Stereoselective Synthesis towards Bullatanocin, towards (+)-*trans*-Kumausyne employing α-Chloro Sulfide Synthons and Catalytic Asymmetric Reactions

A THESIS SUBMITTED

TO

UNIVERSITY OF HYDERABAD

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)

BY

L. RAJU CHOWHAN

(Enroll No: 09CHPH20)

SUPERVISOR

Dr. S. RAGHAVAN

NATURAL PRODUCTS CHEMISTRY DIVISION
CSIR-INDIAN INSTITUTE OF CHEMICAL TECHNOLOGY
(An Associate Institution of UNIVERSITY OF HYDERABAD)
HYDERABAD-500 007, INDIA
July, 2015

DECLARATION

I hereby declare that the work presented in the thesis entitled **“Stereoselective Synthesis towards Bullatanocin, towards (+)-*trans*-Kumausyne employing α-Chloro Sulfide Synthons and Catalytic Asymmetric Reactions”** is entirely original and was carried out by me independently at Indian Institute of Chemical Technology, Hyderabad under the supervision of **Dr. S. Raghavan**, Senior Principal Scientist, Indian Institute of Chemical Technology. I declare that this thesis has not formed the basis for the award of any degree or diploma, fellowship or associate ship or similar title of any university or institution.

Date: **(L. RAJU CHOWHAN)**

CSIR-INDIAN INSTITUTE OF CHEMICAL TECHNOLOGY
HYDERABAD-500 007, INDIA
Telephone: +91- 040 - 2719 1627
E-mail: sraghavan@iict.res.in

Dr. S. Raghavan
Senior Principal Scientist
Natural Products Chemistry Division,
CSIR-Indian Institute of Chemical Technology,
Uppal Road, Hyderabad - 500 007, AP, India.

CERTIFICATE

This is to certify that the research work presented in the thesis entitled **"Stereoselective Synthesis towards Bullatanocin, towards (+)-*trans*-Kumausyne employing α-Chloro Sulfide Synthons and Catalytic Asymmetric Reactions"** has been carried out under my supervision and is a bonafide work of **Mr. L. Raju Chowhan**. This work is original and has not been submitted for any other degree or diploma to this or any other University.

Date: **[Dr. S. RAGHAVAN]**

Research Guide

CSIR-INDIAN INSTITUTE OF CHEMICAL TECHNOLOGY
HYDERABAD-500 007, INDIA
Telephone: +91- 040 - 2719 1627
E-mail: sraghavan@iict.res.in

Dr. S. Raghavan
Head & Senior Principal Scientist
Natural Products Chemistry Division,
CSIR-Indian Institute of Chemical Technology,
Uppal Road, Hyderabad - 500 007, AP, India.

CERTIFICATE

This is to certify that the thesis **“Stereoselective Synthesis towards Bullatanocin, towards (+)-*trans*-Kumausyne employing α-Chloro Sulfide Synthons and Catalytic Asymmetric Reactions”** that is being submitted by **Mr. L. Raju Chowhan** in partial fulfilment for the award of Ph.D. in the Department of Chemistry to the University of Hyderabad is a record of bonafide work carried out by him at our institution

Signature of Head of the Department

Date:

[Dr. S. RAGHAVAN]

Senior Principal Scientist & Head

Dedicated to

My beloved family

ACKNOWLEDGEMENTS

It gives me great pride and honour to express my gratitude towards my research guide **Dr. S. Raghavan**, Senior Principal Scientist, Indian Institute of Chemical Technology, Hyderabad. I thank him for his excellent guidance, unstinted support, consistent encouragement, invaluable suggestions and scintillating discussions that he has offered me during my entire period of stay. I consider myself fortunate in that he has given a decisive turn, a significant boost to my career.

I express my sincere thanks to **Dr. H. M. Meshram**, **Dr. B. China Raju, Dr. V. J. Rao, Dr. Nagaiah, Dr. Venkatnarsaiah, Dr. Narsaiah, Dr. Mohapatra, Dr. B. Jagadeesh, A. V. S. Sharma, Dr. Prabhakar, Dr. Vijaya Sarathi, Ramulu, Venkat and Ramesh** for their support and encouragement.

I am also indebted to **Dr. S. Chandrashekar**, former Head Natural Products Chemistry Division, **Dr. J. M. Rao, Dr. Ahmed Kamal, Dr. G. Sabitha, Dr. A. Bhaskar Rao, Dr. G. V. M. Sharma, Dr. B. V. Rao, Dr.Biswanath Das, Dr Subash Ghosh and Dr. B. V. Subba Reddy** for their immense help and support during my tenure at IICT.

I thank all my senior colleagues, **Dr. Kailash Rathore, Dr. Shaik Mustafa Mr. Krishnaiah, Dr. Aravind, Dr. Prasad, Dr. Sudheer, Ms. Pushpa,** for helpful discussions.

I thank my colleagues **Vinoth Kumar, Render, Pradeep, Ravi Kumar, Anil, Javed Patel, Satyanarayana, Mahesh, Raju Yalla, Satish, Somnath, Ramesh, Santhosh, Nageshwara Rao, Pramod, Satish Kumar, Chandrashekar, Swetha, Madhu, lab assistants Mani, Kishore, Sridhar and all other juniors** for their help.

My thanks are also due to my other colleagues **Patil, Chakravarthy, Srinivas, Sandip, Nagender, Animesh and other colleagues** for their whole hearted co-operation during my research work.

I take this opportunity to thank my M. Sc. Professor **Prof. M Periasamy, Prof. Basavaiah, Prof. Durgaprasad, Prof. L. Guruprasad, Prof. Ramachary, Prof. A. K. Bhuyan, Prof. Radhakrishnan and Prof. Nagarajan** for his continuous encouragement, support and motivation.

It gives me immense pleasure to express my heartfelt thanks to my friends **Balu, Ravi, Rama, Isra, Chandar, Ramdas, Khanda, Shan Musre, Rukmini** for their friendship, love and support.

My heart lingers with joy and happiness when I think of my parents **Mr. Badrya Naik** and **Mrs. Pathyali Bai** to whom I owe a lot for having showered love, moral support and encouragement on me and whose blessings made the journey worth the effort. My special thanks go to my father-in-law **Mr. Sevya Naik** and mother-in-law **Mrs. Parwathamma**. My special thanks to my brother **Ramesh**, brother-in-law **Tukaram, Neelya and Srikanth** for their love and moral support. I take this opportunity to express my love towards my wife **Vasantha** who is continuously encouraging me by her inspiring words helped me to fulfill my duties in my final stage of research.

It is impossible task to mention every individuals name and his/her contribution to my career at IICT. I thank all of them personally.

Financial assistance from CSIR, in the form of Senior Research Fellowship is gratefully acknowledged.

Last but not least, I thank **Dr. S. Chandrashekar** (Director IICT) **Dr. M. Lakshmi Kantam** (Ex. Director, CSIR-IICT), **Dr. J. S. Yadav** (Ex. Director, CSIR-IICT) for providing sophisticated laboratory facilities, the **Council of Scientific and Industrial Research** (CSIR-India) for financial support and **University of Hyderabad** for permitting me to submit my research work in the form of a thesis.

Glossary of abbreviations

Aq	:	Aqueous
Ac	:	Acetyl
Ac_2O	:	Acetic anhydride
AIBN	:	Azobisisobutyronitrile
Ar	:	Aryl
BAIB	:	Bis(acetoxy)iodobenzene
$BF_3.Et_2O$	:	Boran trifluride diethylether
Bn	:	Benzyl
Boc	:	*tert*-Butoxycarbonyl
BOP-Cl	:	Bis(2-oxo-3-oxazolidinyl)phosphonic chloride
Bu	:	Butyl
^{t}Bu	:	*tert*-Butyl
CSA	:	Camphor-10-sulfonic acid
DCC	:	Dicyclohexylcarbodimide
DCE	:	Dichloroethane
DCM	:	Dichloromethane
DET	:	Diethyl tartrate
DDQ	:	2,3-Dichloro-5,6-dicyano-1,4- benzoquinone
DIBAL-H	:	Diisobutylaluminum hydride
DIPA	:	*N*,*N*-Diisopropylamine
DIPEA	:	*N*,*N*-Diisopropylethylamine
DMAP	:	4-(Dimethylamino)pyridine
DMF	:	Dimethyl formamide
DMP	:	2,2-Dimethoxypropane
DMS	:	Dimethyl sulphide
DMSO	:	Dimethyl sulfoxide
dr	:	Distereomeric ratio
ESI	:	Electro spray ionization
Et	:	Ethyl
EtOAc	:	Ethylacetate
FAB	:	Fast atom bombardment
g	:	Gram
h	:	Hour
HAc	:	Acetic acid

HMPA	:	Hexamethylphosphoramide
Hz	:	Hertz
IBX	:	2-Iodoxybenzoic acid
IR	:	Infra red
KHMDS	:	Potasiumhexamethyldisilazane
LAH	:	Lithium aluminium hydride
LCB	:	Long chain base
LDA	:	Lithiumdi*iso*propylamine
LHMDS	:	Lithium hexamethyldisilazide
*m*CPBA	:	*meta*-Chloroperbenzoic acid
Me	:	Methyl
min	:	Minute
mL	:	Milliliter
MOM	:	Methoxy methyl
Mp	:	Melting point
Ms	:	Methane sulfonyl
NBS	:	*N*-Bromosuccinimide
nM	:	Nano molar
NMR	:	Nuclear magnetic resonance
NOESY	:	Nuclear overhauser enhancement spectroscopy
PCC	:	Pyridinium chlorochromate
Ph	:	Phenyl
PMB	:	*para*-Methoxy benzile
PMP	:	*para*-Methoxy phenyl
PMR	:	Proton magnetic resonance
PPTS	:	Pyridinium *p*-toluenesulfonate
*p*TSA	:	*para*-Toluenesulfonic acid
Py	:	Pyridine
rt	:	Room temperature
TBAF	:	*n*- tetrabutylammonium fluoride
TBAI	:	*n*-tetrabutylammoniun iodide
TBS	:	*tert*-Butyldimethylsilyl
TBDPS, BPS	:	*tert*-Butyldiphenylsilyl
TBP	:	Tributylphosphine
TEMPO	:	2,2,6,6-tetramethyl- piperidinyloxy
TEA	:	Triethylamine

Tf	:	Trifluoromethanesulfonyl
TFA	:	Trifluoroacetic acid
TFAA	:	Trifluoroacetic anhydride
THF	:	Tetrahydrofuran
TLC	:	Thin layer chromatography
Tol	:	Tolyl
TPP	:	Triphenylphosphine
Ts	:	Tosyl

GENERAL REMARKS

- Melting points were recorded on either Buchi R-535 apparatus or a Kofler hot plate and are uncorrected.
- Infrared spectra were recorded on Perkin-Elmer Infrared–683 spectrophotometer with NaCl optics. Spectra were calibrated against the polystyrene absorption at 1610 cm^{-1}. Samples were scanned neat, KBr wafers or in chloroform as a thin film.
- PMR and ^{13}C NMR spectra were recorded on Varian Gemini 200, AV-300 or Varian Unity 400 spectrometers making a solution of samples in $CCl_4/CDCl_3$ (1:1) solvent using tetramethylsilane (TMS) as the internal standard unless otherwise mentioned, and are given in the δ scale. The standard abbreviations s, d, t, q, m, dd, dt, brs, bd refer to singlet, doublet, triplet, quartet, multiplet, doublet of a doublet, doublet of a triplet, broad singlet and broad doublet respectively.
- Mass spectra were recorded on either Finnigan MAT 1020B or Micro Mass VG 70-70H spectrometer operating at 70eV using direct inlet system.
- The optical rotations were measured on JASCO DIP-360 digital polarimeter.
- CD-spectra recorded on JASCO J-715 spectropolarimeter.
- CHN analysis was performed on a Vario EL analyzer.
- Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel-60 F_{254} (0.5 mm) glass plates. Visualization of the spots on TLC plates was achieved either by exposure to iodine vapour or UV light or by dipping the plates to sulphuric acid-α-napthol or to ethanolic anisaldehyde-sulphuric acid-acetic acid or to phosphomolybdic acid-sulphuric acid solution and heating the plates at 120 ^{0}C. Column chromatography was performed using silica gel (60-120 mesh) and the column was usually eluted with ethyl acetate-petroleum ether.
- Moisture sensitive reactions were carried out by using standard syringe-septum techniques.
- All solvents and reagents were purified by standard techniques. All evaporation of solvents was carried out under reduced pressure on Buchi-RE-121 rotary evaporator below 50 ^{0}C.
- Yields reported are isolated yields of material judged homogeneous by TLC and NMR spectroscopy.
- The names of some compounds given in the experimental section were taken from ACD/Name, Version 1.0 and Chem. Draw Ultra, Version 10.0.

CONTENTS

Chapter-III *Stereoselective Synthesis Toward (+)-trans-Kumausyne*

SYNOPSIS

The thesis entitled **"Stereoselective Synthesis towards Bullatanocin, towards (+)-*trans*-Kumausyne employing α-Chloro Sulfide Synthons and Catalytic Asymmetric Reactions"** consists of three chapters.

CHAPTER I

Stereoselective Preparation of Chiral α-Substituted Sulfides from α-Chloro Sulfides via 1,2-Asymmetric Induction

This sections deals with the preparation of chiral α-substituted sulfides from α-chloro sulfides and organozinc reagents.

CHAPTER II

Stereoselective Synthesis towards Bullatanocin

In this chapter a brief account of the synthesis of **Bullatanocin** reported by Mootoo and coworkers is described followed by an elaborate account of the present work.

CHAPTER III

Stereoselective Synthesis towards (+)-*trans*-Kumausyne

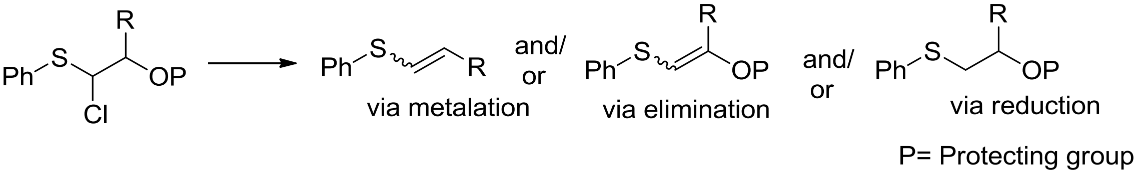
In this chapter the earlier synthesis of **(+)-*trans*-Kumausyne** by various research groups is described briefly followed by an elaborate account of the present work.

CHAPTER I

Stereoselective Preparation of Chiral α-Substituted Sulfides from α-Chloro Sulfides via 1,2-Asymmetric Induction.

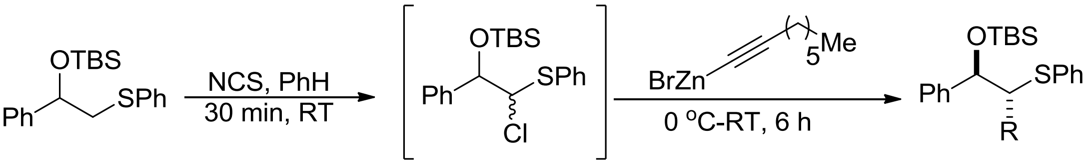
α-Chloro sulfides are potential intermediates for the synthesis of various functional group containing molecules and it is useful as aldehyde, ketone equivalent. α-Chloro sulfides act as electrophile which can be reacted with various nucleophiles to generate multifunctional compounds. The reactions of simple α-chloro sulfides with Grignard reagents have been reported. In the reaction of β-functionalised α-chloro sulfide many side products could result as a consequence elimination, metalation and reduction reactions, (Scheme 1.1). To avoid these undesired reactions softer organozinc reagents have been employed successfully to synthesize α-substituted sulfides.

Scheme 1.1



The investigation started with racemic sulfide **1.1** which was reacted with 1 equivalent of NCS in dry benzene to furnish α-chlorosulfide **1.2** which without isolation was reacted with 1-octynylzinc bromide to furnish α-branched sulfide **1.3**, (Scheme 1.2).

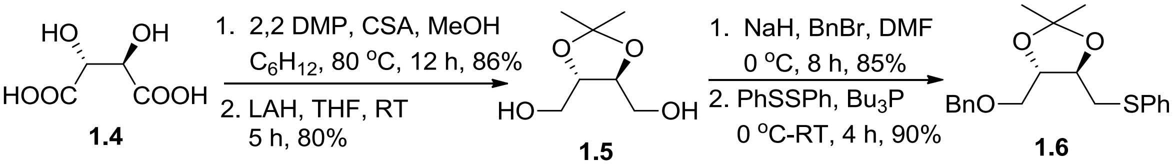
Scheme 1.2



1.1 **1.2** **1.3**

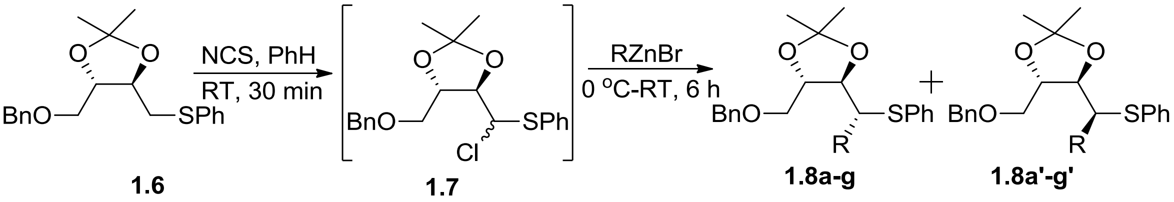
Further reactions were attempted on optically active sulfide **1.6** which was prepared from L-tartaric acid. L-tartaric acid **1.4** was reacted with 2,2-DMP, MeOH in presence of catalytic amount of CSA to afford acetonide diester which was reduced to diol **1.5** using LAH. Selective protection as the monobenzyl ether followed by reaction with PhSSPh in presence of Bu_3P yielded the sulfide **1.6**, (Scheme 1.3).

Scheme 1.3



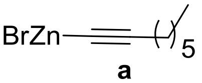
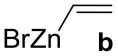
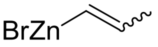
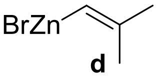
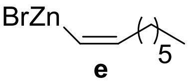
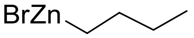
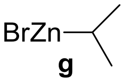
Sulfide **1.6** was reacted with NCS in dry benzene to yield α-chlorosulfide **1.7** which without isolation was added to the organozinc reagents prepared from corresponding Grignard reagents, (Scheme 1.4).

Scheme 1.4



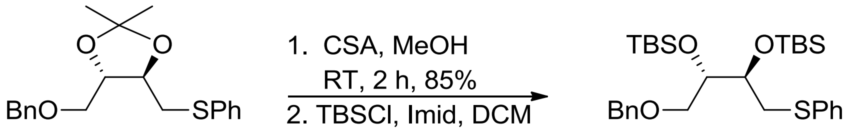
Reactions of α-chloro sulfide **1.6** with various organozinc reagents is summarized in Table 1. Long chain alkynes afforded products with poor selectivity, entry 1. This is probably due to their linear structure and less steric crowding. Good stereoselectivity in bond formation was observed using alkenyl and alkylzinc reagents, entries 2-7.

Table 1

Entry	RZnBr	Product, yield% **(1.8a-g:1.8a'g')**
1	 **a**	**1.8a**, **a'**, 76 (3:1)
2	 **b**	**1.8b, b'**, 78 (>95:<5)
3	 **c**	**1.8c, c'**, 80 (>95:<5)
4	 **d**	**1.8d, d'**, 86 (>95:<5)
5	 **e**	**1.8e, e'**, 66 (>95:<5)
6	 **f**	**1.8f, f'**, 60 (>95:<5)
7	 **g**	**1.8g, g'**, 60 (>95:<5)

In an effort to obtain better selectivity using long chain alkynes, the steric bulk of the β-substituent was increased. Sulfide **1.9** was prepared from sulfide **1.6** by initial treatment with CSA in MeOH to furnish the corresponding diol and subsequently reacted with TBSCl, (Scheme 1.5).

Scheme 1.5



1.6

1. CSA, MeOH RT, 2 h, 85%
2. TBSCl, Imid, DCM 3 h, RT, 95%

1.9

Reactions of sulfide **1.9** with various nucleophiles are summarized in Table 2. Excellent selectivity was observed with unbranched alkynyl, alkenyl and alkylzinc reagents by 1,2 asymmetric induction, (Scheme 1.6).

Scheme 1.6

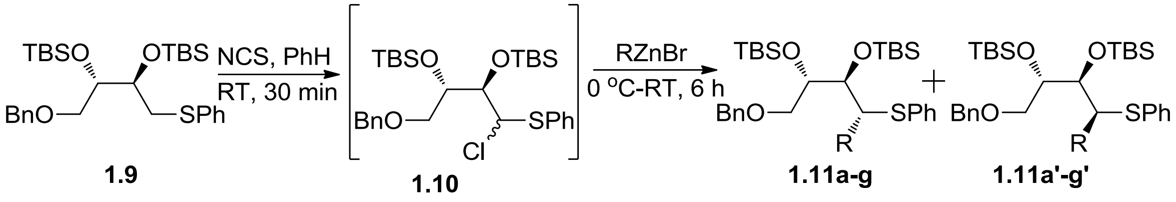
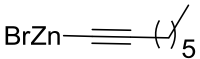
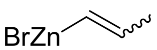
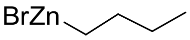
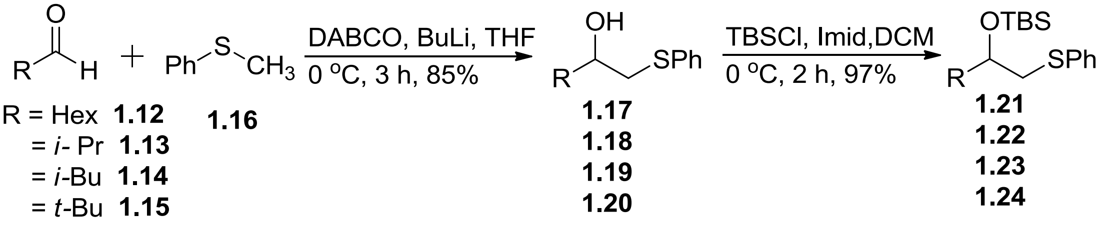


Table 2

Entry	RZnBr	Product, yield%, **(1.11a-c:1.11a'-c')**
1	 **a**	**1.11a**, **a'**, 70 (98:2)
2	 **b**	**1.11b**, **b'**, 80 (98:2)
3	 **c**	**1.11c**, **c'**, 60 (98:2)

To explore further the effect of nature of the β-substitution and steric factors on the stereoselectivity of C-C bond formation, various sulfide derivatives were prepared. β-siloxy thioethers **1.21-1.24** were prepared by reaction of aldehydes **1.12-1.15** with phenylthiomethyl lithium in THF at 0 °C to afford the alcohols **1.17-1.20** which were subsequently protected as their TBS ethers, (Scheme 1.7).

Scheme 1.7



The result of the reaction of α-chloro sulfides, prepared from the corresponding sulfides is summarized in Table 3. Poor selectivity was observed in the reaction of alkynyl nucleophiles with α-chloro sulfide generated from sulfides **1.21-1.23**. Excellent selectivity was obtained with alkenyl and alkyl nucleophiles. Sulfide **1.24** furnished exceptionally high *de* with all types of nucleophiles due to the bulky *t*-butyl group.

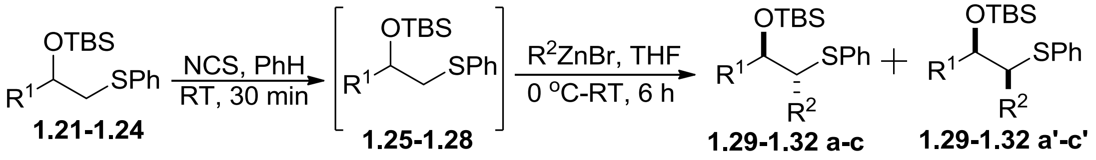
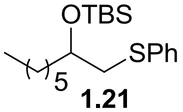
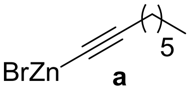
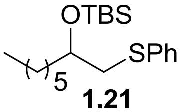
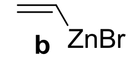
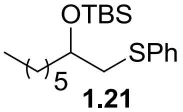
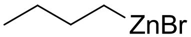
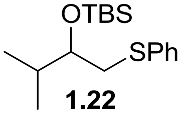
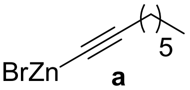
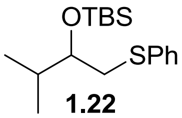
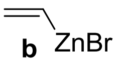
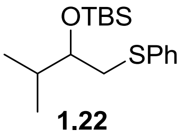
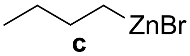
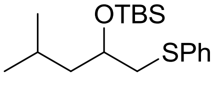
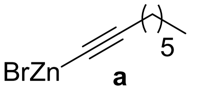
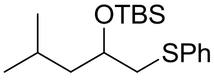
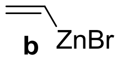
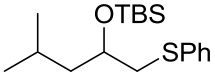
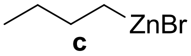
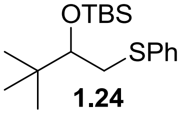
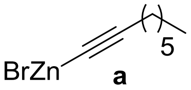
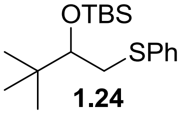
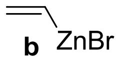
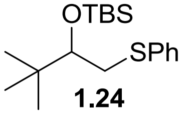
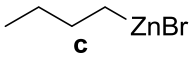
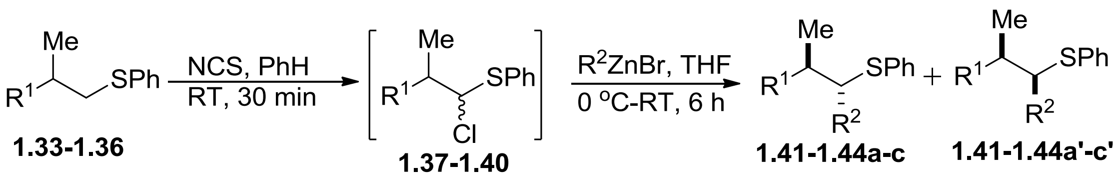


Table 3

Entry	Sulfide	Organometallic reagent (R^{2}ZnBr)	Product,Yield% (**1.29-1.32a-c**:**1.29-1.32a'-c'**)
1	 **1.21**	 **a**	**1.29a**, **a'**, 78 (70:30)
2	 **1.21**	 **b**	**1.29b**, **b'**, 75 (>95:<5)
3	 **1.21**	 **c**	**1.29c**, **c'**, 70 (>95:<5)
4	 **1.22**	 **a**	**1.30a**, **a'**, 75 (75:25)
5	 **1.22**	 **b**	**1.30b**, **b'**, 75 (>95:<5)
6	 **1.22**	 **c**	**1.30c**, **c'**, 75 (>95:<5)

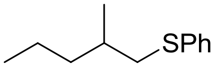
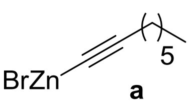
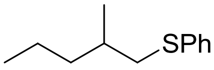
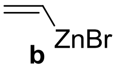
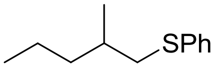
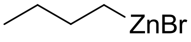
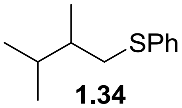
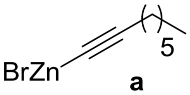
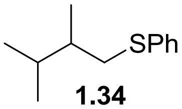
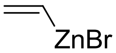
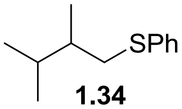
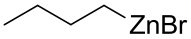
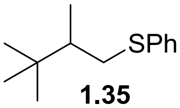
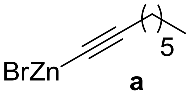
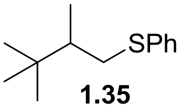
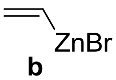
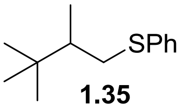
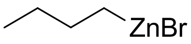
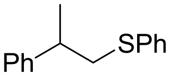
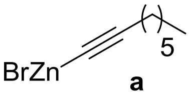
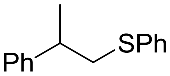
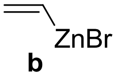
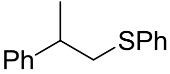
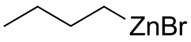
7	 **1.23**		**1.31a**, **a'**, 80 (80:20)
8	 **1.23**		**1.31b**, **b'**, 85 (>95:<5)
9	 **1.23**		**1.31c**, **c'**, 70 (>95:<5)
10	 **1.24**		**1.32a**, **a'**, 65 (>95:<5)
11	 **1.24**		**1.32b**, **b'**, 73 (>95:<5)
12	 **1.24**		**1.32c**, **c'**, 65 (>95:<5)

The influence of a β-methyl substituent was then explored. Sulfides **1.33-1.36** were prepared by a standard sequence of reactions. The reaction of α-chloro β-alkyl methyl sulfides prepared from the corresponding sulfides with various nucleophiles is summarized in Table 4. A general noticiable trend is that alkenyl and alkylzinc nucleophiles afford products with better stereoselectivity. Superior selectivities were observed for a β-siloxy substituent in comparison to β-methyl substituent. Substrate **1.34** with *i*-Pr group fared better than **1.36** with a phenyl substituent. The stereochemistry of major product was assigned by comparison of its ^{1}H NMR data with known compounds.



1.33-1.36 **1.37-1.40** **1.41-1.44a-c** **1.41-1.44a'-c'**

Table 4

Entry	Sulfide	Organo zinc reagent (R^2ZnBr)	Product, Yield% (**1.41-1.44a-c:1.41-1.44a'-c'**)
1	 **1.33**	 **a**	**1.41a**, **a'**, 82 (55:45)
2	 **1.33**	 **b**	**1.41b**, **b'**, 73 (78:22)
3	 **1.33**	 **c**	**1.41c**, **c'**, 40 (75:25)
4	 **1.34**	 **a**	**1.42a**, **a'**, 75 (75:25)
5	 **1.34**	 **b**	**1.42b**, **b'**, 80 (>95:<5)
6	 **1.34**	 **c**	**1.42c**, **c'**, 44 (82:18)
7	 **1.35**	 **a**	**1.43a**, **a'**, 73 (80:20)
8	 **1.35**	 **b**	**1.43b**, **b'**, 70 (>95:<5)
9	 **1.35**	 **c**	**1.43c**, **c'**, 55 (>95:<5)
10	 **1.36**	 **a**	**1.44a**, **a'**, 80 (55:45)
11	 **1.36**	 **b**	**1.44b**, **b'**, 78 (80:20)
12	 **1.36**	 **c**	**1.44c**, **c'**, 40 77:23

Key Features of the Methodology

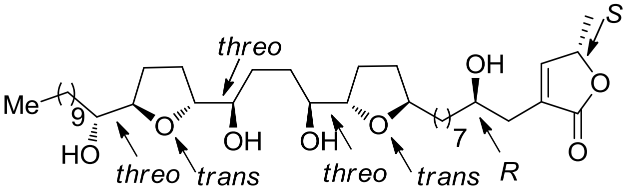
- A C–S stereogenic center is created with efficient stereocontrol by 1,2-asymmetric induction due to a vicinal C–O, C-C stereogenic center.
- The allylic sulfide can be converted to the corresponding sulfoxide/ sulfilimine/sulfur ylide and subjected to [2,3]-sigmatropic rearrangement. The efficient 1,3-chirality transfer observed in this reaction eventually results in a net 1,4-chirality transfer.
- Methodology would be useful for the synthesis of natural products possessing a 1,4-diol, 1,4 amino alcohol subunits, tetrahydrofuran, pyrrolidine, pyran and piperidine rings from appropriate starting materials.
- A very versatile method for the synthesis of chiral α-branched propargylic, allylic and alkyl sulfides.

CHAPTER II

Stereoselective Synthesis towards Bullatanocin

Bullatanocin 2.1 also known as Squamostatin C is an annonaceous acetogenin isolated from the bark of *Annona bullata Rich* by McLaughlin and co-workers. Bullatanocin belongs to non adjacently linked bis-THF family. It shows ED_{50} of less than 10^{-8} µg/mL against the colon cell line HT-29 and the lung cell line A-549. It possseses *threo, trans, threo, threo, trans, R* and *S* absolute configuration. In view of its interesting structure and important biological activity in vivo, Bullatanocin has attracted the attention of synthetic chemists and Mootoo *et.al*, reported the first synthesis in 2003.

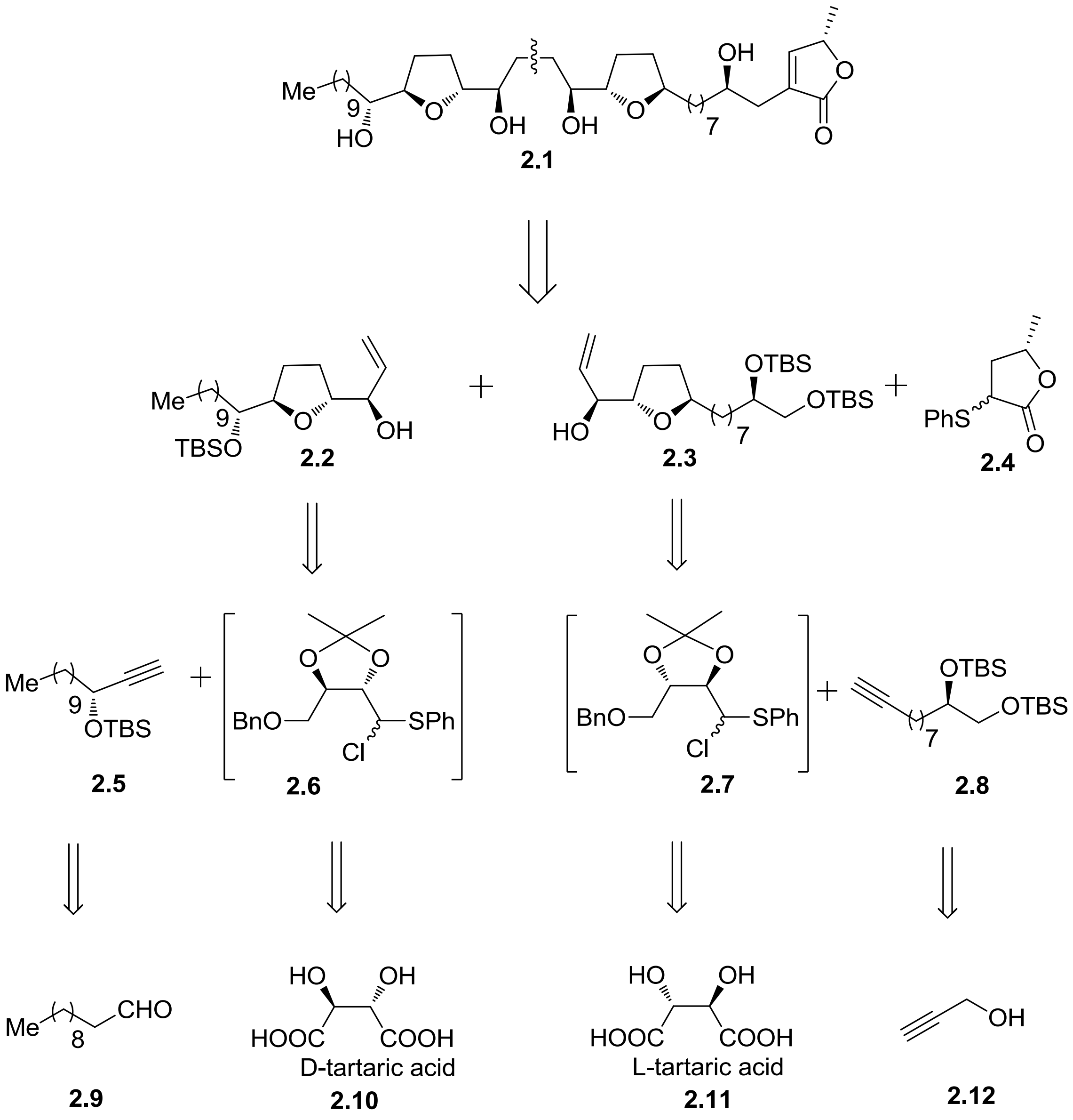
Figure 2.1



Bullatanocin **2.1**

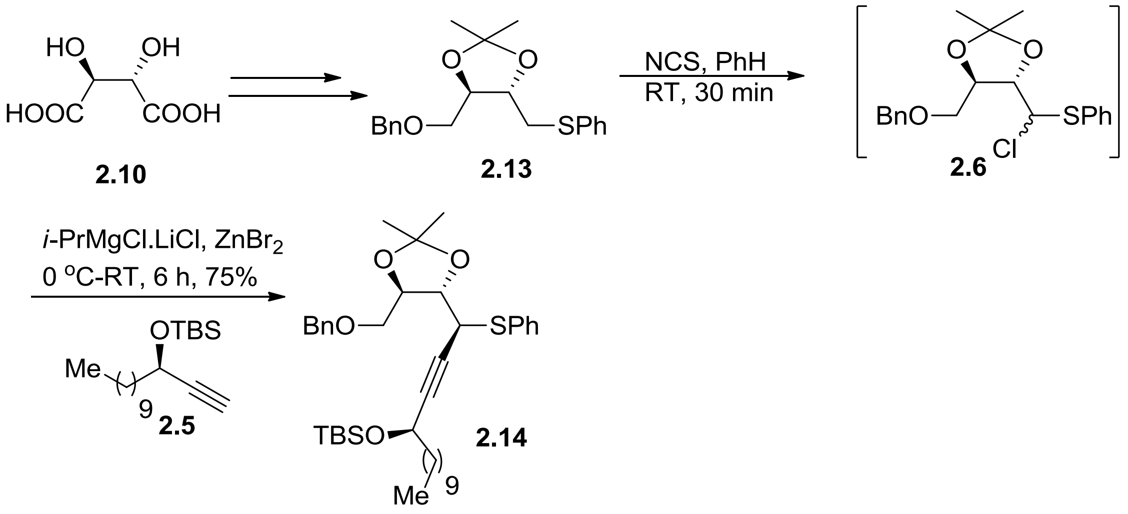
It was proposed to synthesize bullatanocin using a different srtrategy. The disconnective analysis is shown in Scheme 2.1. It was envisoned to unite allyl alcohol **2.3** and butyrolactone **2.4** and further unite the resulting subunit with allyl alcohol **2.2** by an intermolecular or intramolecular olefin cross metathesis reaction. The allylic alcohol **2.2** and **2.3** were envisoned to be obtained from α-chloro sulfide **2.6** and **2.7** respectively. The key step in the synthesis is based on utilizing the α-chloro sulfide synthons **2.6**, **2.7** to prepare propargylic sulfides via 1,2 asymmetric induction. α-Chloro sulfide **2.6** and **2.7** can be traced to (D)-tartaric acid **2.10** and (L)-tartaric acid **2.11** respectively. Alkyne **2.5** was envisaged to be prepared from undecanal **2.9** and alkyne **2.8** from propargyl alcohol **2.12**, (Scheme 2.1).

Scheme 2.1



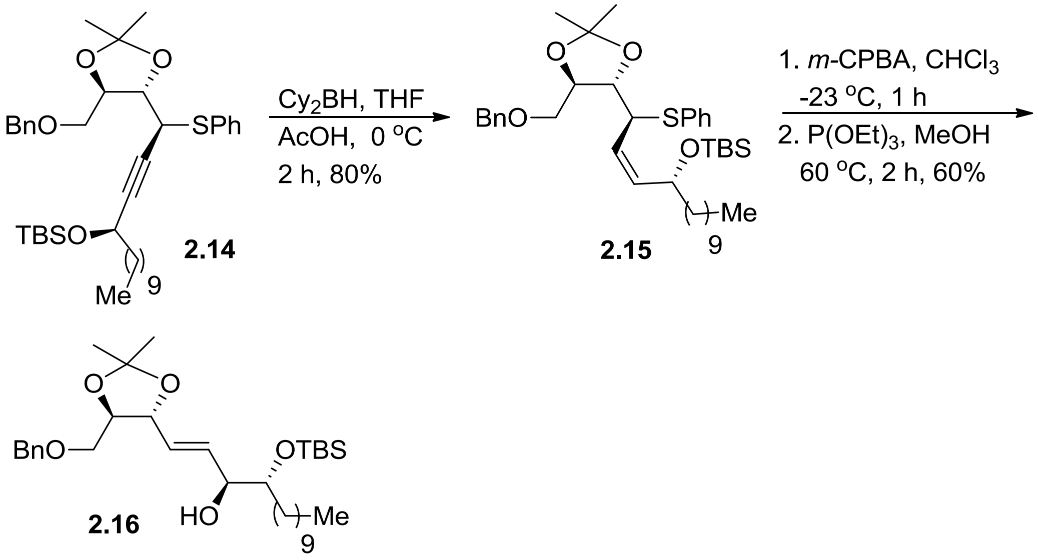
The synthesis commenced with D-tartaric acid **2.10** which was transformed to sulfide **2.13** as described earlier. Sulfide **2.13** was reacted with NCS to furnish the α-chlorosulfide **2.6** which without isolation was reacted with an excess alkynylzinc reagent of alkyne **2.5** to yield the chiral propargyl sulfide **2.14** (>95% *de*) by 1,2 asymmetric induction, (Scheme 2.2).

Scheme 2.2



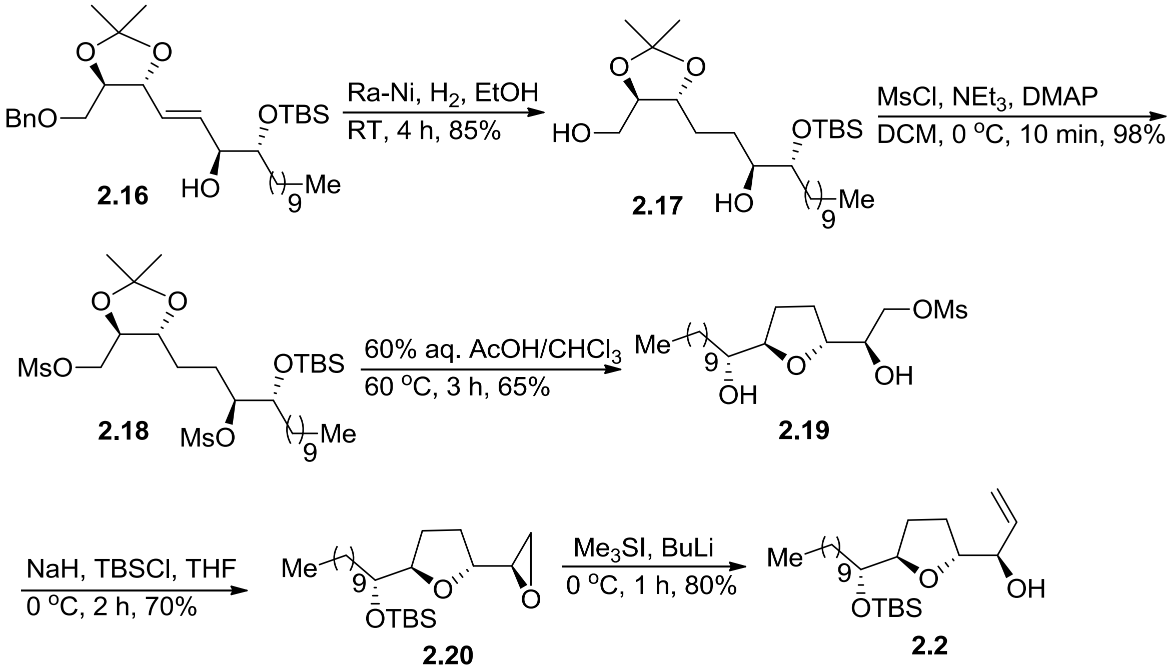
Propargylic sulfide **2.14** was converted to allylic sulfide **2.15** by treatment with Cy_2BH. Further treatment of allylic sulfide with *m*-CPBA at -30 ºC to form the corresponding sulfoxide and heating in the presence of an excess of $P(OEt)_3$ afforded allylic alcohol **2.16** by sulfoxide-sulfinate [2,3] sigmatropic rearrangement (Mislow-Evans-Braverman rearrangement), (Scheme 2.3).

Scheme 2.3



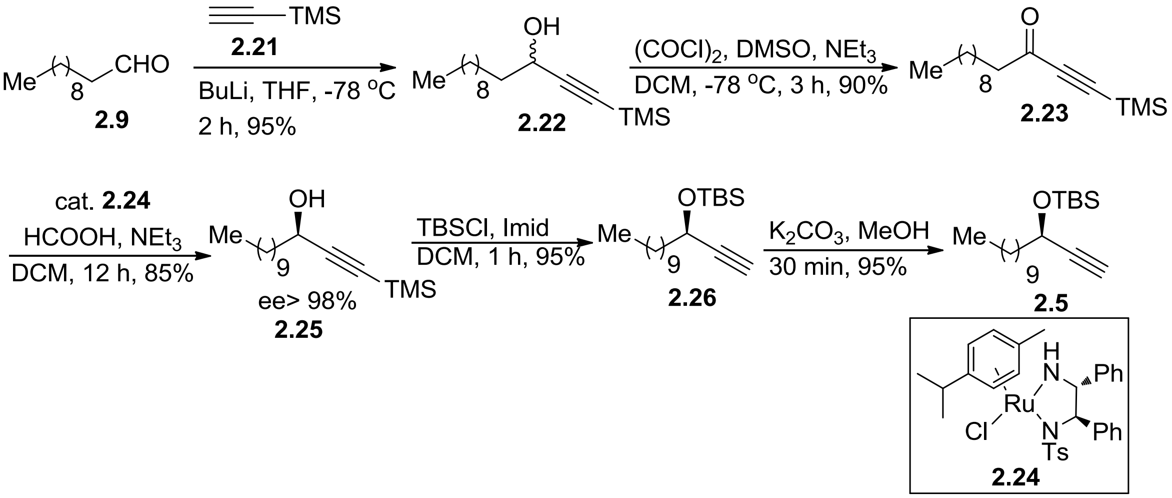
Benzylic ether **2.16** on treatment with freshly prepared Raney-Ni under hydrogen atmosphere afforded diol **2.17** which was further converted to dimesylate **2.18**. Hydrolysis of acetonide using 60% aq. AcOH yielded THF derivative **2.19** which was converted to epoxide **2.20** using NaH and TBSCl in an one pot operation. Opening of epoxide **2.20** using Falck's protocol furnished allylic alcohol **2.2**. Fragment **2.2** was synthesized in an overall yield of 6.5%, (Scheme 2.4).

Scheme 2.4



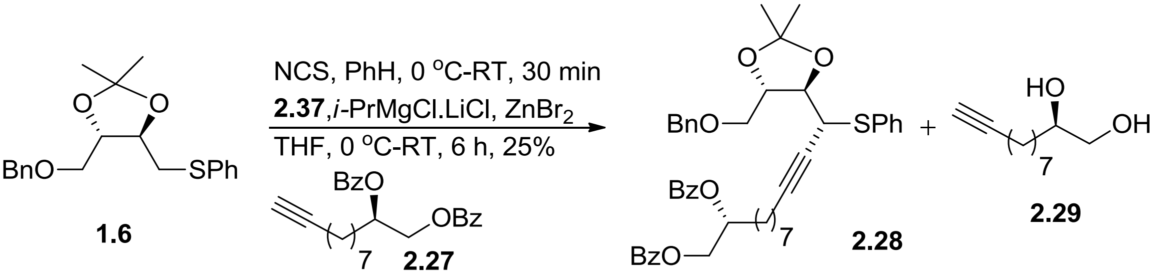
Propargylic ether **2.5** was synthesized from undecyl aldehyde **2.9**. Reaction of aldehyde **2.9** with TMS acetylene **2.21** afforded racemic proporgylic alcohol **2.22** which was oxidized to proporgylic ketone **2.23**. Enantioselective reduction of compound **2.23** using (*R,R*)-Noyori's catalyst **2.24** afforded proporgylic alcohol **2.25** (*er*> 98:2). Compound **2.25** was protected as its TBS ether **2.26**. Removal of TMS using catalytic amount of K_2CO_3 in MeOH afforded alkyne **2.5** in excellent yield, (Scheme 2.5).

Scheme 2.5



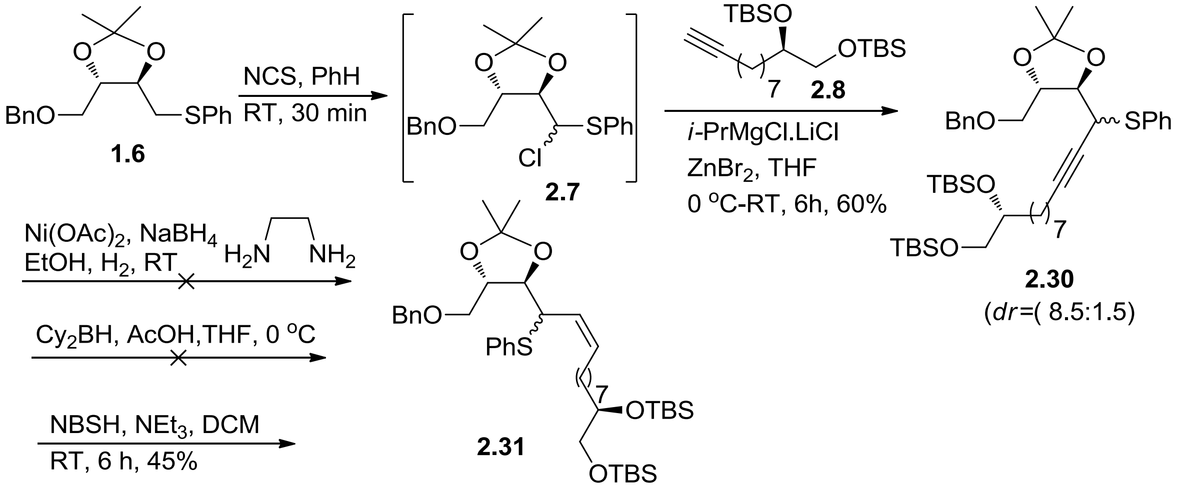
The synthesis of **2.3** commenced with L-tartaric acid **1.3**. α-chloro sulfide **2.7** obtained from sulfide **1.6** reacted with an excess of alkynylzinc reagent prepared from **2.27** to furnish the proporgylic sulfide **2.28** in 25% yield, (Scheme 2.6).

Scheme 2.6



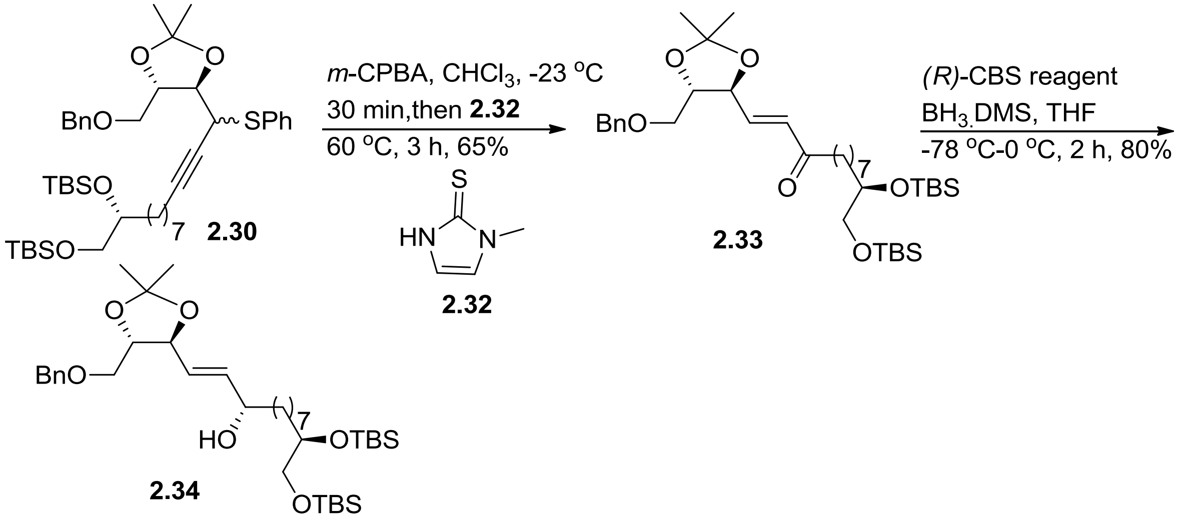
A similar reaction carried out using alkynylzinc reagent prepared from the di silyl ether **2.8** furnished proporgylic sulfide **2.30** in 60% yield (*dr* 8.5:1.5). Attempted partial reduction of the triple bond in **2.31** using Cy$_2$BH and Lindlar's cataltyst resulted in recovery of unreacted starting material. Reduction using *o*-nitrobenzenesulfonyl hydrazide (NBSH) afforded allyl sulfide **2.31** in 45% yield. A draw back using this reagent was that complete conversion could not be achieved even using an excess of NBSH, (Scheme 2.7).

Scheme 2.7



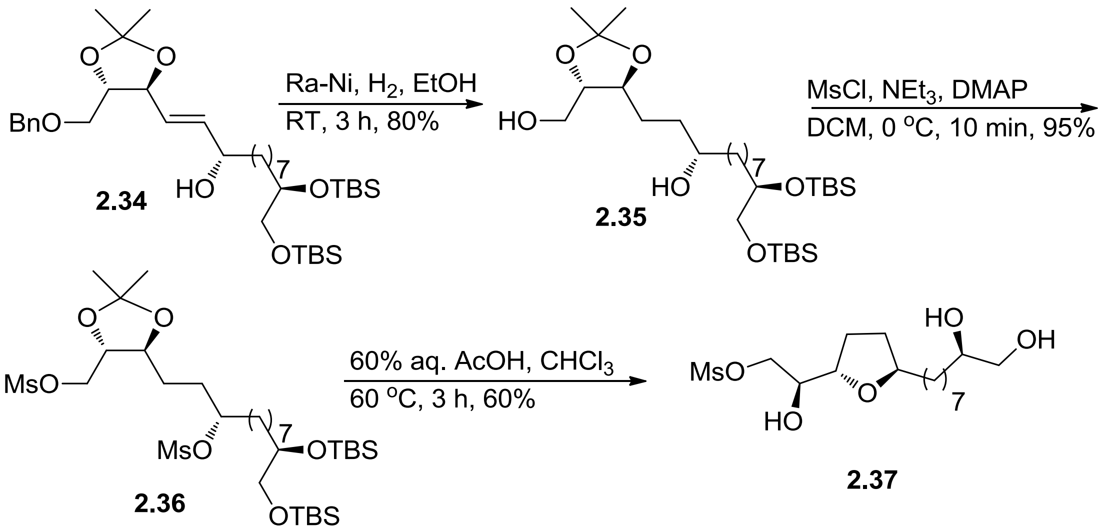
An alternate route was therefore explored. The propargyl sulfide **2.30** was oxidized using *m*-CPBA to furnish an equimolar epimeric mixture of sulfoxides which was treated with an excess of thio imidazole **2.32** to afford unsaturated ketone **2.33**. Stereoselective reduction using CBS catalyst and $BH_3.Me_2S$ furnished allylic alcohol **2.34** (*dr* >95%), (Scheme 2.8).

Scheme 2.8



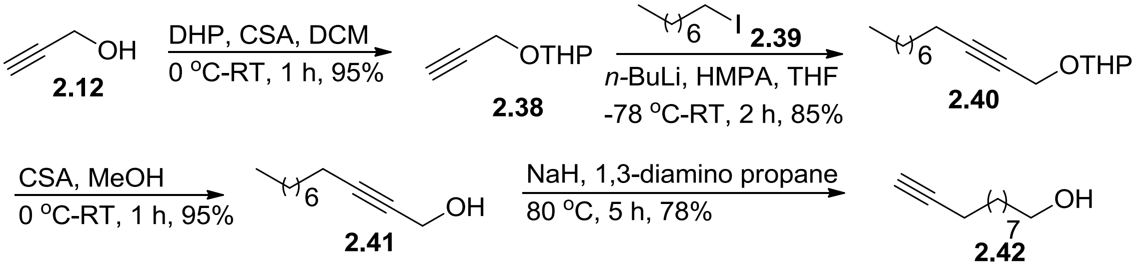
The allylic alcohol **2.34** was hydrogenated and hydrogenolyzed in the same pot using Raney-Nickel under hydrogen atmosphere to furnish the diol **2.35**. The diol was further converted to dimesylate **2.36** and reacted with 60% aq. AcOH leading to the deprotection of acetonide and silyl ethers to furnish the tetrahydrofuran derivative **2.37**, (Scheme 2.9).

Scheme 2.9



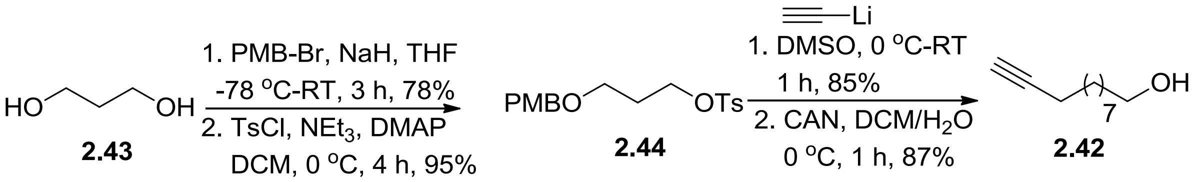
The synthesis of the silyl ether **2.8** commenced by converting propargyl alcohol **2.12** to its THP ether **2.38**. Treatment of **2.38** with *n*-BuLi and alkylation with 1-iodo octane **2.39** furnished internal alkyne **2.40**. Deprotection of THP in acidic condition afforded the corresponding proporgylic alcohol **2.41** which was transformed to alcohol **2.42** by triple bond isomerization using zipper reaction, (Scheme 2.10).

Scheme 2.10



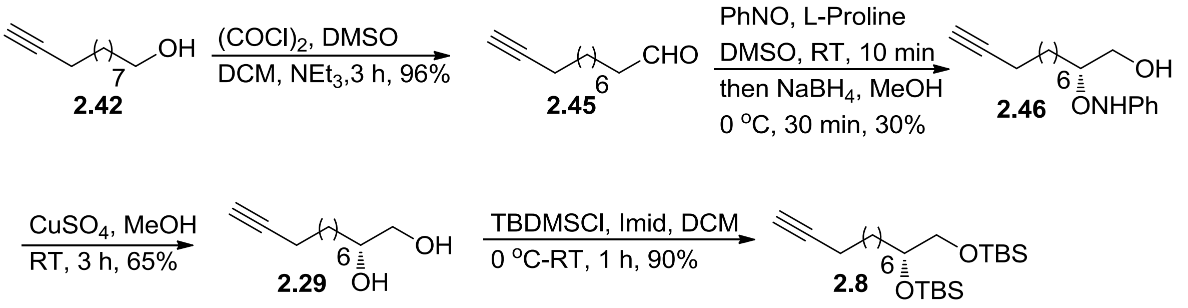
Alcohol **2.42** was alternatively more readily synthesized from nonane diol **2.43**. Selective mono-protection as its *p*-methoxy benzyl ether followed by tosylation yielded compound **2.44**. Alkylation with lithium acetylide ethylenediamine complex followed by deprotection of PMB ether furnished alcohol **2.42**, (Scheme 2.11).

Scheme 2.11



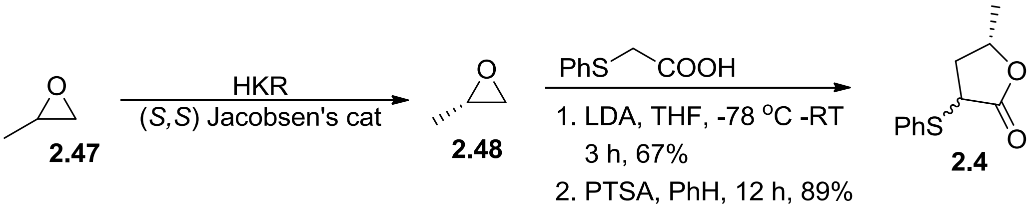
The alcohol **2.42** was oxidized to the corresponding aldehyde **2.45** employing the Swern protocol and further subjected to α-hydroxylation reaction to yield the oxyaminated product **2.46** in 30% and diol **2.29** in 20% yield respectively. The compound **2.46** on treatment with $CuSO_4$ in MeOH afforded the diol **2.29** which was protected as its TBS ether **2.8**, (Scheme 2.12).

Scheme 2.12



The synthesis of the butenolide fragment **2.4** commenced from racemic propylene oxide **2.47** which was resolved by hydrolytic kinetic resolution using Jacobsen's catalyst to afford epoxide **2.48**. Reaction of **2.48**, 2-(phenylthio)acetic acid and LDA followed by refluxing with PTSA in benzene yielded the lactone **2.4**, (Scheme 2.13).

Scheme 2.13



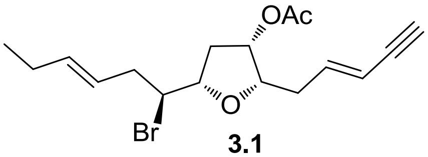
CHAPTER III

Stereoselective Synthesis towards (+)-*trans*-Kumausyne

This section deals with a brief account of the synthesis of (+)-*trans*-Kumausyne reported by the various groups and an elaborate account of the present work.

Trans-Kumausyne **3.1**, (Figure 3.1) was isolated from the red alga *Laurencia nipponica* Yamada by Kurosawa and co-workers.

Figure 3.1

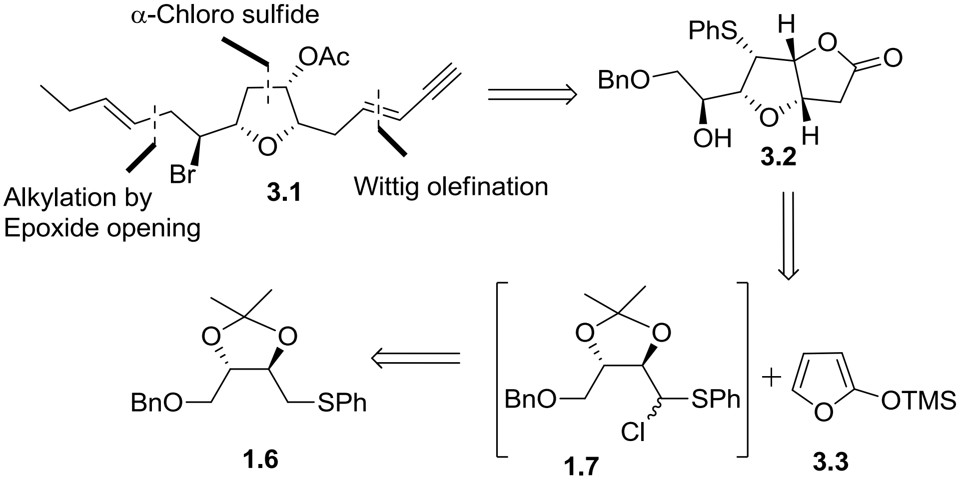


3.1

(+)-*trans*-Kumausyne

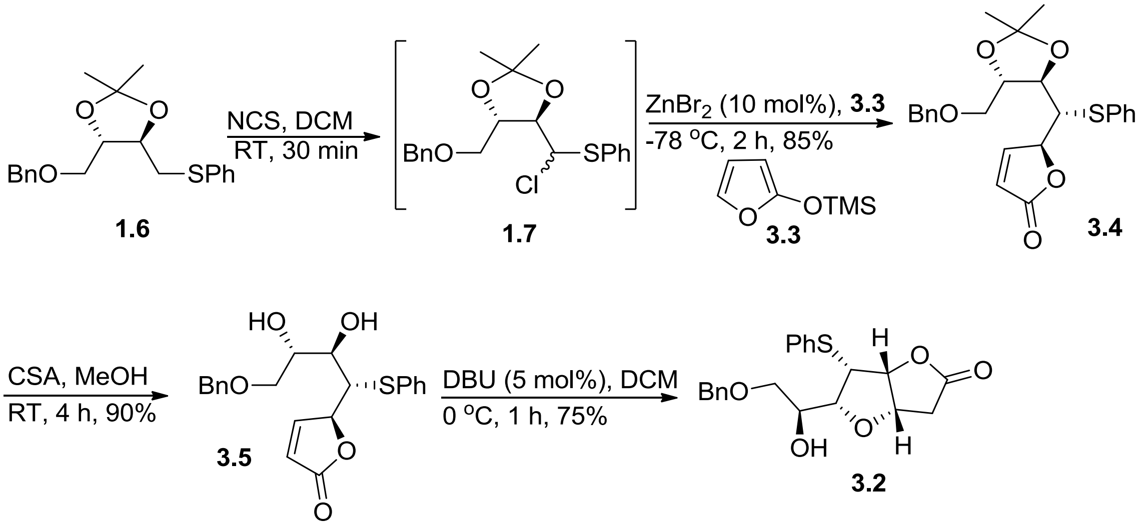
The retrosynthetic analysis is depicted in Scheme 3.1. *trans*-Kumausyne was envisioned to be obtained from lactone **3.2** via opening of epoxide and Wittig olefination reaction. Lactone **3.2** was envisioned to be obtained by vinologus Mukaiyama type reaction of 2-trimethylsiloxy furan with α-chloro sulfide **1.6**, (Scheme 3.1).

Scheme 3.1



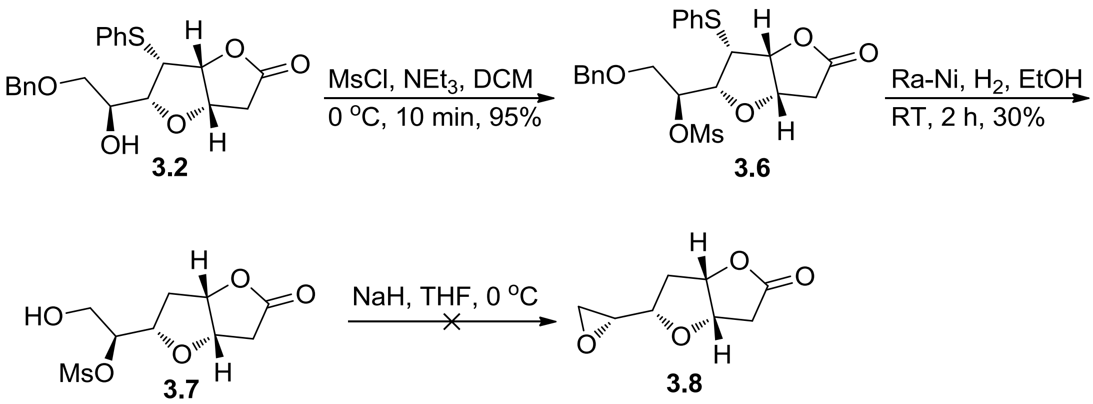
The synthesis commenced with the sulfide **1.6** prepared as detailed earlier. Reaction of α-chloro sulfide **1.7** with 2-trimethylsiloxy furan **3.3** in presence of catalytic $ZnBr_2$ at -78 ^{o}C afforded the lactone **3.4** in 85% yield as mixture of *anti:syn* diastereomers in 1:4 ratio.Treatment of this mixture with catalytic amount of CSA in methanol yielded the diol **3.5**. Intramolecular cyclization was effected using catalytic amount of DBU to furnish lactone **3.2**, (Scheme 3.2).

Scheme 3.2



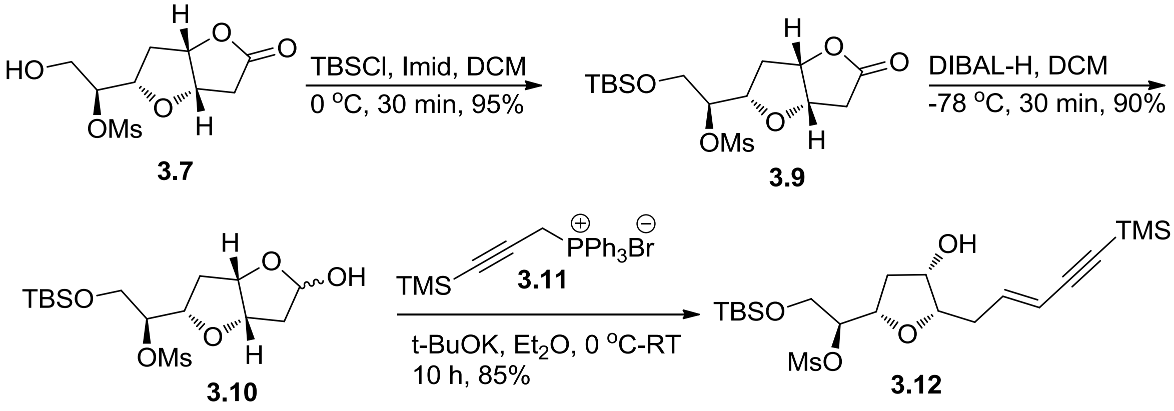
Towards this end the bicyclic lactone **3.2** was converted to corresponding mesylate **3.6** and subsequently treated with freshly prepared Raney-Nickel to afford alcohol **3.7**. The next step called for the epoxide formation and introduction of butenyl side chain. Attempted formation of epoxide **3.8** by treatment with NaH failed to yield any epoxide, (Scheme 3.3).

Scheme 3.3



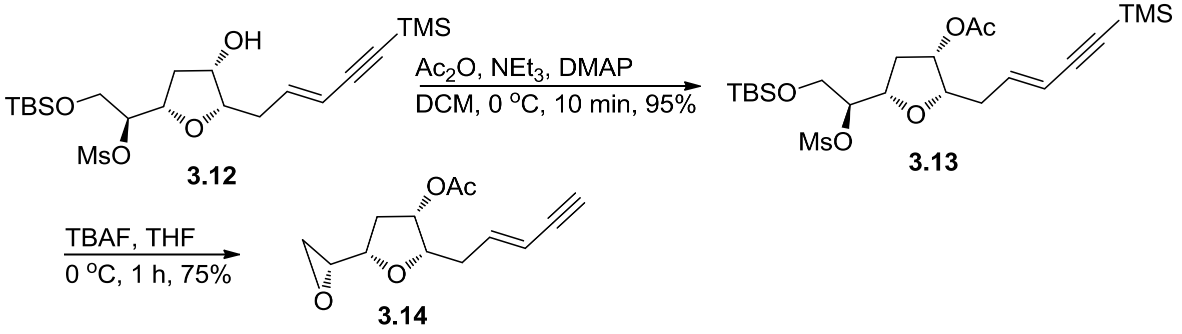
It was therefore decided to first introduce the eneyne side chain. The hydroxy group in **3.7** was protected as its TBS ether **3.9** and the lactone was reduced to lactal **3.10** using DIBAL-H. Reaction of **3.10** with the ylide generated from the salt **3.11** afforded enyne derivative **3.12**, (Scheme 3.4).

Scheme 3.4



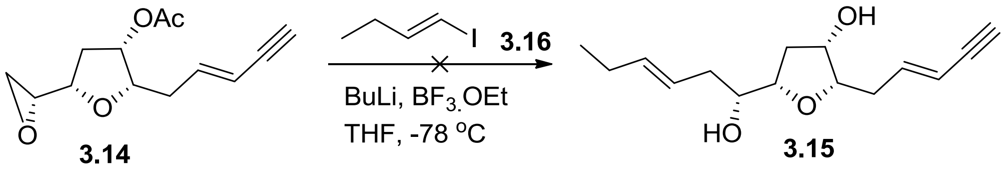
The eneyne derivative **3.12** was converted to acetate **3.13** which on treatment with TBAF led to the deprotection of TBS ether and concomitant epoxide formation to afford the compound **3.14**, (Scheme 3.5).

Scheme 3.5



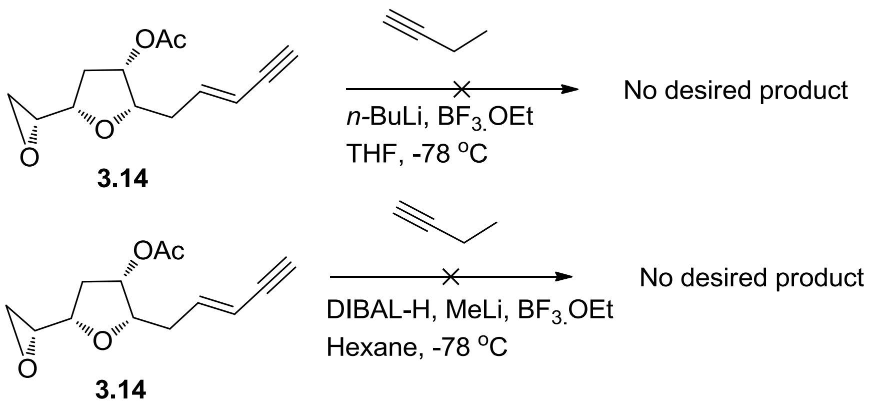
Attempted opening of epoxide **3.14** by reaction with alkenyl lithium prepared from *trans*-1-iodobutene **3.16** and *n*-BuLi in the presence of $BF_3.OEt_2$ failed to afford the expected homoallylic alcohol **3.15**, (Scheme 3.6).

Scheme 3.6



Attempted opening of epoxide with lithio butyne in presence of $BF_3.OEt_2$ failed to yield the desired product. Also opening of epoxide following Alexakis protocol did not yield any desired product, (Scheme 3.7).

Scheme 3.7



CHAPTER I

Stereoselective Preparation of Chiral α-Substituted Sulfides from α-Chloro Sulfides via 1,2-Asymmetric Induction

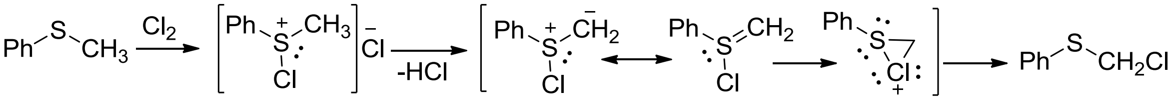
Stereoselective Preparation of Chiral α-Substituted Sulfides from α-Chloro Sulfides via 1,2-Asymmetric Induction

1.1. Introduction

α-Chloro sulfides, possessing a chlorine atom α to the sulfide, can be prepared by direct chlorination of an alkyl sulfide possessing at least one α-hydrogen. In initial study, Cl_2 gas was used to prepare the α-chloro sulfides.[1] Mono chlorodimethyl sulfide was prepared from dimethyl sulphide with one equivalent of chlorine in CCl_4 at -20 ^{o}C.[2] Later chlorine was replaced by more convenient alternative reagents such as NCS,[3] trichloro isocynuric acid,[4] iodobenzene dichloride[5] and benzenesulfenyl chloride,[6] sulfuryl chloride[7] and $SOCl_2$.[7]

The mechanism for the formation of α-chloro sulfide was proposed by Pitt[8] as involving an initial attack of chlorine on sulfur to afford chloro sulfonium ion **1.1**, followed by abstraction of proton by chloride ion to furnish intermediate **I** and **II** which readily rearrange to α-chloro sulfide **1.2** by delivering chlorine from sulfide to adjacent carbon, Scheme 1.1.

Scheme 1.1



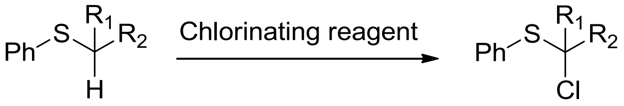
1.1 **I** **II** **1.2**

1.2. Preparation of α-chloro sulfides

1.2.1. Form alkyl sulfides

Most widely used and straight forward rout to prepare α-chlorosulfide is direct chlorination of corresponding alkyl sulfides which has at least one α-hydrogen, Scheme 1.2.

Scheme 1.2

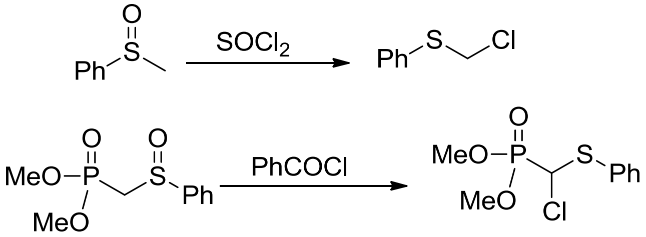


This method has an advantage as many alkyl sulfides can be easily prepared from commercially available compounds such as thiols or alcohols.[9] However this method cannot be used for regioselective chlorination of unsymmetrical sulfides having more than one α-hydrogen.

1.2.2. From Sulfoxides

An α-chloro sulfide can also be prepared from corresponding sulfoxide by treatment with chlorinating agents such as thionyl chloride, benzoyl chloride, acetyl chloride[8] and hydrogen chloride[10] in presence of molecular sieves. Sulfoxides are prepared from the corresponding sulfides, thus this route requires an extra step, Scheme 1.3.

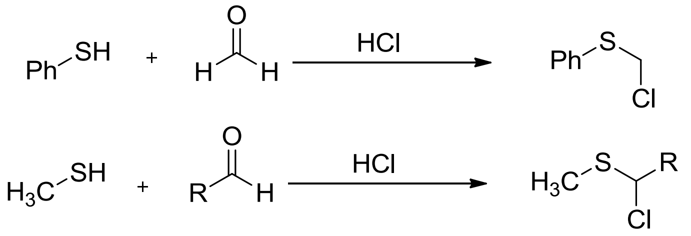
Scheme 1.3



1.2.3. From aldehydes and thiols

Bohme and co-workers[11] revealed a regioselective method for the preparation of α-chloro sulfide by the condensation reaction of an aldehyde with a thiol in the presence of hydrogen chloride. This synthetic method is quite useful for the preparation of a wide range of α-chloro sulfides. Homologation of sulfide is possible by using appropriate aldehyde component. The use of formaldehyde afford primary chloride while higher aldehydes results in secondary chlorides, Scheme 1.4.

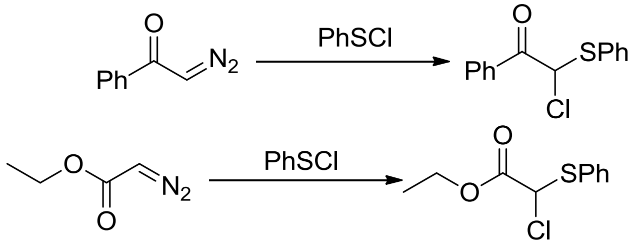
Scheme 1.4



1.2.4. From α-diazocarbonyl compounds

Weygand and Etestmann found a regiospecific method to prepare α-chloro sulfide unit adjacent to the carbonyl group of a ketone by subjecting diazoketones to reaction with various sulfenyl chlorides.[12] The diazoketone can be prepared form acyl chloride and diazomethane, Scheme 1.5.

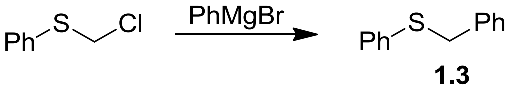
Scheme 1.5



1.3. Carbon-Carbon bond formation by employing α-chloro sulfides

Carbon-carbon bond formation employing α-chloro sulfide is known. In an early study by Bohme and co-workers,[2] simple α-chloro sulfides were reacted with phenyl magnesium bromide to furnish the coupled product **1.3**. The α-chloro sulfide was employed as an electrophile, Scheme 1.6.

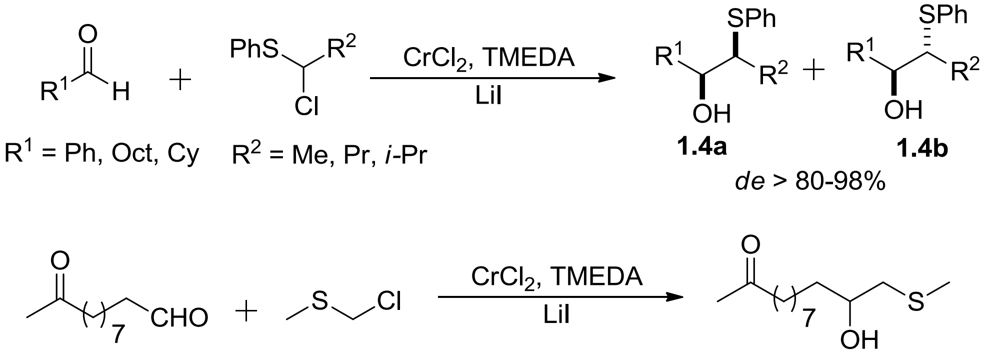
Scheme 1.6



1.3

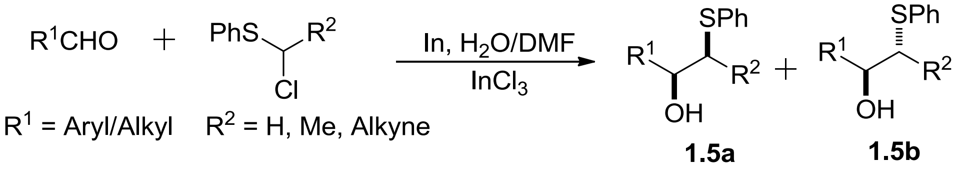
Takai *et. al.*, reported chemo and stereoselective addition of alkyl/aryl α-chloro sulfides to aldehydes. $CrCl_2$ reduced the chloro sulfide to generate a thio carbanion. The reaction is highly chemoselective as under the reaction condition ketones remained intact, Scheme 1.7.[13]

Scheme 1.7



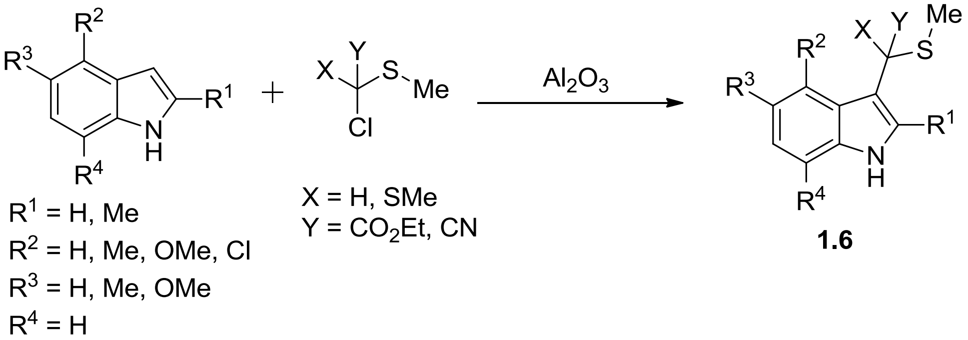
Mitzel *et. al.*, reported C-C coupling of α-chloro sulfide and aldehyde under Barbier type conditions using In metal and $InCl_3$. Mixed solvent system H_2O/DMF resulted in better yield. In presence of $InCl_3$ the reaction proceeds via a chelated transition state to furnish the *syn* diastereomer as the major product and in absence of $InCl_3$ the reaction follows noncheleted pathway which results in *anti* as the major product. Propargylic chloro sulfide furnished homo propargylic alcohol without isomerization to allene, Scheme 1.8.[14]

Scheme 1.8



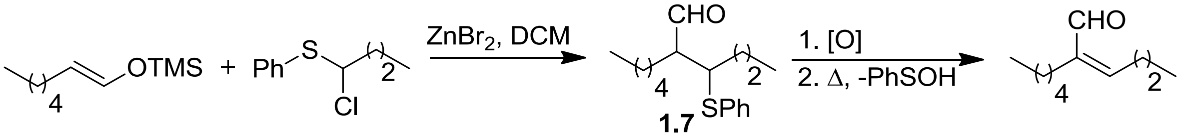
α-Chloro sulfides undergo electrophilic substitution reactions with aromatic compounds in presence of Lewis acids. Generally α-chloro carbonyls are inert towards electrophilic substitution reaction but this is not the case with α-chloro sulfide containing carbonyl counterparts. Ishibashi *et. al.*, reported electrophilic substitution on indole by α-chloro sulfide using neutral alumina as the Lewis acid. Various indole derivatives reacted with several α-chloro sulfides to afford the desired product, Scheme 1.9.[15]

Scheme 1.9



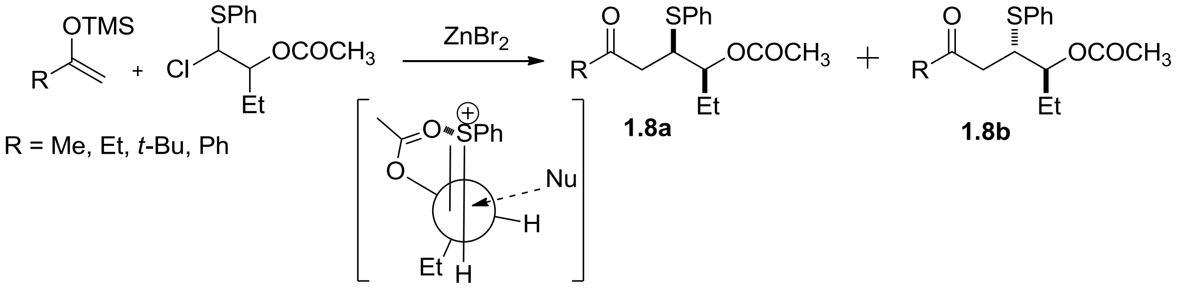
A regiospecific method for the introduction of a thioalkyl substituent α to the carbonyl group was studied by Fleming and Paterson.[16] The reaction of α-chloro sulfides with silyl enol ethers furnished thioalkylated carbonyl compounds **1.7** under mild Lewis acid conditions, subsequent thermal elimination after oxidation to sulfoxide afforded α,β unsaturated carbonyl compounds, Scheme 1.10.

Scheme 1.10



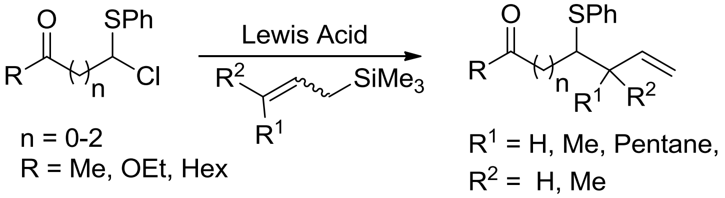
α-Chloro sulfide with a β-substituent reacted with silyl enol ethers in presence of anhydrous zinc bromide to give predominantly the corresponding *syn* products. The high *syn* selectivity of these reactions is explained by nucleophilic addition to chelated chiral thioniun ion, Scheme 1.11.[17]

Scheme 1.11



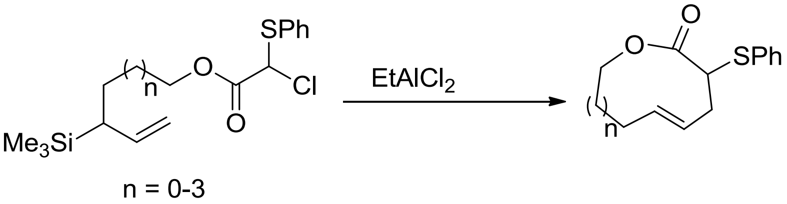
Akiba *et. al.*, reported the first chemoselective allylation of α-chloro sulfide. Allylsilanes reacted with α-chloro sulfides containing a carbonyl group either at α, β or γ positions to furnish α-allylsulfides in high yields, Scheme 1.12.[18a]

Scheme 1.12



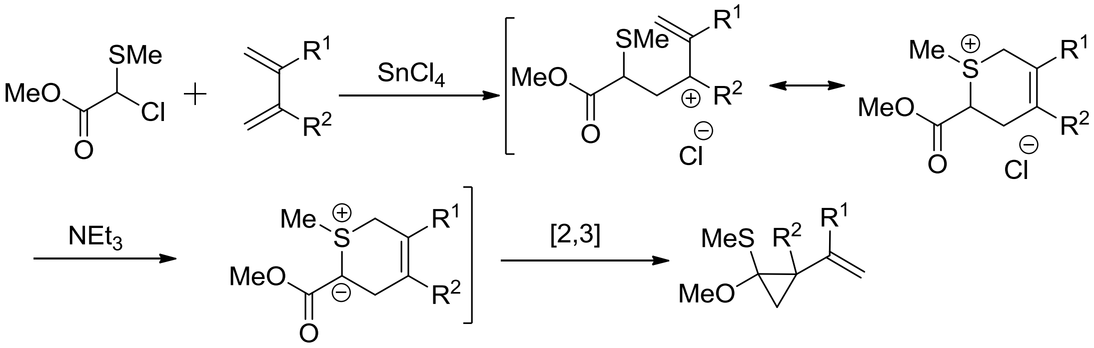
This method was further used to prepare medium-membered lactones (8-11 membered rings) in good yields by $EtAlCl_2$ promoted intramolecular condensation of α-chloro sulfides containing an ester group and allylsilanyl moiety without the need for high dilution conditions, Scheme 1.13.[18b]

Scheme 1.13



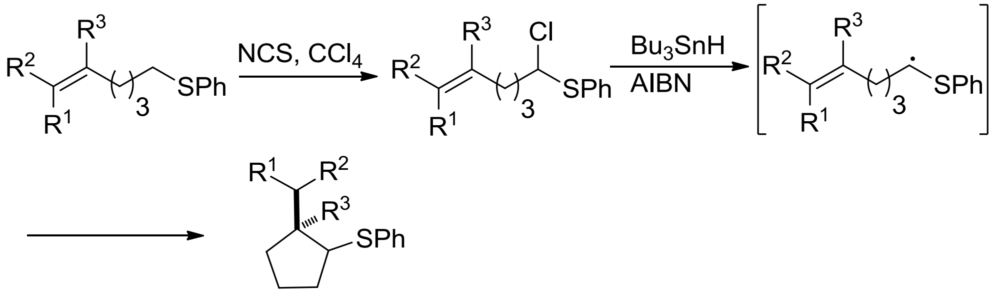
α-Acyl or α cyano-α-chloro sulfide have been utilized in the reaction with conjugated diene in [2+4] fashion to afford cyclo adducts which were further converted insitu to vinyl cyclopropanes under basic condition, Scheme 1.14.[19]

Scheme 1.14



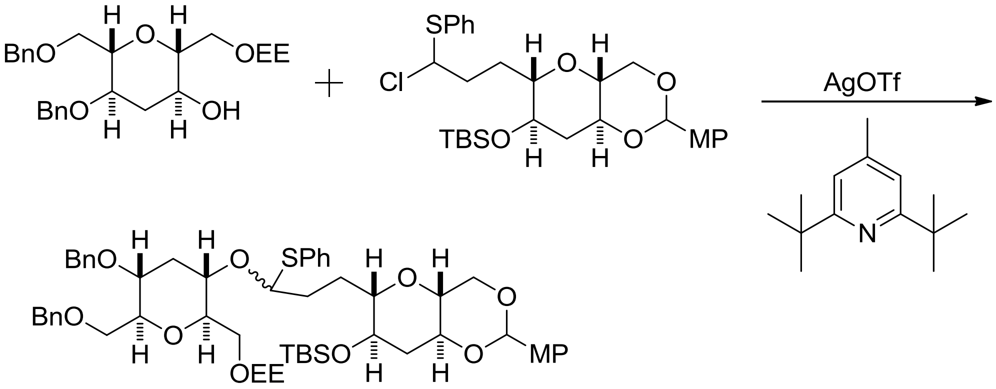
α-Chloro sulfide have been used as precursors of α-sulfenyl radical that undergo intramolecular cyclization as reported Tsai *et. al.*, Scheme 1.15.[20]

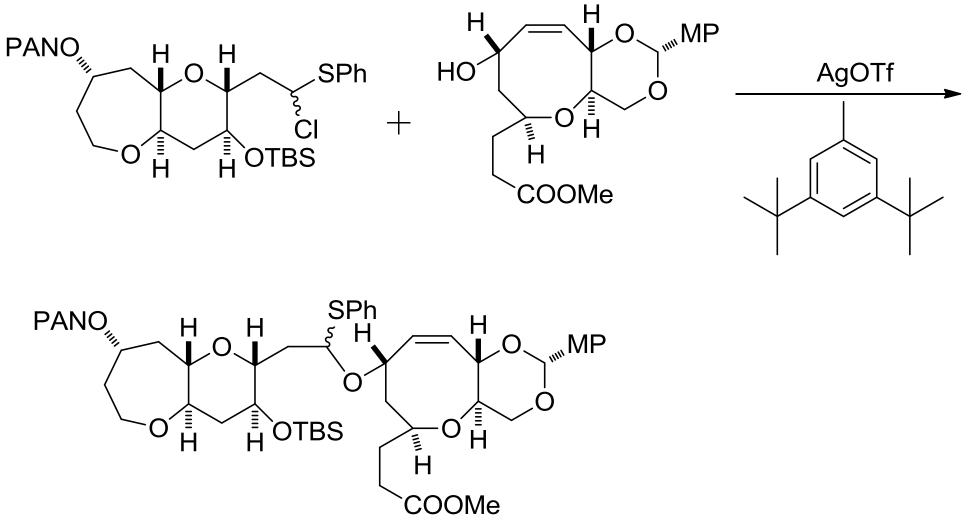
Scheme 1.15



Hirama *et. al.*, have employed α-chloro sulfide for the synthesis of various *O,S* acetal using AgOTf as the catalyst. α-Chloro sulfide were prepared by reacting the corresponding sulfides with NCS and subsequent reaction with an alcohol furnished the corresponding *O,S* acetal as a 2:1 mixture of epimers, Scheme 1.16.[21]

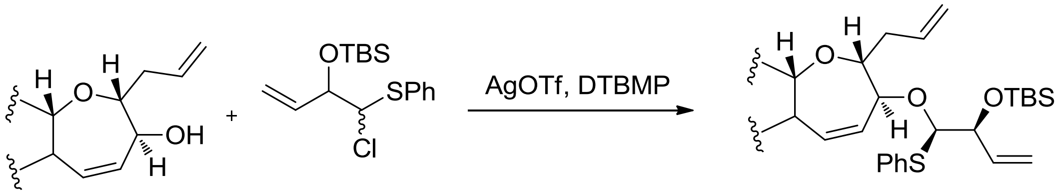
Scheme.1.16





α-Chloro sulfides with β-substitution yielded *O,S* acetal in a 6:1 diastereomeric ratio due to induction of vicinyl chiral centre. Under the reaction condition various acid labile functional groups such as ethers, esters and silyl ethers were found to be inert, Scheme 1.17.

Scheme 1.17



1.4. Stereoselective Carbon-Carbon bond formation by employing α-chloro sulfides

The formation of stereogenic centers in acyclic systems as compared to cyclic systems is particularly challenging due to the many available degrees of freedom. Chiral α-branched propargylic and allylic sulfides are versatile building blocks as a source of epoxy alkynes,[22] epoxydiynes,[23] allylic alcohols,[24] allylic amino derivatives,[25] and γ,δ-unsaturated acids.[26] α-Chloro sulfides are valuable synthetic intermediates as reactive electrophiles,[27] nucleophiles in metal-promoted carbon–carbon bond-forming reactions[28] and as aldehydes or ketone equivalents.[29]

To explore stereoselective creation of C-C bond using α-chloro sulfides and organozinc reagents, an investigation was initiated with racemic sulfide **1.9**. Sulfide **1.9** was reacted with stoichiometric amount of NCS in dry benzene to form α-chloro sulfide **1.10** which without further purification was reacted with 1-octynylzinc bromide to afford the propargylic sulfide **1.11a** and **a'** in a 9:1 ratio, Table 1.1. The reaction of **1.10** with vinylzinc bromides was very stereoselective and afforded products **1.11b** with greater than 95% *de* in good yield. Likewise butylzinc bromide yielded **1.11c** with excellent diastereoselectivity in moderate yield, Scheme 1.18.

Scheme 1.18

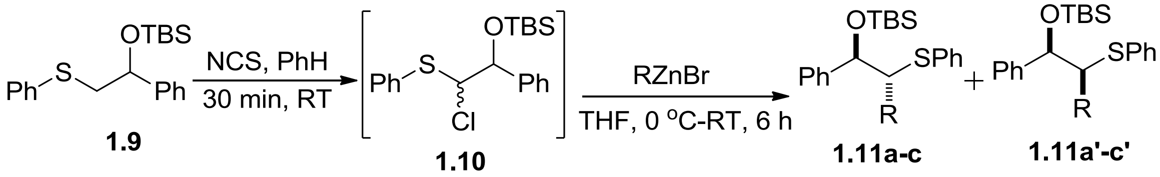
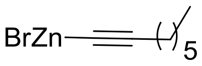
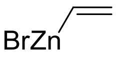
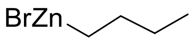
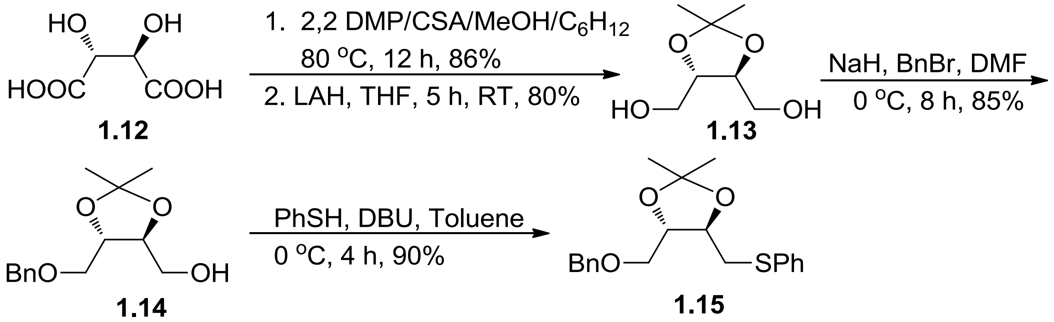


Table 1.1

Entry	RZnBr	Product, yield% **(1.11a-c:1.11a'-c')**
1		**1.11a**, **a'**, 86 (9:1)
2		**1.11b, b'**, 80 (>95:<5)
3		**1.11c, c'**, 64 (>95:<5)

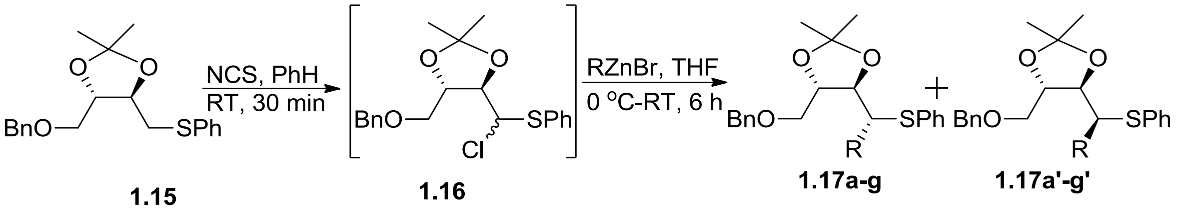
Subsequently, further reactions were attempted on optically active sulfide **1.15**, which was prepared from L-tartaric acid. L-tartaric acid **1.12** was reacted with 2,2-dimethoxy propane (DMP) in MeOH in the presence of catalytic amount of CSA to afford acetonide diester which was reduced to diol **1.13** using LAH. Selective protection as the monobenzyl ether **1.14**[30] followed by reaction with PhSSPh in presence of Bu_3P yielded the sulfide **1.15**, Scheme 1.19.

Scheme 1.19



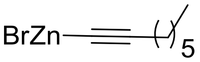
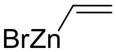
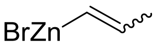
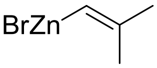
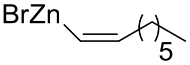
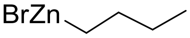
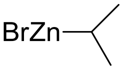
Sulfide **1.15** was reacted with NCS in dry benzene to form α-chloro sulfide **1.16** which was found to be highly moisture sensitive. Therefore α-chloro sulfide needed to be reacted with suitable nucleophiles without isolation and under inert conditions. Thus the supernatant benzene layer containing the α-chloro sulfides was transferred to the organozinc reagent, Scheme 1.20.

Scheme 1.20



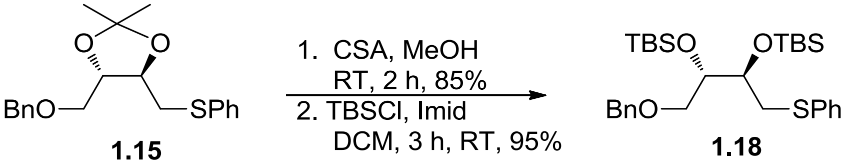
The result of the reactions of α-chloro sulfide **1.16** with various organozinc reagents is summarized in Table 1.2 Long chain alkynes afforded products with poor selectivity, entry 1. This is probably due to their linear geometry and less steric crowding. Good stereoselectivity in bond formation was observed using alkenyl and alkylzinc reagents, entries 2-7.

Table 1.2

Entry	RZnBr	Product, yield% (**1.17a-g:1.17a'-g'**)
1		**1.17a**, **a'**, 76 (3:1)
2		**1.17b, b'**, 78 (>95:<5)
3		**1.17c, c'**, 80 (>95:<5)
4		**1.17d, d'**, 86 (>95:<5)
5		**1.17e, e'**, 66 (>95:<5)
6		**1.17f, f'**, 60 (>95:<5)
7		**1.17g, g'**, 60 (>95:<5)

In an effort to obtain better selectivity using alkynes, the steric bulk of the β-substituent in the sulfide component was increased. Sulfide **1.18** was prepared from sulfide **1.15** by an initial treatment with catalytic amount of CSA in MeOH to furnish the corresponding diol which was subsequently reacted with TBSCl, Scheme 1.21.

Scheme 1.21



1.15

1. CSA, MeOH RT, 2 h, 85%
2. TBSCl, Imid DCM, 3 h, RT, 95%

1.18

Sulfide **1.18** was treated with NCS to furnish α-chloro sulfide **1.19** with was reacted with various nucleophiles. The results are summarized in Table 1.3. Excellent stereoselectivity was obtained with unbranched alkynyl, alkenyl, and alkyl zinc reagents, Scheme 1.22.

Scheme 1.22

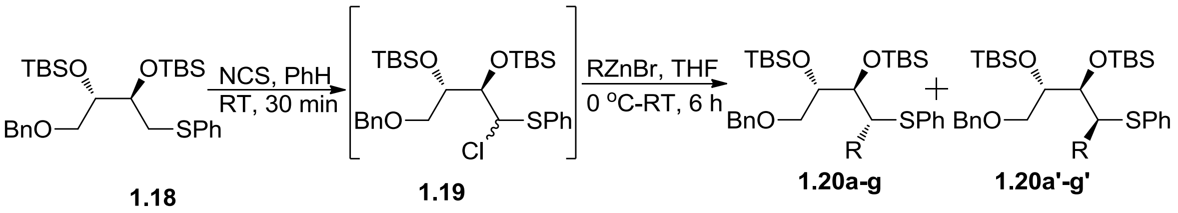
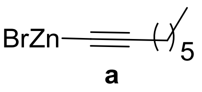
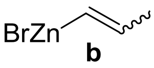
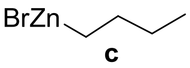


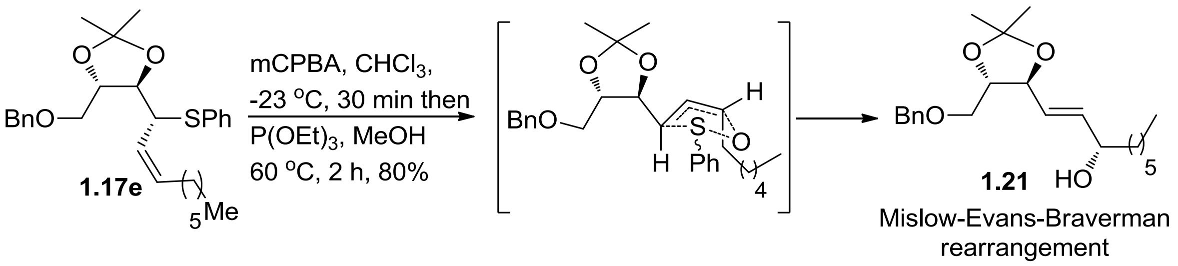
Table 1.3

Entry	RZnBr	Product, yield% **(1.20a-c:1.20a'-c')**
1		**1.20a**, **a'**, 70 (98:2)
2		**1.20b**, **b'**, 80 (98:2)
3		**1.20c**, **c'**, 60 (98:2)

1.5.Assignment of configuration

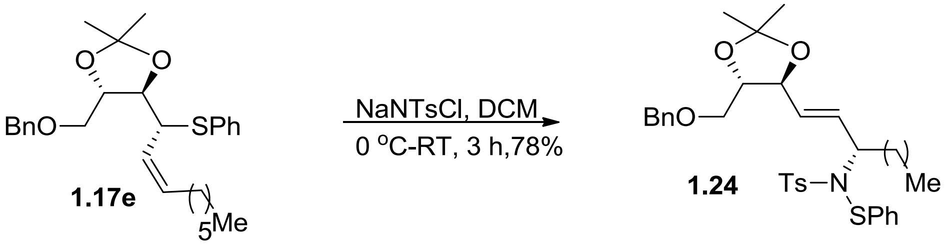
Sulfide **1.17e** was oxidized to the corresponding sulfoxide and treated with an excess of $P(OEt)_3$ in the same pot to afford allylic alcohol **1.21** by a [2,3]-sigmatropic rearrangement (Mislow-Evans-Braverman rearrangement).[30] The rearrangement proceeds efficiently resulting in a net 1,3 chirality transfer, Scheme 1.23.

Scheme 1.23



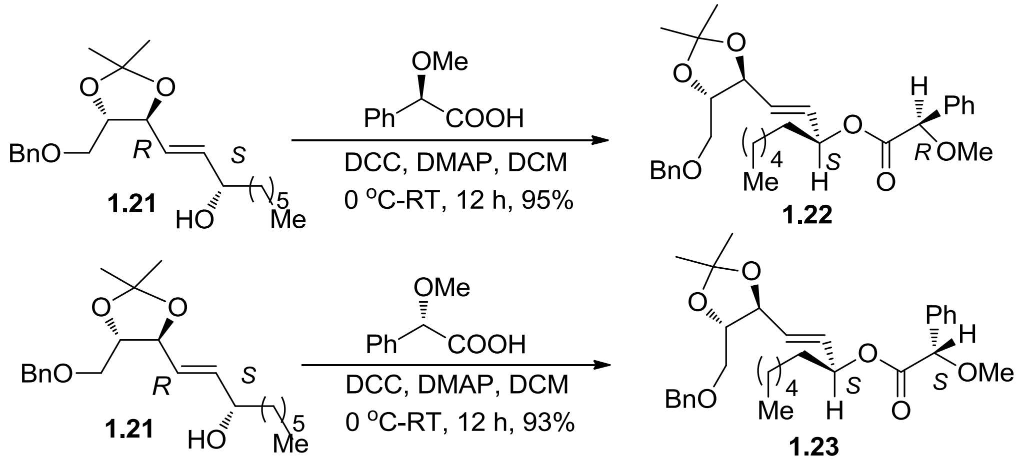
Similarly sulfide **1.17e** was reacted with chloramine-T which furnished an epimeric mixture of sulfilimines. The sulfilimines underwent [2,3]-sigmatropic shift readily at rt to yield allylic amino derivative **1.24**, Scheme 1.24.[31]

Scheme 1.24



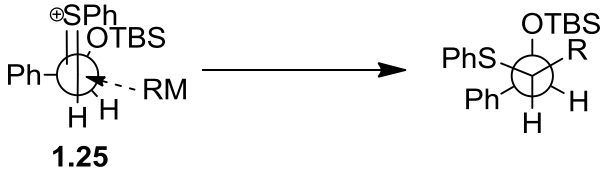
The configuration at the newly generated stereogenic center in **1.17e** was assigned by preparation of mandelate esters of allylic alcohol **1.21**. Allylic alcohol **1.21** on reaction with (*R*)-methoxy mandelic acid and (*S*)-methoxy mandelic acid afforded the corresponding esters **1.22** and **1.23**. Comparision of ^{1}H NMR data of **1.22** and **1.23** revealed that the olefinic protons of **1.22** appeared more down field compared to the olefinic protons of **1.23**, confirming as *S* configuration for the carbinol carbon. Since the [2,3]-sigmatropic rearrangement proceeds with excellent transfer of chirality, the configuration at carbon bearing sulfur in **1.17e** should be *R* configuration. The structure of other products were assigned based on analogy, Scheme 1.25.

Scheme 1.25



The observed stereoselectivity can be rationalized by invoking a model depicted in Scheme 1.12. The nucleophile attacks the sulfenium ion **1.25** from the side opposite to the phenyl group, Scheme 1.26.

Scheme 1.26

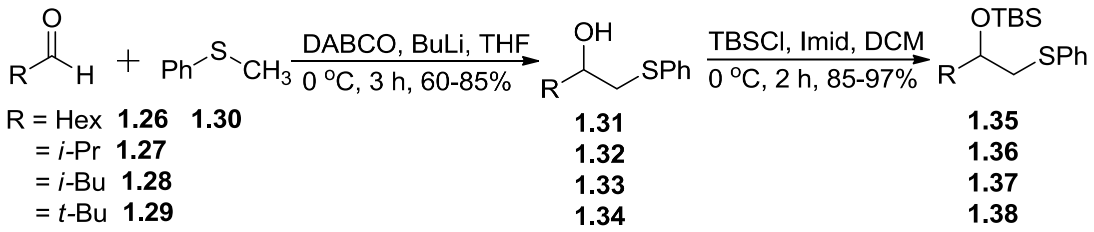


1.6. Diastereoselective synthesis of α-substituted sulfides by employing α-chloro sulfides

It is apparent from the above discussion that α-Chloro sulfides with a β-substituent afforded α-substituted sulfides in excellent diastereoselctivity by 1,2 asymmetric induction. α-Chloro sulfides with a TBS substituent afforded products with better diastereoselectivity compared to isopropylidene moiety. It was of interest to investigate the diastereoselectivity of carbon bond formation by varying the steric bulk of the alkyl substitution on β-siloxy sulfides and also study β-methyl sulfides.

Sulfide **1.35-1.38** were prepared from the corresponding aldehydes.[33] Aldehyde **1.26-1.29** were reacted with phenylthiomethyl lithium in THF at 0 °C to afford the corresponding alcohols **1.31-1.34** which were subsequently protected as their TBS ethers, Scheme 1.27.

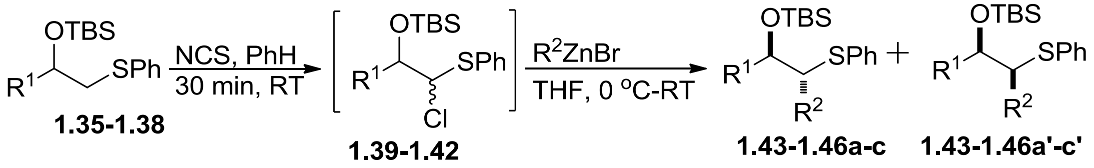
Scheme 1.27



1.7. Preparation of α-substituted sulfides.

Sulfide **1.35-1.38** were treated with stoichiometric amount of *N*-chlorosuccinimide in dry benzene at room temperature to yield the corresponding α-chloro sulfides **1.39-1.42** which were subsequently reacted with various organozinc reagents. The results are summarized in Table 1.4, Scheme 1.28.

Scheme 1.28



Reaction of α-chloro sulfides **1.39-1.41** with 1-octylzinc bromide afforded propargylic sulfide **1.43-1.45a** in good yield with moderate stereoselectivity, entry 1, 4, 7. Interestingly α-chloro sulfide **1.42** afforded propargylic sulfide **1.46a** with excellent stereoselectivity, entry 10. α-Chloro sulfide **1.39-1.42** reacted highly stereoselectively with vinylzinc bromide to yield allylic sulfides **1.43-1.46b** in excellent yield, entry 2, 5, 8, 11.

Similarly reaction with butylzinc bromide yielded corresponding α-substituted sulfides **1.43c-1.46c** as single isomer, entry 3, 6, 9, 12. The stereoselectivity of the reaction of octynylzinc bromide with chloro sulfides **1.10** and **1.39-1.42** correlates with the size of substituent, poorer selectivity being obtained in the reaction with **1.39** having *n*-pentyl substituent and better selectivity being observed for alkyl group with α or β branching. The reaction with vinyl and alkylzinc reagents proceeded with all the chloro sulfides with good stereocontrol.

The poor stereoselectivity observed in the reaction with alkynylzinc reagents is probably due to its *sp* hybridization and lesser steric bulk. Vinylzinc bromide and *n*-butylzinc bromide possessing trigonal and tetrahedral geometry respectively are sterically more bulky compared to the alkynylzinc reagent and furnish products with high selectivity. However excellent selectivity was observed in the reaction of α-chloro sulfide **1.42** with 1-octynylzinc bromide. This is probably due to the bulky tertiary butyl group which directs the incoming nucleophile away from itself and from the side of hydrogen, Scheme 1.26. The stereochemistry of the newly generated centre was assigned by comparing the chemical shift values and coupling constants of the methine protons of the products **1.43-1.46a-c** and **a'-c'** with the data reported for known compounds.[22,] The vicinal coupling constant for the major isomer **1.43-1.46a-c** are in the range of 5.2 to 6.6 Hz while for the minor isomer the coupling constant are in the range of 3.0 to 5.1 Hz.

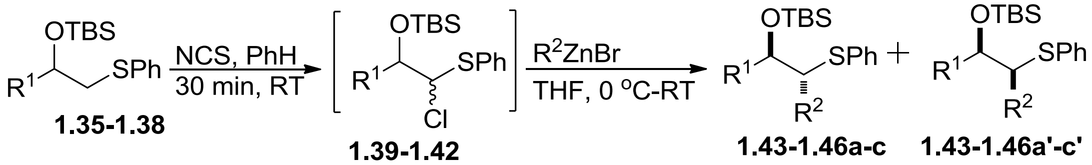
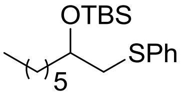
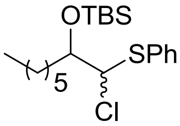
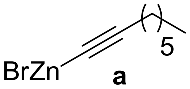
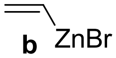
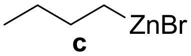
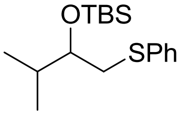
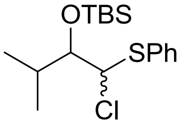
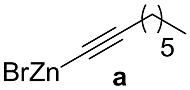
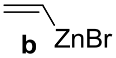
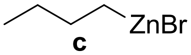
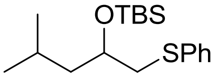
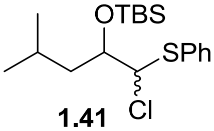
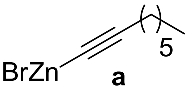
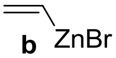
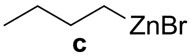
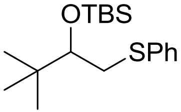
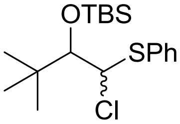
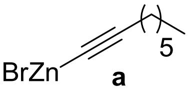
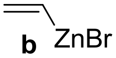
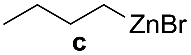


Table 1.4

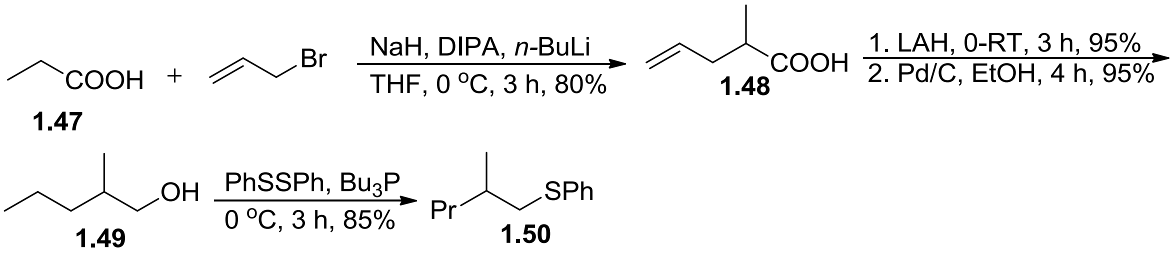
Entry	Sulfide	α-Chloro Sulfide	Organometallic reagent (R^2ZnBr)	Product,Yield% (*Syn:Anti*)
1	 **1.35**	 **1.39**	 **a**	**1.43a**, 78 (70:30)
2			 **b**	**1.43b**, 75 (>95:<5)
3			 **c**	**1.43c**, 70 (>95:<5)
4	 **1.36**	 **1.40**	 **a**	**1.44a**, 75 (75:25)
5			 **b**	**1.44b**, 75 (>95:<5)
6			 **c**	**1.44c**, 75 (>95:<5)
7	 **1.37**	 **1.41**	 **a**	**1.45a**, 80 (80:20)
8			 **b**	**1.45b**, 85 (>95:<5)
9			 **c**	**1.45c**, 70 (>95:<5)
10	 **1.38**	 **1.42**	 **a**	**1.46a**, 65 (>95:<5)
11			 **b**	**1.46b**, 73 (>95:<5)
12			 **c**	**1.46c**, 65 (>95:<5)

1.8. Preparation of β-methyl sulfides

To investigate the influence of the β-methyl substituent on the stereoselectivity of carbon bond formation, few sulfides with a β-methyl group were prepared as described here under.

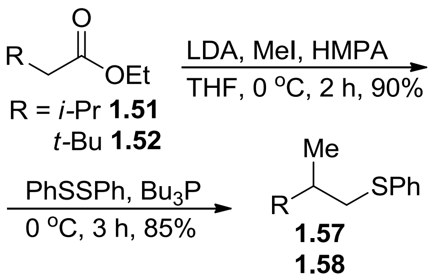
Sulfide **1.50** was prepared from propionic acid **1.47**. Propionic acid **1.47** was treated initially with NaH and subsequently with LDA to afford the dianion that on treatment with allyl bromide afforded the acid **1.48**.[34] Reduction of carboxylic acid using LAH followed by treatment with Pd/C afforded alcohol **1.49**. Treatment with diphenyl disulfide and tributyl phosphine furnished sulfide **1.50**, Scheme 1.29.

Scheme 1.29



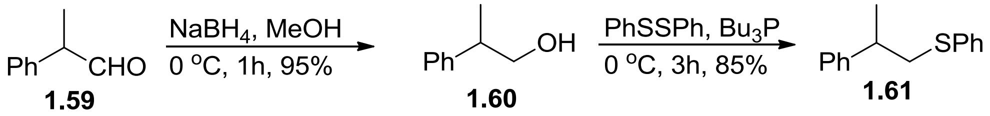
Sulfides **1.57**, **1.58** were prepared from readily available esters **1.51** and **1.52**. Treatment with LDA followed by quenching with MeI at 0 °C afforded α-methyl esters **1.53** and **1.54**.[35] Subsequently reduction using LAH furnished alcohols **1.55** and **1.56** which on treatment with PhSSPh and PBu_3 yielded sulfides **1.55** and **1.56**, Scheme 1.30.

Scheme 1.30



Sulfide **1.61** was prepared from commercially available 2-phenyl propanal **1.59**. Reduction of **1.59** using $NaBH_4$ furnished the alcohol **1.60** which on treatment with PhSSPh and Bu_3P furnished the sulfide **1.61**, Scheme 1.31.

Scheme 1.31



α-Chloro sulfides **1.62-1.65** were prepared from the corresponding sulfides in dry benzene and treated with various organozinc reagents to afford the α-substituted sulfide **1.66-1.69a-c**. The results are summarised in Table 1.5. α-Chloro sulfides **1.62** and **1.65** prepared from **1.50** and **1.61** respectively reacted with 1-octynylzinc bromide to afford approximately equal amount of isomeric of propargylic sulfides **1.66a**,**a'** and **1.69a,a'** in good yield, entry 1, 9. Reaction of octynylzinc bromide with α-chloro sulfides **1.63** and **1.64** furnished proporgylic sulfide **1.67 a**,**a'**, **1.68 a**,**a'** in a ratio of 75:25, entry 4, 7. It is interesting to note that sulfide **1.57** with an isopropyl substituent furnished the propargylic sulfide **1.67a** with better selectivity than sulfide **1.61** with a phenyl substituent though they are sterically similar.

α-Chloro sulfide **1.62** and **1.65** reacted with vinylzinc bromide to afford allylic sulfide **1.66b,b'** and **1.69b,b'** in good yield as a 4:1 mixture of diastereomers, entry 2, 11. α-Chloro sulfides **1.63** and **1.64** yielded allylic sulfides **1.67b,b'** and **1.68b,b'** with excellent stereoselectivity and in good yield, entry 5, 8. α-Chloro sulfides **1.62**, **1.63** and **1.65** reacted with *n*-butylzinc bromide to yield α-substituted sulfides **1.66c,c', 1.67 c,c'** and **1.69c,c'** in moderate yield and selectivity, entry 3, 6, 12. In the reaction of butylzinc bromide with α-chloro sulfides, vinyl sulfides were obtained as side products in variable yield due to elimination. Expectedly, α-chloro sulfide **1.64** reacted with *n*-butylzinc bromide to afford the product **1.68c,c'** with excellent stereoselectivity, entry 9. It is important to keep the amount of THF to a minimum in order to decrease the eliminated product, replacement of THF by Et_2O significantly improved the yield of desired product. The ratio of diasteoremers were determined by examination of crude NMR spectra, Scheme 1.32.

Scheme 1.32

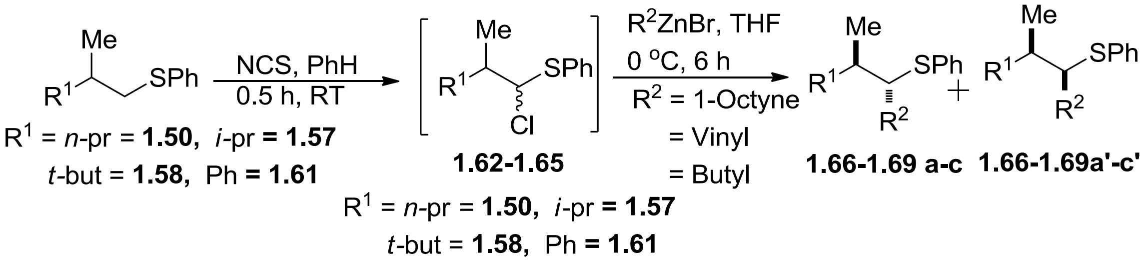
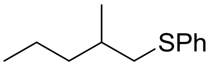
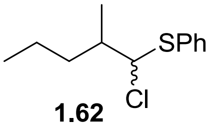
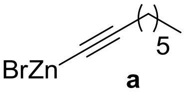
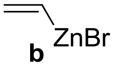
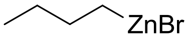
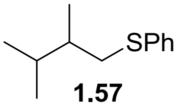
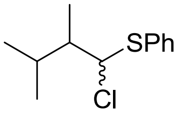
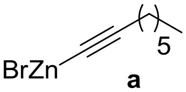
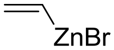
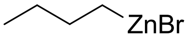
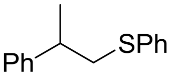
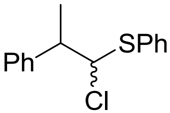
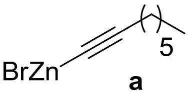
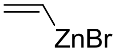
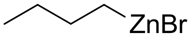
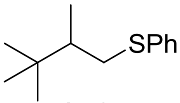
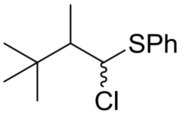
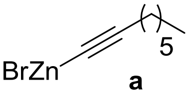
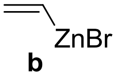
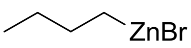


Table 1.5

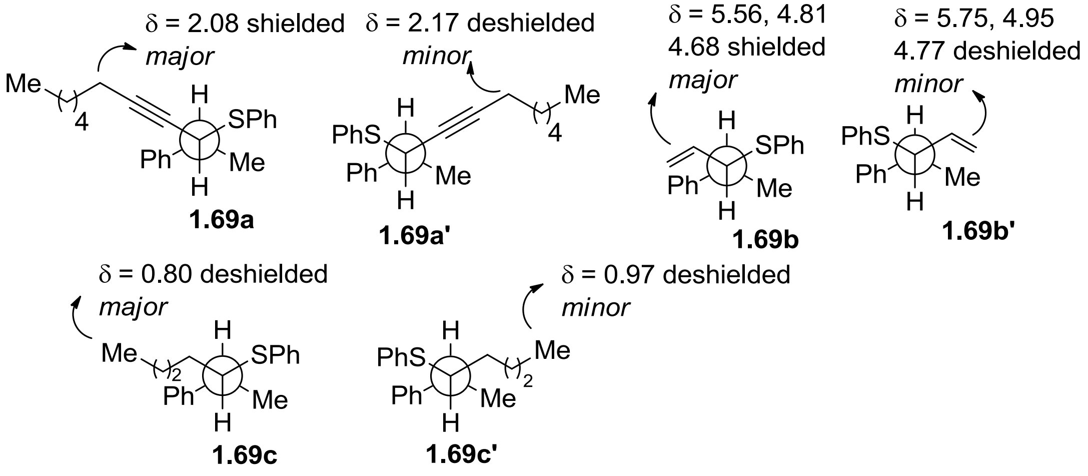
Entry	Sulfide	α-Chloro Sulfide	Organozinc reagent (R^{2}ZnBr)	Product, Yield **(1.66-1.69a-c:1.66-1.69a'-c')**
1	 **1.50**	 **1.62**	 **a**	**1.66a**,**a'** 82 (55:45)
2			 **b**	**1.66b**,**b'** 73 (78:22)
3			 **c**	**1.66c**,**c'** 40 (75:25)
4	 **1.57**	 **1.63**	 **a**	**1.67a**,**a'** 75 (75:25)
5			 **b**	**1.67b**,**b'** 80 (>95:<5)
6			 **c**	**1.67c**,**c'** 44 (82:18)
7	 **1.61**	 **1.65**	 **a**	**1.69a**,**a'** 80 (55:45)
8			 **b**	**1.69b**,**b'** 78 (80:20)
9			 **c**	**1.69c**,**c'** 40 77:23
10	 **1.58**	 **1.64**	 **a**	**1.68a**,**a'** 73 (80:20)
11			 **b**	**1.68b**,**b'** 70 (>95:<5)
12			 **c**	**1.68c**,**c'** 55 (>95:<5)

1.9. Assignment of configuration

It is known that acyclic compounds having vicinal stereocenters, each bearing one hydrogen exist predominantly in the conformation having the hydrogens anti so as to minimize gauche interactions.[36] In such a preferred conformation adopted by sulfide **1.69**, the alkyl group orientated gauche to the phenyl substituent would have resonances upfield due to the shielding effect of the aromatic ring in comparison to alkynyl group resonances of the isomer **1.69a'** (Scheme 1.33). The observed chemical shifts of the propargylic CH_2 for major **1.69a** and minor **1.69a'** isomers are 2.08 and 2.17 ppm respectively, supporting this assignment. Similarly the olefin protons signals for the major isomer **1.69b** as expected resonate upfield (5.56, 4.81 and 4.68) relative to signals for the same protons for the minor isomer (5.75, 4.95 and 4.77). The structure assigned to the major isomer **1.69c** is supported by the observed upfield resonance for the end methyl group of the butyl chain (0.80 ppm) in comparison to the resonance for the methyl group of **1.69c'** (0.97ppm).

The structure of the major isomers **1.66a-1.68a** were assigned based on the analogy. The model depicted in Scheme 1.26 would rationalize the observed stereoselectivity.

Scheme 1.33



1.10. Conclusion

The α-chloro sulfides serve as excellent electrophiles which can be coupled with various nucleophiles.

1. A C–S stereogenic center is created with efficient stereocontrol by 1,2-asymmetric induction due to a vicinal C–O, C-C stereogenic center.
2. The allylic sulfide can be converted to the corresponding sulfoxide/ sulfilimine/sulfur ylide and subjected to [2,3]-sigmatropic rearrangement. The efficient 1,3-chirality transfer observed in this reaction eventually results in a net 1,4-chirality transfer.
3. The methodology would be useful for the synthesis of natural products possessing a 1,4-diol, 1,4 amino alcohol subunits, tetrahydrofuran, pyrrolidine, pyran and piperidine rings from appropriate starting materials.
4. Chiral α-branched propargylic, allylic and alkyl sulfides can be synthesized with moderate to excellent stereoselectivity.

1.11. References

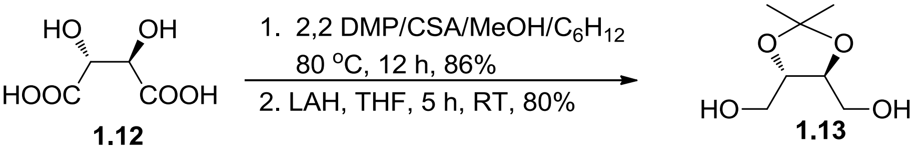
1. (a) Riche, M. A. *Annls Chim. Phys.* **1855**, *43*, 283.
2. (a) Bohme, H. *Ber. Dtsch. Chem. Ges.* **1936**, *69*, 1610. (b) Vedejs, E.; Mullins, M. J.; Renga, J. M.; Singer, S. P. *Tetrahedron Lett.* **1978**, 519. (c) Arai, K.; Iwamura, H.; Oki, M. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3319.
3. Tuleen, D. L.; Stephens, T. B. *Chem. Ind. London*, **1966**, 1555.
4. Mura, J. Jr.; Bennett, D. A.; Cohen, T. *Tetrahedron Letters,* **1975,** *16*, 4433.
5. Schreiber, K. C.; Fernandez, V. P. *J. Org. Chem*. **1961**, *26*, 2478.
6. Oki, M.; Kobayashi, K. *Bull. Chem. Soc. Japan*. **1970**, *43***,** 1223**.**
7. Truce, W. E.; Birum, G. H.; Mc bee, E. T. *J. Am. Chem. Soc*. **1952,** *74*, 3594.
8. Bordwell, F. G.; Pitt, B. M. *J. Am. Chem. Soc*. **1955**, *77*, 572.
9. Bamtt, G. C.; *Comprehensive Organic Chemistry Pergamon Press, Oxford*. **1979**, *3*, 33.
10. Rynbrandt, R. H.; *Tetrahedron Lett.* **1971**, 3553.
11. (a) Bohme, H.; Fisher, H.; Frank, R. *Annln Chem*. **1949**, *563*, 54. (b) Bohme, H.; Gran, H. J. *Annln. Chem*. **1952**, *577,* 68.
12. (a) Weygand, F.; Bestmann, H. J. Z. *Noturf.* **1955**, *106*, 296. (b) Petrov, K. A.; Sokolovsky G. A.; Neimysheva, A. A. *J. Ger. Chem. U.S.S.R.* **1957**, *27*, 855.
13. Nakatsukasa, S.; Takai, K.; Utimoto, K. *J. Org. Chem.* **1986**, *51*, 5045.
14. (a) Engstorm, G.; Meisha, M.; Carolyn, P.; Mitzel, P. *Tetrahedron Lett*. **1999**, *40*, 5967. (b) Mitzel, T. M.; Palomo, C.; Jendza, K. *J. Org. Chem.* **2002**, *67*, 136.
15. Ishibashi, H.; Mita, N.; Matsuba, N.; Kubo, T.; Nakanishi, M.; Ikeda, M. *J. Chem. Soc. Perkins Trans. 1*. **1992**, 2821.

16. (a) Paterson, I.; Fleming, I.; *Tetrahedron Lett.* **1979**, 993, 995, 2179. (b) Fleming, I.; Goldhill, J.; Paterson, I. *Tetrahedron Lett.* **1979**, 3205, 3209.
17. Iqbal, J.; Shukla, A. *Tetrahedron.* **1991**, *47*, 8753.
18. (a) Wada, M.; Shigehisa, T.; Akiba, K. *Tetrahedron Lett.* **1983**, *24*, 1714. (b) Wada, M.; Shigehisa, T.; Akiba, K. *Tetrahedron Lett.* **1985**, *26*, 5191.
19. Ishibashi, H.; Kitano, Y.; Nakatani, H.; Okada, M.; Ikeda, M. *Tetrahedron Lett.* **1984**, *25*, 4231.
20. (a) Tsai, Y.; Chang Chang, F.; Huang, J.; Shiu, C. *Tetrahedron Lett.* **1989**, *30*, 2121. (a) Tsai, Y.; Chang Chang, F.; Huang, J.; Shiu, C.; Kao, C.; Liu, J. *Tetrahedron Lett.* **1997**, *53*, 4291.
21. (a) Inoue, M.; Wang, J.; Wang, G.; Ogasawara, Y.; Hirama, M. *Tetrahedron*. **2003**, *59*, 5645. (b) Kobayashi, S.; Takahashi, Y.; Komano, K.; Alizadeh, B. H.; Kawada, Y.; Oishi, T.; Tanaka, S.; Ogasawara, Y.; Sasaki, S.; Hirama, M.; *Tetrahedron*. **2004**, *60*, 8375. (c) Inoue, M.; Saito, F.; Iwatsu, M.; Ishihara, Y.; Hirama, M. *Tetrahedron Lett.* **2007**, *48*, 2171.
22. Frimpong, K.; Wzorek, J.; Lawlor, C.; Spencer, K.; Mitzel, T. *J. Org. Chem.* **2009,** *74*, 5861.
23. Pelc, M. J.; Zakarian, A. *Tetrahedron Lett.* **2006**, *47*, 7519.
24. Armstrong, A.; Challinor, L.; Moir, J. H. *Angew. Chem. Int. Ed.* **2007**, *46*, 5369.
25. Ma, M.; Peng, L.; Li, C.; Zhang, X.; Wang, J. *J. Am. Chem. Soc.* **2005**, *127*, 15016.
26. (a) Inoue, M.; Miyazaki, K.; Uehara, H.; Maruyama, M.; Hirama, M. *Proc. Natl. Sci. U.S.A.* **2004**, *101,* 12013. (b) For a review, see: Dilworth, B. M.; McKervey, M. A. *Tetrahedron*. **1986**, *42*, 3731.

27. (a) Normant, H.; Castro, C. R. *C. R. Hebd. Seances Acad. Sci.* **1964**, *259*, 830. (b) Gross, H.; Hoft, E. *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 335. (c) Ogura, K.; Fujitha, M.; Takahashi, K.; Iida, H. *Chem. Lett.* **1982**, *11*, 1697. (d) Nakatsuka, S.; Takai, K.; Utimoto, K. *J. Org. Chem.* **1986**, *51*, 5045.
28. Chu, D. T. H. *J. Org. Chem.* **1983**, *48*, 3571.
29. Rodney A. Fernandes. *Eur. J. Org. Chem.* **2007**, 5064.
30. (a) Miller, E. G.; Rayner, D. R.; Mislow, K. *J. Am. Chem. Soc.* **1966**, *88*, 3139. (b) Braverman, S.; Stabinsky, Y. *Chem. Commun.* **1967**, 270. (c) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147.
31. Petranek, J.; Vecera, M. *Collect. Czech. Chem. Commun.* **1959**, *24*, 2191.
32. (a) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M. *J. Org. Chem.* **1986**, *51*, 2370. (b) Trost, B. M.; Bunt, R. C.; Pulley, S. R. *J. Org. Chem.* **1994**, *59*, 4202.
33. Corey E. J.; Seebach, D. *J. Org. Chem.* **1966,** *31*, 4097.
34. (a) Taillier, C.; Gille, B.; Bellosta, V.; Cossy, J. *J. Org. Chem.* **2005**, *70*, 2097.
35. (a) Anthony M. J.; Dubois, J. E. *J. Chem. Soc. Perkin Trans.1*. **1977**, 694. (b) Heathcock, C. H.; Lampe, J. *J. Org. Chem*. **1983**, *48*, 4330.
36. (a) Mori, I.; Bartlett, P. A.; Heathcock, H. C. *J. Am. Chem. Soc.* **1987**, *109*, 7200 (b). Heathcock, H. C.; Kiyooka, S.; Blumenkopf, T. A. *J.* Org. *Chem.***1984**, *49*, 4214. (c) Mori, I.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.***1990,** *55***,** 5966. (d) Binnun, P. E. D.; Schaus, J. V.; Velentino, N. M.; Panek J. S. *J. Org. Chem*, **2002**, *67*, 1705.

Experimental Section

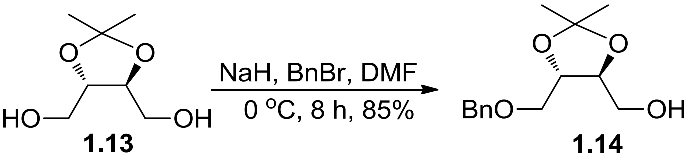
Preparation of diol 1.13



In a round bottom flask L-tartaric acid (12.6 g, 150 mmol), 2,2-dimethoxy propane (23.5 mL, 192 mmol), *p*-toluenesulfonic acid (50 mg, 0.26 mmol) and MeOH (5 mL) were added. The mixture was stirred and heated at 80 °C for 1 h. Additional 2,2-dimethoxy propane (12 mL) and cyclohexane (56 mL) were added. The mixture was heated to reflux with internal stirring. The azeotrope of acetone cyclohexane and methanol cyclohexane were slowly removed by vigruex column over a period of 6 h. The reaction mixture was cooled to rt and K_2CO_3 (120 mg, 0.9 mmol) was added and stirred for 30 min at rt. The reaction mixture was diluted with DCM (100 mL) and washed with saturated aq $NaHCO_3$ (10 mL), brine (10 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford a crude compound which was purified by column chromatography using 20% EtOAc/hexanes (v/v) to afford the pure diester as a viscous oil in 86% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.75 (s, 2H), 3.84 (s, 6H), 1.49 (s, 6H).

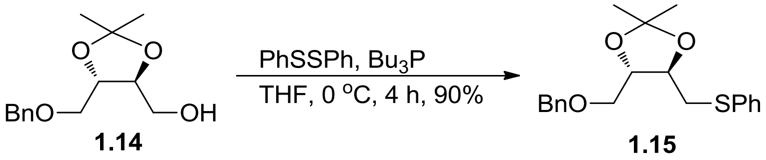
To a suspension of $LiAlH_4$ (11.56 g, 304.6 mmol, 2.5 equiv.) in THF (400 mL) cooled at 0 °C, the solution of diester (30 g, 121.82 mmol) in THF (50 mL) was added dropwise over 30 min. The reaction mixture was refluxed for 8 h. It was then cooled to 0 °C and quenched with ice pieces. The precipitate was filtered through a pad of Celite and washed with a mixture of MeOH (500 mL). The filtrate was concentrated under reduced pressure to give the corresponding acetonide diol as a colourless oil (18.9 g) in 80% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.96–3.90 (m, 2H), 3.70 (dd, *J* = 4.0, 2.7 Hz, 4H) , 2.80 (s, 2H), 1.40 (s, 6H).

Preparation of monobenzyl ether 1.14



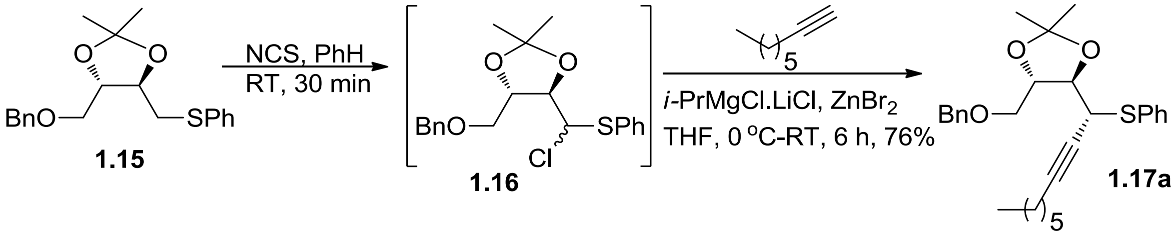
To a suspension of NaH (662 mg, 27.5 mmol) in DMF (25 mL) cooled at 0 °C was added the solution of the diol (4.0 g, 25 mmol) in DMF (50 mL) and the mixture stirred for 1 h at the same temperature. BnBr (4.2 g, 25 mmol) in dry DMF (25 mL) was added the mixture gradually allowed to attain rt and stirred further for 7 h. The reaction mixture was cooled at 0 °C, quenched by adding ice pieces and further diluted with water (100 mL) and extracted with EtOAc (4×50 mL). The combined organic layers were washed with water (15 mL), brine (15 mL) dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford a crude compound which was purified by column chromatography using 20% EtOAc/hexanes (v/v) to afford the pure mono benzyl ether as a viscous oil in 85% yield. TLC, R_f 0.41 (40% EtOAc/hexanes); $[\alpha]^{20}_{D}$ +9.1 (*c* 1, $CHCl_3$); IR (KBr) 3464, 3031, 2987, 2932, 2872, 1496, 1454, 1375, 1251, 1215, 1166, 1082, 991, 907, 847, 741, 700, 608 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33-7.23 (m, 5H), 4.57 (s, 2H), 4.01 (dt, *J* = 8.4, 5.4 Hz, 1H), 3.91-3.98 (m, 1H), 3.76 (dd, *J* = 11.9, 4.1 Hz, 1H), 3.63-3.67 (m, 2H), 3.56 (dd, *J* = 10.2, 5.4 Hz, 1H), 2.63 (s, 1H), 1.42 (s, 3H), 1.41 (s, 3H).

Preparation of sulfide 1.15



To the mixture of mono benzyl ether **1.14** (5.04 g, 20 mmol) and diphenyl disulfide (5.23 g, 24 mmol) in dry THF (80 mL) cooled at 0 °C was added Bu_3P (30 mL, 30 mmol, 1 M in EtOAc) dropwise and the mixture stirred for 4 h allowing it to warm to rt gradually. The reaction mixture was diluted with water (10 mL), the layers were separated and the aq layer was extracted with EtOAc (3×15 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and the solvent evaporated under reduced pressure to afford the crude sulfide which was purified by column chromatography using 2% EtOAc/Hexanes (v/v) as the eluent to afford the pure sulfide **1.15** as viscous oil in 90% yield; TLC, R_f 0.45 (5% EtOAc/Hexanes); $[\alpha]^{25}_{D}$ -14.5 (*c* 1, MeOH); IR (KBr) 2982, 2923, 2861, 1737, 1584, 1449, 1373, 1221, 1085, 1026, 740, 693 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.32-7.09 (m, 10H), 4.53 (s, 2H), 4.04-3.99 (m, 2H), 3.60 (d, *J* = 3.6 Hz, 2H), 3.15 (d, *J* = 4.4 Hz, 2H), 1.41 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 136.0, 129.3, 129.0, 128.5, 127.8, 126.3, 109.8, 79.6, 77.2, 73.7, 70.9, 36.8, 27.3, 27.2; MS $[M+Na]^+$ 367; HRMS (ESI) *m/z* calcd for $C_{20}H_{24}O_3SNa$ 367.1349. Found: 367.1343.

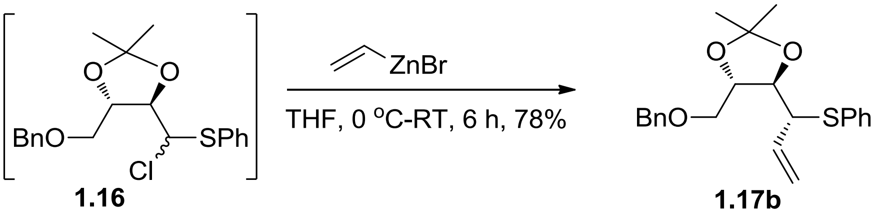
Preparation of propargylic sulfide 1.17



To a solution of sulfide **1.15** (172 mg, 0.5 mmol) in anhydrous benzene (5 mL) was added *N*-chlorosuccinimide (NCS, 75 mg, 0.55 mmol) at rt and stirred for 45 min at the same temperature. Stirring was discontinued and the clear supernatant solution of chloro sulfide **1.16** was siphoned using a syringe and used in the next step. The yield of the chloro sulfide was assumed to be quantitative.

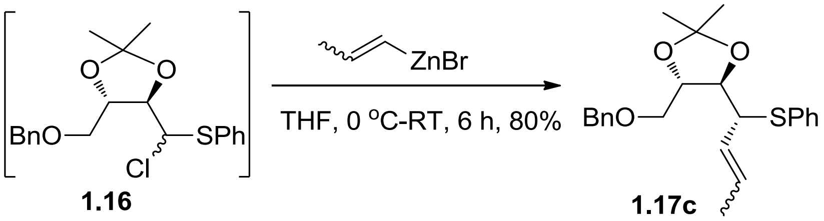
To a solution of 1-octyne (165 mg, 1.5 mmol) in dry THF (0.8 mL) cooled at -10 °C was added *i*-PrMgCl.LiCl (1 mL, 1.5 mmol, 1.5 M in THF) and stirred for 30 min at the same temperature. To the so generated alkynyl Grignard reagent, $ZnBr_2$ (1.1 mL, 1.65 mmol, 1.5 M in THF) was added at 0 °C and stirred for 30 min. To the organozinc reagent maintained at 0 °C was added a solution of chloro sulfide **1.16** (0.5 mmol) in benzene (5 mL) and the reaction mixture was stirred gradually allowing it to attain rt. The reaction mixture was stirred further for a period of 6 h until the TLC indicated complete consumption of the chloro sulfide. The reaction mixture was cooled to 0 °C, quenched by the addition of an aq saturated NH_4Cl solution (5 mL), allowed to warm to rt and diluted with ether. The layers were separated and the aq layer was extracted with ether (3×15 mL). The combined organic layers were washed with water (5 mL), brine (5 mL), dried over Na_2SO_4 and the solvent evaporated under reduced pressure to afford a crude compound which was purified by column chromatography using 2% EtOAc/Hexanes (v/v) as the eluent to afford the pure product **1.17a** as a viscous oil (171 mg, 0.38 mmol) in 76% yield; TLC, R*f* 0.67 (5% EtOAc/Hexanes); IR (KBr) 2927, 2856, 1742, 1683, 1581, 1457, 1373, 1242, 1214, 1084, 860, 738, 694 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.48-7.42 (m, 2H), 7.30-7.20 (m, 8H), 4.57 (s, 2H), 4.25 (ddd, *J* = 8.4, 5.4, 2.8 Hz, 1H), 3.95 (dd, *J* = 10.0, 6.0 Hz, 1H), 3.75 (dd, *J* = 10.5, 2.8 Hz, 1H), 3.62-3.59 (m, 2H), 2.08 (dt, *J* = 10.1, 1.8 Hz, 2H), 1.43 (s, 3H), 1.40 (s, 3H), 1.30-1.20 (m, 8H), 0.90 (t, *J* = 6.9, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 138.1, 133.1, 132.4, 128.7, 128.3, 127.7, 127.6, 127.5, 110.0, 87.6, 79.1, 78.0, 75.6, 73.4, 71.3, 42.6, 31.3, 28.5, 28.4, 27.3, 27.2, 27.1, 22.5, 14.0; MS [M+Na]$^+$ 475; HRMS (ESI) *m/z* calcd for $C_{28}H_{36}O_3SNa$ 475.2289. Found: 475.2282.

Preparation of allylic sulfide 1.17b



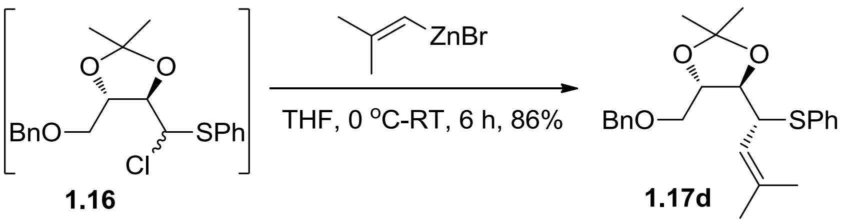
Following the general procedure detailed above, the chloro sulfide **1.16** (0.5 mmol) was reacted with the organozinc reagent, prepared from vinylmagnesium bromide (1.5 mmol), at rt (6 h) to afford the crude product which was purified by column chromatography using 2% EtOAc/Hexanes (v/v) as the eluent to furnish the pure product **1.17b** as a viscous oil (144 mg 0.39 mmol) in 78% yield; TLC, R*f* 0.56 (5% EtOAc/Hexanes); $[\alpha]^{25}_{D}$ -30.1 (*c* 1, MeOH); IR (KBr) 3061, 2986, 2926, 2859, 1758, 1716, 1634, 1581, 1476, 1447, 1373, 1242, 1214, 1163, 1089, 916, 740 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 7.37-7.17 (m, 10H), 5.80 (ddd, *J* = 16.9, 10.2, 8.8 Hz, 1H), 4.96 (d, *J* = 10.2 Hz, 1H), 4.94 (d, *J* = 16.8 Hz, 1H), 4.55 (s, 2H), 4.30-4.21 (m, 1H), 4.05 (dd, *J* = 7.3, 4.4 Hz, 1H), 3.72 (dd, *J* = 8.8, 4.4 Hz, 1H), 3.60 (d, *J* = 5.1 Hz, 2H), 1.47 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 135.2, 134.1, 132.8, 129.2, 128.7, 128.3, 127.6, 127.2, 117.2, 109.8, 79.3, 77.9, 73.4, 70.6, 55.3, 27.1; MS $[M+Na]^+$ 393; HRMS (ESI) *m/z* calcd for $C_{22}H_{26}O_3SNa$ 393.1509 found: 393.1500.

Preparation of allylic sulfide 1.17c



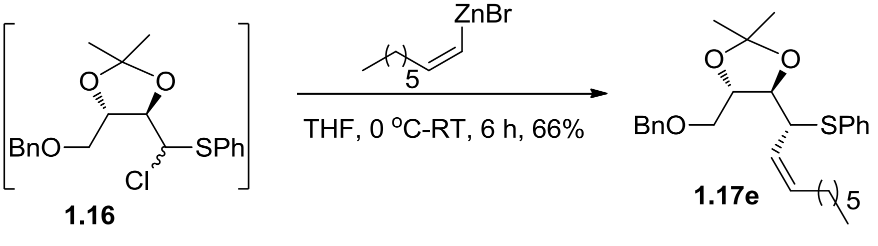
Following the general procedure, the chloro sulfide **1.16** (0.5 mmol) was reacted with 1-propenylzinc bromide (1.5 mmol), at rt (6 h) to afford the crude product which was purified by column chromatography using 2% EtOAc/Hexanes (v/v) as the eluent to furnish the pure product **1.17c** as a viscous oil (153 mg, 0.4 mmol) in 80% yield; TLC, R_f 0.53 (5% EtOAc/Hexanes); IR (KBr) 3061, 3026, 2985, 2926, 2860, 1758, 1716, 1582, 1448, 1371, 1216, 1089, 1026, 739 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.42-7.18 (m, 10H), 5.50-5.30 (m, 2H), 4.56 (s, 2H), 4.20 (ddd, *J* = 8.8, 7.3, 4.4 Hz, 1H), 4.10 (dd, *J* = 9.5, 5.1 Hz, 1H), 3.96 (dd, *J* = 7.3, 5.1 Hz, 1H), 3.60 (d, *J* = 4.4 Hz, 2H), 1.48 (s, 3H), 1.40 (s, 3H), 1.28 (d, *J* = 5.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 133.8, 133.0, 128.6, 128.3, 127.6, 127.5, 127.4, 126.9, 109.8, 79.8, 78.3, 73.4, 70.8, 49.1, 27.1, 12.8; MS $[M+Na]^+$ 407; HRMS (ESI) *m/z* calcd for $C_{23}H_{28}O_3SNa$ 407.1653 Found: 407.1656.

Preparation of allylic sulfide 1.17d



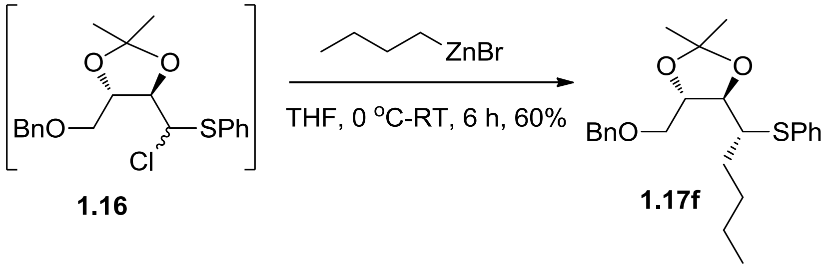
Following the general procedure, the chloro sulfide **1.16** (0.5 mmol) was reacted with the organozinc reagent prepared from 2-methyl-1-propenylmagnesium bromide (1.5 mmol), at rt (6 h) to afford the crude product which was purified by column chromatography using 2% EtOAc/Hexanes (v/v) as the eluent to furnish the pure product **1.17d** as a viscous oil (171 mg, 0.43 mmol) in 86% yield; TLC, R_f 0.54 (5% EtOAc/Hexanes); $[\alpha]^{25}_{D}$ -22.3 (*c* 1, MeOH); IR (KBr) 3061, 3030, 2985, 2931, 2862, 1721, 1666, 1583, 1496, 1478, 1453, 1373, 1242, 1214, 1165, 1089, 1026, 738, 695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.19 (m, 10H), 5.07 (d, *J* = 12.0 Hz, 1H), 4.54 (s, 2H), 4.15 (td, *J* = 9.8, 4.5 Hz, 1H), 3.97 (dd, *J* = 9.8, 5.2 Hz, 1H), 3.92 (dd, *J* = 12.0, 5.2 Hz, 1H), 3.57-3.55 (m, 2H), 1.59 (s, 3H), 1.44 (s, 3H), 1.39 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 135.7, 134.1, 132.2, 128.9, 128.4, 128.3, 127.6, 127.4, 121.7, 109.7, 79.8, 78.5, 73.3, 70.7, 50.7, 27.1, 27.0, 25.4, 17.9; MS $[M+Na]^+$ 421; HRMS (ESI) *m/z* calcd for $C_{24}H_{30}O_3SNa$ 421.1802. Found: 421.1813.

Preparation of allylic sulfide 1.17e



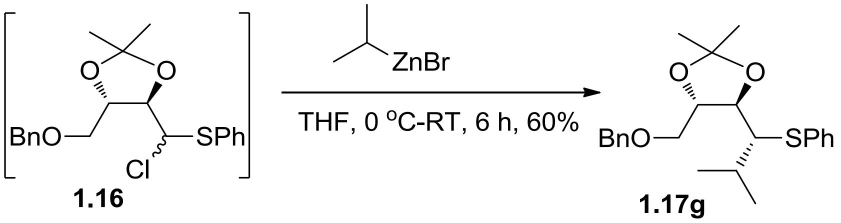
Following the general procedure, the chloro sulfide **1.16** (2.0 mmol) was reacted with the organozinc reagent which is prepared from (*Z*)-1-iodo-1-octenylmagnesium iodide at rt (10 h) to afford the crude product which was purified by column chromatography using 2% EtOAc/Hexanes (v/v) as the eluent to furnish the pure product **1.17e** as a viscous oil (599 mg, 1.32 mmol) in 66% yield; TLC, R_f 0.62 (5% EtOAc/Hexanes); $[\alpha]^{25}_{D}$ +15.5 (*c* 1, MeOH); IR (KBr) 3062, 2985, 2926, 2856, 1582, 1457, 1438, 1373, 1241, 1216, 1166, 1091, 1027, 740, 695 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.4-7.08 (m, 10H), 5.4-5.22 (m, 2H), 4.53 (s, 2H), 4.17 (dt, *J* = 9.0, 5.2 Hz, 1H), 4.05 (dd, *J* = 9.8, 5.2 Hz 1H), 3.93 (dd, *J* = 8.3, 5.2 Hz, 1H), 3.58 (d, *J* = 5.2 Hz, 2H), 1.78-1.5 (m, 2H), 1.44 (s, 3H), 1.38 (s, 3H), 1.36-0.9 (m, 8H), 0.85 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 134.4, 134.0, 133.0, 128.6, 128.3, 127.6, 127.5, 127.2, 126.4, 109.7, 79.8, 78.3, 73.4, 70.8, 49.8, 31.6, 29.2, 28.9, 27.5, 27.1, 22.5, 14.0; MS $[M+Na]^+$ 477; HRMS (ESI) *m/z* calcd for $C_{28}H_{38}O_3SNa$ 477.2464. Found: 477.2439.

Preparation of sulfide 1.17f



Following the general procedure, the chloro sulfide **1.16** (2.0 mmol) was reacted with the organozinc reagent prepared from *n*-butylmagnesium bromide (6 mmol), at rt (10 h) to afford the crude product which was purified by column chromatography using 2% EtOAc/Hexanes (v/v) as the eluent to furnish the pure product **1.17f** as a viscous oil (480 mg, 1.2 mmol) in 60% yield; TLC, R_f 0.53 (5% EtOAc/Hexanes); $[\alpha]^{25}_{D}$ -12.5 (*c* 1, MeOH); IR (KBr) 3063, 2927, 2861, 1637, 1452, 1372, 1218, 1082, 1026, 771, 741, 695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.10 (m, 10H), 4.52 (s, 2H), 4.29 (dt, *J* = 8.1, 5.0 Hz, 1H), 4.05 (dd, *J* = 8.1, 2.6 Hz, 1H), 3.64-3.62 (m, 2H), 3.18 (dt, *J* = 5.0, 2.6 Hz, 1H), 1.90-1.78 (m, 2H), 1.70-1.50 (m, 2H), 1.43 (s, 3H), 1.35 (s, 3H), 1.30-1.24 (m, 2H), 0.87 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.3, 132.5, 131.1, 128.9, 128.4, 127.9, 127.7, 126.5, 109.4, 80.1, 77.2, 73.5, 71.3, 50.7, 32.4, 29.6, 27.2, 27.1, 22.5, 14.0; MS $[M+Na]^+$ 423; HRMS (ESI) *m/z* calcd for $C_{24}H_{32}O_3SNa$ 423.1989. Found: 423.1969.

Preparation of sulfide 1.17g



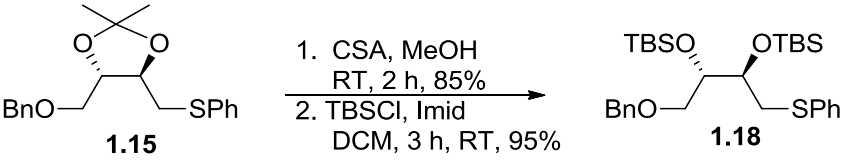
1.16

1.17g

Following the general procedure, the chloro sulfide **1.16** (2.0 mmol) was reacted with the organozinc reagent prepared from *iso*-propylmagnesium chloride (6 mmol), at rt (10 h) to afford the crude product which was purified by column chromatography using 2% EtOAc/Hexanes (v/v) as the eluent to furnish the pure product **1.17g** as a viscous oil (463 mg, 1.2 mmol) in 60% yield; TLC, R_f 0.52 (5% EtOAc/Hexanes); $[\alpha]^{25}_{D}$ -8.0 (*c* 1, MeOH); IR (KBr) 2958, 2925, 2865, 1636, 1458, 1372, 1218, 1080, 770, 740 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.23 (m, 8H), 7.15-7.05 (m, 2H), 4.51 (s, 2H), 4.34-4.32 (m, 1H), 4.12 (dd, *J* = 8.1, 1.3 Hz, 1H), 3.66 (dd, *J* = 9.8, 4.5 Hz, 1H), 3.52 (dd, *J* = 9.8, 5.8 Hz, 1H), 3.11 (dd, *J* = 5.2, 1.5 Hz, 1H), 2.10-1.98 (m, 1H), 1.44 (s, 3H), 1.36 (s, 3H), 1.05 (d, *J* = 4.7

Hz, 3H), 1.01 (d, *J* = 4.7 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.8, 130.5, 129.0, 128.7, 128.3, 127.7, 127.6, 126.0, 109.3, 79.4, 77.5, 73.4, 70.6, 58.0, 29.6, 27.1, 26.8, 20.4, 20.3; MS $[M+Na]^+$ 409; HRMS (ESI) *m/z* calcd for $C_{20}H_{30}O_3SNa$ 409.1815. Found: 409.1813.

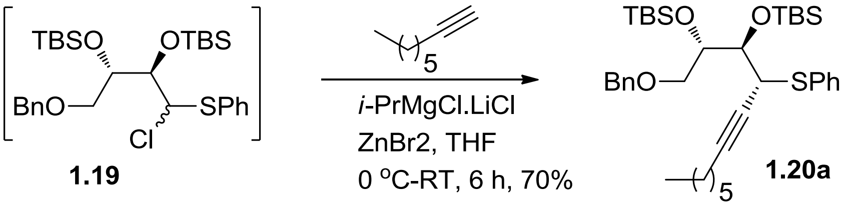
Preparation of sulfide 1.18



To the solution of sulfide **1.15** (1.7 g, 5 mmol) in MeOH (10 mL) was added CSA (58 mg, 0.25 mmol) at 0 °C and gradually allowed to attain rt and stirred for 3 h. The solvent was evaporated under reduced pressure and the crude diol was purified by column chromatography using 20% EtOAc/Hexanes (v/v) as the eluent to afford the pure product as a viscous colorless oil in 85% yield. To the solution of the above diol (1.29 g, 4.25 mmol) in dry DCM (12 mL) cooled to 0 °C, imidazole (693 mg, 10.2 mmol) and TBS-Cl (1.4 g 9.35 mmol) were added and the mixture stirred for 4 h gradually allowing it to attain rt. The reaction mixture was diluted with water (40 mL) and the mixture extracted with DCM (3×25 mL). The combined organic layers were washed with water (5 mL), brine (5 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude sulfide **1.18** as a oil which was purified by column chromatography using hexanes as the eluent to afford the pure product **1.18** as a viscous colorless oil (2.1 g, 4.0 mmol) in 95% yield; TLC, R_f 0.35 (Hexanes); $[\alpha]^{30}_D$ -33.0 (*c* 1, MeOH); IR (KBr) 3064, 2953, 2929, 2890, 2856, 1583, 1470, 1364, 1253, 1108, 835, 776, 736 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.30 (m, 10H), 4.51 (d, *J* = 12 Hz, 1H), 4.49 (d, *J* = 15 Hz, 1H), 3.95

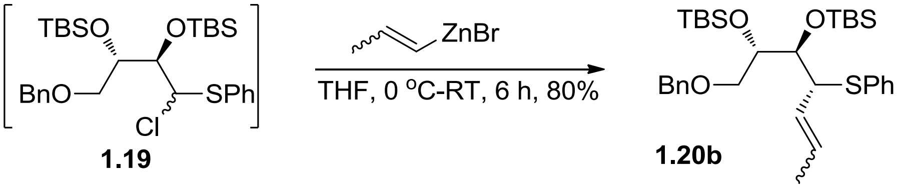
(td, *J* = 7.1, 3.3 Hz, 1H), 3.79 (td, *J* = 7.1, 3.7 Hz, 1H), 3.68 (dd, *J* = 9.6, 2.9 Hz, 1H), 3.42 (dd, *J* = 9.5, 7.4 Hz, 1H), 3.35 (dd, *J* = 13.6, 3.5 Hz, 1H), 2.71 (dd, *J* = 13.7, 8.6 Hz, 1H), 0.89 (s, 9H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 136.8, 128.7, 128.6, 128.1, 127.3, 127.2, 125.5, 73.9, 73.2, 73.0, 71.0, 36.0, 25.9, 25.8, 18.2, 18.1, -4.2, -4.3, -4.6, - 4.7; MS $[M+Na]^+$ 555; HRMS (ESI) *m/z* calcd for $C_{29}H_{48}O_3Si_2SNa$ 555.2769 Found: 555.2760.

Preparation of propargylic sulfide 1.20a



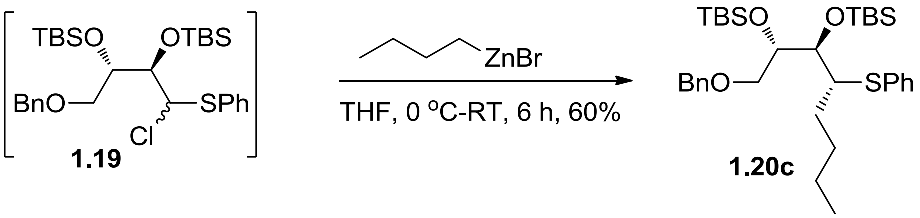
Following the general procedure, α-chloro sulfide **1.19** (0.5 mmol) was prepared and reacted with organozinc reagent (1.5 mmol), prepared from 1-octyne to afford the crude compound which was purified by column chromatography using hexanes as the eluent to afford the pure product **1.20a** as a viscous colorless oil (224 mg, 0.35 mmol) in 70% yield; TLC, R_f 0.45 (Hexanes); $[\alpha]^{30}_D$ -76 (*c* 1, MeOH); IR (KBr) 2953, 2929, 2856, 1589, 1520, 1467, 1365, 1251, 1218, 1112, 1025, 835, 773, 740 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.20 (m, 10H), 4.56 (s, 2H), 4.23 (dt, *J* = 5.1, 3.5 Hz, 1H), 4.17 (dt, *J* = 7.1, 3.5 Hz, 1H), 4.07 (dd, *J* = 4.9, 3.5 Hz, 1H), 3.85 (dd, *J* = 9.8, 3.5 Hz, 1H), 3.63 (dd, *J* = 9.8, 7.1 Hz, 1H), 2.17 (dt, *J* = 6.9, 2.2 Hz, 2H), 1.50-1.20 (m, 8H), 0.97 (s, 9H), 0.94 (s, 9H), 0.2 (s, 3H), 0.16 (s, 3H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 136.1, 131.1, 128.5, 128.2, 127.5, 127.3, 126.3, 85.3, 79.8, 76.6, 74.0, 73.1, 71.9, 42.2, 31.3, 28.5, 28.4, 26.0, 25.9, 25.8, 22.5, 18.9, 18.4, 14.1, -3.8, -4.3, -4.4, -4.9; MS [M+Na]$^+$ 663; HRMS (ESI) *m/z* calcd for $C_{37}H_{60}O_3Si_2SNa$ 663.3721 Found: 663.3699.

Preparation of allylic sulfide 1.20b



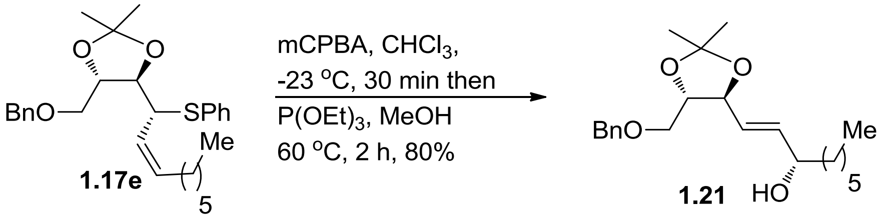
Following the general procedure, the α-chloro sulfide **1.19** (0.5 mmol) was reacted with the organozinc reagent prepared from 1-propenylmagnesium bromide (1.5 mmol), at rt (6 h) to afford the crude product which was purified by column chromatography using hexanes as the eluent to furnish the pure product **1.20b** as a viscous oil (228 mg, 0.4 mmol) in 80% yield; TLC, R_f 0.44 (Hexanes); IR (KBr) 3027, 2953, 2929, 2856, 1584, 1468, 1364, 1253, 1110, 1006, 834, 774, 742 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.10 (m, 10H), 5.59-5.41 (m, 1H), 5.30-5.20 (m, 1H), 4.52 (s, 2H), 4.19 (dd, *J* = 10.5, 3.0 Hz, 1H), 3.89 (dd, *J* = 9.8, 1.5 Hz, 1H), 3.85-3.78 (m, 2H), 3.70 (dd, *J* = 9.8, 8.3 Hz, 1H), 1.09 (dd, *J* = 6.7, 1.5 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H), 0.07 (s, 3H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8, 135.7, 133.5, 132.1, 128.5, 128.2, 127.5, 127.2, 125.7, 122.9, 76.9, 75.6, 73.1, 72.1, 54.4, 29.7, 25.8, 17.5, 12.6, -4.2, -4.5, -4.8, -4.9; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.10 (m, 10H), 5.59-5.41 (m, 1H), 5.13-5.02 (m, 1H), 4.49 (s, 2H), 3.97-3.93 (m, 1H), 3.85-3.83 (m, 2H), 3.75 (dd, *J* = 9.8, 5.2 Hz, 1H), 3.64 (dd, *J* = 9.8, 8.3 Hz, 1H), 1.55 (dd, *J* = 6.7, 1.5 Hz, 3H), 0.92 (s, 9H), 0.91 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.3, 131.3, 131.1, 128.4, 128.2, 127.5, 127.2, 126.9, 125.7, 122.9, 76.9, 75.1, 73.1, 72.0, 49.0, 29.7, 25.9, 17.5, 12.6, -4.2, -4.4, -4.8, -4.9; MS $[M+Na]^+$ 595; HRMS (ESI) *m/z* calcd for $C_{32}H_{52}O_3Si_2SNa$ 595.3057. Found: 595.3073.

Preparation of sulfide 1.20c



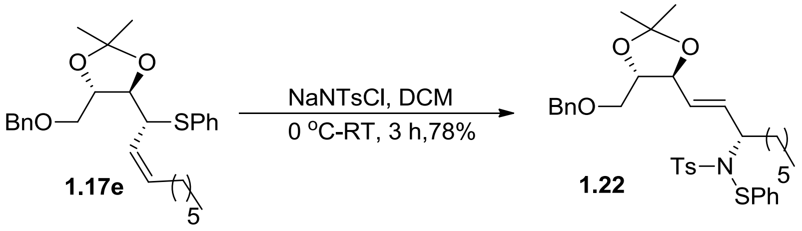
Following the general procedure, the chloro sulfide **1.19** (0.5 mmol) was reacted with the butylzinc bromide (1.5 mmol), at rt (6 h) to afford the crude product which was purified by using hexanes as the eluent to furnish the pure product **1.20c** as a viscous oil (706 mg, 0.3 mmol) in 60% yield; TLC, R_f 0.42 (Hexanes); $[\alpha]^{30}_D$ +7.6 (*c* 1, MeOH); IR (KBr) 2925, 2854, 1734, 1639, 1462, 1373, 1253, 1093, 1018, 834, 774, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.10 (m, 10H), 4.46 (d, *J* = 16.6 Hz, 1H), 4.45 (d, *J* = 12.0 Hz, 1H), 4.03 (ddd, *J* = 7.9, 4.9, 2.2 Hz, 1H), 3.90 (dd, *J* = 10.0, 2.2 Hz, 1H), 3.87 (dd, *J* = 4.9, 2.0 Hz, 1H) 3.65 (dd, *J* = 10.0, 7.9 Hz, 1H), 3.45 (td, *J* = 7.5, 1.8 Hz, 1H), 1.32-1.22 (m, 6H) 0.9-0.85 (s, 21H), 0.08 (s, 3H), 0.07 (s, 3H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.0, 138.0, 130.0, 129.0, 128.1, 127.2, 127.5, 125.5, 75.0, 74.7, 73.0, 72.1, 50.4, 35.0, 29.7, 29.3, 25.3, 22.4, 18.1, 18.0, 13.9, -4.2, -4.3, -4.7, -4.8; MS $[M+Na]^+$ 611; HRMS (ESI) *m/z* calcd for $C_{33}H_{56}O_3Si_2SNa$ 611.3408. Found: 611.3386.

Preparation of allylic alcohol 1.21



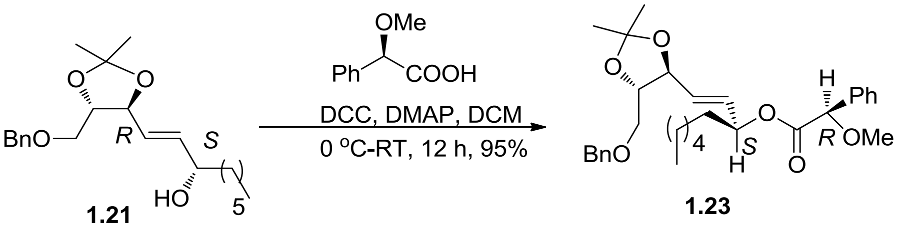
To a solution of **1.17e** (45 mg, 0.1 mmol) in DCM (1 mL) cooled at -23 °C was added *m*-CPBA (25 mg, 0.11 mmol) and the reaction mixture stirred at the same temperature for another 1 h. Methanol (0.5 mL) and triethylphosphite (0.16 mL, 1 mmol) were added. The temperature was raised to 60° C and stirring continued for 1 h. The reaction was quenched by adding aqueous saturated $NaHCO_3$ (0.5 mL). The mixture was diluted with DCM (4 mL) and the layers were separated. The organic layer was washed successively with water (1 mL), brine (1 mL), dried over Na_2SO_4 and the solvent evaporated under reduced pressure to furnish the crude compound which was purified by column chromatography using 5% EtOAc/Hexanes (v/v) as the eluent to afford the product **1.21** (29 mg, 0.08 mmol) in 80% yield as a liquid. TLC, R_f 0.32 (15% EtOAc/Hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35-7.25 (m, 5H), 5.75 (dd, *J* = 15.8, 6.0 Hz, 1H), 5.62 (dd, *J* = 15.8, 6.0 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.57 (d, *J* = 15.8 Hz, 1H), 4.22 (dd, *J* = 8.3, 6.0 Hz, 1H), 4.07 (dt, *J* = 8.3, 6.0 Hz, 1H), 3.80-3.87 (m, 1H), 3.56 (d, *J* = 3.5 Hz 2H), 1.50-1.20 (m, 16H), 0.90 (t, *J* = 6.0 Hz, 3H).

Preparation of allyl amino derivative 1.22



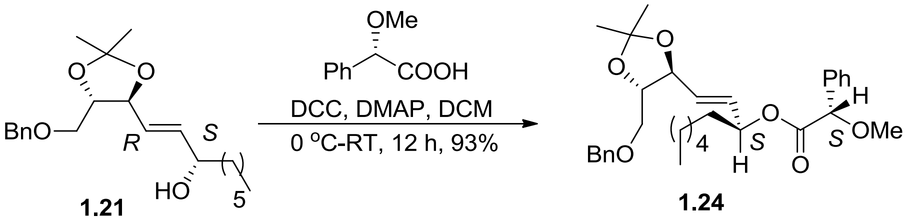
To a solution of **1.17e** (36 mg, 0.1 mmol) in DCM (1 mL) maintained at rt was added anhydrous chloramine-T (28 mg, 0.12 mmol) and the mixture stirred for 3 h. The solvent was removed under reduced pressure and the residue purified by column chromatography using 5% EtOAc/Hexanes (v/v) as the eluent to furnish the product **1.22** (48 mg, 0.078 mmol) in 78% yield as a liquid. TLC, R$_f$ 0.31 (5% EtOAc/Hexanes); ^{1}H NMR (CDCl$_3$, 300 MHz) 7.70 (d, *J* = 8.3 Hz, 2H), 7.30-7.14 (m, 12H), 5.50-5.42 (m, 2H), 4.52-4.45 (m, 3H), 3.95 (dd, *J* = 8.1, 6.4 Hz, 1H), 3.45-3.37 (m, 1H), 3.33 (dd, *J* = 10.6, 3.1 Hz, 1H), 3.22 (dd, *J* = 10.6, 5.1 Hz, 1H), 2.32 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H), 1.22-1.17 (m, 10H), 0.75 (t, *J* = 6.9 Hz, 3H).

Preparation of Mandelate ester 1.23



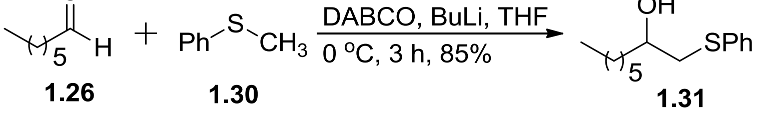
To a solution of **1.21** (36 mg, 0.1 mmol) in DCM (0.4 mL) cooled at 0 ° C was added DCC (30 mg, 0.15 mmol), DMAP (1.2 mg), and (*R*)-methoxymandelic acid (20 mg, 0.12 mmol). The reaction mixture was gradually allowed to attain rt and stirred at the same temperature overnight. The solvent was evaporated under reduced pressure to furnish the crude compound which was purified by column chromatography using 5% EtOAc/Hexanes (v/v) as the eluent to afford the product **1.23** (40 mg, 0.08 mmol) in 80% yield as a liquid. TLC, R$_f$ 0.32 (15% EtOAc/Hexanes); ^{1}H NMR (CDCl$_3$, 200 MHz) δ 7.40-7.20 (m, 10H), 5.59 (m, 1H), 5.19 (dd, *J* = 15.2, 5.1 Hz, 1H), 4.61 (s, 1H), 4.51 (d, *J* = 11.7 Hz, 1H), 4.49 (d, *J* = 15.3 Hz, 1H), 4.16 (td, *J* = 4.4, 2.2 Hz, 1H), 3.78-3.68 (m, 1H), 3.48-3.42 (m, 2H), 3.31 (s, 3H), 1.47-1.37 (m, 2H), 1.35 (s, 3H), 1.33 (s, 3H), 1.28-1.00 (m, 8H), 0.77 (t, *J* = 6.5 Hz, 3H).

Preparation of mandelate ester 1.24



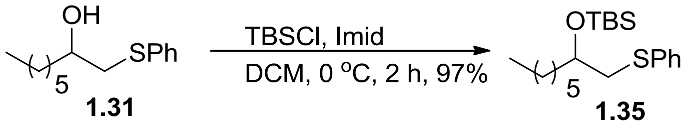
The ester **1.24** was prepared following the procedure detailed for the preparation of **1.23**. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.40-7.20 (m, 10H), 5.46 (dd, *J* = 15.1, 6.0 Hz, 1H), 5.23 (dd, *J* = 15.1, 6.0 Hz, 1H), 4.64 (s, 1H), 4.47 (d, *J* = 12.0 Hz, 1H), 4.45 (d, *J* = 19.6 Hz, 1H) 4.03 (dd, *J* = 8.3, 6.0 Hz, 1H), 3.32 (s, 3H), 3.60-3.55 (m, 1H), 3.40-3.24 (m, 2H), 1.54-1.44 (m, 2H), 1.32 (s, 3H), 1.28 (s, 3H), 1.22-1.12 (m, 8H), 0.81 (t, *J* = 6.7 Hz, 3H).

Preparation of alcohol 1.31



To a solution of thioanisole **1.30** (1.2 mL, 10 mmol), DABCO (1.1 g, 10 mmol) in dry THF (16 mL) was added *n*-BuLi (7.3 mL, 1.5 M in Hexanes, 11 mmol) at 0 °C and gradually allowed to warm to rt and stirred for 2 h. The reaction mixture was cooled to 0 °C, the solution of heptaldehyde **1.26** (1.4 mL, 10 mmol) in THF (10 mL) was added and stirred at the same temperature for 1 h. The reaction mixture was quenched with aq. NH_4Cl, the layers were separated and aqueous layer was extracted with EtOAc (3x10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography using 10% EtOAc/Hexanes (v/v) as the eluent to afford the product **1.31** (2.0 g, 8.5 mmol) in 85% yield as a colourles oil. TLC, R_f 0.32 (10% EtOAc/Hexanes); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.32 (d, J = 7.1 Hz, 2H), 7.24 (t, J = 7.1 Hz, 2H), 7.16 (t, J = 7.1 Hz, 1H), 3.64-3.56 (m, 1H), 3.06 (dd, J = 13.5, 3.3 Hz, 1H), 2.80 (dd, J = 13.5, 8.6 Hz, 1H), 1.49-1.40 (m, 2H), 1.36-1.22 (m, 8H), 0.87 (t, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.8, 128.9, 128.3, 125.5, 69.2, 41.0, 35.7, 31.4, 28.9, 25.2, 22.2, 13.7; MS $[M]^+$ 238.

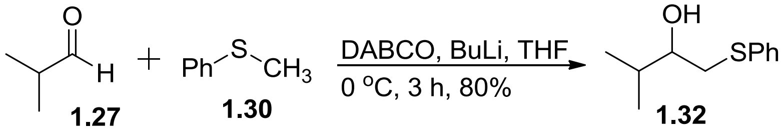
Preparation of sulfide 1.35



To a solution of the alcohol **1.31** (2.0 g, 8.5 mmol) in dry DCM (34 mL) maintained at 0 °C was added imidazole (867 mg, 12.7 mmol) followed by TBS-Cl (1.4 g, 9.35 mmol) and the mixture stirred for a period of 2 h. The reaction mixture was diluted with DCM (30 mL), washed successively with water (10 mL), brine (10 mL), dried over Na_2SO_4 and the solvent evaporated under reduced pressure to yield the crude product which was purified by column chromatography using hexanes to furnish the product **1.35** (2.9 g, 8.2 mmol) in

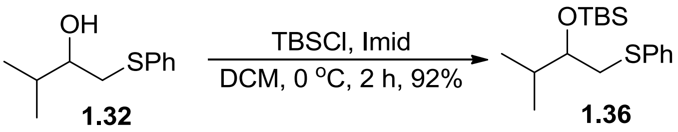
97% yield as a liquid. TLC, R$_f$ 0.81 (Hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.28 (d, *J* = 7.8 Hz, 2H), 7.19 (t, *J* = 7.8 Hz, 2H), 7.08 (t, *J* = 7.8 Hz, 1H), 3.77 (m, 1H), 2.95 (dd, *J* = 13.6, 5.8 Hz, 1H), 2.90 (dd, *J* = 12.6, 5.8 Hz, 1H), 1.71-1.62 (m, 1H), 1.51-1.44 (m, 1H), 1.32-1.24 (m, 8H), 0.91-0.86 (bs, 12H), 0.03 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.3, 129.3, 128.6, 125.7, 71.4, 40.9, 36.4, 31.9, 29.4, 25.9, 25.8, 22.8, 18.1, 14.2, -4.3, -4.5; MS $[M+O+H]^+$ 369.

Preparation of alcohol 1.32



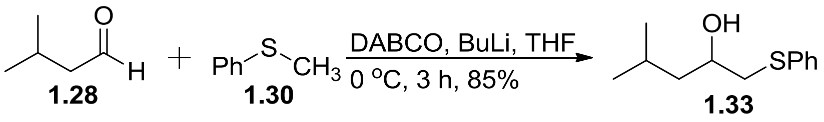
Following the procedure detailed for the preparation of **1.31**, thioanisole (10 mmol) furnished **1.32** (1.5 g, 8.0 mmol) in 80% yield as a liquid. TLC, R$_f$ 0.35 (10% EtOAc/Hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (d, *J* = 7.8 Hz, 2H), 7.28 (t, *J* = 7.8 Hz, 2H), 7.18 (d, *J* = 7.8 Hz, 1H), 3.40-3.34 (m, 1H), 3.15 (dd, *J* = 13.6, 2.9 Hz, 1H), 2.80 (dd, *J* = 13.6, 5.8 Hz, 1H), 2.32 (s, 1H), 1.79-1.72 (m, 1H), 0.95 (d, *J* = 7.8 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.5, 130.1, 129.2, 126.7, 73.9, 40.0, 34.0, 17.8, 17.2; MS $[M+Na]^+$ 235; HRMS (ESI) *m/z* calcd for $C_{11}H_{16}O_2SNa$ 235.0763. Found: 235.0756.

Preparation of sulfide 1.36



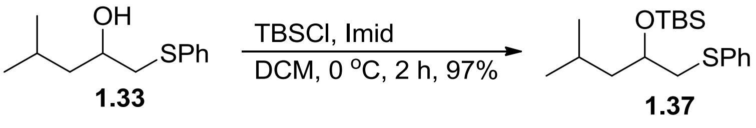
Following the procedure detailed for the preparation of **1.18**, the alcohol **1.32** (1.5 g, 7.9 mmol) furnished the product **1.36** (2.2 g, 7.3 mmol) in 92% yield as a liquid. TLC, R_f 0.81 (Hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.24 (d, *J* = 7.5 Hz, 2H), 7.28 (t, *J* = 7.5 Hz, 2H), 7.18 (t, *J* = 7.5 Hz, 1H), 3.45-3.44 (m, 1H), 3.14 (dd, *J* = 9.2, 3.1 Hz, 1H), 2.80 (dd, *J* = 9.2, 3.1 Hz, 1H), 1.81-1.67 (m, 1H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.79 (d, *J* = 6.7 Hz, 3H), 0.06 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.4, 129.2, 128.9, 125.9, 75.6, 38.1, 32.5 26.0, 25.8, 18.9, 16.4, -4.0, -4.5; MS $[M+O_2+NH_4]^+$ 362.

Preparation of alcohol 1.33



Following the general procedure thioanisole (10 mmol) furnished the product **1.33** (1.7 g, 8.5 mmol) in 85% yield as a liquid. TLC, R_f 0.39 (EtOAc/Hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34 (d, *J* = 7.9 Hz, 2H), 7.25 (t, *J* = 7.9 Hz, 2H), 7.16 (t, *J* = 7.9 Hz, 1H), 3.74-3.65 (m, 1H), 3.06 (dd, *J* = 13.4, 3.5, Hz, 1H), 2.80 (dd, *J* = 13.4, 8.4, Hz, 1H), 2.32 (s, 1H), 1.85-1.72 (m, 1H), 1.31-1.24 (m, 2H) 0.95-0.85 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.0, 129.6, 128.9, 126.2, 67.7, 45.3, 24.7, 23.4, 22.1, 14.2; MS $[M+NH_4]^+$ 234.

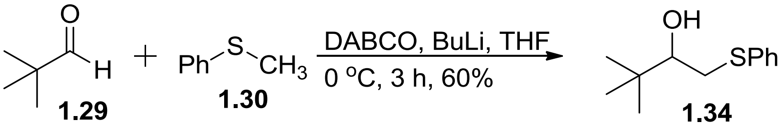
Preparation of sulfide 1.37



Following the procedure detailed for the preparation of **1.18**, the alcohol **1.32** (2.8 g, 8.9 mmol) furnished the product **1.37** (2.6 g, 8.2 mmol) in 92% yield as a liquid. TLC, R_f

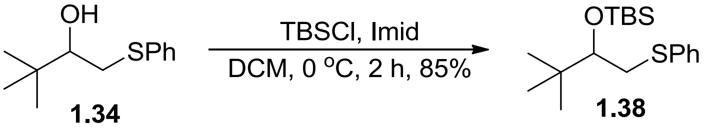
0.82 (Hexanes); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.31 (d, *J* = 7.9 Hz, 2H), 7.22 (t, *J* = 7.9 Hz, 2H), 7.12 (t, *J* = 7.9 Hz, 1H), 3.85-3.79 (m, 1H), 2.97 (dd, *J* = 12.8, 4.9, Hz, 1H), 2.89 (dd, *J* = 12.8, 6.9, Hz, 1H), 1.75-1.65 (m, 1H), 1.55-1.48 (m, 2H) 0.95-0.82 (m, 15H), 0.04 (s, 3H, 0.03 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 137.2, 129.7, 128.8, 126.0, 69.9, 46.1, 27.4, 26.1, 24.5, 23.7, 22.5, 18.4, -4.0, -4.4; [M+O+H]$^+$ 341.

Preparation of alcohol 1.34



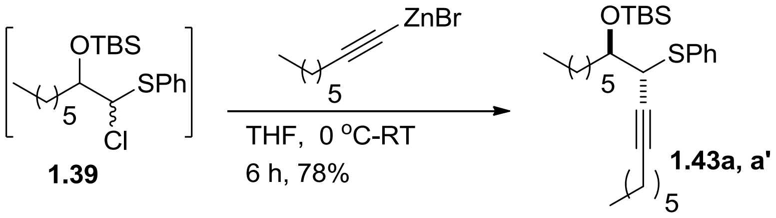
Following the general procedure thioanisole (10 mmol) furnished the product **1.34** (1.2 g, 6.0 mmol) in 60% yield as a liquid. TLC, R$_f$ 0.35 (10% EtOAc/Hexanes); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.34 (d, *J* = 7.4 Hz, 2H), 7.26 (t, *J* = 7.4 Hz, 2H), 7.17 (t, *J* = 7.4 Hz, 1H), 3.25 (dd, *J* = 11.7, 1.9 Hz, 1H), 3.22 (dd, *J* = 13.6, 1.9 Hz, 1H), 2.70 (dd, *J* = 13.6, 11.7 Hz, 1H), 0.90 (bs, 9H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 135.3, 129.8, 129.0, 126.5, 76.3, 38.0, 34.7, 25.9; MS [M+O+Na]$^+$ 249; HRMS (ESI) *m/z* calcd for $C_{12}H_{18}O_2SNa$ 249.0919. Found: 249.0931.

Preparation of sulfide 1.38



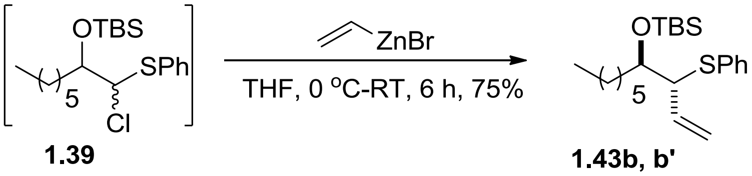
Following the procedure detailed for the preparation of **1.18**, the alcohol **1.32** (1.1 g, 5.6 mmol) furnished the product **1.38** (1.5 g, 4.8 mmol) in 85% yield as a liquid. TLC, R$_f$ 0.86 (Hexanes); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.38 (d, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.22 (t, *J* = 7.5 Hz, 1H), 3.54 (dd, *J* = 6.5, 3.1 Hz, 1H), 3.31 (dd, *J* = 13.0, 3.1 Hz, 1H), 2.86 (dd, *J* = 13.0, 6.5 Hz, 1H), 1.01 (bs, 9H), 0.97 (bs, 9H), 0.12 (s, 6H); MS $[M+H]^+$ 325.

Preparation of propargylic sulfide 1.43a, a'



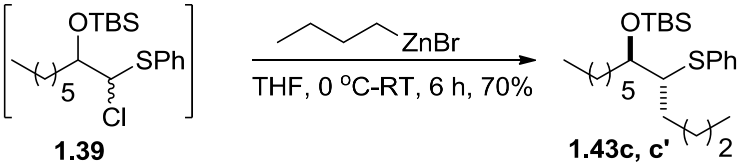
Following the general procedure, the α-chloro sulfide **1.39** (0.5 mmol) was reacted with the organozinc reagent prepared from 1-octyne (1.5 mmol) at rt (6 h) to afford the crude product which was purified by column chromatography using hexanes as the eluent to furnish the pure product **1.43a** (179 mg, 0.39 mmol) in 78% yield as a liquid. TLC, R_f 0.88 (Hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45 (d, *J* = 6.9 Hz, 2H), 7.30-7.18 (m, 3H), 3.87-3.82 (m, 1H), 3.73 (dt, *J* = 4.5, 2.2 Hz, 1H), 2.16 (dt, *J* = 6.7, 2.2 Hz, 2H), 1.78-1.69 (m, 2H), 1.50-1.20 (m, 16H), 0.92-0.87 (bs, 15H), 0.01 (s, 3H), 0.0 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.3, 132.1, 128.7, 127.1, 86.1, 77.5, 74.0, 46.3, 33.6, 31.8, 31.3, 29.3, 28.6, 28.4, 25.8, 25.1, 22.6, 22.5, 18.9, 18.1, 14.1, 14.0, -4.5,-4.6; MS $[M+Na]^+$ 483.

Preparation of allylic sulfide 1.43b, b'



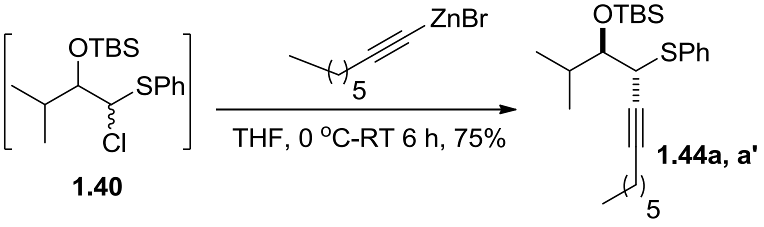
Following the general procedure the α-chloro sulfide **1.39** (0.5 mmol) was reacted with vinylzinc bromide (1.5 mmol) at rt (6 h) to afford the crude product which was purified by column chromatography using hexanes as the eluent to furnish the pure product **1.43b** (141 mg, 0.37 mmol) in 75% yield as a liquid. TLC, R_f 0.84 (Hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40 (d, *J* = 6.9 Hz, 2H), 7.30-7.16 (m, 3H), 5.90 (ddd *J* = 17.0, 10.2, 8.5 Hz, 1H), 5.15-5.01 (m, 2H), 3.87-3.8 (m, 1H), 3.60 (dd, *J* = 8.5, 4.1 Hz, 1H), 1.82-1.60 (m, 2H), 1.30 (bs, 8H), 0.90 (bs, 12H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.7, 132.2, 129.5, 128.7, 126.8, 116.7, 74.5, 43.8, 33.6, 29.3, 25.9, 25.7, 25.6, 22.6, 18.2, 14.1, -3.6, -4.4; MS $[M+O+Na]^+$ 417.

Preparation of sulfide 1.43c, c'



Following the general procedure, the α-chloro sulfide **1.39** (0.5 mmol) was reacted with *n*-butylzinc bromide (1.5 mmol) at rt (6 h) to afford the crude product which was purified by column chromatography using hexanes as the eluent to furnish the pure product **1.43c, c'** (142 mg, 0.35 mmol) in 70% yield as a liquid. TLC, R_f 0.85 (Hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38 (d, *J* = 8.0 Hz, 2H), 7.24 (t, *J* = 8.0 Hz, 2H), 7.18 (t, *J* = 8.0 Hz, 1H), 3.69-3.64 (m, 1H), 3.12 (dt, *J* = 6.0, 3.0 Hz, 1H), 1.92-1.84 (m, 1H), 1.83-1.77 (m, 1H), 1.67-1.58 (m, 1H), 1.44-1.20 (m, 13H), 0.94-0.88 (m, 6H), 0.85 (s, 9H), -0.09 (s, 3H), -0.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.6, 132.0, 128.8, 126.7, 74.1, 55.7, 32.0, 31.5, 30.4, 29.8, 29.4, 28.7, 26.7, 26.0, 22.8, 18.0, 14.3, 14.2, -4.3, -4.4; MS $[M]^+$ 380.

Preparation of propargylic sulfide 1.44a, a'

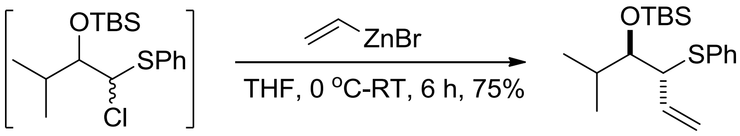


1.40

1.44a, a'

Following the general procedure, the α-chloro sulfide **1.40** (0.5 mmol) was reacted with the 1-octynylzinc bromide at rt (6 h) to afford the crude product which was purified by column chromatography using hexanes as the eluent to furnish the pure product **1.44a, a'** (156 mg, 0.37 mmol) in 75% yield as a liquid. TLC, R_f 0.85 (Hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46 (d, *J* = 7.5 Hz, 2H), 7.30-7.10 (m, 3H), 3.89 (dt, *J* = 4.9, 2.4 Hz, 1H), 3.62 (dd, *J* = 4.7, 2.4 Hz, 1H), 2.14 (td, *J* = 6.7, 2.2 Hz, 2H), 1.40-1.20 (m, 8H), 0.91-0.72 (m, 19H), 0.10 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.1, 131.9, 128.8, 126.9, 86.3, 79.3, 78.9, 45.7, 32.2, 31.5, 29.8, 28.7, 26.3, 22.7, 20.8, 19.1, 18.6, 17.5, 14.2, -3.6, -4.0; MS $[M+Na]^+$ 441.

Preparation of allylic sulfide 1.44b, b'

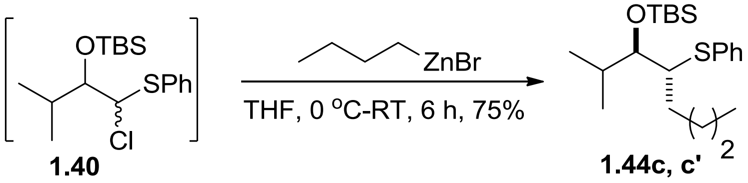


1.40

1.44b, b'

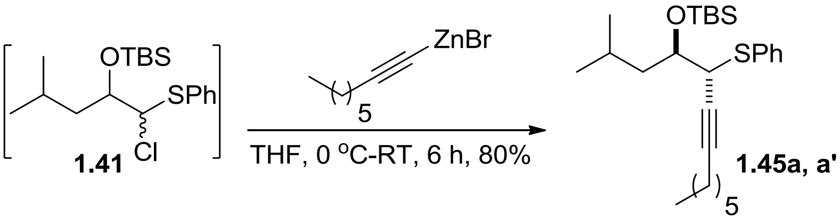
Following the general procedure, the α-chloro sulfide **1.40** (0.5 mmol) was reacted with vinylzinc bromide (1.5 mmol) at rt (6 h) to afford the crude product which was purified by column chromatography using hexanes as the eluent to furnish the pure product **1.44b, b'** (126 mg, 0.37 mmol) in 75% yield as a liquid. TLC, R_f 0.82 (Hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (d, *J* = 6.8 Hz, 2H), 7.27-7.16 (m, 3H), 5.86 (ddd, *J* = 16.6, 9.7, 8.7 Hz, 1H), 4.94 (d, *J* = 9.7 Hz, 1H), 4.86 (d, *J* = 16.6 Hz, 1H), 3.65 (dd, *J* = 8.7, 4.8 Hz, 1H), 3.59 (t, *J* = 4.8 Hz, 1H), 2.04 (m, 1H), 0.99-0.93 (m, 15H). 0.10 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.9, 135.4, 132.3, 128.5, 126.7, 115.6, 79.5, 59.0, 32.1, 29.8, 26.3, 20.7, 17.9, -3.5, -3.8.

Preparation of sulfide 1.44c, c'



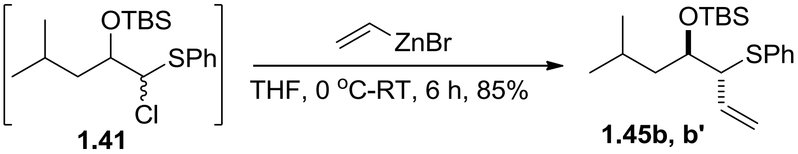
Following the general procedure, the α-chloro sulfide **1.40** (0.5 mmol) was reacted with the *n*-butylzinc bromide (1.5 mmol) at rt (6 h) to afford the crude product which was purified by column chromatography using hexanes as the eluent to furnish the pure product **1.44c, c'** (137 mg, 0.37 mmol) in 75% yield as a liquid. TLC, R_f 0.83 (Hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38 (d, *J* = 7.1 Hz, 2H), 7.30-7.18 (m, 3H), 3.56 (dd, *J*= 4.9, 3.2 Hz, 1H), 3.12-3.06 (m, 1H), 1.90-1.80 (m, 1H), 1.40-1.20 (m, 2H), 1.02-0.85 (m, 22H), -0.01(s, 3H), -0.03(s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.3, 131.2, 128.8, 126.2, 78.4, 55.4, 31.2, 30.4, 29.7, 26.0, 25.6, 22.6, 21.5, 19.0, 14.0, -4.1, -4.2.

Preparation of propargylic sulfide 1.45a, a'



Following the general procedure the α-chloro sulfide **1.41** (0.5 mmol) was reacted with 1-octynylzinc bromide (1.5 mmol) at rt (6 h) to afford the crude product which was purified by column chromatography using hexanes as the eluent to furnish the pure product **1.45a, a'** (172 mg, 0.4 mmol) in 80% yield as a liquid. TLC, R_f 0.86 (Hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.49 (d, *J* = 6.7 Hz, 2H), 7.30-7.20 (m, 3H), 3.89 (dt, *J* = 4.5, 2.2 Hz, 1H), 3.78 (td, *J* = 7.5, 5.2 Hz, 1H), 2.15 (dt, *J* = 5.2, 2.2 Hz, 2H), 1.80-1.70 (m, 2H), 1.52-1.25 (m, 12H), 0.97-0.91 (bs, 15H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.5, 132.3, 128.8, 127.2, 86.3, 77.5, 74.2, 46.5, 33.8, 32.0, 31.5, 29.5, 28.8, 28.6, 26.0, 25.3, 22.8, 19.1, 18.3, 14.2, -4.3, -4.4; MS $[M+Na]^+$ 455; HRMS (ESI) *m/z* calcd for $C_{26}H_{44}OSSiNa$ 455.2779. Found: 455.2765.

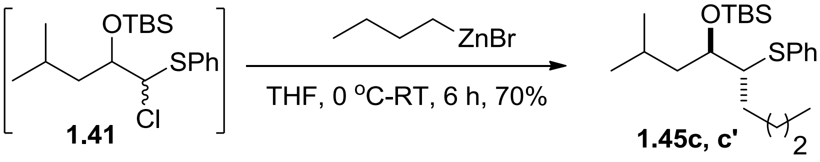
Preparation of allylic sulfide 1.45b, b'



Following the general procedure, the α-chloro sulfide **1.41** (0.5 mmol) was reacted vinylzinc bromide (1.5 mmol) at rt (6 h) to afford the crude product which was purified by column chromatography using hexanes as the eluent to furnish the pure product **1.45b, b'** (148 mg, 0.42 mmol) in 85% yield as a liquid. TLC, R_f 0.85 (Hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36 (d, *J* = 7.0 Hz, 2H), 7.24 (t, *J* = 7.0 Hz, 2H), 7.19 (t, *J* = 7.0 Hz, 1H), 5.92 (ddd, *J* = 17.0, 10.0, 8.0 Hz, 1H), 5.10-5.01 (m, 2H), 3.91 (td, *J* = 8.0, 4.0 Hz, 1H), 3.65 (dd, *J* = 8.0, 4.0 Hz, 1H), 1.73-1.65 (m, 1H), 1.59-1.53 (m, 1H), 1.44-1.38 (m, 1H), 0.94 (d, *J* = 7.0 Hz, 6H), 0.89 (bs, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75

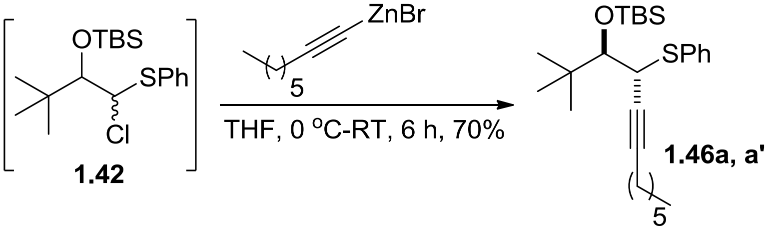
MHz) δ 135.6, 135.5, 132.4, 128.8, 126.9, 117.0, 72.7, 58.7, 42.6, 26.1, 24.4, 23.8, 22.2, 18.3, -4.1, -4.3; MS $[M+Na]^+$ 373; HRMS (ESI) *m/z* calcd for $C_{20}H_{34}OSSiNa$ 373.1997. Found: 373.1986.

Preparation of sulfide 1.45c, c'



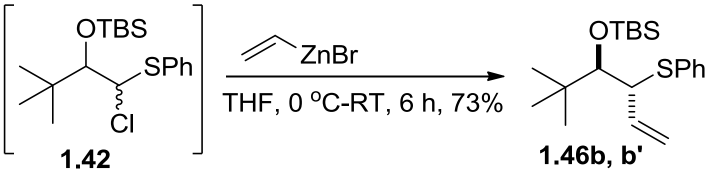
Following the general procedure, the α-chloro sulfide **1.41** (0.5 mmol) was reacted with *n*-butylzinc bromide (1.5 mmol) at rt (6 h) to afford the crude product which was purified by column chromatography using hexanes as the eluent to furnish the pure product **1.45c, c'** (133 mg, 0.35 mmol) in 70% yield as a liquid. TLC, R_f 0.85 (Hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.52 (d, *J* = 7.5 Hz, 2H), 7.42-7.31 (m, 3H), 3.87 (td, *J* = 5.2, 3.0, Hz, 1H), 3.14 (td, *J* = 6.0, 3.0 Hz, 1H), 2.08-1.95 (m, 1H), 1.84-1.66 (m, 2H), 1.53-1.33 (m, 4H), 1.15-0.97 (m, 20H), 0.0 (s, 3H), -0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 132.5, 129.2, 129.0, 127.0, 71.9, 56.0, 40.6, 30.6, 28.5, 26.0, 24.5, 24.2, 22.9, 21.8, 18.2, 14.3, -4.3, -4.5; MS $[M+O+Na]^+$ 419.

Preparation of propargylic sulfide 1.46a, a'



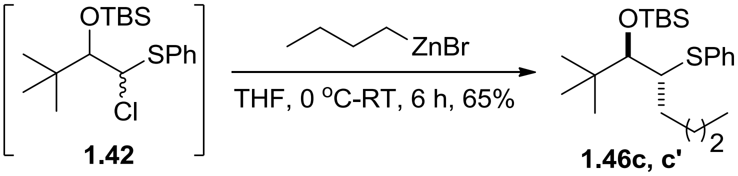
Following the general procedure, the α-chloro sulfide **1.42** (0.5 mmol) was reacted with octynylzinc bromide (1.5 mmol) at rt (6 h) to afford the crude product which was purified by column chromatography using hexanes as the eluent to furnish the pure product **1.46a, a'** (140 mg, 0.32 mmol) in 70% yield as a liquid. TLC, R*f* 0.88 (Hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.46 (d, *J* = 7.7 Hz, 2H), 7.25-7.15 (m, 3H), 4.02 (dt, *J* = 3.7, 2.2 Hz, 1H), 3.71 (d, *J* = 3.7 Hz, 1H), 2.16 (td, *J* = 6.0, 2.2 Hz, 2H), 1.49-1.42 (m, 2H), 1.32-1.23 (m, 6H), 1.02 (s, 9H), 1.00 (s, 9H), 0.90 (t, *J* = 6.7 Hz, 3H), 0.27 (s, 3H), 0.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.0, 131.4, 128.6, 126.4, 84.6, 83.3, 82.2, 43.4, 37.0, 31.6, 29.9, 28.7, 27.2, 26.5, 22.8, 19.1, 14.3, -2.9, -4.5; MS [M+Na]$^+$ 455; HRMS (ESI) *m/z* calcd for $C_{26}H_{44}OSSiNa$ 455.2779. Found: 455.2765.

Preparation of allylic sulfide 1.46b, b'



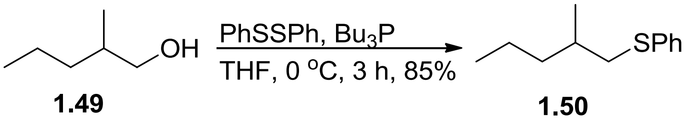
Following the general procedure, the α-chloro sulfide **1.42** (0.5 mmol) was reacted with vinylzinc bromide (1.5 mmol) at rt (6 h) to afford the crude product which was purified by column chromatography using hexanes as the eluent to furnish the pure product **1.46b, b'** (127 mg, 0.36 mmol) in 73% yield as a liquid. TLC, R*f* 0.83 (Hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35-7.11 (m, 5H), 5.95 (ddd, *J* = 17.3, 10.5, 9.0 Hz, 1H), 4.88 (d, *J* = 10.5 Hz, 1H), 4.72 (d, *J* = 17.3 Hz, 1H), 3.75 (dd, *J* = 9.0, 2.2 Hz, 1H), 3.52 (d, *J* = 2.2 Hz, 1H), 0.97 (s, 9H), 0.92 (s, 9H), 0.15 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.8, 132.4, 129.1, 128.8, 126.7, 114.8, 82.8, 57.2, 37.5, 27.6, 26.7, 19.1, -2.7, -3.8.

Preparation of sulfide 1.46c, c'



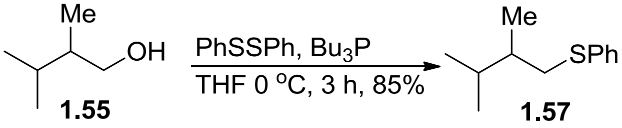
Following the general procedure, the α-chloro sulfide **1.42** (0.5 mmol) was reacted with *n*-butylzinc bromide (1.5 mmol) at rt (6 h) to afford the crude product which was purified by column chromatography using hexanes as the eluent to furnish the pure product **1.46c, c'** (123 mg, 0.32 mmol) in 65% yield as a liquid. TLC, R$_f$ 0.84 (Hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.26 (d, *J* = 7.5 Hz, 2H), 7.19 (t, *J* = 7.5 Hz, 2H), 7.06 (t, *J* = 7.5 Hz, 1H), 3.49 (s, 1H), 3.20 (dd, *J* = 8.8, 5.4 Hz, 1H), 1.82-1.72 (m, 1H), 1.69-1.56 (m, 2H), 1.28-1.20 (m, 6H) 0.98 (s, 12H), 0.94 (s, 9H), 0.10 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.3, 130.4, 128.8, 125.7, 81.1, 51.8, 36.8, 35.8, 30.6, 27.8, 26.6, 22.7, 19.1, 14.2, -2.9, -3.8.

Preparation of sulfide 1.50



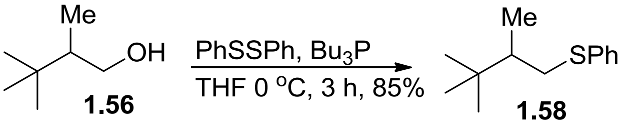
Alcohol **1.49** was prepared by following literature procedure. Sulfide **1.50** was prepared by from alcohol **1.49** (510 mg, 5 mmol) following the procedure employed for the preparation of sulfide **1.15** from alcohol **1.14**. The crude sulfide was purified by column chromatography using 2% EtOAc/Hexanes (v/v) as the eluent to afford the pure sulfide **1.50** as a viscous oil (824 mg, 4.25 mmol) in 85% yield; TLC, R$_f$ 0.81 (Hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.26 (d, *J* = 7.4 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 2H), 7.09 (t, *J* = 7.4 Hz, 1H), 2.89 (dd, *J* = 12.8, 5.9 Hz, 1H), 2.74 (dd, *J* = 12.8, 7.9 Hz, 1H), 1.75-1.70 (m, 1H), 1.50-1.43 (m, 1H), 1.40-1.19 (m, 3H), 1.10 (d, *J* = 6.6 Hz, 3H), 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.2, 128.9, 128.8, 125.6, 41.1, 38.6, 32.8, 20.1, 19.5, 14.4.

Preparation of sulfide 1.57



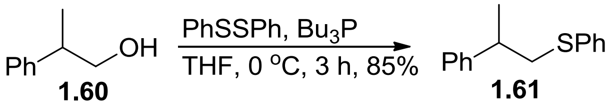
Sulfide **1.57** was prepared by from alcohol **1.55** (510 mg, 5 mmol) following the general procedure. The crude sulfide was purified by column chromatography using 2% EtOAc/Hexanes (v/v) as the eluent to afford the pure sulfide **1.57** as a viscous oil (824 mg, 4.25 mmol) in 85% yield as a liquid. TLC, R_f 0.84 (Hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.31 (d, *J* = 7.2 Hz, 2H), 7.25 (t, *J* = 7.2 Hz, 2H), 7.14 (t, *J* = 7.2 Hz, 1H), 3.01 (dd, *J* = 12.7, 5.4 Hz, 1H), 2.71 (dd, *J* = 12.7, 8.2 Hz, 1H), 1.85-1.78 (m, 1H), 1.68-1.62 (m, 1H), 1.01 (d, *J* = 6.3 Hz, 3H) 0.95 (d, *J* = 7.2, Hz, 3H), 0.90 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.8, 129.0, 128.8, 125.5, 39.0, 38.6, 31.6, 20.5, 18.0, 15.4; MS $[M]^+$ 116.

Preparation of sulfide 1.58



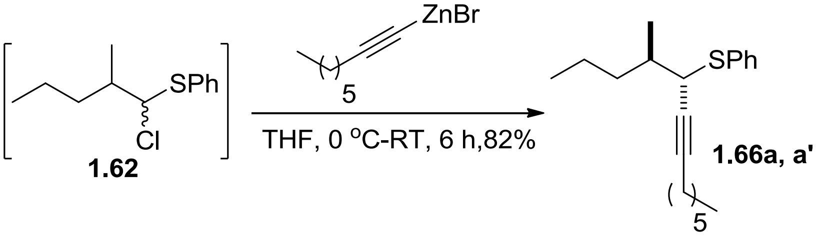
Sulfide **1.58** was prepared by from alcohol **1.56** (580 mg, 5 mmol) following the general procedure. The crude sulfide was purified by column chromatography using 2% EtOAc/Hexanes (v/v) as the eluent to afford the pure sulfide **1.58** as a viscous oil (884 mg, 4.25 mmol) in 85% yield as a liquid. TLC, R_f 0.84 (Hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30-7.17 (m, 4H), 7.10 (t, *J* = 6.9 Hz, 1H), 3.20 (d, *J* = 12.2 Hz, 1H), 2.40 (dd, *J* = 12.5, 1.8 Hz, 1H), 1.49-1.39 (m, 1H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.91-0.88 (bs, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.7, 128.8, 128.6, 125.4, 42.7, 36.9, 33.2, 27.3, 14.2; MS $[M]^+$ 208.

Preparation of sulfide 1.61



Sulfide **1.61** was prepared by from alcohol **1.60** (680 mg, 5 mmol) following the general procedure. The crude sulfide was purified by column chromatography using 2% EtOAc/Hexanes (v/v) as the eluent to afford the pure sulfide **1.61** as a viscous oil (969 mg, 4.25 mmol) in 85% yield as a liquid. TLC, R$_f$ 0.84 (Hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.28-7.09 (m, 10H), 3.18 (dd, *J* = 12.8, 5.4 Hz, 1H), 3.12-2.92 (m, 2H), 1.39 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.3, 136.8, 128.8, 128.7, 128.3, 126.8, 126.4, 125.6, 41.8, 39.2, 20.8; MS $[M+O+H]^+$ 267.

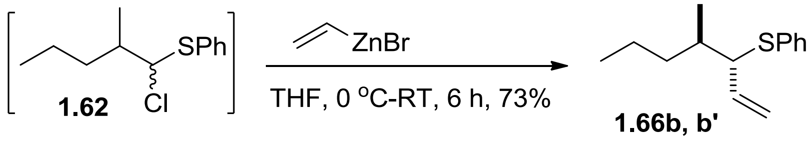
Preparation of propagylic sulfide 1.66a, a'



Following the general procedure, the α-chloro sulfide **1.62** (0.5 mmol) was reacted with 1-octynylzinc bromide (1.5 mmol) at rt (6 h) to afford the crude product which was purified by column chromatography using hexanes as the eluent to furnish the pure product **1.66a** as a viscous oil (123 mg, 0.41 mmol) in 82% yield; TLC, R$_f$ 0.90 (Hexanes); **1.66a:**

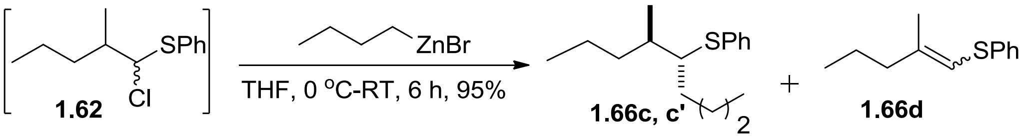
^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.45 (d, *J* = 6.9 Hz, 2H), 7.25 (t, *J* = 7.9 Hz, 2H), 7.19 (t, *J* = 6.9 Hz, 1H), 3.75 (t, *J* = 1.9 Hz, 1H), 2.16 (dt, *J* = 6.9, 1.9 Hz, 2H), 1.82-1.76 (m, 1H), 1.72-1.66 (m, 1H), 1.50-1.42 (m, 3H), 1.38-1.22 (m, 8H), 1.09 (d, *J* = 5.9 Hz, 3H), 0.92 (t, *J* = 6.9, 3H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 137.0, 132.0, 128.6, 127.1, 85.6, 78.8, 46.2, 37.6, 37.4, 36.9, 35.2, 31.4, 29.8, 28.5, 22.7, 20.5, 18.9, 14.2; **1.66a':** ^{1}H NMR (CDCl$_3$, 500 MHz) δ 3.84 (t, *J* = 1.9 Hz,1H); ^{13}C NMR (CDCl$_3$, 75 MHz) 136.4, 131.8, 128.7, 126.9, 86.0, 77.6, 45.2, 37.6, 37.5, 31.4, 29.8, 28.8, 28.5, 22.7, 20.5, 20.4, 17.9, 14.4.

Preparation of allylic sulfide 1.66b, b'



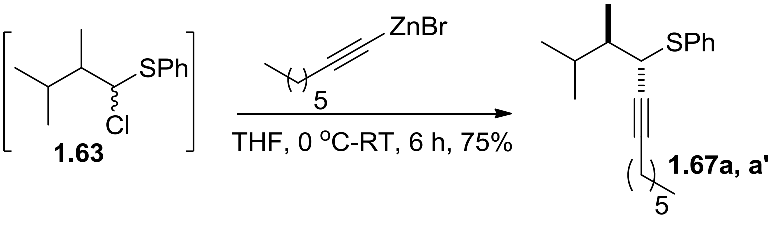
Following the general procedure, the α-chloro sulfide **1.62** (0.5 mmol) was reacted with vinylzinc bromide (1.5 mmol) at rt (6 h) to afford the crude product which was purified by column chromatography using hexanes as the eluent to furnish the pure product **1.66b, b'** as a viscous oil (80 mg, 0.36 mmol) in 73% yield; TLC, R$_f$ 0.90 (Hexanes); **1.66b:** ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.29-7.21 (m, 5H), 5.78-5.70 (m, 1H), 4.94 (d, *J* = 9.0 Hz, 1H), 4.88 (d, *J* = 16.2 Hz, 1H), 3.51 (dd, *J* = 9.0, 5.0 Hz, 1H), 1.30-1.20 (m, 5H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.90 (t, *J* = 7.0, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 137.4, 132.3, 128.6, 127.5, 126.8, 115.9, 59.4, 37.0, 29.7, 20.4, 17.2, 14.2; **1.66b':** ^{1}H NMR (CDCl$_3$, 500 MHz) δ 4.84 (d, *J* = 16.2 Hz, 1H), 3.55 (dd, *J* = 9.0, 5.0 1H), 1.00 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) 136.2, 132.5, 129.0, 127.1, 126.6, 116.4, 58.4, 35.9, 29.7, 20.2, 16.2, 14.2.

Preparation of sulfide 1.66c, c'



Following the general procedure, the α-chloro sulfide **1.62** (0.5 mmol) was reacted with *n*-butylzinc bromide (1.5 mmol) at rt (6 h) to afford the crude product which was purified by column chromatography using hexanes as the eluent to furnish the pure product **1.66c, c'** as a viscous oil (100 mg, 0.45 mmol) in 90% yield in 40:45 ratio of sulfide **1.66c, c'** and vinyl sulfide **1.66d**; TLC, R_f 0.90 (Hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39 (t, *J*= 7.7 Hz, 2H), 7.26 (t, *J* = 7.7 Hz, 2H), 7.28 (t, *J* = 7.7 Hz, 1H), 3.12-3.07 (m, 1H) 1.70-1.44 (m, 4H) 1.40-1.20 (m, 7H), 0.96 (d, *J*= 6.8 Hz, 3H), 0.89 (t, *J*= 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.5, 128.7, 128.6, 125.4, 41.0, 38.4, 32.6, 29.9, 20.0, 19.9, 19.3, 19.2, 14.3, 14.2. **1.66d:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39 (t, *J*= 7.7 Hz, 2H), 7.26 (t, *J* = 7.7 Hz, 2H), 7.28 (t, *J* = 7.7 Hz, 1H), 5.95 (s, 1H), 2.15 (t, *J* = 6.5 Hz, 2H), 1.85 (s, 3H), 1.40-1.20 (m, 2H), 0.89 (t, *J*= 6.8 Hz, 3H).

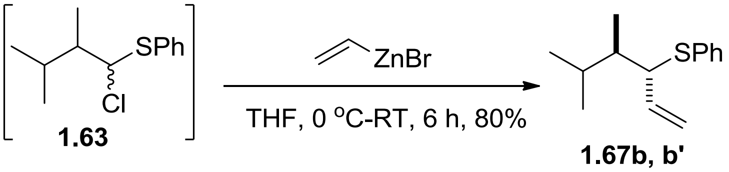
Preparation of propargylic sulfide 1.67a, a'



Following the general procedure, the α-chloro sulfide **1.63** (0.5 mmol) was reacted with 1-octynylzinc bromide (1.5 mmol) at rt (6 h) to afford the crude product which was purified by column chromatography using hexanes as the eluent to furnish the pure product

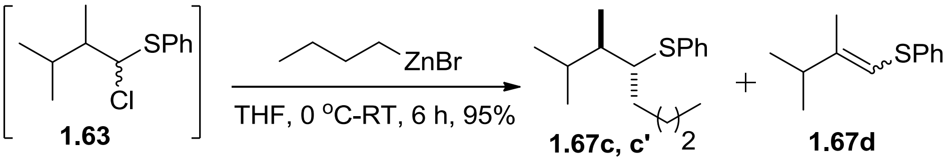
1.67a, a' as a viscous oil (113 mg, 0.37 mmol) in 75% yield; TLC, R_f 0.90 (Hexanes); **1.67a**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.4 (d, *J* = 7.1, 2H), 7.29-7.18 (m, 3H), 3.75-3.69 (m, 1H), 2.13 (td, *J* = 6.8, 2.2 Hz, 1H), 1.3-1.2 (m, 10H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.90 (t, *J* = 6.7 Hz, 3H), 0.85 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 132.3, 129.2, 128.6, 127.0, 85.5, 79.8, 44.9, 43.6, 31.6, 29.8, 28.7, 28.5, 22.6, 21.7, 18.9, 17.6, 14.1, 12.8; **1.67a'**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.95 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.5, 131.9, 128.1, 127.5, 85.5, 79.8, 43.4, 39.4, 31.6, 31.3, 22.5, 21.1, 20.3, 19.4, 19.3, 18.0, 14.5, 12.9; MS $[M]^+$ 302.

Preparation of allylic sulfide 1.67b, b'



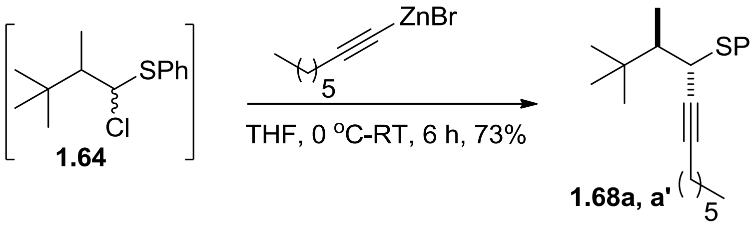
Following the general procedure, the α-chloro sulfide **1.63** (0.5 mmol) was reacted with vinylzinc bromide (1.5 mmol) at rt (6 h) to afford the crude product which was purified by column chromatography using hexanes as the eluent to furnish the pure product **1.67b, b'** as a viscous oil (88 mg, 0.4 mmol) in 80% yield; TLC, R_f 0.90 (Hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27 (d, *J* = 6.9 Hz, 2H), 7.20-7.10 (m, 3H), 5.63 (ddd, *J* = 17.0, 9.8, 9.4 Hz, 1H), 4.78 (d, *J* = 9.8 Hz, 1H), 4.66 (*J* = 17.0 Hz, 1H), 3.42 (dd, *J* = 9.4, 8.3 Hz, 1H) 1.90-1.80 (m, 1H) 1.50-1.40 (m, 1H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.9 (d, *J* = 6.7 Hz, 3H), 0.74 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.7, 133.0, 128.7, 128.6, 126.9, 115.1, 58.7, 43.1, 29.9, 22.0, 17.2, 12.4; MS $[M+O+H]^+$ 237.

Preparation of sulfide 1.67c, c'



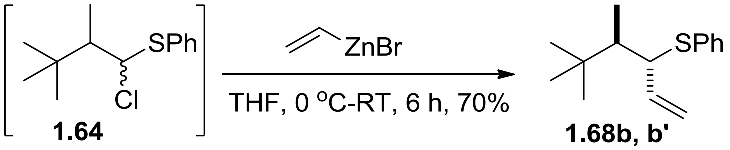
Following the general procedure, the α-chloro sulfide **1.63** (0.5 mmol) was reacted with *n*-butylzinc bromide (1.5 mmol) at rt (6 h) to afford the crude product which was purified by column chromatography using hexanes as the eluent to furnish the pure product **1.67c, c'** as a viscous oil (116 mg, 0.47 mmol) in 95% yield in 44:51 ratio of sulfide **1.67c, c'** and vinyl sulfide **1.67d**; TLC, R_f 0.90 (Hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30-7.10 (m, 5H), 3.25-3.10 (m, 1H), 1.70-1.60 (m, 2H), 1.10 (d, *J* = 6.7 Hz, 6H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.99-0.85 (m, 9H); **1.67d:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30-7.10 (m, 5H), 5.92 (s, 1H), 2.48-2.38 (m, 1H), 1.79 (s, 3H), 1.05 (d, *J* = 6.7 Hz, 6H).

Preparation of propargylic sulfide 1.68a, a'



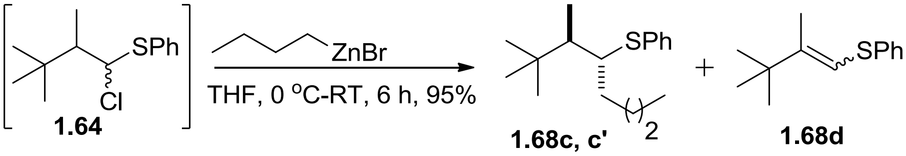
Following the general procedure, the α-chloro sulfide **1.64** (0.5 mmol) was reacted with 1-octynylzinc bromide (1.5 mmol) at rt (6 h) to afford the crude product which was purified by column chromatography using hexanes as the eluent to furnish the pure product **1.68a, a'** as a viscous oil (115 mg, 0.36 mmol) in 73% yield; TLC, R_f 0.93 (Hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.44 (d *J* = 7.2 Hz, 2H), 7.25-7.21 (m, 3H), 4.05 (d, *J* = 2.0 Hz, 1H), 2.10 (dt, *J* = 7.2, 2.0 Hz, 2H), 1.86-1.82 (m, 1H), 1.42-1.34 (m, 2H) 1.3-1.2 (m, 6H), 1.18 (d *J* = 7.2 Hz, 3H), 1.04 (bs, 9H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 136.2, 131.9, 128.6, 126.8, 84.1, 81.9, 48.6, 43.0, 33.9, 31.5, 28.8, 28.8, 27.4, 22.7, 19.0, 14.2, 12.1; MS [M]$^+$ 316.

Preparation of allylic sulfide 1.68b, b'



Following the general procedure, the α-chloro sulfide **1.64** (0.5 mmol) was reacted with vinylzinc bromide (1.5 mmol) at rt (6 h) to afford the crude product which was purified by column chromatography using hexanes as the eluent to furnish the pure product **1.68b, b'** as a viscous oil (82 mg, 0.35 mmol) in 70% yield; TLC, R$_f$ 0.92 (Hexanes); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.30-7.08 (m, 5H), 5.85 (ddd *J* = 15.8, 9.8, 8.3 Hz, 1H), 4.78 (m, 2H), 3.76 (dd, *J* = 8.3, 1.7 Hz, 1H), 1.66-1.56 (m, 1H), 1.10-1.04 (m, 12H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 140.0, 136.2, 132.1, 128.7, 126.6, 113.9, 55.5, 47.7, 29.2, 28.8, 27.5; MS [M]$^+$ 234

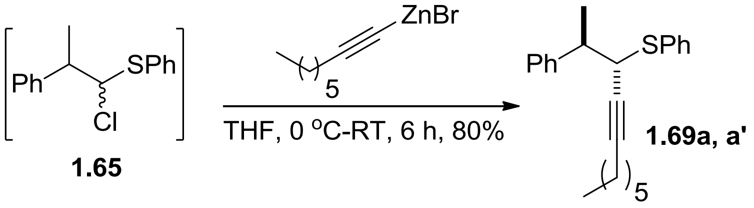
Preparation of sulfide 1.68c, c'



Following the general procedure, the α-chloro sulfide **1.64** (0.5 mmol) was reacted with *n*-butylzinc bromide (1.5 mmol) at rt (6 h) to afford the crude product which was purified by column chromatography using hexanes as the eluent to furnish the pure product

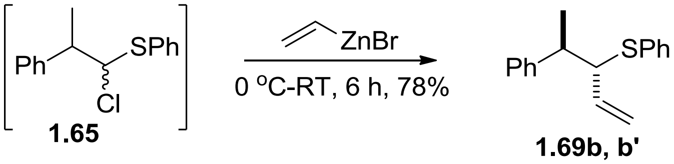
1.68c, c' as a viscous oil (72 mg, 0.27 mmol) in 95% yield in 55:40 ratio of sulfide **1.67c, c'** and vinyl sulfide **1.68d**; TLC, R*f* 0.91 (Hexanes); ^{1}H NMR (CDCl$_3$, 500 MHz) 7.33-7.10 (m, 5H), 3.37 (m, 1H), 1.65-1.55 (m, 7H), 1.13 (s, 9H), 1.01 (s, 3H), 1.0 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 137.5, 129.0, 128.9, 128.3, 44.9, 36.9, 30.0, 29.1, 28.5, 27.4, 22.7, 15.2, 14.1; **1.68d:** ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.33-7.10 (m, 5H), 5.97 (s, 1H), 1.85 (s, 3H), 1.0 (s, 9H).

Preparation of propargylic sulfide 1.69a, a'



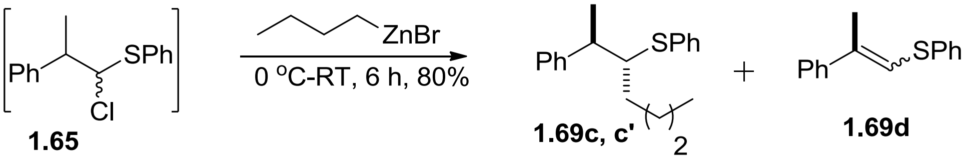
Following the general procedure, the α-chloro sulfide **1.65** (0.5 mmol) was reacted with 1-octynylzinc bromide (1.5 mmol) at rt (6 h) to afford the crude product which was purified by column chromatography using hexanes as the eluent to furnish the pure product **1.69a, a'** as a viscous oil (134 mg, 0.4 mmol) in 80% yield; TLC, R*f* 0.91 (Hexanes); **1.69a:** ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.43-7.36 (m, 4H), 7.29-7.15 (m, 6H), 4.01 (dt, *J* = 4.5, 2.2 Hz, 1H), 3.07 (q, *J* = 6.7 Hz, 1H), 2.17 (td, *J* = 6.7, 2.2 Hz, 2H), 1.48 (d, *J* = 6.7 Hz, 3H), 1.37-1.18 (m, 8H), 0.9 (t, *J* = 6.0 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 143.0, 134.6, 129.4, 128.9, 128.4, 127.7, 127.1, 126.9, 87.2, 78.7, 46.7, 44.0, 31.5, 28.7, 28.6, 19.7, 19.1, 19.0, 14.3; **1.69a':** ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.43-7.36 (m, 4H) 7.29-7.15 (m, 6H), 3.95 (dt, *J* = 4.5, 2.2 Hz, 1H), 2.98 (m, 1H), 2.08 (dt, *J* = 6.7, 2.2 Hz, 2H), 1.48 (d, *J* = 6.7 Hz, 3H) 1.37-1.18 (m, 11H), 0.80 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 144.1, 135.2, 132.2, 129.2, 128.8, 128.0, 127.3, 126.9, 86.9, 77.4, 46.6, 43.4, 28.8, 28.7, 22.7, 19.1, 19.0, 17.3, 14.3; MS $[M]^+$ 336.

Preparation of allylic sulfide 1.69b, b'



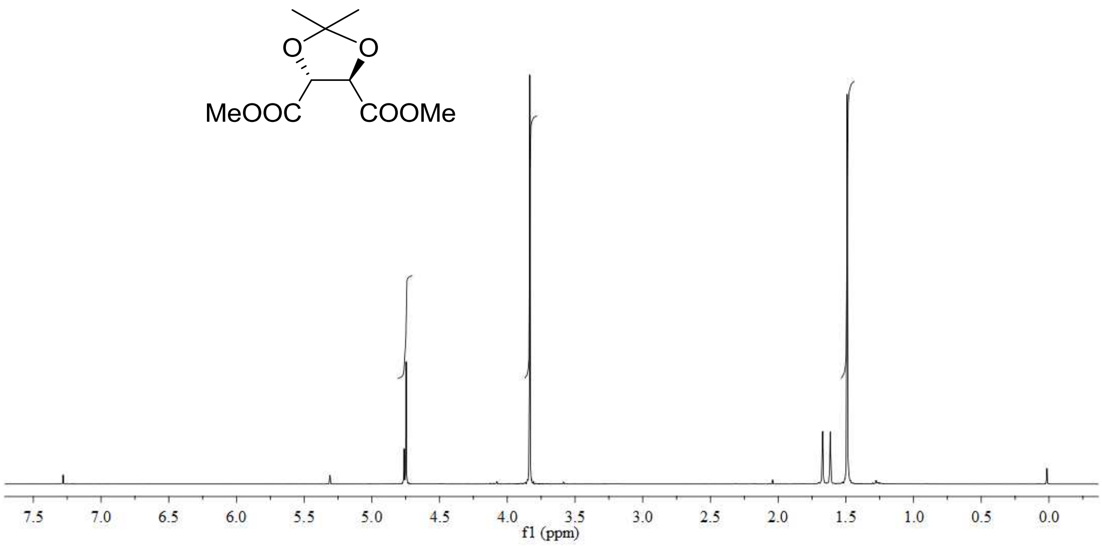
Following the general procedure the α-chloro sulfide **1.65** (0.5 mmol) was reacted with the organozinc reagent prepared from vinylmagnesium bromide (1.5 mmol) at rt (6 h) to afford the crude product which was purified by column chromatography using hexanes as the eluent to furnish the pure product **1.69b, b'** as a viscous oil (82 mg, 0.39 mmol) in 70% yield; TLC, R_f 0.91 (Hexanes); **1.69b:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.42-7.21 (m, 10H), 5.56 (ddd, *J* = 16.9, 9.9, 7.0 Hz, 1 H), 4.81 (d, *J* = 10.0 Hz, 1H), 4.68 (d, *J* = 16.9 Hz, 1H), 3.71 (dd, *J* = 9.3, 7.0 Hz, 1H), 3.01-3.11 (m, 1H), 1.48 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.7, 132.9, 132.8, 128.9, 128.8, 128.2, 127.86, 127.1, 126.7, 116.26, 60.04, 43.92, 29.85; **1.69b':** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.42-7.21 (m, 10H), 5.75 (ddd, *J* = 16.9, 9.9, 9.0 Hz, 1H), 4.95 (d, *J* = 9.9 Hz, 1H), 4.77 (d, *J* = 16.9 Hz 1H), 3.75 (dd, *J* = 6.7, 9.0 Hz, 1H), 3.22 (q, *J* = 6.7 Hz, 1H), 1.39 (d, *J* = 6.7 Hz, 3H); 137.2, 132.9, 128.9, 128.8, 128.3, 128.2, 127.9, 127.1, 126.7, 116.9, 59.8, 43.7, 19.8; MS $[M]^+$ 254.

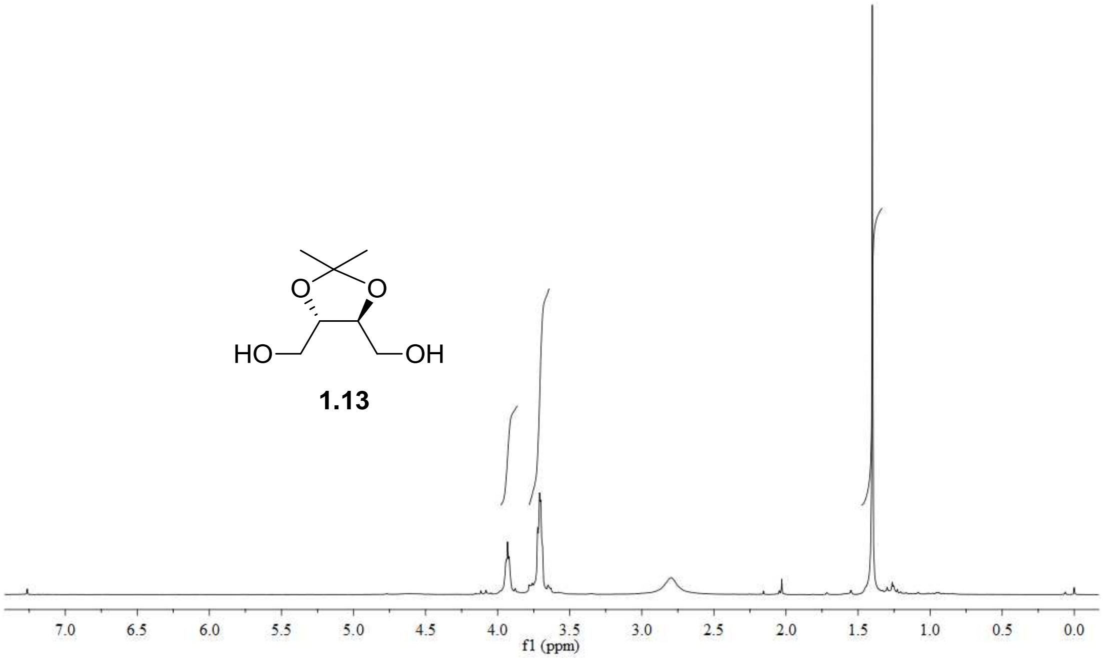
Preparation of sulfide 1.69c, c'



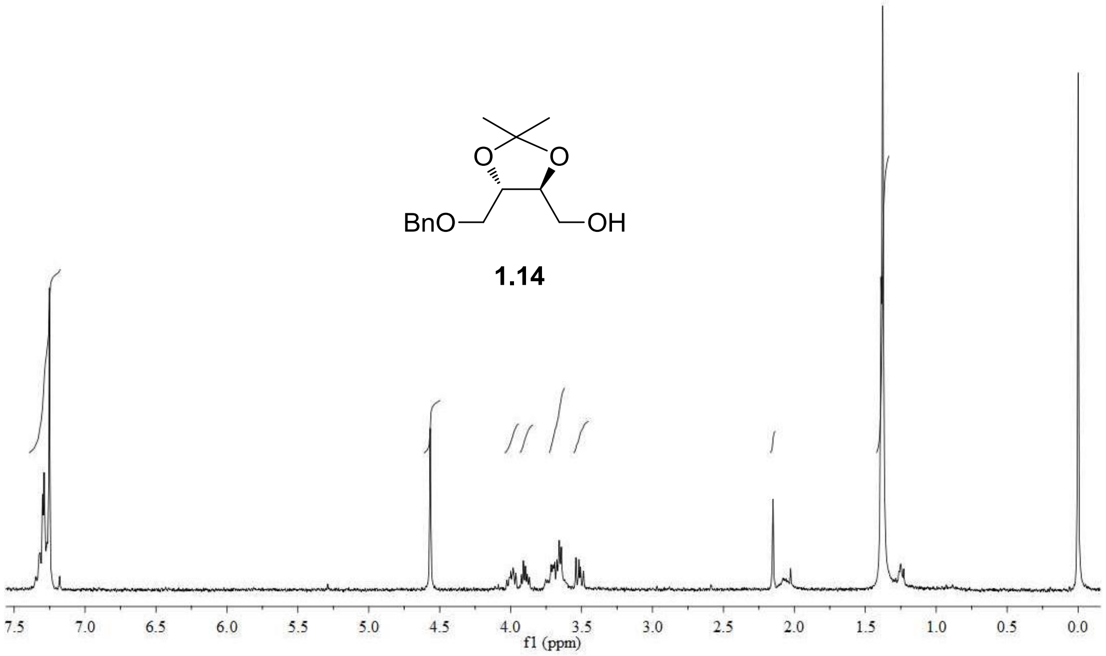
Following the general procedure the α-chloro sulfide **1.65** (0.5 mmol) was reacted with the organozinc reagent prepared from 1-butyl bromide (1.5 mmol) at rt (6 h) to afford the crude product which was purified by column chromatography using hexanes as the eluent to furnish the pure product **1.69c, c'** as a viscous oil (113 mg, 0.4 mmol) in 40% yield; TLC, R_f 0.90 (Hexanes); **1.69c:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.5-7.2 (m, 10H), 3.14 (q, J = 6.7 Hz, 1H), 2.95-2.85 (m, 1H), 1.55-1.47 (m, 2H), 1.42 (d, J = 6.7 Hz, 3H), 1.25-1.15 (m, 4H), 0.80 (t, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 131.7, 129.2, 129.0, 128.5, 128.2, 127.9, 127.6, 126.5, 57.6, 44.0, 33.2, 29.6, 25.3, 18.9, 14.1; **1.69c':** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.5-7.2 (m, 10H), 3.39-3.34 (m, 1H), 3.04 (q, J = 6.7 Hz, 1H), 1.65-1.60 (m, 2H), 1.37 (d, J = 6.7 Hz, 2H), 1.25-1.15 (m, 2H), 0.97 (t, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 131.7, 129.2, 129.0, 128.5, 128.2, 127.9, 127.6, 126.5, 56.7, 42.5, 33.2, 29.9, 25.3, 17.9, 14.1; **1.69d:** in 40% yield, ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.5-7.2 (m, 10H), 6.51 (s, 1H), 2.24 (d, J = 0.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 131.7, 128.8, 128.3, 128.2, 128.0, 27.9, 127.7, 127.3, 126.4, 121.5, 22.54.

Spectral Data

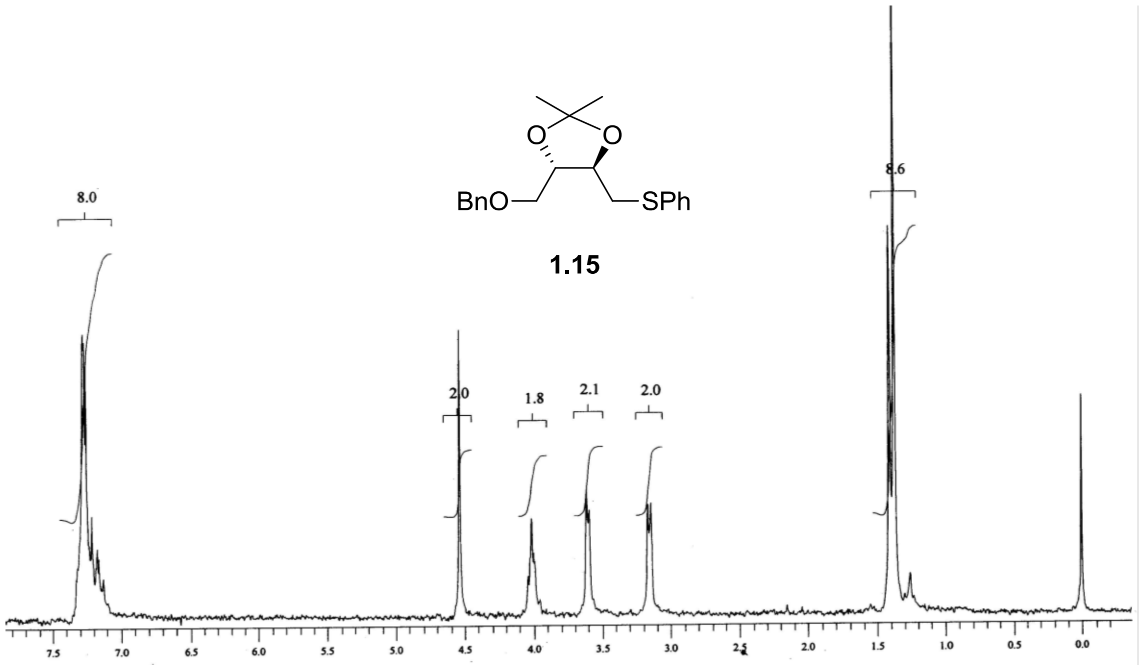

O
O
MeOOC
COOMe
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


O
O
HO
OH
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
f1 (ppm)

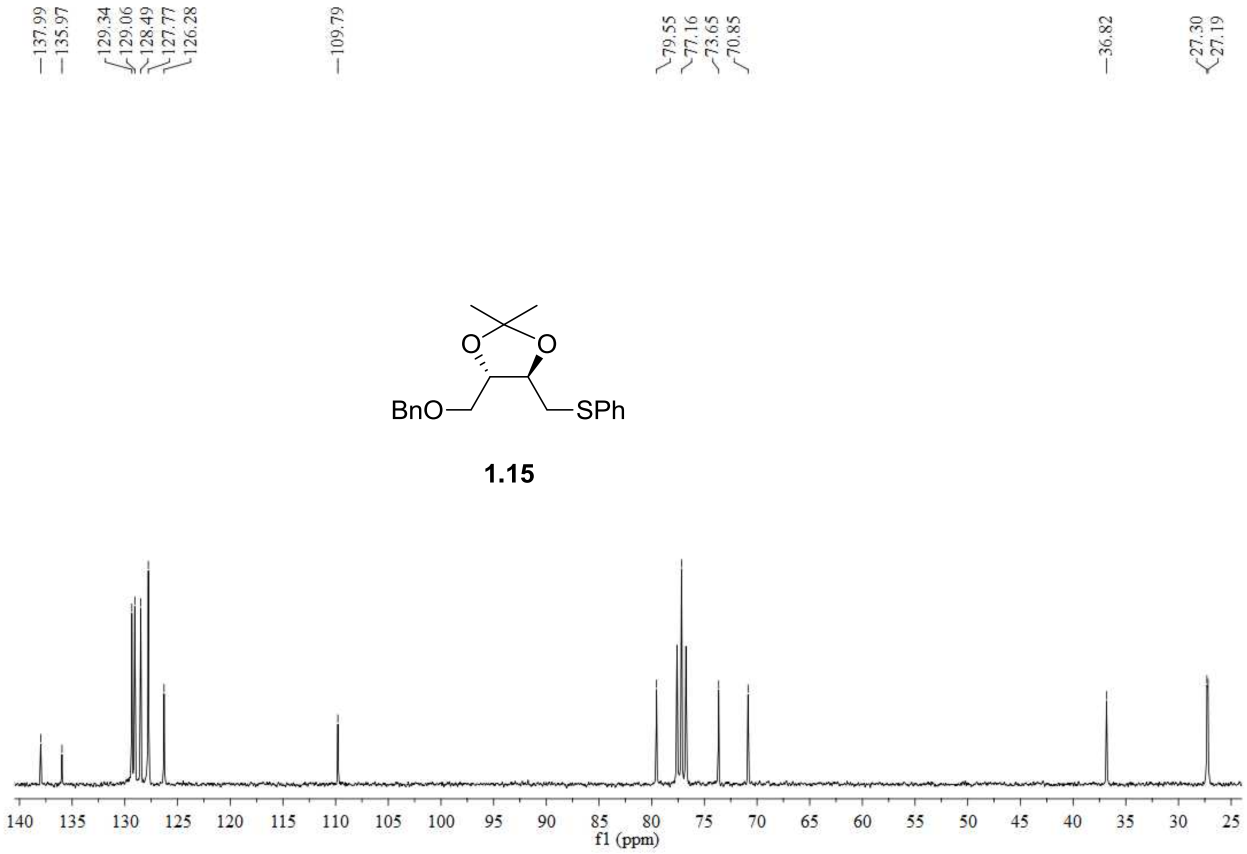
1.13

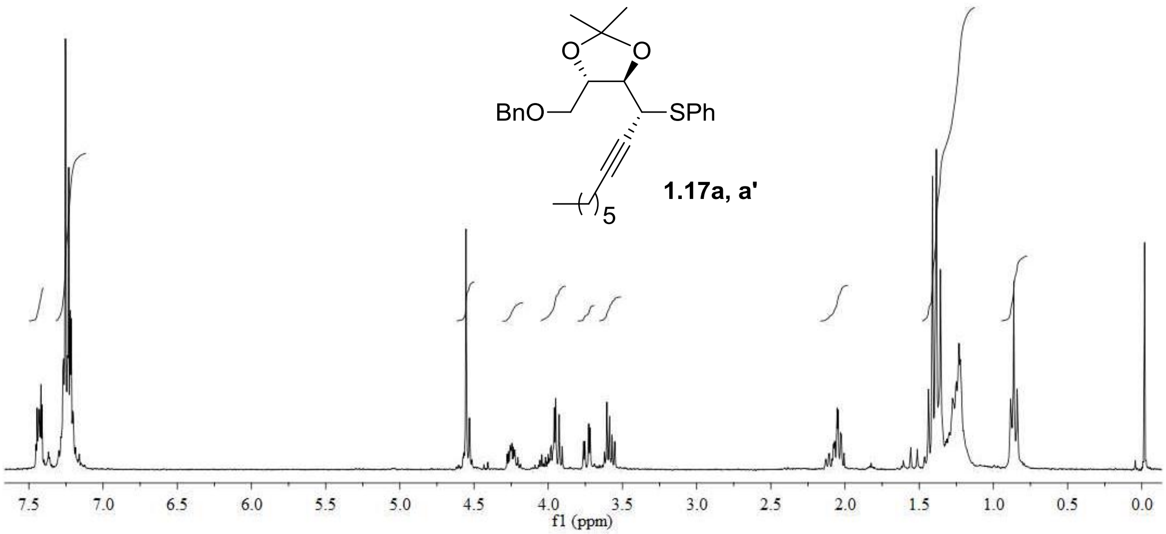

BnO
OH
O
O
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

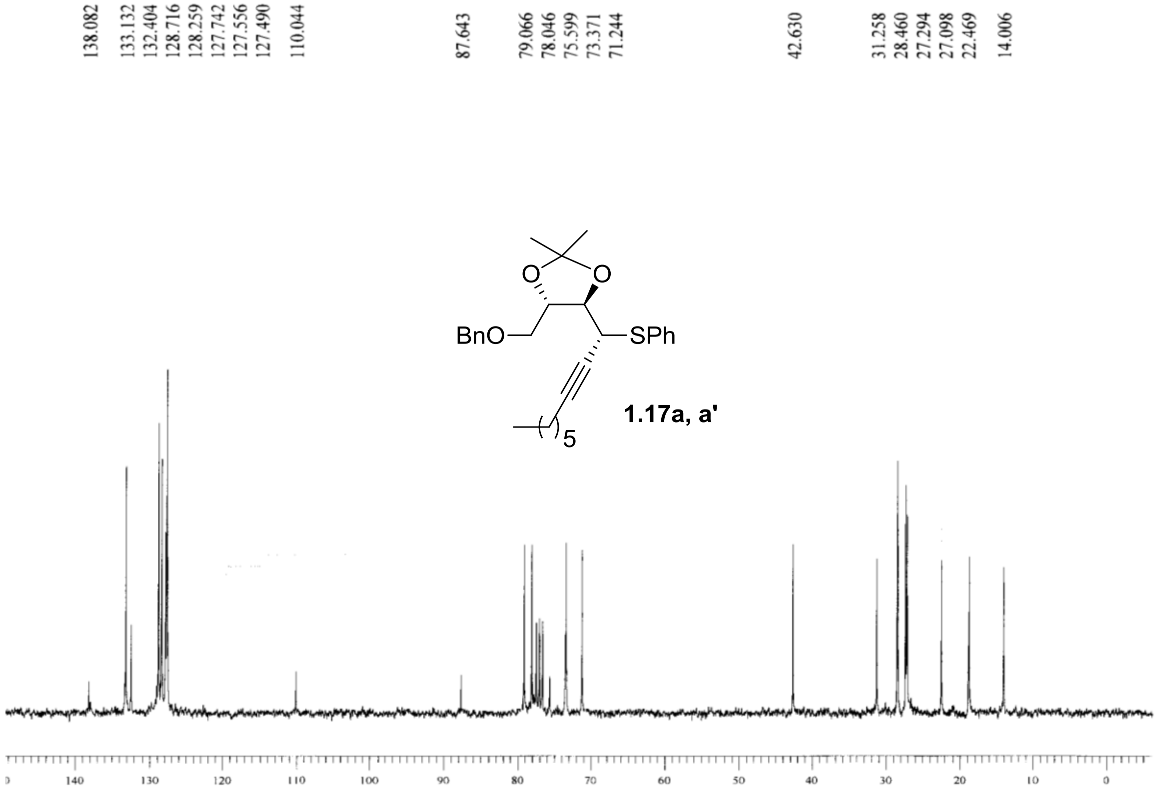
1.14

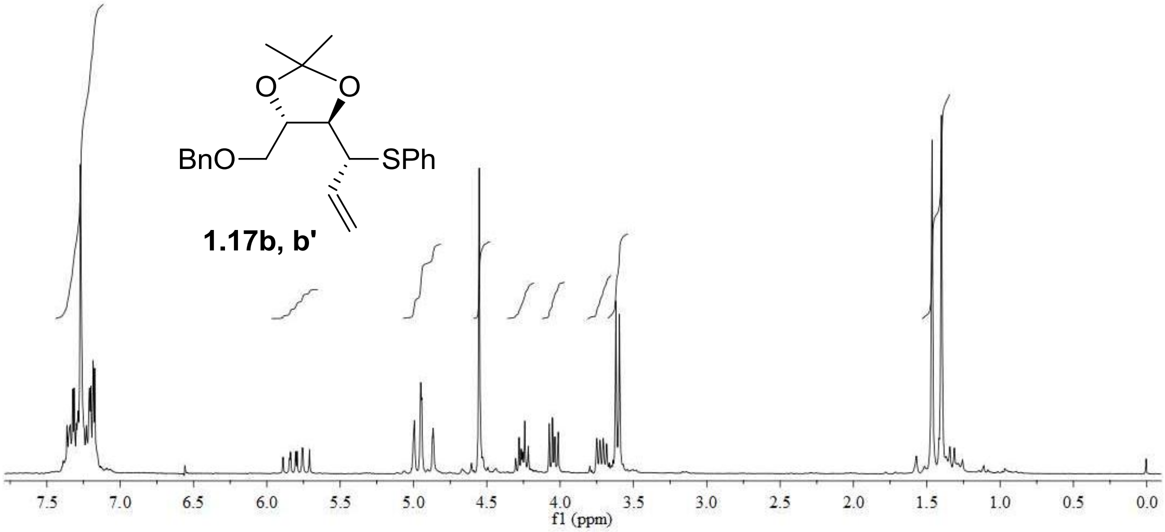

BnO
SPh
O
O
8.0
2.0
1.8
2.1
2.0
8.6
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

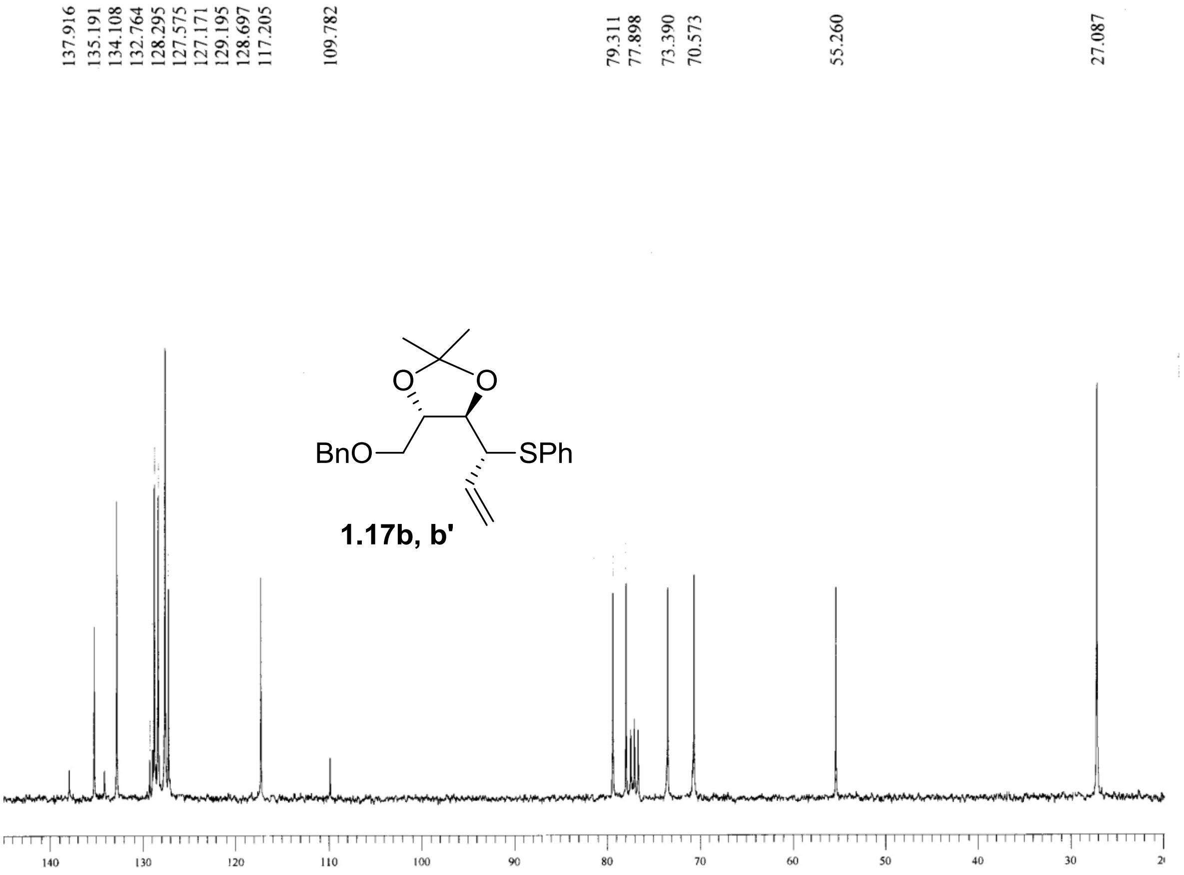
1.15


137.99
135.97
129.34
129.06
128.49
127.77
126.28
109.79
79.55
77.16
73.65
70.85
36.82
27.30
27.19
O
O
BnO
SPh
1.15
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
f1 (ppm)

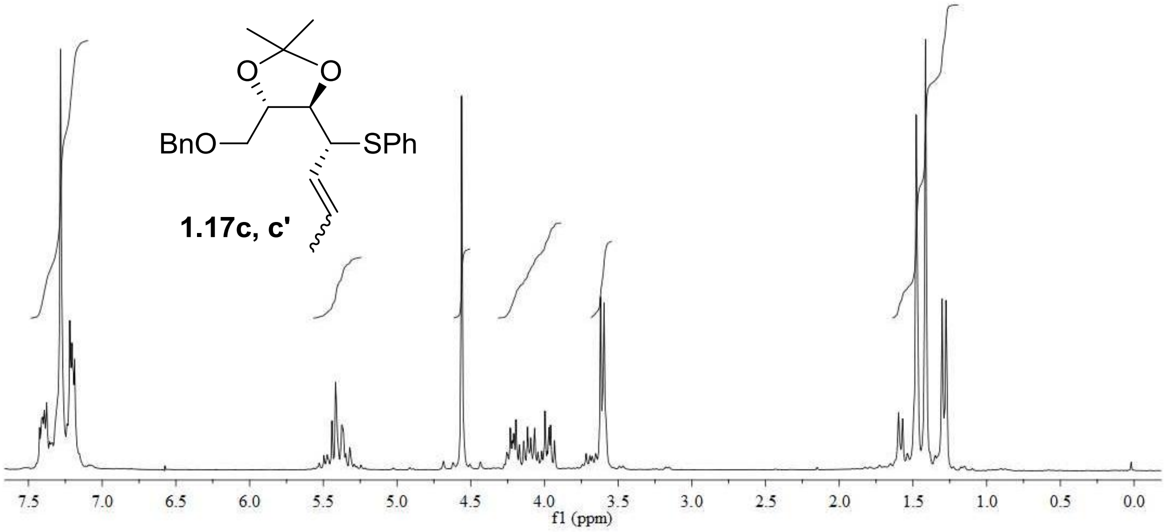

O
O
BnO
SPh
5
1.17a, a'
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


138.082
133.132
132.404
128.716
128.259
127.742
127.556
127.490
110.044
87.643
79.066
78.046
75.599
73.371
71.244
42.630
31.258
28.460
27.294
27.098
22.469
14.006
BnO
O
O
SPh
5
1.17a, a'
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

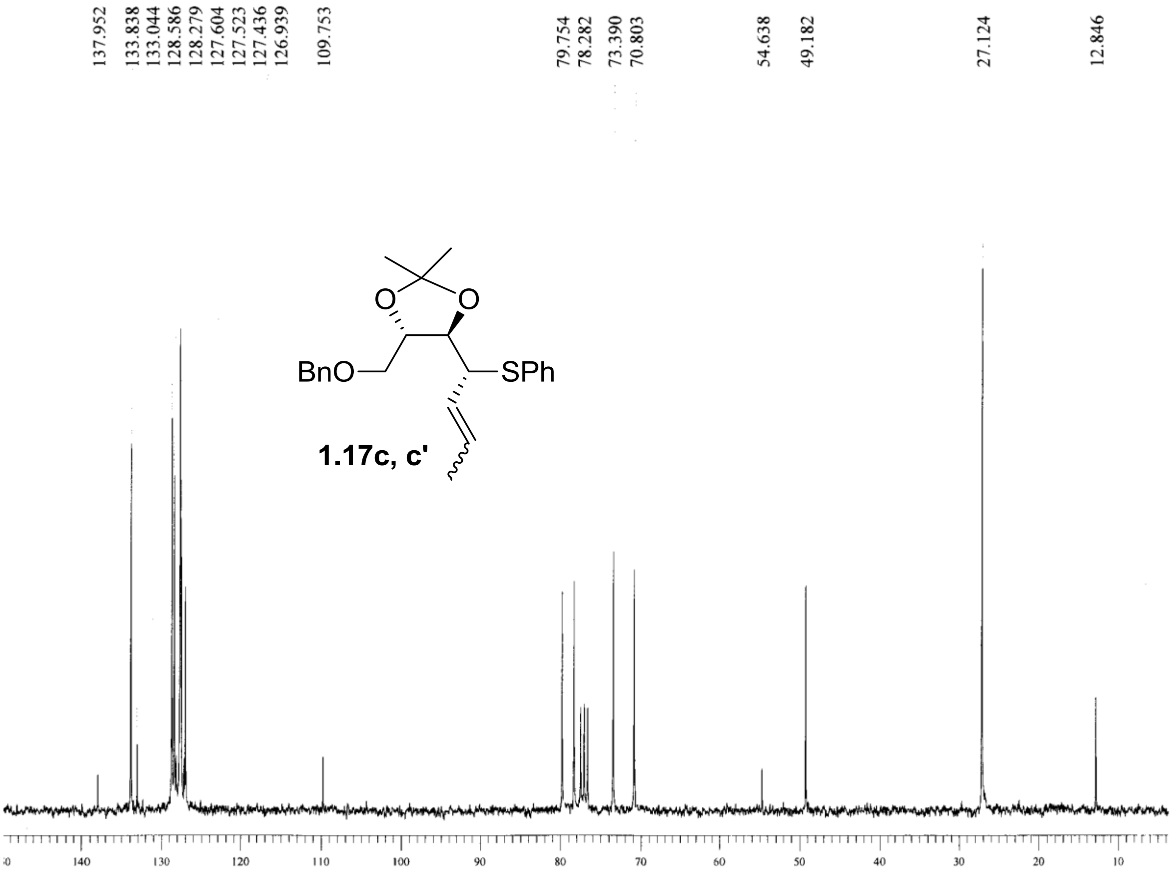

O
O
BnO
SPh
1.17b, b'
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

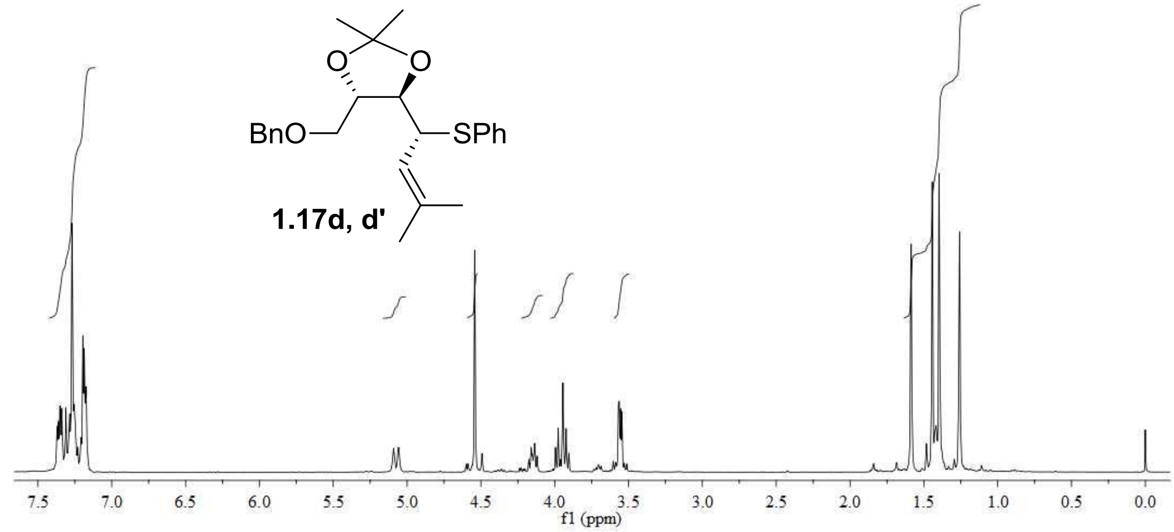

137.916
135.191
134.108
132.764
128.295
127.575
127.171
129.195
128.697
117.205
109.782
79.311
77.898
73.390
70.573
55.260
27.087
BnO
SPh
O
O
140
130
120
110
100
90
80
70
60
50
40
30
20

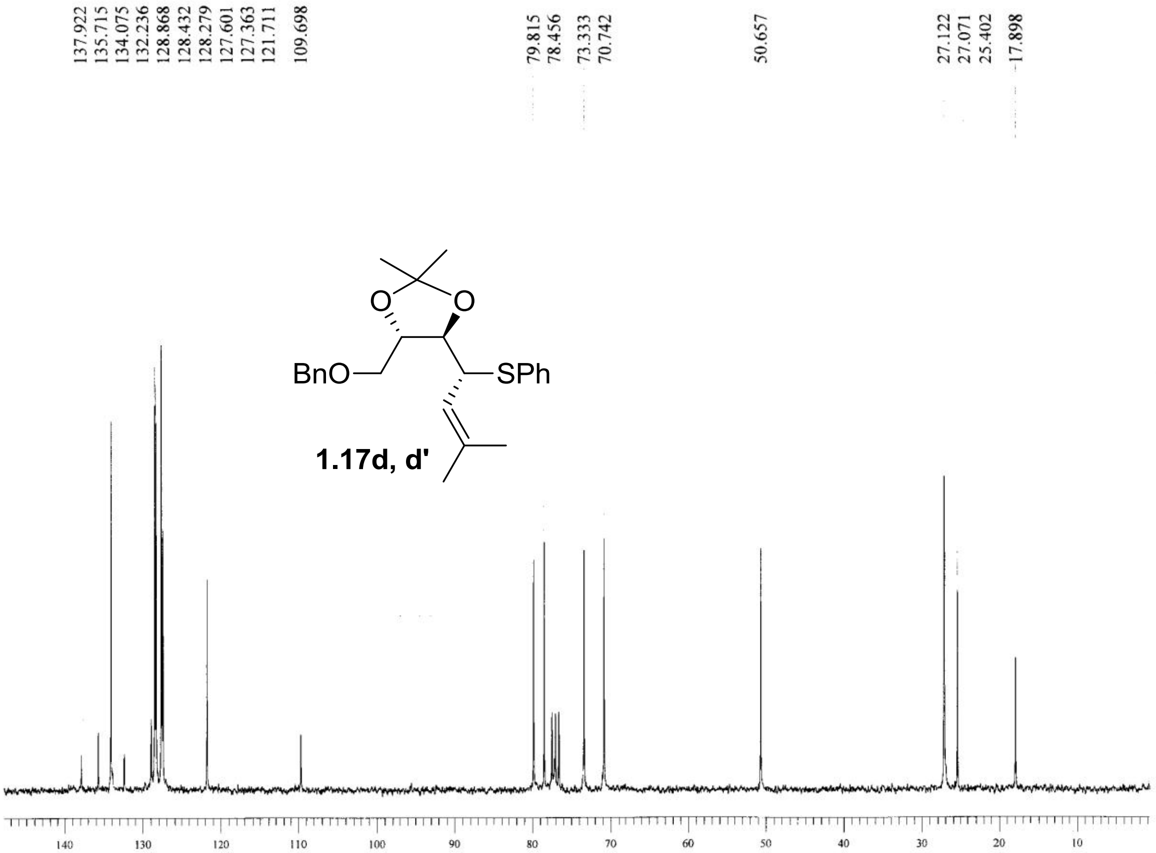
1.17b, b'


BnO
SPh
O
O
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
f1 (ppm)

1.17c, c'

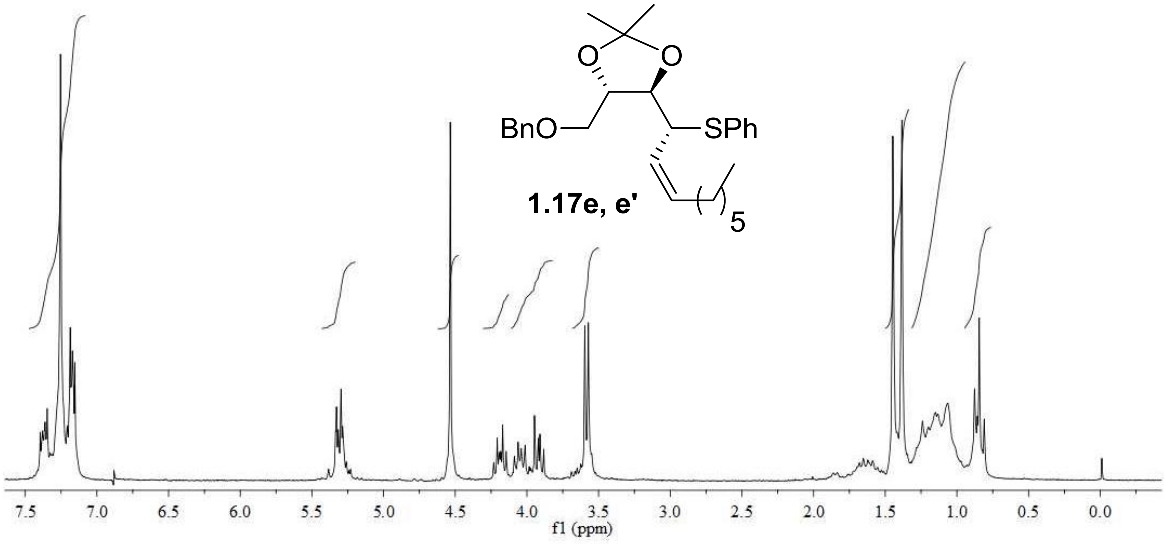

1.17c, c'
137.952
133.838
133.044
128.586
128.279
127.604
127.523
127.436
126.939
109.753
79.754
78.282
73.390
70.803
54.638
49.182
27.124
12.846
BnO
O
O
SPh
140
130
120
110
100
90
80
70
60
50
40
30
20
10


1.17d, d'
BnO
O
O
SPh
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
f1 (ppm)



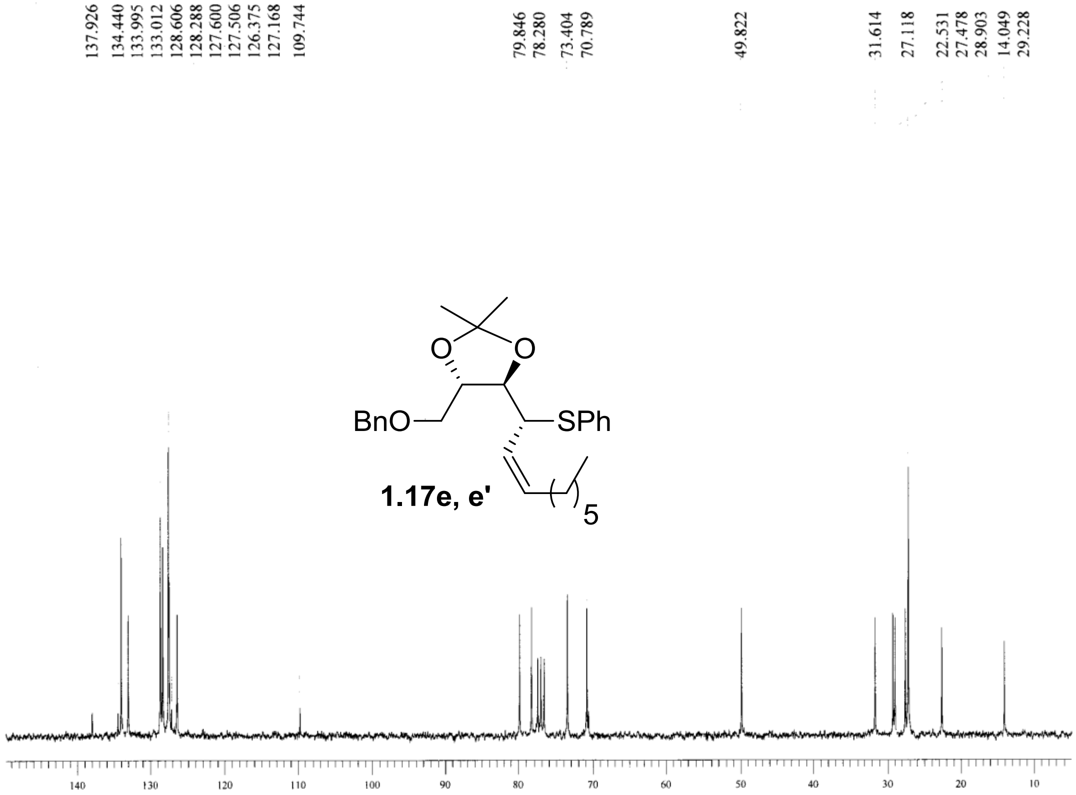
1.17d, d'

137.922
135.715
134.075
132.236
128.868
128.432
128.279
127.601
127.363
121.711
109.698
79.815
78.456
73.333
70.742
50.657
27.122
27.071
25.402
17.898
BnO
O
O
SPh
140
130
120
110
100
90
80
70
60
50
40
30
20
10

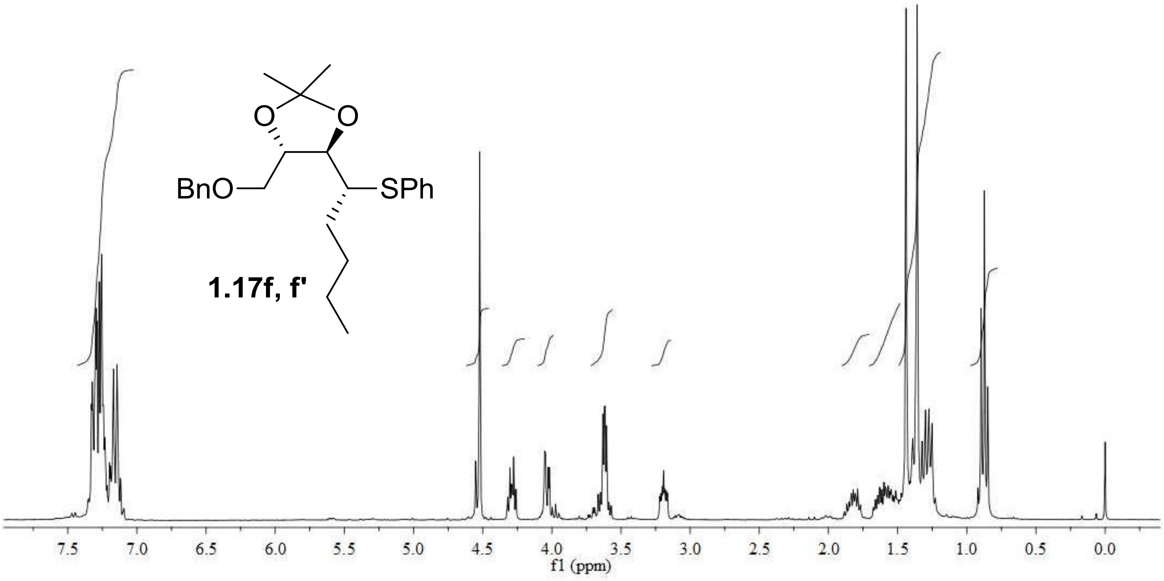


1.17e, e'

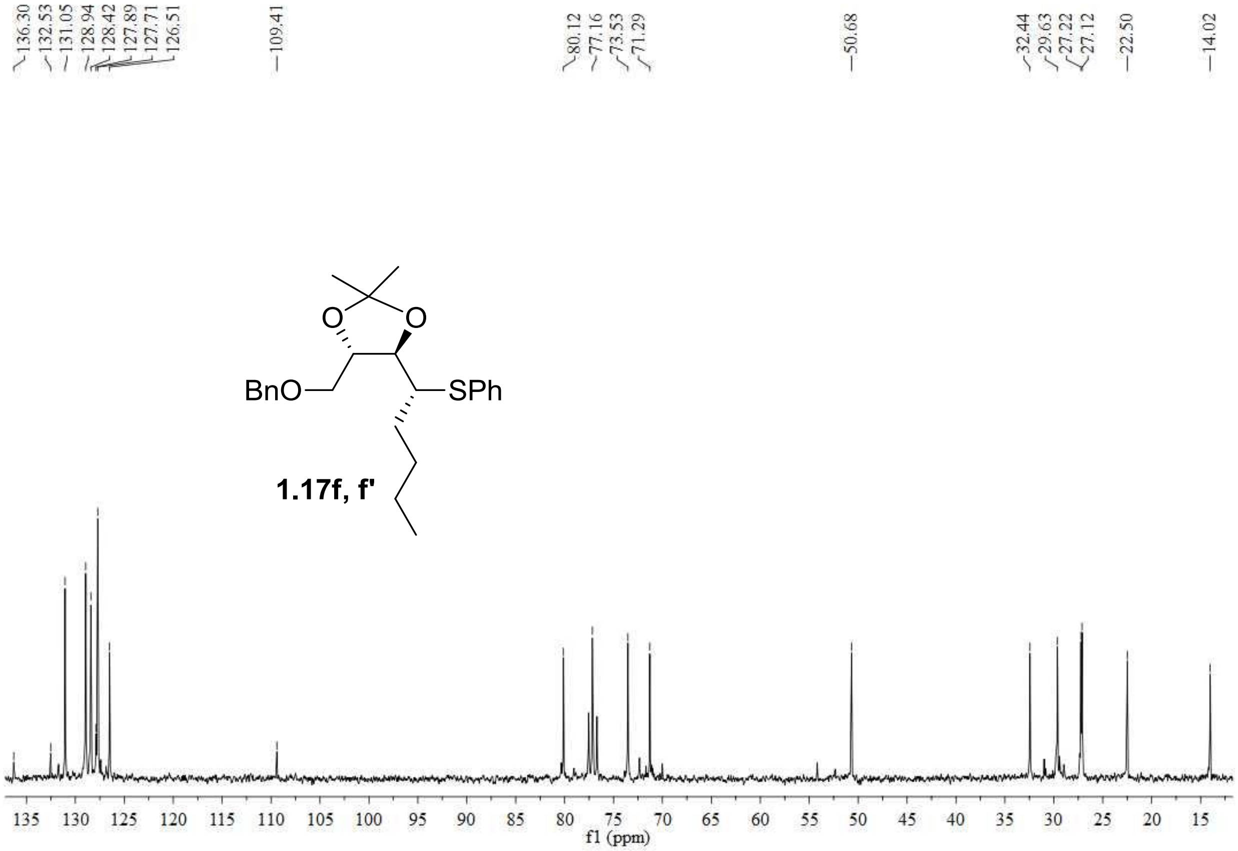
BnO
O
O
SPh
5
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

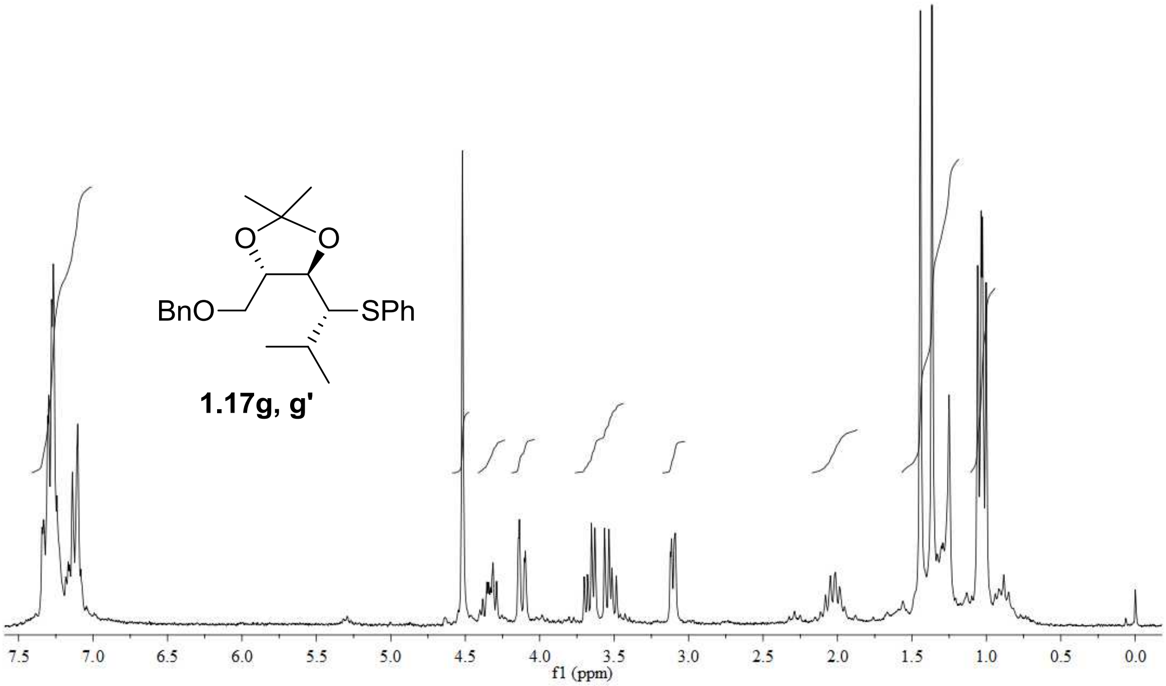

137.926
134.440
133.995
133.012
128.606
128.288
127.600
127.506
126.375
127.168
109.744
79.846
78.280
73.404
70.789
49.822
31.614
27.118
22.531
27.478
28.903
14.049
29.228
O
O
BnO
SPh
5
140
130
120
110
100
90
80
70
60
50
40
30
20
10

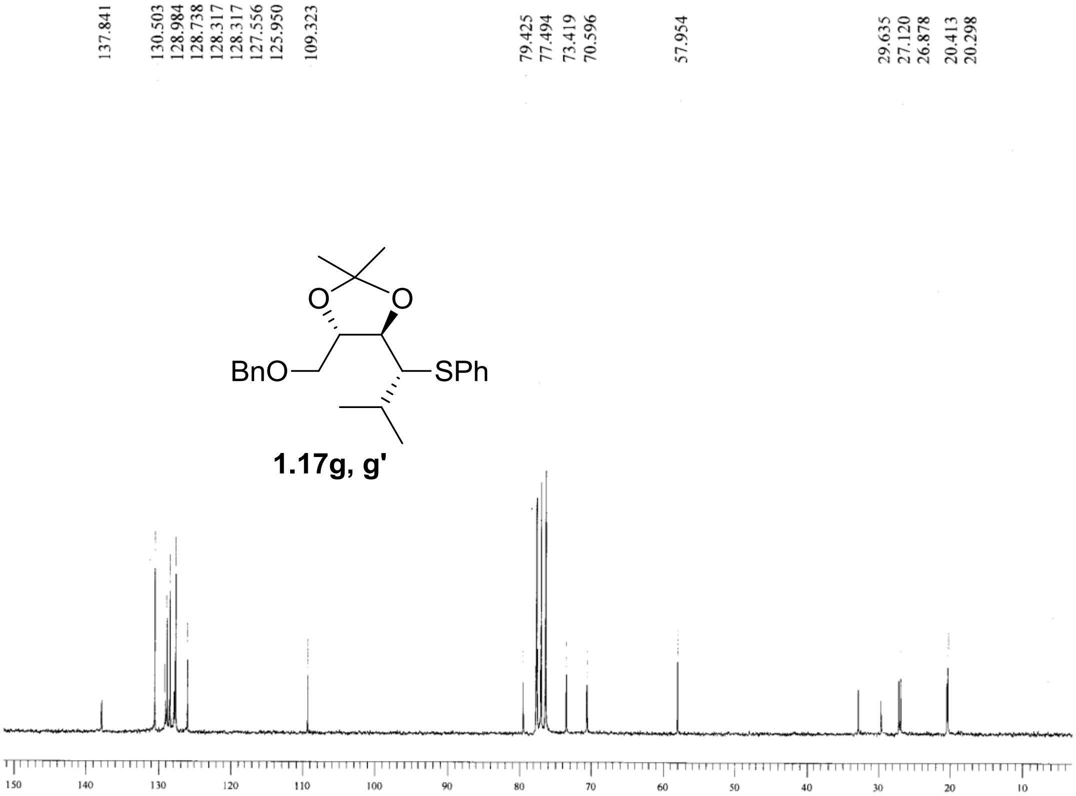
1.17e, e'


O
O
BnO
SPh
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
f1 (ppm)

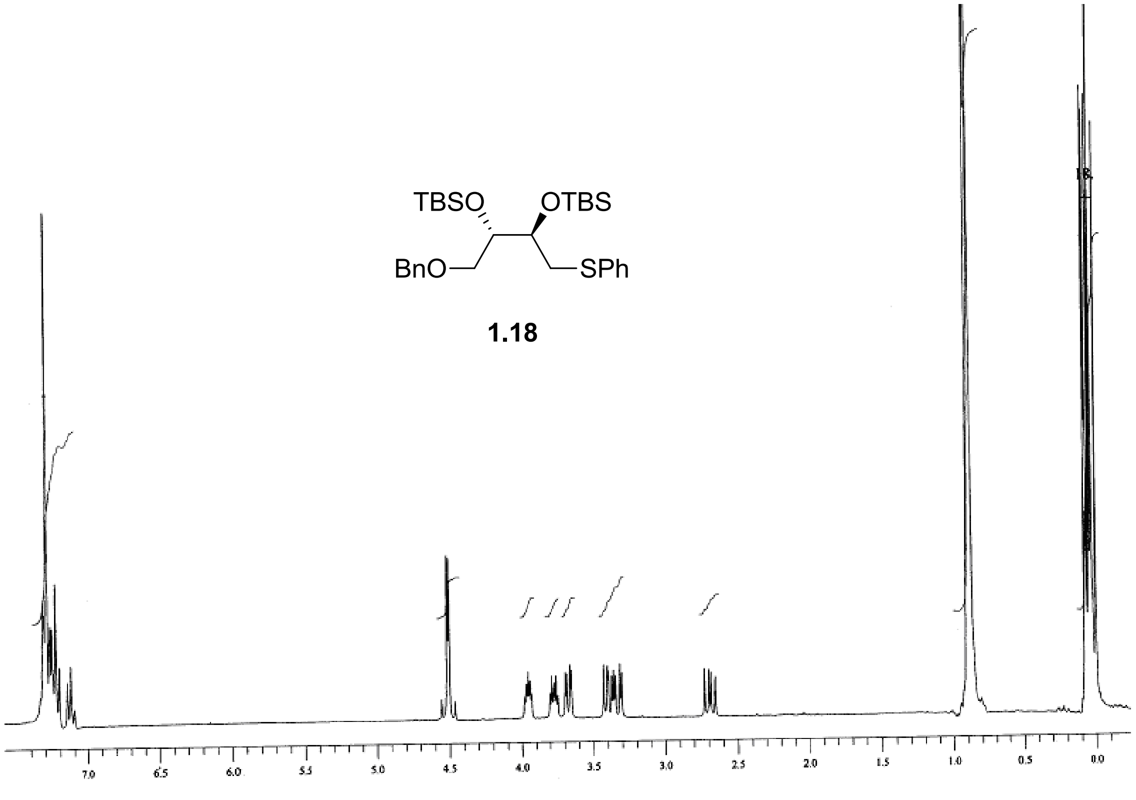
1.17f, f'


1.17f, f'
136.30
132.53
131.05
128.94
128.42
127.89
127.71
126.51
109.41
80.12
77.16
73.53
71.29
50.68
32.44
29.63
27.22
27.12
22.50
14.02
BnO
O
O
SPh
135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15
f1 (ppm)

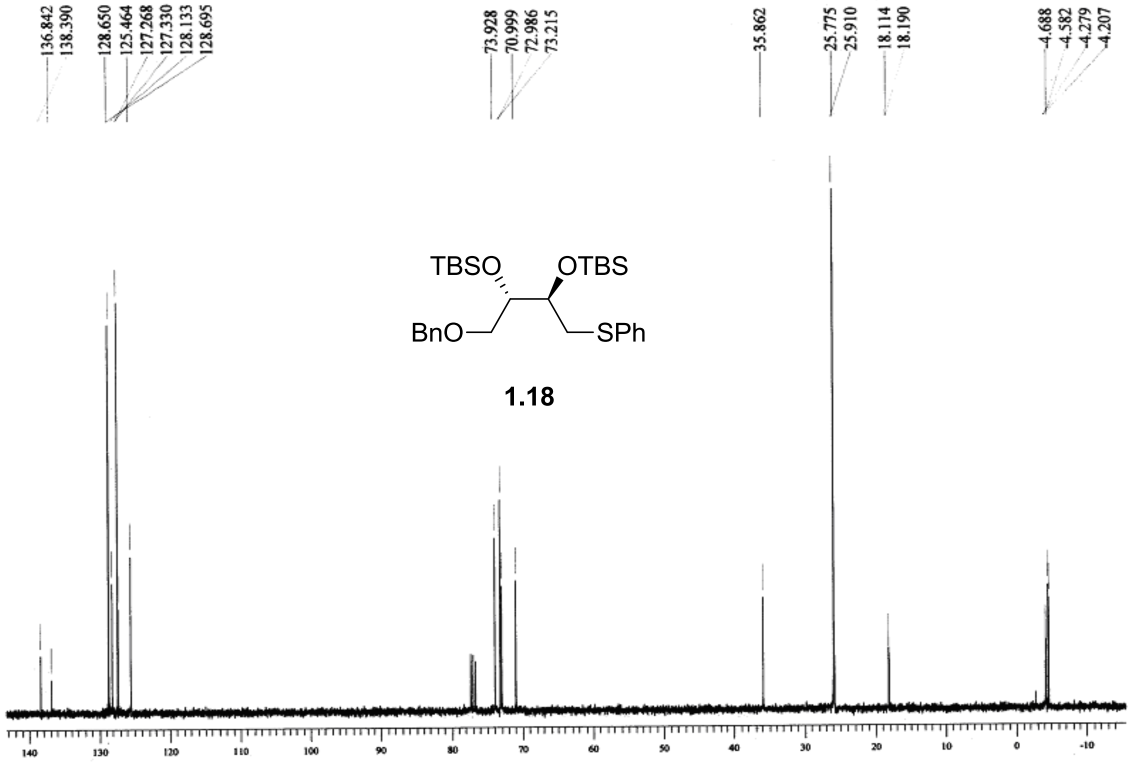

1.17g, g'
BnO
O
O
SPh
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


137.841
130.503
128.984
128.738
128.317
128.317
127.556
125.950
109.323
79.425
77.494
73.419
70.596
57.954
29.635
27.120
26.878
20.413
20.298
BnO
O
O
SPh
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

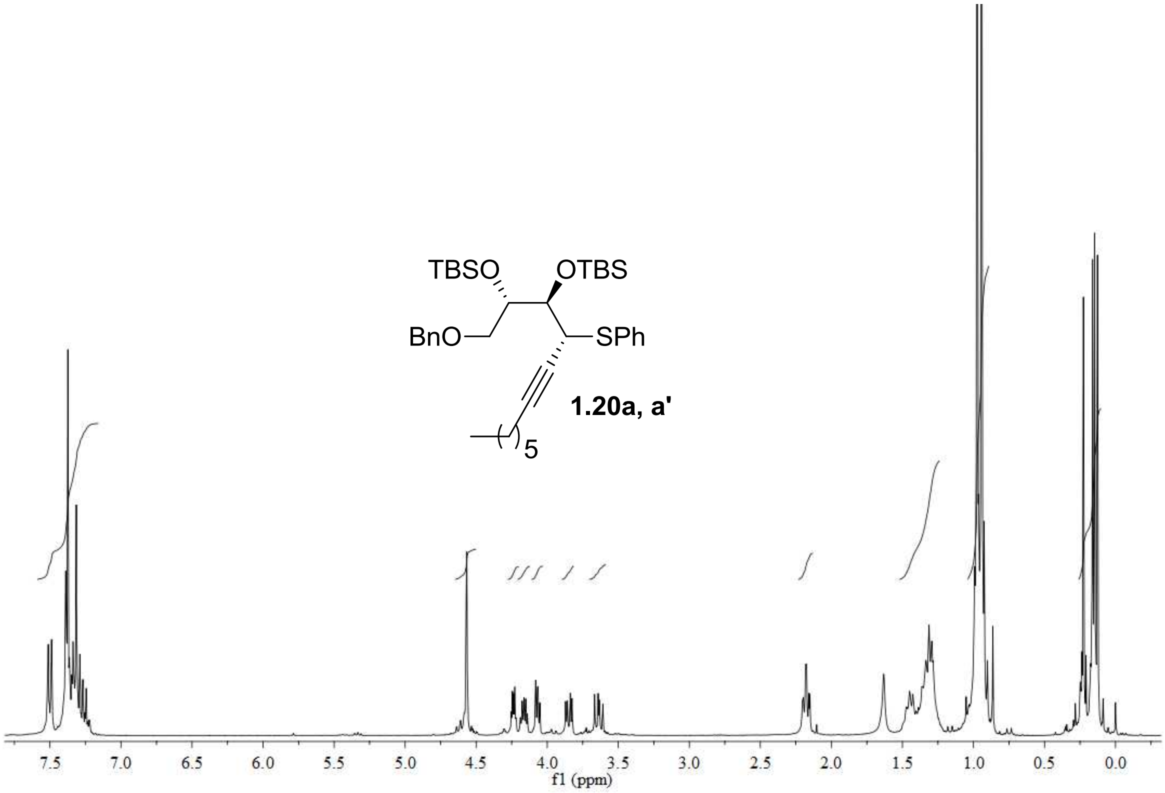
1.17g, g'


TBSO
OTBS
BnO
SPh
18
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

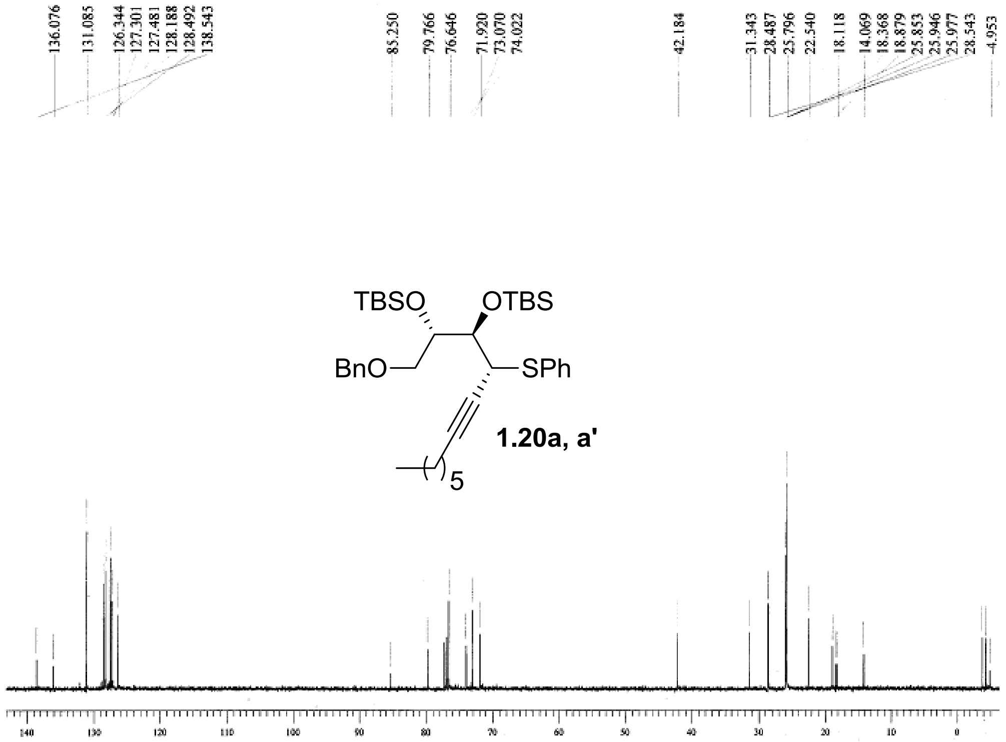
1.18


136.842
138.390
128.650
125.464
127.268
127.330
128.133
128.695
73.928
70.999
72.986
73.215
35.862
25.775
25.910
18.114
18.190
-4.688
-4.582
-4.279
-4.207
TBSO
OTBS
BnO
SPh
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

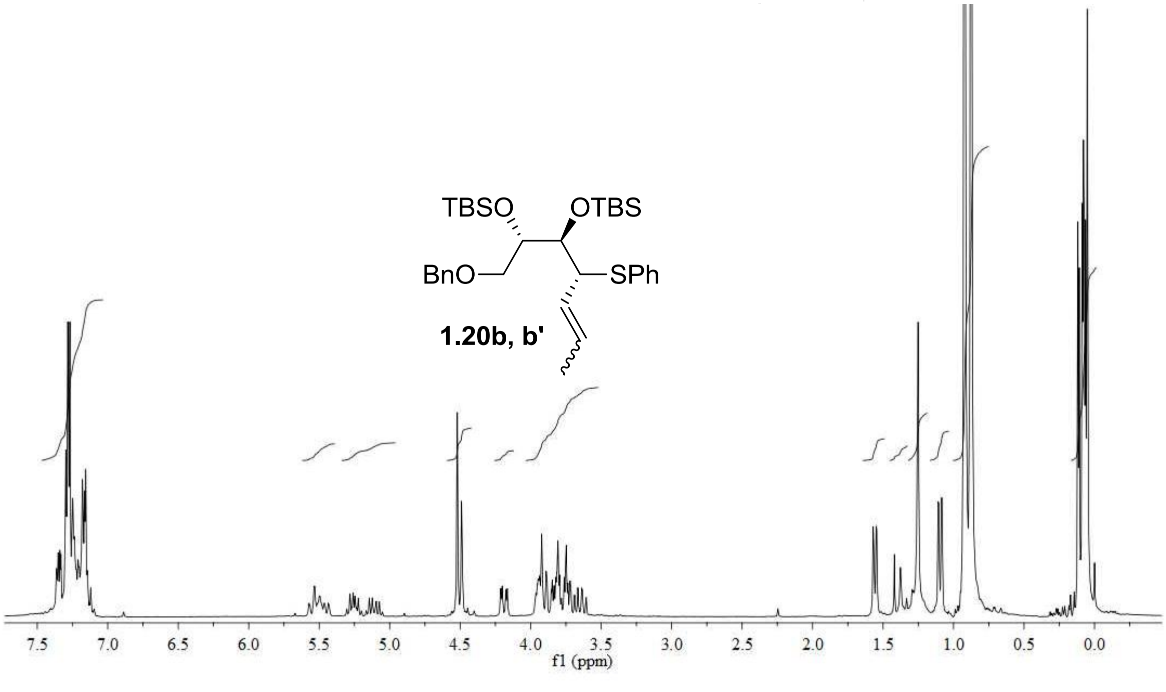
1.18


TBSO
OTBS
BnO
SPh
5
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
f1 (ppm)

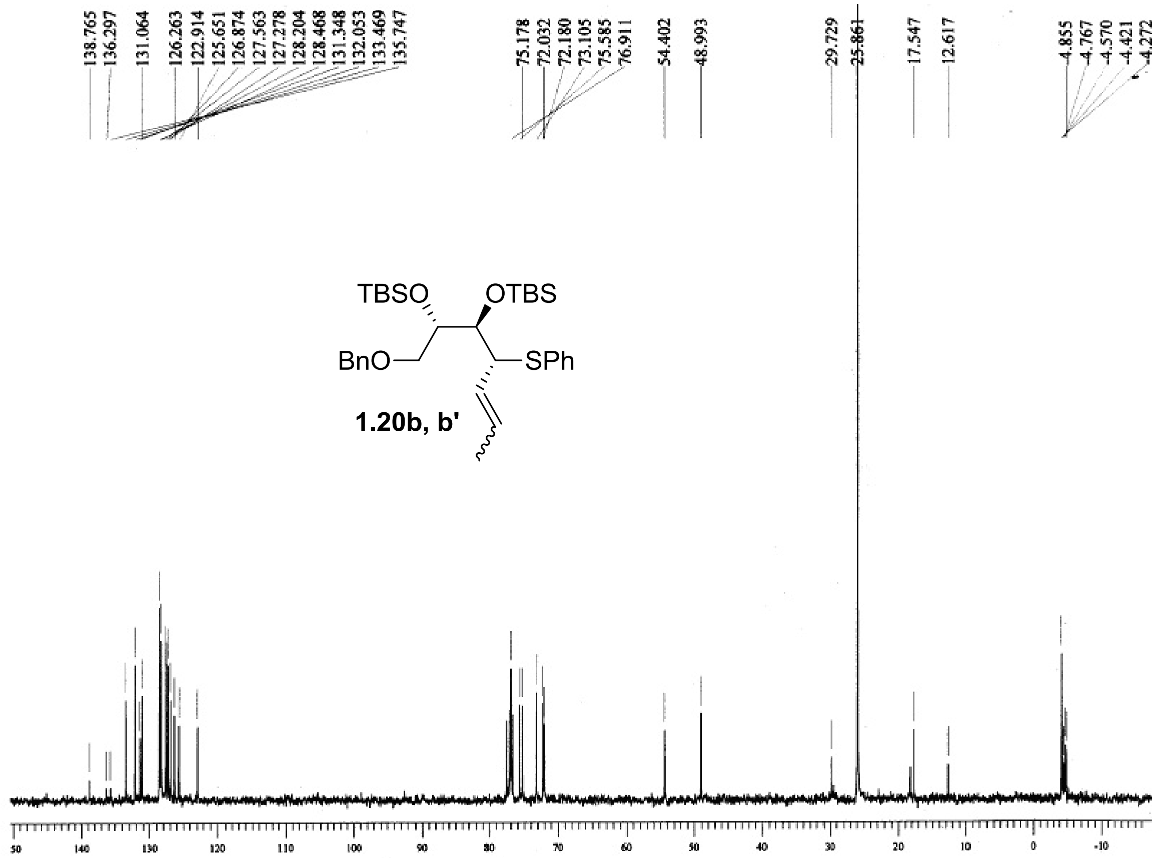
1.20a, a'

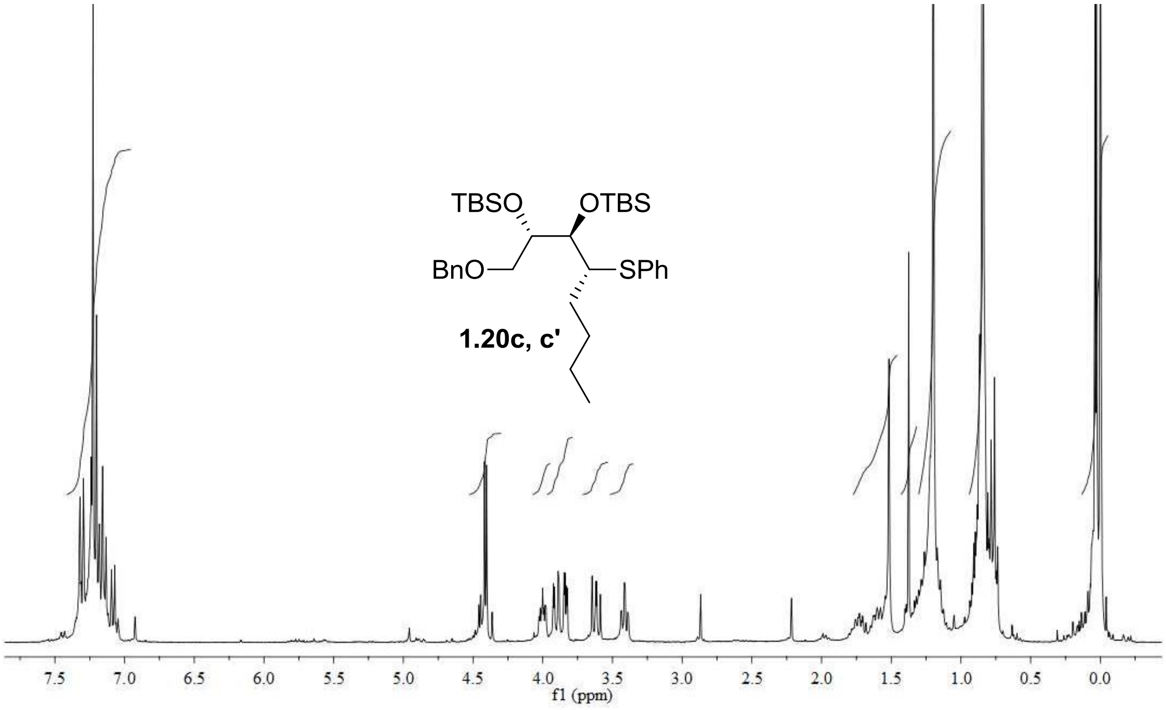

136.076
131.085
126.344
127.301
127.481
128.188
128.492
138.543
85.250
79.766
76.646
71.920
73.070
74.022
42.184
31.343
28.487
25.796
22.540
18.118
14.069
18.368
18.879
25.853
25.946
25.977
28.543
-4.953
TBSO
OTBS
BnO
SPh
5
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

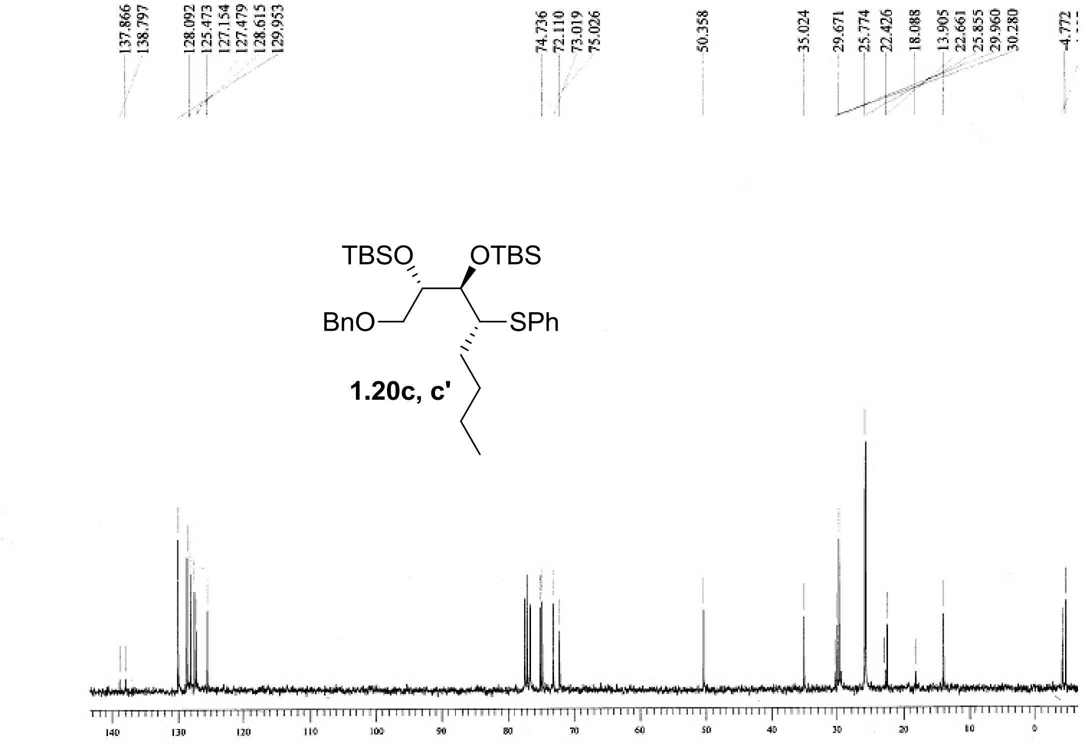
1.20a, a'


TBSO
OTBS
BnO
SPh
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
f1 (ppm)

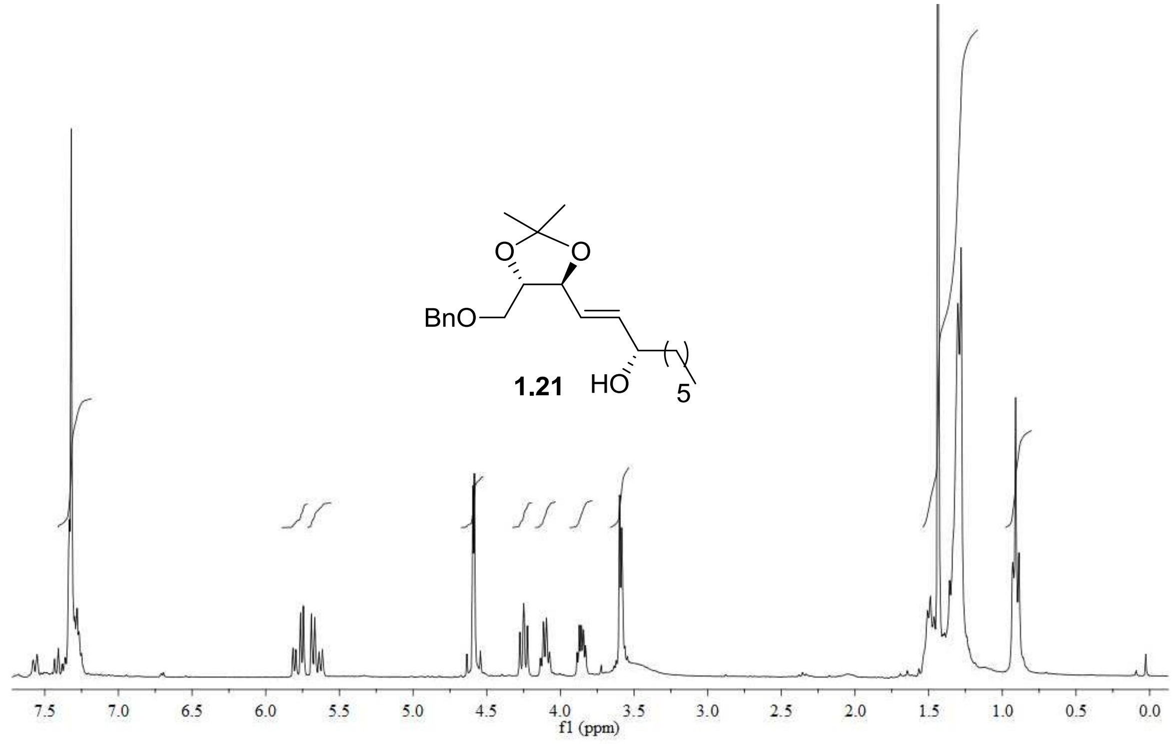
1.20b, b'


138.765
136.297
131.064
126.263
122.914
125.651
126.874
127.563
127.278
128.204
128.468
131.348
132.053
133.469
135.747
75.178
72.032
72.180
73.105
75.585
76.911
54.402
48.993
29.729
25.861
17.547
12.617
-4.855
-4.767
-4.570
-4.421
-4.272
TBSO
OTBS
BnO
SPh
1.20b, b'
50
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

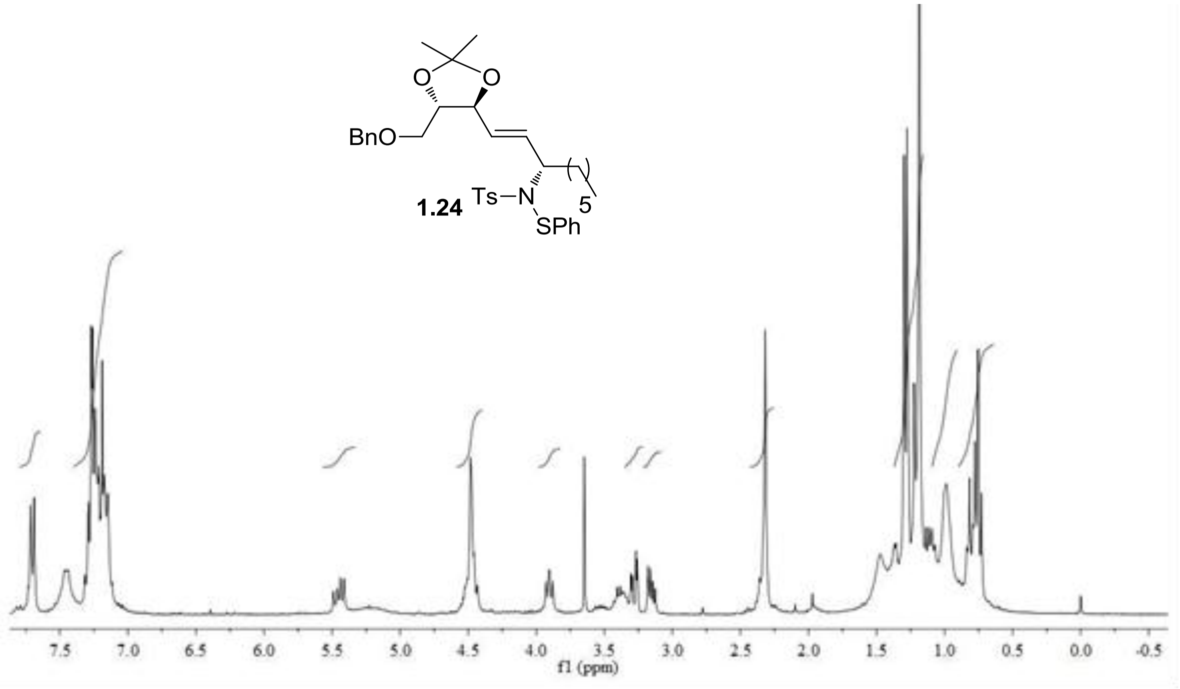

TBSO
OTBS
BnO
SPh
1.20c, c'
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


137.866
138.797
128.092
125.473
127.154
127.479
128.615
129.953
74.736
72.110
73.019
75.026
50.358
35.024
29.671
25.774
22.426
18.088
13.905
22.661
25.855
29.960
30.280
-4.772
TBSO
OTBS
BnO
SPh
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

1.20c, c'

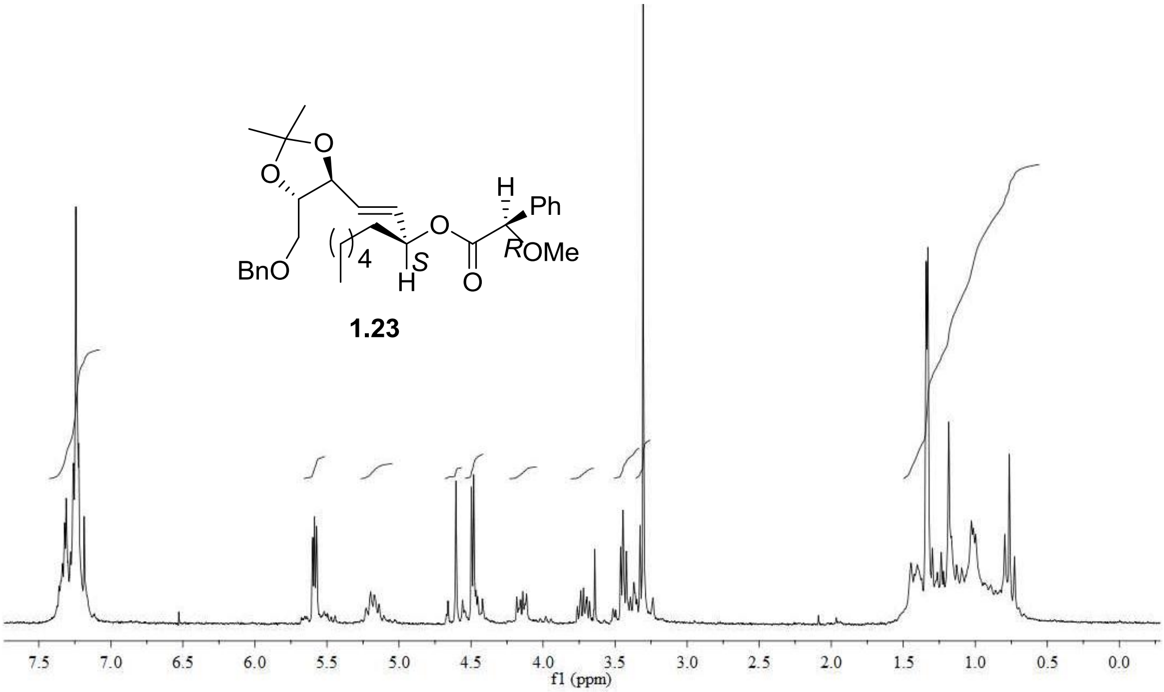

O
O
BnO
HO
5
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

1.21



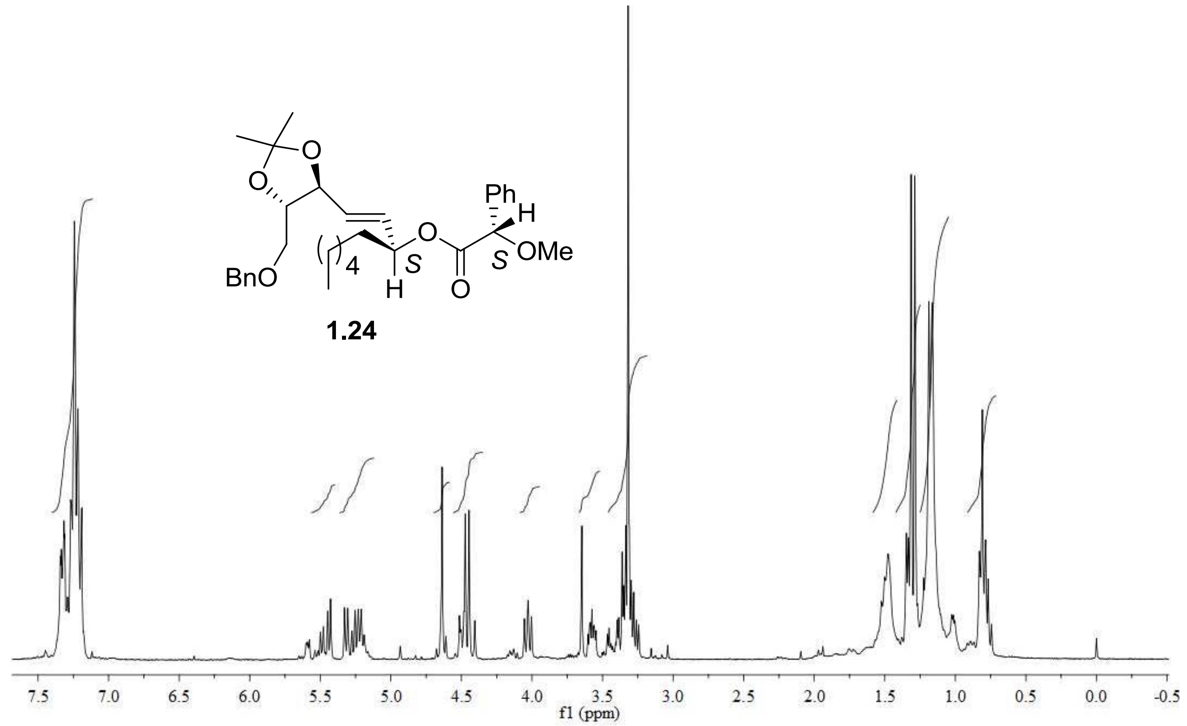
1.24

BnO
O
O
Ts—N
SPh
5
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
-0.5
f1 (ppm)

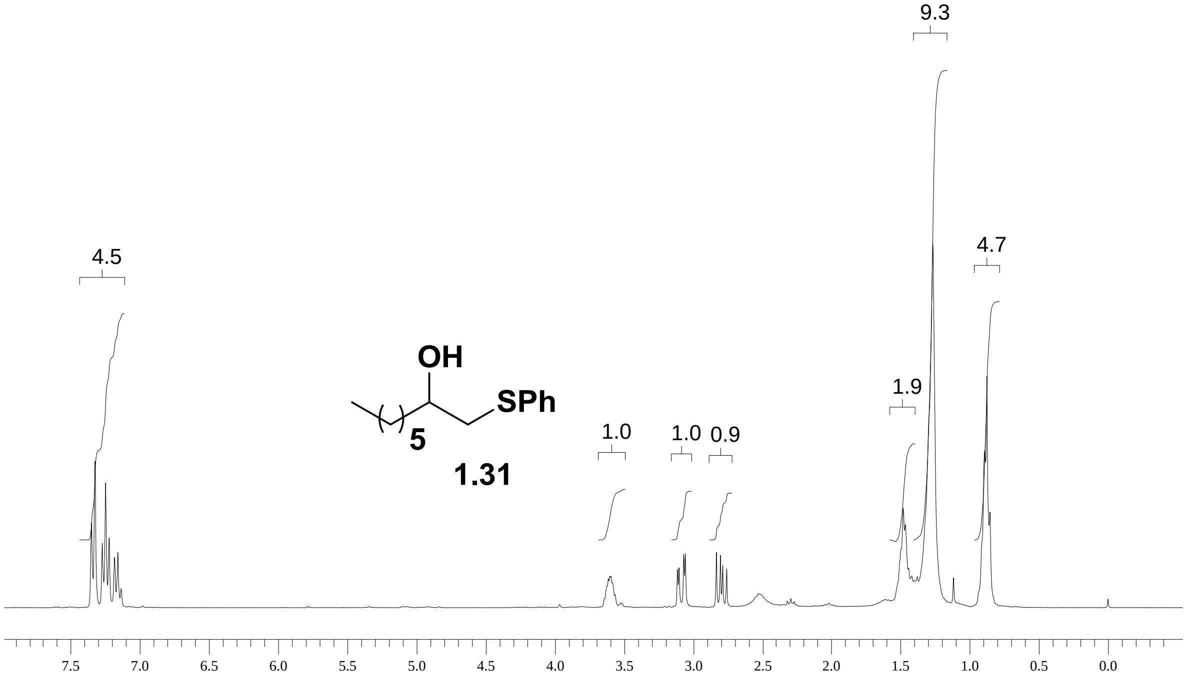


1.23

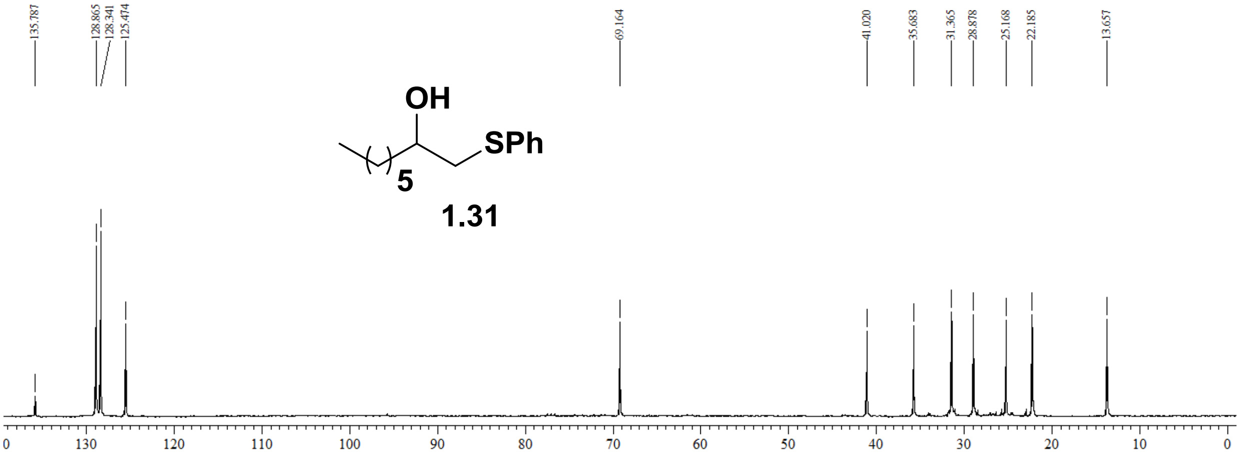
O
O
BnO
4
S
H
O
O
H
Ph
R
OMe
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


O
O
BnO
4
H
S
O
O
Ph
H
S
OMe
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
-0.5
f1 (ppm)

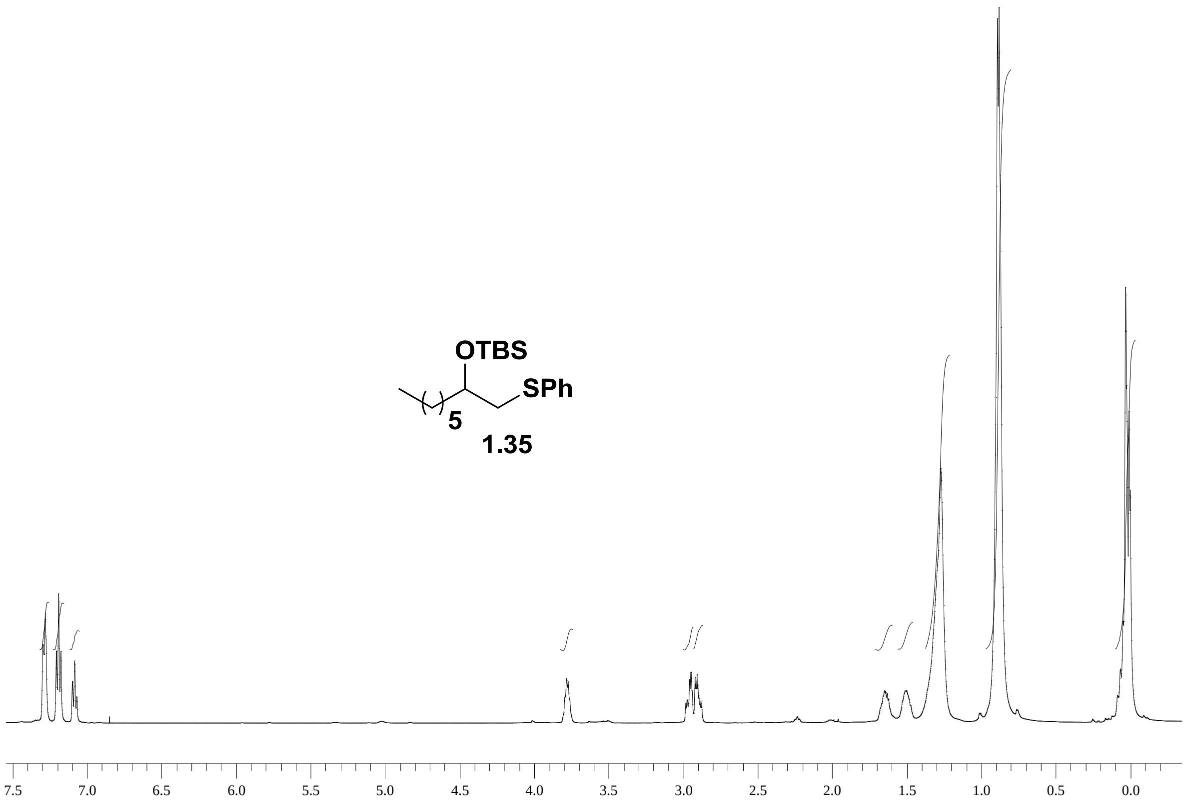
1.24


OH
SPh
5
4.5
1.0
1.0
0.9
1.9
9.3
4.7
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

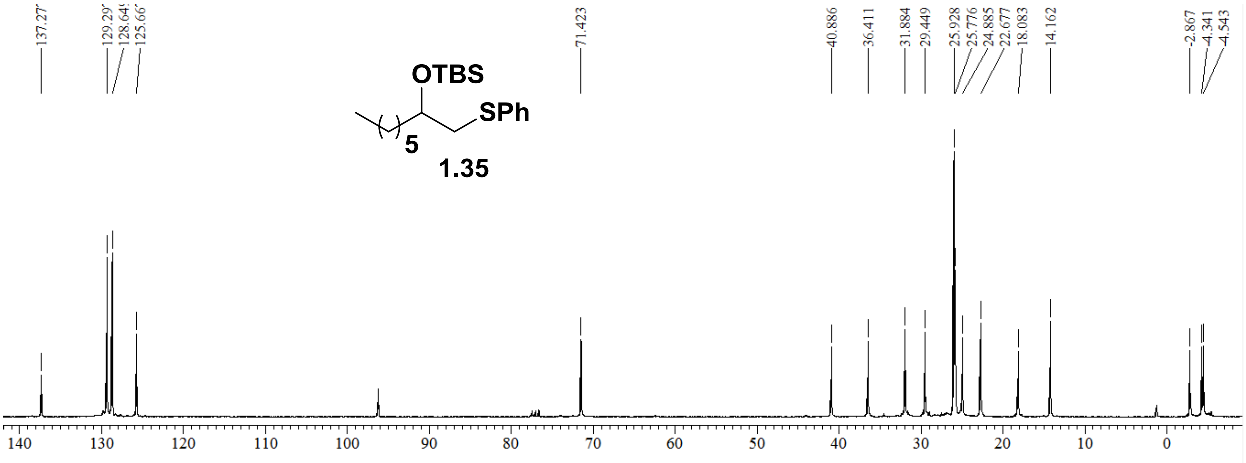
1.31

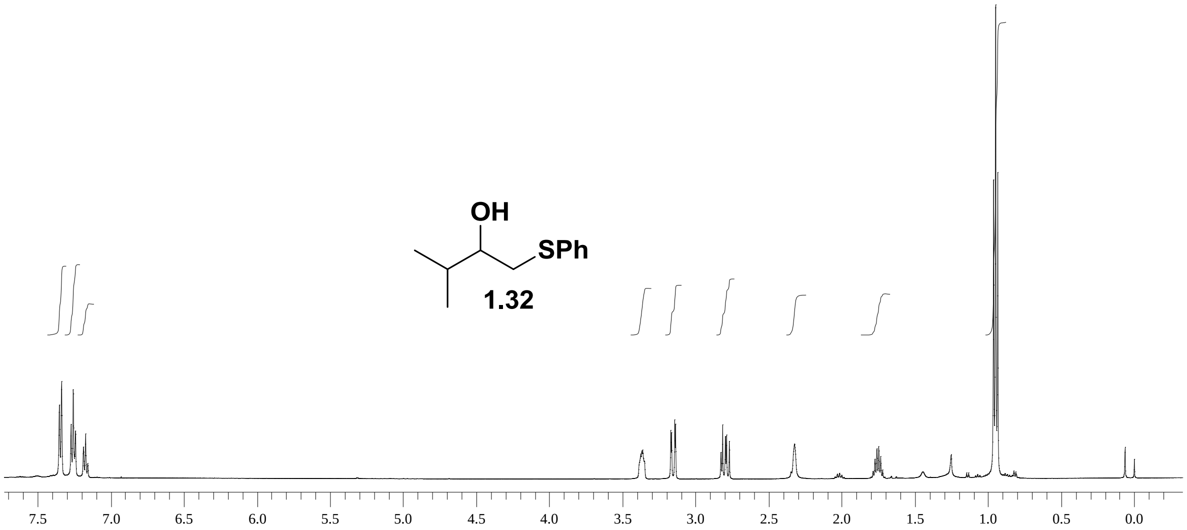

135.787
128.865
128.341
125.474
69.164
41.020
35.683
31.365
28.878
25.168
22.185
13.657
OH
SPh
5
0
130
120
110
100
90
80
70
60
50
40
30
20
10
0

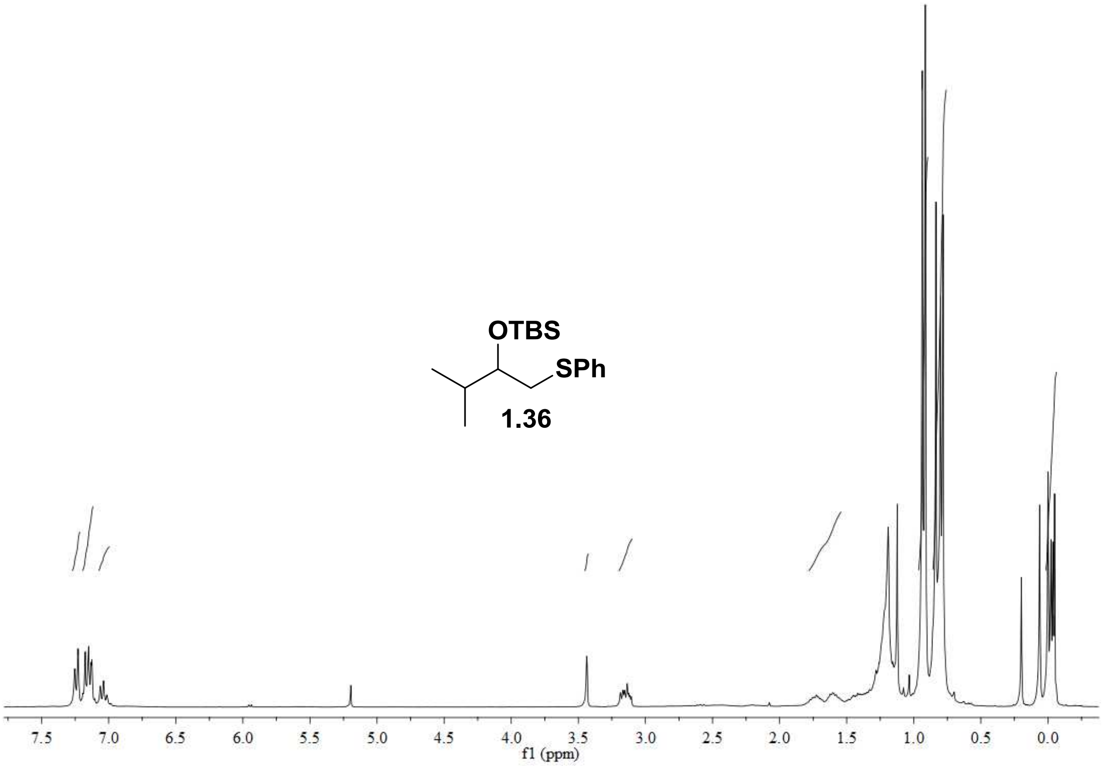
1.31

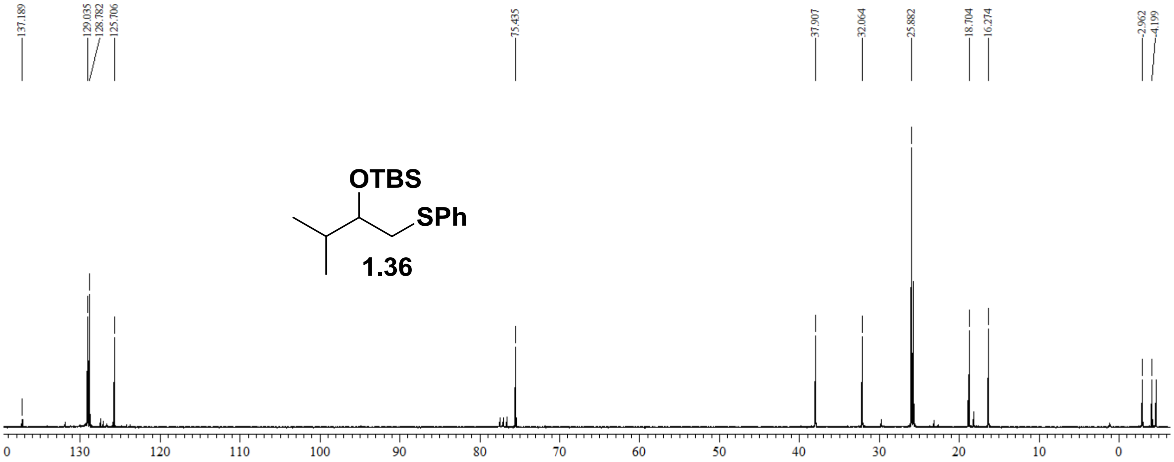

OTBS
SPh
5
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

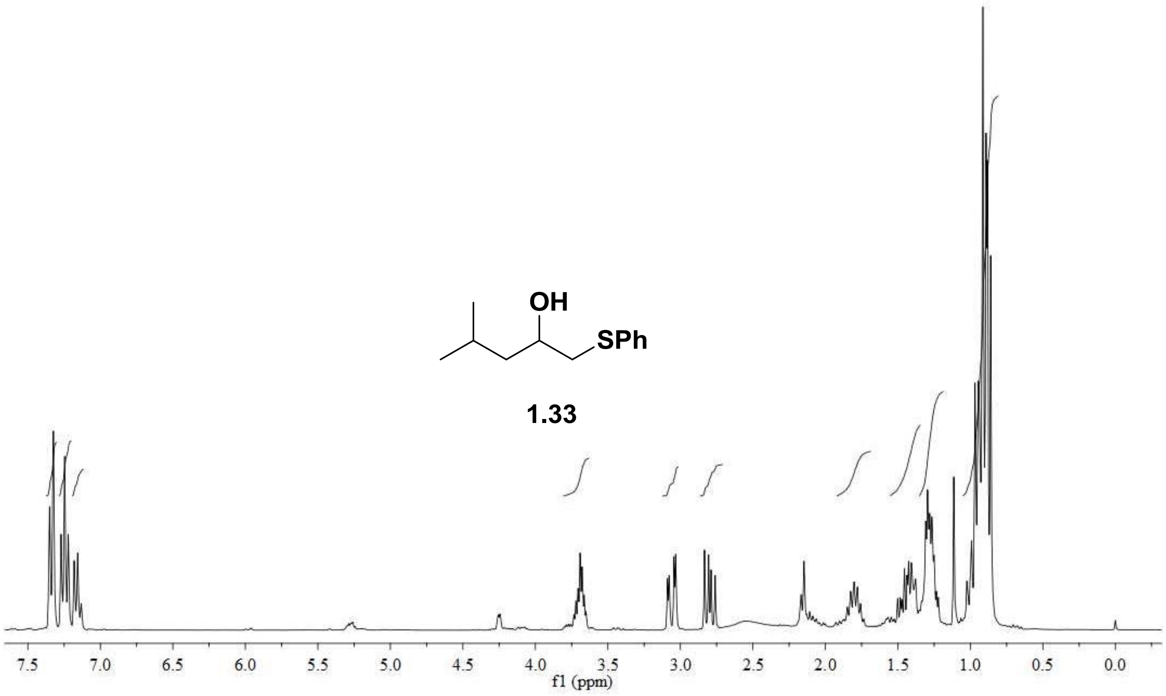
1.35

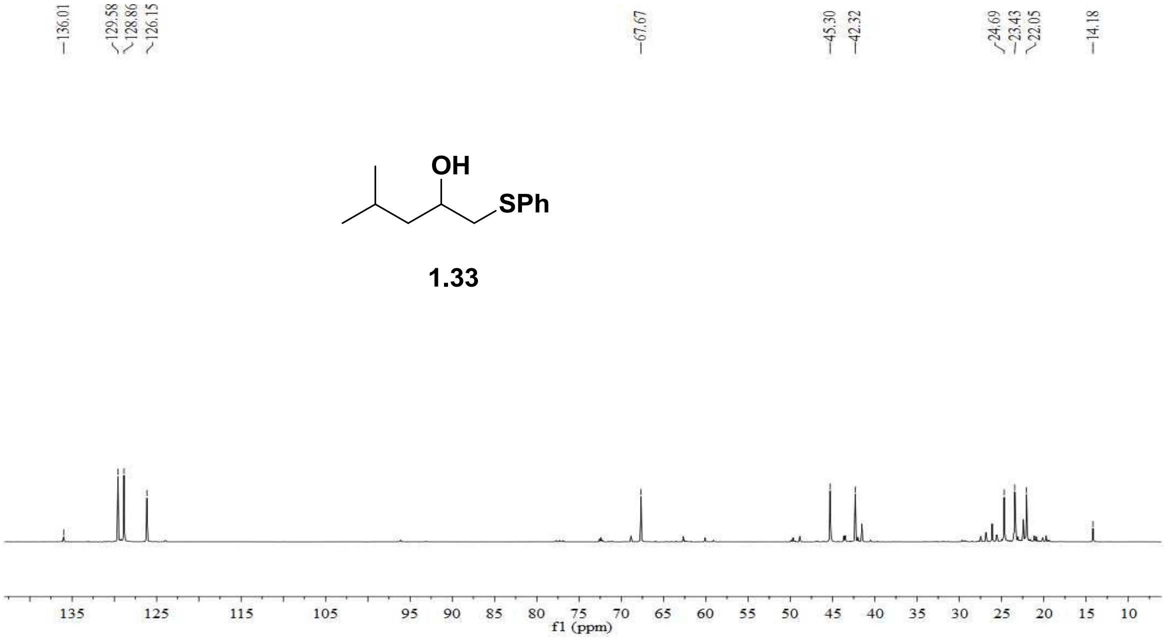

137.27
129.29
128.64
125.66
71.423
40.886
36.411
31.884
29.449
25.928
25.776
24.885
22.677
18.083
14.162
-2.867
-4.341
-4.543
OTBS
SPh
5
1.35
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

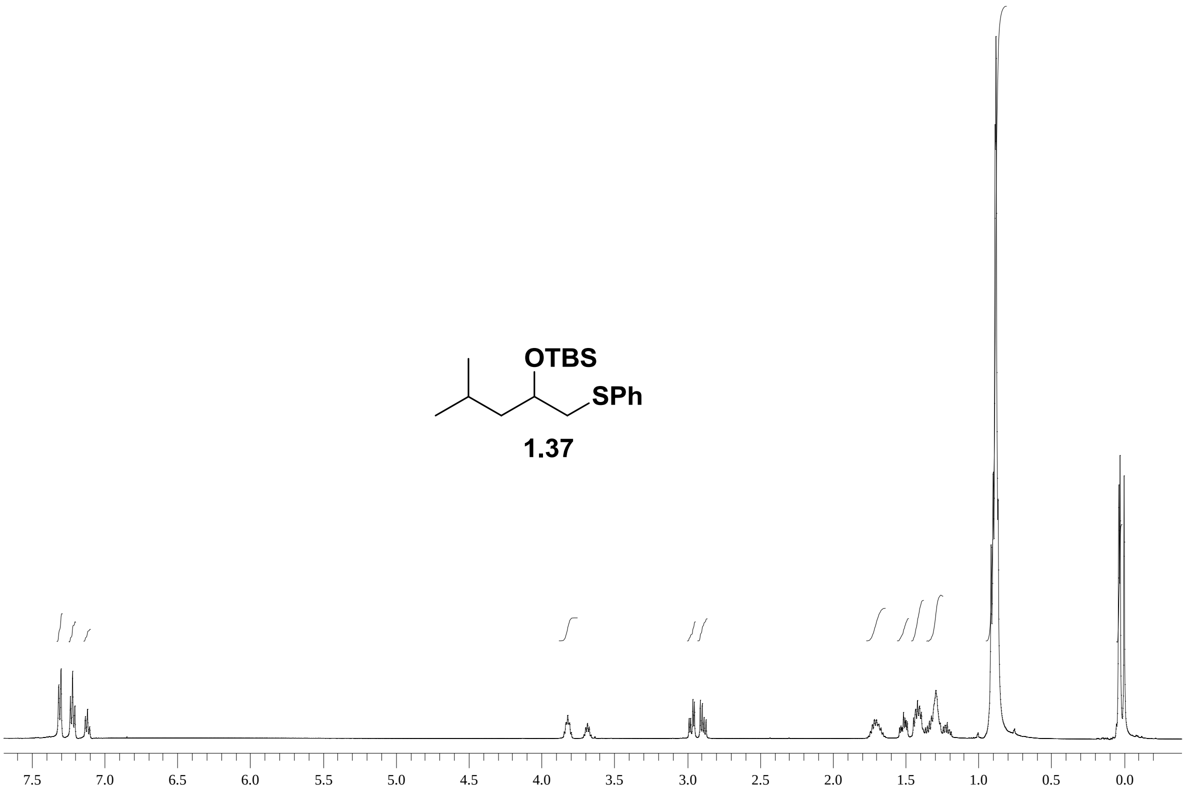

OH
SPh
1.32
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


OTBS
SPh
1.36
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
f1 (ppm)

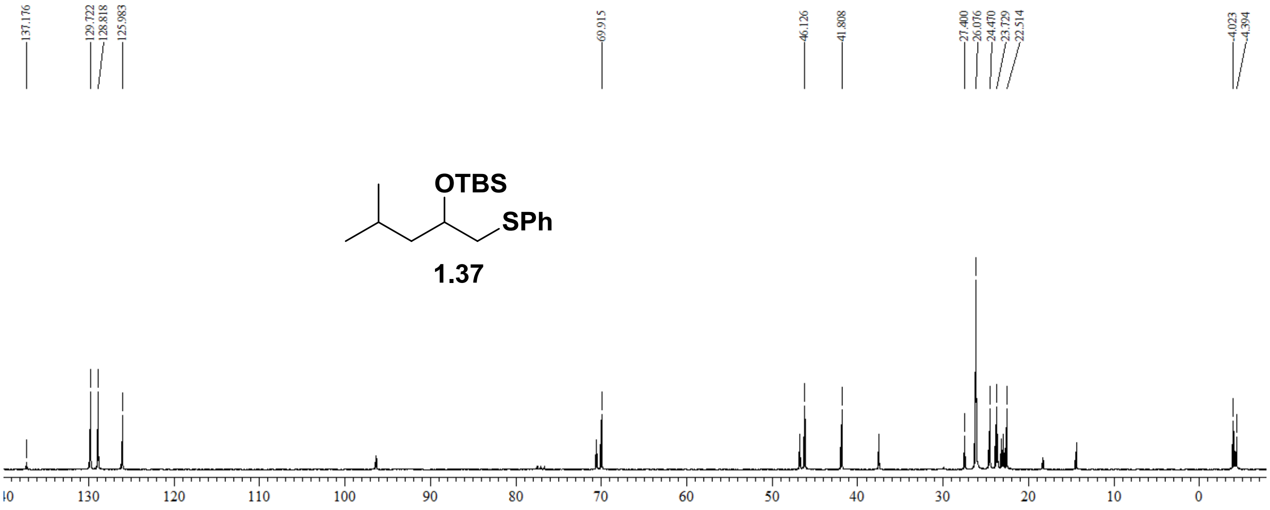

137.189
129.035
128.782
125.706
75.435
37.907
32.064
25.882
18.704
16.274
-2.962
-4.199
OTBS
SPh
1.36
0
130
120
110
100
90
80
70
60
50
40
30
20
10
0


OH
SPh
1.33
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
f1 (ppm)

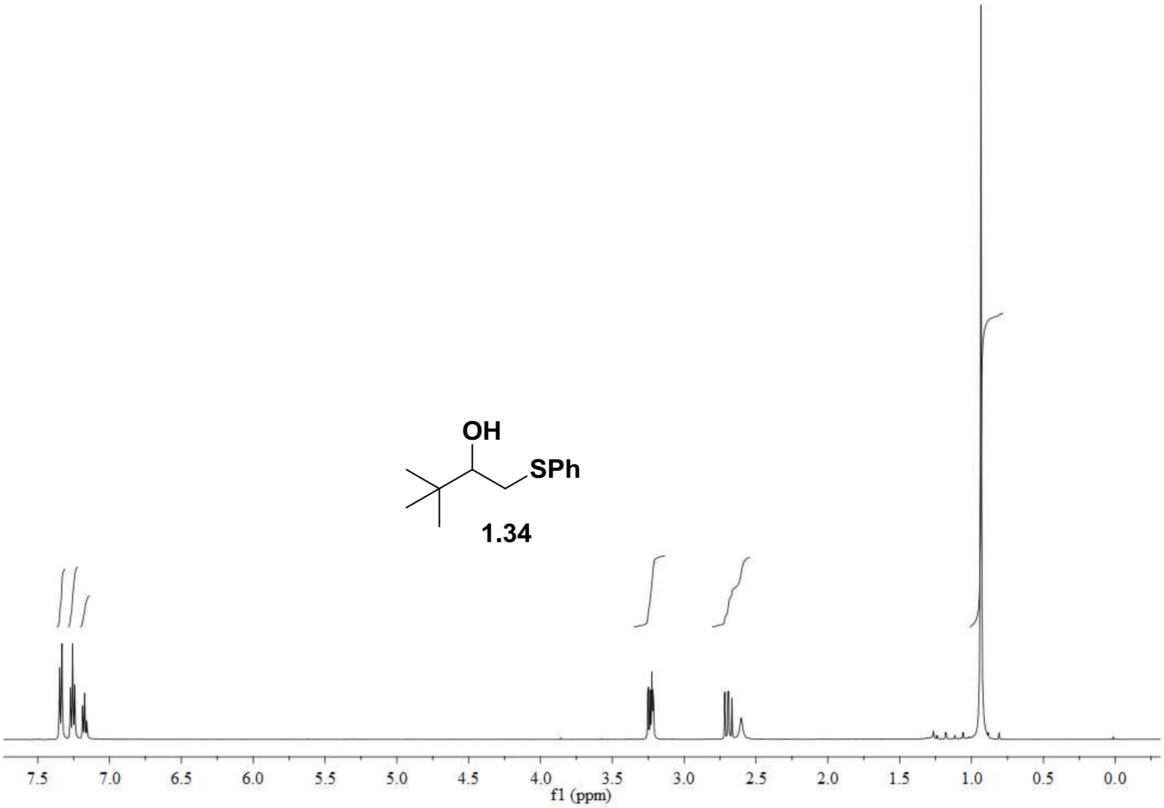

136.01
129.58
128.86
126.15
67.67
45.30
42.32
24.69
23.43
22.05
14.18
OH
SPh
1.33
135
125
115
105
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
f1 (ppm)

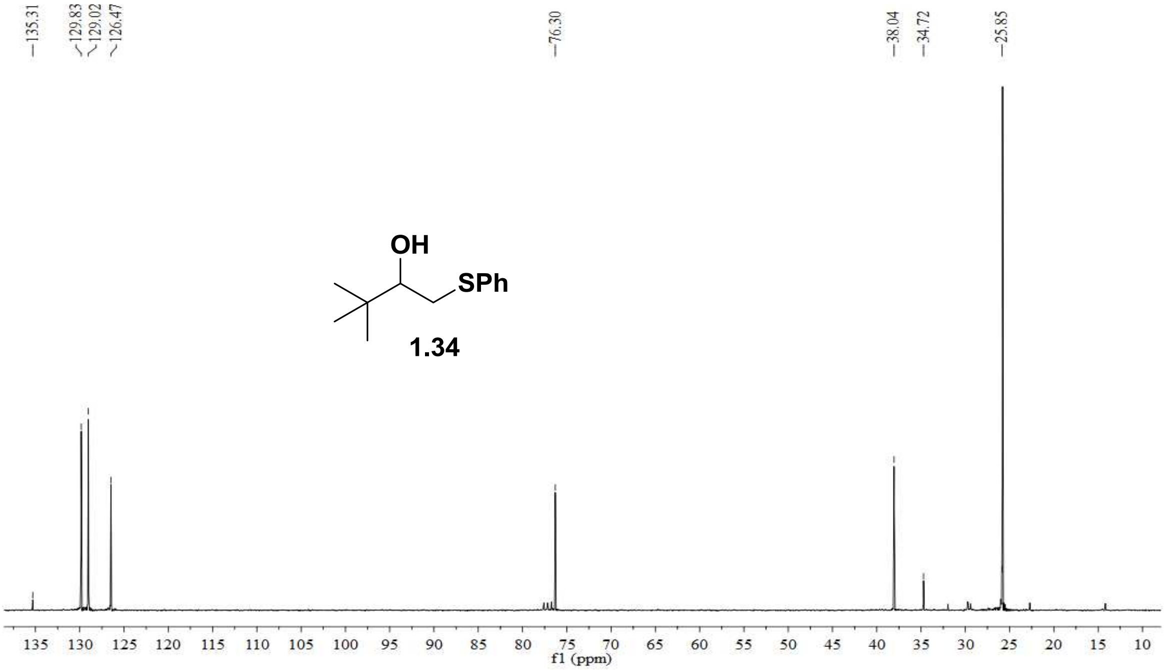

OTBS
SPh
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

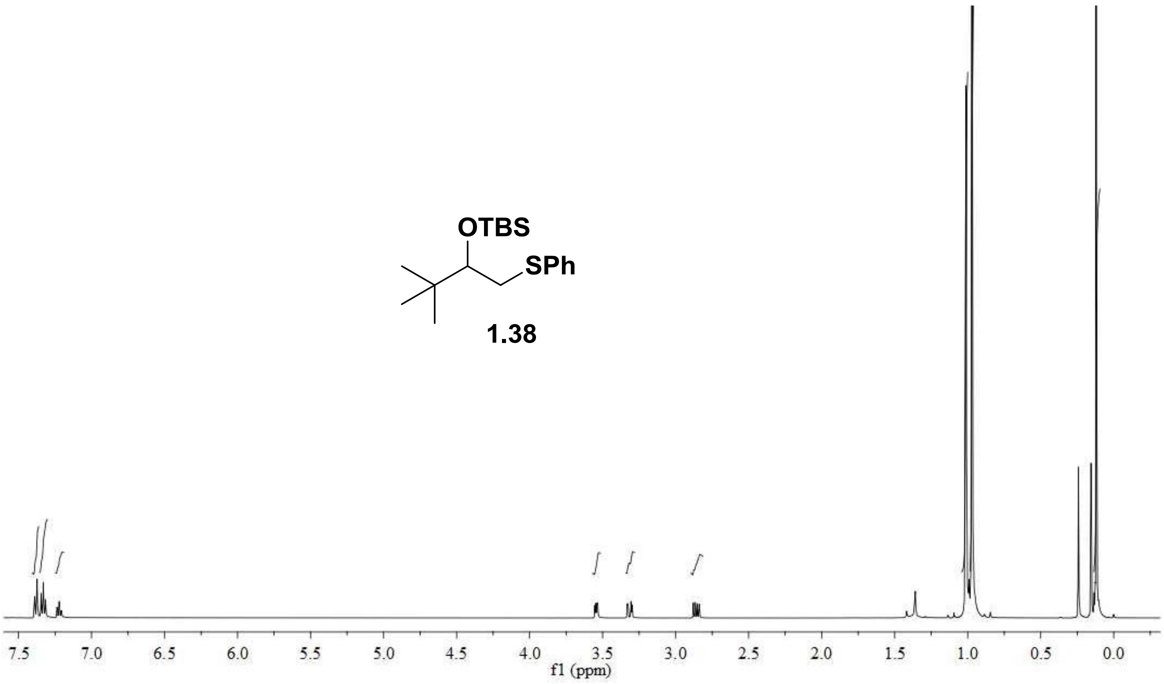
1.37


137.176
129.722
128.818
125.983
69.915
46.126
41.808
27.400
26.076
24.470
23.729
22.514
-4.023
-4.394
OTBS
SPh
40
130
120
110
100
90
80
70
60
50
40
30
20
10
0

1.37

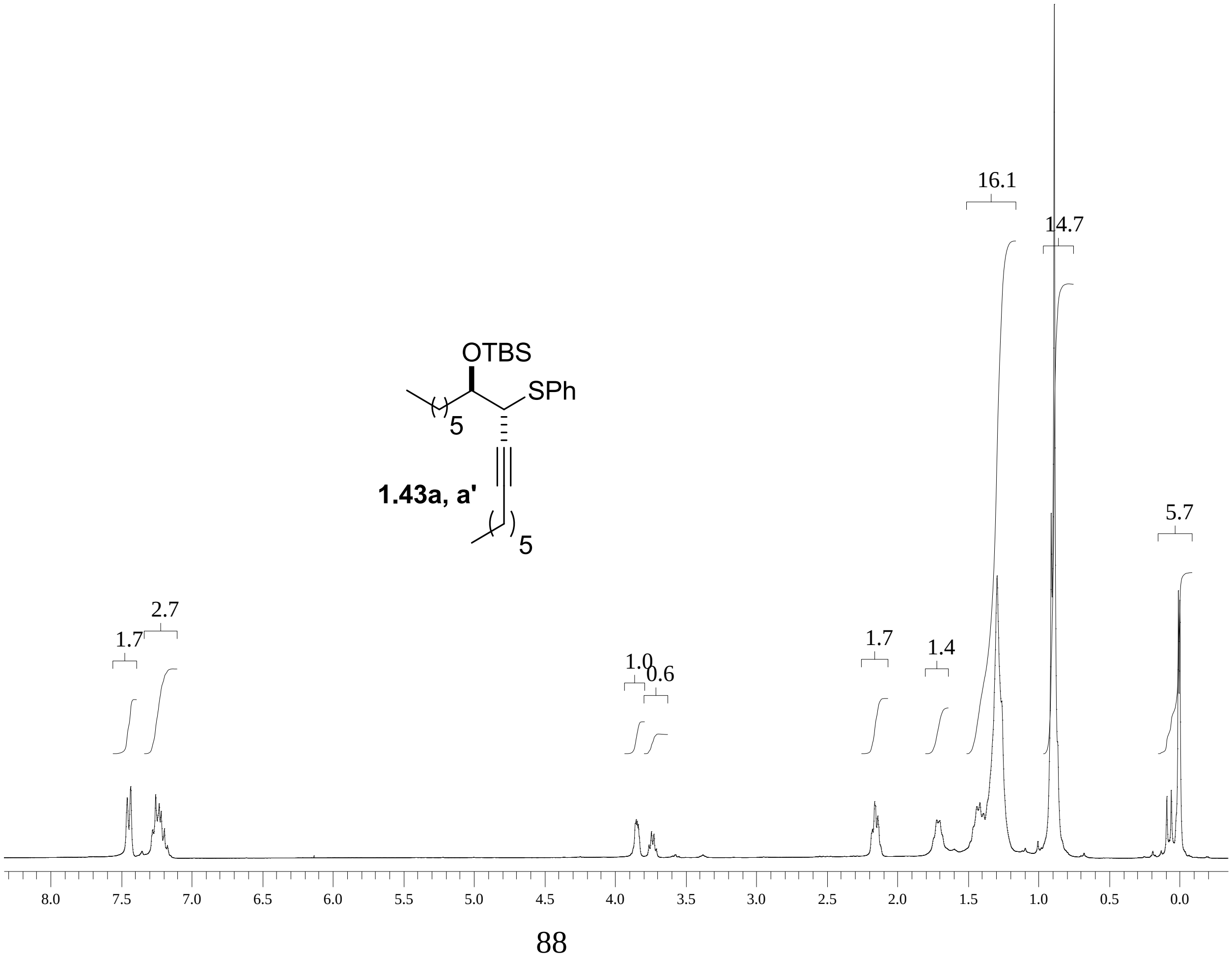

OH
SPh
1.34
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


135.31
129.83
129.02
126.47
76.30
38.04
34.72
25.85
OH
SPh
1.34
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
f1 (ppm)



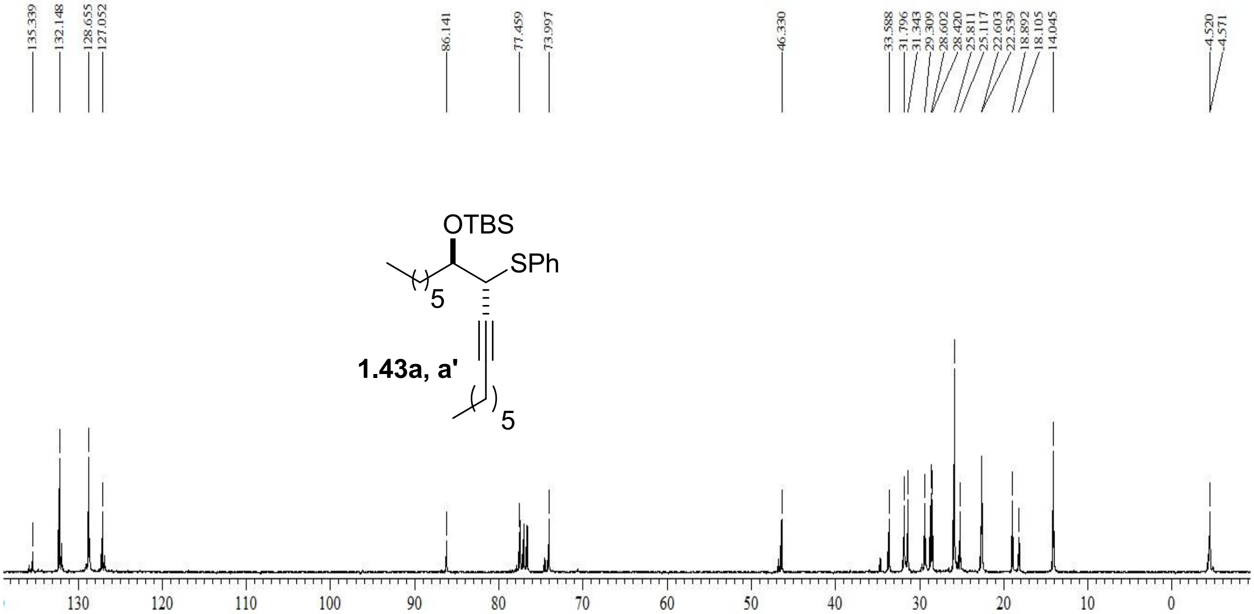
1.38

OTBS
SPh
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
f1 (ppm)



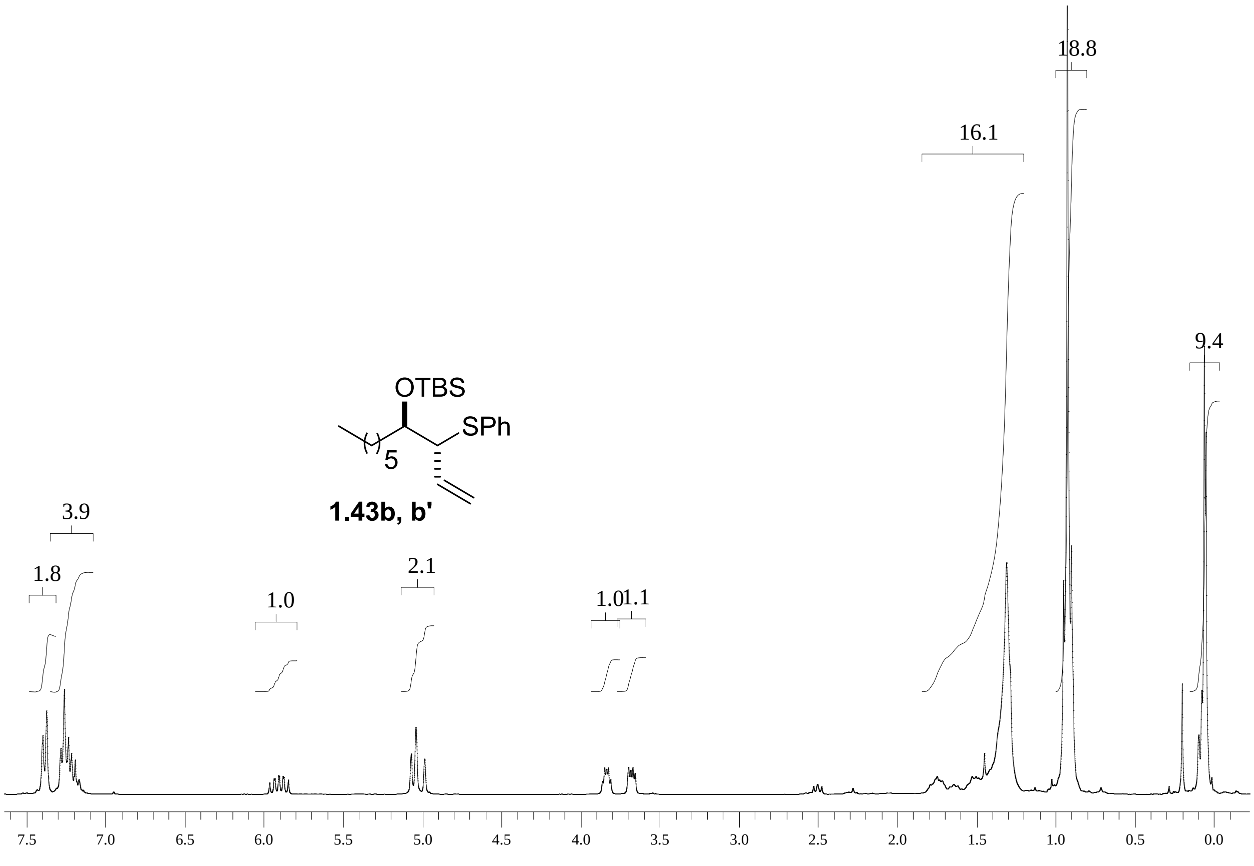
1.43a, a'

OTBS
SPh
5
5
16.1
14.7
5.7
2.7
1.7
1.0
0.6
1.7
1.4
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0



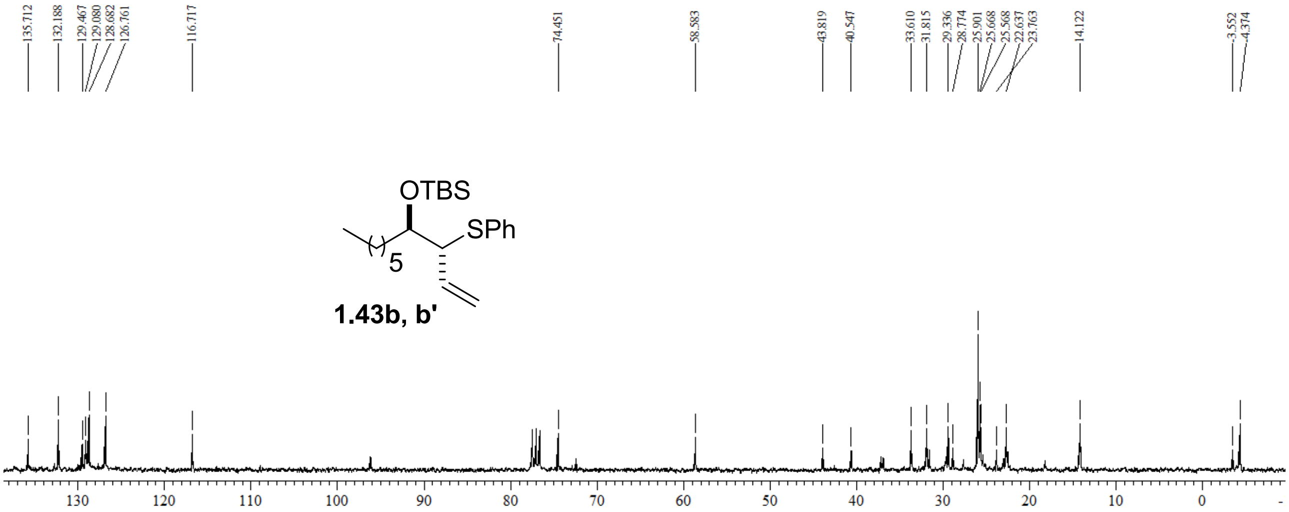
1.43a, a'

135.339
132.148
128.655
127.052
86.141
77.459
73.997
46.330
33.588
31.796
31.343
29.309
28.602
28.420
25.811
25.117
22.603
22.539
18.892
18.105
14.045
-4.520
-4.571
OTBS
SPh
5
5
130
120
110
100
90
80
70
60
50
40
30
20
10
0

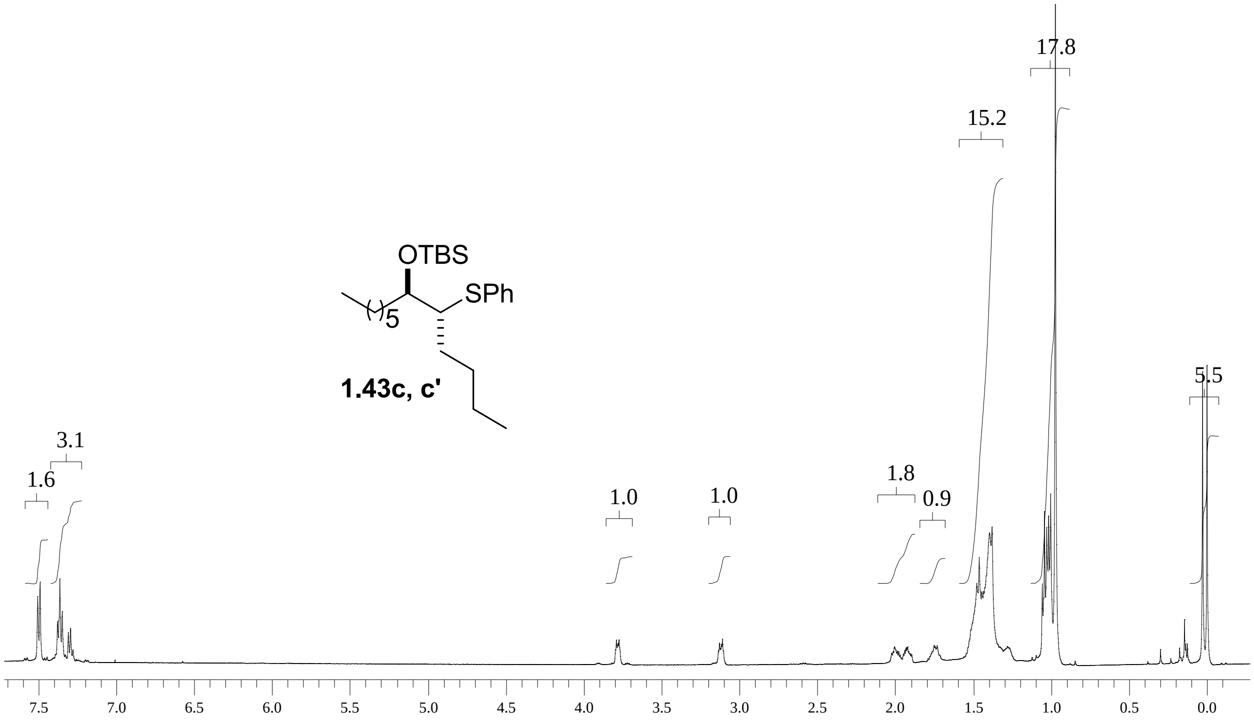


1.43b, b'

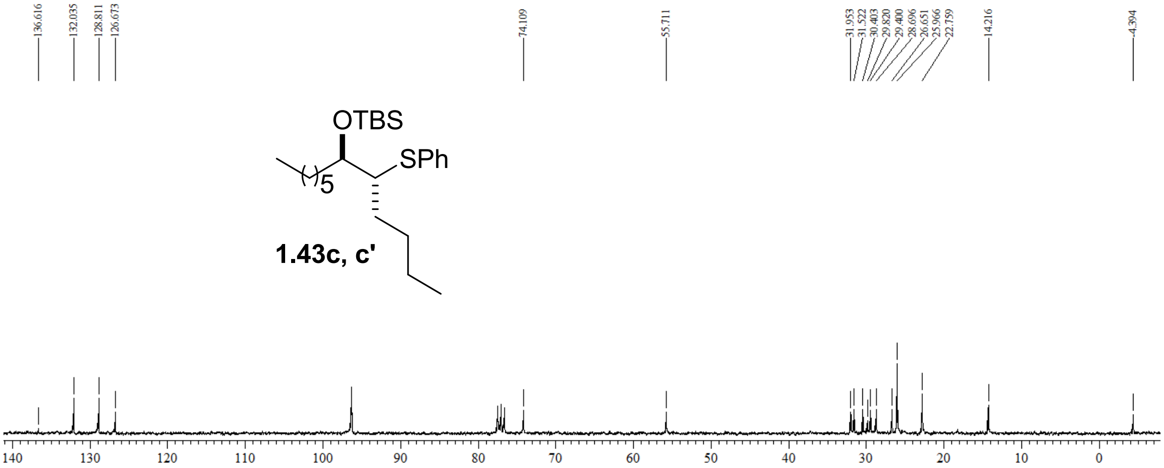
OTBS
SPh
5
18.8
16.1
9.4
3.9
1.8
1.0
2.1
1.0
1.1
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


135.712
132.188
129.467
129.080
128.682
126.761
116.717
74.451
58.583
43.819
40.547
33.610
31.815
29.336
28.774
25.901
25.668
25.568
22.637
23.763
14.122
-3.552
-4.374
OTBS
SPh
5
130
120
110
100
90
80
70
60
50
40
30
20
10
0

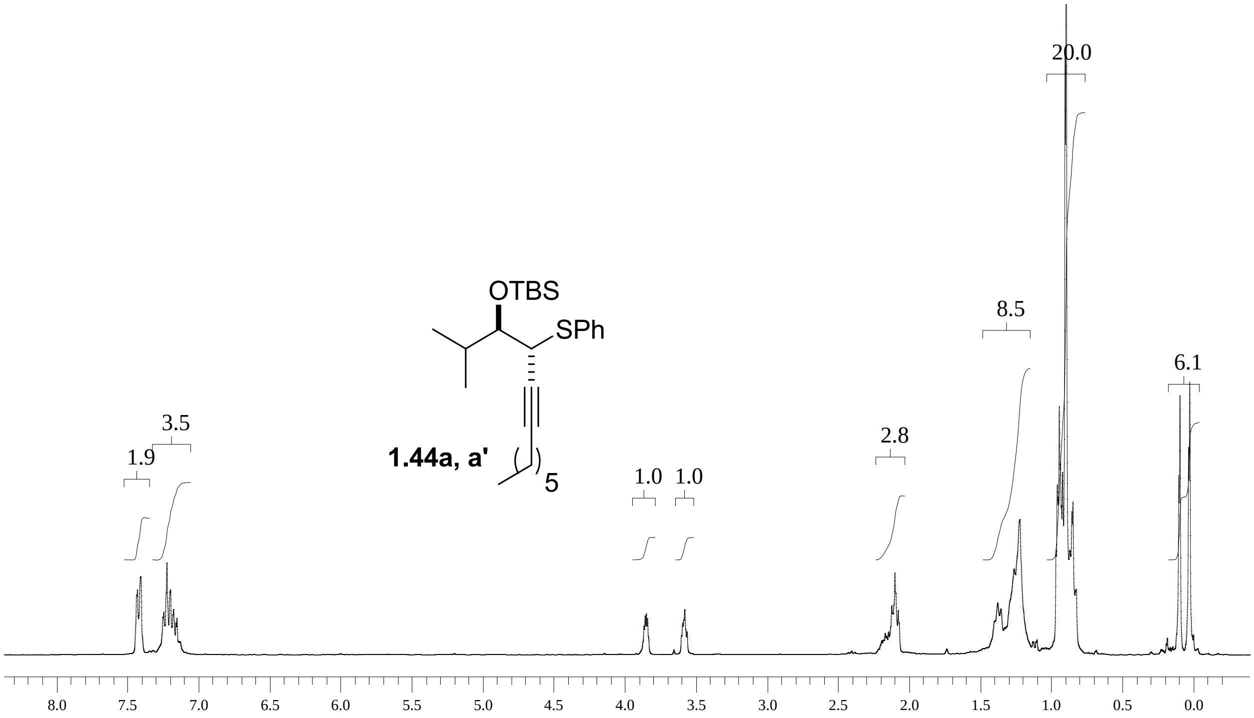
1.43b, b'


OTBS
SPh
5
17.8
15.2
5.5
3.1
1.6
1.0
1.0
1.8
0.9
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

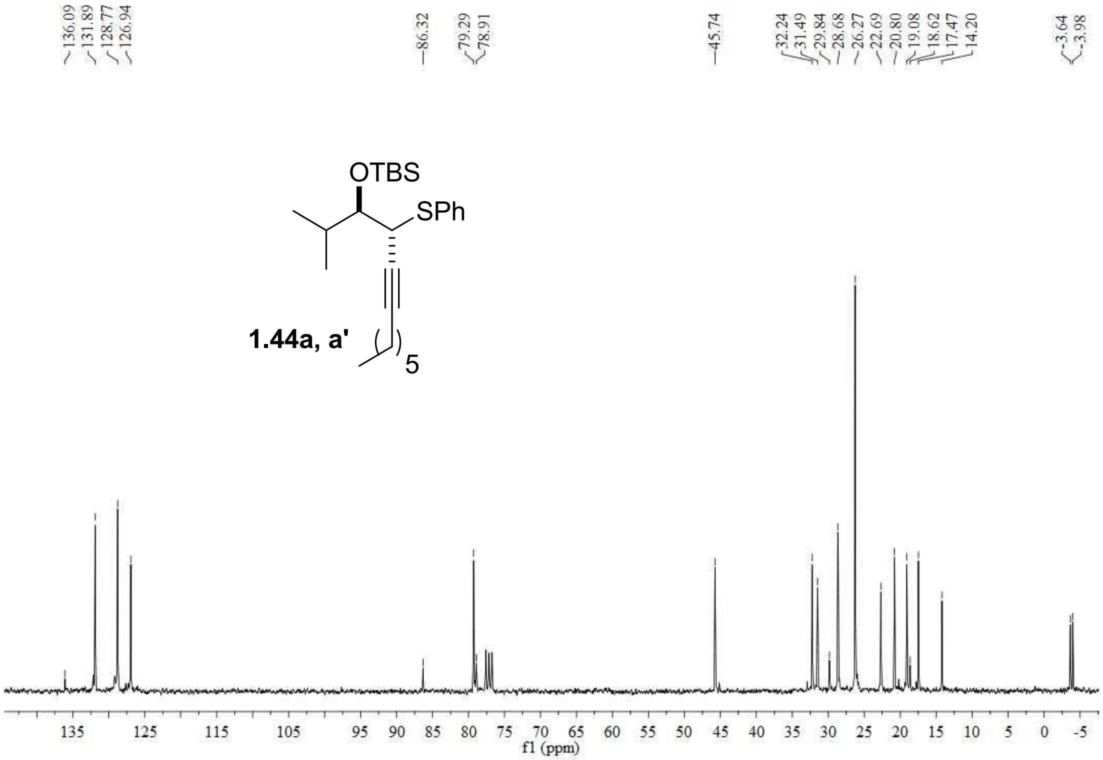
1.43c, c'


136.616
132.035
128.811
126.673
74.109
55.711
31.953
31.522
30.403
29.820
29.400
28.696
26.651
25.966
22.759
14.216
-4.394
OTBS
SPh
5
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

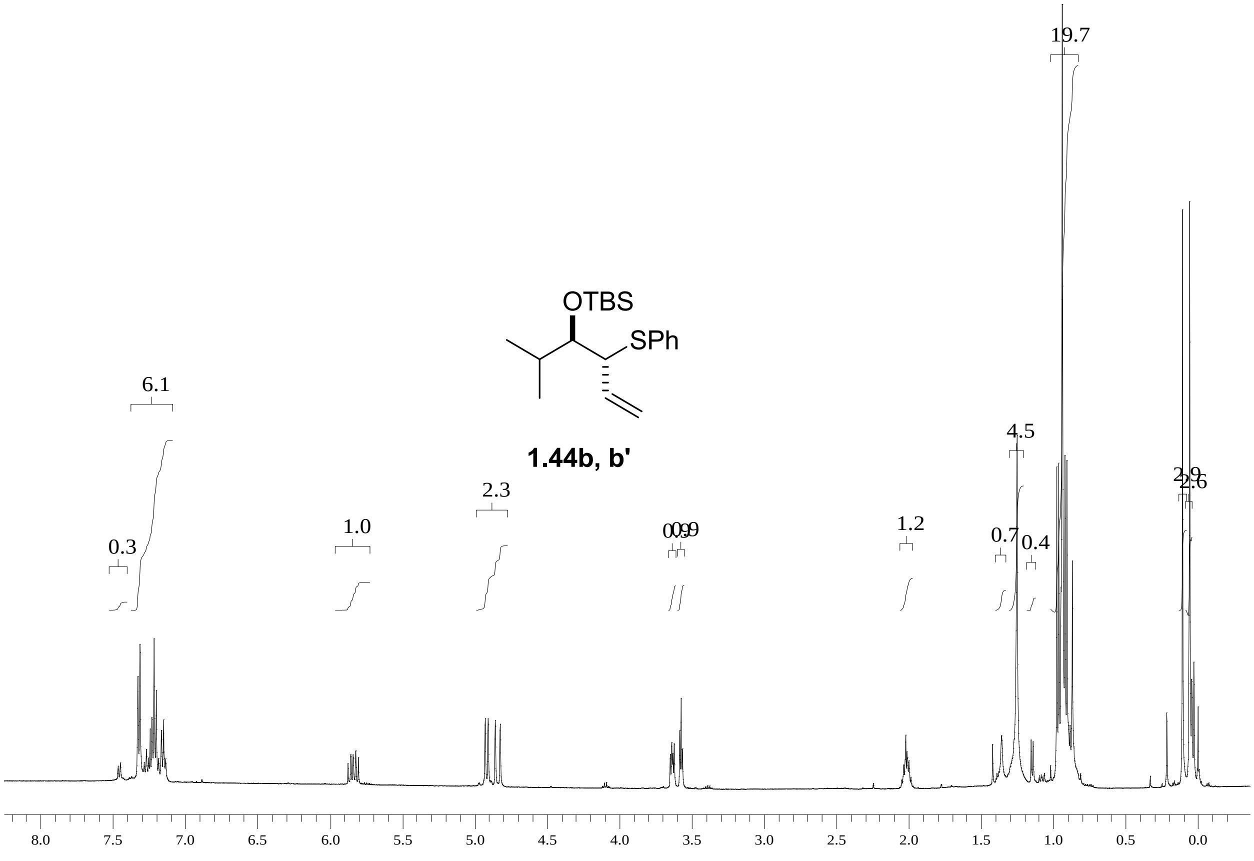
1.43c, c'


20.0
8.5
6.1
3.5
1.9
2.8
1.0
1.0
OTBS
SPh
5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

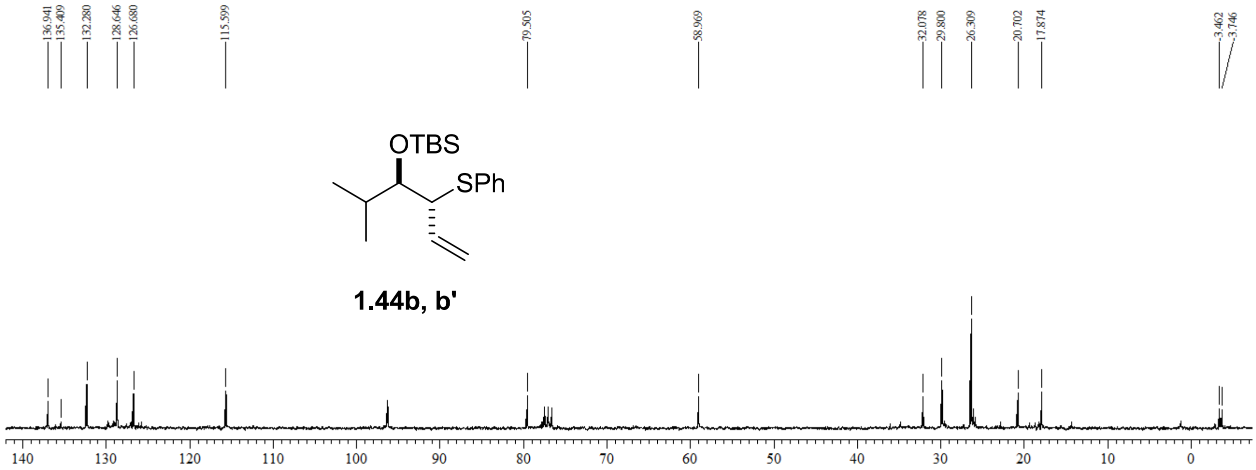
1.44a, a'


136.09
131.89
128.77
126.94
86.32
79.29
78.91
45.74
32.24
31.49
29.84
28.68
26.27
22.69
20.80
19.08
18.62
17.47
14.20
-3.64
-3.98
OTBS
SPh
5
135 125 115 105 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 -5
f1 (ppm)

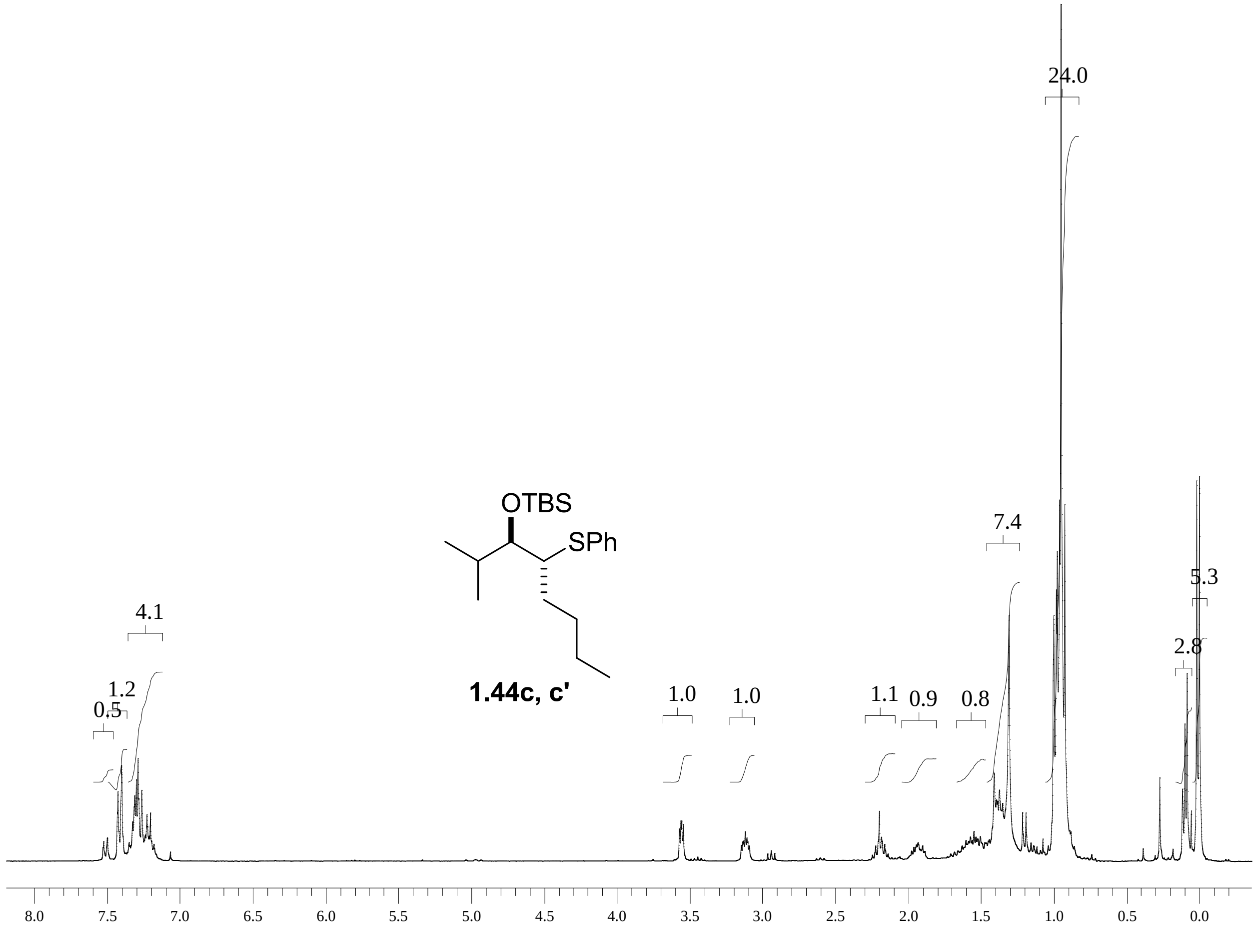
1.44a, a'


OTBS
SPh
0.3
6.1
1.0
2.3
0.9
0.9
1.2
0.7
4.5
0.4
19.7
2.9
2.6
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

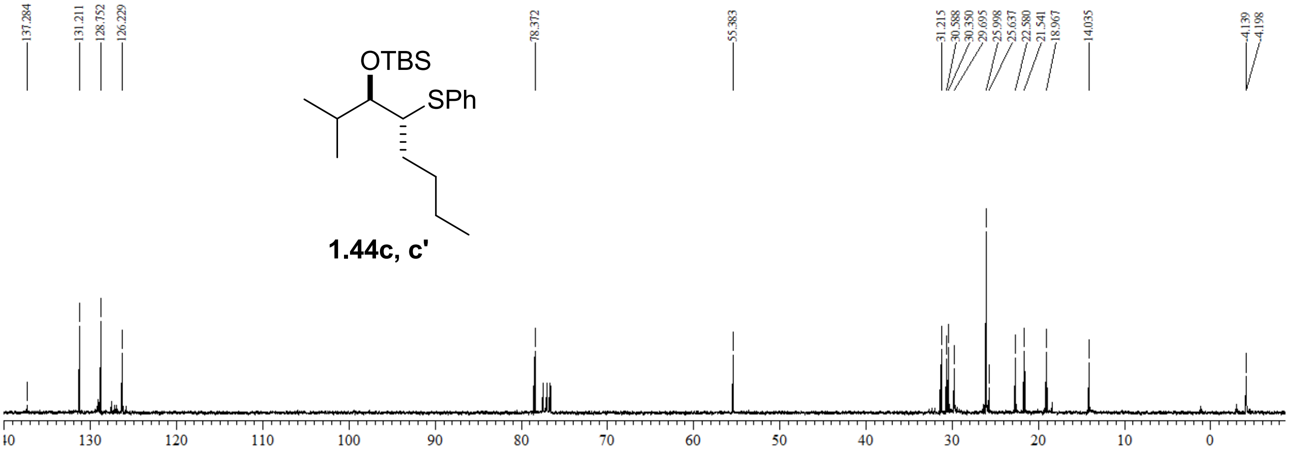
1.44b, b'


136.941
135.409
132.280
128.646
126.680
115.599
79.505
58.969
32.078
29.800
26.309
20.702
17.874
-3.462
-3.746
OTBS
SPh
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

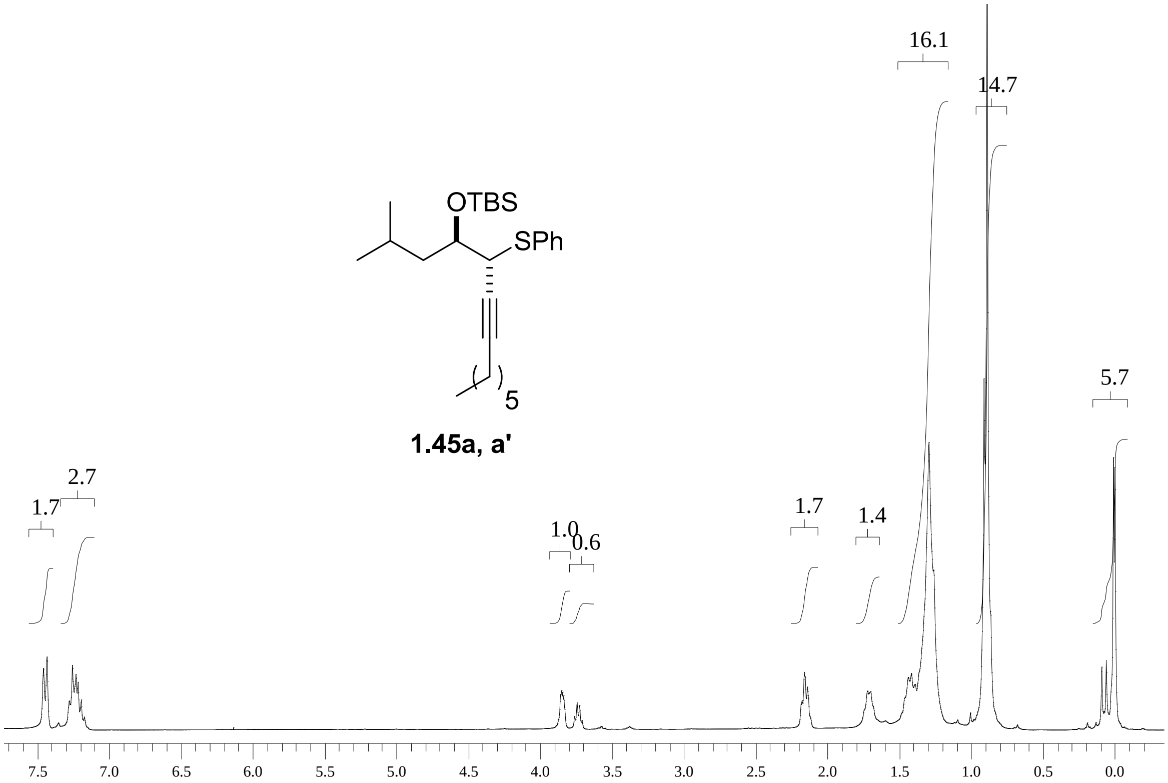
1.44b, b'


24.0
7.4
5.3
2.8
4.1
1.2
0.5
1.0
1.0
1.1
0.9
0.8
OTBS
SPh
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

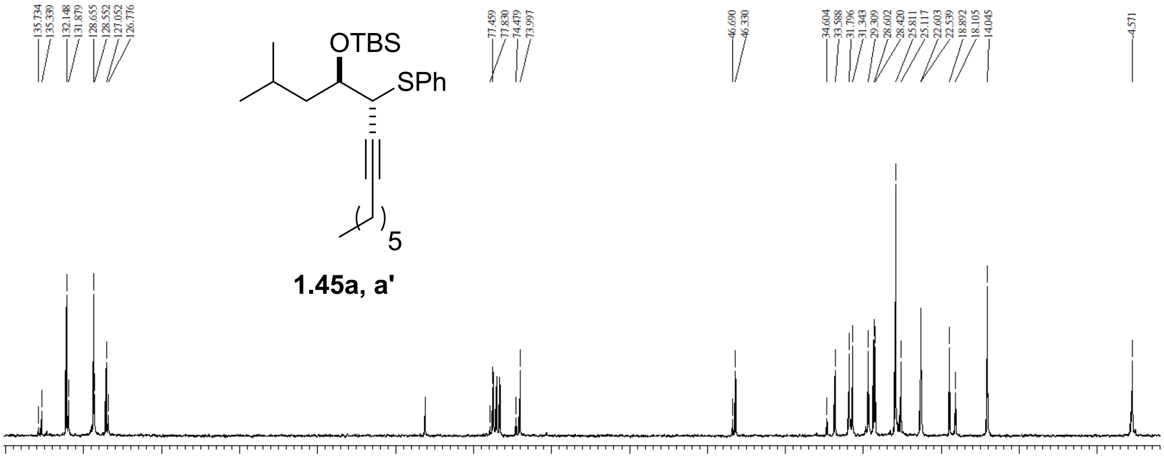
1.44c, c'


137.284
131.211
128.752
126.229
78.372
55.383
31.215
30.588
30.350
29.695
25.998
25.637
22.580
21.541
18.967
14.035
-4.139
-4.198
OTBS
SPh
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

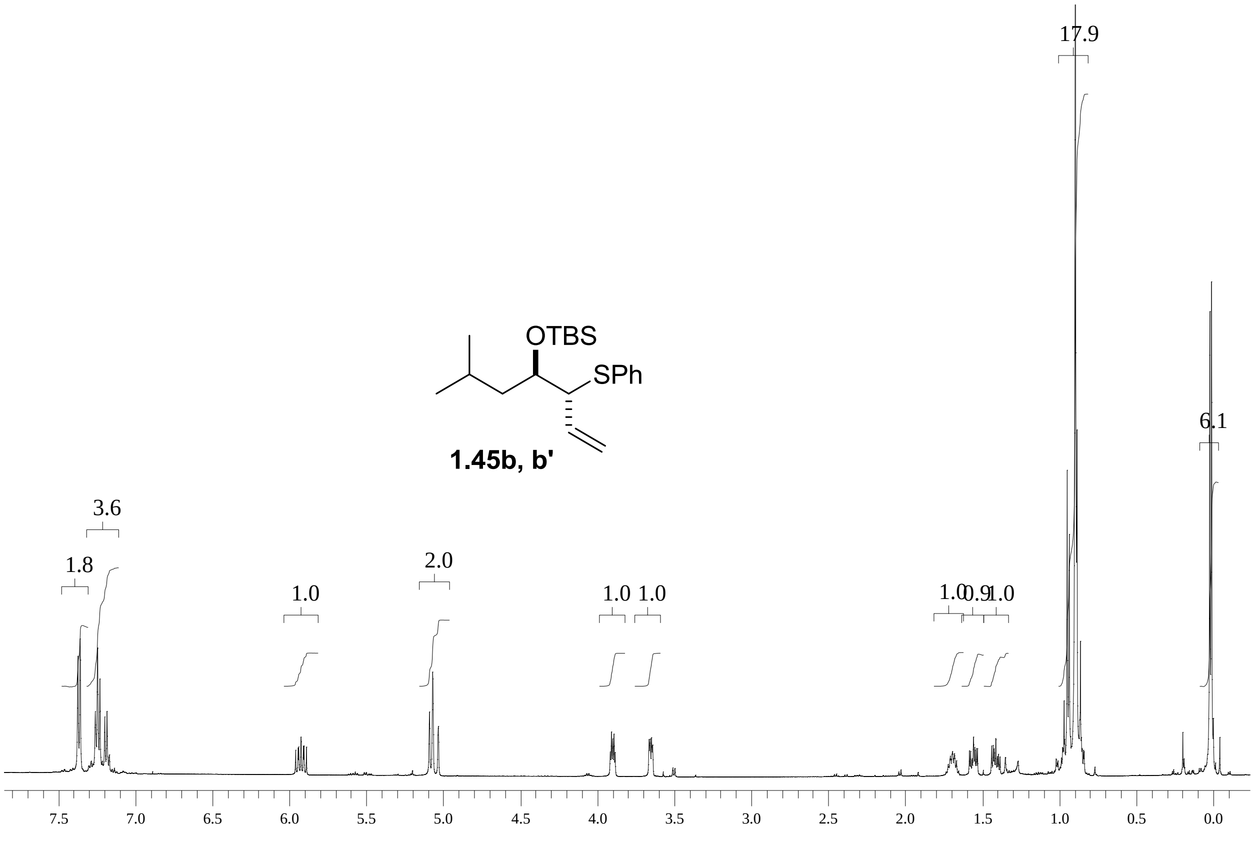
1.44c, c'


OTBS
SPh
5
16.1
14.7
5.7
2.7
1.7
1.0
0.6
1.7
1.4
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

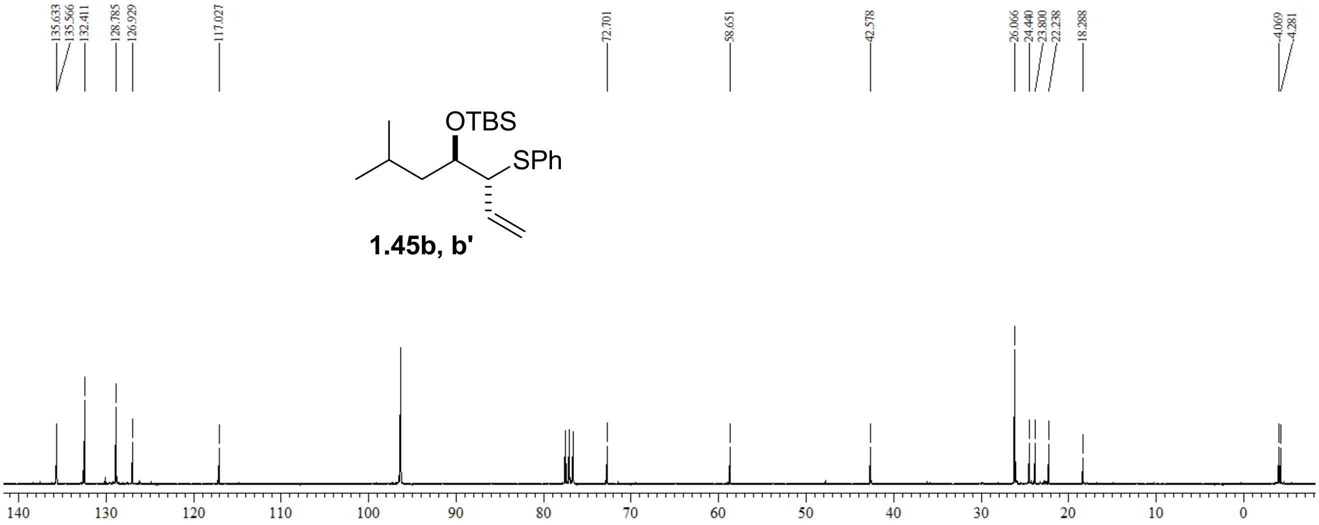
1.45a, a'


135.734
135.339
132.148
131.879
128.655
128.552
127.052
126.776
77.459
77.830
74.479
73.997
46.690
46.330
34.604
33.588
31.796
31.343
29.309
28.602
28.420
25.811
25.117
22.603
22.539
18.892
18.105
14.045
-4.571
OTBS
SPh
5
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

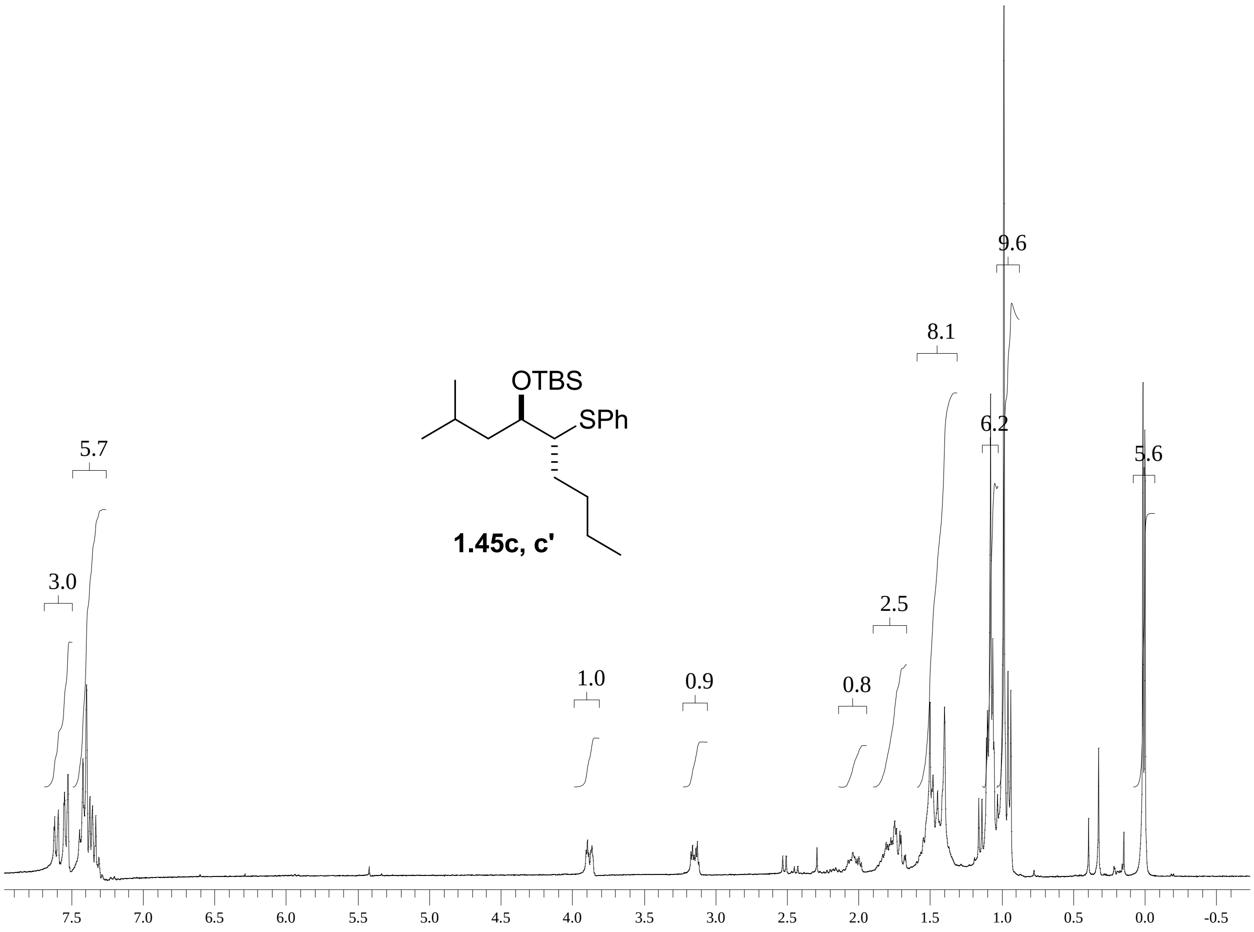
1.45a, a'


OTBS
SPh
17.9
6.1
3.6
1.8
1.0
2.0
1.0
1.0
1.0
0.9
1.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

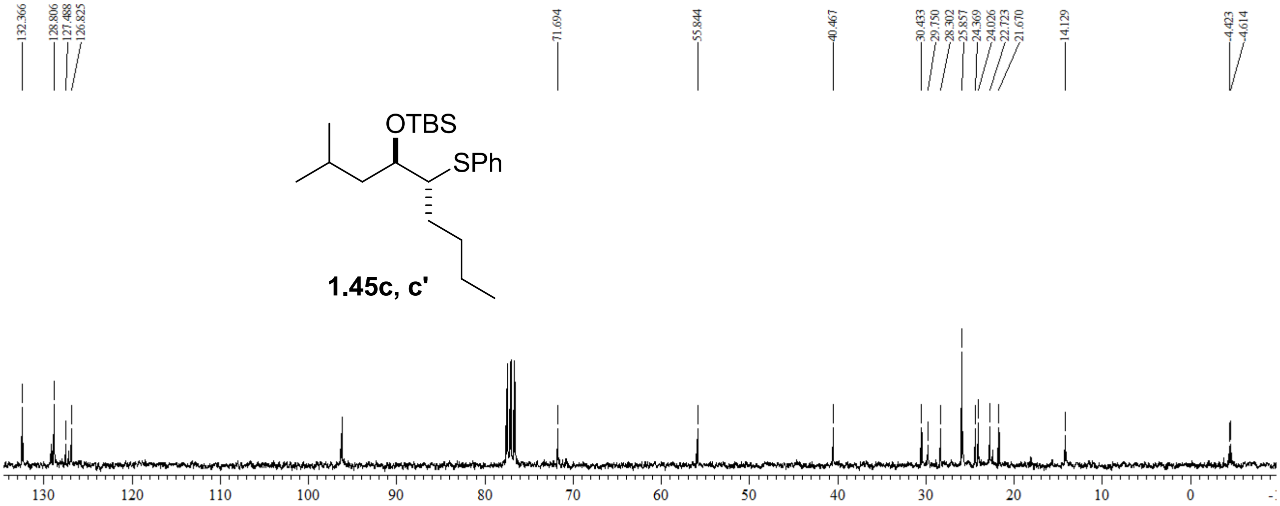
1.45b, b'

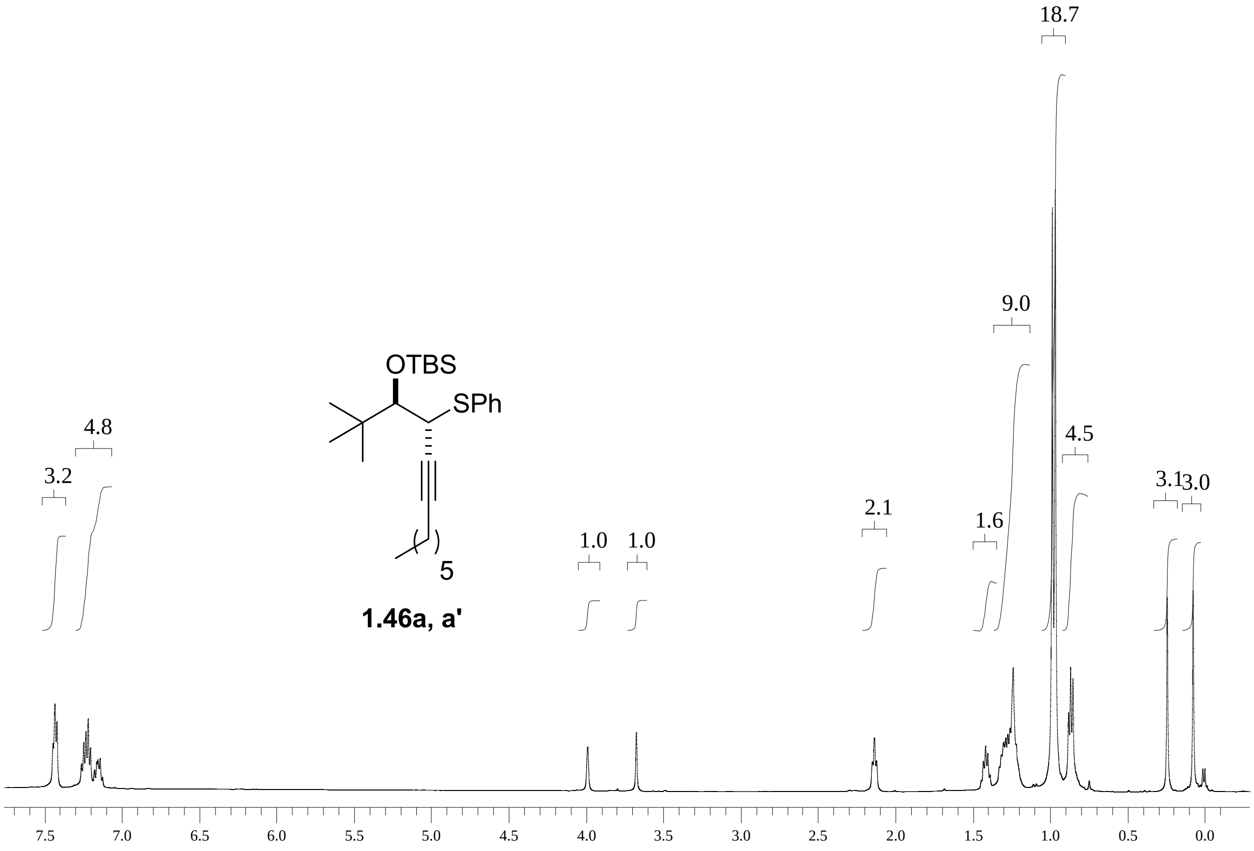

135.633
135.566
132.411
128.785
126.929
117.027
72.701
58.651
42.578
26.066
24.440
23.800
22.238
18.288
-4.069
-4.281
OTBS
SPh
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

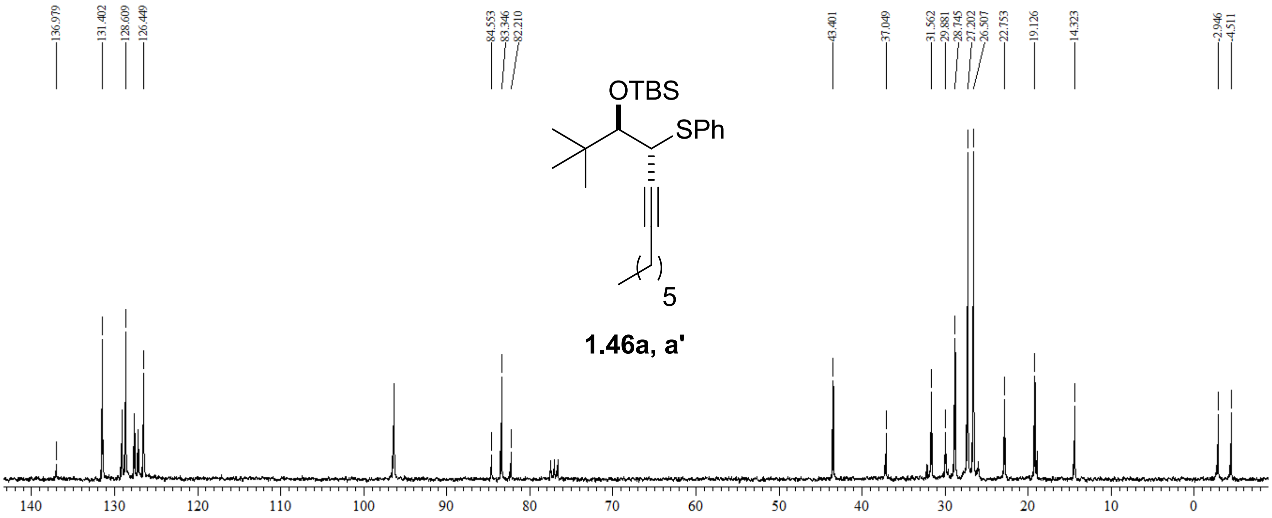
1.45b, b'


9.6
8.1
6.2
5.7
5.6
3.0
2.5
1.0
0.9
0.8
OTBS
SPh
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
-0.5

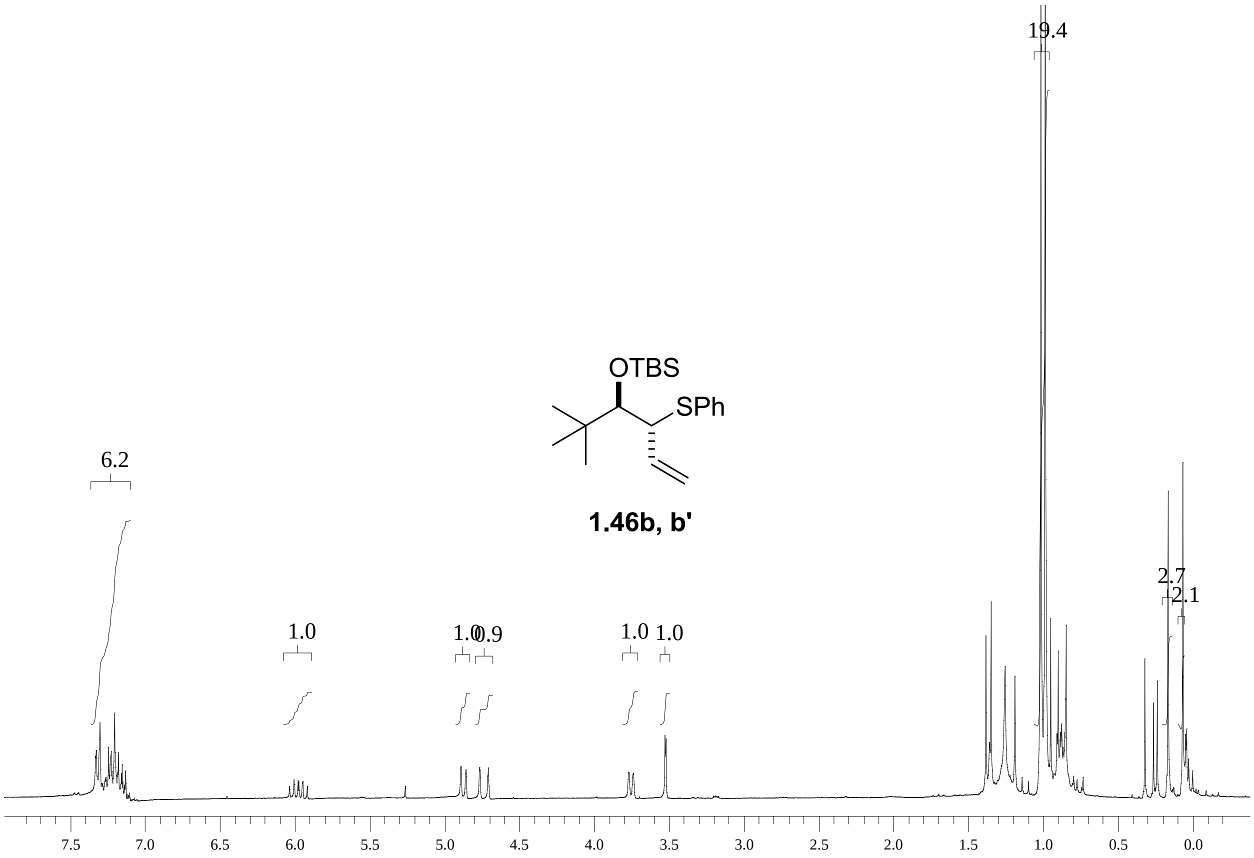
1.45c, c'


1.45c, c'
132.366
128.806
127.488
126.825
71.694
55.844
40.467
30.433
29.750
28.302
25.857
24.369
24.026
22.723
21.670
14.129
-4.423
-4.614
OTBS
SPh
130
120
110
100
90
80
70
60
50
40
30
20
10
0

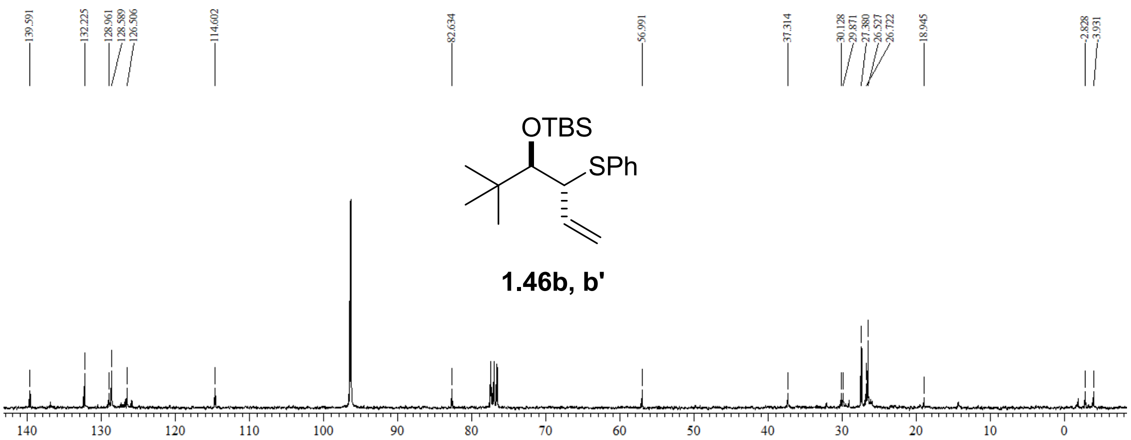

1.46a, a'
18.7
9.0
4.8
3.2
4.5
3.1
3.0
2.1
1.6
1.0
1.0
OTBS
SPh
5
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


136.979
131.402
128.609
126.449
84.553
83.346
82.210
43.401
37.049
31.562
29.881
28.745
27.202
26.507
22.753
19.126
14.323
-2.946
-4.511
OTBS
SPh
5
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

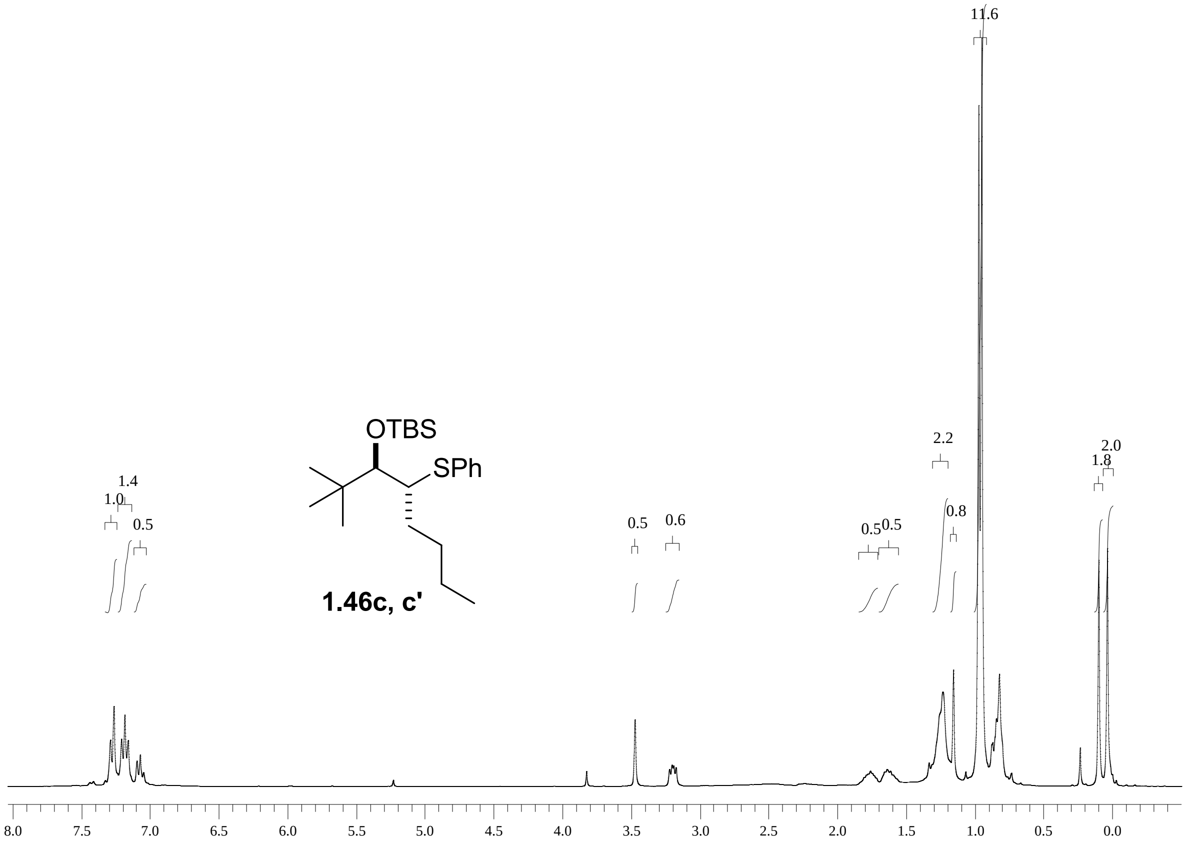
1.46a, a'


OTBS
SPh
6.2
1.0
1.0
0.9
1.0
1.0
19.4
2.7
2.1
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

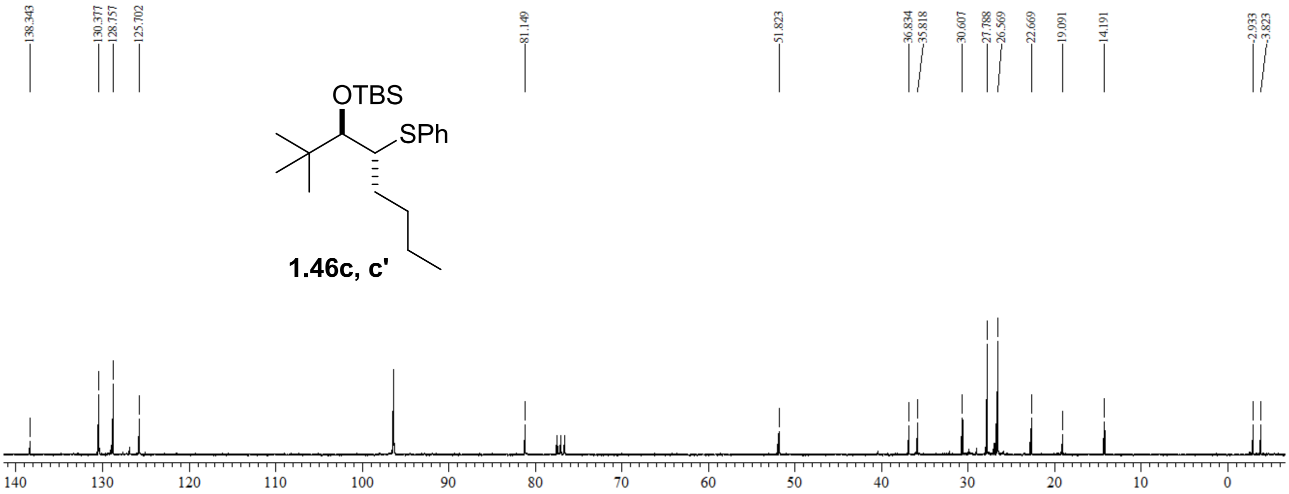
1.46b, b'


139.591
132.225
128.961
128.589
126.506
114.602
82.634
56.991
37.314
30.128
29.871
27.380
26.527
26.722
18.945
-2.828
-3.931
OTBS
SPh
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

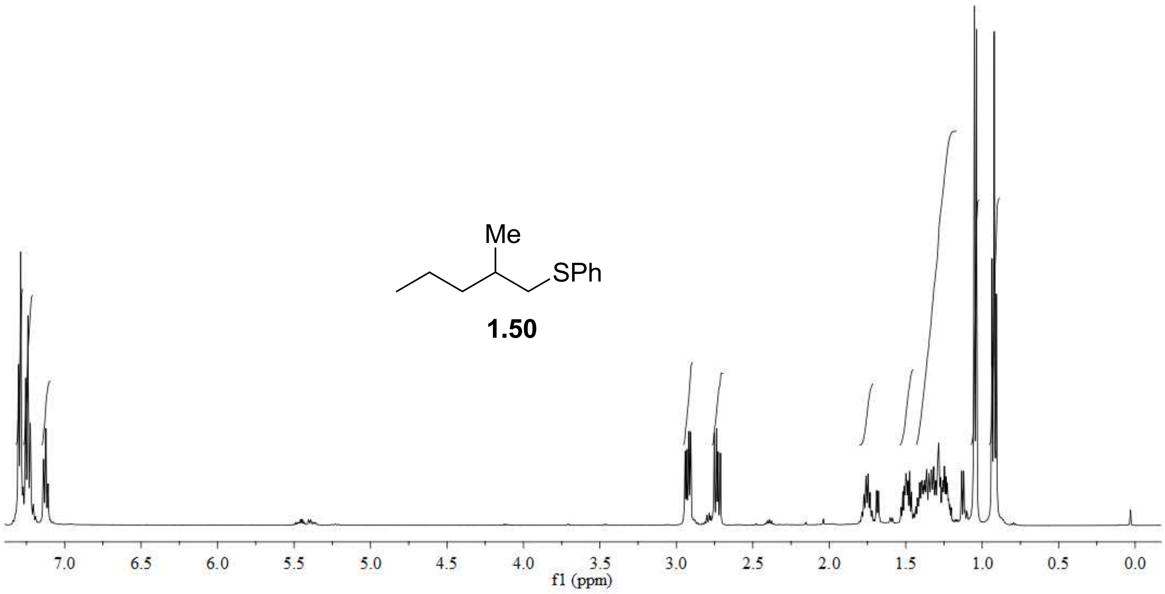
1.46b, b'


11.6
2.2
2.0
1.8
1.4
1.0
0.5
0.5
0.6
0.5
0.5
0.8
OTBS
SPh
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

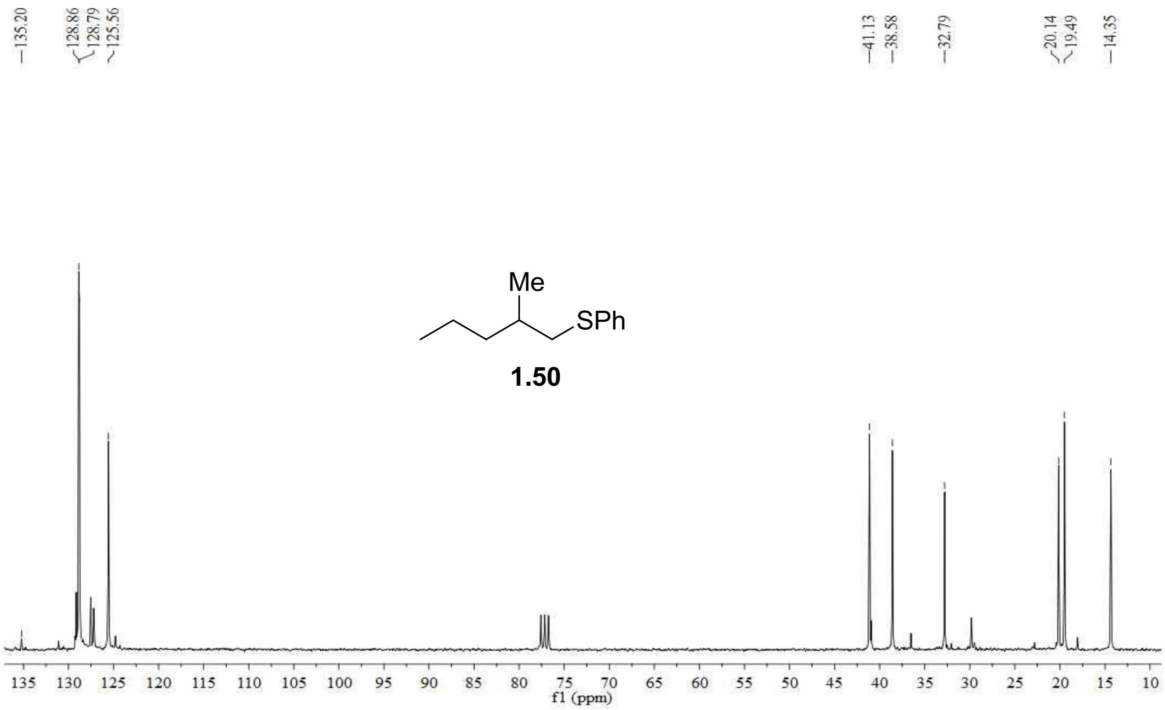
1.46c, c'


138.343
130.377
128.757
125.702
81.149
51.823
36.834
35.818
30.607
27.788
26.569
22.669
19.091
14.191
-2.933
-3.823
OTBS
SPh
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

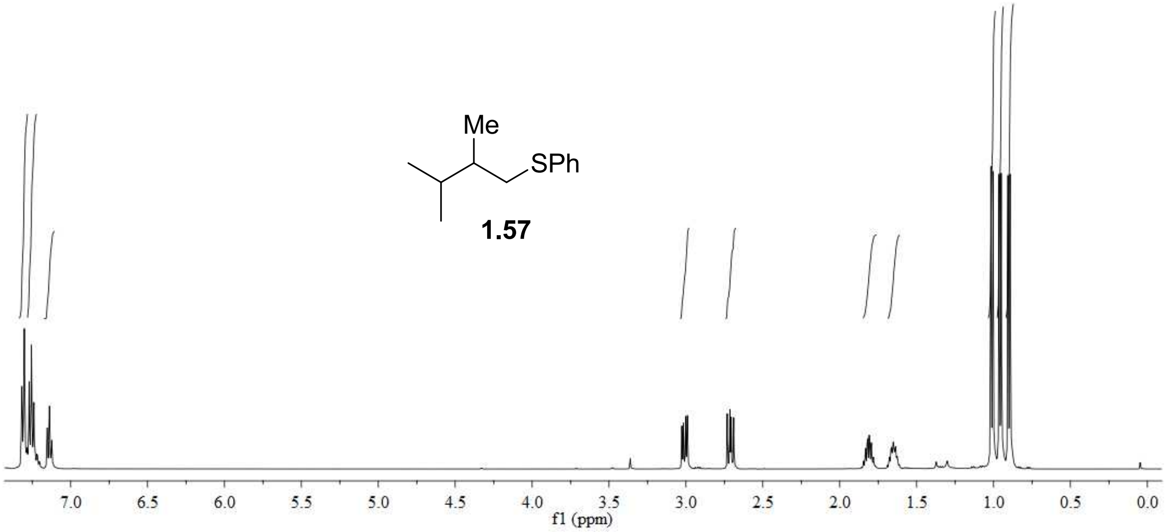
1.46c, c'


Me
SPh
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
f1 (ppm)

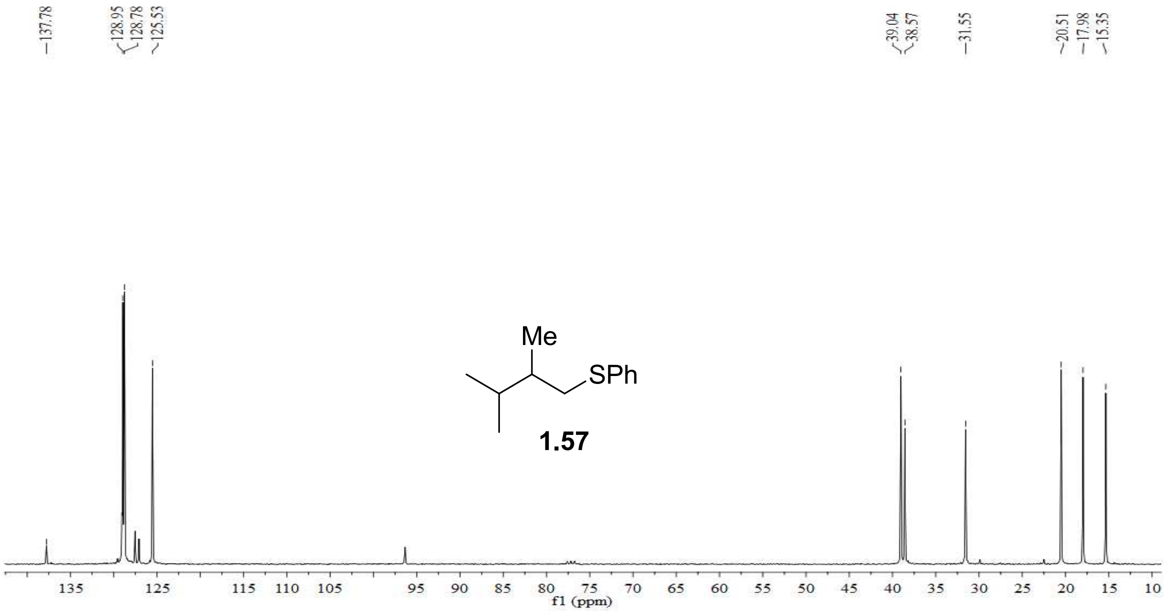
1.50


135.20
128.86
128.79
125.56
41.13
38.58
32.79
20.14
19.49
14.35
Me
SPh
135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10
f1 (ppm)

1.50

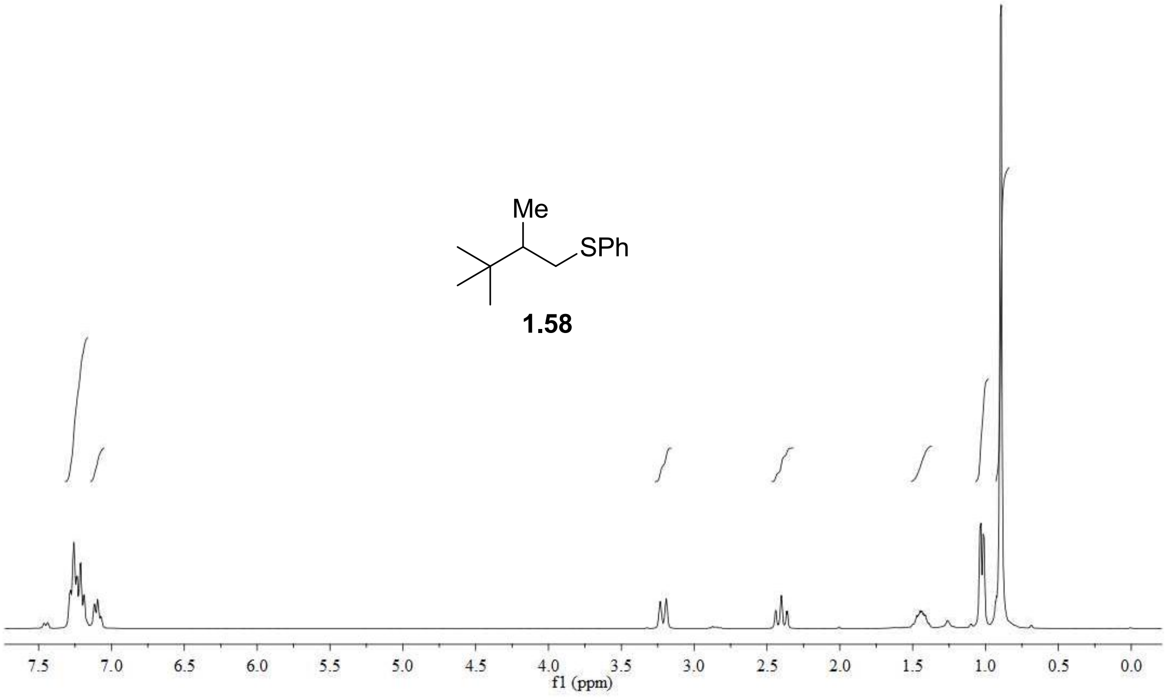

Me
SPh
7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

1.57



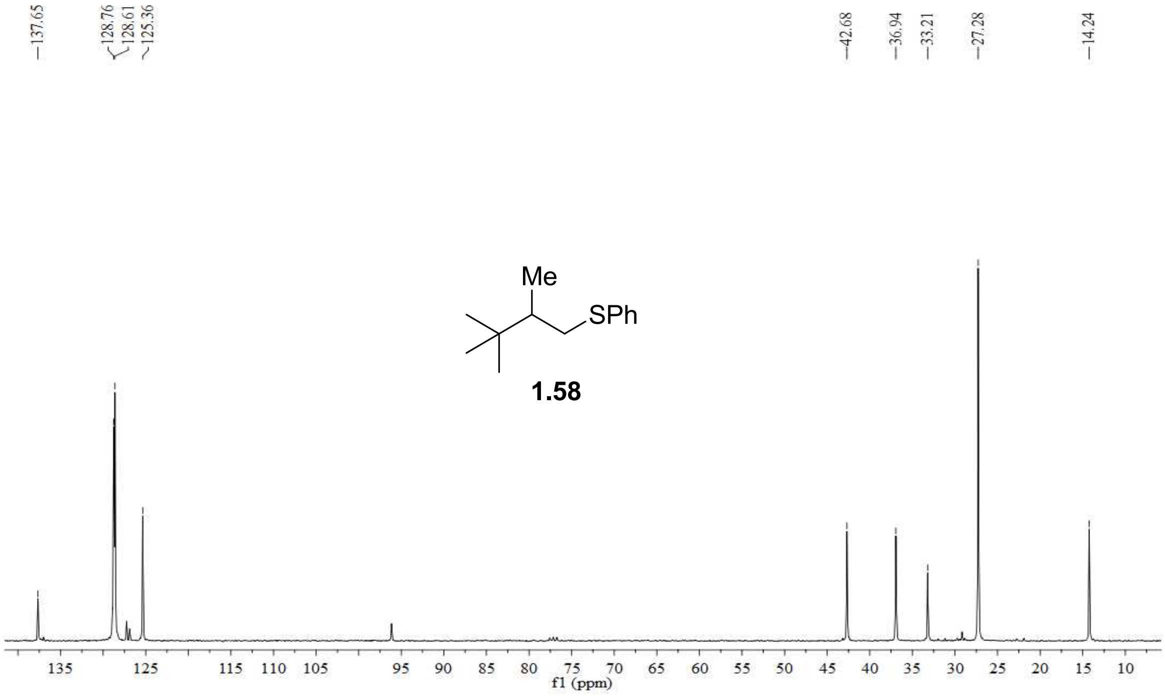
137.78
128.95
128.78
125.53
39.04
38.57
31.55
20.51
17.98
15.35
Me
SPh
135
125
115
110
105
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
f1 (ppm)

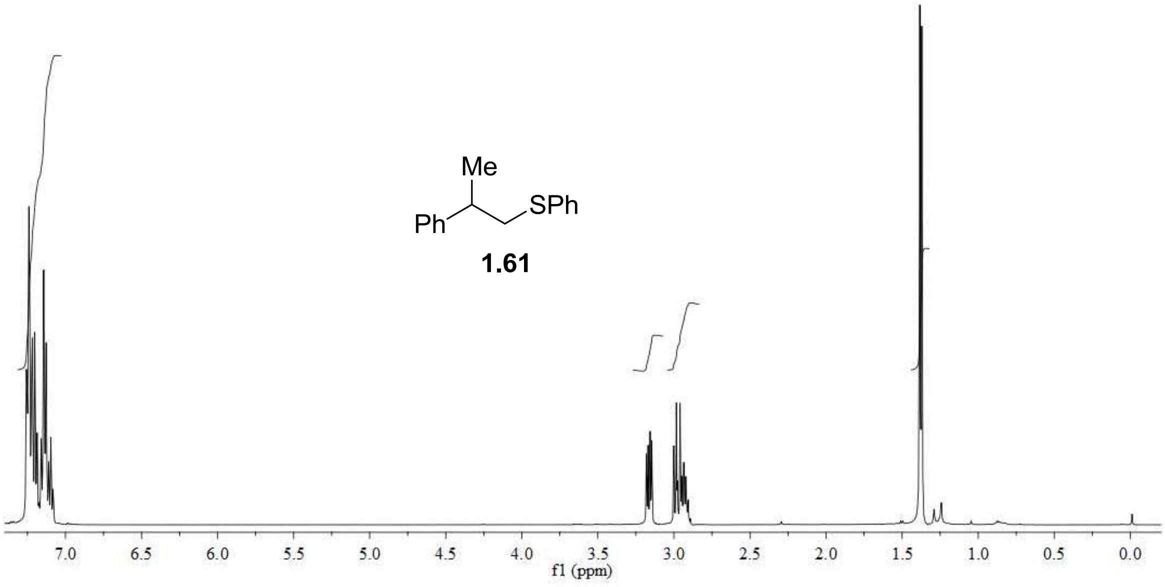
1.57

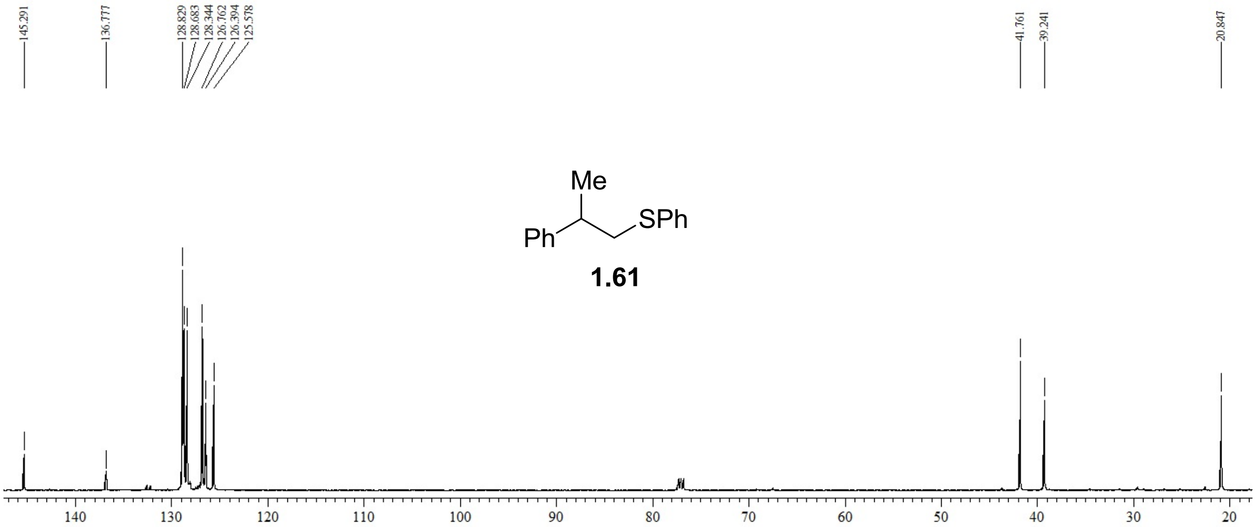


Me
SPh
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

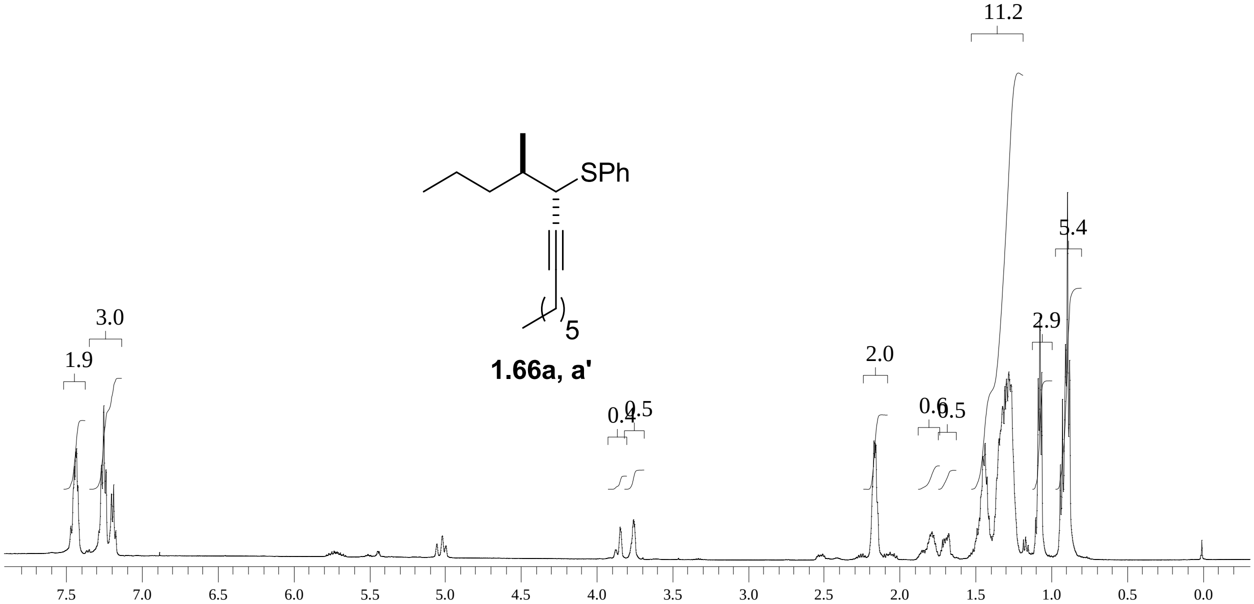
1.58


1.58
137.65
128.76
128.61
125.36
42.68
36.94
33.21
27.28
14.24
Me
SPh
135
125
115
110
105
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
f1 (ppm)

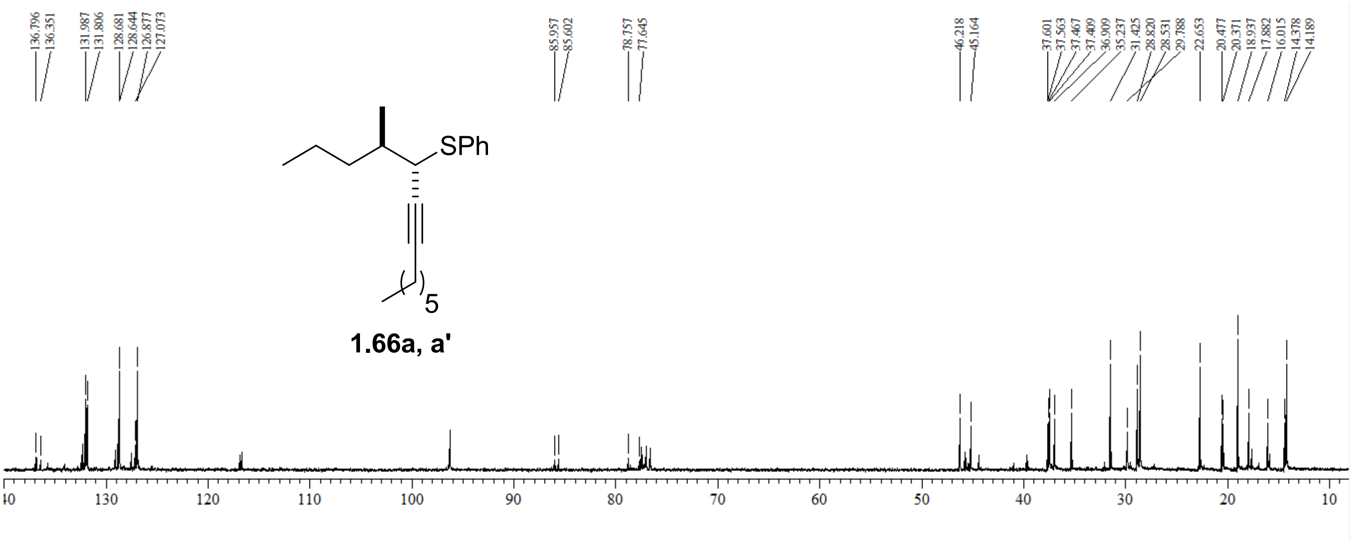

1.61
Me
Ph
SPh
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


145.291
136.777
128.829
128.683
128.344
126.762
126.394
125.578
41.761
39.241
20.847
Me
SPh
Ph
140
130
120
110
100
90
80
70
60
50
40
30
20

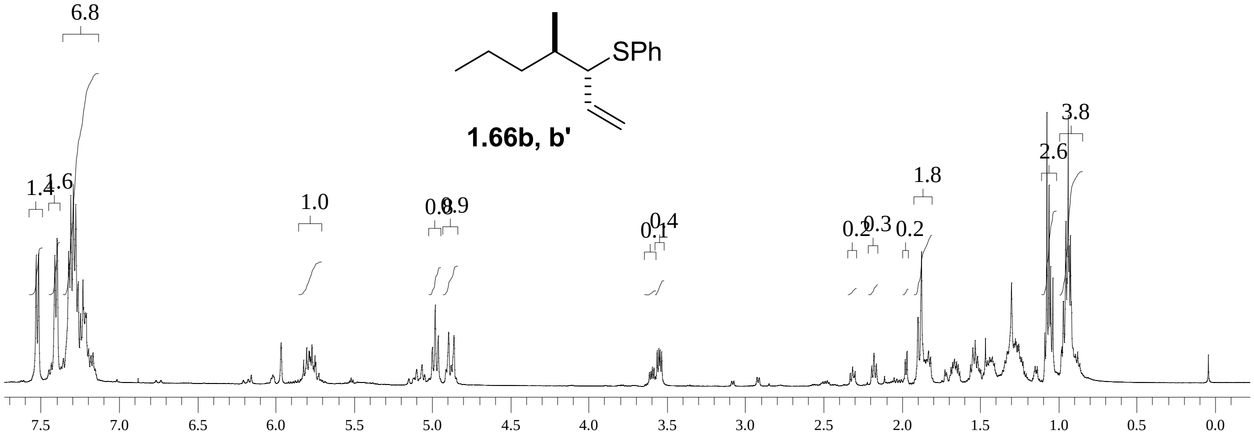
1.61


11.2
5.4
3.0
1.9
2.9
2.0
0.4
0.5
0.6
0.5
SPh
5
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

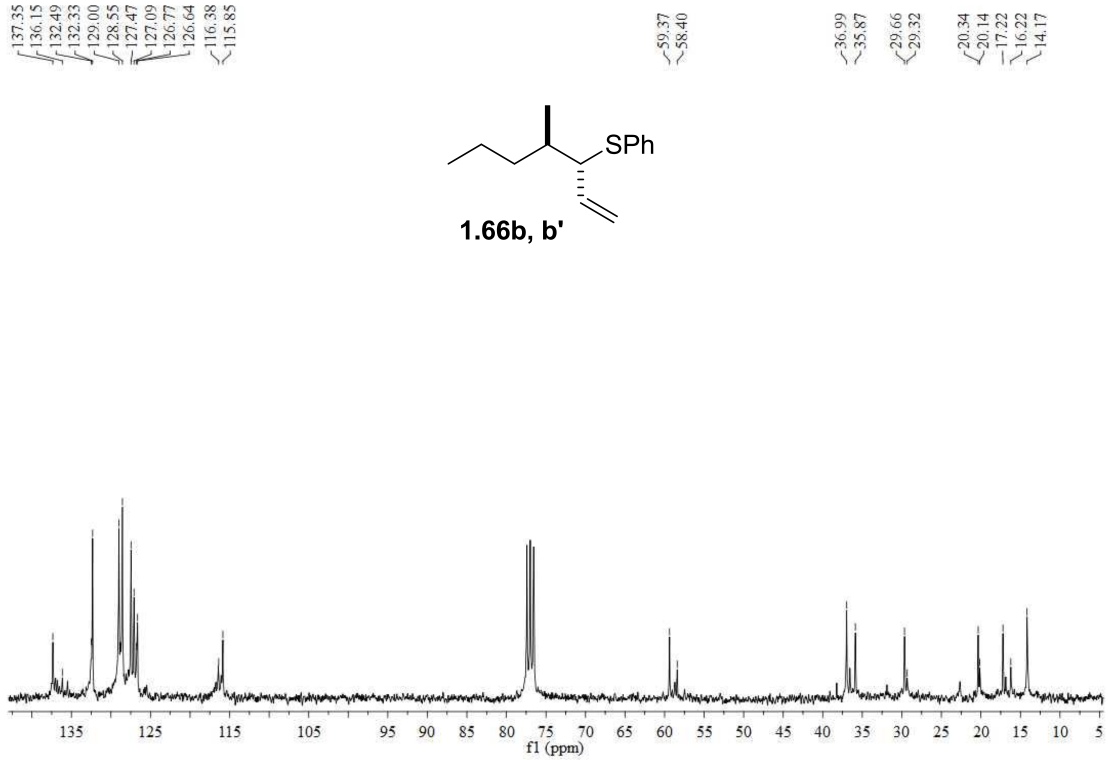
1.66a, a'

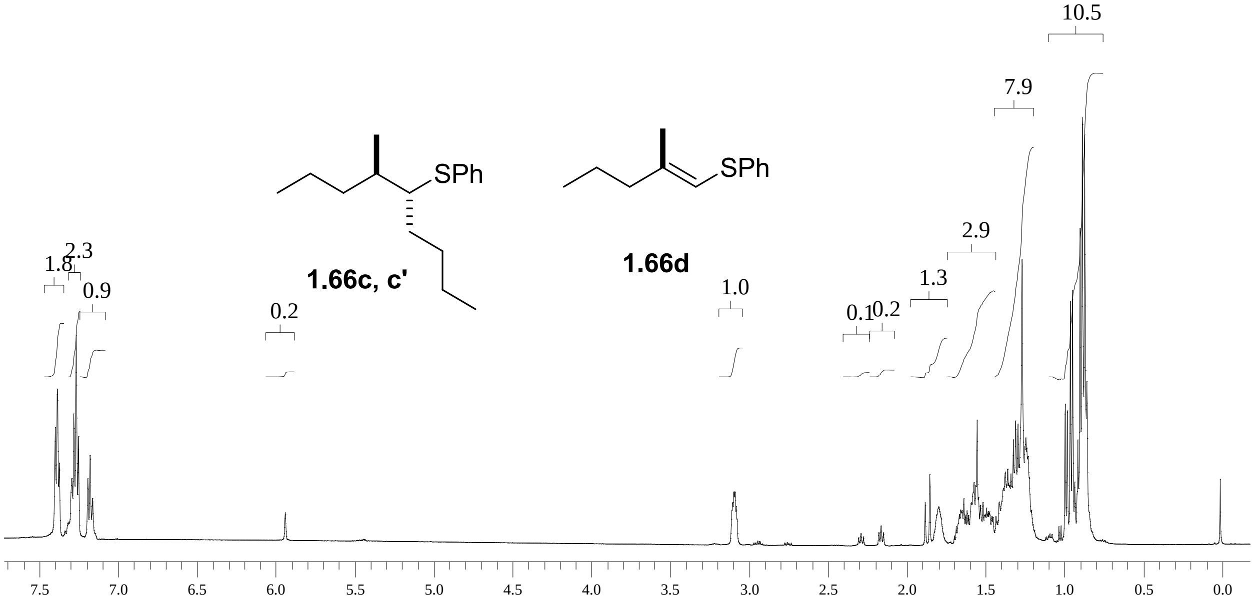

136.796
136.351
131.987
131.806
128.681
128.644
126.877
127.073
85.957
85.602
78.757
77.645
46.218
45.164
37.601
37.563
37.467
37.409
36.909
35.237
31.425
28.820
28.531
29.788
22.653
20.477
20.371
18.937
17.882
16.015
14.378
14.189
SPh
5
40
130
120
110
100
90
80
70
60
50
40
30
20
10

1.66a, a'

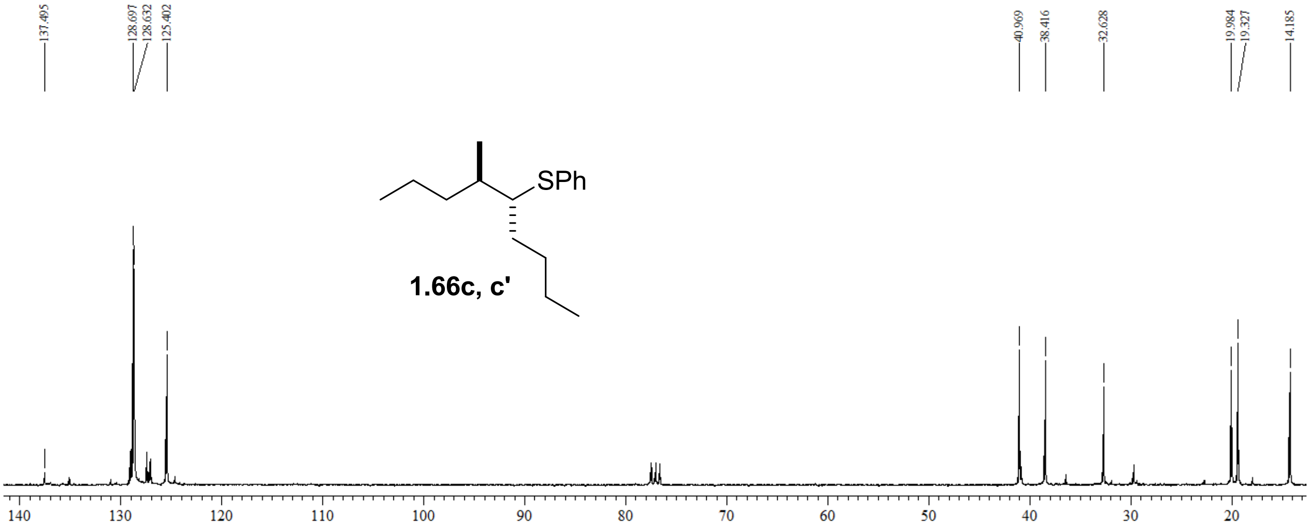

6.8
SPh
3.8
2.6
1.8
1.4
1.6
1.0
0.9
0.9
0.4
0.1
0.2
0.3
0.2
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

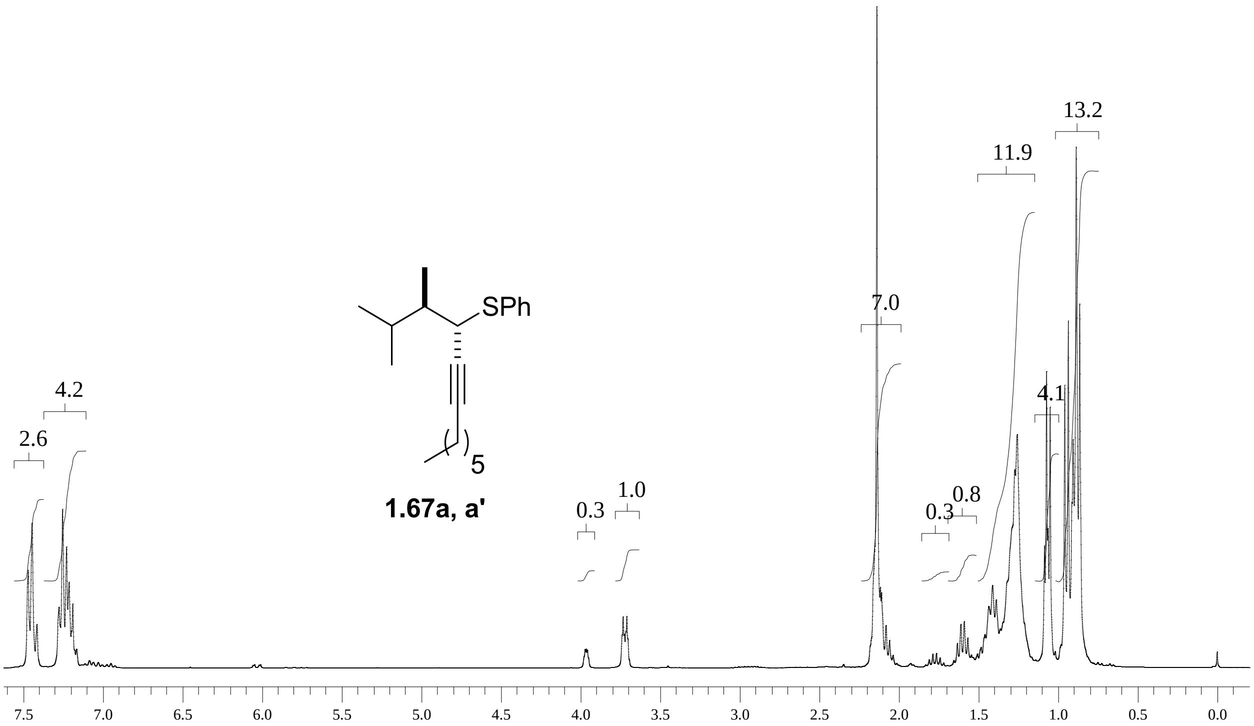
1.66b, b'

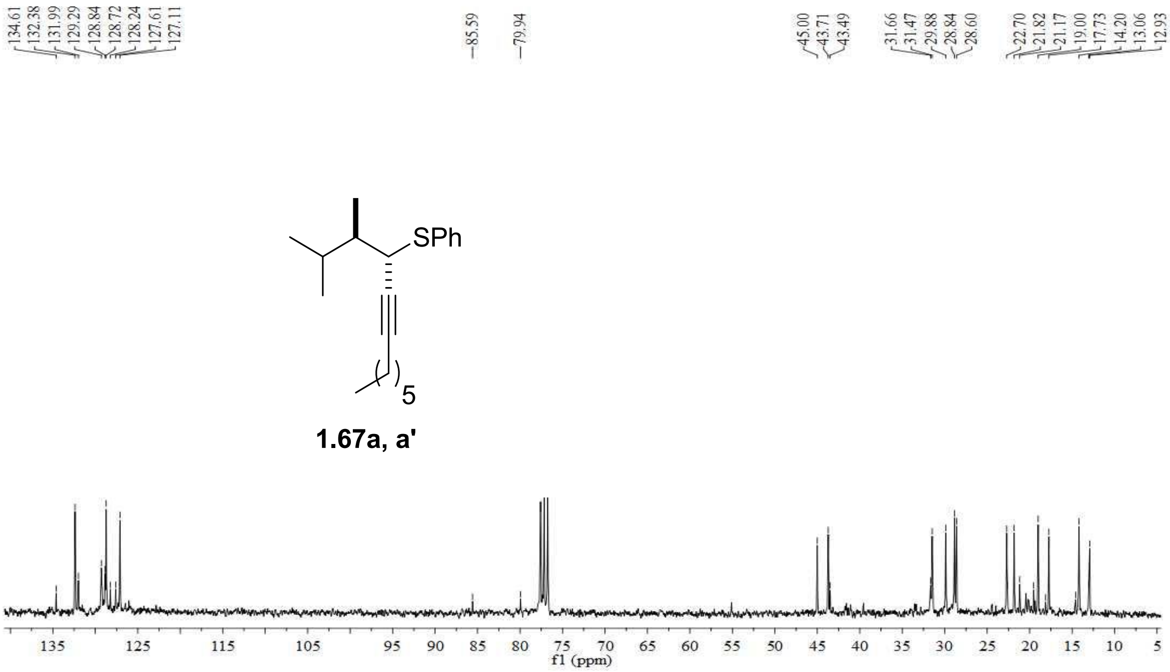

1.66b, b'


1.66c, c'

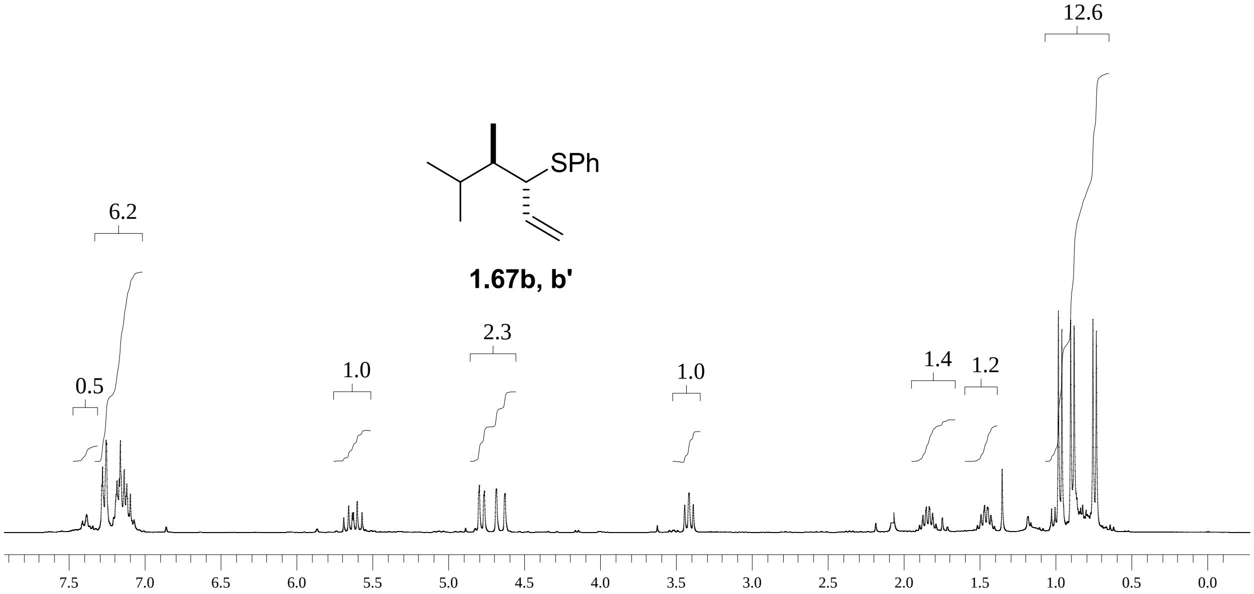
1.66d


1.66c, c'
137.495
128.697
128.632
125.402
40.969
38.416
32.628
19.984
19.327
14.185
SPh
140
130
120
110
100
90
80
70
60
50
40
30
20

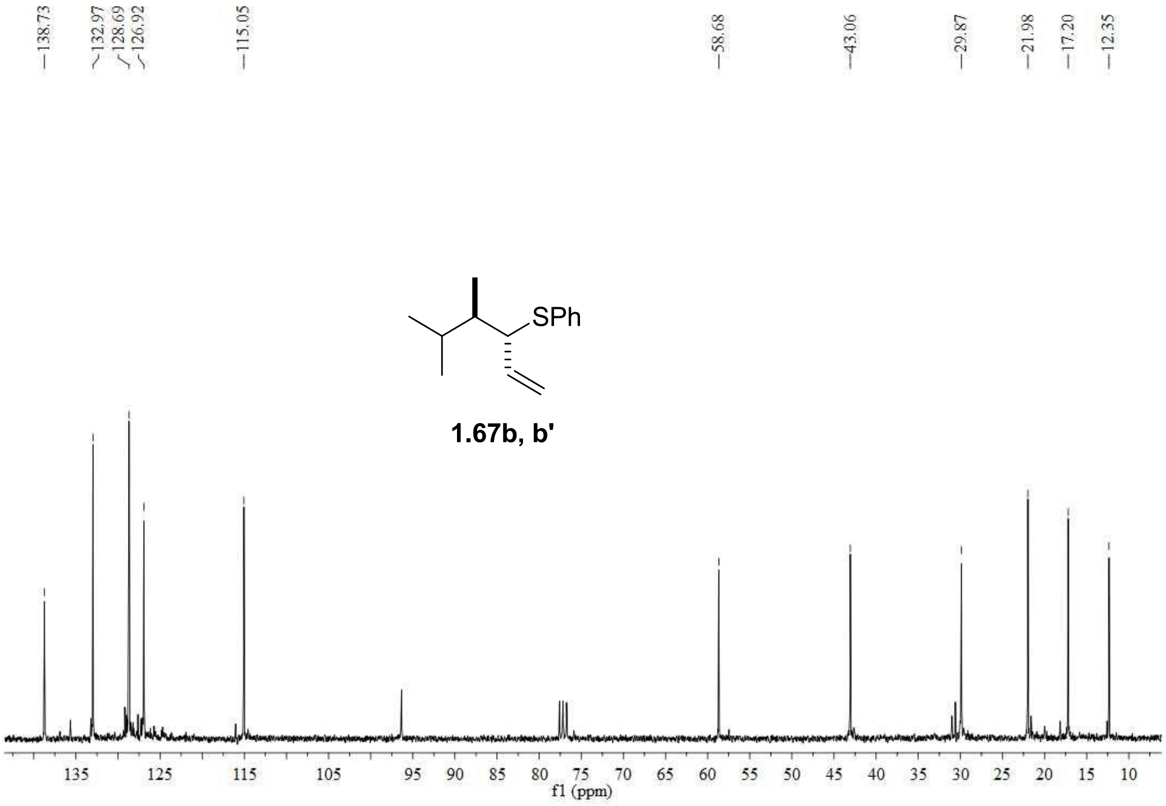

1.67a, a'
SPh
5
2.6
4.2
0.3
1.0
7.0
0.3
0.8
11.9
4.1
13.2
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


134.61
132.38
131.99
129.29
128.84
128.72
128.24
127.61
127.11
85.59
79.94
45.00
43.71
43.49
31.66
31.47
29.88
28.84
28.60
22.70
21.82
21.17
19.00
17.73
14.20
13.06
12.93
SPh
5
135
125
115
105
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
f1 (ppm)

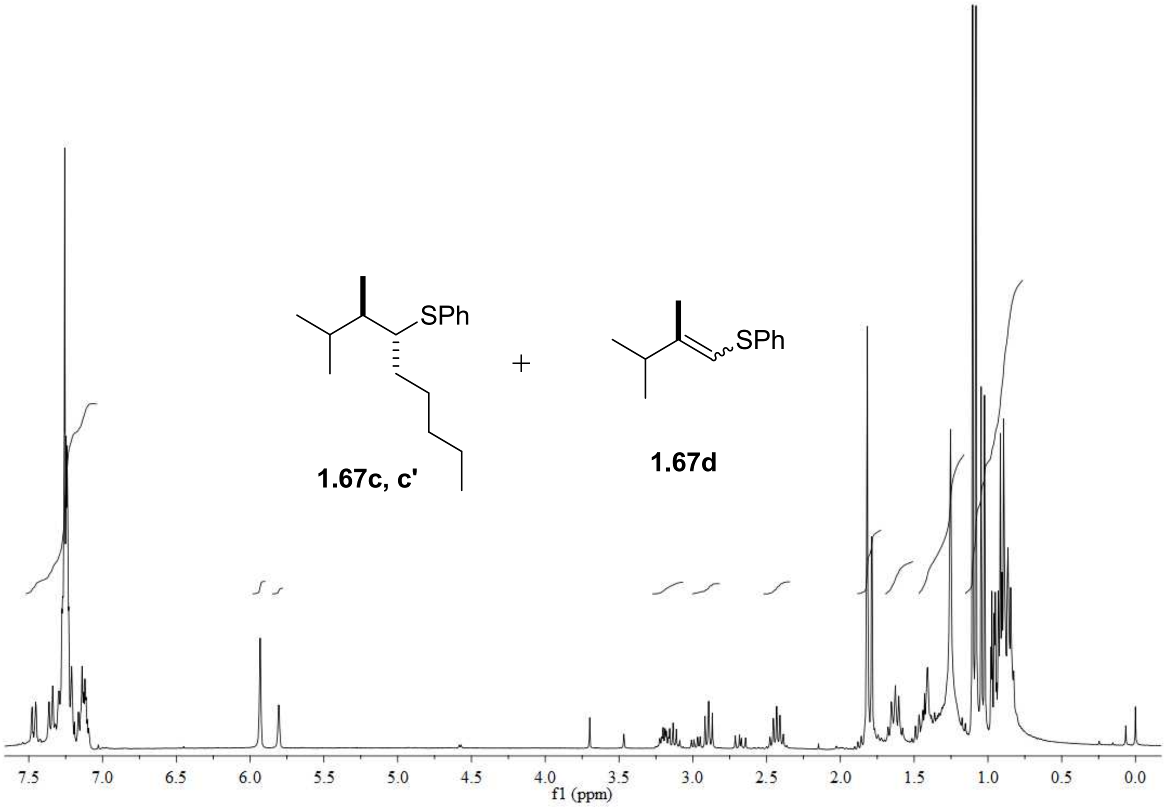
1.67a, a'


12.6
6.2
0.5
1.0
2.3
1.0
1.4
1.2
SPh
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

1.67b, b'

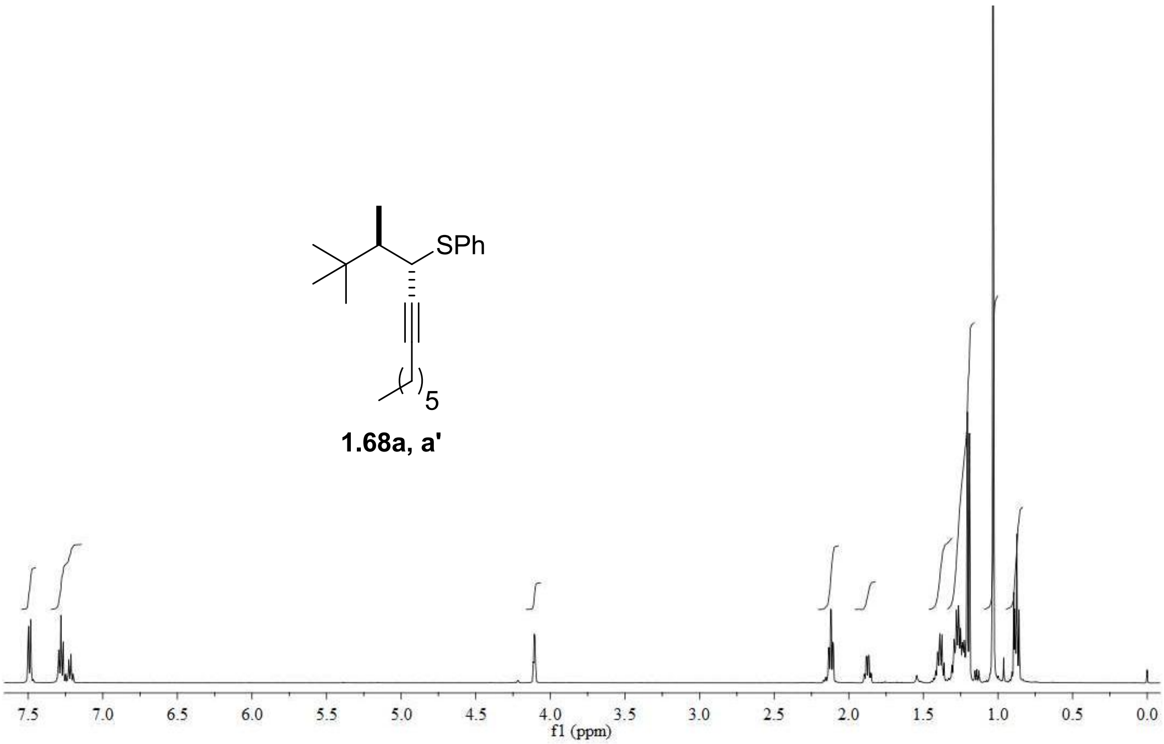


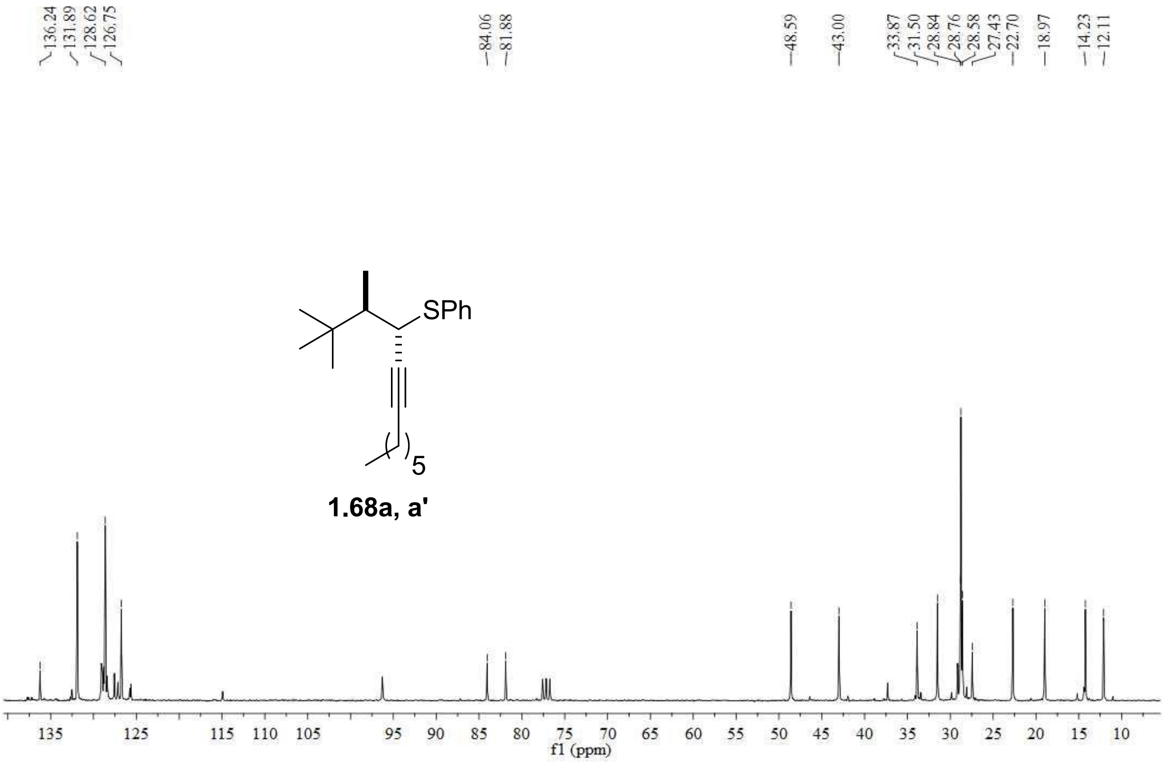
1.67b, b'

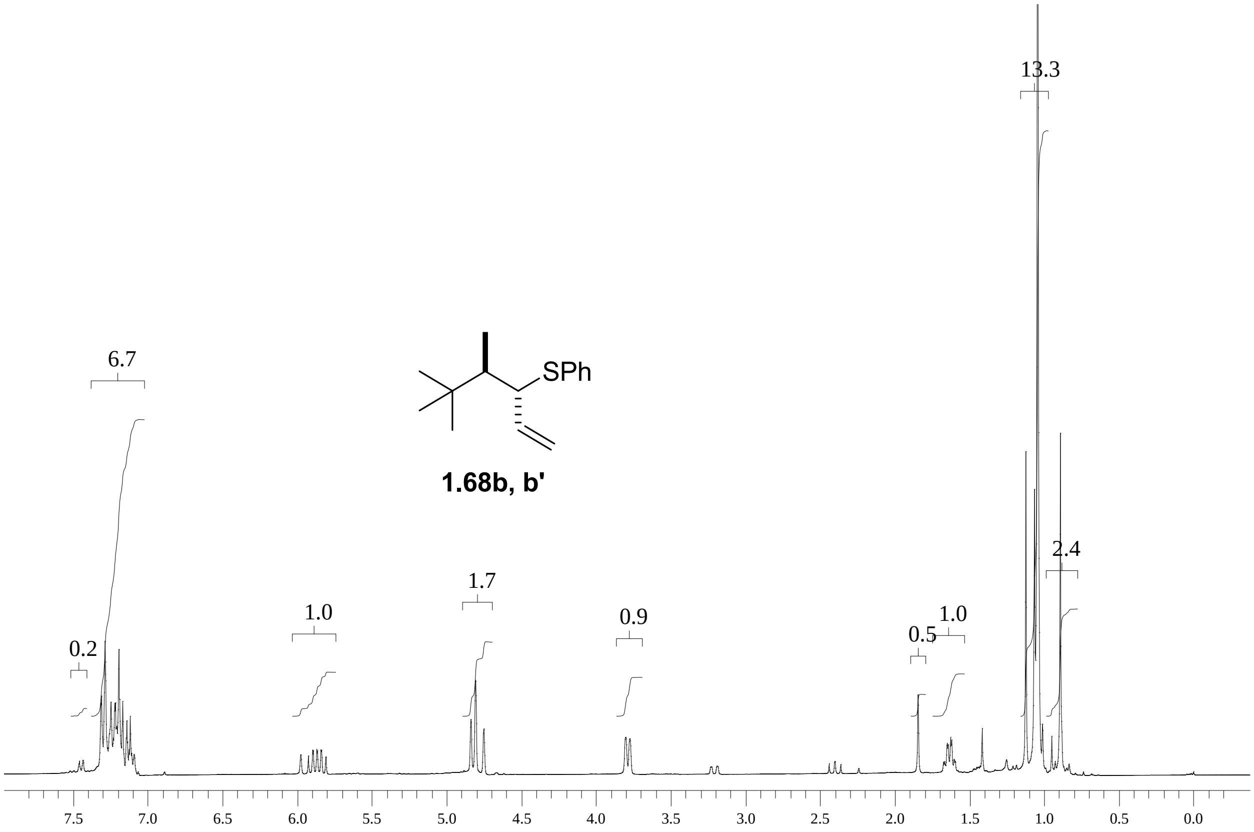


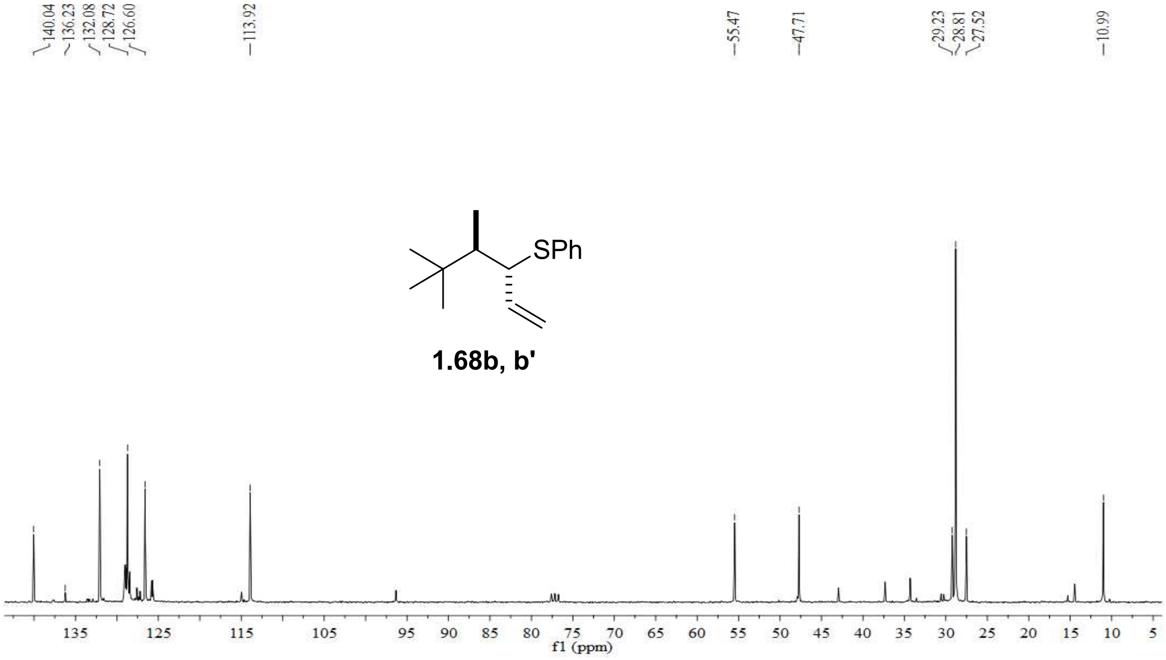
1.67c, c'

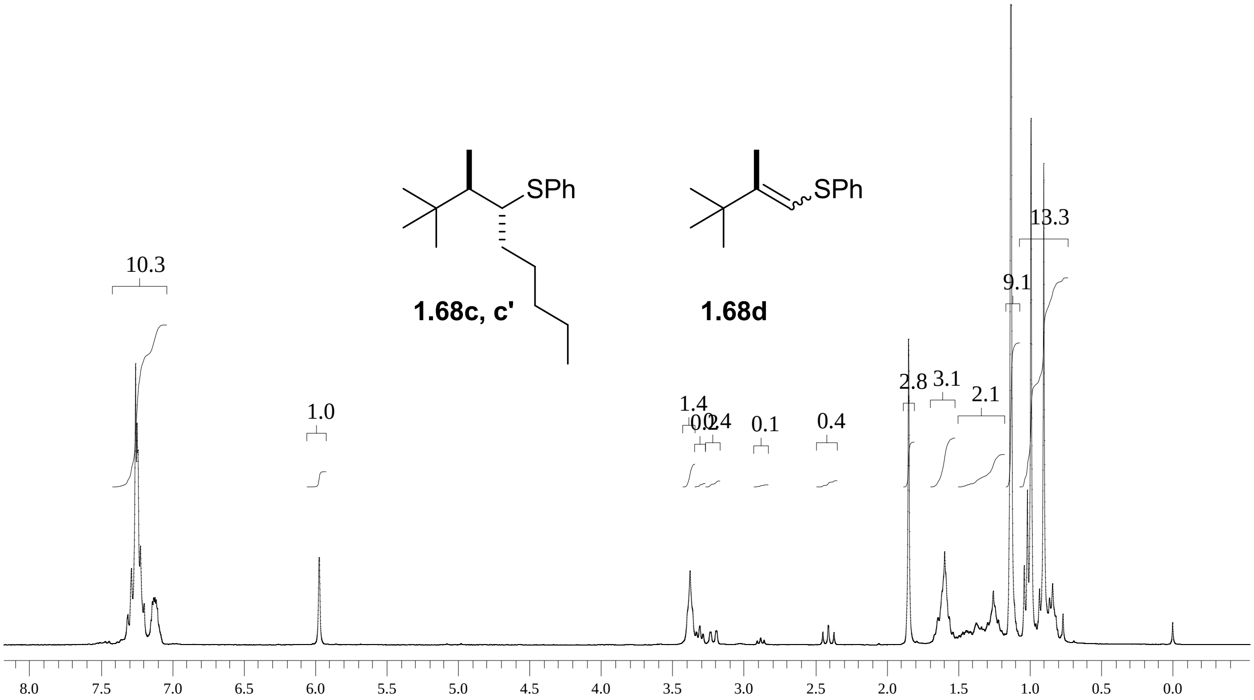
1.67d

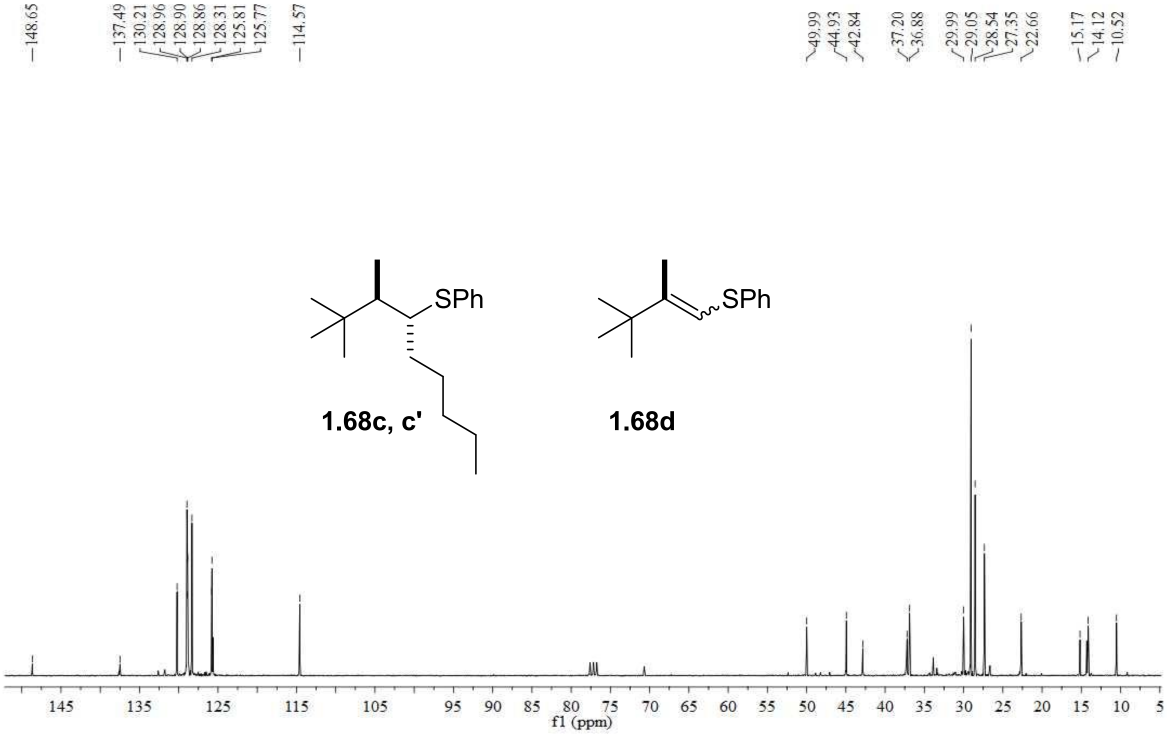

1.68a, a'
SPh
5
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

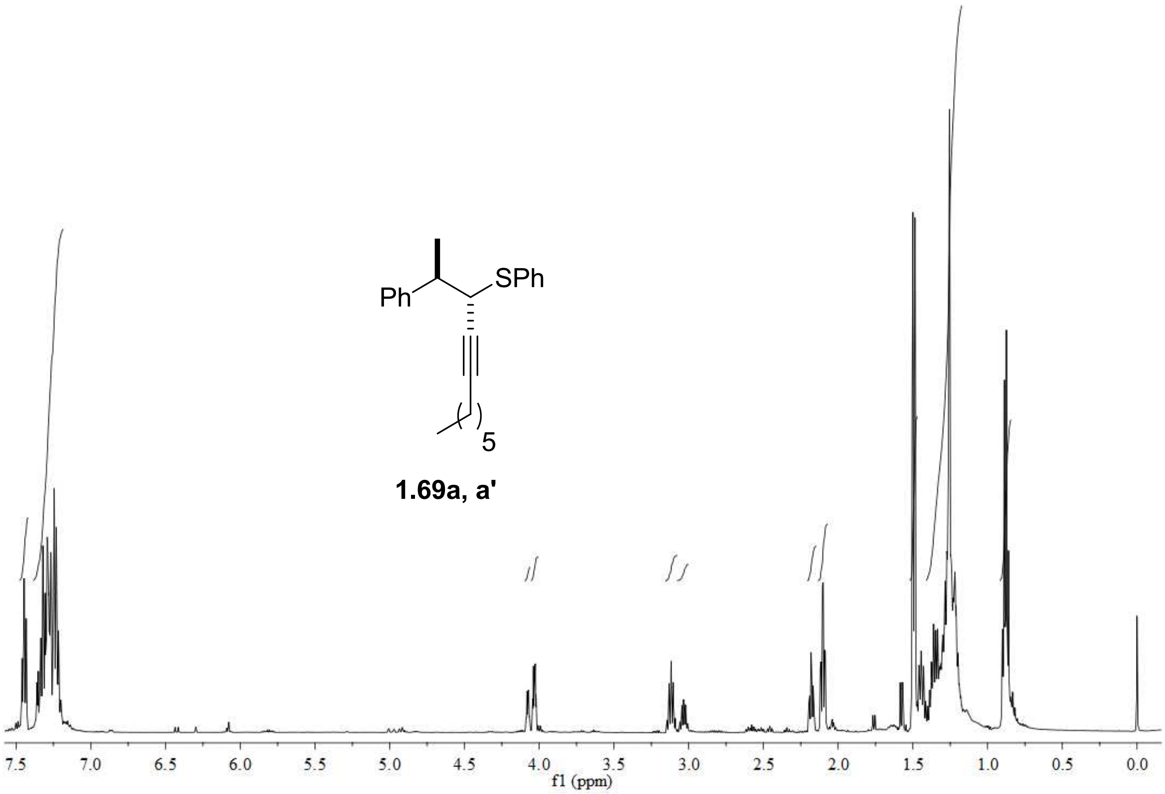

1.68a, a'
136.24
131.89
128.62
126.75
84.06
81.88
48.59
43.00
33.87
31.50
28.84
28.76
28.58
27.43
22.70
18.97
14.23
12.11
SPh
5
135
125
115
110
105
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
f1 (ppm)


1.68b, b'
SPh
13.3
6.7
2.4
1.7
1.0
0.9
1.0
0.5
0.2
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


1.68b, b'
140.04
136.23
132.08
128.72
126.60
113.92
55.47
47.71
29.23
28.81
27.52
10.99
SPh
135
125
115
105
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
f1 (ppm)

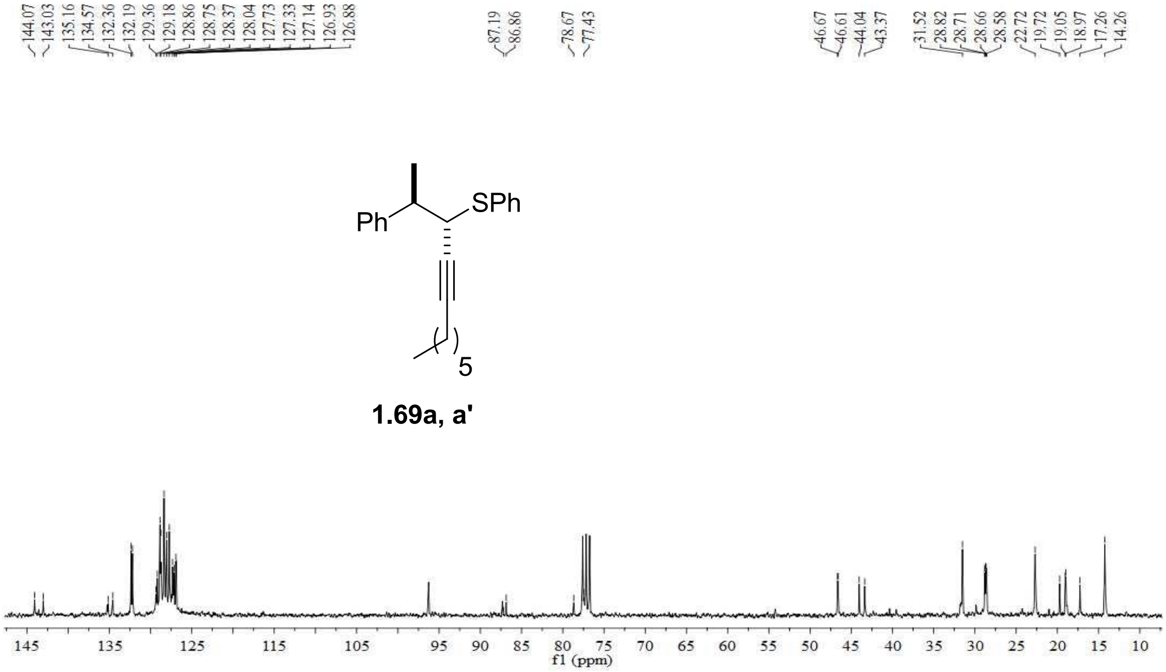

SPh
1.68c, c'
SPh
1.68d
10.3
1.0
1.4
0.2
0.4
0.1
0.4
2.8
3.1
2.1
9.1
13.3
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


148.65
137.49
130.21
128.96
128.90
128.86
128.31
125.81
125.77
114.57
49.99
44.93
42.84
37.20
36.88
29.99
29.05
28.54
27.35
22.66
15.17
14.12
10.52
SPh
1.68c, c'
SPh
1.68d
145
135
125
115
105
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
f1 (ppm)



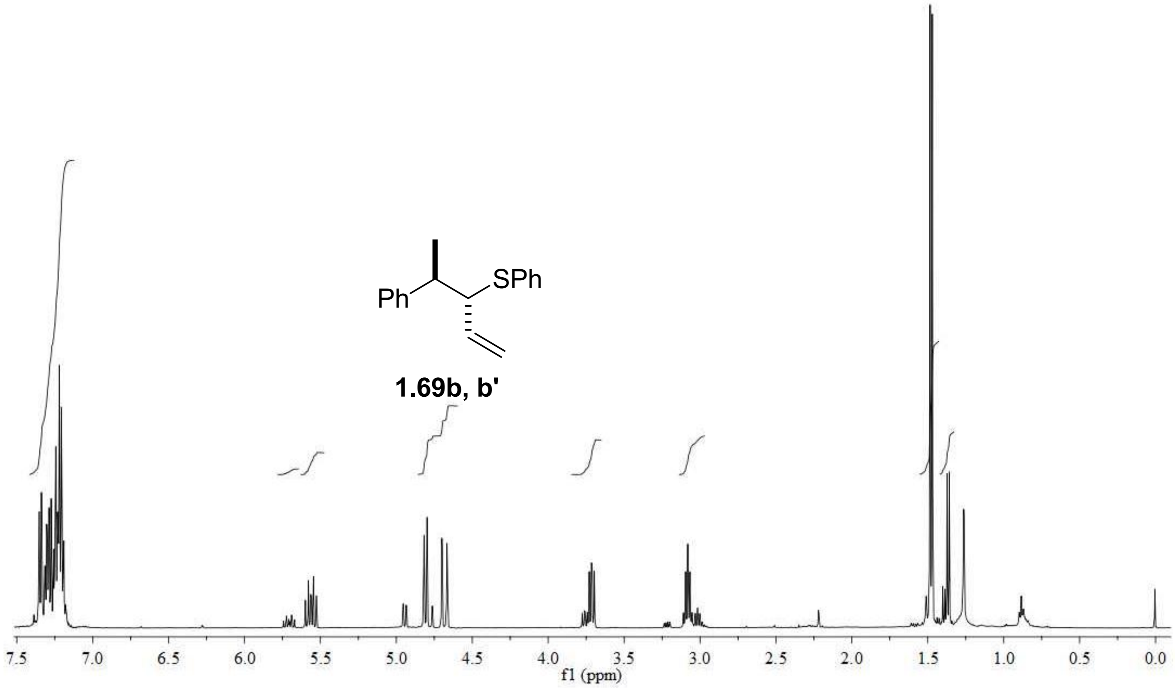
1.69a, a'

SPh
Ph
5
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
f1 (ppm)

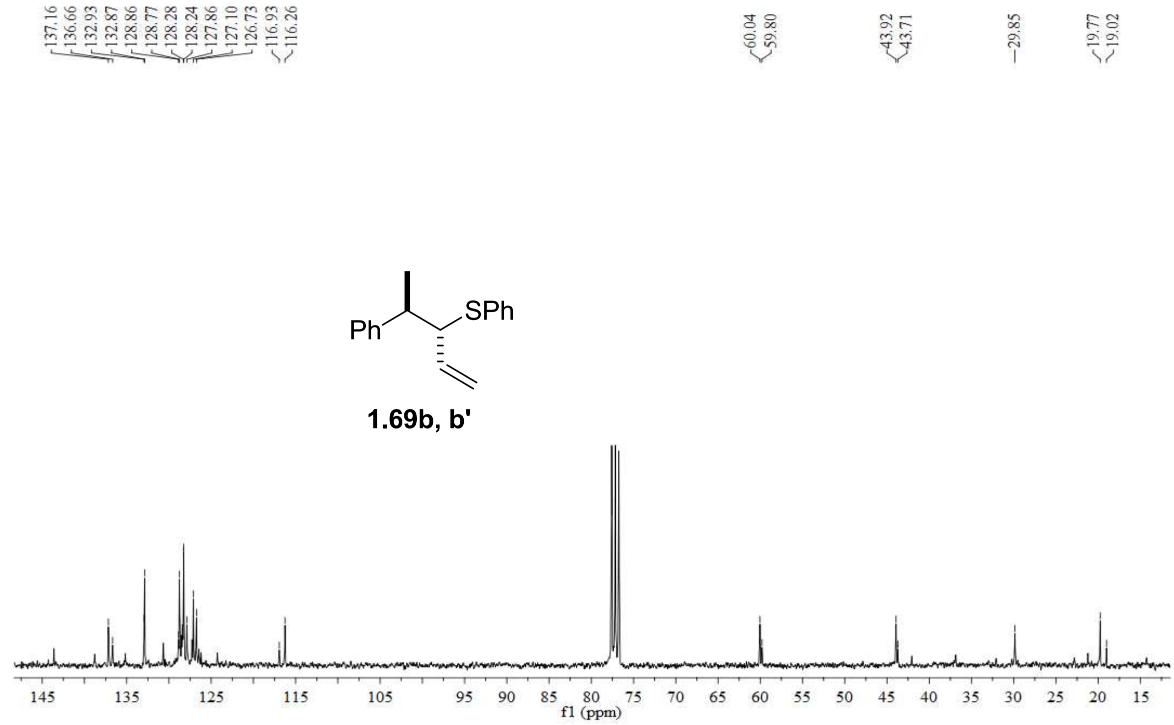


1.69a, a'

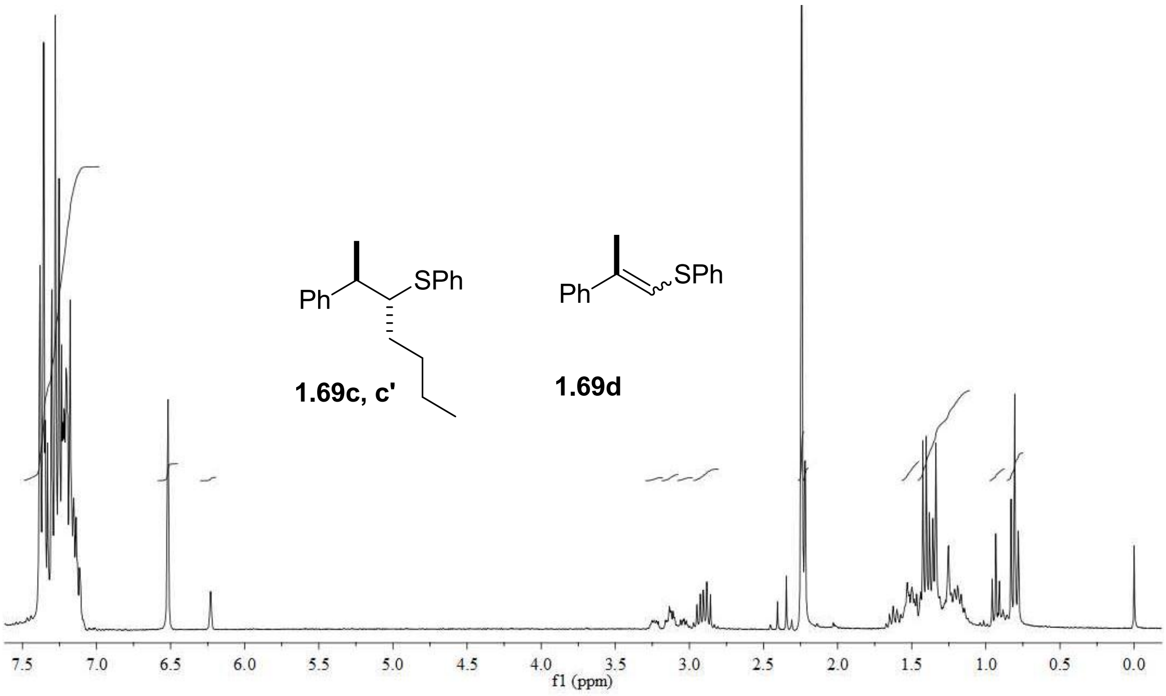
144.07
143.03
135.16
134.57
132.36
132.19
129.36
129.18
128.86
128.75
128.37
128.04
127.73
127.33
127.14
126.93
126.88
87.19
86.86
78.67
77.43
46.67
46.61
44.04
43.37
31.52
28.82
28.71
28.66
28.58
22.72
19.72
19.05
18.97
17.26
14.26
SPh
Ph
5
145 135 125 115 105 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10
f1 (ppm)

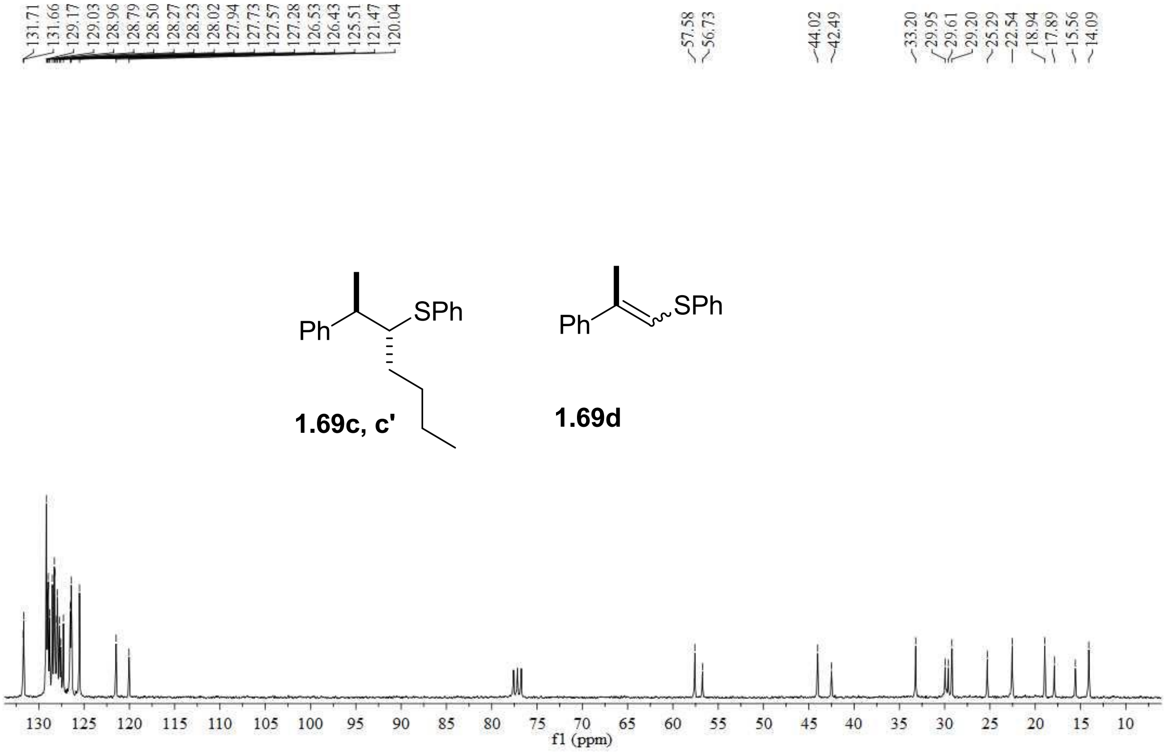

Ph
SPh
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

1.69b, b'


137.16
136.66
132.93
132.87
128.86
128.77
128.28
128.24
127.86
127.10
126.73
116.93
116.26
60.04
59.80
43.92
43.71
29.85
19.77
19.02
Ph
SPh
145
135
125
115
105
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
f1 (ppm)

1.69b, b'


Ph
SPh
1.69c, c'
Ph
SPh
1.69d
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
f1 (ppm)


131.71
131.66
129.17
129.03
128.96
128.79
128.50
128.27
128.23
128.02
127.94
127.73
127.57
127.28
126.53
126.43
125.51
121.47
120.04
57.58
56.73
44.02
42.49
33.20
29.95
29.61
29.20
25.29
22.54
18.94
17.89
15.56
14.09
Ph
SPh
1.69c, c'
Ph
SPh
1.69d
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
f1 (ppm)

CHAPTER II

Stereoselective Synthesis towards Bullatanocin

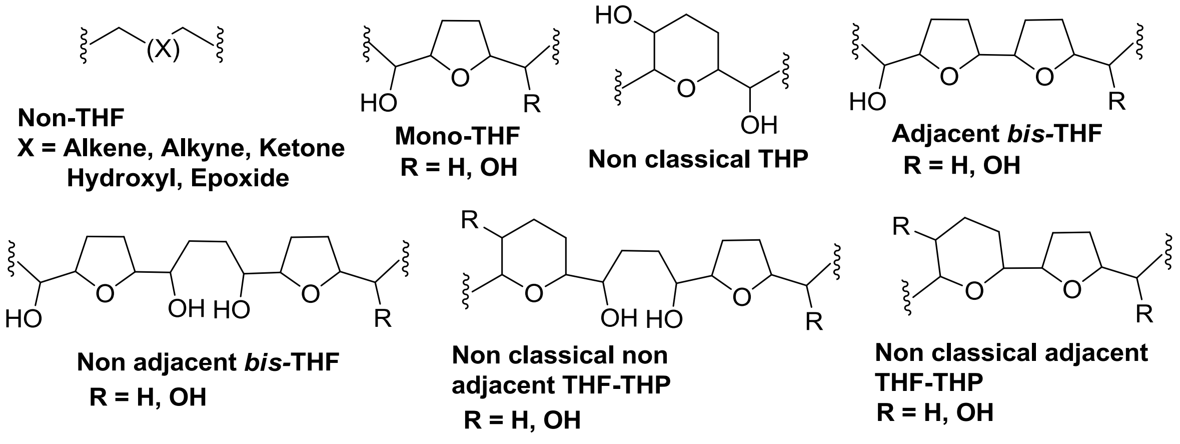
Stereoselective synthesis towards Bullatanocin

In this chapter a brief account of the structure and bioactivity of the *Annonaceous* acetogenin family of natural products and total synthesis of Bullatanocin reported by Mootoo and coworkers followed by an elaborate account of the present work is discolsed.

2.1 . Introduction

Annonaceous acetogenins are a group of natural products isolated from the plant family, *Annonacea* family plant (custard apple family), especially from the seeds, leaves and twigs of these plants. So far more than 400 acetogenins have been isolated. Structurally, *Annonaceous* acetogenins have unbranched C32/34 fatty acid chains with a terminal γ-lactone. Based on THF or THP rings and their connectivity acetogenins are classified into various categories. (1) Non-THF (2) Mono-THF (3) Non classical-THP (4) Adjacently linked *bis*-THF (5) Non classical adjacently linked THF-THP (6) Non adjacently linked *bis*-THF (7) Non classical non adjacently linked THF-THP, Figure 2.1.

Figure 2.1



Non-THF
X = Alkene, Alkyne, Ketone Hydroxyl, Epoxide

Mono-THF
R = H, OH

Non classical THP

Adjacent *bis*-THF
R = H, OH

Non adjacent *bis*-THF
R = H, OH

Non classical non adjacent THF-THP
R = H, OH

Non classical adjacent THF-THP
R = H, OH

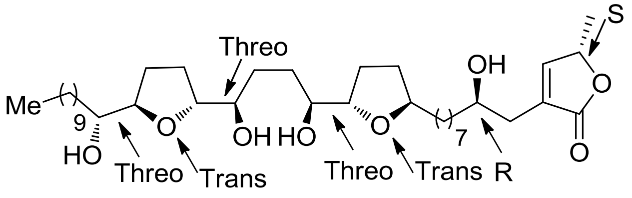
The proposed pathway for the biosynthesis of acetogenins starts with by installing the terminal γ-lactone to the long chain unsaturated fatty acid, then the double bonds in the fatty acid chain are partially or completely epoxidised which are subsequently opened by intermolecular/intramolecular ring opening reactions to result in various acetogenins with THF and THP ring diols. In addition to these cyclic ethers (THF, THP), other functional groups are also found in *Annonaceous* acetogenins such as epoxides, ketones, alkenes and alkynes.

2.2. Biological activity

The *Annonaceous* acetogenins display many interesting biological activities *in vivo* as well as *in vitro* such as antitumor, anti-parasitic, pesticidal, antimalarial and antibacterial activities.[2-9] Most importantly *Annonaceous* acetogenins act as cytotoxic and antitumour agents. Interestingly this activity extends to multi-drug resistant (MDR) cancer cell lines.[11,12] The *Annonaceous* acetogenins trilobacin and asiminocin are amongst the most potent cytotoxic compounds known in several human tumor cell lines ($ED_{50} > 10^{-12}$ μg/mL).[13,14] The cytotoxic and anti-tumour properties are thought to be due to potent inhibition of mitochondrial complex 1.[15-18]

Bullatanocin belongs to non adjacently linked bis THF family of acetogenins. It shows ED_{50} of less than 10^{-8} *μg*/mL against the colon cancer cell line HT-29 and the lung cancer cell line A-549. It possesses *threo, trans, threo, threo, trans* disposition of oxygen. In view of the interesting structure and important biological activity in vivo, bullatanocin has attracted the attention of synthetic chemists and Mootoo *et.al* reported the first total synthesis in 2003.[2]

Figure 2.2

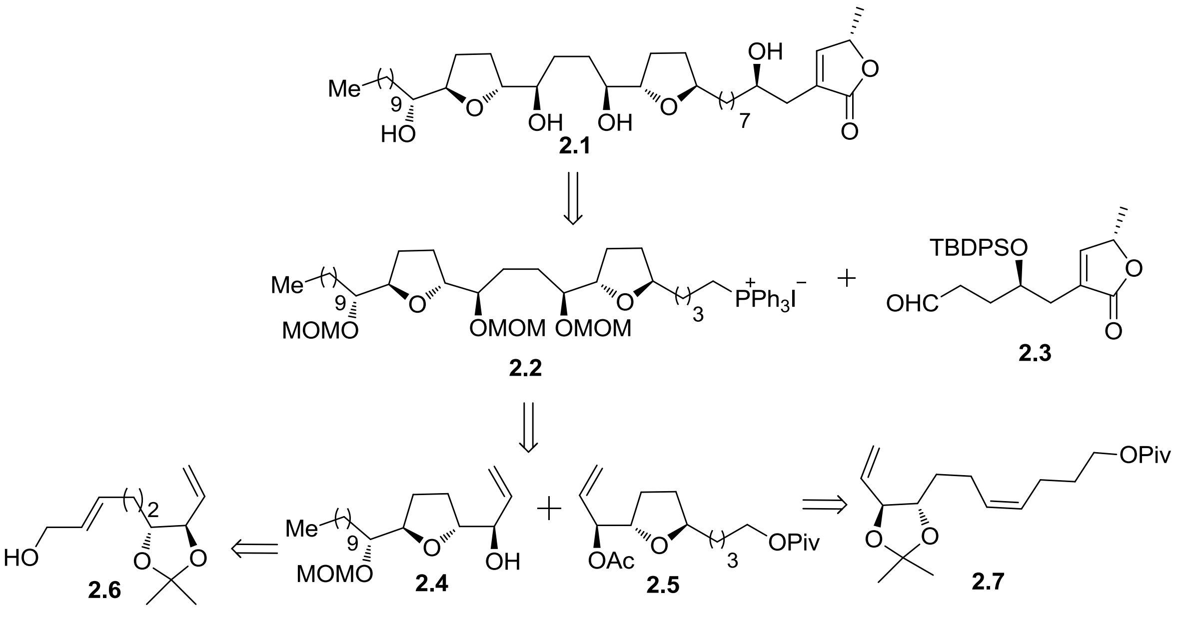


Bullatanocin 2.1

2.3. Mootoo's Approach

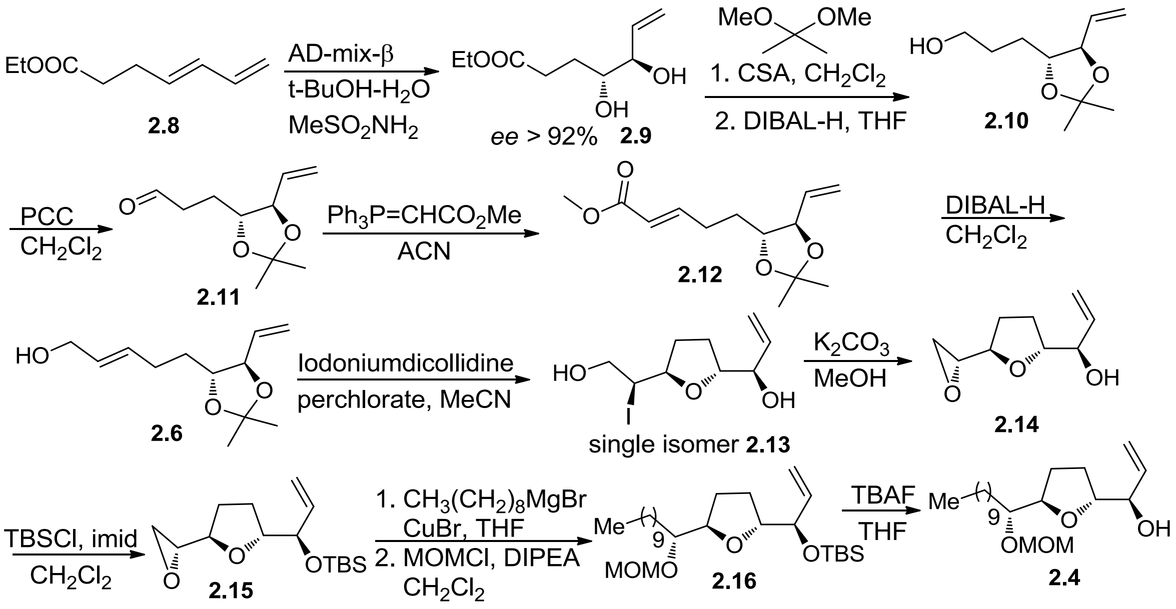
The first total synthesis of bullatanocin **2.1** was achieved by Mootoo and co-workers utilizing an iodoetherification methodology and olefin-metathesis reaction.[3] The target molecule was subdivided into three main fragments **2.3-2.5**. The ring in fragments **2.4** and **2.5** were created by iodoetherification reaction developed by Mootoo. The coupling strategy was to unite the THF fragments **2.4** and **2.5** by cross-metathesis and further couple it with the butenolide fragment **2.3** by a Wittig reaction, Scheme 2.1.

Scheme 2.1. Retrosynthetic analysis employed by Mootoo



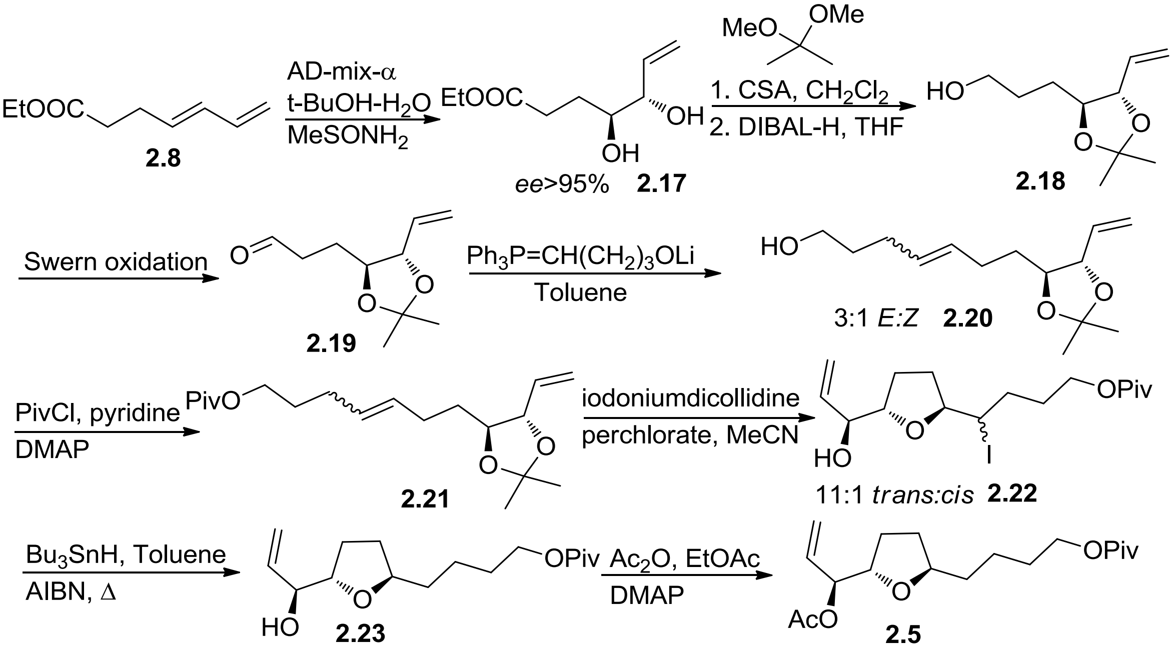
The synthesis of THF fragment **2.4** began with ester **2.8** which was converted to diol **2.9** employing Sharpless' asymmetric dihydroxylation reaction. The diol was protected as its acetonide and subjected to reduction with DIBAL-H to yield alcohol **2.10**. Oxidation using PCC furnished aldehyde **2.11**, which was further converted to unsaturated ester **2.12** by Wittig olefination reaction. The compound **2.12** on reduction with DIBAL-H yielded alcohol **2.6** which on treatment with iodoniumdicollidine perchlorate afforded the THF derivative **2.13** stereoselectively. The iodide **2.13** on treatment with anhydrous K_2CO_3 in methanol yielded epoxide **2.14.** The free hydroxyl of **2.14** was protected as its TBS ether **2.15** and subsequently reacted with nonyl Grignard reagent in presence of CuBr to furnish the secondary carbinol that on MOM protection afforded MOM ether **2.16**. Compound **2.16** on treatment with TBAF afforded the fragment **2.4**, Scheme 2.2.

Scheme 2.2 Synthesis of THF fragment **2.4**



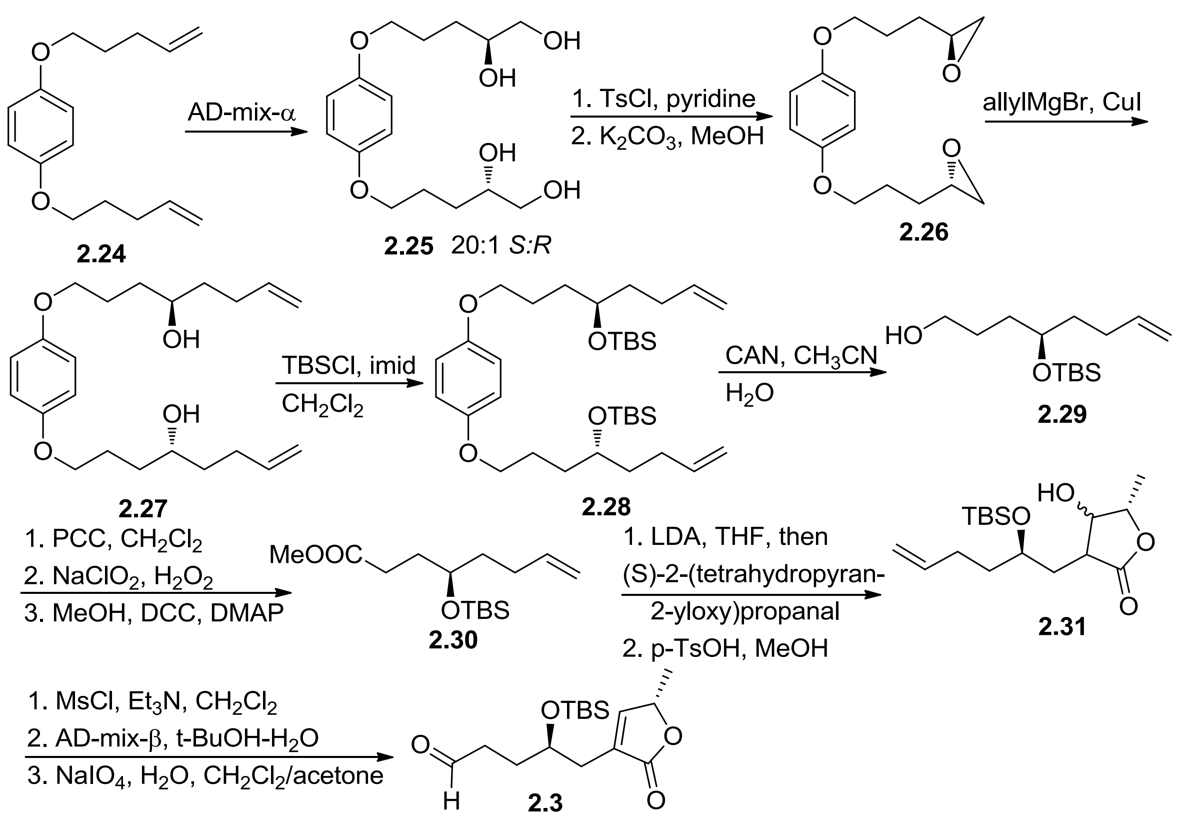
The synthesis of fragment **2.5** again commenced from diene ester **2.8**. Asymmetric dihydroxylation of **2.8** using AD-mix-α afforded the diol **2.17**. The aldehyde **2.19** was prepared as earlier and subjected to Wittig olefination with an unstabilized ylide to afford olefin **2.20** as a 3:1 *Z:E* mixture. The primary hydroxyl was protected as its pivalate ester **2.21** and subsequently treated with iodoniumdicollidine perchlorate in ACN to yield the THF derivative **2.22**. Reductive deiodinization using Bu_3SnH yielded the compound **2.23** which was further converted to its acetate **2.5**, Scheme 2.3.

Scheme 2.3 Synthesis of THF fragment **2.5**.



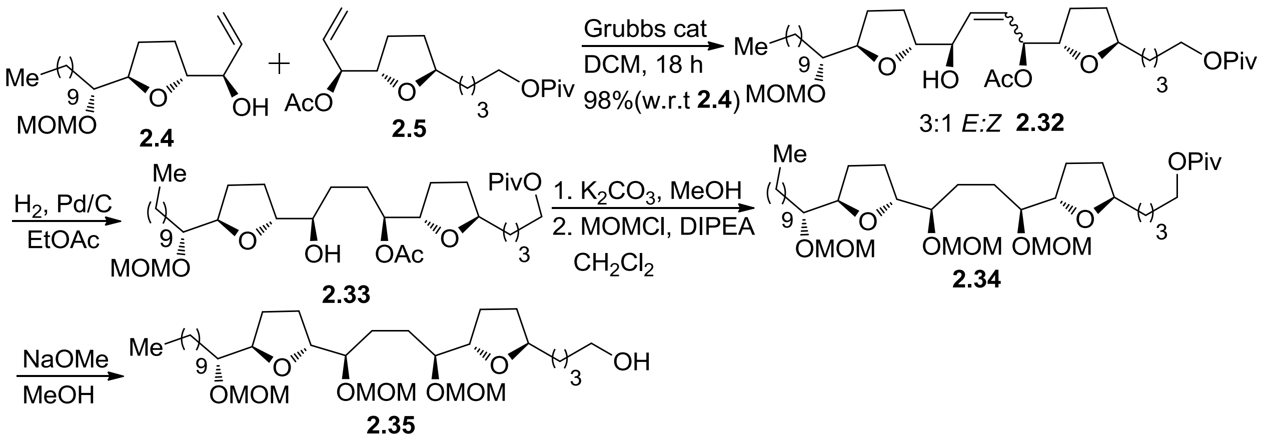
The synthesis of butenolide fragment **2.3** commenced with diene **2.24**. The diene **2.24** was synthesised in one step from 5-iodo-1-pentene. Dihydroxylation of diene **2.24** using AD-mix-α followed by recrystallisation afforded tetraol **2.25**. Compound **2.25** was converted to *bis*-epoxide **2.26** by selective mono tosylation of primary alcohol followed by treatment with K_2CO_3. Opening of *bis* epoxide **2.26** with vinylmagnesium bromide in presence of CuI afforded the diol **2.27** which was subsequently protected as its silyl ether **2.28**. Compound **2.28** on treatment with CAN afforded the alcohol **2.29** which was oxidized to ester **2.30**. Deprotonation of **2.30** with LDA followed by reaction with (*S*)-2-(tetrahydropyran-2-yloxy)propanal and subsequent treatment with PTSA furnished lactone **2.31**. Dehydration of lactone **2.31**, regioselective dihydroxylation of terminal double bond followed by periodate cleavage of the diol yielded aldehyde **2.3**, Scheme 2.4.

Scheme 2.4 Synthesis of butenolide fragment **2.3**



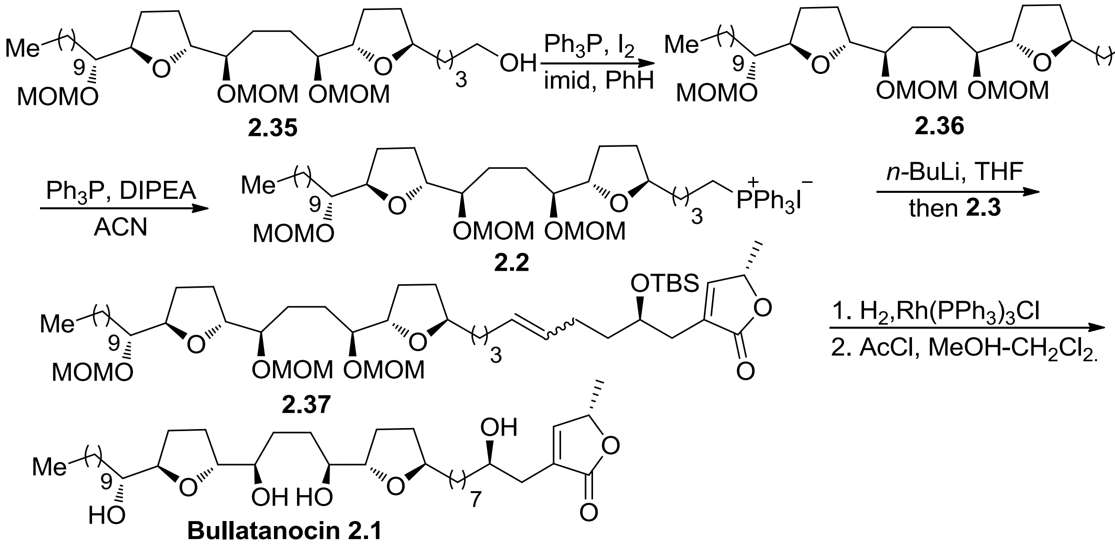
The key step in the synthesis of Bullatanocin was the cross-metathesis reaction between alkenes **2.4** and **2.5** using Grubbs' catalyst. This process relied on employing an excess of allylic alcohol **2.5** relative to alcohol **2.4** to furnish alkene **2.32**. Best results were obtained by using 1:3/4 ratios of fragments **2.4** & **2.5** respectively. Alkene **2.32** was reduced to compound **2.33** using Pd/C. The acetate group was selectively deprotected and the resulting diol was protected as its MOM ether **2.34**. The pivalate group was deptotected using NaOMe to furnish alcohol **2.35**, Scheme 2.5.

Scheme 2.5 Total synthesis of alcohol **2.35**



Alcohol **2.35** was converted to iodide **2.36** and subsequently treated with Ph_3P to afford the phosphonium salt **2.2**. Butenolide **2.3** was coupled with the ylide generated from **2.2** to afford olefin **2.37**. Selective reduction followed by deprotection of the protecting group afforded bullatanocin **2.1**, Scheme 2.6.

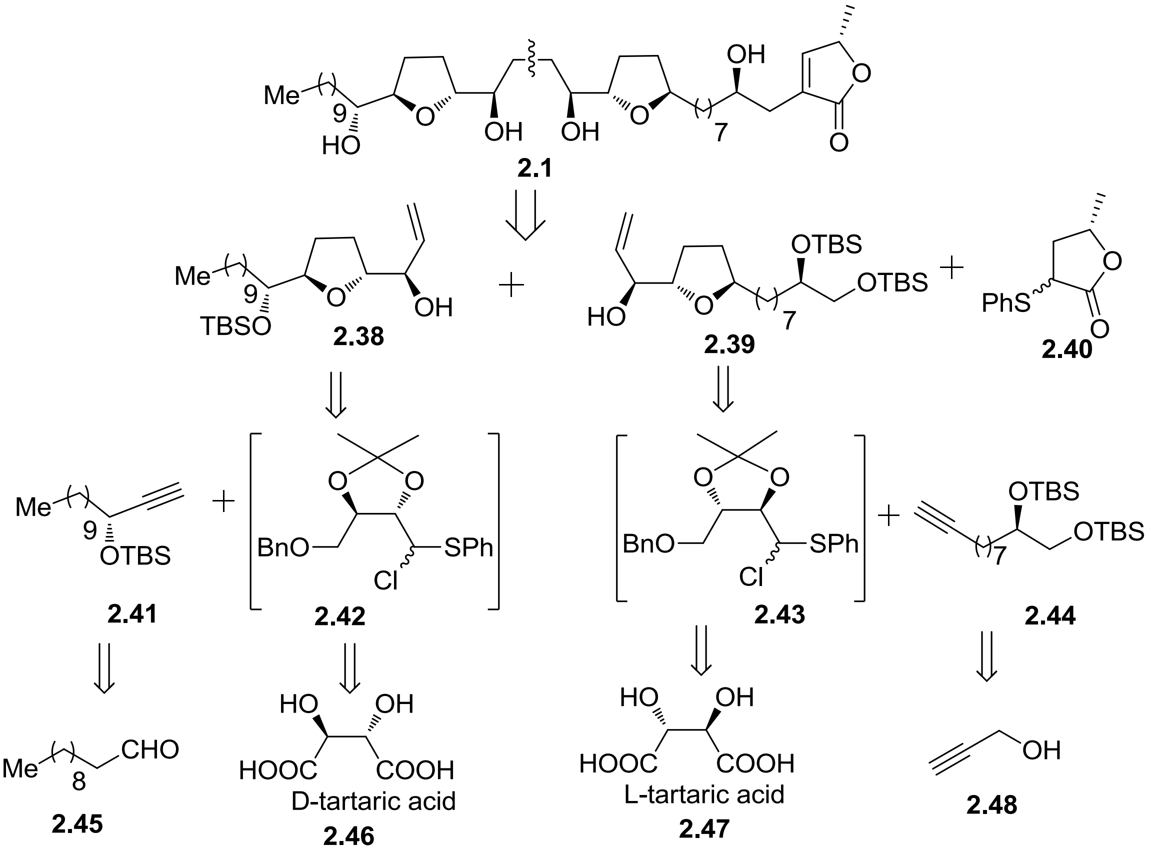
Scheme 2.6 Total synthesis of Bullatanocin **2.1**



2.4. Towards the Synthesis of Bullatanocin: Present Study

It was proposed to synthesize bullatanocin employing α-chloro sulfides as reactive intermediate for C-C bond formation. The synthesis of the target was envisioned by uniting subunits **2.38**, **2.39** and **2.40**. The tetrahydrofuran derivatives **2.38** and **2.39** were envisaged to be obtained from the reaction of α-chloro sulfides **2.42** and **2.43** by reaction with alkynylzinc reagents. The sulfides can be obtained from (D)-tartaric acid **2.46** and (L)-tartaric acid **2.47** respectively. The key step in the synthesis is based on utilizing the α-chloro sulfide synthons **2.42**, **2.43** to prepare propargylic sulfides via 1,2 asymmetric induction. Alkyne **2.41** was envisaged to be prepared from undecanal **2.45** and alkyne **2.44** from propargyl alcohol **2.49**, Scheme 2.7.

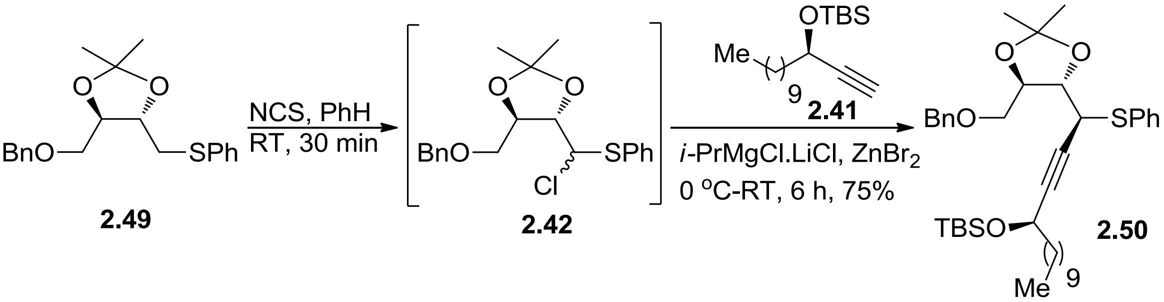
Scheme 2.7 Retrosynthetic Analysis



The synthesis of THF derivative **2.38** commenced from D-tartaric acid **2.46**. The sulfide **2.49**, was prepared as detailed in Scheme 1.18 in chapter 1.

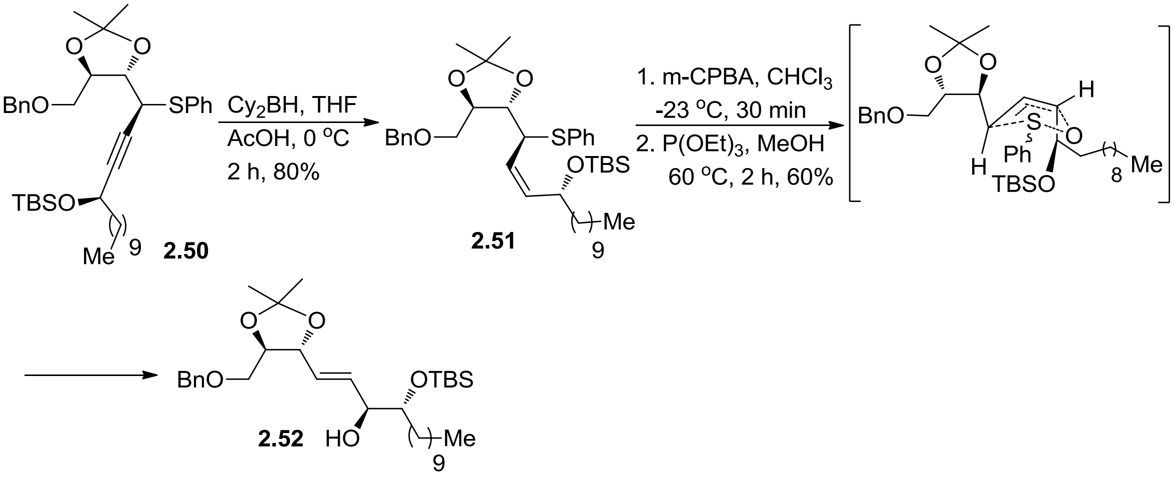
Sulfide **2.49** was reacted with one equivalent of NCS in dry benzene to form α-chloro sulfide intermediate **2.42**[5] which without isolation was allowed to react with an excess of alkynylzinc reagent bromide, prepared form alkyne **2.41** by treatment with *i*-PrMgCl.LiCl and and subsequent transmetallation[6], to afford the propargylic sulfide **2.50** (*de* >95%) by 1,2 asymmetric induction due to its vicinal stereogenic center. The identity of **2.50** was confirmed by its ^{1}H NMR wherein the resonances for the terminal alkyne proton was absent and spectrum showed resonances at δ 4.10-4.01 (m, 1H) for PhS-C*H*-, the tertiary butyl signal for the TBS moiety appeared at δ 0.90-0.84 (s, 9H) while the methyl groups of the silyl ether appeared at 0.05 (s, 3H), 0.04 (s, 3H). The ESI mass spectrum of **2.50** showed a molecular ion peak at 675 [M+Na]$^+$ supporting the structural assignment, Scheme 2.8.

Scheme 2.8 Synthesis of propargylic sulfide **2.50**



Propargylic sulfide **2.50** was reduced to allylic sulfide **2.51** by treatment with one equivalent of Cy_2BH.[7] The identity of **2.51** was confirmed by its ^{1}H NMR spectrum that revealed the presence of olefinic protons at δ 5.70-5.45 (m, 2H). The ESI mass spectrum of **2.51** showed the molecular ion peak at 677 [M+Na]$^+$. The allylic sulfide was treated with *m*-CPBA at -23 °C to furnish an epimeric mixture of sulfoxides which without isolation was reacted with an excess P(OEt)$_3$ at 60 °C to afford allylic alcohol **2.52** via sulfoxide-sulfinate [2,3] sigmatropic rearrangement reaction also popularly known as Mislow-Evans-Braverman rearrangement.[8] The identity of **2.52** was confirmed by its ^{1}H NMR spectrum which showed resonances at δ 4.25 (dd, *J* = 6.0, 3.0 Hz, 1H) for -O-C*H*-CH=CH- and 4.08 (dd, *J* = 6.0, 3.0 Hz, 1H) for -CH=CH-C*H*(OH)-. The ESI mass spectrum of **2.52** showed the molecular ion peak at 580 [M+NH$_4$]$^+$, Scheme 2.9.

Scheme 2.9 Synthesis of allylic alcohol **2.52**

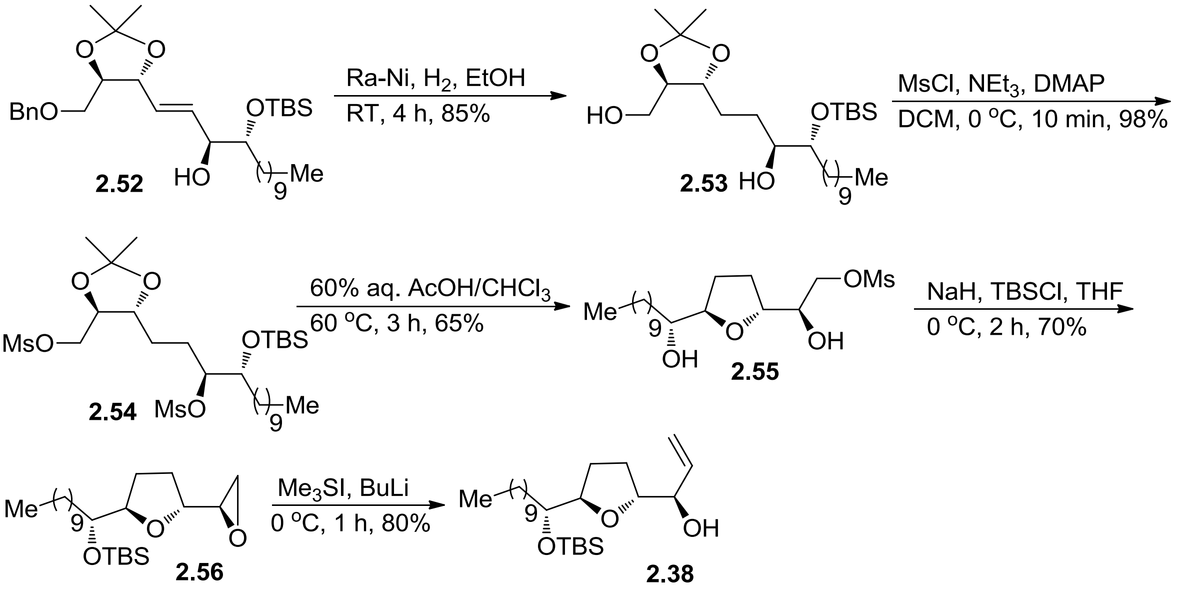


Benzylic ether **2.52** on treatment with freshly prepared Raney-Ni[9] under hydrogen atmosphere afforded the diol **2.53**. The identity of **2.53** was confirmed by its ^{1}H NMR spectrum, wherein the resonances for the benzylic group were absent. The ESI mass spectrum of **2.53** showed the molecular ion peak at 471 [M+H]$^+$. The compound **2.53** was converted to dimesylate **2.54** by reaction with MsCl/NEt$_3$. The identity of **2.54** was confirmed by its ^{1}H NMR spectrum which showed resonances at δ 4.68-4.64 (m, 1H) for -C*H*-SO$_2$-CH$_3$, 4.27 (d, *J* = 11.3 Hz, 1H), 4.26 (d, *J* = 9.13 Hz, 1H) for –C*H$_2$*-SO$_2$-CH$_3$, δ

3.10 (s, 3H) and 3.04 (s, 3H) for -O-SO_2-CH_3. The ESI mass spectrum of **2.54** showed the molecular ion peak at 648 $[M+NH_4]^+$.

Hydrolysis of acetonide **2.54** using 60% aq AcOH yielded THF derivative **2.55**.[10] The hydroxy mesylate was converted to epoxide **2.56** using NaH and TBSCl in an one pot operation. One carbon homologation following Falck's protocol furnished allylic alcohol **2.38**. The identity of **2.38** was confirmed by its ^1H NMR spectrum that revealed the presence of protons for the mono substituted alkene at δ 5.81-5.71 (m, 1H), 5.33 (d, *J* = 17.5 Hz, 1H) and 5.31 (d, *J* = 10.9 Hz, 1H). The ESI mass spectrum of **2.38** showed the molecular ion peak at 435 $[M+Na]^+$, Scheme 2.10.[11]

Scheme 2.10 Synthesis of THF fragment **2.38**

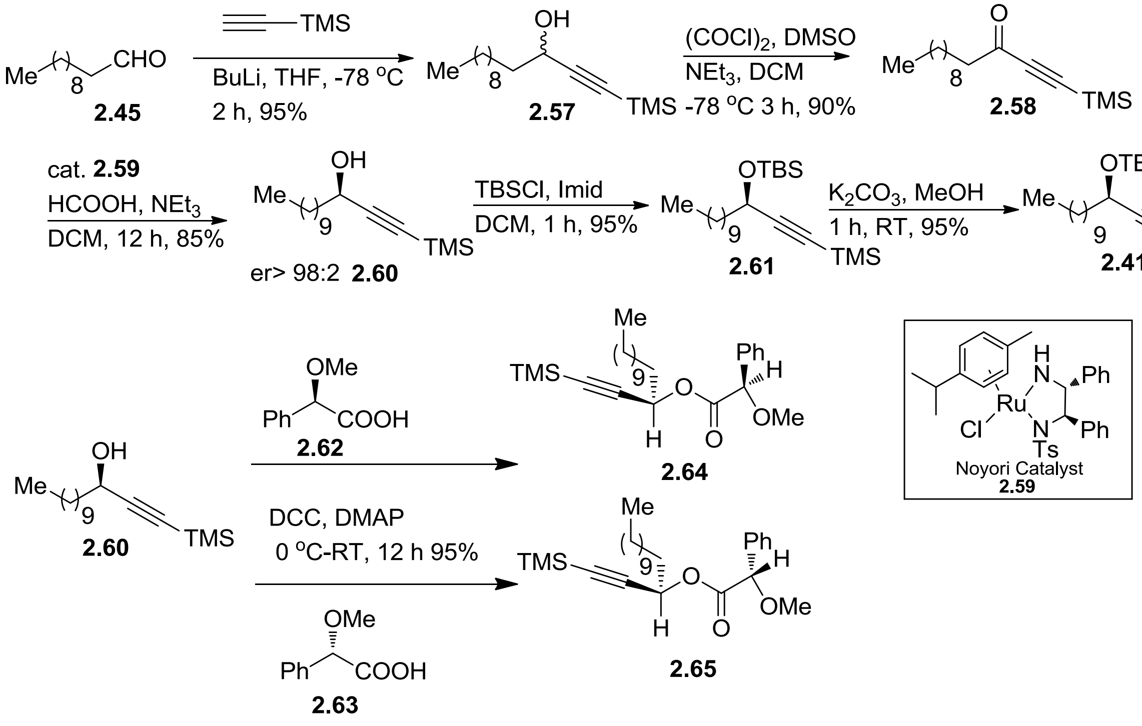


The propargylic ether **2.41** was synthesized beginning from undecyl aldehyde **2.45**. Reaction of commercially available aldehyde **2.45** with the lithium anion of TMS acetylene afforded racemic propargylic alcohol **2.57** which was oxidized to propargylic ketone **2.58**. Enantioselective reduction of **2.58** using (*R*,*R*)-Noyori catalyst

2.59[14] afforded propargylic alcohol **2.60** (*er* = 98:2).[12] The hydroxyl group in **2.60** was protected as its TBS ether **2.61**. Removal of TMS group using catalytic amount of K_2CO_3 in MeOH afforded alkyne **2.41** in excellent yield. The identity of **2.41** was confirmed by its ^{1}H NMR spectrum which showed resonances at δ 2.30 (d, *J* = 1.5 Hz, 1H) for *H*CC-CH(OTBS)-.

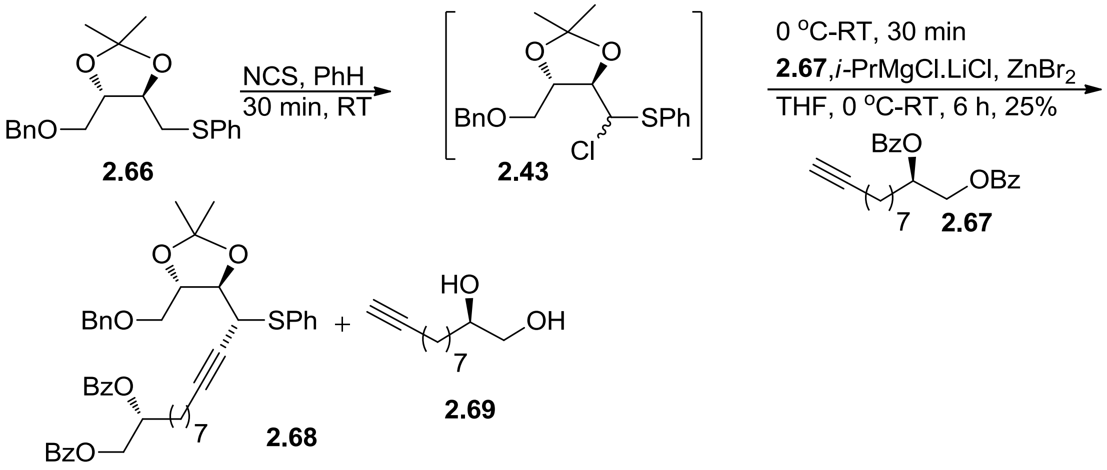
The enantiomeric purity and absolute configuration of alcohol **2.60** was determined by conversion to its mandelate derivatives **2.64**, **2.65** by reacting with enantiomerically pure methoxy mandelic acid **2.62, 2.63**.[13] The ^{1}H NMR spectrum of **2.64** showed resonances at δ 1.02 (t, *J* = 6.0 Hz, 3H) for -CH_2-CH_3, 0.30 (s, 9H) for –CC-Si(CH_3)$_3$ and the ^{1}H NMR spectrum of **2.65** showed resonances at δ 0.99 (t, *J* = 6.9 Hz, 3H) for -CH_2-CH_3 and 0.26 (s, 9H) for –CC-Si(CH_3)$_3$, Scheme 2.11.

Scheme 2.11 Synthesis of alkyne **2.41**



The synthesis of **2.39** commenced with L-tartaric acid **2.47**. Sulfide **2.66** was prepared as described earlier. Sulfide **2.66** was reacted with NCS in dry benzene to furnish α-chloro sulfide intermediate **2.43** which without isolation was allowed to react with an excess of an organozinc reagent prepared from alkyne **2.67** to furnish the propargylic sulfide **2.68** in 25% yield and diol **2.69** resulting from deprotection of benzoate group, Scheme 2.12.

Scheme 2.12 Synthesis of propargylic sulfide **2.68**

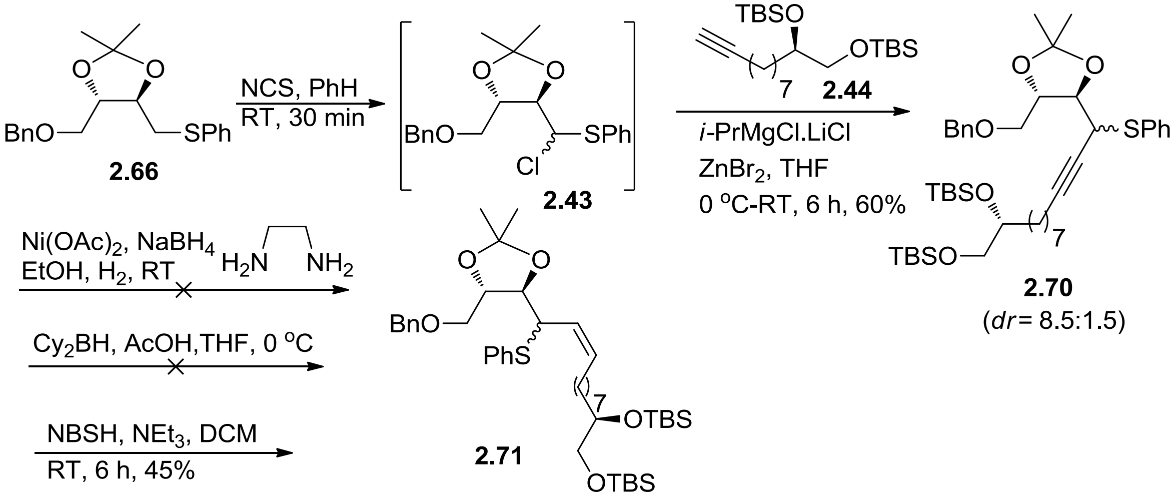


The reaction with chloro sulfide **2.43** was attempted with the disilyl ether derivative **2.44** to furnish the propargylic sulfide **2.70** was obtained in 60% yield (*dr* = 8.5:1.5). The identity of **2.70** was confirmed by its ^{1}H NMR spectrum which showed resonances at 4.10-4.02 (m, 1H), for PhS-C*H*-, 2.13 (dt, *J* = 6.9, 1.9 Hz, 2H) for –CC-CH_2-, the tertiary butyl signal for the TBS moiety appeared at δ 0.96 (s, 9H) while the methyl groups of the silyl ether appeared at 0.11 (s, 6H). The ESI mass spectrum of **2.70** showed the molecular ion peak at MS $[M+Na]^+$ 777.

Attempted partial reduction of the triple bond in **2.70** using Cy$_2$BH and nickel boride resulted in recovery of unreacted starting material. Reduction using *o*-

nitrobenzenesulfonyl hydrazide (NBSH) afforded allyl sulfide **2.71** in 45% yield. A draw back using this reagent was that complete conversion could not be achieved even using an excess of NBSH, Scheme 2.13.[15]

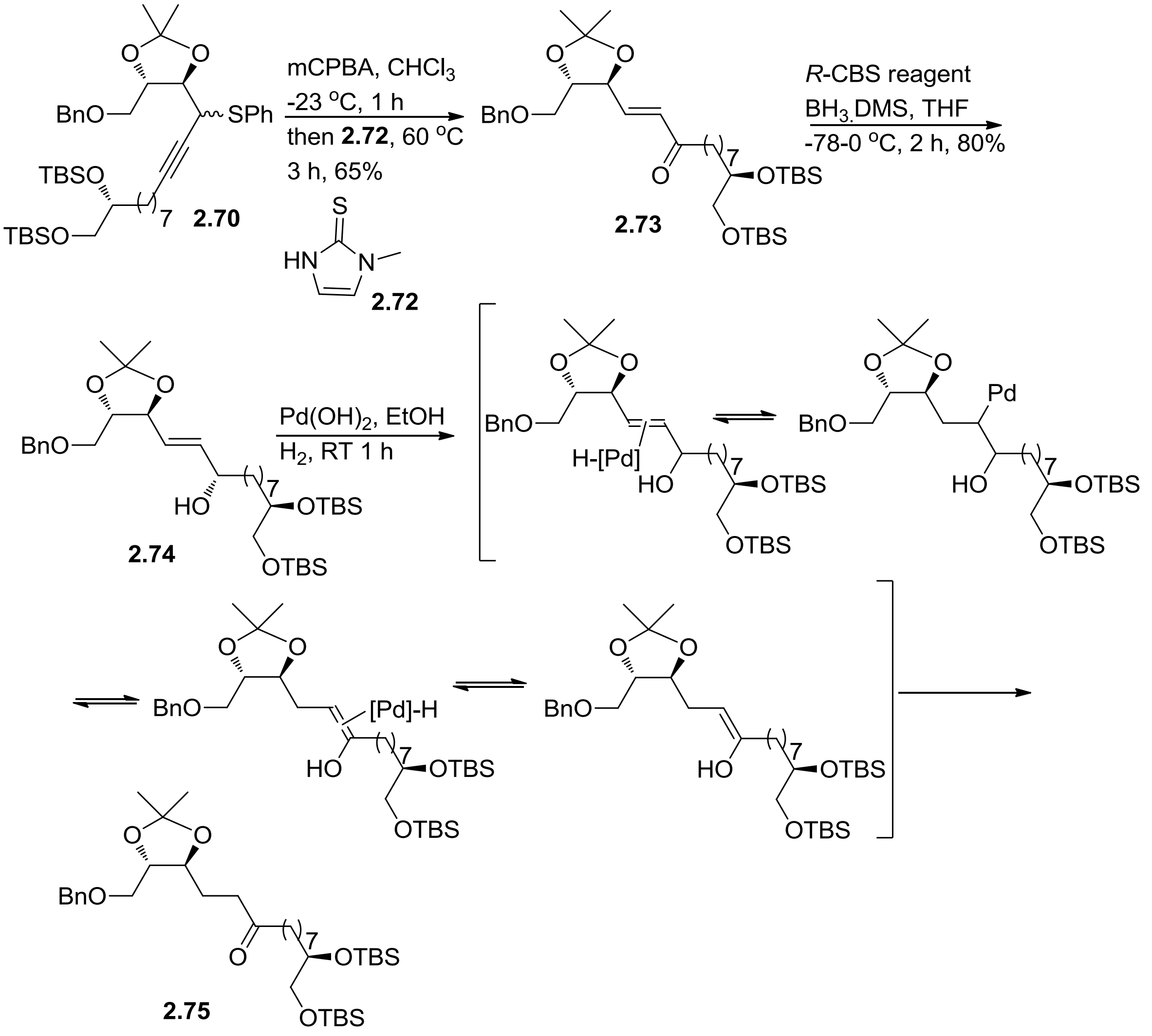
Scheme 2.13 Synthesis of allylic sulfide **2.71**



An alternate route to **2.39** was therefore explored. Propargylic sulfide **2.70** was oxidized using *m*-CPBA to furnish an equimolar epimeric mixture of sulfoxides which on heating in presence of an excess of thio imidazole **2.72**[16] afforded unsaturated ketone **2.73** by Braverman rearrengement.[8e,17] The identity of **2.73** was confirmed by its ^{1}H NMR spectrum that revealed the presence of olefinic protons at δ 6.77 (dd, *J* = 16.0, 5.0 Hz, 1H) and 6.37 (d, *J* = 16.0 Hz, 1H). The ESI mass spectrum of **2.73** showed the molecular ion peak at 663 $[M+H]^+$.

Stereoselective reduction of ketone **2.73** using (*R*)-Methyl CBS catalyst and $BH_3.SMe_2$ furnished allylic alcohol **2.74.**[18] The identity of **2.74** was confirmed by its ^{1}H NMR spectrum that revealed the presence of olefinic protons at δ 5.87 (dd, *J* = 15.0, 6.0 Hz, 1H), 5.75 (dd, *J* = 16.0, 7.0 Hz, 1H). The ESI mass spectrum of **2.74** showed the molecular ion peak at 687 [M+Na]$^+$. Attempted hydrogenation and hydrogenolysis using Pd/ and Pd(OH)$_2$ were unsuccessful, instead the ketone **2.75** was obtained, probably by isomerization of the double bond followed by tautomerization,[19] Scheme 2.14.

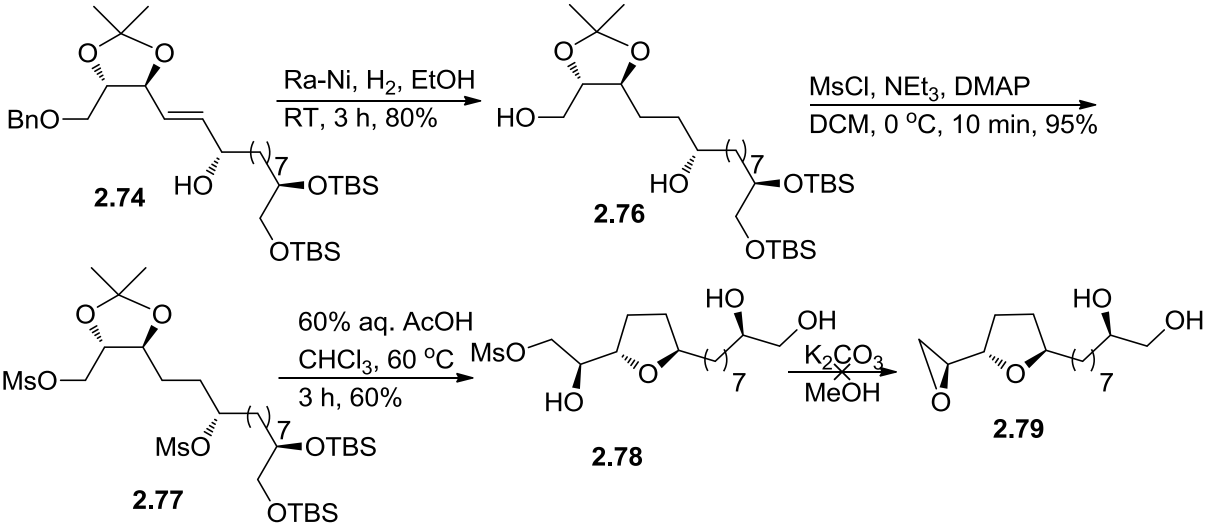
Scheme 2.14 Synthesis of allylic alcohol **2.74**



The allylic alcohol **2.74** could however be hydrogenated and hydrogenolyzed without incident using Raney-Nickel under hydrogen atmosphere to furnish the diol **2.76**. The identity of **2.76** was confirmed by its ^{1}H NMR spectrum, wherein the resonances for the benzylic and olefinic protons were absent. The ESI mass spectrum of **2.76** showed the molecular ion peak at 599 $[M+Na]^+$. The formation of diol **2.76** was further confirmed by conversion to its di acetate.

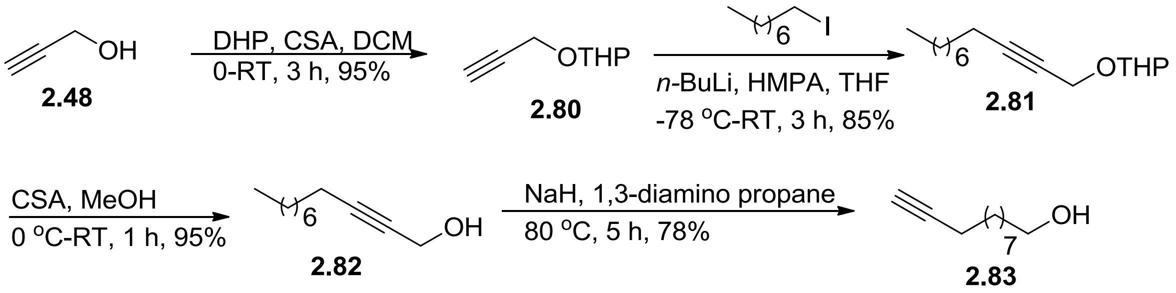
The diol **2.76** was converted to dimesylate **2.77**. The identity of **2.77** was confirmed by its ^{1}H NMR spectrum, which revealed signals at δ 3.07 (s, 3H) and 3.01 (s, 3H) for $-O-SO_2-CH_3$. The ESI mass spectrum of **2.77** showed the molecular ion peak at 755 $[M+Na]^+$. The compound **2.77** on treatment with 60% aq AcOH resulted in the deprotection of acetonide and silyl ethers to furnish the tetrahydrofuran derivative **2.78**. The formation THF **2.78** was confirmed by conversion to a tri acetate derivative and by ^{1}H NMR, Mass and HRMS analysis. The ^{1}H NMR spectrum of **2.78** revealed resonances at δ 4.31-4.23 (m, 2H) for $–CH_2-O-SO_2-CH_3$, δ 4.01-3.90 (m, 2H) for –C*H*-O-C*H*- and δ 3.08 (s, 3H) for $–CH-O-SO_2-CH_3$. The ESI mass spectrum of **2.78** showed the molecular ion peak at 391 $[M+Na]^+$. Attempted formation epoxide **2.79** in K_2CO_3 MeOH/EtOH and NaH, THF resulted in mixture of compounds or degradation of starting materials, Scheme 2.15.

Scheme 2.15 Synthesis of THF fragment **2.79**



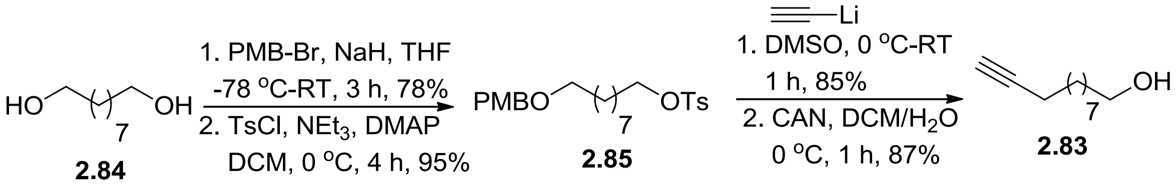
The synthesis of disilyl ether **2.44** commenced with propargyl alcohol **2.48**. Protection of the carbinol as its THP ether **2.80** followed by treatment with *n*-BuLi and 1-iodooctane furnished internal alkyne **2.81**. Deprotection of THP under acidic conditions afforded the corresponding propargylic alcohol **2.82** which was transformed to terminal alkyne **2.83** by using the Zipper reaction.[20] The identity of **2.83** was confirmed by its ^{1}H NMR spectrum, wherein the signals at δ 2.16 (dt, *J* = 6.9, 2.6 Hz, 2H) for -H_2C-CCH and δ 1.84 (t, *J* = 2.6 Hz, 1H) -H$_2$C-CC*H* were observed, Scheme 2.16.

Scheme 2.16 Synthesis of alcohol **2.83**



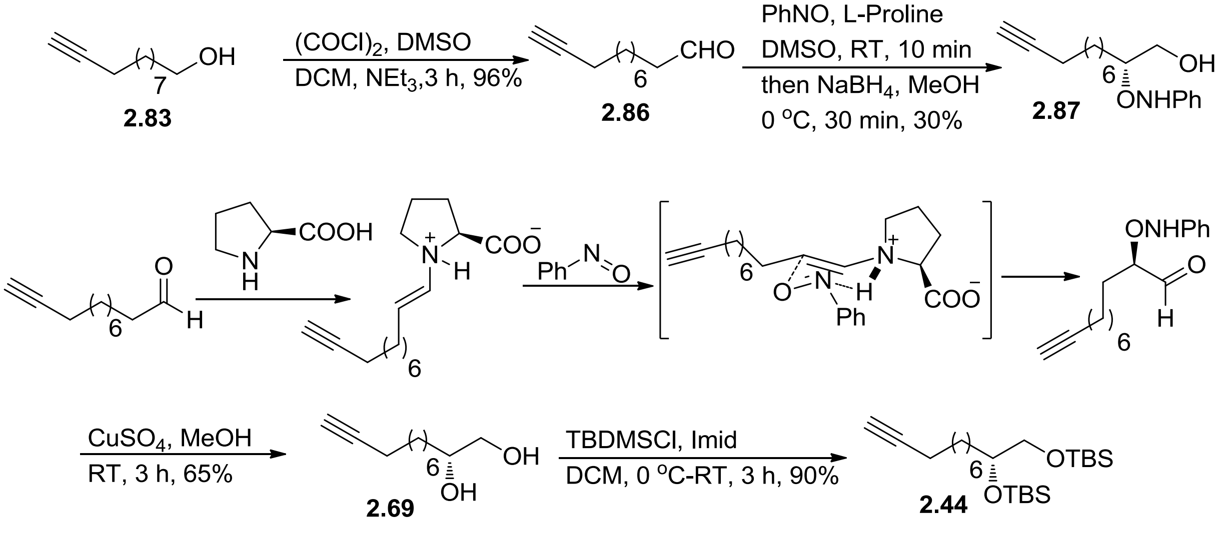
Alcohol **2.83** was alternatively synthesized more readily from nonane diol **2.84**. Selective mono-protection as its *p*-methoxybenzyl ether followed by tosylation yielded compound **2.85**. Alkylation with lithium acetylide ethylenediamine complex followed by deprotection of PMB ether furnished alcohol **2.83**, Scheme 2.17.

Scheme 2.17 Synthesis of alcohol **2.83**



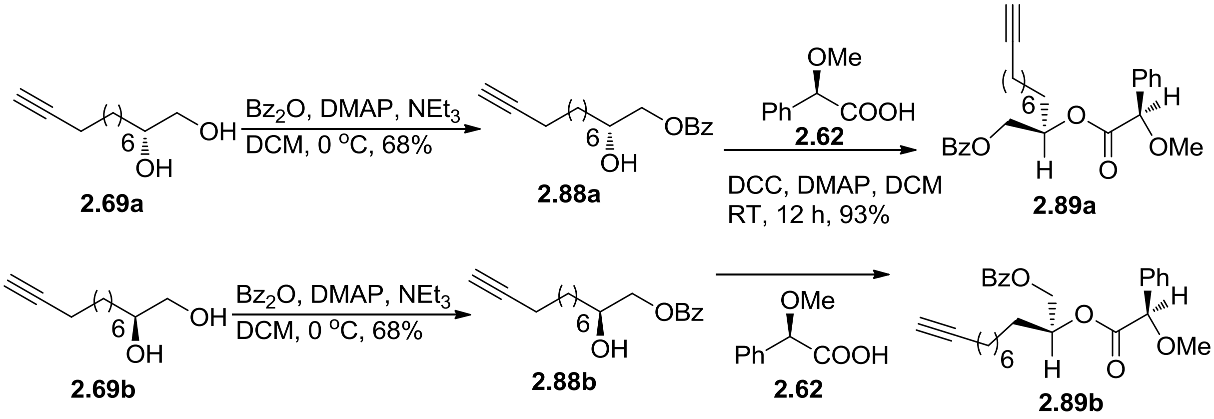
The alcohol **2.83** was oxidized to corresponding aldehyde **2.86** employing the Swern protocol. The identity of **2.86** was confirmed by its ^{1}H NMR spectrum, which revealed signals at δ 9.73 (s, 1H) for -C*H*O. Aldehyde **2.86** was further subjected to α-hydroxylation reaction using nitrosobenzene which in addition to the expected oxyaminated product **2.87 (**30% yield) yielded the diol **2.69** (50%) after reduction of the product mixture with $NaBH_4$ in 20% yield. [21] The compound **2.87** on treatment with $CuSO_4$ in MeOH afforded the diol **2.69** which was protected as its TBS ether **2.44**. The identity of **2.44** was confirmed by its ^{1}H NMR spectrum which showed resonances at δ 3.61 (m, 1H), for –CH_2-C*H*(OTBS)-CH_2(OTBS), δ 3.48 (dd, *J* = 10.1, 7.1 Hz, 1H), 3.38 (dd, *J* = 10.1, 7.1 Hz, 1H) for -C*H*$_2$(OTBS), the tertiary butyl signal for the TBS moiety appeared at δ 0.98 and 0.82 (2s, 18H), while the methyl groups of the silyl ether appeared at δ 0.2 (s, 12H), Scheme 2.18.

Scheme 2.18 Synthesis of alkyne **2.44**



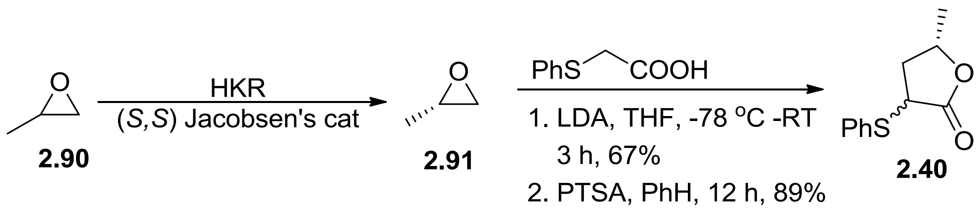
The optical purity and the absolute configuration of the diol **2.69** was determined as *R* by comparing the chemical shift values of its mandelate derivatives **2.89a**, **2.89b**. The diol **2.69a, b** was protected as its mono benzoate **2.88a, b** which was further converted to its mandelate derivatives by reacting with (*R*)-methoxy mandelic acid **2.62**. The diol **2.69b** was prepared in the same manner as the diol **2.69a** by using D-Proline as the catalyst from the aldehyde **2.85**.The ^{1}H NMR spectrum of **2.89a** showed resonances at δ 4.32-4.12 (m, 2H) for –O-C*H*$_2$-O-C(O)Ph, 2.15 (dt, *J* = 6.9, 2.6 Hz, 2H) for –C*H*$_2$-CCH and 1.84 (t, *J* = 2.6 Hz, 1H) for –CH$_2$-CC*H*. The ^{1}H NMR spectrum of **2.89b** showed resonances at δ 4.33 (dd, *J* = 7.2, 5.1 Hz, 1H), 4.20 (dd, *J* = 7.2, 6.2 Hz, 1H) for –O-C*H*$_2$-O-C(O)Ph, 2.07 (dt, *J* = 6.9, 2.6 Hz, 2H) for –C*H*$_2$-CCH, 1.78 (t, *J* = 2.6 Hz, 1H) for –CH$_2$-CC*H*, Scheme 2.19.

Scheme 2.19 Synthesis of mandelate ester **2.89a**, **2.89b**



The synthesis of the butenolide fragment **2.40** commenced from racemic propylene oxide **2.90** which was resolved by hydrolytic kinetic resolution using Jacobsen's catalyst to afford epoxide **2.91**. Reaction of **2.91**, 2-(phenylthio)acetic acid and LDA followed by refluxing with PTSA in benzene yielded the lactone **2.40**, Scheme 2.20.[22]

Scheme 2.20 Synthesis of lactone **2.40**



2.5. Conclusion

In conclusion, a new stereoselective route to the THF subunit of Bullatanocin has been developed by employing α-chloro sulfide intermediate for C-C bond formation, [2,3] sigmatropic rearrangement for transformation of C-S to C-O bond stereoselectively and catalytic asymmetric reactions is disclosed. The synthetic route is characterized by high stereoselectivity in the creation of the stereogenic centres.

2.6. References

1. (a) Gu, Z. G.; Fang, X.; Rieser, M. J.; Hui, Y.; Miesbauer, L. R.; Smith, D. L.; Wood, K. V.; McLaughlin, J. L. *Tetrahedron.* **1993**, *49*, 745-754. (b) Gu, Z.; Zeng, L.; Fang, X.; Colman Saizarbitoria, T.; Huo, M.; McLaughlin, J. L. *J. Org. Chem*. **1994**, *59*, 5162-5172. (c) Squamostatin C: Shimada, H.; Nishioka, S.; Singh, S.; Sahai, M.; Fujimoto, Y. *Tetrahedron Lett*. **1994**, *35*, 3961-3964. (d) Fujimoto, Y.; Murasaki, C.; Shimada, H.; Nishioka, S.; Kakinuma, K.; Singh, S.; Singh, M.; Gupta, Y. K.; Sahai, M. *Chem. Pharm. Bull*. **1994**, *42*, 1175-1184.
2. (a) Lei Zhu.; David R. Mootoo. *Org. Lett.* **2003**, *5*, 3475. (b) Lei Zhu.; David R. Mootoo. *J. Org. Chem*. **2004**, *69*, 3154.
3. (a) Zhang, H.; Mootoo, D. R. *J. Org. Chem*. **1995**, *60*, 8134. (b) Zhang, H.; Seepersaud, M.; Seepersaud, S.; Mootoo, D. R. *J. Org. Chem*. **1998**, *63*, 2049. (c) Ruan, Z.; Mootoo, D. R. *Tetrahedron Lett*. **1999**, *40*, 49. (d) Dabideen, D.; Ruan, Z.; Mootoo, D. R. *Tetrahedron.* **2002**, *58*, 2077.
4. (a) Eugene, A. Mash.; Keith, A. Nelson; Shawne Van Deusen.; Susan, B. Hemperly. *Org. Syn.* **1990**, *68*, 92. (b) Rodney A. Fernandes. *Eur. J. Org. Chem.* **2007**, 5064.
5. Sadagopan Raghavan.; Vinoth, V. Kumar.; Raju, L. Chowhan. *Synlett.* **2010**. *12*, 1807.
6. Ren, H.; Krasovskiy, A.; Knochel, P. *Org. Lett.* **2004**, *6*, 4215.
7. (a) Brown, H. C.; Ganesan, K.; Dhar, R. K. *J. Org. Chem.* **1993**, *58*, 147. (b) Atsushi Abiko. *Organic Syntheses,* **2002**, *79*, 103.
8. (a) Rayner, D. R.; Miller, E. G.; Bickart, P.; Gordon, A. J.; Mislow, K. *J. Am. Chem. Soc*. **1966**, *88*, 3138; (b) Braverman, S.; Stabinsky, Y. *J. Chem. Soc., Chem.*

Commun. **1967**, 270. (c) Bickart, P.; Carson, F. W.; Jacobus, J.; Miller, E. G.; Mislow, K. *J. Am. Chem. Soc*. **1968**, *90*, 4869. (d) Evans, D. A.; Andrews, G. C.; Sims, C. L. *J. Am. Chem. Soc*. **1971**, *93*, 4956. (e) David A. Evans.; Glenn C. Andrews *Accounts of Chemical Research*. **1974**, *7*, 174. (f) Tsuyoshi Satoh.; Toshifumi Miyagawa. *Tetrahedron Letters* **2006**, *47*, 1981.

9. Harry R. Billica.; Homer Adkins. *Organic Syntheses*. **1949**, *29*, 24.
10. (a) Hanessian, S.; Delorme, D.; Tyler, P. C.; Demailly, G.; Chapleur, Y. *Can. J. Chem*. **1983**, *61*, 634. (b) Sadagopan Raghavan.; Ganapathy, S. Subramanian.; Tony, K. A. *Tetrahedron Letters.* **2008**, *49*, 1601.
11. (a) Alcaraz, L.; Hamett, J. J.; Mioskowski, C.; Martel, J. P.; Le Gall, T.; Dong Soo Shin.; Falk, J. R. *Tetrahedmn Letters.* **1994**, *35*, 5449. (b) Ryan J. Davoille.; David T. Rutherford.; Steven D. R. Christie. *Tetrahedron Letters.* **2000**, *41*, 1255. (c) Lynda J. Brown.; Ian B. Spurr.; Stephen C. Kemp.; Nicholas P. Camp.; Karl R. Gibson.; Richard C. D. Brown. *Org. Lett*. **2008**, *10*, 2489. (d) Sadagopan Raghavan.; Ganapathy, S. Subramanian. *Tetrahedron*. **2011**, *67*, 7529.
12. (a) Akio Fujii.; Shohei Hashiguchi.; Nobuyuki Uematsu.; Takao Ikariya.; Ryoji Noyori. *J. Am. Chem. Soc.* **1996,** *118*, 2521. (b) Karl Josef Haack.; Shohei Hashiguchi.; Akio Fujii.; Takao Ikariya.; Ryoji Noyori. *Angew. Chem Int. Ed.* **1997**, *36*, 285. (c) Kazuhiko Matsumura.; Shohei Hashiguchi.; Takao Ikariya.; Ryoji Noyori. *J. Am. Chem. Soc.* **1997**, *119*, 8738. (d) Masashi Yamakawa.; Issaku Yamada.; Ryoji Noyori. *Angew. Chem. Int. Ed.* **2001**, *40*, 2818. (e) Ryoji Noyori.; Masashi Yamakawa.; Shohei Hashiguchi. *J. Org. Chem.* **2001**, *66*, 7931.

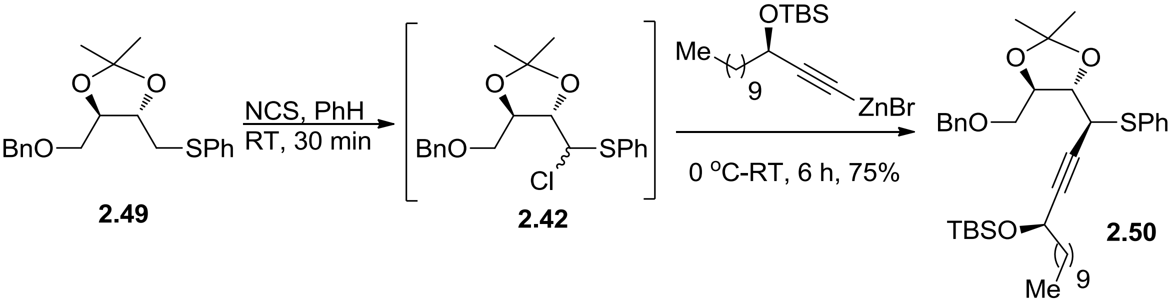
13. (a) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M. *J. Org. Chem.* **1986**, *51*, 2370. (b) Trost, B. M.; Bunt, R. C.; Pulley, S. R. *J. Org. Chem.* **1994**, *59*, 4202.
14. Pikul, S.; Corey, E. J. *Organic Syntheses,* **1993**, *71*, 22.
15. (a) Andrew, G. Myers.; Bin Zheng.; Mohammad Movassaghi. *J. Org. Chem.* **1997**, *62,* 7507. (b) Barrie, J. Marsh.; David R. Carbery. *J. Org. Chem.* **2009**, *74*, 3186.
16. Lynn James Guziec.; Frank S. Guziec, Jr. *J. Org. Chem.* **1994***, 59*, 4691.
17. Raghavan, S.; Pradip, K. S. *Synlett*. **2013**. *24*, 1983.
18. (a) Corey, E. J.; Bakashi, R. K.; Shibata, S. *J. Am. Chem. Soc*. **1987**, *109*, 7925. (b) Corey, E. J.; Saizo Shibata.; Bakshi, R, K. *J. Org. Chem.* **1988**, *53*, 2861. (c) Corey, E. J.; John, O. Link. *J. Am. Chem. Soc*. **1992**, *114*, 1906.
19. Gowravaram Sabitha.; Sambit Nayak.; M. Bhikshapathi.; Yadav, J.S. *Org. Lett.* **2011**, *13*, 382.
20. (a) Brown, C. A.; Yamashita, A. *J. Am. Chem. Soc.* **1975**, *97*, 891–892. (b) Abrams, S. R.; Nucciarone, D. D.; Steck, W. F. *Can. J. Chem.* **1983**, *61*, 1073–1076. (c) Suzanne R. Abrams.; Angela C. Shaw. *Organic Syntheses*, **1988**, *66,*127.
21. (a) Yujiro Hayashi.; Junichiro Yamaguchi.; Kazuhiro Hibino.; Mitsuru Shoji. *Tetrahedron Letters.* **2003**, *44*, 8293. (b) Zhong, G. Angew. *Chem., Int. Ed*. **2003**, *42*, 4247 (c) Sean P. Brown.; Michael P. Brochu.; Christopher J. Sinz.; David W. C. MacMillan. *J. Am. Chem. Soc.* **2003**, *125*, 10808. (d) Dhevalapally B. Ramachary.; Carlos F. Barbas. *Org. Lett*. **2005**, *7*, 1577. (e) Ismail Ibrahem.; Gui-Ling Zhao.; Henrik Sunden.; Armando Cordova. *Tetrahedron Letters*. **2006**, *47,* 4659. (f) Shyla George.; Arumugam Sudalai. *Tetrahedron Asymmetry*. **2007**, *18,* 975.

22. White, J. D.; Somers, T. C.; Reddy, G. N. *J. Org. Chem*. **1992**, *57*, 4991.

Experimental Section

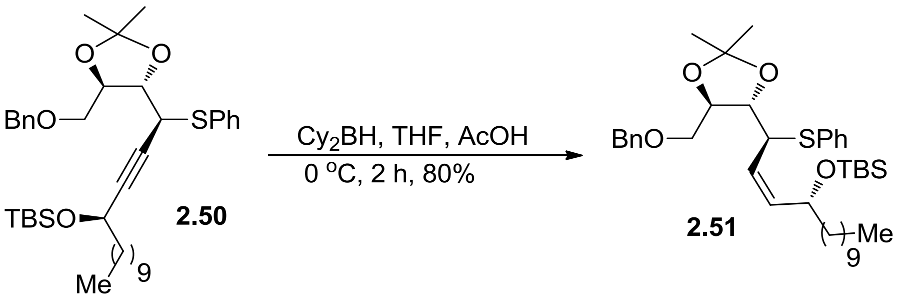
Preparation of propargylic sulfide 2.50

To a solution of sulfide **2.49** (1.72 g, 5 mmol) in anhydrous benzene (50 mL) was added *N*-chlorosuccinimide (NCS, 750 mg, 5.5 mmol) at rt and stirred for 30 min at the same temperature. Stirring was discontinued and the clear supernatant solution of chloro sulfide **2.42** was siphoned using a syringe and used in the next step. The yield of the chloro sulfide was assumed to be quantitative.



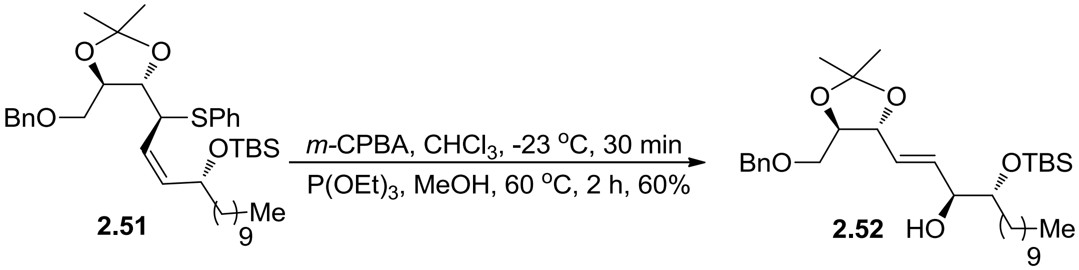
Separately the alkynylzinc bromide was prepared from alkyne **2.41**. To a solution of alkyne **2.41** (3.1 g, 10 mmol) in dry THF (8 mL) cooled at 0 °C was added *i*-PrMgCl.LiCl (5 mL, 10 mmol, 2 M in THF) and the mixture stirred for 30 min at the same temperature. A solution of $ZnBr_2$ (10 mL, 10 mmol, 1 M in THF) was added and the mixture stirred for 30 min. To the organozinc reagent so generated and maintained at 0 °C was added a solution of chloro sulfide **2.42** (5 mmol) in benzene (50 mL) and the reaction mixture stirred for a period of 6 h gradually allowing it to attain rt. The reaction mixture was cooled to 0 °C, quenched by the addition of aq saturated NH_4Cl solution (5 mL) and allowed to warm to rt. The aqueous layer was separated and extracted with ether (3×15 mL). The combined organic layers were washed with water (5 mL), brine (5 mL), dried over Na_2SO_4 and the solvent evaporated under reduced pressure to afford a crude compound which was purified by column chromatography using 2% EtOAc/Hexanes (v/v) as the eluent to afford the pure product **2.50** as a viscous oil (2.41 g, 3.7 mmol) in 75% yield; TLC, R_f 0.51 (5% EtOAc/Hexanes); $[\alpha]^{25}_{D}$ (+) 60.1 (*c* 1, MeOH); IR (KBr) 2927, 2855, 1637, 1462, 1372, 1251, 1215, 1087 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.2 Hz, 2H), 7.31-7.20 (m, 8H), 4.57 (s, 2H), 4.32-4.22 (m, 2H), 4.10-4.01 (m, 2H), 3.75 (dd, *J* = 11.0, 3.9 Hz, 1H), 3.63 (dd, *J* = 10.2, 4.7 Hz, 1H), 1.60-1.47 (m, 2H), 1.42 (s, 3H), 1.37 (s, 3H), 1.30-1.22 (m, 16H), 0.90-0.84 (bs, 12H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 133.2, 132.8, 132.3, 128.8, 128.2, 127.7, 127.4, 110.0, 88.4, 79.6, 78.8, 77.9, 73.4, 71.1, 62.9, 42.4, 38.6, 32.0, 29.7, 29.6 29.4, 29.3, 27.3, 25.9, 25.2, 22.7, 18.3, 14.2, -4.3, -5.0; MS $[M+Na]^+$ 675; HRMS (ESI) *m/z* calcd for $C_{39}H_{60}O_4SSiNa$ 675.3879. Found: 675.3887.

Preparation of allylic sulfide 2.51



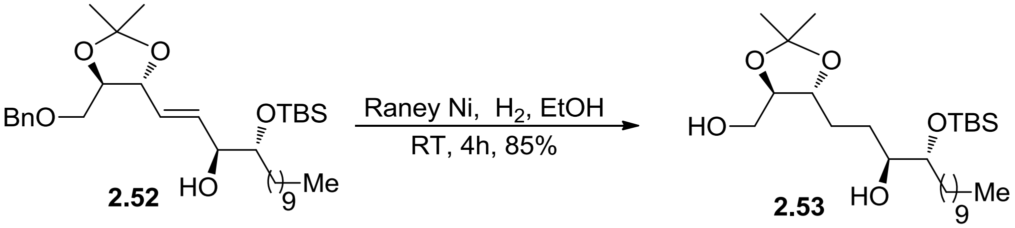
To the solution of cyclohexene (0.1 mL, 1 mmol) in dry THF (2 mL) cooled at 0 °C added $BH_3.SMe_2$ (0.05 mL, mL, 0.5 mmol, 10 M in DMS) and the mixture stirred for 1 h at the same temperature. To the so generated dicyclohexylborane, was added the solution of sulfide **2.50** (327 mg, 0.5 mmol) in 2 mL THF and the mixture stirred for 1 h at 0 °C. The reaction mixture was quenched by adding acetic acid (0.1 mL) and gradually allowed it to attain rt over a period of 30 min. The reaction mixture was diluted with ether (5 mL) and water (5 mL). The aqeous layer was separated and extracted with ether (3×5 mL). The combined organic layers were washed with water (5 mL), brine (5 mL), dried over Na_2SO_4 and the solvent evaporated under reduced pressure to afford the crude compound which was purified by column chromatography using 2% EtOAc/Hexanes (v/v) as the eluent to afford the pure product **2.51** as a viscous oil (261 mg, 0.4 mmol) in 80% yield, TLC, R_f 0.52 (5% EtOAc/Hexanes); $[\alpha]^{25}_D$ (+) 20.3 (*c* 1, MeOH); IR (KBr) 3061, 3026, 2925, 2856, 1723, 1582, 1455, 1379, 1273, 1114, 741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65-7.30 (m, 10H), 5.70-5.45 (m, 2H), 4.80-4.66 (m, 3H), 4.28-4.10 (m, 3H), 3.87 (dd, *J* = 10.2, 4.3 Hz, 1H), 3.75 (dd, *J* = 9.4, 5.8 Hz, 1H), 1.65-1.38 (m, 24H), 1.05 (t, *J* = 6.5 Hz, 3H), 0.98 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.2, 134.2, 134.1, 129.0, 128.5, 127.9, 127.8, 126.6, 126.5, 125.7, 109.8, 80.7, 77.3, 73.6, 71.1, 69.0, 49.7, 38.2, 32.1, 29.8, 29.6, 29.5, 27.7, 27.3, 27.2, 26.0, 25.9, 25.3, 22.8, 18.2, 14.3, -4.0, -4.4; MS $[M+Na]^+$ 677; HRMS (ESI) *m/z* calcd for $C_{39}H_{62}O_4SSiNa$ 677.4035. Found: 677.4015.

Preparation of allylic alcohol 2.52



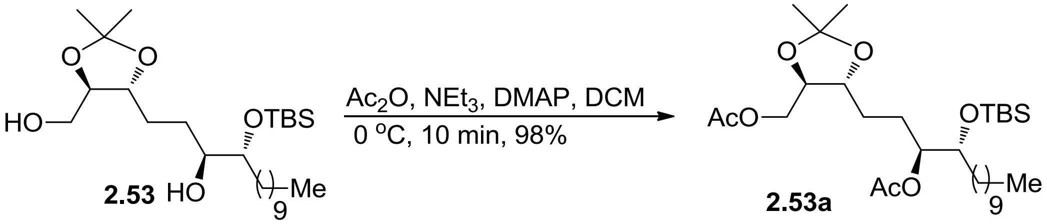
To the solution of allyl sulfide **2.51** (654 mg, 1 mmol) in $CHCl_3$ (4 mL) cooled at -23 °C was added *m*-CPBA (223 mg, 1 mmol, 77% assay) and the mixture stirred at the same temperature for 30 min. Methanol (4 mL) and $P(OEt)_3$ (0.83 mL, 5 mmol) were added and the mixture heated at reflux for 2 h. The solvent was evaporated under reduced pressure. The residue was diluted with $CHCl_3$ (10 mL), washed with Na_2CO_3 (5 mL), water (5 mL), brine (5 mL), dried over Na_2SO_4 and the solvent evaporated under reduced pressure to afford the crude compound which was purified by column chromatography using 5% EtOAc/Hexanes (v/v) as the eluent to afford the pure product **2.52** as a viscous oil (337 mg, 0.6 mmol) in 60% yield, TLC, R_f 0.31 (10% EtOAc/Hexanes); $[\alpha]^{25}_{D}$ (+) 7.1 (*c* 1, MeOH); IR (KBr) 3448, 2926, 2855, 1636, 1460, 1378, 1250, 1215, 1089, 1026, 843 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.32-7.24 (m, 5H), 5.74-5.66 (m, 2H), 4.57 (d, *J* = 14.8 Hz, 1H), 4.56 (d, *J* = 12.4 Hz, 1H), 4.25 (dt, *J* = 6.0, 3.0 Hz, 1H), 4.08 (dd, *J* = 6.0, 3.0 Hz, 1H), 3.90-3.78 (m, 1H), 3.68-3.60 (m, 1H), 3.57-3.55 (m, 2H), 1.41 (s, 6H), 1.28-1.22 (m, 19H), 0.90 (s, 12H), 0.08 (s, 3H) 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 133.0, 129.2, 128.5, 127.8, 127.8, 109.6, 80.4, 78.6, 75.4, 74.7, 73.7, 69.5, 32.0, 31.6, 30.0, 29.9, 29.8, 29.7, 29.6, 29.5, 27.1, 26.0, 25.8, 22.8, 18.2, 14.3, -4.1, -4.3; MS $[M+NH_4]^+$ 580; HRMS (ESI) *m/z* calcd for $C_{33}H_{58}O_5SiNa$ 585.3951. Found: 585.3977.

Preparation of diol 2.53



To the solution of allylic alcohol **2.52** (1.1 g, 2 mmol) in EtOH (8 mL) was added freshly prepared Raney-Ni (5 g in EtOH) at ambient temparature and the mixture stirred for 4 h under an atmosphere of hydrogen. The reaction mixture was filtered through a pad of Celite and the residue washed with EtOH (3x20 mL). The combined organic layers were evaporated under reduced pressure to furnish the crude compound which was purified by column chromatography using 20% EtOAc/Hexane (v/v) as the eluent to afford the pure product **2.53** as a viscous oil (805 mg, 1.7 mmol) in 85% yield, TLC, R_f 0.20 (20% EtOAc/Hexanes); $[\alpha]^{25}_D$ (+) 6.5 (*c* 1, MeOH); IR (KBr) 3443, 2926, 2855, 1637, 1462, 1375, 1251, 1217, 1163, 1071, 835, 771 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.89 (dt, *J* = 8.7, 3.6 Hz, 1H), 3.79 (dd, *J* = 11.7, 2.9 Hz, 1H), 3.74-3.68 (m, 1H), 3.63-3.54 (m, 3H), 1.42 (s, 3H), 1.40 (s, 3H), 1.35-1.20 (m, 22H), 0.94-0.87 (bs, 12H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 113.4, 86.3, 82.1, 80.1, 79.3, 66.6, 36.6, 35.6, 34.7, 34.6, 34.6, 34.3, 34.1, 33.9, 32.1, 31.8, 30.6, 30.4, 27.4, 22.8, 18.8, 14.6, 0.6, 0.3; MS $[M+1]^+$ 471; HRMS (ESI) *m/z* calcd for $C_{26}H_{54}O_5SiNa$ 497.3638. Found: 497.3644.

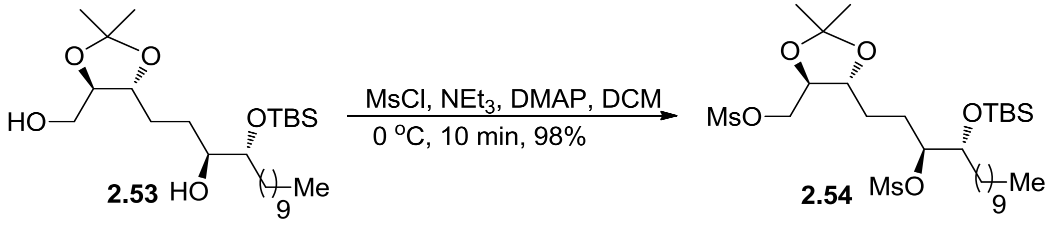
Preparation of acetate 2.53a



To the solution of diol **2.53** (47 mg, 0.1 mmol) in dry DCM (1 mL) cooled at 0 °C was added NEt_3 (43 µL, 0.3 mmol), DMAP (2 mg), Ac_2O (20 µL, 0.2 mmol) and the mixture stirred for 10 min at the same temperature. The reaction mixture was diluted with DCM (5 mL) and the organic phase was washed with water (2 mL), aq Na_2CO_3 (2 mL) brine (3 mL), dried over Na_2SO_4 and the solvent evaporated under reduced pressure to afford the crude compound which was purified by column chromatography using 15% EtOAc/Hexanes (v/v) as the eluent to afford the pure product **2.53a** as a viscous oil (59 mg, 0.98 mmol) in 98% yield, TLC, R_f 0.32 (20% EtOAc/Hexane); ^1H NMR (200 MHz, $CDCl_3$) δ 4.81 (dt, *J* = 5.8, 2.1 Hz, 1H), 4.22 (dd, *J* = 11.7, 3.6 Hz, 1H), 4.04 (dd, *J* = 11.7, 5.8 Hz, 1H), 3.82-3.76

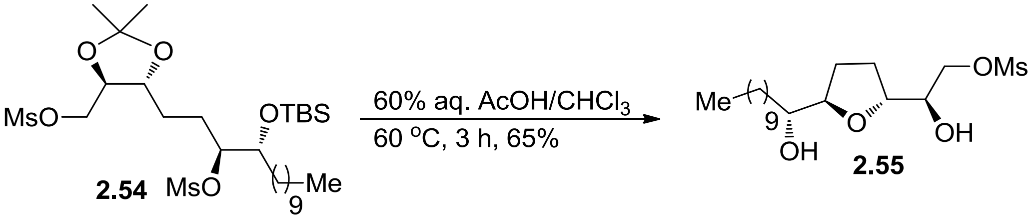
(m, 1H), 3.74-3.68 (m, 2H), 2.10 (s, 3H), 2.05 (s, 3H), 1.75-1.50 (m, 2H), 1.39 (s, 3H), 1.37 (s, 3H), 1.27-1.24 (m, 20H), 0.90-0.88 (bs, 12H), 0.05 (s, 3H), 0.02 (s, 3H).

Preparation of dimesylate 2.54



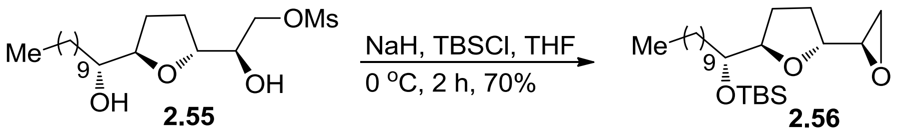
To the solution of diol **2.53** (474 mg, 1 mmol) in dry DCM (4 mL) cooled at 0 ^{o}C was added NEt$_3$ (432 µL, 3 mmol), DMAP (12 mg), MsCl (228 µL, 2 mmol) and the mixture stirred for 10 min at the same temperature. The reaction mixture was diluted with DCM (5 mL) and washed successively with water (5 mL), brine (5 mL) and dried over Na$_2$SO$_4$. The solvent was evaporated under reduced pressure to afford the crude compound which was purified by column chromatography using 15% EtOAc/Hexanes (v/v) as the eluent to afford the pure product **2.54** as a viscous oil (617 mg, 0.98 mmol) in 98% yield, TLC, R$_f$ 0.32 (20% EtOAc/hexanes); $[\alpha]^{25}_{D}$ 10.8 (*c* 1, MeOH); IR (KBr) 2924, 2853, 1638, 1461, 1356, 1252, 1174, 911, 834, 721 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.68-4.64 (m, 1H), 4.27 (d, *J* = 11.3 Hz, 1H), 4.26 (d, *J* = 9.1 Hz, 1H), 3.88-3.81 (m, 3H), 3.10 (s, 3H), 3.04 (s, 3H), 1.86-1.75 (m, 4H), 1.40 (s, 3H), 1.37 (s, 3H), 1.30-1.22 (m, 18H), 0.91 (s, 9H), 0.89 (t, *J* = 6.5 Hz, 3H), 0.11 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 109.6, 86.5, 78.1, 77.6, 74.4, 68.2, 45.8, 38.6, 37.5, 31.4, 29.6, 29.4, 29.2, 29.0, 27.2, 27.1, 26.6, 25.8, 25.7, 22.5, 18.0, 14.0, -4.8, -4.4; MS [M+NH$_4$]$^+$ 648; HRMS (ESI) *m/z* calcd for C$_{28}$H$_{58}$O$_9$S$_2$SiNa 653.3189. Found: 653.3171.

Preparation of tetrahydrofuran derivative 2.55



The solution of dimesylate **2.54** (630 mg, 1 mmol) in 60% aq AcOH:$CHCl_3$ (1:1, 4 mL) was heated at reflux for 4 h. The reaction mixture was cooled to 0 ^{o}C and aq saturated $NaHCO_3$ (4 mL) was added. The aqueous layer was separated and extracted with DCM (3X10 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4 and the solvent evaporated under reduced pressure to afford the crude compound which was purified by column chromatography using 15% EtOAc/Hexanes (v/v) as the eluent to furnish the pure product **2.55** as a viscous oil (247 mg, 0.65 mmol) in 65% yield, TLC, R_f 0.41 (40% EtOAc/Hexanes); $[\alpha]^{25}_{D}$ 0.5 (*c* 1, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.32-4.20 (m, 2H), 4.08-4.0 (m, 1H), 3.88 (m, 2H), 3.80-3.72 (m, 1H), 3.04 (s, 3H), 2.08-1.96 (bs, 4H), 1.38-1.18 (bs, 20H), 0.88 (t, *J* = 6.7, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 83.4, 78.3, 74.1, 71.3, 70.9, 37.6, 33.3, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 28.5, 28.4, 25.5, 22.6, 14.1; MS $[M+Na]^+$ 403; HRMS (ESI) *m/z* calcd for $C_{18}H_{36}O_6SNa$ 403.2130. Found: 403.2137.

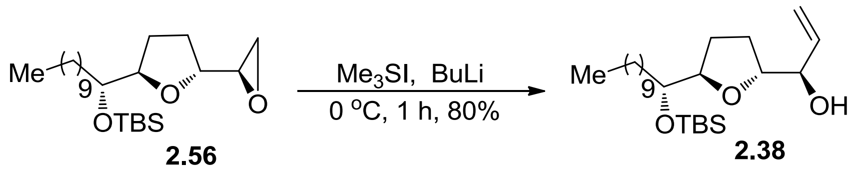
Preparation of epoxide 2.56



To the solution of mesylate **2.55** (380 mg, 1 mmol) in dry THF (4 mL) cooled at 0 ^{o}C was added NaH (70 mg, 2 mmol, 60% assay) and the mixture stirred for 30 min when

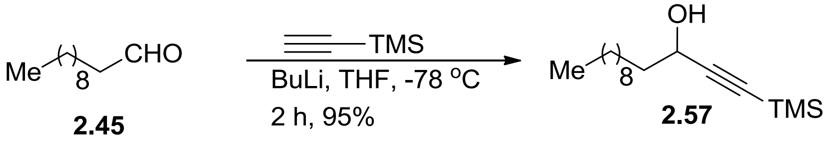
TBSCl (150 mg, 1 mmol) was added and the mixture gradually allowed to warm to rt and the mixture stirred for 1 h. The reaction mixture was cooled to 0 °C and quenched by adding ice pieces. The aq layer was separated and extracted with ether (3x5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4 and the solvent evaporated under reduced pressure to afford the crude compound which was purified by column chromatography using 5% EtOAc/hexanes (v/v) as the eluent to afford the pure product **2.56** as a viscous oil (278 mg, 0.7 mmol) in 70% yield, TLC, R_f 0.5 (10% EtOAc/hexanes); $[\alpha]^{25}_{D}$ (+) 12.5 (*c* 1, MeOH); IR (KBr) 2925, 2854, 1731, 1633, 1556, 1463, 1252, 1076, 835, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.92-3.76 (m, 2H), 3.34 (dt, *J* = 6.7, 5.8 Hz, 1H), 2.94 (dt, *J* = 4.1, 2.6 Hz, 1H), 2.72 (dd, *J* = 5.2, 4.1 Hz, 1H), 2.67 (dd, *J* = 5.2, 2.6 Hz, 1H), 2.15-1.85 (m, 4H), 1.40-1.22 (m, 18H), 0.89 (t, *J* = 6.9 Hz, 3H); MS $[M+NH_4]^+$ 416; HRMS (ESI) *m/z* calcd for $C_{23}H_{46}O_3SiNa$ 421.3113. Found: 421.3110.

Preparation of allylic alcohol 2.38



To the solution of Me_3SI (215 mg, 1 mmol) in dry THF (4 mL) cooled at 0 °C was added *n*-BuLi (0.6 mL, 1.5 M in Hexanes) and the mixture stirred at same temparature for 30 min (heterogenous solution becomes homogenous). The solution of epoxide **2.56** (206 mg, 0.5 mmol) in dry THF (2 mL) was added to the above generated ylide and the mixture stirred for 30 min. The mixture was quenched by adding aq saturated NH_4Cl (2 mL). The layer were separated and the aq layer extracted with ether (3x5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4 and the solvent evaporated under reduced pressure to afford the crude compound which was purified by column chromatography using 10% EtOAc/Hexanes (v/v) as the eluent to afford the pure product **2.38** as a viscous oil (164 mg, 0.4 mmol) in 80% yield, TLC, R*f* 0.21 (10% EtOAc/Hexanes); $[\alpha]^{25}_{D}$ (+) 9.1 (*c* 1, MeOH); IR (KBr) 2854, 1732, 1637, 1463, 1376, 1251, 1073, 925, 834, 774 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81-5.71 (m, 1H), 5.33 (d, *J* = 17.5 Hz, 1H), 5.31 (d, *J* = 10.9 Hz, 1H), 3.87 (dd, *J* = 10.9, 5.8 Hz, 1H) 3.81 (dd, *J* = 10.9, 5.8 Hz, 1H), 3.77-3.70 (m, 1H), 3.56-3.50 (m, 1H), 1.96-1.90 (m, 2H), 1.72-1.60 (m, 2H), 1.30-1.24 (bs, 18H), 0.89 (s, 12H), 0.07 (s, 3H), 0.05 (s, 3H); MS $[M+Na]^+$ 435; HRMS (ESI) *m/z* calcd for $C_{24}H_{48}O_3SiNa$ 435.3270. Found: 435.3262.

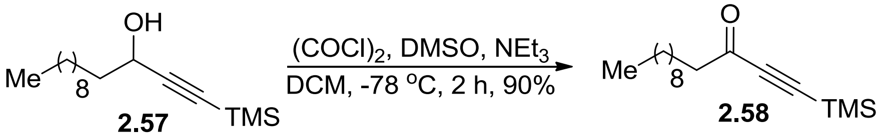
Preparation of racemic alcohol 2.57



To the solution of TMS acetylene (1.34 mL, 11 mmol) in THF (40 mL) cooled at -78 °C was added *n*-BuLi (7.3 mL, 11 mmol, 1.5 M in hexane) and the mixture stirred for 1 h. The solution of aldehyde **2.45** (2.12 mL, 10 mmol) in THF (5 mL) was added dropwise and the mixture gradually allowed to warm to rt and stirred for 1 h. The reaction mixture was cooled to 0 °C and was quenched by adding saturated aq NH_4Cl (5 mL). The layers were separated and extracted with ether (3x15 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and the solvent evaporated under reduced pressure to afford the crude compound which was purified by column chromatography using 5% EtOAc/Hexanes (v/v) as the eluent to afford the pure product **2.57** as a viscous oil (2.41 g, 9 mmol) in 90% yield, TLC, R*f* 0.2 (10% EtOAc/Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ

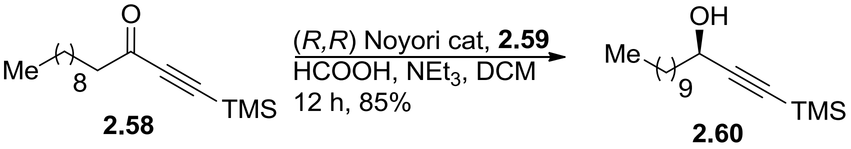
4.27 (t, *J* = 6.0 Hz, 1H), 1.85 (s, 1H), 1.70-1.60 (m, 2H), 1.50-1.20 (m, 16H), 0.87 (t, *J* = 6.7 Hz, 3H), 0.16 (s, 9H).

Preparation of propargylic ketone 2.58



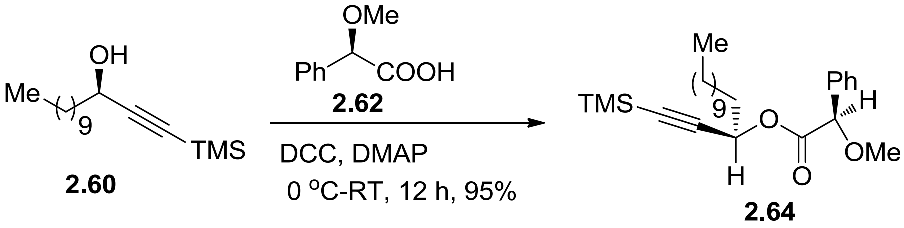
To the solution of anhydrous oxalyl chloride (0.65 mL, 7.5 mmol) in dry DCM (20 mL) cooled at -78 °C, was added anhydrous DMSO (0.78 mL, 10 mmol) and the mixture stirred for 45 min at the same temperature. A solution of propargylic alcohol **2.57** (1.3 g, 5 mmol) in dry DCM (2 mL) was added at the same temparature and the mixture stirred for 45 min. NEt_3 (3.5 mL, 25 mmol) was added and the reaction mixture allowed to warm gradually to 0 °C. The reaction mixture was diluted with DCM (20 mL) and washed with 2N HCl (15 mL), water (5 mL), brine (5 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude compound which was purified by column chromatography using 2% EtOAc/Hexanes (v/v) as the eluent to afford the pure product **2.58** as a viscous oil (1.1 g, 4.5 mmol) in 90% yield, TLC, R_f 0.51 (10% EtOAc/Hexanes); IR (KBr) 2925, 2855, 1678, 1461, 1252, 1134, 1094 847 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.52 (t, *J* = 6.7 Hz, 2H), 1.70-1.60 (m, 2H), 1.32-1.22 (m, 14H), 0.88 (t, *J* = 6.7 Hz, 3H), 0.16 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 188.2, 102.2, 97.6, 45.4, 32.0, 29.7, 29.6, 29.5, 29.4, 29.1, 24.1, 22.8, 14.2, -0.6; MS $[M+NH_4]^+$ 289.

Preparation of chiral propargylic alcohol 2.60



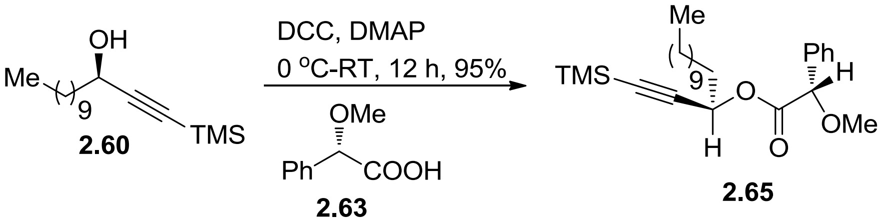
Formic acid (1.5 mL, 40 mmol) was cooled to 0 °C and NEt_3 (2.2 mL, 16 mmol) was added dropwise. A solution of propargylic ketone **2.58** (1.0 g, 4 mmol), (*R,R*) Noyori catalyst (25 mg, 0.04 mmol) in DCM (2 mL) was added and the mixture stirred overnight at rt. The reaction mixture was filtered through a pad of Celite and the residue washed with EtOAc. The combined filtrates were evaporated under reduced pressure to afford the crude compound which was purified by column chromatography using 5% EtOAc/Hexanes (v/v) as the eluent to afford the pure product **2.60** as a viscous oil (0.91 g, 3.4 mmol) in 85% yield, TLC, R_f 0.2 (10% EtOAc/Hexanes); $[\alpha]^{25}_D$ (+) 20.1 (*c* 1, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.27 (t, *J* = 6.0 Hz, 1H), 1.85 (s, 1H), 1.70-1.60 (m, 2H), 1.50-1.20 (m, 16H), 0.87 (t, *J* = 6.7 Hz, 3H), 0.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 107.0, 89.2, 62.9, 37.7, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 25.1, 22.7, 14.1, -0.1.

Preparation of Mandelate ester 2.64



To the solution of propargylic alcohol **2.60** (26 mg, 0.1 mmol) in DCM (1 mL) cooled at 0 °C was added DCC (30 mg, 0.15 mmol), DMAP (1.2 mg), and (*R*)-methoxymandelic acid (20 mg, 0.12 mmol). The reaction mixture was stirred overnight while gradually allowing the the temperature to rise to rt. The solvent was evaporated under reduced pressure to furnish the crude compound which was purified by column chromatography using 5% EtOAc/Hexanes (v/v) as the eluent to afford the product **2.64** (40 mg, 0.08 mmol) in 80% yield as a liquid. TLC, R_f 0.32 (10% EtOAc/Hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.49-7.27 (m, 5H), 5.50 (t, *J* = 6.5 Hz, 1H), 4.88 (s, 1H), 3.55 (s, 3H), 1.36-1.08 (m, 18H), 1.02 (t, *J* = 6.0 Hz, 3H), 0.30 (s, 9H)

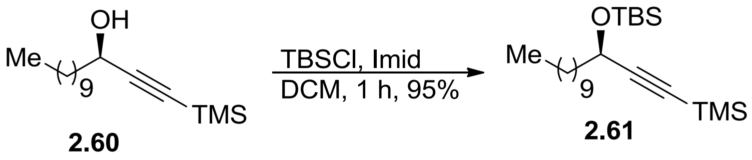
Preparation of Mandelate ester 2.65



Prepared following the procedure detailed above using (*S*)-methoxymandelic acid as the acid partner.

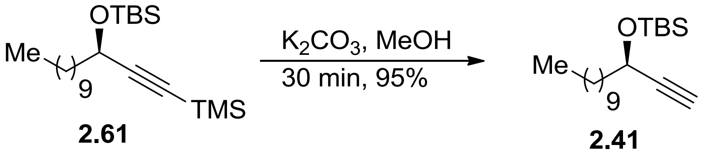
^{1}H NMR ($CDCl_3$, 300 MHz) δ ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.53-7.39 (m, 5H), 5.44 (dd, *J* = 8.6, 6.5 Hz, 1H), 4.84 (s, 1H), 3.52 (s, 3H), 1.49-1.23 (m, 18H), 0.99 (t, *J* = 6.9 Hz, 3H), 0.26 (s, 9H);

Preparation of TBS ether 2.61



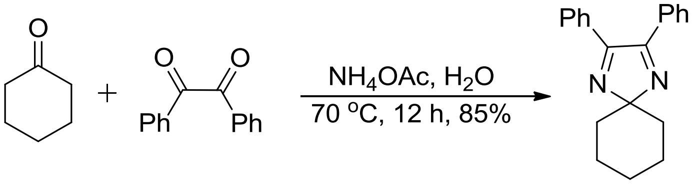
To the solution of alcohol **2.60** (268 mg, 1 mmol) in dry DCM (4 mL) maintained at 0 °C was added imidazole (102 mg, 1.5 mmol) followed by TBS-Cl (165 mg, 1.1 mmol) and the mixture stirred for a period of 1 h. The reaction mixture was diluted with DCM (5 mL), washed successively with water (2 mL), brine (4 mL), dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to yield the crude product which was purified by column chromatography using Hexanes to furnish the product **2.61** (362 mg, 0.95 mmol) in 95% yield as a liquid; TLC, R_f 0.84 (Hexanes); $[\alpha]^{25}_D$ (+) 23.5 (*c* 1, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.28 (t, *J* = 6.0 Hz, 1H), 1.68-1.58 (m, 2H), 1.40-1.22 (m, 16H), 0.94-0.86 (bs, 12H), 0.16 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.2, 88.4, 63.6, 38.7, 29.8, 29.7, 29.5, 29.4, 28.5, 26.0, 25.9, 25.4, 22.5, 18.5, 14.3, 0.0, -4.3, -4.8.

Preparation of alkyne 2.41



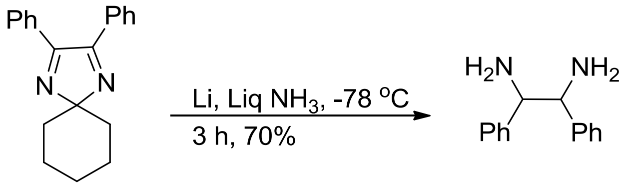
To the solution of silyl ether **2.61** (382 mg, 1 mmol) in MeOH (4 mL) cooled at 0 ^oC was added K_2CO_3 (138 mg, 1 mmol) and the mixture stirred for 1 h gradually allowing it to warm to rt. Methanol was evaporated under reduced pressure and the residue was diluted with ether (10 mL). The organic layer was washed with water (5 mL), brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude compound which was purified by column chromatography using Hexanes as the eluent to afford the pure product **2.41** as a viscous colourless oil (293 mg, 0.95 mmol) in 95% yield, TLC, R_f 0.83 (Hexanes); $[\alpha]^{25}_D$ (+) 31.7 (*c* 1, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.30 (td, *J* = 6.7, 2.2 Hz, 1H), 2.30 (d, *J* = 2.2 Hz, 1H), 1.70-1.60 (m, 2H), 1.45-1.25 (m, 16H), 0.95-0.85 (bs, 12H), 0.15 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 86.0, 72.0, 63.0, 38.8, 32.2, 29.9, 29.8, 29.6, 29.5, 26.0, 25.4, 22.9, 18.5, 14.4, -4.3, -4.8.

Preparation of 2,2-Spirocyclohexane-4,5-diphenyl-2H-imidazole



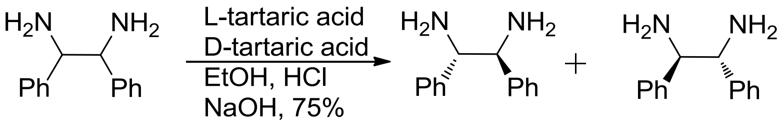
The mixture of benzil (158 g, 0.75 mol), ammonium acetate (400 g, 5 mol) and cyclohexanone (80 mL, 0.77 mol) in glacial acetic acid (1 L, 16 mol) was heated at reflux for 1.5 h. While hot, the reaction mixture was poured into a 3 L of vigorously stirred water. The mixture was left overnight to cool to ambient temperature. The crystals were collected by filtration, washed with distilled water (4x300 mL) and dried under reduced pressure to give imidazole as (205 g) as yellowish-green crystals in 95% yield, M. P. 105–106 °C.

Preparation of (±)-1,2-Diphenyl-1,2-ethylenediamine



To the solution of ammonia (400 mL) in THF (400 mL) cooled at -78 °C was added lithium granules (6.94 g, 1.00 mol) followed by a solution of imidazole (72.0 g, 0.250 mol) in THF (50 mL). The mixture was stirred for 2.5 h and ethanol (30 mL, 1.0 mol) was added slowly. The mixture was stirred for an additional 30 min and solid ammonium chloride (70 g) was added. The cooling bath was removed and the reaction mixture was allowed to warm to 0 °C. Water (400 mL) was added and the phases were separated. The aqueous phase was washed with ether (3x300 mL) and the combined organic extracts are washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure until a final volume of 200 mL. The reaction mixture was cooled to 0 °C and treated with HCl (2N, 300 mL). The biphasic mixture was vigorously stirred at ambient temperature for 1 h, water (500 mL) was added and phases were separated. The organic phase was washed with water (150 mL) and the combined phases were extracted dichloromethane (3x300 mL). The solution was then carefully treated with sodium hydroxide (2N, 300 mL) and the mixture was extracted DCM (4x150 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, concentrated under reduced pressure to afforded diamine as a yellow solid (49 g) in 94% yield, M. P. 81–82 °C

Resolution of racemic diamine

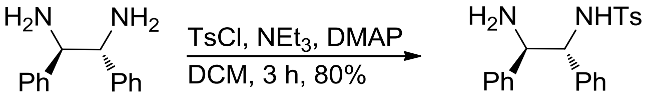


To the solution of racemic diamine (42.5 g, 200 mmol) in ethanol (230 mL), a homogenous solution of L-(+)-tartaric acid (30.0 g, 200 mmol) in ethanol (230 mL) was added. The tartrate salts precipitate immediately. The crystals were collected by filtration, washed twice with ethanol (60 mL) and dried under reduced pressure. The solids were dissolved in boiling water (230 mL) and ethanol (230 mL) was added. The homogenous solution is allowed to cool slowly to rt. The crystals are collected by filtration, washed with ethanol (40 mL) and dried under reduced pressure. The recrystallization procedure was then repeated twice using the same volumes of solvents. The tartrate salt of as colorless crystals was dissolved in water (300 mL) and the mixture was vigorously stirred and cooled at 0-5 °C, 50% aqueous sodium hydroxide (23 mL) was added dropwise followed by DCM (150 mL) and the mixture was stirred for 30 min. The layers were separated extraxted with DCM

(2x50 mL), combined organic extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the crude (*S,S*)-(-)-diamine which was recrystalized using hexane to furnish the white solid in 40% yield (8.5 g), $[\alpha]^{23}_{D}$ (-) 108° (MeOH, *c* 1.1).

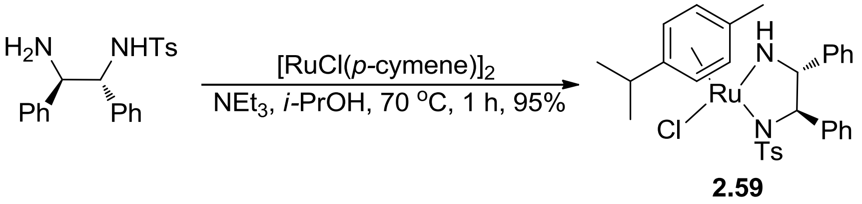
The filtrates from all crystallizations are combined and the solvent was evaporated under reduced pressure. To the residual solid distilled water (250 mL) was added and vigorously stirred, 50% NaOH solution (25 mL) was added dropwise followed by DCM (200 mL) and the mixture was stirred for 30 min. The layer was separated and extracted with DCM (2x50 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, concentrated under reduced pressure to yield crude diamine as a pale yellow crystals. This material is treated with D-(-)-tartaric acid and the resulting salt is recrystallized in exactly the same manner as described earlier to give (*R,R*)-diamine (7.5 g, 35%) of a white crystals, $[\alpha]^{23}_{D}$ (+) 5 ° (H_2O, *c* 1.3).

Preparation of monotosylate of diamine



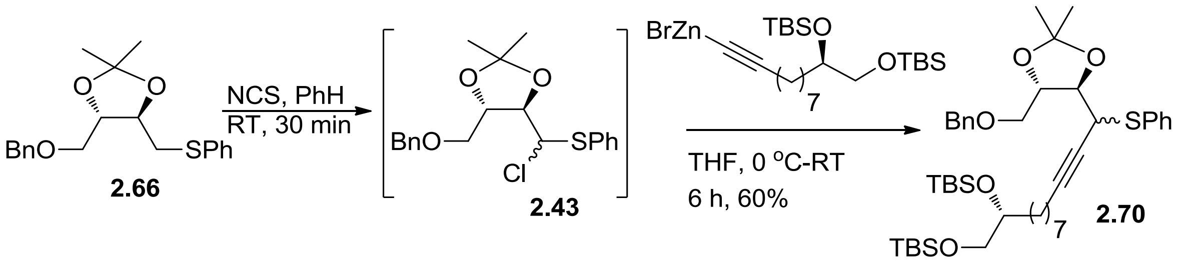
To the solution of diamine (0.87 g, 4.1 mmol) in dry DCM (16 mL) cooled at 0 ^{o}C was added *p*-Toluene sulfonyl chloride (0.78 g, 4.15 mmol), NEt_3 (1.1 mL, 8.2 mmol), DMAP (25 mg). The reaction mixture stirred for 3 h gradually allowing to warm rt. The reaction mixture washed with water (5 mL), brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford a crude compound which was purified by column chromatography using hexanes as the eluent to afford the pure product as a white solid (1.2 g, 0.34 mmol) in 85% yield, TLC,R_f 0.51 (5% MeOH/EtOAc).

Preparation of Noyori catalyst 2.59



To the solution of amine (764 mg, 2 mmol) in *i*-PrOH (15 mL) ruthenium chloro *p*-cymene dimer (612 mg, 1 mmol) and NEt_3 (0.57 mL, 4 mmol) were added and the mixture refluxed for 1 h. The reaction mixture was filtered and washed with cold acetone, dried under reduced pressure to afford the ruthenium diamine complex **2.59** as brick red colour solid (1.8 g, 1.9 mmol) in 95% yield.

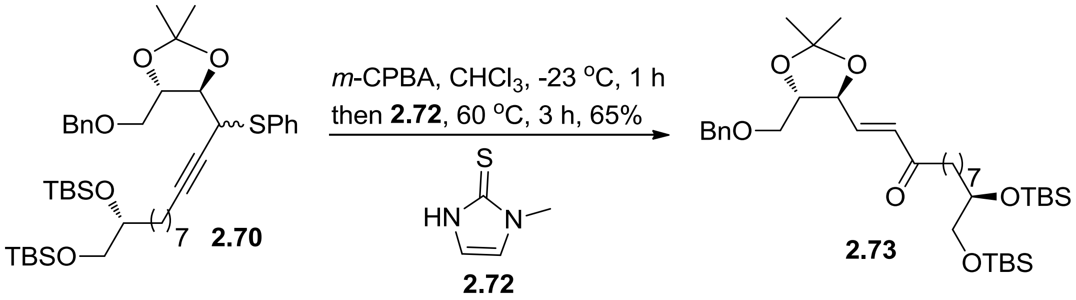
Preparation of propargylic sulfide 2.70



The chloro sulfide **2.43** was prepared as described earlier. To a solution of alkyne **2.44** (410 mg, 1 mmol) in dry THF (0.8 mL) cooled at 0 °C was added *i*-PrMgCl.LiCl (0.5 mL, 1 mmol, 2 M in THF) and the mixture stirred for 30 min at the same temperature. A solution of $ZnBr_2$ (1 mmol, 1 mL, 1 M in THF) was added and the mixture stirred for 30min. To the so generated organozinc reagent maintained at 0 °C was added a solution of chloro sulfide **2.43** (0.5 mmol) in benzene (5 mL) and the reaction mixture stirred for a period of 6 h gradually allowing it to attain rt. The reaction mixture was cooled to 0 °C, quenched by the addition of aq saturated NH_4Cl solution (5 mL) and allowed to warm to rt. The aqueous layer was extracted with ether (3x15 mL). The combined organic layers were washed with water (5 mL), brine (5 mL), dried over Na_2SO_4 and the solvent evaporated under reduced pressure to afford a crude compound which was purified by column chromatography using 2% EtOAc/Hexanes (v/v) as the eluent to afford the pure product **2.70** as a viscous oil (452 mg, 0.6 mmol) in 60% yield, ^{1}H NMR indicated the presence of two isomers in a 8.5:1.5 ratio. TLC, R_f 0.62 (5% EtOAc/Hexanes); Major isomer: IR (KBr) 3060, 2960, 2929, 2856, 1723, 1582, 1454, 4110, 1373, 1260, 1215, 1025 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.9 Hz, 2H), 7.38-7.26 (m, 8H), 4.63 (s, 2H), 4.34 (td, *J* = 5.9, 2.9 Hz, 1H), 4.10-4.02 (m, 2H), 3.70-3.64 (m, 3H), 3.54 (dd, *J* = 9.8, 5.9 Hz, 1H), 3.44 (dd, *J* = 9.8, 6.9 Hz, 1H), 2.13 (dt, *J* = 6.9, 1.9 Hz, 2H), 1.65-1.25 (m, 18H), 0.96 (s, 9H), 0.94 (s, 9H), 0.11 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2, 133.3, 132.6, 130.7, 128.9, 128.4, 127.7, 127.6, 110.2, 87.8, 79.2, 78.1, 73.6, 73.5, 73.2, 71.3, 67.6, 42.8, 34.4, 29.8, 29.2, 29.0, 28.6, 27.4, 27.3, 26.1, 26.0, 25.8, 20.5, 18.8, 18.3, -4.1,

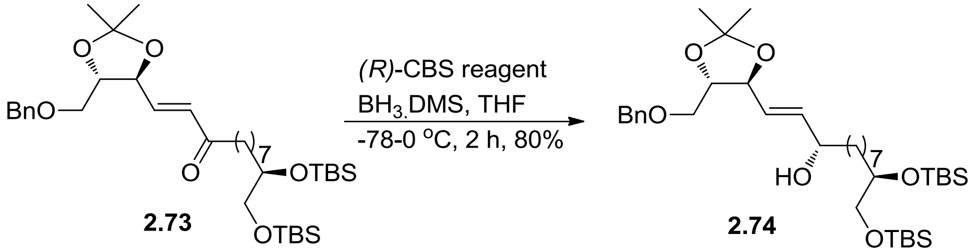
-4.6, -5.1, -5.2. Minor isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.9 Hz, 2H), 7.38-7.26 (m, 8H), 4.61 (s, 2H), 4.30 (td, *J* = 6.9, 1.9 Hz, 1H), 4.10-4.02 (m, 2H), 3.70-3.64 (m, 3H), 3.54 (dd, *J* = 9.8, 5.9 Hz, 1H), 3.44 (dd, *J* = 9.8, 6.9 Hz, 1H), 2.18 (dt, *J* = 6.9, 1.9 Hz, 2H), 1.65-1.25 (m, 18H), 0.96 (s, 9H), 0.94 (s, 9H), 0.11 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 133.2, 132.5, 131.0, 129.0, 128.5, 128.0, 127.8, 110.3, 87.5, 79.5, 78.0, 73.6, 73.5, 73.0, 70.8, 66.3, 42.0, 34.0, 29.8, 29.2, 28.9, 28.6, 27.4, 27.2, 26.1, 26.0, 25.2, 20.6, 19.0, 18.5, -3.5, -4.3, -5.2, -5.3; MS $[M+Na]^+$ 777; HRMS (ESI) *m/z* calcd for $C_{43}H_{70}O_5SSi_2Na$ 777.43747, Found: 777.43786.

Preparation of unsaturated ketone 2.73



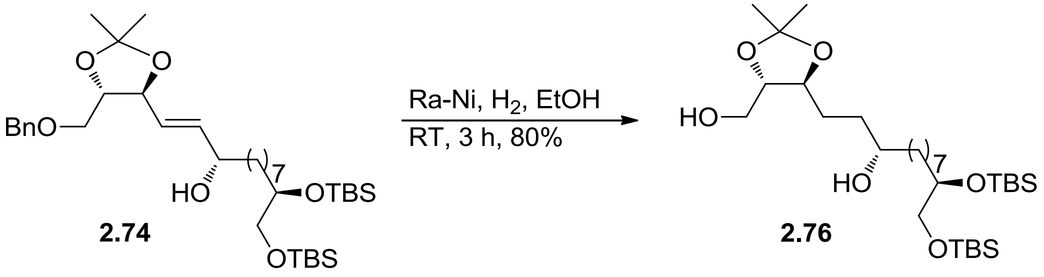
To the solution of propargylic sulfide **2.7** (754 mg, 1 mmol) in $CHCl_3$ (4 mL) cooled at -23 °C was added *m*-CPBA (223 mg, 1 mmol, 77% assay) and the mixture stirred for a period of 1 h. Mercapto imidazole (570 mg, 5 mmol) was added the mixture was heated at reflux for 2 h. The solvent was evaporated under reduced pressure and the crude compound was purified by column chromatography using 5% EtOAc/Hexanes (v/v) as the eluent to afford the pure product **2.73** as a viscous oil (430 mg, 0.65 mmol) in 65% yield, TLC, R_f 0.21 (10% EtOAc/Hexanes); $[\alpha]^{25}_{D}$ (+) 11.3 (*c* 1, $CHCl_3$); IR (KBr) 2956, 2929, 2856, 1697, 1636, 1580, 1466, 1377, 1258, 1026, 834 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42-7.32 (m, 5H), 6.77 (dd, *J* = 16.0, 5.0 Hz, 1H), 6.37 (d, *J* = 16.0 Hz, 1H), 4.66 (d, *J* = 15.3 Hz, 1H), 4.65 (d, *J* = 12.4 Hz, 1H), 4.50 (m, 1H), 3.95 (td, *J* = 8.0, 4.0 Hz, 1H), 3.73-3.63 (m, 3H), 3.55 (dd, *J* = 10.0, 6.0 Hz, 1H), 3.43 (dd, *J* = 10.0, 6.0 Hz, 1H) 2.56 (t, *J* = 7.0 Hz, 2H), 1.70-1.52 (m, 2H), 1.51 (s, 3H), 1.49 (s, 3H), 1.44-1.30 (m, 10H), 0.97 (s, 9H), 0.95 (s, 9H), 0.12 (s, 12H); ^{13}C NMR (300 MHz, $CDCl_3$) 199.8, 141.4, 137.7, 130.1, 128.4, 127.7, 127.6, 110.0, 79.5, 77.7, 73.5, 73.1, 69.2, 67.4, 40.7, 34.2, 29.6, 29.3, 29.1, 26.9, 26.7, 26.0, 25.9, 25.0, 23.9, 18.3, 18.1, -4.2, -4.7, -5.3, -5.4; MS $[M+H]^+$ 663; HRMS (ESI) *m/z* calcd for $C_{37}H_{67}O_6Si_2$ 663.44707. Found: 663.44912.

Preparation of allylic alcohol 2.74



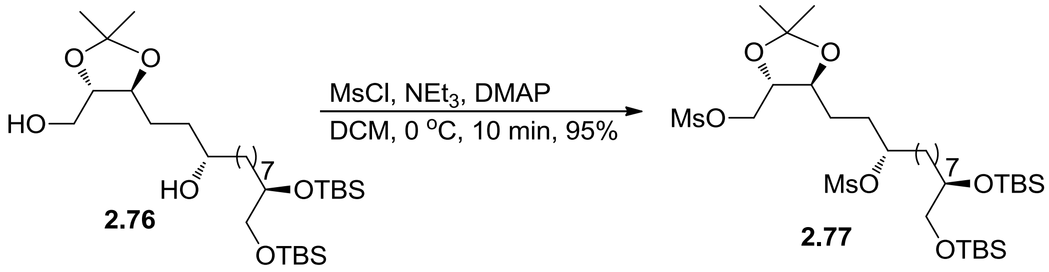
To the solution of $BH_3.SMe_2$ (0.2 mL, 2 mmol, 10 M in DMS) in dry THF (4 mL) cooled at 0 °C was added CBS catalyst (0.2 mL, 0.2 mmol, 1 M in Toluene) and the mixture stirred for 30 min. It was then cooled to -78 °C and the solution of unsaturated ketone **2.73** (662 mg, 1 mmol) in dry THF (1 mL) was added slowly maintaining the same temperature and stirred further for a period of 1.5 h. The reaction mixture was quenched by adding MeOH (4 mL). The solvents were evaporated under reduced pressure, the residue was diluted with ether (10 mL) and washed with water (5 mL), brine (5 mL). The solvent was evaporated under reduced pressure to afford the crude compound which was purified by column chromatography using 5% EtOAc/Hexanes (v/v) as the eluent to afford the pure product **2.74** as a viscous oil (531 mg, 0.8 mmol) in 80% yield, TLC, R_f 0.41 (20% EtOAc/Hexanes); $[\alpha]^{25}_{D}$ (+) 11.2 (*c* 1, $CHCl_3$); (KBr) 2929, 2857, 1630, 1463, 1370, 1252, 1100, 835 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45-7.32 (m, 5H), 5.87 (dd, *J* = 15.0, 6.0 Hz, 1H), 5.75 (dd, *J* = 16.0, 7.0 Hz, 1H), 4.66 (d, *J* = 15.5 Hz, 1H), 4.65 (d, *J* = 12.6 Hz, 1H), 4.32 (dd, *J* = 8.0, 7.0 Hz, 1H), 4.17 (dd, *J* = 10.0, 7.0 Hz, 1H), 4.00-3.95 (m, 1H), 3.75-3.65 (m, 3H), 3.58 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.47 (dd, *J* = 10.0, 6.0 Hz, 1H), 1.65-1.30 (m, 20H), 0.98 (s, 9H), 0.97 (s, 9H), 0.13 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 138.0, 128.4, 127.7, 127.0, 126.3, 109.4, 80.2, 78.7, 73.5, 73.2, 69.3, 69.2, 67.5, 37.1, 34.4, 29.8, 29.7, 29.6, 27.0, 26.0, 25.3, 25.1, 18.4, 18.2, -4.2, -4.7, -5.2, -5.3; MS $[M+Na]^+$ 687; HRMS (ESI) *m/z* calcd for $C_{37}H_{68}O_6Si_2Na$ 687.44466. Found: 687.44492.

Preparation of diol 2.84



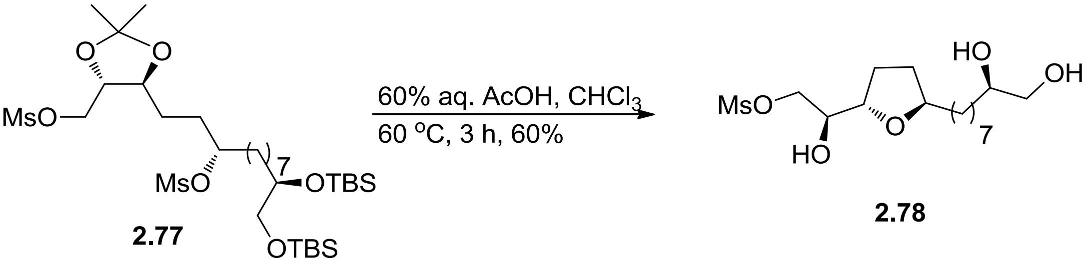
To the solution of allylic alcohol **2.74** (664 mg, 1 mmol) in EtOH (4 mL) was added freshly prepared Raney-Ni (3 g in EtOH) at ambient temparature and the mixture stirred for a period of 3 h under an atmosphere of hydrogen. The reaction mixture was filtered through a pad of Celite and the residue washed with EtOH (3x10 mL), the combined organic layers were evaporated under reduced pressure to afford the crude compound which was purified by column chromatography using 20% EtOAc/Hexanes (v/v) as the eluent to afford the pure product **2.76** as a viscous oil (460 mg, 0.8 mmol) in 80% yield, TLC, R_f 0.26 (30% EtOAc/Hexanes); $[\alpha]^{25}_D$ (+) 16.5 (*c* 1, $CHCl_3$); IR (KBr) 3436, 3061, 2922, 2857, 1750, 1592, 1446, 1260, 1161, 1092, 900, 804 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.96-3.93 (m, 1H), 3.78 (dd, *J* = 11.8, 3.1 Hz, 1H), 3.73-3.69 (m, 1H), 3.65-3.56 (m, 3H), 3.49 (dd, *J* = 9.8, 4.9 Hz, 1H), 3.39 (dd, *J* = 9.8, 5.9 Hz, 1H), 1.80-1.60 (m, 4H), 1.42 (s, 3H), 1.39 (s, 3H), 1.38-1.24 (m, 14H), 0.90 (s, 9H), 0.88 (s, 9H), 0.05 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.9, 81.6, 79.3, 77.4, 73.3, 67.6, 61.9, 37.8, 34.5, 34.1, 31.1, 29.9, 29.8, 29.1, 27.5, 27.2, 26.1, 25.9, 25.2, 18.5, 18.3, -4.1, -4.6, -5.1, -5.2; MS $[M+Na]^+$ 599; HRMS (ESI) *m/z* calcd for $C_{30}H_{64}O_6Si_2Na$ 599.41336. Found: 599.41428.

Preparation of dimesylate 2.77



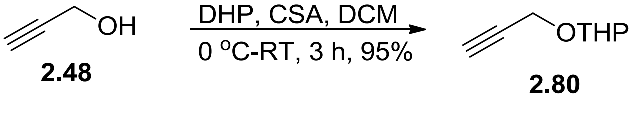
To the solution of diol **2.76** (576 mg, 1 mmol) in dry DCM (4 mL) cooled at 0 °C was added NEt_3 (432 µL, 3 mmol), DMAP (12 mg), MsCl (228 µL, 2 mmol) and stirred for 10 min at the same temperature. The reaction mixture was diluted with DCM (5 mL) and washed successively with water (5 mL), brine (5 mL), dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to afford the crude compound which was purified by column chromatography using 20% EtOAc/Hexanes (v/v) as the eluent to afford the pure product **2.77** as a viscous oil (695 mg, 0.95 mmol) in 95% yield, TLC, R_f 0.31 (30% EtOAc/hexanes); $[\alpha]^{25}_{D}$ (+) 17.8 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.48-4.47 (m, 1H), 4.37-4.25 (m, 2H), 3.95-3.85 (bs, 2H), 3.62 (dd, *J* = 10.0, 4.9 Hz, 1H), 3.50 (m, 1H), 3.40 (dd, *J* = 10.3, 3.9 Hz, 1H), 3.07 (s, 3H), 3.01 (s, 3H), 1.80-1.50 (m, 4H), 1.41 (s, 3H), 1.38 (s, 3H), 1.33-1.25 (m, 14H), 0.89 (s, 9H), 0.87 (s, 9H), 0.05 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 109.8, 83.7, 83.0, 78.3, 73.3, 67.6, 66.4, 38.9, 37.9, 37.7, 37.5, 34.5, 31.7, 29.9, 29.6, 28.6, 27.4, 26.9, 26.1, 25.9, 25.2, 18.5, 18.3, -4.1, -4.6, -5.2, -5.2; MS $[M+Na]^+$ 755; HRMS (ESI) *m/z* calcd for $C_{32}H_{68}O_{10}S_2Si_2Na$ 755.36846. Found: 755.36938.

Preparation of tetrahydrofuran derivative 2.78



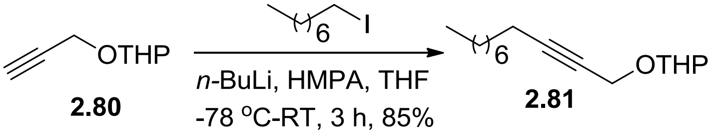
The solution of dimesylate **2.77** (336 mg, 0.5 mmol) in 2 mL of 60% aq AcOH:$CHCl_3$ (1:1) was heated at reflux for 3 h. The reaction mixture was cooled to 0 °C and aq saturated $NaHCO_3$ (2 mL) was added. The aqueous layer was separated and extracted with DCM (3x5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4 and the solvent evaporated under reduced pressure to afford the crude compound which was purified by column chromatography using 15% EtOAc/Hexanes (v/v) as the eluent to furnish the pure product **2.78** as a viscous oil (110 mg, 0.3 mmol) in 60% yield, TLC, R*f* 0.21 (50% EtOAc/Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.31-4.23 (m, 2H), 4.01-3.90 (m, 2H), 3.79-3.62 (m, 3H), 3.54 (dd, *J* = 10.5, 7.5 Hz, 1H), 3.08 (s, 3H), 2.11-1.97 (m, 4H), 1.70-1.20 (m, 14H); MS $[M+Na]^+$ 391; MS $[M+Na]^+$ 391; HRMS (ESI) *m/z* calcd for $C_{16}H_{32}O_7SNa$ 391.17610. Found: 391.17790.

Preparation of THP ether 2.80



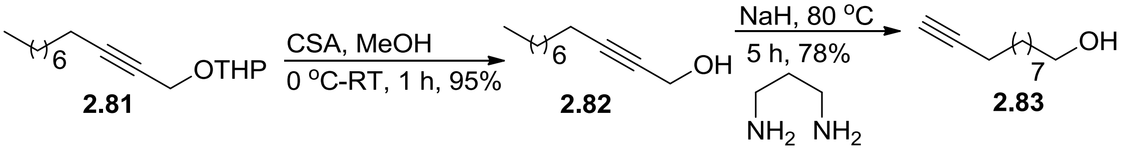
To the solution of propargylic alcohol **2.48** (3.1 g, 50 mmol) in DCM (400 mL) cooled at 0 °C was added DHP (4.6 mL, 50 mmol), CSA (580 mg, 2.5 mmol) and the mixture stirred for 3 h. The reaction mixure was washed with aq Na_2CO_3 (10 mL), brine (5 mL), dried over Na_2SO_4 and solvent was evaporated under reduced pressure to afford crude compound which was purified by column chromatography using 2% EtOAc/Hexanes (v/v) as the eluent to yield ether **2.80** as a colourless oil (6.6 g, 47.5 mmol) in 95% yield, TLC, R_f 0.52 (5% EtOAc/Hexanes); ^1H NMR (200 MHz, $CDCl_3$) δ 4.80 (t, *J* = 3.2 Hz, 1H), 4.21 (t, *J* = 2.2 Hz, 2H), 3.85-3.75 (m, 1H), 3.55-3.47 (m, 1H), 2.31 (t, *J* = 2.2 Hz, 1H), 1.90-1.50 (m, 6H).

Preparation of Alkyne 2.88



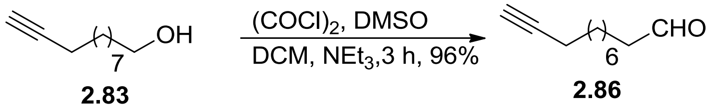
To the solution of THP ether **2.80** (6.3 g, 45 mmol) in THF (135 mL) cooled at -78 °C was added *n*-BuLi (45 mL, 45 mmol, 1 M in Hexane) and the mixture stirred at the same temperature for 1 h. The solution of octyl iodide (10.8 g, 45 mmol) in HMPA (8.0 mL) was added and stirred for 2 h allowing the temperature to raise to rt. The mixture was cooled to 0 °C, then quenched with aq saturated NH_4Cl. The aq layer was separated and extracted with ether (3x50 mL). The combined organic layer was washed with brine (25 mL), dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to afford the crude ether which was purified by column chromatography using 2% EtOAc/Hexanes (v/v) as the eluent to yield pure **2.81** as an oil (9.6 g, 38 mmol) in 85% yield, TLC, R_f 0.61 (5% EtOAc/Hexanes); ^1H NMR (200 MHz, $CDCl_3$) δ 4.78 (t, *J* = 2.8 Hz, 1H), 4.21 (td, *J* = 4.4, 2.2 Hz, 2H), 3.87-3.74 (m, 1H), 3.56-3.44 (m, 1H), 2.25-2.15 (m, 6H), 1.75-1.24 (m, 14H), 0.90 (t, *J* = 6.9 Hz, 3H).

Preparation of alkyne 2.83



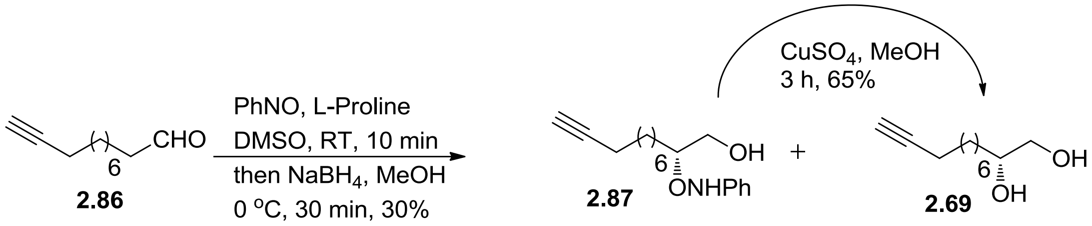
To the solution of THP ether **2.81** (9.6 g, 38 mmol) in MeOH (115 mL) cooled at 0 °C was added CSA (440 mg, 1.9 mmol) and the mixture stirred for 1 h. The solvent was evaporated under reduced pressure and the residue diluted with DCM (115 mL). The reaction mixture was washed successively with aq Na_2CO_3 (10 mL), brine (5 mL), dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to afford crude product which was purified by column chromatography using 8% EtOAc/Hexanes (v/v) as the eluent to yield alcohol **2.82** as an oil (6.0 g, 36 mmol) in 95% yield, TLC, R_f 0.32 (10% EtOAc/Hexanes). Sodium hydride (5.7 g, 252 mmol, 60% Nujol) was taken in a flame dried round bottom flask. The reaction was freed of mineral oil by successively washing with petroleum ether. 1,3-Diaminopropane (110 mL) was added to the reaction and the mixture was stirred at 70 °C. After 1 h the resultant brown solution was cooled to 50 °C. The solution of substrate **2.82** (6.0 g, 36 mmol) in 1,3-diaminopropane (20 mL) was injected into the flask. After completion of the reaction the reaction mixture was poured into ice water and extracted with ether (3x50 mL). The combined ether layers were washed successively with water (10 mL), HCl (5 mL), brine (15 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product which was purified by column chromatography using 15% EtOAc/Hexanes (v/v) to give pure **2.83** (4.6 g, 28 mmol) in 78% yield. TLC, R_f 0.28 (10% EtOAc/Hexanes); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.60 (t, J = 6.7 Hz, 2H), 2.16 (dt, J = 6.9, 2.6 Hz, 2H), 1.84 (t, J = 2.6 Hz, 1H), 1.60-1.48 (m, 4H), 1.44-1.28 (m, 10H);); ^{13}C NMR (100 MHz, $CDCl_3$) δ 84.8, 68.2, 63.1, 32.9, 29.6, 29.5, 29.2, 28.9, 25.6, 18.6.

Preparation of aldehyde 2.86



To the solution of anhydrous oxalyl chloride (0.65 mL, 7.5 mmol) in dry DCM (20 mL) cooled at -78 °C, was added anhydrous DMSO (0.78 mL, 10 mmol) and the mixture stirred for 45 min at the same temperature. A solution of alcohol **2.83** (1.3 g, 5 mmol) in dry DCM (2 mL) was added at the same temparature and the mixture stirred for 45 min. NEt_3 (3.5 mL, 25 mmol) was added and the reaction mixture allowed to warm gradually to 0 °C. The reaction mixture was diluted with DCM (20 mL) and washed with 2N HCl (15 mL), water (5 mL), brine (5 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude compound which was purified by column chromatography using 2% EtOAc/Hexanes (v/v) as the eluent to afford the pure product **2.86** as a viscous oil (1.1 g, 4.5 mmol) in 90% yield, TLC, R_f 0.52 (10% EtOAc/Hexanes); ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.73 (s, 1H), 2.39 (dt, J = 7.2, 1.6 Hz, 2H), 2.15 (dt, J = 6.9, 2.6 Hz, 2H), 1.83 (t, J = 2.6 Hz, 1H), 1.68-1.24 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 84.3, 68.1, 43.9, 29.2, 29.1, 28.9, 28.6, 28.4, 22.1.

Preparation of diol 2.69

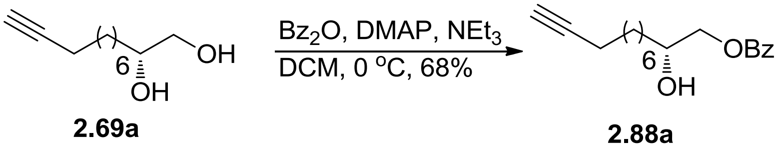


DMSO (4 mL) was added to L-proline (55.2 mg, 0.48 mmol) at rt under nitrogen atmosphere and the suspension was stirred for 10 min. Nitrosobenzene (257 mg, 2.4 mmol) was added in one portion at which time the solution became green. Aldehyde **2.86** (436 mg, 2.63 mmol) in DMSO (6 mL) was added in one portion to the above greenish suspension and stirring continued at rt until the reaction was determined to be complete by TLC (the change of color of the green colour solution to a yellow homogeneous solution was observed). The reaction mixture was then transferred to a suspension of $NaBH_4$ (365 mg, 9.6 mmol) in ethanol (5 mL) at 0 ^oC. After 30 min of stirring, the reaction mixture was treated with saturated aq $NaHCO_3$ (15 mL) and extracted with dichloromethane (3x10 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford the crude diol **2.69** and anilinoxy compound **2.87** which was used immediately for the next reaction.

To a solution of the above crude compound in methanol (8 mL), was added $CuSO_4.5H_2O$ (174 mg, 0.61 mmol). The reaction mixture was stirred at rt for 3 h and then quenched with a cold saturated NH_4Cl solution (5 mL). The mixture was filtered on a Celite pad and washed thoroughly with ethyl acetate (15 mL). The volatiles were removed under reduced pressure. The residue was extracted with ethyl acetate (3x15 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product which was purified by column chromatography using 30% EtOAc/Hexanes (v/v) to give pure diol 2.90 (214 mg, 1.26 mmol) in 60% yield as viscous oil TLC: R_f 0.24 (40% EtOAc/Hexanes). $[\alpha]^{25}_D$ (+) 8.6 (*c* 1.02, $CHCl_3$); IR (neat) 3405, 2933, 2858, 1639, 1460, 1061, 770 cm^{-1}. ^1H NMR (400

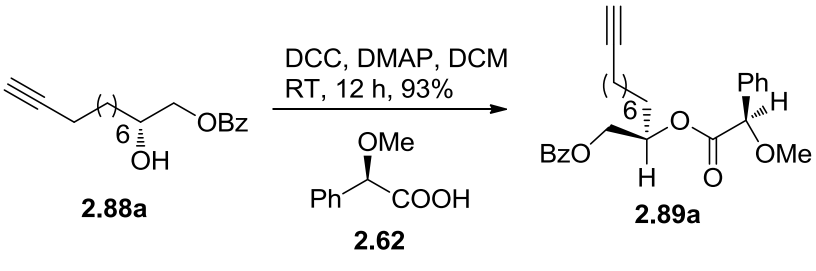
MHz, $CDCl_3$) δ 4.39 (m, 1H), 4.20 (dd, *J* = 11.4, 7.3 Hz, 1H), 3.95 (dd, *J* = 11.4, 7.3 Hz 1H), 2.17 (td, *J* = 7.0, 2.2 Hz, 2H), 1.85 (t, *J* = 2.2, 1Hz), 1.53-1.23 (m, 12H).

Preparaion of Mandelate 2.88a



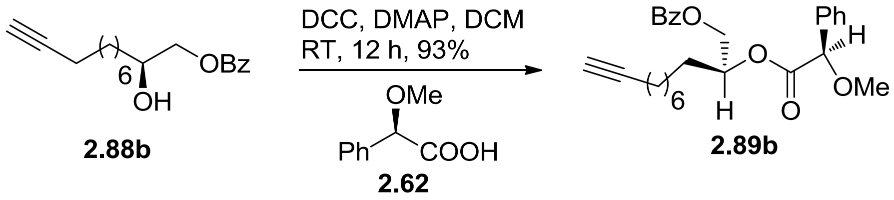
To a solution of diol **2.69a** (85 mg, 0.5 mmol) in DCM (2 mL) was added benzoic anhydride (125 mg, 0.55 mmol) and Et_3N (0.15 ml, 1.1 mmol) at 0 °C and the reaction mixture was stirred at the same temperature for 30 min. The reaction mixture was diluted with DCM (5 mL) and washed with water, brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude benzoate which was purified by column chromatography using 20% EtOAc/Hexanes (v/v) to give the pure benzoate (123 mg, 0.45 mmol) in 68% yield. TLC, R_f 0.47 (10% EtOAc/Hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.1 Hz, 2H), 7.53 (d, *J* = 7.1 Hz, 1H), 7.46 (d, *J* = 7.1 Hz, 2H), 4.35 (dd, *J* = 7.2, 5.1 Hz, 1H), 4.20 (dd, *J* = 7.2, 6.2 Hz, 1H), 4.01-3.92 (m, 1H), 2.20 (dt, *J* = 6.9, 2.6 Hz, 2H), 1.80 (t, *J* = 2.6 Hz, 1H), 1.60-1.25 (m, 12H).

Preparaion of Mandelate 2.89a



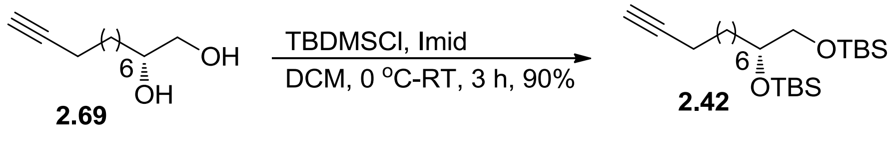
To the solution of alcohol **2.88a** (28 mg, 0.1 mmol) in DCM (1 mL) cooled at 0 ° C was added DCC (30 mg, 0.15 mmol), DMAP (1.2 mg), and (*R*)-methoxymandelic acid (20 mg, 0.12 mmol). The reaction mixture was stirred overnight while gradually allowing the the temperature to rise to rt. The solvent was evaporated under reduced pressure to furnish the crude compound which was purified by column chromatography using 5% EtOAc/Hexanes (v/v) as the eluent to afford the product **2.89a** (39 mg, 0.09 mmol) in 93% yield as a liquid. TLC, R_f 0.32 (10% EtOAc/Hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.75 (d, J = 8.0 Hz, 2H), 7.45-7.10 (m, 8H), 5.30-5.20 (m, 1H), 4.73 (s, 1H), 4.32-4.12 (m, 2H), 3.40 (s, 3H), 2.15 (dt, J = 6.9, 2.6 Hz, 2H), 1.84 (t, J = 2.6 Hz, 1H), 1.74-1.18 (m, 12H).

Preparaion of Mandelate 2.89b



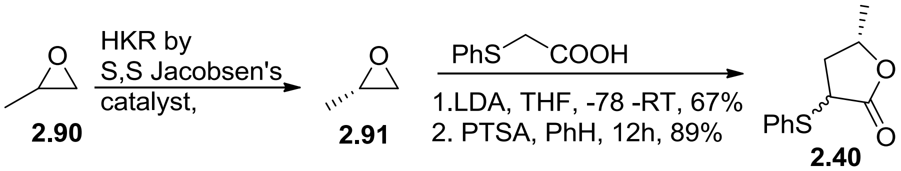
Prepared following the detailed above using the diol **2.89b** and (*R*)-methoxymandelic acid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.92 (d, J = 7.1 Hz, 2H), 7.50 (d, J = 7.1 Hz, 1H), 7.40-7.20 (m, 7H), 5.25-5.20 (m, 1H), 4.70 (s, 1H), 4.33 (dd, J = 7.2, 5.1 Hz, 1H), 4.20 (dd, J = 7.2, 6.2 Hz, 1H), 3.30 (s, 3H), 2.07 (dt, J = 6.9, 2.6 Hz, 2H), 1.78 (t, J = 2.6 Hz, 1H), 1.53-1.10 (m, 12H).

Preparation of Alkyne 2.42



To the solution of alcohol **2.69** (1.8 g, 10 mmol) in dry DCM (40 mL) maintained at 0 °C was added imidazole (2.0 g, 30 mmol) followed by TBS-Cl (3.3 g, 22 mmol) and stirred for a period of 3 h. The reaction mixture was washed with water (10 mL), brine (5 mL), dried over Na_2SO_4, and the solvent evaporated under reduced pressure to yield the crude product which was purified by column chromatography using hexanes to furnish the product **2.42** (3.7 g, 9 mmol) in 90% yield as a liquid; TLC, R_f 0.81 (Hexanes); $[\alpha]^{25}_D$ 23.5 (*c* 1, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.61 (m, 1H), 3.48 (dd, *J* = 10.1, 7.1 Hz, 1H), 3.38 (dd, *J* = 10.1, 7.1 Hz, 1H), 2.18 (td, *J* = 6.9, 2.6 Hz, 2H), 1.83 (t, *J* = 2.6 Hz, 1H), 1.60-1.22 (m, 12H), 0.98-0.82 (s, 18H), 0.2 (s, 12H).

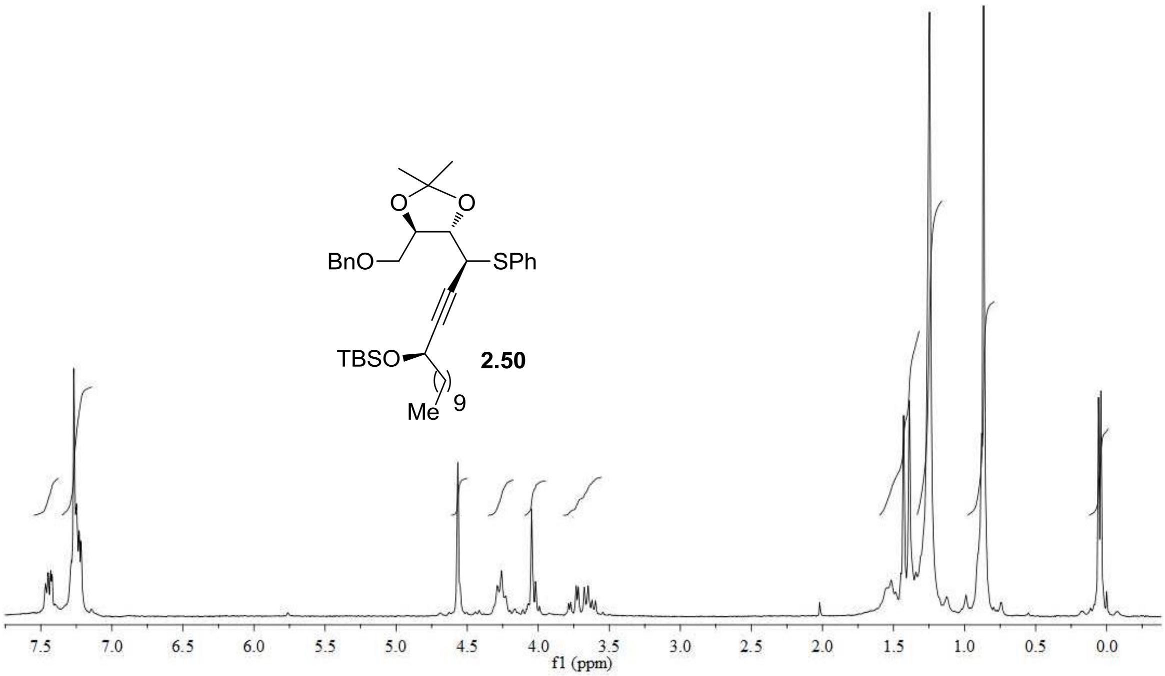
Preparation of Butenolide 2.40

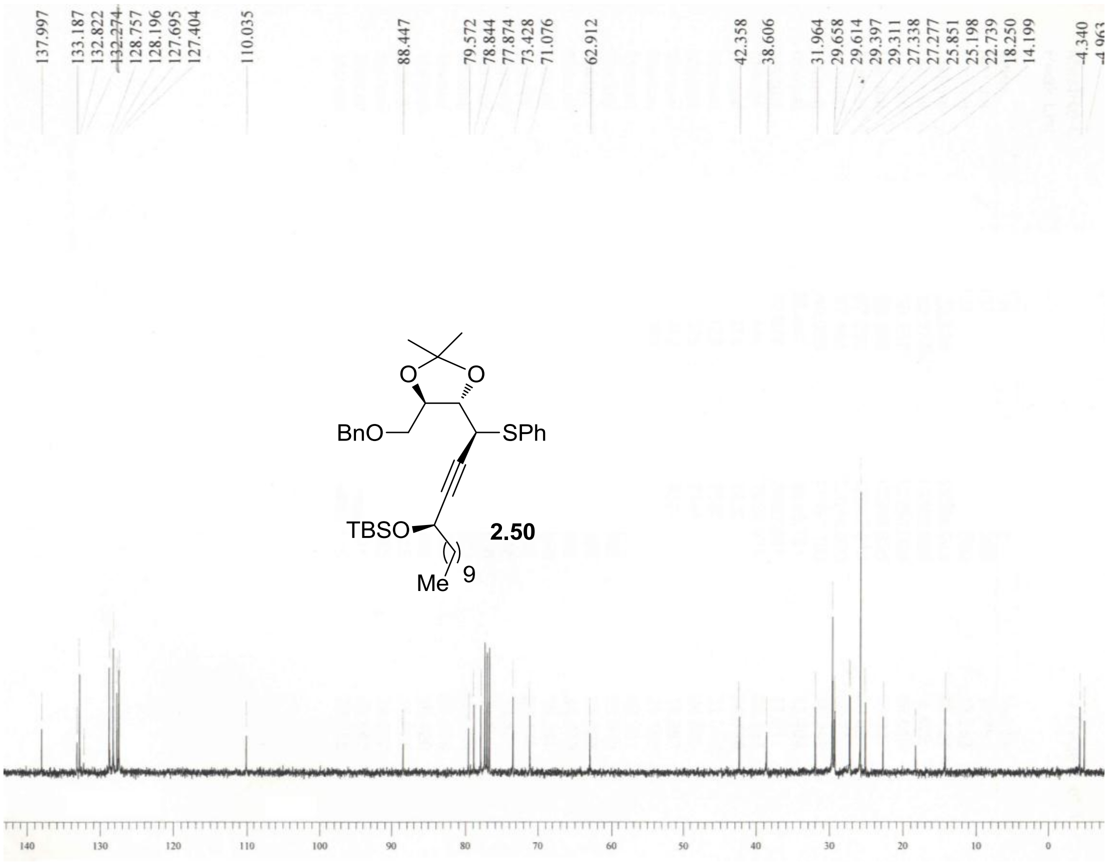


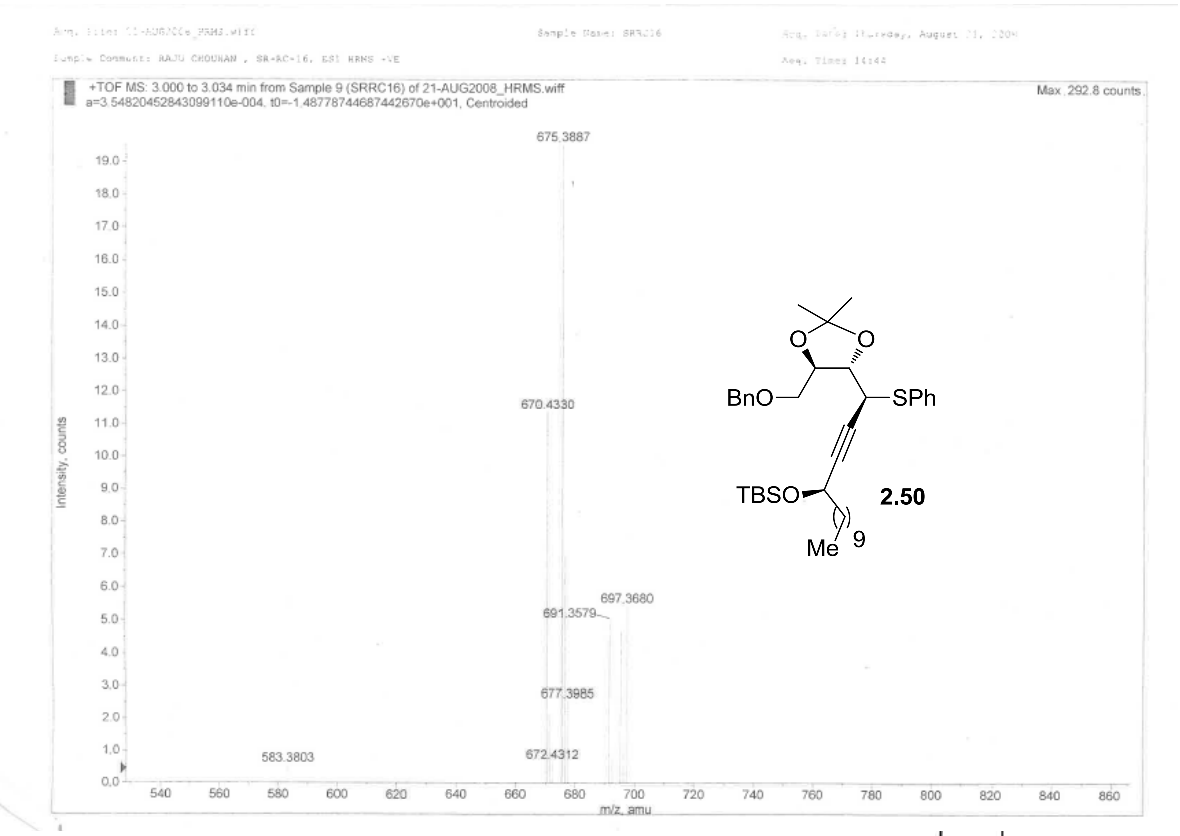
A mixture of (*S,S*)-(+)-*N,N*^{1}-Bis (3,5-di-*tert*-butylsacylidine)-1-2-cyclohexanediamino-Co(II) complex (0.434 g, 0.72 mmol), toluene (7.0 mL) and acetic acid (0.08 mL, 1.44 mmol) was stirred in open air for 1 h at rt. The solvent was removed in a rotary evaporator under reduced pressure and the brown residue [(*S,S*)-(+)-*N,N*^{1}-Bis (3,5-di-tert-butylsacylidine)-1-2-cyclohexanediamino-Co(III) acetate, (salen)-Co(III) (OAc) complex] was dried under vacuum. The brown residue was then added to propylene oxide (8.3 g, 143.8 mmol) and the mixture then cooled in an ice bath. Water (1.42 mL, 79.1 mmol) was slowly added keeping the bath temperature at 15 °C. After 1 h addition was completed, the ice water bath was removed and the reaction mixture was stirred at rt for 12 h. The crude reaction mixture was then purified by distillation to yield **2.91** (3.5 g, 40%), liquid b.p. 37 °C, $[\alpha]^{25}_D$ -7.7 (*c* 1, $CHCl_3$).

To the solution of DIPA (0.8 mL, 5.0 mmol) in THF (10 mL) cooled at -78 °C was added *n*-BuLi (3.2 mL, 1.5 M in Hexanes, 4.8 mmol) and the mixture stirred for 15 minutes. A solution of phenylthioacetic acid (420 mg, 2.5 mmol) in THF (2.0 mL) was then added and the mixture stirred for 15 minutes at -78 ^{o}C. To the resulting dianion, epoxide **2.91** (300 mg, 5.0 mmol) was added. The reaction mixture was allowed to warm to rt over a period of 3 h and stirred for another 16 h. The reaction mixture was quenched with aq NaOH (2 N, 3 mL) and extracted with ether (25 mL). The aq layer was acidified and extracted with ether (50 mL). The organic layer was washed with brine and dried over Na_2SO_4. The solvent was evaporated to yield the hydroxy acid which was dissolved in dry benzene (8.0 mL), *p*-toluenesulfonic acid (20 mg) was added and the mixture stirred for 12 h at rt. The solvent was evaporated under reduced pressure and residue was purified by column chromatography using 25% EtOAc/Hexane (v/v) to yield butenolide **2.40** (333 mg, 60%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.55-7.50 (m, 4H), 7.35-7.25 (m, 6H), 4.60-4.45 (m, 2H), 3.95-3.82 (m, 2H), 2.75-2.25 (m, 4H), 1.40-1.30 (m, 6H).

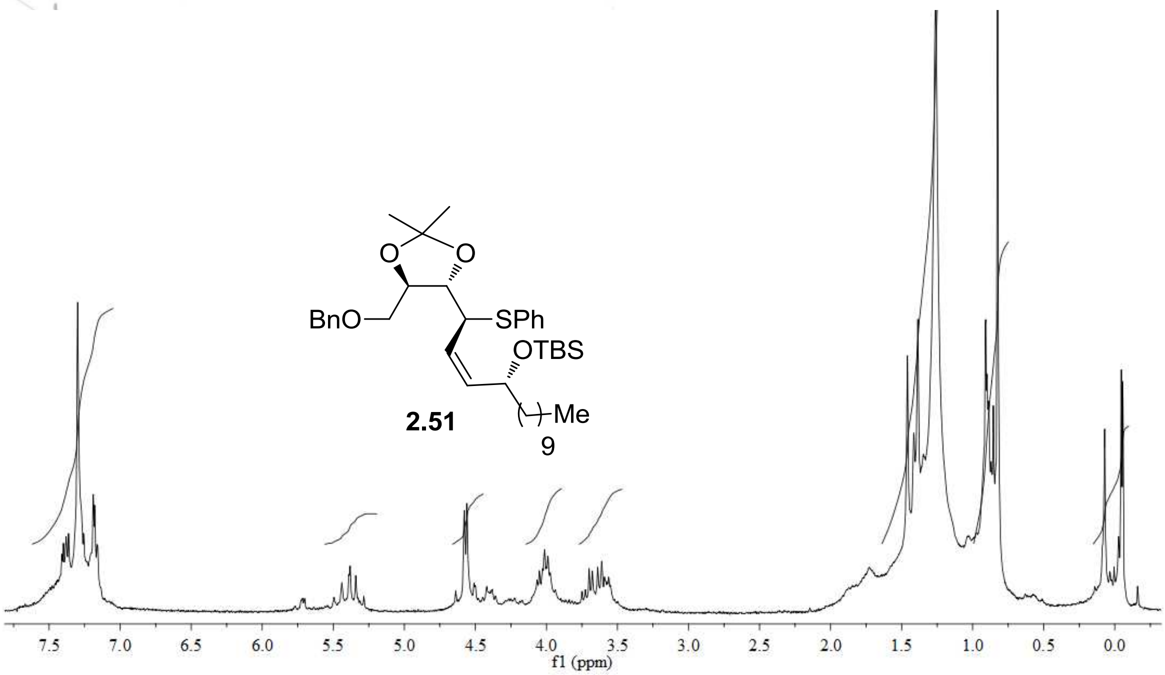
Spectral Data


BnO
O
O
SPh
TBSO
2.50
9
Me
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
f1 (ppm)

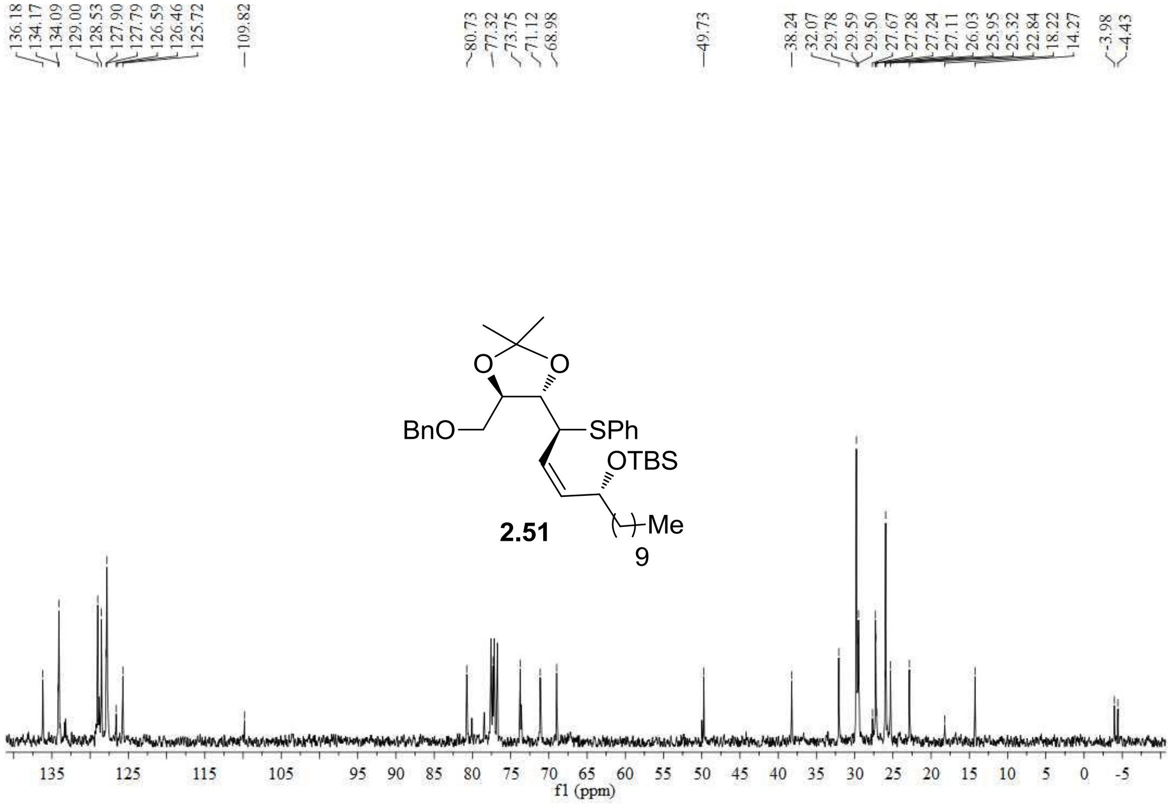

137.997
133.187
132.822
132.274
128.757
128.196
127.695
127.404
110.035
88.447
79.572
78.844
77.874
73.428
71.076
62.912
42.358
38.606
31.964
29.658
29.614
29.397
29.311
27.338
27.277
25.851
25.198
22.739
18.250
14.199
-4.340
-4.963
BnO
O
O
SPh
TBSO
2.50
9
Me
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

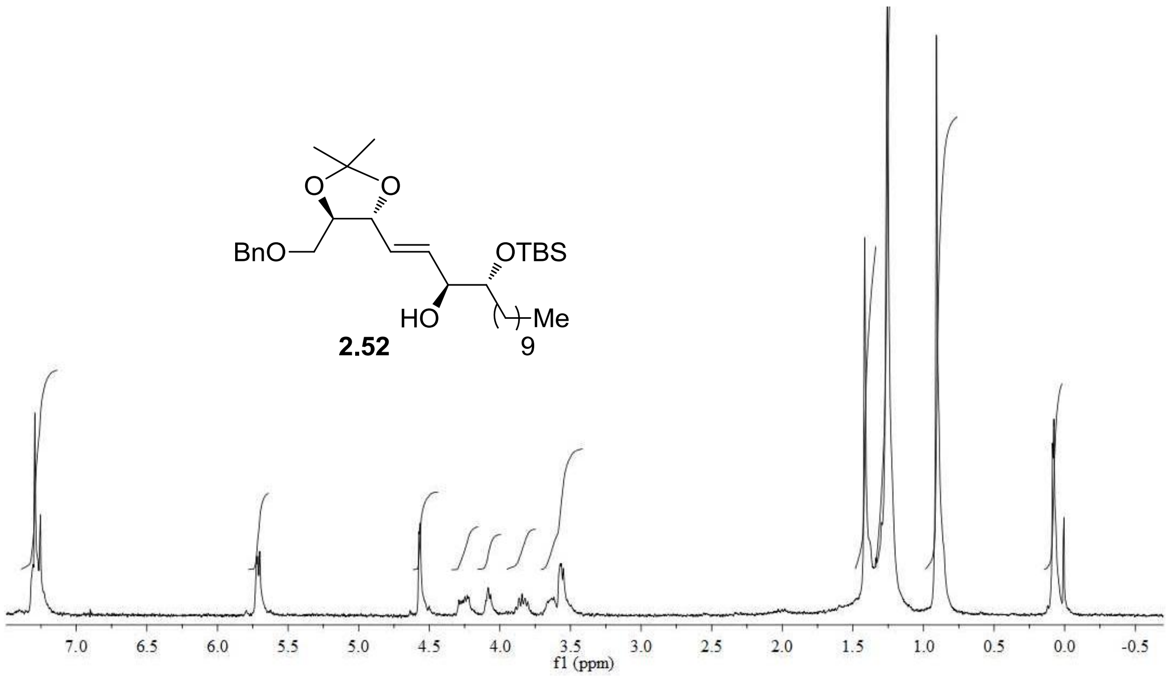

Acq. File: 21-AUG2008_HRMS.wiff
Sample Name: SRRC16
Acq. Date: Thursday, August 21, 2008
Sample Comment: RAJU CHOUHAN , SR-RC-16, ESI HRMS -VE
Acq. Time: 14:44
+TOF MS: 3.000 to 3.034 min from Sample 9 (SRRC16) of 21-AUG2008_HRMS.wiff
a=3.54820452843099110e-004, t0=-1.48778744687442670e+001, Centroided
Max. 292.8 counts.
675.3887
670.4330
697.3680
691.3579
677.3985
672.4312
583.3803
Intensity, counts
m/z, amu
19.0
18.0
17.0
16.0
15.0
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
540
560
580
600
620
640
660
680
700
720
740
760
780
800
820
840
860
O
O
BnO
SPh
TBSO
Me
9

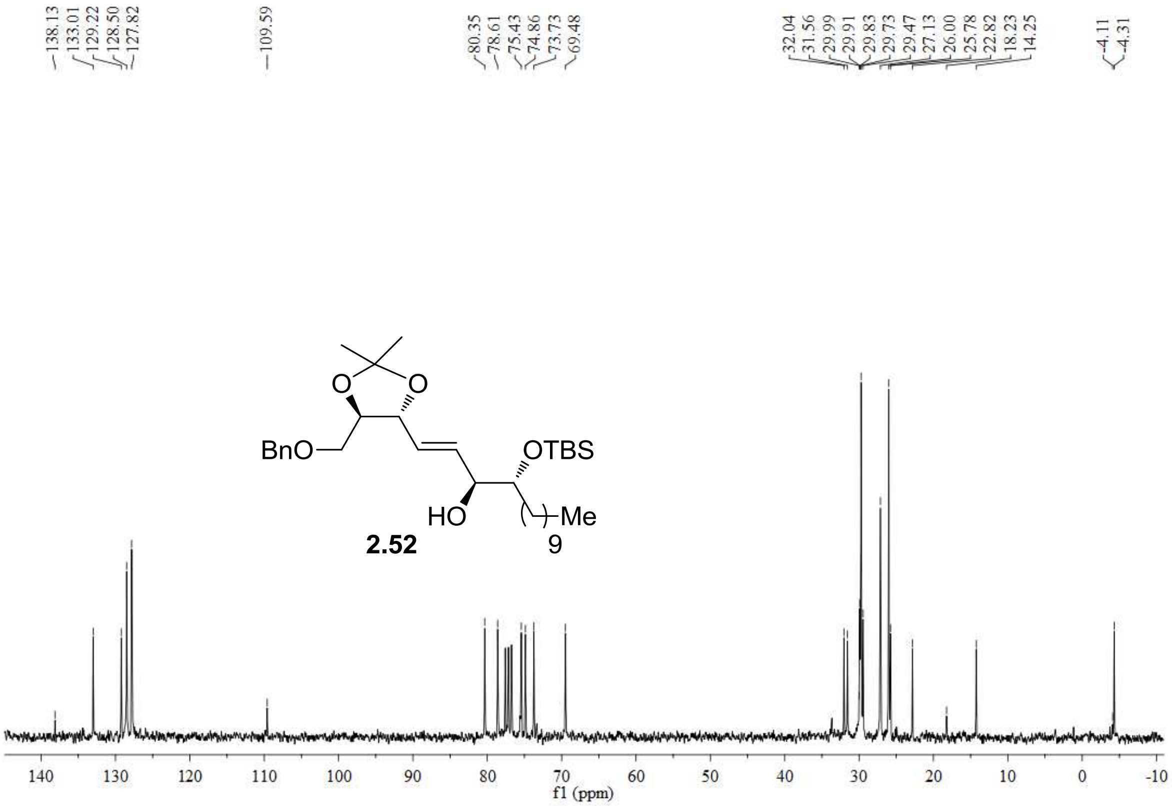
2.50

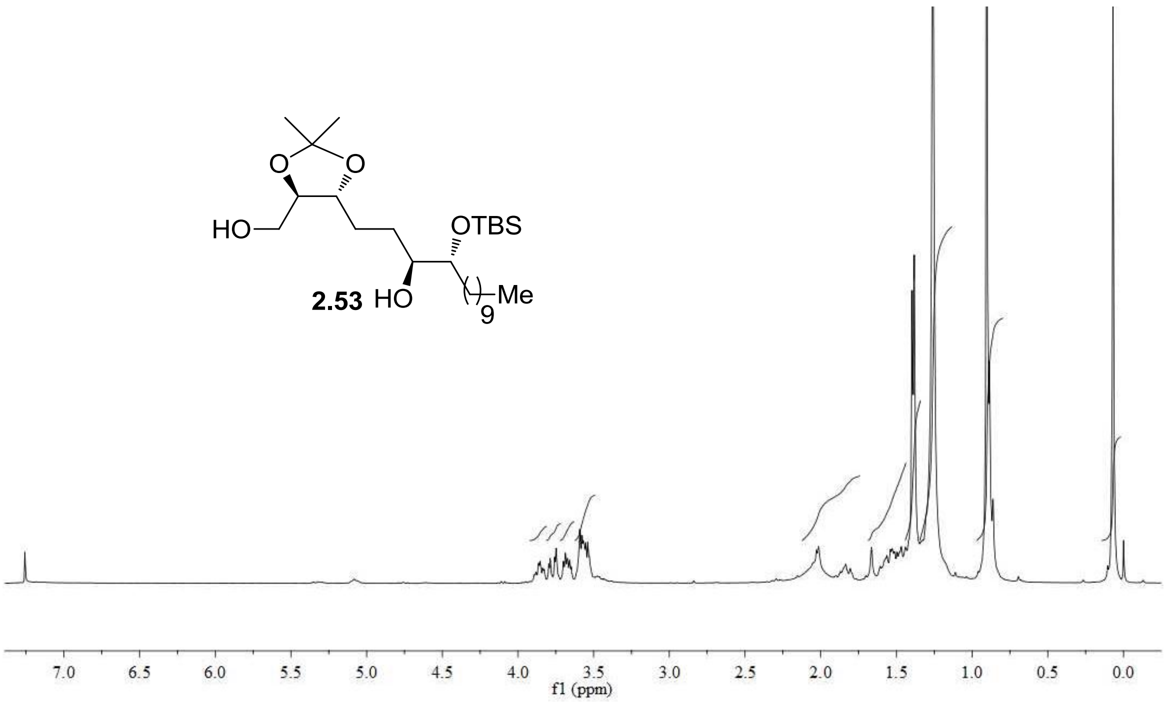

O
O
BnO
SPh
OTBS
Me
9
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

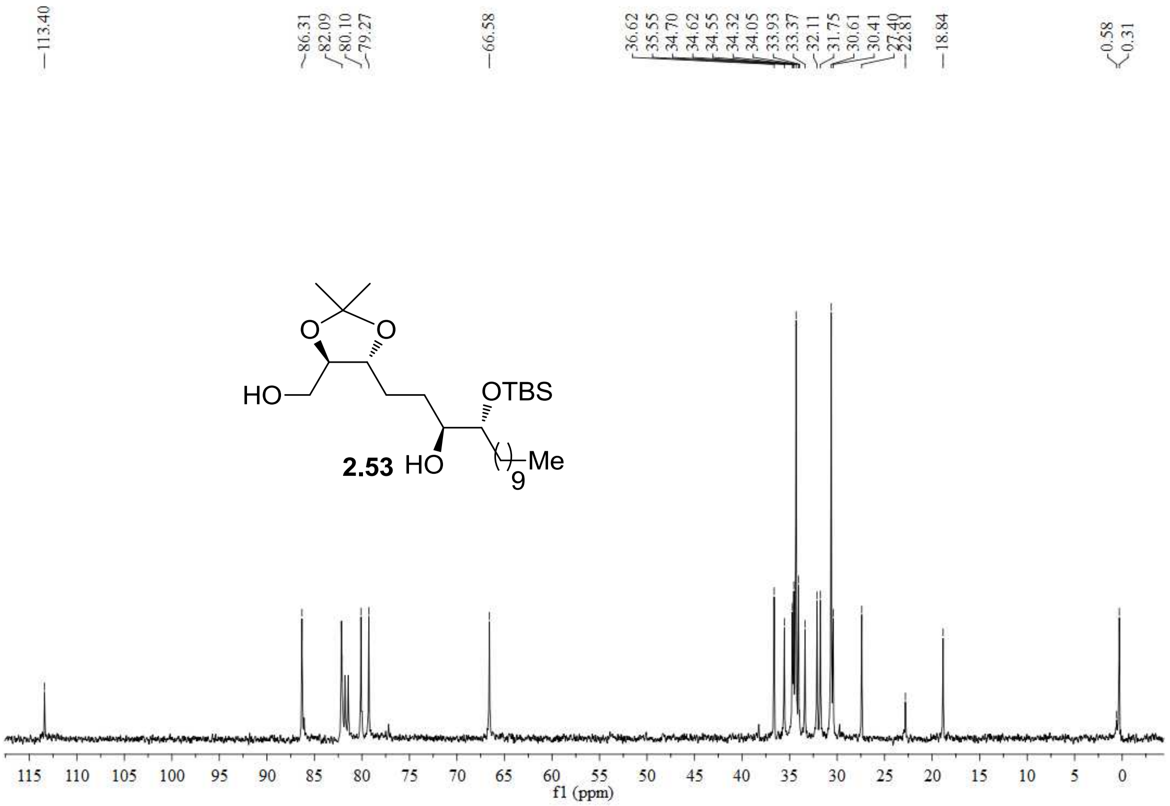
2.51

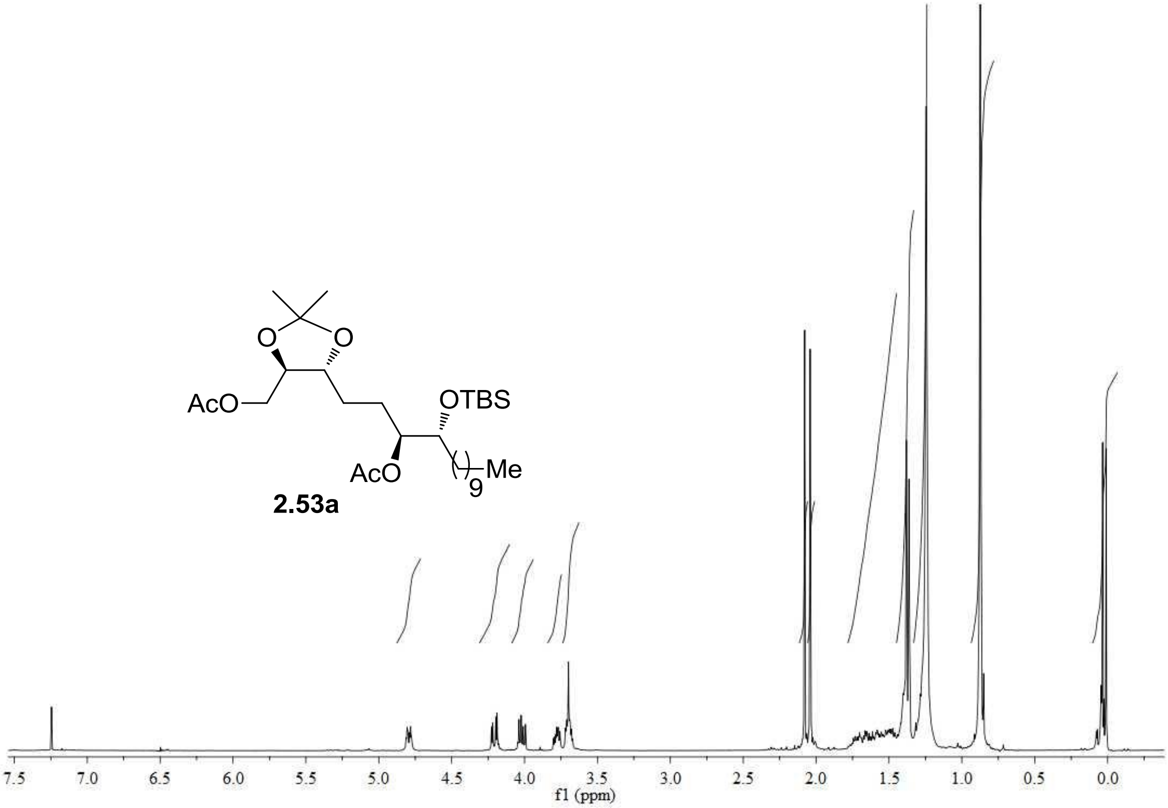

136.18
134.17
134.09
129.00
128.53
127.90
127.79
126.59
126.46
125.72
109.82
80.73
77.32
73.75
71.12
68.98
49.73
38.24
32.07
29.78
29.59
29.50
27.67
27.28
27.24
27.11
26.03
25.95
25.32
22.84
18.22
14.27
-3.98
-4.43
O
O
BnO
SPh
OTBS
Me
9
2.51
135
125
115
105
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
f1 (ppm)

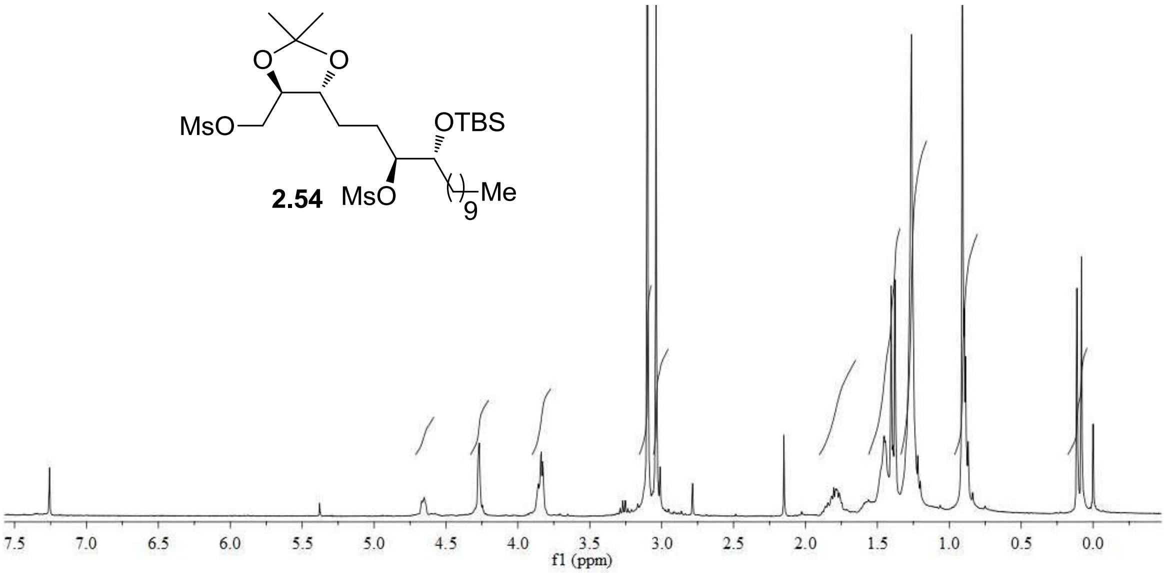

O
O
BnO
OTBS
HO
Me
9
2.52
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


138.13
133.01
129.22
128.50
127.82
109.59
80.35
78.61
75.43
74.86
73.73
69.48
32.04
31.56
29.99
29.91
29.83
29.73
29.47
27.13
26.00
25.78
22.82
18.23
14.25
-4.11
-4.31
O
O
BnO
OTBS
HO
Me
9
2.52
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

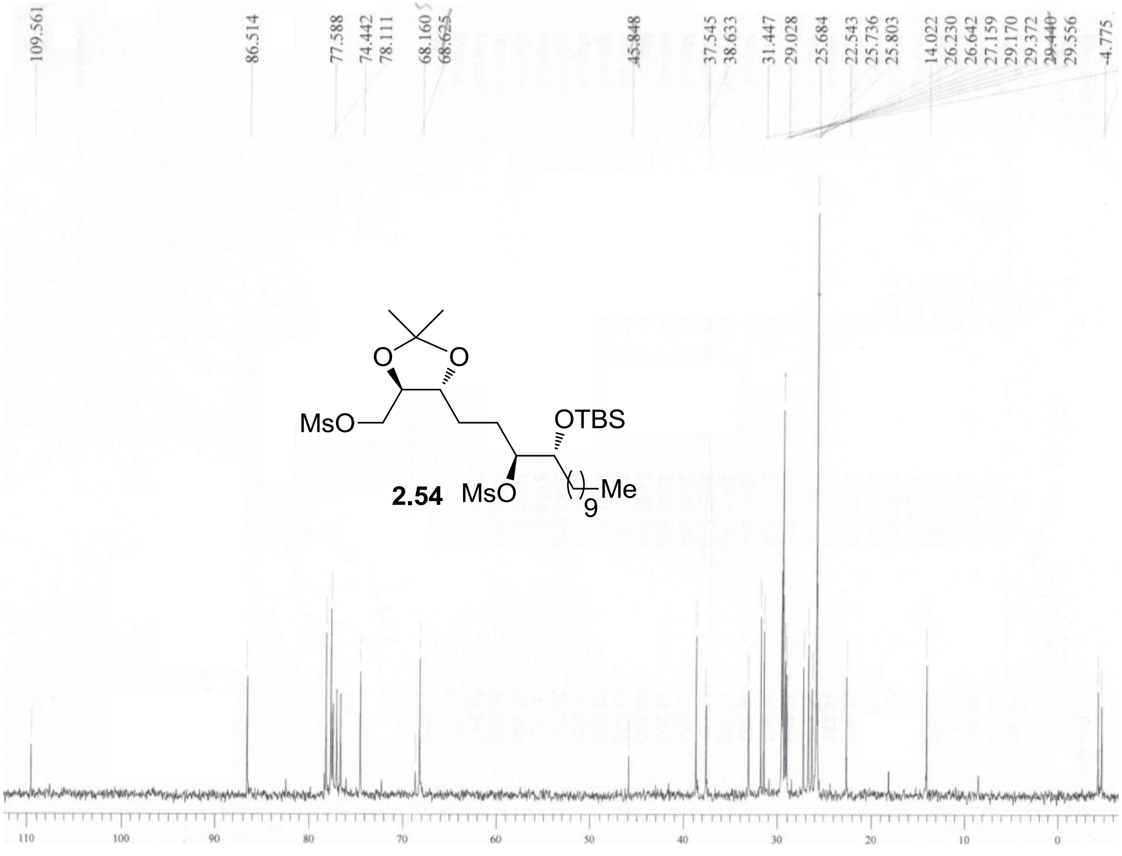

O
O
HO
OTBS
2.53
HO
9
Me
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


113.40
86.31
82.09
80.10
79.27
66.58
36.62
35.55
34.70
34.62
34.55
34.32
34.05
33.93
33.37
32.11
31.75
30.61
30.41
27.40
22.81
18.84
0.58
0.31
HO
O
O
OTBS
HO
Me
9
2.53
115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0
f1 (ppm)

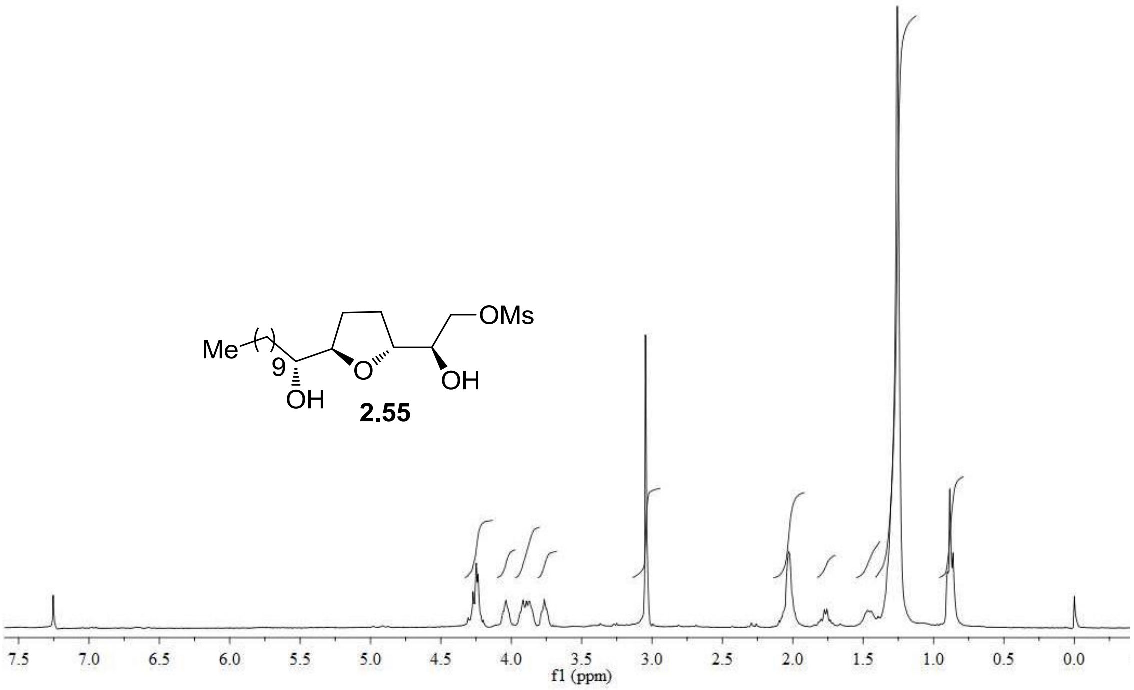

AcO
O
O
OTBS
AcO
Me
9
2.53a
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


O
O
MsO
OTBS
MsO
9
Me
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
f1 (ppm)

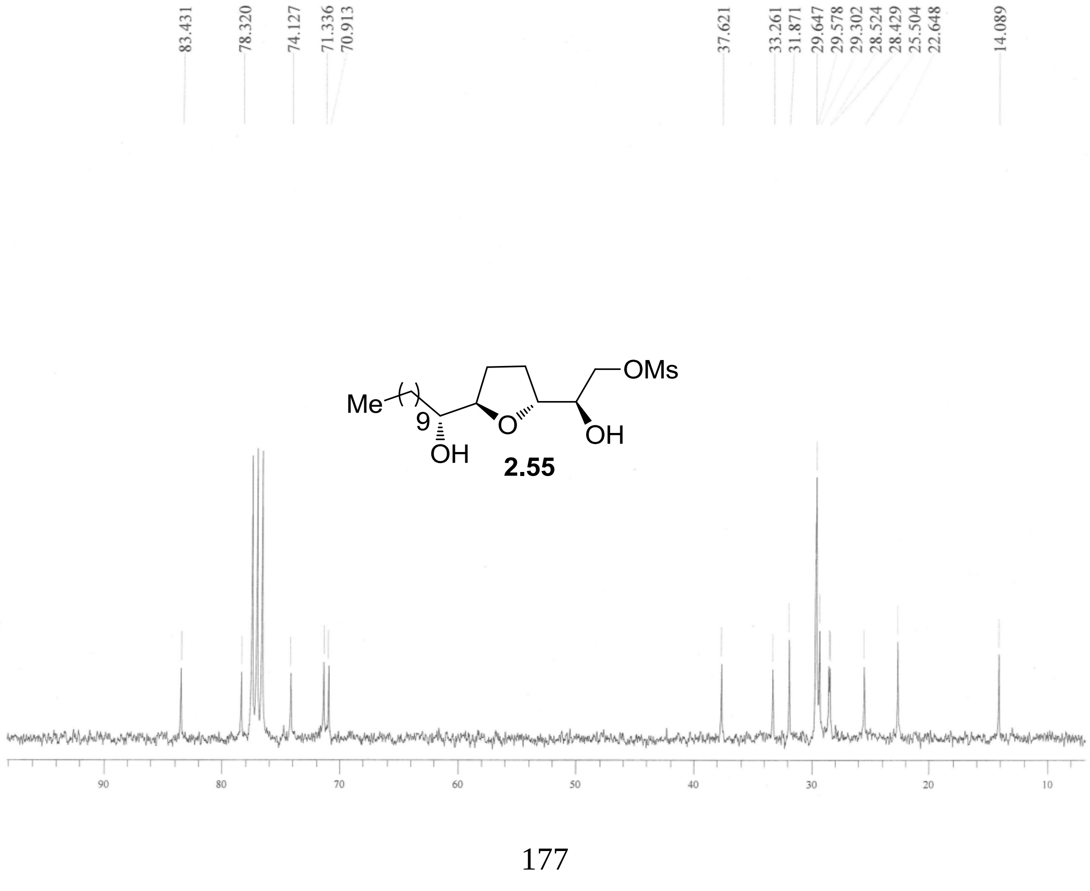
2.54


109.561
86.514
77.588
74.442
78.111
68.160
68.625
45.848
37.545
38.633
31.447
29.028
25.684
22.543
25.736
25.803
14.022
26.230
26.642
27.159
29.170
29.372
29.440
29.556
-4.775
O
O
MsO
OTBS
MsO
9
Me
110
100
90
80
70
60
50
40
30
20
10
0

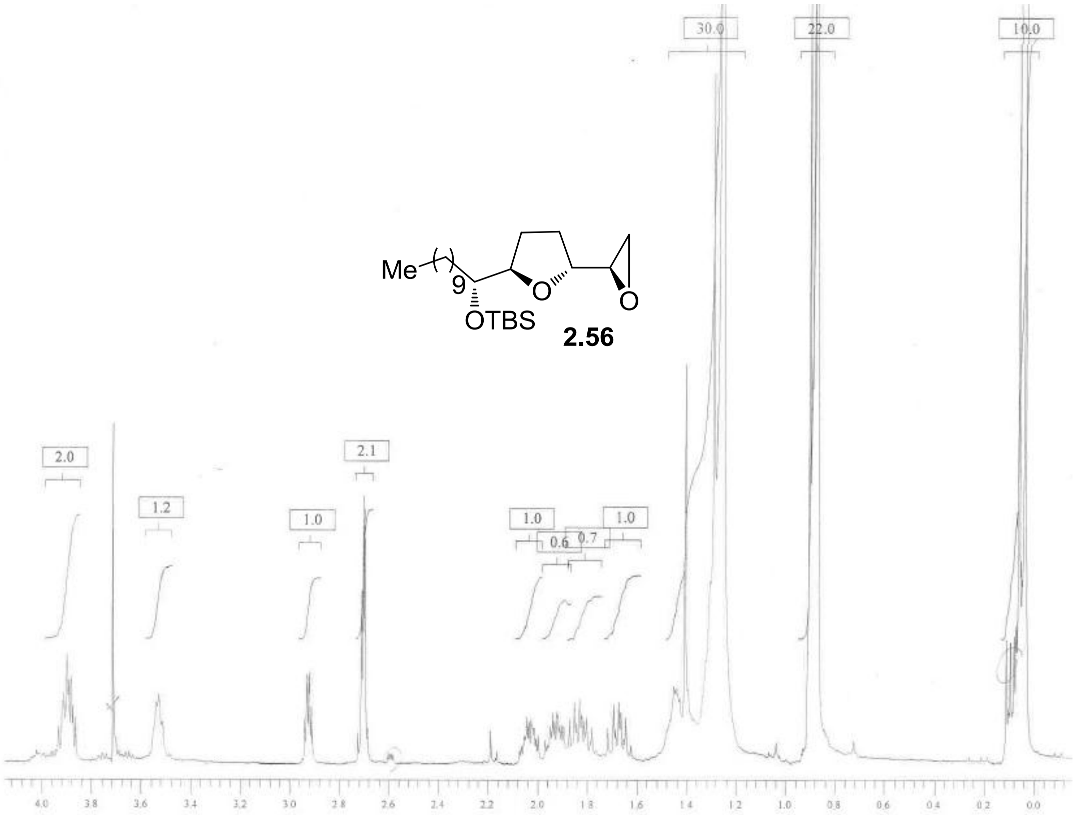
2.54


Me
9
OH
O
OMs
OH
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
f1 (ppm)

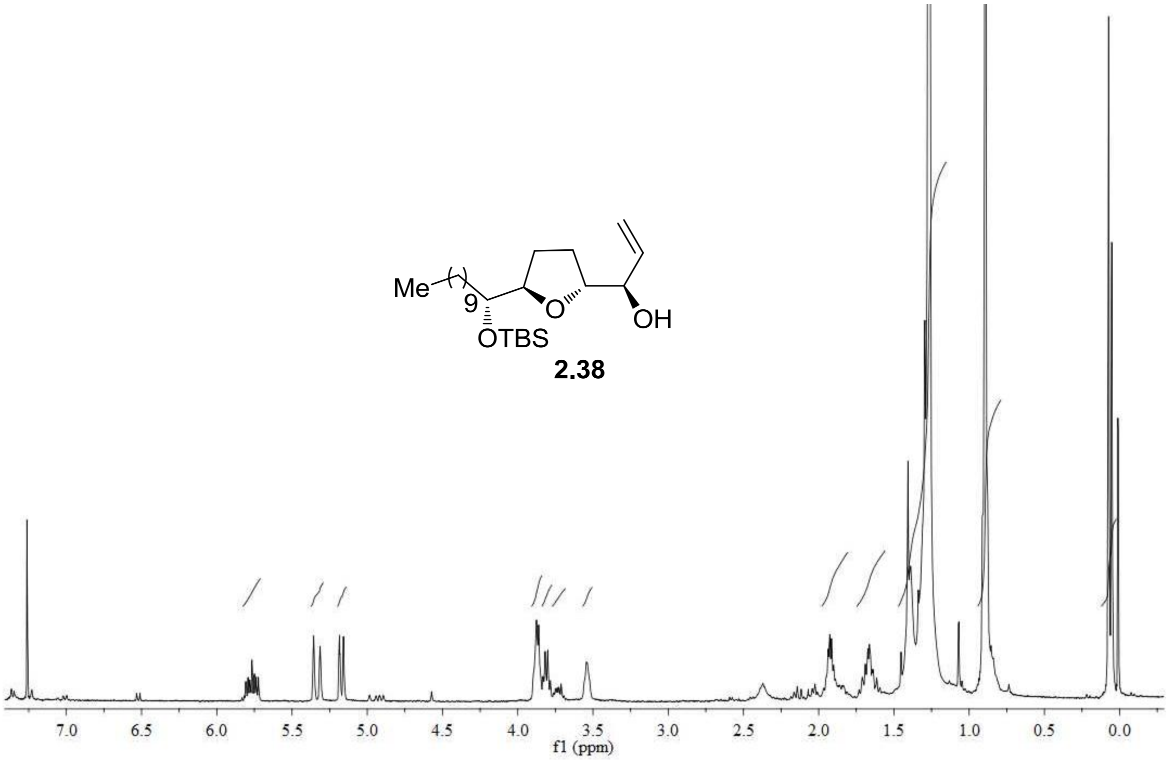
2.55


83.431
78.320
74.127
71.336
70.913
37.621
33.261
31.871
29.647
29.578
29.302
28.524
28.429
25.504
22.648
14.089
Me
9
OH
O
OMs
OH
90
80
70
60
50
40
30
20
10

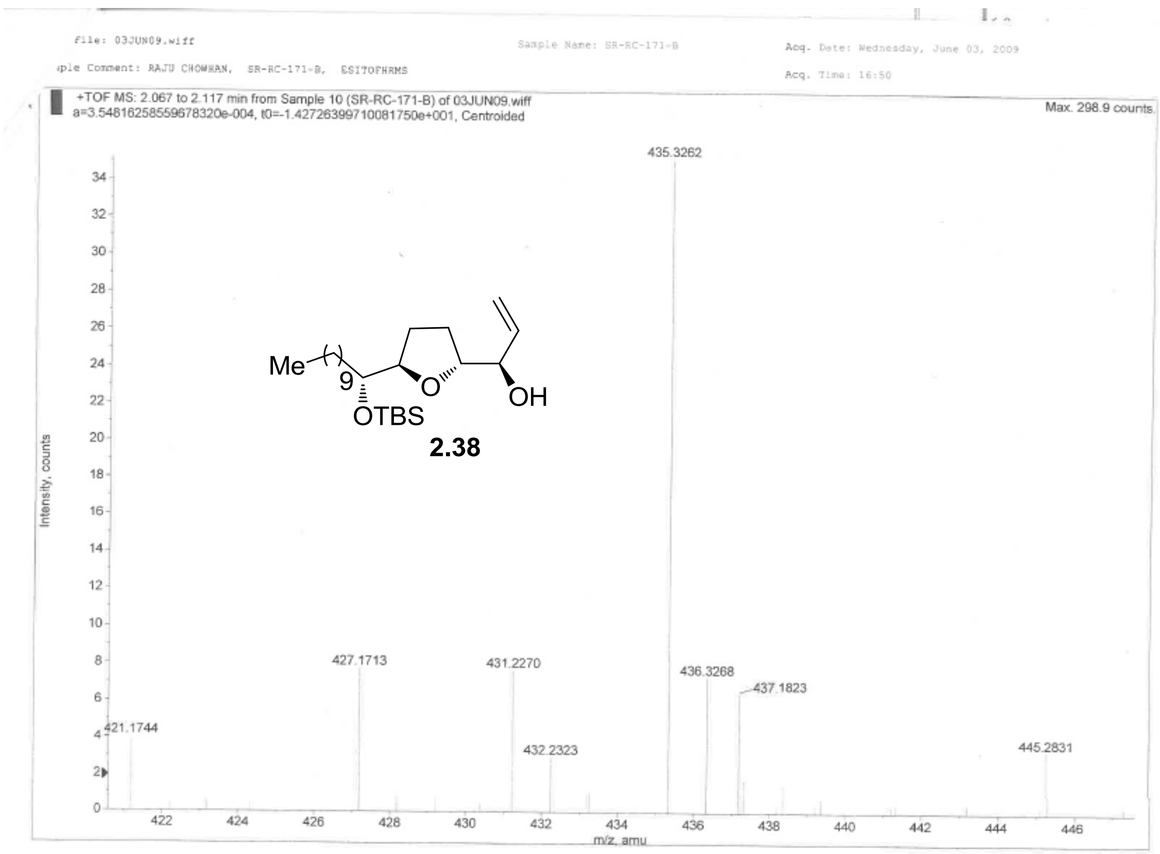
2.55


30.0
22.0
10.0
2.0
1.2
1.0
2.1
1.0
0.6
0.7
1.0
Me
9
OTBS
O
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0

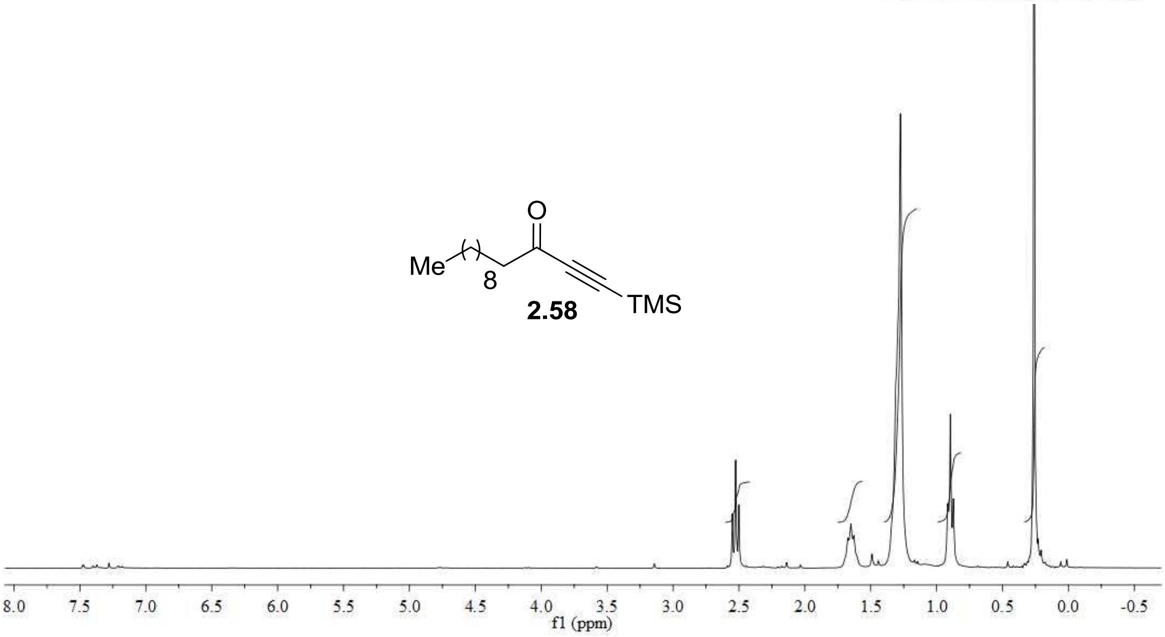
2.56


Me
9
OTBS
O
OH
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
f1 (ppm)

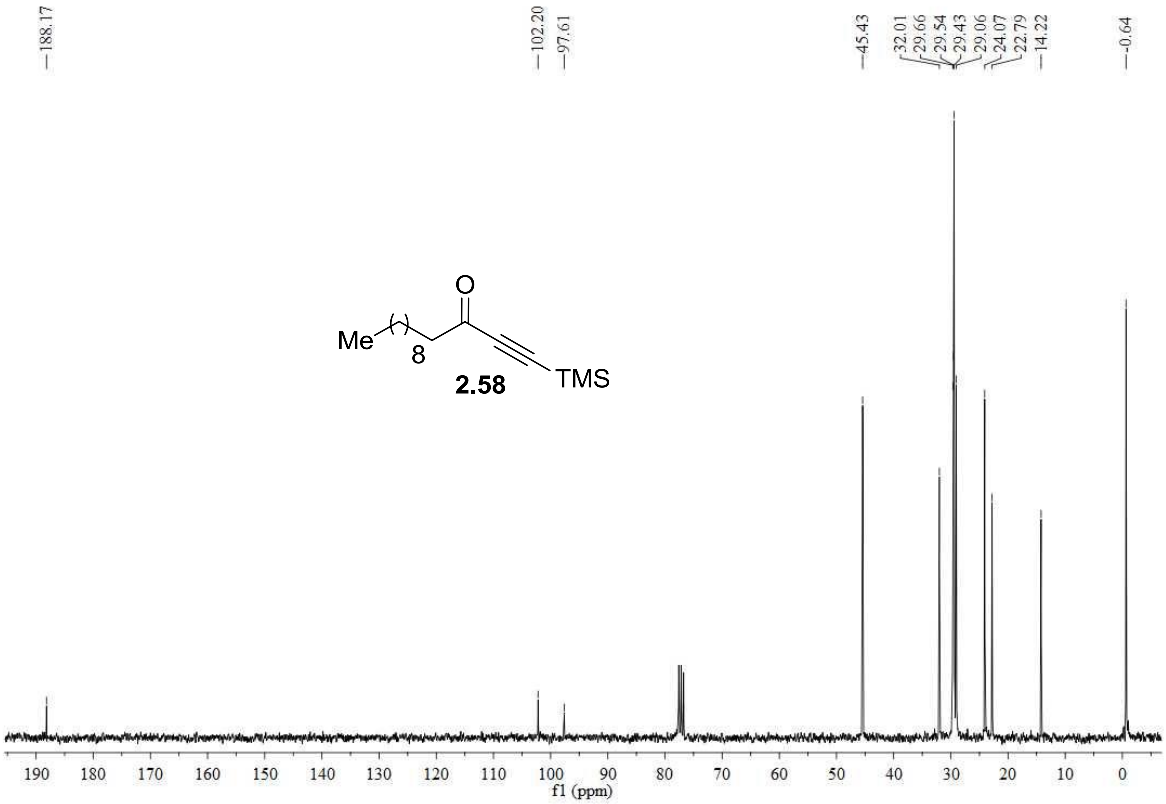
2.38

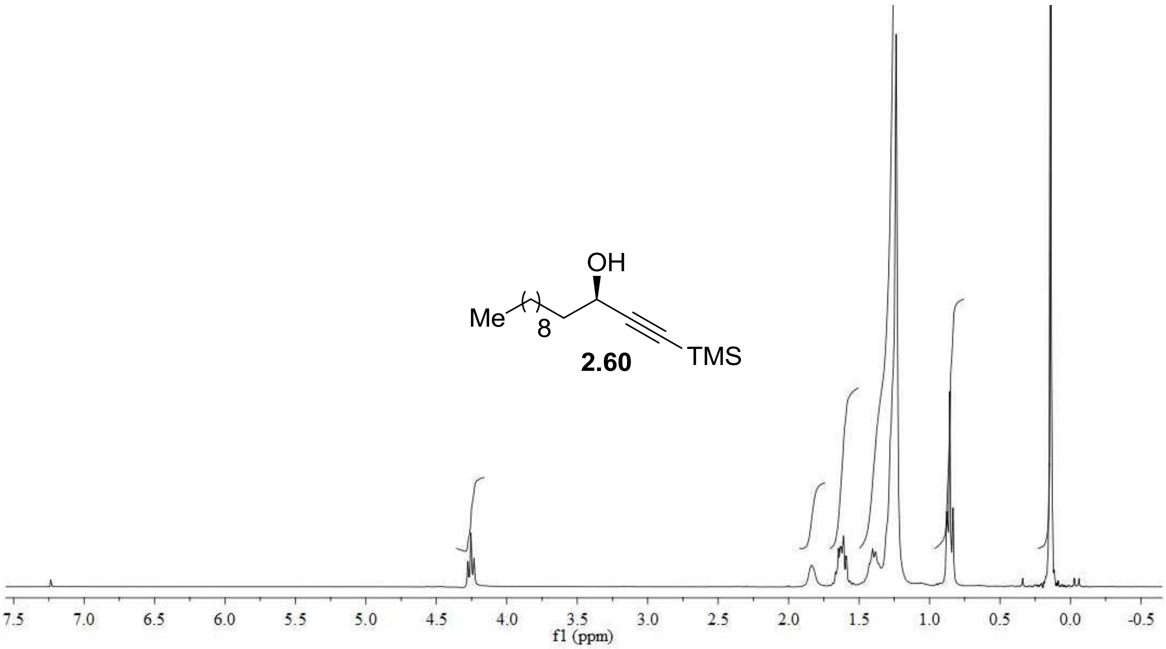

File: 03JUN09.wiff
Sample Name: SR-RC-171-B
Acq. Date: Wednesday, June 03, 2009
ple Comment: RAJU CHOWHAN, SR-RC-171-B, ESITOFHRMS
Acq. Time: 16:50
+TOF MS: 2.067 to 2.117 min from Sample 10 (SR-RC-171-B) of 03JUN09.wiff
a=3.54816258559678320e-004, t0=-1.42726399710081750e+001, Centroided
Max. 298.9 counts.
435.3262
427.1713
431.2270
436.3268
437.1823
421.1744
432.2323
445.2831
Intensity, counts
m/z, amu
Me
9
O
OH
OTBS

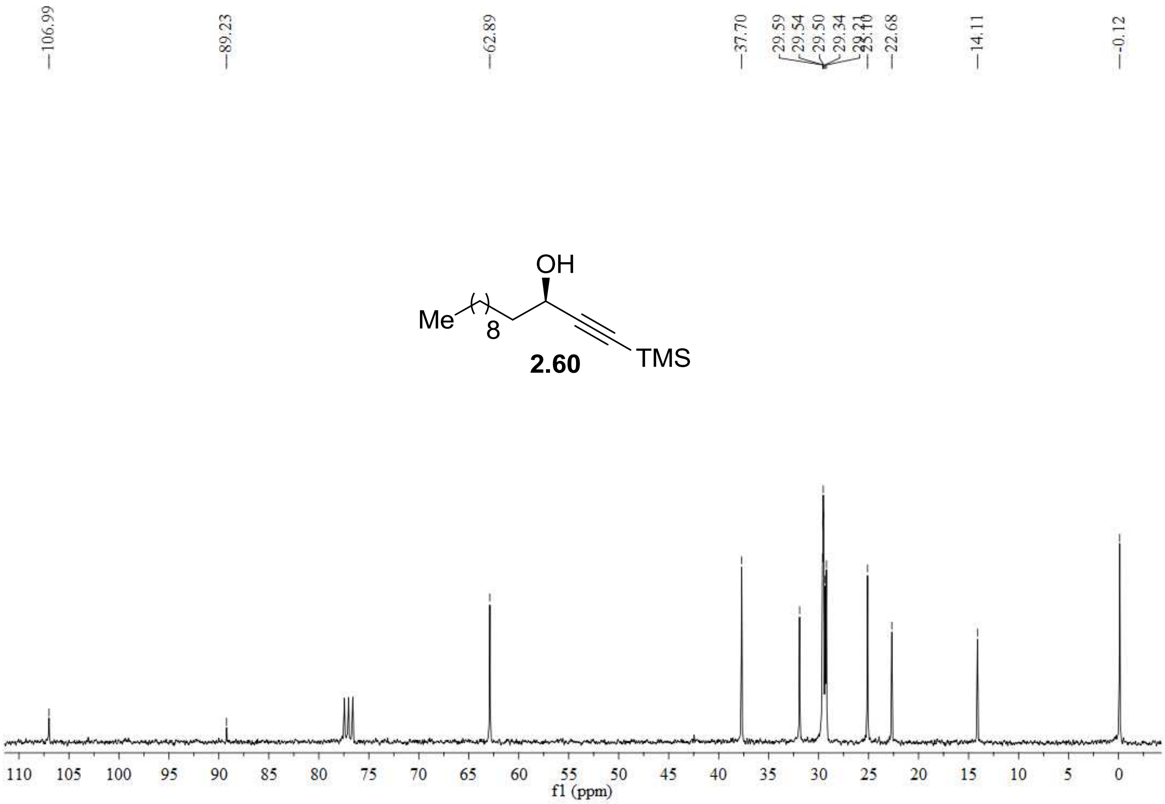
2.38


O
Me
8
TMS
f1 (ppm)

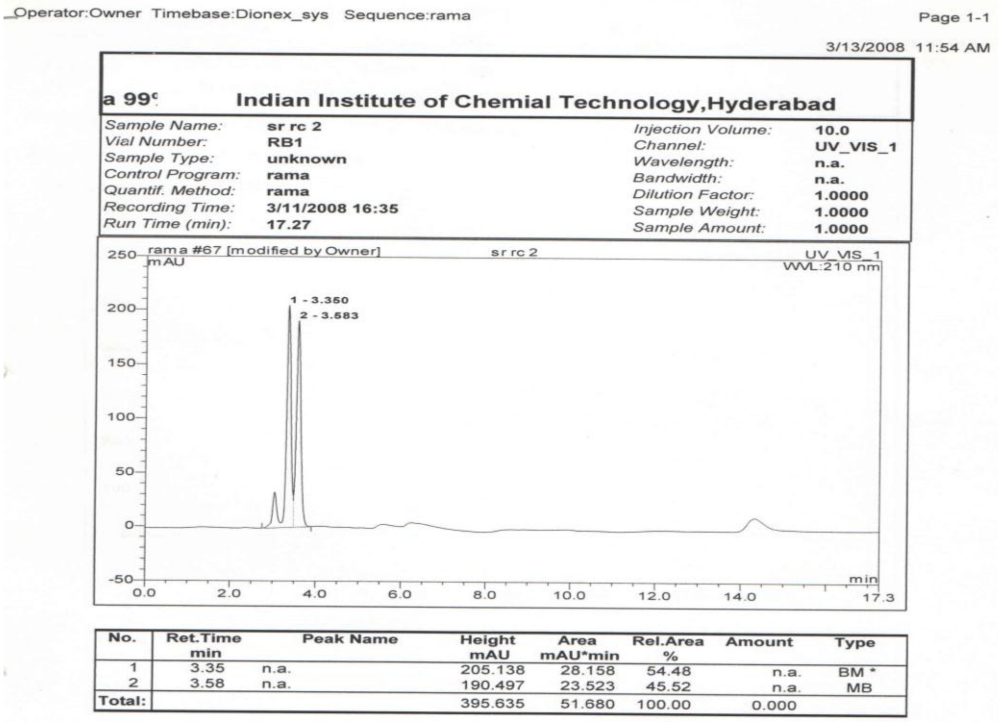
2.58


188.17
102.20
97.61
45.43
32.01
29.66
29.54
29.43
29.06
24.07
22.79
14.22
-0.64
O
Me
8
2.58
TMS
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


OH
Me
8
2.60
TMS
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 -0.5
f1 (ppm)



2.60



Operator:Owner Timebase:Dionex_sys Sequence:rama

Page 1-1

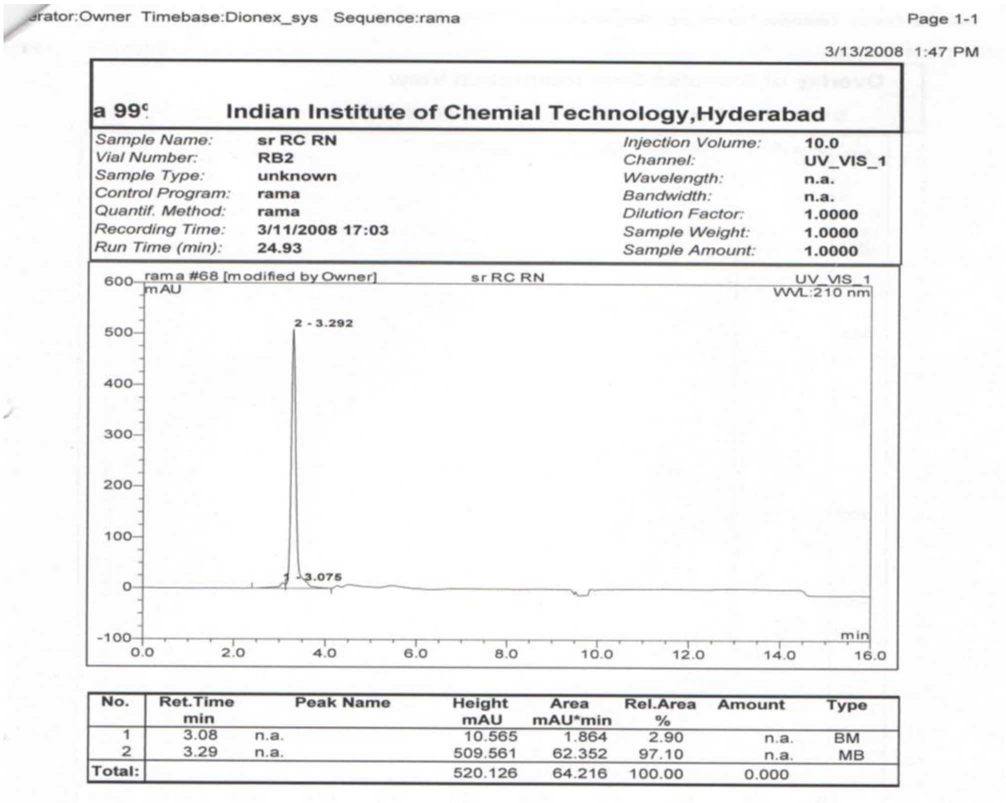
3/13/2008 11:54 AM

a 99

Indian Institute of Chemial Technology,Hyderabad

Sample Name:	**sr rc 2**	*Injection Volume:*	**10.0**
Vial Number:	**RB1**	*Channel:*	**UV_VIS_1**
Sample Type:	**unknown**	*Wavelength:*	**n.a.**
Control Program:	**rama**	*Bandwidth:*	**n.a.**
Quantif. Method:	**rama**	*Dilution Factor:*	**1.0000**
Recording Time:	**3/11/2008 16:35**	*Sample Weight:*	**1.0000**
Run Time (min):	**17.27**	*Sample Amount:*	**1.0000**

No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	3.35	n.a.	205.138	28.158	54.48	n.a.	BM *
2	3.58	n.a.	190.497	23.523	45.52	n.a.	MB
Total:			395.635	51.680	100.00	0.000	



erator:Owner Timebase:Dionex_sys Sequence:rama Page 1-1

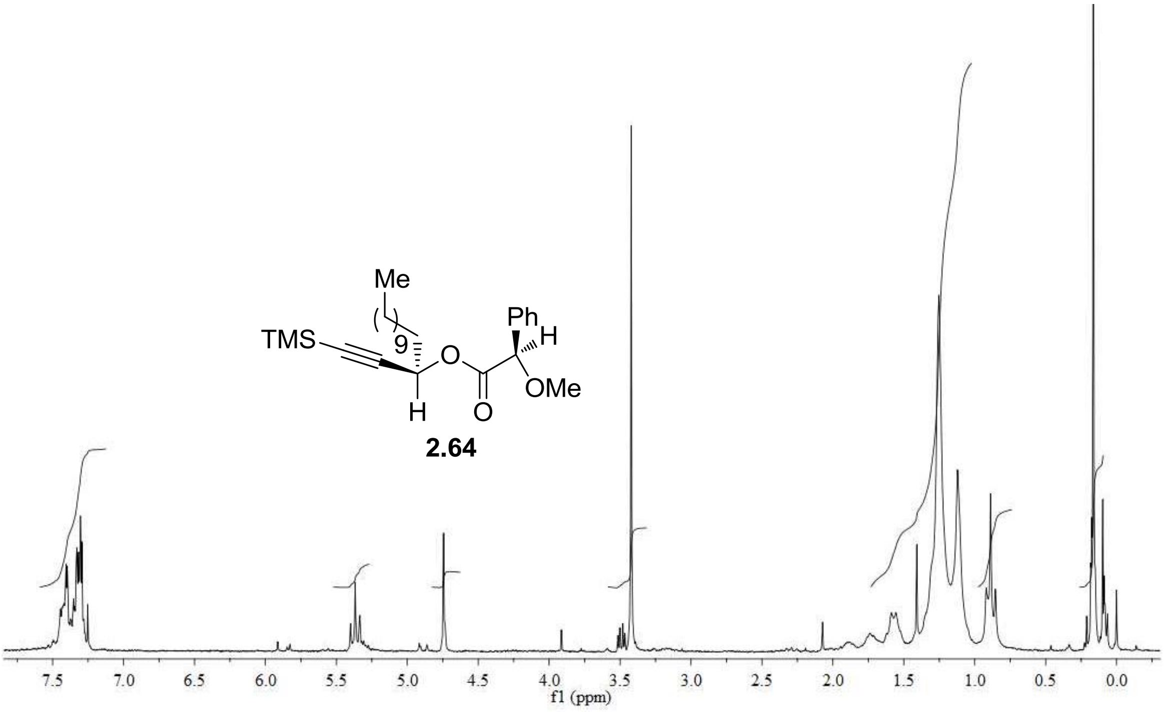
3/13/2008 1:47 PM

a 99 **Indian Institute of Chemial Technology,Hyderabad**

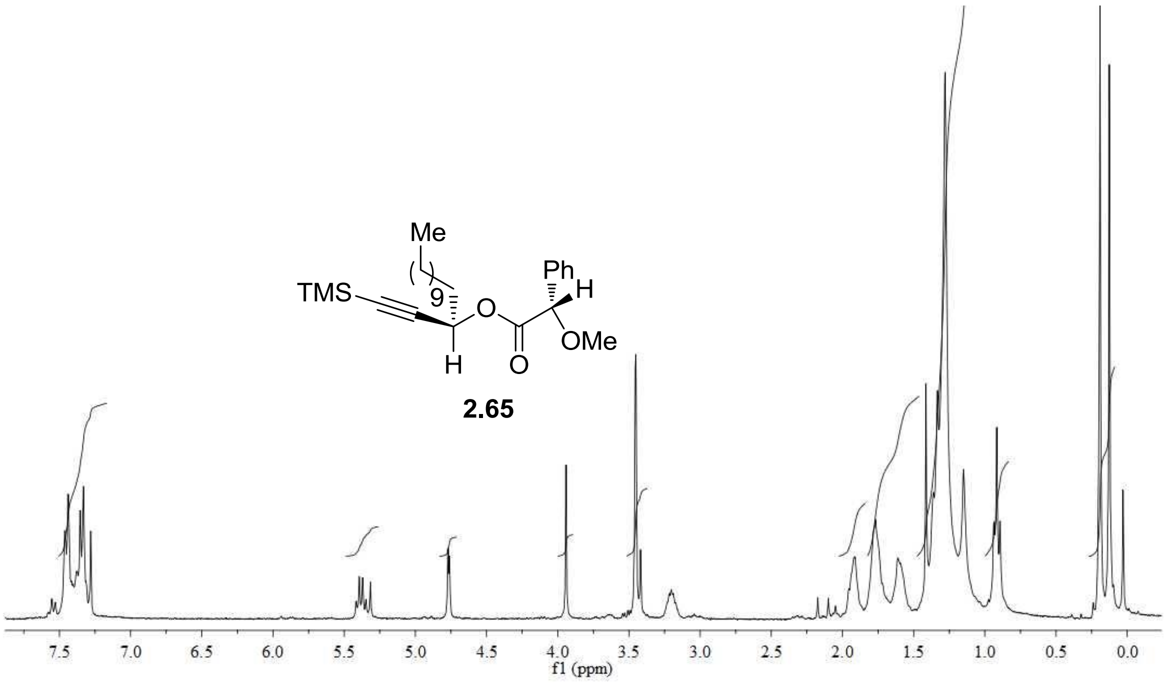
Sample Name:	sr RC RN	Injection Volume:	10.0
Vial Number:	RB2	Channel:	UV_VIS_1
Sample Type:	unknown	Wavelength:	n.a.
Control Program:	rama	Bandwidth:	n.a.
Quantif. Method:	rama	Dilution Factor:	1.0000
Recording Time:	3/11/2008 17:03	Sample Weight:	1.0000
Run Time (min):	24.93	Sample Amount:	1.0000

No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	3.08	n.a.	10.565	1.864	2.90	n.a.	BM
2	3.29	n.a.	509.561	62.352	97.10	n.a.	MB
Total:			520.126	64.216	100.00	0.000	

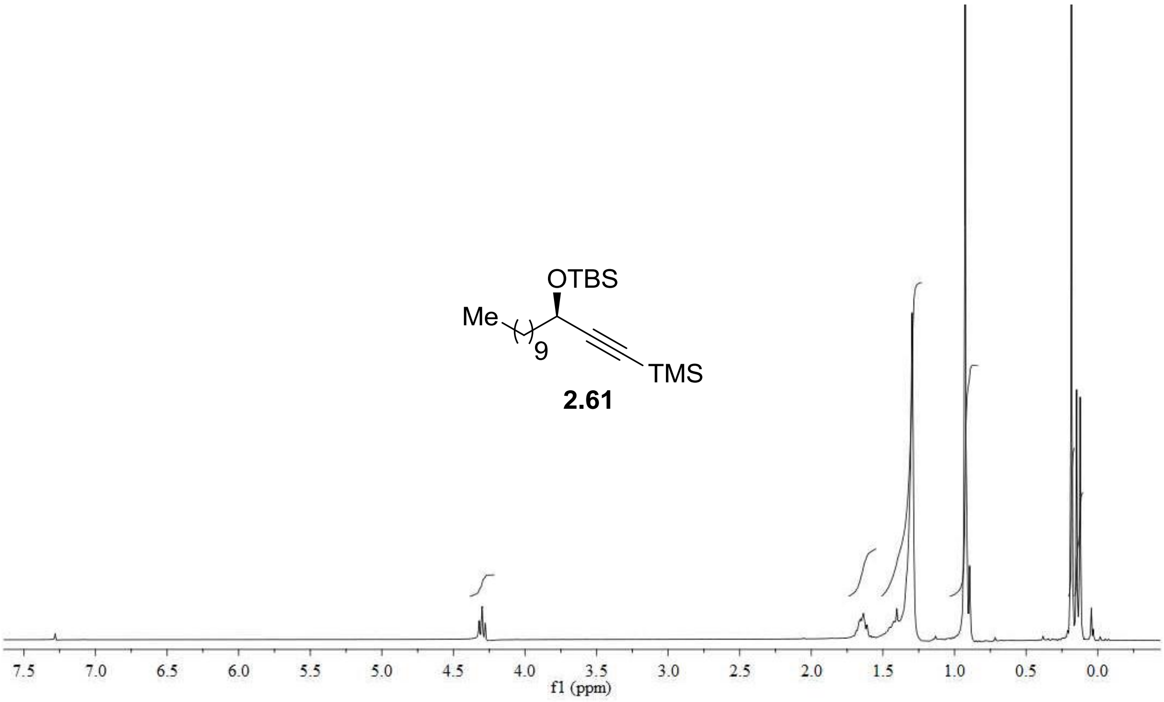
HPLC conditions: Eurocol Column 01 VEE 110, 250X4.6mm, 5µ. Mobile phase 1% IPA+99% Hexanes. Flow rate 1 mL/min. PDA Detector



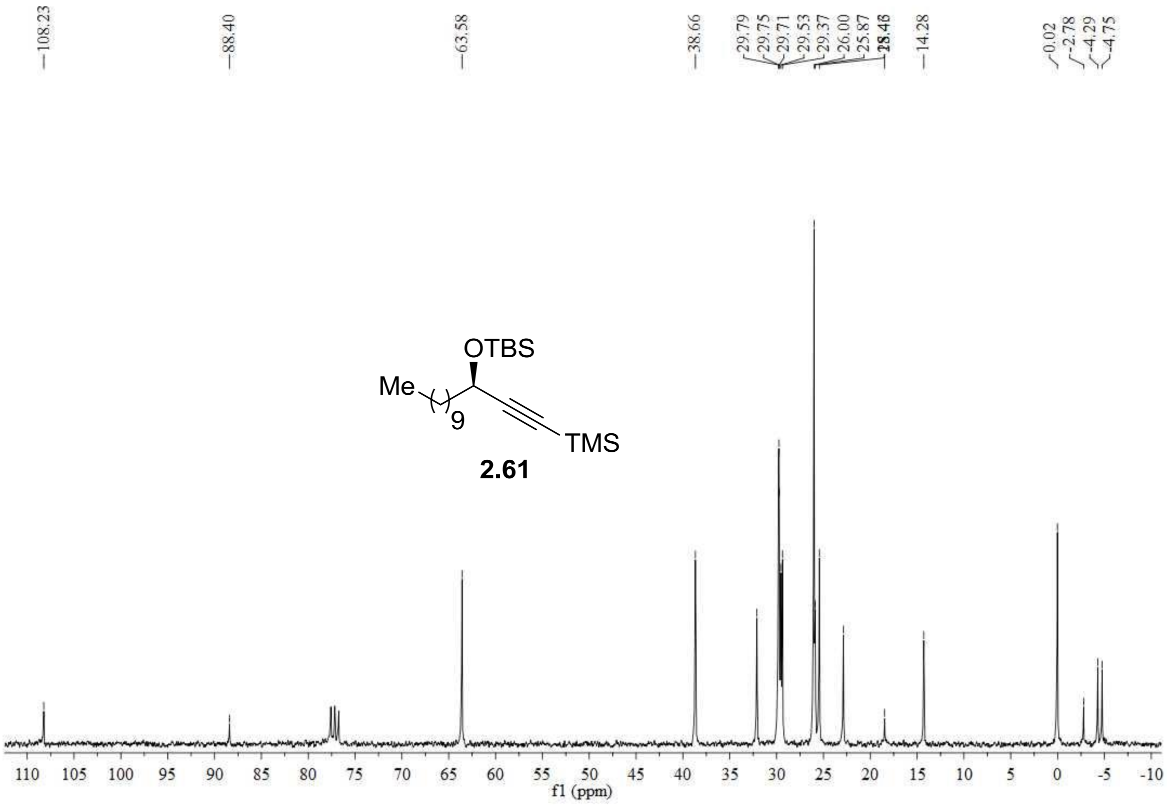
2.64


Me
9
TMS
O
Ph
H
OMe
H
O
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
f1 (ppm)

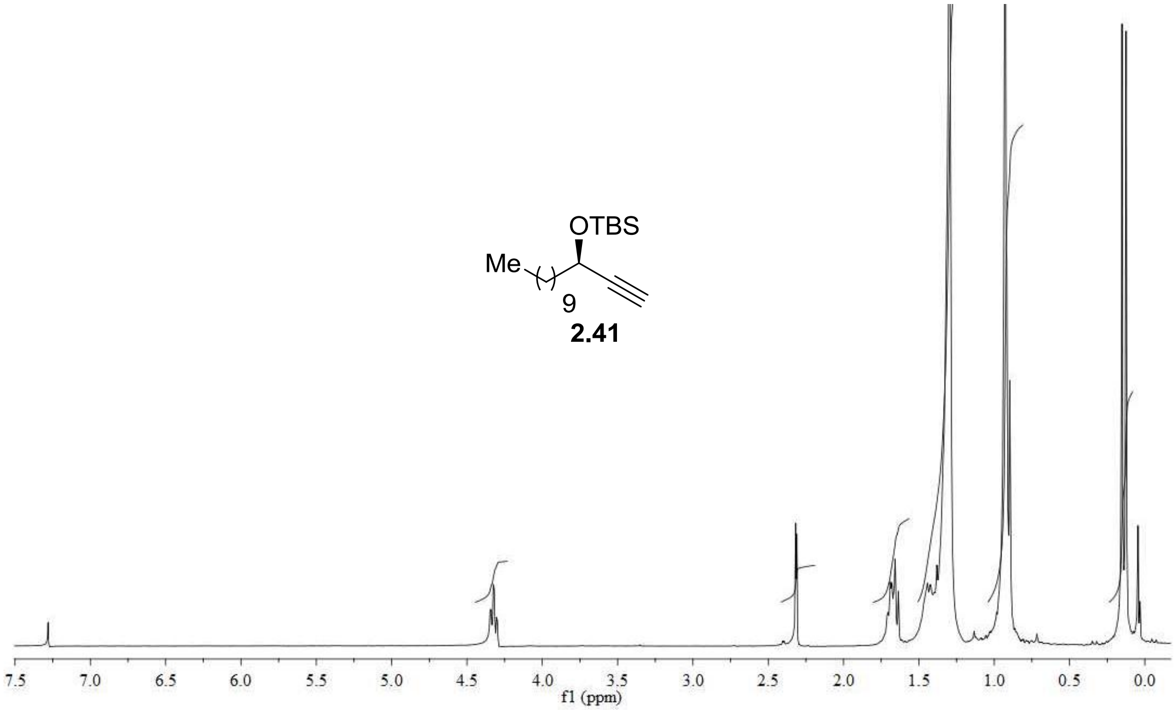
2.65


OTBS
Me
9
TMS
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
f1 (ppm)

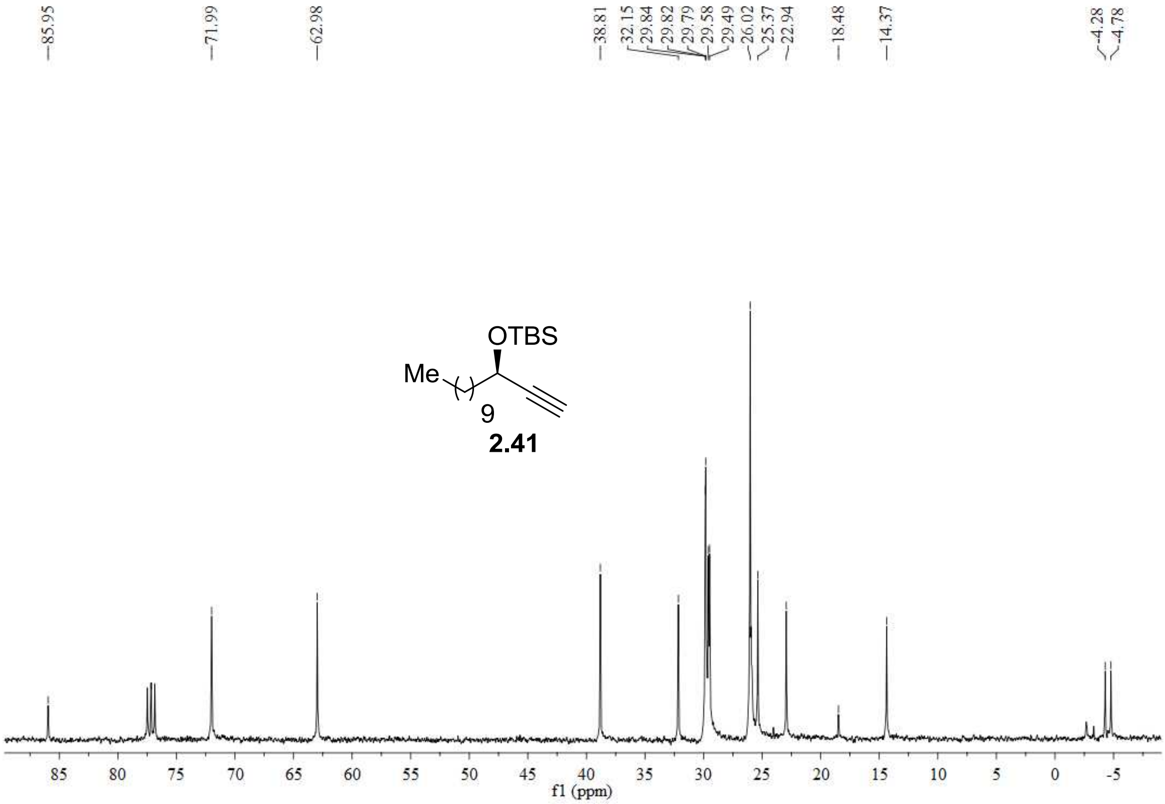
2.61


108.23
88.40
63.58
38.66
29.79
29.75
29.71
29.53
29.37
26.00
25.87
18.46
14.28
0.02
-2.78
-4.29
-4.75
OTBS
Me
9
TMS
110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 -5 -10
f1 (ppm)

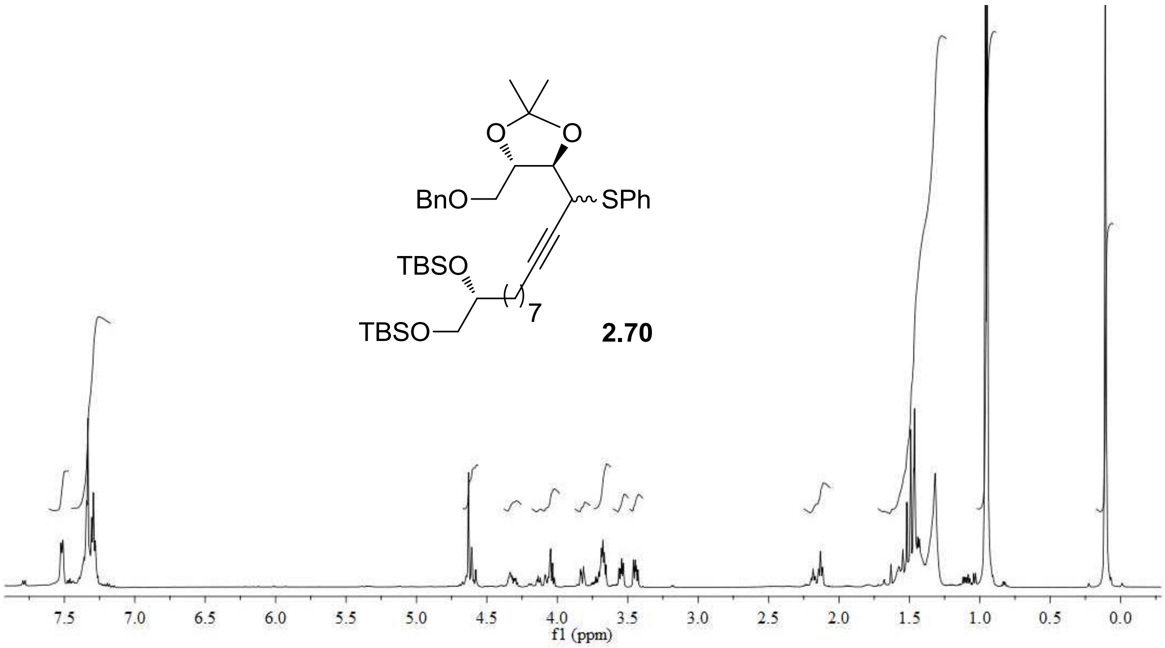
2.61


OTBS
Me
9
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
f1 (ppm)

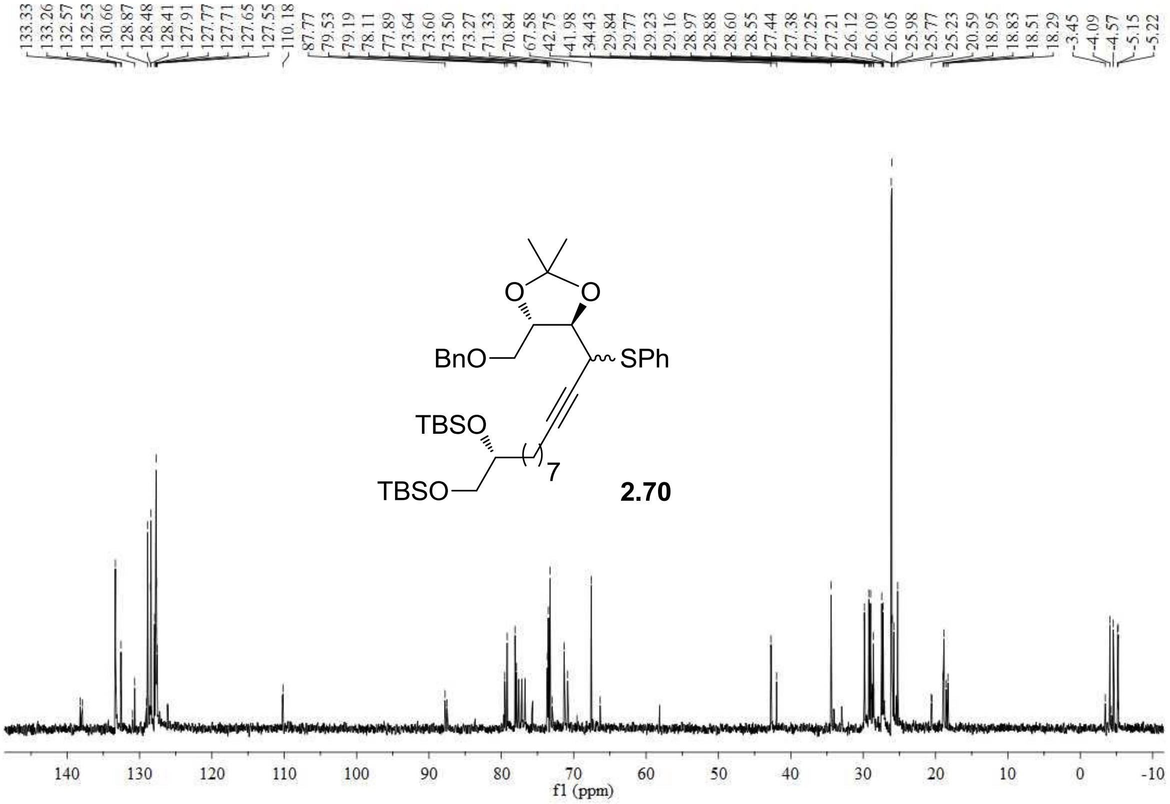
2.41


85.95
71.99
62.98
38.81
32.15
29.84
29.82
29.79
29.58
29.49
26.02
25.37
22.94
18.48
14.37
-4.28
-4.78
OTBS
Me
9
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
f1 (ppm)

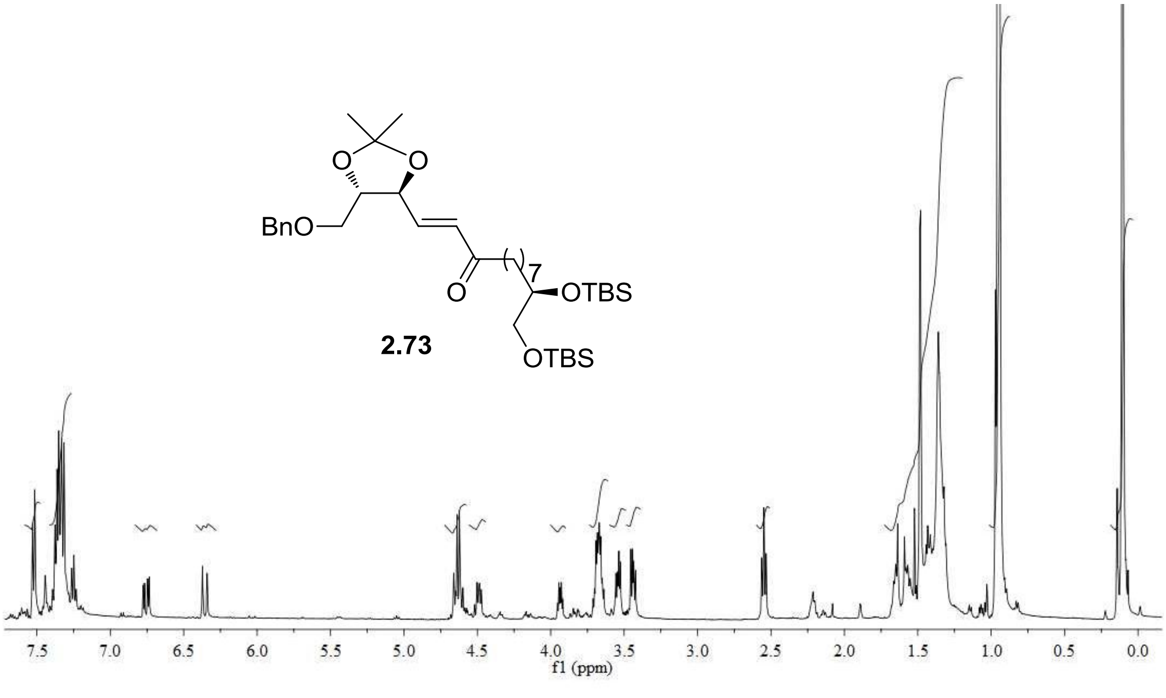
2.41


O
O
BnO
SPh
TBSO
TBSO
7
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

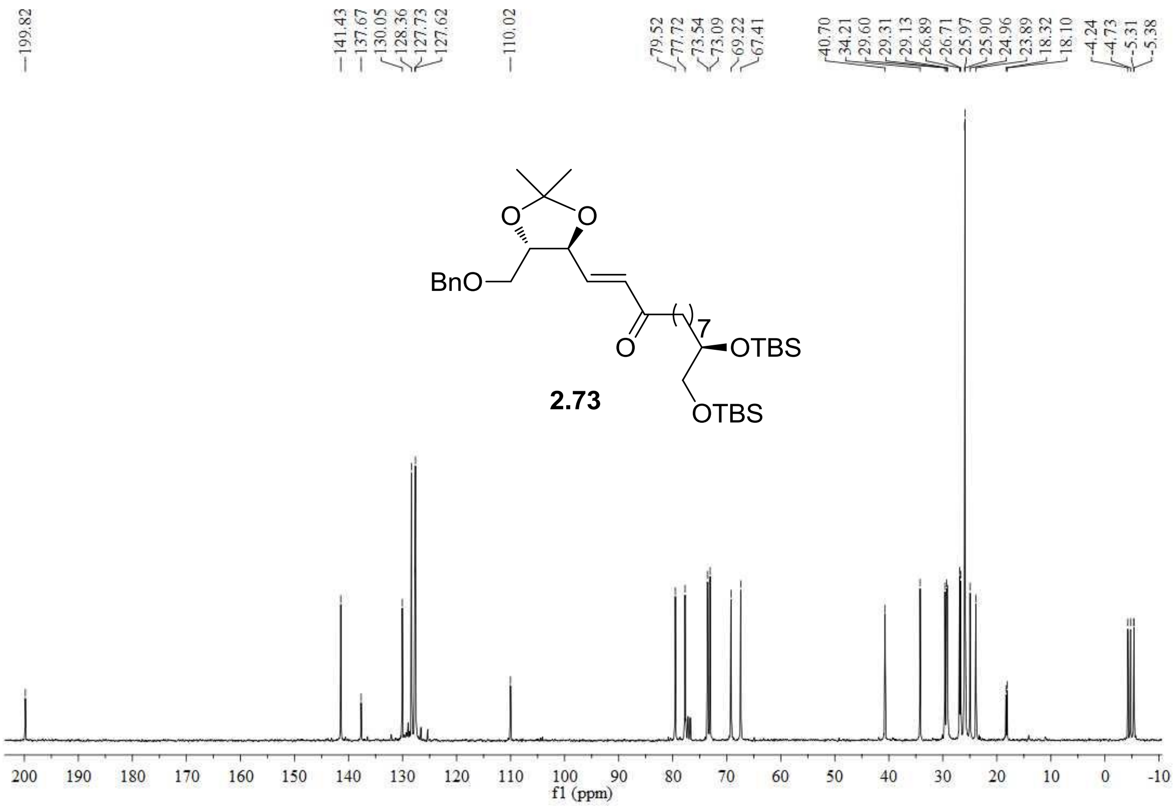
2.70


133.33
133.26
132.57
132.53
130.66
128.87
128.48
128.41
127.91
127.77
127.71
127.65
127.55
110.18
87.77
79.53
79.19
78.11
77.89
73.64
73.60
73.50
73.27
71.33
70.84
67.58
42.75
41.98
34.43
29.84
29.77
29.23
29.16
28.97
28.88
28.60
28.55
27.44
27.38
27.25
27.21
26.12
26.09
26.05
25.98
25.77
25.23
20.59
18.95
18.83
18.51
18.29
-3.45
-4.09
-4.57
-5.15
-5.22
BnO
O
O
SPh
TBSO
TBSO
7
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

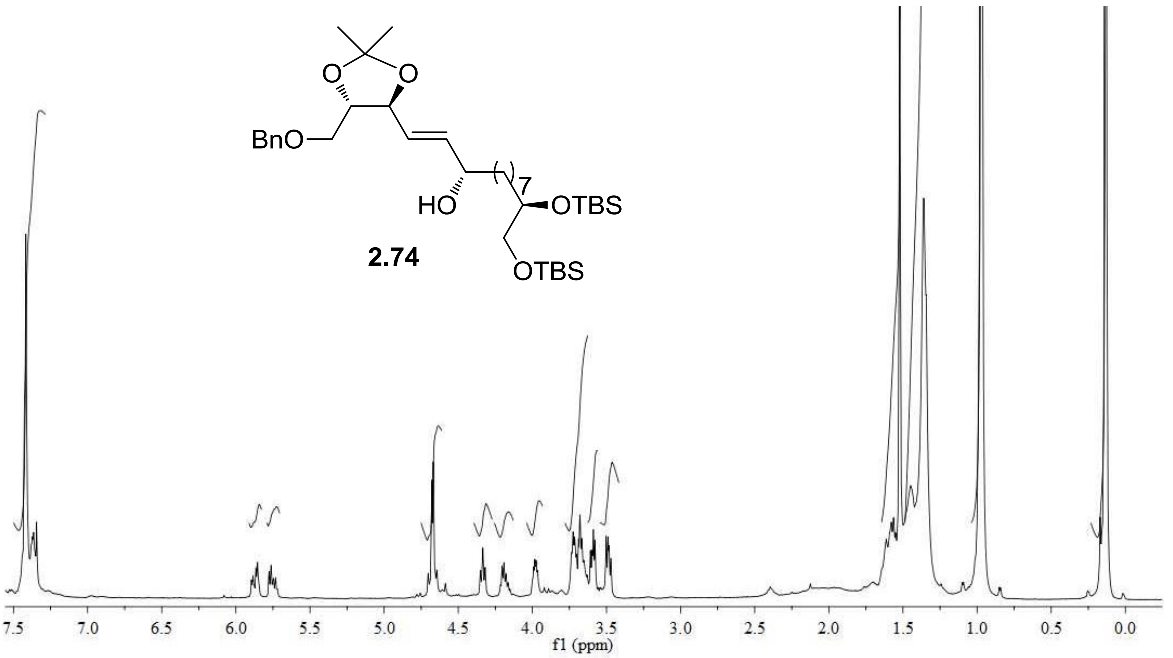
2.70


BnO
O
O
O
7
OTBS
OTBS
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
f1 (ppm)

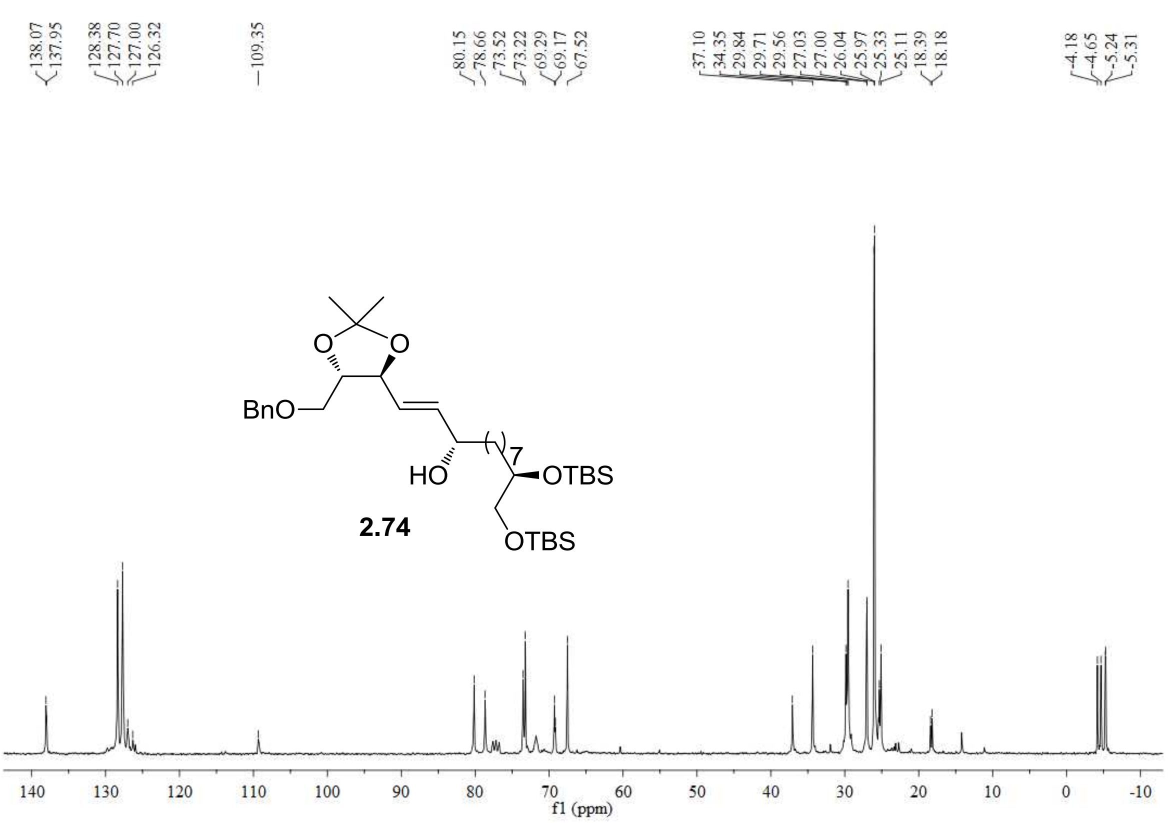
2.73

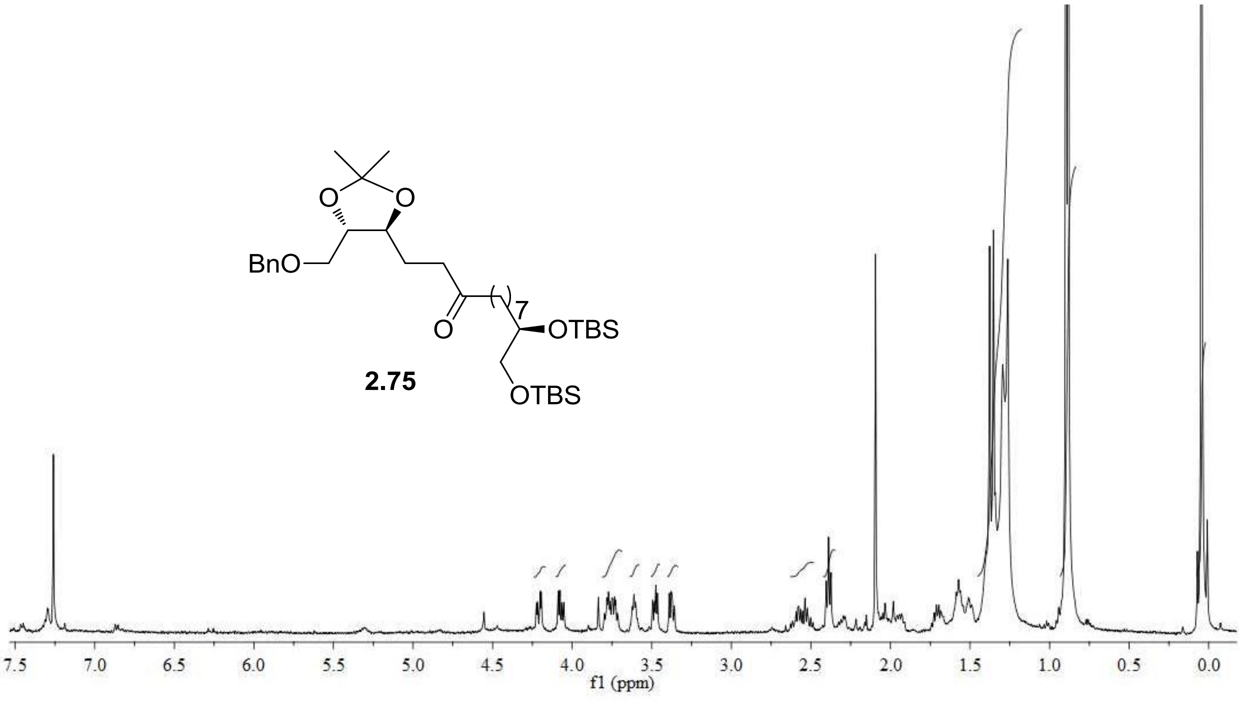

199.82
141.43
137.67
130.05
128.36
127.73
127.62
110.02
79.52
77.72
73.54
73.09
69.22
67.41
40.70
34.21
29.60
29.31
29.13
26.89
26.71
25.97
25.90
24.96
23.89
18.32
18.10
-4.24
-4.73
-5.31
-5.38
BnO
O
O
O
7
OTBS
OTBS
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

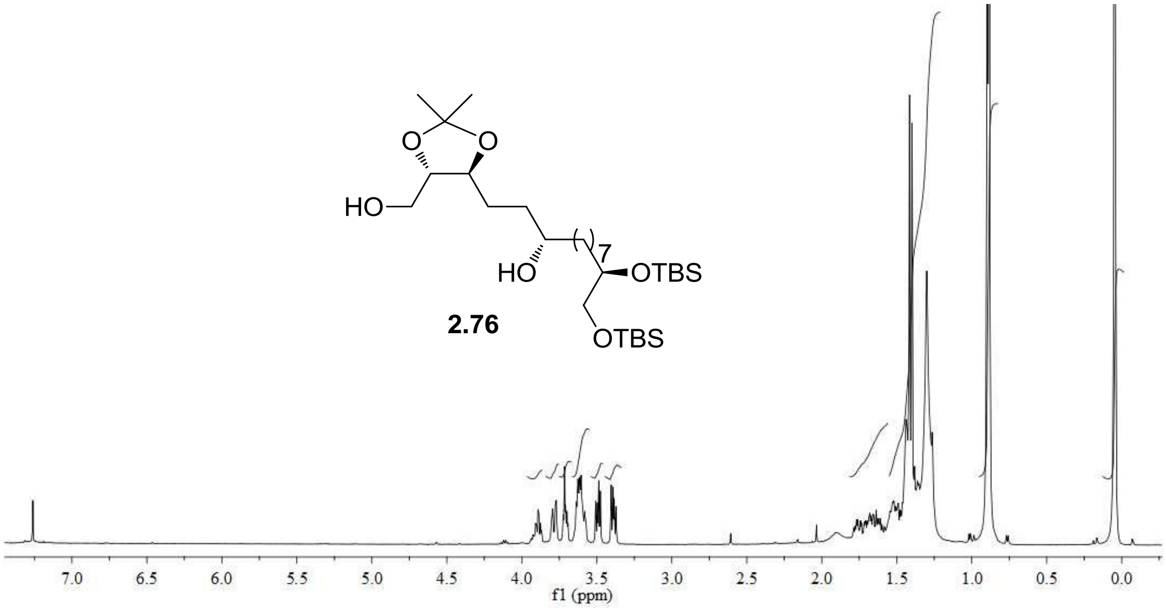
2.73

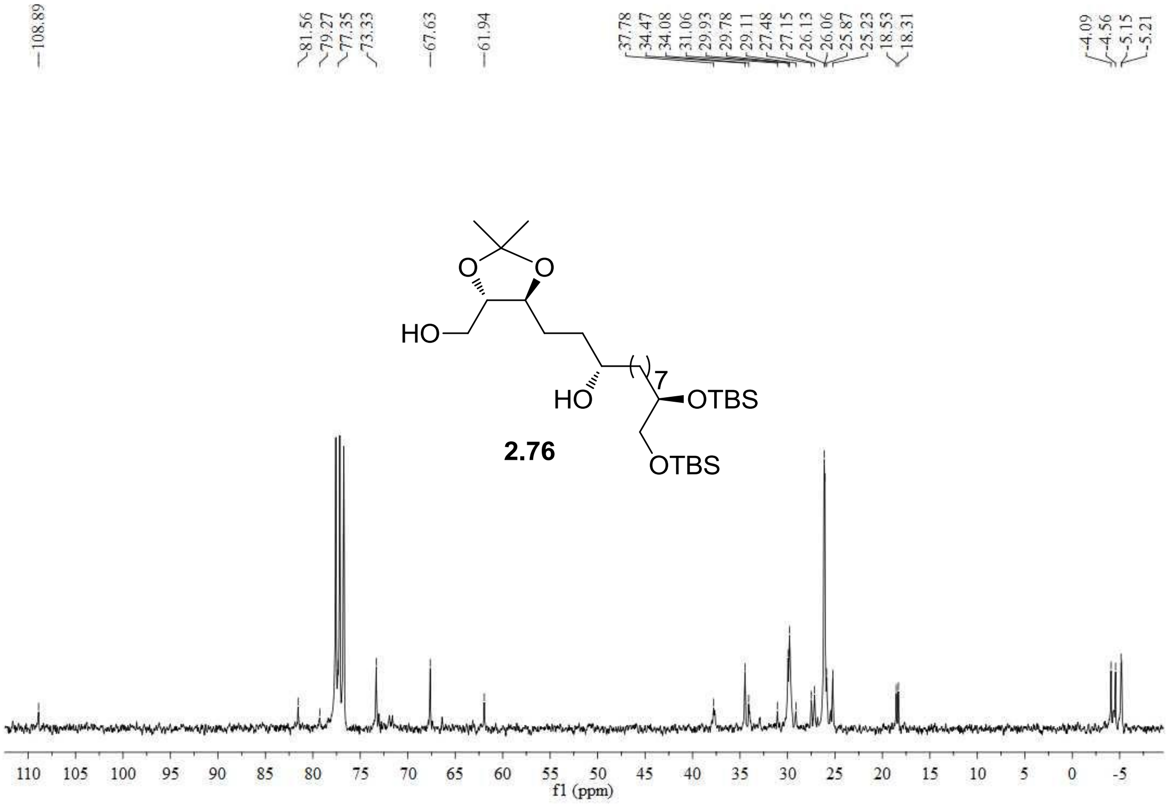

BnO
O
O
HO
7
OTBS
OTBS
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

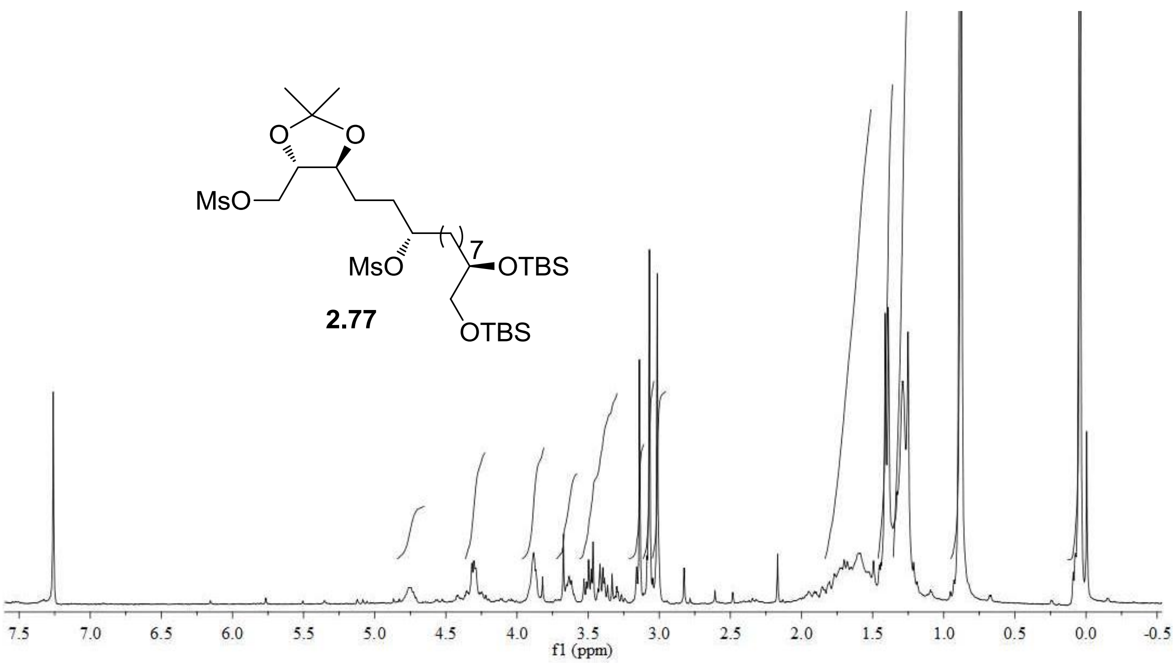
2.74

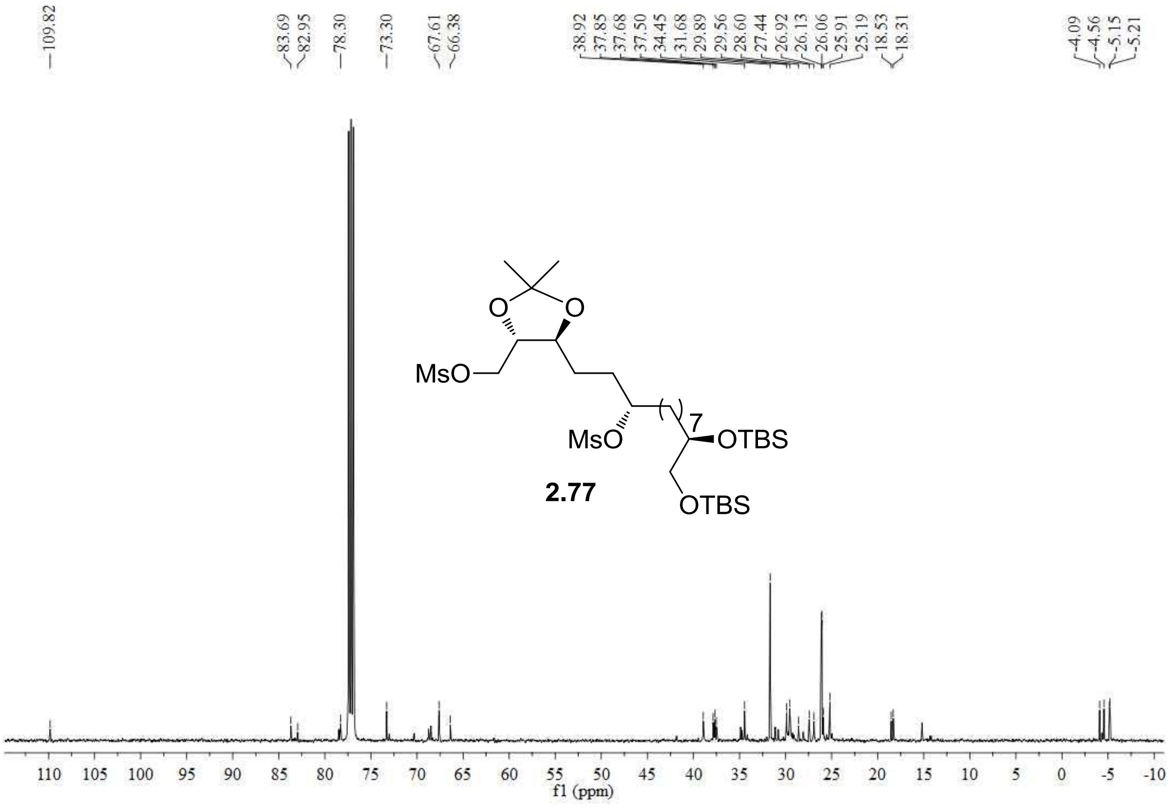

2.74
138.07
137.95
128.38
127.70
127.00
126.32
109.35
80.15
78.66
73.52
73.22
69.29
69.17
67.52
37.10
34.35
29.84
29.71
29.56
27.03
27.00
26.04
25.97
25.33
25.11
18.39
18.18
-4.18
-4.65
-5.24
-5.31
BnO
O
O
HO
7
OTBS
OTBS
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

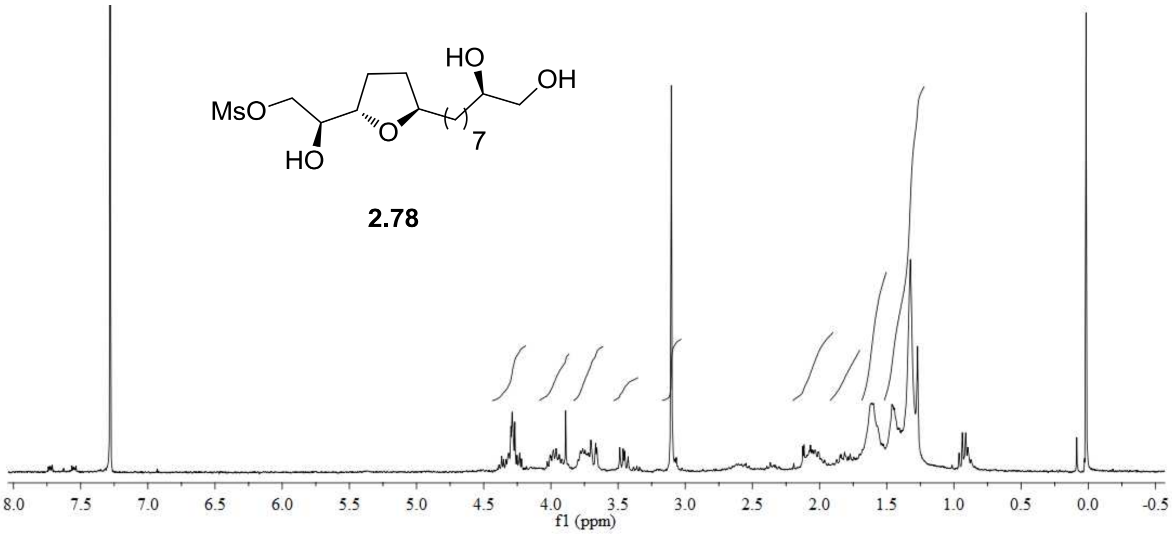

2.75
BnO
O
O
O
7
OTBS
OTBS
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


HO
O
O
HO
7
OTBS
OTBS
2.76
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
f1 (ppm)

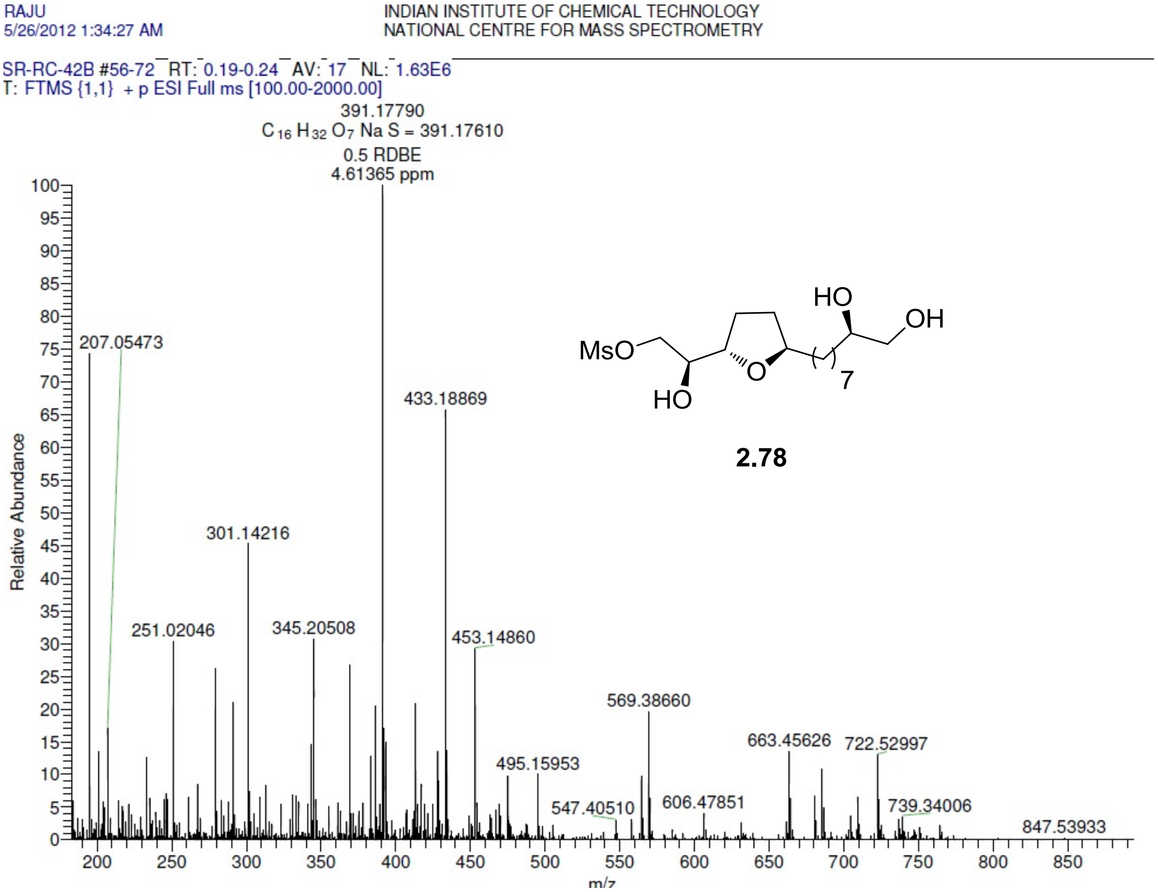

108.89
81.56
79.27
77.35
73.33
67.63
61.94
37.78
34.47
34.08
31.06
29.93
29.78
29.11
27.48
27.15
26.13
26.06
25.87
25.23
18.53
18.31
-4.09
-4.56
-5.15
-5.21
HO
O
O
HO
7
OTBS
OTBS
2.76
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
f1 (ppm)

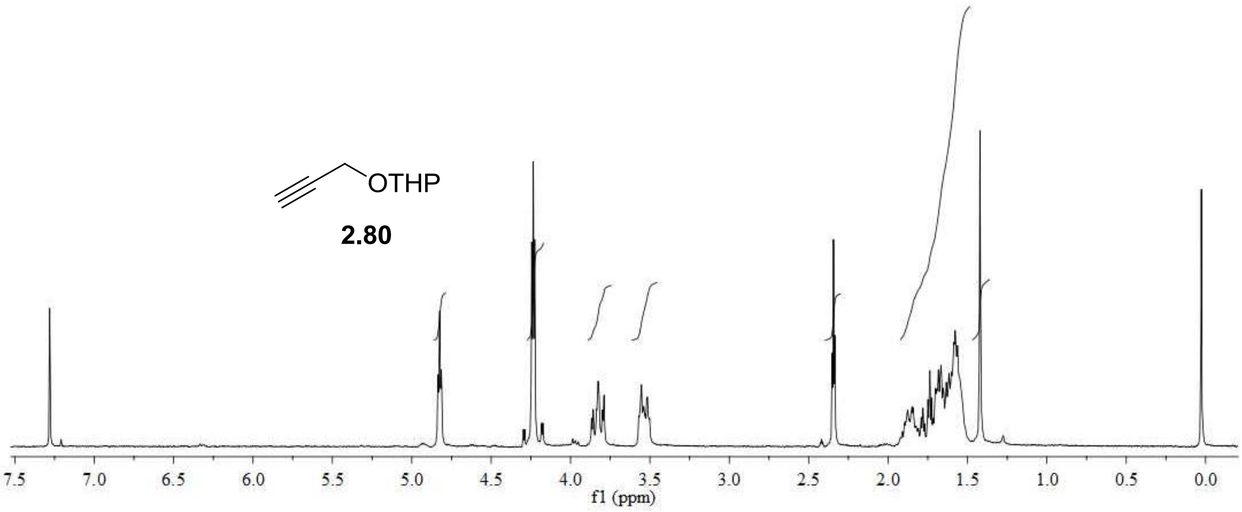

MsO
O
O
MsO
7
OTBS
OTBS
2.77
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

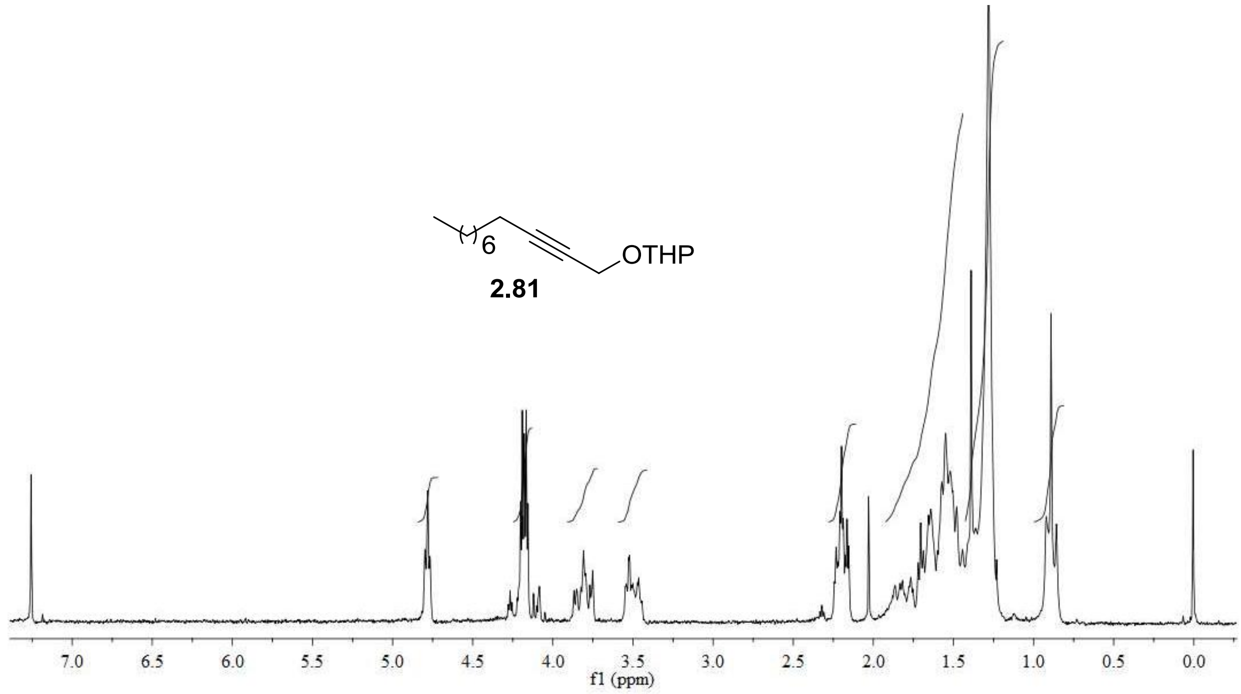

109.82
83.69
82.95
78.30
73.30
67.61
66.38
38.92
37.85
37.68
37.50
34.45
31.68
29.89
29.56
28.60
27.44
26.92
26.13
26.06
25.91
25.19
18.53
18.31
-4.09
-4.56
-5.15
-5.21
MsO
O
O
MsO
7
OTBS
OTBS
2.77
110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 -5 -10
f1 (ppm)

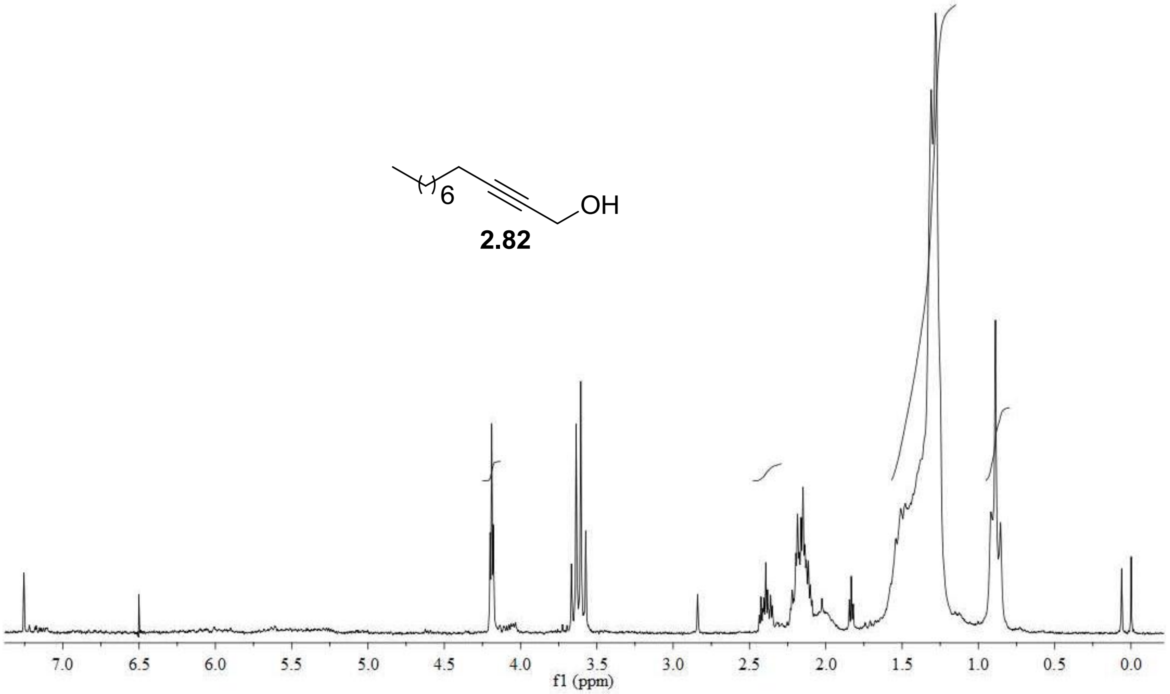

MsO
HO
HO
OH
O
7
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

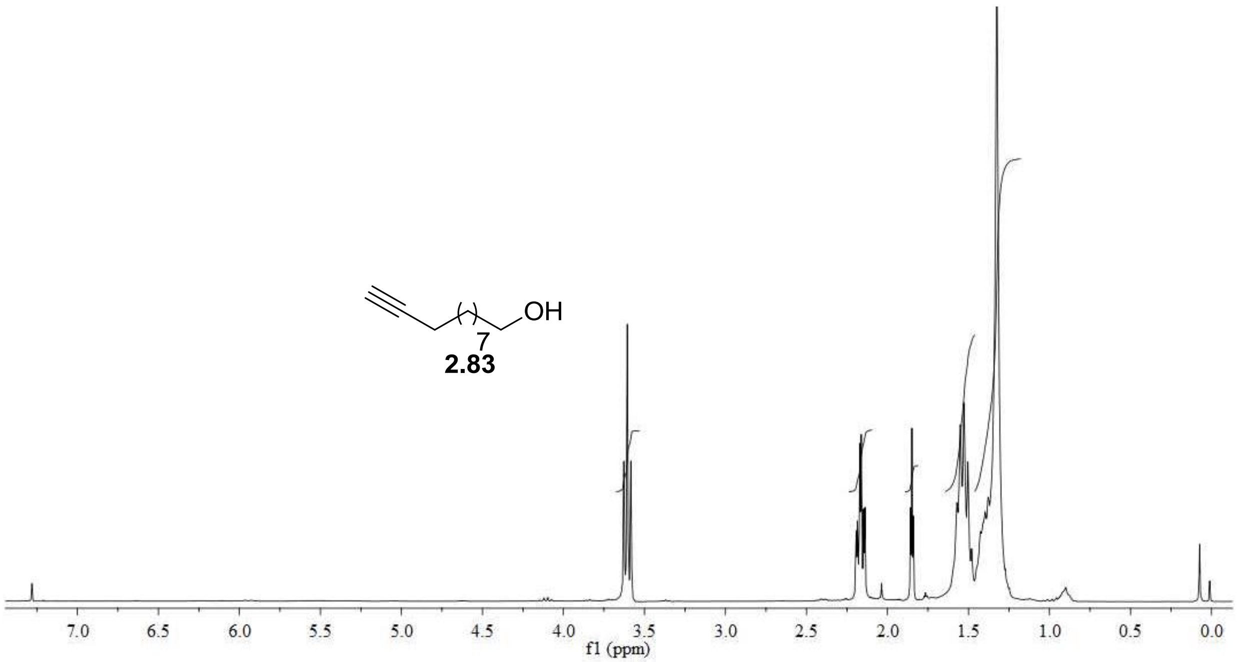
2.78

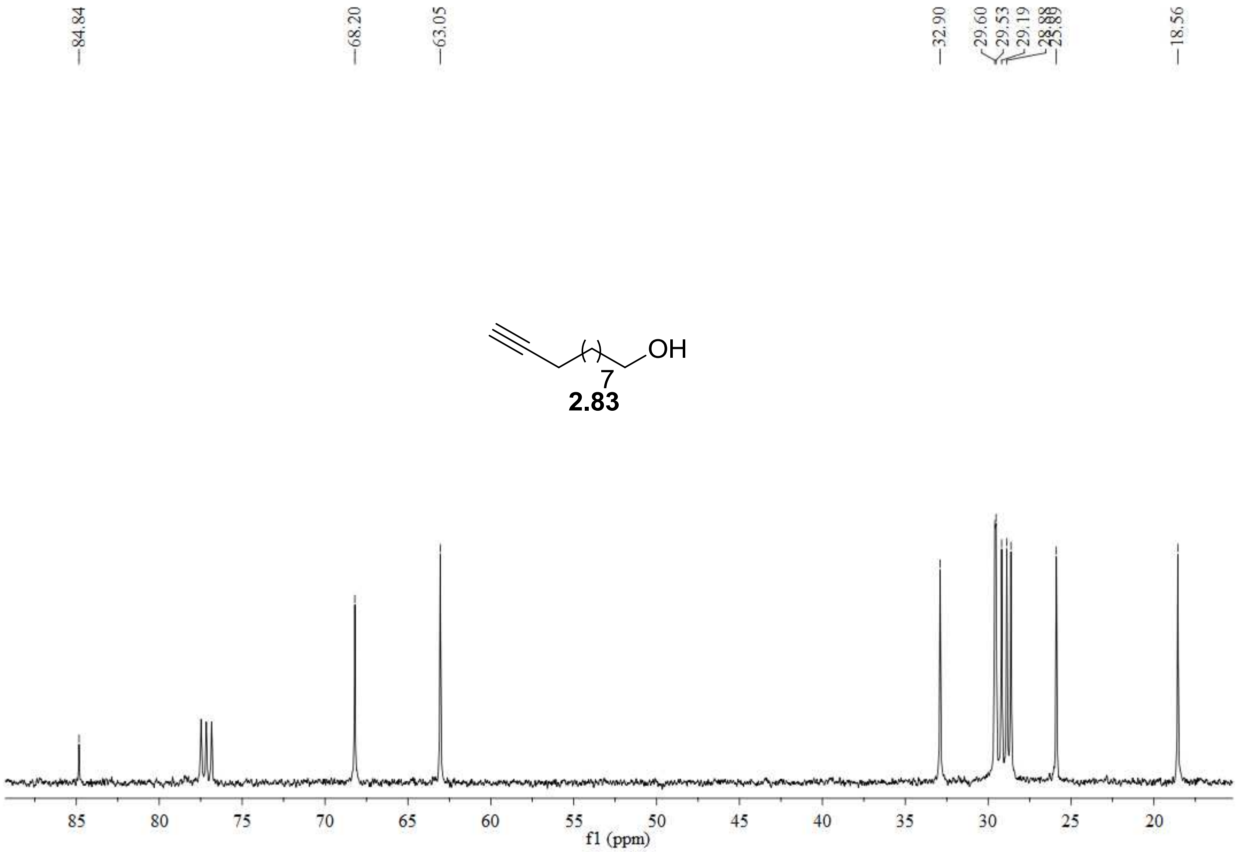

RAJU
5/26/2012 1:34:27 AM
INDIAN INSTITUTE OF CHEMICAL TECHNOLOGY
NATIONAL CENTRE FOR MASS SPECTROMETRY
SR-RC-42B #56-72 RT: 0.19-0.24 AV: 17 NL: 1.63E6
T: FTMS {1,1} + p ESI Full ms [100.00-2000.00]
391.17790
C 16 H 32 O 7 Na S = 391.17610
0.5 RDBE
4.61365 ppm
207.05473
433.18869
301.14216
251.02046
345.20508
453.14860
569.38660
663.45626
722.52997
495.15953
547.40510
606.47851
739.34006
847.53933
Relative Abundance
m/z
MsO
HO
HO
OH
O
7
2.78


2.80
OTHP
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
f1 (ppm)


2.81
6
OTHP
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
f1 (ppm)

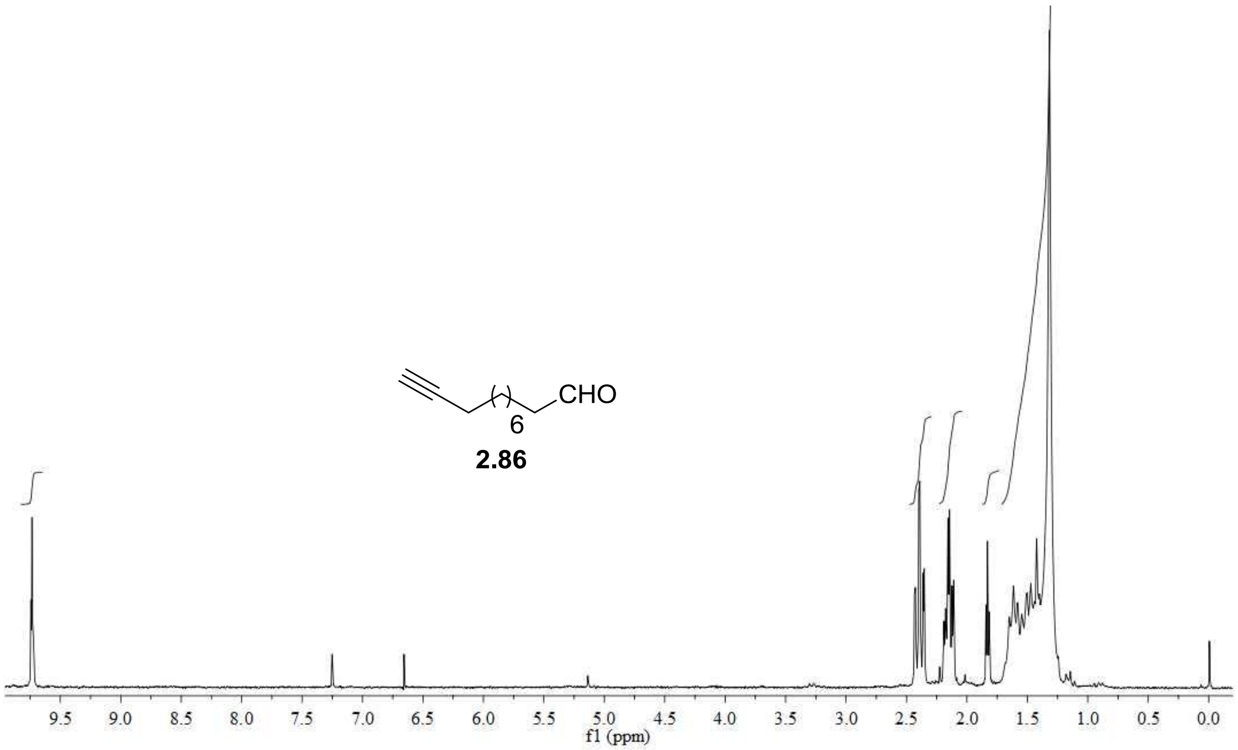

2.82
6
OH
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


2.83
OH
7
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
f1 (ppm)



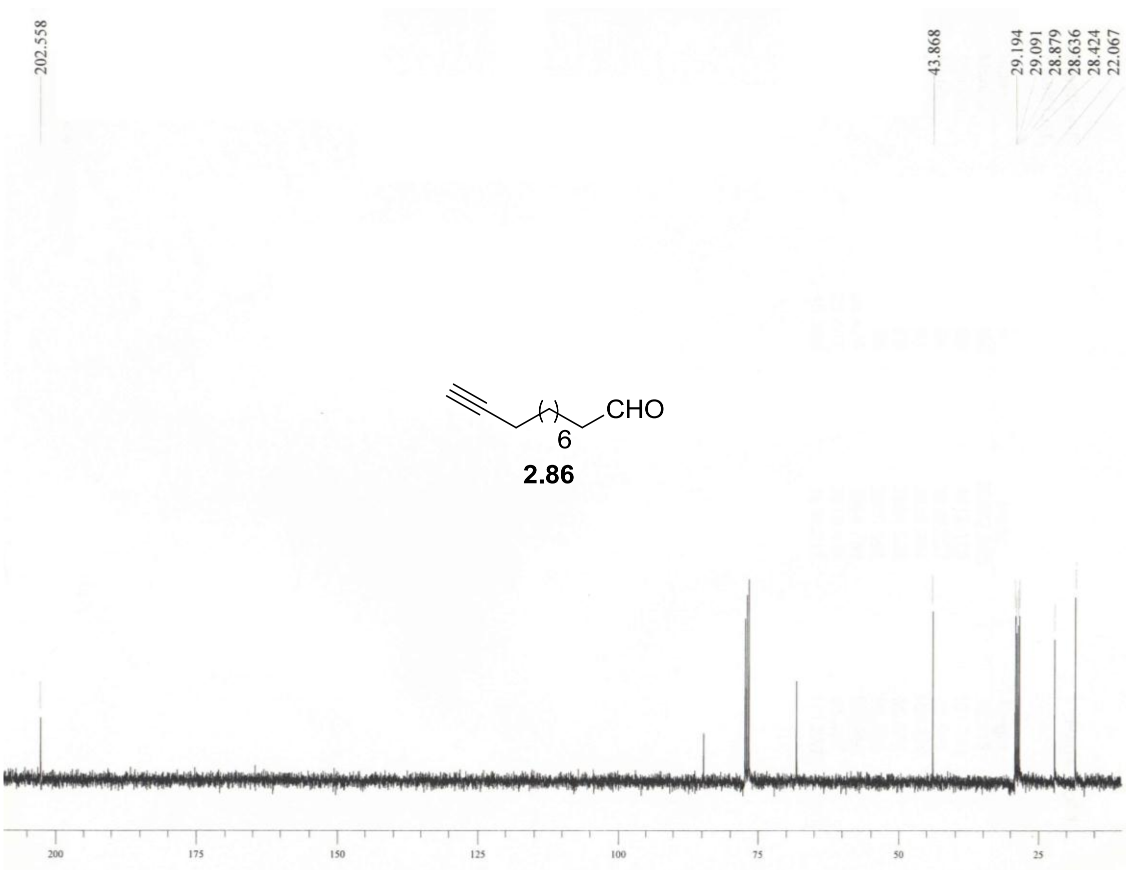
2.83

84.84
68.20
63.05
32.90
29.60
29.53
29.19
28.88
25.89
18.56
OH
7
85
80
75
70
65
60
55
50
45
40
35
30
25
20
f1 (ppm)

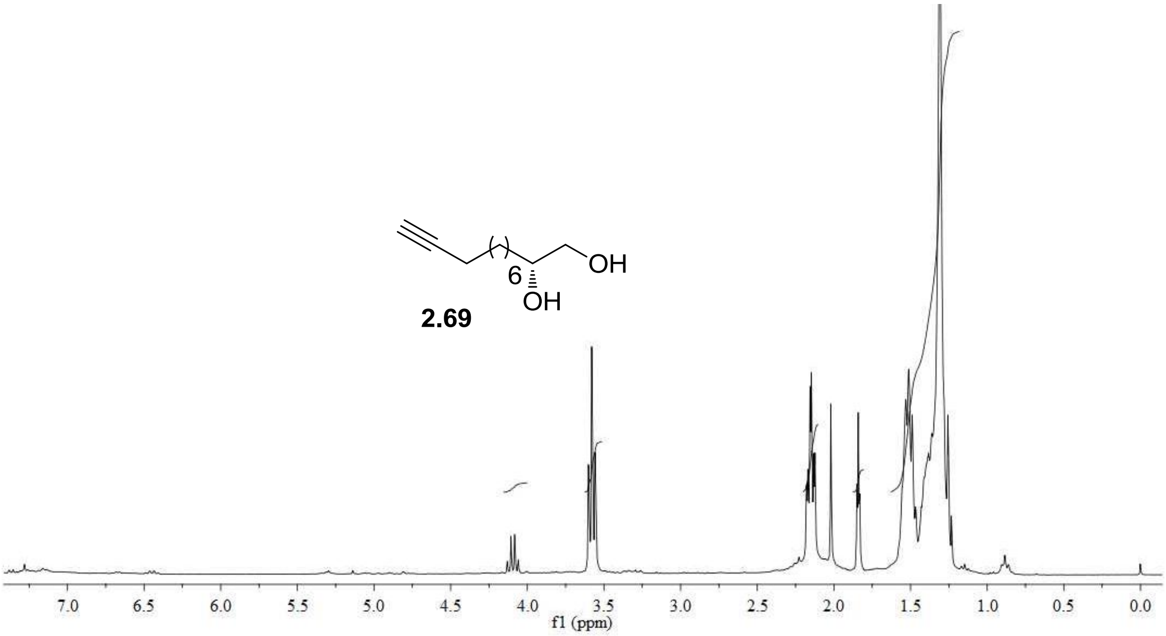


2.86

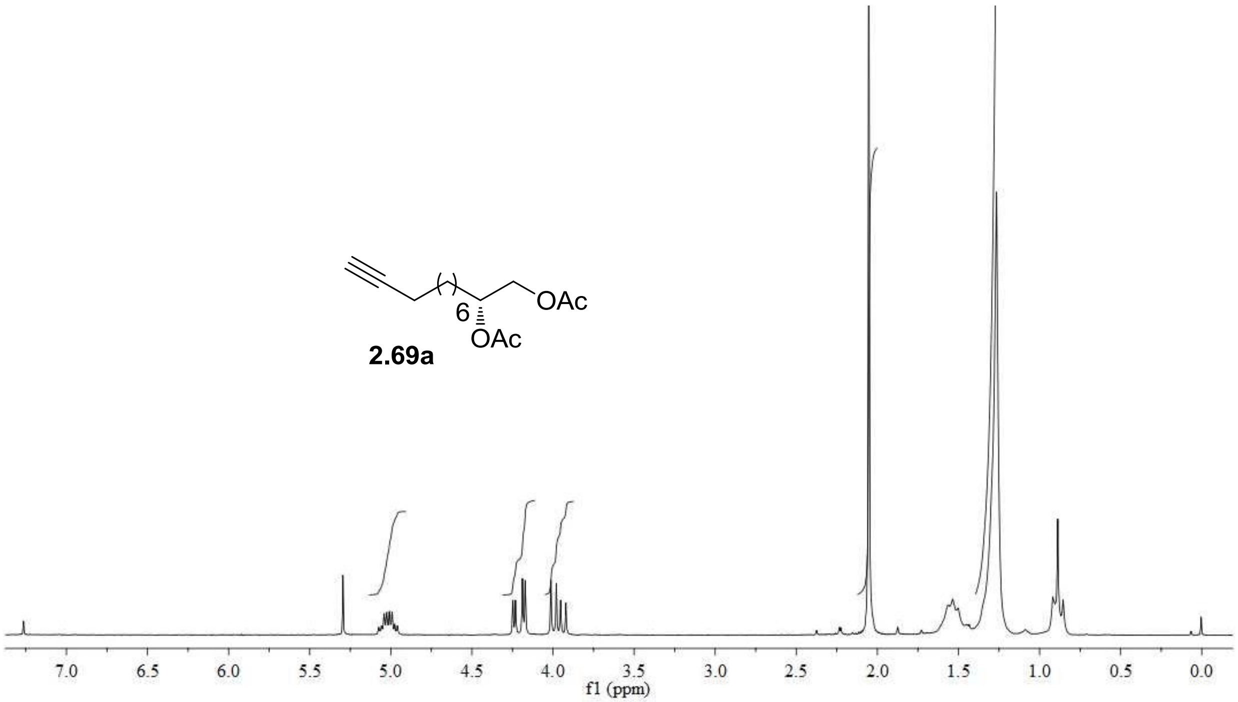
CHO
6
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

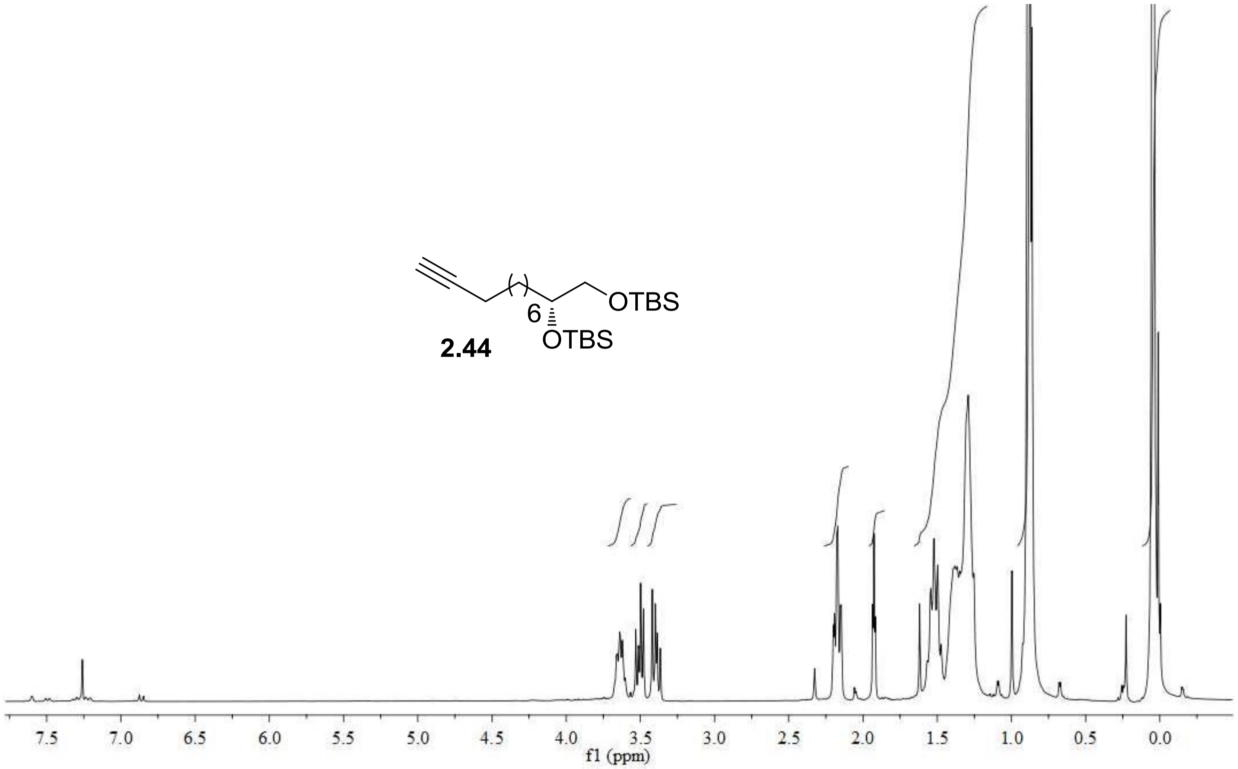

202.558
43.868
29.194
29.091
28.879
28.636
28.424
22.067
CHO
6
200
175
150
125
100
75
50
25

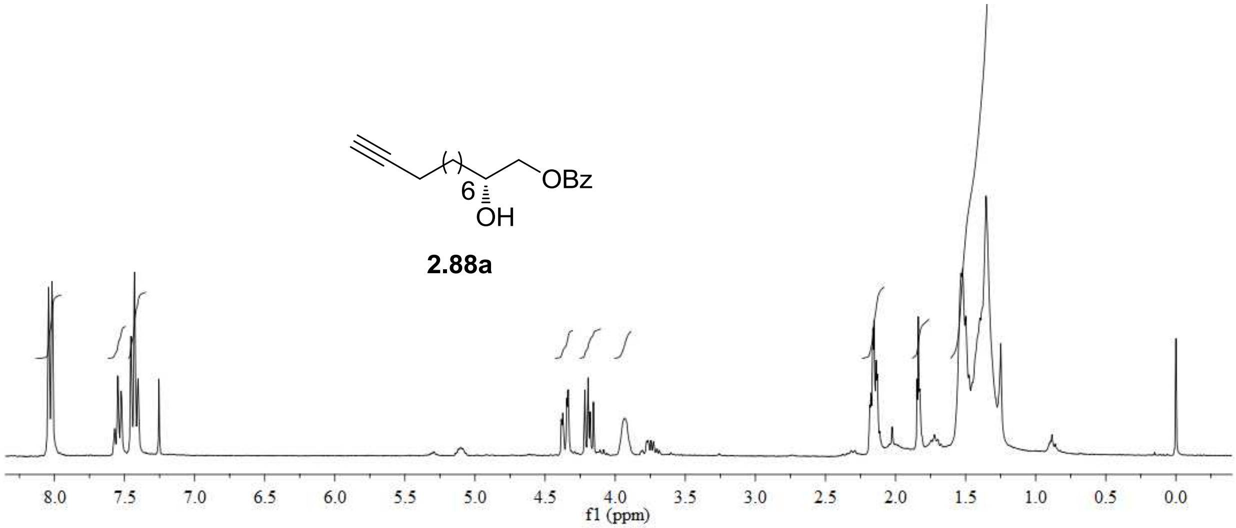
2.86


OH
6
OH
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
f1 (ppm)

2.69

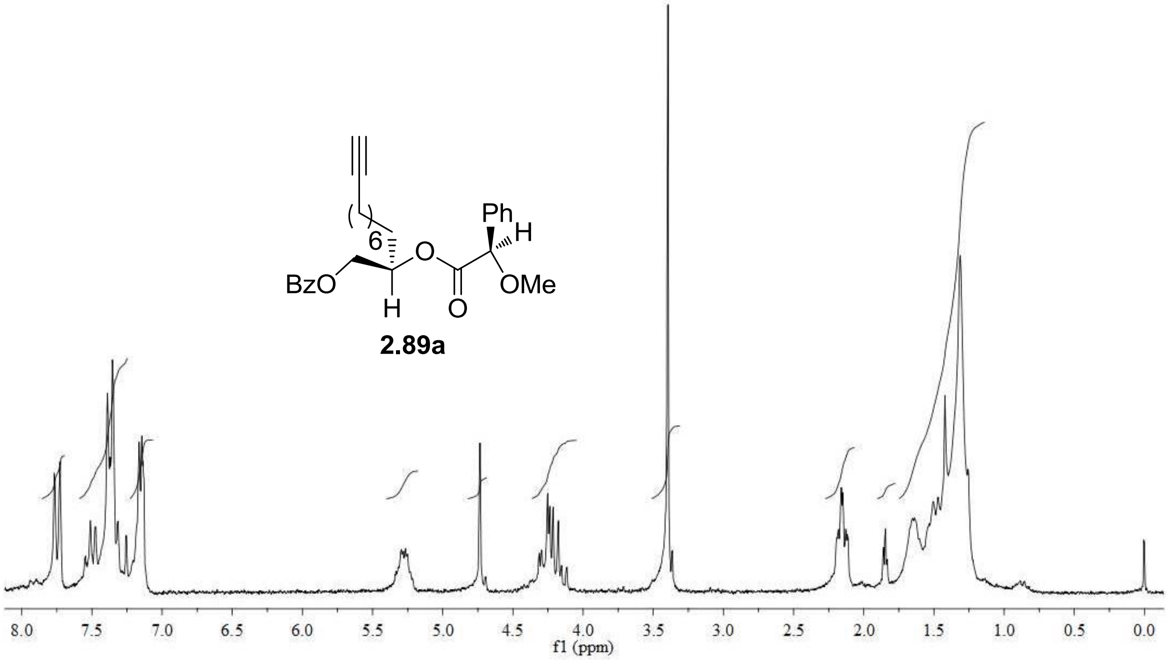

2.69a
6
OAc
OAc
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


2.44
6
OTBS
OTBS
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
f1 (ppm)



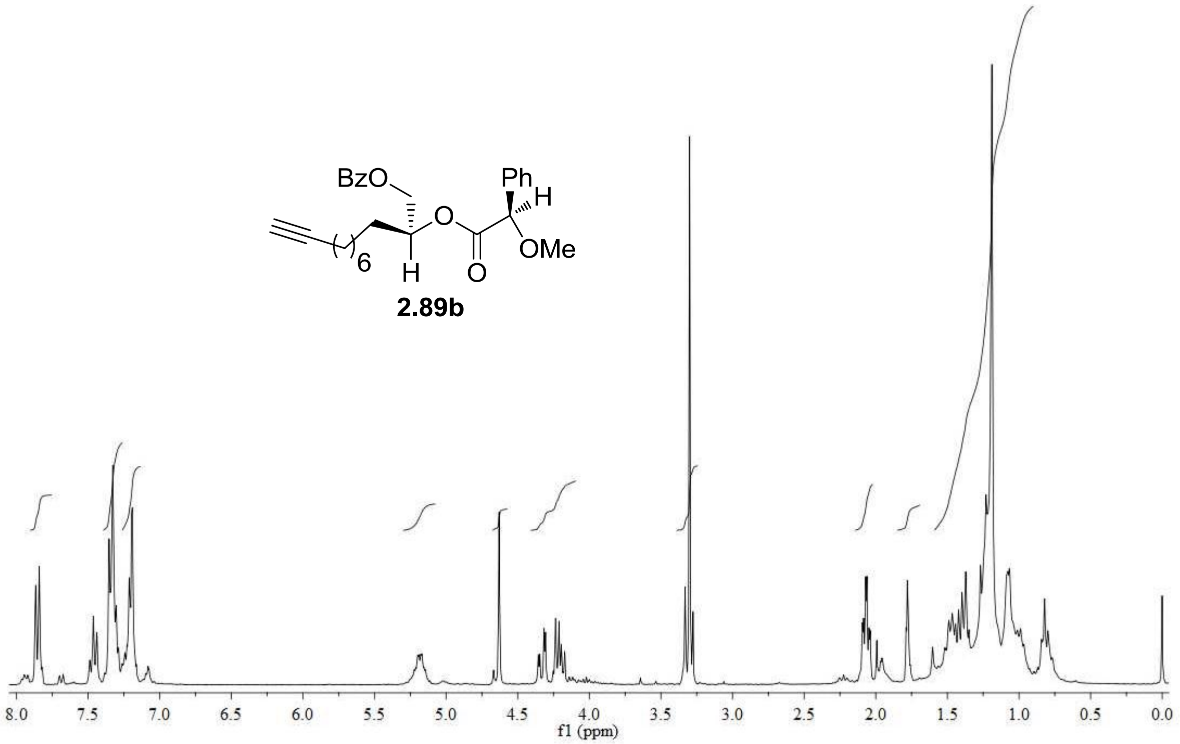
2.88a

OBz
6
OH
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

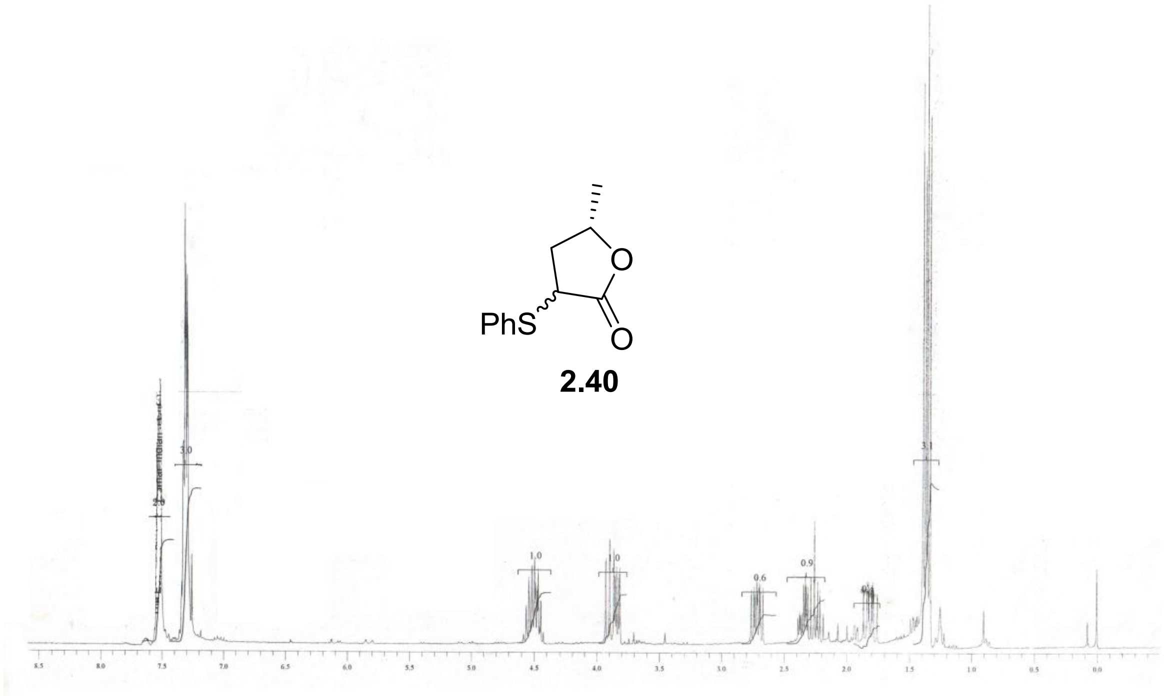


2.89a

Ph
H
6
O
BzO
H
O
OMe
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


BzO
Ph
H
O
OMe
6
H
O
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

2.89b


O
PhS
O
2.0
3.0
1.0
1.0
0.6
0.9
3.1
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

2.40

CHAPTER III

Stereoselective Synthesis towards (+)-trans-Kumausyne

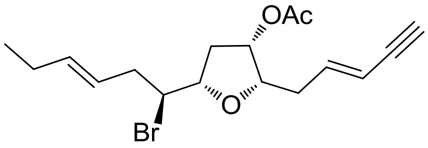
CHAPTER III

Stereoselective Synthesis towards (+)-*trans*-Kumausyne

3.1. Introduction

trans-Kumausyne **3.1** was isolated from the red alga *Laurencia nipponica* Yamada by Kurosawa and coworkers.[1] A large number of these *Laurencia* lipids contain at least one tetrahydrofuran ring. In many of these the oxygen of the tetrahydrofuran ring is flanked by *cis* side chains which are also *cis* related to an oxygen substituent. These compounds have attracted substantial interest from the synthesis community and efforts made to date have resulted in completed the total syntheses of *(±)-trans*-kumausyne **3.1** and kumausallene by several groups.[2]

Figure 1

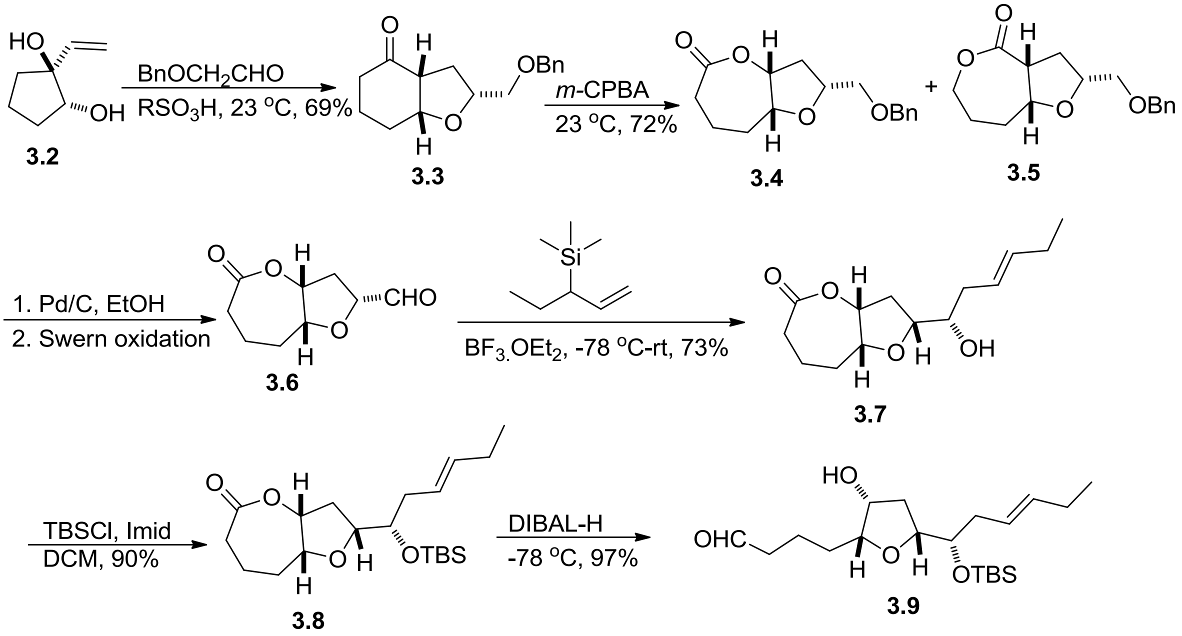


(+)-*trans*-Kumausyne **3.1**

3.2. Overman's approach

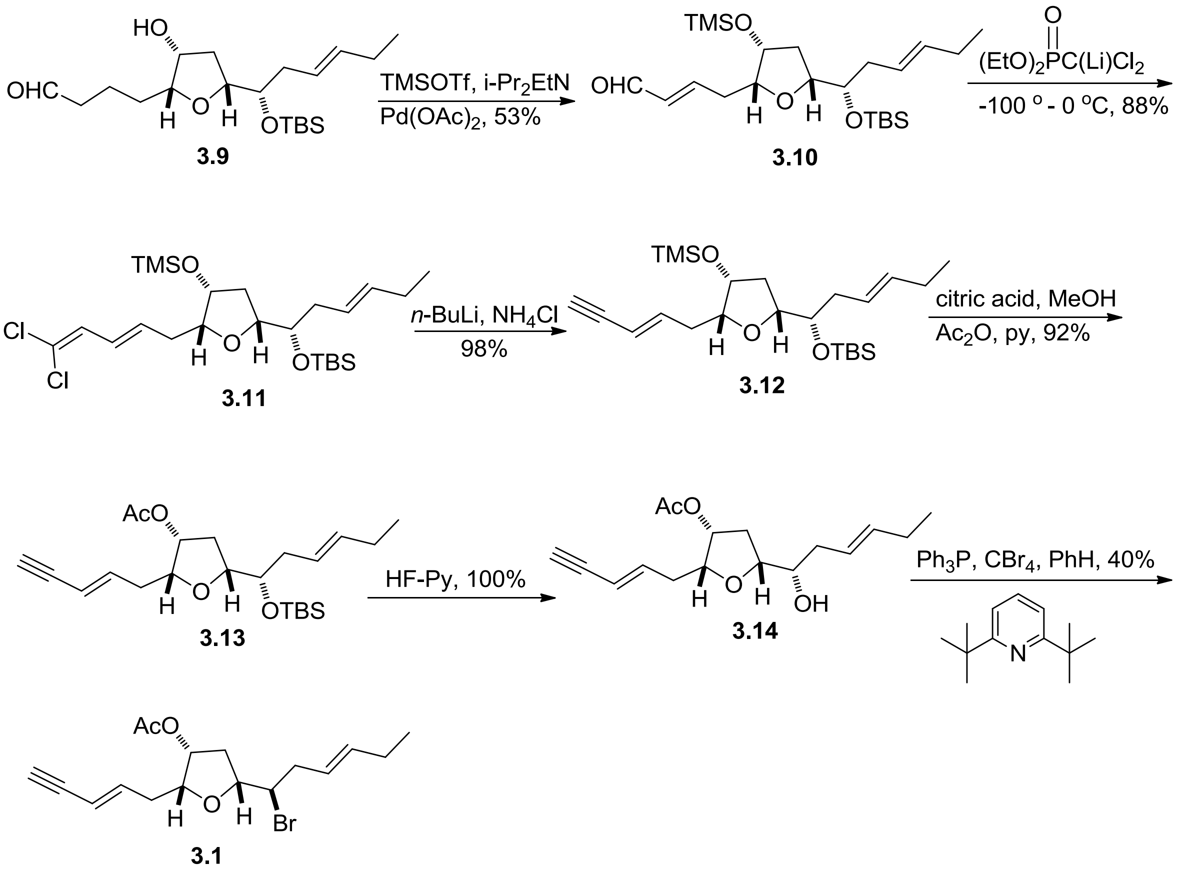
The first total synthesis *(±)-trans*-kumausyne **3.1** was reported by Overman *et.al.*[2a] The synthesis started with the *cis*-hydrobenzofuranone **3.3** which was prepared from the reaction of (*1R,2S*)-l-vinylcyclopentane-l,2-diol **3.2** and α-(benzyloxy)-acetaldehyde. Oxidation of **3.3** with *m*-chloroperoxybenzoic acid provided a 4:1 mixture of regioisomeric lactones **3.4** and **3.5**. Debenzylation of compound **3.4** using Pd/C under H_2 atmosphere afforded the primary alcohol which was oxidised under Swern conditions to provide the aldehydes **3.6**. Reaction of lactone aldehyde **3.6** with 3-(trimethylsilyl)-1-pentene in the presence of $BF_3.OEt_2$ afforded a single crystalline alcohol **3.7** which was protected as its silyl ether **3.8**. Subsequent treatment with DIBAL-H yielded hydroxy aldehyde **3.9**, Scheme 3.1**.**

Scheme 3.1 synthesis of aldehyde **3.9**



Treatment of compound **3.9** with Me_3SiOTf, *i*-Pr_2EtN resulted in silylation of the secondary hydroxyl and enolization of the aldehyde to furnish the enoxysilane which was oxidized using $Pd(OAc)_2$ to afford the unsaturated aldehyde **3.10**. One carbon homologation of **3.10** employing the Horner-Emmons reagent generated from diethyl trichloromethane phosphonate afforded the dichloro diene **3.11** was further treated with *n*-BuLi to give enyne **3.12**. Selective cleavage of the TMS group followed by acylation provided the acetate **3.13**. Desilylation of compound **3.13** using HF.pyridine afforded alcohol **3.14** which was treated with Ph_3P and CBr_4, in the presence of 2,6-di-*tert*-butylpyridine in benzene to afford *(±)-trans*-kumausyne **3.1**, Scheme 3.2.

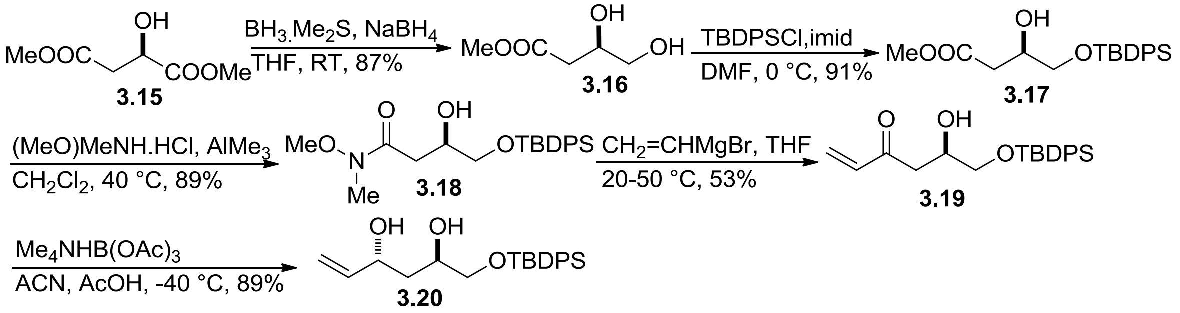
Scheme 3.2 Total synthesis of **3.1**



3.3. Boukouvalas' approach

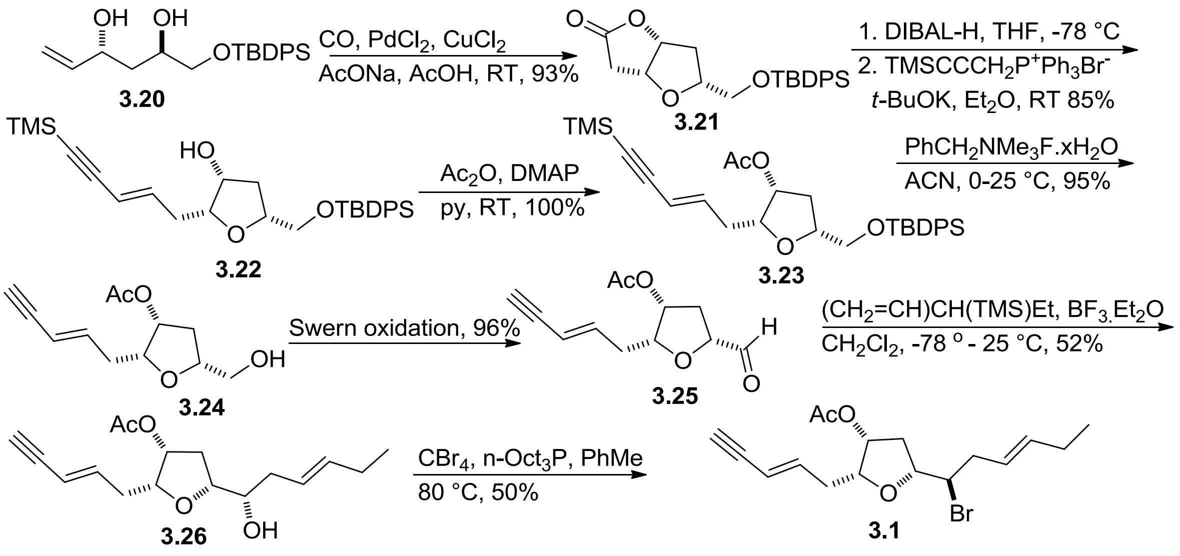
Boukouvalas *et al.*[2c] have synthesised (-)-*trans*-Kumausyne **3.1** by employing Pd catalysed tandem intramolecular alkoxycarbonylation-lactonization strategy. The synthesis began with the selective reduction of dimethyl (*R*)-malate **3.15** to diol **3.16**. Selective protection of primary hydroxyl of **3.16** as its TBDPS ether **3.17** and further reaction with *N*,*O*-dimethylhydroxylamine hydrochloride in the presence of trimethylaluminum furnished Weinreb amide **3.18**. Reaction of **3.18** with vinylmagnesium bromide yielded enone **3.19**, which was reduced using $Me_4NHB(OAc)_3$ to afford the diol **3.20**, Scheme 3.3.

Scheme 3.3 Synthesis of diol **3.20**



Treatment of diol **3.20** with carbon monoxide in the presence of $PdCl_2$ and $CuCl_2$ afforded the bicyclic lactone **3.21**[3] which was reduced to the lactal and subjected to Wittig-olefination reaction with the [3-(trimethylsilyl)-2-propynyl]triphenylphoshonium bromide to afford the enyne **3.22**.[4] Compound **3.22** was converted to its acetate **3.23** and deprotection of both the silyl groups of **3.23** by using benzyltrimethylammonium fluoride hydrate afforded alcohol **3.24** which was oxidized using the Swern protocol to furnish aldehyde **3.25**. Reaction of aldehyde **3.25** with 3-(trimethylsilyl)-1-pentene provided alcohol **3.26** which was treated with CBr_4 and tri-*n*-octylphosphine to afford (-)-*trans*-kumausyne **3.1**, Scheme 3.4.

Scheme 3.4 Total synthesis of **3.1**

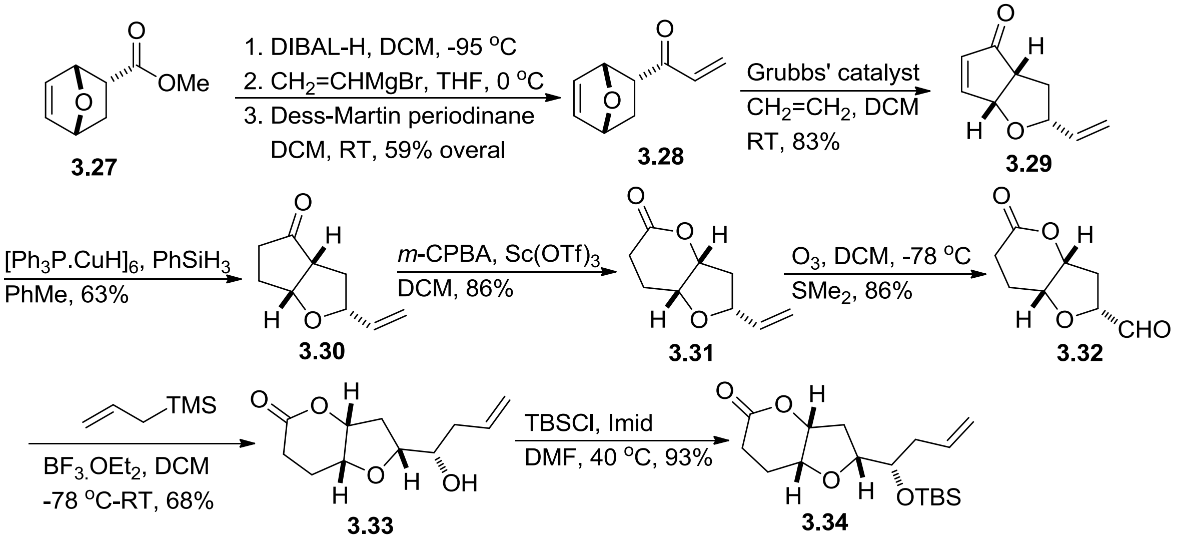


3.4. Phillips's approach

Phillips *et al.*[2f] have synthesized *(±)-trans*-kumausyne **3.1** employing tandem ring-opening-ring-closing (ROM-RCM) and ring-opening-ring-closing-cross metathesis (ROM-RCMCM) strategy.[5]

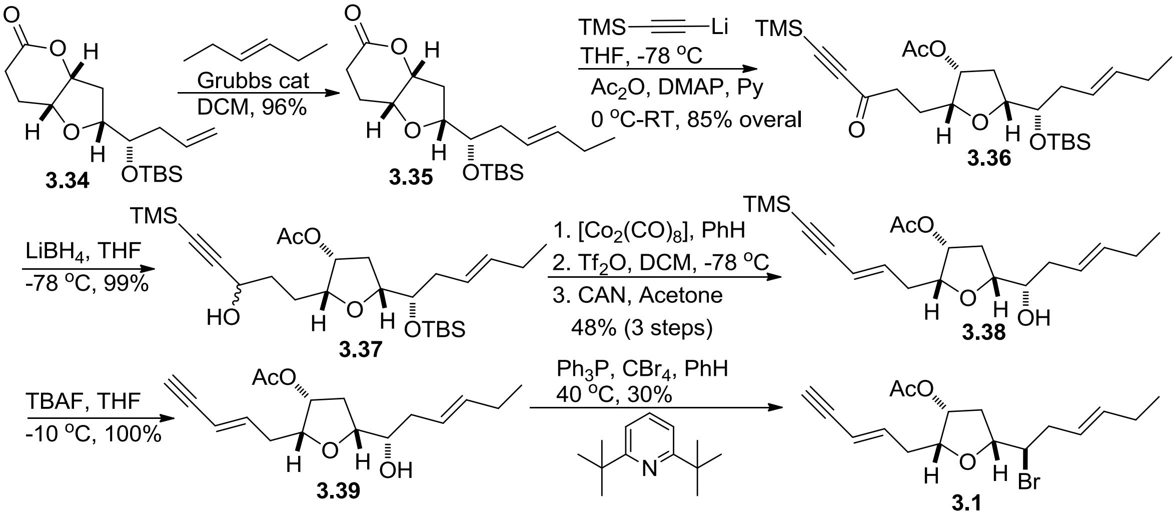
The synthesis was commenced from ester **3.27** which was readily prepared by Diels-Alder reaction of furan and methyl acrylate.[6] Ester **3.27** was selectively reduced to the aldehyde, reaction with vinylmagnesium bromide and subsequent oxidation of the crude mixture of allylic alcohols with DMP provided enone **3.28**. Compound **3.28** was reacted with ethylene gas in presence of Grubbs' catalyst to afford unsaturated ketone **3.29** which was subsequently reduced to ketone **3.30** using $[Ph_3P.CuH]_6$, $PhSiH_3$. Baeyer-Villiger oxidation of ketone **3.30** afforded bicyclic lactone **3.31.** Ozonolysis of the olefin **3.31** afforded aldehyde **3.32** which was reacted with allyltrimethylsilane in the presence of $BF_3.OEt_2$ to give homoallylic alcohol **3.33** which was subsequently protected as its TBS ether **3.34**, Scheme 3.5.

Scheme 3.5 Synthesis of lactone **3.34**



Homoallyl ether **3.34** was reacted with excess of *trans*-3-hexene in the presence Grubbs' catalyst to give the alkene **3.35**. The lactone was reacted with the lithium anion of TMS acetylene followed by conventional acetylation provided alkynyl ketone **3.36** which was reduced to corresponding alcohol **3.37** using $LiBH_4$. Treatment of compound **3.37** with $Co_2(CO)_8$, followed by triflic anhydride mediated elimination, and decomplexation with ceric ammonium nitrate (CAN) provided enyne **3.38**. Removal of silyl group with TBAF in THF afforded alcohol **3.39** which was treated with Ph_3P and CBr_4 in the presence of 2,6-di-*tert*-butylpyridine to afford (±)-*trans*-kumausyne **3.1**, Scheme 3.6.

Scheme 3.6 Total synthesis of **3.1**

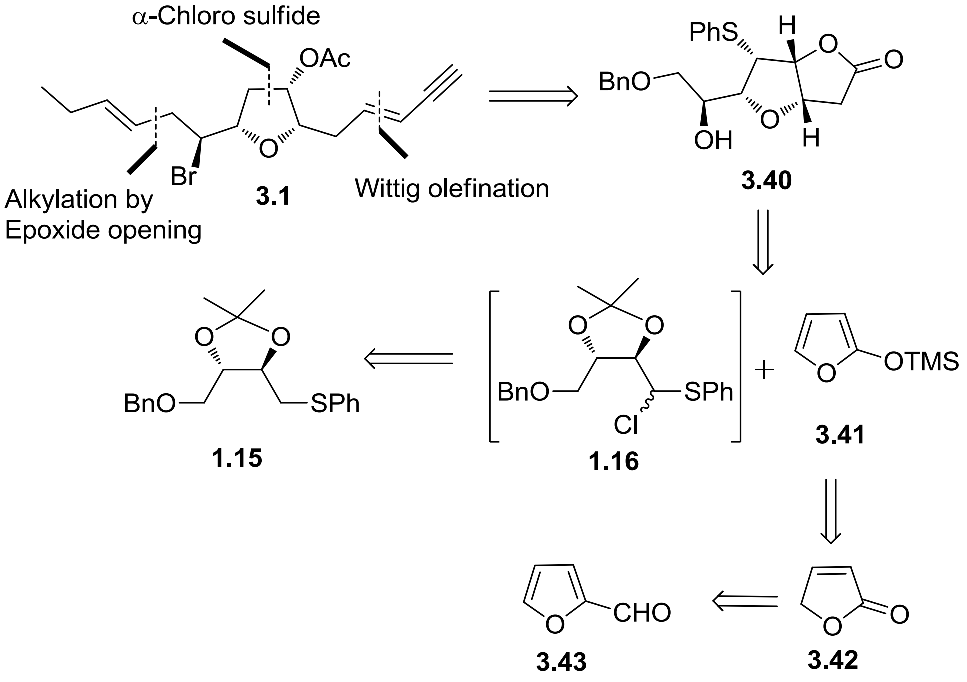


3.5. Present approach

The synthesis of *trans*-kumausyne **3.1** was envisaged as a testing ground for the potential of α-chloro sulfide as synthon for C-C bond formation. By a retrosynthetic analysis, *trans*-kumausyne **3.1** was envisioned to be obtained from lactone **3.40** *via* opening of epoxide to introduce the butenyl side chain and Wittig olefination reaction to introduce the eneyne side chain. Lactone **3.40** was envisioned to be obtained by vinylogus

Mukaiyama type reaction of 2-trimethylsiloxy furan **3.42** with α-chloro sulfide **1.16** Retron **1.15** can be secured from (L)-tartaric acid and 2-trimethylsiloxy furan **3.41** which is commercially available, can be prepared from furanone **3.42** which in turn can be obtained from furfural **3.43**, Scheme 3.7.

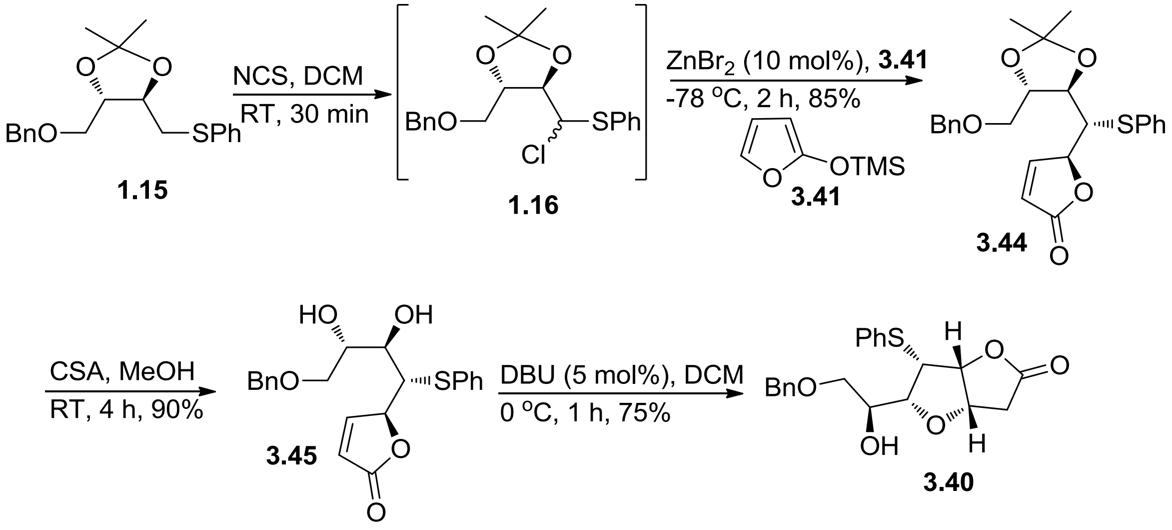
Scheme 3.7. Retrosynthetic analysis



The synthesis commenced with the sulfide **1.16** prepared as described in chapter I, Scheme 1.7. Reaction of α-chlorosulfide **1.16** with 2-trimethylsiloxy furan **3.41** in presence of catalytic $ZnBr_2$ at -78 °C afforded the lactone **3.44**[7] in 85% yield as a inseperable mixture of C_4-C_5 *erythro:threo* diastereomers in a 1:4 ratio. The identity of **3.44** was confirmed by its ^{1}H NMR spectrum which showed the presence of olefinic protons which resonates at δ 6.14 (dd, *J* = 8.2, 6.1 Hz, 1H), δ 5.27 (d, *J* = 8.2 Hz, 1H) for *syn* isomer and δ 6.07 (dd, *J* = 7.2, 5.1 Hz, 1H), δ 5.22 (d, *J* = 5.6 Hz, 1H) for *anti* isomer. The ESI mass spectrum of **3.44** showed the molecular ion peak at 449 [M+Na]$^+$.

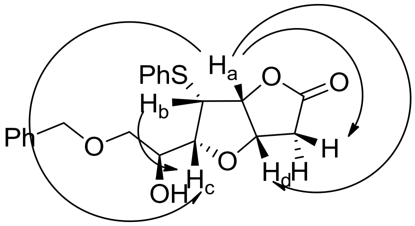
Treatment of this mixture with catalytic amount of CSA in methanol yielded diol **3.45**. The identity of **3.45** was confirmed by its ^{1}H NMR spectrum, wherein the resonances for the acetonide protons were absent. The ESI mass spectrum of **3.45** showed the molecular ion peak at 409 [M+Na]$^+$. Intramolecular cyclization was effected using catalytic amount of DBU to furnish lactone **3.40**. The identity of **3.40** was confirmed by its ^{1}H NMR spectrum, wherein the resonances for the olefinic protons were absent and there appeared resonances at δ 5.01 (ddd, J = 5.1, 4.3, 0.7 Hz, 1H) for -CH$_2$-C*H*(O)-CH(O)-, δ 4.91 (dd, J = 4.3, 0.7 Hz, 1H) for -CH$_2$-CH(O)-C*H*(O)- and δ 2.66 (d, J = 4.3 Hz, 2H) for -C*H*$_2$-COO-. The ESI mass spectrum of **3.40** showed the molecular ion peak at 409 [M+Na]$^+$. The relative stereochemistry of the bicyclic compound was confirmed by NOE analysis. It is noteworthy that under the condition of cyclization the unsaturated lactone undergoes epimerization to yield the *erythro* isomer which undergoes cyclization to furnish the bicyclic lactone exclusively, Scheme 3.8.

Scheme 3.8 synthesis of lactone **3.40**



The NOE studies revealed that H_a shows NOE with H_c, H_b and H_d, similarly H_b shows NOE with H_a, H_c, thus proving that H_a, H_b, H_c, H_d were on the same side, Figure 3.2.

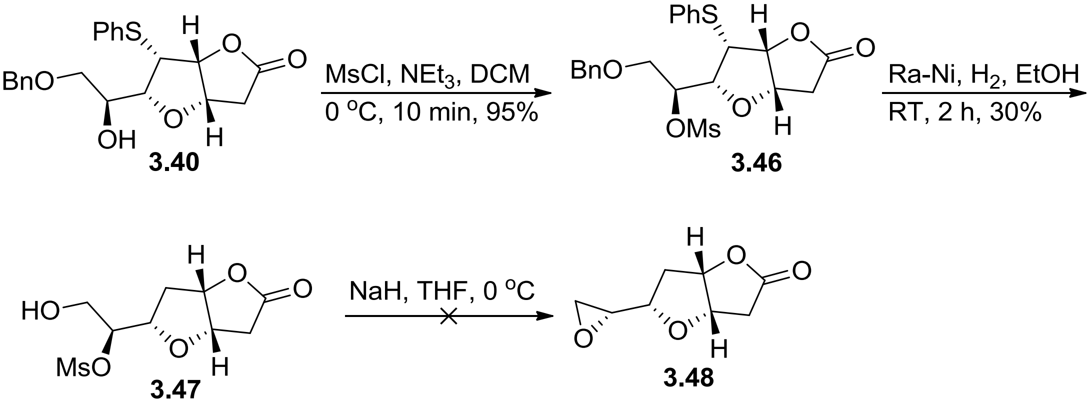
Figure 3.2



3.40

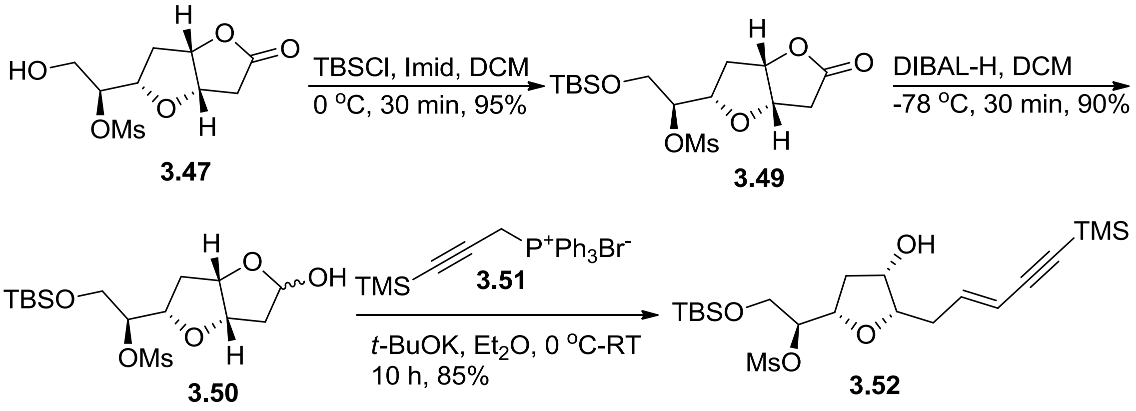
Progressing, the hydroxyl in bicyclic lactone **3.40** was converted to its mesylate **3.46** by treatment of MsCl/NEt3. The identity of **3.46** was confirmed by its ^{1}H NMR spectrum which revealed resonances at δ 5.07 (t, *J* = 5.1 Hz, 1H) for -C*H*-O-SO2-CH3, δ 3.10 (s, 3H) for –CH-O-SO2-C*H3*. The ESI mass spectrum of **3.46** showed the molecular ion peak at 487 $[M+Na]^+$. The compound **3.46** was treated with freshly prepared Raney-Ni to afford alcohol **3.47**. The identity of **3.47** was confirmed by its ^{1}H NMR spectrum, wherein the resonances for the benzylic and aromatic protons were absent. The ESI mass spectrum of **3.47** showed the molecular ion peak at 289 $[M+Na]^+$. The next step called for the epoxide formation and introduction of butenyl side chain. Attempted formation of epoxide **3.48** by treatment with NaH failed to yield the epoxide cleanly, a complex mixture resulted. Repeated trials using a variety bases consistently failed to yield the expected epoxide **3.48** cleanly, Scheme 3.9. Therefore it was decided to initially introduce the enyne side chain.

Scheme 3.9 Synthesis of epoxide **3.48**



Towards this end the hydroxy group in lactone **3.47** was protected as its TBS ether **3.49**. The structure of compound **3.49** was confirmed by its ^{1}H NMR spectrum which showed resonances at δ 3.92 (dd, *J* = 12.0, 7.0 Hz, 1H), 3.83 (dd, *J* = 11.0, 4.0 Hz, 1H) for the methylene protons alcohol of the silyl ether. The tertiary butyl signal for the TBS moiety appeared at δ 0.90 (s, 9H) while the methyl groups of the silyl ether appeared at 0.09 (s, 3H) and 0.08 (s, 3H). The ESI mass spectrum of **3.49** showed the molecular ion peak at 403 $[M+Na]^+$. The lactone **3.49** was reduced to the lactal **3.50** using DIBAL-H. Reaction of compound **3.50** with the ylide generated from the salt **3.51** afforded the enyne derivative **3.52**. The identity of **3.52** was confirmed by its ^{1}H NMR spectrum that revealed the presence of olefinic protons at δ 6.18 (td, *J* = 15.8, 7.4 Hz, 1H) and δ 5.62 (d, *J* = 15.8 Hz, 1H). The ESI mass spectrum of **3.52** showed the molecular ion peak at 499 $[M+Na]^+$, Scheme 3.10.

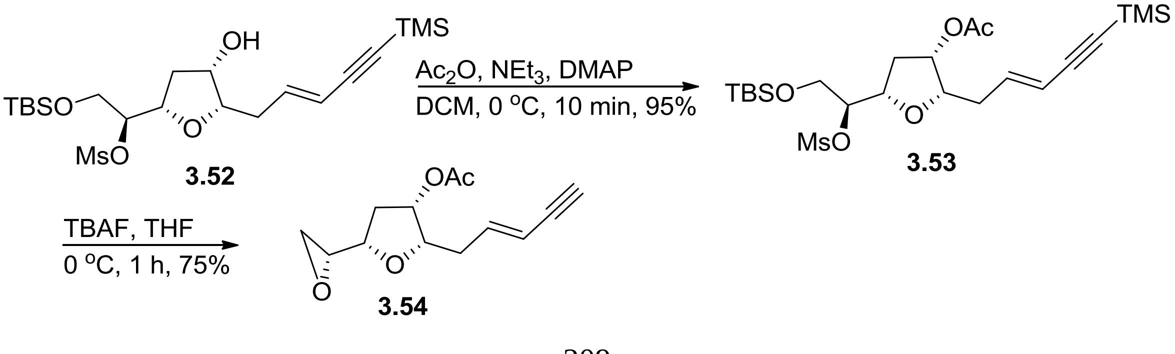
Scheme 3.10 Synthesis of eneyne **3.52**



The eneyne derivative **3.52** was converted to acetate **3.53** using Ac_2O/NEt_3. The identity of **3.53** was confirmed by its ^{1}H NMR spectrum, which showed resonances at δ 5.33 (m, 1H) for -C*H*-OC(O)-CH_3, δ 2.09 (s, 3H) for -CH_2-OC(O)-CH_3. The ESI mass spectrum of **3.53** showed the molecular ion peak at 541 $[M+Na]^+$.

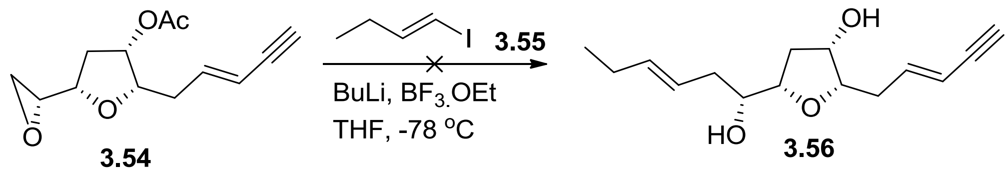
The compound **3.53** on treatment with TBAF led to the deprotection of TBS ether and concomitant epoxide formation to afford the epoxide **3.54**. The identity of **3.54** was confirmed by its ^{1}H NMR spectrum, wherein resonances for epoxide protons were observed at δ 2.83-2.76 (m, 1H) and δ 2.46-2.32 (m, 2H). The ESI mass spectrum of **3.54** showed the molecular ion peak at 259 $[M+Na]^+$, Scheme 3.11.

Scheme 3.11 Synthesis of epoxide **3.54**



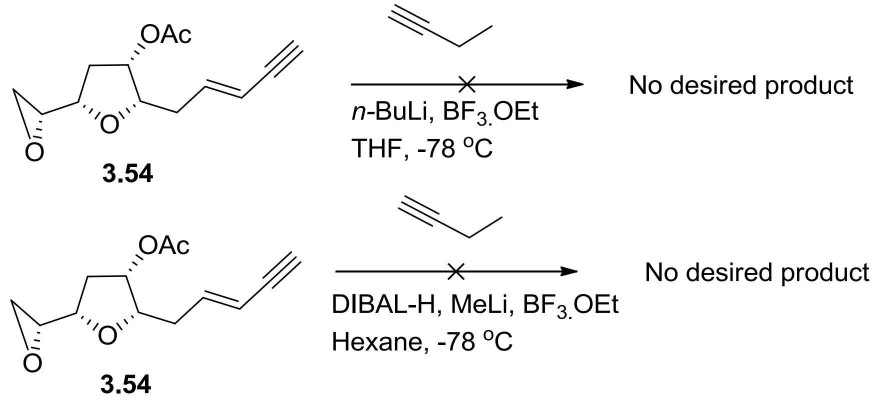
The epoxide was obtained and it remained to introduce the butenyl side chain and bromine with inversion of configuration. Attempted opening of epoxide **3.54** by reaction with an excess of alkenyl lithium, prepared from *trans*-1-iodo butene **3.55** and BuLi, in presence of $BF_3.OEt_2$ failed to afford homoallylic alcohol **3.56**, Scheme 3.12.

Scheme 3.12 Opening of epoxide **3.54**



Attempted opening of epoxide **3.54** with lithio butyne in presence of $BF_3.OEt_2$ also failed to yield the desired product. Also opening of epoxide following Alexakis' protocol[8] did not yield any desired product, Scheme 3.13.

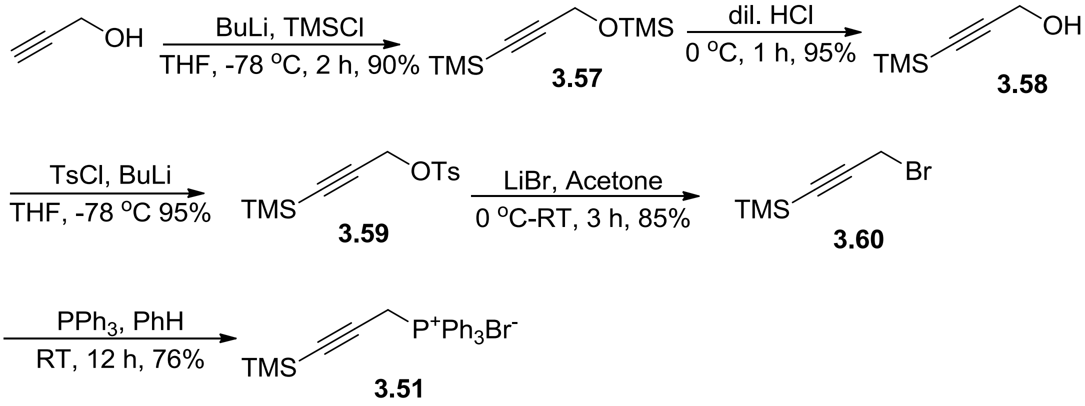
Scheme 3.13 Opening of epoxide **3.54**



Thus the synthesis of *trans*-kumausyne could not be completed. Alternate routes are being explored presently.

Wittig salt **3.51** was prepared from propargyl alcohol by converting it to its di TMS derivative **3.57** followed by acid hydrolysis to afford the propargyl alcohol **3.58**, which was further treated with TsCl in presence of BuLi to furnish **3.59**. Treatment with LiBr to afford the propargyl bromide **3.60** followed by reaction with PPh_3 in benzene furnished the compound **3.51**, Scheme 3.14.[4]

Scheme 3.14 Synthesis of Wittig salt **3.51**



3.6. Conclussion

In conclusion, a new stereoselective route towards (+)-*trans*-kumausyne was explored using vinylogus Mukaiyama type reaction for C-C bond formation on a α-chloro sulfide. The synthetic route is characterized by high stereoselectivity in the creation of the stereogenic centres.

3.7. References:

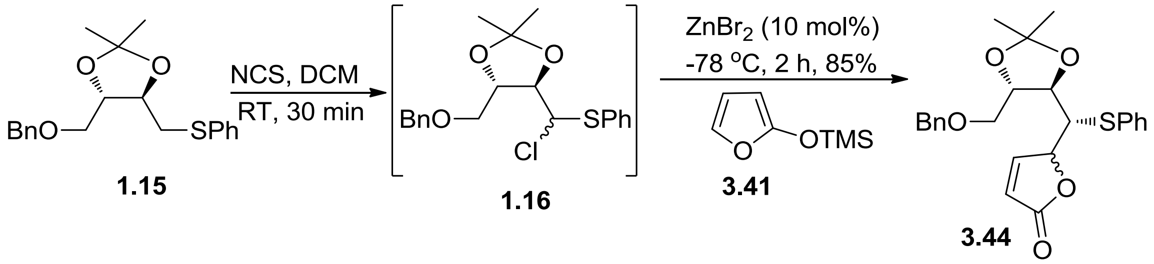
1. (a) Suzuki, T.; Koizumi, K.; Suzuki, M.; Kurosawa, E. *Chem. Lett*. **1983**, 1639. (b) Suzuki, T.; Koizumi, K.; Suzuki, M.; Kurosawa, E. *Chem. Lett*. **1983**, 1643.
2. (a) Brown, M. J.; Harrison, T.; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5378. (b) Osumi, K.; Sugimura, H. *Tetrahedron Letters*, **1995**, *36*, 5789. (c) Boukouvalas, J.; Fortier, G.; Radu, I. I. *J. Org. Chem.* **1998**, *63*, 916. (d) Pradilla, R. F; Montero, C.; Priego, J.; Martınez, L. A. *J. Org. Chem.* **1998**, *63*, 9612. (e) Rajendrakumar, R. G.; Christopher, S. C.; Lowary, T. L. *J. Org. Chem.* **2001**, *66*, 9046. (f) Carley, L. Chandler.; Phillips, A. J. *Org. Lett.* **2005**, *7*, 3493. (g) Pradilla, R. F.; Alhambra, C.; Castellanos, A.; Fernandez, J.; Manzano, P.; Montero, C.; Urena, M.; Viso, A. *J. Org. Chem*. **2005**, *70*, 10693. (h) Marko, D. M.; Dario, A. B.; Rudroff, F. *Chem. Commun.* **2006**, 3214.
3. (a) Gregory C. P. J.; Christopher J. M.; Douglas J. B.; Wilfried, A. K.; William, K. *Tetrahedron Letters*. **1997**, *38*, 3479. (b) Gregory C. P. J.; Christopher S. P. M.; Patricia H.; Christopher J. M.; Wilfried, A. K.; William, K. *J. Org. Chem*. **2001**, *66*, 7487.
4. (a) Corey, E. J.; Ronald A. R. *Tetrahedron Letter*. **1973**, *8*, 1495. (b) Jones, E. R. H.; Ahmed, M.; Barley, G.; Hearn, M. T. W.; Thaller, V.; Yates, J. *J. Chem. Soc., Perkin Trans. 1*. **1974**, 1981. (c) Nicolaou, K. C.; Webber, S. E. *J. Am. Chem. Soc.* **1984**, *106*, 5734.
5. (a) Minger, T. L.; Phillips, A. J. *Tetrahedron Lett*. **2002**, *43*, 5357. (b) Pfeiffer, M. W. B.; Phillips, A. J. *J. Am. Chem. Soc*. **2005**, *127*, 5334.

6. (a) Kotsuki, H.; Asao, K.; Ohnishi, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3339. (b) Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; von Matt, P.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582.
7. (a) Makoto, W.; Takahide, S.; Kin-ya A. *Tetrahedron Letters*. **1983**, *24*, 1711. (b) Javed, I.; Alka S. *Tetrahedron*. **1991**, 41, 8153.
8. Alexakis, A.; Jachiete, O. *Tetrahedron*. **1989**, *45*, 6197.
9. Nasman, J. A. H.; Pensar, K. G. *Synthesis*. **1985**, 786.
10. Brimble, M. A.; Brimble, M. T,; Gibson, J. J. *J. Chem. Soc. Perkins Trans. I.* **1989**, 179.
11. Ren, H.; Krasovskiy, A.; Knochel, P. *Org. Lett.* **2004**, *6*, 4215.

Experimental Section

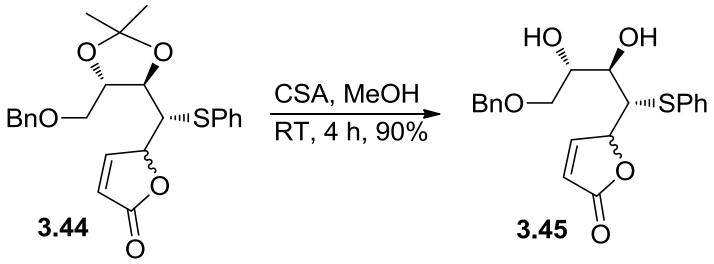
(+)-*trans*-Kumausyne Experimental Procedure

Preparation of lactone 3.44



To a solution of sulfide **1.15** (1.72 g, 5 mmol) in anhydrous DCM (20 mL) was added *N*-chlorosuccinimide (NCS, 750 mg, 5.5 mmol) at rt and stirred for 30 min at the same temperature to afford α-chloro sulfide **1.16**. The reaction mixture was cooled to -78 °C and $ZnBr_2$ (660 μL, 1 mmol, 1.5 M in THF) followed by 2-trimethylsilyloxy furan **3.41** (1.2 mL, 7.5 mmol) were added and the mixture stirred for 2 h at the same temperature. The reaction was quenched by adding saturated aq NH_4Cl (5 mL) and extracted with DCM (3x15 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude sulfide which was purified by column chromatography using 10% EtOAc/Hexanes (v/v) as the eluent to furnish the pure epimeric mixture of sulfide **3.44** (*dr* 1:4) as a viscous oil (1.81 g, 4.2 mmol) in 85% yield; TLC, R_f 0.32 (20% EtOAc/Hexanes); IR (KBr) 3062, 2924, 2858, 1747, 1573, 1450, 1373, 1259, 1099, 1026, 823, 744 cm^{-1}; ***Threo:*** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45-7.22 (m, 8H), 7.20-7.16 (m, 2H), 6.00 (dd, *J* = 8.2, 2.0 Hz, 1H), 5.12 (d, *J* = 8.2 Hz, 1H), 4.45 (d, *J* = 12.3 Hz, 1H), 4.37 (d, *J* = 12.3 Hz, 1H), 4.27 (dd, *J* = 8.2, 2.0 Hz, 1H), 3.80 (dd, *J* = 8.2, 1.7 Hz, 1H), 3.68-3.66 (m, 2H), 3.46-3.45 (m, 1H), 3.31 (dd, *J* = 8.2, 4.1 Hz, 1H), 1.34 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 155.5, 137.5, 133.8, 131.6, 130.6, 129.2, 129.1, 128.3, 127.6, 122.1, 109.8, 84.1, 79.2, 75.7, 73.4, 70.4, 54.8, 27.0, 26.7; ***Eryrhro:*** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45-7.22 (m, 8H), 7.20-7.16 (m, 2H), 5.92 (dd, *J* = 6.1, 2.0 Hz, 1H), 5.07 (d, *J* = 6.1 Hz, 1H), 4.31 (d, *J* = 11.3 Hz, 1H), 4.30 (m, 2H), 3.73 (d, *J* = 4.1, 1.7 Hz, 1H), 3.67 (m, 2H), 3.45 (m, 1H), 3.31 (d, *J* = 8.2 Hz, 1H), 1.19 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 155.4, 137.4, 135.2, 131.6, 129.2, 129.1, 128.3, 127.6, 127.0, 121.2, 109.8, 82.6, 76.0, 75.5, 73.4, 70.2, 51.8, 26.8, 26.6; MS $[M+Na]^+$ 449; HRMS (ESI) *m/z* calcd for $C_{24}H_{26}O_5SNa$ 449.1398. Found: 449.1382.

Preparation of diol 3.45

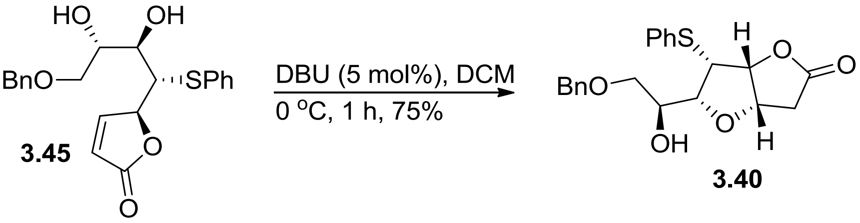


3.44

3.45

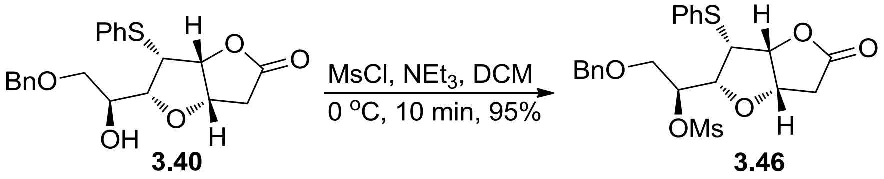
To a solution of sulfide **3.44** (426 mg, 1 mmol) in MeOH (1 mL) was added CSA (5 mol%) and stirred for 4 h. MeOH was evaporated under reduced pressure and the crude compound was purified by column chromatography using 30% EtOAc/Hexanes (v/v) as the eluent to afford the pure diol (epimeric mixture) **3.45** as viscous oil (347 mg, 0.9 mmol) in 90% yield; TLC, R_f 0.25 (50% EtOAc/Hexanes); IR (KBr) 3446, 3060, 3028, 2923, 2864, 1784, 1754, 1600, 1582, 1478, 1439, 1309, 1160, 1096, 897, 824; ***Threo:*** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.12 (m, 10H), 6.10 (dd, *J* = 8.7, 4.9 Hz, 1H), 5.30 (d, *J* = 8.7 Hz, 1H), 4.67 (dd, *J* = 8.7, 4.9 Hz, 1H) 4.41 (s, 2H), 3.71-3.67 (m, 3H), 3.50-3.46 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 156.1, 137.6, 134.6, 132.7, 130.3, 128.3, 127.9, 127.8, 127.6, 121.9, 83.6, 73.2, 71.7, 70.7, 69.9, 54.8; ***Erythro:*** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45-7.29 (m, 10H), 6.07 (dd, *J* = 8.7, 4.9 Hz, 1H), 5.63 (d, *J* = 8.7 Hz, 1H), 4.94-4.90 (m, 1H), 4.36 (s, 2H), 4.10 (dd, *J* = 14.2, 7.1 Hz, 1H), 3.73-3.68 (m, 2H), 3.50-3.47 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 156.0, 137.4, 134.0, 131.6, 129.1, 128.3, 127.9, 127.3, 126.9, 121.1, 82.7, 73.1, 71.5, 70.5, 70.3, 54.2; MS $[M+Na]^+$ 409; HRMS (ESI) *m/z* calcd for $C_{21}H_{22}O_5SNa$ 409.10802. Found: 409.10761.

Preparation of bicyclic lactone 3.40



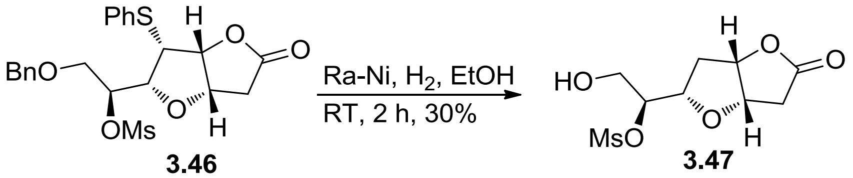
To the solution of diol **3.45** (386 mg, 1 mmol) in DCM (10 mL) cooled at 0 °C, DBU (46 *μL*, 0.05 mmol) was added and stirred for 1 h at the same temperature. The reaction was quenched by adding 1N HCl (1 mL). The layer was separated and aqueous layer extracted with DCM (3×10 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4 and solvent evaporated under reduced pressure to afford the crude compound which was purified by column chromatography using 20% EtOAc/Hexanes (v/v) as the eluent to afford the pure sulfide **3.40** as white solid (289 mg, 0.75 mmol) in 75% yield; M. P. 82 °C; TLC, R_f 0.32 (50% EtOAc/Hexanes); $[\alpha]^{25}_{D}$ (+) 26.5 (*c* 1, MeOH); IR (KBr) 3448, 2922, 2853, 1782, 1631, 1462, 1290, 1146, 1073, 896, 744, 695; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.18 (m, 10H), 5.01 (ddd, *J* = 5.1, 4.3, 0.7 Hz, 1H), 4.91 (dd, *J* = 4.3, 0.7 Hz, 1H), 4.57 (d, *J* = 12.4 Hz, 1H), 4.45 (d, *J* = 12.4 Hz, 1H), 4.30 (dd, *J* = 5.8, 0.7 Hz, 1H), 4.07 (dd, *J* = 5.1, 2.9 Hz, 1H), 3.67 (dd, *J* = 5.1, 2.9 Hz, 1H), 3.60-3.57 (m, 2H), 2.66 (d, *J* = 4.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 137.6, 133.2, 131.1, 129.4, 128.5, 127.9, 127.8, 127.6, 88.6, 80.2, 76.9, 73.4, 70.6, 70.5, 53.2, 35.9; MS $[M+Na]^+$ 409; HRMS (ESI) *m/z* calcd for $C_{21}H_{22}O_5SNa$ 409.1085. Found: 409.1082.

Preparation of mesylate 3.46



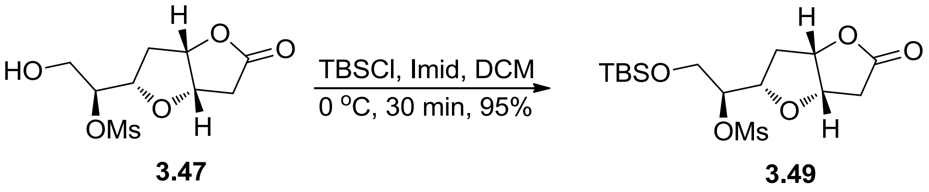
To the solution of alcohol **3.40** (386 mg, 1 mmol) in DCM (4 mL) cooled at 0 °C was added DMAP (6 mg), NEt_3 (207 µL, 1.5 mmol) and MsCl (89 µL, 1.1 mmol) and the mixture stirred for 10 min at the same temparature. The reaction mixture was diluted with DCM (5 mL), washed with water (5 ml), brine (5 mL), dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The crude mesylate was purified by column chromatography using 20% EtOAc/Hexanes (v/v) as the eluent to afford the pure compound **3.46** as a liquid (440 mg, 0.95 mmol) in 95% yield; TLC, R_f 0.4 (50% EtOAc/Hexanes); $[\alpha]^{25}_D$ (+) 1.7 (*c* 1, MeOH); IR (KBr) 2923, 2855, 1786, 1586, 1448, 1354, 1172, 1038, 974, 924, 811, 743, 696; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.20 (m, 10H), 5.07 (t, *J* = 5.1 Hz, 1H), 5.02-4.92 (m, 2H), 4.70 (d, *J* = 12.4 Hz, 1H), 4.58-4.55 (m, 1H), 4.45 (d, *J* = 12.4 Hz, 1H), 3.80 (dd, *J* = 7.0, 3.6 Hz, 1H), 3.72-3.69 (m, 2H), 3.10 (s, 3H), 2.76 (dd, *J* = 4.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 136.9, 131.5, 129.4, 128.4, 128.1, 128.0, 127.9, 127.8, 87.3, 81.5, 77.6, 76.8, 73.2, 68.6, 52.7, 38.6, 35.6; MS $[M+Na]^+$ 487; HRMS (ESI) *m/z* calcd for $C_{22}H_{24}O_7SNa$ 487.08557. Found: 487.08518.

Preparation of alcohol 3.47



To the solution of benzyl ether **3.46** (464 mg, 1 mmol) in EtOH (4 mL) was added Raney-Nickel (2 g in EtOH) and stirred for 2 h at rt under an atmospheare of hydrogen. The reaction was filtered through Ceilite, washed with EtOAc and concentrated under reduced pressure to afford the crude compound which was purified by column chromatography using EtOAc as the eluent to afford the pure hydroxy mesylate **3.47** as a liquid (133 mg, 0.5 mmol) in 50% yield; TLC, R$_f$ 0.2 (EtOAc); $[\alpha]^{25}_D$ (+) 1.5 (*c* 1, MeOH); IR (KBr) 3448, 2927, 2857, 1739, 1461, 1358, 1244, 1175,1119, 1031, 926, 842, 770; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.15 (dt, *J* = 4.8, 0.9 Hz, 1H), 4.85 (m, 1H), 4.67 (dd, *J* = 8.7, 4.8 Hz, 1H), 4.40 (m, 1H), 3.90-3.88 (m, 2H), 3.17 (s, 3H), 2.75 (m, 2H), 2.56-2.46 (m, 1H), 2.22-2.16 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 84.1, 83.8, 78.9, 77.8, 62.7, 38.9, 36.6, 34.8; MS $[M+Na]^+$ 289; HRMS (ESI) *m/z* calcd for $C_9H_{14}O_7SNa$ 289.03524. Found: 289.03565.

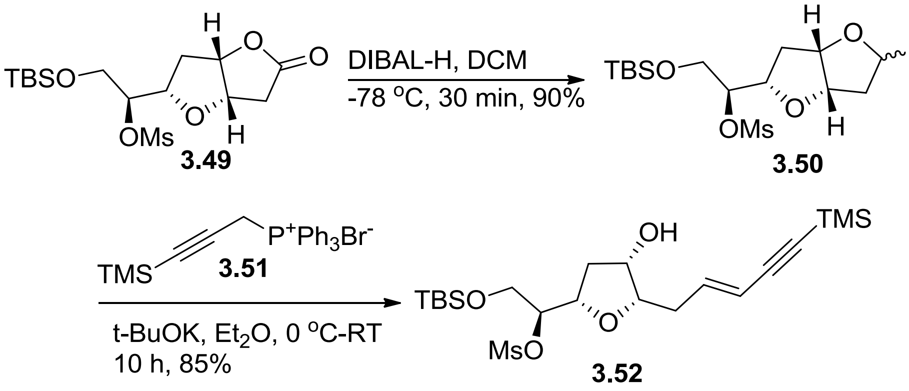
Preparation of silyl ether 3.49



To the solution of hydroxy mesylate **3.47** (266 mg, 1 mmol) in dry DCM (4 mL) maintained at 0 °C was added imidazole (102 mg, 1.5 mmol), TBS-Cl (165 mg, 1.1 mmol) and the mixture stirred for a period of 30 min. The reaction mixture was diluted with DCM (5 mL), washed successively with water (2 mL), brine (4 mL), dried over Na_2SO_4 and the solvent evaporated under reduced pressure to yield the crude product which was purified by column chromatography using 10% EtOAc/Hexanes (v/v) to furnish the pure product **3.49** (361 mg, 0.95 mmol) in 95% yield as a liquid; TLC, R$_f$ 0.35 (20% EtOAc/Hexanes); $[\alpha]^{25}_D$ (+) 24.8 (*c* 1, $CHCl_3$); IR (KBr) 2933, 2858, 1784, 1741, 1461, 1351, 1257, 1173, 1092, 923, 834, 796; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.13 (dt, *J* =

5.0, 1.0 Hz, 1H), 4.82-4.81 (m, 1H), 4.60 (m, 1H), 4.40-4.35 (m, 1H), 3.92 (dd, *J* = 12.0, 7.0 Hz, 1H), 3.83 (dd, *J* = 11.0, 4.0 Hz, 1H), 3.11 (s, 3H), 2.74-2.70 (m, 2H), 2.47-2.45 (m, 1H), 2.22 (m, 1H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 84.3, 84.1, 78.8, 77.5, 63.4, 38.8, 36.7, 34.8, 25.8, 18.2, -5.5; MS $[M+Na]^+$ 403; HRMS (ESI) *m/z* calcd for $C_{15}H_{28}O_7SSiNa$ 403.12172. Found: 403.12170.

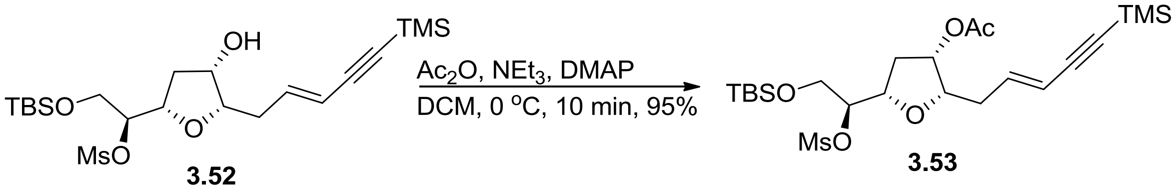
Preparation of enyne 3.52



To the solution of lactone **3.49** (380 mg, 1 mmol) in dry DCM (4 mL) cooled at -78 °C was added DIBAL-H (0.88 mL, 1.1 mmol, 1.25 M in toluene) dropwise and the reaction mixture was stirred for 30 min at same temperature. The reaction mixture was allowed to warm 0 °C and quenched by adding ice pieces and stirred further for 15 min at the same temperature. The mixture was diluted with DCM (5 mL). The aqueous layer was separated and extracted with DCM (3x5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford the lactol **3.50** as liquid in 95% yield; TLC, R_f 0.3 (50% EtOAc/Hexanes). The lactol **3.50** was used for the next step without purification.

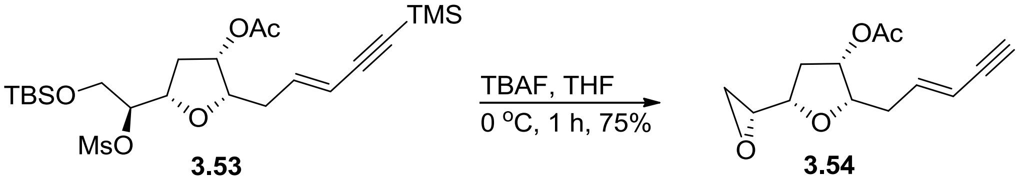
To the solution of *t*-BuOK (168 mg, 1.5 mmol) in ether (75 mL) was added 3-trimethylsilyl-2-propynyl-triphenylphosphonium bromide **3.51** (679 mg, 1.5 mmol) at rt. The reaction mixture was stirred for 3 h and then the solution of the lactol **3.50** (382 mg, 1 mmol) in ether (20 mL) was added and stirring continued for 7 h. The reaction mixture was cooled to 0 ^{o}C and quenched with ice, the layers were separated and the aqueous layer extracted with ether (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and the solvent evaporated under reduced pressure to afford the crude product which was purified by column chromatography using 10% EtOAc/Hexanes (v/v) as the eluent to afford the pure enyne **3.52** as oil in 85% yield; TLC, R_f 0.5 (20% EtOAc/Hexanes); $[\alpha]^{25}_{D}$ (+) 11.4 (*c* 1, $CHCl_3$); IR (KBr) 2925, 2854, 1709, 1460, 1376, 1254, 1175 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.18 (td, *J* = 15.8, 7.4 Hz, 1H), 5.62 (d, *J* = 15.8 Hz, 1H), 4.55 (dd, *J* = 10.6, 4.6 Hz 1H), 4.44-4.39 (m, 1H), 4.26-4.17 (m, 1H), 3.97-3.87 (m, 2H), 3.83 (dd, *J* = 11.4, 3.8 Hz, 1H), 3.12 (s, 3H), 2.51-2.37 (m, 2H), 2.14-2.02 (m, 2H), 0.90 (s, 9H), 0.18 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.3, 131.0, 128.9, 112.4, 85.5, 81.9, 76.1, 72.7, 63.6, 39.0, 37.8, 33.1, 26.0, 18.1, 0.1, -5.3; MS $[M+Na]^+$ 499; HRMS (ESI) *m/z* calcd for $C_{21}H_{40}O_6SSi_2Na$ 499.19763. Found: 499.19966.

Preparation of acetate 3.53



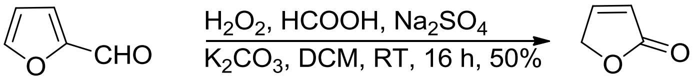
To the solution of alcohol **3.52** (476 mg, 1 mmol) in anhydrous DCM (4 mL) cooled at 0 ^{o}C was added DMAP (6 mg), NEt_3 (206 µL, 1.5 mmol) and acetic anhydride (112 µL, 1.1 mmol) and the mixture stirred at rt for 10 min. The reaction mixture was diluted with DCM (5 mL), washed with water (5 mL), brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product which was purified by column chromatography using 10% EtOAc/Hexanes (v/v) as the eluent to afford the pure acetate **3.53** as an oil (492 mg, 0.95 mmol) in 95% yield; TLC, R*f* 0.42 (20% EtOAc/Hexanes); $[\alpha]^{25}_D$ (+) 2.3 (*c* 1, $CHCl_3$); IR (KBr) 2923, 2853, 2380, 1732, 1627, 1462, 1352, 1251, 1173, 1121, 965, 923, 841, 776; ^1H NMR (500 MHz, $CDCl_3$) δ 6.13 (td, *J* = 15.9, 6.9 Hz, 1H), 5.56 (d, *J* = 15.9 Hz, 1H), 5.33 (m, 1H), 4.56 (dd, *J* = 8.9, 4.9 Hz ,1H), 4.41-4.35 (m, 1H), 4.25-4.17 (m, 1H), 3.92-3.80 (m, 2H), 3.12 (s, 3H), 2.38-2.32 (m, 2H), 2.22-2.13 (m, 2H), 2.09 (s, 3H), 0.89 (s, 9H), 0.17 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 140.9, 112.5, 103.5, 93.9, 84.9, 80.5, 76.3, 74.9, 63.5, 39.0, 35.4, 33.3, 29.8, 26.0, 18.1, 0.0, -5.3; MS $[M+Na]^+$ 541; HRMS (ESI) *m/z* calcd for $C_{23}H_{42}O_7SSi_2Na$ 541.20820. Found: 541.20955.

Preparation of epoxide 3.54



To the solution of the TBS ether **3.53** (518 mg, 1 mmol) in THF (10 mL) at 0 °C was added TBAF (3 mL, 3 mmol, 1 M in THF) and the mixture stirred at rt for 1 h. The reaction mixture was cooled to 0 °C and quenched by adding saturated aq NH_4Cl (3 mL). The layers were separated and the aq layer was extracted with EtOAc (3x5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product which was purified by column chromatography using 10% EtOAc/Hexanes (v/v) as the eluent to afford the pure epoxide **3.54** as oil (177 mg, 0.75 mmol) in 75% yield; TLC, R*f* 0.2 (20% EtOAc/Hexanes); IR (KBr) 2924, 2856, 2380, 1736, 1626, 1457, 1381, 1243, 1079, 759; ^1H NMR (500 MHz, $CDCl_3$) δ 6.21 (td, *J* = 15.9, 7.9 Hz, 1H), 5.55 (d, *J* = 15.8 Hz, 1H), 5.33-5.31 (m, 1H), 4.24 (dd, *J* = 7.9, 3.9 Hz, 1H), 4.10-4.00 (m, 1H), 3.08 (d, *J* = 2.9 Hz, 1H), 2.83-2.76 (m, 1H), 2.46-2.32 (m, 2H), 2.10-2.02 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 141.7, 111.2, 83.4, 80.3, 76.8, 76.7, 75.0, 53.0, 44.7, 34.2, 33.2, 21.1; MS $[M+Na]^+$ 259.

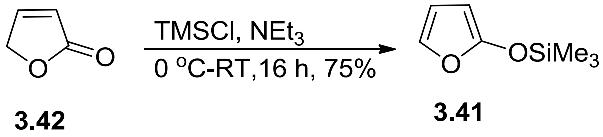
Preparation of Furanone 3.42



3.43 **3.42**

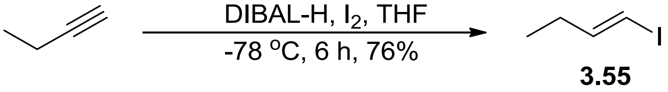
A two neck round bottom flask with reflux condenser was charged with furfural **3.43** (43 g, 500 mmol), formic acid (46 g, 1 mmol), Na_2SO_4 (50 g, 352 mmol), K_2CO_3 (17.5 g, 126 mmol) in DCM (250 mL) and added 30% H_2O_2 (37.5 mL) in one portion and stirred for 30 min at rt, after which the mixture was started refluxing. Then 30% H_2O_2 (62.5 mL) was added over a period of 2 h drop wise. The mixture was further stirred for 10 h at rt. The phases were separated and aq phase was extracted with DCM (3x50 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Toluene (100 mL) was added and formic acid was remove by azeotropic distillation. To the residue, toluene (100 mL) was added followed by NEt_3 (1.3 mL, 10 mmol) and stirred for 1 h at rt. The solvent was removed under reduced pressure and the crude compound was purified by vacuum distillation to yield the furanone **3.42** as colorless viscous oil in in 50% yield. B. P. 96 °C /19 torr; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (dt, *J* = 5.8, 1.7 Hz, 1H), 6.18 (d, *J* = 5.8 Hz, 1H), 4.95 (dd, *J* = 2.1, 1.7 Hz, 2H).[1]

Preparation of 2-trimethylsiloxy furan 3.41



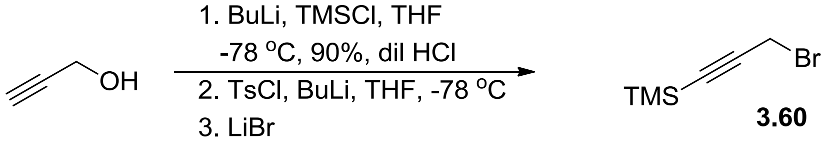
Furanone **3.42** (8.4 g, 100 mmol) was cooled to 0 °C and added NEt_3 (14.1 mL, 101 mmol), TMSCl (12.9 mL, 101 mmol) and stirred at RT for 16 h. Dry hexane (100 mL) was added and filtered through celite under inert condition followed by distillation afforded the pure 2-trimethylsiloxy furan **3.41** as a colorless liquid (11.7 g, 75 mmol) in 75% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 (s, 1H), 6.13 (s, 1H), 5.03 (s, 1H), 0.22 (s, 9H).[2]

Preparation of *trans*-1-iodobutene 3.55



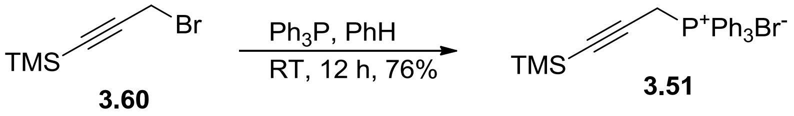
1-Butyne gas (8.0 mL, 100 mmol) was collected in a round bottom flask fitted with a Deewar condenser at -78 °C, THF (200 mL) was added followed by DIBAL-H (80.8 mL, 101 mol, 1.25 M in toluene) and the mixture stirred for 4 h at -78 °C. Iodine (25 g, 100 mmol) in THF (100 mL) was added and the mixture gradually allowed to attain rt and stirred for 2 h. The reaction mixture was cooled to 0 °C and quenched by adding aq $Na_2S_2O_3$ (20 mL). The layers were separated and the organic layer was washed with brine dried over Na_2SO_4 and purified by distillation to afford *trans*-1-iodobutene **3.55** as a colorless liquid in 80% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.55 (dt, *J* = 17.5, 5.2 Hz, 1H), 5.95 (d, *J* = 17.5 Hz, 1H), 2.15 (q, *J* = 6.5 Hz, 2H), 1.02 (t, *J* = 6.5 Hz, 3H).

Preparation of bromide 3.60



To the solution of propargyl alcohol (2.8 g, 2.9 mL, 50 mmol) in THF (100 mL) was added *n*-butyllithium (58.4 mL, 105 mmol, 1.8 M in hexanes) maintaining the temperature at -78 °C, and the mixture stirred at the same temperature for 30 min. Trimethylchlorosilane (11.4 g, 13.3 mL, 105 mmol) was added and the mixture was allowed to warm to rt and stirred for 30 min to furnish the disilylated compound **3.57**. Aq hydrochloric acid (3 N, 600 mL) was added and the solution was stirred for 1 h to afford the alcohol **3.58**. Water (30 mL) was added and aqueous layer was extracted with ether (3x100 mL), the combined organic layers were washed with sodium bicarbonate (20 mL), brine (10 mL) and dried over sodium sulfate. The solvent was evaporated under reduced pressure until the volume was about 70 mL. The mixture was cooled to -78 °C and *n*-butyllithium (30.6 mL, 55 mmol, 1.8 M in hexane) was added and stirred for 30 min at the same temperature. *p*-Toluenesulfonyl chloride (104.8 g, 550 mmol) in THF (300 mL) was added. The mixture was allowed to warm to room temperature during a period of 1 h. The reaction mixture was cooled to 0 °C and water (20 mL) was added and aqueous layers were extracted with ether (3x100 mL). The combined organic layers were washed with brine (20 mL) and dried over sodium sulfate. The solvent was evaporated under vacuum to afford the tosylated compound **3.59**. To the compound **3.59** in acetone (1 L) was added lithium bromide (87.0 g, 1 mol) at room temperature and stirred for 3 h. The reaction mixture was diluted with water (150 mL), the layers were separated and the aq layer extracted with ether (3x100 mL). The combined organic layers were washed with brine (10 mL) and dried over sodium sulfate. The solvent was evaporated under reduced pressure to afford the crude compound which was distilled at 62.5-64.5 °C at 15 mm Hg to afford propargyl bromide **3.60** in 55.88 g in 59% yield as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.88 (s, 2 H), 0.15 (s, 9 H).

Preparation of Wittig salt 3.51

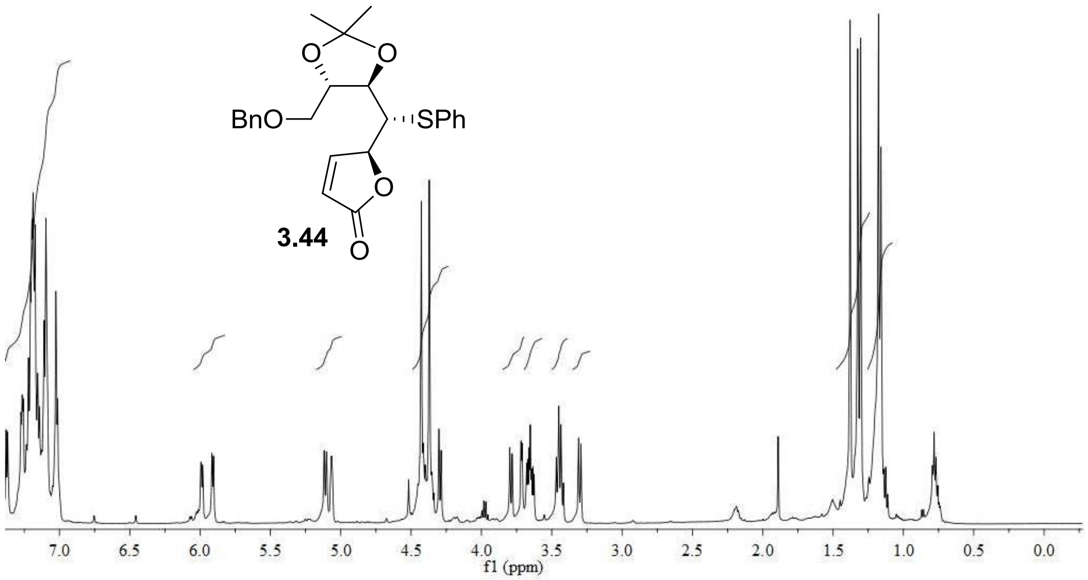


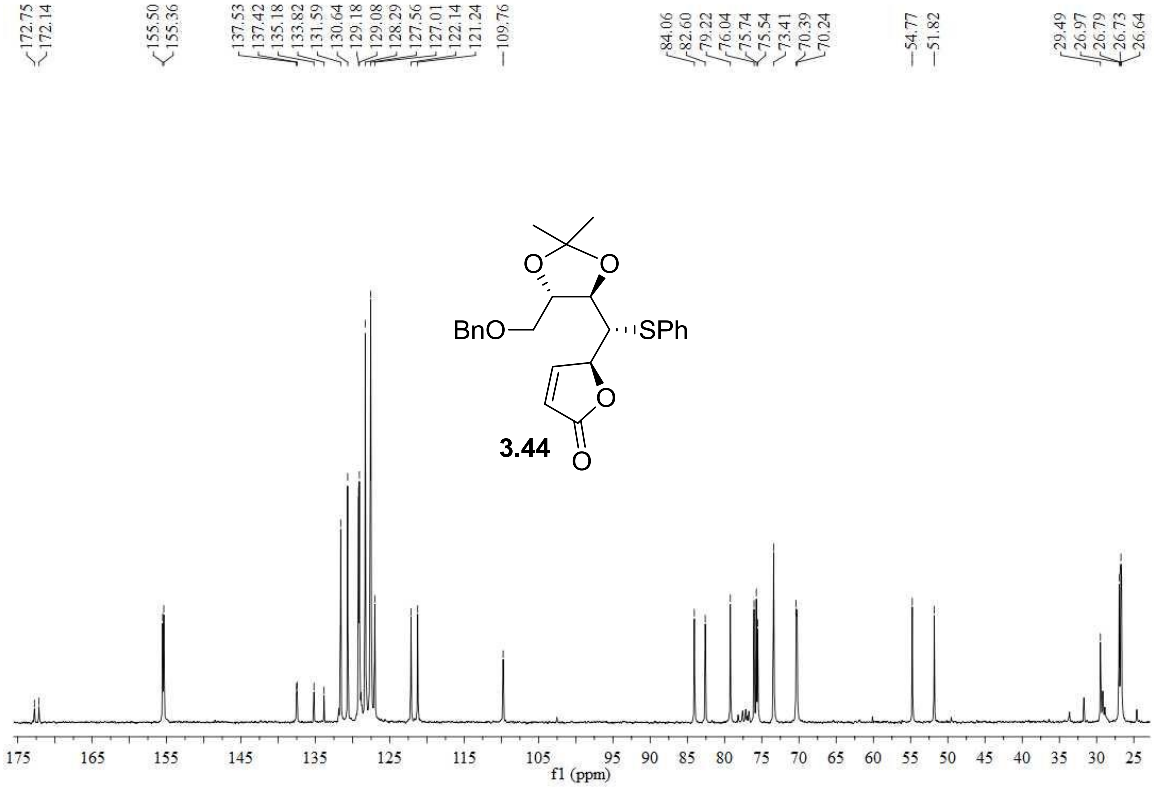
To a solution of 3-bromo-1-trimethylsilylprop-1-yne **3.60** (20 mmol, 4 g) in benzene (20 mL) was added triphenylphosphine (27 mmol, 7.2 g) and the mixture was stirred at room temperature for 12 h. The precipitate was filtered off, washed with hexanes and dried under vacuum to yield the pure compound **3.51** in 6.5 g in 70% yield, M. P. 155-159 °C (lit., 154-156 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89-7.87 (m, 15H), 5.92 (d, J = 11.4, 2H), 0.07 (s, 9 H).

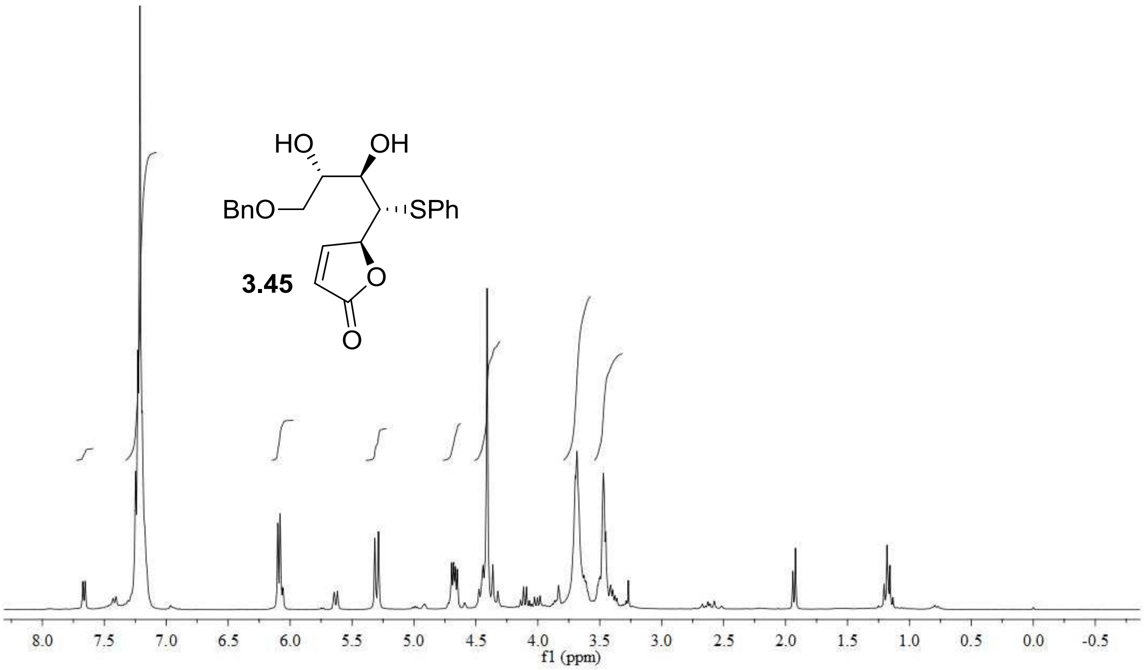
References

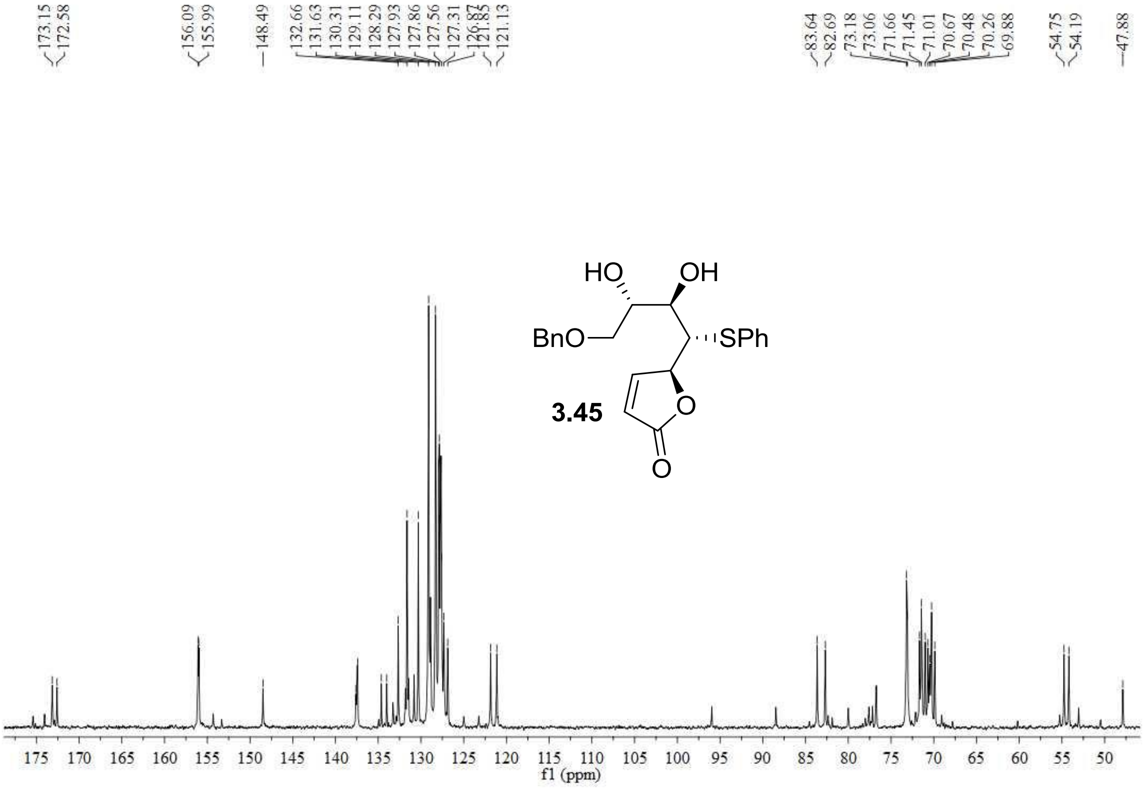
1. Nasman, J. A. H.; Pensar, K. G. *Synthesis.* **1985**, 786.
2. Brimble, M. A.; Brimble, M. T.; Gibson, J. J. *J. Chem. Soc. Perkins Trans. I.* **1989**, 179.

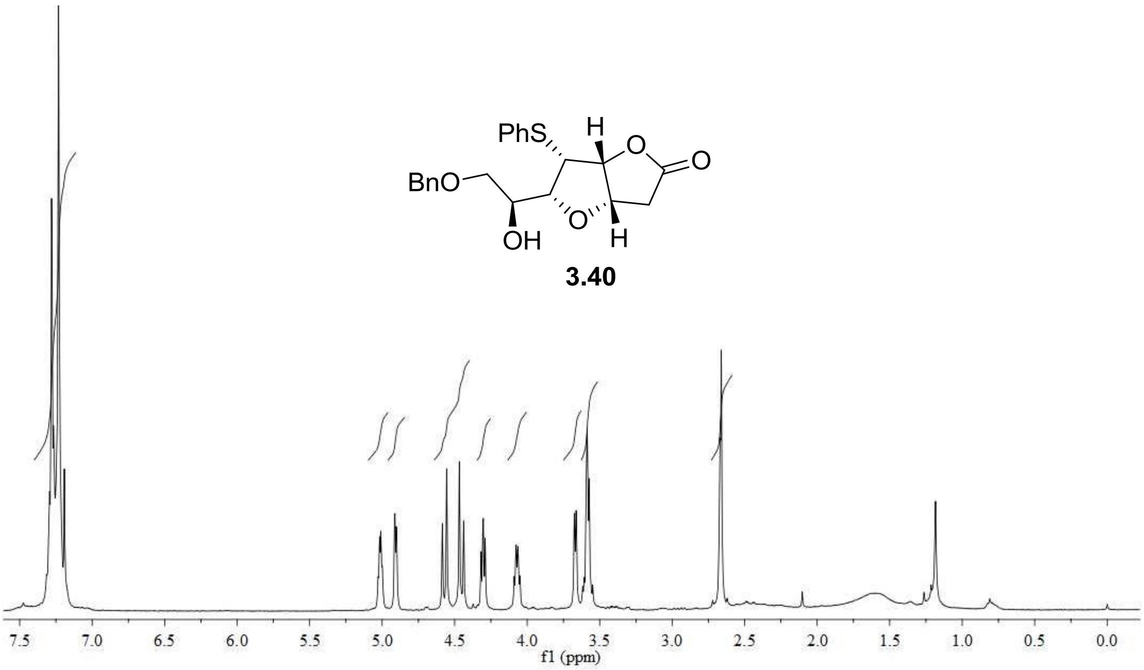
Spectral Data


BnO
SPh
O
O
O
O
3.44
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
f1 (ppm)

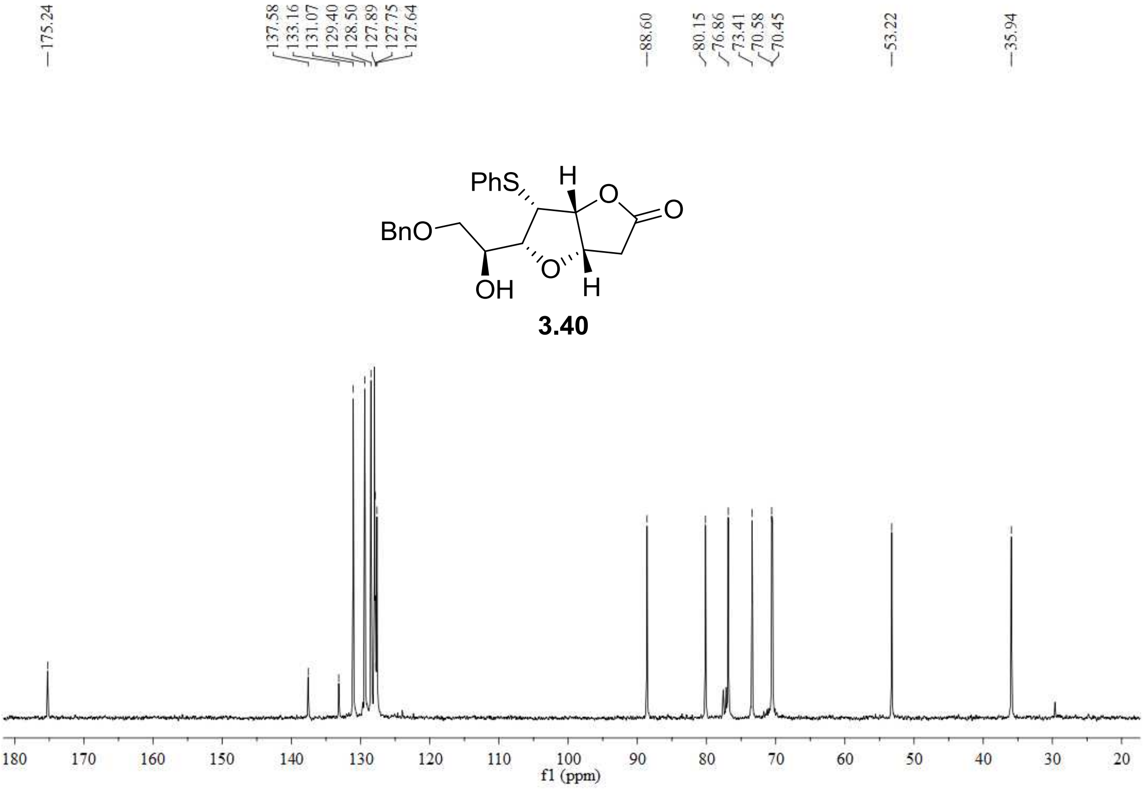

172.75
172.14
155.50
155.36
137.53
137.42
135.18
133.82
131.59
130.64
129.18
129.08
128.29
127.56
127.01
122.14
121.24
109.76
84.06
82.60
79.22
76.04
75.74
75.54
73.41
70.39
70.24
54.77
51.82
29.49
26.97
26.79
26.73
26.64
BnO
SPh
O
O
O
O
3.44
175
165
155
145
135
125
115
105
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
f1 (ppm)


HO
OH
BnO
SPh
O
O
3.45
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


173.15
172.58
156.09
155.99
148.49
132.66
131.63
130.31
129.11
128.29
127.93
127.86
127.56
127.31
126.87
121.85
121.13
83.64
82.69
73.18
73.06
71.66
71.45
71.01
70.67
70.48
70.26
69.88
54.75
54.19
47.88
HO
OH
BnO
SPh
O
O
3.45
175
170
165
160
155
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
f1 (ppm)


PhS
H
O
O
BnO
O
H
OH
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
f1 (ppm)

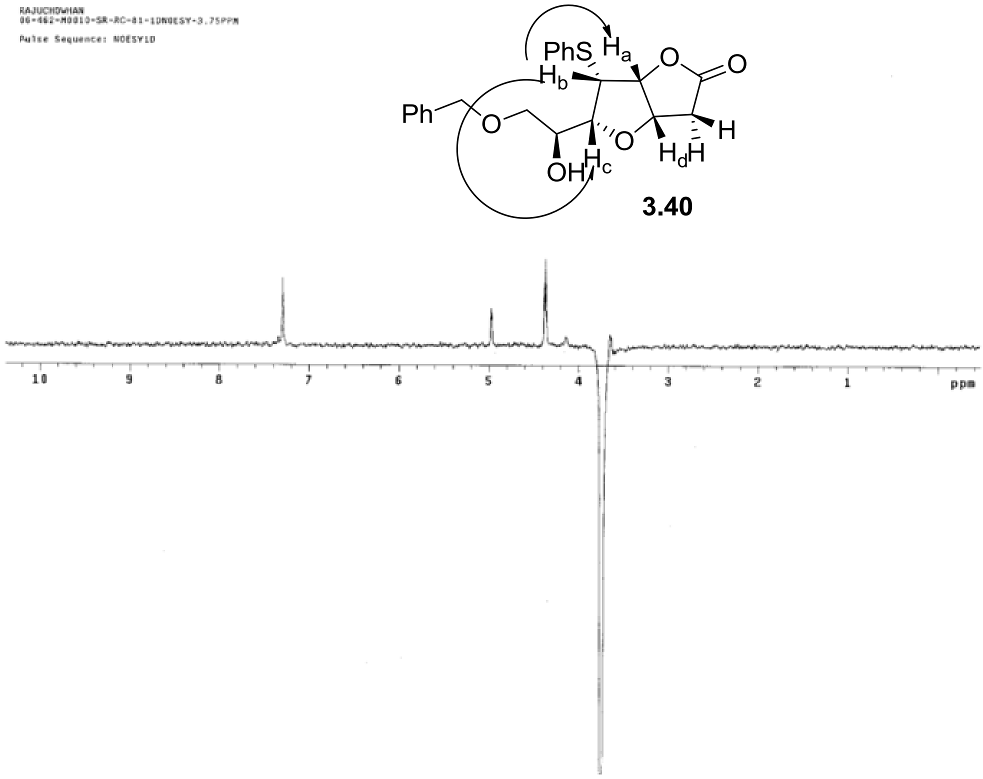
3.40


175.24
137.58
133.16
131.07
129.40
128.50
127.89
127.75
127.64
88.60
80.15
76.86
73.41
70.58
70.45
53.22
35.94
PhS
H
O
O
BnO
O
H
OH
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

3.40

RAJUCHOWHAN
06-462-M0010-SR-RC-81-1DNOESY-3.75PPM

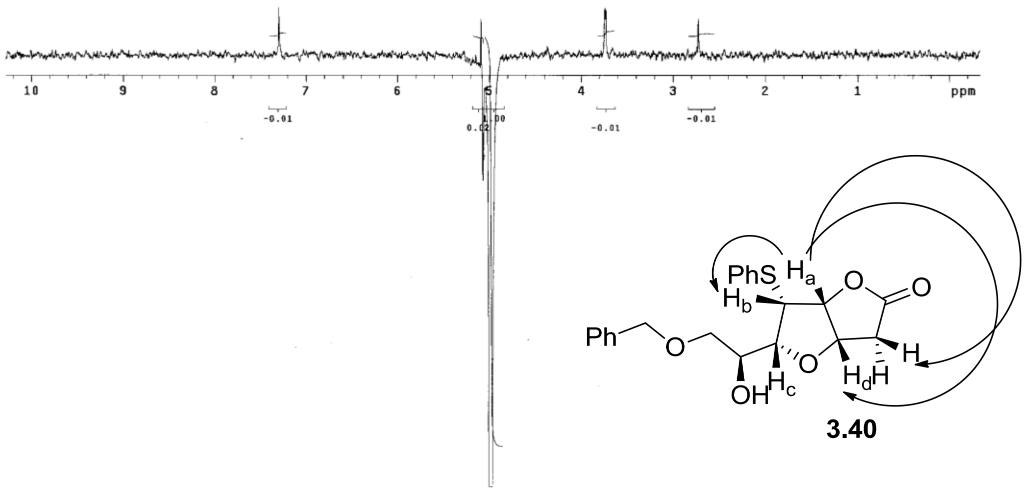
Pulse Sequence: NOESY1D



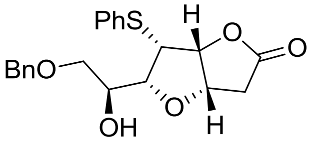
3.40

RAJUCHOWHAN
06-462-M0010-SR-RC-81-1DNOESY-4.95PPM

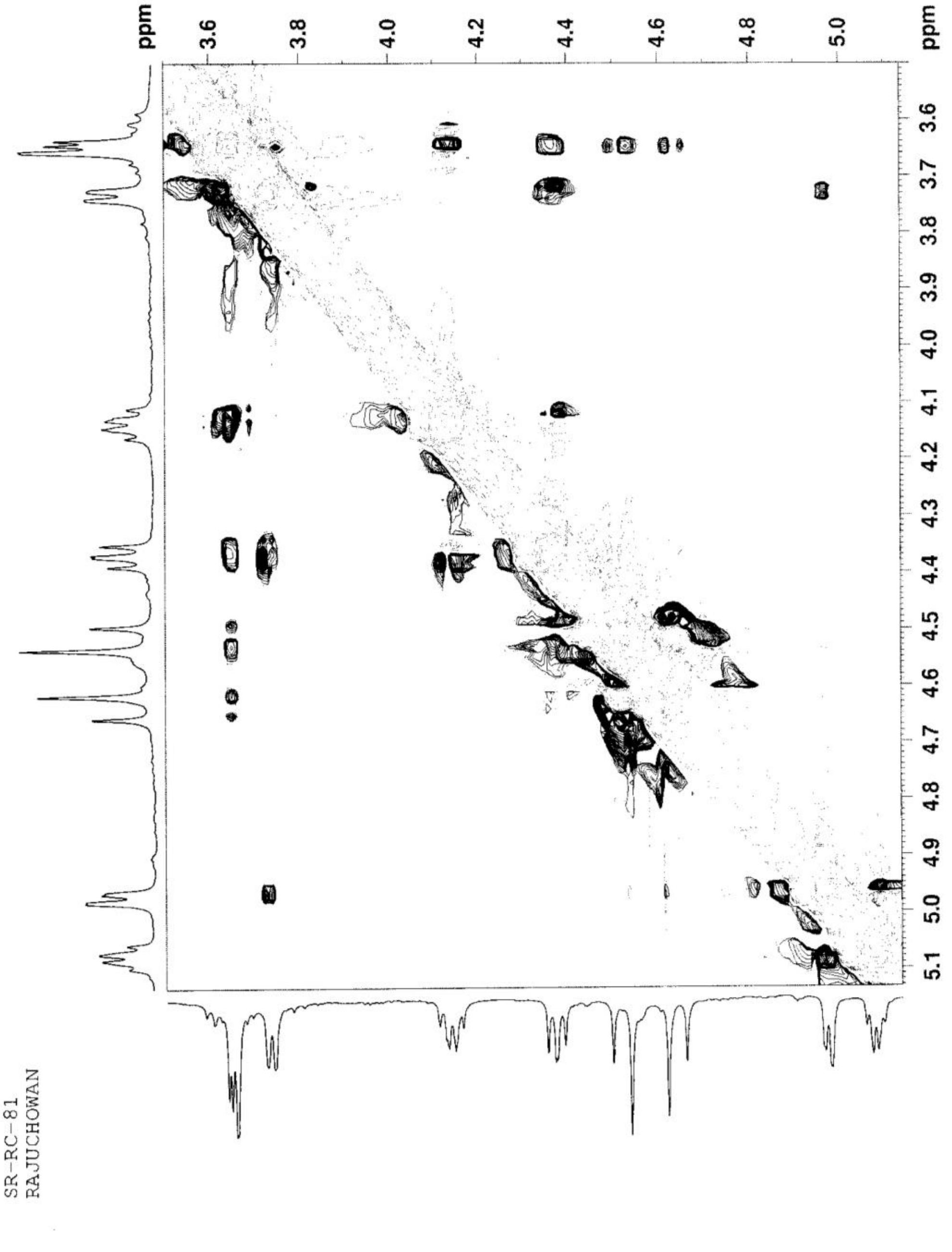
Pulse Sequence: NOESY1D

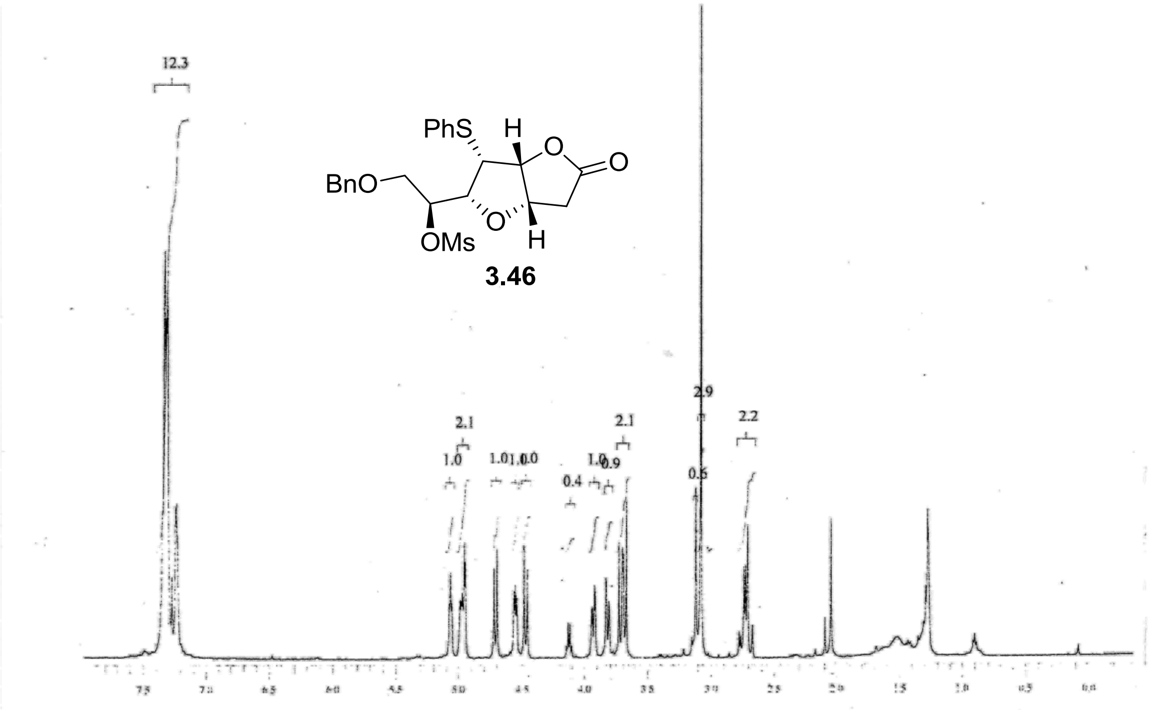


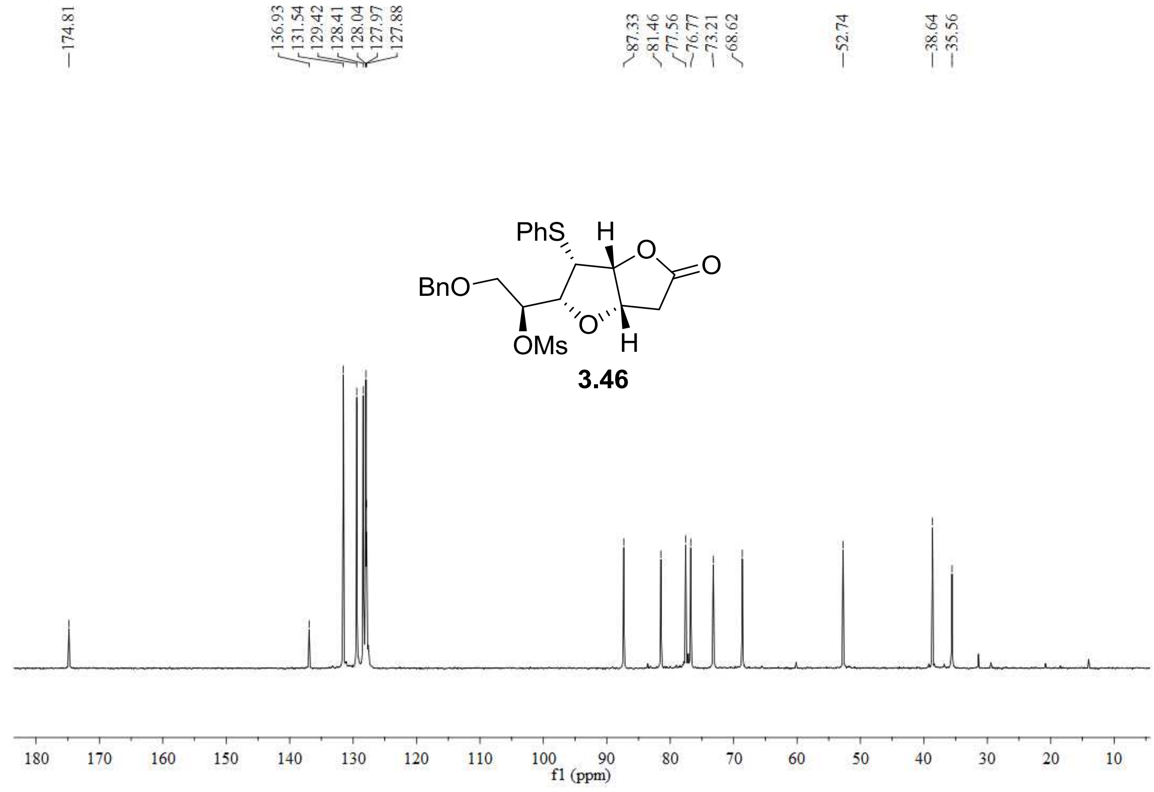
3.40

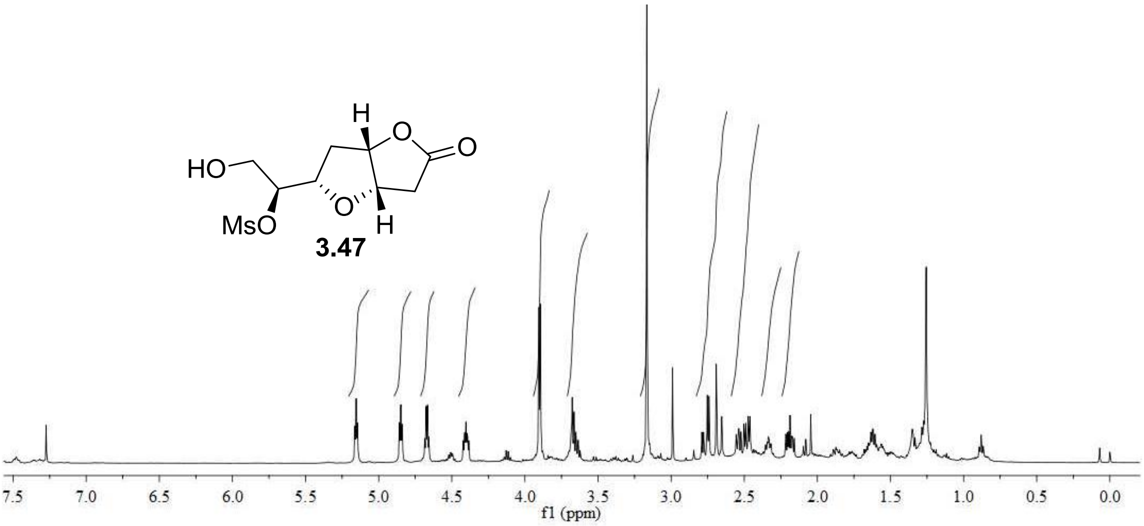

PhS
H
O
O
BnO
OH
O
H

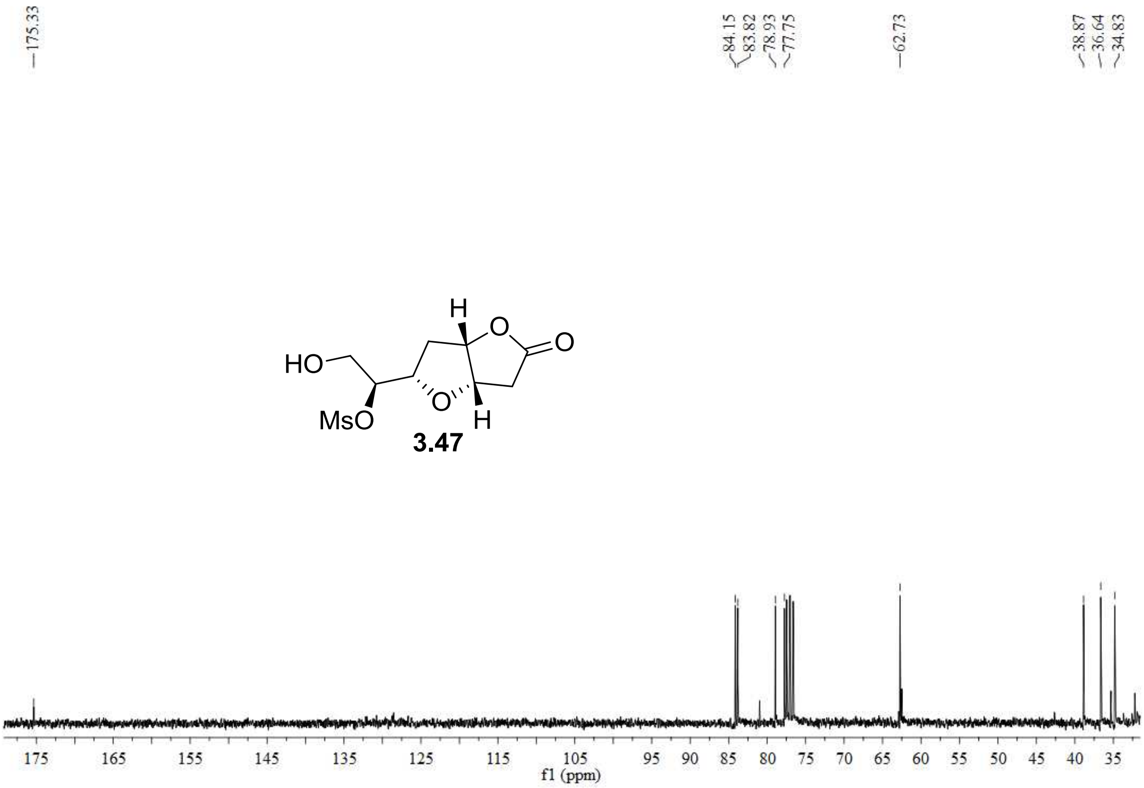
3.40

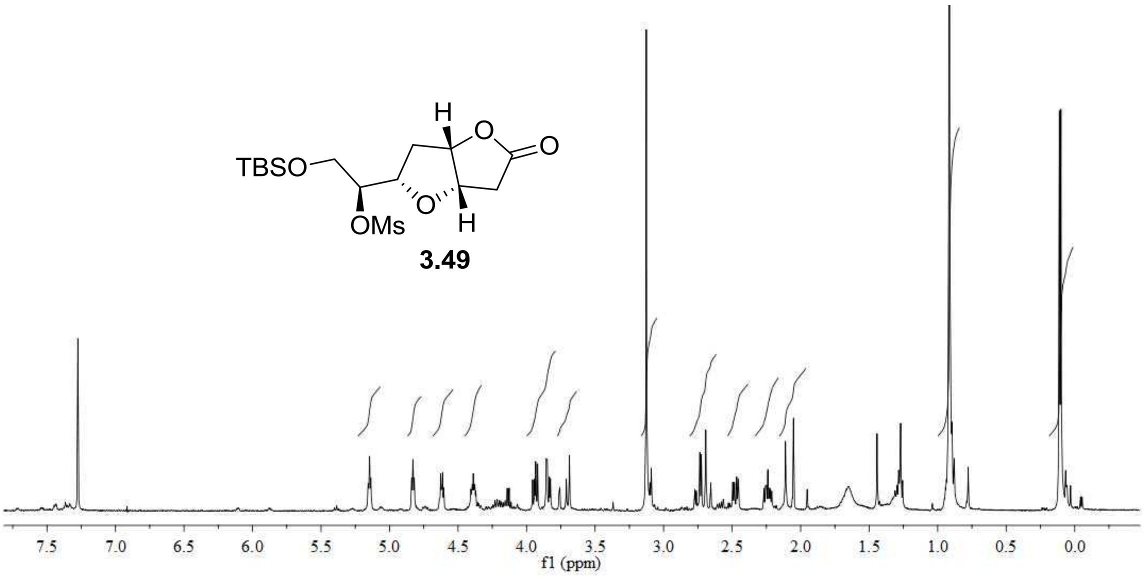

ppm
3.6
3.8
4.0
4.2
4.4
4.6
4.8
5.0
ppm
3.6
3.7
3.8
3.9
4.0
4.1
4.2
4.3
4.4
4.5
4.6
4.7
4.8
4.9
5.0
5.1
SR-RC-81
RAJUCHOWAN

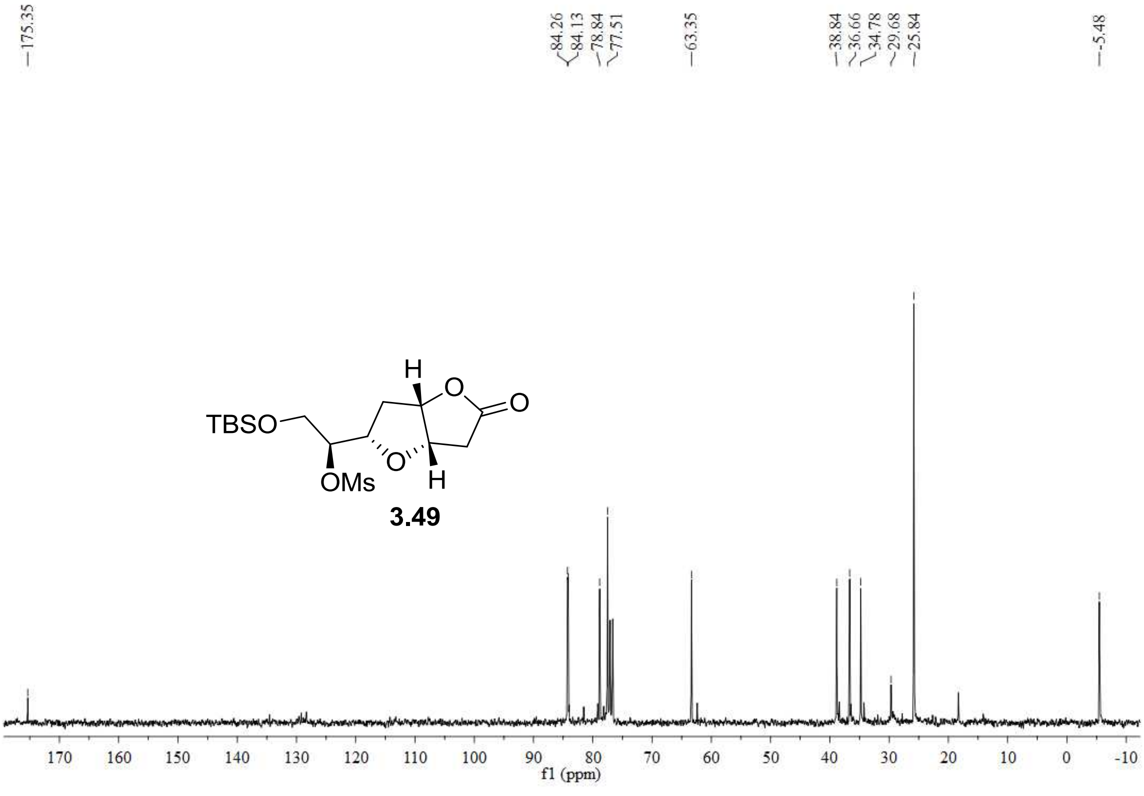

PhS
H
O
O
BnO
O
OMs
H
3.46
12.3
2.1
1.0
1.0
1.0
1.0
0.4
1.0
0.9
2.1
2.9
0.6
2.2
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

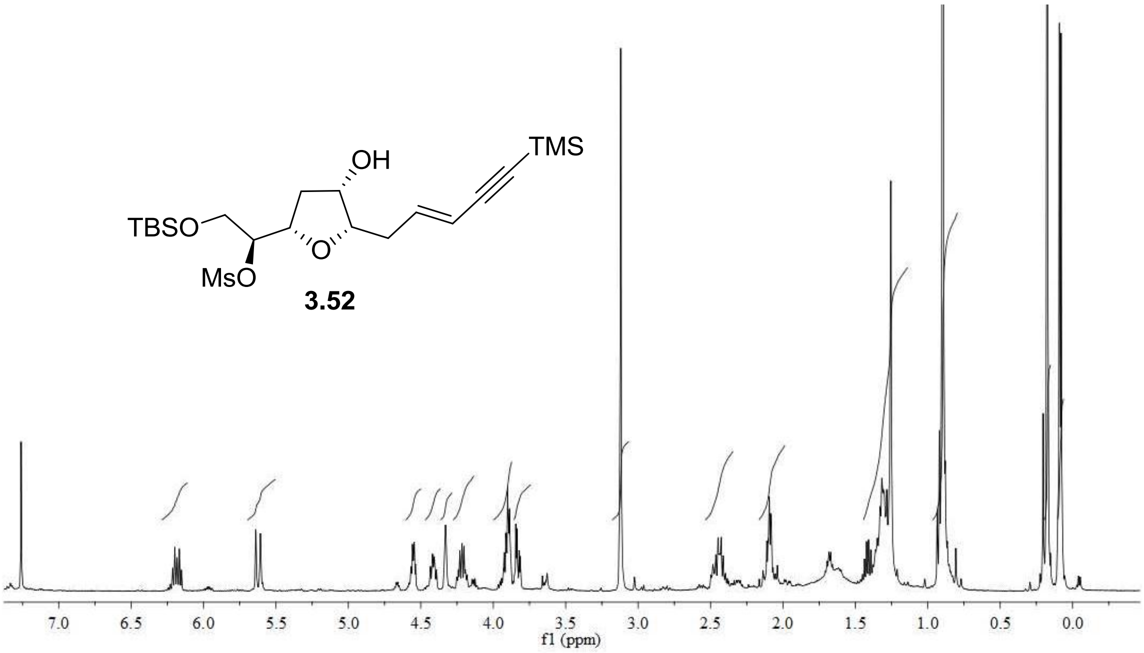

174.81
136.93
131.54
129.42
128.41
128.04
127.97
127.88
87.33
81.46
77.56
76.77
73.21
68.62
52.74
38.64
35.56
PhS
H
O
O
BnO
O
OMs
H
3.46
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


H
O
O
HO
MsO
O
H
3.47
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
f1 (ppm)

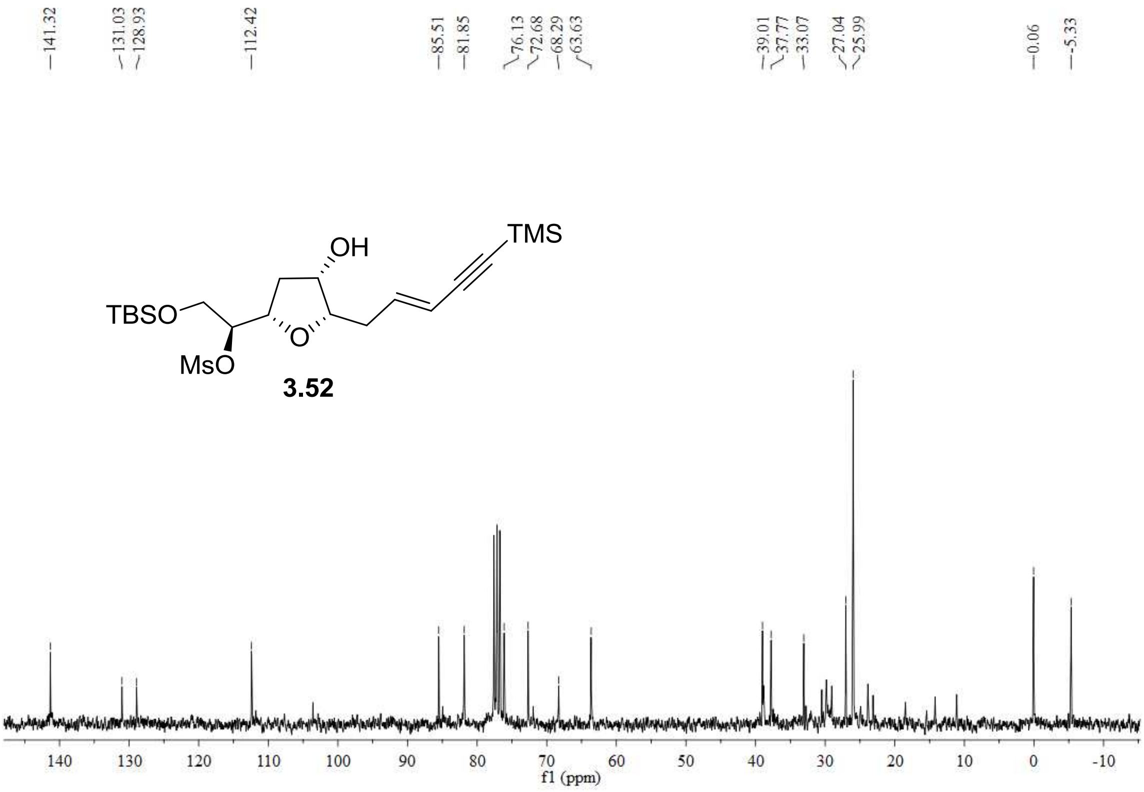

175.33
84.15
83.82
78.93
77.75
62.73
38.87
36.64
34.83
H
O
O
HO
MsO
O
H
3.47
175
165
155
145
135
125
115
105
95
90
85
80
75
70
65
60
55
50
45
40
35
f1 (ppm)


TBSO
OMs
O
H
O
O
H
3.49
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
f1 (ppm)

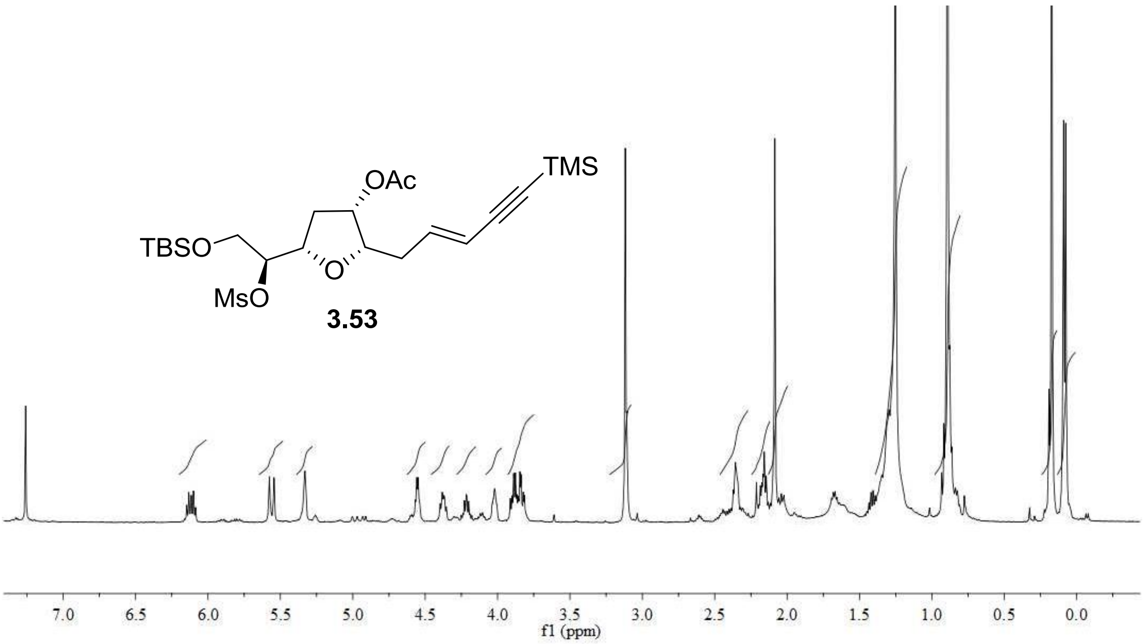

175.35
84.26
84.13
78.84
77.51
63.35
38.84
36.66
34.78
29.68
25.84
-5.48
TBSO
OMs
O
H
O
O
H
3.49
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


OH
TMS
TBSO
O
MsO
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
f1 (ppm)

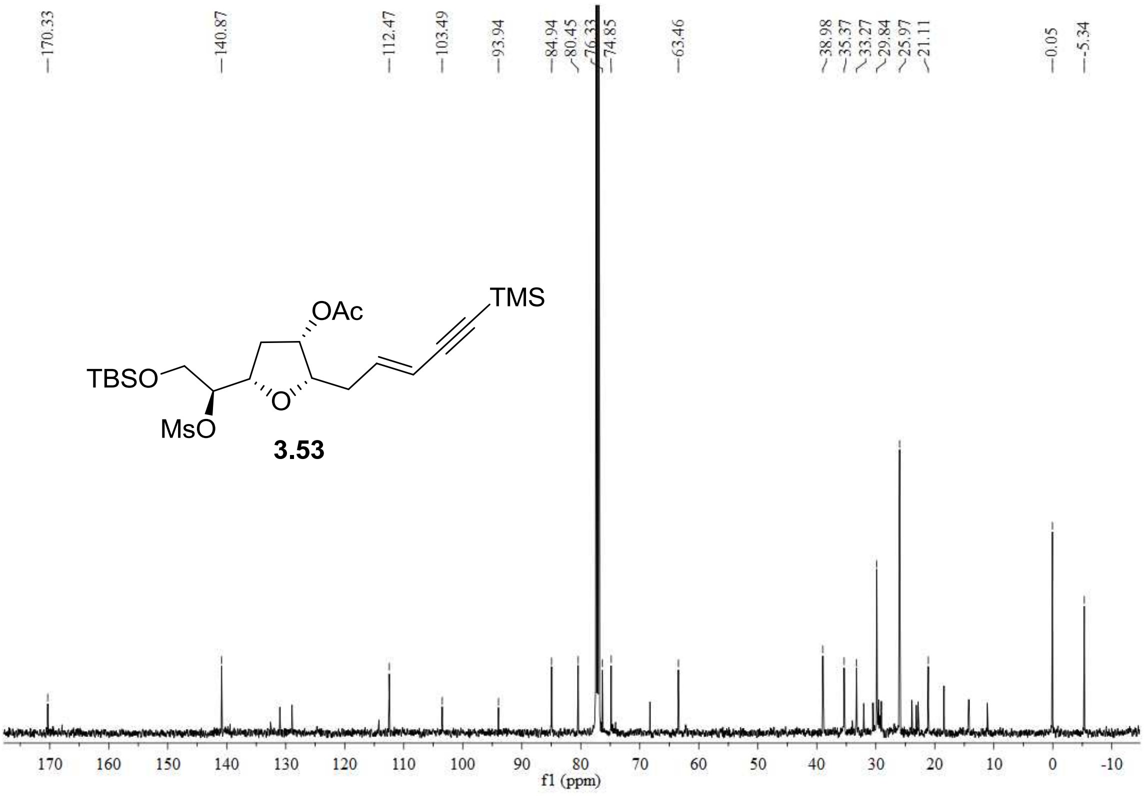
3.52


141.32
131.03
128.93
112.42
85.51
81.85
76.13
72.68
68.29
63.63
39.01
37.77
33.07
27.04
25.99
0.06
-5.33
OH
TMS
TBSO
O
MsO
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

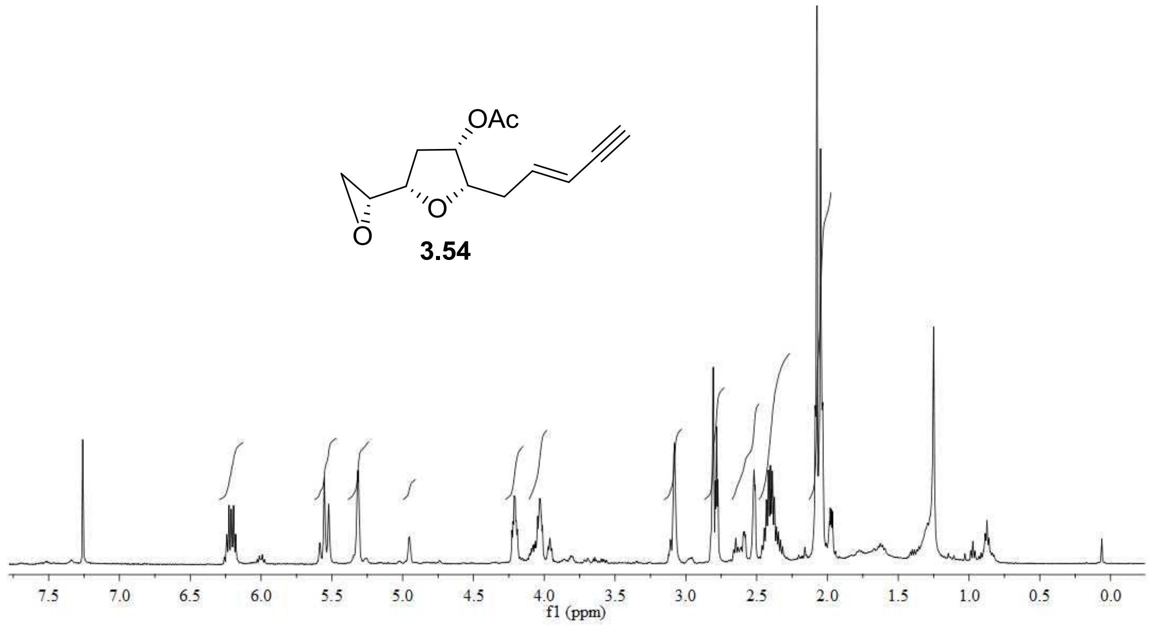
3.52


OAc
TMS
TBSO
O
MsO
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
f1 (ppm)

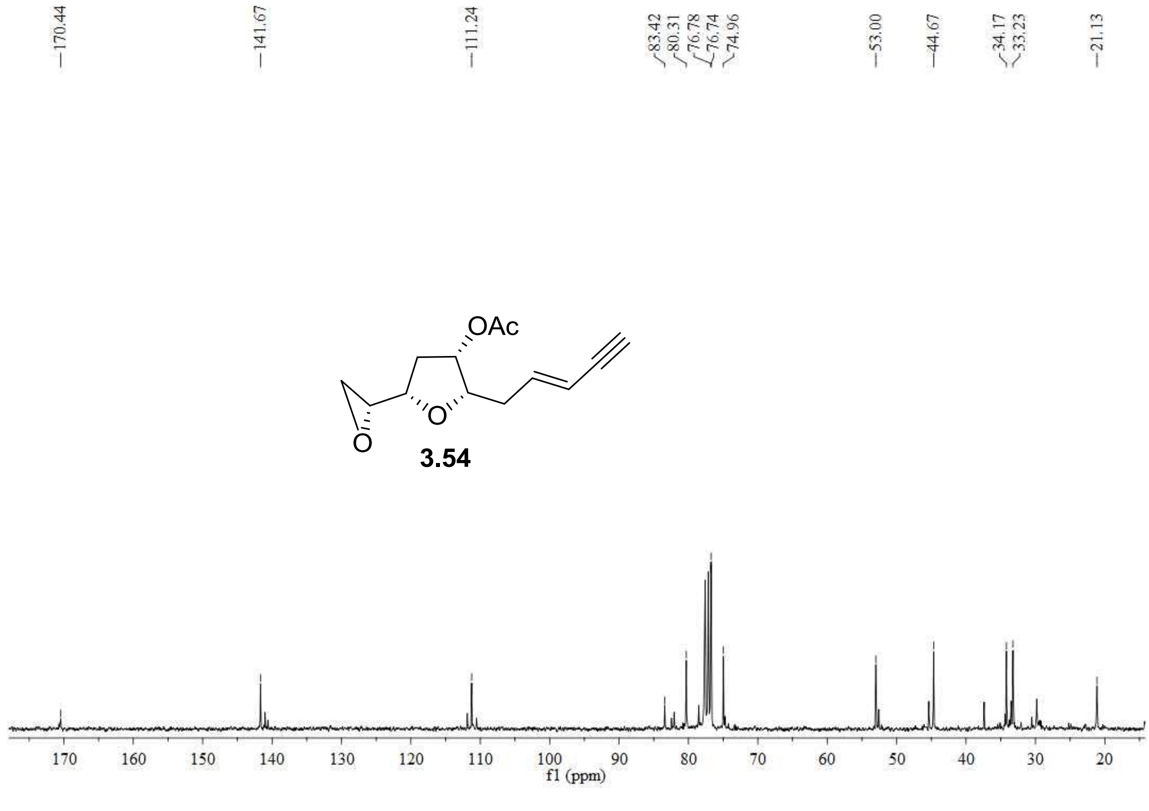
3.53


170.33
140.87
112.47
103.49
93.94
84.94
80.45
76.33
74.85
63.46
38.98
35.37
33.27
29.84
25.97
21.11
0.05
-5.34
OAc
TMS
TBSO
O
MsO
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

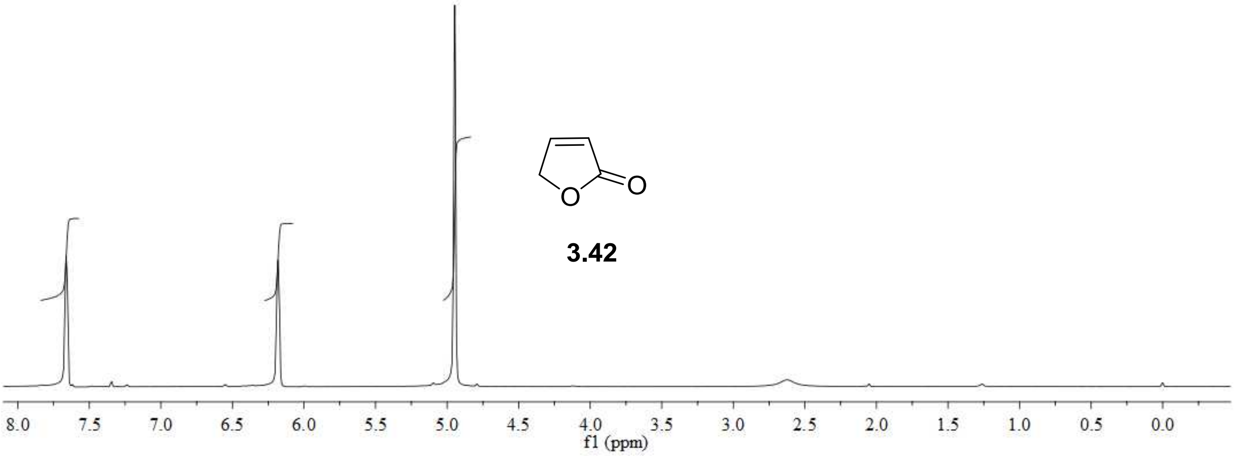
3.53


OAc
O
O
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
f1 (ppm)

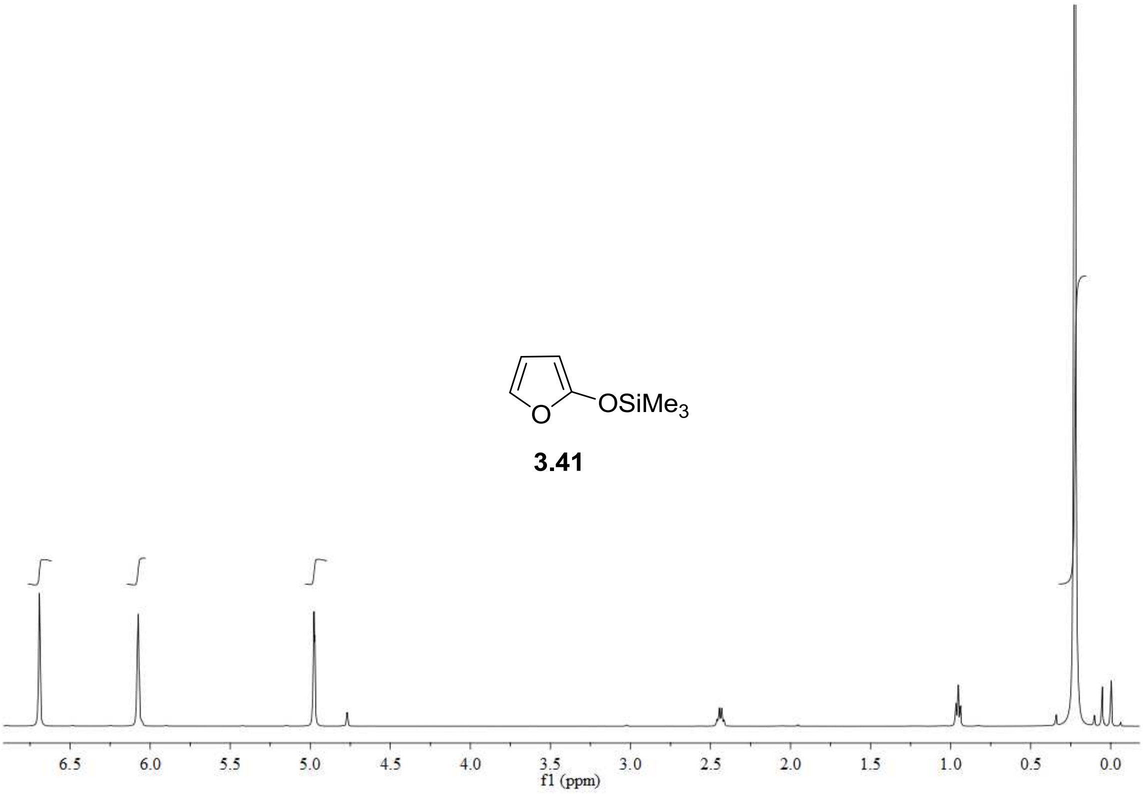
3.54


170.44
141.67
111.24
83.42
80.31
76.78
76.74
74.96
53.00
44.67
34.17
33.23
21.13
OAc
O
O
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

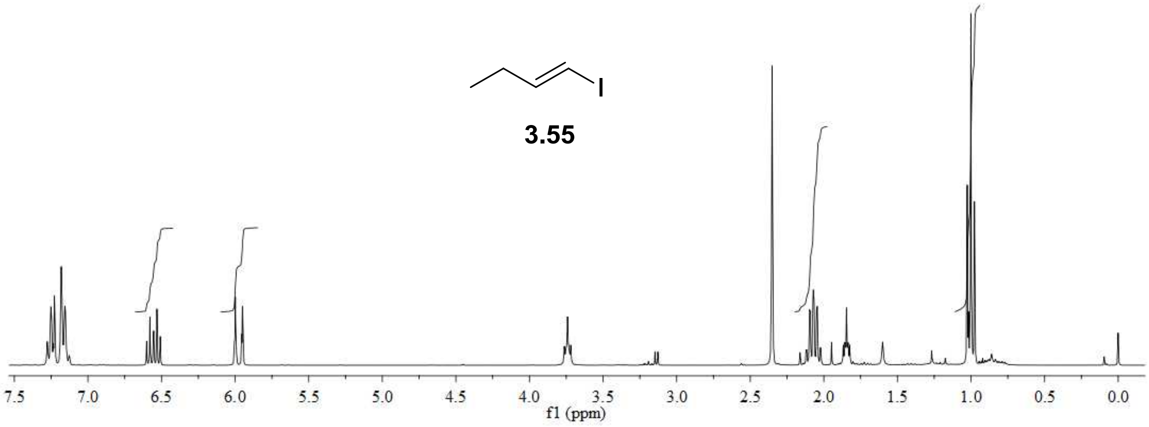
3.54


O
O
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

3.42

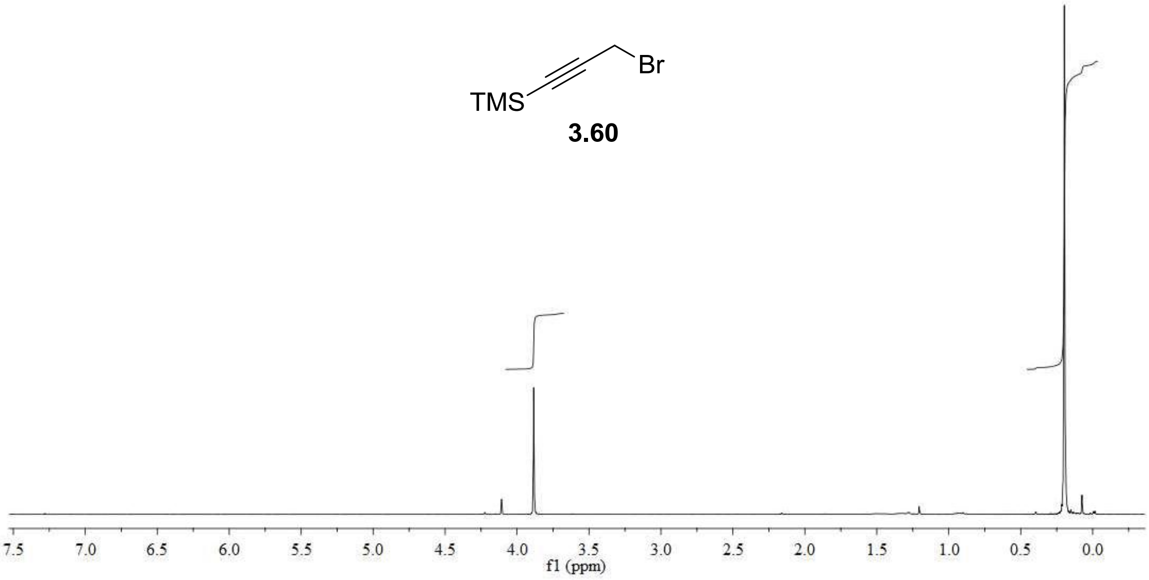

O
OSiMe3
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

3.41



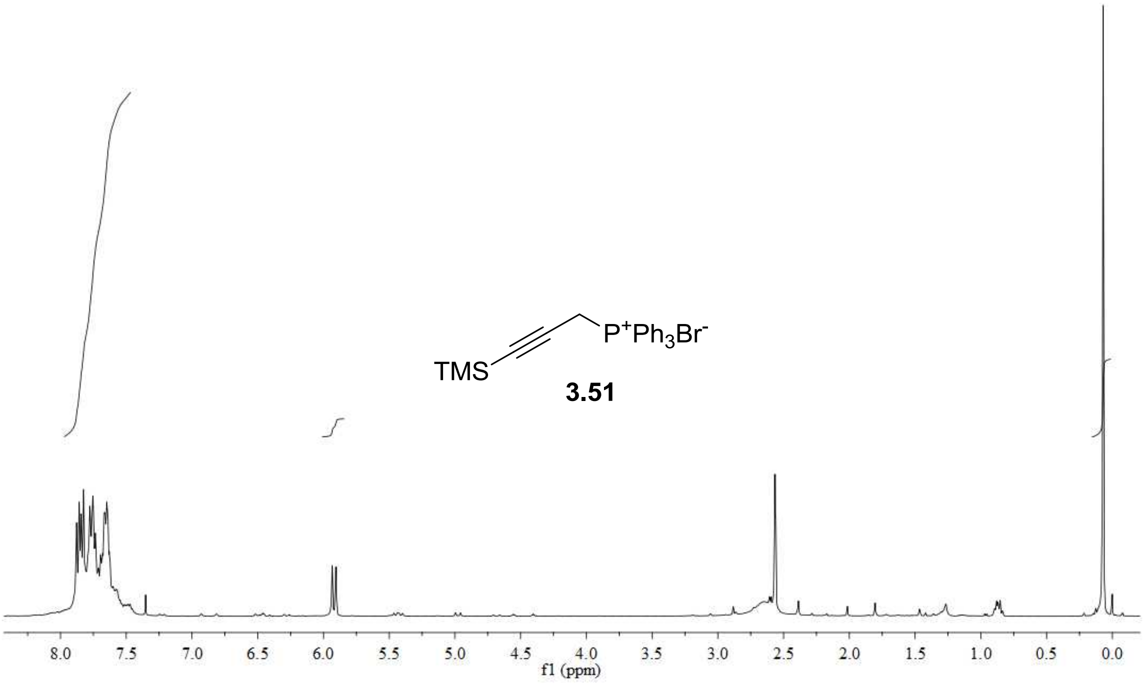
3.55

I
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
f1 (ppm)



3.60

TMS
Br
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
f1 (ppm)



3.51

List of Publications

The research work described in this thesis has been published in the following journals.

1. "Highly Stereoselective Preparation of Chiral α-Substituted Sulfides from α -Chloro Sulfides via 1,2-Asymmetric Induction". Sadagopan Raghavan, V. V. Kumar, L. Raju Chowhan. *Synlett.* **2010**, *12*, 1807–1810.
2. Diastereoselective Synthesis of Chiral α-Substituted Sulfides from α -Chloro Sulfides via 1,2-Asymmetric Induction". Sadagopan Raghavan, L. Raju Chowhan, V. V. Kumar. Manuscript under preparation.
3. Stereoselective synthesis towards Bullatanocin. Sadagopan Raghavan, L. Raju Chowhan. Manuscript under preparation.
4. Stereoselective synthesis towards (+) *trans*-Kumausyne. Sadagopan Raghavan, L. Raju Chowhan. Manuscript under preparation.

Participated Symposia

1. Poster presented in "International symposium on "Chemistry and Chemical Biology of Natural Products, (CCBNP–2012", August 2-4, 2012, at Indian Institute of Chemical Technology, Hyderabad, India.

2. "Nature Inspired Initiatives in Chemical Trends (NIICT)", August 1-4, 2013 at Indian Institute of Chemical Technology, Hyderabad, India.

Oral Presentation

1. Delivered a lecture on "Stereoselective synthesis of Bullatanocin employing α-chloro sulfide as intermediate", in "Dr. K.V.Rao Scientific society Award" on 25th April 2012.