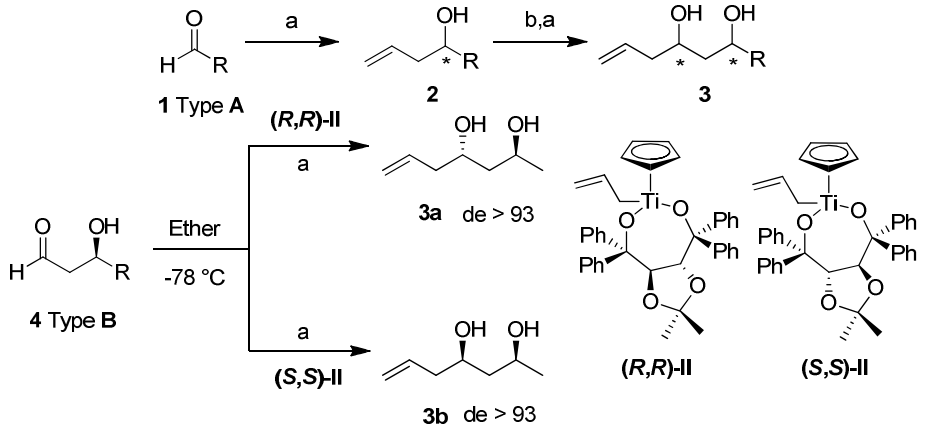
## 4.2. Review of Literature

***A. Selected approaches for stereoselective construction of 1,3,5-Polyols:***

**Cossy *et al.* (2000)[10]**

Cossy *et al.*[10] developed an enantioselective synthesis of *syn*- and *anti*-1,3-diols *via* allyltitanation of unprotected *β*-hydroxyaldehyde (Scheme 1). Thus *syn*- or *anti*-1,3-diols were obtained with good to excellent enantiomeric excess by allyltitanation of nonprotected *β*-hydroxyaldehydes of **4** (type **B)** with

cyclopentadienyldialkoxyallyltitanium complexes (*R,R*)-**II** or (*S,S*)-**II**[11] (Scheme 1). *β*-Hydroxyaldehydes **4** (type **B**) were prepared in two steps by allyltitanation of aldehydes of **1** (type **A)**. Treatment of aldehydes **1** with either complex (*R,R*)-**II** or (*S,S*)-**II** in ether at -78 °C afforded homoallylic alcohols **2** with good enantiomeric excess (*ee*) 93-96% [12, 13] and in high yield (85-92%). The transformation of these homoallylic alcohols to the corresponding *β*-hydroxyaldehydes **4** (type **B**) was achieved by using sodium periodate in the presence of a catalytic amount of osmium tetroxide.[14] These *β*-hydroxyaldehydes were unstable and treated directly with the allytitanium complexes. When the unprotected *β*-hydroxyaldehydes **4** (type **B**) was treated with (*S,S*)-**II** complexes, the *syn*-1,3-diols were obtained in high yield (78-85%) and with diastereoisomeric excesses up to 93%.



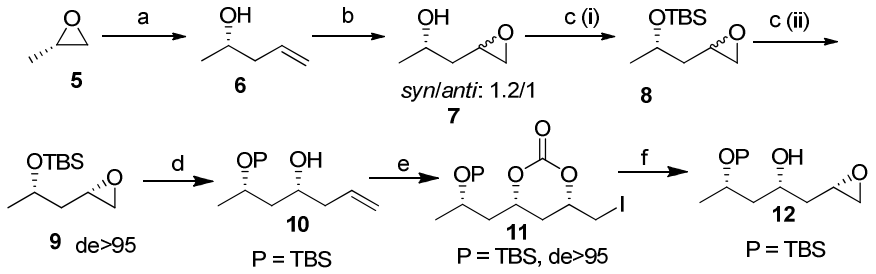

**Scheme 1.** *Reactions and conditions*: (a) cyclopentadienyldialkoxyallyltitanium complex **(*R*,*R*)-II** or **(*S*,*S*)-II** , Ether, –78 °C; (b) $NaIO_4$, $OsO_4$.

When *β*-hydroxyaldehydes **4** (type **B**) was treated with the same allyltitanium complex (*R,R*)-**II**, the *anti*-1,3-diols were isolated in high yield (75-83%) and with diastereoisomeric excesses up to 93% (Scheme 1).

### Kumar *et al.* (2006)[3a]

Pradeep Kumar *et al.*[3a] developed an efficient method for the synthesis of *syn*-/*anti*-1,3-polyols using Jacobsen's hydrolytic kinetic resolution and regioselective opening of epoxide by vinyl magnesium bromide. Thus optically pure propylene oxide **5** easily obtained by Jacobsen's hydrolytic kinetic resolution (HKR) of racemate, was regioselectively opened using vinyl magnesium bromide to furnish homoallyl alcohol

**6** which was then subjected to *m*-CPBA epoxidation to furnish epoxy alcohol **7**. The epoxide **7** on TBS protection furnished the TBS ether **8** which serves as a precursor for the next Jacobsen's hydrolytic kinetic resolution. Compound **8** was then subjected to Jacobsen's HKR to give enantiomerically pure epoxide **9**. The *syn*-and *anti*-configuration of 1,3-polyol moiety can be manipulated simply by changing the Jacobsen's catalyst in the hydrolytic kinetic resolution step. The epoxide **9** on ring-opening with vinyl magnesium bromide led to homoallylic alcohol **10** which on iodolactonisation furnished *syn*/*syn*-1,3,5-polyols **11** which was directly treated with $K_2CO_3$ in methanol to give the desired *syn*-epoxy alcohol **12** (Scheme 2)**.**




**Scheme 2.** *Reactions and conditions*: a) Vinylmagnesium bromide, CuI, THF, -20 °C, 12 h, 87%; b) *m*CPBA, $CH_2Cl_2$, 0 °C to rt, 10 h, 96%; (c) (i) TBS-Cl (TBS=tert-butyldimethylsilyl), imidazole, $CH_2Cl_2$, 0 °C to rt, 4 h, 95%. (ii) (*S*,*S*)-Salen- Co-(OAc) (0.5 mol%), dist. $H_2O$ (0.55 equiv), THF, 0 °C, 24 h; (d) Vinylmagnesium bromide, THF, CuI, –20 °C, 1 h, 82%; (e) (i) $Boc_2O$, DMAP, $CH_3CN$, rt, 5 h, 90%; (ii) IBr, PhMe, –85 °C, 1 h; (f) $K_2CO_3$, MeOH, RT, 2 h, 81%.

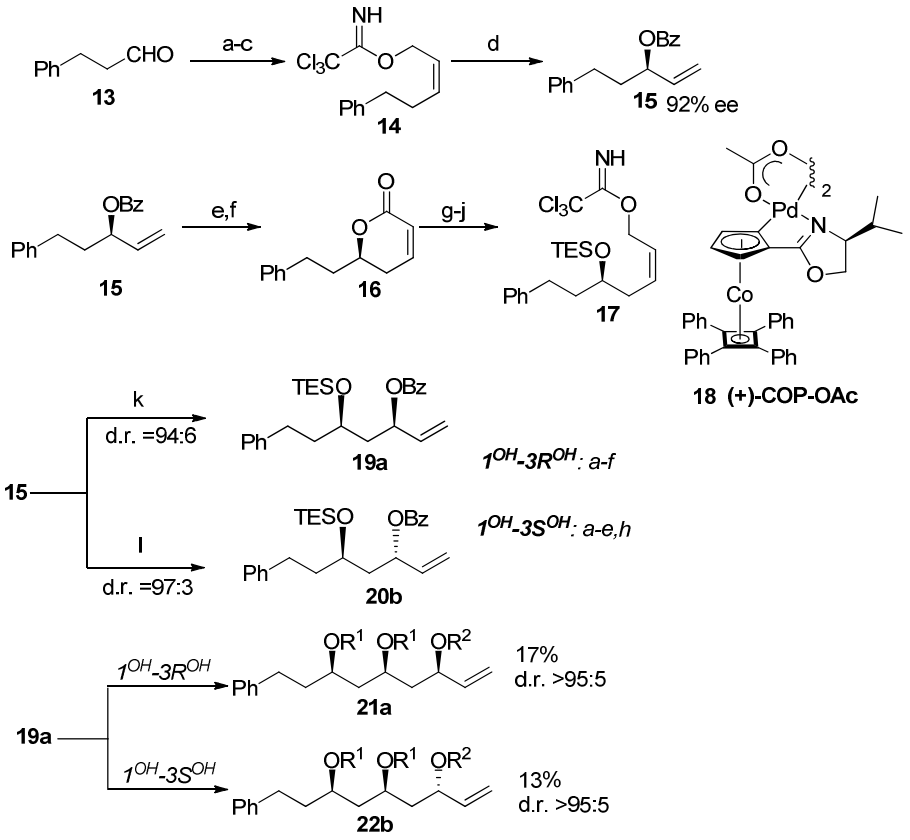
**Kirsch *et al.* (2007)[15]**

Kirsch *et al.*[15] developed an iterative systematic approach to the 1,3-polyol motif to provide access to all possible stereoisomers by utilizing the catalytic asymmetric Overman esterification for the construction of all stereogenic centres. The first stereogenic center was introduced by reaction of trichloroacetimidate **14**[16] with benzoic acid in the presence of palladacycle (+)-COP-OAc **18** (1 mol%).[17] The conversion in $CH_2Cl_2$ at 23 °C provided (*R*)-allylic ester **15** in 93% yield and 92% *ee* after 16 h (Scheme 3).

A series of transformations consisting of transesterification,[18] ring-closing metathesis,[19] and base-catalyzed double bond isomerization[20] led to the formation of

*α,β*-unsaturated *δ*-lactone **16**.[21] The lactone ring was opened with $NaBH_4$/ $CeCl_3.7H_2O$ followed by the formation of the corresponding bis silyl ether. The protecting group on the primary alcohol was removed selectively, and then the *Z*-configured allylic alcohol was converted into trichloroacetimidate **17**. The imidate was subsequently reacted with benzoic acid in the presence of (+)-COP-OAc **18** (1 mol%) to create the next stereogenic center. Under catalyst control, *syn*-1,3-diol **19a** was produced in high diastereoselectivity (dr = 94 : 6).

The sequence with (-)-COP-OAc ***ent*-18** ($1^{OH}$-$3S^{OH}$), resulted in the formation of *anti*-1,3-diol in excellent yield and diastereoselectivity (dr = 97 : 3). The feasibility of this approach was further illustrated by synthesizing 1,3-polyols in this way (Scheme 3).

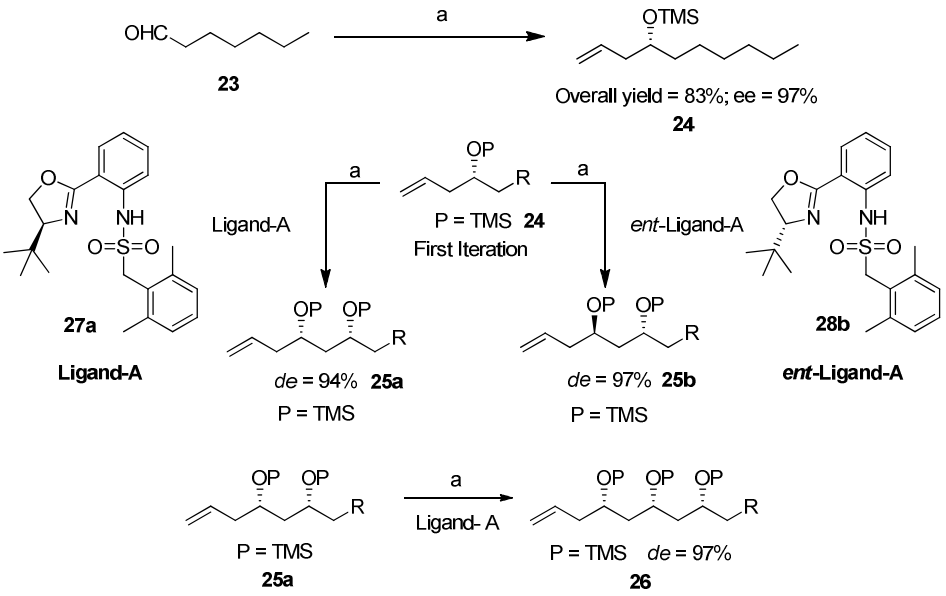



**Scheme 3:** Synthesis of allylic ester. *Reagents and conditions*: (a) (i) $(PhO)_2P(O)CH_2CO_2Et$, NaH, 0 °C, THF; then 3-phenylpropionaldehyde, –78 °C, 85%, dr . 95 : 5; (b) DIBAL-H, –78 °C, $CH_2Cl_2$; (c) $Cl_3CCN$, DBU (10 mol%), 23 °C, $CH_2Cl_2$; (d) PhCOOH (3 equiv.), (+)-COP-OAc (1 mol%) **18**, 23 °C, $CH_2Cl_2$, 93%, 92% *ee*. Synthesis of (*R*,*R*)-diol **19a** (*via* $1^{OH}$-$3R^{OH}$) and (*R*,*S*)-diol **19b** (*via* $1^{OH}$-$3S^{OH}$). (e) (i) DIBAL-H, –78 °C, $CH_2Cl_2$; (ii) $CH_2$=$CHCH_2CO_2H$, DCC, DMAP (15

mol%), 23 °C, $CH_2Cl_2$, 88%; (f) (i) Grubbs II (1 mol%), 38 °C, $CH_2Cl_2$; (ii) DBU (10 mol%), 23 °C, $CH_2Cl_2$, 82%; (g) $NaBH_4$, $CeCl_3.7H_2O$, 0 °C, MeOH, 91%; (h) (i) TESOTf, lutidine, 0 °C, $CH_2Cl_2$; (ii) $K_2CO_3$, 0 °C, MeOH, 90%; (j) $Cl_3CCN$, DBU (10 mol%), 23 °C, $CH_2Cl_2$, 94%; (k) PhCOOH (3 equiv), (+)-COP-OAc (1 mol%), 23 °C, $CH_2Cl_2$, 95%, dr = 94 : 6; (l) PhCOOH (3 equiv.), (-)- COP-OAc (1 mol%), 23 °C, $CH_2Cl_2$, 94%, dr = 97 : 3.

**Kishi *et al.* (2008)[22]**

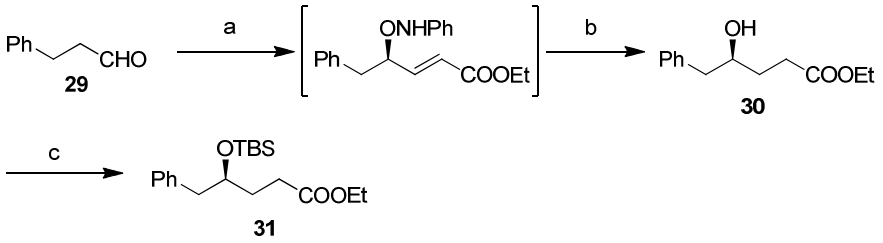
Kishi *et al.*[22] recently developed iterative Cr-mediated catalytic asymmetric allylation approch for the synthesis of *syn-/anti*-1,3-polyols (Scheme 4). Thus **23** was subjected to the Cr-mediated catalytic asymmetric allylation in the presence of sulfonamide ligand-A **27a**, followed by TMS protection, to furnish the anticipated, protected allylic alcohol **24** in 83% yield and 97% *ee*. One cycle of iteration is composed of a three-step operation, i.e., oxidative cleavage of the olefin to form an aldehyde, catalytic asymmetric allylation, and protection of the resultant alcohol. After oxidative cleavage of the olefin, **24** was subjected to the first cycle of iteration which involves the Cr-mediated catalytic asymmetric allylation in the presence of sulfonamide ligand **A** or its enantiomer ***ent*-A**, followed by TMS protection and product isolation by passing through a short silica gel column. The $^1$H NMR analysis revealed that the diastereomeric purity of resultant ***syn*-25a** and ***anti*-25b** was de > 94% and de > 97%, respectively. Similarly the second iteration of the alcohol **25a** furnished the *syn/syn*-triol **26** in good yield and de>97.




**Scheme 4:** *Reagents and conditions*: (a) **(**i) CrBr, Mn, $Et_3N$, 2,6-lutidine, allyl bromide, Ligand-A, $Zr(Cp)_2Cl_2$ (ii) TMS-Cl, $Et_3N$.

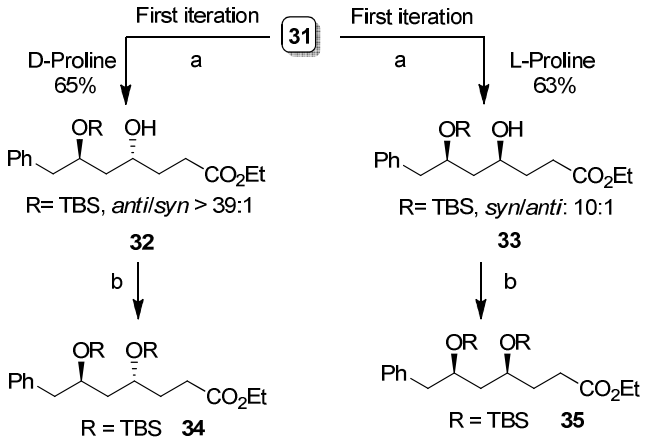
**Kumar *et al.* (2009)[3b]**

Our group has developed an iterative organocatalytic approach to synthesize both *syn/anti* 1,3-polyols starting from an appropriate aldehyde and using proline as catalyst and nitrosobenzene as oxygen source.[3b] Thus, when the commercially available phenyl propanal **29** was subjected to sequential $\alpha$-aminoxylation (L-proline as a catalyst) followed by HWE-olefination reaction, it furnished *O*-amino-substituted allylic alcohol, which was directly subjected to hydrogenation conditions using catalytic amounts of Pd/C to furnish the $\gamma$-hydroxy ester **30** in good yield (Scheme 5).



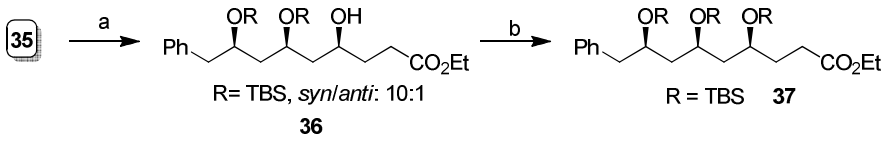

**Scheme 5:** Synthesis of γ-hydroxy ester*: Reagents and conditions*: (a) Nitrosobenzene, L-proline, DMSO, HWE salt, DBU, LiCl, $CH_3CN$; (b) $H_2$/Pd-C, EtOAc; (c) TBSCl, 2,6-lutidine, DCM.

The free hydroxy group of *γ*-hydroxy ester **30** was protected as TBS ether using TBSOTf to furnish compound **31**.




**Scheme 6.** First iteration for synthesis of diol: *Reagents and conditions*: (a) (i) DIBAL-H, –78 °C; (ii) Nitroso benzene, D/L-Proline, DMSO, HWE salt, DBU, LiCl, $CH_3CN$; (iii) $H_2$/Pd-C, EtOAc; (b) TBSOTf, 2,6-lutidine, DCM.

With a substantial amount of the TBS ether **31** in hand, we then proceeded toward the first cycle of iteration (Scheme 6) to produce **32** and **33** by using either D-Proline or L-proline respectively. Each cycle of iteration consists of four steps, viz. DIBAL-H reduction of ester to aldehyde, sequential *α*-aminoxylation, HWE olefination, and $H_2$-Pd/C reduction, followed by TBS protection of the hydroxy group to eventually furnish the TBS protected *γ*-hydroxy ester. Since the stereochemical outcome of the reaction can be predicted on the basis of the catalyst used, this method gives an easy access to 1,3- *syn*/*anti*-diols with predictable and useful stereocontrol in good yield.




**Scheme 7.** Second iteration for synthesis of triol: *Reagents and Conditions*: (a) (i) DIBAL-H, –78 °C; (ii) Nitroso benzene, L-Proline, DMSO, HWE salt, DBU, LiCl, $CH_3CN$, 61%; (iii) $H_2$/Pd-C, EtOAc; (b) TBSOTf, 2,6-lutidine, DCM, 88%.

To illustrate the feasibility of this approach for preparing 1,3,5-polyols, we further attempted the synthesis of a *syn*/*syn*-1,3,5-triol as a representative example (Scheme 7). Thus, by subjecting *syn*-diol **35** to a second cycle of iteration using the L-proline-

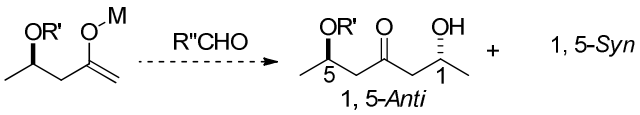
catalyzed sequence of reactions, triol **36** was obtained as a 10:1 unseparable mixture of diastereomers in 61% yield as determined from $^1$H NMR.

***B. Selected approaches for stereoselective construction of 1,5-diols:***

**Evans *et al.* (1997)[9b]**

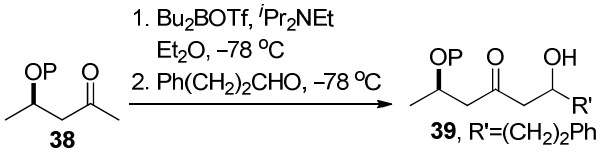
Evans *et al.*[9b] developed a highly diastereoselective aldol addition of methyl ketone enolates and used this control element into double-stereodifferentiating aldol reactions for the synthesis of 1,5-diol motif (Scheme 8) .

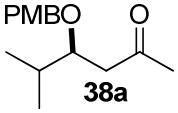
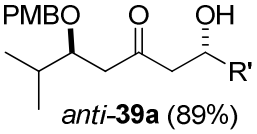
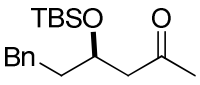
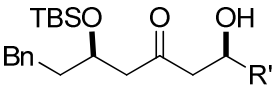
The double-stereodifferentiating reactions of these enolates with chiral *β*-alkoxy aldehydes offer the possibility of controlling the absolute stereochemistry of the aldol process from the proximal alkoxy substituent on either the aldehyde (1,3-induction) or the enolate fragment (1,5-induction) since face selectivity in either reaction component can be regulated by the proper selection of aldol reaction type.




**Scheme 8**: 1,5-induction.

**Table 1.** Stereoselective aldol Reactions with representative ketones

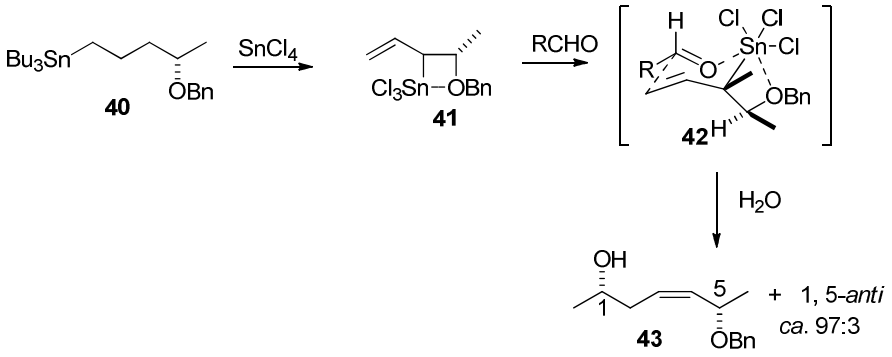



| entry | ketone | product[a] | *anti:syn*[b] |
|---|---|---|---|
| 1 |   **38a** |   *anti*-**39a** (89%) | 95:05 |
| 2 |   **38b** |   *syn*-**39b** (85%) | 40:60 |

[a]Major product (%, yield of aldol adducts). [b]Ratios determined by HPLC or $^1$H NMR analysis of the unpurified product mixture.

**Thomas *et al.* (1997)[9c]**

Thomas *et al.*[9c] developed a diastereoselective synthesis of 1,5-diols by the reaction of allyltintrihalides and aldehydes. Alk-2-enylstannanes with heteroatom substituents at the 4-, 5- and 6-positions undergo stereoselective transmetallation on treatment with tin(IV)halides to generate allyltintrihalides which react with aldehydes and imines with useful levels of 1,5-, 1,6- and 1,7-asymmetric induction.[23] For example, transmetallation of 4-benzyloxypent-2-enylstannane **40** with tin(IV) chloride generates the allyltin trichloride **41** which reacts with aldehydes, *via* the transition structure **42**, to give the *1,5-syn-(Z)*-products **43** (Scheme 9).[24] The stereoselectivity of transmetallation is believed to be predominantly due to kinetic control.[25]



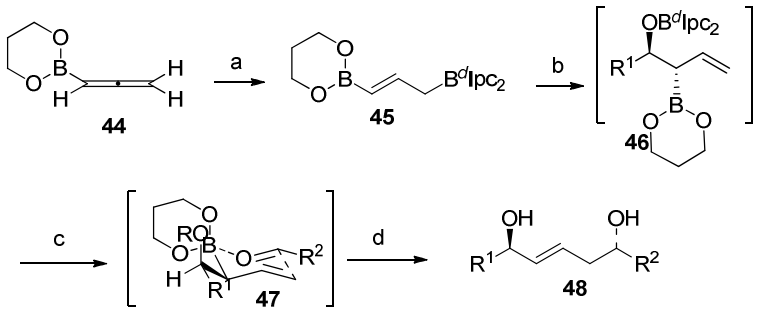

**Scheme 9**: Synthesis of 1,5-*syn*-(*Z*)-product.

**Roush *et al.*[9d]**

Roush *et al.*[9d] developed an enantioselective synthesis of 1,5-*anti*- and 1,5-*syn*-diols using a highly diastereoselective one-pot double allylboration reaction sequence (Scheme 10). They have visualized that if intermediate **46**, or surrogates with different diol units on boron, could be induced to combine with a second aldehyde with control over the equatorial nature of the substituent R to boron in the second allylboration transition state (cf., transition state **47**),[26] then stereoselective access to **48** would be achieved.

These reactions, performed by adding the aldehydes at –78 °C to a solution of the in situ generated reagent **45** and then allowing the reaction mixture to stir at ambient

temperature for 24 h, provided the 1,5-*anti*-diol **48** with ≥20:1 diastereoselectivity and 84-95% *ee*.




**Scheme 10:** *Reactions and conditions*: (a) $^{d}Ipc_2BH$, $Et_2O$, 0 $^{o}C$; (b) $R^1CHO$, –78 $^{o}C$; (c) $R^2CHO$, 23 $^{o}C$, 24 h; (d) $H_2O_2$, NaOH, 0 $^{o}C$, 60-75%.

## 4.3. Present work

### *Objective*

Hydrolytic kinetic resolution (HKR) developed by Jacobsen[27] to resolve the racemic terminal epoxide into enantiopure epoxide and diol using (salen)Co(OAc) complexes (Figure 3) focuses mainly on simple terminal mono-epoxides.[28] In this connection HKR of terminal bis-epoxides would offer not only an interesting opportunity to create long distance stereocentres through desymmetrization of a meso precursor but also open up avenue to utilize these functionalized precursor for the synthesis of polyketides and several other biologically active natural products. However, the literature survey reveals that there has been only limited research work on desymmetrization and synthetic application of functionalized bis-epoxide by HKR.[29]

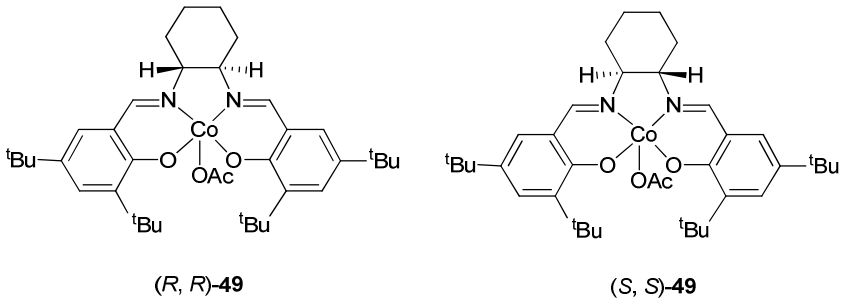



**Figure 3.** Structures of Co(III)-OAc salen complexes.

In view of above, we considered developing a new protocol for *syn/anti*-1,5-diols by hydrolytic kinetic resolution of bis-epoxide. We now describe for the first time that the structurally diverse and complex terminal bis-epoxide can smoothly be resolved using HKR method by desymmetrizing a meso precursor to generate both *syn/anti*-1,5-diols. These synthetic precursors can be further manipulated to get 1,3,5-triols simply by stereoselective reduction which can subsequently be utilized to the total synthesis of cryptocarya diacetate, an *α*,*β*-unsaturated-*δ*-lactone containing 1,3-polyol.

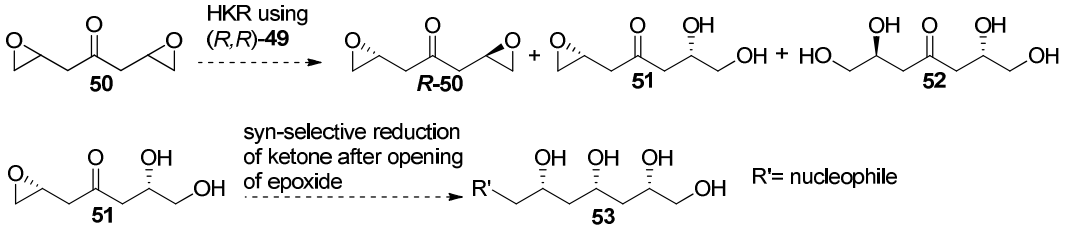
## 4.4. Results and discussion

### *A. Originally proposed strategy for the preparation of syn/anti-1,5-diols and syn/syn-1,3,5-triols*

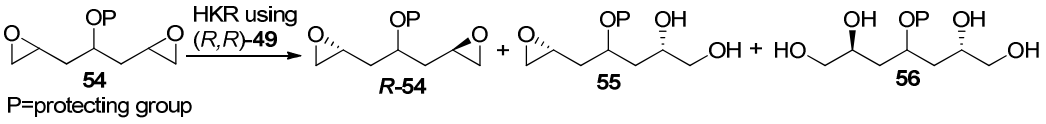
With an aim towards generating *syn/anti*-1,5-diols and subsequent manipulation to 1,3,5-triols by desymmetrization approach, we envisaged keto-bis-epoxide **50** as a substrate for HKR because the pro-chiral carbonyl functionality would provide a handle to generate yet another chiral hydroxyl centre in a stereoselective manner from the resolved component at later stage. We note in advance that the HKR of bis-epoxide **50** using (*R*, *R*)-**49** catalyst would generate two stereocentres providing three products namely bis-epoxide ***R*-50**, epoxy diol **51**, and tetrol **52** (Scheme 11).

### *B. Failed attempt to synthesize keto bis-epoxide & Alternative strategy by replacing the keto group with protected hydroxy group*

The proposed scheme **11** relies on the generation of a third stereogenic centre through stereoselective *syn*-reduction of keto group in the epoxy-diol **51**, which should form as a major enantiomer in the resolution step. Unfortunately we were unable to prepare the keto-bis-epoxide **50** from hepta-1,6-dien-4-ol, by the oxidation and epoxidation reaction sequence which could presumably be due to the unstable nature of keto compound **50.** Therefore we considered replacing the keto group with protected hydroxy group (Scheme 12).



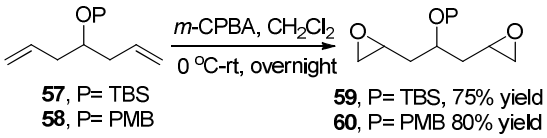

**Scheme 11.** Proposed strategy for the preparation of *syn/anti*-1,5-diols and *syn*-1,3,5-triols.



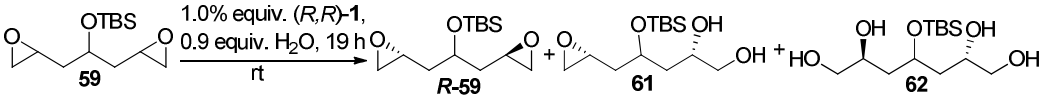

**Scheme 12.** Resolution of bis-epoxide **54**.

### *C. Preparation of bis-epoxides and resolution of differently protected bis-epoxides*

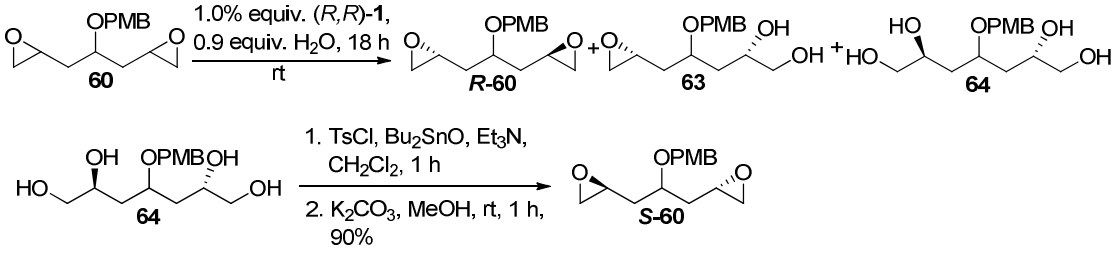
Eventually we prepared bis-epoxides **59** & **60** with differently protected hydroxy group starting from diene **57** & **58** respectively (Scheme 13). The $^1$H NMR spectrum of **59** showed epoxide peaks at δ 3.09-2.99 (multiplet, two protons), 2.82-2.73 (multiplet, two protons), 2.51-2.42 (multiplet, two protons) and for **60** at 3.12-2.98 (multiplet, two protons), 2.81-2.71 (multiplet, two protons), 2.51-2.43 (multiplet, two protons) in $^1$H NMR spectrum. We began with the resolution of compound **59** which was subjected to Jacobsen HKR conditions using 1.0% equiv. of (*R*, *R*)-**49** and 0.9 equiv. of $H_2O$. To our delight, the desired resolution occurred, giving a mixture of the expected bis-epoxide ***R*-59**, epoxy-diol **61** and tetrol **62** in 23%, 45% and 20% yields respectively (Scheme 14).




**Scheme 13.** Preparation of bis-epoxides **59** & **60**.




**Scheme 14.** Resolution of bis-epoxide **59**.



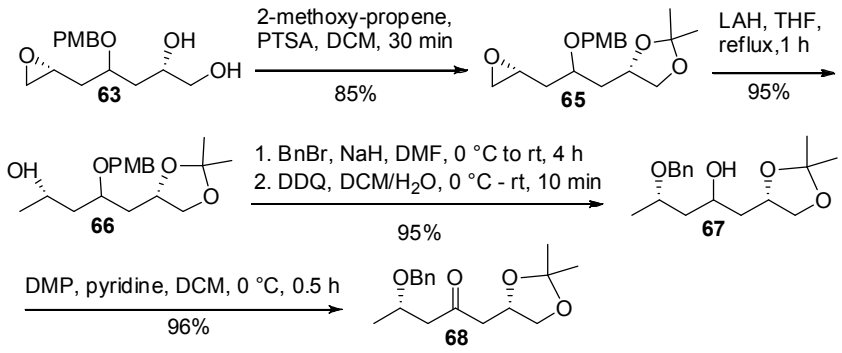

**Scheme 15.** Resolution of bis-epoxide **60** and conversion of tetrol **64** to ***S*-60**.

The difference in polarity makes these compounds easily separable by chromatography. Similarly PMB-protected bis-epoxide **60** on HKR under the similar conditions afforded bis-epoxide ***R*-60**, epoxy-diol **63** and tetrol **64** in 22%, 46% and 18% yields respectively (Scheme 15).

As anticipated in each case, epoxy-diol was obtained in major amount. However we preferred to use PMB-protected bis-epoxide **60,** over TBS-protected epoxide **59** for chiral resolution and further manipulation due to the labile nature of TBS group in the reaction conditions employed.

### *D. Measurement of enantioselectivities & diastereoselctivity*

Our attempt to measure the enantioselectivity (*ee*) of the major component epoxy-diol **63** proved to be a difficult task due to diastereomeric nature of epoxy-diol. Therefore to minimize the number of diastereomers, epoxy-diol **63** was converted to its keto analogue **68** (Scheme 16).



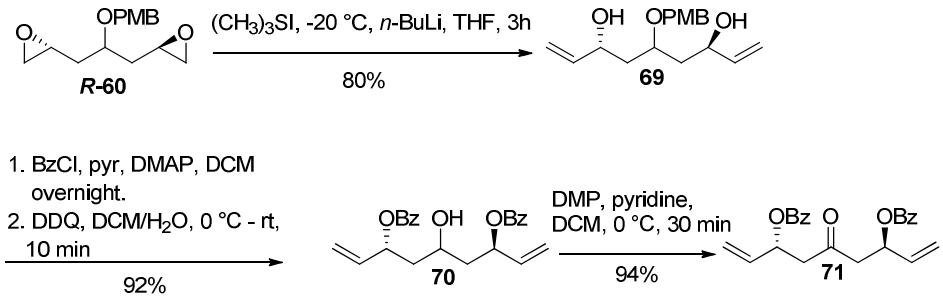

**Scheme 16.** Preparation of keto compound **68**.

We began with the protection of the epoxy-diol **63** as its acetonide **65.** Appearance of multiplet in the range of δ 1.41-1.33 (six protons) in $^1$H NMR and disappearance of

peaks at 3390 $cm^{-1}$ in IR spectrum confirmed the formation of product. Subsequent reductive ring-opening of the epoxide **65** using $LiAlH_4$ in refluxing THF produced **66** in 95% yield. The disappearance of the epoxide peak which appered at δ 3.11-2.98, 2.81-2.72, 2.52-2.45 as multiplet of one proton each and appearance of peaks at 3315 $cm^{-1}$ in IR spectrum confirmed the formation of product. The secondary alcohol was then protected with benzyl bromide as its benzyl-ether, which was directly subjected to removal of PMB group using DDQ to give **67** in 95% yield. In the $^1H$ NMR spectra, the peaks owing to PMB group disappeared and Bn group appeared. Oxidation of secondary alcohol was carried out by Dess Martin Periodinane (DMP) to obtain **68** having the requisite keto group in 96% yield. The IR spectra of **68** showed the appearance of keto absorption at 1710 $cm^{-1}$ and absence of hydroxyl absorption at 3301 $cm^{-1}$. In $^{13}C$ NMR, peak owing to carbonyl carbon was present at δ 207.1.

Eventually we could successfully measure the *ee* through HPLC analysis at this stage. The *ee* of major diastereomer was 95.5% and that of minor was 88%. We also measured the diastereomeric ratio of compound **68**, which was found to be ≈80:20. Tetrol **64** resulted after the resolution of bis-epoxide **60**, was easily converted to chiral bis-epoxide ***S*-60** by primary hydroxyl group conversion to tosylate and subsequent treatment with potassium carbonate (Scheme 15). ***S*-60** also served as an important compound for measurement of *ee* of bis-epoxide ***R*-60** and tetrol **64**.

As experienced in epoxy-diol case, we transformed the $C_2$-symmetric bis-epoxide ***R*-60** into its keto analogue **71** (Scheme 17) for the measurement of *ee*.




**Scheme 17.** Preparation of keto compound **71**.

We then attempted at the ring opening of bis-epoxide ***R*-60** on either side by dimethylsulfonium methylide mediated (Corey–Chaykovsky's condition)[30] reaction to give diol **69** in 80% yield. The IR spectrum of **69** gave broad hydroxyl absorption at

3315 $cm^{-1}$. The $^{1}H$ NMR spectrum of **69** gave olefin peaks at δ 5.91-5.73 (multiplet, two protons) and 5.26-5.02 (multiplet, four protons). The diol **69** was protected as its di-benzoate and subsequently subjected to removal of PMB group using DDQ to produce the secondary alcohol **70** in 92% yield. In the $^{1}H$ NMR spectra, the peaks owing to PMB group disappeared and Bz group appeared i.e. at δ 7.99-7.75 (multiplet, four protons), 7.53-7.19 (multiplet, six protons). The IR spectra of **70** showed ester carbonyl at 1725 $cm^{-1}$. In $^{13}C$ NMR, peak owing to carbonyl carbons were present at δ 166.7 and 165.6. Finally the secondary alcohol **70** was oxidized to keto by using DMP to produce **71** in 94% yield. The IR spectra of **71** showed the appearance of keto absorption at 1712 $cm^{-1}$ and absence of hydroxyl absorption at 3300 $cm^{-1}$. In $^{13}C$ NMR, peak owing to carbonyl carbon was present at δ 196.5. Eventually the *ee* at this stage was successfully measured through HPLC analysis and was found to be 95.99%.

To summarize the above findings, a concise strategy for the preparation of asymmetric 1,5-*syn*-diol **68** (Scheme 16) and $C_2$-symmetric 1,5-*anti*-diol **71** (Scheme 17) as hydroxy protected derivatives has been developed in high enantioselectivities, starting from meso bis-epoxide **60** and by utilizing desymmetrization technique which allows for further manipulations in terms of keto reduction to prepare various 1,3,5-triols.

### *E. Construction of syn/syn-1,3,5-Triols and its Application to the Formal Synthesis of Cryptocarya Diacetate 72*

After having established a novel approach for the stereoselective synthesis of 1,5-diol motif, we turned our attention towards extending this protocol to 1,3,5-triols and further apply to the formal synthesis of cryptocarya diacetate **72**, a natural product isolated from the leaves and bark of the South African plant, *Cryptocarya latifolia* which is noted for its medicinal properties.[31] These properties range from the treatment of headaches and morning sickness to that of cancer, pulmonary diseases and various bacterial and fungal infections etc. Motivated by these claims, van Staden has tested crude extracts of *C. latifolia* and found significant activity as cyclooxygenase inhibitors (COX-2/COX-1).[32] In a search to find the molecular origins of these effects, Horn found a series of related 6-substituted 5,6-dihydropyran-

2-ones in the biologically active hexane and acetone extracts, including cryptocarya diacetate **72** and cryptocarya triacetate 7**3**,[33] along with two bicyclic pyranone/polyol structures cryptocaryolone **74** and cryptocaryolone diacetate **75** (Figure 4).[33b]

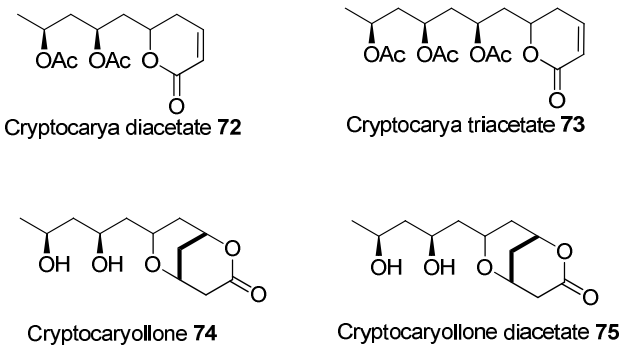



**Figure 4.** Structures of 6-substituted 5,6-dihydropyran-2-ones.

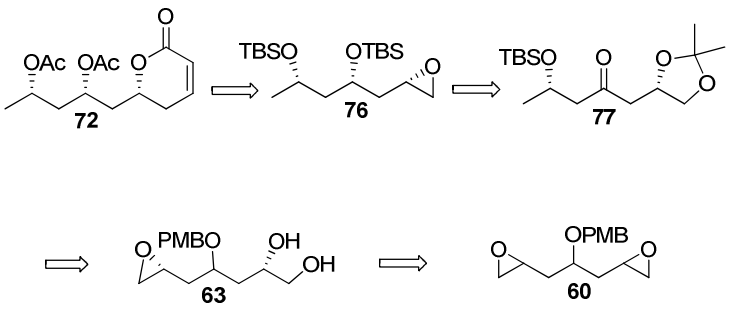
Horn has determined the absolute and relative stereochemistry of the cryptocarya acetates **72** and 7**3** by a combination of Mosher ester analysis and Rychnovsky $^{13}C$ NMR/ acetonide analysis.[33b] Finally Nakata confirmed their result by an enantioselective total synthesis of both cryptocarya diacetate and cryptocarya triacetate.[34]

The unique structural features of this class of compounds and their high medicinal value have aroused great interest among synthetic organic chemists, resulting in an onslaught of activity directed at the stereo- and enantiocontrolled synthesis of the target molecule. Various methods for the synthesis of Cryptocarya diacetate 7**2** have been described in the literature. Most of the approaches to the 1,3-diol system are based on asymmetric methods such as Sharpless asymmetric dihydroxylation,[35] Prins cyclization[36] and iterative Jacobsen's hydrolytic kinetic resolution.[37]

As part of our research program aimed at developing syntheses of biologically active natural products based on HKR,[38] we further demonstrate the usage of the methodology developed by us to the formal synthesis of cryptocarya diacetate.

Our retrosynthetic strategy for the synthesis of **72** is outlined in Scheme 18. Since transformation of **76** to the target molecule **72** has been reported previously from our group[3a] itself, we have designed a route for the synthesis of epoxide **76**. We envisioned that the second stereogenic centre could be obtained by *syn*-selective

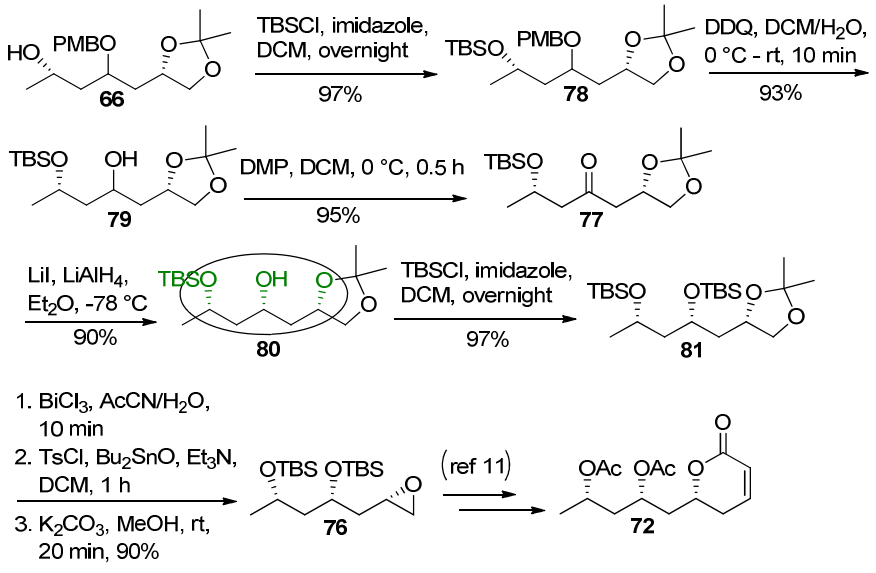
reduction of acyclic *β*-alkoxy ketone **77**, which could in turn be prepared from epoxy-diol **63**, a major resolved component of bis-epoxide **60**.




**Scheme 18.** Retrosynthetic analysis for cryptocarya diacetate **72**

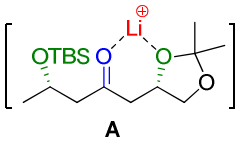
Towards the synthesis of target molecule **72**, the first objective was to generate *syn/syn*-1,3,5-triol from the synthetic precursor **66**. We began with the protection of the secondary alcohol **66** with TBSCl to furnish **78** in 97% yield. PMB group was then removed easily by DDQ to give the alcohol **79** in 93% yield.

The IR spectra of **79** showed hydroxyl absorption at 3385 $cm^{-1}$. In the $^{1}H$ NMR spectra, the peaks owing to PMB group disappeared. Oxidation of secondary alcohol was carried out by DMP to obtain **77** having the requisite keto group. The IR spectra of **77** showed the appearance of keto absorption at 1720 $cm^{-1}$ and absence of hydroxyl absorption at 3385 $cm^{-1}$. In $^{13}C$ NMR, peak owing to carbonyl carbon was present at δ 207.6. Now the platform was set to create the desired *syn*-1,3,5-triols using *syn*-selective reduction conditions. The system here represents an acyclic *β*-alkoxy ketone.



**Scheme 19.** Formal synthesis of cryptocarya diacetate **72**.

The *syn*-selective reduction of such acyclic *β*-alkoxy ketones with $LiAlH_4$ in the presence of LiI as reported by Mori and co-workers[39] (Figure 5) went smoothly affording **80** as a major diastereomer along with minor (10:1) which was determined from $^{1}H$ & $^{13}C$-NMR spectroscopy (Figure 6).

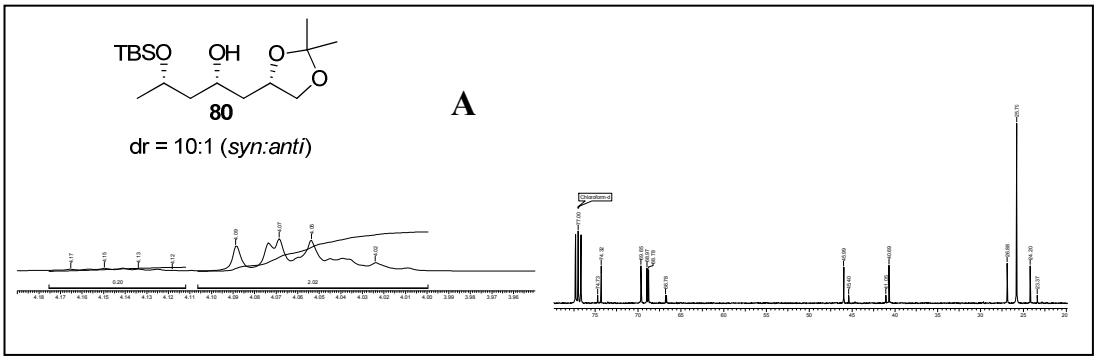



A

**Figure 5.** Chelation controlled transition models

The highly *syn*-selectivity arises from *β*-chelation of both the ketone and ether oxygens of compound **77** with lithium cation to form an intermediate complex **A** (Figure 5). This locks the conformation of the *β*-alkoxy ketone chain and hydride then attacks from less hindered side, resulting in the formation of the *syn*-product **80**.

The *syn* relationship of 1,3,5-triol **80** was determined using 1D and 2D NMR spectrum analysis. In compound **80**, methyne -CH ($H_2$) proton appears at δ 3.89 ($H_2$) ppm. The $H_2$ peak at δ 3.89 ppm shows NOESY correlation with $H_3$ proton appearing at δ 4.24 ppm.



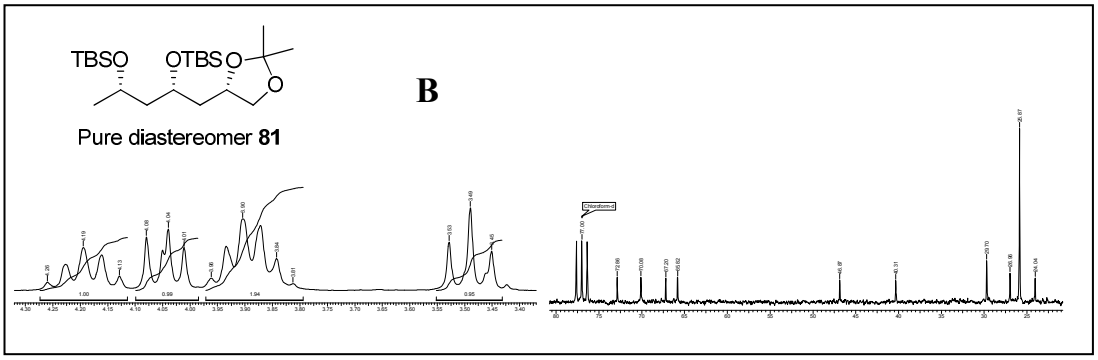



**Figure 6.** (**A**) Partial $^{1}$H NMR and $^{13}$C NMR spectra of diastereomeric mixture (10:1) **80**. (**B**) Partial $^{1}$H NMR and $^{13}$C NMR spectra of pure diasteomer **81**.

This may probably be also attributed to the weak hydrogen-bonding between hydrogen atom of the free hydroxyl group and oxygen atom of the acetonide group responsible for the restriction of the free-rotation in this part of molecule and thus indicating the *syn*-relationship between $H_2$ and $H_3$ protons (Figure 7, shown in red color). The $H_1$ and $H_3$ protons already being *syn* to each other establishes the relative *syn*-stereochemistry of these protons.

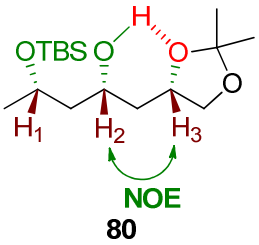



**Figure 7.** Structure of compound **80** showing partial hydrogen bonding (red color).

At this stage one might feel uncomfortable to think about the more number of steps involved in this case to generate the 1,3,5-triol motif than in the proposed scheme, where we planned to proceed with keto functionality itself. However we want to make it clear that the unmasked keto group is precarious to handle under the reaction conditions employed.

Towards the synthesis of target molecule, we then first carried out the protection of secondary hydroxyl group as TBS ether to produce **81** in 97% yield. To our delight at this stage the major diastereomer was separated from the minor one in chromatography and hence we proceeded further with single diastereomer. We next examined the acetonide deprotection of **81** under variety of reaction conditions. It was

gratifying to note that acetonide group deprotected smoothly in the presence of TBS group on treatment with catalytic amount of bismuth trichloride[40] affording the diol, which was directly converted to known di-TBS proteceted epoxide **76** through selective monotosylation and subsequent base promoted $S_N2$ displacement of tosyl group. The $^1$H NMR spectrum of **76** showed epoxide peaks at δ 3.05-2.98 (multiplet, one proton), 2.80-2.75 (multiplet, one proton), 2.49-2.43 (multiplet, one proton) in $^1$H NMR spectrum. Since transformation from **76** to the target molecule **72** is already reported,[3a] this completes the formal synthesis of cryptocarya diacetate.

It may be pertinent to mention here that our present method of polyol synthesis is either comparable or better with some of the known literature methods. The overall yield upto generation of three stereocenters in our case is ≈31% with six steps and no iterative cycles in comparison to Kishi's method[1b] (overall yield≈34%, 4 steps involving two cycles of iteration) and Bruckner's method[1a] (overall yield ≈7% with six steps).

### 4. 5. Conclusion

Thus starting from a meso precursor we have successfully synthesized both *syn/anti*-1,5-diols with further extension of this methodology to *syn*-1,3,5-triol and its application to cryptocarya diacetate. A short reaction sequence, excellent enantio- and diastereoselectivity and high overall yield of the products renders our strategy a good alternative to the boron mediated aldol reactions and other known methods. One of the most noteworthy aspect of this method is that resolved components can be used in two directional chain elongation as they have got both the epoxide and diol handles to access several important polyketide having 1,3-polyols array.

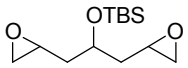
## 4. 6. Experimental Section

***General information:***

All reactions were carried out under argon or nitrogen in oven-dried glassware using standard gas-light syringes, cannulas and septa. Solvents and reagents were purified and dried by standard methods prior to use. Optical rotations were measured at room temperature. IR spectra were recorded on an FT-IR instrument. $^1$H NMR spectra were recorded on 200 MHz, 300 MHz and 500 MHz and are reported in parts per million

(δ) downfield relative to $CDCl_3$ as internal standard and $^{13}C$ NMR spectra were recorded at 50 MHz, 75 MHz and 125 MHz and assigned in parts per million (δ) relative to $CDCl_3$. Column chromatography was performed on silica gel (100-200 and 230-400 mesh) using a mixture of petroleum ether and ethyl acetate as the eluent.

**Preparation of racemic bis-epoxides**




**59**

***Tert*-butyl ((1,3-di(oxiran-2-yl)propan-2-yl)oxy)dimethylsilane (59):** At 0 °C, *m*-CPBA (60%, 3.0 g, 10.6 mmol) was added in portions to *tert*-butyl (hepta-1,6-dien-4-yloxy) dimethylsilane **57** (1.0 g, 4.4 mmol) in $CH_2Cl_2$ (15 mL). The suspension was stirred at rt overnight. The mixture was filtered through a sintered glass funnel, washed repeatedly with saturated $NaHCO_3$, dried ($Na_2SO_4$) and concentrated. After flash chromatography, the bis-epoxide **59** was obtained as colorless liquid

**Yield:** 0.85 g, 75%

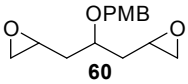
**Mol. Formula**: $C_{13}H_{26}O_3Si$

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 1265, 917, 837.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 4.17-4.05 (m, 1H), 3.09-2.99 (m, 2H), 2.82-2.73 (m, 2H), 2.51-2.42 (m, 2H), 1.93-1.74 (m, 2H), 1.68-1.52 (m, 2H), 0.89 (s, 9H), 0.09-0.07 (m, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 68.1, 49.6, 48.8, 47.6, 46.5, 40.8, 40.4, 25.7, 17.9, -4.6, -4.9.

**HRMS** ($ESI^+$) m/z calcd for $C_{13}H_{27}O_3Si$ $[M + H]^+$ 259.1729, found 259.1729.




**60**

**2,2'-(2-((4-Methoxybenzyl)oxy)propane-1,3-diyl)bis(oxirane) (60):** Based on the procedure for the formation of **59**, 1-((hepta-1,6-dien-4-yloxy)methyl)-4-

methoxybenzene **58** (2.0 g, 12.0 mmol) was treated with *m*-CPBA (50%, 13.5 g, 39.1 mmol) to give bis-epoxide **60** as a colorless liquid after flash chromatography.

**Yield:** 1.1 g, 80%

**Mol. Formula**: $C_{15}H_{20}O_4$

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 1250, 1070, 840.

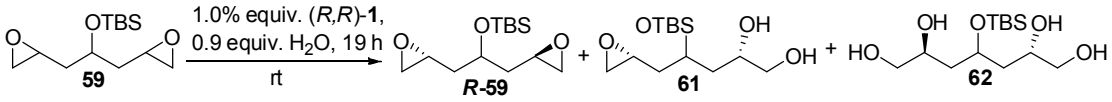
**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.29-7.24 (m, 2H,), 6.90-6.82 (m, 2H), 4.57-4.46 (m, 2H), 3.91-3.70 (m, 4H), 3.12-2.98 (m, 2H), 2.81-2.71 (m, 2H), 2.51-2.43 (m, 2H), 2.02-1.72 (m, 3H), 1.72-1.53 (m, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 159.2, 130.3, 129.3, 113.8, 74.5, 71.1, 55.2, 49.6, 49.1, 47.5, 46.6, 37.9, 37.2.

**HRMS** ($ESI^+$) m/z calcd for $C_{15}H_{20}O_4Na$ $[M + Na]^+$ 287.1259, found 287.1259.

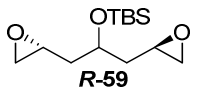
**HKR of bis-epoxide (59)**

**Scheme**




**Experimental Procedures and Compound Characterization Data:**

Bis-epoxide **59** (2.0 g, 7.4 mmol), (*R, R*)-**49** (51 mg, 77.4 μmol) and $H_2O$ (0.12 mL, 6.6 mmol) were stirred for 19 h. The products were separated by flash chromatography to afford bisepoxide ***R*-59**, epoxy-diol **61** and tetrol **62**.

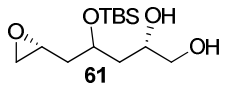



***Tert*-butyl((1,3-di((*R*)-oxiran-2-yl)propan-2-yl)oxy)dimethylsilane (*R*-59):**

**Yield:** 0.46 g, 23%

$[\alpha]_D^{25}$: +82.75 (*c* 0.24, $CHCl_3$).

The spectral data exactly matched with the racemic bis-epoxide **59**.




61

**(2*S*)-4-((*Tert*-butyldimethylsilyl)oxy)-5-((*R*)-oxiran-2-yl)pentane-1,2-diol (61):**

**Yield:** 0.96 g, 45%

**Mol. Formula**: $C_{13}H_{28}O_4Si$

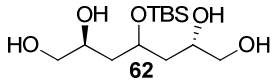
$[\alpha]_D^{25}$: +65.7 (*c* 0.35, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3410, 3050, 1255, 950.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 4.26-4.06 (m, 1H), 4.02-3.81 (m, 1H), 3.67-3.57 (m, 2H), 3.48-3.36 (m, 1H), 3.06-2.90 (m, 1H), 2.64-2.72 (m, 1H), 2.49-2.42 (m, 1H), 2.01-1.70 (m, 2H), 1.68-1.48 (m, 2H), 0.87-0.84 (m, 9H), 0.10-0.06 (m, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 68.6, 68.4, 66.7, 49.4, 47.2, 40.0, 39.3, 25.6, 17.7, -4.8, -4.9.

**HRMS** ($ESI^+$) m/z calcd for $C_{13}H_{28}O_4SiNa$ $[M + Na]^+$ 299.1655, found 299.1657.




62

**(2*S*,6*S*)-4-((*Tert*-butyldimethylsilyl)oxy)heptane-1,2,6,7-tetrol (62):**

**Yield:** 0.45 g, 20%

**Mol. Formula**: $C_{13}H_{30}O_5Si$

$[\alpha]_D^{25}$: –8.57 (*c* 0.82, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3400, 3370, 3100.

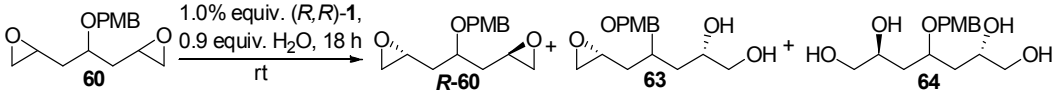
**$^1$H NMR** (400 MHz, $CDCl_3$): δ 4.38-4.07 (m, 4H), 4.03-3.63 (m, 5H), 3.57-3.36 (m, 2H), 1.43-1.17 (m, 4H), 0.86 (s, 9H), 0.07-0.03 (m, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 69.1, 67.8, 67.0, 66.9, 40.3, 38.9, 29.6, 25.8, 17.9, -4.4, -4.6.

**HRMS** ($ESI^+$) m/z calcd for $C_{13}H_{31}O_5Si$ $[M + H]^+$ 295.1941, found 295.1944.

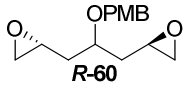
**HKR of bisepoxide (60)**

**Scheme**




**Experimental Procedures and Compound Characterization Data:**

Bis-epoxide **60** (5.0 g, 18.9 mmol), (*R*, *R*)-**49** (0.12 g, 0.18 mmol) and $H_2O$ (0.3 mL, 17.0 mmol) were stirred for 18 h. The products were separated by flash chromatography to afford bis-epoxide ***R*-60**, epoxy-diol **63** and tetrol **64**.

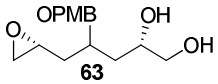



**(2*R*,2'*R*)-2,2'-(2-((4-Methoxybenzyl)oxy)propane-1,3-diyl)bis(oxirane) (*R*-60)**:

**Yield:** 1.1 g, 22%

$[\alpha]_D^{25}$: +15.34 (*c* 0.74, $CHCl_3$).

The spectral data exactly matched with the racemic bis-epoxide **60**.




**(2*S*)-4-((4-Methoxybenzyl)oxy)-5-((R)-oxiran-2-yl)pentane-1,2-diol (63):**

**Yield:** 2.4 g, 46%

**Mol. Formula**: $C_{15}H_{22}O_5$

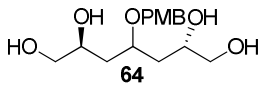
$[\alpha]_D^{25}$: +13.21 (*c* 1.0, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3390, 3050, 1255, 925.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.29-7.24 (m, 2H), 6.91-6.86 (m, 2H), 4.64-4.38 (m, 2H), 4.01-3.85 (m, 2H), 3.79 (s, 3H), 3.71-3.61 (m, 1H), 3.49-3.40 (m, 1H), 3.07-2.98 (m, 1H), 2.83-2.73 (m, 1H), 2.53-2.49 (m, 1H), 2.05-1.83 (m, 2H), 1.75-1.54 (m, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 159.3, 130.0, 129.5, 113.9, 74.3, 71.5, 68.9, 66.8, 55.2, 49.6, 47.3, 37.4, 37.1.

**HRMS** ($ESI^+$) m/z calcd for $C_{15}H_{22}O_5Na$ $[M + Na]^+$ 305.1365, found 305.1360.




**64**

**(2*S*,6*S*)-4-((4-Methoxybenzyl)oxy)heptane-1,2,6,7-tetraol (64):**.

**Yield:** 1.0 g, 18%

**Mol. Formula**: $C_{15}H_{24}O_6$

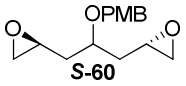
$[\alpha]_D^{25}$: –11.30 (*c* 0.65, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3395, 3310, 3065.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.25-7.20 (m, 2H,), 6.88-6.84 (m, 2H), 4.51-4.52 (m, 2H), 4.16-3.86 (m, 3H), 3.79 (s, 3H), 3.67-3.43 (m, 5H), 3.18-2.79 (m, 3H), 2.08-1.61 (m, 4H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 159.2, 129.1, 128.9, 113.8, 73.7, 72.7, 70.2, 69.7, 69.3, 65.8, 55.2, 31.9, 29.6.

**HRMS** ($ESI^+$) m/z calcd for $C_{15}H_{24}O_6Na$ $[M + Na]^+$ 323.1471, found 323.1469.




***S*-60**

**(2*S*, 2'*S*)-2,2'-(2-((4-Methoxybenzyl)oxy)propane-1,3-diyl)bis(oxirane) (*S*-60):** To a mixture of tetrol **64** (0.5 g, 1.66 mmol), in dry $CH_2Cl_2$ (5 mL) was added dibutyltin oxide (0.008 g, 0.03 mmol) followed by the addition of *p*-toluenesulfonyl chloride (0.63 g, 3.32 mmol) and triethylamine (0.46 mL, 3.32 mmol) and reaction was stirred at room temperature under nitrogen for 1h. The reaction was monitored by TLC, after completion of reaction the mixture was quenched by adding water. The solution was extracted with $CH_2Cl_2$ (3 x 10 ml) and then combined organic phase was washed with water, dried ($Na_2SO_4$) and concentrated. To this crude mixture in MeOH at 0 °C was added $K_2CO_3$ (0.69 g, 4.99 mmol) and the resultant mixture was allowed to stir for 15 min at rt. After completion of reaction as indicated by TLC, the reaction was quenched by addition of ice pieces and methanol was evaporated. The concentrated

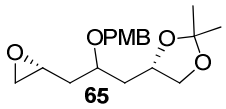
reaction mixture was then extracted with ethyl acetate (3 x 20 mL), the combined organic layer was washed with brine, dried ($Na_2SO_4$) and concentrated. The column chromatography of crude product using pet ether:ethyl acetate (90:10) gave the bis-epoxide ***S*-60** as a colorless liquid.

**Yield:** 0.39 g, 90%

$[\alpha]_D^{25}$: –16.05 (*c* 0.8, $CHCl_3$).

The spectral data matched exactly with the racemic bis-epoxide **60**.

**Determination of enantioselectivity (*ee*) & proof of relative stereochemistry of epoxy-diol (63)**




**65**

**(4*S*)-4-(2-((4-Methoxybenzyl)oxy)-3-((*R*)-oxiran-2-yl)propyl)-2,2-dimethyl-1,3-dioxolane (65):** Epoxy-diol **63** (1.0 g, 3.5 mmol), 2-methoxy-propene (1.0 mL, 10.6 mmol) and a few crystals of PTSA in $CH_2Cl_2$ (10 mL) were stirred at 25 °C for 30 min, then quenched with solid $NaHCO_3$ and stirred for 30 min. The reaction mixture was filtered through a pad of celite and concentrated. Silica gel column chromatography using petroleum ether:ethyl acetate (24:1) gave **65** as a colorless liquid.

**Yield:** 0.97 g, 85%

**Mol. Formula**: $C_{18}H_{26}O_5$

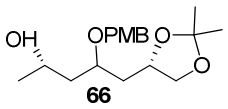
$[\alpha]_D^{25}$: –6.39 (*c* 0.75, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3068, 1255, 925, 735.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.28-7.24 (m, 2H), 6.90-6.84 (m, 2H), 4.60-4.39 (m, 2H), 4.30-4.13 (m, 1H), 4.06-3.39 (m, 1H), 3.88-3.82 (m, 1H), 3.79 (s, 3H), 3.55-3.45 (m, 1H), 3.11-2.98 (m, 1H), 2.81-2.72 (m, 1H), 2.52-2.45 (m, 1H), 1.89-1.66 (m, 4H), 1.41-1.33 (m, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 159.2, 130.4, 129.5, 113.8, 108.5, 74.3, 73.1, 71.9, 69.9, 55.2, 49.4, 47.4, 39.4, 38.0, 27.0, 25.9.

**HRMS** ($ESI^+$) m/z calcd for $C_{18}H_{26}O_5Na$ $[M + Na]^+$ 345.1678, found 345.1676.




**66**

**(2*S*)-5-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-4-((4-methoxybenzyl)oxy)pentan-2-ol (66):** To a solution of 0.42 g. (11.16 mmol) of lithium aluminum hydride in THF (7 mL) at 0 $^oC$ was added a solution of 0.9 g. (2.79 mmol) of epoxide **65** in THF drop- wise. The mixture was stirred under refluxing conditions for 1 h, then cooled to 0 $^oC$ and quenched with the dropwise addition of satd aq $Na_2SO_4$ solution. The reaction mixture was filtered through a pad of celite and concentrated. Silica gel column chromatography using petroleum ether:ethyl acetate (24:1) gave **66** as a colorless liquid.

**Yield:** 0.86 g, 95%

**Mol. Formula**: $C_{18}H_{28}O_5$

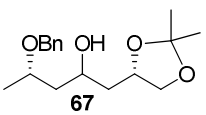
$[\alpha]_D^{25}$: – 13.97 (*c* 0.9, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3315, 3068, 1040 and 745.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.29-7.24 (m, 2H), 6.91-6.84 (m, 2H), 4.62-4.37 (m, 2H), 4.29-3.84 (m, 4H), 3.80 (s, 3H), 3.57-3.44 (m, 1H), 2.05-1.51 (m, 4H), 1.43-1.35 (m, 6H), 1.20-1.14 (m, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 159.3, 130.0, 129.6, 113.9, 108.5, 74.7, 73.3, 71.6, 69.8, 64.6, 55.2, 41.9, 38.4, 26.9, 25.8, 23.7.

**HRMS** ($ESI^+$) m/z calcd for $C_{18}H_{28}O_5Na$ $[M + Na]^+$ 303.2355, found 303.2349.




**67**

**(4*S*)-4-(Benzyloxy)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)pentan-2-ol (67):** To the alcohol **66** (0.156 g, 0.48 mmol) in DMF (1.5 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 0.02 g, 0.53 mmol). After 15 min, benzyl bromide (0.06 mL,

0.53 mmol) was introduced and the reaction mixture further stirred for 4 h at room temperature. Water was carefully added to the reaction mixture, extracted with diethyl ether, washed with water, dried ($Na_2SO_4$) and evaporated to afford benzyl protected compound, which was used immediately in the next step without further purification. To a stirring solution of this newly formed compound (0.1 g, 0.24 mmol) in $CH_2Cl_2/H_2O$ (0.9:0.1) was added DDQ (0.12 g, 0.29 mmol) at 0 °C. The resulting mixture was stirred for 10 min at r.t. The mixture was poured into saturated aqueous $NaHCO_3$ and further diluted with $CH_2Cl_2$. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 5 mL). The combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated. The solvents were removed under reduced pressure to give the crude product mixture as yellow oil. Silica gel column chromatography of the crude product using pet ether:ethyl acetate (95:5) as eluent gave **67**.

**Yield:** 0.06 g, 95%

**Mol. Formula**: $C_{17}H_{26}O_4$

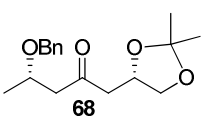
$[\alpha]_D^{25}$: +12.35 (*c* 0.4, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3301, 3100, 2924, 2860, 1613, 1513.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.25-7.18 (m, 5H), 4.62-4.52 (m, 1H), 4.41-4.31 (m, 1H), 4.28-4.13 (m, 1H), 4.06-3.95 (m, 1H), 3.91-3.67 (m, 2H), 3.51-3.41 (m, 1H), 1.76-1.53 (m, 4H), 1.32-1.28 (m, 6H), 1.21-1.16 (m, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 138.3, 128.5, 127.8, 127.4, 108.6, 73.8, 72.7, 70.6, 69.8, 66.0, 43.2, 40.7, 25.7, 19.2.

**HRMS** ($ESI^+$) m/z calcd for $C_{17}H_{27}O_4$ $[M + H]^+$ 295.1909, found 295.1902.




**68**

**(*S*)-4-(Benzyloxy)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)pentan-2-one (68):** Dess–Martin periodinane (0.05 g, 0.17 mmol) was added to a solution of compound **67** (0.08 g, 0.18 mmol) in $CH_2Cl_2$ (0.5 ml) followed by addition of one drop of pyridine

at 0 $^{o}$C. The reaction was stirred at rt for 30 min, before being quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. The organic layer was washed with satd NaCl solution and dried over $Na_2SO_4$ and concentrated. Silica gel column chromatography of the crude product using petroleum ether: ethyl acetate (98:2) gave the keto compound **68**.

**Yield:** 0.047 g, 96%

**Mol. Formula**: $C_{17}H_{24}O_4$

$[\alpha]_D^{25}$: +29.78 (*c* 0.5 $CHCl_3$).

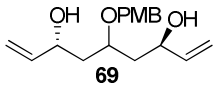
**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 2724, 1710, 1513, 1013.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.31-7.22 (m, 5H), 4.54-4.51 (m, 1H), 4.44-4.38 (m, 2H), 4.14-4.11 (m, 1H), 4.03-3.97 (m, 1H), 3.48-3.44 (m, 1H), 2.90-2.85 (m, 1H), 2.78-2.74 (m, 1H), 2.60-2.52 (m, 1H), 2.48-2.44 (m, 1H), 1.35-1.31 (m, 6H), 1.21 (d, *J*=6.10 Hz, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 207.1, 138.3, 128.4, 127.7, 108.8, 71.4, 70.8, 69.4, 50.4, 48.0, 26.8, 25.4, 19.8.

**HRMS** ($ESI^+$) m/z calcd for $C_{17}H_{24}O_4Na$ $[M + Na]^+$ 315.1572, found 315.1573.

**Determination of enantioselectivity (*ee*) of bis-epoxide (*R*-60)**




**69**

**(3*R*, 7*R*)-5-((4-Methoxybenzyl)oxy)nona-1,8-diene-3,7-diol (69):** To a suspension of trimethylsulfonium iodide (1.26 g, 6.62 mmol) in dry THF (3 mL) at −20 $^{o}$C was added *n*-BuLi (4.13 mL, 1.6 M solution in hexane, 6.62 mmol) dropwise over 20 min and stirred for 30 min. Then the epoxide ***R*-60** (0.25 g, 0.94 mmol) in dry THF (2 mL) was added to the above reaction mixture and stirred for 3 h. After consumption of the starting material the reaction mixture was quenched with $H_2O$ (10 mL) and extracted with EtOAc. The combined extracts were washed with brine, dried over $Na_2SO_4$ and

concentrated. The column chromatography of crude product using pet ether:ethyl acetate (90:10) gave **69** as a colorless liquid.

**Yield:** 0.22 g, 80%

**Mol. Formula**: $C_{17}H_{24}O_4$

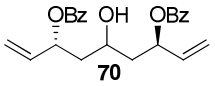
$[\alpha]_D^{25}$: – 7.74 (*c* 0.4, $CHCl_3$.

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3315, 2983, 1580, 780.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.25-7.21 (m, 2H), 6.86- 6.81 (m, 2H), 5.91-5.73 (m, 2H), 5.26-5.02 (m, 4H), 4.54-4.50 (m, 2H), 4.38-4.32 (br, m, H), 4.25-4.16(br, m, 1H), 4.01- 3.81 (m, 2H), 3.75 (s, 3H), 2.60-2.53 (m, 1H), 1.82-1.67 (m, 4H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 159.4, 140.8, 129.8, 129.7, 114.4, 114.3, 113.9, 75.5, 71.1, 70.9, 69.8, 55.2, 41.1, 40.3;.

**HRMS** ($ESI^+$) m/z calcd for $C_{17}H_{24}O_4Na$ $[M + Na]^+$ 315.1572, found 315.1574.




**70**

**(3*R*, 7*R*)-5-Hydroxynona-1,8-diene-3,7-diyl dibenzoate (70):** To a stirred solution of **69** (0.2 g, 0.68 mmol) in dry pyridine (2.5 mL) was added dropwise benzoyl chloride (0.31 mL, 2.73 mmol) and the resulting solution was stirred overnight at room temperature. The solvent was removed and the residue was partitioned between $CH_2Cl_2$ and water. The organic layer was washed with brine, dried over $Na_2SO_4$, filtered and concentrated and was used immediately in the next step without further purification. To a stirring solution of dibenzoate (0.2 g, 0.39 mmol) in $CH_2Cl_2/H_2O$ (1.2:0.07) was added DDQ (0.1 g, 0.48 mmol) at $0^oC$. The resulting mixture was stirred for 10 min at r.t. The mixture was poured into saturated aqueous $NaHCO_3$ and further diluted with $CH_2Cl_2$. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 10 mL). The combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated. The solvents were removed under reduced pressure to give the crude product mixture as yellow oil. Silica gel column

chromatography of the crude product using pet ether:ethyl acetate (96:4) as eluent gave **70**.

**Yield:** 0.14 g, 92%

**Mol. Formula**: $C_{23}H_{24}O_5$

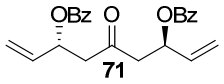
$[\alpha]_D^{25}$: –6.65 (*c* 0.54, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3300, 3080, 2970, 1725, 1125.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.99-7.75 (m, 4H), 7.53-7.19 (m, 6H), 5.97- 5.59 (m, 4H), 5.35-5.09 (m, 4H), 3.96-3.73 (m, 1H), 2.08-1.76 (m, 4H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 166.7, 165.6, 136.3, 136.1, 133.1, 132.9, 130.2, 129.6, 129.5, 128.4, 117.1, 116.6, 73.0, 72.1, 64.5, 42.6, 41.5.

**HRMS** ($ESI^+$) m/z calcd for $C_{23}H_{24}O_5Na$ $[M + Na]^+$ 403.1521, found 403.1523.




71

**(3*R*, 7*R*)-5-Oxonona-1,8-diene-3,7-diyl dibenzoate (71):** Dess–Martin periodinane (0.06 g, 0.14 mmol) was added to a solution of compound **70** (0.05 g, 0.13 mmol) in $CH_2Cl_2$ (0.8 ml) followed by addition of one drop of pyridine at 0 $^oC$. The reaction was stirred at rt for 30 min, before being quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. The organic layer was washed with satd NaCl solution and dried over $Na_2SO_4$ and concentrated. The column chromatography of crude product using pet ether:ethyl acetate (90:10) gave **71** as a colorless liquid. found 401.1365.

**Yield:** 0.046 g, 94%

**Mol. Formula**: $C_{23}H_{22}O_5$

$[\alpha]_D^{25}$: – 10.30 (*c* 0.75, $CHCl_3$).

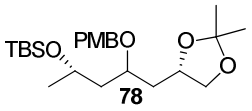
**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3078, 1730, 1712, 1545.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 8.02-7.97 (m, 4H), 7.47-7.39 (m, 6H), 6.52- 6.42 (m, 2H), 6.02-5.89 (m, 4H), 5.25-5.19 (m, 2H), 3.21-2.83 (m, 4H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 196.5, 165.4, 135.0, 133.7, 130.2, 129.6, 128.4, 117.2, 71.3, 44.9.

**HRMS** ($ESI^+$) m/z calcd for $C_{23}H_{22}O_5Na$ $[M + Na]^+$ 401.1365, found 401.1365.

**Formal Synthesis of Cryptocarya diacetate**




**78**

***Tert*-butyl(((2*S*)-5-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-((4 methoxybenzyl)oxy)pentan-2-yl)oxy)dimethylsilane (78):** To an ice-cold stirred solution of alcohol **66** (0.8 g, 2.46 mmol) in $CH_2Cl_2$ (5 mL) imidazole (0.41 g, 6.16 mmol) was added followed by TBSCl (0.56 g, 3.69 mmol) at 0 °C. The resulting mixture was stirred overnight at rt before $H_2O$ (20 mL) was added. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic layer was washed with brine, dried ($Na_2SO_4$), and concentrated under reduced pressure. Silica gel column chromatography of the crude product using petroleum ether: ethyl acetate (99:1) gave the TBS ether **78**.

**Yield:** 1.04 g, 97%

**Mol. Formula**: $C_{24}H_{42}O_5Si$

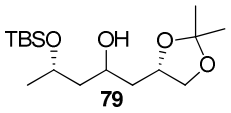
$[\alpha]_D^{25}$: +1.04 (*c* 1.07, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3073, 1035, 738.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.25-7.19 (m, 2H), 6.84 (d, *J*=8.75 Hz, 2H), 4.50-4.31 (m, 2H), 4.25-4.12 (m, 1H), 4.05-3.86 (m, 2H), 3.76 (s, 3H), 3.70-3.57 (m, 1H), 3.54-3.41 (m, 1H), 1.96-1.55 (m, 4H), 1.37-1.31 (m, 6H), 1.14-1.08 (m, 3H), 0.86-0.83 (m, 9H), 0.06-0.00 (m, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 159.1, 130.7, 129.3, 113.8, 108.3, 73.8, 73.4, 71.0, 70.0, 55.8, 55.2, 45.5, 39.1, 26.9, 25.9, 24.3, 18.0, -4.0, -4.7.

**HRMS** ($ESI^+$) m/z calcd for $C_{24}H_{43}O_5Si$ $[M + H]^+$ 439.2880, found 439.2886.




**79**

**(4*S*)-4-((*Tert*-butyldimethylsilyl) oxy)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)pentan-2-ol (79):** To a stirring solution of PMB ether **78** (0.9 g, 2.0 mmol) in $CH_2Cl_2/H_2O$ (6.3:0.4) was added DDQ (0.56 g, 2.46 mmol) at $0^oC$ . The resulting mixture was stirred for 10 min at r. t. The mixture was poured into saturated aqueous $NaHCO_3$ and further diluted with $CH_2Cl_2$. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 10 mL). The combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated. The solvents were removed under reduced pressure to give the crude product mixture as yellow oil. Silica gel column chromatography of the crude product using pet ether:ethyl acetate (96:4) as eluent gave **79**.

**Yield:** 0.6 g, 93%

**Mol. Formula**: $C_{16}H_{34}O_4Si$

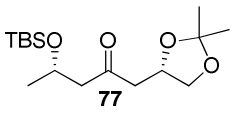
$[\alpha]_D^{25}$: +5.75 (*c* 0.7, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3385, 3055, 1032, 738.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 4.38-4.03 (m, 4H), 3.65 (s, 1H), 3.58-3.48 (m, 1H), 1.68-1.51 (m, 4H), 1.39 (s, 3H), 1.35 (s, 3H), 1.23 (d, J=6.12 Hz, 3H), 0.87 (s, 9H), 0.10-0.05 (m, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 108.6, 73.4, 69.8, 67.6, 65.5, 44.6, 41.2, 26.9, 25.8, 22.8, 17.9, -4.5, -5.0.

**HRMS** ($ESI^+$) m/z calcd for $C_{16}H_{35}O_4Si$ $[M + H]^+$ 319.2305, found 319.2303.




**77**

**(*S*)-4-((*Tert*-butyldimethylsilyl)oxy)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)pentan-2-one (77):** Dess–Martin periodinane (0.732 g, 1.73 mmol) was added to a solution of compound **79** (0.5 g, 1.57 mmol) in $CH_2Cl_2$ (10.0 ml) followed by addition of two drops of pyridine at $0\ ^oC$. The reaction was stirred at rt for 30 min, before being

quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. The organic layer was washed with satd NaCl solution and dried over $Na_2SO_4$ and concentrated. Silica gel column chromatography of the crude product using petroleum ether: ethyl acetate (99 : 1) gave the keto compound **77**.

**Yield:** 0.47 g, 95%

**Mol. Formula**: $C_{16}H_{32}O_4Si$

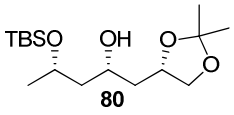
$[\alpha]_D^{25}$: +18.36 (*c* 0.6, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 2992, 1720.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 4.52-4.13 (m, 3H), 3.54-3.46 (m, 1H), 2.89-2.86 (m, 1H), 2.70-2.37 (m, 3H), 1.38 (s, 3H), 1.33 (s, 3H), 1.15 (d, *J*=6.05 Hz, 3H), 0.87-085 (m, 9H), 0.05-0.02 (m, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 207.6, 108.7, 71.5, 69.4, 65.4, 52.7, 48.7, 26.8, 25.8, 25.4, 23.9, 17.9, -4.5, -5.0.

**HRMS** ($ESI^+$) m/z calcd for $C_{16}H_{33}O_4Si$ $[M + H]^+$ 317.2148, found 317.2146.




**80**

**(2*R*, 4*S*)-4-((*Tert*-butyldimethylsilyl)oxy)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)pentan-2-ol (80):** To a stirred solution of ketone **77** (0.45 g, 1.41 mmol) in ether (28 mL) was added LiI (1.89 g, 14.21 mmol), and the resulting mixture was stirred at -40 °C for 5 min. After this period, the mixture was cooled to -78 °C, and $LiAlH_4$ (0.54 g, 14.21 mmol) was added and the mixture was stirred for 30 min. The reaction mixture was then allowed to reach 0 °C, diluted with $Et_2O$ and quenched by the dropwise addition of sat. aq $Na_2SO_4$. The solid material was collected by filtration and washed thoroughly with hot EtOAc several times. The combined organic layers were dried ($Na_2SO_4$). The solvent was removed under reduced pressure and the residue was purified by column chromatography (EtOAc–hexane, 3:7) to afford alcohol **80** as a colourless liquid.

**Yield:** 0.4 g, 90%

**Mol. Formula**: $C_{16}H_{32}O_4Si$

$[\alpha]_D^{25}$: +21.20 (*c* 1.77, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 3390, 3052, 1032, 745.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 4.28-4.21 (m, 1H), 4.09-4.02 (m, 2H), 3.93-3.87 (m, 1H), 3.62-3.52 (m, 2H), 1.78-1.49 (m, 4H), 1.39 (s, 3H), 1.33 (s, 3H), 1.17 (d, *J*=6.01 Hz, 3H), 0.87 (s, 9H), 0.07-0.06 (m, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 108.6, 73.4, 69.8, 67.6, 65.5, 44.6, 41.2, 26.9, 25.8, 22.8, 17.9, -4.5, -5.0.

**HRMS** ($ESI^+$) m/z calcd for $C_{16}H_{35}O_4Si$ $[M + H]^+$ 319.2305, found 319.2303.

**Determination of relative configuration**

In compound **80**, methyne -CH ($H_2$) proton appears at δ 3.89 ($H_2$) ppm. The $H_2$ peak at δ 3.89 ppm shows NOESY correlation with $H_3$ proton appearing at δ 4.24 ppm (**Fig. 2**).

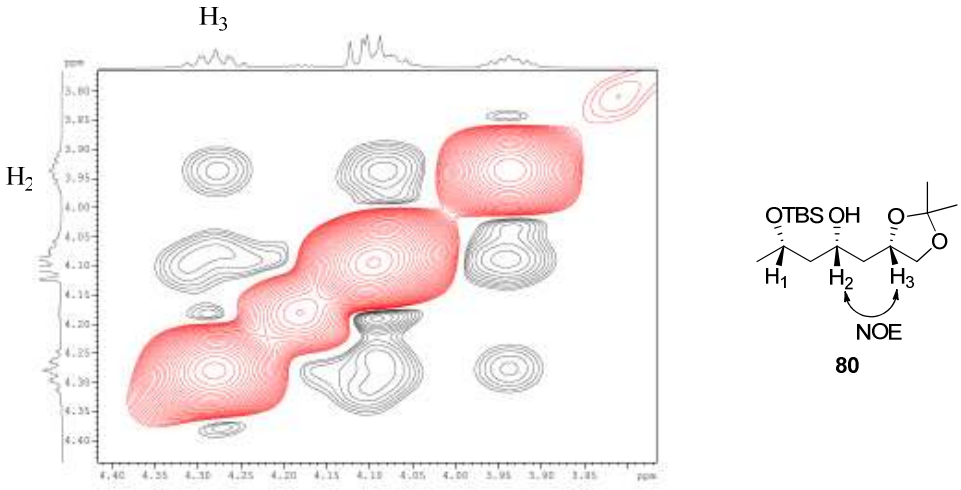



**Fig. 2.** NOE between $H_2$ proton and $H_3$ proton

This may probably be also attributed to the weak hydrogen-bonding between hydrogen atom of the free hydroxyl group and oxygen atom of the acetonide group responsible for the restriction of the free-rotation in this part of molecule and thus indicating the *syn*-relationship between $H_2$ and $H_3$ protons. The $H_1$ and $H_3$ protons

already being *syn* to each other establishes the relative *syn*-stereochemistry of these protons.

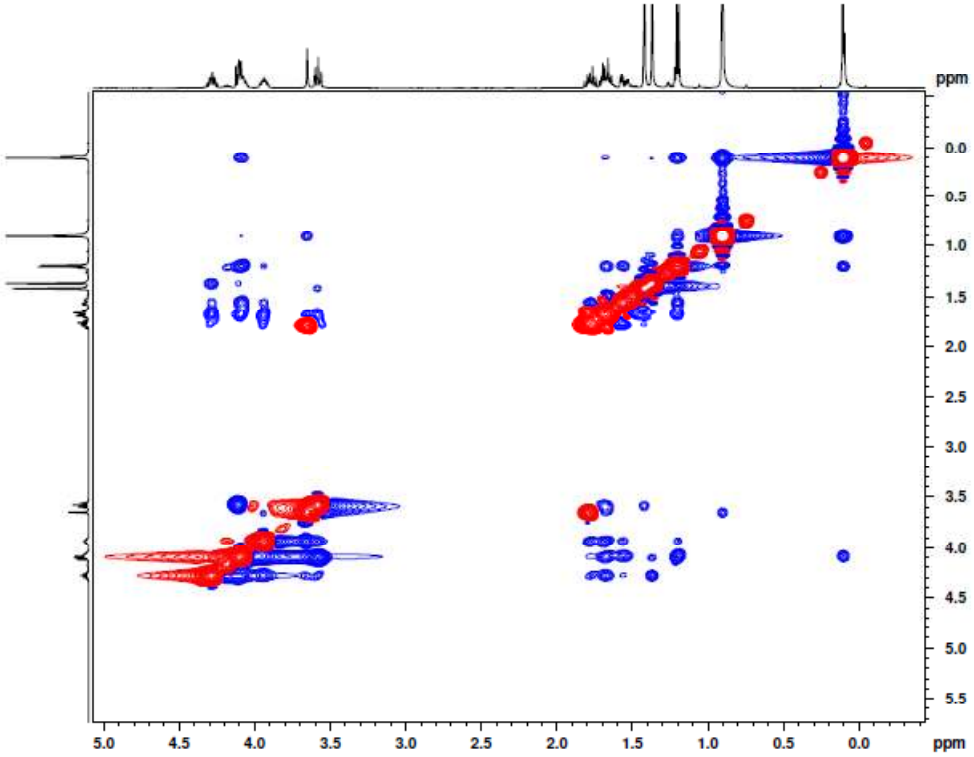
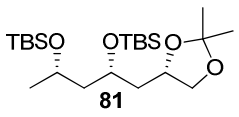



**Fig 3.** NOESY of syn 1,3,5- triol **80**




**81**

**(5*R*, 7*S*)-5-(((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)methyl)-2,2,3,3,7,9,9,10,10-nonamethyl-4,8-dioxa-3,9-disilaundecane (81):** Compound **81** was prepared following the procedure as described for **78** (colorless liquid).

**Yield:** 12.6 mg, 97%

**Mol. Formula**: $C_{22}H_{48}O_4Si_2$

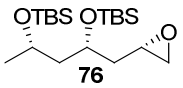
$[\alpha]_D^{25}$: +5.63 (*c* 1.28 $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 2957, 2931, 2888, 1619, 1473, 1464, 761.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 4.26-4.13 (m, 1H), 4.08-4.01 (m, 1H), 3.96-3.81 (m, 2H), 3.53-3.45 (m, 1H), 1.93-1.56 (m, 4H), 1.38 (s, 3H), 1.33 (s, 3H), 1.12 (d, *J*=5.94 Hz, 3H), 0.87 (s, 18H), 0.04-0.03 (m, 12H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 108.1, 72.9, 70.0, 67.2, 65.8, 46.9, 40.3, 29.7, 26.9, 25.9, 24.0, 18.0, -4.1, -4.5, -4.7.

**HRMS** ($ESI^+$) m/z calcd for $C_{22}H_{49}O_4Si_2$ $[M + H]^+$ 433.3169, found 433.3169.




**76**

**(5*S*, 7*R*)-2,2,3,3,5,9,9,10,10-Nonamethyl-7-((*S*)-oxiran-2-ylmethyl)-4,8-dioxa-3,9-disilaundecane (76):** A solution of the acetonide **82** (0.35 g, 0.8 mmol) in MeCN (8 mL) was treated with bismuth trichloride (12.6 mg, 5 mol%) and two drops of water and stirred for 10 min at rt. After completion of the reaction, $NaHCO_3$ was added and the solvent was removed under reduced pressure, water was added and the mixture extracted into EtOAc, washed with brine, dried over anhydrous $Na_2SO_4$ and concentrated to give the crude diol that was used immediately in the next step without further purification.

To a mixture of diol in dry $CH_2Cl_2$ (4 mL) was added dibutyltin oxide (4.0 mg, 16.0 μmol) followed by the addition of *p*-toluenesulfonyl chloride (0.15 g, 0.81 mmol) and triethylamine (0.11 mL, 0.81 mmol) and reaction was stirred at room temperature under nitrogen. The reaction was monitored by TLC, after completion of reaction the mixture was quenched by adding water. The solution was extracted with $CH_2Cl_2$ and then combined organic phase was washed with water, dried ($Na_2SO_4$) and concentrated. To this crude mixture in MeOH at 0 °C was added $K_2CO_3$ (0.22 g, 1.6 mmol) and the resultant mixture was allowed to stir for 20 min at rt. After completion of reaction as indicated by TLC, the reaction was quenched by addition of ice pieces and methanol was evaporated. The concentrated reaction mixture was then extracted with ethyl acetate, the combined organic layer was washed with brine, dried ($Na_2SO_4$) and concentrated. The column chromatography of crude product using pet ether:ethyl acetate (90:10) gave the epoxide **76** as a colorless liquid.

**Yield:** 0.27 g, 90%

**Mol. Formula**: $C_{16}H_{33}O_3Si$

$[\alpha]_D^{25}$: +13.82 (*c* 1.2 $CHCl_3$), lit.[3a] $[\alpha]_D^{25}$ +10.62 (*c* 0.84, $CHCl_3$).

**IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$ 2957, 2931, 1619, 1473, 1362, 1265, 915, 820.

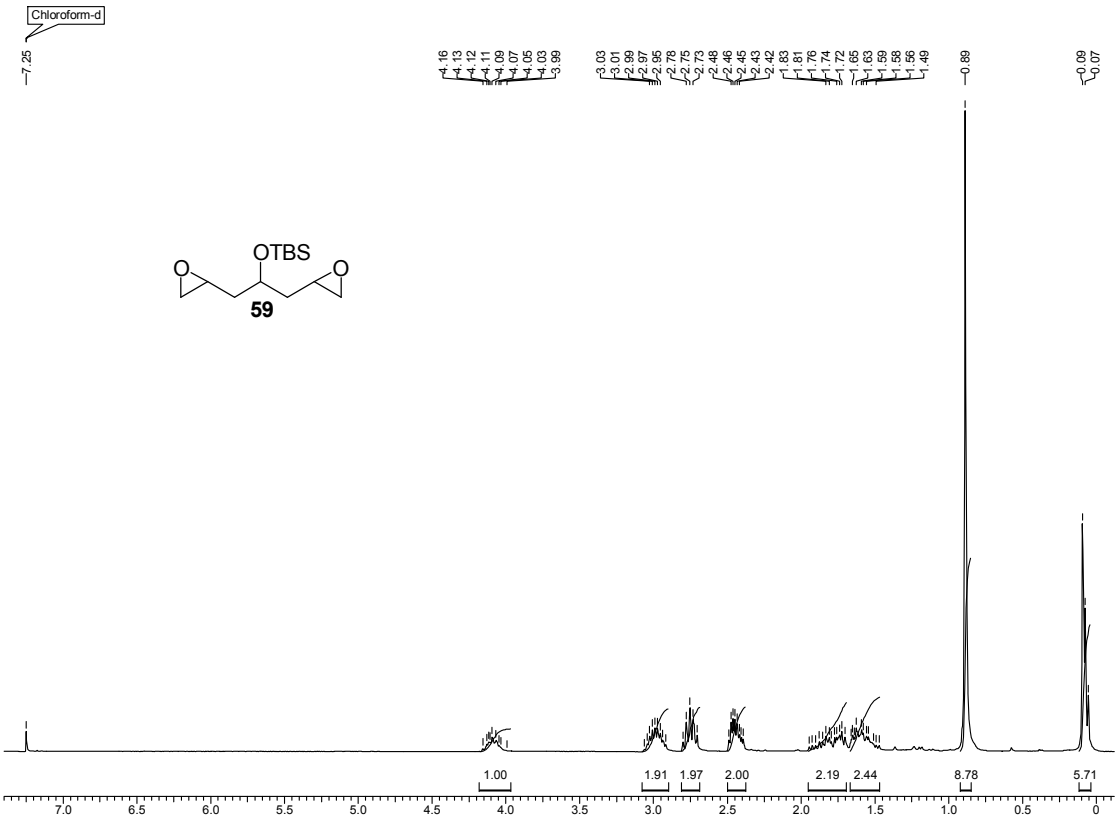
**$^1$H NMR** (400 MHz, $CDCl_3$): δ 4.04-3.83 (m, 2H), 3.05-2.98 (m, 1H), 2.80-2.75 (m, 1H), 2.49-2.43 (m, 1H), 1.73-1.61 (m, 4H), 1.14 (d, *J*=6.41 Hz, 3H), 0.88-0.86 (m, 18H), 0.07-0.03 (m, 12H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 68.1, 66.2, 49.7, 49.3, 47.9, 40.7, 29.7, 25.9, 25.8, 24.5, 18.0, -3.8, -4.3, -4.3.

**HRMS** ($ESI^+$) m/z calcd for $C_{16}H_{34}O_3Si$ $[M + H]^+$ 303.2355, found 303.2351.

## 4. 7. Spectra

| | |
|---|---|
| $^{1}H$ and $^{13}C$ spectra of compound | **59** |
| $^{1}H$ and $^{13}C$ spectra of compound | **61** |
| $^{1}H$ and $^{13}C$ spectra of compound | **62** |
| $^{1}H$ and $^{13}C$ spectra of compound | **60** |
| $^{1}H$ and $^{13}C$ spectra of compound | **63** |
| $^{1}H$ and $^{13}C$ spectra of compound | **64** |
| $^{1}H$ and $^{13}C$ spectra of compound | **65** |
| $^{1}H$ and $^{13}C$ spectra of compound | **66** |
| $^{1}H$ and $^{13}C$ spectra of compound | **67** |
| $^{1}H$ and $^{13}C$ spectra of compound | **68** |
| $^{1}H$ and $^{13}C$ spectra of compound | **69** |
| $^{1}H$ and $^{13}C$ spectra of compound | **70** |
| $^{1}H$ and $^{13}C$ spectra of compound | **71** |
| $^{1}H$ and $^{13}C$ spectra of compound | **78** |
| $^{1}H$ and $^{13}C$ spectra of compound | **79** |
| $^{1}H$ and $^{13}C$ spectra of compound | **77** |
| $^{1}H$ and $^{13}C$ spectra of compound | **80** |
| $^{1}H$ and $^{13}C$ spectra of compound | **81** |
| $^{1}H$ and $^{13}C$ spectra of compound | **76** |
| HPLC data of keto | **68** |
| HPLC data of keto | **71** |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4.03
3.99
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2.42
1.83
1.81
1.76
1.74
1.72
1.65
1.63
1.59
1.58
1.56
1.49
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OTBS
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2.00
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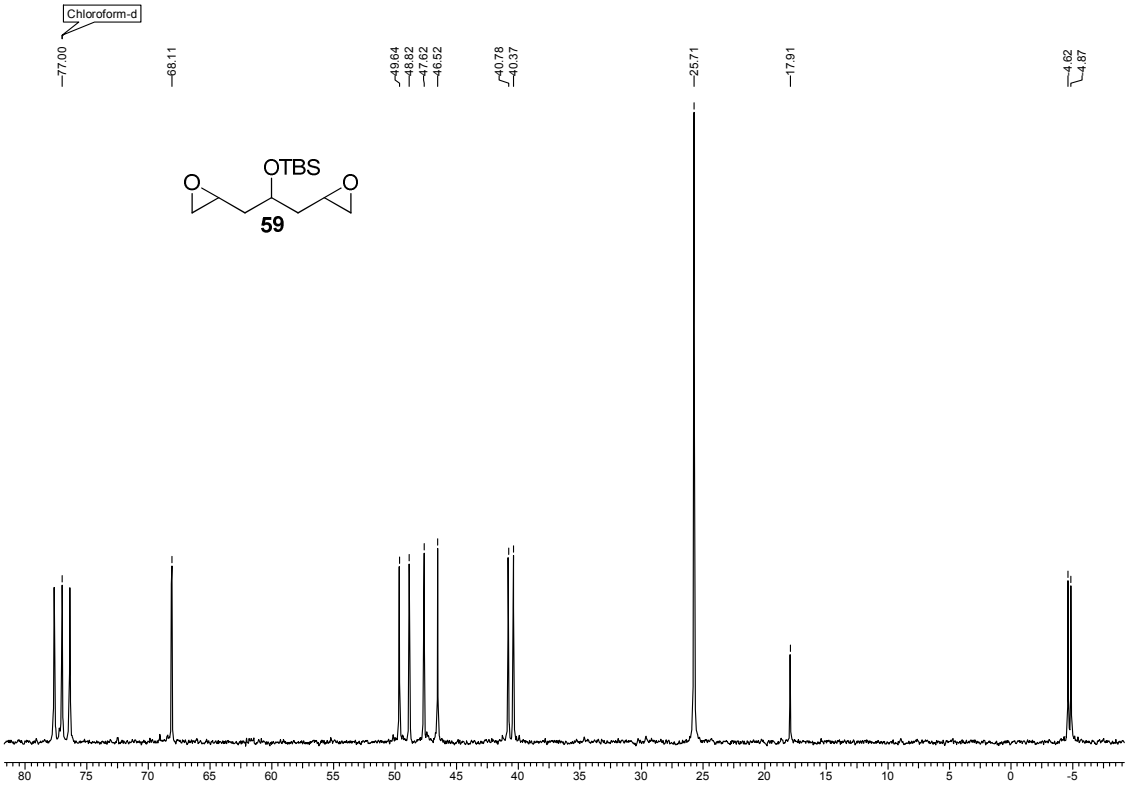
5.71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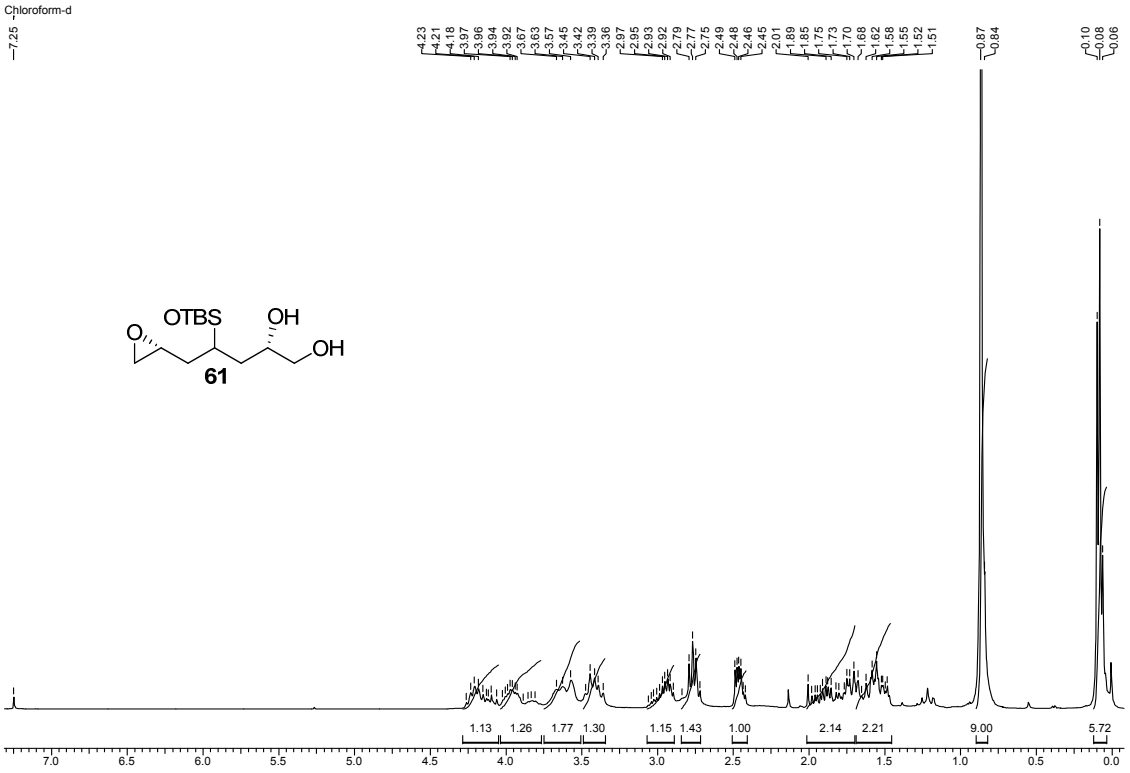
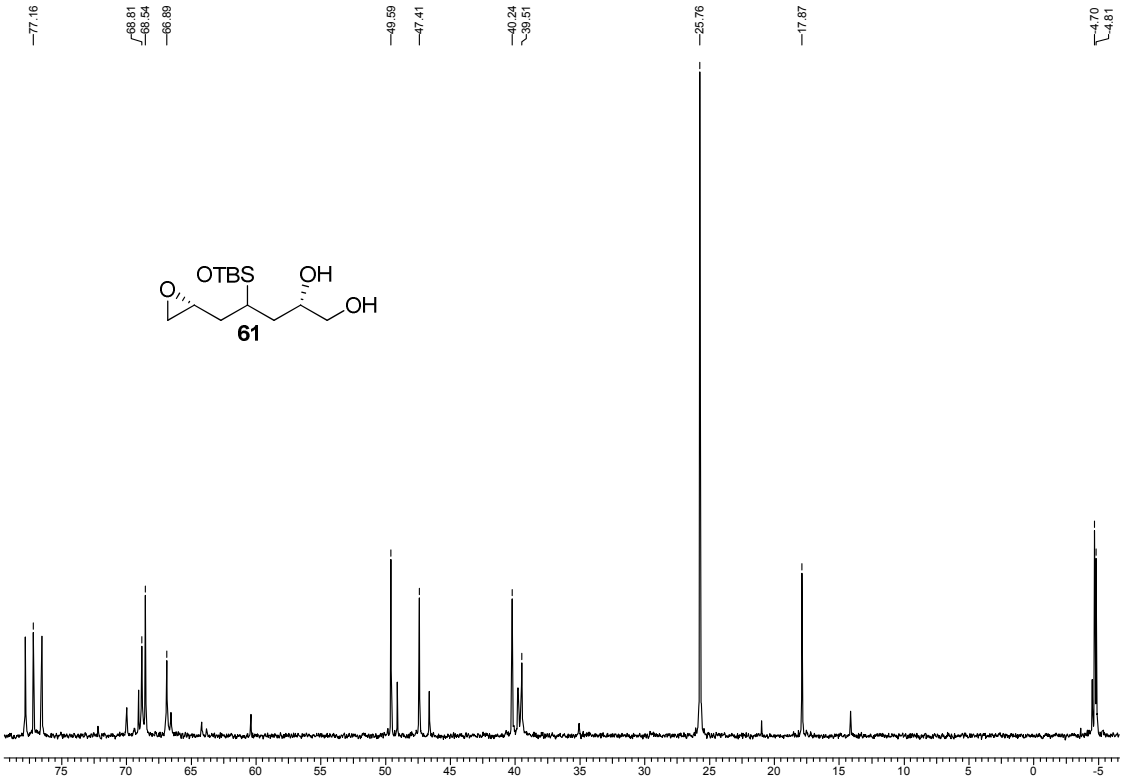
17.91
4.62
4.87
OTBS
59


Chloroform-d
OTBS
OH
OH
61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OH
OH
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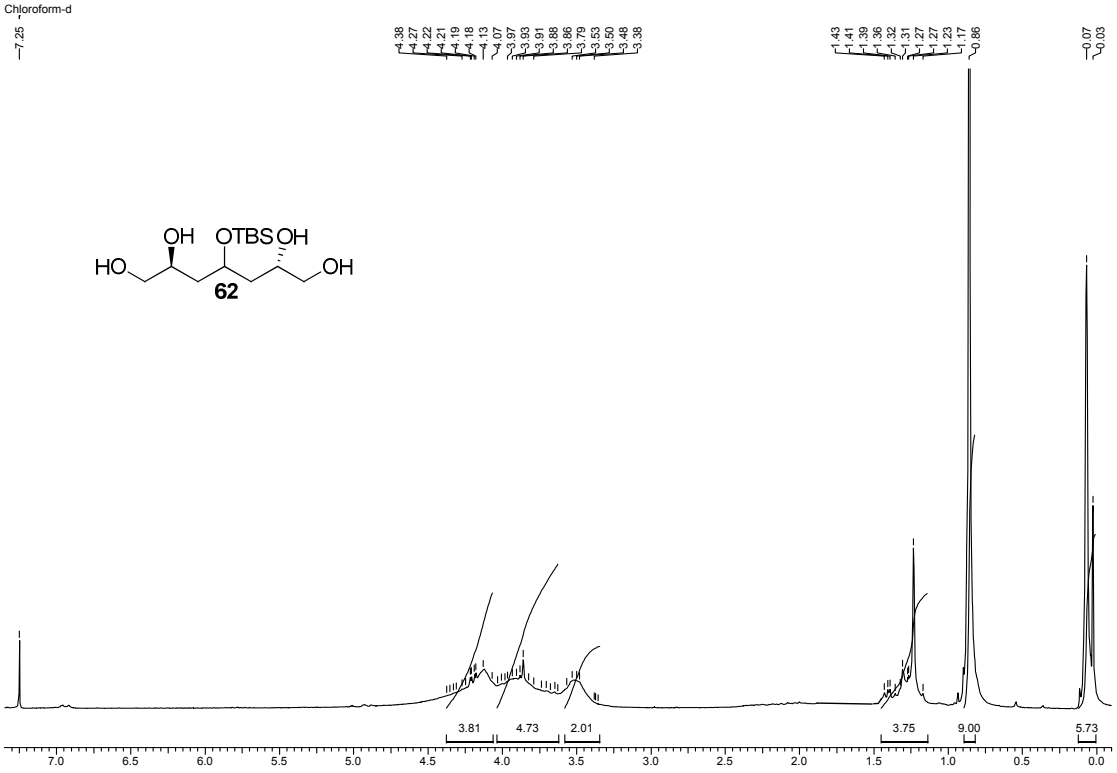
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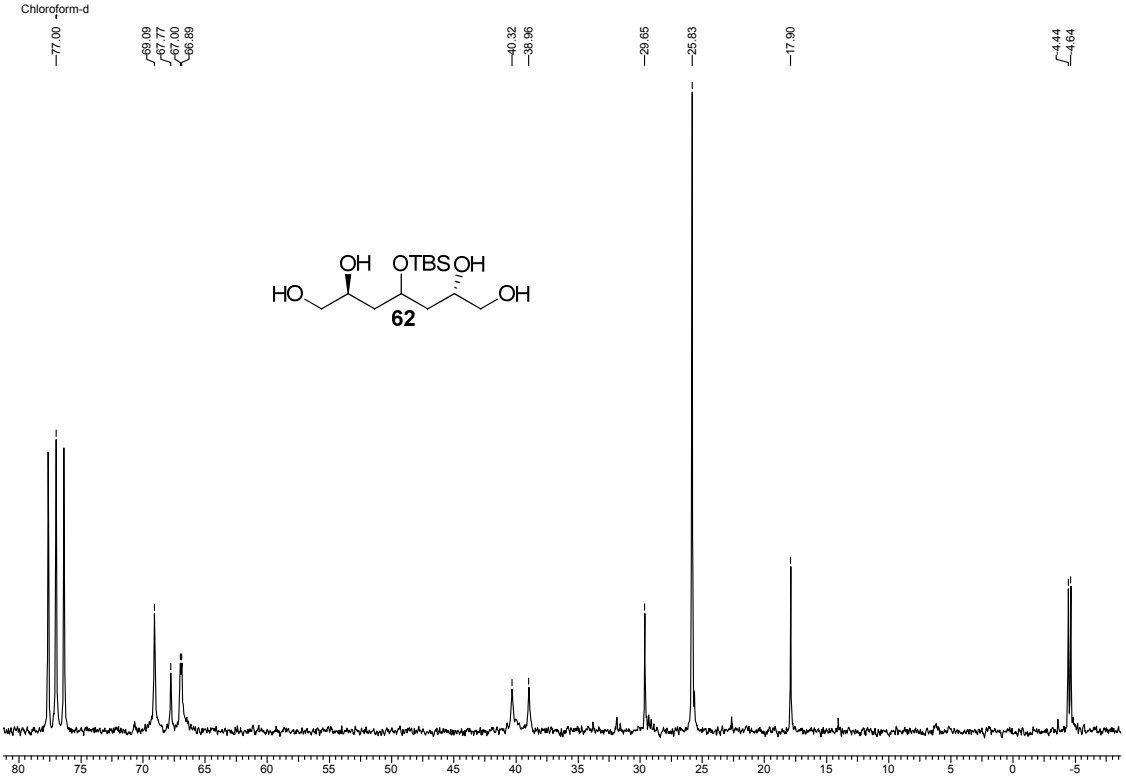
3.79
3.53
3.50
3.48
3.38
1.43
1.41
1.39
1.36
1.32
1.31
1.27
1.27
1.23
1.17
0.86
0.07
0.03
OH
OTBS
OH
HO
OH
62
3.81
4.73
2.01
3.75
9.00
5.73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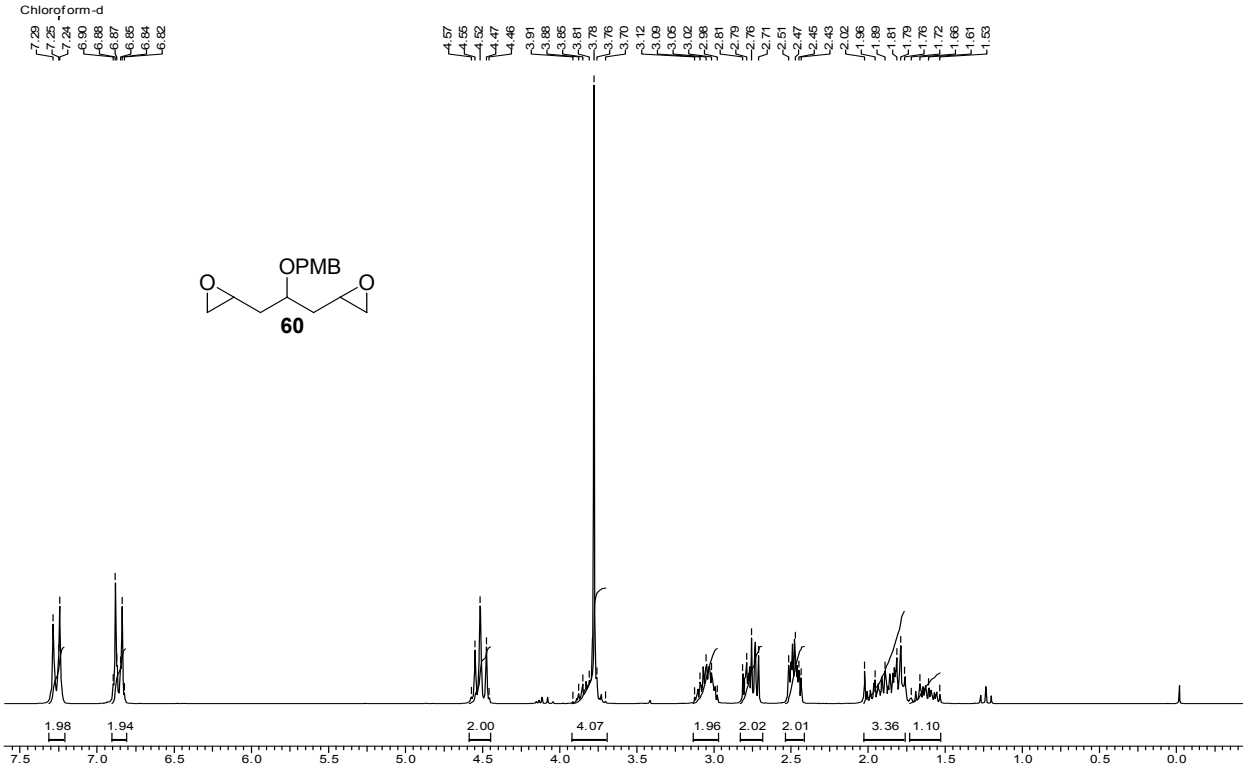
HO
OH
62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3.02
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1.89
1.81
1.79
1.76
1.72
1.66
1.61
1.53
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O
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1.94
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2.02
2.01
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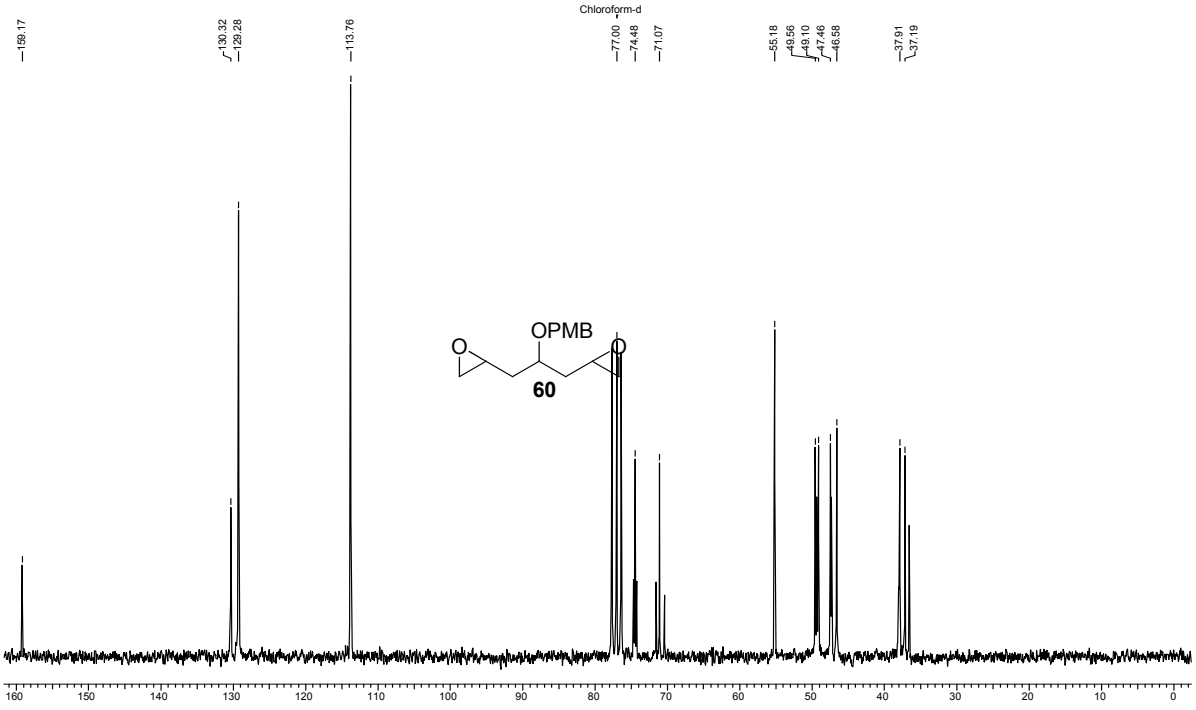
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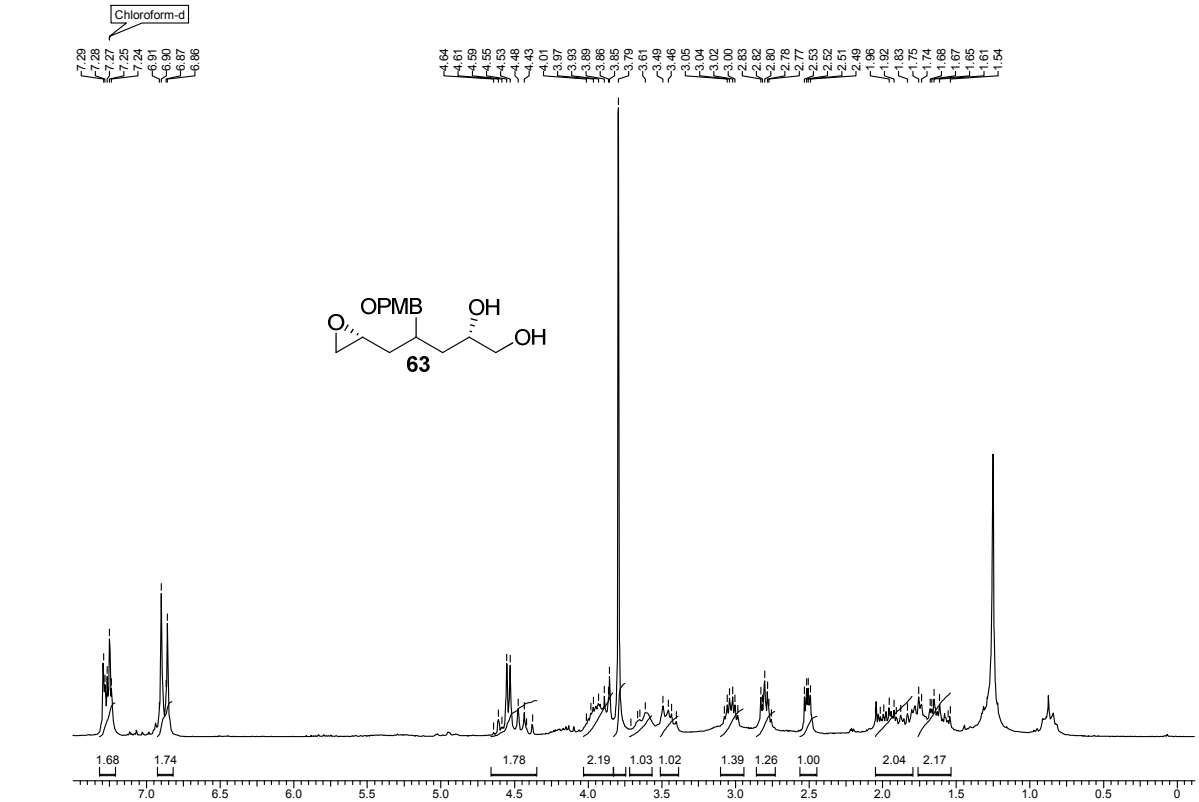
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3.86
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3.49
3.46
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2.51
2.49
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1.68
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1.65
1.61
1.54
OPMB
OH
O
OH
63
1.68
1.74
1.78
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1.03
1.02
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1.26
1.00
2.04
2.17
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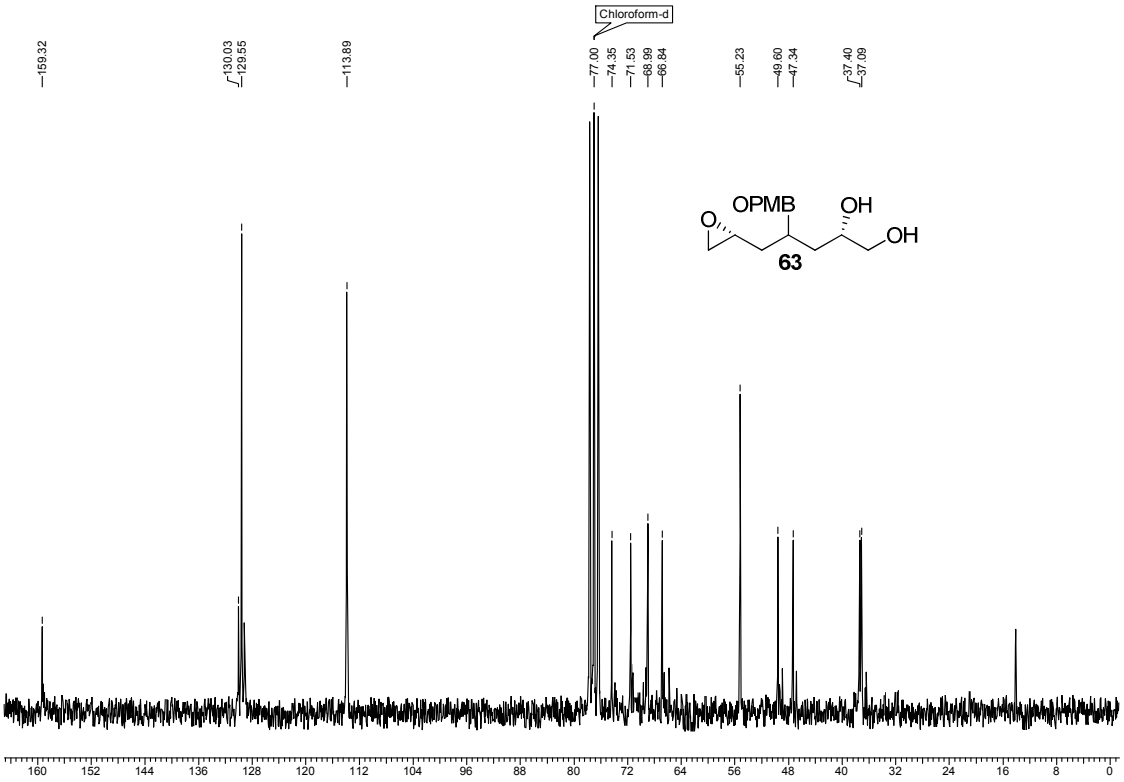
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37.09
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O
OH
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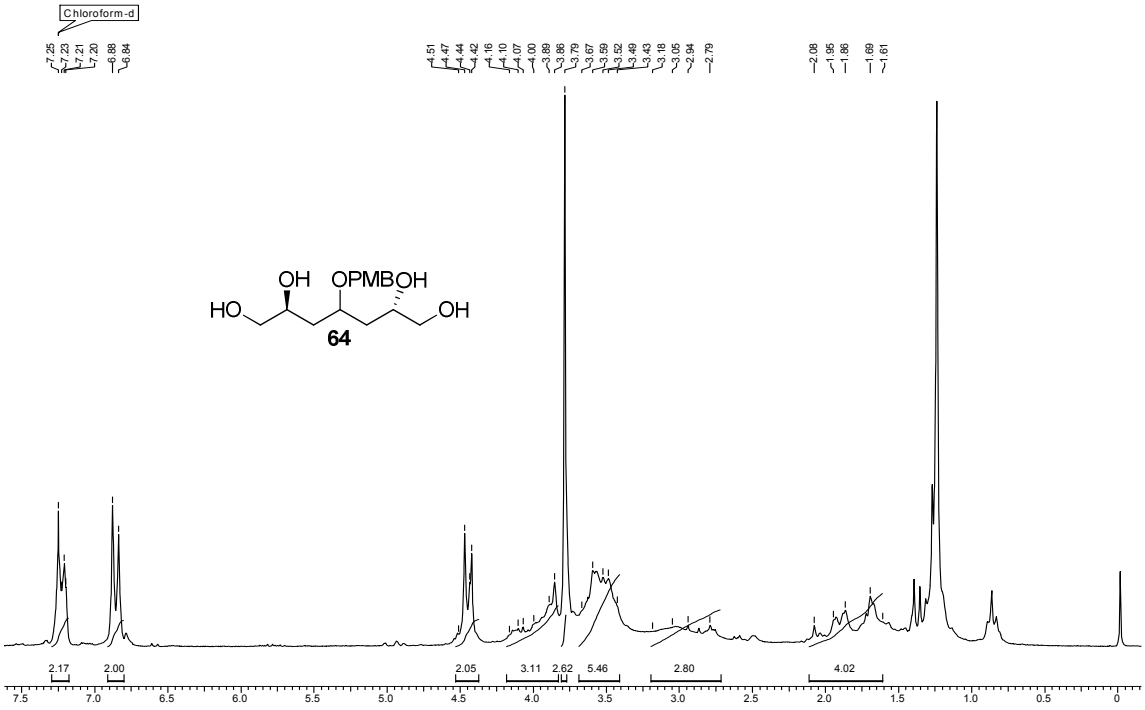
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4.44
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4.07
4.00
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3.86
3.79
3.67
3.59
3.52
3.49
3.43
3.18
3.05
2.94
2.79
2.08
1.95
1.86
1.69
1.61
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HO
OH
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3.11
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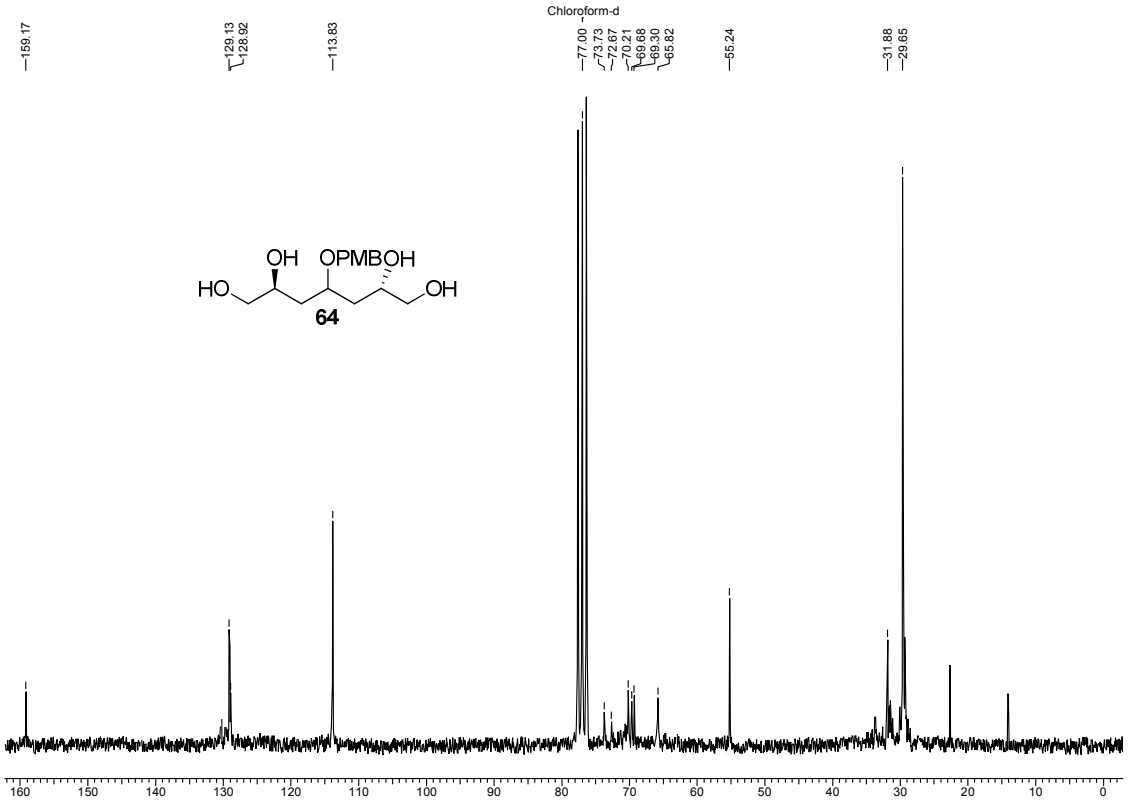
2.80
4.02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55.24
31.88
29.65
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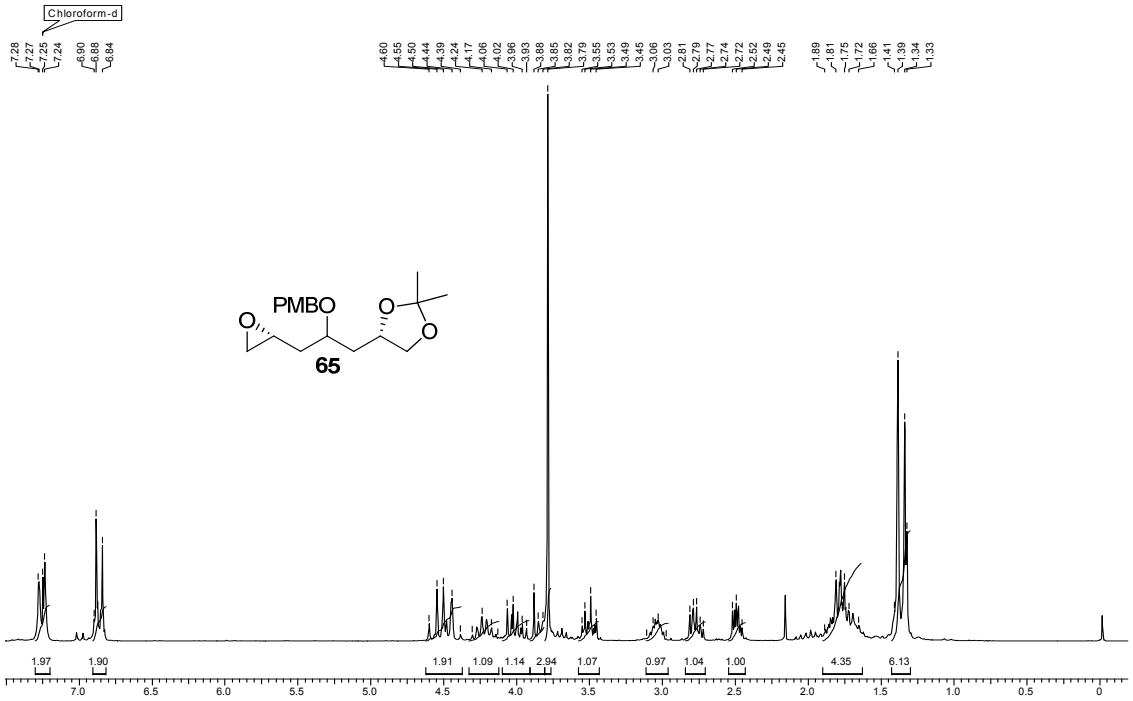
OPMBOH
HO
OH
64


Chloroform-d
PMBO
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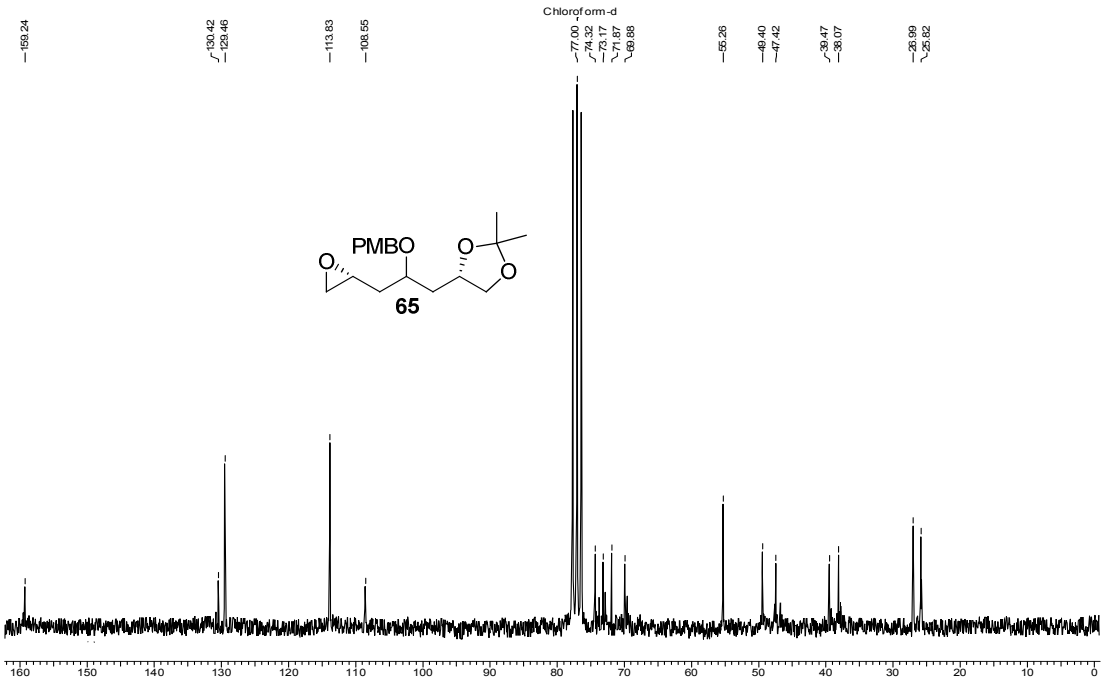
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PMBO
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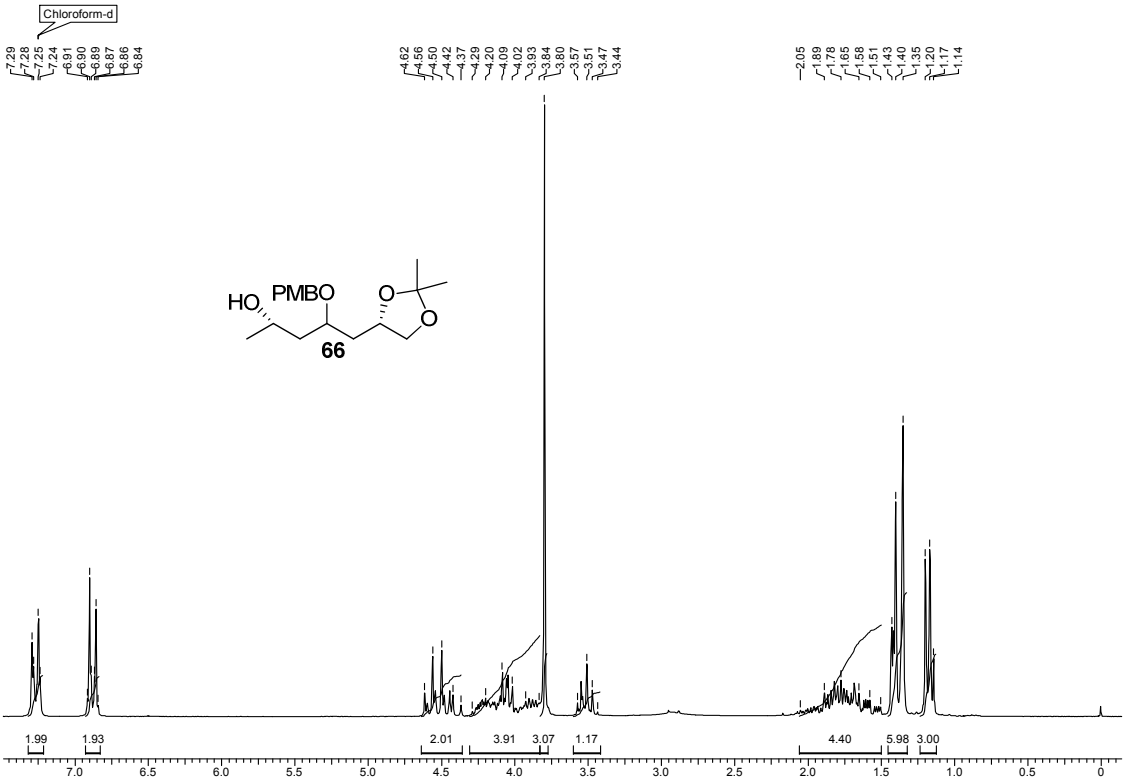
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6.88
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6.86
6.84
4.62
4.56
4.50
4.42
4.37
4.29
4.20
4.09
4.02
3.93
3.84
3.80
3.57
3.51
3.47
3.44
2.05
1.89
1.78
1.65
1.58
1.51
1.43
1.40
1.35
1.20
1.17
1.14
HO
PMBO
O
O
66
1.99
1.93
2.01
3.91
3.07
1.17
4.40
5.98
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6.5
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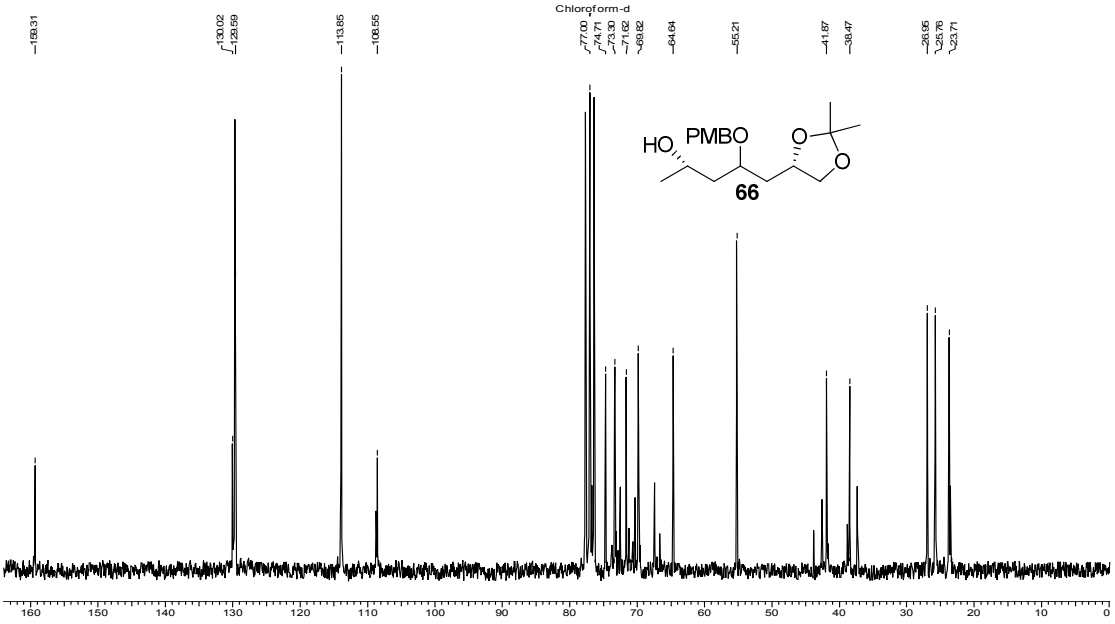
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69.62
64.64
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41.67
38.47
26.95
25.76
23.71
HO
PMBO
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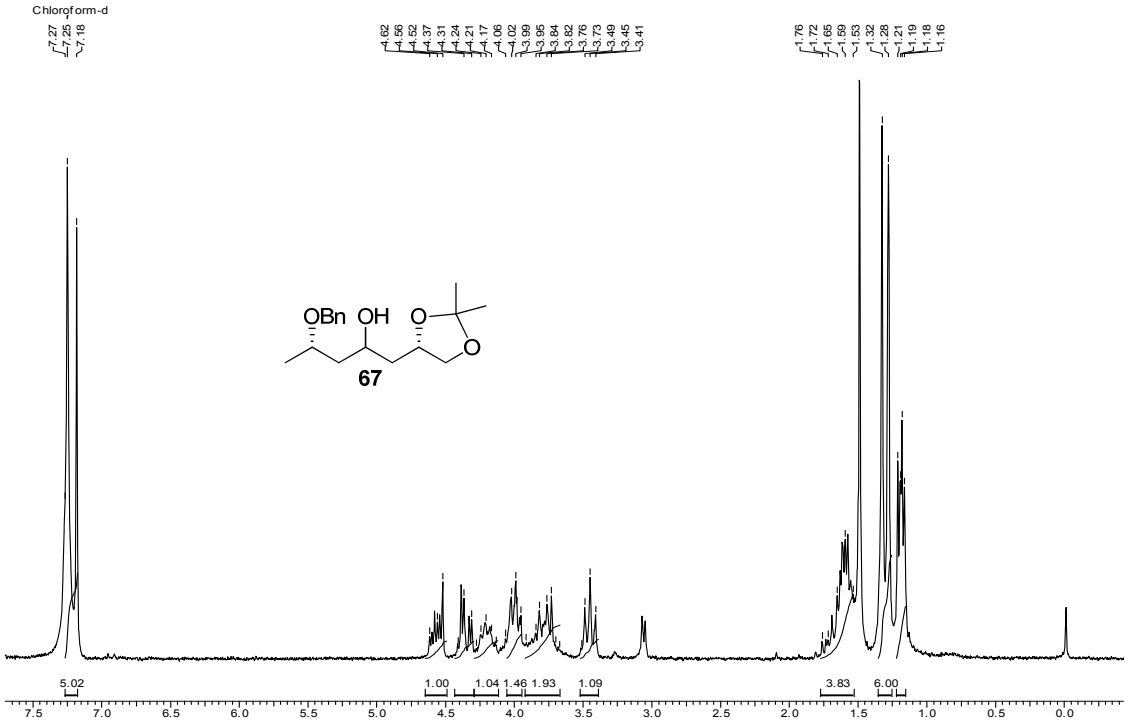
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4.24
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4.06
4.02
3.99
3.95
3.84
3.82
3.76
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3.49
3.45
3.41
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1.59
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1.28
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1.19
1.18
1.16
OBn OH O
O
67
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1.04
1.46
1.93
1.09
3.83
6.00
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7.0
6.5
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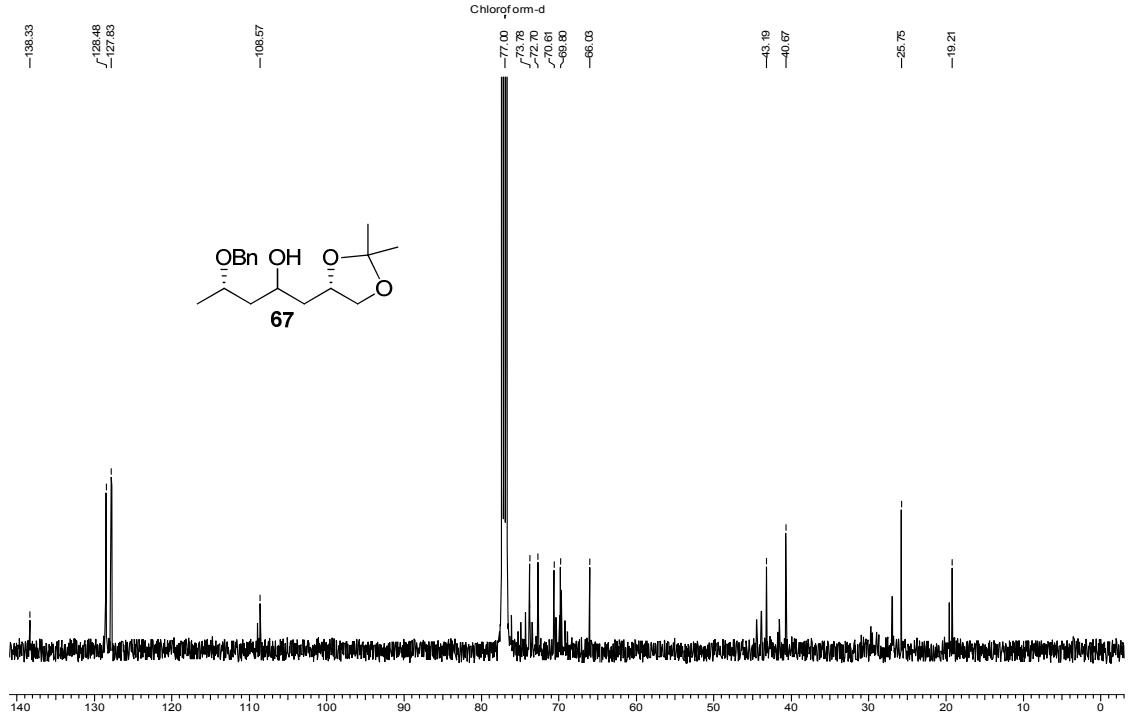
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73.78
72.70
70.61
69.80
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40.67
25.75
19.21
OBn OH O
O
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130
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110
100
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70
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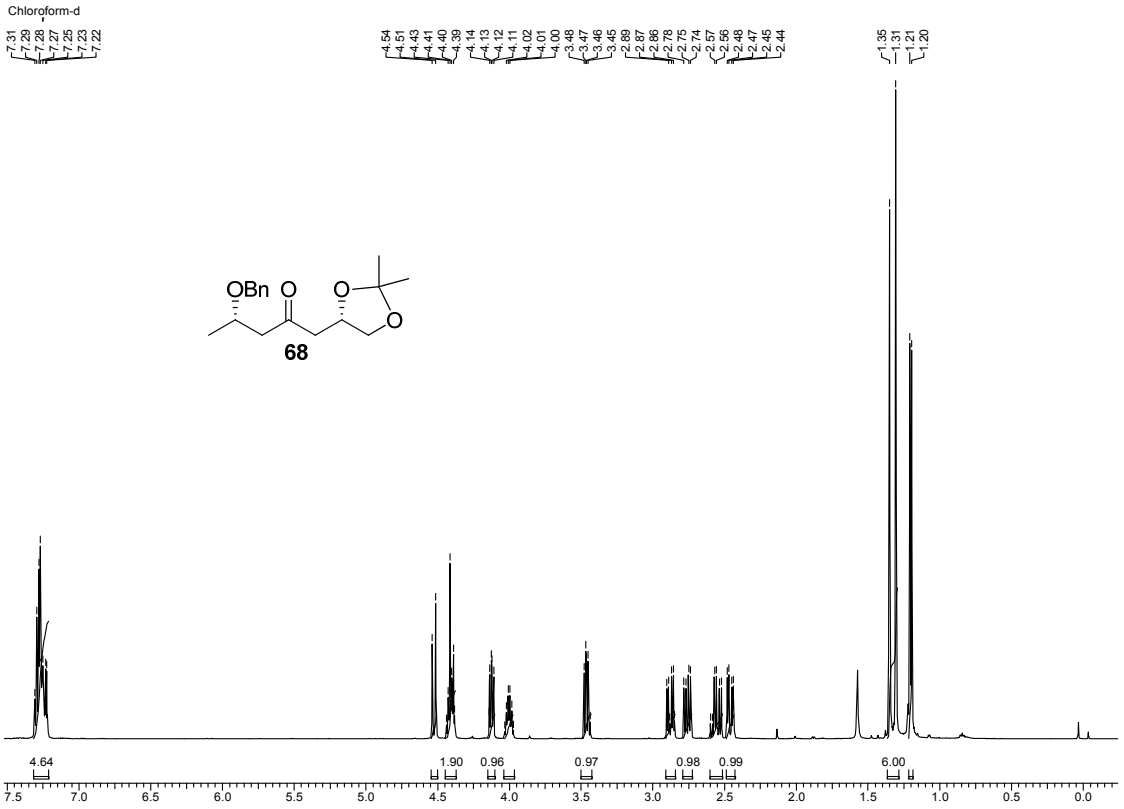
20
10
0


Chloroform-d
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4.41
4.40
4.39
4.14
4.13
4.12
4.11
4.02
4.01
4.00
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3.47
3.46
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2.78
2.75
2.74
2.57
2.56
2.48
2.47
2.45
2.44
1.35
1.31
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O
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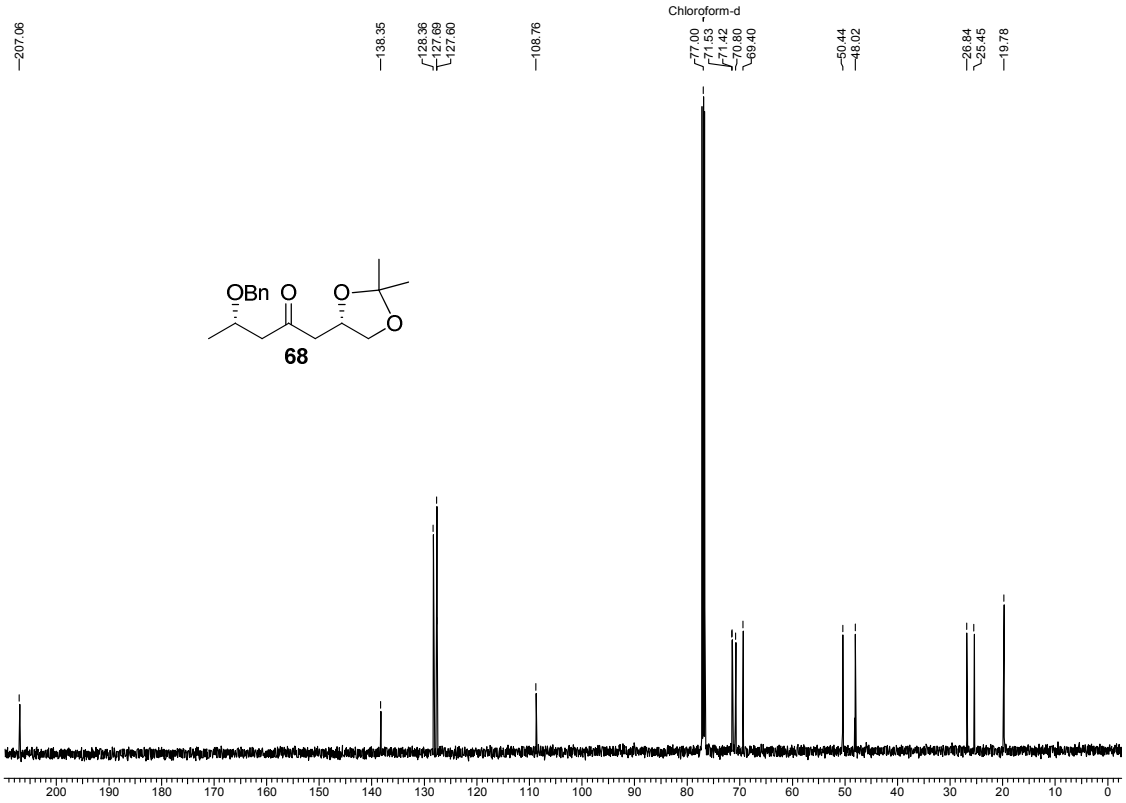
6.00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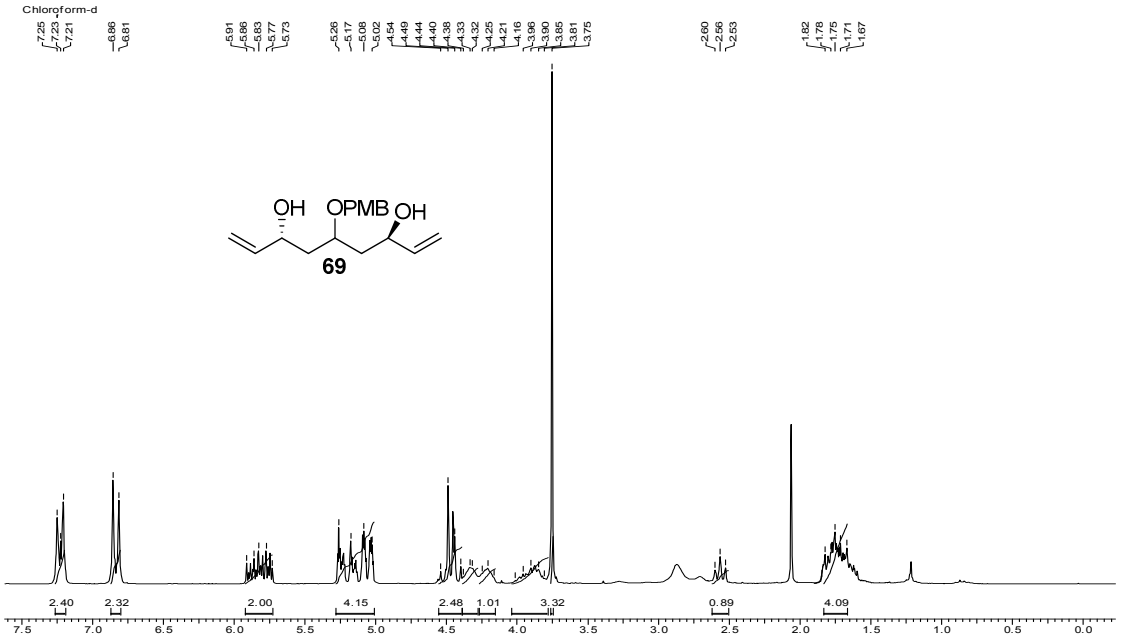
O
68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5.17
5.08
5.02
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4.49
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3.85
3.81
3.75
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2.56
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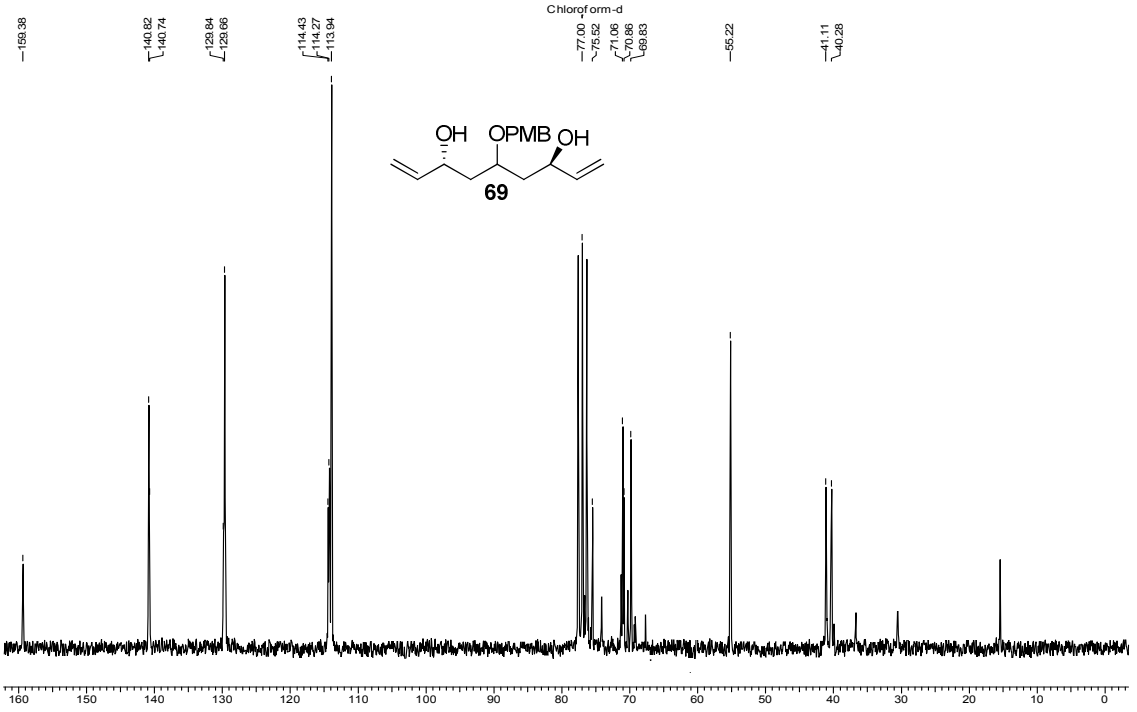
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113.94
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41.11
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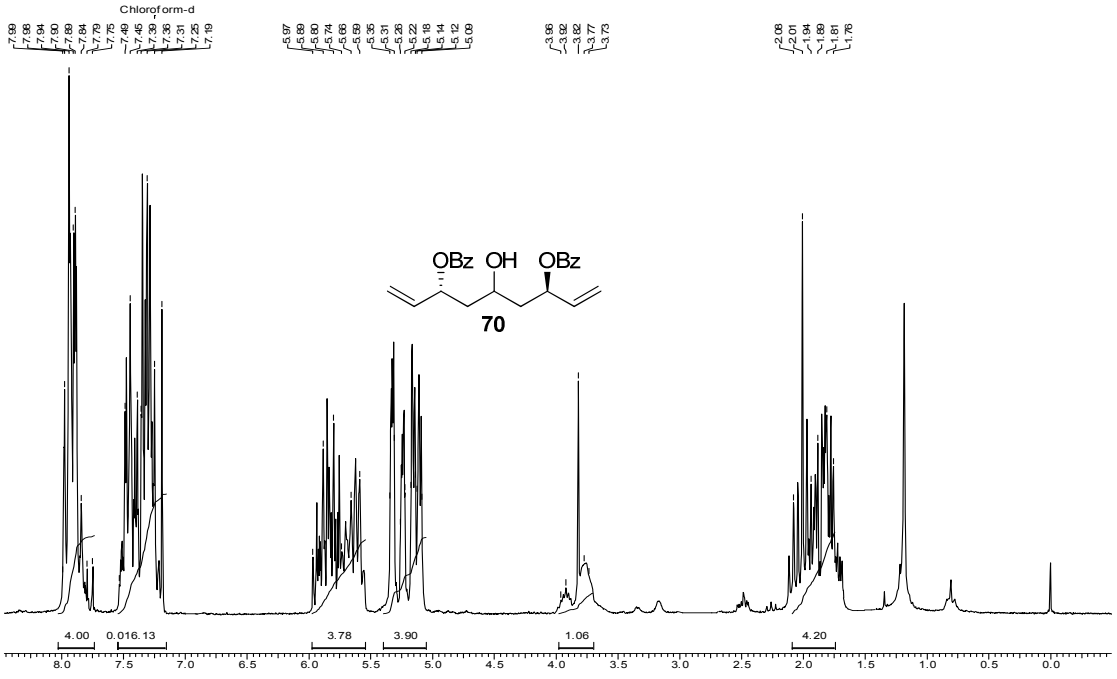
OPMB
OH
69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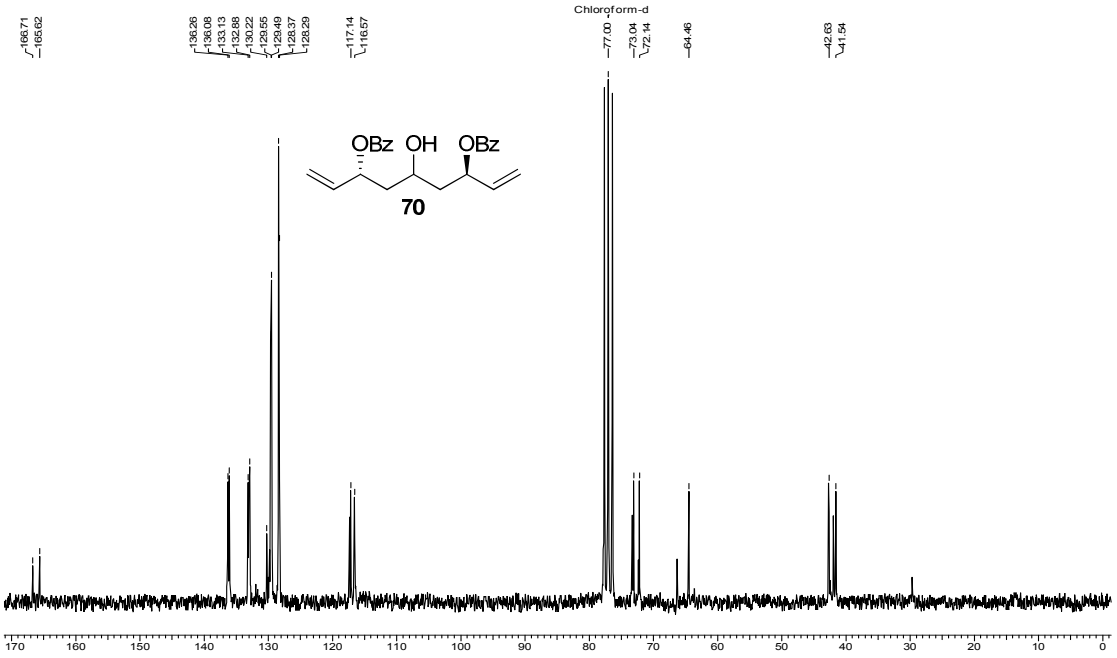
Chloroform-d
OBz OH OBz
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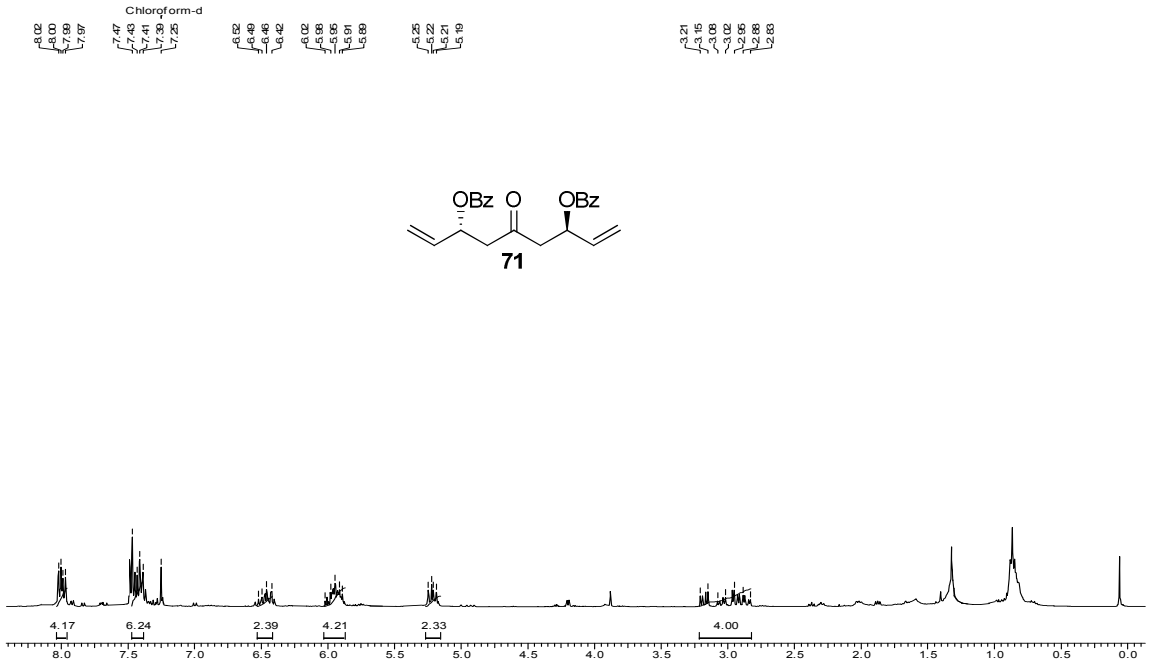
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6.49
6.46
6.42
6.02
5.98
5.95
5.91
5.89
5.25
5.22
5.21
5.19
3.21
3.15
3.08
3.02
2.95
2.88
2.83
OBz
O
OBz
71
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6.24
2.39
4.21
2.33
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7.5
7.0
6.5
6.0
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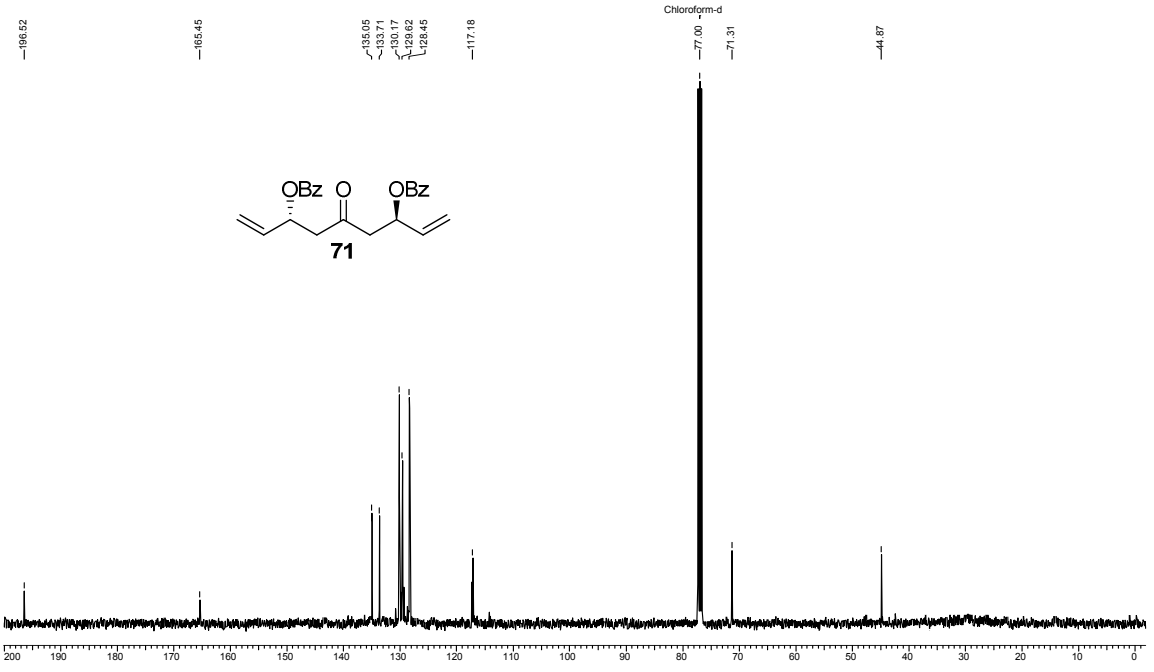
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OBz
O
OBz
71
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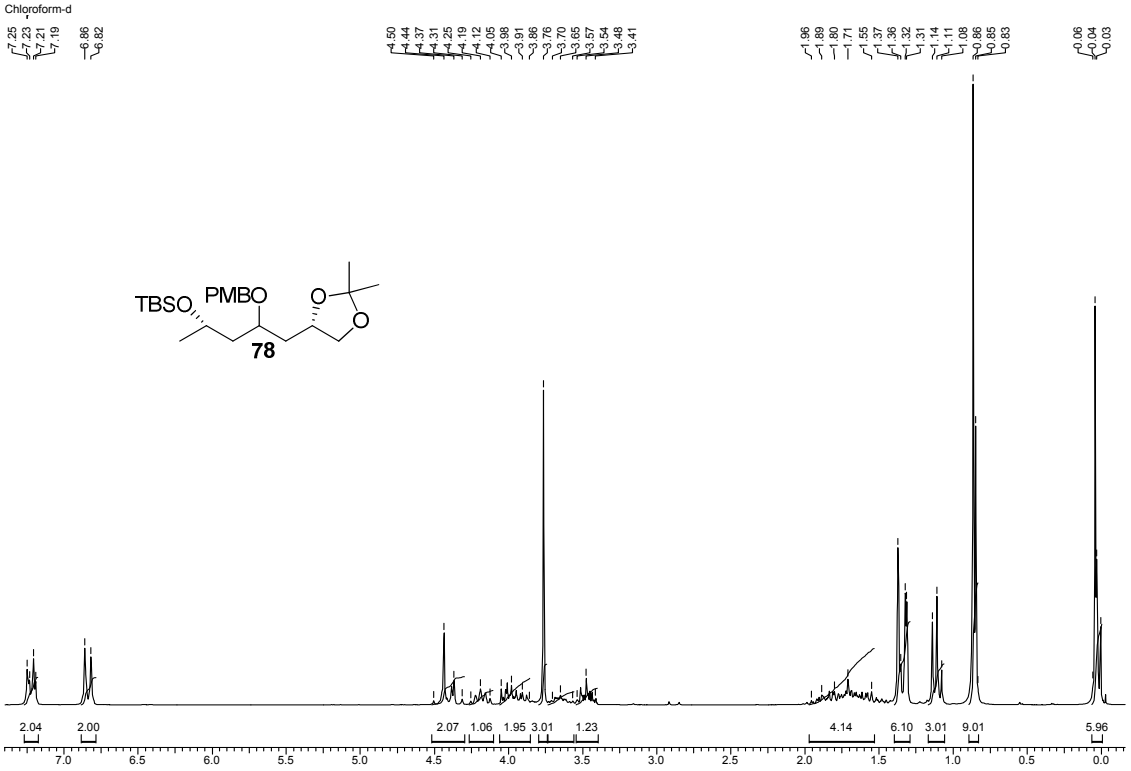
Chloroform-d
TBSO
PMBO
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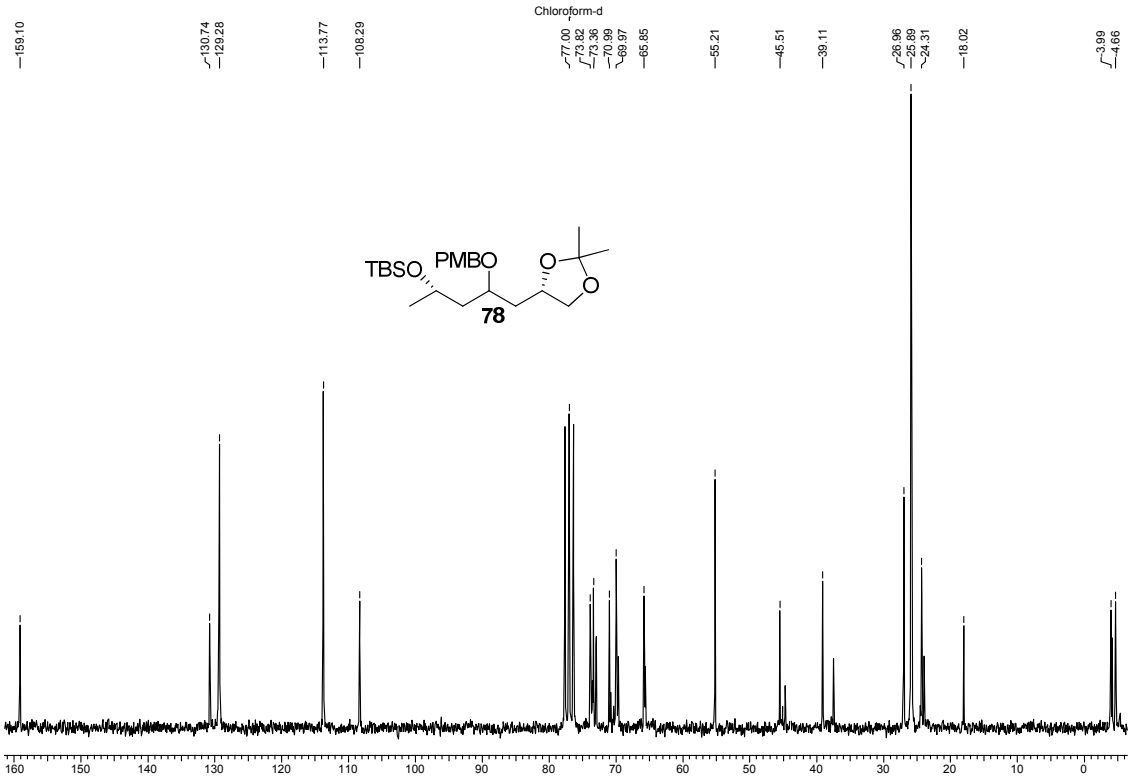
Chloroform-d
TBSO
PMBO
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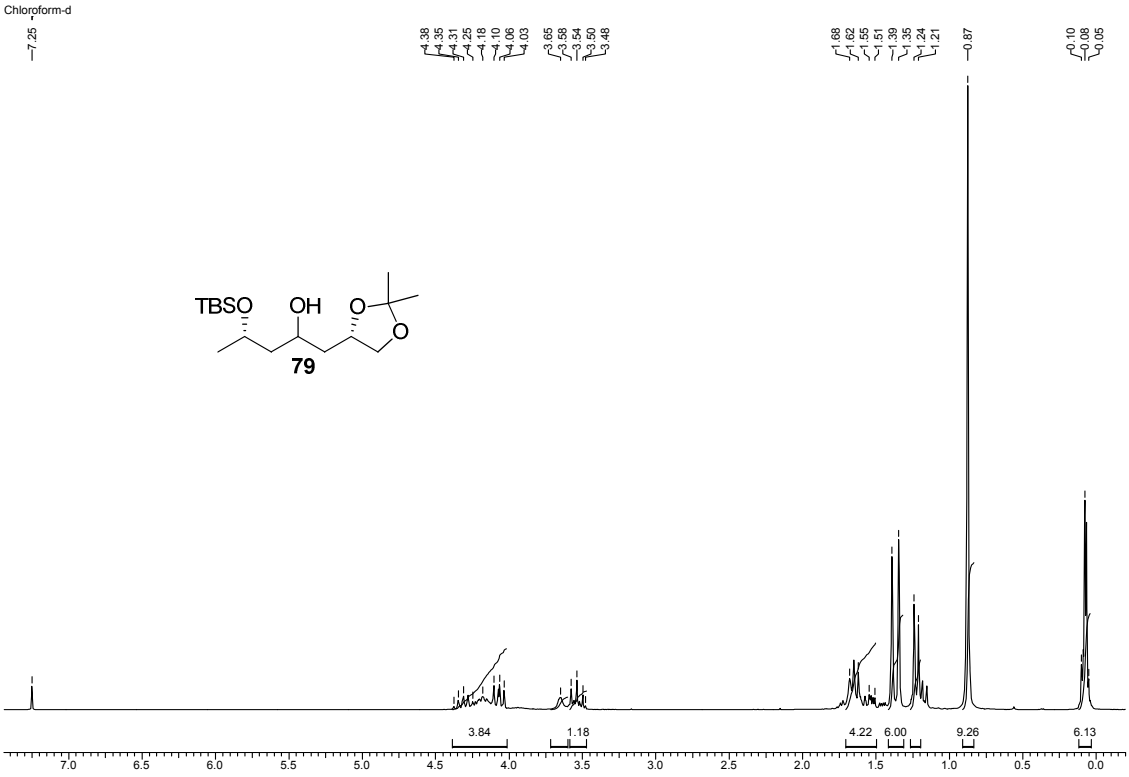
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3.50
3.48
1.68
1.62
1.55
1.51
1.39
1.35
1.24
1.21
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O
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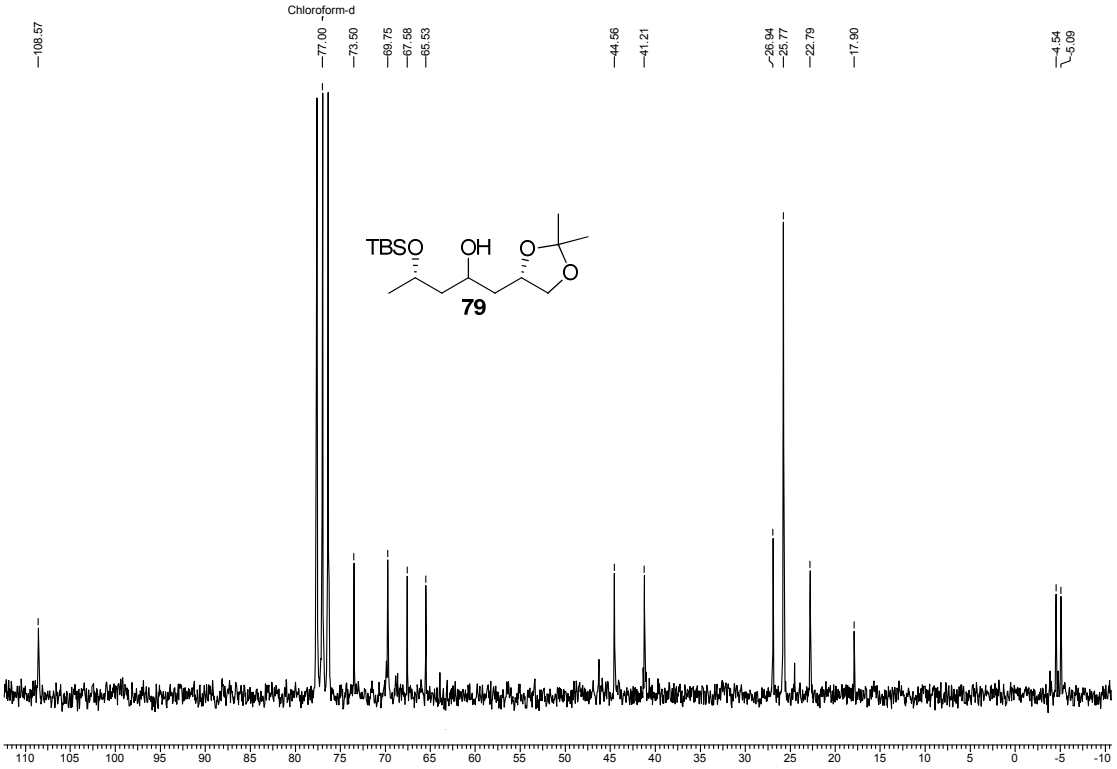
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TBSO
OH
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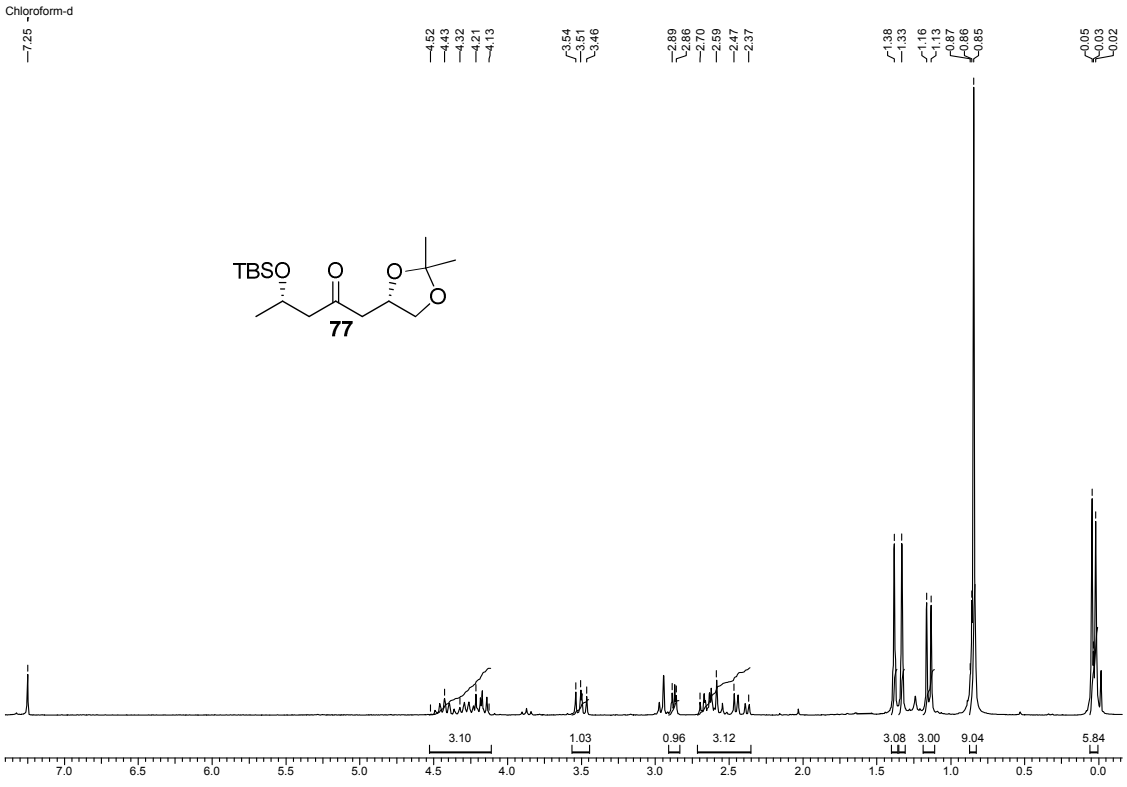
O
79


Chloroform-d
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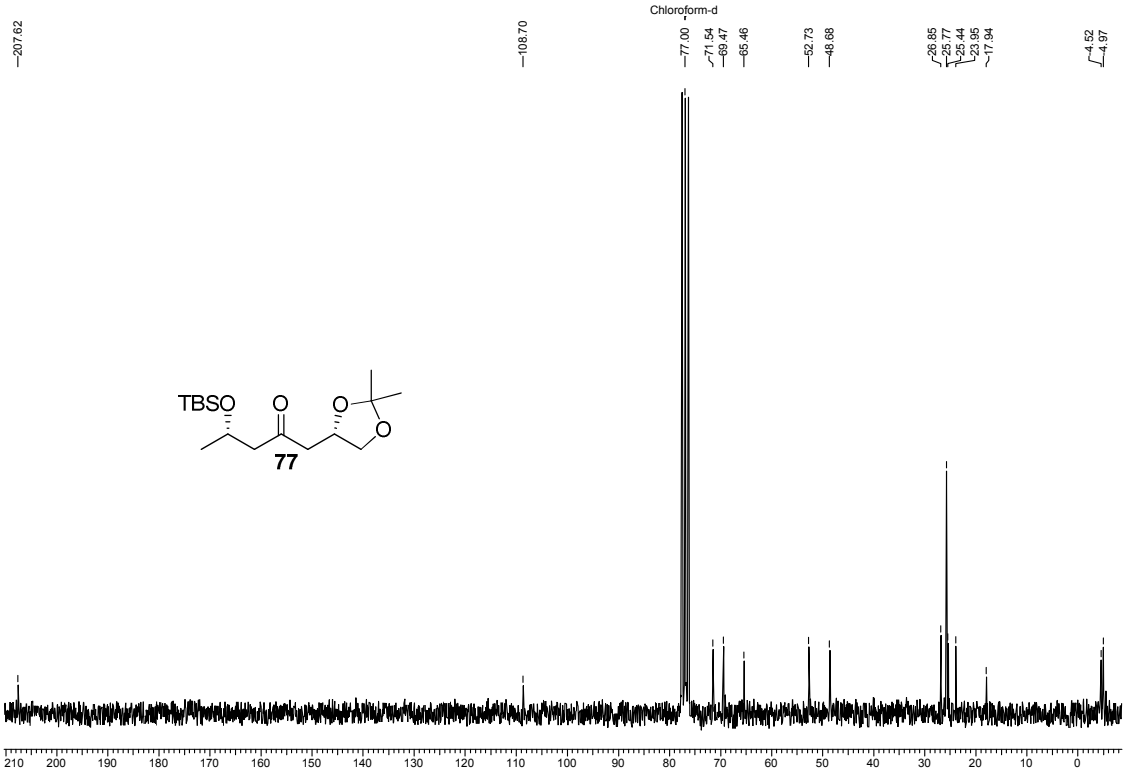
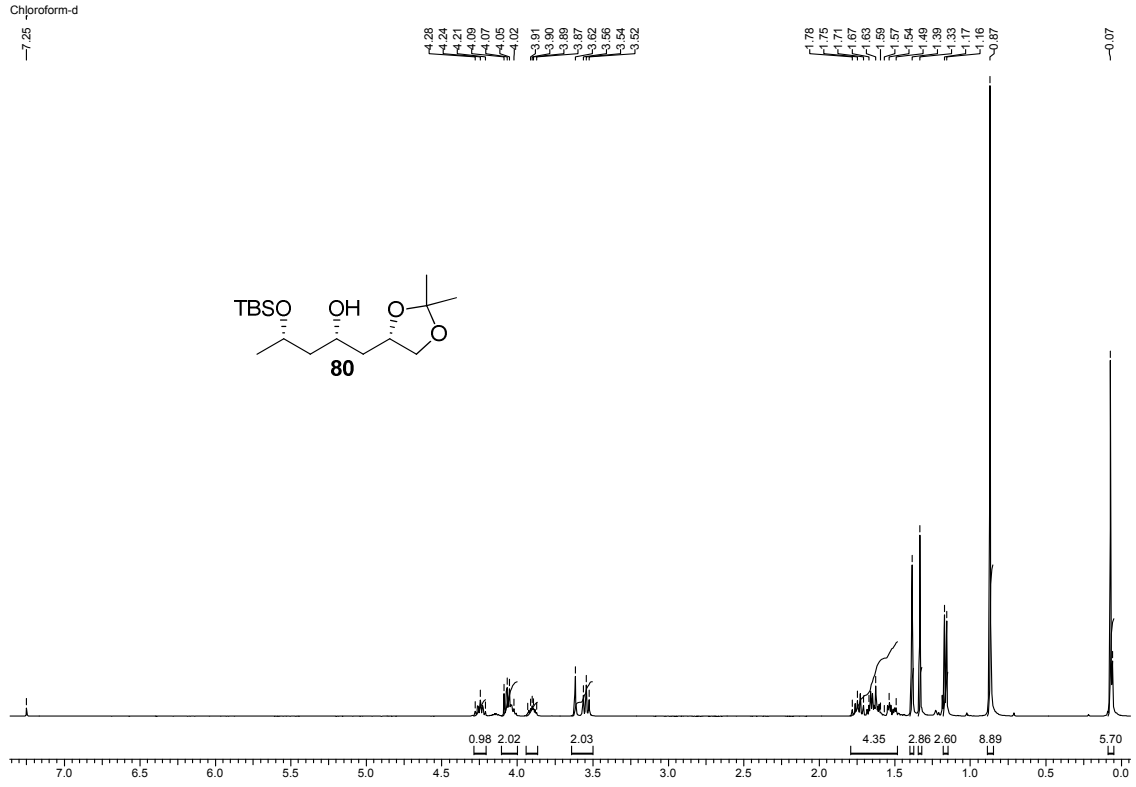
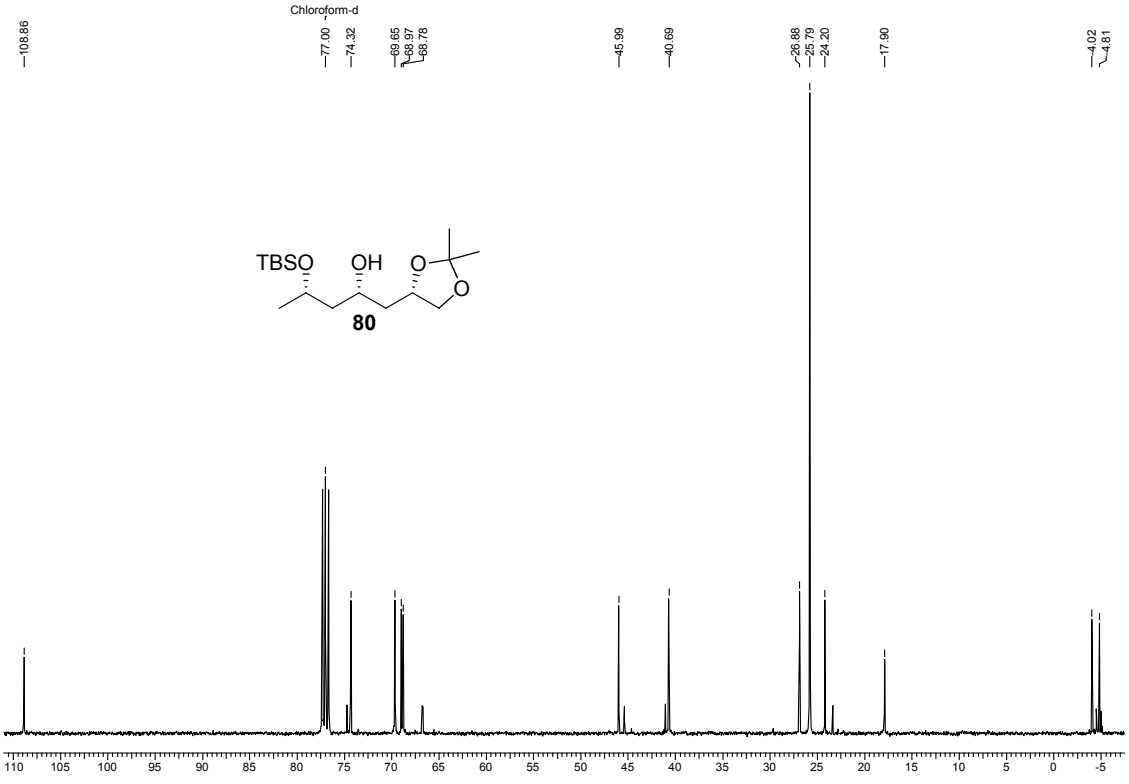
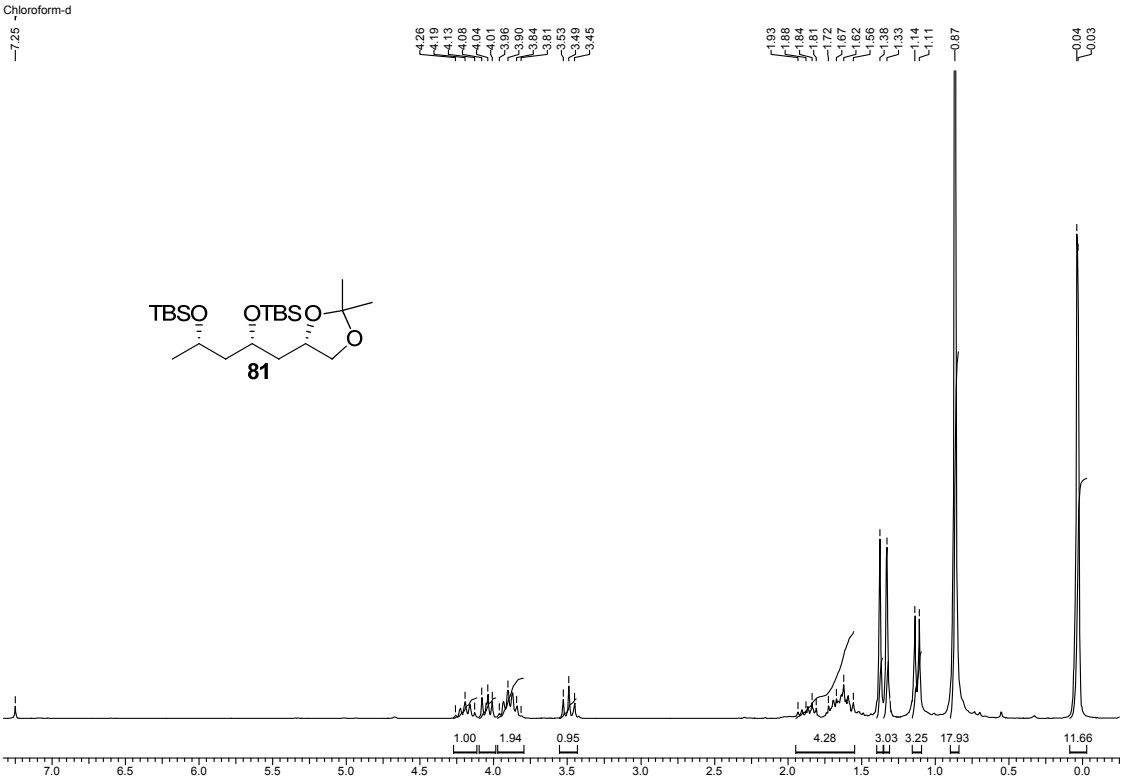
2.70
2.59
2.47
2.37
1.38
1.33
1.16
1.13
0.87
0.86
0.85
0.05
0.03
0.02
TBSO
O
O
O
77
3.10
1.03
0.96
3.12
3.08
3.00
9.04
5.84


Chloroform-d
207.62
108.70
77.00
71.54
69.47
65.46
52.73
48.68
26.85
25.77
25.44
23.95
17.94
4.52
4.97
TBSO
O
O
O
77


Chloroform-d
7.25
4.28
4.24
4.21
4.09
4.07
4.05
4.02
3.91
3.90
3.89
3.87
3.62
3.56
3.54
3.52
1.78
1.75
1.71
1.67
1.63
1.59
1.57
1.54
1.49
1.39
1.33
1.17
1.16
0.87
0.07
TBSO
OH
O
O
80
0.98
2.02
2.03
4.35
2.86
2.60
8.89
5.70


Chloroform-d
108.86
77.00
74.32
69.65
68.97
68.78
45.99
40.69
26.88
25.79
24.20
17.90
4.02
4.81
TBSO
OH
O
O
80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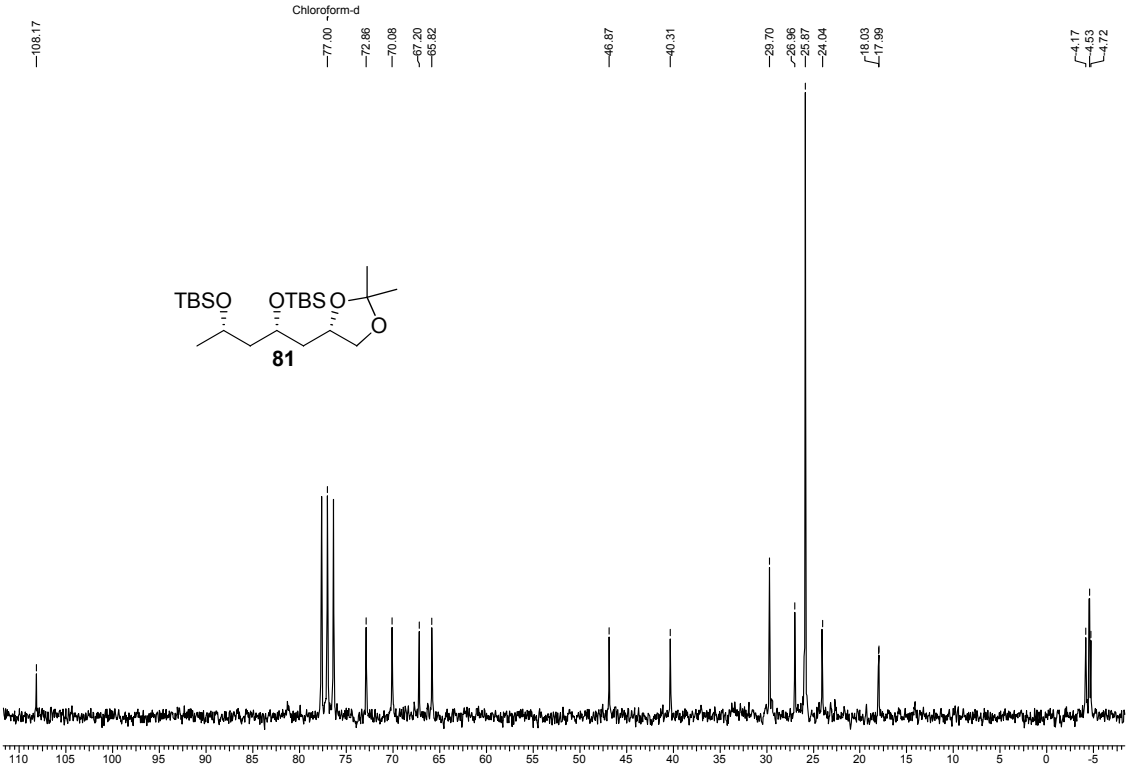
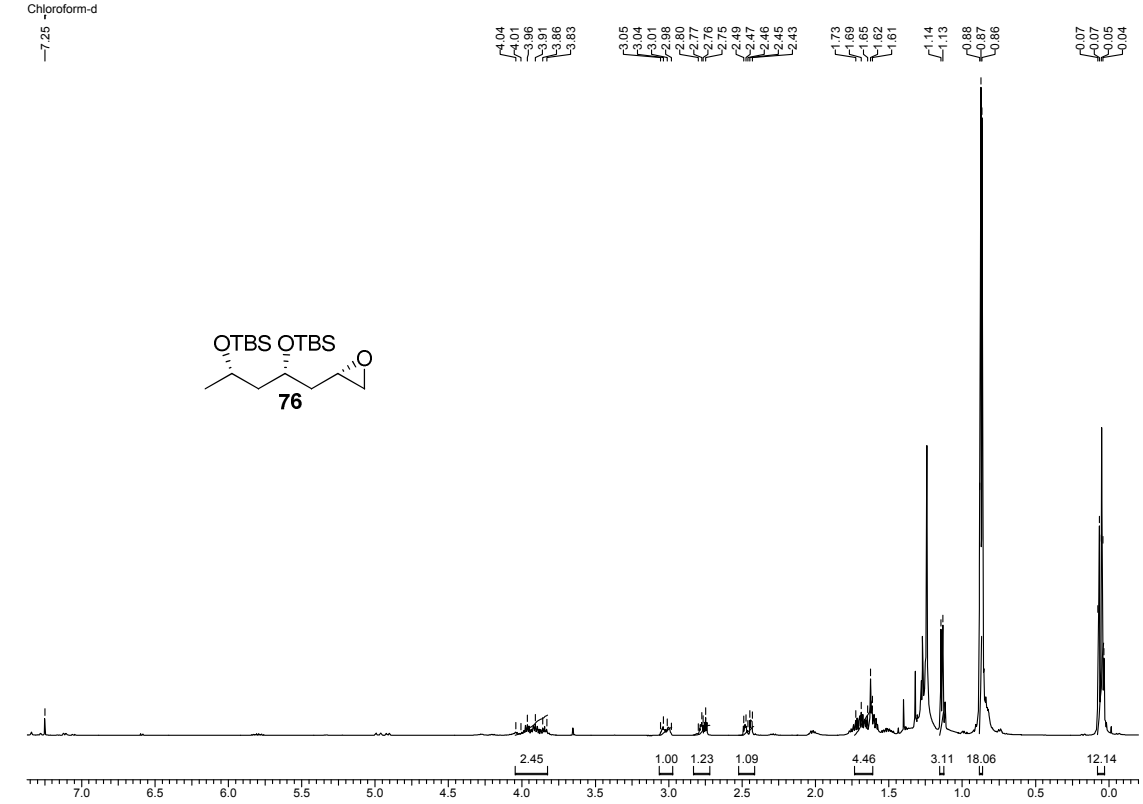
7.25
4.26
4.19
4.13
4.08
4.04
4.01
3.96
3.90
3.84
3.81
3.53
3.49
3.45
1.93
1.88
1.84
1.81
1.72
1.67
1.62
1.56
1.38
1.33
1.14
1.11
0.87
0.04
0.03
TBSO
OTBS
O
O
81
1.00
1.94
0.95
4.28
3.03
3.25
17.93
11.66


Chloroform-d
108.17
77.00
72.86
70.08
67.20
65.82
46.87
40.31
29.70
26.96
25.87
24.04
18.03
17.99
4.17
4.53
4.72
TBSO
OTBS
O
O
81


Chloroform-d
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4.04
4.01
3.96
3.91
3.86
3.83
3.05
3.04
3.01
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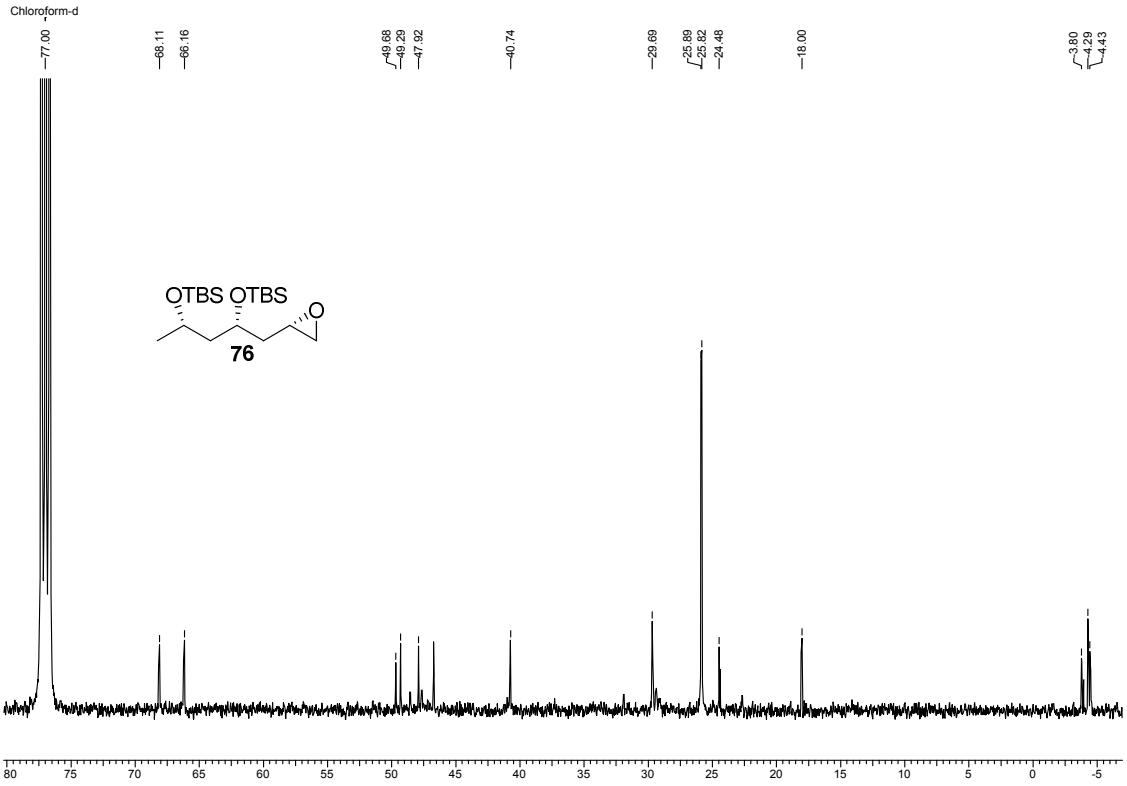
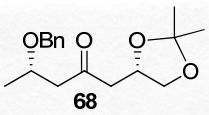
2.80
2.77
2.76
2.75
2.49
2.47
2.46
2.45
2.43
1.73
1.69
1.65
1.62
1.61
1.14
1.13
0.88
0.87
0.86
0.07
0.07
0.05
0.04
OTBS OTBS
O
76
2.45
1.00
1.23
1.09
4.46
3.11
18.06
12.14
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

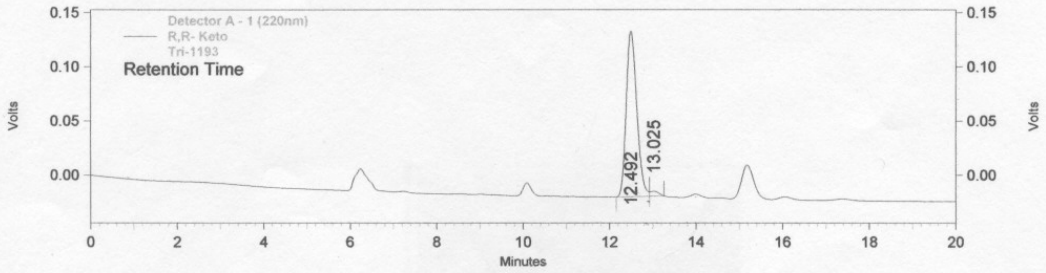

Chloroform-d
77.00
68.11
66.16
49.88
49.29
47.92
40.74
29.69
25.89
25.62
24.48
18.00
3.80
4.29
4.43
OTBS OTBS
O
76
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5

**Enantiomeric excess of major diastereomer of keto compound 68:**

**Shimadzu CLASS-VP V6.12 SP5**
**Method Name:** C:\CLASS-VP\Method ch 2.met
**Data Name:** C:\CLASS-VP\Data\Dr Tripathi\Tri-1193
**User:** System
**Acquired:** 12/30/11 4:11:28 PM
**Printed:** 12/30/11 5:22:26 PM
**Sample Name** R,R- Keto



68



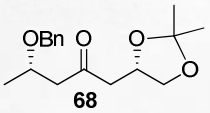

**Detector A - 1 (220nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 12.492 | 2614589 | 97.758 |
| 13.025 | 59953 | 2.242 |
| Totals | 2674542 | 100.000 |

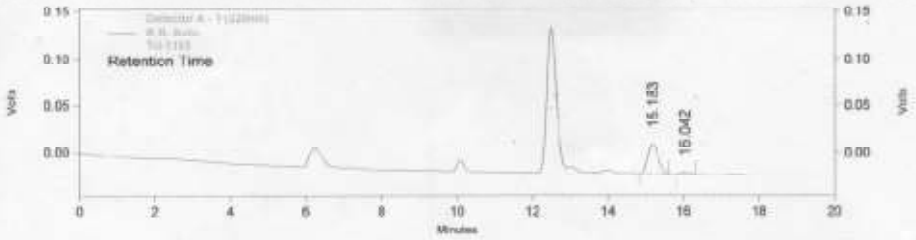
Project Leader :Dr.Tripathi
Column :Kromasil 5-Cellucoat(250x4.6 mm)
Mobile Phase :IPA:Pet Ether (10:90)
Wavelength : 220 nm
Flow Rate :0.5 ml/min (23Kgf)
conc. :.1 mg/1.0mL
Inj vol- : 5 ul

**Enantiomeric excess of minor diastereomer of keto compound 68:**

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\Dr Tripathi\Tri-1193
User: System
Acquired: 12/30/11 4:11:28 PM
Printed: 12/30/11 5:24:46 PM
Sample Name R,R- Keto




68

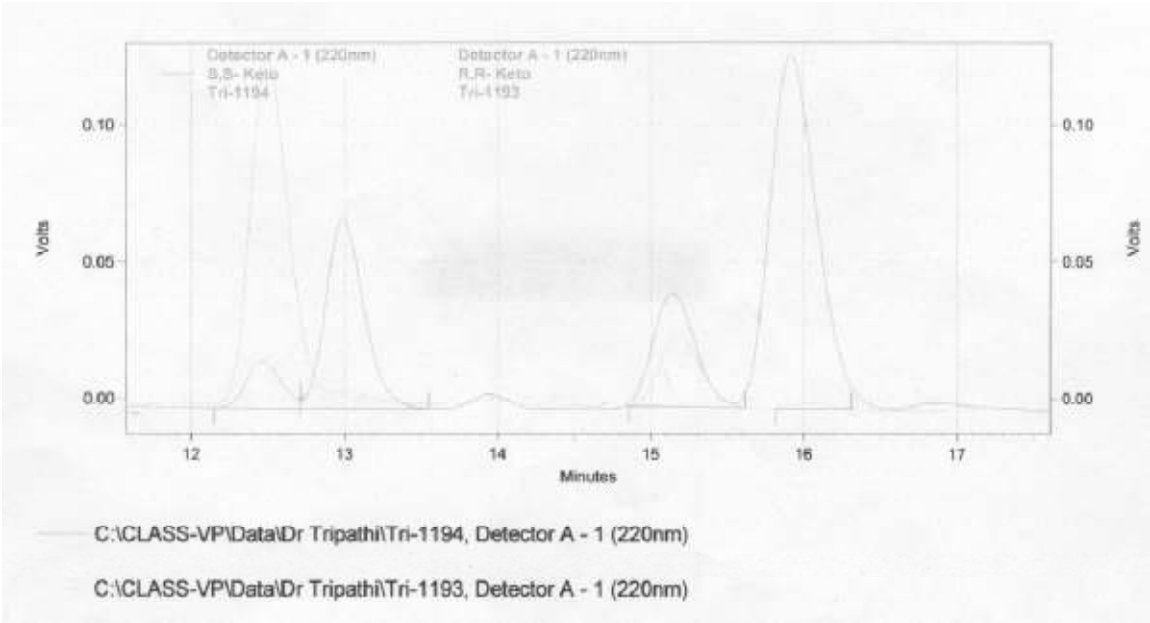



Detector A - 1 (220nm)

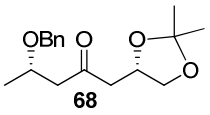
| Retention Time | C Area | Area % |
|---|---|---|
| 15.183 | 592085 | 94.046 |
| 16.042 | 37483 | 5.954 |
| Totals | 629568 | 100.000 |

Project Leader :Dr.Tripathi
Column :Kromasil 5-Cellucoat(250x4.6 mm)
Mobile Phase :IPA:Pet Ether (10:90)
Wavelength : 220 nm
Flow Rate :0.5 ml/min (23Kgf)
conc. :.1 mg/1.0mL
Inj vol- : 5 ul

**Racemic**

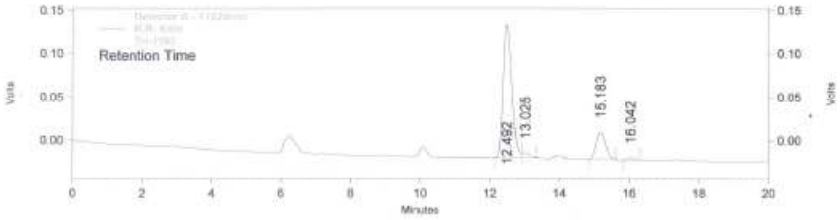


**Diastereomeric excess of keto compound 68**




**68**

**Shimadzu CLASS-VP V6.12 SP5**
**Method Name:** C:\CLASS-VP\Method ch 2.met
**Data Name:** C:\CLASS-VP\Data\Dr Tripathi\Tri-1193
**User:** System
**Acquired:** 12/30/11 4:11:28 PM
**Printed:** 12/30/11 5:24:03 PM
**Sample Name** R,R- Keto




**Detector A - 1 (220nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 12.492 | 2627531 | 78.853 |
| 13.025 | 75089 | 2.253 |
| 15.183 | 592085 | 17.769 |
| 16.042 | 37483 | 1.125 |
| Totals | 3332188 | 100.000 |

Project Leader :Dr.Tripathi
Column :Kromasil 5-Cellucoat(250x4.6 mm)
Mobile Phase :IPA:Pet Ether (10:90)
Wavelength : 220 nm
Flow Rate :0.5 ml/min (23Kgf)
conc. :.1 mg/1.0mL
Inj vol- : 5 ul

**Enantiomeric excess of compound 71:**

**NATIONAL CHEMICAL LABORATORY**

ORGANIC CHEMISTRY TECHNOLOGY

Analyzed: 04/11/12 03:03 PM Reported: 04/11/12 03:58 PM

Data Path: f:\win32app\hsm\NCLOC\DATA\4701\

Processing Method: Lichrosphere RP-18 (250-4) Acquisition Method: Lichrosphere RP-18 (250-4)

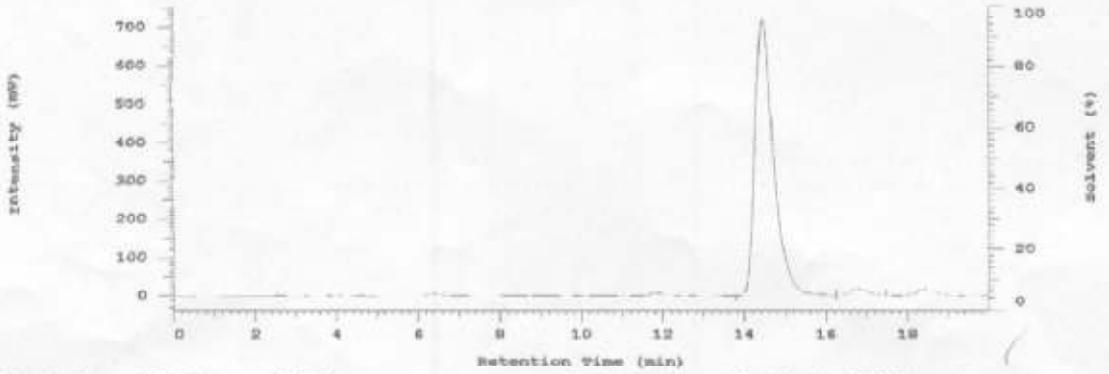
System(acquisition): Sys 1 Series:4701

Sample Name: Bis Epoxide R, R Chiral Vial Number: 1

Injection from vial: 1 of 1 Vial Type: UNK

Volume: 10.0 ul

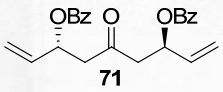
Chrom Type: HPLC Channel : 1




Peak Quantitation: AREA Calculation Method: AREA%

| No. | RT | Height | Area | Area % |
|---|---|---|---|---|
| 1 | 14.44 | 710285 | 22764273 | 97.995 |
| 2 | 16.90 | 15198 | 465875 | 2.005 |
| | | 733483 | 23230148 | 100.000 |

Peak rejection level: 0




**71**

Group Leader :Dr.Pradeep Kumar

Column : Chiralcel OJ-RH(150 X 4.6 mm)

M.P. :ACN:H2O (60:40)

Flow Rate :0.5 ml/min (766 psi)

Sample conc: 1mg/1 ml

Inj vol: 2 ul

WAVELENGTH : 254 nm

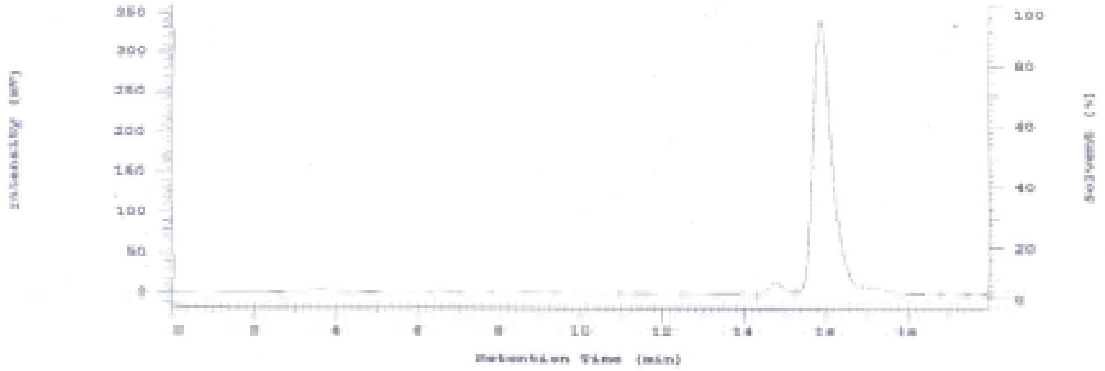
**NATIONAL CHEMICAL LABORATORY**

ORGANIC CHEMISTRY TECHNOLOGY

Analyzed: 04/11/12 03:28 PM Reported: 04/11/12 03:53 PM
Data Path: f:\win32app\hsm\NCLOCC\DATA\4702\
Processing Method: Lichrosphere RP-18 (250-4) Acquisition Method: Lichrosphere RP-18 (250-4)

System(acquisition): Sys 1 Series:4700
Sample Name: Rik Epoxide 0, 0 Chiral Vial Number: 2
Injection from vial: 1 of 1 Vial Type: UNK
Volume: 10.0 ul

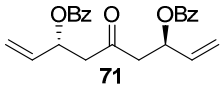
Chrom Type: HPLC Channel : 1




Peak Quantitation: AREA Calculation Method: AREA

| No. | RT | Height | Area | Area % |
|---|---|---|---|---|
| 1 | 14.74 | 13418 | 333935 | 3.059 |
| 2 | 15.87 | 350151 | 10580768 | 96.941 |
| | | 351569 | 10914703 | 100.000 |

Peak rejection level: 0




**71**

Group Leader :Dr.Pradeep Kumar
Column : Chiralcel OJ-RH(150 X 4.6 mm)
M.P. :ACN:H2O (60:40)

Flow Rate :0.5 ml/min (700 psi)
Sample conc: 1mg/1 ml
Inj vol: 2 ul
WAVELENGTH : 254 nm

## 4. 8. Reference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# Curriculum Vitae

# Partha Sarathi Chowdhury

## Education

**2007- present** Ph.D. Organic Chemistry, National Chemical Laboratory, Pune, India.

**2007** M. Sc. Chemistry, Banaras Hindu University, Varanasi, India (**1st Class** with **distinction**)

**2005** B. Sc. University of Calcutta, Kolkata, India (**1st Class**)

## Fellowships

**2007-2009** Junior Research Fellowship awarded by Council of Scientific and Industrial Research (CSIR), India (www.csir.res.in).

**2009-2012** Senior Research Fellowship awarded by Council of Scientific and Industrial Research (CSIR), India.

## Examination Qualified

**2006** Qualified *National Eligibility Test* (NET) conducted by **Council of Scientific and Industrial Research (CSIR),**

**2007** Qualified *Graduate Aptitude Test* in Engineering (GATE) conducted by **Indian Institute of Technology (IIT) Kharagpur,** India with 420 score

## Publications

**1** A desymmetrization approach to the enantiopure *syn/anti*-1,5-diols *via* hydrolytic kinetic resolution (HKR) of functionalized meso bis-epoxides: further elaboration to *syn*/*syn*-1,3,5-triols and application to the formal synthesis of cryptocarya diacetate.
Pradeep Kumar,* **Partha Sarathi Chowdhury**, Menaka Pandey
*Advanced Synthesis and Catalysis* **2013**, *355,* 1719–1723.

**2** Total synthesis of umuravumbolide and hyptolide via silicon-tethered ring closing metathesis.
**Partha Sarathi Chowdhury**, Pradeep Kumar*
*European Journal of Organic Chemistry* **2013,** 4586–4593.

**3** First asymmetric total synthesis of aspinolide A.
**Partha Sarathi Chowdhury**, Priti Gupta, Pradeep Kumar*
*Tetrahedron Letters* **2009**, *50,* 7018-7020.

**4** Enantioselective synthesis of decarestrictine J.
**Partha Sarathi Chowdhury**, Priti Gupta, Pradeep Kumar*
*Tetrahedron Letters* **2009**, *50,* 7188–7190.

**5** A highly concise and practical route to clavaminols, sphinganine and (+)-spisulosine *via* Indium mediated allylation of α-hydrazino aldehyde and a

theoretical insight into the stereochemical aspect of the reaction.
Menaka Pandey[1a], **Partha Sarathi Chowdhury**[1a], Achintya Kumar Dutta[1b], Pradeep Kumar*[1a] and Sourav Pal[1b]
*RSC Advances* **2013**, *3*, 15442–15448.

**6** Enantio- and diastereoconvergent total synthesis of antifungal sphingofungin B
Menaka Pandey, **Partha Sarathi Chowdhury**, Pradeep Kumar*
**(To be Communicated)**

## Research experience

**Ph.D. thesis Title** "Studies Directed Towards Enantioselective Total Synthesis of Some Naturally Occurring Lactones and Hydrolytic Kinetic Resolution (HKR) of Terminal Mono and Bis-Epoxides."

**Supervisor** Dr. Pradeep Kumar (National Chemical Laboratory)

**Description** Asymmetric Total Synthesis of Naturally Occurring 10-Membered Lactones such as **Decarestrictine J** and **Aspinolide A.**

Total Synthesis of **Umuravumbolide, Hyptolide and Hypurticin** *via* Temporary Silicon Tethered-Ring Closing Metathesis.

A Desymmetrization Approach to The Enantiopure ***syn/anti*-1,5-Diols** *via* Hydrolytic Kinetic Resolution (HKR) of Functionalized Meso Bis-Epoxides: Further Elaboration to ***syn*/*syn*-1,3,5-Triols** and Application to The Formal Synthesis of **Cryptocarya Diacetate**.

## Conference & Presentations

**2011** Oral presentation at **"6th Junior National Organic Symposium Trust (JNOST)**" conference University of Hyderabad, Hyderabad, India.

**2012** Poster presentation at **"Zing Natural Products Conference"** Lanzarote, Spain.

## Technical Skills

**1** Excellent experience in conducting reactions under inert conditions.

**2** Purification, and characterization of various organic and organometallic compounds in milligram and multigram scale.

**3** Experience in handling HPLC, IR, GC.

**4** Skilled in the interpretation of spectroscopic data (NMR, IR, MS, LCMS, TOF Mass, HRMS, IR, UV-VIS, GC, HPLC) towards the characterization of unknown compounds.