SYNTHETIC STUDIES TOWARD NEW α-GLUCOSIDASE INHIBITORS PENAROLIDE SULFATE A_1, SCHULZEINES B AND C

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Synthetic Studies Toward New α-Glucosidase Inhibitors Penarolide Sulfate A_1, Schulzeines B And C

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OCTOBER 2008

DEDICATED

TO MY BELOVED

PARENTS

DECLARATION

The research work embodied in this thesis has been carried out at National Chemical Laboratory, Pune under the supervision of **Dr. M. K. Gurjar**, Division of Organic Chemistry, National Chemical Laboratory, Pune- 411008. This work is original and has not been submitted part or full, for any degree or diploma of this or any other University.

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CERTIFICATE

The research work presented in thesis entitled "**Synthetic Studies Toward New α-Glucosidase Inhibitors Penarolide Sulfate A_1, Schulzeines B And C**" has been carried out under my supervision and is a bonafide work of **Mr. Debabrata Bhattasali**. This work is original and has not been submitted for any other degree or diploma of this or any other University.

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Debabrata Bhattasali

ABBREVIATIONS

AcOH	-	Acetic acid
Ac_2O	-	Acetic anhydride
Boc	-	*tert*-Butyloxycarbonyl
Bn	-	Benzyl
BnBr	-	Benzyl bromide
m-CPBA	-	*meta*-Chloroperbenzoic acid
DBU	-	1,8-diazabicyclo[5,4,0]undec-7-ene
DCC	-	*N*,*N*′-Dicyclohexylcarbodiimide
DCM	-	Dichloromethane
DDQ	-	2,3-Dichloro-5,6-dicyano-*para*-benzoquinone
DET	-	Diethyl tartrate
DIPT	-	Diisopropyl tartrate
DIBAL-H	-	Diisobutylaluminium hydride
DIPEA	-	Diisopropylethyl amine
DME	-	Dimethoxyethane
DMF	-	*N*,*N*-Dimethyl formamide
DMAP	-	*N*,*N*-Dimethylamino pyridine
DMP	-	Dimethoxypropane
DMSO	-	Dimethyl sulfoxide
EDC	-	1-Ethyl-3-(3′-dimethylaminopropyl)-carbodiimide
Eqv	-	Equivalent
EtOAc	-	Ethyl acetate
EtOH	-	Ethanol
Et_3N	-	Triethyl amine
Et	-	Ethyl
FGT	-	Functional group transformations
HKR	-	Hydrolytic kinetic resolution

HMPA	-	Hexamethylphosphoricacid triamide
HOBt	-	1-Hydroxybenzotriazole
HWE	-	Horner-Wadsworth-Emmons
Im-H	-	Imidazole
LAH	-	Lithium aluminium hydride
LDA	-	Lithium diisopropylamide
LiHMDS	-	Lithium hexamethyldisilazide
MeOH	-	Methanol
MsCl	-	Methanesulfonyl chloride
MEM	-	Methoxyethoxymethyl
Me	-	Methyl
MOM	-	Methoxymethyl
NMO	-	*N*-Methylmorpholine-*N*-oxide
PCC	-	Pyridinium chlorochromate
Pd/C	-	Palladium on carbon
Ph	-	Phenyl
PMB	-	*para*-Methoxybenzyl
Py	-	Pyridine
rt	-	Room temperature
SAD	-	Sharpless aymmetric dihydroxylation
SAE	-	Sharpless asymmetric epoxidation
TBAF	-	Tetra-*n*-butylammonium fluoride
TBDPSCl	-	*tert*-Butyl diphenylchlorosilane
TBHP	-	*tert*-Butyl hydroperoxide
TBSCl	-	*tert*-Butyl dimethylchlorosilane
TMEDA	-	*N*,*N*,*N*′,*N*′-*Tet*ramethylethylenediamine
TMSOI	-	Trimethylsulfoxonium iodide
TMSI	-	Trimethylsilyl iodide
TMSOTf	-	Trimethylsilyl triflate
TPP	-	Triphenylphosphine
p-TSA	-	*para*-Toluenesulfonic acid
THF	-	Tetrahydrofuran

GENERAL REMARKS

❋ ^{1}H NMR spectra were recorded on AV-200 MHz, AV-400 MHz, and DRX-500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.

❋ ^{13}C NMR spectra were recorded on AV-50 MHz, AV-100 MHz, and DRX-125 MHz spectrometer

❋ ESI Mass spectra were recorded on Finngan MAT-1020 spectrometer at 70 *eV* using a direct inlet system.

❋ Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.

❋ Optical rotations were measured with a JASCO DIP 370 digital polarimeter.

❋ Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected.

❋ All reactions are monitored by Thin Layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV light, I_2 and anisaldehyde in ethanol as development reagents.

❋ All solvents and reagents were purified and dried by according to procedures given in Vogel's Text Book of Practical Organic Chemistry. All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.

❋ All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 40 °C.

❋ Silica gel (60–120) used for column chromatography was purchased from ACME Chemical Company, Mumbai, India.

❋ Independent numbering of compounds, schemes and figures has been employed for Abstract and each individual chapter.

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ABSTRACT

The thesis entitled **"Synthetic Studies Toward New α-Glucosidase Inhibitors Penarolide Sulfate A_1, Schulzeines B And C"** consists of three chapters. The first chapter deals with the basic introduction regarding various glycosidase inhibitors. The second chapter deliberates the synthetic efforts toward the total synthesis of penarolide sulfate A_1. The third chapter outlines the synthetic studies toward the total syntheses of schulzeines B and C. Chapter 2 and 3 are subdivided into the following sections; Present work, Experimental, Spectra and References.

Chapter 1: An Introduction to Glycosidase Inhibitors

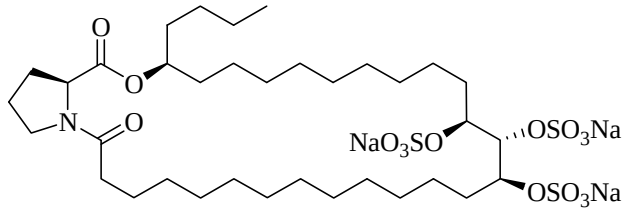
The first chapter of this dissertation summarizes the role of glycosidases in hydrolyzing the most stable covalent bond found within natural biopolymers, the glycosidic bond. It presents an overview of the classification and mechanistic approach of glycosidases. However, glycosidase inhibitors are of mere current interest since they describe the mechanism of enzyme-catalysed glycoside hydrolysis which has a direct application in medicinal chemistry. Thus, the chapter outlines the importance of glycosidase inhibitors as drugs and therapeutic agents. Glycosidases are involved in the biosynthesis of the oligosaccharide chains and quality control mechanisms in the endoplasmic reticulum of the N-linked glycoproteins. Inhibition of these glycosidases can have profound effects on quality control, maturation, transport, and secretion of glycoproteins that alters the cell-cell or cell-virus recognition processes. This principle is the basis for the potential use of glycosidase inhibitors as drugs in viral infection, diabetes, cancer, and genetic disorders. The chapter also gives a brief synopsis about the structure-activity relation of drugs and identification of the pharmacophore, in particular glycosidase inhibitors.

Chapter 2: Total Synthesis of Penarolide Sulfate A_1

In 2000, Fusetani and co-workers reported the isolation, structure elucidation, and biological activity of new α-glucosidase inhibitors penarolide sulfate A_1 (**1**) and A_2 (**2**),

from the marine sponge *Penares* sp., with IC_{50} values of 1.2 and 1.5 μg/mL, respectively (Figure 1). The constitution and the relative stereochemistry of penarolide sulfate A_1 and A_2 were elucidated by chemical degradation and extensive 2D-NMR studies; the absolute configuration was established by application of Mosher's method. Penarolide Sulfate A_1 and A_2 are 30- and 31-membered macrolides encompassing a proline residue and three sulfate groups.

Figure 1. *Penarolide sulfate A_1 (**1**) and A_2 (**2**).*



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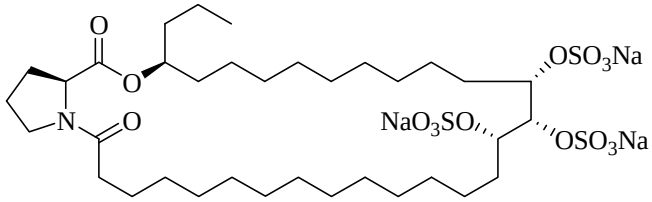

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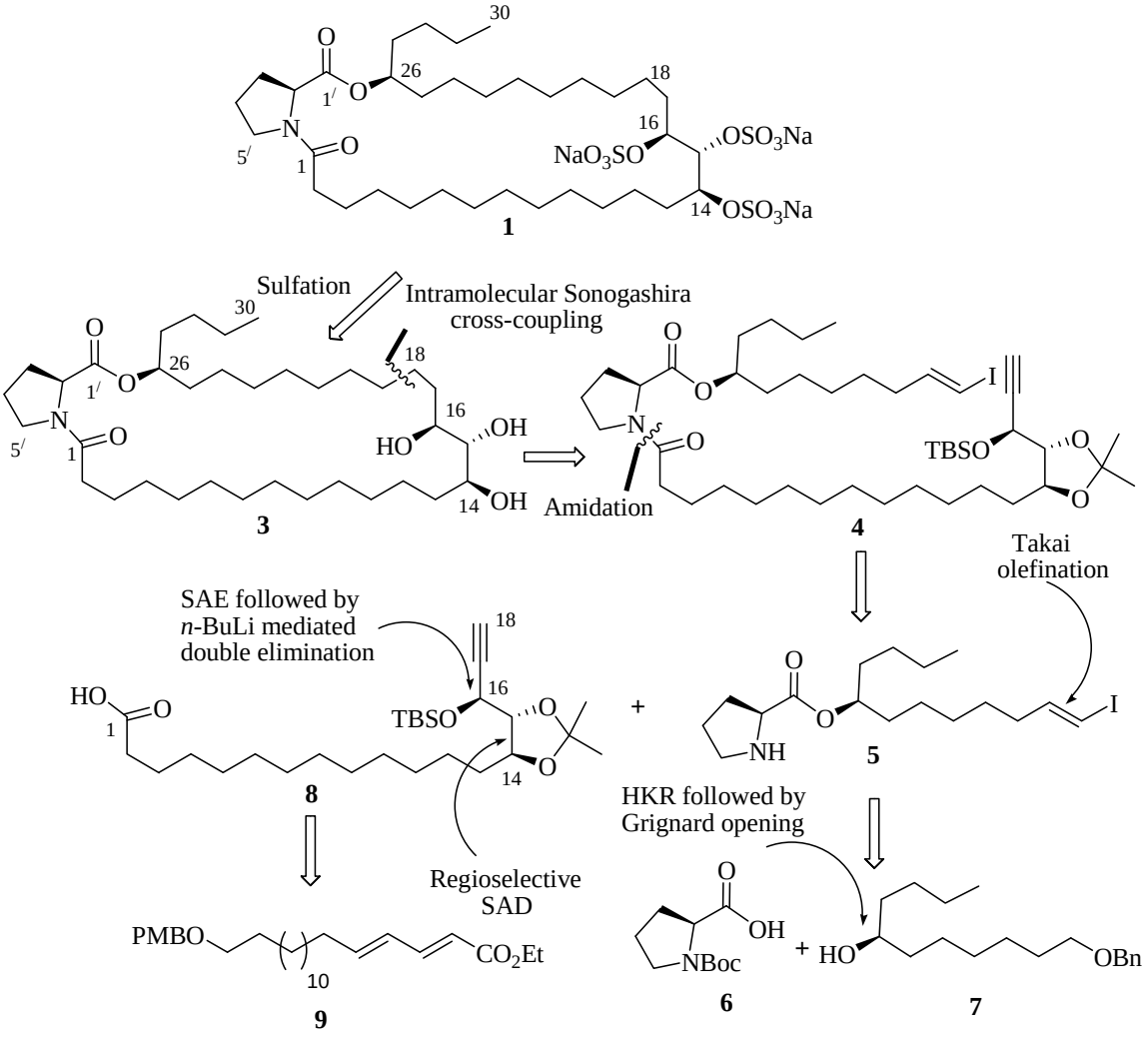
The intriguing structural features, noteworthy biological profiles, and limited availability make penarolide sulfate A_1 (**1**) and A_2 (**2**) attractive targets for total synthesis. No report has yet appeared on the total synthesis of any of these natural products. We report herein a novel convergent strategy towards the total synthesis of penarolide sulfate A_1. The highlight of this effort is an efficient assembly of its 30-membered macrolide core through sequential amidation and macrocyclization *via* intramolecular Sonogashira cross-coupling reaction.

Retrosynthesis carried on the compound **1** into three segments **6, 7** and **8** provided the impetus for our work (Scheme 1). The assembly of the 30-membered macrocyclic core was envisioned to be a sequence of amidation between the C_1-C_{18} acid **8** and amine **5** segments followed by intramolecular Sonogashira reaction of the amide **4** thus formed. The key segment **5** would be elaborated from a chiral building block **7** by simple esterification reaction with commercially available N-Boc-L-proline **6**. Our plan for the

synthesis of C_1-C_{18} subunit **8** is based upon the regioselective Sharpless asymmetric dihydroxylation (SAD) and Sharpless asymmetric epoxidation (SAE) reactions.

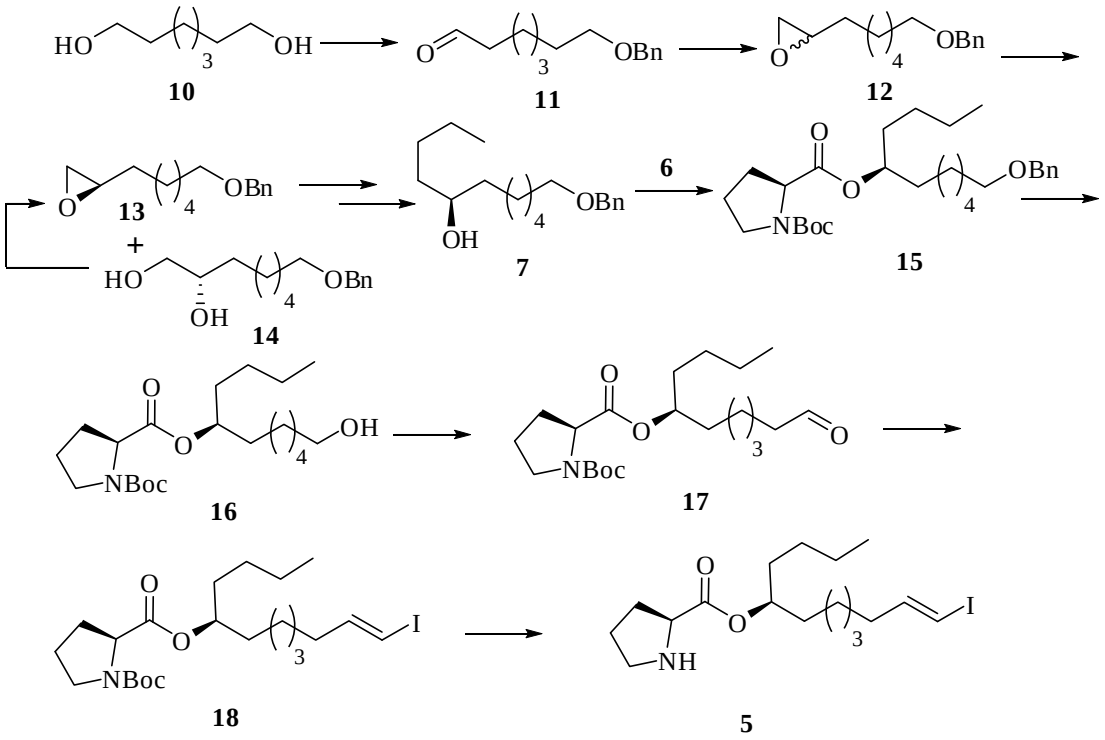
Scheme 1. *Retrosynthetic analysis*.



Synthesis of the amine building block **5** was started by the reaction of the known aldehyde **11** by following the Corey-Chakovsky reaction condition to produce the racemic terminal epoxide **12** (Scheme 2). Compound **12** was then subjected to hydrolytic kinetic resolution (HKR) using 0.5 mol% of (*R*,*R*)-salen-Co(III)OAc and 0.55 eqv of distilled water at 0 °C to afford the chiral epoxide **13** with 98.8% *ee* along with the diol **14** with 93.3% *ee*. The undesired diol **14** was converted to the required epoxide **13** following a known strategy. Secondary alcohol **7** was derived by the regioselective ring opening of **13** with the *n*-propylmagnesium bromide in the presence of CuCN in dry

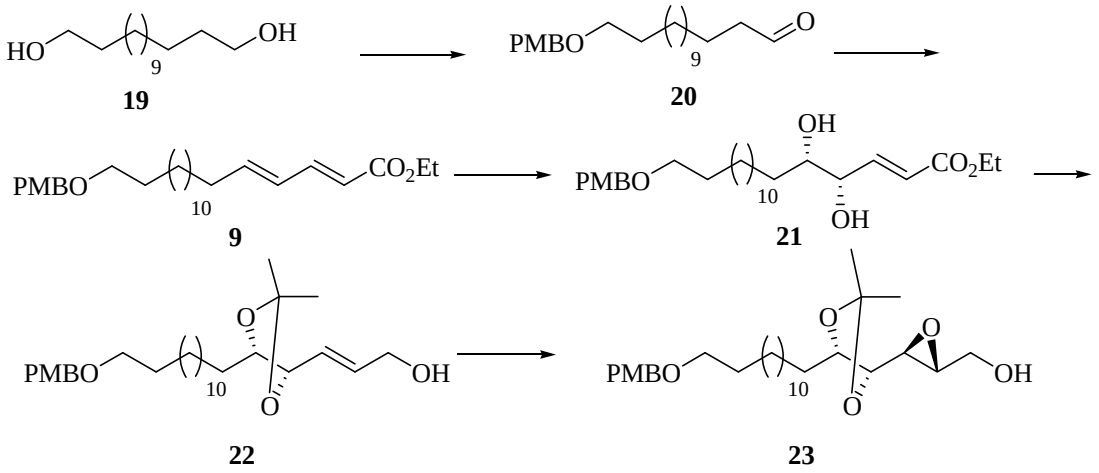
THF. Esterification of compound **7** with commercially available N-Boc-L-proline under standard EDC, DMAP conditions afforded compound **15** in 96% yield. In a sequence of three simple chemical transformation *viz.* hydrogenolysis, IBX oxidation and Takai olefination, compound **15** was transformed to compound **18** in 70% yield over three steps. Deprotection of the *t*-butyloxycarbonyl protecting group under acidic condition gave the target amine building block **5** in 81% yield.

Scheme 2



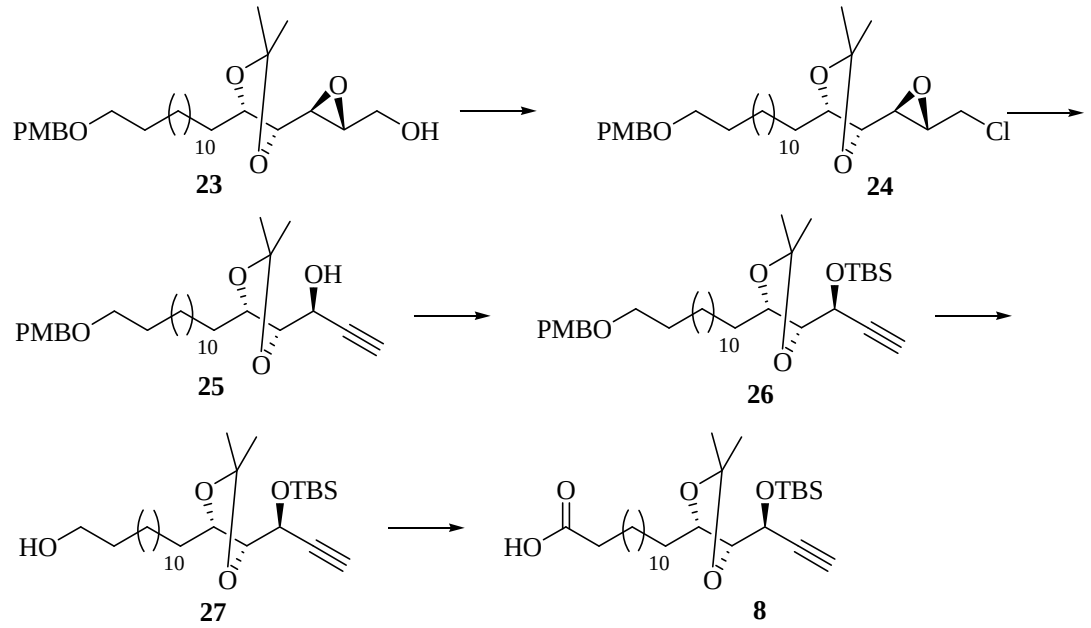
We next turned our attention to the synthesis of the acid segment **8**. The synthesis of the C_1-C_{18} segment **8** was initiated with the introduction of the diene appendage at C_{14} of the aldehyde **20** *via* a Horner-Wadsworth-Emmons reaction (Scheme 3). Asymmetric dihydroxylation of **9** (*E*, *E*-dienoate) using $(DHQ)_2PHAL$ as the chiral ligand at 0 °C for 6 h gave exclusively the regioselective dihydroxy derivative **21** (*ee* = 98.4%) in 70% yield. Protection of the diol group present in compound **21** as an isopropylidene derivative followed by reduction with DIBAL-H gave the alcohol **22**.

Scheme 3



Sharpless asymmetric epoxidation on **22** produced **23** as the single diastereomer (confirmed from its ^{13}C NMR spectra). The epoxy chloride **24** was then prepared from **23** by treating with TPP and CCl_4 under reflux condition (Scheme 4). Compound **24** on treatment with excess *n*-BuLi (3 eqv) afforded the alkynol **25**.

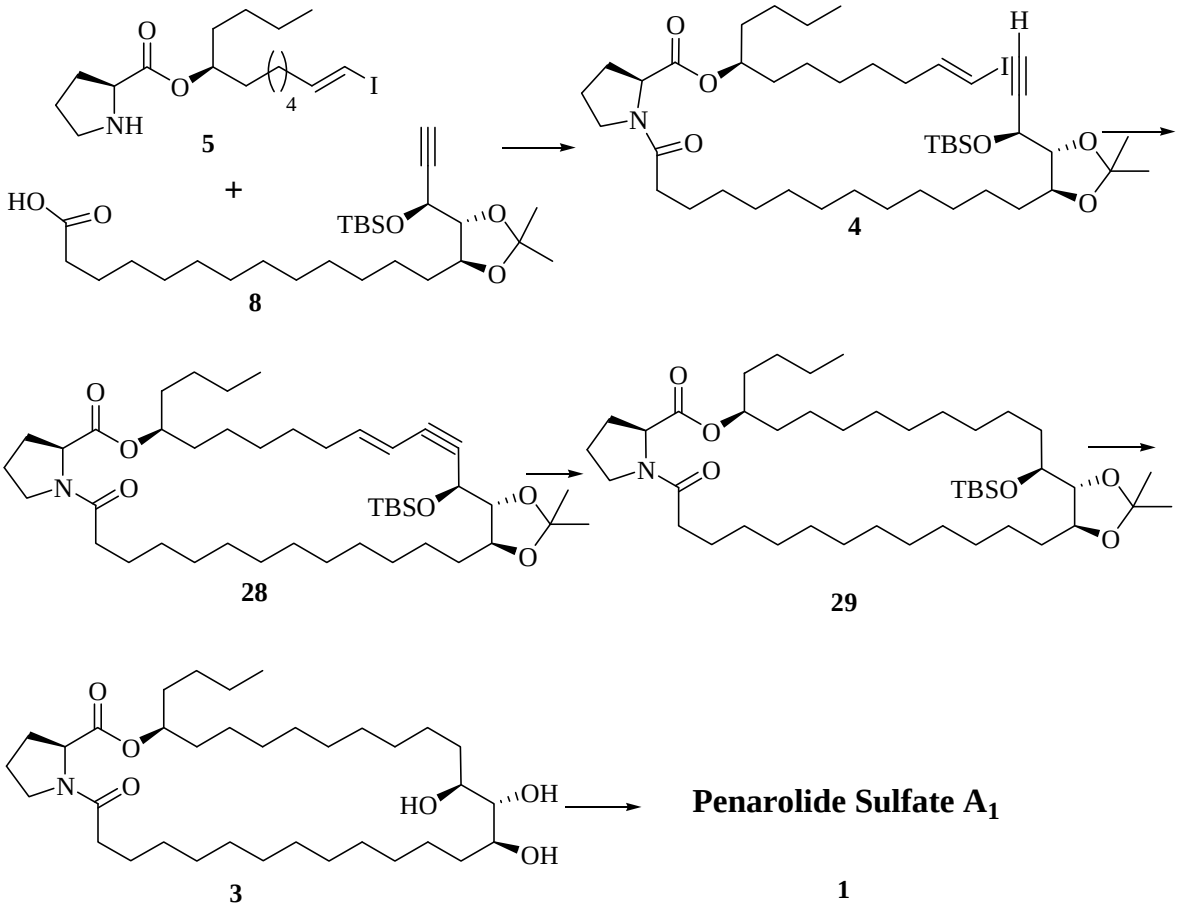
Scheme 4



Protection of the secondary alcohol as its TBS ether followed by oxidative removal of the PMB ether with DDQ yielded the penultimate C_{18} alcohol **27**. Oxidation

of **27** to the corresponding aldehyde with IBX followed by further oxidation with $NaClO_2$ in *t*-BuOH at 0 °C gave the required C_{18} acid **8** in 88% yield.

Scheme 5



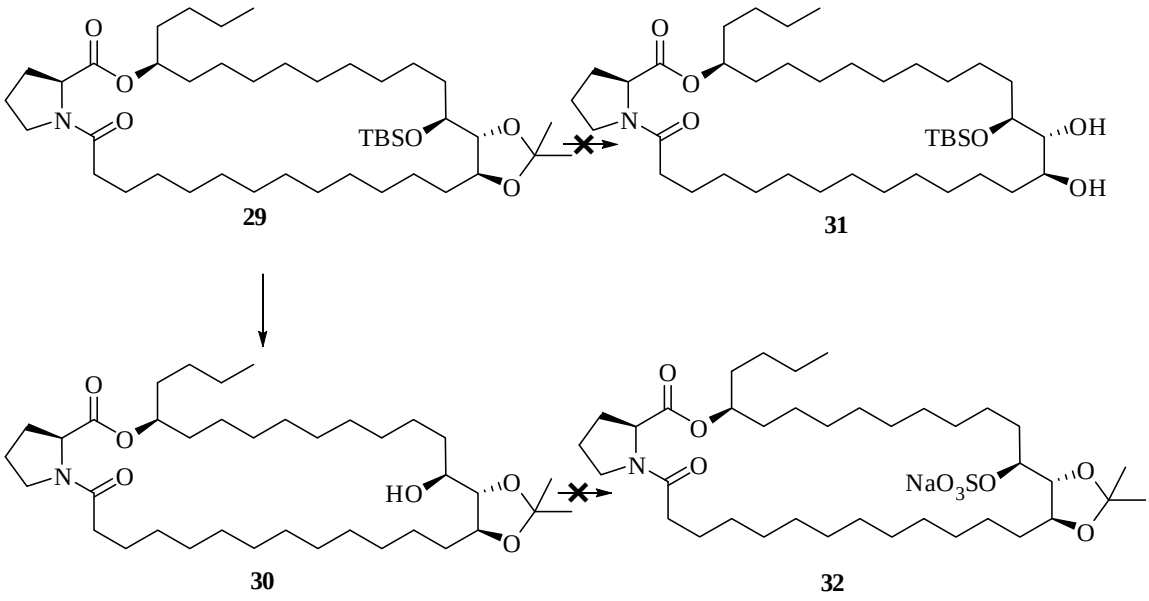
Assembly of fragments (**5** and **8**) to the target molecule **1** was our next goal. EDC-HOBt-mediated coupling of amine **5** with the carboxylic acid **8** was facile and afforded the coupled product **4** in 95% yield (Scheme 5). Formation of the 30-membered macrocyclic ring following intramolecular Sonogashira cross-coupling reaction was attempted next. Several reaction conditions to tune the macrocyclization under Sonogashira coupling conditions were performed. Finally, the reagent combination of tetrakis(triphenylphosphine)-palladium(0) and CuI in anhydrous diethyl amine at 0 ^{o}C for 30 min gave the best result. Reduction of both double and triple bond present in the macrocyle by Raney Ni in ethanol under hydrogen atmosphere and complete deprotection using *p*-TSA in methanol led to the formation of the triol **3**. The spectral as well as

analytical data of synthetic **3** was in good agreement with the assigned structure. Next we attempted persulfation on compound **3**. After exploiting various standard reaction conditions for persulfation we were dismayed to obtain complex intractable reaction mixtures in all cases. Finally, reaction of compound **3** with $Py.SO_3$ complex for 36 h followed by quenching the reaction with water and subsequent basification (pH = 9) using saturated solution of $NaHCO_3$ leads to the formation of the natural product penarolide sulfate A_1 in 84% yield. The spectral and analytical data of synthetic **1** were in complete conformity with that isolated by Fusetani *et al.*

At this stage, we thought it would be pertinent to evaluate the enzyme inhibition activity of compound **3** too, because then we would be able to rationalize the importance of sulfate groups toward biological activity for these classes of molecules.

Thus, enzyme inhibition assays were performed on desulfated penarolide sulfate **3**. From the enzyme inhibition studies it was concluded that compound **3** also acts as α-glucosidase inhibitor (IC_{50} = 166 μM); the extent of inhibition is much less than that of the parent molecule **1**. Compound **3** inhibited β-glucosidase, β-mannosidase and β-galactosidase, but the extent of inhibition towards the corresponding α-analogs was negligible at 1mM inhibitor concentration.

Scheme 6



Since compound **3** being found weakly active in comparison with compound **1**, we attempted the preparation of the partially sulfated derivatives of **3**. For this endeavor, controlled deprotection of compound **29** using TBAF in THF resulted in the formation of compound **30** in 94% yield (Scheme 6).

Following our earlier method of sulfation, compound **30** furnished number of products which we failed to characterize. Similarly, controlled deprotection of isopropylidene group present in compound **29** in presence of TBS group was tried to obtain the dihydroxy derivative **31**. Various Lewis acid [$Zn(NO_3)_2.6H_2O$, $CuCl_2.2H_20$ in ethanol, $FeCl_3.6H_2O/SiO_2$] mediated reaction conditions at room temperature were found to be futile and we ended up with unreacted starting material. However, by employing harsh reaction conditions (heating from 70 ^oC to 110 ^oC in the presence of earlier mentioned Lewis acids) furnished the completely deprotected triol **3**. TMSOTf mediated opening of isopropylidene group also failed to furnish the desired product **31**. Since, we were unable to prepare the partially sulfated derivatives of compound **3** their bioevaluation was not possible and the role of sulfate groups toward biological activity remained inconclusive for this class of natural product.

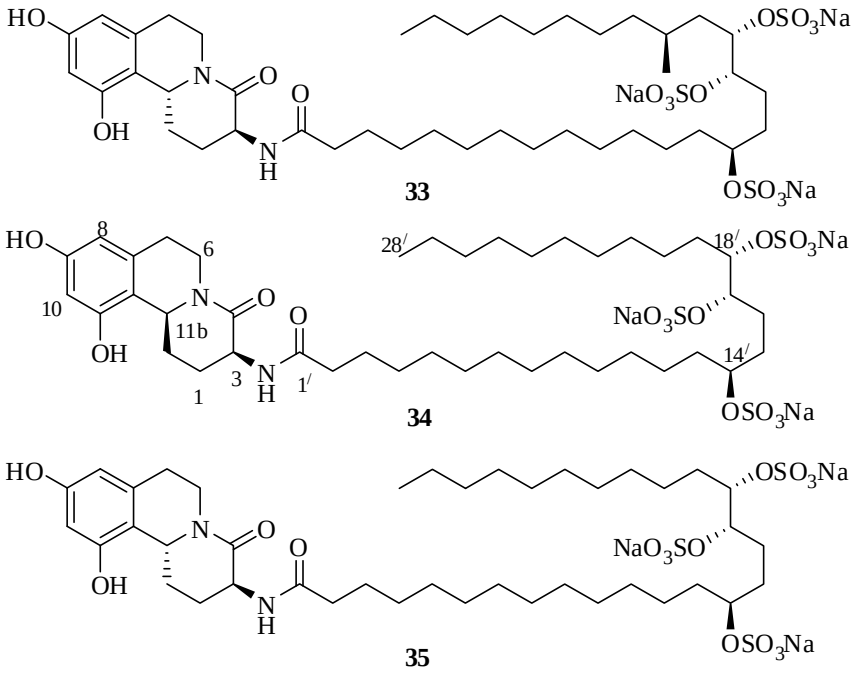
In conclusion, the first total synthesis of penarolide sulfate A_1 is documented. The salient feature of our synthetic protocol was intramolecular Sonogashira cross-coupling reaction for the construction of key 30-membered macrocyclic ring. Regioselective Sharpless asymmetric dihydroxylation, Sharpless asymmetric epoxidation and Jacobsen HKR were employed for the generation of four asymmetric centers present in the molecule. A biological activity profile of the desulfated penarolide sulfate A_1 (**3**) has also been disclosed. The reported approach is convergent in nature and provides considerable flexibility for the synthesis of related unnatural analogues.

Chapter 3: Studies toward the Total Syntheses of Schulzeines B and C

Three new α-glucosidase inhibitors, schulzeines A-C (**33**-**35**), (Figure 2) were isolated by Fusetani and co-workers from the marine sponge, *Penares schulzei* in 2004. From the structural standpoint, schulzeines belong to the family of isoquinoline alkaloids, encompassing two amino acids, and C_{28} fatty acid side chain, the last of which is sulfated. Inspection of structures revealed that compound **33** and **34** have a common C_{28} fatty acid

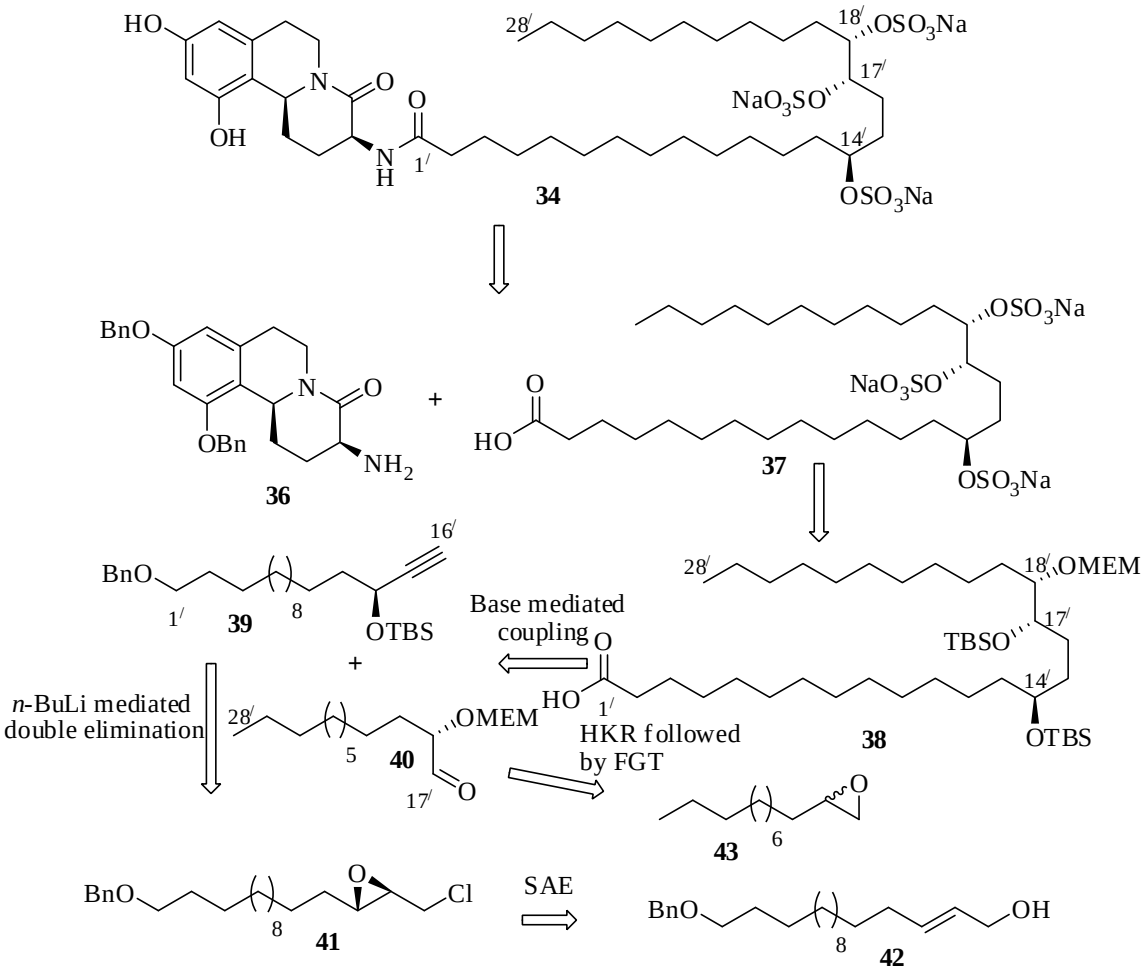
side chain and are epimeric at C_{11b} of the tetrahydroisoquinoline unit. Absolute stereochemistry of schulzeines was determined by application of the modified Mosher analysis to fragments obtained by chemical degradation. Schulzeines A-C inhibits α-glucosidase with IC_{50} values of 48-170 nM.

Figure 2. *Schulzeines A-C (**33-35**).*



Fascinated by the intriguing biological activity, we selected these isoquinoline alkaloids as targets for the total synthesis. Herein we describe the stereoselective synthesis of the C_{28} fatty acid fragments of schulzeine B (**34**) and C (**35**). As shown in the retrosynthetic Scheme 7, the key reactions in our intended total synthesis are (i) Sharpless asymmetric epoxidation reaction of the olefin **42**, (ii) *n*-BuLi mediated double elimination reaction of the epoxy Chloride **41**, (iii) resolution of the racemic epoxide **43** by means of Jacobsen hydrolytic kinetic resolution and finally (iv) coupling of the alkyne compound **39** with the α-substituted aldehyde **40**.

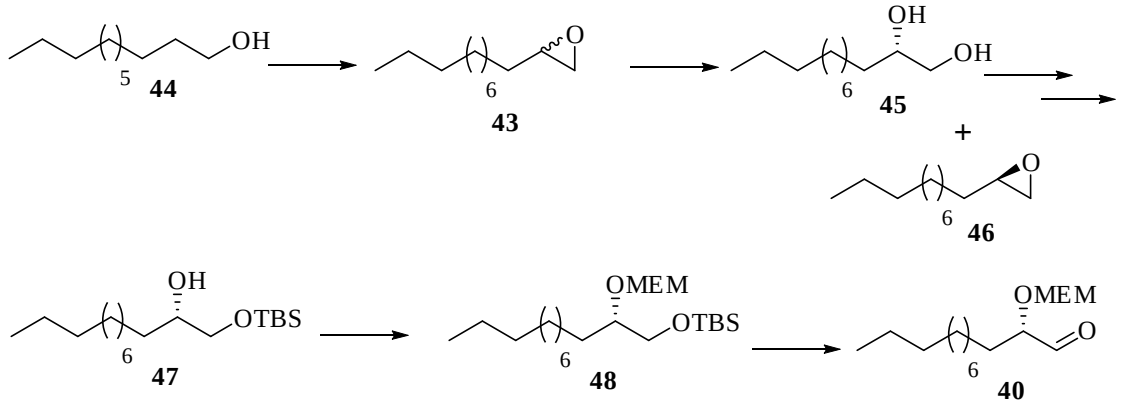
Scheme 7. *Retrosynthetic analysis*.



Our synthesis towards the aldehyde **40** commenced with commercially available 1-undecanol (**44**). Oxidation of **44** by means of IBX in DMSO, followed by treatment with trimethylsulfoxonium iodide and sodium hydride resulted in the formation of the racemic epoxide **43** (Scheme 8). This racemic epoxide **43** was then resolved by treating with H_2O 0.55 eqv. and (*R*,*R*)-Co(III)-Salen acetate complex (Jacobsen's hydrolytic kinetic resolution). Separation of the resolved epoxide **46** and the diol **45** was carried out by silica gel column chromatography. The diol **45** was obtained as a white solid and the enantiomeric purity of the diol was determined by comparing optical rotation values from the literature. Primary hydroxyl group of compound **45** was protected selectively as the TBS ether by means of TBSCl and imidazole in anhydrous CH_2Cl_2 to produce compound **47**. Secondary hydroxyl group present in compound **47** was protected as MEM ether by

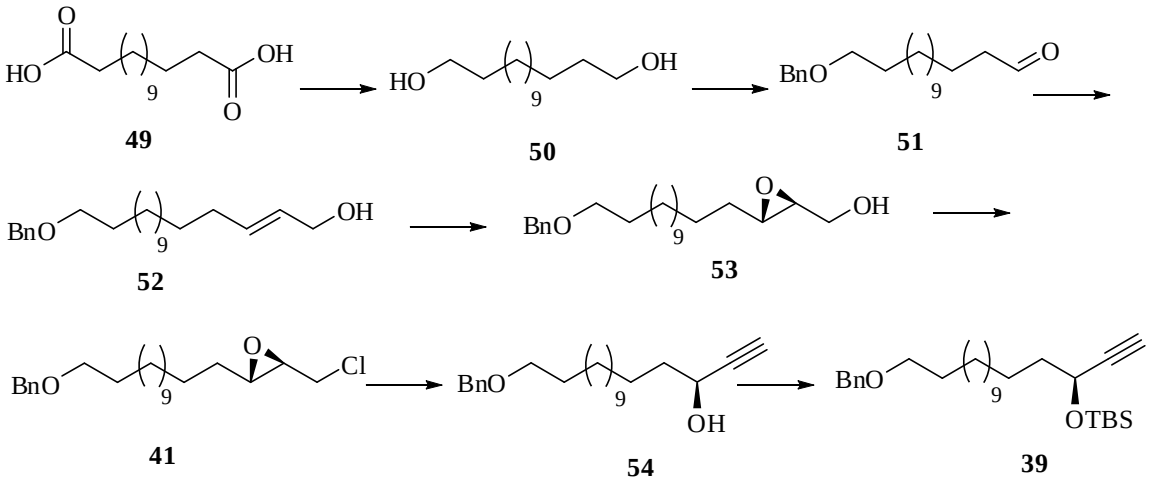
reacting with MEMCl in presence of DIPEA to produce compound **48**. Deprotection of TBS group by TBAF followed by oxidation using IBX afforded the requisite aldehyde **40**.

Scheme 8



Synthesis of the α-substituted alkyne **39** was started from commercially available 1,12-dodecanedicarboxylic acid (**49**). Compound **49** was reduced to the corresponding diol **50**, which was then protected selectively as the monobenzyl ether by treating it with benzyl bromide and sodium hydride in a solvent system of THF: DMF (7:3) (Scheme 9). Oxidation of monobenzyl ether to **51** was affected by reacting it with iodoxybenzoic acid in DMSO. Two carbon Wittig homologation of the aldehyde **51** was carried out by using the Wittig ylide $Ph_3P{=}CHCO_2Et$ in benzene under refluxing condition to produce the corresponding α,β-unsaturated ester. This ester on treatment with DIBAL-H at –78 ^{o}C

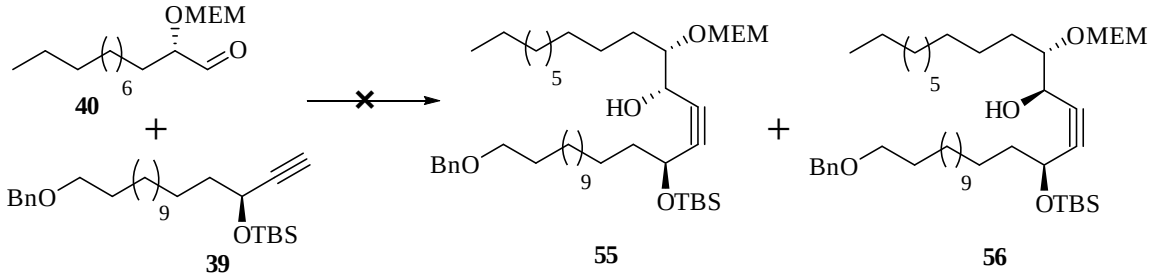
Scheme 9



produced the allylic alcohol **52** in 76% overall yield in two steps from the compound **51**. Our next goal was to generate stereocenter at the C_2-C_3 position of this α,β-unsaturated alcohol **52**. This was done by adopting Sharpless asymmetric epoxidation protocol. In doing so, compound **52** was treated with (+)-DET in presence of titaniumtetraisopropoxide and *t*-butyl hydroperoxide in anhydrous CH_2Cl_2 at –20 ^oC to produce epoxy alcohol **53**. Epoxy alcohol **53** was transformed to the epoxy chloride **41** by means of triphenylphosphine and CCl_4 under reflux. The hydroxy alkyne **54** was obtained by *n*-BuLi mediated ring opening followed by elimination reaction of the epoxy chloride **41**. Finally the secondary hydroxyl group present in compound **54** was protected as TBS ether to produce compound **39**.

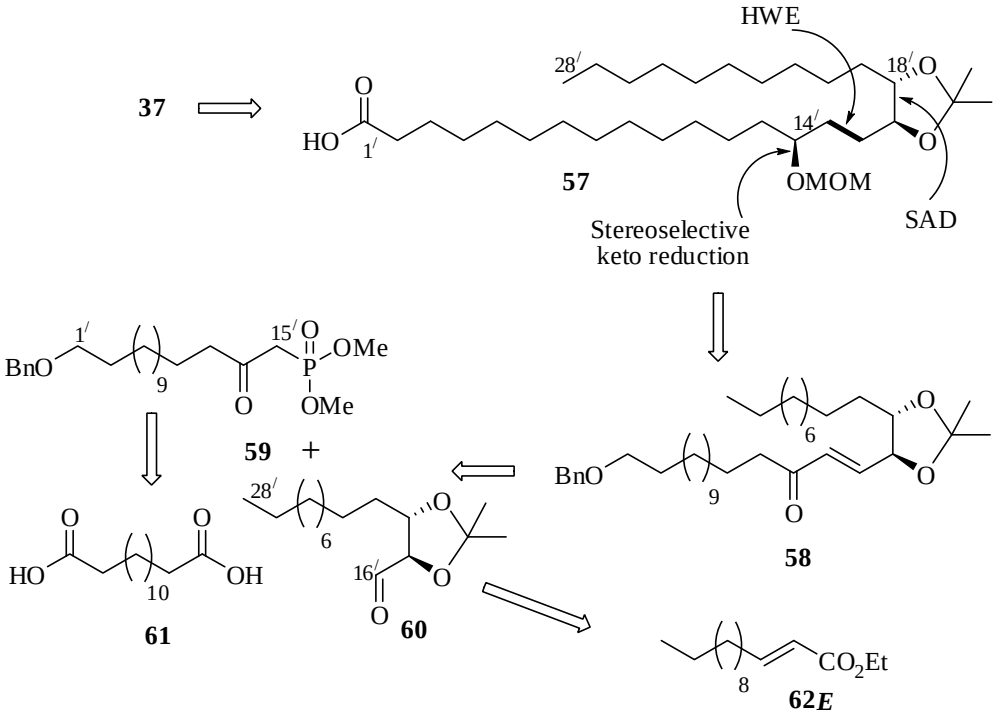
As the two fragments **39** and **40** were in our hand, our next strategy was to unite them. Generation of the lithiated alkyne under various basic conditions (*n*-BuLi, *s*-BuLi) and then coupling this with the aldehyde **40** was attempted. However we failed to isolate the required coupling product. We had also tried zinc triflate mediated coupling of the alkyne **39** with the aldehyde **40** and that attempt was also turned to be futile (Scheme 10).

Scheme 10



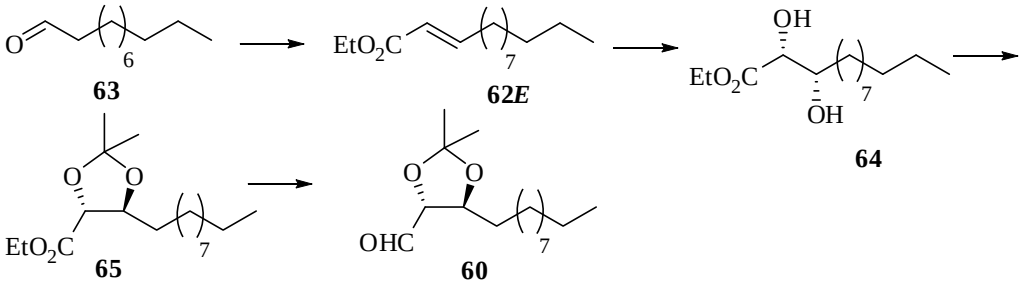
Since we were unsuccessful to couple the alkyne **39** with the aldehyde **40** we planned the modified retrosynthetic strategy shown below that would furnish the C_{28} fatty acid segment of schulzeine B-C. A convergent strategy toward the suitably protected C_{28} fatty acid was envisaged by the coupling of $C_1^{/}$-$C_{15}^{/}$ (**59**) and $C_{16}^{/}$-$C_{28}^{/}$ (**60**) building blocks *via* a HWE-reaction. The resulting enone **58** *en route* should additionally provide access to the $C_{14}^{/}$-OH group. Our plan for the synthesis of $C_{16}^{/}$-$C_{28}^{/}$ subunit **60** is founded upon the Sharpless asymmetric dihydroxylation (Scheme 11).

Scheme 11. *Modified Retrosynthetic analysis.*



The construction of the C_{28} fatty acid side chain **57** began with the syntheses of the C_{15} and C_{13} subunits (**59** and **60**). Synthesis of the C_{13} subunit **60** started with the two carbon homologation of undecan-1-al (**63**) using (ethoxycarbonylmethylene)-triphenylphosphorane in CH_2Cl_2, affording **62** as a mixture of *E*/*Z*-isomers (85:15) (Scheme 12). Asymmetric dihydroxylation of **62***E* using $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, and $K_2OsO_4.2H_2O$ in *t*-BuOH:H_2O (1:1) at 0 °C for 6 h gave the dihydroxy derivative **64** in 98.5% *ee* and 85% yield. Protection of **64** as an isopropylidene derivative followed by controlled reduction with DIBAL-H gave the C_{13} aldehyde **60**.

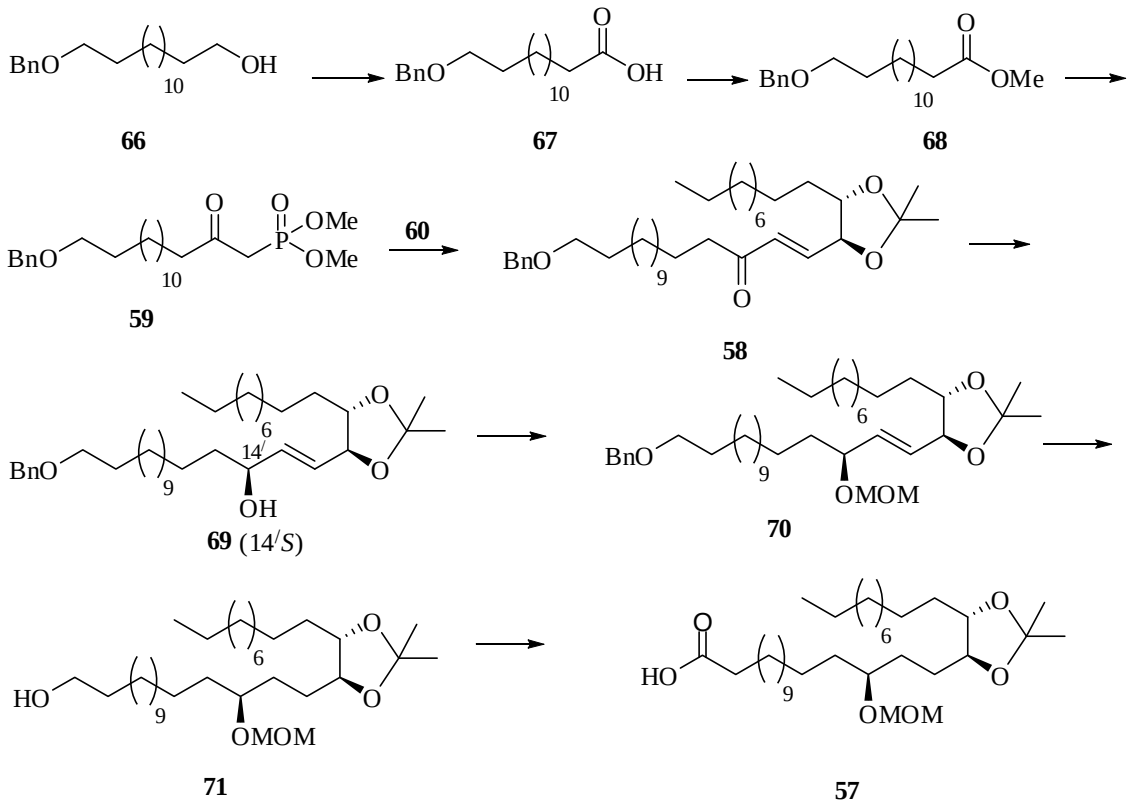
Scheme 12



Following our earlier work (Scheme 9) we have transformed the dicarboxylic acid **49** to compound **66** in two steps with an overall yield of 73%. Mono *O*-benzyl protected alcohol **66** on treatment with $RuCl_3$-$NaIO_4$ in CCl_4:CH_3CN:H_20 (1:1:2) furnished the acid **67**. Compound **67** was subjected to acid-catalyzed esterification to afford the methyl ester **68**. Treatment of **68** with lithiated methyldimethylphosphonate provided the requisite C_{15} subunit **59** in excellent yield (Scheme 13).

With both the C_{15} and C_{13} subunits in hand, we addressed the HWE coupling that would provide the side chain fatty acid unit. After exploring a variety of bases, we concluded that the key HWE-reaction between **59** and **60** can be successfully carried out using DBU-LiCl that would lead to the exclusive formation of enone **58** with *E*-configuration.

Scheme 13

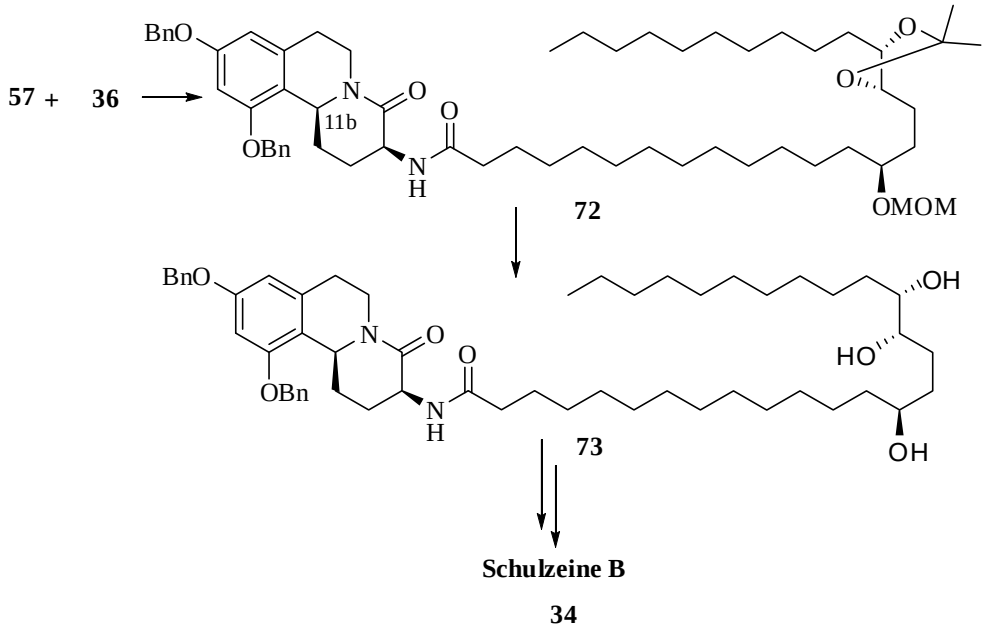


The resulting enone **58** was reduced with (*S*)-(–)-BINAL-H in THF at −78 °C to afford **69** (14′*S*) and its (14′*R*)-epimer in 11:1 ratio. Separations of both the epimers are done by flash silica gel column chromatography. The absolute configuration of the newly

created center in the major isomer **69** (14′*S*) was established by application of Mosher method. Protection of the free hydroxyl group in **69** as its MOM ether **70** followed by hydrogenolysis gave **71** in 78% yield over two steps. Oxidation of **71** to the corresponding aldehyde with IBX followed by further oxidation with $NaClO_2$ in *t*-BuOH at 0 °C gave the C_{28} fatty acid **57**.

The next and the final step would be to couple the acid **57** with the amine **36** (prepared by one of the colleague in our research group). This was done successfully by using EDC and HOBt to afford the coupled product **72** in an excellent yield (Scheme 14). Trimethylsilyl iodide (TMSI) mediated deprotection of the acetonide and MOM-protecting groups in **72** gave the triol **73** in 47% yield. Finally, persulfation of triol **73** using SO_3.Py in DMF followed by debenzylation afforded schulzeine B (**34)** in 80% yield over two steps. Similarly, starting with C_{11b} epimer of **36** and coupling it with the acid **57** and following a same sequence of reactions (deprotection, sulfation and debenzylation), the synthesis of schulzeine C (**35**) was accomplished.

Scheme 14



In summary, the first total syntheses of schulzeines B and C are documented. For the synthesis of the key C_{28} fatty acid segment, Sharpless asymmetric dihydroxylation, Horner-Wadsworth-Emmons reaction and BINAL-H mediated asymmetric reduction of

the enone were employed as the key reactions. The reported synthetic sequence gave sufficient amount of natural compound that might be useful for further biological investigations.

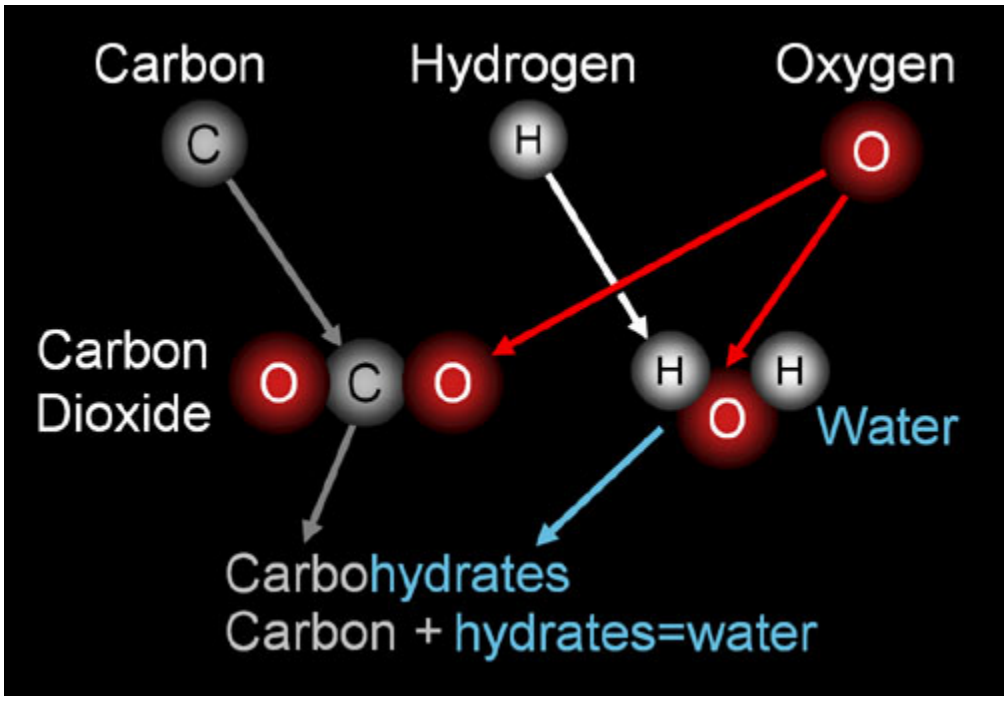
Note: Compound numbers in the abstract are different from those in individual chapters of the thesis.

Chapter 1

An introduction to Glycosidase inhibitors

Introduction

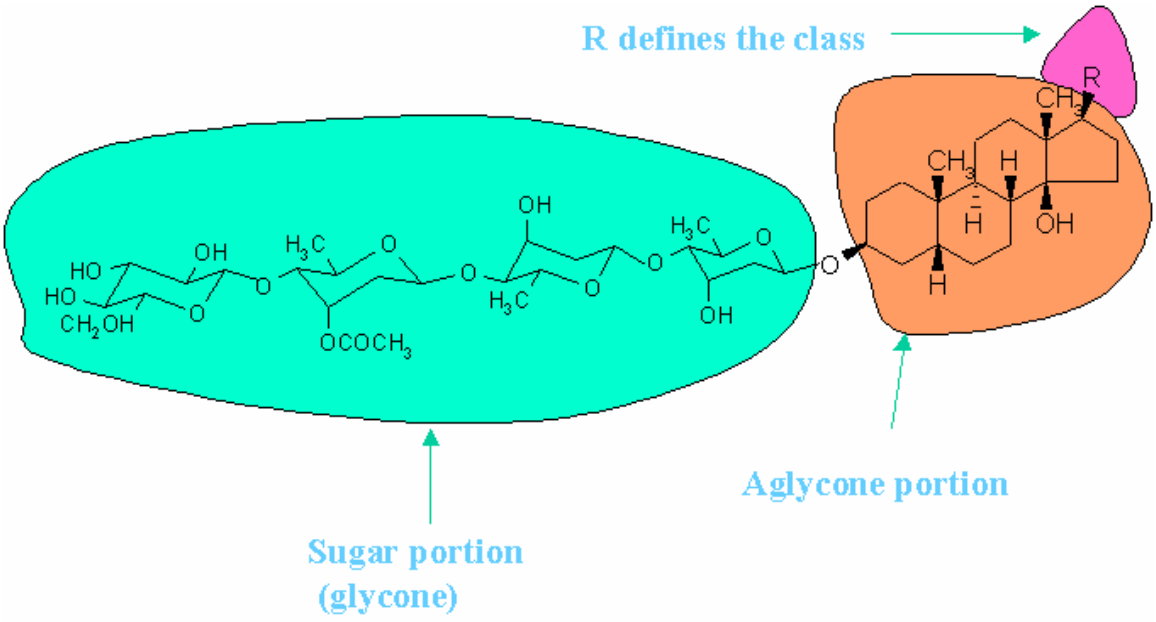
Carbohydrates are the building blocks of life serving two main roles in the cell; they are the store-house of energy (eg. glycogen) and also the structural units (eg. starch and cellulose).They play pivotal in various cellular processes such as cell recognition, regulation and growth. Various disease states are associated with these cellular processes. For example, bacteria and viruses have to recognize host cells before they can infect them and so the carbohydrate molecules involved in this cell recognition are crucial to the process.



Many of the important cell recognition roles played by carbohydrates are not acted out by pure carbohydrates, but by the glycoconjugates like glycoproteins or glycolipids. The carbohydrate portion serves the role of a molecular 'tag' which labels and identifies the cell, sometimes also acting as a receptor whereby it binds other molecules or cells.[1] There is actually good sense in having a carbohydrate as a molecular tag rather than a peptide or a nucleic acid. This is because far more variations are possible in the structure for carbohydrates than for DNA and even proteins. For example, there is only one possible dipeptide which can be formed between two molecules of alanine but there are eleven possible disaccharides which can be formed from two glucose molecules.

Carbohydrate structures offer tremendous potential for novel drugs, they are 'loaded' with hydroxyl groups and asymmetric centers as a result of which carbohydrate synthesis is a demanding 'sport'.

A very interesting chapter of carbohydrate chemistry comprises of the formation and breakdown of one of the most stable covalent linkages ($\Delta G^{\#} \sim 30$ kcal mol^{-1}) found within natural biopolymers-the glycosidic bond.[2,3] In chemistry, the glycosidic bond is a certain type of functional group that joins a carbohydrate (sugar) molecule to another, which may or may not be another carbohydrate. These acetal derivatives come under the generic name of glycosides; those of glucose are known as glucosides, of fructose, fructosides etc. Glycosides are compounds containing a carbohydrate and a non-carbohydrate residue in the same molecule. The non-sugar component is called aglycon which may be methyl alcohol, glycerol, sterol, phenol, etc. The sugar component is called glycon. The carbohydrate residue is attached by glycosidic bond at the anomeric carbon to a non carbohydrate residue or aglycon. Glycosidic bond particularly that between two glucose residues, is the most stable of the linkages within naturally occurring biopolymers, with half-lives for spontaneous hydrolysis of cellulose and starch being in the range of 5 million years.[4]



Enzymes, the glycosidases carrying out the hydrolyses of these materials therefore face a challenging task, yet they accomplish this with rate constants up to 1000

s^{-1}. As such they are able to accelerate hydrolysis by factors approaching 10^{17} and therefore are in a class of enzymes described as being some of the most proficient of known catalysts.[4] When rate constants for spontaneous cleavage of glycosides are compared with other covalent bonds in biological polymers, the glycosidic bonds that join polysaccharides appear to be more stable to spontaneous hydrolysis than the phosphodiester bonds that join the nucleotides of DNA[5] by roughly 2 orders of magnitude. In contrast, proteins[6] are less stable to hydrolysis than DNA by roughly 2 orders of magnitude in neutral solution and RNA is even less stable.[7] Thus, at physiological pH values, the two major classes of biological polymers used by organisms for long-term storage of energy and information are distinguished by their resistance to hydrolytic attack.

Glycosidases are found essentially in all domains of life. The fundamental roles they play include the control of metabolism including the breakdown and reassembly of edible carbohydrates, the processing of various oligosaccharide-containing proteins and lipids, the formation of cell walls and other barrier structures and they also function as immuno-determinants on cell. Glycoside hydrolases are found in the intestinal tract and in saliva where they degrade complex carbohydrates such as lactose, starch, sucrose and trehalose. In the gut they are found as glycosylphosphatidyl anchored enzymes on endothelial cells. The enzyme lactase is required for degradation of the milk sugar lactose and is present at high levels in infants, but in most populations will decrease after weaning or during infancy, potentially leading to lactose intolerance in adulthood. The enzyme O-GlcNAcase is involved in removal of N-acetylglucoamine groups from serine residues in the cytoplasm and nucleus of the cell. The glycoside hydrolases are involved in the biosynthesis and degradation of glycogen in the body. These enzymes are also involved in a variety of metabolic disorders and other carbohydrate mediated diseases such as diabetes, viral infections and cancer. In bacteria and prokaryotes, they are found both as intracellular and extracellular enzymes largely involved in nutrient acquisition. One of the important occurrences of glycoside hydrolases in bacteria is the enzyme beta-galactosidase (LacZ), which is involved in regulation of expression of the *lac* operon in *E. coli*. In higher organisms glycoside hydrolases are found within the endoplasmic reticulum and Golgi apparatus where they are involved in processing of N-linked

glycoproteins, and in the lysozome as enzymes involved in the degradation of carbohydrate structures. Deficiency in specific lysozomal glycoside hydrolases can lead to a range of lysosomal storage disorders that result in developmental problems or death.

Any medicament that renders the function of glycosidases are called glycosidase inhibitors. Inhibition of these enzyme systems reduces the rate of glucose absorption from the intestine as the carbohydrates are not broken down into simple glucose molecules, resulting in a slower and lower rise in the blood glucose level through the day. For example, the α-glucosidase inhibitors belong to a class of oral medication for Type 2 diabetes. Glycosidase inhibitors are important tools for studying glycosidase mechanisms and many have great potential in therapeutic applications.[8] Based on the understanding of the glycosidase mechanism, a trigonal anomeric center, positive charge between the ring oxygen and anomeric carbon, half chair-like conformation, and proper hydroxyl group configurations are all proposed to be important characteristics of a good inhibitor. Many naturally occurring glycosidase inhibitors[9] such as deoxynojirimycin, deoxymannonojirimycin, castanospermine and swainsonine in which the ring oxygen is replaced by a nitrogen atom, generally known as iminoalditols or aza-sugars, have been found to inhibit several hundred to more than 10^5-fold better than their oxygen analogs. They are believed to be able to mimic the ground state conformation and the positive charge by protonation of the basic nitrogen atom at physiological pH. The potential medical uses of the iminoalditols and their derivatives are numerous and range from diabetes[10] through antimicrobials,[11] cancer,[12] autoimmune diseases,[13] neurological[14] and metabolic disorders.[15] Despite their promise, those glycosidase inhibitors have not realized their full clinical potential. This is largely because of a lack of commercially viable syntheses and difficulty in preparing a comprehensive palette of variant structures. In some cases such as deoxynojirimycin there is also the problem of too low specificity. The developments of these possible drug candidates are limited because most of them are available in only small exploratory amounts.

Classification of Glycosidases

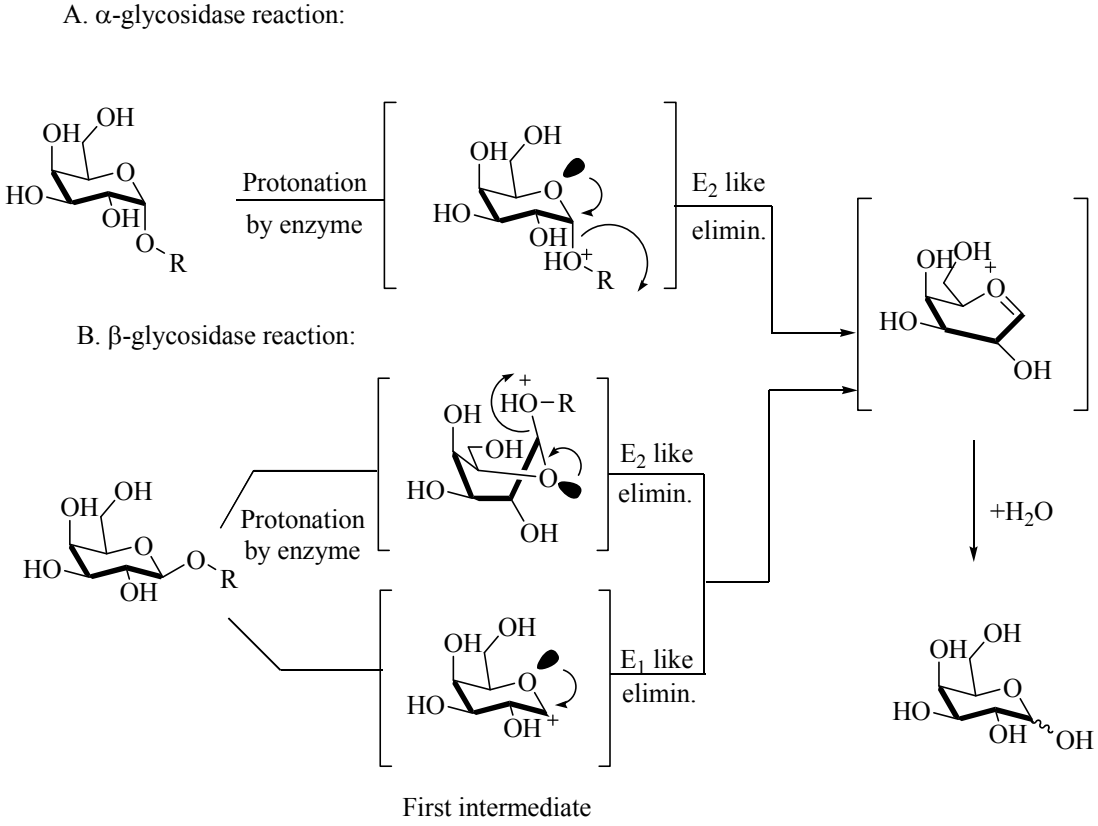
There has been a veritable explosion of structural information on glycosidases in recent years both in terms of sequences and in terms of three-dimensional structures. The

predicted amino acid sequences of well over 2000 different glycoside hydrolases are now available, and, at last count, these were divided into 76 different families on the basis of sequence similarities, this information being currently available on an excellent Web site (http:// afmb.cnrs-mrs.fr/_pedro/CAZY/db.html)[16] and having been reviewed recently.[17] Three-dimensional structures have now been determined for representatives of at least 30 of these families, revealing incredible structural diversity despite the fact that all these enzymes catalyze the same reaction, hydrolysis of an acetal. Nonetheless, some families adopt similar folds and on this basis have been assigned to so-called "clans", as also reviewed recently.[18, 19]

(1) Glycosidases are more importantly classified based on the stereochemistry of the anomeric glycosidic bond that they cleave. Enzymes catalyzing the cleavage of α-glycosidic bond are termed as α-glycosidases while those cleaving a β-glycosidic bond are termed as β-glycosidases (Figure 1). A similar mechanism appears to exist in α-retaining glycosidases, but of course with the complementary stereochemical itinerary involving a β-linked intermediate. Good evidence for this has come from kinetic studies,[20] from the trapping of intermediates, and from the three-dimensional structure of one such intermediate.[21] Several lines of evidence, however, point toward a subtle difference in the oxocarbenium ion character of the transition structures formed on α- and β-glycosidases. On β-glycosidases, the *syn* interaction of the nucleophile carboxyl oxygens with the anomeric center and the 2-hydroxyl will tend to favor a greater share of the positive charge on the anomeric carbon. This interaction is not possible for an α-glucosidase, where instead a *syn* interaction of the nucleophile carboxyl oxygens with the anomeric center and the endocyclic oxygen is observed in the intermediate.[21] This interaction will favor positive charge development on the endocyclic oxygen. Experimental support for this hypothesis is drawn from observations with two classes of inhibitors, as follows. The efficacy of the 2-fluorosugar inhibitors with β-glycosidases, but not with α-glycosidases, could be due to the fact that only with the β-glycosidases, wherein the charge is localized to a greater extent on the adjacent anomeric carbon, is there sufficient inductive destabilization to affect rates significantly. By contrast, the 5-fluoro inhibitors function with both α- and β-glycosidases, consistent with the proximity

of the fluorine to the developing charge on the endocyclic oxygen. The specificities of the reversible azasugar inhibitors of the deoxynojirimycin and isofagomine classes could be explained in this way too. As has been pointed out previously,[22,23] the deoxynojirimycins, which apparently mimic charge developed on the ring oxygen, are potent α-glycosidase inhibitors but very modest inhibitors of β-glycosidases. iminopentitol, penarolide sulfates, schulzeines are some other newly isolated α-glycosidase inhibitors. By contrast, the isofagomines, which arguably mimic charge development on the anomeric carbon, have the complementary inhibitory profile.

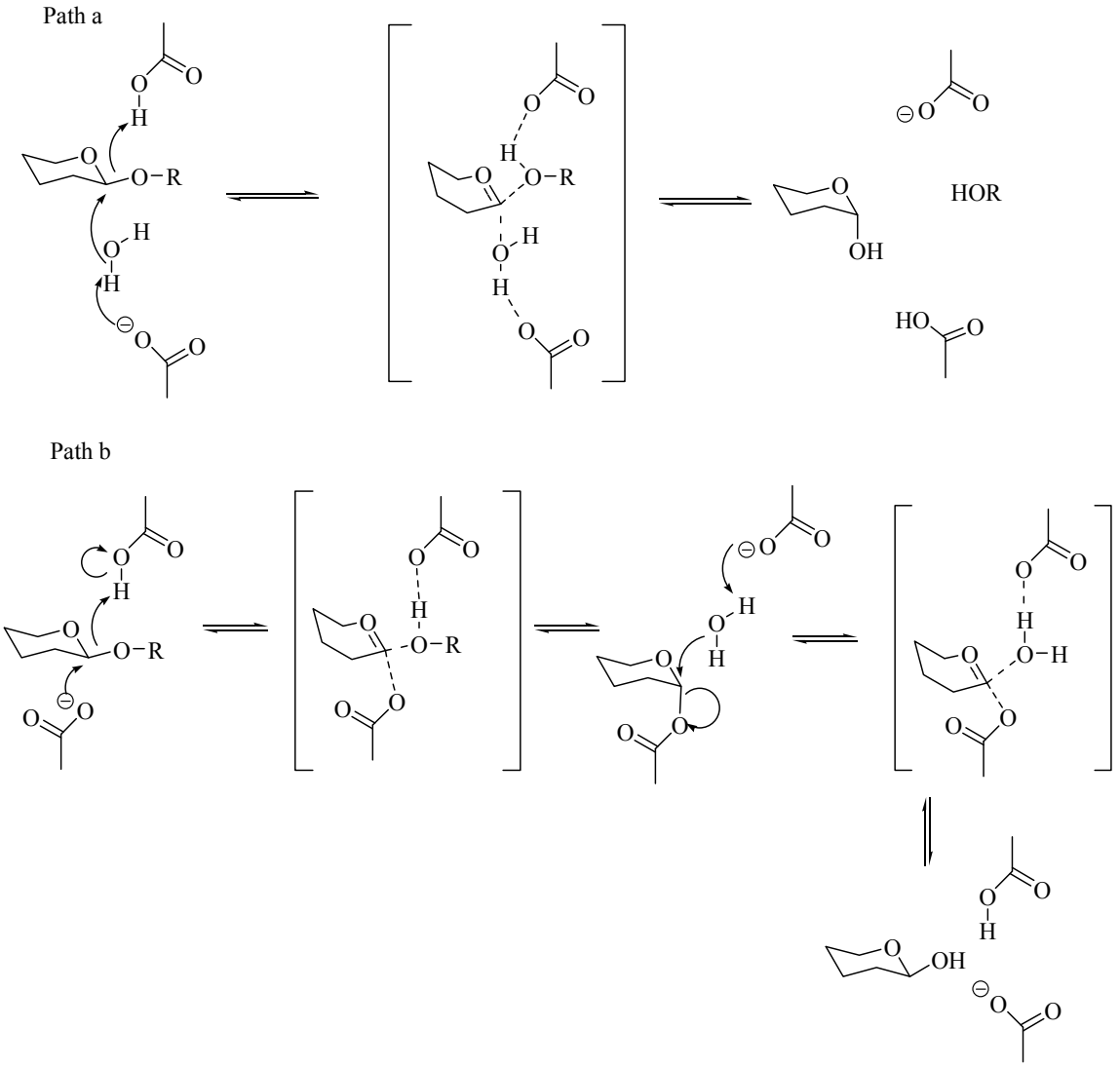
Figure 1. *Glycosidase reaction mechanism involved in α-glycosidases and β-glycosidases.*



(2) At least in terms of simple tonnage, glycosyl transfer must be accounted one of the most important biochemical reactions, since around two-thirds of the carbon in the biosphere exist as carbohydrate (largely cellulose and hemicellulose).[24] The reaction is formally a nucleophilic substitution at the saturated carbon of the anomeric center and can take place with either retention or inversion of the anomeric configuration. We

therefore have two basic types of glycosyl-transferring enzymes-"retaining" and "inverting" (Figure 2).[25]

Figure 2. *General mechanism for inverting (path a) and retaining (path b) glycosidases.*

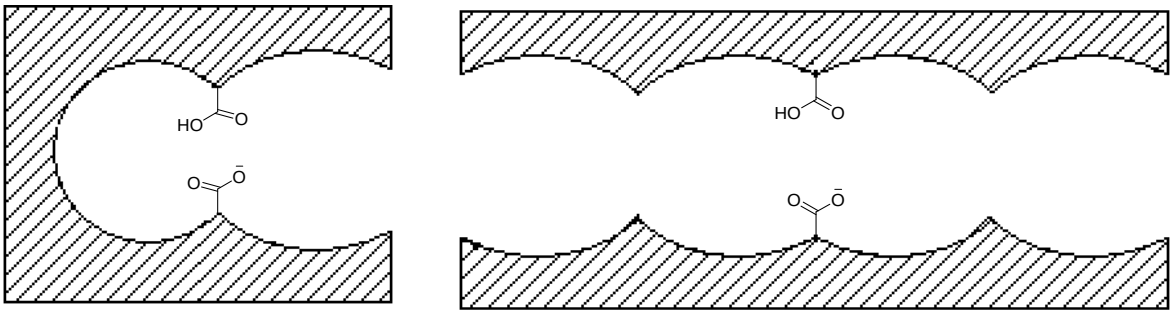


Glycosidases employ two separate and distinct mechanisms.[26] In one set of enzymes, direct displacement leads to net inversion of anomeric configuration. In the other set, anomeric configuration is retained via a double displacement mechanism involving a glycosyl-enzyme intermediate. While the two mechanisms are quite distinct, there are significant similarities: both involve oxocarbenium ion-like transition states,[27] and both involve a pair of carboxylic acids, which have different roles in the two cases. In

"*inverters*" one functions as an acid catalyst and the other as a base catalyst, whereas in "*retainers*" one functions as an acid/base catalyst and the other as a nucleophile/leaving group. Furthermore, the two residues are further apart in the inverting than in the retaining glycosidases to allow the intervention of a water molecule. The average separation in retaining α- and β-glycosidases is 4.8 ± 0.5 and 5.3 ± 0.2 Å, respectively, but in the inverting α- and , β-glycosidases it is 9.0 ± 1.0 and 9.5 Å, respectively.[28] The similar transition state raises the possibility of converting an enzyme from one mechanism to the other by changing the separation by mutation.

(3) Another determinant factor is the position of the glycosidic bond that is cleaved by the enzyme. The glycosidases that remove sugars one at a time, from the non-reducing end of an oligo or polysaccharide are called the exoglycosidases (Figure 3). They are involved in the breakdown of starch and glycogen, the processing of eukaryotic glycoproteins, the biosynthesis and modification of glycosphingolipids and the catabolism of peptidoglycans and other glycoconjugates. If the glycosidic bonds are situated within the polysaccharides, they are cleaved by the endoglycosidases. They are involved in the catabolism and clearance of the aged glycoproteins, in catalyzing the alteration of bacterial and plant cell walls and also in the hydrolysis of highly insoluble structural polysaccharides like chitin and cellulose.[29]

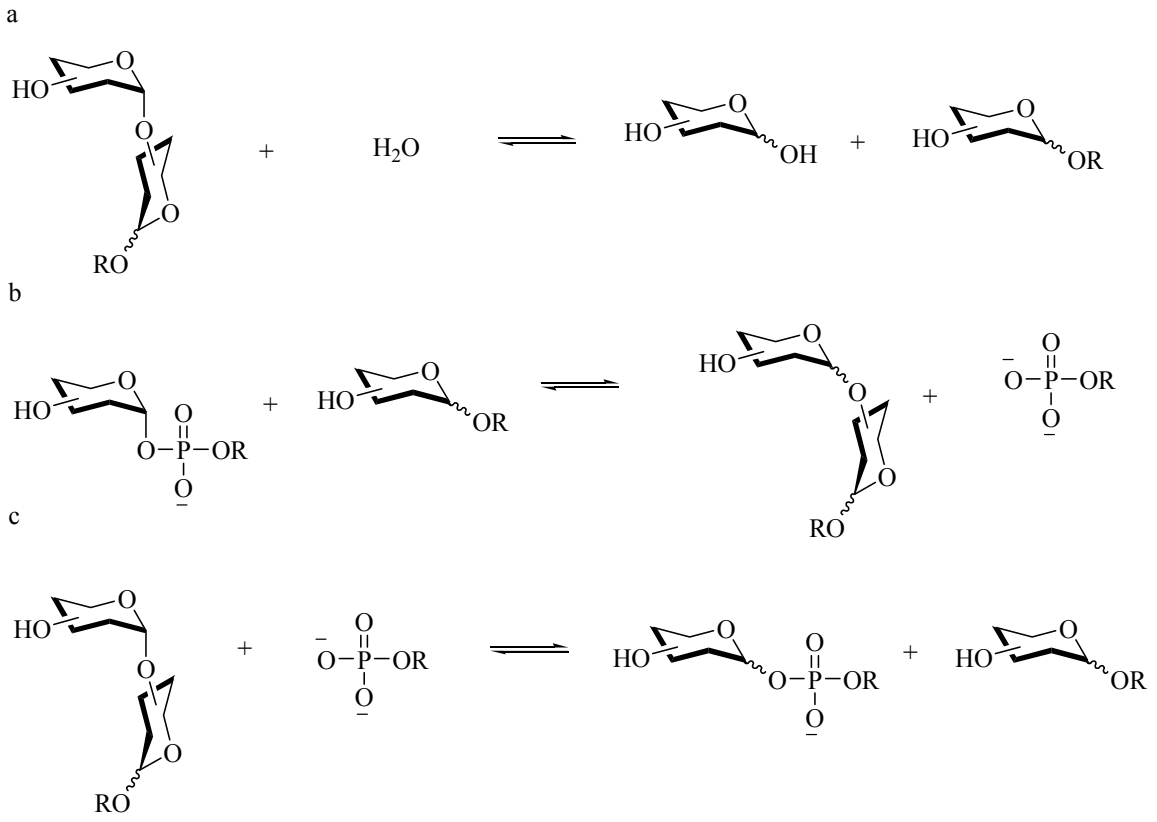
Figure 3. *Exo and Endo glycosidases.*



(4) The mechanistic strategies involved in the functioning of the enzymes have resulted in another set of categorization. Glycosidases have evolved well-defined and characteristic active sites that allow them to catalyse glycosidic bond hydrolysis with rate constants of up to 1000 s^{-1}. As such they are able to accelerate hydrolysis by factors approaching 10^{17}. Primary amino acid sequences are used to classify glycosidases into

one of 94 different families. Structural characterization of representatives from a large number of these families has been achieved, revealing an extraordinary degree of diversity in overall fold, despite sharing several identical active site features.

Figure 4. *Overall reactions catalyzed by (a) glycosidases, (b) glycosyltransferases, and (c) Phosphorylases.*



This would indicate a convergent evolution of mechanism. Transglycosidases are enzymes that share homologous structure, catalytic machinery and mechanistic strategies with various glycosidases and are therefore classified amongst the glycosidase families. However, instead of catalysing the hydrolysis of glycosidic linkages between sugars, they facilitate the transfer of the glycone moiety to the hydroxyl of another sugar (transglycosylation) (Figure 4).

Glycosyltransferases catalyse the transfer of glycosyl moieties from activated donor sugars to an acceptor. The activating group of the donor is a nucleoside

diphosphate (NDP) or monophosphate, phosphate, or a lipid phosphate and the acceptor is a hydroxyl group from another sugar, a lipid, a serine or threonine residue or the amide of an asparagine residue in a protein. As with the glycosidases, glycosyltransferases are classified as either retaining or inverting depending on the stereochemical outcome at the anomeric centre relative to that of the donor sugar and are also classified into sequence similarity-based families. Depending on the direction of the reaction being catalyzed, phosphorylase enzymes serve to either degrade or polymerize oligosaccharide substrates. The degradation process proceeds via phosphorolysis of a glycosidic linkage, while in the synthetic direction a sugar phosphate acts as the donor substrate.

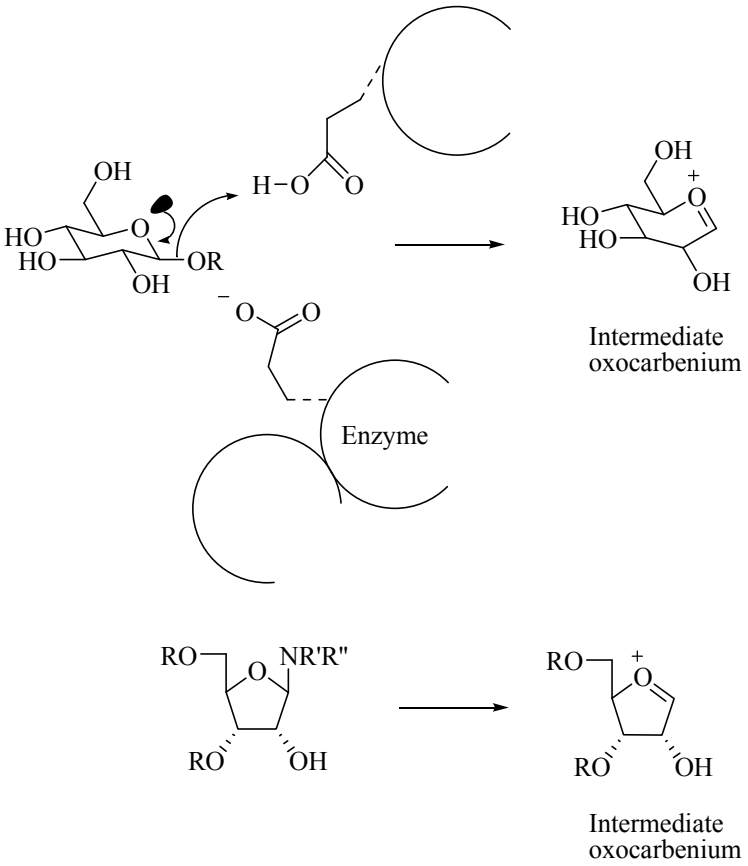
Another interesting and much less explored class comprises of the Cyanogenic glycosides.[30] Some few plant species have the ability to produce cyanides. They are strong cytotoxins, competitive inhibitors of the Fe^{III} of the heme group. The cells detoxify them by glycosylation, i.e. by linking them β-glycosidically to sugar residues (usually glucose).

Mechanistic approach

The nonenzymic chemistry of the glycosidic linkage, especially in water, is dominated by electron release from the lone pairs of the oxygen atom, resulting in departure of the anomeric substituent,[31] and generation of a glycosyl cation. In solvents less polar than water glycosyl cations are too unstable to exist,[32] but in aqueous solution they are just on the border line of a real existence. By analogy with the reaction in free solution, and as a consequence of many probes of enzymic transition-state structure which indicate considerable glycosyl cation character, glycosyl cation intermediates are often drawn for enzymic processes. These intermediates are often considered not to accumulate - they are high-energy intermediates in the traditional physical organic sense. However, it is not meaningful to talk of high-energy glycosyl cation intermediates, which do not accumulate, in enzyme active sites, for the following reason. In the context of the physical organic chemistry of reactions in solution, it is now realized that,[33] once a high-energy intermediate has become so unstable as to have a lifetime shorter than that of an encounter complex, the other components of the encounter complex, and the solvent shell, are necessarily involved in the reaction mechanism. In aqueous solution, the

glucosyl cation is so unstable as to be on the border line of a real existence, estimates of its lifetime varying from 10^{-10} s to 10^{-12} s.[34,35] Any glycosyl cations generated in enzyme active sites would be generated in the vicinity of the catalytic groups, and therefore any reactions supposedly involving them would necessarily be preassociation reactions: the only way a nonaccumulating, high-energy intermediate could be said to exist is if it came off the enzyme surface and became solvent equilibrated, but glucosyl cations are too unstable for that to happen.

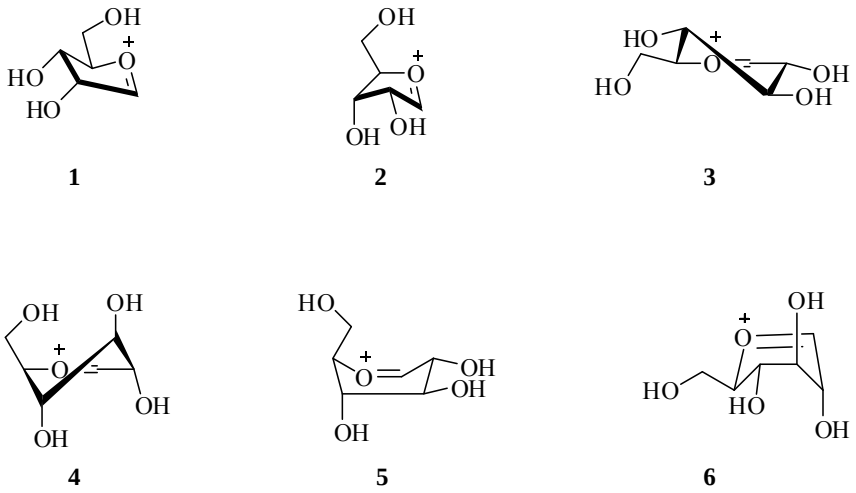
Figure 5. *Reaction mechanism.*



The consequences of the direction of the lone pairs on the glycosidic oxygen in space have received much attention, and the idea has received currency that for the aglycon-glycon bond to break, the sugar ring must be a conformation such that this bond is antiperiplanar to an sp^3 lone pair on the ring oxygen atom.[36,37] Indeed, it has been firmly stated that "α-glycosides must hydrolyze via their ground state conformation, whereas β-glycosides must first assume a boat conformation in order to fulfill the

stereoelectronic requirement". Such distortion, which is likely driven by interactions between the enzyme and the substrate, can assist bond cleavage in several ways. First, it permits an in-line attack of the enzymic nucleophile at the anomeric center, unencumbered by the repulsive diaxial interactions otherwise present when displacing an equatorial leaving group. It also moves the substrate closer to the conformation of the oxocarbenium ion transition state, as well as placing the glycosidic oxygen in an appropriate position for protonation by the general acid catalyst. In fact, in the case of the acid-catalyzed hydrolysis of methyl α- and β-glycosides, precisely the reverse happens, and the antiperiplanar lone pair hypothesis (ALPH) requires quite implausible contortions of the pyranose ring when applied to retaining glycosidases going through covalent intermediates of opposite anomeric configuration to the substrate, since the oxocarbonium ion like transition states must, according to the dictates of ALPH, be generated in either direction from covalent intermediates with an antiperiplanar lone pair.[38] The case has been made that the "theory of stereoelectronic control" in fact represents an overinterpretation of small and elusive least motion effects,[39] and even one of its protagonists now considers that "it is not necessary to take literally the earliest formulation of stereoelectronic theory".[40]

Figure 6. *Conformations necessary to permit ALPH theory.*



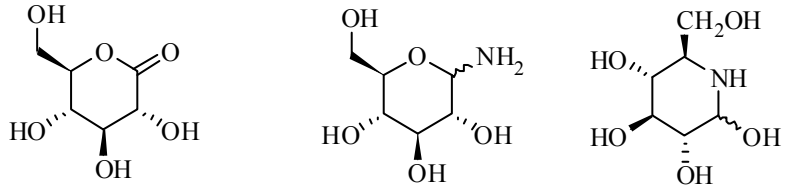
It must be emphasized, however, that the stereoelectronic requirement for planarity of an oxocarbonium ion (and hence presumably of an oxocarbonium-like

transition state) is unambiguous. Thus, in the case of furanosyl cations, the conformation of the ring is probably an envelope, with C_1, C_2, C_4, and 0_4 coplanar, whereas in the case of pyranosyl cations, the analogy with aldono-lactones (which can adopt halfchair or classical boat conformations in a way that varies with solvent and substitution pattern)[41] suggests that half-chair and classical boat conformations which both enable C_1, C_2, 0_5, and C_5 to be coplanar must be considered. In figure 6, the conformations of a ribofuranosyl cation, (**1**) and (**2**), and of a glucopyranosyl cation, (**3**), (**4**), (**5**), and (**6**) permitted by these requirements are illustrated.

Examples of natural structurally interesting α-glycosidase inhibitors

Glycosidases catalyse chemical transformations at the C_1 position of carbohydrates, and a number of metabolic processes rely on these enzymes for their efficiency, selectivity and control. Glycosidase inhibitors are of interest both in studies on the mechanism of enzyme-catalysed glycoside hydrolysis[42] and in medicinal chemistry.[43,44] For example, the potent glycosidase inhibitor 1-deoxynojirimycin, a 5-amino-1,5-dideoxy-D-glucopyranose derivative, has been shown to inhibit human immunodeficiency virus (HIV) replication *in vitro*.[11a] In addition, immobilized glycosidase inhibitors are becoming increasingly popular in affinity chromatography for the purification of a wide range of glycohydrolases and glycosyltransferases.[45]

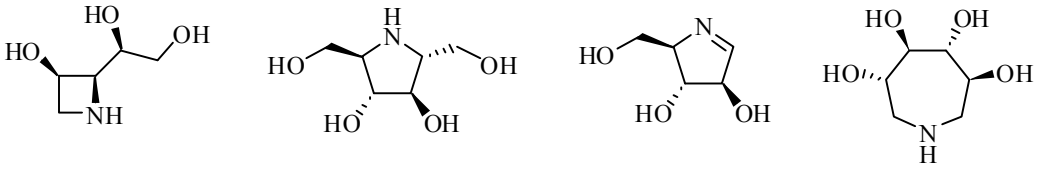
Figure 7. *The classical glycosidase inhibitors.*



Historically, the first glycosidase inhibitors were the families of the monosaccharide-derived δ-aldonolactones (such as D-gluconolactone **7**),[46] and glycosyl amines (1-amino-1-deoxy pyranoses such as D-glucosyl amine **8**)[47] (Figure 7).

Although, lacking long-term stability in aqueous solution, these families of compounds typically display competitive inhibition against glycosidases whose substrates they most closely resemble. Ever since the pioneering work by Paulsen on sugar analogues with basic nitrogen instead of oxygen in the ring (also called the azasugars or iminosugars)[48] and the discovery of such a natural product (nojirimycin **9**),[49] many other naturally occurring iminosugars have been identified and additional analogues and homologs have been synthesized, opening a dynamic research area.[50]

Figure 8. *Azasugars of various ring size.*



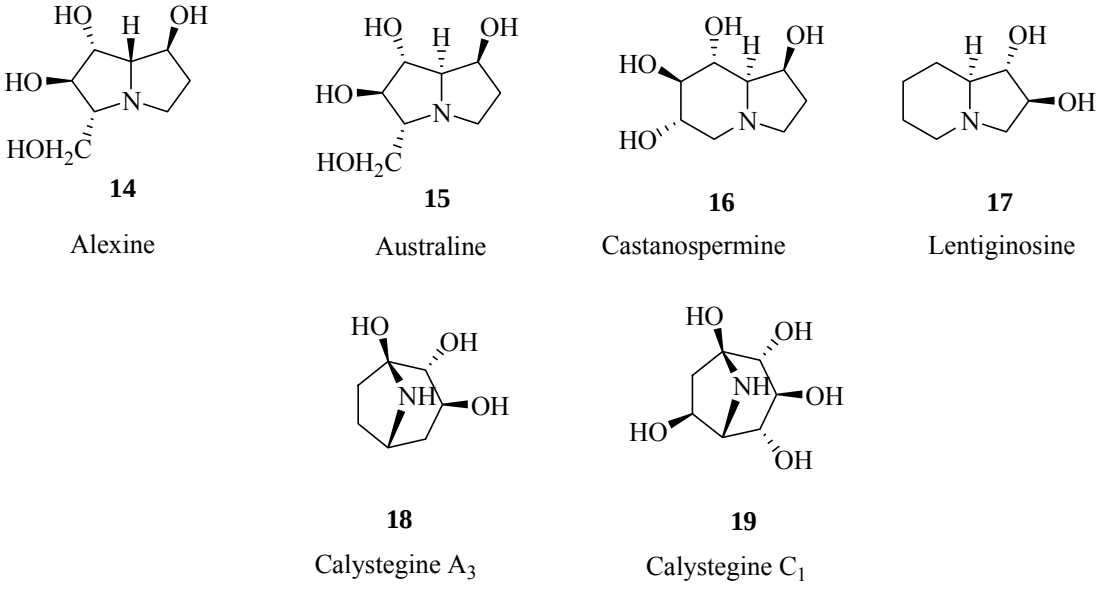
10 1,3-dideoxy-1,3-imino-L-xylitol

11 DMDP

12 Nectricine

13 (3*S*,4*R*,5*R*,6*S*)-3, 4, 5, 6-tetrahydroxyazepane

Figure 9. *Bicyclic azasugars.*



14 Alexine

15 Australine

16 Castanospermine

17 Lentiginosine

18 Calystegine A_3

19 Calystegine C_1

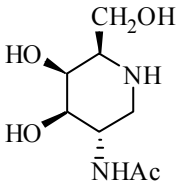
The search for more potent and selective inhibitors has led to isolation and synthesis of azasugars of various ring sizes (Figure 8).[51] The aim has been to mimic the transition state (oxycarbenium ion). While the small rings (like azitidine **10**) provide tight

transition state upon protonation, the bigger rings (like azepane **13)** provide more flexibility to bind the active site of enzyme.

Bicyclics like pyrrolizidines (alexine **14**, australine **15**) indolizidines (castenospermine **16**, lentigenosine **17**) and nortropanes (calystegine A_3 **18**, calystegine C_1 **19**) are shown in Figure 9.

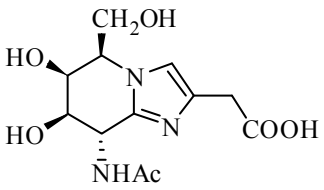
There are also entities incorporating a nitrogen in more than one position, including the one in the ring, e.g.; siastatin **20**, nagstatin **21** and aminocyclitols like mannostatin **22** (Figure 10). Polyhydroxypiperidine derivatives comprise the main class of glucosidase inhibitors, with a great variety of compounds of natural origin, isolated from fungi, bacteria, and plants, besides the synthetic derivatives, and several of them show high inhibitory constants for both α- and β-glucosidases.

Figure 10



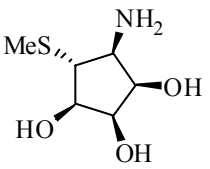
20

Siastatin B



21

Nagstatin

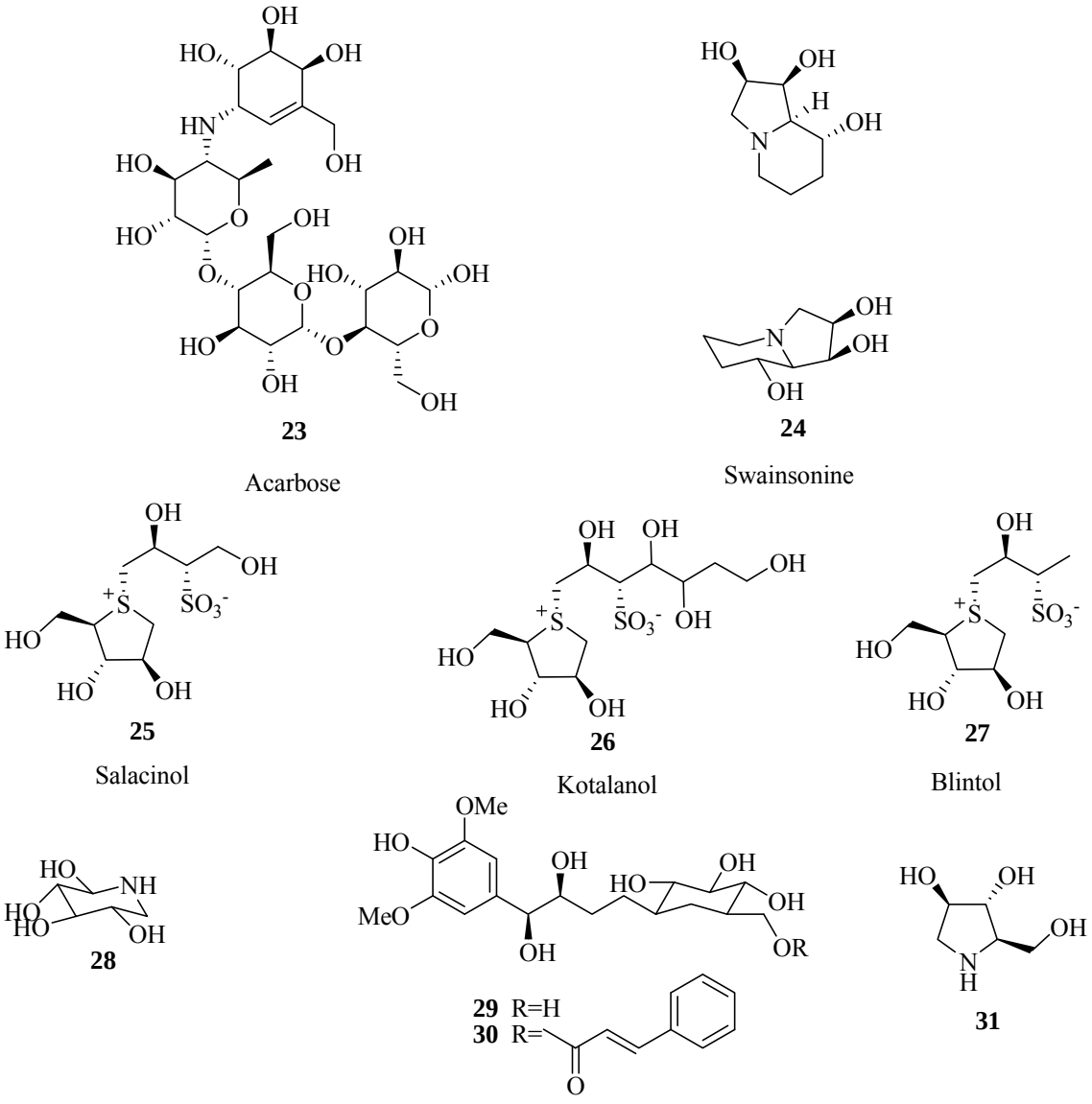


22

Mannostatin

α-Glucosidase inhibitors have also been isolated from various food materials e.g. ougon, hijiki, tochu-cha, welsh onion and clove. Some naturally occurring compounds such as acarbose (**23**) and swaninsonine (**24**) are potent glycosidase inhibitors (Figure 11). A new class of α-glucosidase inhibitors, namely salacinol (**25**)[52,53] and kotalanol (**26**) with an intriguing inner-salt sulfonium-sulfate structure was isolated from the roots and stems of the plant *salacis reticulate* which has been used as an antidiabetic ayurvedic traditional medicine.[54-56] Salacinol showed the competitive inhibition for the intestinal α-glucosidase *in vitro*; IC_{50} values were 3.2 μg/mL to maltose, 0.84 μg/mL to sucrose, and 0.59 μg/mL to isomaltose. It is believed that the inhibition of glucosidases by salacinol (**25**) and kotalanol (**26**) is in fact due to their ability to mimic both the shape and charge

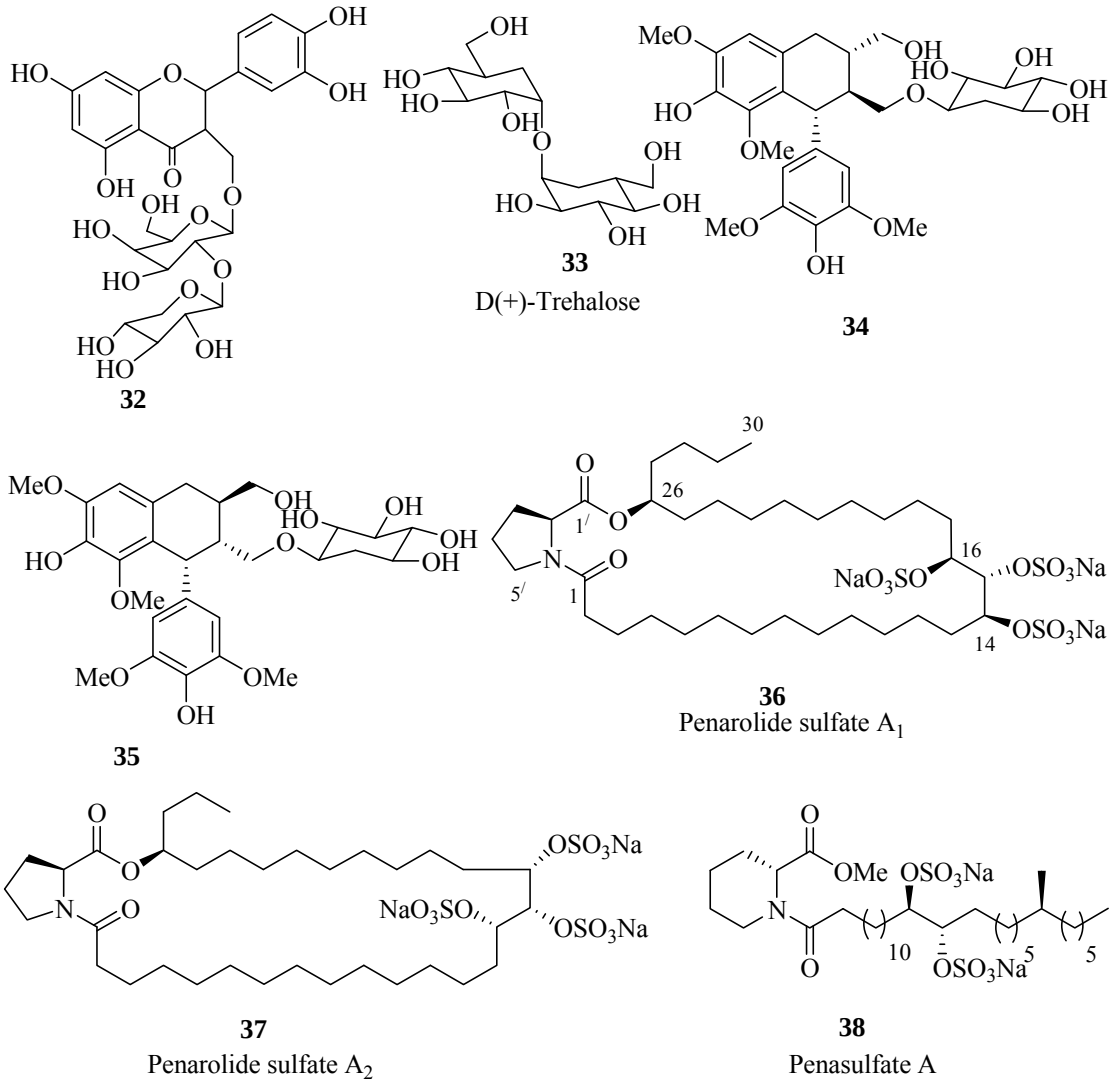
Figure 11



of the oxocarbenium ion like transition state involved in the enzymatic reactions. The selenium congener of the salacinol was synthesized[57-59] and it was found that blintol (**27**) exhibited stronger inhibitory activities than salacinol. Moranoline (**28**),[60] another one α-glucosidase inhibitor, which was isolated from culture filtrates of a *Streptomyces* sp. Compounds **29** and **30** were isolated from aqueous methanol extract of *hyssop* (*Hyssopus officinalis*) leaves and showed considerable α-glucosidase inhibitory activity.[61]

Iminopentitol (**31**),[62] an α-glucosidase inhibitor was isolated as a natural product from fruits of *Angylocalyx boutiqueanus*, the leaves and roots of *Morus spp* and also from two marine sponges collected in Western Australia[63,64] (Figure 11). Compound **33** was isolated from the water extracts of the seeds of *balsam pear* and the fruitbodies of *G. frondosa*, both of which were known as health promoting foods and antibiotic activities. Compounds **32**, **34**, and **35**, which were isolated from the *Devil tree* (traditional Thai medicinal plant) showed potent α-glucosidase activity (Figure 12).[65]

Figure 12

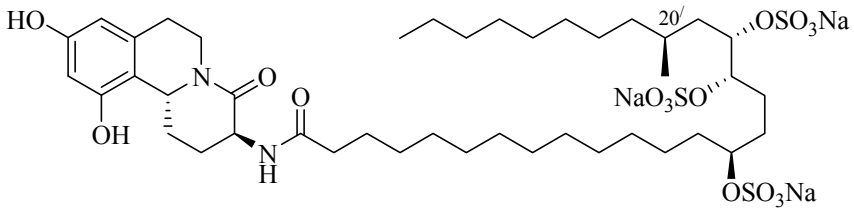


Fusetani *et al.* while screening for α-glucosidase inhibitors from Japanese marine invertebrates, encountered a marine sponge *Penares* sp. collected off Hachijo-jima Island

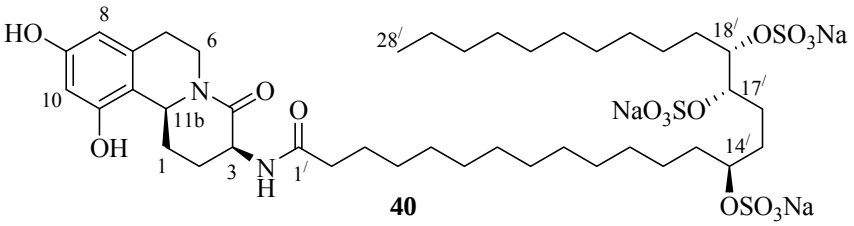
whose hydrophilic extract was highly active. Bioassay-guided fractionation led to the isolation of two active compounds, penarolide Sulfates A_1 and A_2 whose structures were assigned as proline-containing macrolide trisulfates (Figure 12). Penarolide sulfates A_1 (**36**) and A_2 (**37**) inhibit α-glucosidase with IC_{50} values of 1.2 and 1.5 μg/mL respectively.[66] Another one α-glucosidase inhibitor penasulfate A (**38**) was also isolated from same sponge.[67]

Schulzeines A-C (**39-41**) were isolated by Fusetani *et al.* from the hydrophilic extract of the marine sponge *Penares schulzei*.[68] The structure of the schulzeines can be divided into two major components, namely, the tricyclic core containing tetrahydroisoquinoline fused with δ-lactam and the C_{28} fatty acid side chain. The tricyclic core bears two stereogenic centers at C_3 and C_{11b}. The stereo center at C_3 is assigned as '*S*' in all members of this family whereas schulzeines A (**39**) and C (**41**) have C_{11b} '*R*' and schulzeine B (**40**) has C_{11b} '*S*' configuration (Figure 13).

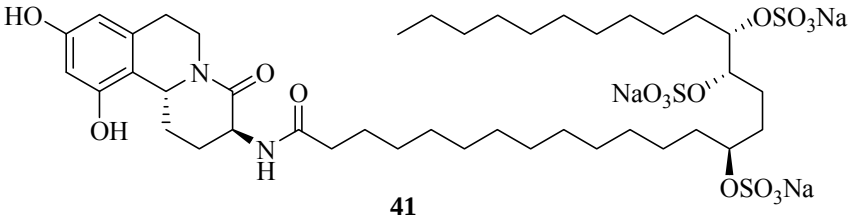
Figure 13



39



40



41

The C_{28} fatty acid side chain of schulzeines bear three stereogenic centers at C_{14}, C_{17} and C_{18} as sodium sulfate salts with the configuration assigned as *S*, *S*, *S*. Schulzeine A has an extra stereogenic centre at C_{20} bearing a methyl substituent These are new class of α-glucosidase inhibitors, inhibited α-glucosidase with IC_{50} values of 48-170 nM. Schulzeines were also having inhibitory activity against viral neuraminidase with IC_{50} values of 60 μM.

Structure-Activity relation of drugs

In recent years, medicinal chemistry has undergone a revolutionary change. A huge investment has to be made towards the research and development of a new drug. Most research projects in the pharmaceutical industry now begin by identifying a suitable target in the body and designing a drug to interact with that target.

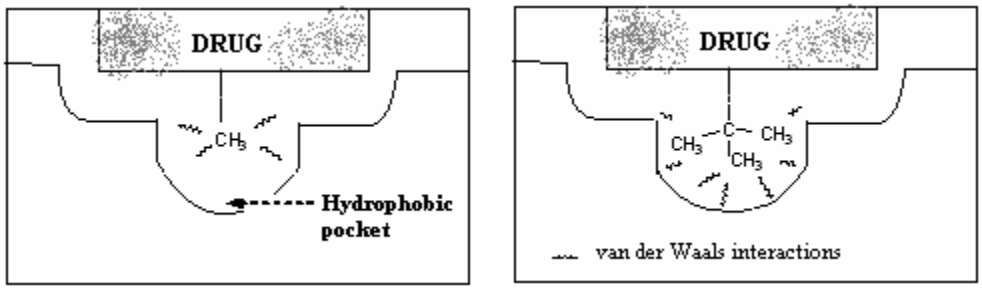
The first step is to isolate and identify the active principle from the natural sources, the lead compound. Once the structure of a biologically active compound is known, the focus is on the structure-activity relationship study of the compound. The aim of such a study is to discover which parts of the molecule are important to biological activity and which are not. The binding role of hydroxyl groups, amino groups, aromatic rings, double bonds, ketones, amides etc. with the receptor sites play crucial role in the drug activity. Once it is established which groups are important for a drug's activity, it is possible to move on to the next stage-the identification of the pharmacophore.[1] The pharmacophore summarizes the important functional groups which are required for activity and their relative positions in space with respect to each other. A drug must have the correct balance of hydrophilic and hydrophobic properties. Without this balance, drugs suffer several disadvantages, drugs which are too polar are easily excreted by the kidneys and do not easily cross the fatty barriers of the cell membranes, while drugs which are too lipophilic are poorly absorbed from the GI tract since they are likely to coagulate in fatty globules and fail to interact with the gut wall.

The biological activity of most drugs is related to a combination of physicochemical properties like hydrophobicity, electronic factors, steric factors etc. Hansch equation, Craig plot, Topliss scheme are some distinct approaches to quantify the structure-activity relationship of drugs.[1] When carrying out structure-activity

relationships, biological testing should involve *in vitro* tests. The results then conclusively show which binding groups are important in drug-target interactions. If *in vivo* testing is done, there may be loss of activity due to the inability of the drug to reach its target rather than reduced drug-target interactions.

There are several strategies which can be used to improve the interactions between a drug and its target, like variation of substituents, extension of the structure, chain extensions/contractions, ring expansions/contractions, ring variations, ring fusions, simplification or rigidification of the structures. For example, alkyl substituents such as methyl, ethyl, propyl, butyl, isopropyl, isobutyl or t-butyl are often used to investigate the effect of chain length and bulk on binding. If these groups are interacting with a hydrophobic pocket present in the target receptor, then varying the alkyl group allows one to probe how deep and wide the pocket might be. Increasing the length and / or bulk of the alkyl chain to take advantage of such a pocket will then increase the binding interaction.

Figure-14. *Variation of alkyl chain to fill a hydrophobic pocket.*



Bello *et al.*[69] presented the inhibitory properties of a series of synthetic epimers and analogues of swainsonine towards the multiple forms of human alpha-mannosidases *in vitro* and in cells in culture. These compounds offer the opportunity to determine which alterations in the chirality of the swainsonine molecule affect its inhibitory specificity. A comparison of their biological activities has identified reagents that will be useful for studying steps in the biosynthesis and catabolism of glycoproteins and that may be of potential value in chemotherapy. Takahashi *et al.*[70] recently prepared α-Glucosidase inhibitors with a phthalimide skeleton. Structure-activity relationship studies indicated a critical role for the hydrophobicity of the substituent at the nitrogen atom of the

phthalimide skeleton. Introduction of electron-withdrawing groups, including a nitro group and chlorine, influenced the activity. 4,5,6,7-tetrachloro-*N*-phenylphthalimide and 4,5,6,7-tetrachloro-N-(4-phenylbutyl)phthalimide proved to be more potent α-glucosidase inhibitors than the known inhibitor 1-deoxynojirimycin. A series of imino sugar derivatives were made and tested for their antiviral activity against HBV by Mehta *et al.*[71]

Penarolide sulfates A_1 and A_2 (**36** and **37** in Figure 12) and schulzeines A-C (**39**, **40** and **41** of figure 13) do not bear slightest resemblance to glucose derivatives structurally, yet they are reportedly potent α-glucosidase inhibitors. This initiates inquisitiveness to find a plausible mechanism for their mode of inhibition. Induced fitting *via* hydrophobic interactions would definitely be a possible route. As for salacinol (**25**, Figure 11), it was found that the sulfate group is important for its increased activity against α-glucosidases,[72] the specificity may be derived from the strong noncovalent binding of its sulfate group to some arginine residues in the binding site. In case of penarolide sulfates A_1 and A_2 and schulzeines A-C sulfate groups might be playing the same role in the inhibition activity.

Therapeutic importance

About 40 years have passed since the classical glycosidase inhibitor nojirimycin was discovered from the cultured broth of the *Streptomyces* sp.[73] Since then, over 100 glycosidase inhibitors have been isolated from plants and microorganisms. Modifying or blocking biological processes by specific glycosidase inhibitors has revealed the vital functions of glycosidases in living systems. Because enzyme-catalyzed carbohydrate hydrolysis is a biologically widespread process, glycosidase inhibitors have many potential applications as agrochemicals and therapeutic agents.

Antidiabetic agents

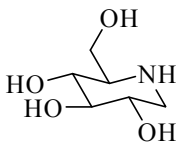
Diabetes mellitus, commonly referred to as diabetes, is a medical condition associated with abnormally high levels of glucose (or sugar) in the blood (hyperglycemia).[74] Diabetes Mellitus is a life-long, chronic condition. In 2006, according to the World Health Organization, at least 171 million people worldwide suffer from

diabetes. Current scientific evidence demonstrates that much of the morbidity and mortality of diabetes can be eliminated by aggressive treatment with diet, exercise, and new pharmacological approaches to achieve better control of blood glucose level. Furthermore, the possibility of preventing the onset of diabetes using dietary supplements and/or herbal medicines has attracted increasing attention.

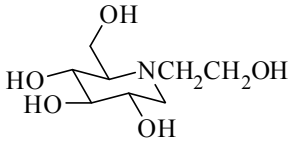
There are two main types of diabetes mellitus. These are known as Type 1 and Type 2. Treatment is aimed at controlling the elevated blood glucose without causing an abnormally low glucose level (hypoglycemia). Type 1 diabetes mellitus is treated with insulin, exercise, and a healthy diet. Type 2 diabetes mellitus is first treated with weight reduction, a healthy diet and regular exercise. In Type 2 diabetes, if the above measures fail to control the elevated blood glucose, oral (by mouth) medicines are used to try to boost insulin production, improve the body's use of it, or reduce the speed at which glucose enters the blood. Treatment with insulin will be considered if these other medicines are insufficient. Gestational diabetes is usually controlled by a healthy diet and regular exercise. Some women may require treatment with insulin.

Besides the use of multiple approaches, α-glucosidase inhibitors are one of the alternative therapeutic approaches. In the 1970s, it was realized that inhibition of all or some of the intestinal disaccharidases and pancreatic α-amylase by inhibitors could regulate the absorption of carbohydrate and these inhibitors could be used therapeutically in the oral treatment of the non-insulin-dependent diabetes mellitus (Type 2 diabetes).

Figure 15



42
Deoxynojirimycin



43
Miglitol

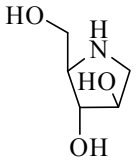
Bayer's researchers found that the *Actinoplanes* strain SE 50 yields a potent sucrase inhibitor, acarbose (**23**, Figure 11), which inhibits pig intestinal sucrase with an IC_{50} value of 0.5 μM.[75] After intensive clinical development, acarbose (Glucobay) was introduced into the market in Germany in 1990 for the treatment of diabetes and has since

been successfully marketed in Europe and Latin America. Thus acarbose provided the physician with the first new therapeutic principle for the treatment of diabetes in nearly 40 years.

In 1966 nojirimycin (**9**, figure 7) was discovered as the first glucose analog with the nitrogen atom in place of the ring oxygen.[76] Nojirimycin was first described as an antibiotic produced by *Streptomyces roseochromogenes* R-468 and *S. lavendulae* SF-425 and was shown to be a potent inhibitor of α- and β-glucosidases from various sources.[77] 1-deoxynojirimycin (DNJ) (**42**, Figure 15)[78] was later isolated from the roots of mulberry trees and called molanoline.[79] DNJ is also produced by many strains in the genera Bacillus and Streptomyces.[80-82] Despite the excellent α-glucosidase inhibitory activity *in vitro*, its efficacy *in vivo* was only moderate.[83] Therefore, a large number of DNJ derivatives were prepared in the hope of increasing the *in vivo* activity. Thus miglitol (BAY m 1099) (**43**, Figure 15) was selected as the most favorable inhibitor out of a large number of *in vitro* active agents. Miglitol differs from acarbose (**23**, Figure 11) in that it is almost completely absorbed from the intestinal tract and may possess systemic effects in addition to the effects in the intestinal border.[84] Salacinol (**25**, Figure 11) and kotalanol (**26**, Figure 11) have been identified as α-glucosidase-inhibiting components from the water-soluble fraction of the roots and stems of *S. reticulata*.[85,86]

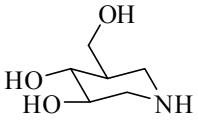
In Type 2 diabetes, hepatic glucose production is increased.[87] A possible way to suppress hepatic glucose production and lower blood glucose in type 2 diabetes patients may be through inhibition of hepatic glycogen phosphorylase.[88] In enzyme assays, 1,4-dideoxy-1,4-imino-D-arabinitol (D-AB1) (**44**, Figure 16), which was first isolated from the fruits of the legume *Angylocalyx boutiquenus*,[62] was found to be a potent inhibitor of hepatic glycogen phosphorylase.[89]

Figure 16



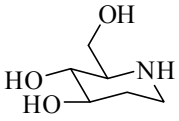
44

D-AB1



45

Isofagomine



46

Fagomine

D-AB1 further inhibited hepatic glycogen breakdown *in vivo* and displayed an accompanying antihyperglycemic effect, which was most pronounced in obese mice.[89] Recently the synthetic piperidine alkaloid isofagomine (**45**), (3*R*,4*R*,5*R*)-5-hydroxymethylpiperidine- 3,4-diol, has been reported to potently inhibit hepatic glycogen phosphorylase with an IC_{50} value of 0.7 μM, and to prevent basal and glucagon-stimulated glycogen degradation in cultured hepatocytes with IC_{50} values of 2-3 μM.[90] However, its N-substitution always resulted in a loss of activity compared to the parent compound, and fagomine ((2*R*,3*R*,4*R*)-5-hydroxymethylpiperidine- 3,4-diol) (**46**) was a weak inhibitor of this enzyme, with an IC_{50} value of 200 μM.[90] The structures of all the discussed inhibitors are shown in Figure 16.

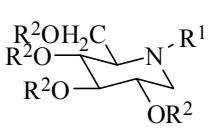
Antiviral agents

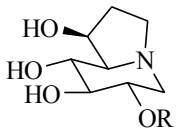
Many animal viruses contain an outer envelope, which is composed of one or more viral glycoproteins. These viral envelope glycoproteins are often essential for virion assembly and secretion and/or infectivity. The glycon attached to these proteins are often vital for the correct performance of these functions. Compounds that interfere with the glycosylation processes of viral glycoproteins can be expected as antiviral agents. Alterations in glycon composition have been employed to investigate the way glycoproteins operate and to develop new ways of treating clinical conditions.

In 1983 scientist led by Luc Monagnier at the Pasture Institute in France first discovered the virus that causes AIDS.[91] Human immunodeficiency virus (HIV) is a retrovirus that can lead to *acquired immunodeficiency syndrome* (AIDS, a condition in humans in which the immune system begins to fail, leading to life-threatening opportunistic infections). As of January 2006, the Joint United Nation Program on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) estimated that AIDS has killed more than 25 million people since it was first recognized on December 1, 1981, making it one of the most destructive pandemics in recorded history. Since the beginning of the pandemic; three main transmission routes for HIV have been identified:[92-98] the sexual route, the blood or blood product route and the mother to child transmission (MTCT) route.

HIV primarily infects vital cells in the human immune system such as helper T cells (specifically $CD4^+$ T cells), macrophages and dendritic cells. HIV infection leads to low levels of $CD4^+$ T cells through three main mechanisms: firstly, direct viral killing of infected cells; secondly, increased rates of apoptosis in infected cells; and thirdly, killing of infected $CD4^+$ T cells by CD8 cytotoxic lymphocytes that recognize infected cells. When $CD4^+$ T cell numbers decline below a critical level, cell-mediated immunity is lost, and the body becomes progressively more susceptible to opportunistic infections. If untreated, eventually most HIV-infected individuals developed AIDS (Acquired Immunodeficiency Syndrome) and die; however about one in ten remains healthy for many years, with no noticeable symptoms. Treatment with anti-retroviral, where available, increases the life expectancy of people infected with HIV. It is hoped that current and future treatments may allow HIV-infected individuals to achieve a life expectancy approaching that of the general public.

Figure 17





47 NB-DNJ $R^1 = C_4H_9$ $R^2 = H$
48 NN-DNJ $R^1 = C_9H_{19}$ $R^2 = H$

49 Castanospermine R = H
50 MDL 28574 $R = CH_3CH_2CH_2CO$

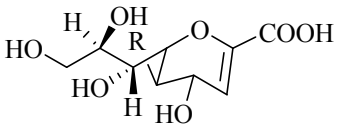
In fact, α-glucosidase inhibitors such as DNJ (**42**) shown in Figure 15, N-butyl-DNJ (NB-DNJ) (**47**), castanospermine (**49**), and 6-*O*-butanoylcastanospermine (MDL 28574) (**50**) as in Figure 17, inhibit human immunodeficiency virus (HIV) replication and HIV mediated syncytium formation *in vitro*.[11a, 99-101] These sugar analogs showing anti-HIV activity have the common property that they are potent processing α-glucosidase inhibitors but not processing α-mannosidase inhibitors. Problems exist in achieving therapeutic serum concentrations of inhibitors needed to inhibit α-glucosidases sufficiently and side effects such as diarrhea occur.

In contrast to the heavily glycosylated HIV envelope glycoproteins, the envelope glycoproteins of hepatitis B virus (HBV) contain only two glycosylation sites.[102] In case of HBV, glucosidase inhibitor prevents the formation and secretion of the virus through

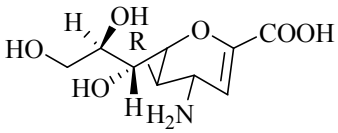
the disruption of the viral envelope. A few misfolding are sufficient to prevent viron formation. However, the HBV glycoproteins are sensitive to inhibitors of the N-linked glycosylation pathway. In this virus, correct glycosylation appears to be necessary for processes involved in transport of the virus out of the host cell. *In vitro* treatment of HBV with NB-DNJ results in a high proportion of virus particles being retained inside the cells.[103] Recent work has shown that N-nonyl-DNJ (NN-DNJ) (**48**, Figure 17) is 100-200 times more potent than NB-DNJ in inhibiting HBV in cell-based assays.[104]

The influenza pandemic of 1918-19, known as Spanish flu that killed more than 20 million people, prompted a substantial research effort to find a preventive agent and/or cure for this oldest and most common disease. There are two major surface antigen proteins, hemagglutinin and neuraminidase (sialidase; NA), which are seen as spikes covering the surface of the viral particle.[105]

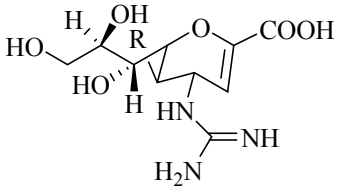
Figure 18



DANA (**51**) R = $NHCOCH_3$
FANA (**52**) R = $NHCOCF_3$



4-Amino-4-deoxy-DANA (**53**) R = $NHCOCH_3$



Zanamivir (**54**) R = $NHCOCH_3$

Figure 18 shows the first substrate-based NA inhibitor described was Neu5Acen (2-deoxy-2,3-dehydro-N-acetylneuraminic acid; DANA) (**51**).[106] Despite *in vivo* less efficacy of DANA[107] and the possibility that such compounds may not be suitable candidates as anti-influenza drugs, considerable research effort has been devoted to the development of substrate-based NA inhibitors. Introduction of the trifluoroacetamido group in place of the acetamido of DANA to give 2-deoxy-2,3-dehydro-N-trifluoroacetylneuraminic acid (FANA) (**52**, Figure 18) resulted in a slight improvement

in inhibitory activity toward influenza NA,[108] but it was ineffective in animal models of influenza infection.[107] Thus was developed a 4-deoxy-4-guanidino derivative of DANA, zanamivir (**54**, Figure 18), which inhibits NA of both influenza A and B.

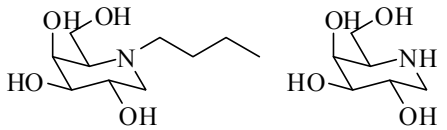
α-Glucosidase inhibitors reduces Dengue virus production by affecting the initial steps of viron morphogenesis in the endoplasmic reticulam.[109] Glucosidase inhibition strongly affects productive folding pathways of the envelope glycoproteins prM (the intracellular glycosylated precursor of M [membrane protein]) and E (envelope protein): the proper folding of prM bearing unprocessed N-linked oligosaccharide is inefficient, and this cause delayed formation of prME heterodimer. The complexes formed between incompletely folded prM and E appears to be unstable, leading to a nonproductive pathway. Inhibition of α-glucosidase-mediated N-linked oligosaccharide trimming may thus prevent the assembly of Den virus by affecting the early stages of envelope glycoprotein processing.

Thus protein crystals enable scientists to determine the three-dimensional structure of the enzyme and to build drugs designed to fit its active site. The success of the structure-based drug design through computational analysis provides encouragement for future efforts targeted at other diseases.

Therapy for lysosomal storage diseases

Glycosphingolipid (GSL) storage diseases are relatively rare hereditary disorders that are severe in nature and frequently fatal.[110] NB-DNJ (**47**, Figure 17), N-butyl-1-deoxygalactonojirimycin (NB-DGJ) (**55**, Figure 19) and 1-deoxygalactonojirimycin (DGJ) (**56**, Figure 19) are used as synthetic inhibitors for the GSL lysosomal storage diseases.

Figure 19



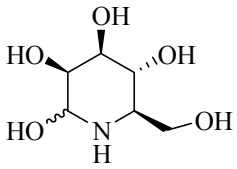
55 NB-DGJ **56** DGJ

Anti-tumor and anti-cancer agents

The membrane cells of malignant cells differ from normal ones in the structure and composition of their glycoproteins, glycolipids and proteoglycans. As a result, the nature of the carbohydrates that participate in the complex process of metastasis is also specific and these sugars are sometimes modified. Although a number of azasugars have been reported to show anticancer activity such as, NJ (**9**, Figure 7), MJ (**57**, Figure 20), DNJ (**42**, Figure 15) and swainsonine (**24**, Figure 11),[110] research has concentrated on developing swainsonine as a candidate for the management of human malignancies. It inhibits the growth of tumor cells and prevents the dissemination of malignant cells from primary tumor to secondary sites (a process known as metastasis) also there is considerable evidence that swainsonine enhances the natural antitumor defense of the body.[111]

The membrane surfaces of malignant cells differ from normal ones in the structure and composition of their glycoproteins, glycolipids, and proteoglycans. A study of the inhibitory effect of imino sugars like nojirimycin (**9**), mannonojirimycin (**57**) and deoxynojirimycin (**42**) has been carried out by Tsuruoka and co-workers in a model of pulmonary metastasis of mouse B16 melanoma. In vitro treatment with 10 mg mL^{-1} of the tested compounds was 98% and 80% effective with NJ and DNJ, respectively, and 57% effective with MJ, thus highlighting the participation of α-glycosidases in metastatic processes.[112]

Figure 20



57

Mannonojirimycin

Conclusion

The alteration of glycosidase activity by inhibitors *in vivo* is of great interest because of the involvement of glycosidases in a wide range of anabolic and catabolic

processes. As already reviewed, glycosidase inhibitors could have many kinds of beneficial effects as therapeutic agents. Recently immense importance has been bestowed on the research of glycosidase inhibitors, the isolation, structure elucidation, synthesis and biological activities of these metabolites. The present dissertation deals with the synthetic studies towards the total synthesis of three newly discovered naturally occurring α-glucosidase inhibitors, the penarolide sulfate A_1 and the schulzeines B-C.

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fimi,[e] *Bacillus Circulans xylanase*, [f] hen egg white lysozyme,[g] glucoamylase from *Aspergillus awamori*,[h] β-amylase from soybean,[i] and endoglucanase E2 from *Thermomonospora fusca*.[j] a) Burk, D.; Wang, Y.; Dombroski, D.; Berhuis, A. M.; Evans, S. V.; Luo, Y.; Withers, S. G.; Brayer, G. D. *J. Mol. Biol.* **1993**, *230*, 1084; (b) Swift, H. J.; Brady, R. L.; Derewenda, S.; Dodson, E. J.; Turemburg, J. P.; Wilkinson, A. *J. Acta Crystallogr.* **1991**, *B47*, 535; (c) Brady, R. L.; Brzozowski, A. M.; Derewenda, S.; Dodson, E. J.; Dodson, G. G. *Acra Crystullogr.* **1991**, *B47*, 527; (d) Larson, S. B.; Greenwood, A.; Cascio, D.; Day, J.; McPherson, A. *J. Mol. Biol.* **1994**, *235*, 1560; (e) White, A.; Withers, S. G.; Gilkes, N. R.; Rose, D. R. *Biochemistry* **1994**, *33*, 12546; (f) Campell, R.; Rose, D.; Wakarchuck, W.; To, R.; Sung, W.; Yagachi, M. In: *Proceedings of the second TRICEL symposium on Tnchodem reesei cellulase and other hydrolase;* Suominen, P., Reinikainen, T., Eds.; Helsinski Foundation for Biotechnical and Industrial Fermentation Research: Espoo, Finland, 1993; pp. 63-72; (g) Imoto, T.; Johnson, L. N.; North, A. C. T.; Phillips, D. C.; Rupley, J. A. In: *The Enzymes;* Boyer, P. D., Ed.; Academic Press: New York, 1972; pp 666-668; (h) Aleshin, A.; Golubev, A.; Firsov, L. M.; Honzatko, R. B. *J. Biol. Chem.* **1993**, *267*, 19291; (i) Mikami, B.; Degano, M.; Hehre, E. J.; Sacchettini, J. C. *Biochemistry* **1994**, *33*, 7779; (j) Spezio, M.; Wilson, D. B.; Karplus, P. A. *Biochemistry* **1993**, *32*, 9906.

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Chapter 2

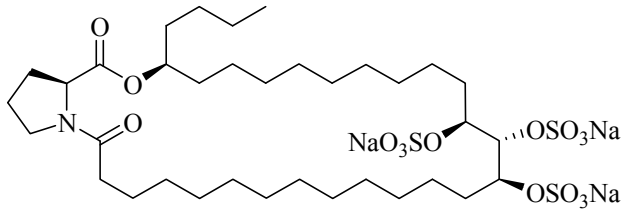
Total Synthesis of Penarolide sulfate A_1

PRESENT WORK

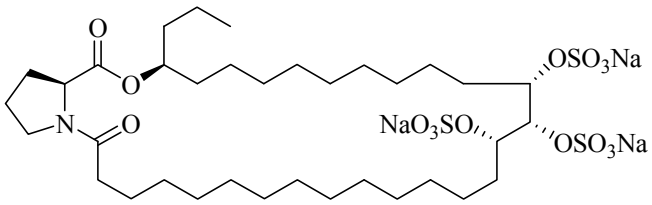
Present work

Recent progresses in glycobiology have shed light on significant roles of glycosidases in various biological functions, including immune response, oncogenesis, metastasis of tumors, viral and bacterial infections, and differentiation of neural cells.[1] Specific inhibitors of glycosidases have potentials for treatment of a variety of diseases. α-glucosidases are involved in glycoprotein processing and glycogenolysis. Their inhibitors can be applied for the treatment of diabetes, obesity, viral infections, and cancer.[2] In fact, several naturally-occurring sugar mimetic inhibitors like acarbose and N-butyl-1-deoxynojirimycin are used or tested in the treatment of diabetes and HIV infection.[2] In the year 2000, during the screening for α-glucosidase inhibitors from Japanese marine invertebrates, Fusetani and co-workers encountered a marine sponge *Penares* sp.[3] from Hachijo-jima Island whose hydrophilic extract was highly active.

Figure 1. *Penarolide sulfate A_1 (**1**) and A_2 (**2**)*.



1

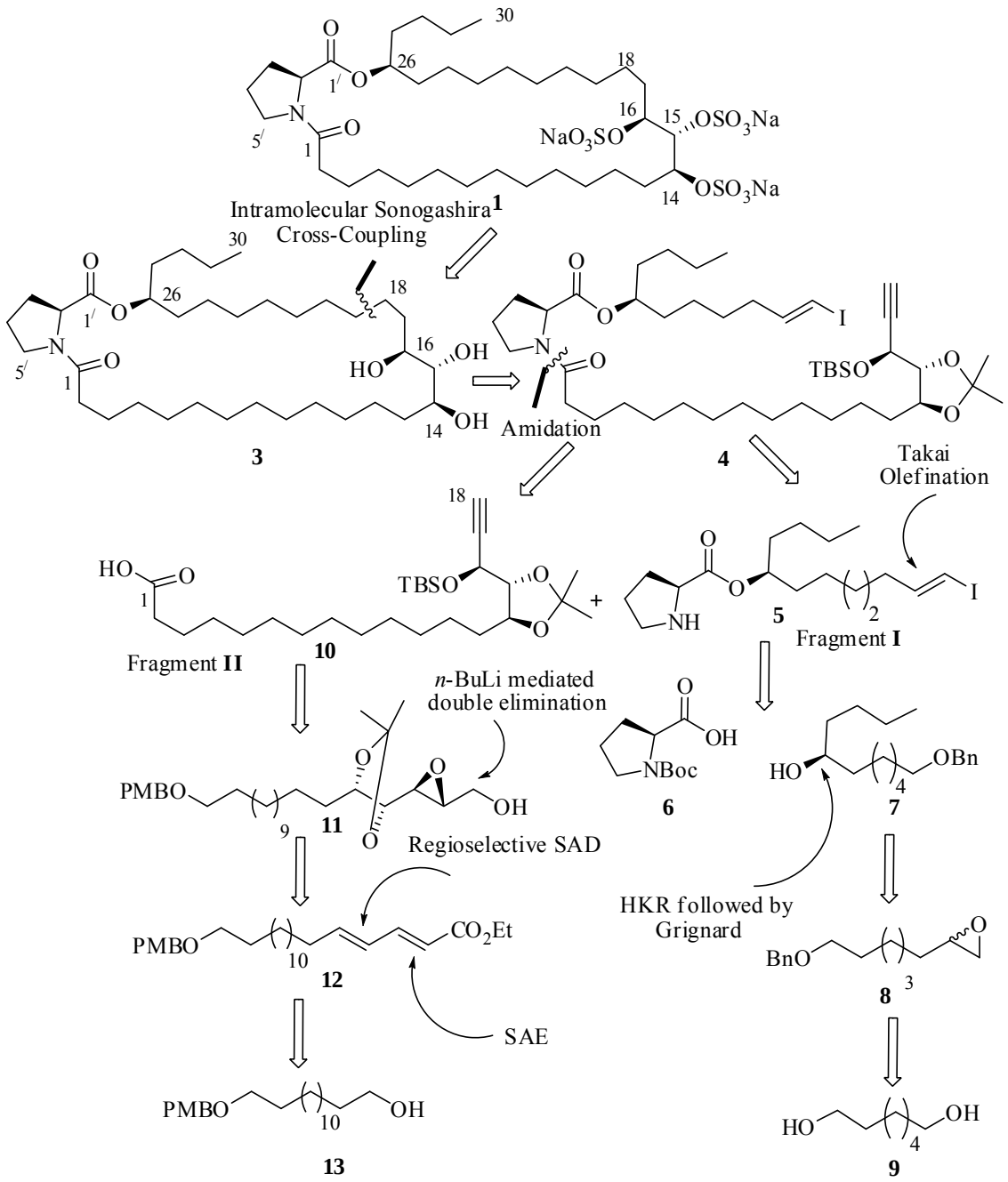


2

Bioassay-guided fractionation led to the isolation of two active compounds, penarolide sulfates A_1 and A_2 whose structures were assigned to proline-containing macrolide trisulfates. Spectral and chemical degradation data indicated an unique 30- and 31-membered macrolide encompassing a proline residue and three sulfate groups (Figure 1). The compound **1** is having three contiguous stereogenic centers on the macrocyclic

skeleton at C_{14}, C_{15} and C_{16} as sodium sulfate salts with the configuration assigned as *S*, *R*, *S* respectively (Scheme 1). The absolute configurations at the C_{26} and $C_2^{/}$ stereocenters are assigned as *S* and *S* respectively. Penarolide sulfates A_1 (**1**) and A_2 (**2**) inhibit α-glucosidase with IC_{50} values of 1.2 and 1.5 μg/mL, respectively.[4]

Scheme 1. *Retrosynthetic strategy*.



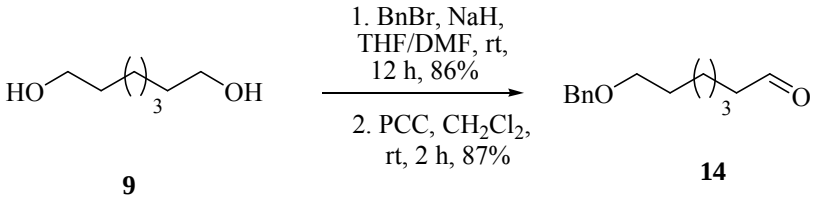
The intriguing structural features, noteworthy biological profiles, and limited availability, make penarolide sulfate A_1 and A_2 attractive targets for total synthesis. No report has yet appeared on the total synthesis of any of these natural products. We initially focused our endeavor towards the first total synthesis of penarolide sulfate A_1 by designing a novel convergent strategy. These includes an efficient assembly of its 30-membered macrolide core through sequential amidation[5] and macrocyclization *via* intramolecular Sonogashira cross-coupling reaction.[6]

Retrosynthesis of compound **1** into three segments **6, 7** and **10** provided the impetus for our work (Scheme 1). The assembly of the 30-membered macrocyclic core was envisioned to be a sequence of amidation between the C_1-C_{18} acid and amine segments (**10** and **5**) followed by intramolecular Sonogashira reaction of the amide thus formed. The key segment **5** would be elaborated from a chiral building block **7** by simple esterification[7] reaction using commercially available N-Boc-L-proline. The building block **7** could be obtained by the application of Jacobsen's hydrolytic kinetic resolution on the racemic epoxide **8** followed by regioselective Grignard opening of the resolved epoxide thus formed. Our plan for the synthesis of C_1-C_{18} subunit is founded upon the regioselective Sharpless asymmetric dihydroxylation[8] on compound **12** followed by simple FGT and Sharpless asymmetric epoxidation[9] would furnish the intermediate **11**, suitable for *n*-BuLi mediated double elimination reaction. Simple functional group manipulations thereafter would produce the protected hydroxy alkyne intermediate **10**.

Synthesis of fragment I

Synthesis of fragment **I** started with commercially available 1,7-heptane diol (**9**), which was protected as its monobenzyl ether by reacting with BnBr and sodium hydride in a solvent system of THF: DMF (7:3). It was then oxidized to the known[10] aldehyde **14** by treating with PCC[11] in DCM at room temperature for 2 h (Scheme 2).

Scheme 2

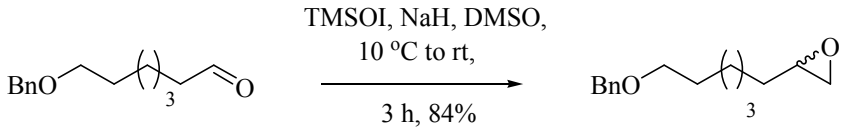


9 **14**

The appearance of a signal in the ^{1}H NMR at δ 9.8 ppm having a coupling constant J = 1.2 Hz confirmed the formation of the aldehyde. The formation of aldehyde was further confirmed by ^{13}C NMR which showed the appearance of a new peak at δ 202 ppm. The spectral data of **14** was consistent with the literature value.[10a]

Our next step involved the synthesis of the racemic epoxide **8** with the extension of one carbon. For this endeavor, **14** was treated with the sulfur ylide [$(CH_3)_2S(O)CH_2$] (prepared from trimethylsulfoxonium iodide and NaH) in DMSO at 10 ^{o}C to rt for 3 h (Corey-Chakovsky reaction)[12] to furnish **8** in 84% yield (Scheme 3).

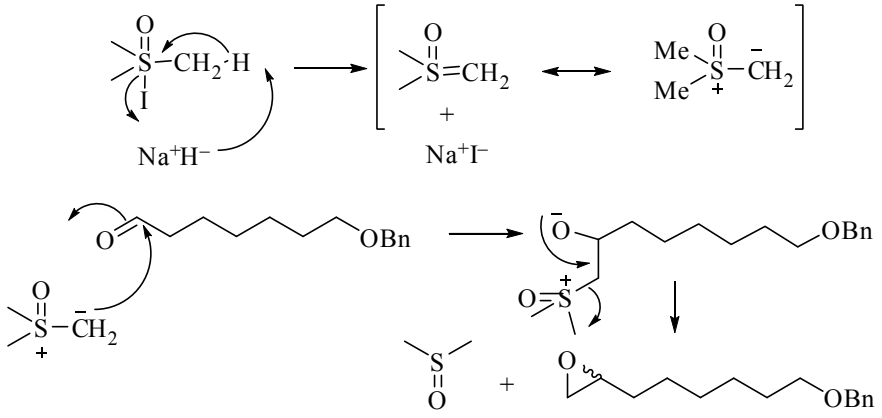
Scheme 3



14 **8**

The reaction mechanism consists of nucleophilic addition of the ylide to the carbonyl group. A negative charge is transferred to the oxygen carbonyl anion and because the sulfonium cation is a good leaving group it gets expelled forming the oxirane (Scheme 4). The ^{1}H and ^{13}C NMR spectra clearly indicated the formation of oxirane ring. The ^{1}H NMR spectrum of **8** showed the three oxirane ring protons at δ 2.90-2.84 ppm (m, 1H), 2.73 ppm (dd, J = 5.1, 4.0 Hz, 1H) and 2.44 (dd, J = 5.1, 2.7 Hz, 1H) ppm. The other protons resonated at their expected respective chemical shift values. The ^{13}C NMR and elemental analysis further supported the assigned structure **8**.

Scheme 4. *Mechanism of oxirane formation*.

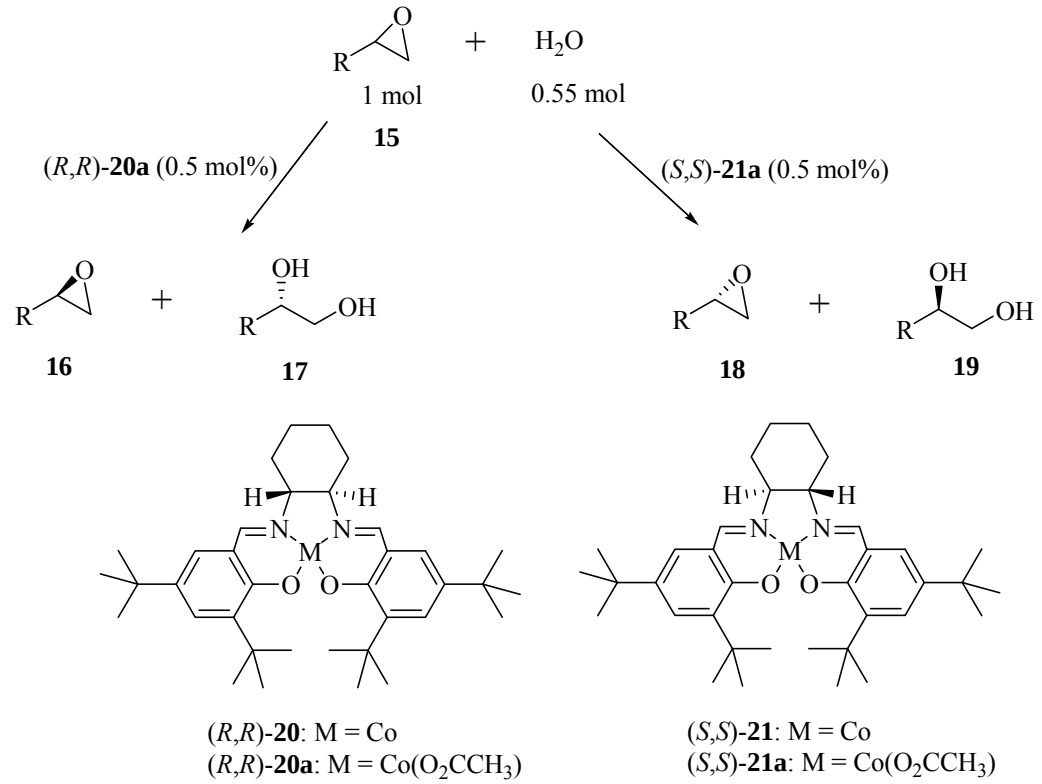


Our next step involved resolution of the racemic epoxide thus formed in the earlier step. To complete this job Jacobsen's Hydrolytic Kinetic Resolution (HKR) was chosen as the synthetic protocol.

A brief overview on Jacobsen's hydrolytic kinetic resolution

Epoxides are versatile building blocks for organic synthesis. However, terminal epoxides are arguably the most important subclass of these compounds, and no general and practical method exists for their production in enantiomereically pure form. In 1997 Jacobsen group reported a powerful tool to resolve the terminal epoxide by describing the hydrolytic kinetic resolution (HKR) process.[13] Terminal epoxides are available very inexpensively as racemic mixtures, and kinetic resolution is an attractive strategy for the production of optically active epoxides, providing an economical and operationally simple method.

Scheme 5

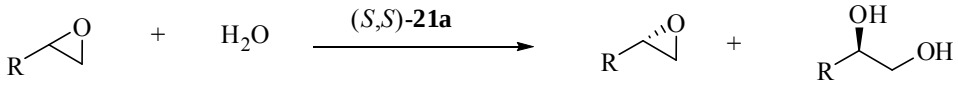


*Readily accessible synthetic catalysts((R,R)-(–)-N,N′-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II)acetate (**20a**) and (S,S)-(+)-N,N′-Bis(3,5-di-tert-*

*butylsalicy-lidene)-1,2-cyclohexanediaminocobalt(II))acetate (**21a**) have been used for the efficient asymmetric hydrolysis of terminal epoxides. This process uses water as the only reagent with no added solvent and low loading of recyclable catalyst (<0.5 mole percent), and it affords highly valuable terminal epoxides and 1,2-diols in high yield with high enantiomeric enrichment. Accordingly, (R,R)-salen Co(III)OAc (HKR catalyst) complex **20a** with 0.55 eqv of H_2O effect the resolution of racemic terminal epoxide **15** providing the optically pure epoxide **16** and corresponding optically pure diol **17** in good chemical and optical purity (Scheme 5).*

*The nonvolatile residue obtained after the distillation of epoxide and diol contained reduced complex **20**, from which active catalyst **20a** can be regenerated by treatment with acetic acid in air. Therefore the catalyst can be recycled with no observable loss in activity or enantioselectivity.[14] By using active catalyst **21a** the other epoxide **18** can be obtained in optically pure form together with the corresponding diol **19** in good chemical and optical purity.*

***Table 1**. Hydrolytic kinetic resolution of terminal epoxides with water catalyzed by **21a**. The values for k_{rel} were calculated using the equation $k_{rel} = ln[(1 - c)(1 - ee)]/ln[(1 - c)(1 + ee)]$, where ee is the enantiomeric excess of the epoxide and c is the fraction of epoxide remaining in the final reaction mixture.*



Entry	R	Concentration		Time	Epoxide		Diol		K_{rel}
		21a (mol%)	Water (eqv)		ee (%)	Isolated yield (%)	ee (%)	Isolated yield (%)	
1	CH_3	0.2	0.55	12	>98	44	98	50	>400
2	CH_2Cl	0.3	0.55	8	98	44	86	38	50
3	$(CH_2)_3CH_3$	0.42	0.55	5	98	46	98	48	290
4	$(CH_2)_5CH_3$	0.42	0.55	6	99	45	97	47	260
5	Ph	0.8	0.70	44	98	38	98*	39*	20
6	$CH{=}CH_2$	0.64	0.55	20	84	44	94	49	30
7	$CH{=}CH_2$	0.85	0.70	68	89	29	88	64	30

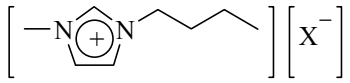
*After recrystallisation

The HKR is an attractive procedure for the preparation of optically enriched terminal epoxides and 1,2-diols. The criteria for evaluating the practicality of chemical processes such as this one have become increasingly stringent. High standards of yield and selectivity in product formation must be met, but additional issues such as reagent cost, volumetric productivity, waste generation, reagent toxicity, and handling risks weigh more heavily than ever before. With these criteria positively met, the HKR appears to hold significant potential for large-scale application.

However, in case of the substrate is epichlorohydrin, the catalyst recycling procedure is not suitable on a large scale applications. Although there are several efforts to overcome the drawback of the HKR procedure, the HKR reactions are appealing still more practical candidates for immobilization.[15] Immobilization on solid support often results in catalysts with lower enantioselectivities or efficiencies than solution phase counterparts and complexity associated with synthesizing the appropriately modified chiral ligands.

Recently a new and highly practical recycling procedure of the Co(salen) catalysts by ionic liquids[16] has been reported . Air and moisture stable room temperature ionic liquids consisting of 1,3-dialkylimidazolium cations and their counter anions, in particular, have attracted growing interest in the last few years. (Figure 2).[17]

***Figure 2**. Typical ionic liquids*.

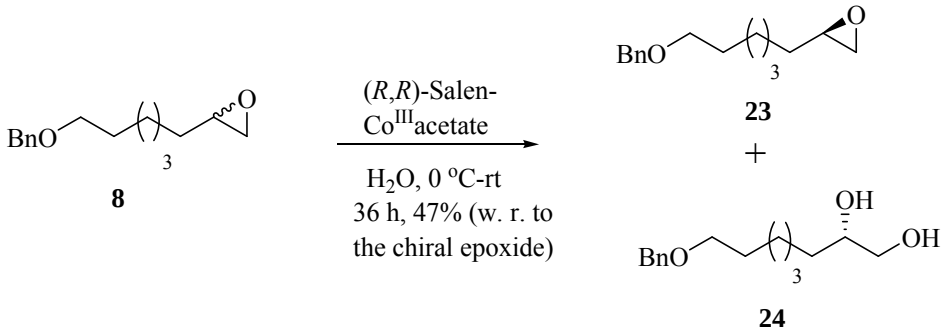


[bmim][X] (**22**); X = PF_6 (**22a**)
SbF_6 (**22b**)
BF_4 (**22c**)
OTf (**22d**)
OAc (**22e**)

1-butyl-3-methyl imidazolium
cations with different
anionic counterparts

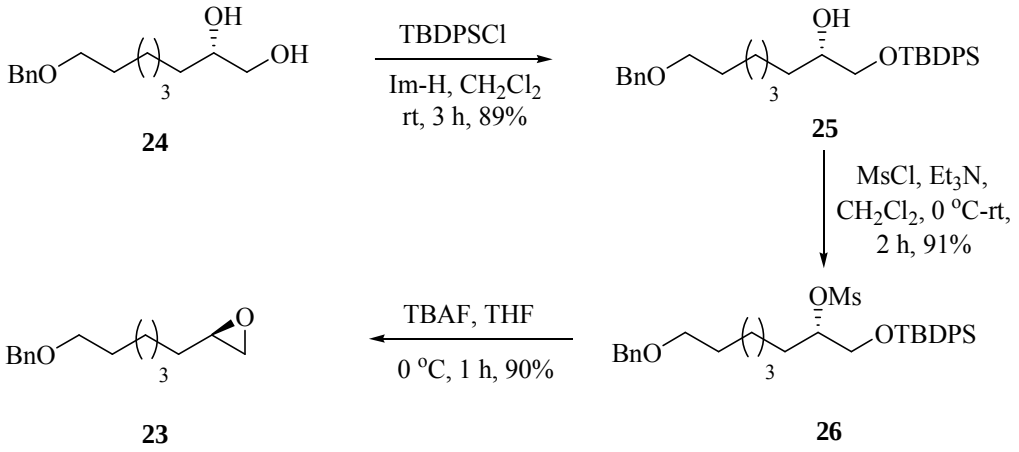
This procedure provides not only simple recycle of catalyst but also the additional advantage of use of catalyst without any modification of the structure.

Scheme 6



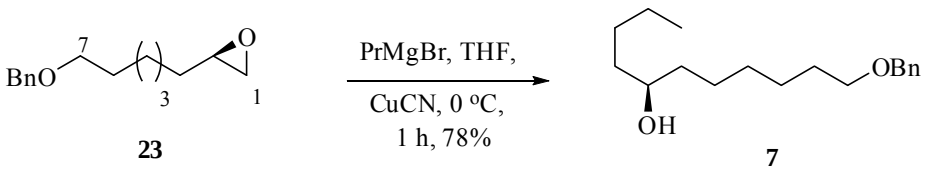
The catalyst (*R,R*)-salen-Co(III)OAc was synthesized as per the literature procedure[18] in good yield. The racemic epoxide **8** was then subjected to hydrolytic kinetic resolution conditions using 0.5 mol% of (*R,R*)-salen-Co(III)OAc and 0.55 eqv of distilled water at 0 ^{o}C to afford the resolved epoxide **23** in 47% yield (Scheme 6)**.** Separation of the resolved epoxide **23** and the 1,2-diol **24** by silica gel column chromatography afforded the chiral diol **24** in 42% yield. The epoxide **23** was obtained as a colorless liquid and the enantiomeric purity of the epoxide was found to be 98.8% *ee* by HPLC analysis using a chiracel OD-H column (eluent 100% *n*-hexane, flow rate 1 mL/min, λ = 214 nm). The diol **24** was obtained with 93.3% *ee* (eluent 7% *i*-propanol/*n*-hexane, flow rate 0.7 mL/min, λ = 220 nm). The ^{1}H and ^{13}C NMR spectra of **23** and **24** were in full agreement with the assigned structures.

Scheme 7



The undesired 1,2-diol **24** was transformed to the required epoxide **23** by a sequence of three simple chemical transformations[19] (Scheme 7). First protection of the primary alcohol as its TBDPS ether followed by protection of the secondary one as its mesyl derivative by reacting with MsCl and Et_3N in anhydrous CH_2Cl_2 at room temperature furnished the mesylate **26**. This mesyl derivative **26** was confirmed by the ^1H NMR spectrum, in which the downfield shift of methine proton bearing the methanesulfonyl group was observed as a multiplet at δ 4.75-4.64 ppm compared to that of the starting material. Finally, treatment of compound **26** with TBAF[20] in THF resulted in deprotection of the *t*-butyldiphenylsilyl protecting group and in situ S_N2 displacement of the mesylate furnished the inverted epoxide **23**. The inverted epoxide was confirmed using identical optical rotation value obtained with the resolved compound **23** and having the same enantiomeric purity data. Thus, by virtue of this synthetic sequence the loss of yield due to the formation of the undesired diol was circumvented.

Scheme 8

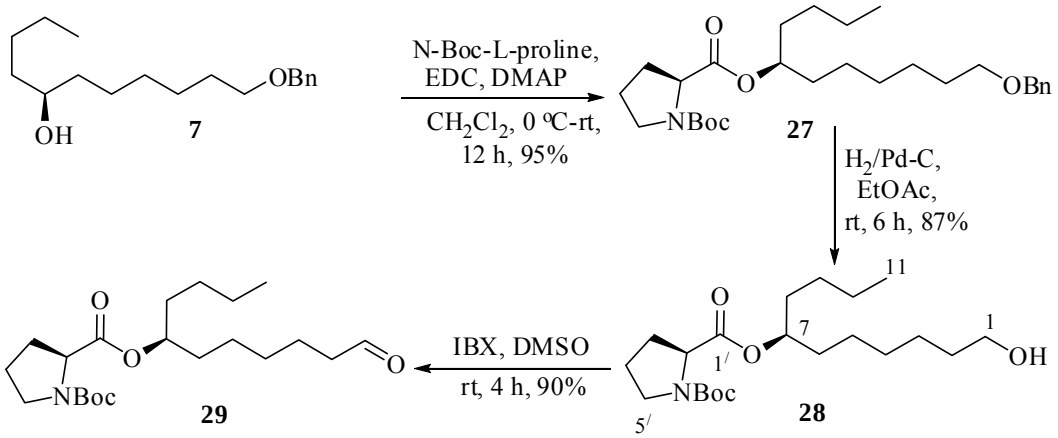


23 **7**

The secondary alcohol **7** was derived by the regioselective ring opening of **23** at less hindered carbon C_1 with *n*-propylmagnesium bromide in the presence of catalytic CuCN in dry THF (Scheme 8).[21] The structure of compound **7** was analyzed by its ^1H NMR spectrum in which the peaks due to epoxide protons (at δ 2.73 and 2.44 ppm respectively) were missing and the secondary hydroxyl group bearing methine proton was present in the downfield region of the spectrum (δ 3.57-3.54 ppm, multiplet). Furthermore, the terminal methyl group resonated at δ 0.91 ppm as triplet. ^{13}C NMR was also in accordance with the predicted structure of the secondary alcohol **7**. In the ^{13}C NMR spectrum, the carbon of the terminal methyl group appeared at δ 14.1 ppm, which in turn proved the insertion of three carbon appendage to the aliphatic segment; while the rest of the carbons were identified at their respective positions in the spectrum. The molecular ion peak at (*m/z*) 301.14 for $[M+Na]^+$ from ESI mass spectrum confirmed its

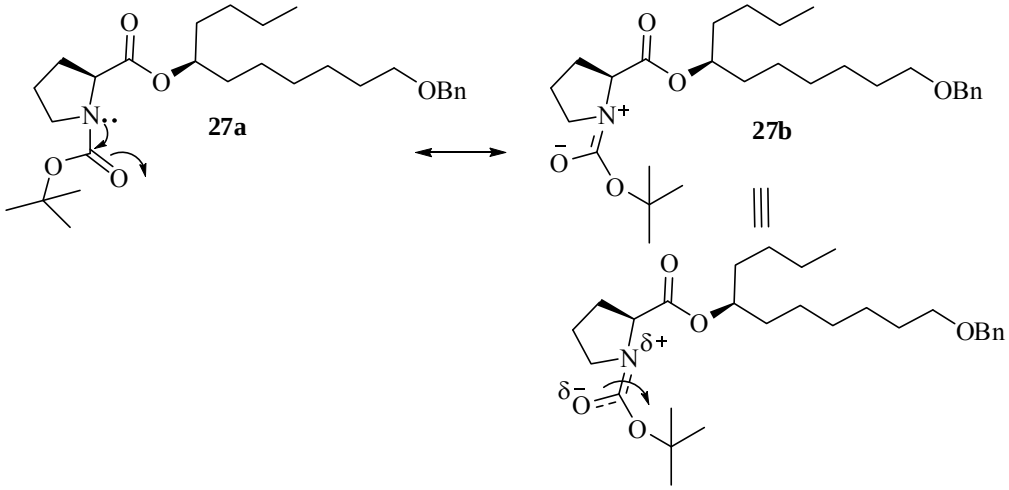
elemental composition. In the IR spectrum, the presence of signal at 3437 cm^{-1} also supported the formation of the secondary alcohol **7**.

Scheme 9



The next task was to attach the proline moiety to the aliphatic hydroxy segment (**7**). The coupling reaction between N-Boc-L-proline with the alcohol **7** was facile, under standard EDC, DMAP condition and produced the coupled compound **27** in 95% yield (Scheme 9).

Figure 3



In the ^{1}H NMR spectrum of compound **27**, the presence of *t*-butyloxycarbonyl (Boc) protected proline leads to formation of rotamers [22] (Any of a set of conformers that arise from the restricted rotation around a single bond (Figure 3). The rotational barrier is the activation energy required to jump from one conformer to the other). Thus at room

temperature the nine methyl protons of the Boc protecting group resonated at δ 1.45 and 1.42 ppm, having integration of three and six protons respectively. The complex pattern observed in the ^{13}C NMR spectrum of compound **27**, can be accounted for the presence of proline rotamers. Furthermore, to confirm this phenomenon, we had taken the ^{1}H NMR spectrum of **27** at 325 ^{o}K. At this higher temperature the free rotation along the propyl amide bond present in compound **27** became so fast that NMR time scale can not distinguish them separately and the nine methyl protons of the Boc protecting group coalesces at the same position of the spectrum and resonated at δ 1.42 ppm. IR, Mass spectrum and elemental analysis of compound **27** was in accordance with the assigned structure. Debenzylation[23] of **27** under hydrogen atmosphere using Pd/C as the catalyst furnished the primary alcohol **28** (Scheme 9). In the IR spectrum, the O-H stretching was observed at 3455 cm^{-1}. In the ^{1}H NMR spectrum, the absence of five proton multiplet at δ 7.33-7.25 ppm and two proton singlet at δ 4.49 ppm clearly suggested the formation of the free alcohol **28**. Again, the downfield shift of the two protons at C_1 of the aliphatic chain from δ 3.44 ppm to δ 3.62 ppm was also strong evidence in favor of debenzylation. In the ^{13}C NMR spectrum, absence of signals at δ 138.5, 129.3, 128.1, 127.3, and 127.2 ppm and the drift of carbon signal from δ 70.1 ppm to the value of δ 62.5 ppm confirmed the formation of the primary alcohol **28**. The complexity in the ^{13}C NMR spectrum of this compound is attributed to the presence of proline rotamers. Oxidation of **28** by IBX in DMSO produced the corresponding aldehyde **29** in 90% yield. In the IR spectrum the carbonyl stetching was observed at 1720 cm^{-1}. In the ^{1}H NMR spectrum of **29**, the aldehyde proton appeared at δ 9.74 ppm and the two protons adjacent to the aldehyde group appeared at δ 2.43-2.39 ppm. All other protons of this compound appeared at the expected position of the NMR spectrum.

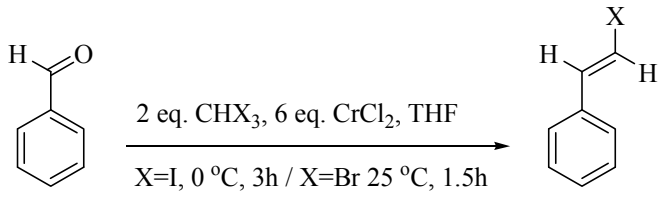
Next, we turned our attention to install the vinyl iodo group to the terminus of the aliphatic chain of compound **29** stereoselectively, by employing Takai olefination[24] protocol. This involves one carbon homologation of the aldehyde to the alkenyl halide stereoselectively to produce the exclusive *E*-isomer.

A brief overview on Takai olefination protocol and mechanistic consideration

Many methods are now available for the stereocontrolled preparation of alkenyl halides from acetylenic precursors.[25] However, the one-carbon homologation of an aldehyde to an alkenyl halide is quite limited.[26] For example, treatment of an aldehyde with the Wittig reagent Ph_3P=CHX usually gives a mixture of Z and E isomers and preparation of the ylide is rather complicated.[27] This is a simple and stereoselective method for the conversion of aldehydes to the corresponding (E)-alkenyl halides by an organochromium reagent.[28]

*Takai olefination in organic chemistry describes the organic reaction of an aldehyde with a diorganochromium compound to form an alkene. In the original 1986 publication the aldehyde is benzaldehyde (**30**) (Scheme 10) and the organochromium species **34** (Scheme 11) is generated from iodoform or bromoform and an excess of chromium(II) chloride. The reaction product is a vinyl halide (**31**) (Scheme 10). The main selling point is the E-configuration of the double bond. According to the principal investigator Kazuhiko Takai, existing alternatives such as the Wittig reaction only yield mixtures.*

Scheme 10



30 **31**

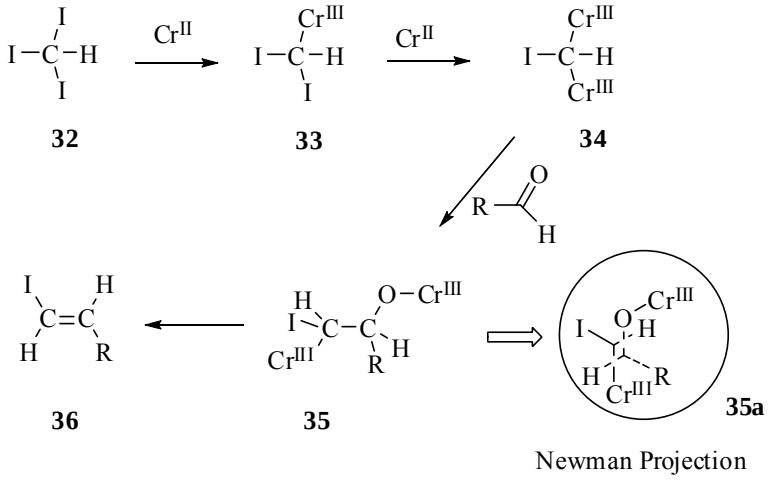
A representative experimental condition of this olefination reaction is as follows.

Anhydrous $CrCl_2$[29] is suspended in THF under an argon atmosphere. A solution of the terminal aldehyde and iodoform in THF was then added dropwise to the suspension at 0 °C. After stirring at 0 °C for 3 h, the reaction mixture was poured into water and extracted with diethyl ether. The combined extracts were dried over anhydrous Na_2SO_4

and concentrated. Purification by column chromatography on silica gel (hexane) affords the E-isomer exclusively.

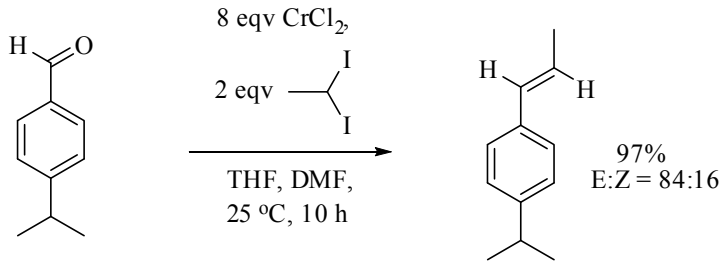
In the reaction mechanism proposed by Takai, chromium(II) is oxidized to chromium(III) when replacing both the halogen atoms. The geminal carbodianion complex ***34*** *thus formed reacts with the aldehyde in a 1,2-addition along one of the carbon to chromium bonds and in the next step both chromium bearing groups engage in an elimination reaction. In the newman projection (****35a****) it can be seen that how the steric bulks of chromium groups and the steric bulks of the alkyl and halogen groups drives this reaction towards anti elimination (Scheme 11) .*[30]

Scheme 11*. Mechanism of Takai olefination reaction.*



Alkenyl halides having an E configuration are produced selectively in all but the case of an α,β-unsaturated aldehyde and iodoform. The E/Z ratios of the alkenyl halides increase in the order I < Br < Cl and the rates of reaction of the haloform are in the sequence I > Br > Cl. Thus, reaction between an aldehyde and chloroform was conducted in THF at 65 °C. When bromoform was employed, a mixture (approximately 1 :1) of an alkenyl chloride and the desired bromide was produced. This difficulty was overcome by using a combination of $CrBr_3$, and $LiAlH_4$ (1:0.5 molar ratio) instead of $CrC1_2$. Although ketones are also converted into the corresponding alkenyl halides, they are less reactive than aldehydes. Selective conversion of an aldehyde into E-iodo olefin was performed without affecting the coexisting ketone group.

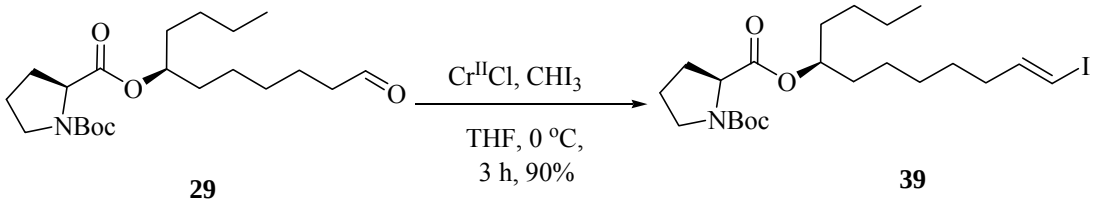
Scheme 12



37 **38**

The scope of the reaction was further extended to diorganochromium intermediates bearing alkyl groups instead of halogens which is shown in the conversion of compound ***37*** *to* ***38*** *(Scheme 12).*[31]

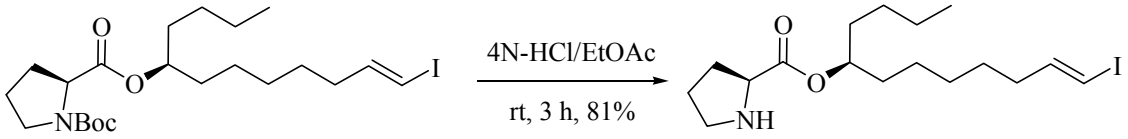
Scheme 13



29 **39**

The treatment of aldehyde **29** with chromous chloride and iodoform in anhydrous THF at 0 °C produced exclusively the *E*-iodo olefin **39** (Scheme 13). In the ^{1}H NMR spectrum, the two olefinic protons appeared at δ 6.48 ppm (dt, J = 14.3, 7.2 Hz, 1H) and 5.98 ppm (d, J = 14.3 Hz, 1H) as doublet of triplet and doublet respectively. In the ^{13}C NMR spectrum, the olefinic protons appeared at δ 146.4 and 146.3 (rotamers), and 79.7 and 79.4 (rotamers) ppm respectively. In the ESI mass spectrum, the appearance of the highest molecular ion peak at 530.21 suggested the formation of the $[M+Na]^{+}$. All other analytical data were in clear accordance with the predicted structure.

Scheme 14



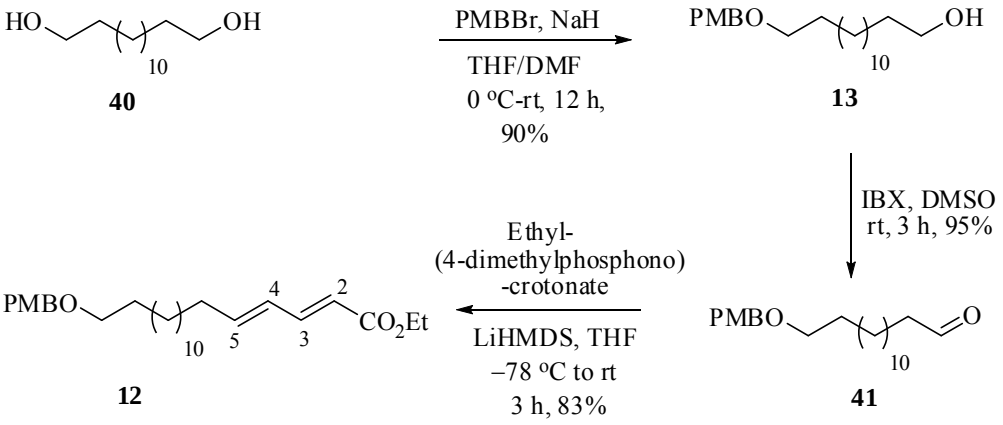
39 **5**

The next task remained to complete the synthesis of the amine building block **5** was the deprotection of the *t*-butyloxycarbonyl protecting group. This was done by reacting **39** with 4N-HCl in ethyl acetate (Scheme 14).[32] In the ^{1}H NMR spectrum, the absence of nine methyl protons of the *t*-butyloxycarbonyl protecting group and in the ^{13}C NMR the absence of complicated signals due to the rotamers clearly confirmed the formation of the free amine **5** (fragment **I**). In the IR spectrum, the secondary amine stretching at 3343 cm^{-1} was observed. Mass spectral data and elemental analysis also supported this observation.

Synthesis of fragment II

We next turned our attention for the synthesis of C_1-C_{18} carboxylic acid segment **10** (fragment **II**). The journey toward the synthesis of the fatty acid segment starts with commercially available 1,14-tetradecane diol (**40**). Selective monoprotection of **40** as its PMB ether[33] produced compound **13** (Scheme 15). In the ^{1}H NMR spectrum of compound **13**, the characteristic resonances for the aromatic ring protons of the PMB group was observed as two doublets at δ 7.25 and 6.86 ppm (J = 8.7 Hz), while the methyl group appeared as a singlet at δ 3.80 ppm. Oxidation of **13** to the corresponding aldehyde **41** by means of IBX in DMSO was the next step employed to derive at the substrate for four carbon homologation. Judicious employment of Horner-Wadsworth-Emmons reaction[34] of the ylide obtained from ethyl-4-(dimethylphosphono)-crotonate[35] in THF and LiHMDS as the base produced exclusively *E,E*-isomer **12** in 83% yield. This was confirmed from its ^{1}H and ^{13}C spectral data. In the ^{1}H NMR spectrum the appearance of four olefinic protons at δ 7.29 (dd, J = 15.4, 9.5 Hz, 1H), 6.21-6.11 (m, 2H) and 5.81 (d, J = 15.4 Hz, 1H) ppm clearly confirmed exclusive *E,E* stereochemistry. ^{13}C NMR, elemental analyis and mass spectra were in accordance with the predicted structure.

Scheme 15

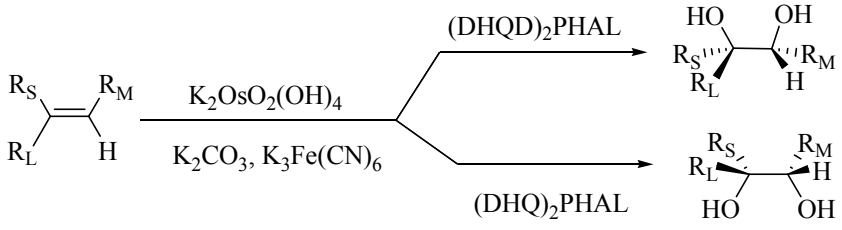


The next goal in the intended total synthesis programme was the installation of stereocenters at C_4 and C_5 of compound **12**. This was done successfully by using the regioselective Sharpless asymmetric dihydroxylation protocol.

A brief overview on Sharpless asymmetric dihydroxylation reaction

The stereospecific cis-dihydroxylation of olefins achieved by OsO_4 is one of the most valued transformations for introducing functionality into organic molecules. Initially the AD[36] using derivatives of cinchona alkaloids were performed under stoichiometric conditions. Later on with the advent of: i) use of two phase conditions with $K_3Fe(CN)_6$ as reoxidant; ii) $MeSO_2NH_2$ for rate acceleration and iii) second generation ligands[37] (phthalazine and diphenylpyrimidine,with two independent cinchona alkaloid units) by Sharpless et al., catalytic AD came into focus.

Scheme 16

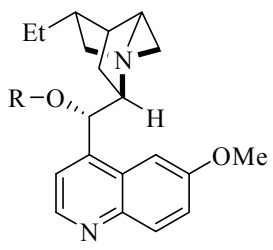


R_L, R_M and R_S are largest, medium sized and smallest substituents respectively.

Sharpless asymmetric dihydroxylation is the chemical reaction of an alkene with OsO_4 in the presence of a chiral quinine ligand to form a vicinal diol (Scheme 16).[38,39,40] The

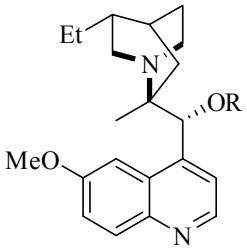
enantioselectivity in the AD reaction is due to the enzyme-like binding pocket present in the dimeric cinchona alkaloid ligands. The Cinchona alkaloid backbone is ideally suited for providing high ligand acceleration and enantioselectivity. The reaction rates are influenced by the nature of O-9 substituent of the Cinchona alkaloid. The rate enhancement is caused by a stabilization of the transition state due to aromatic stacking interactions.

***Figure 4**. Chinchona alkaloid ligands*.



42

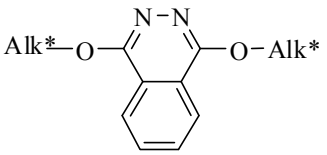
Dihydroquinidine (R=H)
DHQD



43

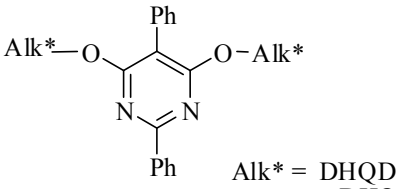
Dihydroquinine (R=H)
DHQ

***Figure 5**. Second generation ligands*.



44

Phthalazine (PHAL)
Ligands

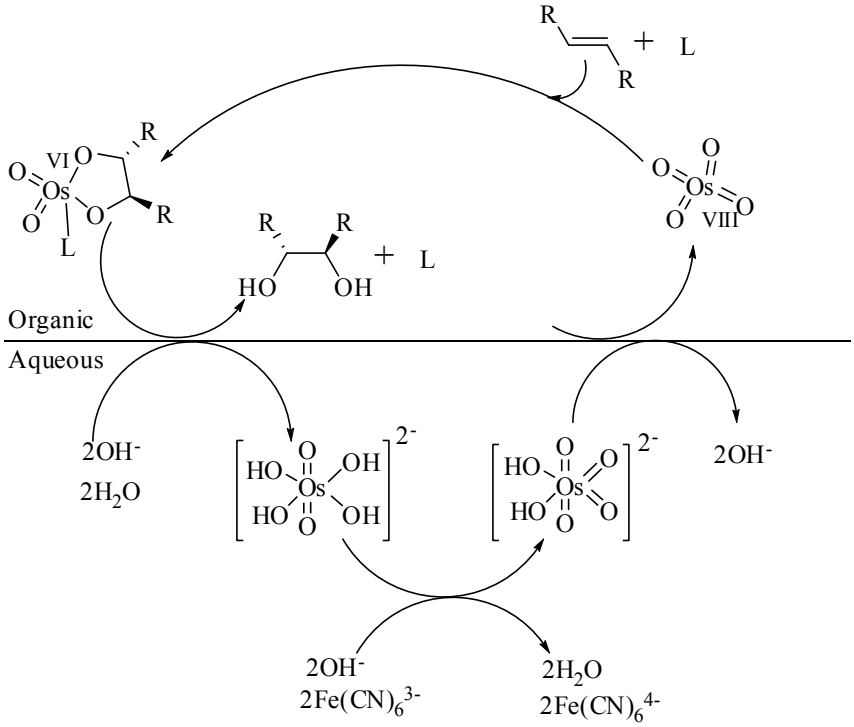


45

Diphenylpyrimidine (PYR)
Ligands

Although this kind of stabilization is operative even in monomeric first generation ligand,[41] it is most effective in the dimeric second-generation ligands due to the presence of a binding pocket. Thus the almost perfect match between the phthalazine ligands and aromatic olefins with respect to rates and enantioselectivities can be readily explained by an especially good transition state stabilization resulting from offset-parallel interactions between the aromatic substituent of the olefin and the phthalazine floor of the ligand, as well as favorable edge-to face interactions with the bystander methoxyquinoline ring.

Scheme 17. *The mechanism involved in the biphasic reaction protocol.*



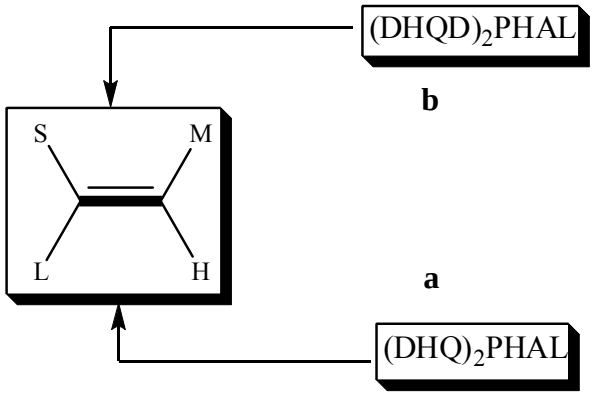
In heterogeneous solvent system, typically t-butanol/water the actual osmylation takes place in the organic layer, giving rise to the Os(VI)glycolate which can not be oxidised to an Os(VIII)glycolate, because of the absence of the inorganic stoichiometric oxidant, $K_3Fe(CN)_6$[42], in the organic layer. Consequently, the second catalytic cycle can not occur. Further, reaction requires hydrolysis of the Os(VI)glycolate to the diol and a water soluble inorganic Os(VI) species which enters the basic aqueous layer ready to be oxidized by $K_3Fe(CN)_6$ to OsO_4. The lat er returns to the organic phase, completing the catalytic cycle (Scheme 17). The enantiomeric purities of diols obtained under these heterogeneous conditions are essentially identical to those obtained under stoichiometric conditions. Sharpless discovered that alkyl sulfonamides[43] *(e.g. $CH_3SO_2NH_2$) accelerates the hydrolysis of the Os(VI) glycolate under heterogeneous conditions, and the reaction times can be up to 50 times shorter in the presence of this additive.*

Emperical rules for predicting the face selectivity

The observations shown in the following figure have led to a revised mnemonic device[44] *for predicting the enantiofacial selectivity in the reaction. An olefin positioned*

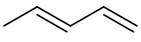
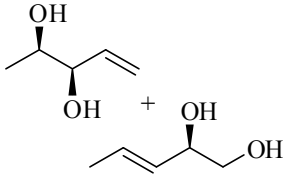
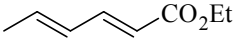
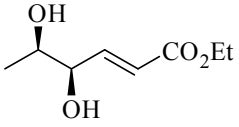
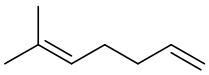
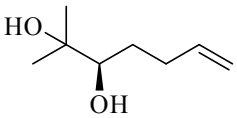
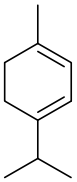
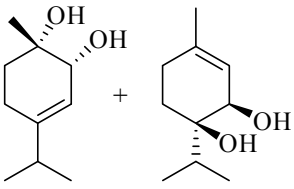
accordingly will be attacked either from the top face (β-face) in the case of dihdroquinidine derivatives or from the bottom face (α-face) in the case of dihydroquinine derived ligands (Figure 6).

***Figure 6**. Mnemonic diagram (S = small group, L = large group, M = medium group, H = proton).*



Regioselectivity

***Table 2**. The AD reactions were performed under standard conditions[8b] using (DHQD)$_2$PHAL and 0.2-1.0 mol% of OsO_4.*

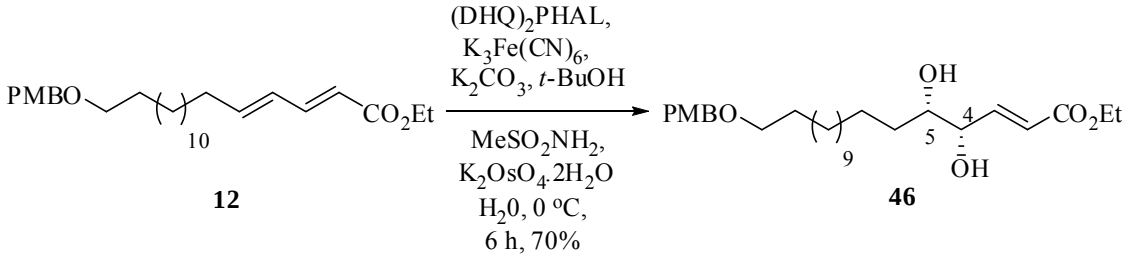
Entry	Substrate	Products	Ratio	%ee	% yield
1			3 : 1	90 72	48
2			Exclusive	92	78
3			Exclusive	98	73
4			8:1	86	78

The regioselectivity[45] of the mono-dihydroxylation of a polyene is determined both by electronic and by steric effects. Recently, it was shown that the rate constants of the dihydroxylation of isolated double bonds are much larger with trans-1,2-disubstituted and trisubstituted olefins than with cis-1,2-disubstituted and terminal alkenes.[46] Similar trends are also observed with polyenes, and the factors governing the regioselectivity are discussed in more detail in the following paragraph.

Electronic factors greatly influence the regioselectivity, and the osmylation of unsymmetrical polyenes preferentially occurs at the more electron-rich double bond. This is true for conjugated polyenes (Entry 1 and 2, Table 2) as well as substrates with isolated double bonds (Entry 3, Table 2). Steric effects may play a decisive role in systems with electronically very similar double bonds, and generally the sterically most accessible site is osmylated preferentially (Entry 4, Table 2).

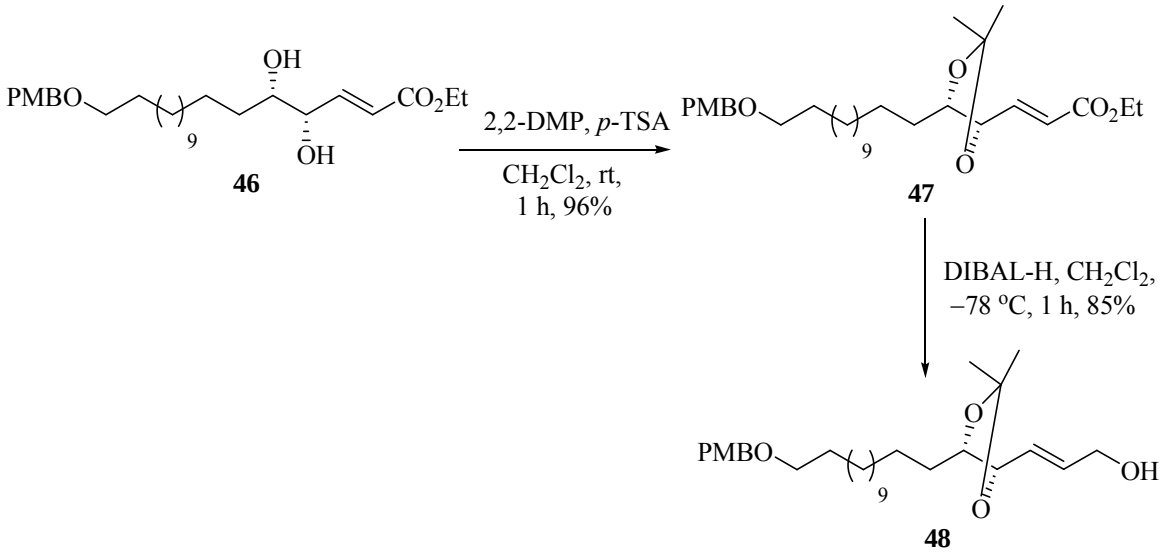
Thus, compound **12** was treated with ligand $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$ and K_2OsO_4. $2H_2O$ in *t*-BuOH-H_2O (1:1) at 0 °C for 6 h to afford the diol **46**. In this reaction exclusive formation of the regioselective isomer **46** was observed in 70% yield (Scheme 18). The formation of this particular product was confirmed after thorough investigation of the ^1H NMR, ^{13}C NMR spectra and elemental analysis of this compound. In the ^1H NMR spectrum, the H-4 and H-5 protons resonated as multiplets at δ 4.16 and 3.59 ppm respectively. The two olefinic protons α to the carboxylate group resonated at δ 6.99 (dd, J = 15.6, 5.0 Hz, 1H) and 6.19 ppm (d, J = 15.6 Hz, 1H). In the ^{13}C NMR spectrum, peaks at 72.5 and 70.2 ppm correspond to C-4 and C-5 of compound **46**. Enatiomeric purity of **46** was estimated to be 98.4% *ee* by HPLC analysis using a chiracel OJ-H column (6% *i*-propanol/*n*-hexane, flow rate 0.5 mL/min, λ = 220 nm).

Scheme 18



The diol **46** was ketalized[47] under acidic condition using 2,2-dimethoxy propane in CH_2Cl_2 in the presence of catalytic *p*-TSA to furnish **47**. Reduction of carboxylate group of **47** was performed by using DIBAL-H[48] in anhydrous CH_2Cl_2 at –78 °C to obtain **48** in 85% yield (Scheme 19).

Scheme 19



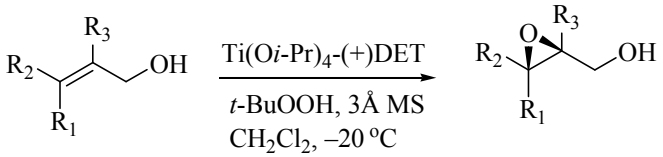
The structure **48** was unambiguously assigned based on the ^{1}H NMR spectrum. Two CH_3 groups of isopropylidene moiety appeared as six proton singlet at δ 1.33 ppm. The doublet due to CH_2OH at δ 4.09 ppm was also observed. The rest of the protons were identified at their respective positions in the spectrum. ^{13}C NMR, mass spectra, IR and elemental analysis were in complete conformity of the assigned structure.

This set the stage for Sharpless asymmetric epoxidation (SAE) that would install the third chiral center relevant to the target. SAE figures prominently in modern asymmetric synthesis for external chiral induction for two contiguous chiral centers under passive substrate control because of the factors like (i) oxidation of wide spectrum of substrates with different substituent patterns including *meso* compounds (ii) inexpensive reagents (iii) compatibility of various functional groups (iv) excellent *ee*'s (v) feasibility of either enantiomeric product and (vi) predictability of product configuration by mnemonic device (Scheme 22).

A brief overview on Sharpless asymmetric epoxidation reaction

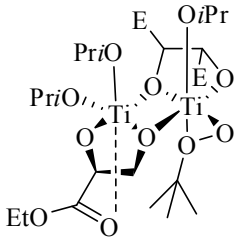
Epoxides are versatile and important intermediates in organic synthesis. The strain of the three-membered heterocyclic ring makes them accessible to a large variety of reagents. This metal catalyzed epoxidation process was discovered by K. Barry Sharpless in 1980 and allows the transformation of a prochiral substrate into an optically active (or optically pure) product using a chiral catalyst. The asymmetric induction is achieved by adding an enantiomerically enriched tartrate derivative. This epoxidation is arguably one of the most important reaction discovered in the last 30 years. This has been recognized by the award of the 2001 Noble Prize to Professor Barry Sharpless.

Scheme 20



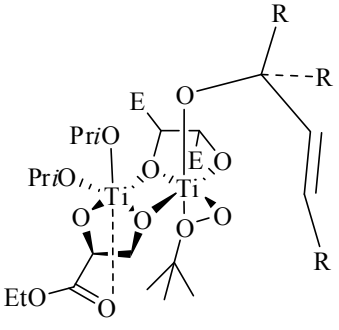
In this enantioselective chemical reaction 2,3-epoxyalcohols are produced from primary and secondary allylic alcohols (Scheme 20).[49,50] *This reaction gives good yields and enantioselectivities over a broad range of substrates. The oxidizing agent is t-butyl hydroperoxide. Enantioselectivity is achieved by a catalyst formed from titanium*

Figure 7*. Putative transition state for Sharpless Asymmetric Epoxidation reaction.*



49

Active species

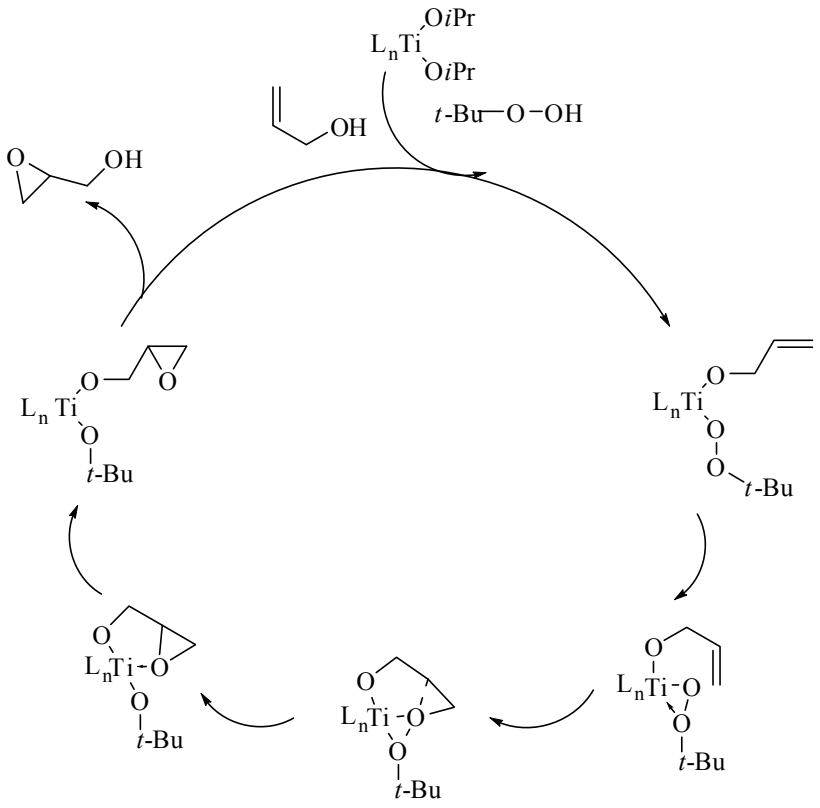


50

Transition state complex

*tetraiospropoxide and diethyl or diisopropyl tartrate. Only 5-10 mol% of the catalyst in the presence of 3Å molecular sieves (3 Å MS) is necessary.[51] It is proposed that, co-ordination of the chiral ligand DET and the oxidant source TBHP to the metal center forms the catalytically active species (**49**) (Figure 7). It is generally belived that this species is dimeric, i. e. two metal centres are bridged via two oxygen ligand giving the overall shape of two edge-fused octahedral. Coordination of the substrate can only occur in one orientation without causing severe steric interactions (Figure 7, **50**). Co-ordination in the complex on the left brings the double bond over the peroxide oxygen of the TBHP ligand. Oxidation can only occur from the bottom face, leading overall to a highly enantioselective process (Scheme 21). The Sharpless group has investigated the reaction kinetics[52] and the structure of the catalyst.[53]*

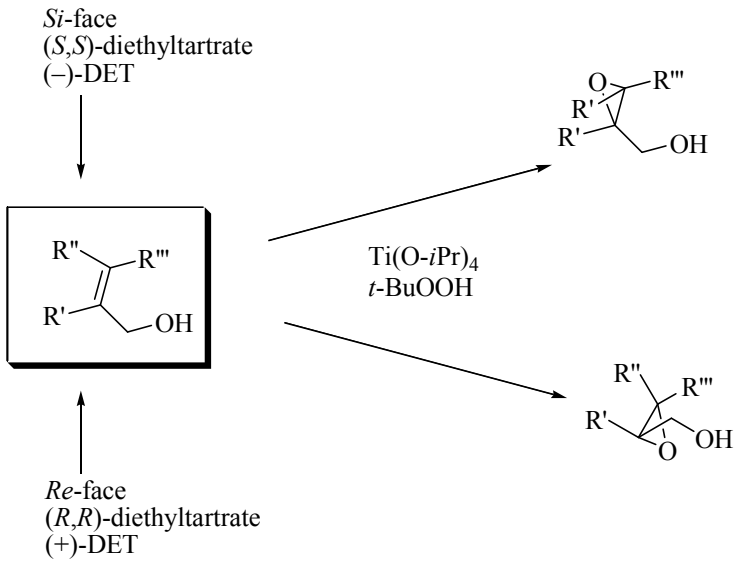
***Scheme 21**. The catalytic cycle for Sharpless asymmetric epoxidation.*



This new chiral epoxidation system possesses two especially striking and useful features. It gives uniformly high asymmetric inductions throughout a range of substitution patterns in the allylic alcohol and, secondly, the absolute configuration of the

epoxide produced can be predicted. Upon use of a given tartrate enantiomer the system delivers the epoxide oxygen to the same face of the double bond regardless of the substitution pattern. As shown in the Scheme 22 if the allylic alcohol is drawn so that the hydroxymethyl group is at the lower right, oxygen is delivered at the bottom face in the presence of (L)-(+)-DET (the natural isomer) and from the top face in the presence of (D)-(–)-DET.[54]

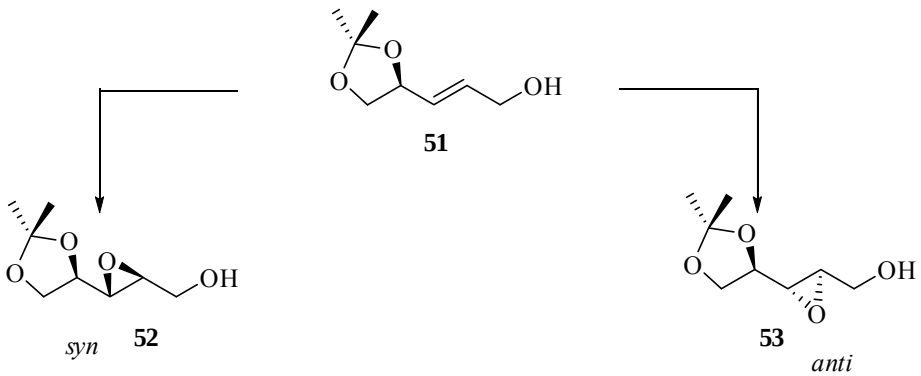
***Scheme 22**. Mnemonic diagram for asymmetric epoxidation pioneered by Sharpless.*



Diastereoselectivity: the case of primary, chiral allylic alcohols

The Sharpless epoxidation has been very extensively studied and the effect of many parameters on the stereochemical outcome of the reaction is well known. Hence, it is now widely used to showcase and exemplify some general and very important concepts of asymmetric synthesis. One of them is referred to as double induction or match/mismatch effect. Consider the following reaction, where the starting material is chiral and enantiopure.

Figure 8



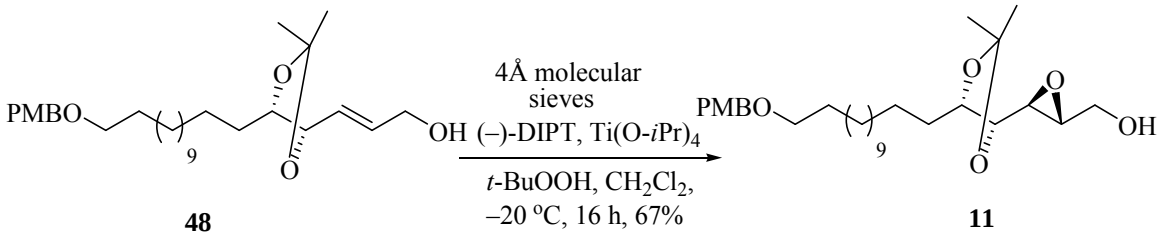
Reagent	*syn* : *anti* (**52**:**53**)	
1.*m*-CPBA	1:1.4	
2.Ti(O-*i*Pr)$_4$-TBHP	1:2.3	
3.Ti(O-*i*Pr)$_4$-TBHP-(–)DIPT	1:90	**Matched**
4.Ti(O-*i*Pr)$_4$-TBHP-(+)DIPT	22:1	**Mismatched**

When the reaction is carried out without chiral ligand (entries 1 and 2), both the syn and the anti diastereoisomer are obtained. However, there is a weak (merely steric) bias towards the anti product. Since, in this case, the starting material is enantiopure, this results in a weak but clear stereoinduction by the substrate itself. When DIPT is added, a second and stronger stereoinduction is observed. If the ligand-induced and the substrate-induced stereochemistries are identical, the result is an overall synergy, resulting in very high selectivity (i.e. higher than any single stereoinduction): it is a matched case. When the stereochemistry induced by the substrate is opposite to that induced by the ligand, the ligand-induced predominates. However, the overall selectivity is not as good as when the ligand alone ruled over the stereochemistry. There is no "team work" anymore: it is a mismatched case.

Asymmetric epoxidation of Compound **48** was conducted at –20 °C in stoichiometric fashion in CH_2Cl_2 with *t*-butyl hydroperoxide as oxo-donor and Ti(O-*i*Pr)$_4$-[(–)-DIPT] complex as chiral adjuvant. Overnight refrigeration of the reaction mixture resulted in the complete consumption of starting material (Scheme 23). The epoxy alcohol **11** gave satisfactory spectral data. The ^{1}H NMR spectrum carried peaks between δ 3.09–3.01 ppm, characteristic of epoxy protons whereas other protons

resonated at their expected chemical shifts. This was further confirmed by appropriate sodiated molecular ion peak $[M+Na]^+$ at (*m/z*) 515.34 in the ESI mass spectrum. The diastereopurity of the product was confirmed from its ^{13}C NMR analysis.

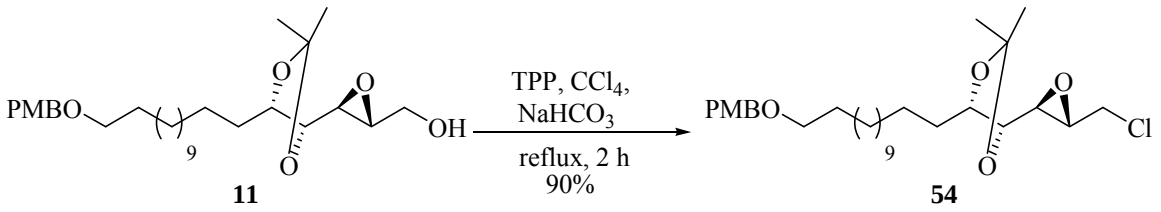
Scheme 23



48 **11**

Conversion of Compound **11** to epoxymethylene chloride **54** was not a smooth affair, as the exposure to triphenylphosphine in refluxing CCl_4 (Appel Reaction)[55] resulted in a mixture of three chromatographically-separable products. The major product formed in 50% yield was the desired product. The other two products were probably the ring-opened products, as evident from the absence of epoxide protons at δ 3.09-3.01 ppm in their ^1H NMR spectra. Attempts to minimize the ring-opened products, by the addition of base, *viz*. $NaHCO_3$, to the reaction medium was successful, as complete conversion of the starting material to the desired product was observed in that case (Scheme 24). The yield was improved to 90% in the later case.

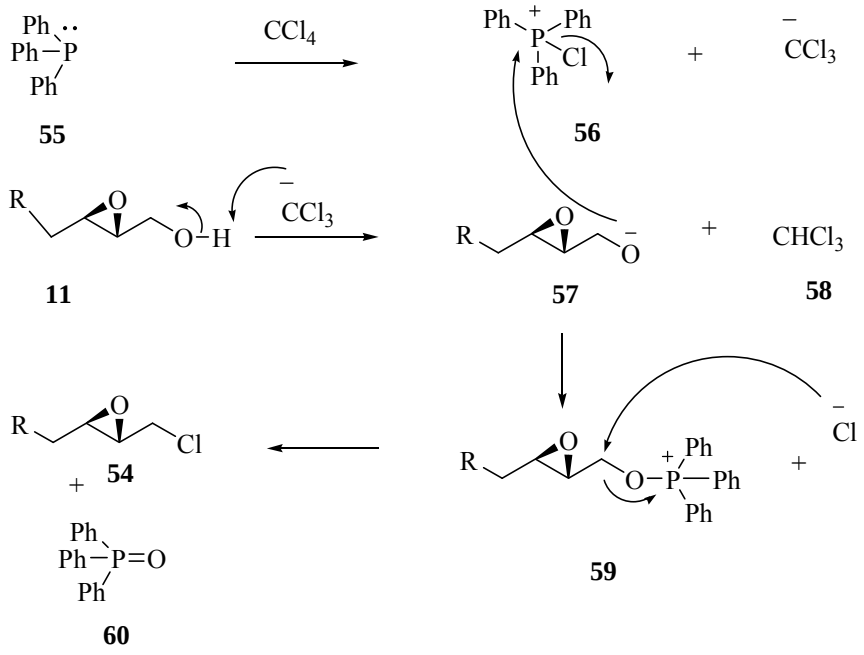
Scheme 24



11 **54**

The initial step of the Appel reaction is the formation of the phosphonium salt pair **56** (Scheme 25). Deprotonation of the alcohol **11**, forming chloroform (**58**), yields an alkoxide ion pair **57**. The nucleophilic displacement of the chloride by the alkoxide yields intermediate **59**. With primary and secondary alcohols, the chloride anion reacts in a S_N2 process forming the desired alkyl chloride **54** and triphenyl phosphine oxide **60**. Tertiary alcohols form the products **54** and **60** *via* a S_N1 mechanism. The driving force behind this reaction is provided by the formation of solid triphenylphosphine oxide, which phase separates from the reaction mixture.

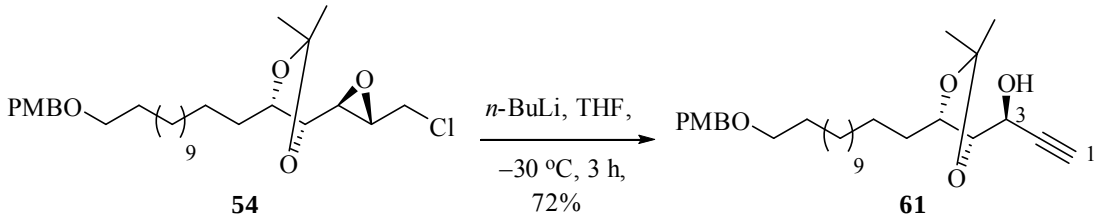
Scheme 25. *Mechanism involved in Appel reaction*.



The product **54** was confirmed by the analysis of the ^{1}H NMR, IR and ESI mass spectra. In the ^{1}H NMR spectrum of **54,** upfield shift of peaks belonging to methylene protons (CH_2–Cl) compared to that of **11** was noticed. This was further confirmed by a sodiated molecular ion peak at (*m*/*z*) 533.20 in the ESI mass spectrum.

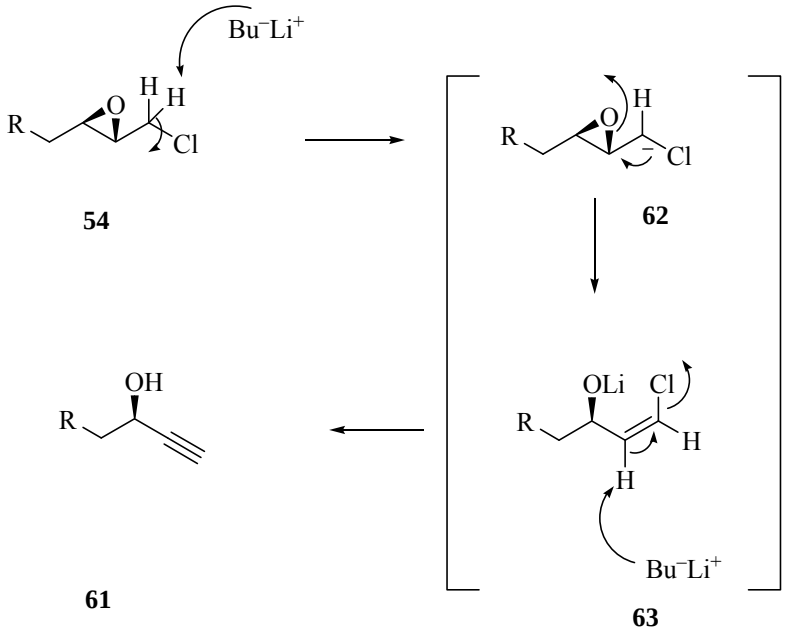
Exposure of the epoxy chloride **54** to *n*-BuLi (3 eqv) in THF at –30 ^{o}C brought about the facile formation of the 3-hydroxy alkyne **61** (Scheme 26)[56] with 72% yield in one step, presumably *via* a sequence triggered by initial generation of the α-chloro carbanion (**62**) as shown in Scheme 27.

Scheme 26



Under these conditions optical integrities introduced in the Sharpless epoxidation were found to be preserved in the acetylenic alcohol formed by this double elimination protocol. Mechanistically the reaction proceeds through the following pathway,

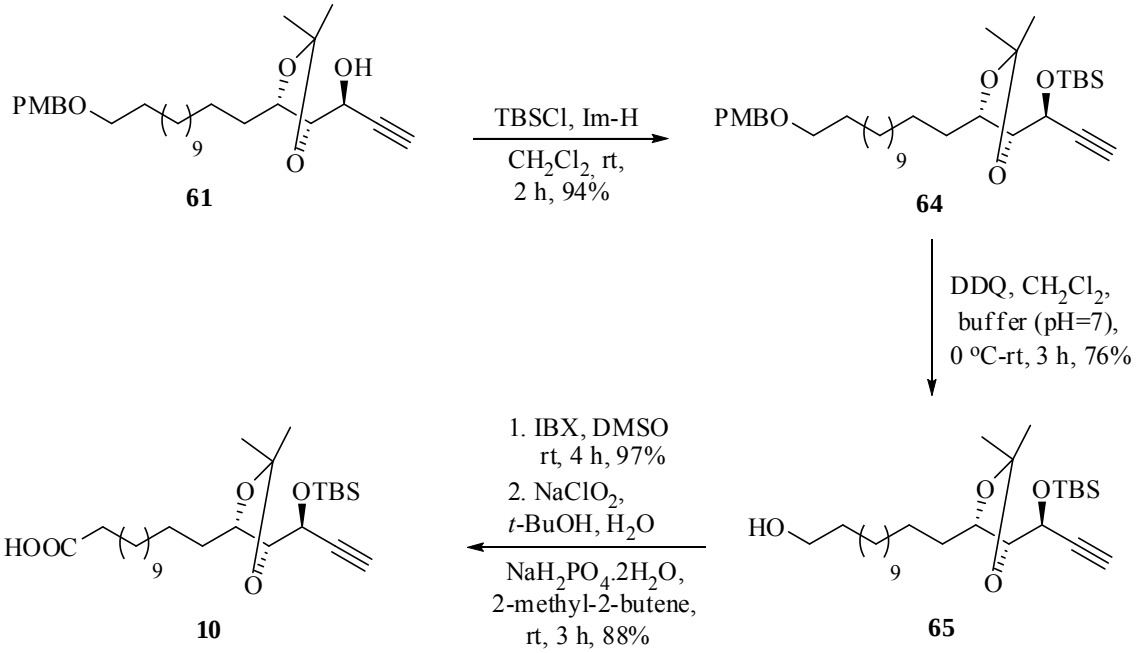
Scheme 27. *Mechanism involved in the double elimination reaction*.



The structure of Compound **61** was completely confirmed on the basis of ^{1}H, ^{13}C NMR, IR and mass spectral analysis. The ^{1}H NMR spectrum of **61** showed a singlet at δ 2.51 ppm integrating for one proton, which was assigned to terminal alkyne.

The secondary hydroxyl group present in compound **61** was protected as silyl ether by using TBS-Cl and imidazole in anhydrous CH_2Cl_2 at room temperature for 4 h to afford **64** in 94% yield (Scheme 28). The structure of product **64** was confirmed by ^{1}H and ^{13}C NMR spectra. In the ^{1}H NMR spectrum two singlets at δ 0.17 (s, 3H) and 0.13 (s, 3H) ppm for Me_2Si and a multiplet at δ 0.91 ppm for $-C(CH_3)_3$ of TBS-group were observed. The peaks at δ –4.7, –5.0, 26.2 and 25.7 ppm in the ^{13}C NMR spectrum were in support of **64**. The next task ahead was to deprotect *p*-methoxybenzyl group and install carboxylic acid at that position. Keeping the thought in mind compound **64** was treated with DDQ[57] in anhydrous CH_2Cl_2 under buffered condition to produce the penultimate alcohol **65** in 76% yield.

Scheme 28



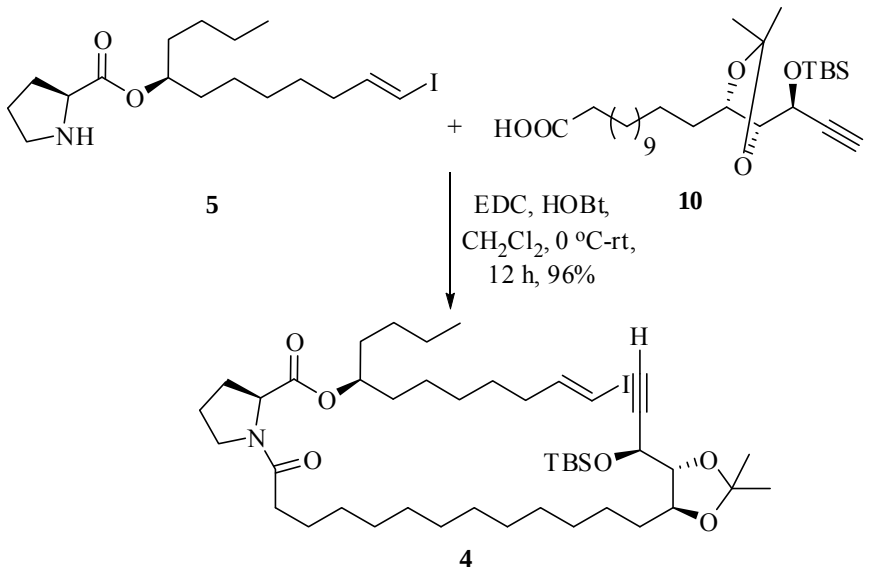
The absence of peaks due to PMB group (in the ^{1}H NMR spectrum peaks at δ 7.25, 6.86, 4.42 and 3.80 ppm and in the ^{13}C NMR resonances at δ 159.0, 130.8, 129.2, 113.7 and 55.2 ppm) was evident for the successful removal of the protecting group. The structure was further supported by the IR spectrum with absorption corresponding to free hydroxyl at 3436 cm^{-1} and elemental analysis (Scheme 28).

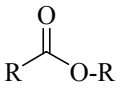
Compound **65** was then oxidized to the corresponding acid by using two step process of oxidation.[58] For that alcohol **65** was treated with iodoxybenzoic acid in DMSO to produce the corresponding aldehyde which was then treated with sodium chlorite in a solvent system of *t*-BuOH:H_2O (3:1) and in the presence of $NaH_2PO_4.2H_2O$ as the buffer and the chlorine quencher 2-methyl-2-butene to the desired carboxylic acid **10** in 88% yield. In the IR spectrum, the O-H stretching was observed at 3310 cm^{-1} and the C=O stretching at 1712 cm^{-1}. In the ^{1}H NMR spectrum, the protons adjacent to the carboxyl group appeared at upfield δ 2.34 ppm (t, J = 7.3 Hz, 2H) in comparison with compound **65**. The carbonyl carbon was observed at δ 179.8 ppm in the ^{13}C NMR spectrum. Other analytical data such as the mass spectrum, and elemental analysis of **10** (Fragment **II**) were in accordance with the proposed structure.

Coupling of acid 10 with amine 5

As both the coupling partners (**5** and **10**) were in our hand our next task was to unite them. The EDC/HOBt mediated condensation reaction between amine **5** and acid **10** proceeded smoothly to produce the amide **4** in 96% yield (Scheme 29).

Scheme 29



In the IR spectrum, the ester carbonyl () and the amide carbonyl (NH-C=O) stretching was observed at 1734 cm^{-1} and 1659 cm^{-1} respectively with concomitant absence of the amine stretching at 3343 cm^{-1}. In the ^1H NMR spectrum, the two olefinic protons resonated at δ 6.49 (dt, J = 14.3, 7.1 Hz, 1H) and 5.98 (d, J = 14.3 Hz, 1H) ppm while the alkyne proton appeared at δ 2.45 ppm (d, J = 2.2 Hz, 1H). NMR signals from both the coupling partners in the product confirmed structure **4**. In the ^{13}C NMR spectrum, resonances due to both the ester and amide carbonyls at δ 172.2 and 171.7 ppm respectively further confirmed in favor of facile coupling. In the ESI mass spectrum the highest molecular ion peak at 894.10 for $[M+Na]^+$ supported that observation.

The next and the most important job in our intended synthetic programme was the formation of the 30-membered macrocyclic ring. To complete this job we had chosen intramolecular Sonogashira cross-coupling reaction as our key step. The main reason for

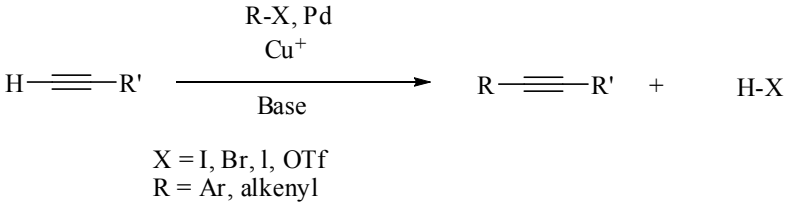
this preferential choice of this particular palladium mediated reaction is that, few number of literature[6b] reports are there for such macrocylization by employing this synthetic protocol. The emergence of the Sonogashira coupling reaction as a powerful method for the formation of carbon–carbon bonds is largely due to the overall mildness of the technique. The Sonogashira reaction conditions are compatible with many types of functional group such as carboxylic acid, ester, amide, nitro, ether, amine, hydroxy ketone and even aldehyde groups. Since the reaction conditions are very mild, a high degree of stereochemical complexity can be tolerated.

A brief overview on Sonogashira cross-coupling reaction

In studying the evolution of organic chemistry and grasping its essence, one comes quickly to the conclusion that no other type of reaction plays as large a role in shaping this domain of science than carbon–carbon bond-forming reactions. The Grignard,[59] Diels–Alder,[60] and Wittig[61] reactions are but three prominent examples of such processes, and are among those which have undeniably exercised decisive roles in the last century in the emergence of chemical synthesis as we know it today. In the last quarter of the 20th century, a new family of carbon–carbon bond-forming reactions based on transition-metal catalysts evolved as powerful tools in synthesis. Among them, palladium-catalyzed cross coupling reactions are the most prominent.

The palladium-catalyzed coupling of terminal alkynes with vinyl or aryl halides was first reported independently and simultaneously by the groups of Cassar[62] and Heck[63] in 1975.

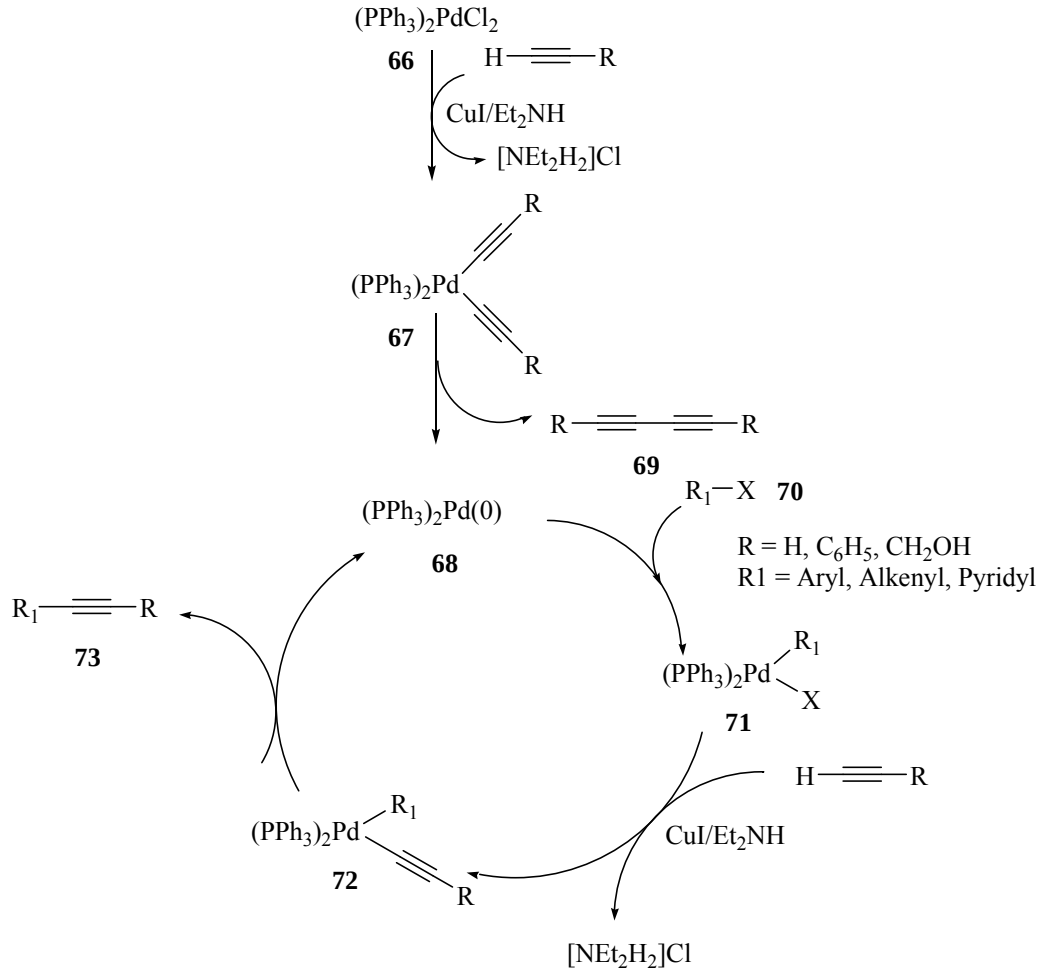
Scheme 30



A few months later, Sonogashira and co-workers demonstrated that, in many cases, this cross-coupling reaction could be accelerated by the addition of cocatalytic CuI salts to the reaction mixtures.[6a,64,65] This protocol, which has become known as the Sonogashira

reaction, (Scheme 30) can be viewed as both an alkyne version of the Heck reaction and an application of palladium catalysis to the venerable Stephens–Castro reaction (the coupling of vinyl or aryl halides with stoichiometric amounts of copper(I) acetylides).[66]

***Scheme 31**. Mechanism of Sonogashira cross-coupling reaction.*

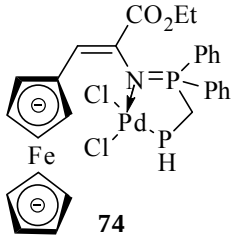


The Sonogashira reaction provides a valuable method for the synthesis of conjugated acetylenic systems, which are used in a diverse array of important applications from natural products and pharmaceuticals to designed molecules of interest in biotechnology and nanotechnology. Interestingly, the utility of the "copperfree" Sonogashira protocol (i.e. the original Cassar–Heck version of this reaction) has subsequently been" rediscovered" independently by a number of other researchers in recent years.[67]

Although the detailed mechanism of the reaction is yet to be clarified, it seems likely that the substitution occurs through an initial formation of bis-(triphenylphosphine)dialkynylpalladium(II) ***67****, which gives a catalytic species bis(triphenylphosphine)palladium(0)* ***68*** *through a reductive elimination of 1,4-diphenylbutadiyne* ***69****. Subsequent oxidative addition of aryl or vinyl halide* ***70*** *to* ***68*** *followed by an alkynylation of the adduct* ***71*** *gives an aryl- or vinyl-alkynyl derivative of palladium* ***72****, which easily regenerates the original bis(triphenylphosphine)palladium(0)* ***68*** *through the reductive elimination of the substitution products. The alkynylation of the starting catalyst* ***66*** *or an oxidative adduct* ***71*** *in the catalytic cycle is catalyzed by cuprous iodide in the presence of diethylamine (Scheme 31).*

The Sonogashira reaction has emerged in recent years as one of the most general, reliable and effective methods for the synthesis of substituted alkynes.[68] *The palladium-catalyzed coupling of a number of preformed metal acetylides (e.g. Zn,*[69]*Mg,*[70] *B,*[71] *Al,*[72]*and Sn*[73] *derivatives) with organic electrophiles also provides a useful access to substituted alkynes. Nevertheless, the Sonogashira protocol (employing cocatalytic CuI salts) is the most widely used of the palladium-catalyzed alkynylation methods, particularly in the context of total synthesis, largely owing to its broad applicability and convenience.*

Figure 9



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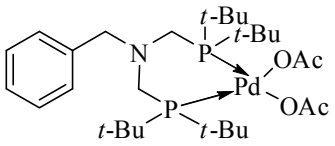

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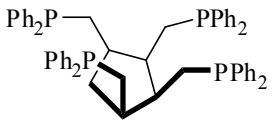

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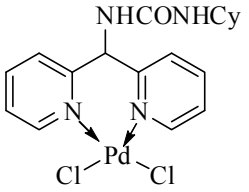
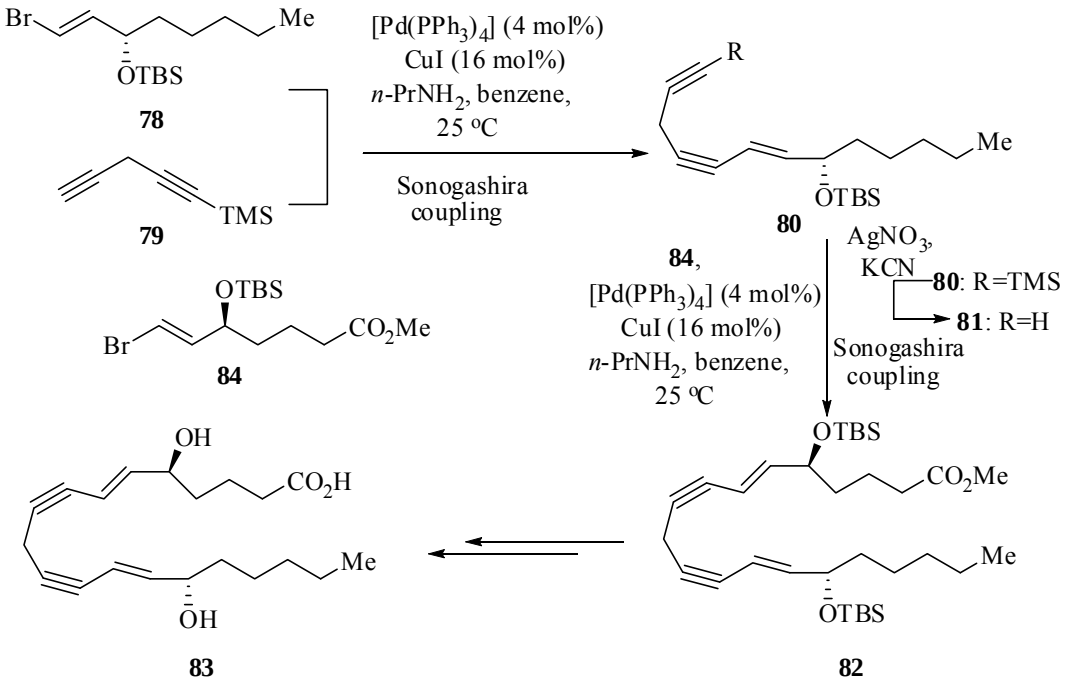


76

This reaction is usually performed using a palladium-phosphine complex. Most widely used are $PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$. Catalyst with bidentate ligands such as $Pd(dppe)Cl_2$, $Pd(dppp)Cl_2$ have also been employed. The change of the triphenylphosphine to more electron rich phosphine ligands increases the rate of the reaction. Steric demand in the phosphines enhances the rate of the reaction $P(t\text{-}Bu)_3$ had been used in combination with weakly ligated palladium source such as $Pd(OAc)_2$, $PdCl_2(PhCN)_2$, or $Pd_2(dba)_3$. For example, the combination of $Pd(PhCN)_2Cl_2$/CuI/$P(t\text{-}Bu)_3$ has been found extremely effective.[74]

*An early application of the Sonogashira reaction in total synthesis can be found in the generalized synthetic route to the biologically significant lipoxins and related eicosanoids pioneered by the Nicolaou group in the early 1980s. As an illustrative example, we highlight the stereospecific synthesis of (5S,15S)-dihydroxy-6,13-trans-8,11-cis-eicosatetraenoic acid (**83**),*[75] *an important metabolite of arachidonic acid. Besides securing the stereochemistry of the remote hydroxybearing stereogenic centers, the central problem in the synthesis of this and similar polyunsaturated compounds resides in the construction of an aliphatic chain that have double bonds of defined geometry in specified positions within the molecule.*

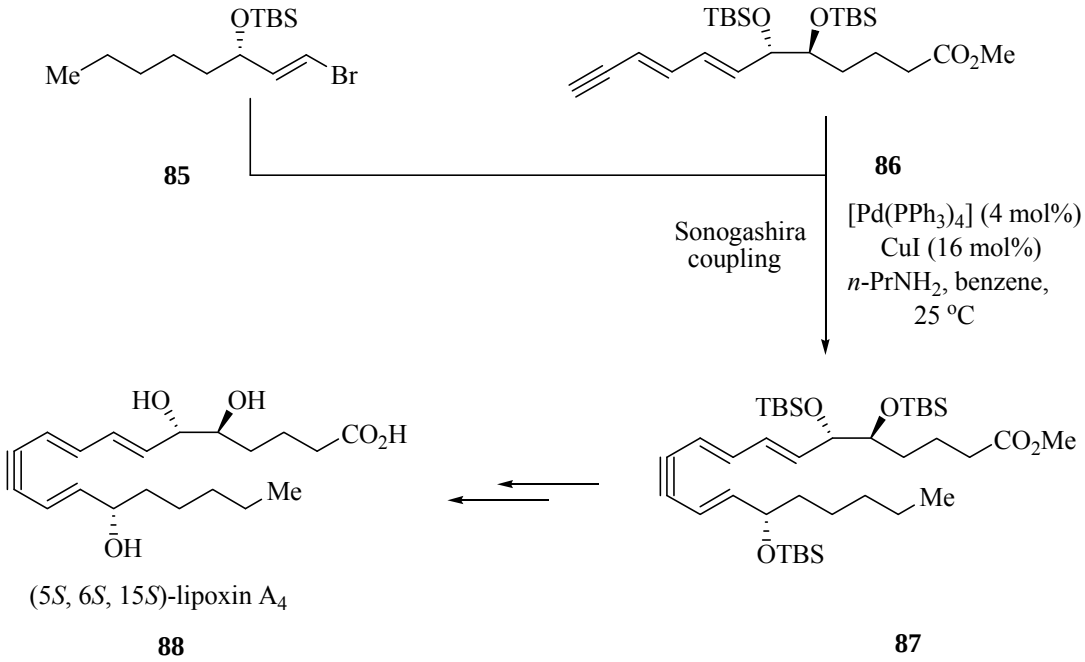
Scheme 32



The solution devised by the Nicolaou group involved the stereospecific formation of the conjugated unsaturated systems through Sonogashira coupling reactions in which the acetylene components function as masked Z alkene motifs.

Thus, as illustrated in Scheme 32, the coupling of (E)-vinyl bromide ***78*** *with the terminal alkyne* ***79*** *upon exposure to [Pd(PPh$_3$)$_4$] (4 mol%), CuI (16 mol%), and n-PrNH$_2$ (1.2 equiv) in benzene proceeded smoothly at room temperature to afford enediyne* ***80*** *in good yield. As expected, compound* ***80*** *was formed as a single geometric isomer, with the anticipated retention of configuration about the E double bond. After the liberation of the terminal acetylene to give compound* ***81****, a second Sonogashira reaction, this time with vinyl bromide* ***84*** *under the same coupling conditions gave bis(enyne)* ***82*** *as a single isomer and again in good yield. With the entire molecular framework of the target natural product thus rapidly assembled through this convergent and flexible approach, the few remaining synthetic steps required only selective hydrogenation of the two alkyne units, under lindlar conditions,*[76] *and removal of protecting groups.*

Scheme 33



*Variations on this general Sonogashira coupling theme allowed the synthesis of a number of other structurally and biosynthetically related eicosanoid natural products, including the lipoxin family of secondary metabolites. For example, (5S,6S,15S)-lipoxin A_4 (**88**) was readily obtained through the smooth union of the enantiomerically pure building blocks **85** and **86**, followed by standard Lindlar reduction and protecting-group cleavage procedures (Scheme 33).[77] A large number of isomeric lipoxin A[78] and lipoxin B[79] derivatives were produced by analogous routes, which enabled not only the identification and structure elucidation of a number of naturally occurring isomers of this series, but also provided meaningful quantities of materials for further biological investigations.[80]*

These instructive examples serve to highlight the fact that the Sonogashira reaction provides an important alternative to the Stille and Suzuki reactions for the stereoselective synthesis of polyene systems, by means of this two-step protocol of alkyne–alkene coupling followed by selective reduction of the triple bond. Such methodology proves to be of particular use when the organostannane or organoboron components, required for the Stille[81] or Suzuki[82] coupling reactions, respectively, are either unavailable or too unstable to be synthetically useful. It is important to note that both the corresponding E- and Z-alkene isomers can be readily prepared in a stereoselective fashion from the parent alkyne. Thus, whereas the Z alkenes are typically prepared by catalytic hydrogenation procedures, a number of routes are available for the synthesis of the corresponding E isomers;[83] the hydrosilylation protocols recently developed by the Furstner[84] and Trost groups[85] are potentially convenient and chemoselective methods.

We tried Sonogashira reaction under several reaction conditions (Table 3), to make this macrocyclisation happen. Finally, the best result was obtained in which tetrakis(triphenylphosphine)palladium(0) and CuI was used in anhydrous diethyl amine at 0 ^{o}C for 30 min to obtain the macrocyclic compound **89** in 35% yield (Scheme 34).

Scheme 34

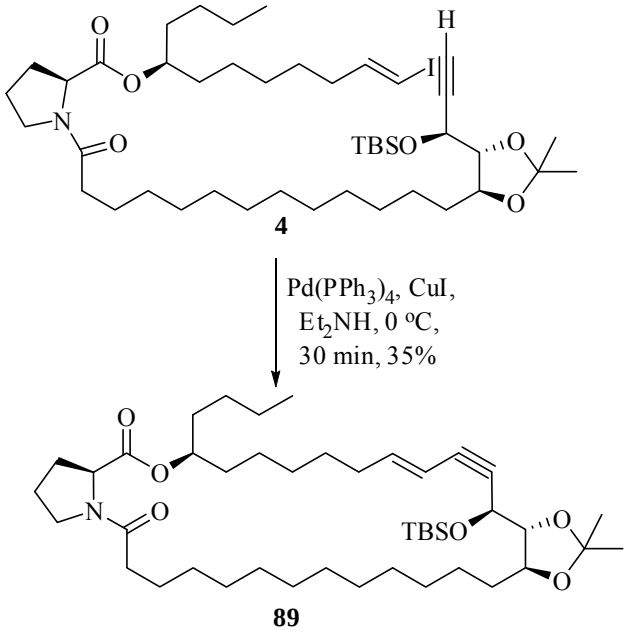


Table 3. *Conditions tried for macrocyclization. In all the cases below CuI (20 mol%) was employed as the co catalyst.*

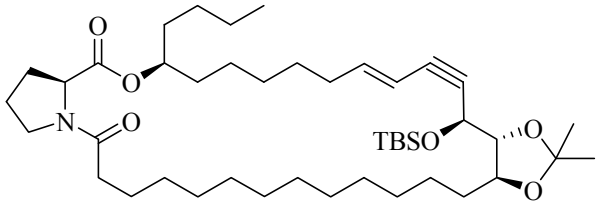
Catalyst (10 mol%)	Solvent	Temp.	Time	Yield
$PdCl_2(PPh_{3)2}$	CH_3CN/Et_2NH (7:3)	0 °C	2 h	No reaction
$PdCl_2(PPh_3)_2$	CH_3CN/Et_2NH (3:7)	0 °C	2 h	No reaction
$PdCl_2(PPh_3)_2$	Et_2NH	0 °C	2 h	5%
$PdCl_2(PPh_3)_2$	Et_2NH	25 °C	2 h	5%
$Pd(PPh_3)_4$	CH_3CN/Et_2NH (3:7)	0 °C	2 h	7%
$Pd(PPh_3)_4$	CH_3CN/Et_2NH (3:7)	25 °C	2 h	7%
$Pd(PPh_3)_4$	**Et_2NH**	**0 °C**	**30 min**	**35%**

In the ^{1}H NMR spectrum, upfield shift of olefinic protons to δ 6.09 (dt, J = 15.8, 7.2 Hz, 1H) and 5.45 (d, J = 15.8 Hz, 1H) ppm in comparison with compound **4** clearly suggested in favor of macrocyclisation. Furthermore, the absence of alkyne proton signal at δ 2.45 ppm (d, J = 2.2 Hz, 1H) confirmed macrocyclisation. In the ESI mass spectrum,

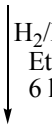
the highest molecular ion peak at 766.85 for $[M+Na]^+$ supported that observation. ^{13}C NMR and elemental analysis were also in complete conformity of the predicted structure.

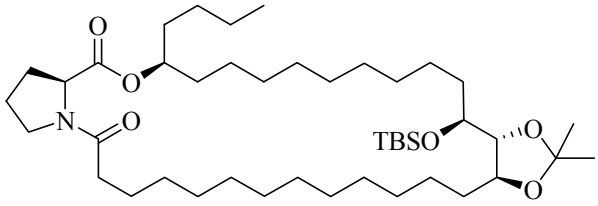
Reduction of both double and triple bond present in the macrocyle by Raney Ni[86] in ethanol under hydrogenation condition gave compound **90** in 92% yield (Scheme 35). In the ^1H NMR absence of olefinic signals at δ 6.09 and 5.45 ppm are seen. In the ^{13}C NMR signals due to resonances at δ 145.2 and 144.7 (rotamers), 109.1 and 108.9 (rotamers), 86.3 and 86.1 (rotamers), 85.1 and 85.0 (rotamers) ppm were missing, indicated complete hydrogenation of compound **89**. In the ESI mass spectrum, the highest molecular ion peak at 772.82 for $[M+Na]^+$ supported that observation. Elemental analysis and IR spectrum were in complete recognition of the predicted structure.

Scheme 35



89



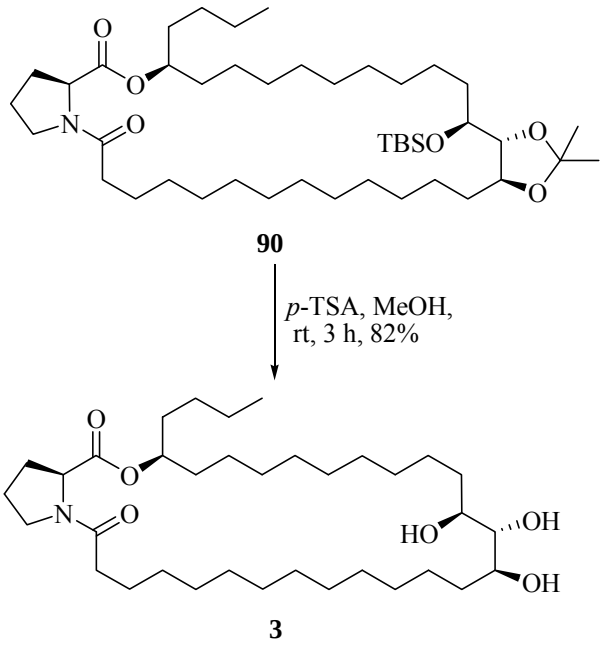


90

Treatment of compound **90** with *p*-TSA[87] in methanol resulted in global deprotection of isopropylidene and TBS protecting groups and furnished the triol compound **3** in 82% yield (Scheme 36). In the ^1H NMR spectrum of compound **3**, the absence of two singlet signals integrating for three protons each at δ 1.40 and 1.39 ppm, six proton signals for Me_2Si group at δ 0.16 (s, 3H) and 0.13 (s, 3H) ppm and nine proton multiplet due to the $-CMe_3$ group at δ 0.94 ppm indicated that the deprotection was

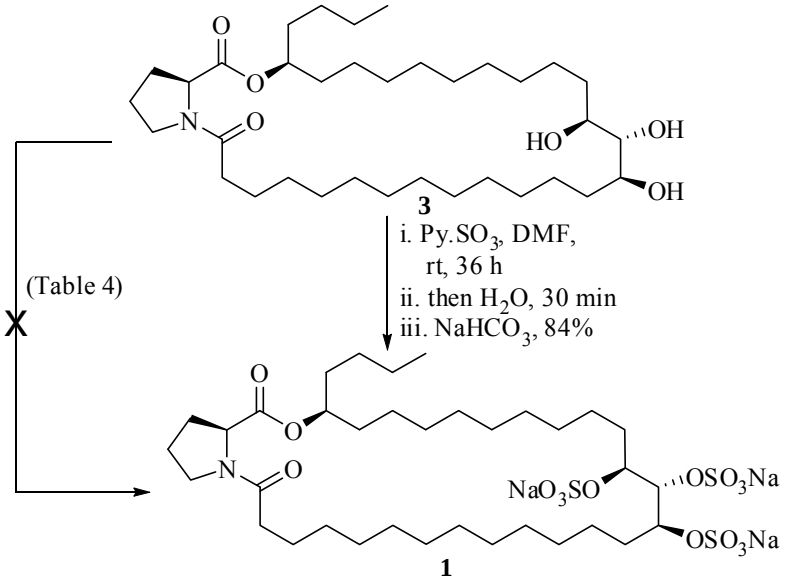
complete. This observation was supported by the appearance of highest molecular ion peak at 618.49 for $[M+Na]^+$ in the ESI mass spectrum.

Scheme 36



Finally, we tried persulfation[88-90] on compound **3** under the following (Table 4) reaction conditions but were dismayed to obtain complex intractable reaction mixtures in all cases. The natural compound **1** could not be isolated (Scheme 37).

Scheme 37



However, we were delighted to see that on modification of procedure 1 (Table 4) for persulfation on **3** as depicted in Scheme 37 yielded the trisulfated natural product **1** (Penarolide sulfate A_1) in 84% yield. The spectral and analytical data of synthetic **1** completely matched with that of the natural product isolated by Fusetani *et al.* (Table 5).

Table 4

Conditions Tried for Persulfation on 3	**Observation**
1. (a) $Py.SO_3$, DMF, rt, 36 h. (b) then $NaHCO_3$.	Complex intractable reaction mixture
2. $Py.SO_3$, Na_2SO_4, Microwave, 10 min.	Complex intractable reaction mixture
3. (a) $Py.SO_3$, DMF, rt, 20 h. (b) Acetone/Methanol(9:1), H_2O. (c) then 1N NaOH.	Complex intractable reaction mixture

Table 5. *Comparative ^1H (selected peaks) (CD_3OD, 400 MHz) and ^{13}C NMR (CD_3OD, 100 MHz) spectral data of synthetic penarolide sulfate A_1 (**1**) with data reported for natural **1** at 25 ^oC. ^{a} Overlap of carbons.*

^1H NMR				**^{13}C NMR**	
Synthetic **1** δ (in ppm) (*J* in Hz)	(m)	Natural **1** δ (in ppm) (*J* in Hz)	(m)	Synthetic **1** δ (in ppm)	Natural **1** δ (in ppm)
5.04 (6.0)	d	5.03 (5.4)	d	174.2	174.3
Merged in CD_3OD		4.86 (6.2)	quint	173.8	173.8
4.66 (8.7)	d	4.66 (9.6)	d	80.7	80.8
4.63-4.61	m	4.63 (4.2)	q	79.4	79.2
4.40 (8.7, 4.5)	dd	4.39 (8.9, 4.6)	dd	78.9	78.8
3.63 (7.2)	t	3.63 (7.7)	t	76.2	76.3
2.43 (15.2, 7.2)	dt	2.43 (15.0, 7.7)	dt	61.0	61.1
0.90 (6.7)	t	0.90 (6.9)	t	Merged in CD_3OD	48.5
				35.2	35.2
				34.7	34.7
				30.9	31.7
				30.8	31.3
				30.6	30.5
				30.4[a]	30.4
				28.5	30.0[a]
				26.4	28.6
				26.0	26.4

				25.8	26.1
				23.4	25.8
				14.3	23.5
					14.3

At this stage, we thought it would be pertinent to evaluate the enzyme inhibition activity of compound **3** too, because then we would be able to rationalize the importance of sulfate groups toward biological activity for these classes of molecules.

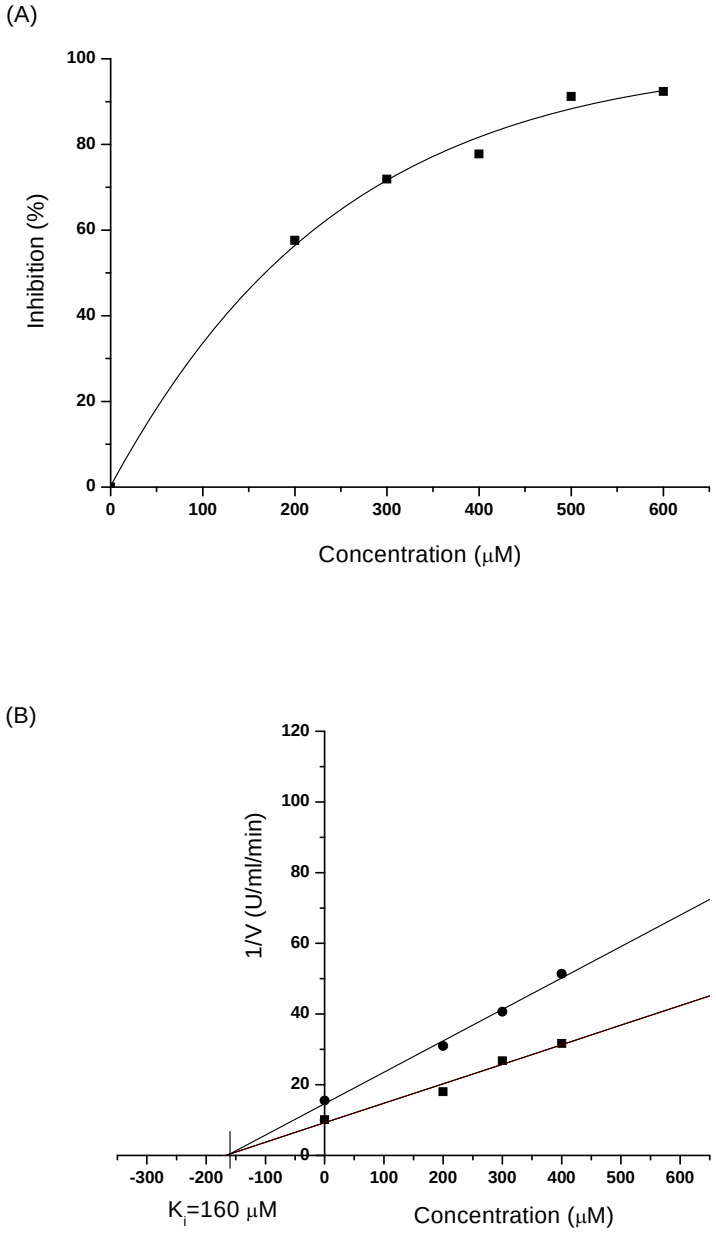
Table 6. *Inhibition (K_i in μM) of various glycosides by desulfated penarolide sulfate A_1 (**3**) as the inhibitor.*[a]

[a] *The enzyme inhibition study was carried out under similar conditions as reported in ref. 91 and the same is detailed in the experimental section;* [b] *Percentage inhibition at 1 mM inhibitor concentration*.

Glucosidase	Ki (μM)
α-glucosidase	160
β-glucosidase	21.0 %[b]
α-galactosidase	7.5 %[b]
β-galactosidase	30.0 %[b]
α-mannosidase	2.4 %[b]
β-mannosidase	35 %[b]

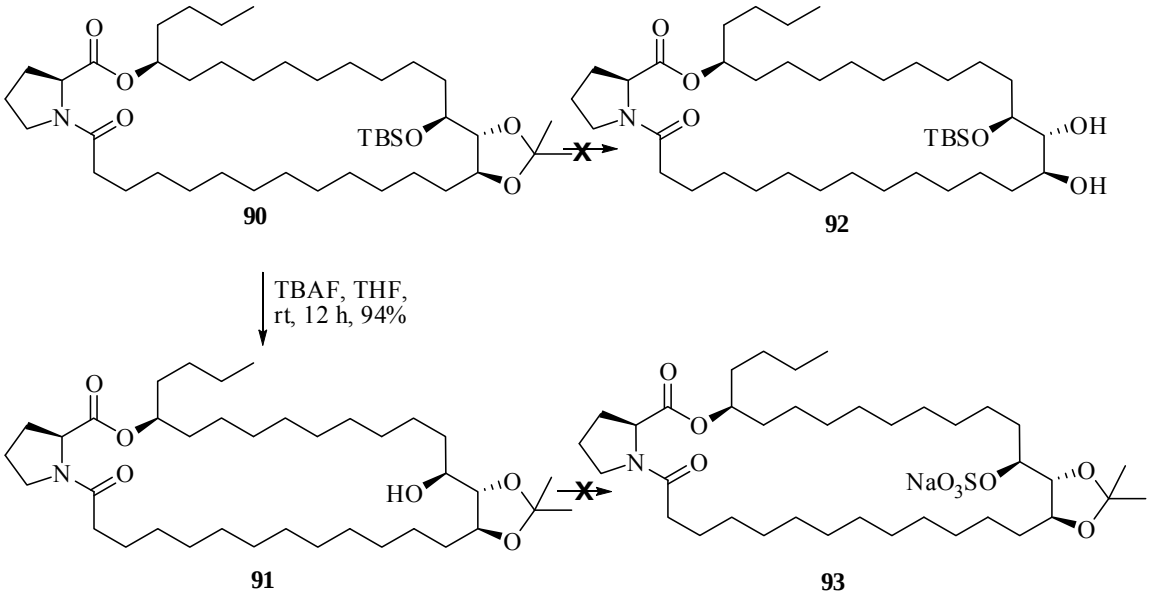
Thus, desulfated penarolide sulfate **3**, was also acted as α-glucosidase inhibitor (IC_{50} = 166 μM); the extent of inhibition is much less than that of the parent molecule **1**. Compound **3** inhibited β-glucosidase, β-mannosidase and β-galactosidase, but the extent of inhibition towards the corresponding α-analogs was negligible at 1mM inhibitor concentration.

Figure 10. *Binding of **3** to α-Glucosidase and kinetics of inhibition. (A) The sigmoidal curve indicates the best fit for the percentage inhibition data obtained, and the IC_{50} value was calculated from the graph. (B) Enzymatic activity of the α-glucosidase was estimated using the substrate p-nitrophenyl-α-D-glucopyaranoside 250 μM (■) and 500 μM (●) at different concentrations of **3**. K_i was determined following Dixon's method.*[92]



Compound **3** being found weakly active in comparison with **1**, we tried for the preparation of the partially sulfated derivatives of **3**. For this endeavor, controlled deprotection of compound **90** using TBAF in THF resulted in the formation of compound **91** in 94% yield (Scheme 38). Sulfation on **91** under the above mentioned conditions were found to be ineffective and we ended up with complex reaction mixtures in all the cases and unable to isolate and characterize the monosulfated derivative of **3**.

Scheme 38



90 **92**

91 **93**

Similarly the controlled deprotection of the isopropylidene group present in compound **90** in presence of TBS group was tried. Various Lewis acid mediated ($Zn(NO_3)_2.6H_2O$,[93] $CuCl_2.2H_2O$ in ethanol,[94] $FeCl_3.6H_2O/SiO_2$[95]) reaction conditions at room temperature were found to be futile and we ended up with unreacted starting material. However, by employing harsh reaction conditions (heating from 70 ^oC-110 ^oC in the presence of earlier mentioned Lewis acids) furnished the completely deprotected triol **3**. We had also tried TMSOTf[96] mediated opening of the isopropylidene group but that attempt was also turned in vain. Since, we were unable to prepare the partially sulfated derivatives of **3** their bioevaluation was not possible and the role of sulfate groups toward biological activity remained inconclusive for these classes of natural products.

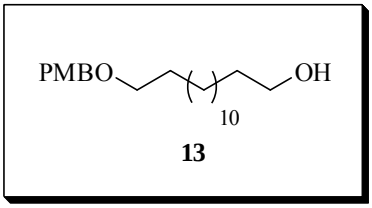
Conclusion

In summary, the first total synthesis of penarolide sulfate A_1 is documented. The salient feature of our synthetic protocol was intramolecular Sonogashira cross-coupling reaction for the construction of key 30-membered macrocyclic ring. Regioselective Sharpless asymmetric dihydroxylation, Sharpless asymmetric epoxidation and Jacobsen HKR were employed for the generation of four asymmetric centers present in the molecule. A biological activity profile of the desulfated penarolide sulfate A_1 (**3**) has also been disclosed. The reported approach is convergent in nature and provides considerable flexibility for the synthesis of related unnatural analogues.

EXPERIMENTAL

Experimental

14-(4-Methoxybenzyloxy)-tetradecan-1-ol (13)

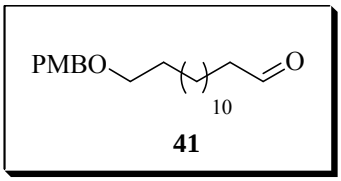


13

To a stirred solution of 1,14-tetradecane diol **40** (26.8 g, 116.3 mmol) in a mixed solvent of THF/DMF (7:3 by volume) (200 mL) at 0 ^{o}C, NaH (4.65 g, 116.3 mmol) was added portion wise followed by the addition of PMBBr (16.96 mL, 116.3 mmol). After 12 h, reaction was quenched by the addition of ice cold water (130 mL) and the reaction mixture was concentrated in the rotavapour. The residue thus obtained was diluted with water and extracted with ethyl acetate (3x 100 mL). The combined organic layer was washed with water (150 mL), brine, dried over anhydrous Na_2SO_4 and evaporated. The residue was purified on silica gel eluting with light petroleum and ethyl acetate (4:1) to afford compound **13** (36.7 g, 90%) as a white solid.

Mol. Formula	: $C_{22}H_{38}O_3$
M. P.	: 63 ^{o}C
IR ($CHCl_3$) υ	: 3421, 1612, 1248, 1036 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	: δ 7.25 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.42 (s, 2H), 3.80 (s, 3H), 3.62 (t, *J* = 6.6 Hz, 2H), 3.42 (t, *J* = 6.6 Hz, 2H), 1.62-1.52 (m, 4H), 1.25 (m, 20H) ppm.
^{13}C NMR ($CDCl_3$)	: δ 159.0, 130.6, 129.1, 113.7 (2C), 72.4, 70.1, 62.8, 55.1, 32.7, 29.7, 29.6 (2C), 29.4 (2C), 26.2, 25.7 ppm.
ESI-MS (*m/z*)	: 373.52 $[M+Na]^{+}$.
Elemental Analysis	: Calcd.: C, 75.38; H, 10.93%. Found: C, 75.16; H, 11.21%.

14-(4-Methoxybenzyloxy)-tetradecanal (41)

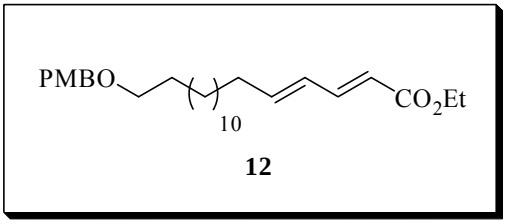


41

Iodoxybenzoic acid (IBX) (28.12 g, 100.4 mmol) in DMSO (200 mL) was stirred at room temperature for 30 min till it become a clear solution. Compound **13** (35.2 g, 100.4 mmol) in THF (150 mL) was added to the clear solution and stirred at room temperature for 3 h. The reaction mixture was then diluted with water (100 mL) and filtered. THF was removed under reduced pressure and the reaction mixture was extracted with diethyl ether (3x 75 mL), washed with $NaHCO_3$, water, brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on silica gel eluting with light petroleum and ethyl acetate (9:1) to afford compound **41** (33.2 g, 95%) as a yellow oil.

Mol. Formula	: $C_{22}H_{36}O_3$
IR ($CHCl_3$) υ	: 2926, 1726, 1613, 1247, 1099 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	: δ 9.75 (t, *J* = 1.9 Hz, 1H), 7.24 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.42 (s, 2H), 3.79 (s, 3H), 3.42 (t, *J* = 6.6 Hz, 2H), 2.41 (dt, *J* = 7.3, 1.9 Hz, 2H), 1.65-1.52 (m, 4H), 1.25 (m, 18H) ppm.
^{13}C NMR ($CDCl_3$)	: δ 202.4, 159.0, 130.7, 129.1, 113.6, 72.4, 70.1, 55.0, 43.8, 29.7, 29.5, 29.4 (2C), 29.3, 29.1, 26.1, 22.0 ppm.
ESI-MS (*m/z*)	: 371.36 $[M+Na]^+$.
Elemental Analysis	: Calcd.: C, 75.82; H, 10.41%. Found: C, 75.59; H, 10.29%.

(2*E*,4*E*)-Ethyl-18-(4-methoxybenzyloxy)-octadeca-2,4-dienoate (12)

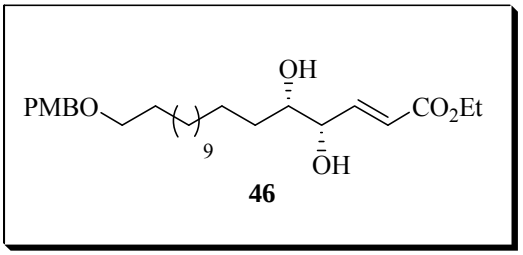


12

To a solution of ethyl-4-(dimethylphosphono)-crotonate (29.45 g, 132.6 mmol) in anhydrous THF (250 mL) at –78 ^{o}C, LiHMDS (132.56 mL, 1.0 M in THF) was added. After 1 h, this solution was transferred *via* cannula into compound **41** (30.8 g, 88.4 mmol) in THF (70 mL) maintained at –78 ^{o}C. The reaction mixture was warmed to room temperature, stirred for 1 h, quenched with saturated aqueous NH_4Cl solution (100 mL) and concentrated. The aqueous layer was extracted with ethyl acetate (3x 100 mL). The combined organic layer was washed with water, brine, dried over anhydrous Na_2SO_4, evaporated. The residue was purified on silica gel eluting with light petroleum and ethyl acetate (9:1) to afford compound **12** (32.6 g, 83%) as a light yellow oil.

Mol. Formula	: $C_{28}H_{44}O_4$
IR ($CHCl_3$) υ	: 2926, 1715, 1247, 1036 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$)	: δ 7.29 (dd, *J* = 15.4, 9.5 Hz, 1H), 7.28 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.21-6.11 (m, 2H), 5.81 (d, *J* = 15.4 Hz, 1H), 4.45 (s, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 3.45 (t, *J* = 6.7 Hz, 2H), 2.18 (q, *J* = 6.9 Hz, 2H), 1.62 (quint, *J* = 6.9 Hz, 2H), 1.45-1.42 (m, 2H), 1.38-1.32 (m, 4H), 1.31-1.28 (m, 17H) ppm.
^{13}C NMR (125 MHz, $CDCl_3$)	: δ 167.3, 159.0, 145.1, 144.7, 130.8, 129.2, 128.3, 119.1, 113.7, 72.4, 70.2, 60.1, 55.2, 33.0, 29.7, 29.6, 29.5 (2C), 29.4 (2C), 29.1, 28.7, 26.2, 14.3 ppm.
ESI-MS (*m/z*)	: 467.52 $[M+Na]^+$.
Elemental Analysis	: Calcd.: C, 75.63; H, 9.97%. Found: C, 75.89; H, 10.11%.

(4*S*,5*S*,*E*)-Ethyl-4,5-dihydroxy-18-(4-methoxybenzyloxy)-octadec-2-enoate (46)

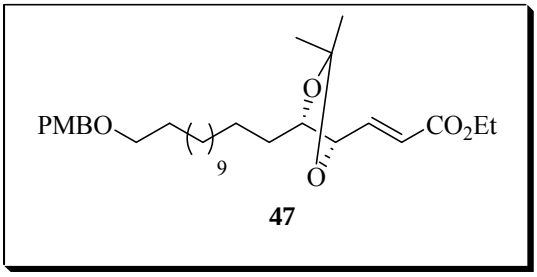


46

To a vigorously stirring mixture of $K_3[Fe(CN)_6]$ (55.98 g, 170.0 mmol), K_2CO_3 (23.50 g, 170.0 mmol), $(DHQ)_2PHAL$ (457 mg, 0.57 mmol), $MeSO_2NH_2$ (5.4 g, 56.7 mmol) and $K_2OsO_4.2H_2O$ (104 mg, 0.28 mmol) in (1:1) *t*-BuOH: H_2O (300 mL) at 0 °C was added compound **12** (25.2 g, 56.7 mmol). After 6 h, the reaction was quenched with sodium sulphite (50 g) and *t*-BuOH was evaporated under reduced pressure. The aqueous phase was extracted with ethyl acetate (3x 100 mL). The combined organic layer was washed with 2N KOH solution, water, brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on silica gel by eluting with light petroleum and ethyl acetate (4:1) to afford compound **46** (19.0 g, 70%) as a white solid.

Mol. Formula	: $C_{28}H_{46}O_6$
M. P.	: 67 ^oC
$[\alpha]_D^{25}$	: –17.1 (*c* = 1.2, $CHCl_3$).
IR ($CHCl_3$) υ	: 3308, 2927, 1713, 1464, 1251 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$)	: δ 7.31 (d, *J* = 8.7 Hz, 2H), 6.99 (dd, *J* = 15.6, 5.0 Hz, 1H), 6.93 (d, *J* = 8.7 Hz , 2H), 6.19 (d, *J* = 15.6 Hz, 1H), 4.49 (s, 2H), 4.27 (q, *J* = 7.2 Hz, 2H), 4.16 (m, 1H) 3.87 (s, 3H), 3.59 (m, 1H), 3.49 (t, *J* = 6.7 Hz, 2H), 2.73 (br s, 2H), 1.66 (quint, *J* = 6.9 Hz, 2H), 1.60-1.51 (m, 2H), 1.39-1.33 (m, 23H) ppm.
^{13}C NMR (125 MHz, $CDCl_3$)	: δ 166.3, 159.1, 147.1, 130.7, 129.2, 122.3, 113.7, 74.1, 74.0, 72.5, 70.2, 60.5, 55.2, 33.1, 29.7, 29.6, 29.5, 26.2, 25.6, 14.2 ppm.
ESI-MS (*m/z*)	: 501.68 $[M+Na]^+$.
Elemental Analysis	: Calcd.: C, 70.26; H, 9.69%. Found: C, 70.37; H, 9.84%.

(*E*)-Ethyl-3-((4*S*,5*S*)-5-(13-(4-methoxybenzyloxy)-tridecyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-acrylate (47)

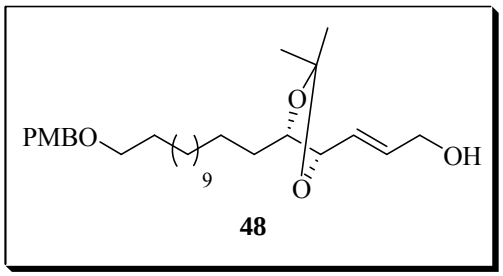


47

To a solution of compound **46** (16.6 g, 34.7 mmol) and 2,2-dimethoxypropane (5.11 mL, 41.6 mmol) in CH_2Cl_2 (125 mL), *p*-TSA (250 mg) was added. The reaction mixture was stirred at room temperature for 1 h. After completion of the reaction (monitored by TLC), the reaction mixture was washed with saturated $NaHCO_3$ solution (75 mL), water, brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on silica gel by using light petroleum and ethyl acetate (9.5:0.5) to afford the acetonide derivative **47** (17.3 g, 96%) as colorless oil.

Mol. Formula	: $C_{31}H_{50}O_6$
$[\alpha]_D^{25}$	: –8.1 (*c* = 1.7, $CHCl_3$).
IR ($CHCl_3$) υ	: 2854, 1724, 1513, 1247 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$)	: δ 7.32 (d, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 6.92 (dd, *J* = 15.7, 5.6 Hz, 1H), 6.18 (dd, *J* = 15.7, 1.5 Hz, 1H), 4.49 (s, 2H), 4.28 (q, *J* = 7.2 Hz, 2H), 4.22-4.18 (m, 1H), 3.87 (s, 3H), 3.79 (dt, *J* = 8.3, 5.9 Hz, 1H), 3.49 (t, *J* = 6.7 Hz, 2H), 1.68-1.63 (m, 4H), 1.58-1.53 (m, 2H), 1.50 (s, 3H), 1.48 (s, 3H), 1.39-1.33 (m, 21H) ppm.
^{13}C NMR (125 MHz, $CDCl_3$)	: δ 165.9, 159.1, 144.2, 130.8, 129.2, 122.6, 113.7, 109.3, 80.6, 80.3, 72.5, 70.2, 60.5, 55.2, 32.1, 29.8, 29.7, 29.6 (2C), 29.5, 27.3, 26.7, 26.2, 26.0, 14.3 ppm.
ESI-MS (*m/z*)	: 541.16 $[M+Na]^+$.
Elemental Analysis	: Calcd.: C, 71.78; H, 9.72%. Found: C, 71.62; H, 9.63%.

(*S*)-1-((4*S*,5*S*)-5-(13-(4-Methoxybenzyloxy)-tridecyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-prop-2-yn-1-ol (48)



48

To a solution of compound **47** (15.9 g, 30.7 mmol) in CH_2Cl_2 (150 mL) at –78 ^oC was added DIBAL-H (1.3 M solution in toluene, 51.91 mL, 67.5 mmol). After 1 h, excess of DIBAL-H was quenched with saturated solution of sodium potassium tartrate. The solid was filtered, the filtrate concentrated to give a residue which was purified on silica gel by eluting with light petroleum and ethyl acetate (4:1) to give compound **48** (12.5 g, 85%) as a colorless oil.

Mol. Formula : $C_{29}H_{48}O_5$

$[\alpha]_D^{25}$: –3.6 (*c* = 1.2, $CHCl_3$).

IR ($CHCl_3$) υ : 3436, 2854, 1464, 1217 cm^{-1}.

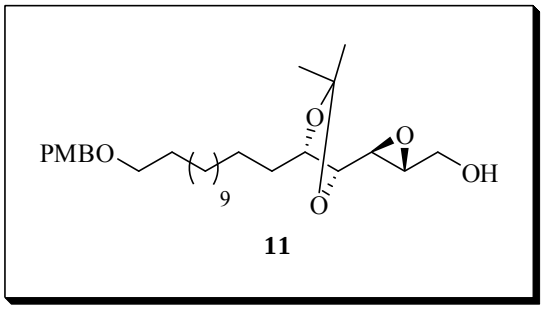
^{1}H NMR (500 MHz, $CDCl_3$) : δ 7.17 (d, *J* = 8.7 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 5.88 (dt, *J* = 15.4, 5.1 Hz, 1H), 5.62 (dd, *J* = 15.4, 7.3 Hz, 1H), 4.35 (s, 2H), 4.09 (d, *J* = 5.1 Hz, 2H), 3.93 (t, *J* = 8.1 Hz, 1H), 3.73 (s, 3H), 3.59 (dt, *J* = 8.1, 5.9 Hz, 1H), 3.35 (t, *J* = 6.7 Hz, 2H), 1.54-1.49 (m, 2H), 1.47-1.44 (m, 2H), 1.33 (s, 3H), 1.33 (s, 3H), 1.28-1.18 (m, 20H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ 159.1, 133.9, 130.8, 129.2, 128.2, 113.8, 108.4, 81.7, 80.8, 72.5, 70.2, 62.7, 55.2, 31.9, 29.8, 29.7, 29.6 (3C), 29.5, 27.3, 27.0, 26.2, 26.1 ppm.

ESI-MS (*m/z*) : 499.21 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 73.07; H, 10.15%.
Found: C, 73.26; H, 10.29%.

((2*R*,3*S*)-3-((4*R*,5*S*)-5-(13-(4-Methoxybenzyloxy)-tridecyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-oxiran-2-yl)-methanol (11)



11

To a solution of titanium tetrakis(isopropoxide) (7.33 mL, 24.8 mmol) and (–)-DIPT (5.18 mL, 24.8 mmol) in CH_2Cl_2 (125 mL) carrying activated molecular sieves (4Å, 12.0 g) at –22 °C, was added *t*-butyl hydroperoxide (3.3 M in toluene) (15.01 mL, 49.5 mmol) dropwise. After 15 minutes, a solution of allylic alcohol **48** (11.8 g, 24.8 mmol) in CH_2Cl_2 (75 mL) was added dropwise over a period of 10 minutes. The reaction mixture was kept at the same temperature for 16 h. Aqueous tartaric acid (10%) was then added to the reaction mixture followed by stirring for 1 h. The reaction mixture was filtered and the filtrate was extracted with CH_2Cl_2 (3x 50 mL) and the combined CH_2Cl_2 extract was concentrated under reduced pressure and was taken up in diethyl ether (125 mL) and treated with 1M NaOH solution (60 mL), stirred for another 1 h and then extracted with diethyl ether (3x 50 mL). The combined organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and evaporated. The residue was purified on silica gel (230-400 mesh) by using light petroleum and ethyl acetate (3:1) to afford the epoxy alcohol **11** (8.2 g, 67%) as a colorless oil.

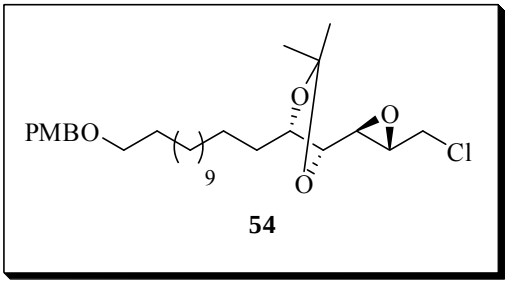
Mol. Formula	: $C_{29}H_{48}O_6$
$[\alpha]_D^{25}$	: +2.3 (*c* = 1.1, $CHCl_3$).
IR ($CHCl_3$) υ	: 3447, 2926, 1513, 1248 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$)	: δ 7.24 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 4.41 (s, 2H), 3.96-3.91 (m, 2H), 3.79 (s, 3H), 3.66 (dd, *J* = 12.8, 4.3 Hz, 1H), 3.41 (t, *J* = 6.7 Hz, 2H), 3.39 (dd, *J* = 7.8, 6.3 Hz, 1H), 3.09 (quint, *J* = 2.3 Hz, 1H), 3.01 (dd, *J* = 6.3, 2.3 Hz, 1H), 2.02 (br s, 1H), 1.62-1.55 (m, 4H), 1.40 (s, 3H), 1.39 (s, 3H), 1.33-1.26 (m, 20H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) : δ 159.1, 130.8, 129.2, 113.7, 109.2, 80.4, 79.8, 72.5, 70.2, 61.0, 56.7, 55.2, 55.0, 33.2, 29.8, 29.7, 29.6, 29.5, 27.3, 26.7, 26.2, 25.9 ppm.

ESI-MS (*m/z*) : 515.34 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 70.70; H, 9.82%.
Found: C, 70.53; H, 9.96%.

(4*R*,5*S*)-4-((2*R*,3*S*)-3-(Chloromethyl)-oxiran-2-yl)-5-(13-(4-ethoxybenzyloxy)-tridecyl)-2,2-dimethyl-1,3-dioxolane (54)



54

A solution of compound **11** (7.5 g, 15.2 mmol) and triphenylphosphine (7.98 g, 30.5 mmol) containing sodium bicarbonate (3.5 g) was refluxed in CCl_4 (100 mL) for 2 h. Removal of solvent under reduced pressure and residue purification by silica gel column chromatography using light petroleum and ethyl acetate (9.5:0.5) gave compound **54** (7.0 g, 90%) as a colorless oil.

Mol. Formula : $C_{29}H_{47}ClO_5$

$[\alpha]_D^{25}$: +1.3 (*c* = 1.5, $CHCl_3$).

IR ($CHCl_3$) υ : 2928, 1612, 1465, 1216 cm^{-1}.

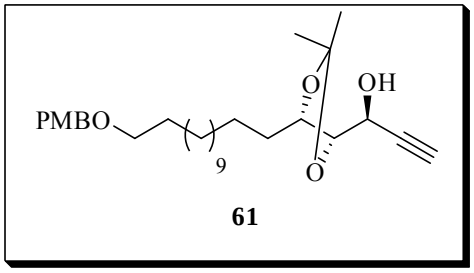
^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.26 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.43 (s, 2H), 4.00-3.90 (m, 1H), 3.80 (s, 3H), 3.67 (dd, *J* = 11.9, 4.7 Hz, 1H), 3.55 (dd, *J* = 11.9, 6.2 Hz, 1H), 3.43 (t, *J* = 6.7 Hz, 2H), 3.42-3.39 (m, 1H), 3.23 (ddd, *J* = 6.2, 4.7, 1.9 Hz, 1H), 2.97 (dd, *J* = 5.8, 1.9 Hz, 1H), 1.63-1.52 (m, 4H), 1.40 (s, 6H), 1.26 (m, 20H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 159.0, 130.8, 129.1, 113.7, 109.3, 79.8, 79.7, 72.4, 70.1, 57.9, 55.4, 55.1, 43.9, 33.1, 29.7, 29.6, 29.4, 27.2, 26.6, 26.2, 25.8 ppm.

ESI-MS (*m/z*) : 533.20 $[M+Na]^+$.

Elemental Analysis : Calcd. C, 68.14; H, 9.27%.
Found C, 68.27; H, 9.47%.

(*S*)-1-((4*S*,5*S*)-5-(13-(4-Methoxybenzyloxy)-tridecyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-prop-2-yn-1-ol (61)



61

n-Butyllithium (25.60 mL, 41.0 mmol, 1.6 M solution in hexane) was added dropwise to a solution of compound **54** (6.98 g, 13.7 mmol) in dry THF (70 mL) at –30 °C under nitrogen atm. After stirring for 1 h at –30 °C, the reaction mixture was gradually warmed to room temperature over a period of 1 h, quenched with aqueous NH_4Cl solution (50 mL), and concentrated. The residue was extracted with ethyl acetate (3x 50 mL), washed with water and brine, dried over anhydrous Na_2SO_4, evaporated. The residue was purified on silica gel by using light petroleum and ethyl acetate (4:1) to afford compound **61** (4.71 g, 72%) as colorless oil.

Mol. Formula : $C_{29}H_{46}O_5$

$[\alpha]_D^{25}$: –8.8 (*c* = 1.7, $CHCl_3$).

IR ($CHCl_3$) υ : 3425, 2926, 1612, 1465, 1247 cm^{-1}.

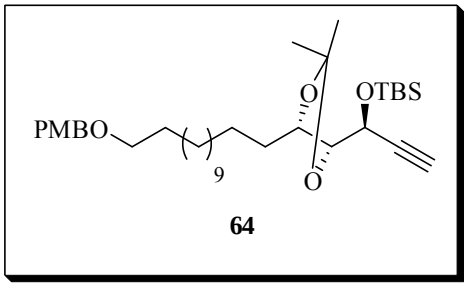
^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.24 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.47 (dd, *J* = 3.8, 2.2 Hz, 1H), 4.42 (s, 2H), 4.05 (ddd, *J* = 8.0, 7.8, 3.8 Hz, 1H), 3.80 (s, 3H), 3.75 (dd, *J* = 7.8, 3.8 Hz, 1H), 3.42 (t, *J* = 6.6 Hz, 2H), 2.51 (d, *J*= 2.2 Hz, 1H), 1.69-1.48 (m, 4H), 1.42 (s, 6H), 1.25 (m, 20H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 159.1, 130.7, 129.2, 113.7, 109.0, 82.4, 81.1, 77.4, 75.0, 72.5, 70.1, 62.3, 55.1, 34.1, 29.8, 29.7, 29.6, 29.5, 27.6, 27.0, 26.2, 26.0 ppm.

ESI-MS (*m/z*) : 496.96 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 73.38; H, 9.77%.
Found: C, 73.63; H, 9.55%.

***tert*-Butyl((*S*)-1-((4*R*,5*S*)-5-(13-(4-methoxybenzyloxy)-tridecyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-prop-2-ynyloxy)-dimethylsilane (64)**



64

To a solution of compound **61** (4.7 g, 9.9 mmol) and imidazole (877 mg, 12.9 mmol) in CH_2Cl_2 (40 mL) was added TBSCl (1.79 g, 11.9 mmol) in portions and the resulting mixture was stirred at room temperature for 2 h. After completion of the reaction (monitored by TLC), the reaction mixture was poured on ice, diluted with water and extracted with ethyl acetate (3x 50 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on silica gel by using light petroleum and ethyl acetate (9:1) to furnish compound **64** (5.52 g, 94%) as a colorless oil.

Mol. Formula : $C_{35}H_{60}O_5Si$

$[\alpha]_D^{25}$: +2.1 (*c* = 1.1, $CHCl_3$).

IR ($CHCl_3$) υ : 2855, 1614, 1513, 1249, 1097 cm^{-1}.

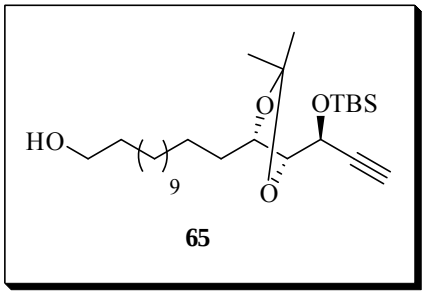
^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.25 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.42 (s, 2H), 4.39 (dd, *J* = 5.7, 2.2 Hz, 1H), 4.01 (ddd, *J* = 8.0, 7.2, 3.3 Hz, 1H), 3.80 (s, 3H), 3.70 (dd, *J* = 7.2, 5.7 Hz, 1H), 3.42 (t, *J* = 6.6 Hz, 2H), 2.45 (d, *J* = 2.2 Hz, 1H), 1.62-1.54 (m, 4H), 1.41 (s, 3H), 1.39 (s, 3H), 1.36-1.25 (m, 20H), 0.91 (m, 9H), 0.17 (s, 3H), 0.13 (s, 3H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 159.0, 130.8, 129.2, 113.7, 108.9, 83.0 (2C), 78.5, 73.9, 72.5, 70.2, 63.9, 55.2, 34.5, 29.8, 29.7, 29.6 (2C), 29.5 (2C), 27.6, 27.1, 26.2, 25.7, 18.2, –4.7, –5.0 ppm.

ESI-MS (*m/z*) : 611.50 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 71.38; H, 10.27%.
Found: C, 71.47; H, 10.08%.

13-((4*S*,5*R*)-5-((*S*)-1-(*tert*-Butyldimethylsilyloxy)-prop-2-ynyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-tridecan-1-ol (65)



65

To a stirred solution of compound **64** (3.47 g, 5.9 mmol) in a mixed solvent system of CH_2Cl_2: buffer (pH = 7) (18:1 by volume) (30 mL), DDQ (1.61 g, 7.1 mmol) was added at 0 ^oC. After 3 h the reaction was quenched by the addition of saturated $NaHCO_3$ solution (50 mL) and extracted with CH_2Cl_2 (3x 50 mL). The combined organic fraction was washed with water, brine, dried over anhydrous Na_2SO_4, evaporated. The residue was purified on silica gel by using light petroleum and ethyl acetate (3:1) to furnish compound **65** (2.1 g, 76%) as a light yellow oil.

Mol. Formula : $C_{27}H_{52}O_4Si$

$[\alpha]_D^{25}$: +2.4 (*c* = 1.0, $CHCl_3$).

IR ($CHCl_3$) υ : 3311, 2856, 2117, 1464, 1253, 1167 cm^{-1}.

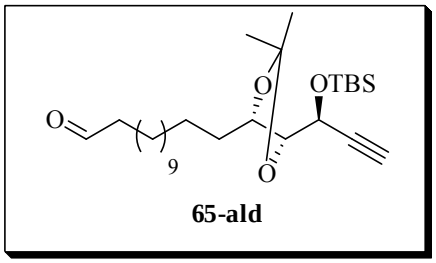
^{1}H NMR (200 MHz, $CDCl_3$) : δ 4.40 (dd, *J* = 5.7, 2.2 Hz, 1H), 4.02 (ddd, *J* = 8.0, 7.2, 3.3 Hz, 1H), 3.72 (dd, *J* = 7.2, 5.7 Hz, 1H), 3.64 (t, *J* = 6.5 Hz, 2H), 2.47 (d, *J*= 2.2 Hz, 1H), 1.63-1.50 (m, 4H), 1.42 (s, 3H), 1.39 (s, 3H), 1.27 (m, 20H), 0.92 (m, 9H), 0.18 (s, 3H), 0.14 (s, 3H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 108.9, 83.1, 83.0, 78.4, 74.0, 63.9, 63.0, 34.5, 32.8, 29.7 (2C), 29.6, 29.5, 27.6, 27.1, 26.2, 25.8, 18.2, –4.6, –4.9 ppm.

ESI-MS (*m/z*) : 491.23 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 69.18; H, 11.18%.
Found: C, 69.24; H, 11.33%.

13-((4*S*,5*R*)-5-((*S*)-1-(*tert*-Butyldimethylsilyloxy)-prop-2-ynyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-tridecanal (65-ald)

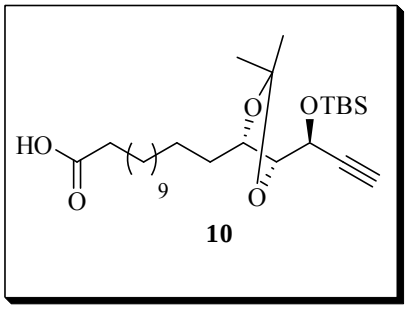


65-ald

Iodoxybenzoic acid (IBX) (1.17 g, 4.2 mmol) in DMSO (15 mL) was stirred at room temperature for 30 min till it become a clear solution. Compound **65** (1.96 g, 4.2 mmol) in THF (10 mL) was added to the clear solution and stirred for 4 h at room temperature. The reaction mixture was then diluted with water (40 mL) and filtered. The filtrate was extracted with diethyl ether (3x 50 mL), washed with $NaHCO_3$, water, brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on silica gel eluting with light petroleum and ethyl acetate (9:1) to afford the corresponding aldehyde **65-ald** (1.9 g, 97%) as yellow oil.

Mol. Formula	: $C_{27}H_{50}O_4Si$
$[\alpha]_D^{25}$	: +3.6 (*c* = 1.4, $CHCl_3$).
IR ($CHCl_3$) υ	: 2855, 2117, 1711, 1463, 1252, 1132 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	: δ 9.77 (t, *J* = 1.9 Hz, 1H), 4.40 (dd, *J* = 5.7, 2.2 Hz, 1H), 4.02 (ddd, *J* = 8.3, 7.2, 3.3 Hz, 1H), 3.72 (dd, *J* = 7.2, 5.7 Hz, 1H), 2.47 (d, *J* = 2.2 Hz, 1H), 2.42 (dt, *J* = 7.3, 1.9 Hz, 2H) 1.77-1.46 (m, 6H), 1.42 (s, 3H), 1.39 (s, 3H), 1.26 (m, 16H), 0.92 (m, 9H), 0.17 (s, 3H), 0.13 (s, 3H) ppm.
^{13}C NMR (50 MHz, $CDCl_3$)	: δ 202.9, 108.9, 83.1, 83.0, 78.5, 73.9, 63.9, 43.9, 34.5, 29.7, 29.6, 29.4 (2C), 29.2, 27.6, 27.1, 26.2, 25.8, 22.1, 18.2, –4.6, –5.0 ppm.
ESI-MS (*m/z*)	: 489.46 $[M+Na]^+$.
Elemental Analysis	: Calcd.: C, 69.48; H, 10.80%. Found: C, 69.32; H, 10.98%.

13-((4*S*,5*R*)-5-((*S*)-1-(*tert*-Butyldimethylsilyloxy)-prop-2-ynyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-tridecanoic acid (10)

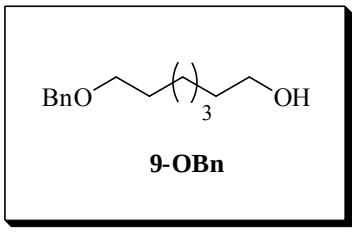


10

To the solution of the above aldehyde (1.43 g, 3.1 mmol), $NaH_2PO_4.2H_2O$ (1.45 g, 9.3 mmol) and 2-methyl-2-butene (2 mL) in *t*-BuOH (20 mL), a solution of $NaClO_2$ (840 mg, 9.3 mmol) in water (10 mL) was added drop wise for a period of 10 minutes at 0 ^oC. After 2 h, the reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (3x 25 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on silica gel by eluting with light petroleum and ethyl acetate (4:1) to give compound **10** (1.3 g, 88%) as a light yellow oil.

Mol. Formula	: $C_{27}H_{50}O_5Si$
$[\alpha]_D^{25}$	: +4.3 (*c* = 1.0, $CHCl_3$).
IR ($CHCl_3$) υ	: 3310, 2928, 1712, 1463, 1217 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$)	: δ 4.40 (dd, *J* = 5.5, 2.3 Hz, 1H), 4.02 (ddd, *J* = 8.3, 7.3, 3.3 Hz, 1H), 3.73 (dd, *J* = 7.3, 5.5 Hz, 1H), 2.47 (d, *J* = 2.3 Hz, 1H), 2.34 (t, *J* = 7.3 Hz, 2H) 1.77-1.51 (m, 6H), 1.42 (s, 3H), 1.39 (s, 3H), 1.26 (m, 16H), 0.91 (m, 9H), 0.17 (s, 3H), 0.13 (s, 3H) ppm.
^{13}C NMR (125 MHz, $CDCl_3$)	: δ 179.8, 108.9, 83.1, 83.0, 78.5, 73.9, 63.9, 34.5, 34.0, 29.7, 29.6, 29.5 (2C), 29.4, 29.2, 29.0, 27.6, 27.1, 26.1, 25.7, 24.7, 18.2, –4.7, –5.0 ppm.
ESI-MS (*m/z*)	: 505.14 $[M+Na]^+$.
Elemental Analysis	: Calcd.: C, 67.17; H, 10.44%. Found: C, 67.08; H, 10.30%.

7-(Benzyloxy)-heptan-1-ol (9-OBn)

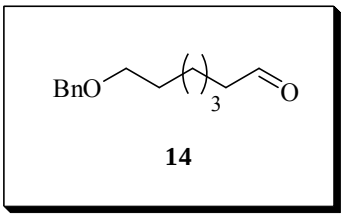


9-OBn

To a solution of 1,7-heptanediol (**9**) (21.23 g, 160.6 mmol) in a mixed solvent of THF and DMF (7:3 by volume, 200 mL) at 0 ^{o}C, sodium hydride (60% in dispersion oil) (6.42 g, 160.6 mmol) was added slowly followed by the addition of benzyl bromide(19.06 mL, 160.6 mmol). After being stirred for 30 min at that temperature the reaction mixture was allowed to warm to room temperature. The reaction mixture was stirred overnight at rt and quenched with water. After the removal of THF under reduced pressure, the residue was partitioned between ether (250 mL) and water (300 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated, and the residue was purified by silica gel column chromatography eluting with light petroleum and ethyl acetate (7:3) to give the monobenzyl derivative **9-OBn** (30.70 g, 86%) as colorless oil.

Mol. Formula	: $C_{14}H_{22}O_2$
IR ($CHCl_3$) υ	: 3433, 2853, 1613, 1586, 1464, 1247 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	: δ 7.34-7.25 (m, 5H), 4.49 (s, 2H), 3.59 (t, *J* = 6.7 Hz, 2H), 3.45 (t, *J* = 6.6 Hz, 2H), 1.85 (br.s, 1H), 1.68-1.48 (m, 4H), 1.33 (m, 6H) ppm.
^{13}C NMR (50 MHz, $CDCl_3$)	: δ 138.4, 128.2, 127.5, 127.4, 72.7, 70.2, 62.5, 32.5, 29.5, 29.1, 26.1, 25.6 ppm.
ESI-MS (*m/z*)	: 245.26 $[M+Na]^+$.
Elemental Analysis	: Calcd.: C, 75.63; H, 9.97%. Found: C, 75.76; H, 10.08%.

7-(Benzyloxy)-heptanal (14)



14

To a stirred solution of 7-benzyloxyheptan-1-ol (**9-OBn**) (21.13 g, 95.0 mmol) in CH_2Cl_2 (250 mL), PCC (40.97 g, 190.1 mmol) was added and the resulting mixture was stirred at rt for 2 h. After the completion of the reaction (monitored by TLC), the reaction mixture was diluted with ether (200 mL) and filtered. The filtrate was concentrated under reduced pressure and the residue thus obtained was purified by silica gel column chromatography eluting with light petroleum and ethyl acetate (4:1) to give compound **14** (18.22 g, 87%) as a colorless oil.

Mol. Formula : $C_{14}H_{20}O_2$

IR ($CHCl_3$) υ : 2926, 1725, 1614, 1462, 1301 cm^{-1}.

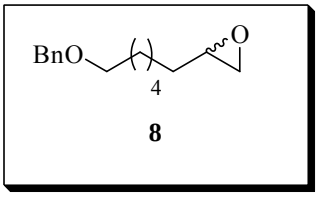
^{1}H NMR (200 MHz, $CDCl_3$) : δ 9.74 (t, *J* = 1.7 Hz, 1H), 7.34-7.25 (m, 5H), 4.49 (s, 2H), 3.45 (t, *J* = 6.6 Hz, 2H), 2.41 (dt, *J* = 7.2, 1.7 Hz, 2H), 1.70-1.55 (m, 4H), 1.46-1.26 (m, 4H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 202.3, 138.5, 128.2, 127.5, 127.4, 72.7, 70.0, 43.7, 29.4, 28.9, 25.9, 21.9 ppm.

ESI-MS (*m/z*) : 243.36 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 76.33; H, 9.15%.
Found: C, 76.19; H, 9.33%.

2-(6-(Benzyloxy)-hexyl)-oxirane (8)



8

To a suspension of NaH (4.33 g, 60% dispersion in oil, 108.3 mmol) and trimethylsulphoxonium iodide (23.82 g, 108.3 mmol) in DMSO (150 mL) under argon at 10 ^oC was added compound **14** (15.9 g, 72.2 mmol) in DMSO (100 mL) over a period of 30 min. After 3 h the reaction was quenched with ice-cold water and

extracted with ethyl acetate (3x 125 mL). The combined organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on silica gel using light petroleum and ethyl acetate (9:1) to afford compound **8** (14.22 g, 84%) as a yellow oil.

Mol. Formula : $C_{15}H_{22}O_2$

IR ($CHCl_3$) υ : 2929, 1603, 1454, 1258 cm^{-1}.

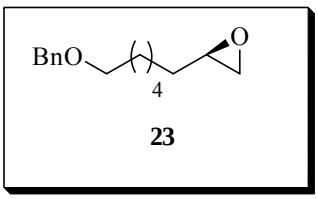
^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.33-7.28 (m, 5H), 4.49 (s, 2H), 3.45 (t, *J* = 6.6 Hz, 2H), 2.90-2.84 (m, 1H), 2.73 (dd, *J* = 5.1, 4.0 Hz, 1H), 2.44 (dd, *J* = 5.1, 2.7 Hz, 1H), 1.63-1.30 (m, 10H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ 138.5, 128.2, 127.5, 127.3, 72.7, 70.2, 52.1, 46.8, 32.3, 29.6 (2C), 29.2, 26.1, 25.9 ppm.

ESI-MS (*m/z*) : 257.45 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 76.88; H, 9.46%.
Found: C, 76.71; H, 9.31%.

(*R*)-2-(6-(Benzyloxy)-hexyl)-oxirane (23) and (*S*)-8-(Benzyloxy)-octane-1,2-diol (24)



23

(*R, R*)-salen-Co(III) catalyst (172 mg, 0.26 mmol) was added to (*R/S)* epoxide **8** (12.18 g, 52.0 mmol), followed by dropwise addition of water (0.51 ml, 28.6 mmol) over 1 h at 0 ^oC. The reaction mixture was allowed to warm to room temperature and stirred for 36 h. The reaction mixture was filtered and the filtrate concentrated. The residue was purified by column chromatography eluting with light petroleum and ethyl acetate (9:1) to afford compound **23** (5.7 g, 47%) as a light yellow oil.

Mol. Formula : $C_{15}H_{22}O_2$

$[\alpha]_D^{25}$: +5.6 (*c* = 2.0, $CHCl_3$).

IR ($CHCl_3$) υ : 2933, 1603, 1454, 1216 cm^{-1}.

^{1}H NMR : δ 7.33-7.28 (m, 5H), 4.49 (s, 2H), 3.45 (t, *J* = 6.6 Hz, 2H),

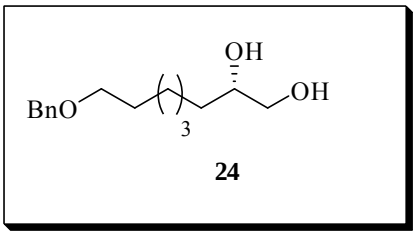
(200 MHz, $CDCl_3$) 2.90-2.84 (m, 1H), 2.73 (dd, J = 5.1, 4.0 Hz, 1H), 2.44 (dd, J = 5.1, 2.7 Hz, 1H), 1.63-1.30 (m, 10H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 138.5, 128.2, 127.5, 127.3, 72.8, 70.2, 52.2, 46.9, 32.4, 29.6 (2C), 29.2, 26.1, 25.9 ppm.

ESI-MS (*m/z*) : 257.45 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 76.88; H, 9.46%.
Found: C, 76.97; H, 9.29%.

Further elution with petroleum ether and ethyl acetate (1:1) gave the diol **24** (5.5 g, 42%) as yellow oil.



24

Mol. Formula : $C_{15}H_{24}O_3$

$[\alpha]_D^{25}$: +2.9 (c = 1.0, $CHCl_3$).

IR ($CHCl_3$) υ : 3392, 2932, 1454, 1216, 1028 cm^{-1}.

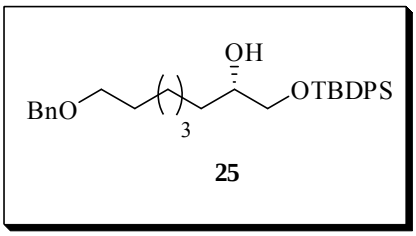
^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.32-7.26 (m, 5H), 4.49 (s, 2H), 3.67 (m, 2H), 3.46 (t, J = 6.6 Hz, 2H), 3.41-3.39 (m, 1H), 2.53 (br s, 2H), 1.64-1.58 (m, 2H), 1.42-1.33 (m, 8H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 138.4, 128.3, 127.5, 127.4, 72.8, 72.1, 70.3, 66.5, 33.0, 29.6, 29.4, 26.0, 25.5 ppm.

ESI-MS (*m/z*) : 275.36 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 71.39; H, 9.59%.
Found: C, 71.68; H, 9.37%.

(*S*)-8-(Benzyloxy)-1-(*tert*-butyldiphenylsilyloxy)-octan-2-ol (25)

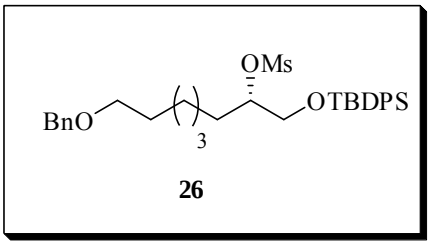


25

To a solution of the diol **24** (5.32 g, 21.1 mmol) and imidazole (1.87 g, 27.4 mmol) in CH_2Cl_2 (75 mL) was added TBDPSCl (6.95 g, 25.3 mmol) in portions followed by the addition of DMAP (103 mg, 0.8 mmol) and the resulting mixture was stirred at room temperature for 3 h. After completion of the reaction (monitored by TLC), the reaction mixture was poured on ice, diluted with water and extracted with diethyl ether (3x 75 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on silica gel by using light petroleum and ethyl acetate (9:1) to produce compound **25** (9.21 g, 89%) as a colorless oil.

Mol. Formula	: $C_{31}H_{42}O_3Si$
$[\alpha]_D^{25}$	: +0.9 (*c* = 1.3, $CHCl_3$).
IR ($CHCl_3$) υ	: 3467, 2857, 1589, 1427, 1362 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	: δ 7.68-7.24 (m, 15H), 4.48 (s, 2H), 3.74-3.60 (m, 2H), 3.50-3.41 (m, 1H), 3.43 (t, *J* = 6.7 Hz, 2H), 2.27 (br.s, 1H), 1.62-1.52 (m, 2H), 1.37-1.26 (m, 8H), 1.06 (m, 9H) ppm.
^{13}C NMR (50 MHz, $CDCl_3$)	: δ 138.6, 135.5, 133.1 (2C), 129.8, 128.3, 127.7, 127.5, 127.4, 72.8, 71.8, 70.3, 68.0, 32.7, 29.7, 29.4, 26.9, 26.1, 25.4, 19.2 ppm.
ESI-MS (*m/z*)	: 513.29 $[M+Na]^+$.
Elemental Analysis	: Calcd.: C, 75.87; H, 8.63%. Found: C, 75.93; H, 8.41%.

(*S*)-8-(Benzyloxy)-1-(*tert*-butyldiphenylsilyloxy)-octan-2-yl-methanesulfonate (26)



26

To a solution of the alcohol **25** (8.94 g, 18.2 mmol) and triethylamine (3.81 mL, 27.3 mmol) at 0 °C in CH_2Cl_2 (75 mL), methanesulphonyl chloride (2.5 g, 21.9 mmol) in CH_2Cl_2 (20 mL) was added dropwise. The reaction mixture was stirred for 2 h. After the completion of the reaction (monitored by TLC), the reaction mixture was washed successively with aqueous sodium bicarbonate and water, dried over anhydrous Na_2SO_4 and concentrated. The residue thus obtained was purified by silica gel column chromatography eluting with light petroleum and ethyl acetate (4:1) to afford compound **26** (9.43 g, 91%) as a colorless oil.

Mol. Formula : $C_{32}H_{44}O_5SSi$

$[\alpha]_D^{25}$: –5.7 (*c* = 0.5, $CHCl_3$).

IR ($CHCl_3$) υ : 2858, 1962, 1589, 1458, 1428, 1242 cm^{-1}.

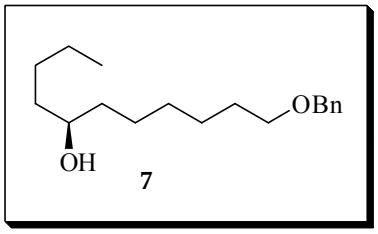
^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.68-7.25 (m, 15H), 4.75-4.64 (m, 1H), 4.48 (s, 2H), 3.83-3.68 (m, 2H), 3.44 (t, *J* = 6.7 Hz, 2H), 2.97 (s, 3H), 1.68-1.52 (m, 4H), 1.39-1.16 (m, 6H), 1.06 (m, 9H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 138.6, 135.5, 135.4, 132.8, 132.6, 130.0, 129.9, 128.3, 127.8, 127.6, 127.4, 83.8, 72.8, 70.2, 65.3, 38.5, 31.4, 29.6, 29.1, 26.8, 25.9, 24.8, 19.2 ppm.

ESI-MS (*m/z*) : 591.37 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 67.57; H, 7.80%.
Found: C, 67.73; H, 7.74%.

(*S*)-11-(Benzyloxy)-undecan-5-ol (7)

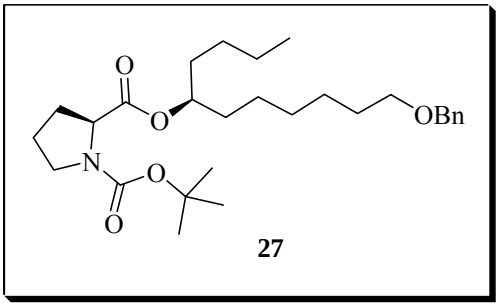


7

To a suspension of magnesium (1.5 g, 61.8 mmol) in dry THF (100 mL) at 0 °C was added a solution of *n*-propyl bromide (5.62 mL, 61.8 mmol) in THF (30 ml). After 0.5 h, CuCN (2.22 g, 24.7 mmol) and compound **23** (4.83 g, 20.6 mmol) in THF (25 mL) were added and stirred for 1 h at 0 ^{o}C. The reaction mixture was then quenched with saturated NH_4Cl solution, concentrated and the residue partitioned between ethyl acetate and water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on silica gel using light petroleum and ethyl acetate (4:1) as an eluent to afford compound **7** (4.5 g, 78%) as colorless oil.

Mol. Formula	: $C_{18}H_{30}O_2$
$[\alpha]_D^{25}$	: +1.5 (*c* = 1.3, $CHCl_3$).
IR ($CHCl_3$) υ	: 3437, 2933, 1454, 1278, 1216 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$)	: δ 7.33-7.25 (m, 5H), 4.49 (s, 2H), 3.57-3.54 (m, 1H), 3.45 (t, *J* = 6.5 Hz, 2H), 1.64-1.58 (m, 2H), 1.45-1.30 (m, 14H), 0.91 (t, *J* = 6.6 Hz, 3H) ppm.
^{13}C NMR (125 MHz, $CDCl_3$)	: δ 138.7, 128.3, 127.6, 127.5, 72.9, 71.9, 70.4, 37.5, 37.2, 29.7, 29.6, 27.9, 26.2, 25.6, 22.8, 14.1 ppm.
ESI-MS (*m/z*)	: 301.14 $[M+Na]^+$.
Elemental Analysis	: Calcd.: C, 77.65; H, 10.86%. Found: C, 77.46; H, 10.69%.

(*S*)-2-((*S*)-11-(Benzyloxy) undecan-5-yl)-1-*tert*-butyl pyrrolidine-1, 2-dicarboxylate (27)



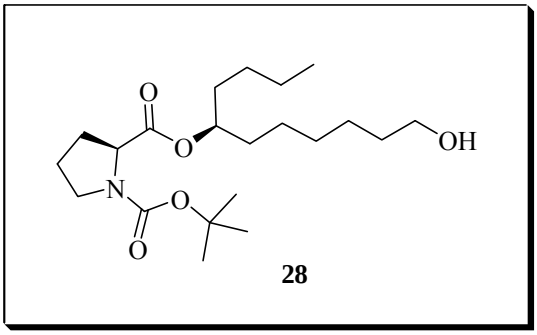
27

A solution of compound **7** (4.31 g, 15.5 mmol) and N-Boc-L-proline (4.0 g, 18.6 mmol) in CH_2Cl_2 (60 mL) was treated sequentially at 0 ^oC with DMAP (946 mg, 7.7 mmol) and EDC (3.86 g, 20.1 mmol). After 12 h at room temperature, the reaction mixture was quenched with water and extracted with ethyl acetate (3x 50 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on silica gel using light petroleum and ethyl acetate (4:1) to afford compound **27** (7.0 g, 95%) as a light yellow oil.

Mol. Formula	: $C_{28}H_{45}NO_5$
$[\alpha]_D^{25}$	: –34.5 (*c* = 1.2, $CHCl_3$).
IR ($CHCl_3$) υ	: 2932, 1736, 1692, 1406, 1163 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	: δ 7.33-7.25 (m, 5H), 4.92-4.80 (m, 1H), 4.49 (s, 2H), 4.34-4.20 (m, 2H), 3.61-3.47 (m, 1H), 3.44 (t, *J* = 6.6 Hz, 2H), 2.21-1.87 (m, 4H), 1.62-1.48 (m, 4H), 1.45 and 1.42 (rotamers, s, s, 9H), 1.30-1.22 (m, 12H), 0.89 (t, *J* = 6.5 Hz, 3H) ppm.
^{13}C NMR (50 MHz, $CDCl_3$)	: δ 172.5 and 172.4 (rotamers), 153.9 and 153.6 (rotamers), 138.5, 132.6, 129.3, 128.1, 127.3, 127.2, 79.5 and 79.2 (rotamers), 74.7 and 74.5 (rotamers), 72.6, 70.1 and 70.1 (rotamers), 58.9, 46.3 and 46.1 (rotamers), 33.8 and 33.7 (rotamers), 33.6, 30.9, 29.6 and 29.5 (rotamers), 29.1 and 29.0 (rotamers), 28.5 and 28.2 (rotamers), 27.3 and 27.2 (rotamers), 25.9 and 25.8 (rotamers), 25.1 and 24.9 (rotamers), 24.1, 23.2, 22.4, 13.8 and 13.7 (rotamers) ppm.
ESI-MS (*m/z*)	: 498.45 $[M+Na]^+$.
Elemental Analysis	: Calcd.: C, 70.70; H, 9.54; N, 2.94%.

Found: C, 70.88; H, 9.41; N, 2.79%.

(*S*)-1-*tert*-Butyl-2-((*S*)-11-hydroxyundecan-5-yl)-pyrrolidine-1,2-dicarboxylate (28)

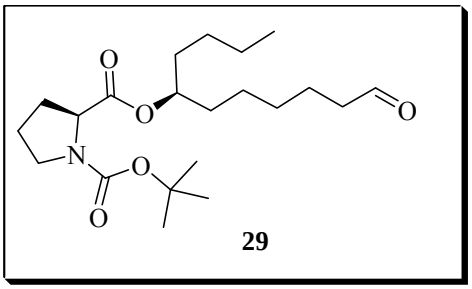


28

A solution of compound **27** (6.71 g, 14.1 mmol) in ethyl acetate (60 mL) was stirred in presence of 10% Pd/C (750 mg, 5 mol%) under hydrogen atmosphere. After 6 h, the reaction mixture was filtered through a pad of celite and concentrated. The residue was purified on silica gel using light petroleum and ethyl acetate (3:2) to provide compound **28** (4.7 g, 87%).

Mol. Formula	: $C_{21}H_{39}NO_5$
$[\alpha]_D^{25}$	: –43.8 (*c* = 1.6, $CHCl_3$).
IR ($CHCl_3$) υ	: 3455, 2934, 1736, 1690, 1406, 1215 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	: δ 4.92-4.79 (m, 1H), 4.32-4.20 (m, 1H), 3.62 (t, *J* = 6.5 Hz, 2H), 3.56-3.35 (m, 2H), 2.25-1.86 (m, 4H), 1.81-1.68 (m, 2H), 1.55-1.49 (m, 4H), 1.46 and 1.42 (rotamers, s, s, 9H), 1.32-1.26 (m, 10H), 0.89 (t, *J* = 6.5 Hz, 3H) ppm.
^{13}C NMR (50 MHz, $CDCl_3$)	: δ 172.7 and 172.6 (rotamers), 154.1 and 153.8 (rotamers), 79.7 and 79.4 (rotamers), 74.9 and 74.6 (rotamers), 62.5, 59.1, 46.4 and 46.2 (rotamers), 33.8 and 33.7 (rotamers), 32.5, 30.9, 30.0, 29.1 and 29.0 (rotamers), 28.4, 28.3, 27.4 and 27.3 (rotamers), 25.5, 25.1 and 25.0 (rotamers), 24.2, 23.3, 22.5, 13.9 and 13.8 (rotamers) ppm.
ESI-MS (*m/z*)	: 408.47 $[M+Na]^+$.
Elemental Analysis	: Calcd.: C, 65.42; H, 10.20; N, 3.63%. Found: C, 65.67; H, 10.01; N, 3.45%.

(*S*)-1-*tert*-Butyl-2-((*S*)-11-oxoundecan-5-yl)-pyrrolidine-1,2-dicarboxylate (29)



29

Iodoxybenzoic acid (IBX) (3.56 g, 12.7 mmol) in DMSO (50 mL) was stirred at room temperature for 30 min till it become a clear solution. Compound **28** (4.08 g, 10.6 mmol) in THF (30 mL) was added to the clear solution and stirred for 4 h at room temperature. The reaction mixture was then diluted with water (70 mL) and filtered. THF was removed under reduced pressure and the reaction mixture was extracted with diethyl ether (3x 50 mL), washed with $NaHCO_3$, water, brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on silica gel eluting with light petroleum and ethyl acetate (9:1) to afford the corresponding aldehyde **29** (3.7 g, 90%) as a yellow oil.

Mol. Formula : $C_{21}H_{37}NO_5$

$[\alpha]_D^{25}$: –39.1 (*c* = 2.0, $CHCl_3$).

IR ($CHCl_3$) υ : 2934, 1733, 1694, 1405, 1215, 1163 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 9.74 (m, 1H), 4.90-4.81 (m, 1H), 4.29-4.21 (m, 1H), 3.56-3.35 (m, 2H), 2.43-2.39 (m, 2H), 2.32-1.86 (m, 4H), 1.65-1.50 (m, 6H), 1.44 and 1.41 (rotamers, s, s, 9H), 1.31-1.24 (m, 8H), 0.87 (t, *J* = 6.6 Hz, 3H) ppm.

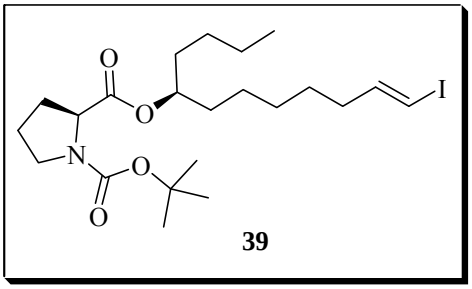
^{13}C NMR (50 MHz, $CDCl_3$) : δ 202.2 and 202.0 (rotamers), 172.7 and 172.6 (rotamers), 154.2 and 153.8 (rotamers), 79.7 and 79.5 (rotamers), 74.8 and 74.5 (rotamers), 59.2, 46.5 and 46.3 (rotamers), 43.7, 33.9 and 33.9 (rotamers), 33.9 and 33.8 (rotamers), 31.0 and 30.1 (rotamers), 29.7 and 29.0 (rotamers), 28.4 (2C), 27.5 and 27.3 (rotamers), 25.1 and 24.9 (rotamers), 24.5 and 24.3 (rotamers), 23.4, 22.5, 21.9, 14.0 and 13.9 (rotamers) ppm.

ESI-MS (*m/z*) : 406.21 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 65.77; H, 9.72; N, 3.65%.

Found: C, 65.65; H, 9.84; N, 3.73%.

(*S*)-1-*tert*-Butyl-2-((*S, E*)-12-iodododec-11-en-5-yl)-pyrrolidine-1, 2-dicarboxylate (39)



39

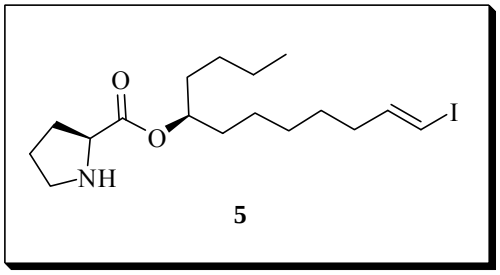
Anhydrous $CrCl_2$ (4.93 g, 40.1 mmol) was suspended in THF (80 mL) under an argon atmosphere. A solution of the above aldehyde (2.56 g, 6.7 mmol) and iodoform (5.28 g, 13.4 mmol) in THF (50 mL) was added dropwise to the suspension at 0 ^oC. After stirring at 0 ^oC for 3 h, the reaction mixture was poured into water (150 mL) and extracted with diethyl ether (3x 75 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on silica gel using light petroleum and ethyl acetate (9:1) to provide compound **39** (3.1 g, 90%) as a light yellow oil.

Mol. Formula	: $C_{22}H_{38}INO_4$
$[\alpha]_D^{25}$	: –35.4 (*c* = 1.2, $CHCl_3$).
IR ($CHCl_3$) υ	: 2400, 1737, 1690, 1405, 1162 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	: δ 6.48 (dt, *J* = 14.3, 7.2 Hz, 1H), 5.98 (d, *J* = 14.3 Hz, 1H), 4.91-4.82 (m, 1H), 4.32-4.21 (m, 1H), 3.58-3.35 (m, 2H), 2.22-1.92 (m, 6H), 1.61-1.49 (m, 4H), 1.46 and 1.43 (rotamers, s, s, 9H), 1.29 (m, 10H), 0.89 (t, *J* = 6.5 Hz, 3H) ppm.
^{13}C NMR (50 MHz, $CDCl_3$)	: δ 172.7 and 172.6 (rotamers), 154.1 and 153.8 (rotamers), 146.4 and 146.3 (rotamers), 79.7 and 79.4 (rotamers), 74.8 and 74.6 (rotamers), 74.5 and 74.4 (rotamers), 60.3 and 59.1 (rotamers), 46.4 and 46.2 (rotamers), 35.9, 33.9, 33.7, 31.0 and 30.0 (rotamers), 28.9 and 28.7 (rotamers), 28.4 (2C), 28.2 and 27.8 (rotamers), 27.4 and 27.3 (rotamers), 25.0 and 24.9 (rotamers), 24.3, 23.4, 22.6, 14.0 and 13.9 (rotamers) ppm.

ESI-MS (*m/z*) : 530.21 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 52.07; H, 7.55; N, 2.76%.
Found: C, 52.25; H, 7.43; N, 3.03%.

(*S*)-((*S*,*E*)-12-Iodododec-11-en-5-yl)-pyrrolidine-2-carboxylate (5)



5

A suspension of compound **39** (2.45 g, 4.8 mmol) and 4N-HCl in ethyl acetate (25 mL) were stirred for 3 h at room temperature. After the completion of the reaction (monitored by TLC), the reaction mixture was diluted with ethyl acetate and neutralized with saturated sodium bicarbonate solution (55 mL). The aqueous phase was extracted with ethyl acetate (3x 75 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated**.** The residue was purified on neutral alumina using ethyl acetate as the eluent to provide the free amine **5** (1.6 g, 81%) as a yellow oil.

Mol. Formula : $C_{17}H_{30}INO_2$

$[\alpha]_D^{25}$: –10.4 (*c* = 3.5, $CHCl_3$).

IR ($CHCl_3$) υ : 3343, 2930, 1730, 1605, 1459, 1377, 1215 cm^{-1}.

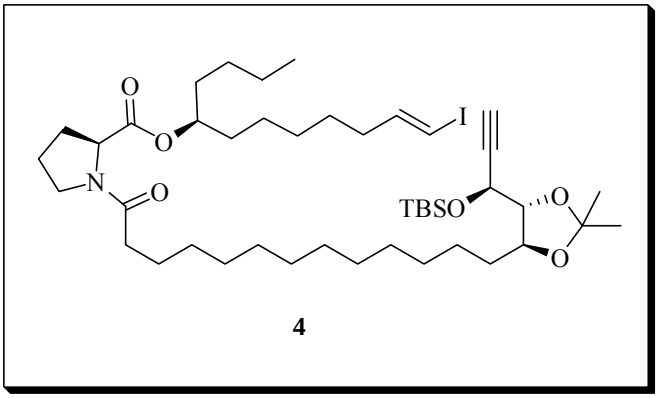
^{1}H NMR (200 MHz, $CDCl_3$) : δ 6.49 (dt, *J* = 14.3, 7.2 Hz, 1H), 5.98 (d, *J* = 14.3 Hz, 1H), 4.95-4.83 (m, 1H), 3.84-3.72 (m, 1H), 3.20-3.08 (m, 1H), 3.00-2.92 (m, 2H), 2.27-1.99 (m, 4H), 1.90-1.70 (m, 4H), 1.58-1.49 (m, 4H), 1.33-1.25 (m, 8H), 0.89 (t, *J* = 6.6 Hz, 3H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 174.2, 146.3, 75.2, 74.6, 59.7, 46.7, 35.9, 33.8, 30.4, 29.7, 28.7, 28.2, 27.4, 25.2, 25.0, 22.5, 14.0 ppm.

ESI-MS (*m/z*) : 430.19 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 50.13; H, 7.42; N, 3.44%.
Found: C, 50.29; H, 7.21; N, 3.32%.

(*S*)-((*S*,*E*)-12-iodododec-11-en-5-yl)-1-(13-((4*S*,5*R*)-5-((*S*)-1-(*tert*-butyl dimethylsilyloxy)-prop-2-ynyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-tridecanoyl)-pyrrolidine -2-carboxylate (4)



4

To a solution of the free amine **5** (1.19 g, 2.9 mmol) and the acid **10** (1.17 g, 2.4 mmol) in CH_2Cl_2 (15 mL) at 0 ^oC was added sequentially HOBt (327 mg, 2.4 mmol) and EDC (604 mg, 3.1 mmol). After 12 h at room temperature, the reaction mixture was quenched with water and extracted with ethyl acetate (3x 50 mL). The combined organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on silica gel using light petroleum and ethyl acetate (4:1) to afford compound **4** (2.0 g, 96%) as a yellow oil.

Mol. Formula : $C_{44}H_{78}INO_6Si$

$[\alpha]_D^{25}$: –19.4 (*c* = 1.3, $CHCl_3$).

IR ($CHCl_3$) υ : 2930, 2206, 2104, 1734, 1659, 1501, 1431, 1215, 1081 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 6.49 (dt, *J* = 14.3, 7.1 Hz, 1H), 5.98 (d, *J* = 14.3 Hz, 1H), 4.94-4.81 (m, 1H), 4.56-4.44 (m, 1H), 4.40 (dd, *J* = 5.6, 2.2 Hz, 1H), 4.02 (dt, *J* = 7.6, 3.1 Hz, 1H), 3.71 (dd, *J* = 7.2, 5.6 Hz, 1H), 3.65-3.44 (m, 2H), 2.45 (d, *J* = 2.2 Hz, 1H), 2.29 (dt, *J* = 7.3, 1.6 Hz, 2H), 2.14-2.00 (m, 6H), 1.77-1.46 (m, 10H), 1.41 (s, 3H), 1.39 (s, 3H), 1.26 (m, 26H), 0.92 (m, 9H), 0.91 (t, *J* = 6.7 Hz, 3H), 0.17 (s, 3H), 0.13 (s, 3H) ppm.

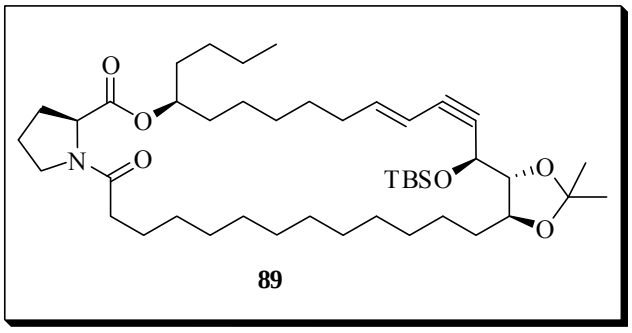
^{13}C NMR (100 MHz, $CDCl_3$) : δ 172.2 and 172.2 (rotamers), 171.7, 146.5 and 146.3 (rotamers), 108.9, 83.1 and 83.1 (rotamers), 78.4, 74.8 and 74.6 (rotamers), 74.5 and 74.4 (rotamers), 73.9, 63.9, 59.7 and 58.9 (rotamers), 47.0 and 46.3 (rotamers), 36.0 and 35.9

(rotamers), 34.1 and 33.9 (rotamers), 34.0 and 33.8 (rotamers), 32.0, 31.7, 29.7, 29.6, 29.5, 29.4, 28.8 and 28.7 (rotamers), 28.4 and 28.3 (rotamers), 27.9 and 27.7 (rotamers), 27.3, 27.2, 26.2, 25.8, 25.0, 24.8 (2C), 22.6 and 22.5 (rotamers), 18.2, 14.1 and 14.0 (rotamers), –4.6, –4.9 ppm.

ESI-MS (*m/z*) : 894.10 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 60.60; H, 9.02; N, 1.61%.
Found: C, 60.39; H, 9.22; N, 1.47%.

Preparation of compound 89



89

Tetrakis(triphenylphosphine)palladium(0) (253 mg, 0.2 mmol) and CuI (83 mg, 0.4 mmol) were added successively to a stirred solution of compound **4** (1.91 g, 2.2 mmol) in anhydrous Et_2NH (10 mL) at room temperature and the reaction mixture was degassed (4x) gently with argon under fringe-throng process. After 30 min the reaction was quenched by the addition of water and extracted with diethyl ether (3x 50 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated. The residue was purified on silica gel (230-400 mesh) eluting with light petroleum and ethyl acetate (7:3) to afford compound **89** (572 mg, 35%) as a yellow oil.

Mol. Formula : $C_{44}H_{77}NO_6Si$

$[\alpha]_D^{25}$: +1.9 (*c* = 1.7, $CHCl_3$).

IR ($CHCl_3$) υ : 2927, 1733, 1646, 1463, 1252, 1161, 1069 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) : δ 6.09 (dt, *J* = 15.8, 7.2 Hz, 1H), 5.45 (d, *J* = 15.8 Hz, 1H), 4.92-4.85 (m, 1H), 4.72-4.71 (m, 1H), 4.51 (dd, *J* = 9.1, 3.5 Hz, 1H), 4.23 (dt, *J* = 7.8, 3.1 Hz, 1H), 3.71 (dd, *J* = 8.0, 2.8 Hz, 1H), 3.67-3.49 (m, 2H), 2.35-2.18 (m, 4H), 2.11 (t, *J* = 6.6

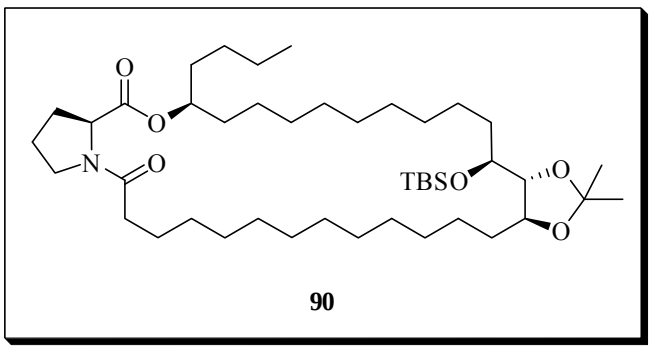
Hz, 2H), 2.02-1.87 (m, 4H), 1.58-1.46 (m, 10H) 1.40 (s, 3H), 1.39 (s, 3H), 1.27 (m, 24H), 0.94 (m, 9H), 0.90 (t, J = 6.7 Hz, 3H), 0.16 (s, 3H), 0.13 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) : δ 172.0 and 171.9 (rotamers), 171.8, 145.2 and 144.7 (rotamers), 109.1 and 108.9 (rotamers), 108.2, 86.3 and 86.1 (rotamers), 85.1 and 85.0 (rotamers), 83.1 and 83.0 (rotamers), 76.0 and 75.5 (rotamers), 74.7, 62.2, 60.2 and 59.4 (rotamers), 47.0 and 46.3 (rotamers), 34.6 and 34.5 (rotamers), 34.0, 33.9 and 33.9 (rotamers), 33.7 and 33.6 (rotamers), 33.2 and 33.0 (rotamers), 32.0 and 31.7 (rotamers), 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 28.9, 28.7, 28.6, 27.9 and 27.7 (rotamers), 27.5, 27.1 and 27.0 (rotamers), 25.9, 25.5, 25.3 and 25.2 (rotamers), 24.9, 24.8, 24.7 and 24.7 (rotamers), 22.7 and 22.7 (rotamers), 22.6 and 22.5 (rotamers), 18.4, 14.2 and 14.1 (rotamers), –4.8 ppm.

ESI-MS (*m/z*) : 766.85 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 71.01; H, 10.43; N, 1.88%.
Found: C, 71.23; H, 10.62; N, 1.67%.

(3a*R*,4*S*,14*S*,16a*S*,33a*S*)-14-Butyl-4-(*tert*-butyldimethylsilyloxy)-2,2-dimethyl-hexacosahydro-3aH-[1,3]dioxolo[4,5-r]pyrrolo[2,1-c][1,4]-oxaazacyclotriacontine-16,21(4H,22H)-dione (90)



90

A suspension of compound **89** (450 mg, 0.6 mmol) and Raney Ni (75 mg) in ethanol (5 mL) was hydrogenated at normal pressure and temperature. After 12 h, the reaction mixture was filtered through a pad of Celite and concentrated. The residue was purified on silica gel using light petroleum and ethyl acetate (7:3) to provide compound **90** (420 mg, 92%) as colorless oil.

Mol. Formula : $C_{44}H_{83}NO_6Si$

$[\alpha]_D^{25}$: –19.8 (*c* = 0.9, $CHCl_3$).

IR ($CHCl_3$) υ : 2929, 1730, 1638, 1463, 1380, 1215 cm^{-1}.

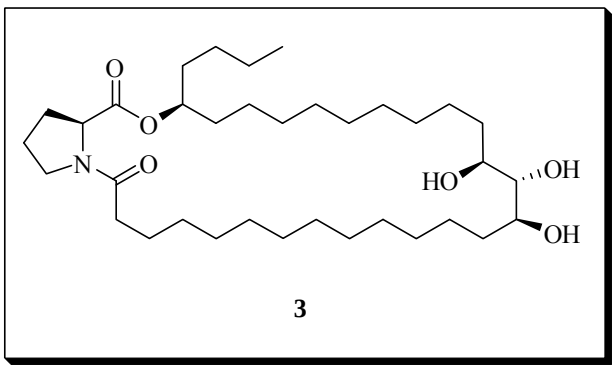
^{1}H NMR (400 MHz, $CDCl_3$) : δ 4.92-4.86 (m, 1H), 4.51 (dd, *J* = 9.1, 3.5 Hz, 1H), 4.00-3.96 (m, 1H), 3.84-3.79 (m, 1H), 3.74-3.65 (m, 1H), 3.62-3.47 (m, 2H), 2.29-2.12 (m, 4H), 2.05-1.86 (m, 4H), 1.66-1.58 (m, 4H), 1.54-1.49 (m, 8H), 1.37 (s, 6H), 1.25 (m, 32H), 0.90 (m, 9H), 0.89 (t, *J* = 6.7 Hz, 3H), 0.07 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) : δ 172.0 and 171.9 (rotamers), 171.8, 107.8, 81.8 and 81.7 (rotamers), 76.1, 75.0 and 74.8 (rotamers), 72.0 and 71.8 (rotamers), 60.1 and 59.3 (rotamers), 47.0 and 46.2 (rotamers), 34.9 and 34.5 (rotamers), 34.1 and 33.9 (rotamers), 33.7, 33.6, 33.5, 33.4, 31.9 and 31.8 (rotamers), 31.6 and 31.6 (rotamers), 30.0, 29.6 (2C), 29.5, 29.3, 29.2, 29.0 and 28.9 (rotamers), 28.6, 27.4 and 27.3 (rotamers), 27.2, 25.9, 25.6 and 25.3 (rotamers), 25.0 (2C), 24.8 and 24.7 (rotamers), 24.6, 24.4, 22.6 and 22.6 (rotamers), 22.5 and 22.4 (rotamers), 18.1, 14.1 and 13.9 (rotamers), –4.3, –4.5 ppm.

ESI-MS (*m/z*) : 772.82 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 70.44; H, 11.15; N, 1.87%.
Found: C, 70.23; H, 11.27; N, 1.77%.

(3*S*,13*S*,15*S*,32a*S*)-3-Butyl-13,14,15-trihydroxyoctacosahydro-1H-pyrrolo[2,1-c][1,4]oxaazacyclotriacontine-1,28(3H)-dione (3)

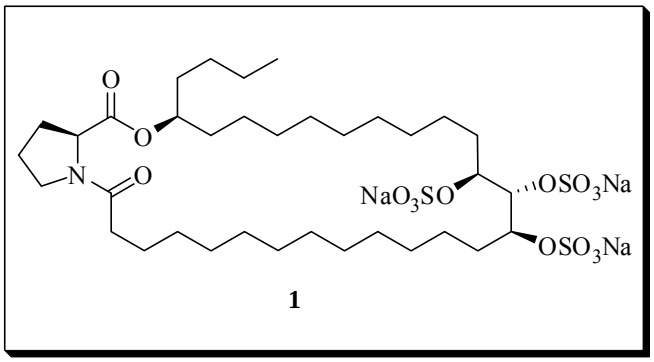


3

A solution of compound **90** (336 mg, 0.45 mmol) and *p*-TSA (50 mg) in Methanol (5 mL) was stirred at room temperature for 4 h. The reaction mixture was neutralized (pH 6) by the addition of Et_3N (0.5 mL) and concentrated. The residue was purified on silica gel by using light petroleum and ethyl acetate (2:3) to afford compound **3** (217 mg, 82%) as light yellow oil.

Mol. Formula	: $C_{35}H_{65}NO_6$
$[\alpha]_D^{25}$	: –19.4 (*c* = 1.0, $CHCl_3$).
IR ($CHCl_3$) υ	: 3413, 2924, 1737, 1631, 1463, 1277, 1193 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$)	: δ 4.92-4.84 (m, 1H), 4.50 (dd, *J* = 9.1, 3.5 Hz, 1H), 3.92-3.80 (m, 2H), 3.63-3.57 (m, 2H), 3.52-3.44 (m, 1H), 2.31-2.09 (m, 8H), 2.03-1.89 (m, 4H), 1.66-1.49 (m, 10H), 1.27 (m, 30H), 0.89 (t, *J* = 6.7 Hz, 3H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	: δ 172.3 and 172.1 (rotamers), 172.0, 76.2, 75.0 and 74.9 (rotamers), 70.3, 60.2 and 59.3 (rotamers), 47.0 and 46.3 (rotamers), 34.6, 34.5, 34.0 and 33.8 (rotamers), 33.6 and 33.5 (rotamers), 32.7 and 32.7 (rotamers), 32.6 and 32.6 (rotamers), 31.9 and 31.6 (rotamers), 29.7, 29.6 (2C), 29.5, 29.4, 29.3, 29.2, 29.0 and 28.8 (rotamers), 28.4 and 28.3 (rotamers), 27.4 and 27.4 (rotamers), 25.5 and 25.5 (rotamers), 24.8 and 24.7 (rotamers), 22.7 and 22.7 (rotamers), 22.5 and 22.4 (rotamers), 14.1 and 14.0 (rotamers) ppm.
ESI-MS (*m/z*)	: 618.49 $[M+Na]^+$.
Elemental Analysis	: Calcd.: C, 70.55; H, 10.99; N, 2.35%. Found: C, 70.41; H, 11.17; N, 2.18%.

Penarolide Sulfate A_1 (1)

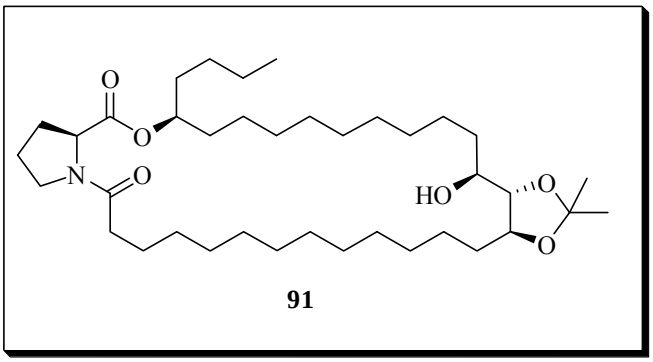


1

Sulfur trioxide/pyridine complex (296 mg, 1.86 mmol) was added to a solution of the triol **3** (37 mg, 0.06 mmol) in dry DMF (3 mL) under nitrogen and then stirred at room temperature for 36 h. Water (4 mL) was added and the reaction mixture was stirred for 30 min, then it was basified (pH 9) by adding saturated $NaHCO_3$ solution (6 mL). After stirring for 30 min, the resulting solution was concentrated in *vacuo.* The residue was triturated with ethyl acetate and filtered. The residue was purified on silica gel column by using methanol and ethyl acetate (3:7) to afford penarolide sulfate A_1 (**1**) (47 mg, 84%) as amorphous solid.

Mol. Formula	: $C_{35}H_{62}NNa_3O_{15}S_3$
$[\alpha]_D^{25}$	: –24.6 (*c* = 0.5, CH_3OH). [Lit. $[\alpha]_D^{25}$ –25.0 (*c* = 0.5, CH_3OH)].
IR (Nujol) υ	: 2927, 1734, 1636, 1248, 1184 cm^{-1}.
^{1}H NMR (400 MHz, CD_3OD)	: δ 5.04 (d, *J* = 6.0 Hz, 1H), 4.66 (d, *J* = 8.7 Hz, 1H), 4.63-4.61 (m, 1H), 4.40 (dd, *J* = 8.7, 4.5 Hz, 1H), 3.63 (t, *J* = 7.2 Hz, 2H), 2.43 (dt, *J* = 15.2, 7.2 Hz, 2H), 2.30-2.23 (m, 2H), 2.14-1.92 (m, 4H), 1.85-1.77 (m, 2H), 1.58-1.45 (m, 14H), 1.30 (m, 28H), 0.90 (t, *J* = 6.7 Hz, 3H) ppm.
^{13}C NMR (100 MHz, CD_3OD)	: δ 174.2, 173.8, 80.7, 79.4, 78.9, 76.2, 61.0, 35.2, 34.7, 30.9, 30.8, 30.6, 30.4, 28.5, 26.4, 26.0, 25.8, 23.4, 14.3 ppm.
ESI-MS (*m/z*)	: 924.69 $[M+Na]^+$.

(3a*S*,4*S*,14*S*,16a*S*,33a*S*)-14-Butyl-4-hydroxy-2,2-dimethylhexacosahydro-3aH-[1,3]dioxolo[4,5-γ]pyrrolo[2,1-c][1,4]oxaazacyclotriacontine-16,21(4H,22H)-dione (91)



91

To a stirred solution of compound **90** (94 mg, 0.13 mmol) in THF (3 mL), TBAF (0.19 mL) (1.0 M in THF) was added dropwise. The reaction mixture was then stirred for 1 h, by which time the reaction was complete (as monitored by TLC). The reaction was then quenched by the addition of water and the reaction mixture was concentrated under reduced pressure. The crude mass was taken up in water and extracted with ethyl acetate (3x 10 mL), washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude residue was then purified by silica gel column chromatography eluting with light petroleum and ethyl acetate (3:2) to furnish compound **91** (75 mg, 94%) as a light yellow oil.

Mol. Formula	: $C_{38}H_{69}NO_6$
$[\alpha]_D^{25}$	: –25.5 (*c* = 0.3, $CHCl_3$).
IR ($CHCl_3$) υ	: 3205, 2854, 1735, 1638, 1404, 1246 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$)	: δ 4.91-4.85 (m, 1H), 4.50 (dd, *J* = 8.7, 3.3 Hz, 1H), 4.03-4.00 (m, 2H), 3.82 (m, 1H), 3.73-3.67 (m, 1H), 3.64-3.50 (m, 2H), 2.32-2.13 (m, 4H), 2.06-1.91 (m, 4H), 1.67-1.61 (m, 4H), 1.52-1.43 (m, 8H), 1.40 (s, 3H), 1.39 (s, 3H), 1.26 (m, 32H), 0.89 (t, *J* = 6.7 Hz, 3H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	: δ 172.0 and 171.9 (rotamers), 171.7, 108.0, 82.9 and 82.8 (rotamers), 76.0 and 75.4 (rotamers), 75.2 and 74.8 (rotamers), 70.2 and 70.0 (rotamers), 60.2 and 59.3 (rotamers), 47.0 and 46.3 (rotamers), 34.6 and 34.5 (rotamers), 34.0, 33.8 and 33.7 (rotamers), 33.6, 32.1, 32.0, 31.7, 29.7, 29.5, 29.4, 29.3 (2C),

29.1 and 29.0 (rotamers), 28.8 and 28.7 (rotamers), 28.6, 27.5 (2C), 27.4 (2C), 27.1, 25.9 and 25.8 (rotamers), 25.4, 25.3, 25.2, 24.9 and 24.8 (rotamers), 22.7 and 22.6 (rotamers), 22.6 and 22.5 (rotamers), 14.2 and 14.1 (rotamers) ppm.

ESI-MS (*m/z*) : 658.57 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 71.77; H, 10.94; N, 2.20%.
Found: C, 71.64; H, 11.03; N, 2.37%.

General procedure for enzyme inhibition assay

Inhibition assay for the inhibitory potencies of the desulfated penarolide sulfate A_1(**3**) was determined by measuring the residual hydrolytic activities of the glycosidases of the corresponding *p*-nitrophenyl glycosides in the presence of desulfated penarolide sulfate A_1(**3**) spectrophotometrically.

In the case of α-glucosidase (Yeast), the assay was performed in a citrate phosphate buffer (50 mM, pH 6.8) with *p*-nitrophenyl α-D-glucopyranoside as the substrate. The enzyme was incubated with the inhibitor at various concentrations for 30 min then the substrate was added and the reaction was carried out at 37 °C for 30 min and then quenched by Na_2CO_3 solution.

In the case of β-glucosidase (Almond), the assay was performed in a citrate phosphate buffer (50 mM, pH 5.5) with *p*-nitrophenyl β-D-glucopyranoside as the substrate. The reaction was carried out at 37 °C for 30 min and then quenched by Na_2CO_3 solution.

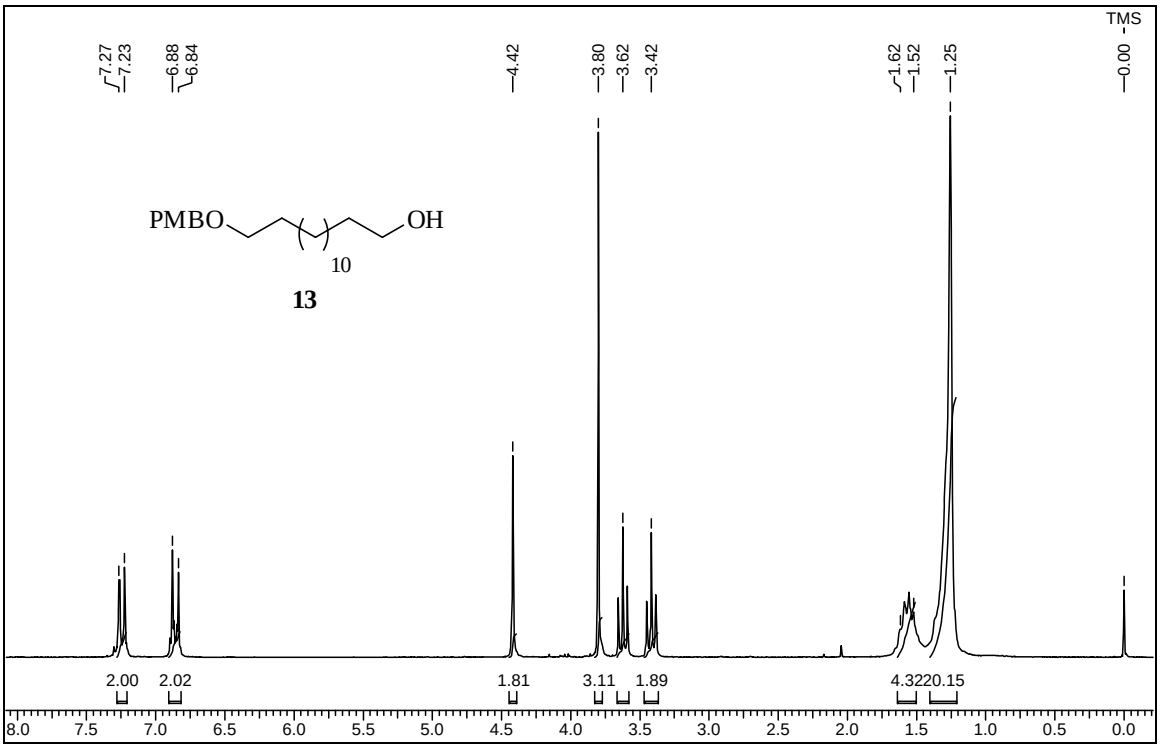
In the case of α-galactosidase (Green coffee beans), the assay was performed in an citrate phosphate buffer (50 mM, pH 6.5) with *p*-nitrophenyl α-D-galactopyranoside as the substrate and the reaction was carried out at 25 °C for 20 min and then quenched by Na_2CO_3 solution.

In the case of β-galactosidase, each assay was performed in citrate buffer (50 mM, pH 4.5) with *p*-nitrophenyl β-D-galactosidase as the substrate and the reaction was carried out at 25 °C for 20 min and then quenched by Na_2CO_3 solution.

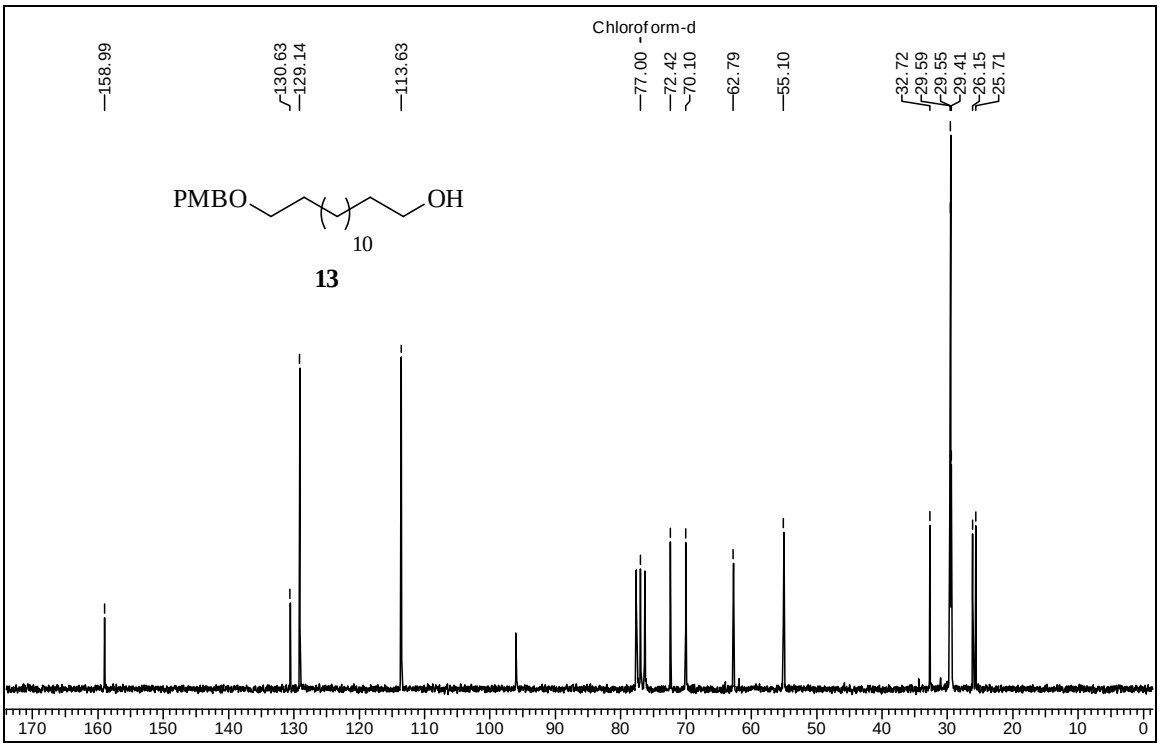
In the case of α-mannosidae (Jack Bean), the assay was performed in an acetate buffer (50 mM, pH 4.5) with *p*-nitrophenyl α-D-mannopyranoside as the substrate and the reaction was carried out at 25 °C for 20 min and then quenched by Na_2CO_3 solution.

In the case of β-mannosidase (Snail acetone), the assay was performed in an acetate buffer (50 mM, pH 4.0) with *p*-nitrophenyl β-D-mannopyranoside as the substrate and the reaction was carried out at 25 °C for 20 min and then quenched by Na_2CO_3 solution.

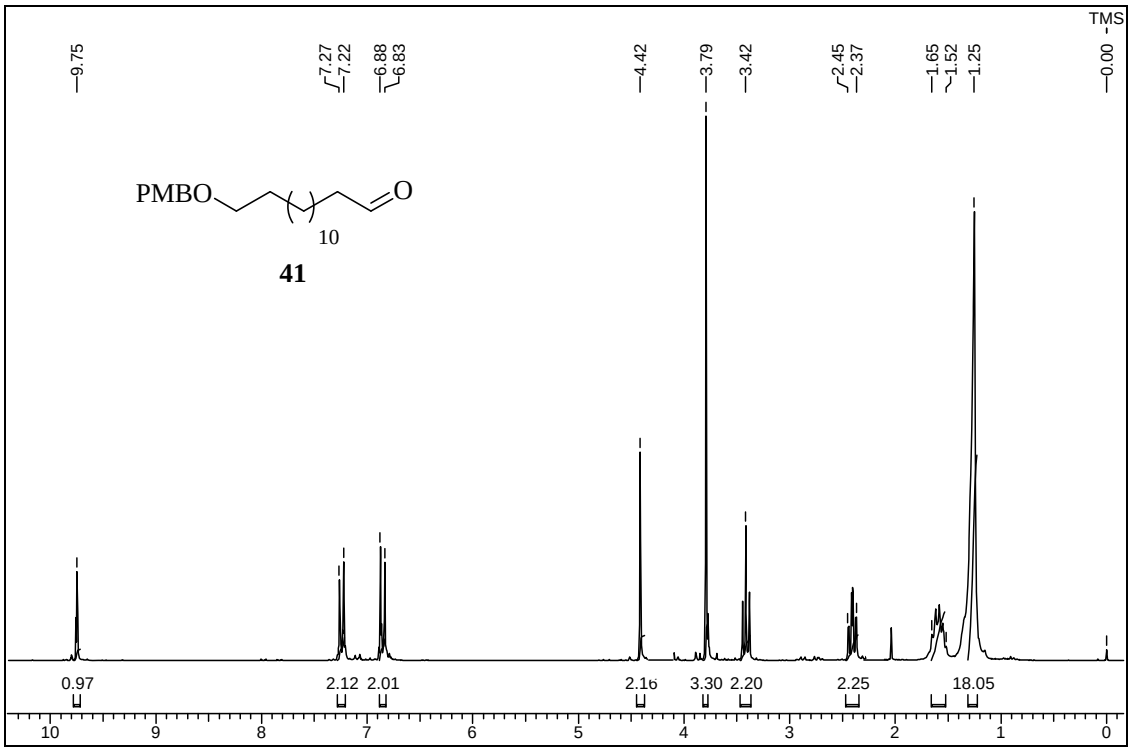
SPECTRA



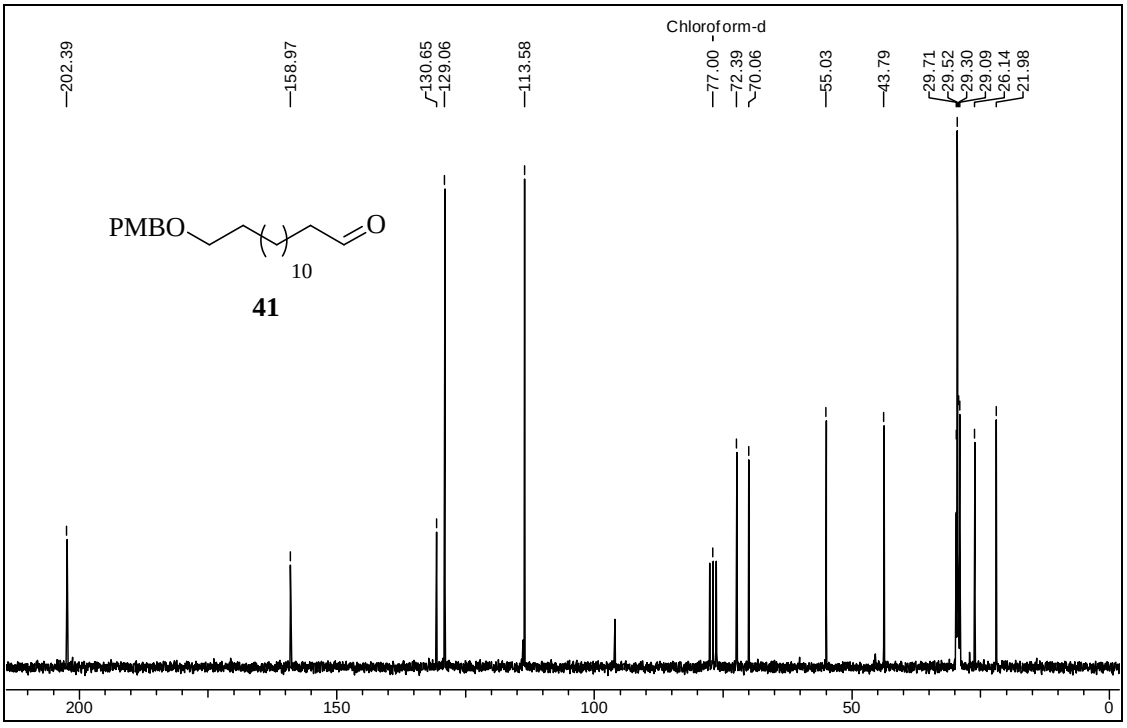
^{1}H NMR spectrum of compound 13 in $CDCl_3$



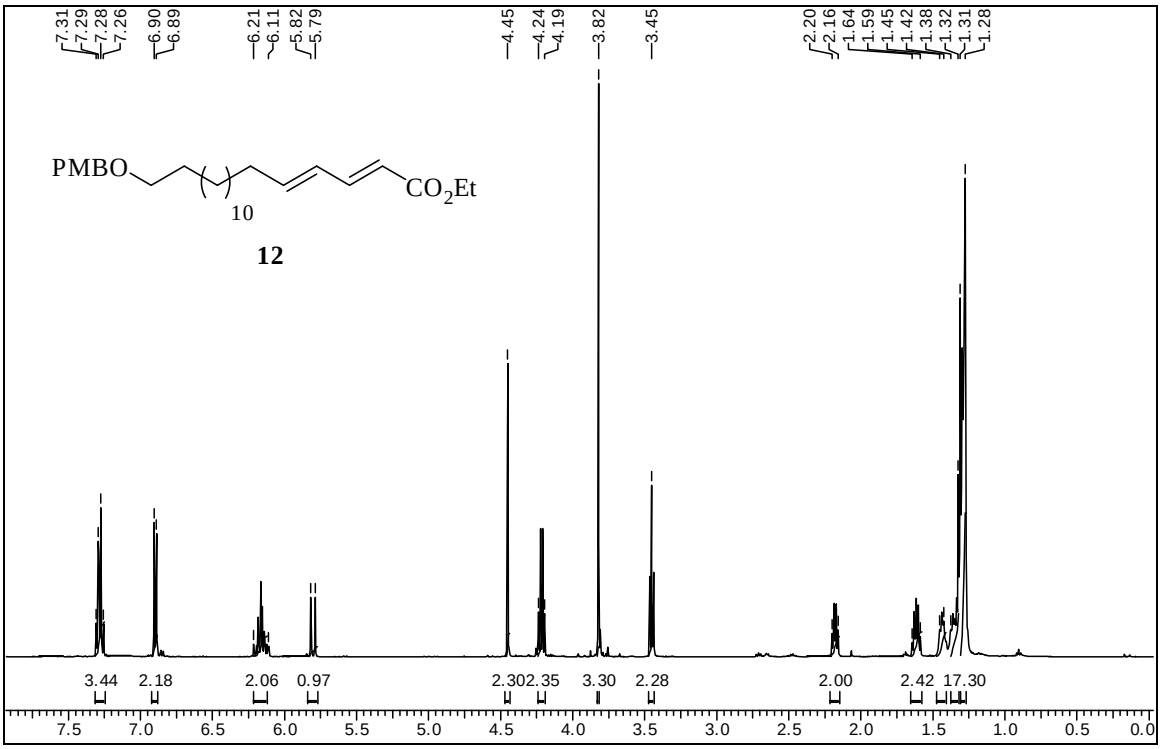
^{13}C NMR spectrum of compound 13 in $CDCl_3$



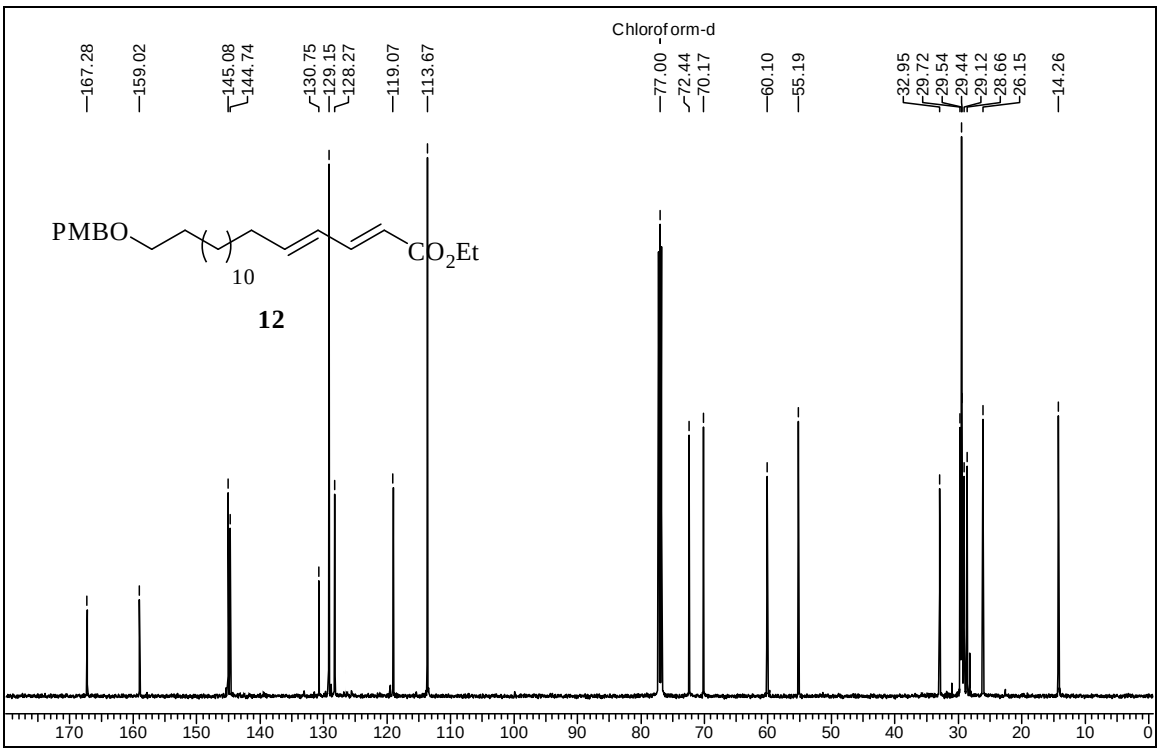
^{1}H NMR spectrum of compound 41 in $CDCl_3$



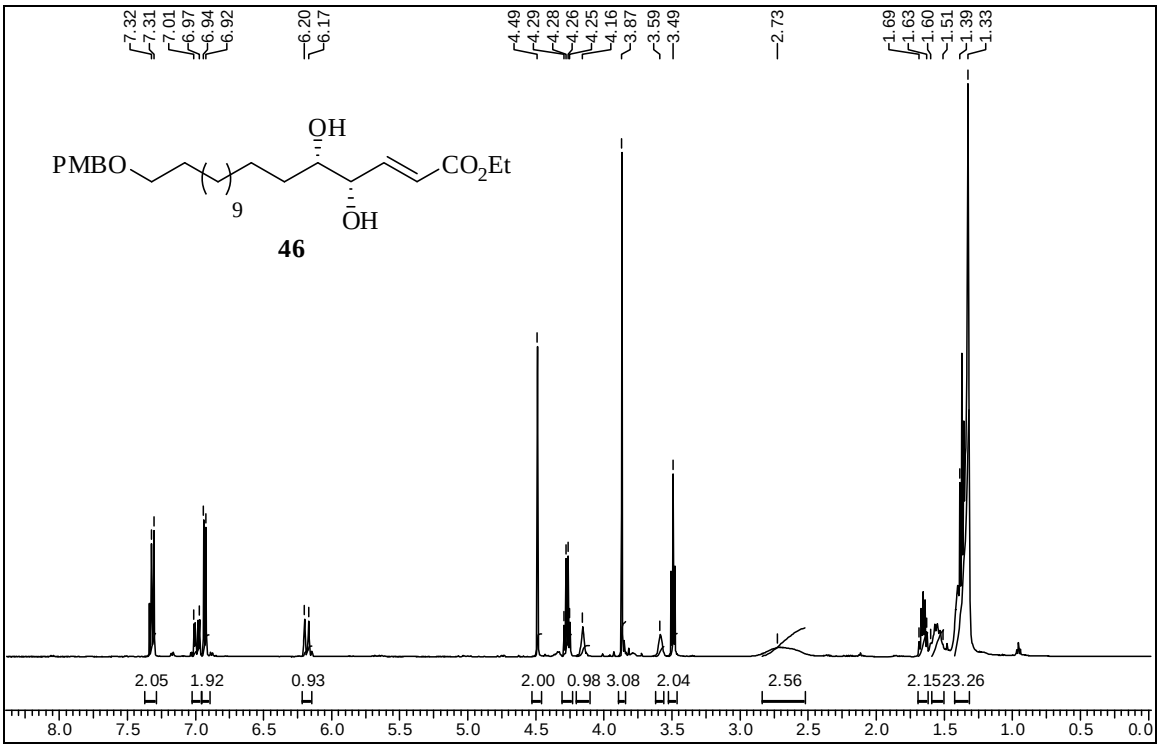
^{13}C NMR spectrum of compound 41 in $CDCl_3$



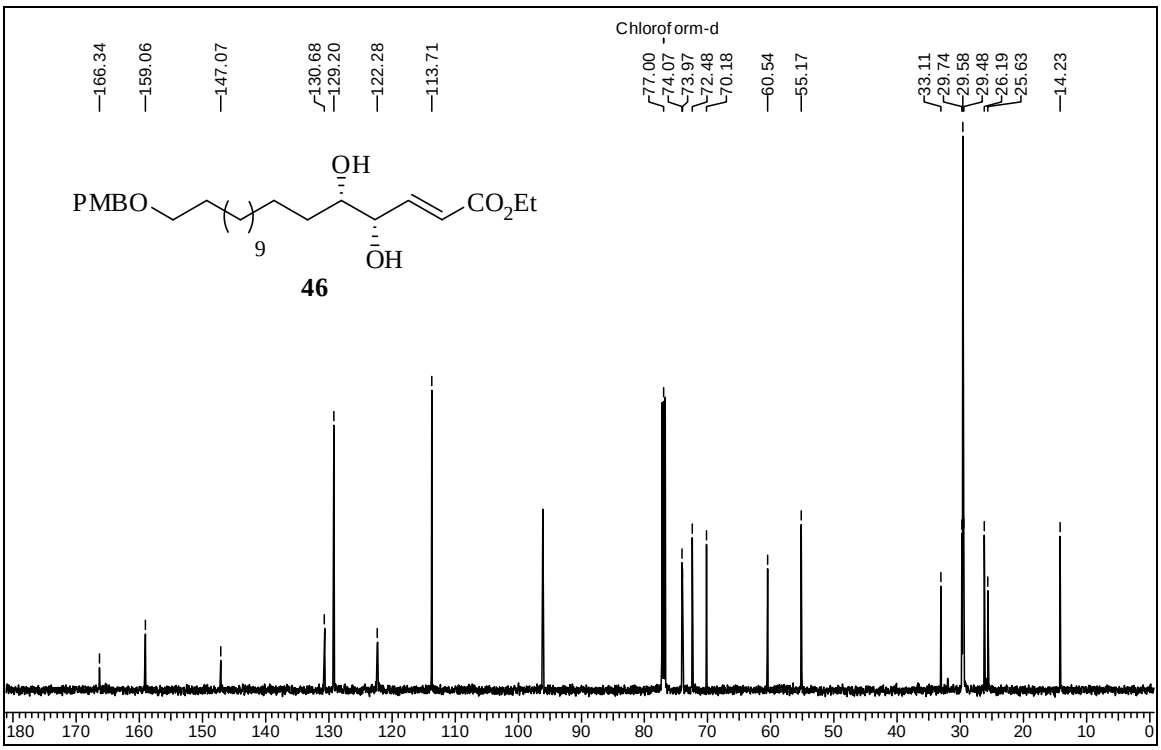
^{1}H NMR spectrum of compound 12 in $CDCl_3$



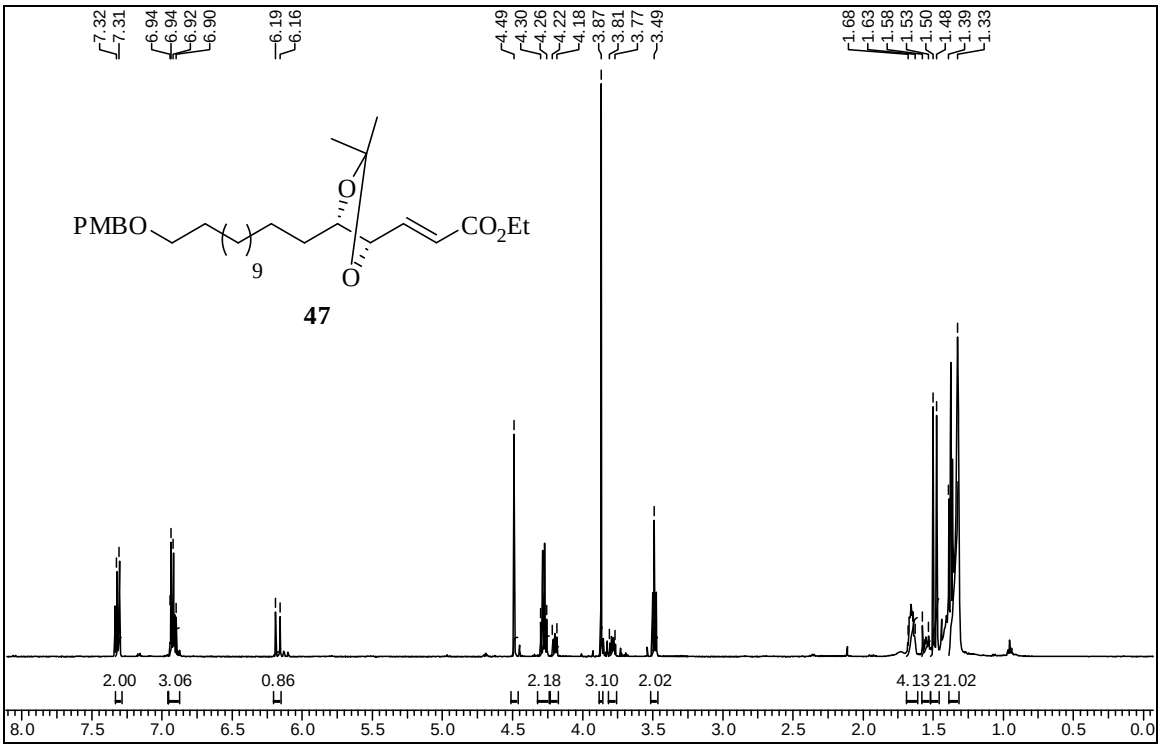
^{13}C NMR spectrum of compound 12 in $CDCl_3$



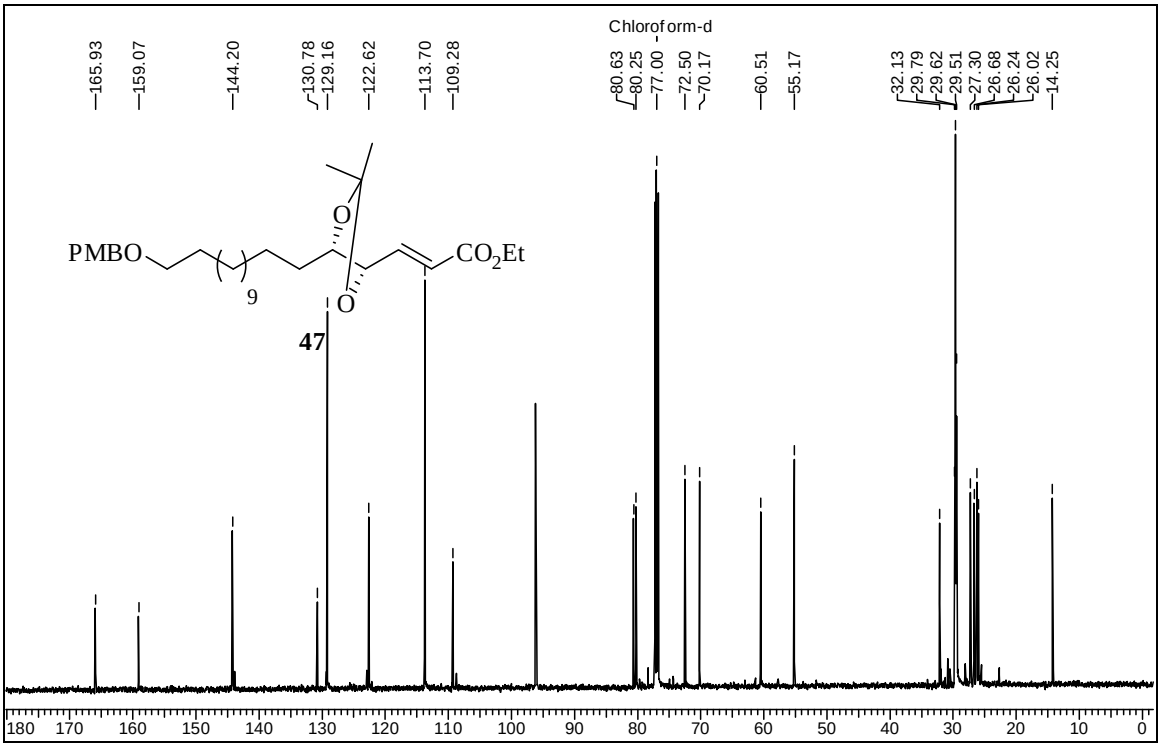
^{1}H NMR spectrum of compound 46 in $CDCl_3$



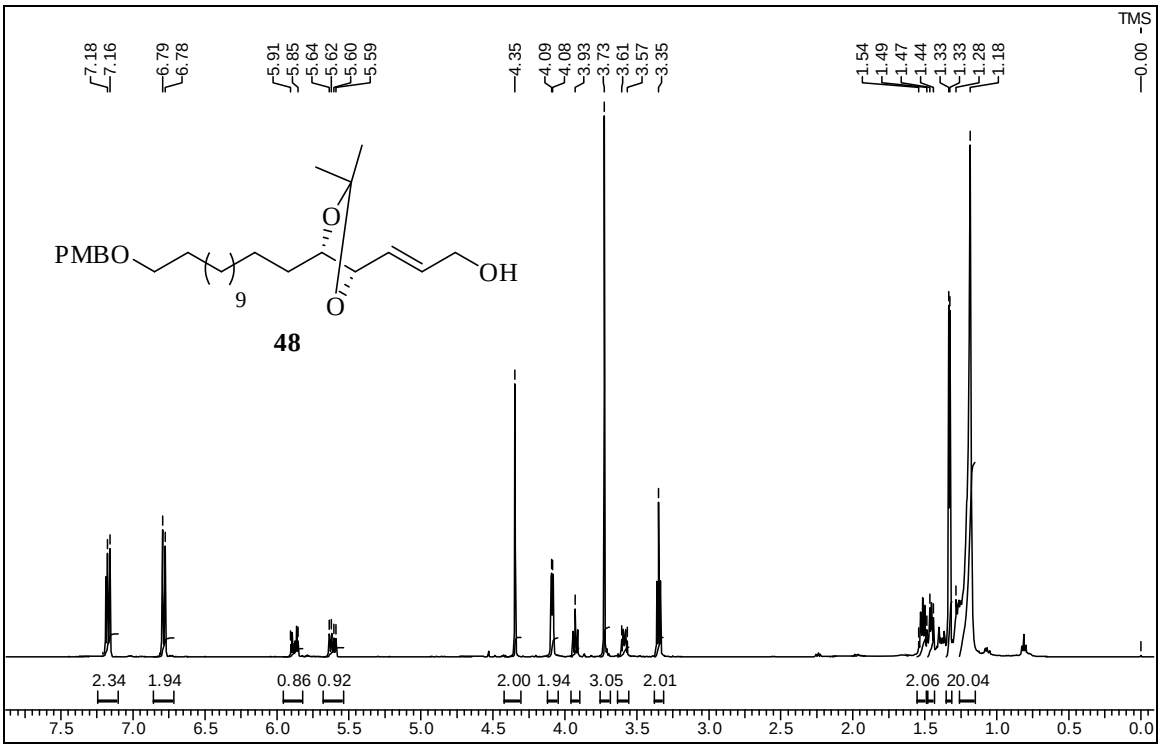
^{13}C NMR spectrum of compound 46 in $CDCl_3$



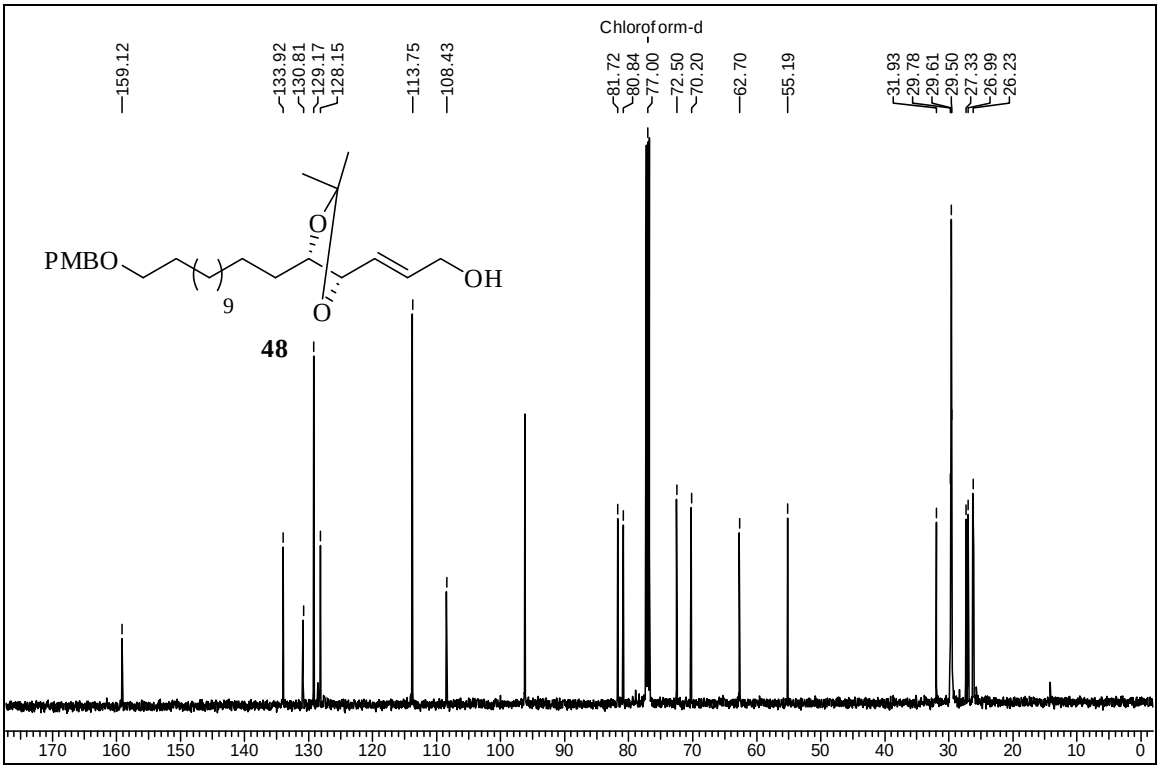
^{1}H NMR spectrum of compound 47 in $CDCl_3$



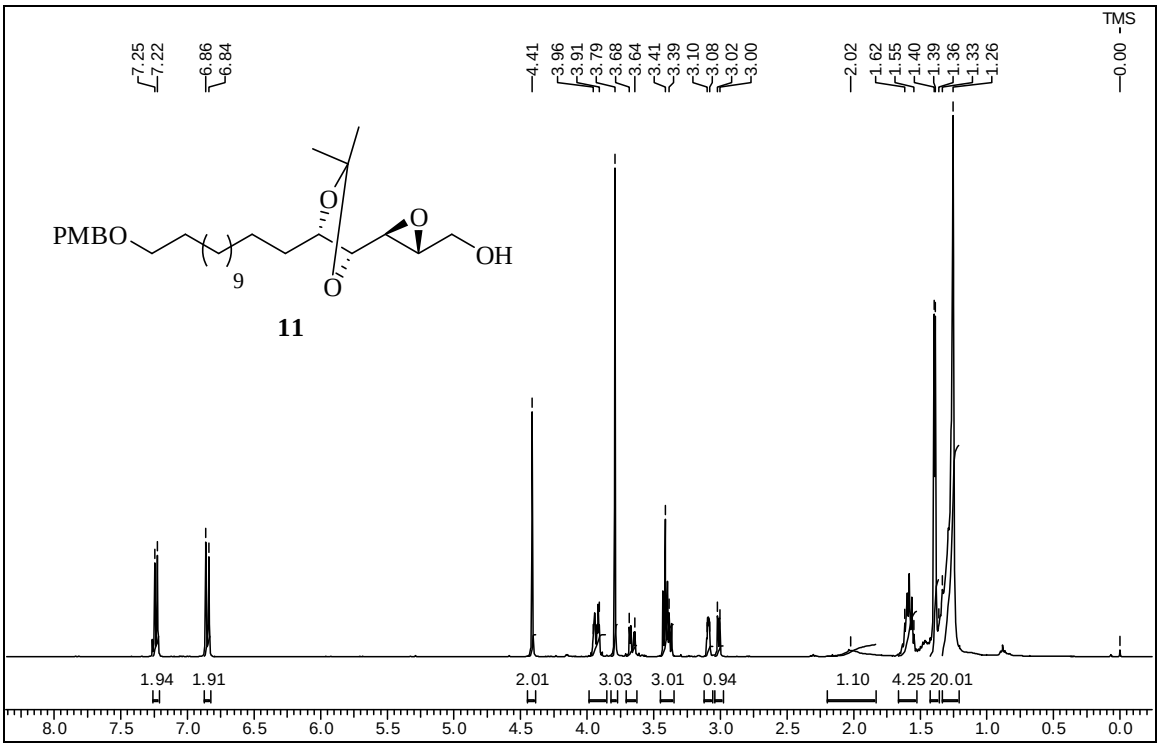
^{13}C NMR spectrum of compound 47 in $CDCl_3$



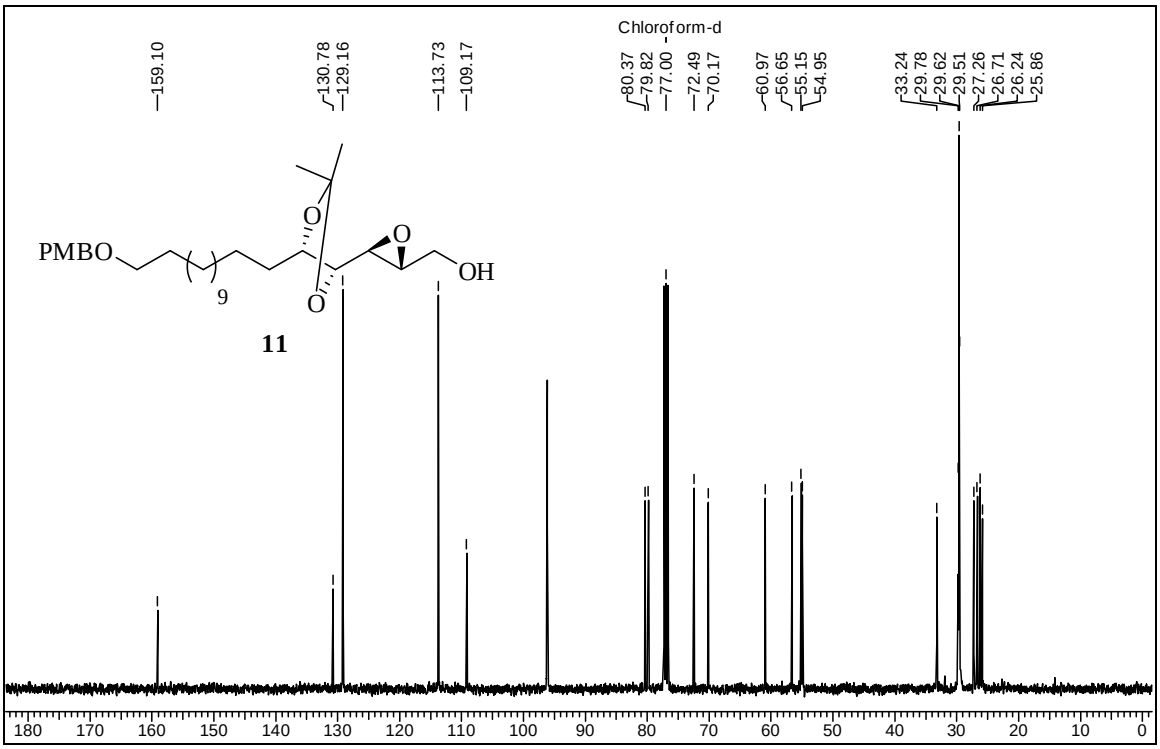
^{1}H NMR spectrum of compound 48 in $CDCl_3$



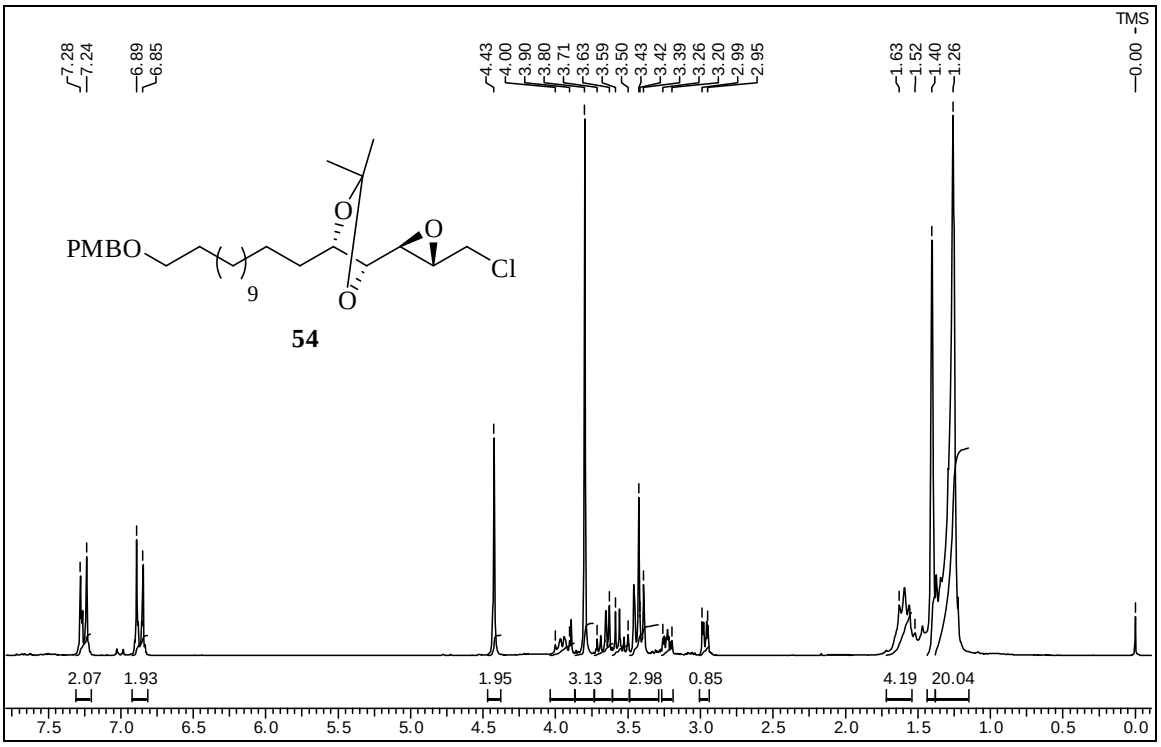
^{13}C NMR spectrum of compound 48 in $CDCl_3$



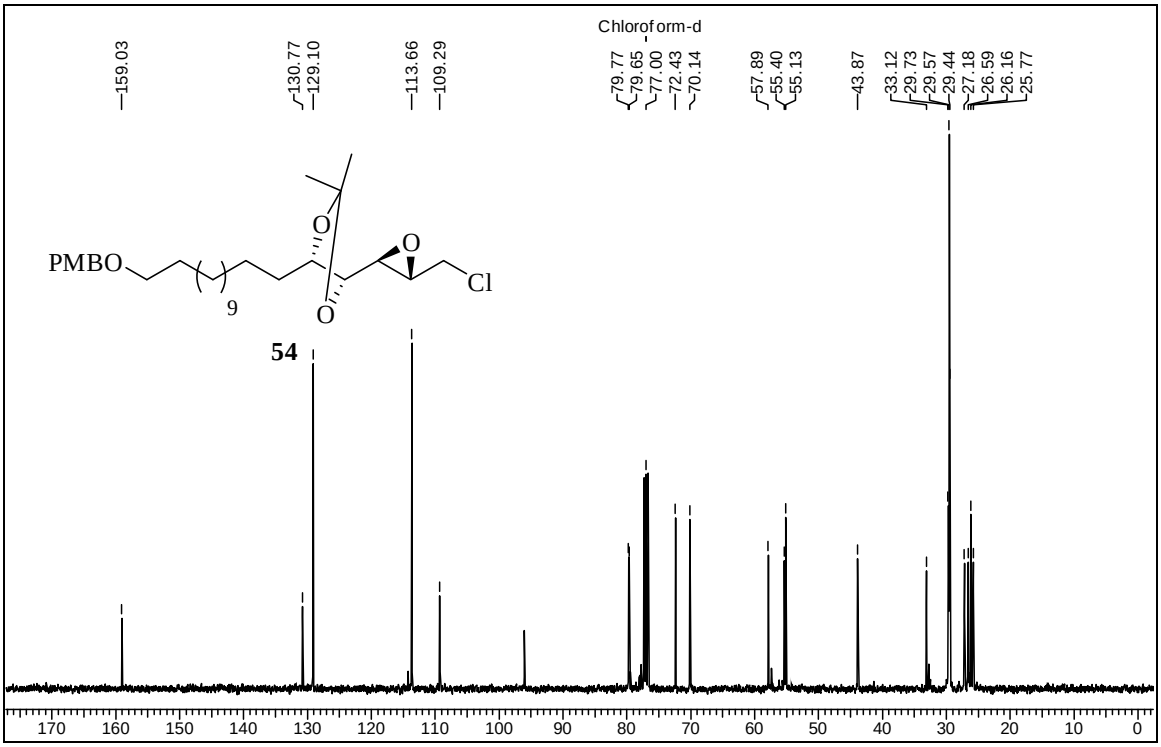
^{1}H NMR spectrum of compound 11 in $CDCl_3$



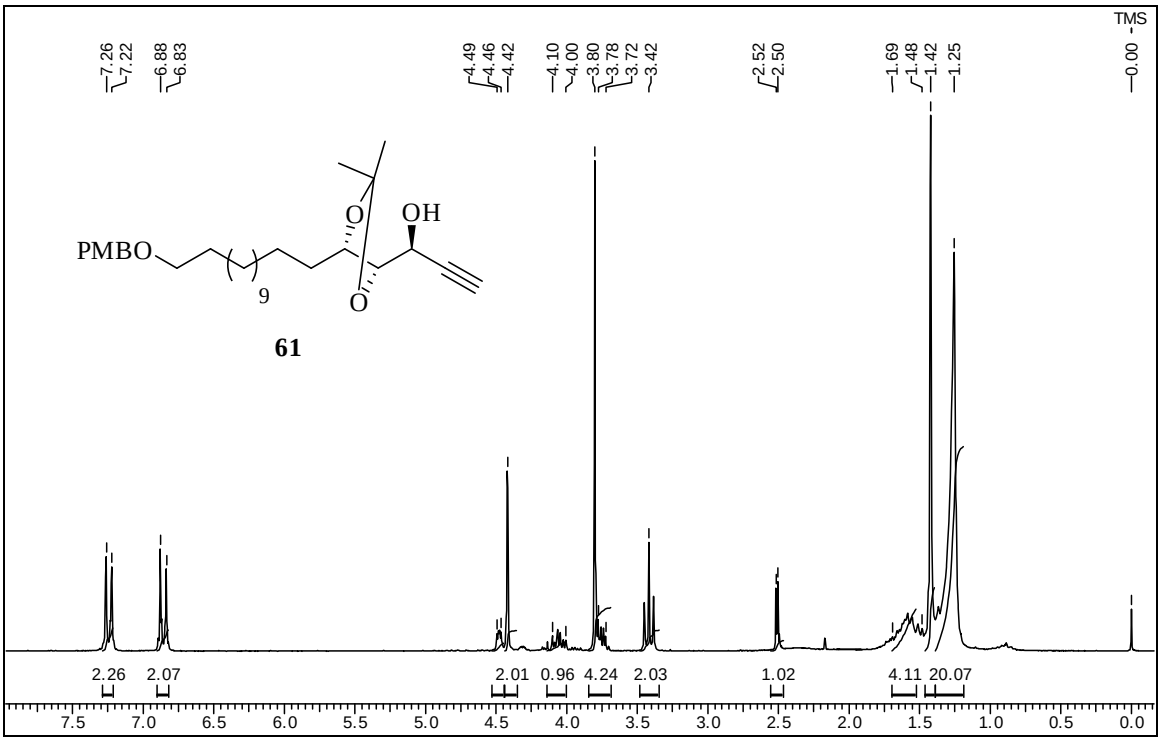
^{13}C NMR spectrum of compound 11 in $CDCl_3$



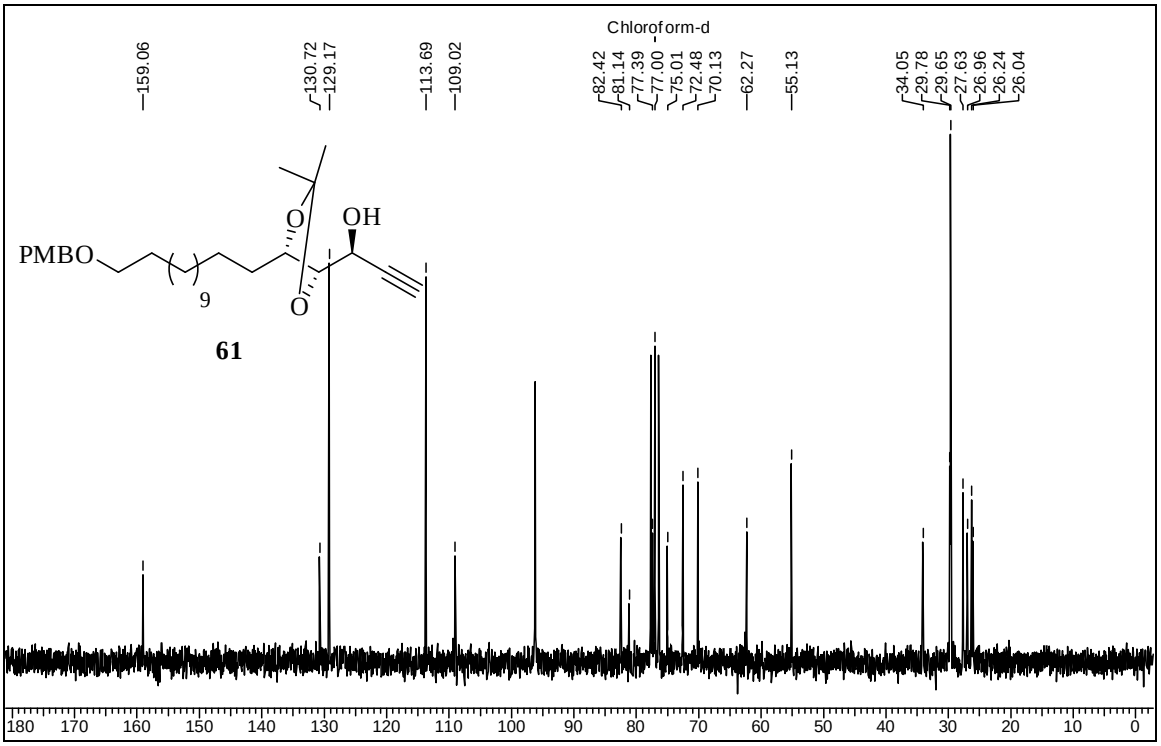
^{1}H NMR spectrum of compound 54 in $CDCl_3$



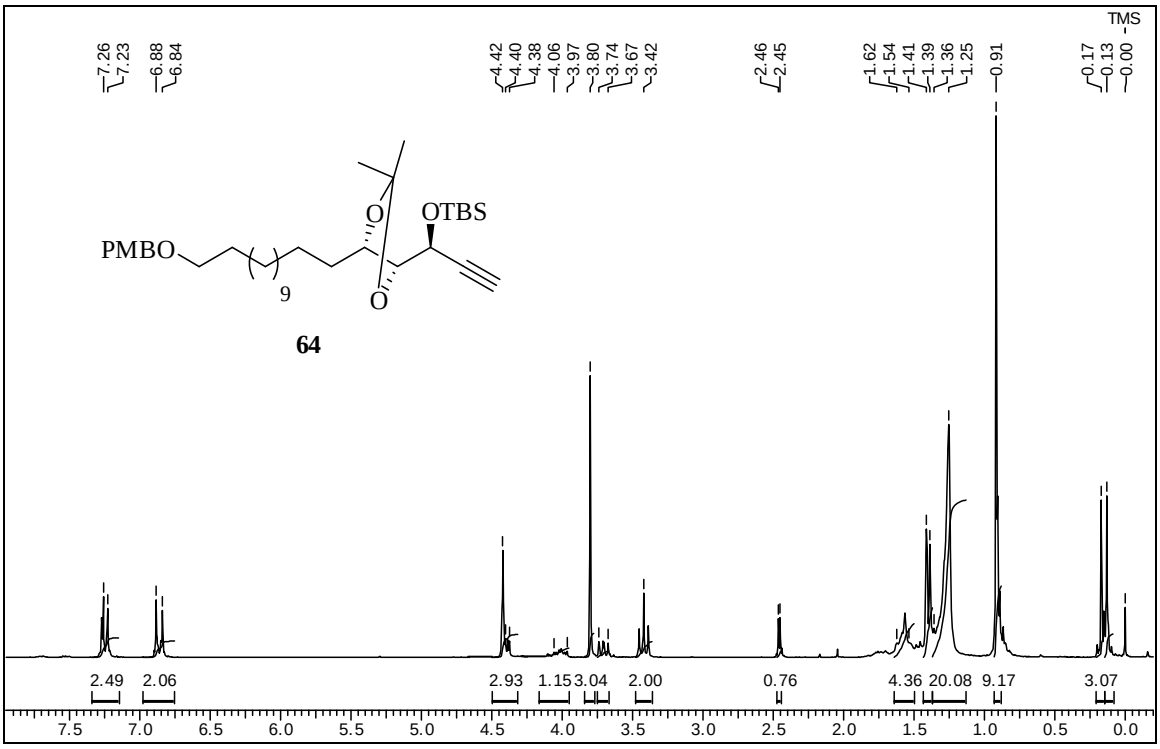
^{13}C NMR spectrum of compound 54 in $CDCl_3$



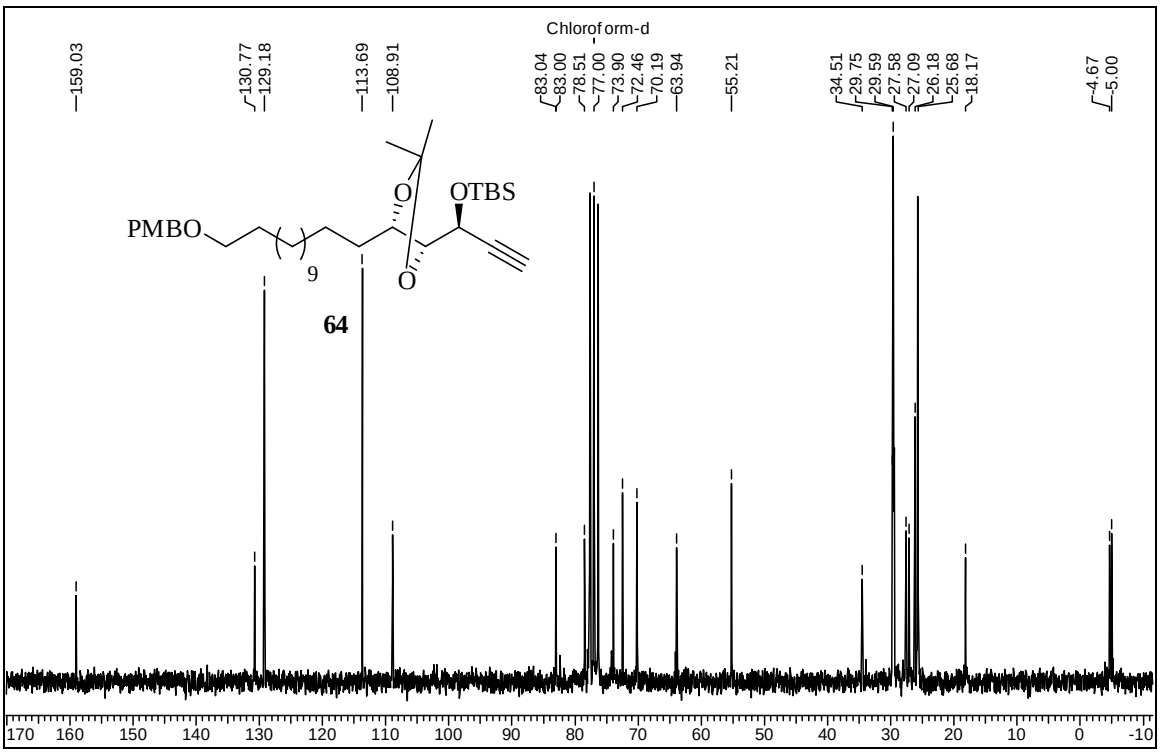
^{1}H NMR spectrum of compound 61 in $CDCl_3$



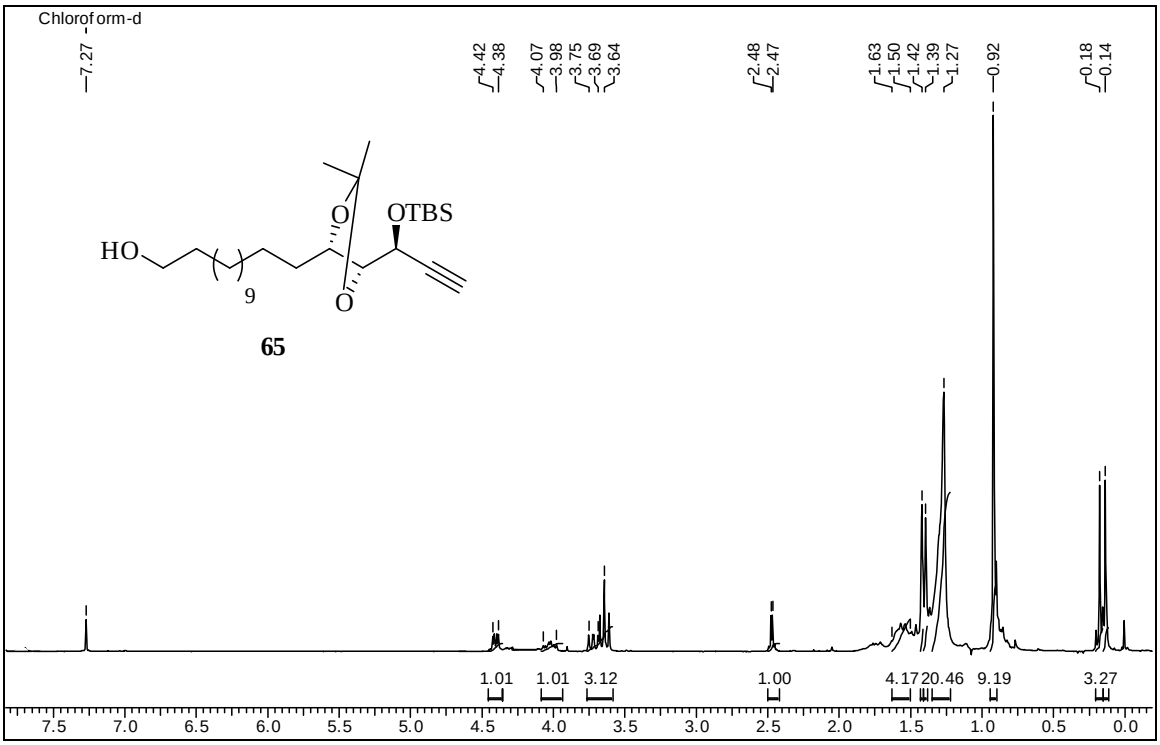
^{13}C NMR spectrum of compound 61 in $CDCl_3$



^{1}H NMR spectrum of compound 64 in $CDCl_3$

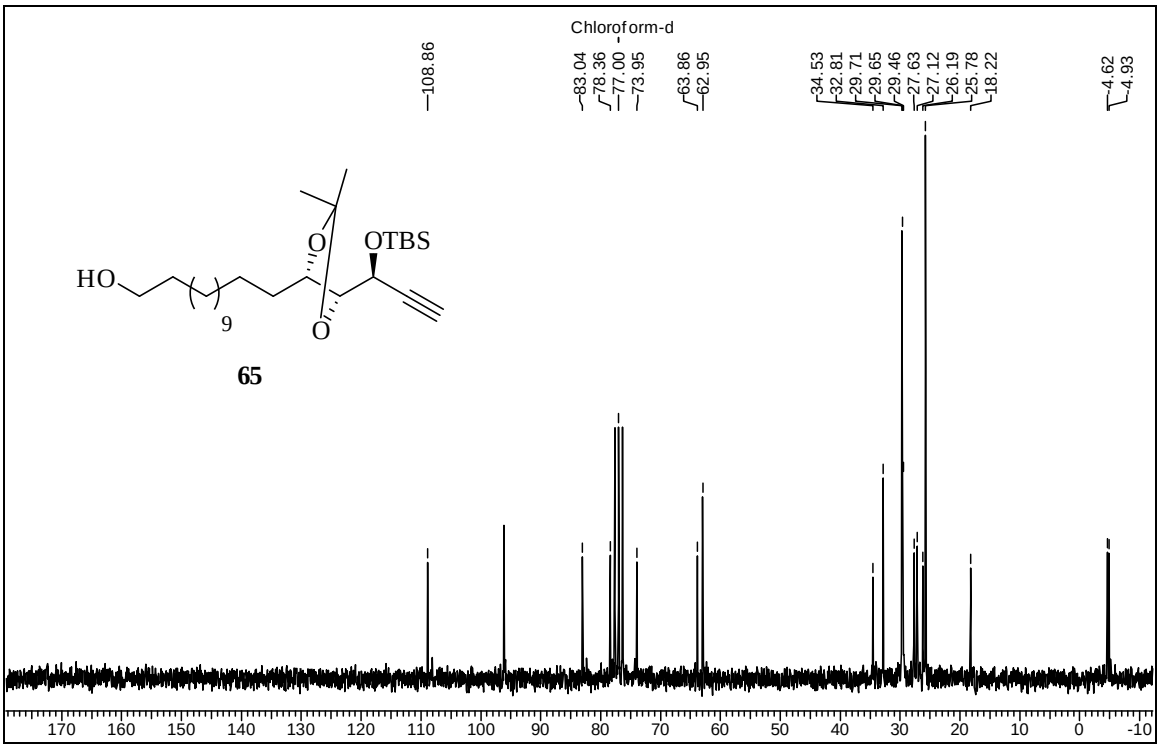


^{13}C NMR spectrum of compound 64 in $CDCl_3$



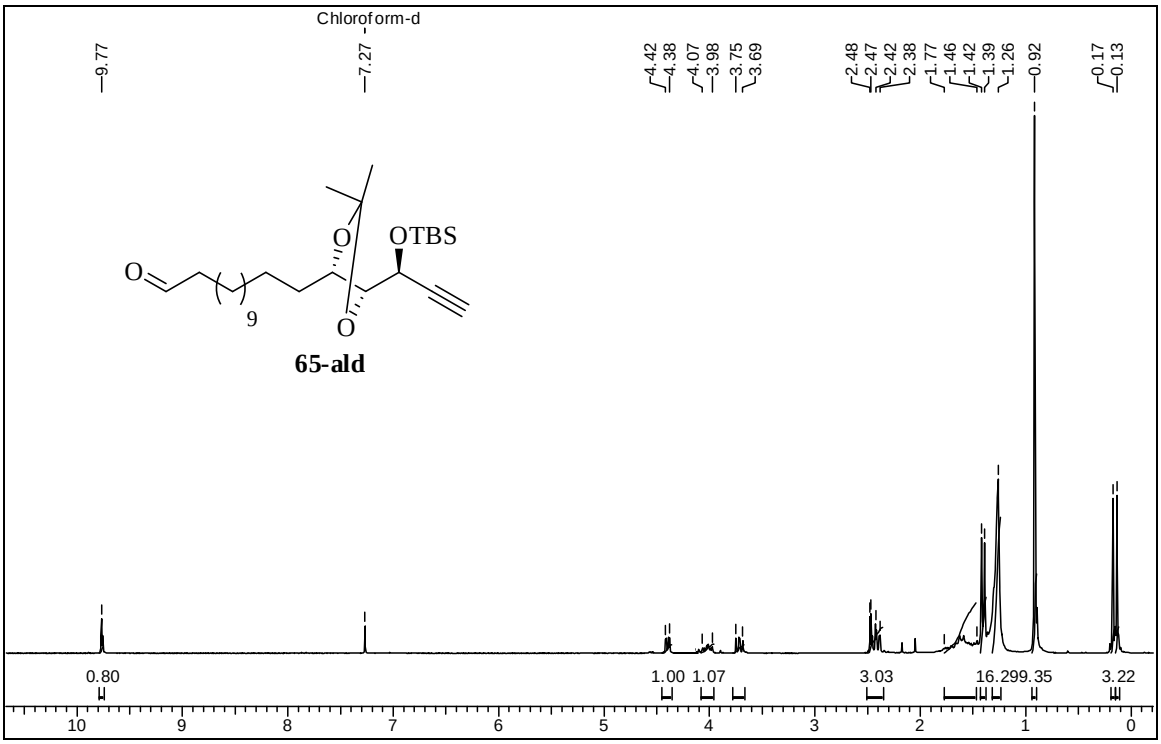
65

^{1}H NMR spectrum of compound 65 in $CDCl_3$

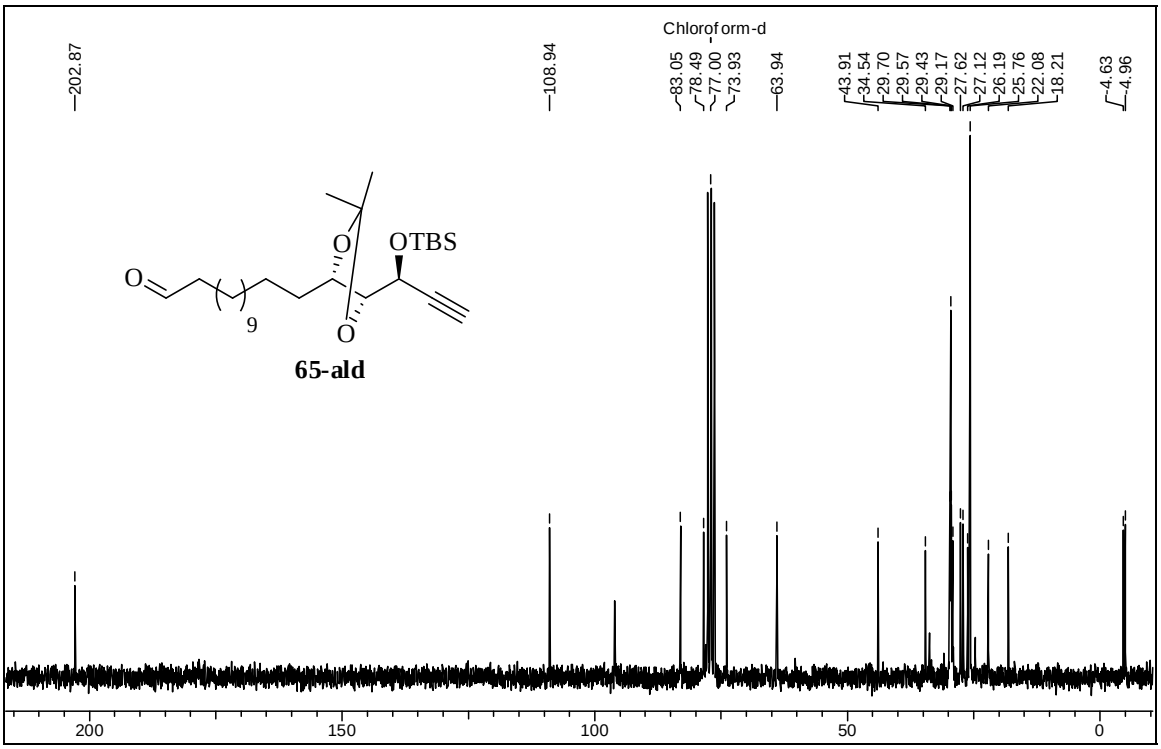


65

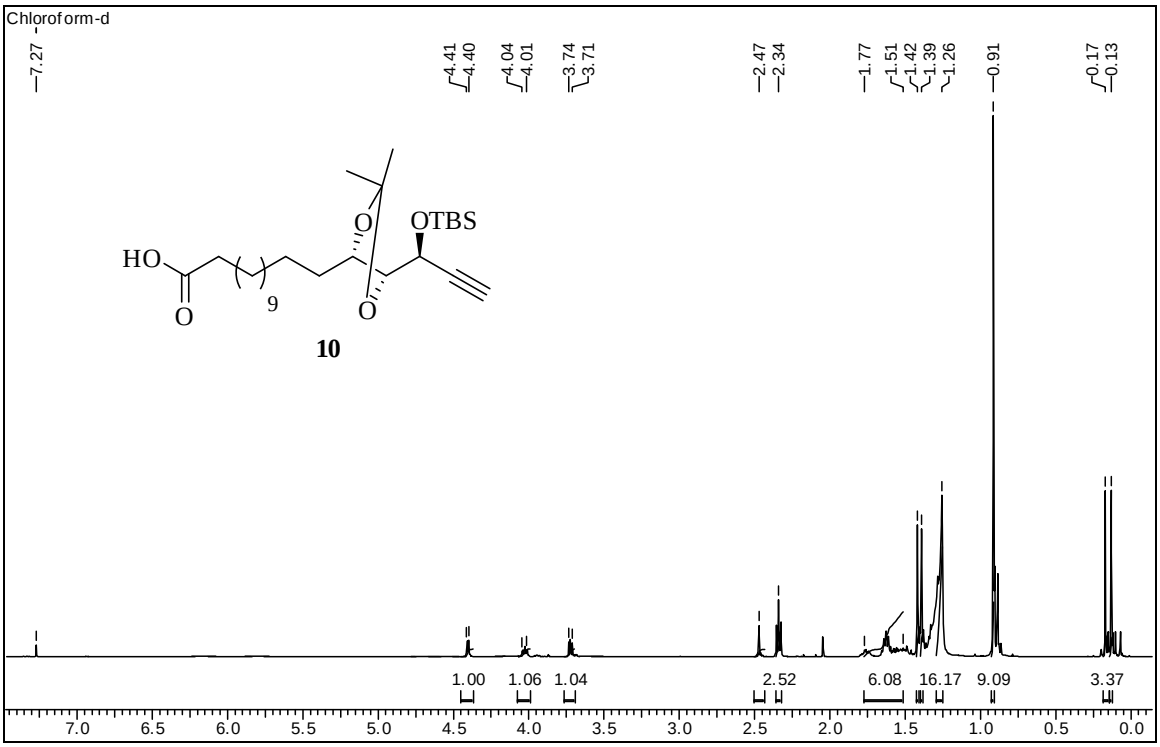
^{13}C NMR spectrum of compound 65 in $CDCl_3$



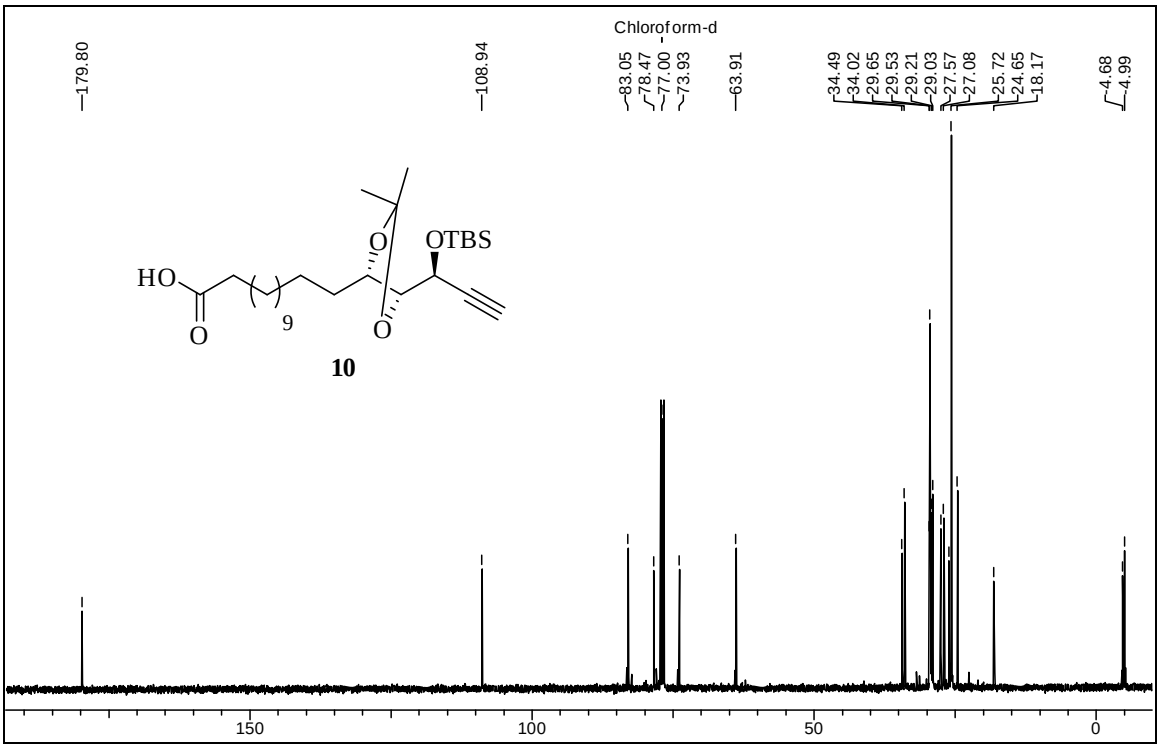
^{1}H NMR spectrum of compound 65-ald in $CDCl_3$



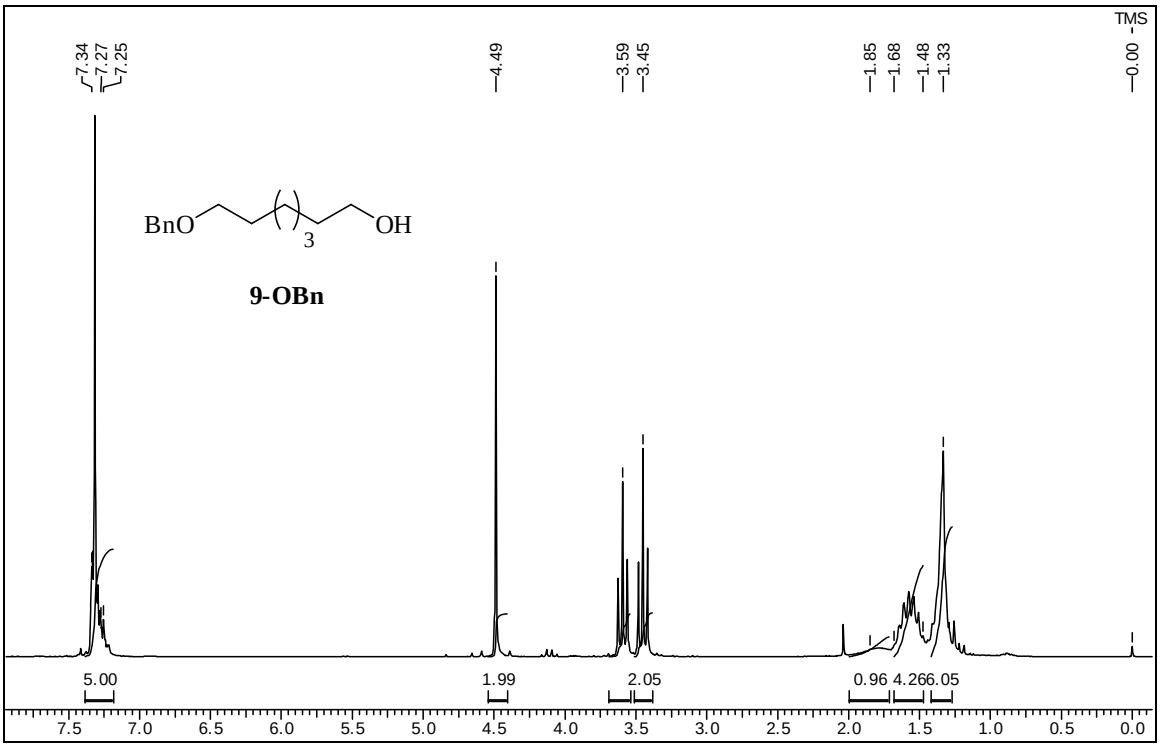
^{13}C NMR spectrum of compound 65-ald in $CDCl_3$



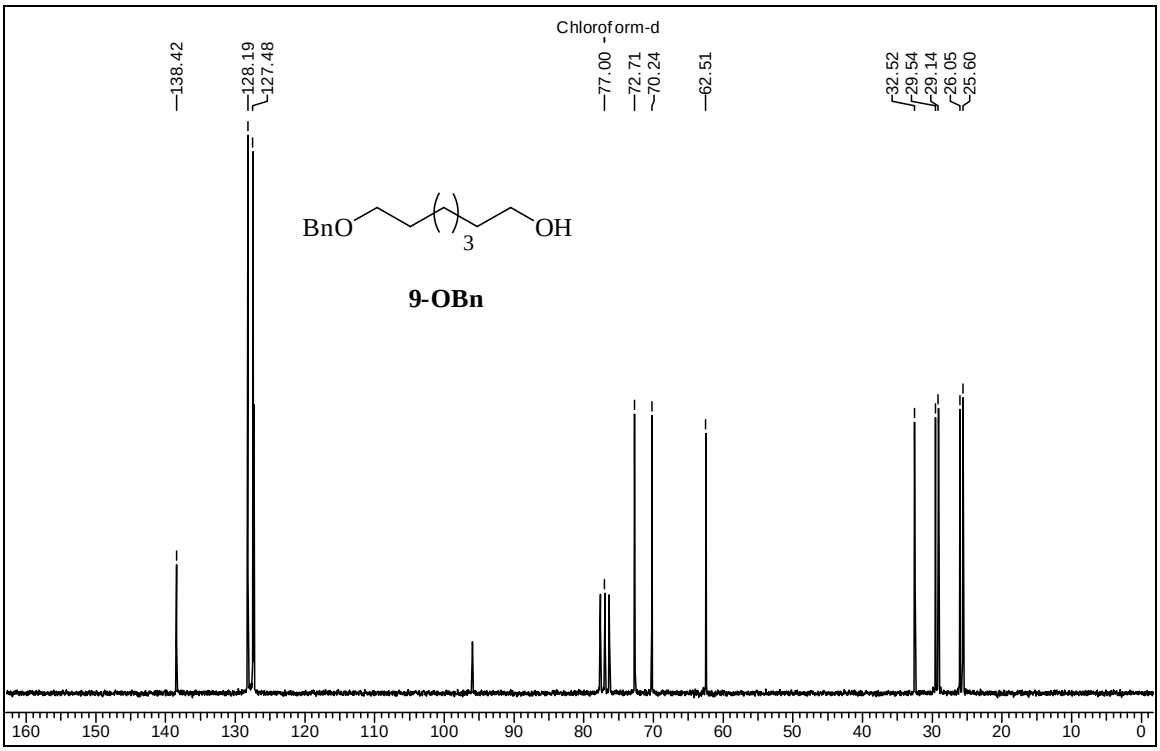
^{1}H NMR spectrum of compound 10 in $CDCl_3$



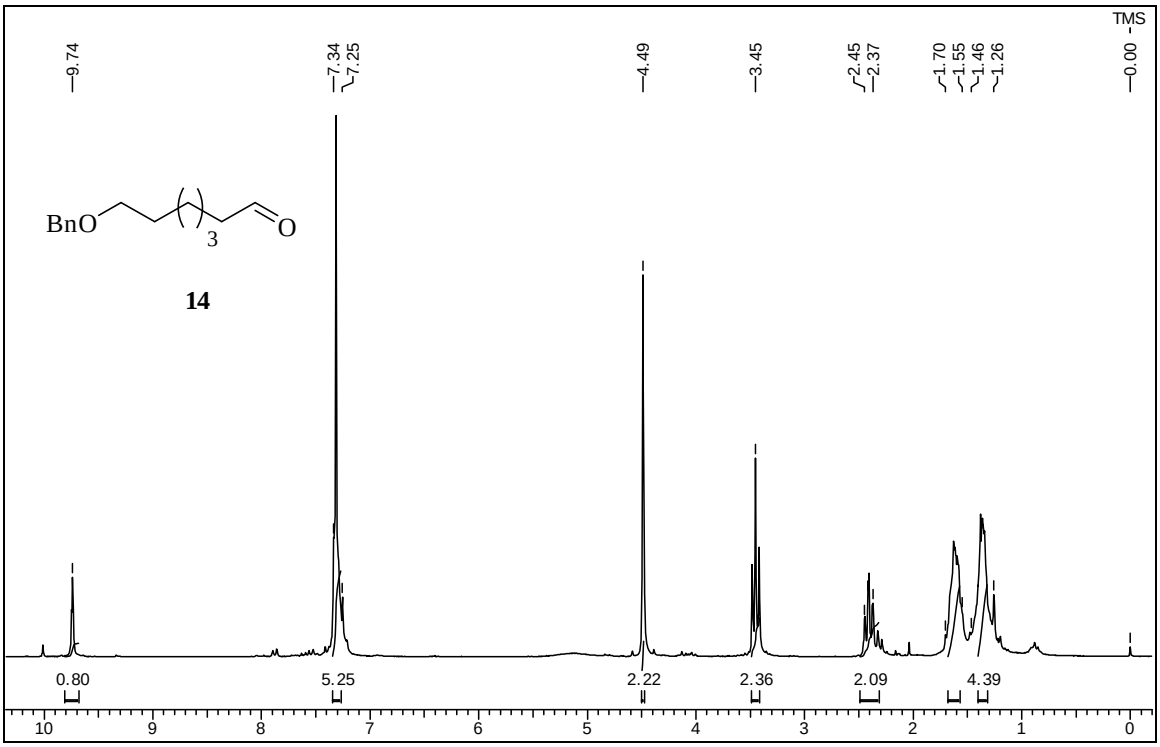
^{13}C NMR spectrum of compound 10 in $CDCl_3$



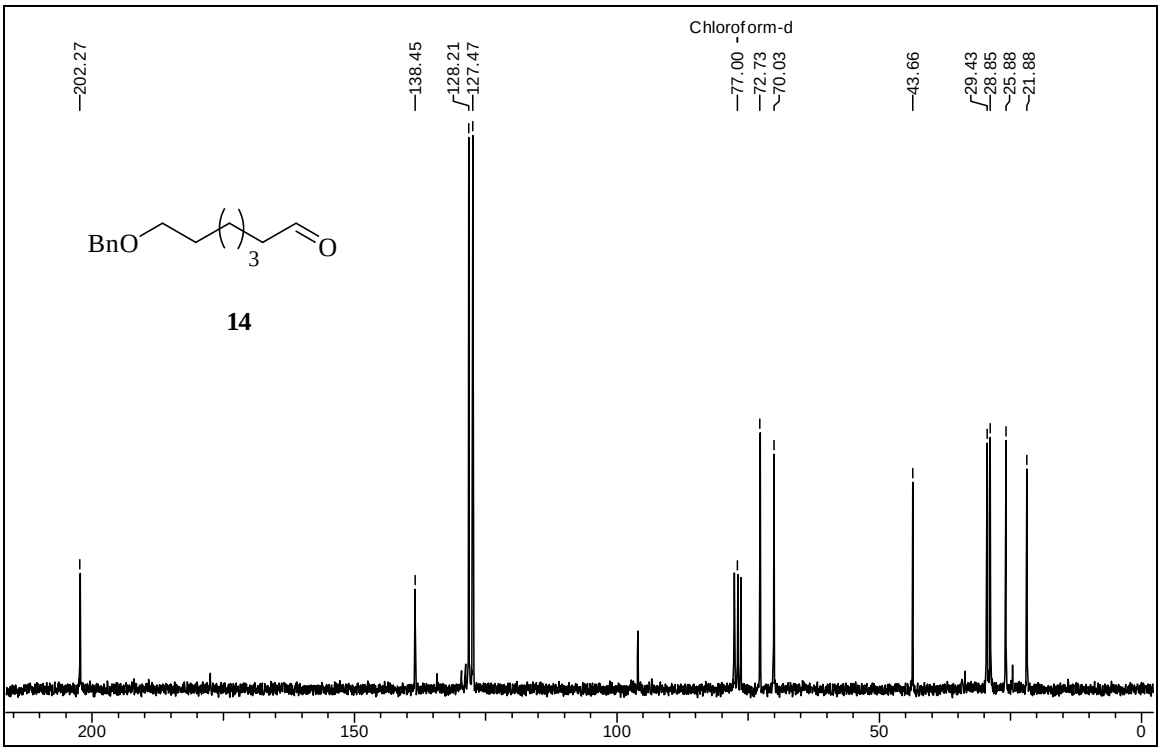
^{1}H NMR spectrum of compound 9-OBn in $CDCl_3$



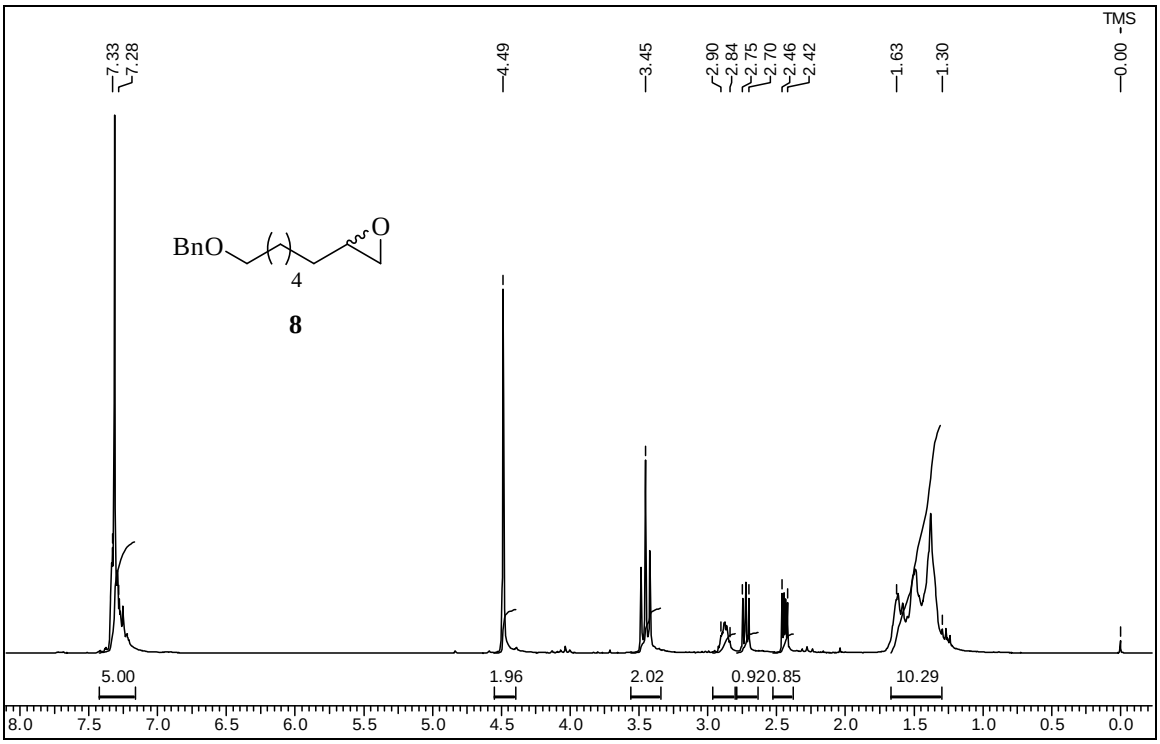
^{13}C NMR spectrum of compound 9-OBn in $CDCl_3$



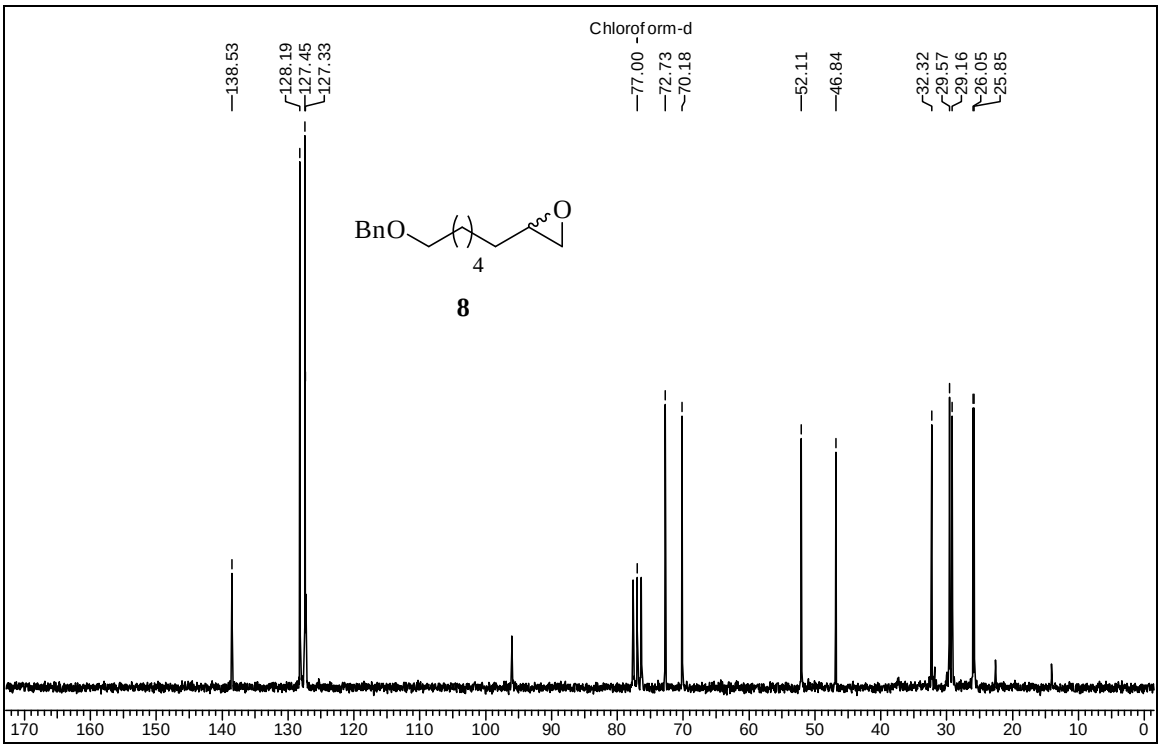
^{1}H NMR spectrum of compound 14 in $CDCl_3$



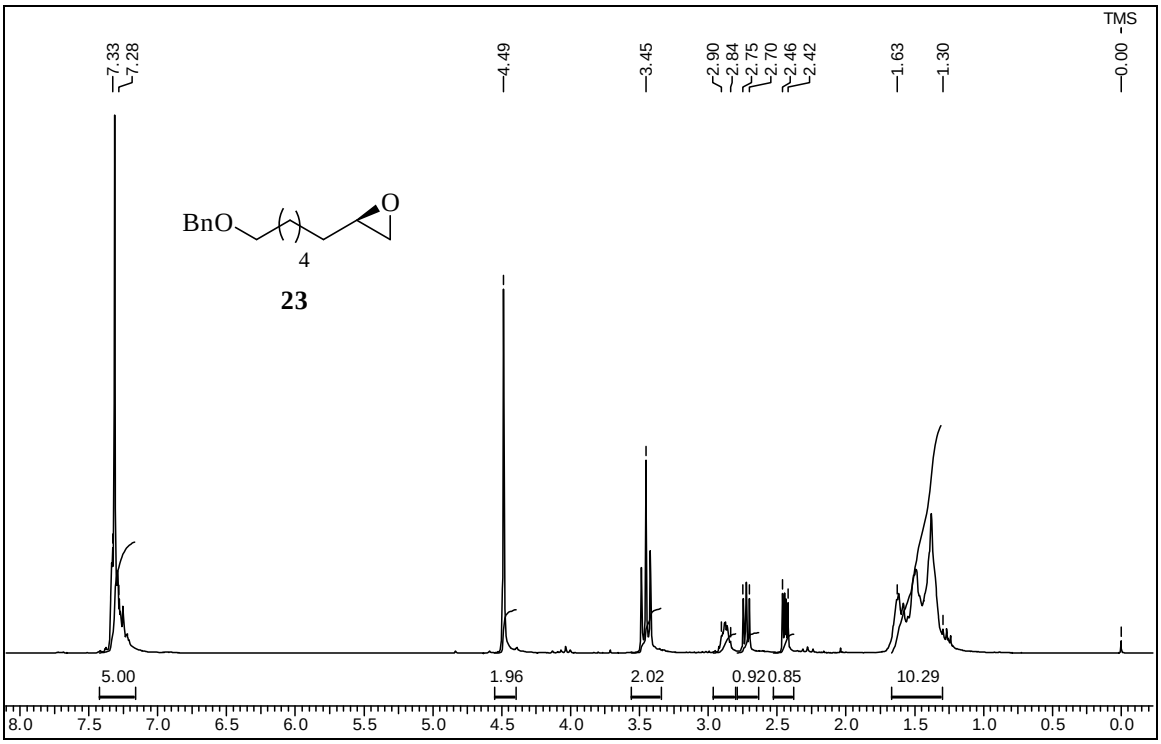
^{13}C NMR spectrum of compound 14 in $CDCl_3$



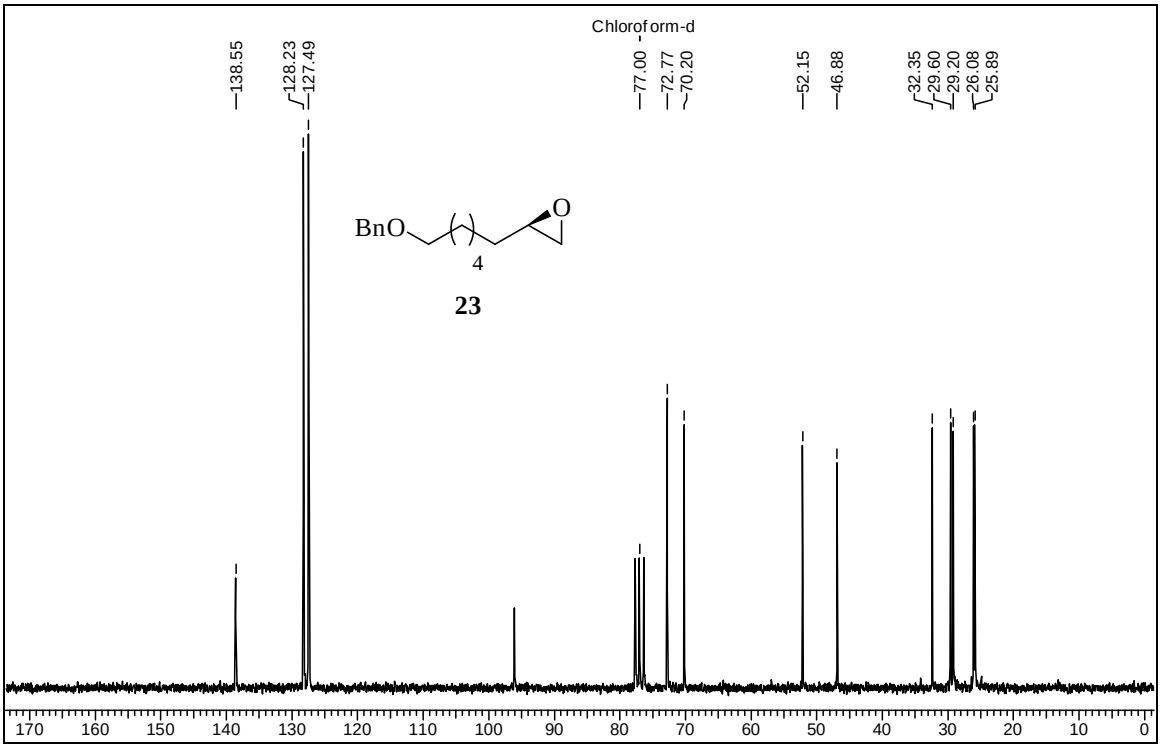
^{1}H NMR spectrum of compound 8 in $CDCl_3$



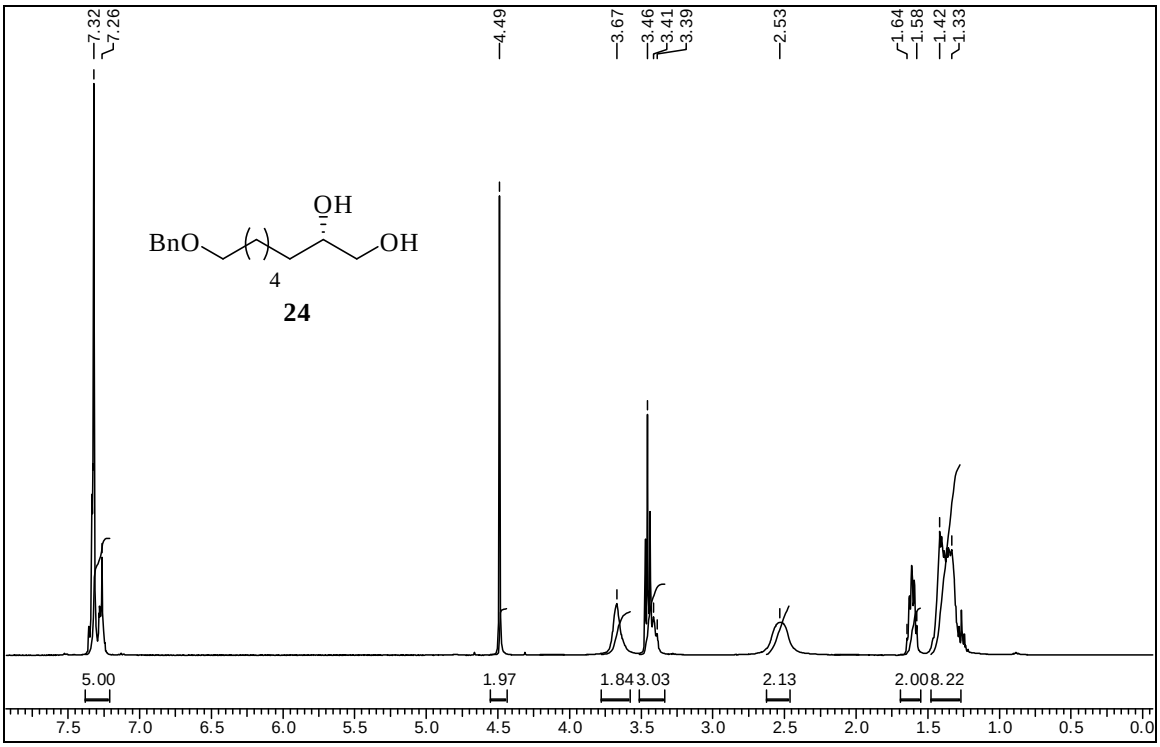
^{13}C NMR spectrum of compound 8 in $CDCl_3$



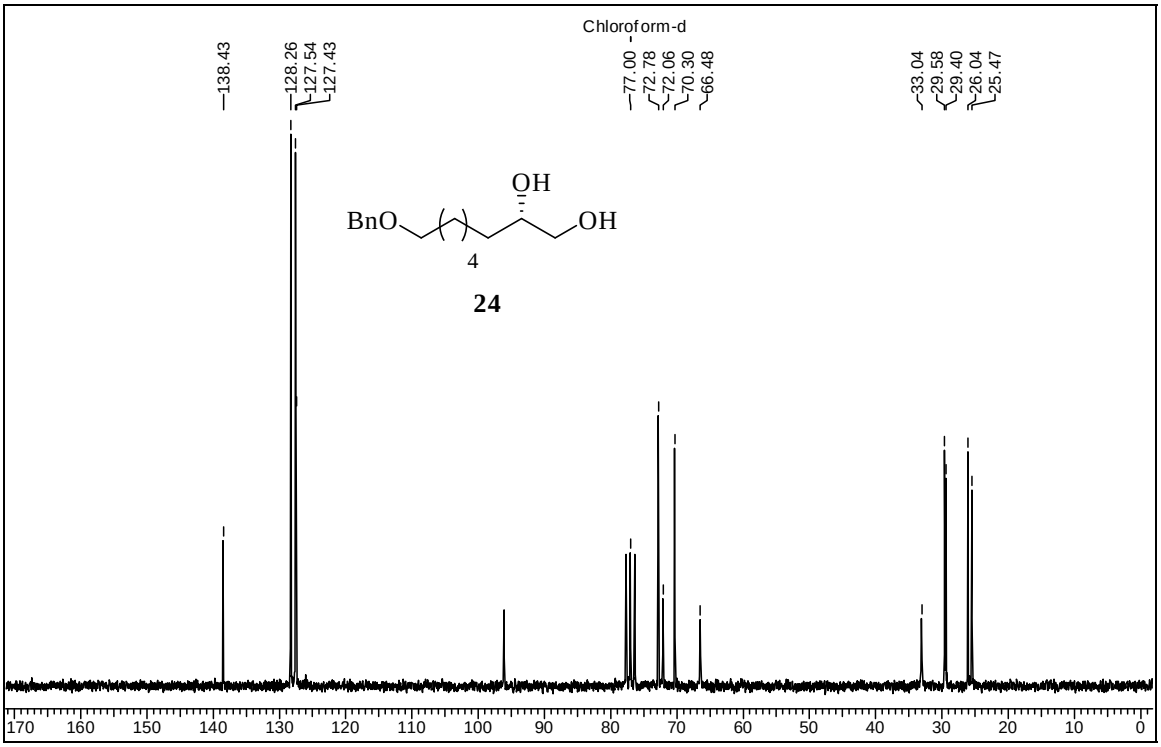
^{1}H NMR spectrum of compound 23 in $CDCl_3$



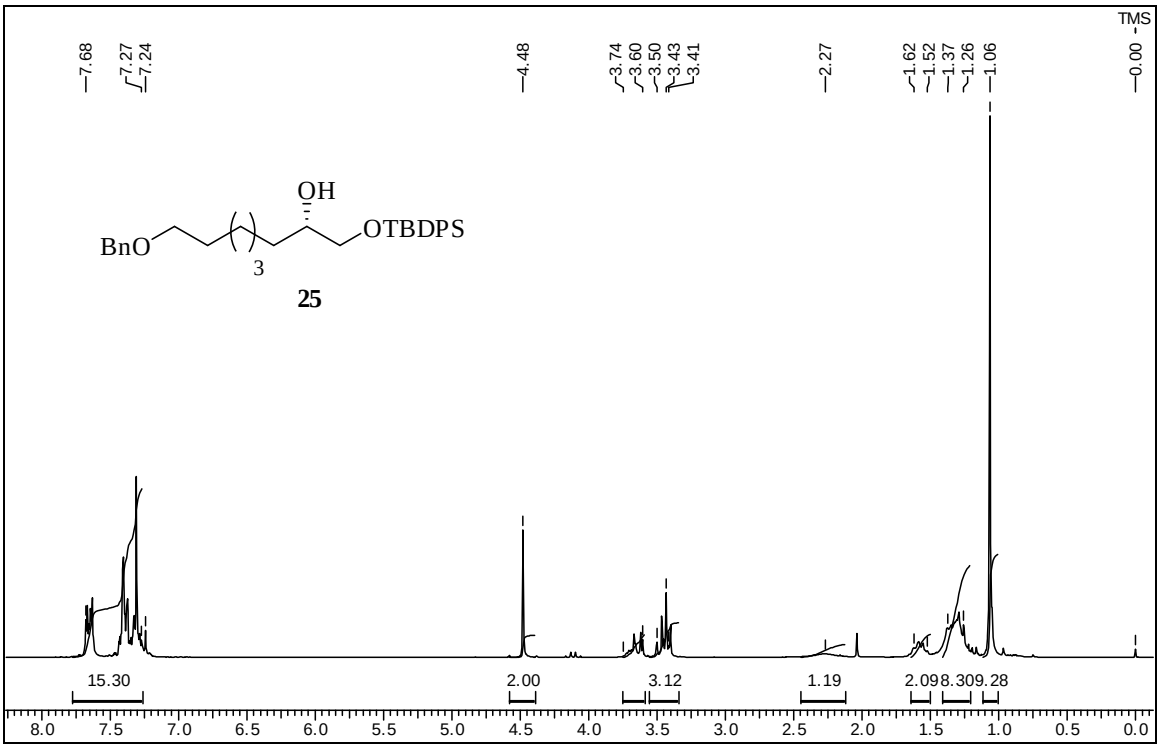
^{13}C NMR spectrum of compound 23 in $CDCl_3$



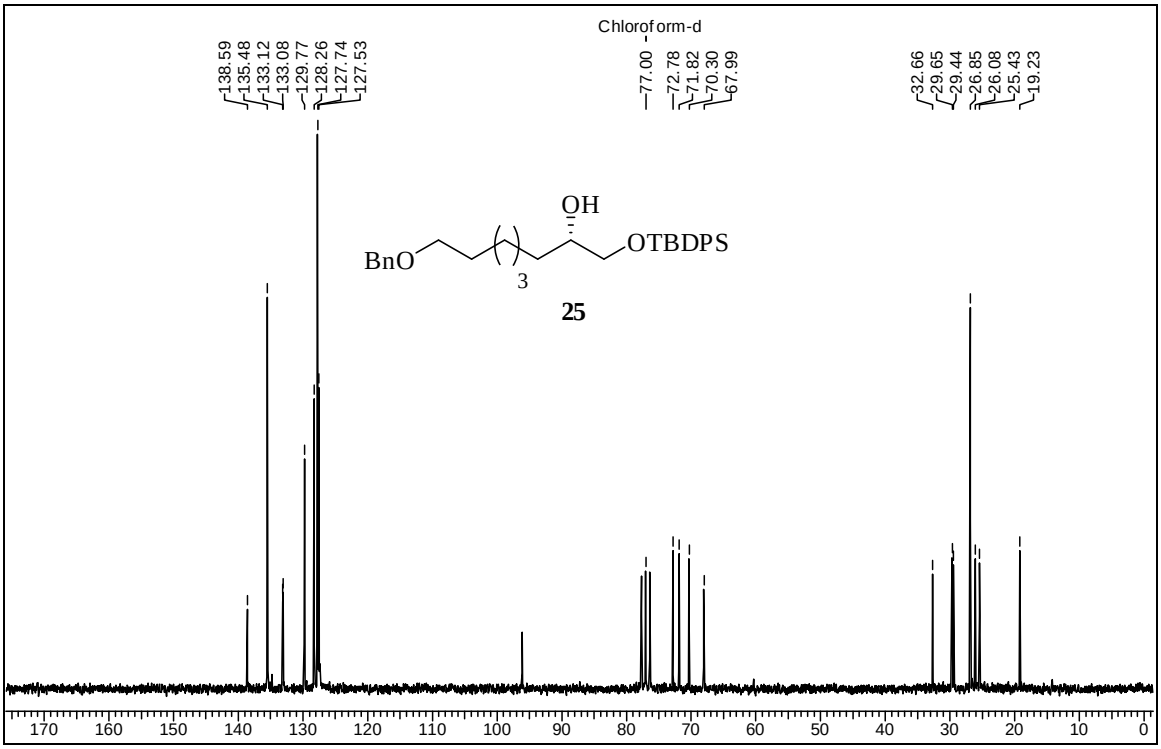
^{1}H NMR spectrum of compound 24 in $CDCl_3$



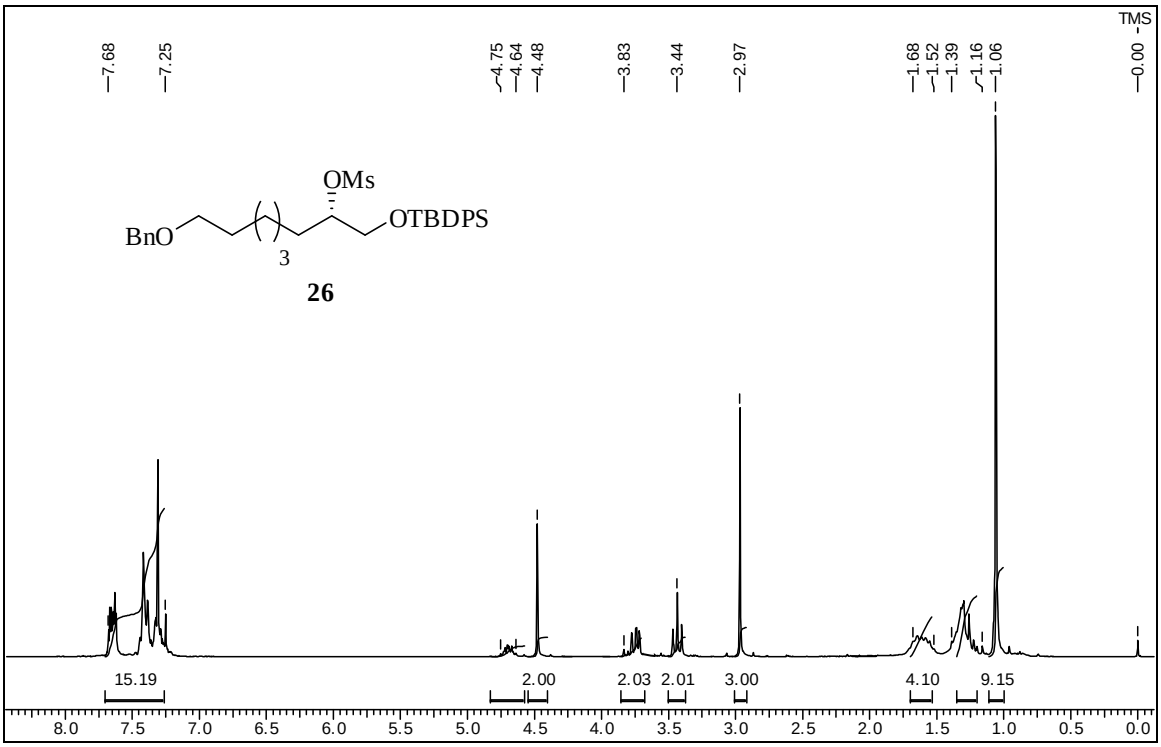
^{13}C NMR spectrum of compound 24 in $CDCl_3$



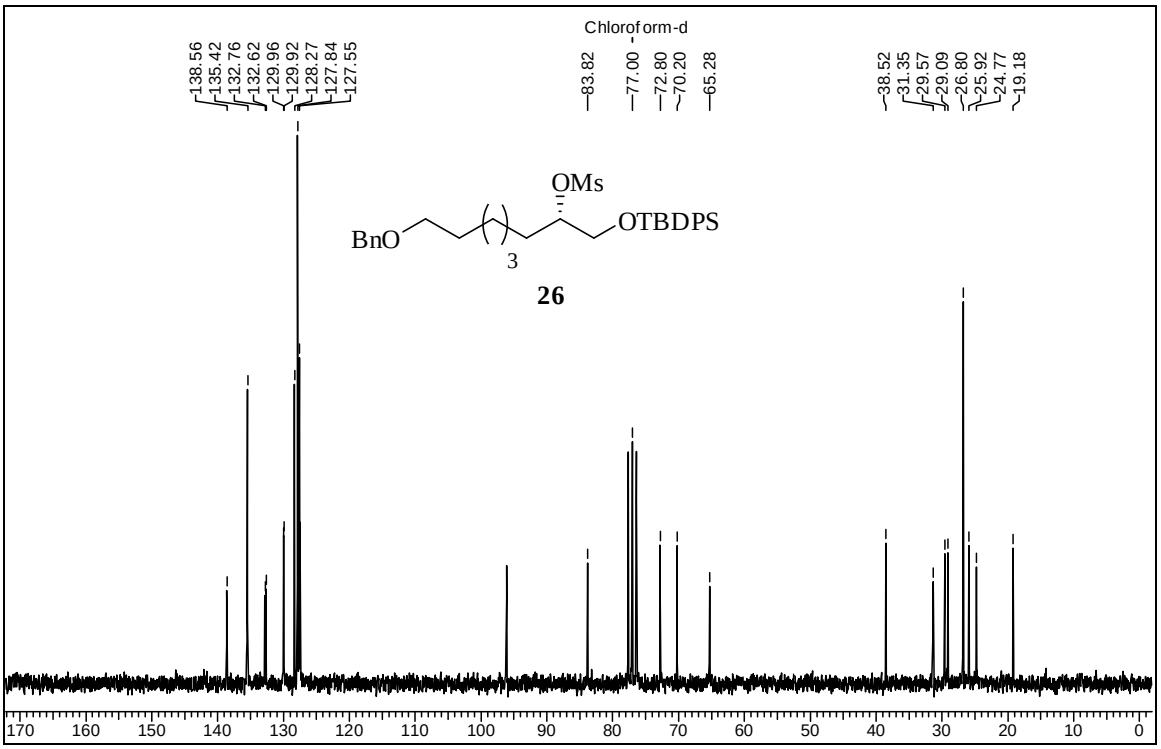
^{1}H NMR spectrum of compound 25 in $CDCl_3$



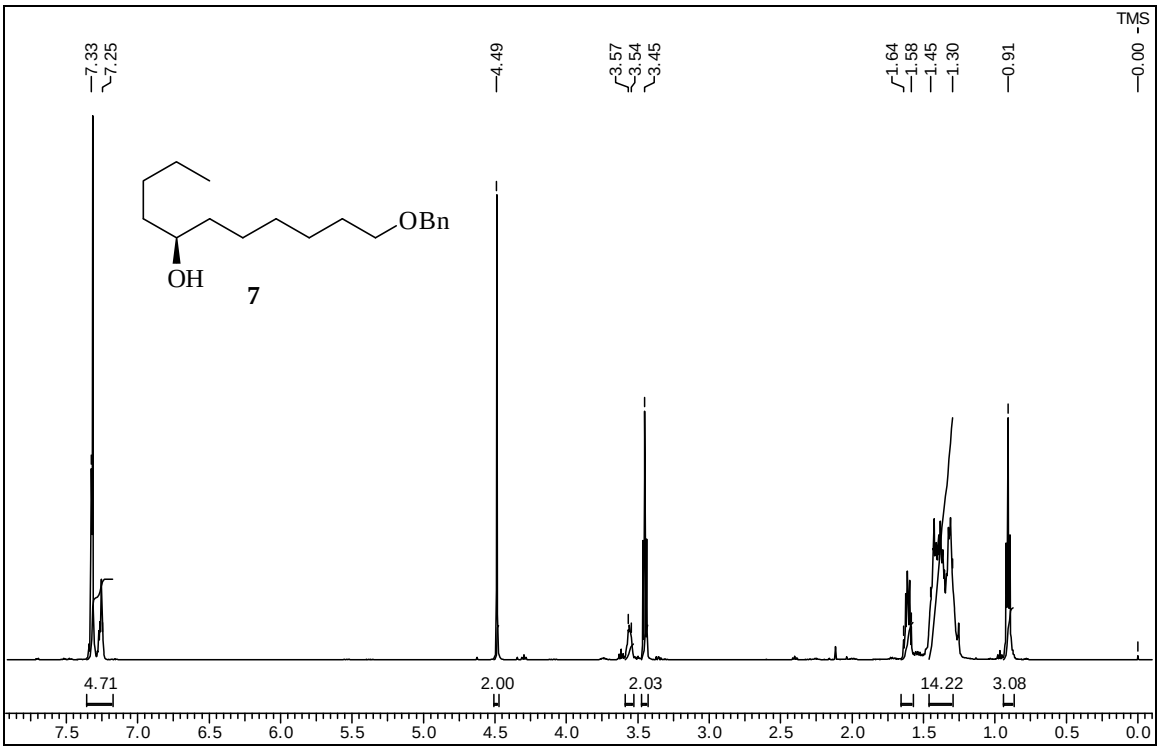
^{13}C NMR spectrum of compound 25 in $CDCl_3$



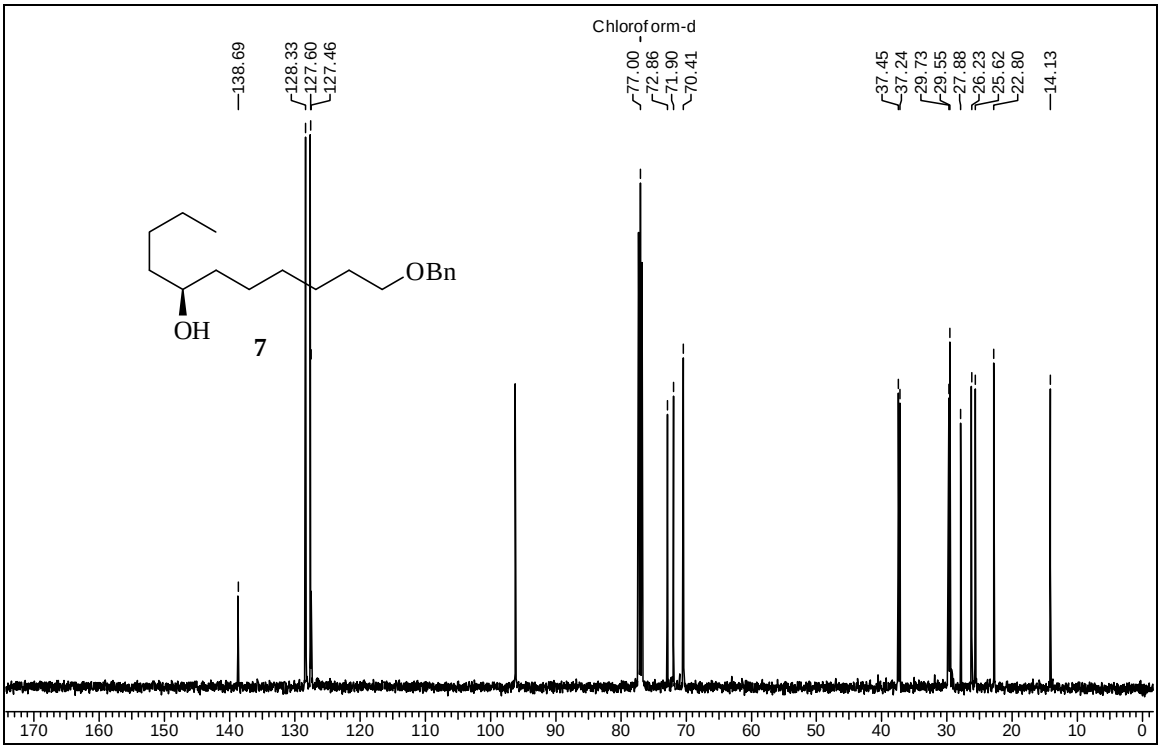
^{1}H NMR spectrum of compound 26 in $CDCl_3$



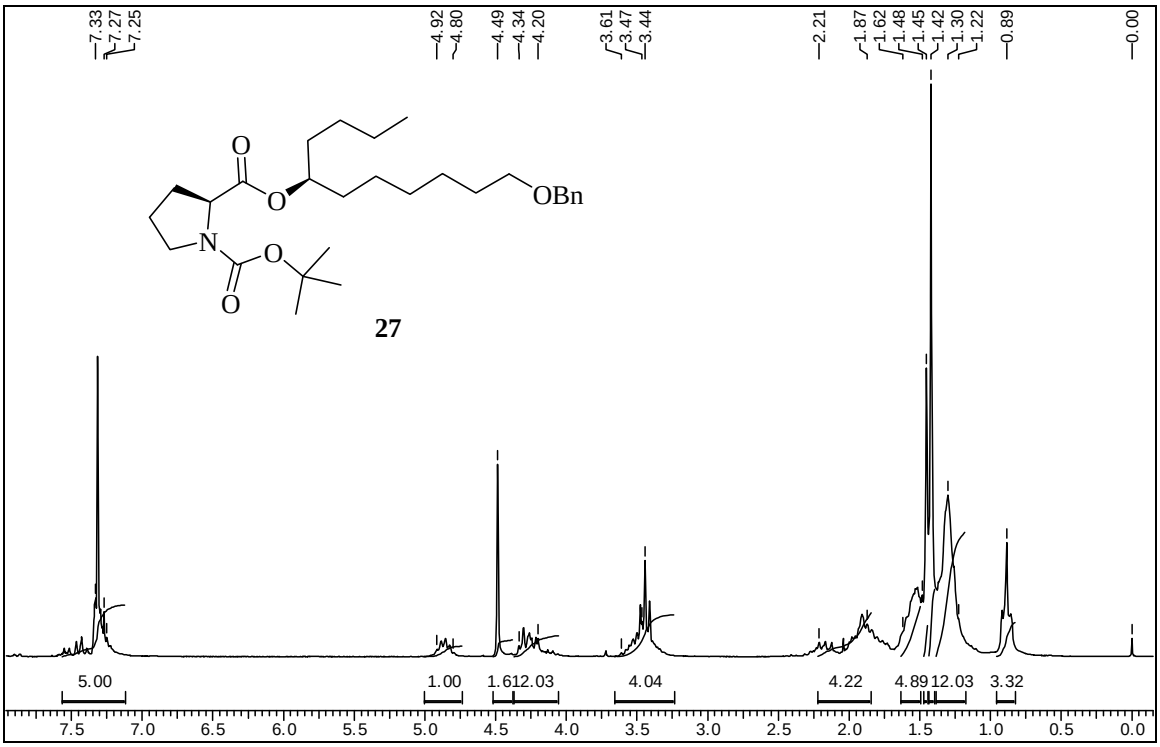
^{13}C NMR spectrum of compound 26 in $CDCl_3$



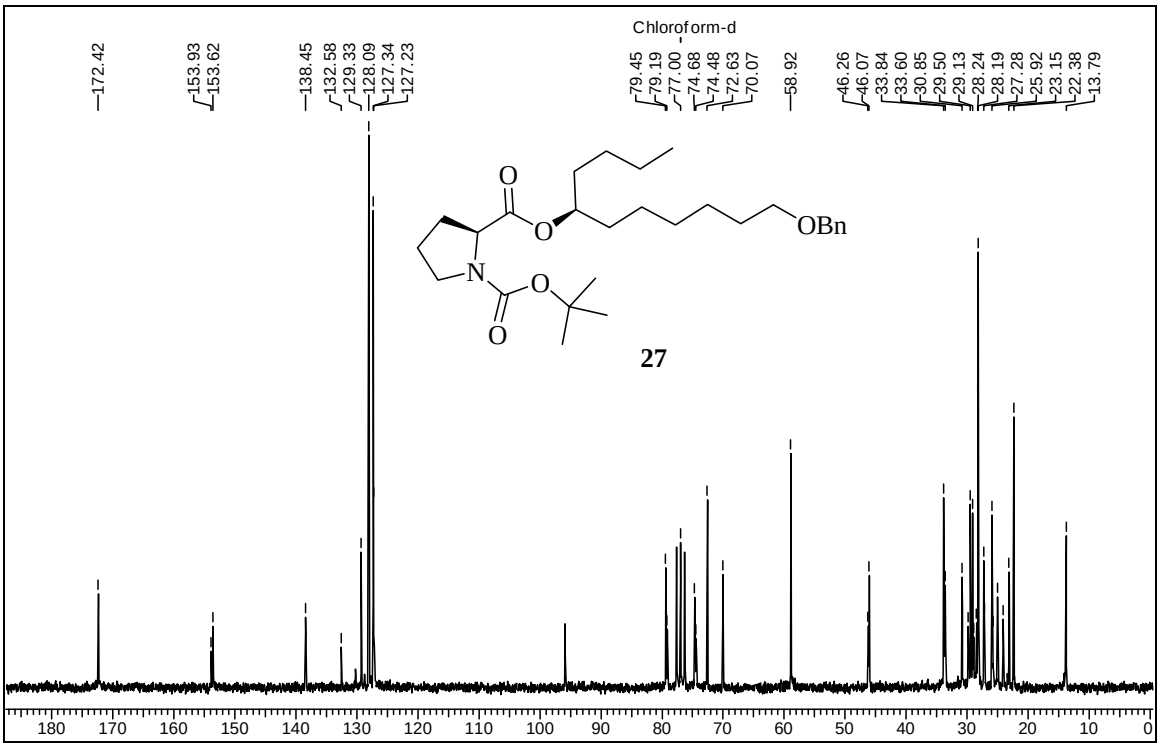
^{1}H NMR spectrum of compound 7 in $CDCl_3$



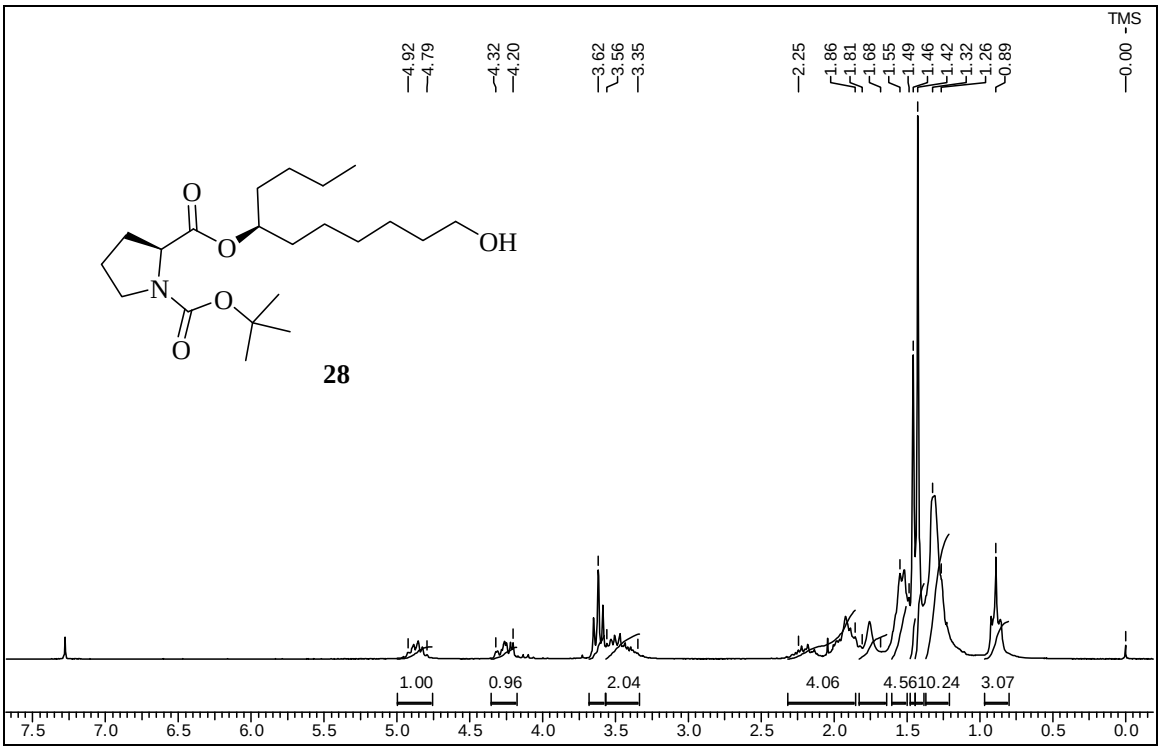
^{13}C NMR spectrum of compound 7 in $CDCl_3$



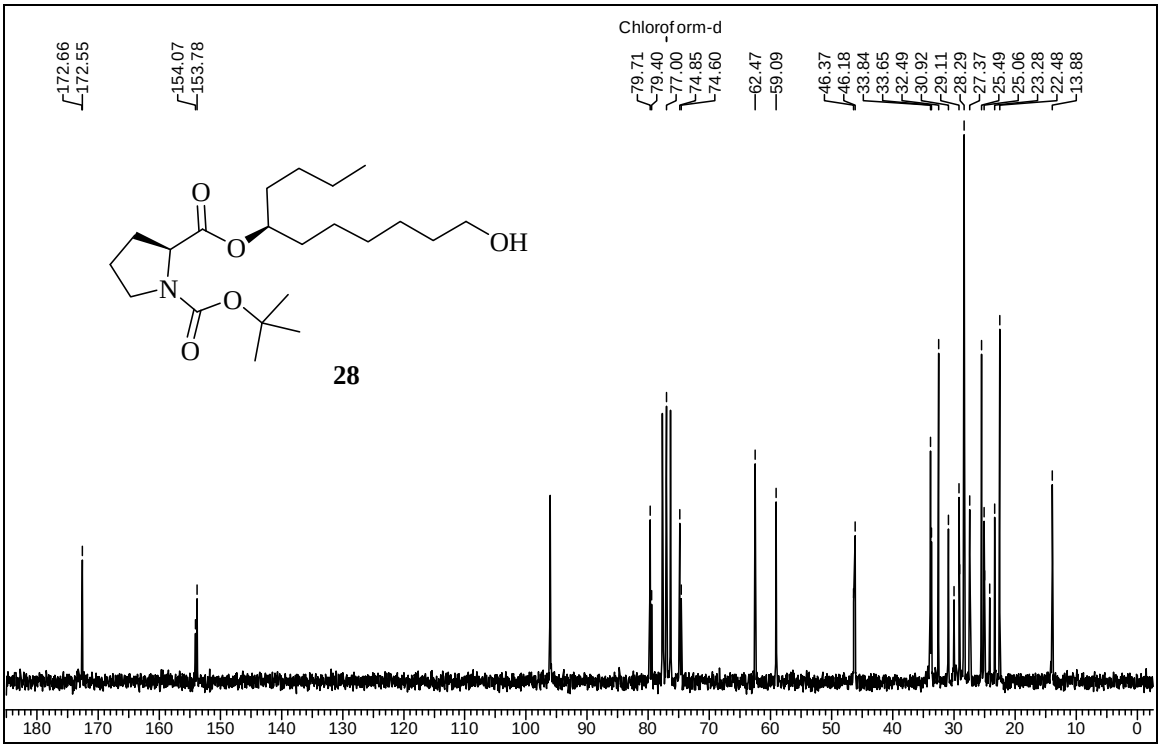
^{1}H NMR spectrum of compound 27 in $CDCl_3$



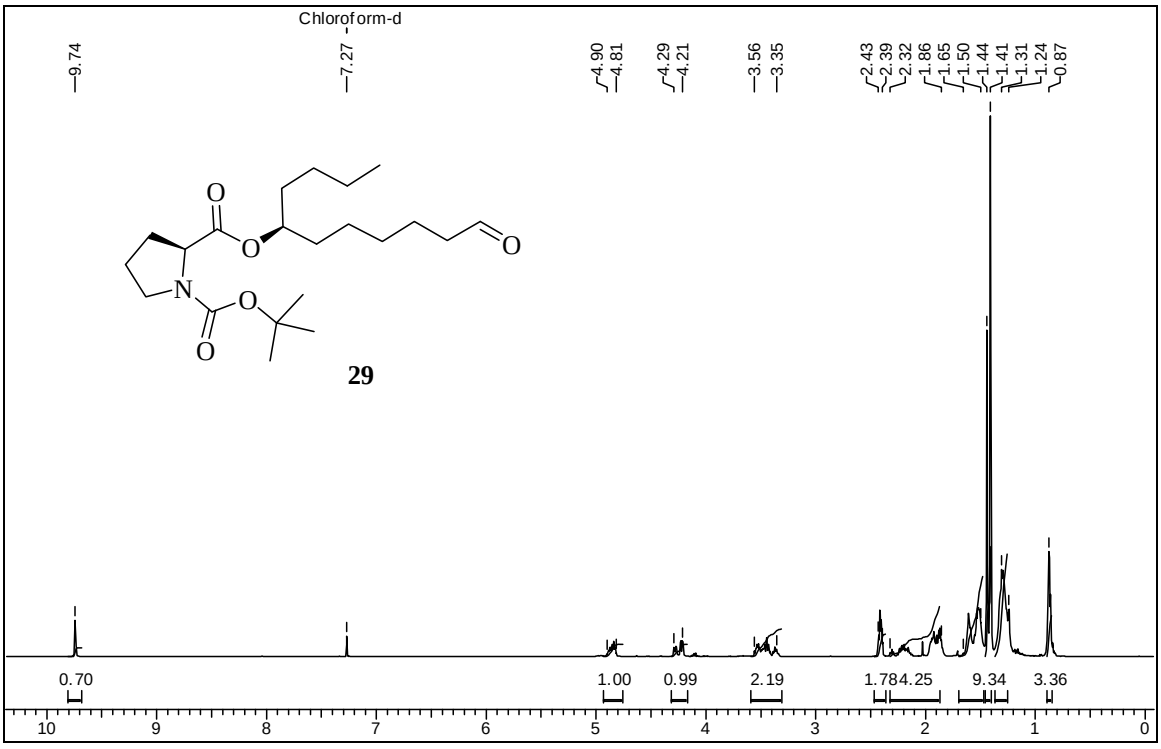
^{13}C NMR spectrum of compound 27 in $CDCl_3$



^{1}H NMR spectrum of compound 28 in $CDCl_3$

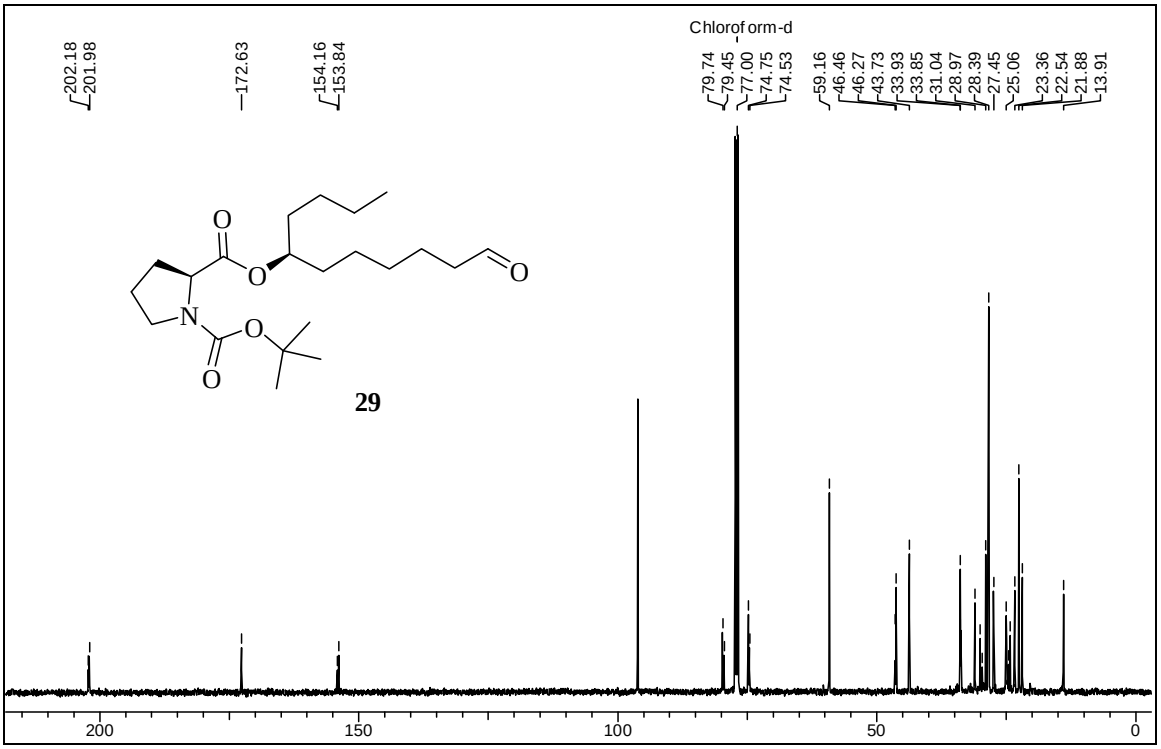


^{13}C NMR spectrum of compound 28 in $CDCl_3$



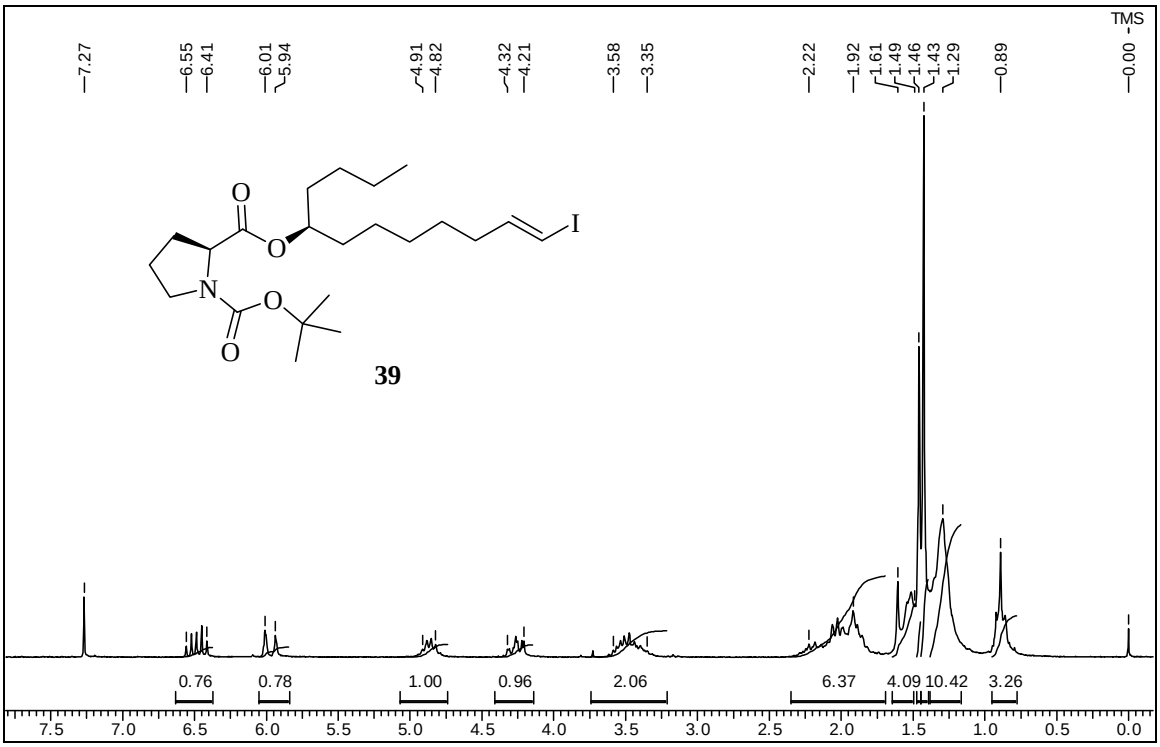
29

^{1}H NMR spectrum of compound 29 in $CDCl_3$

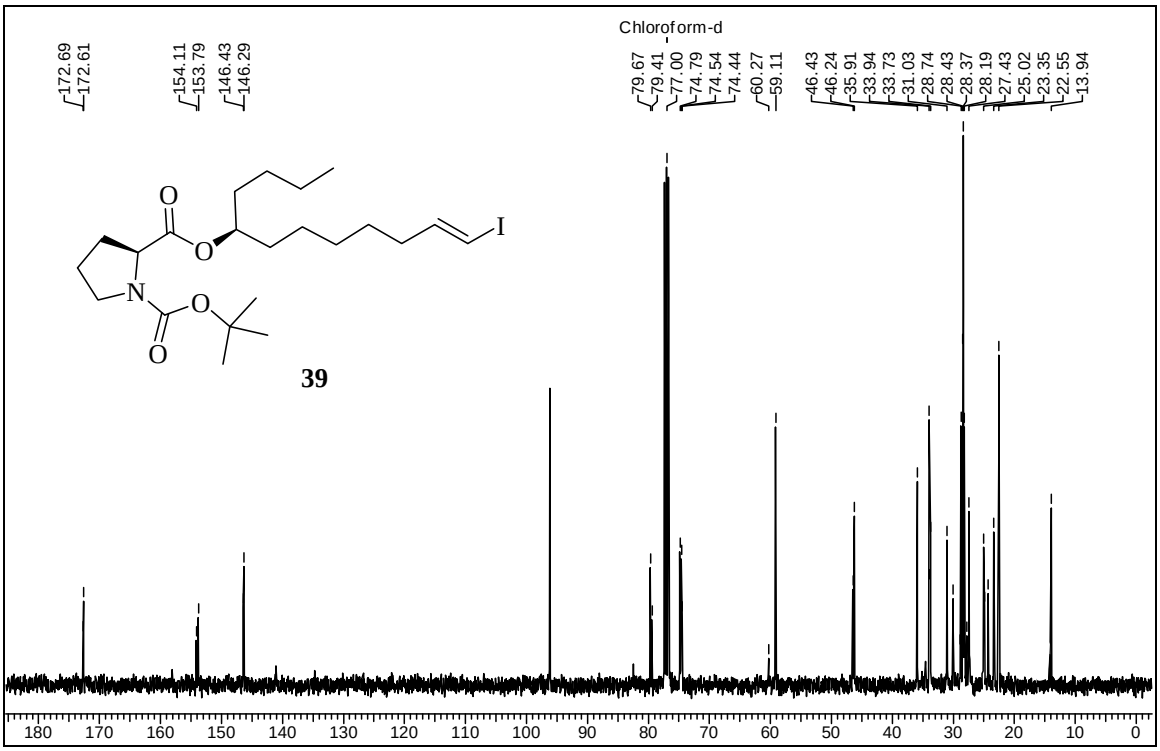


29

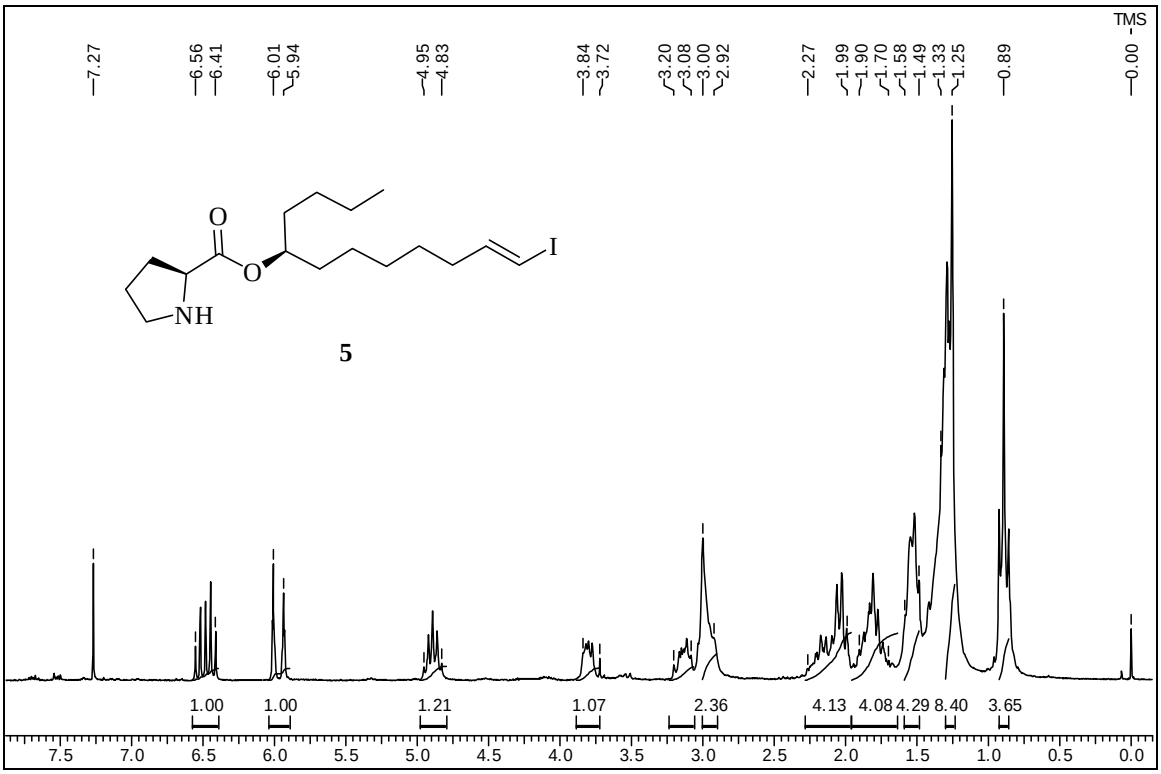
^{13}C NMR spectrum of compound 29 in $CDCl_3$



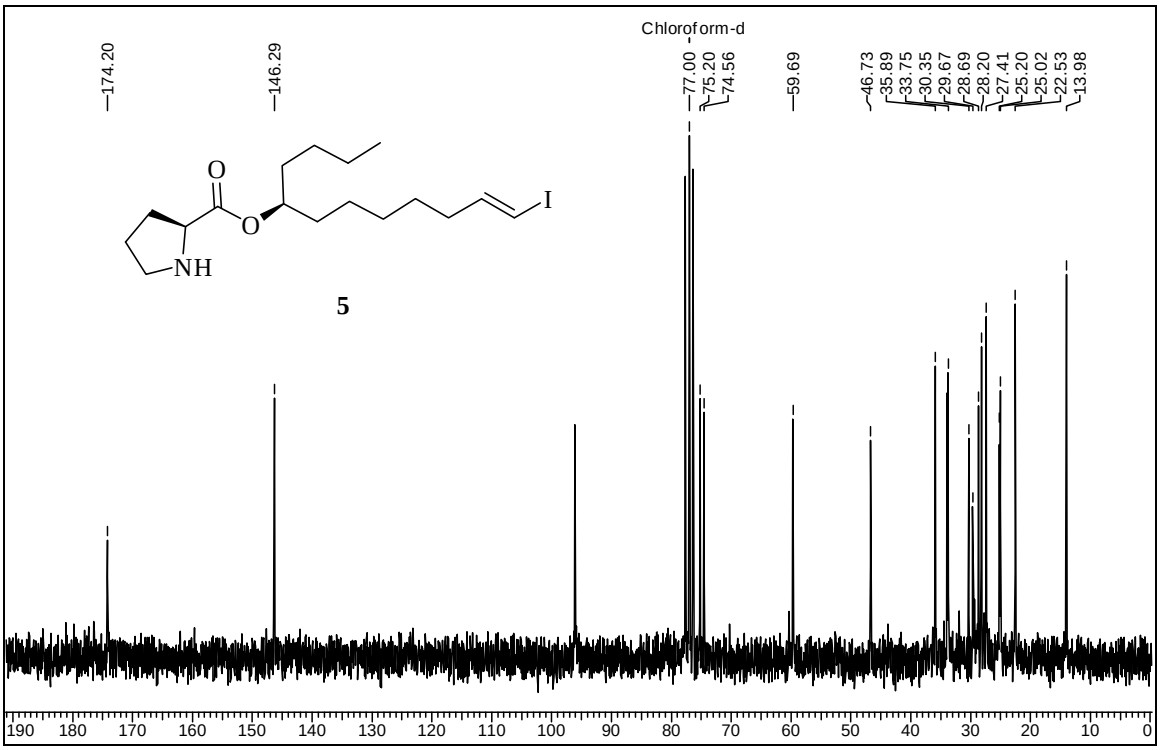
^{1}H NMR spectrum of compound 39 in $CDCl_3$



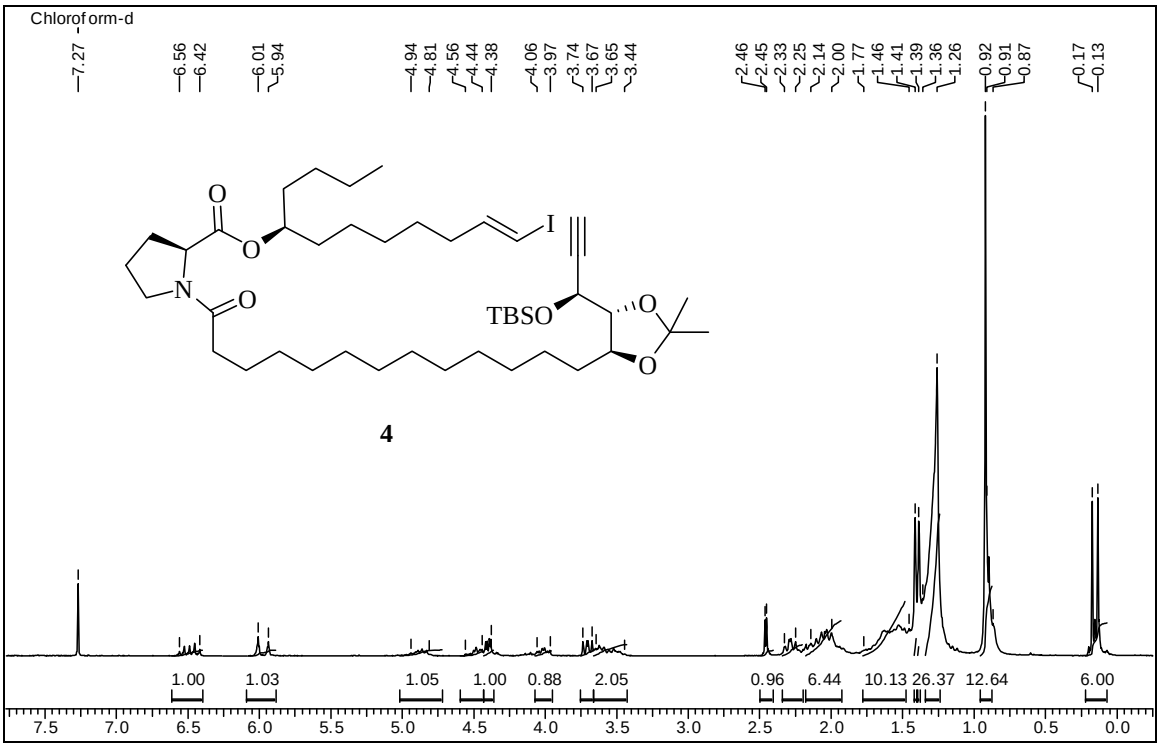
^{13}C NMR spectrum of compound 39 in $CDCl_3$



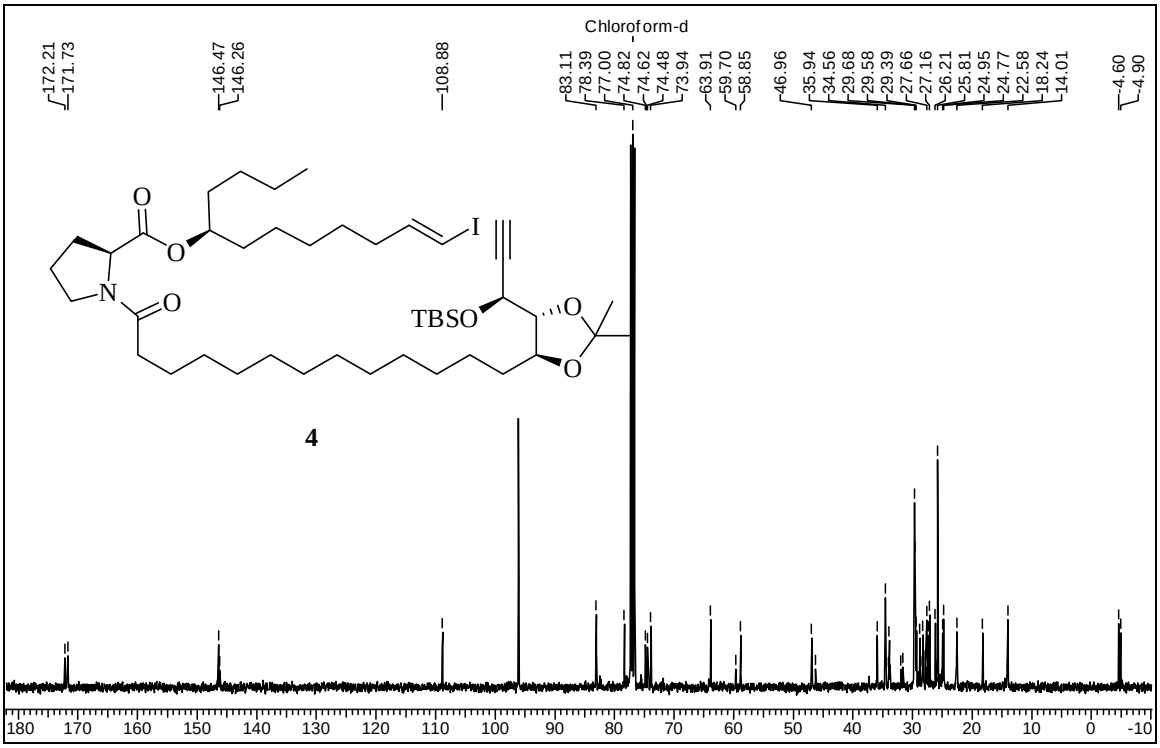
^{1}H NMR spectrum of compound 5 in $CDCl_3$



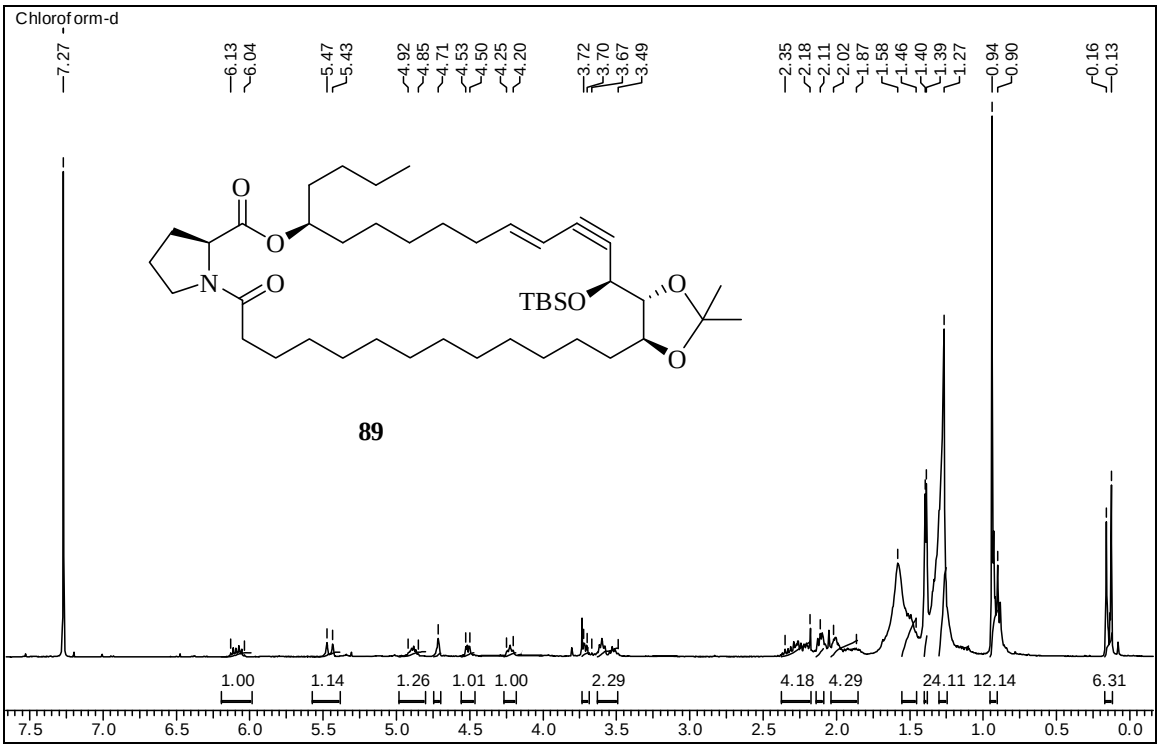
^{13}C NMR spectrum of compound 5 in $CDCl_3$



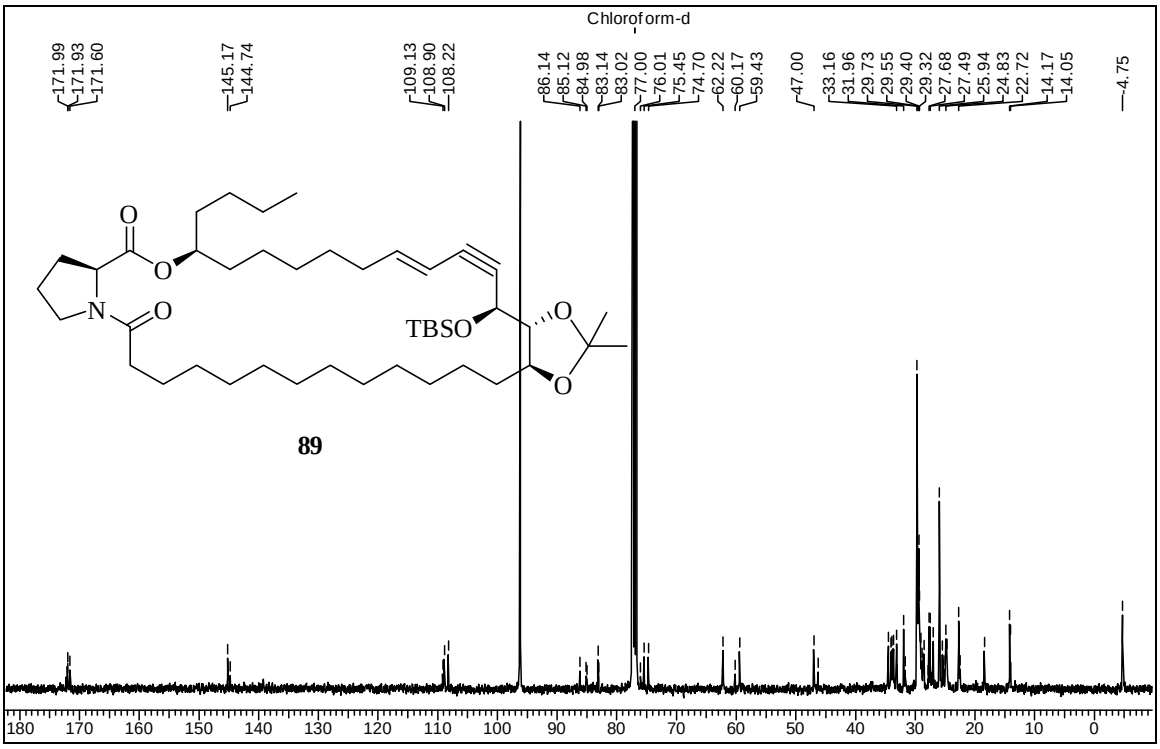
^{1}H NMR spectrum of compound 4 in $CDCl_3$



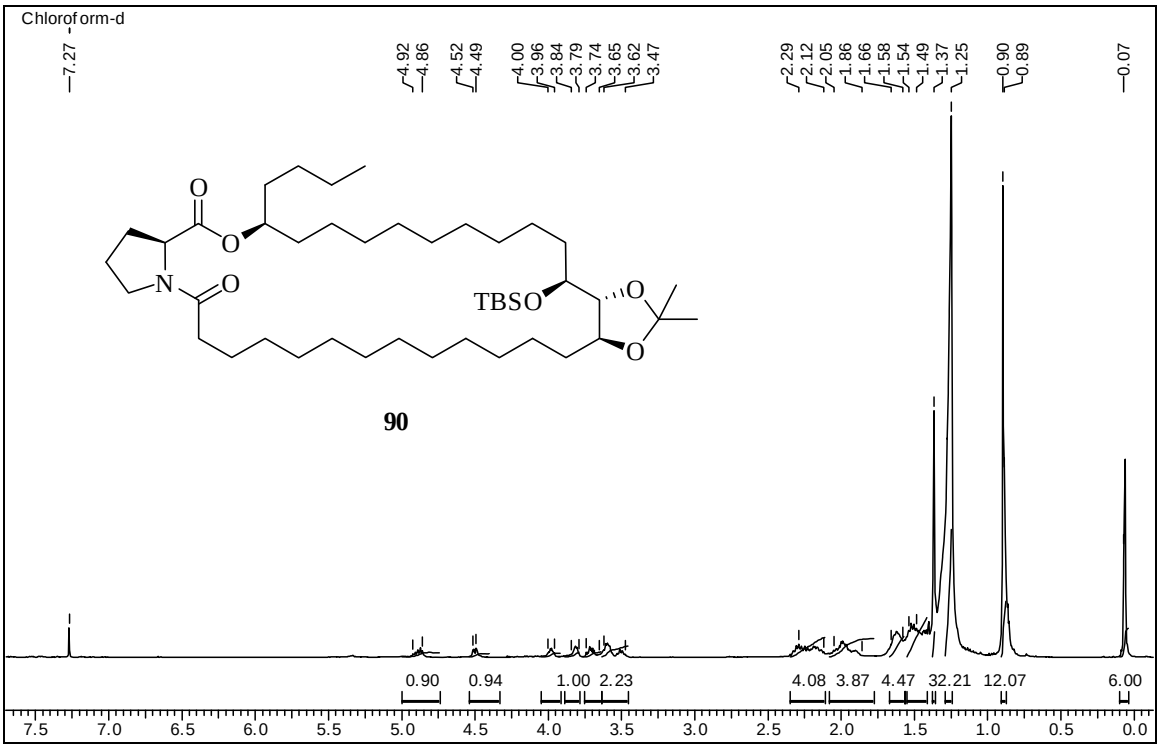
^{13}C NMR spectrum of compound 4 in $CDCl_3$



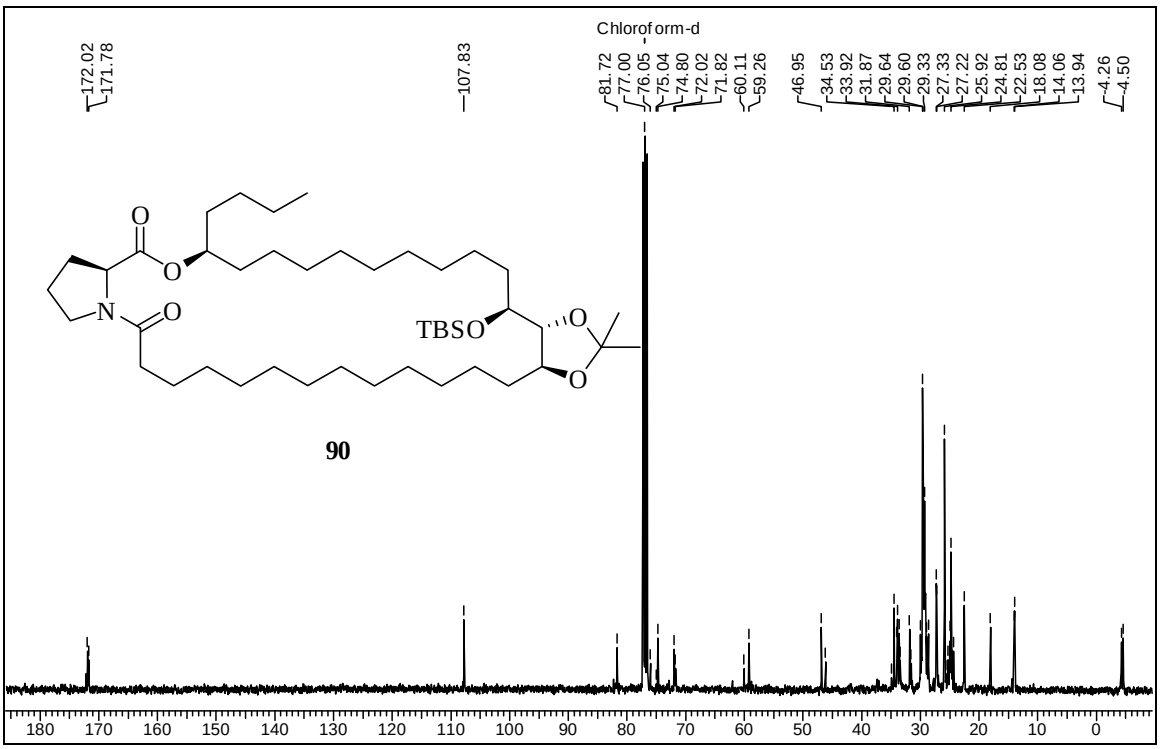
^{1}H NMR spectrum of compound 89 in $CDCl_3$



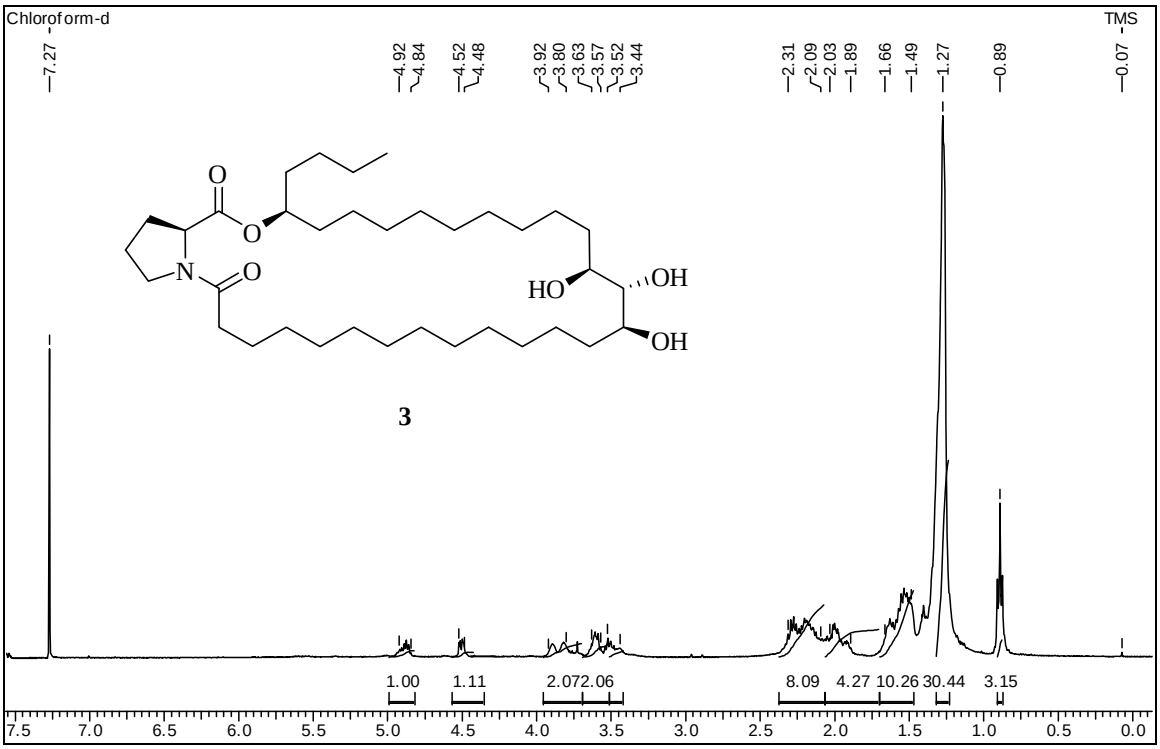
^{13}C NMR spectrum of compound 89 in $CDCl_3$



^{1}H NMR spectrum of compound 90 in $CDCl_3$

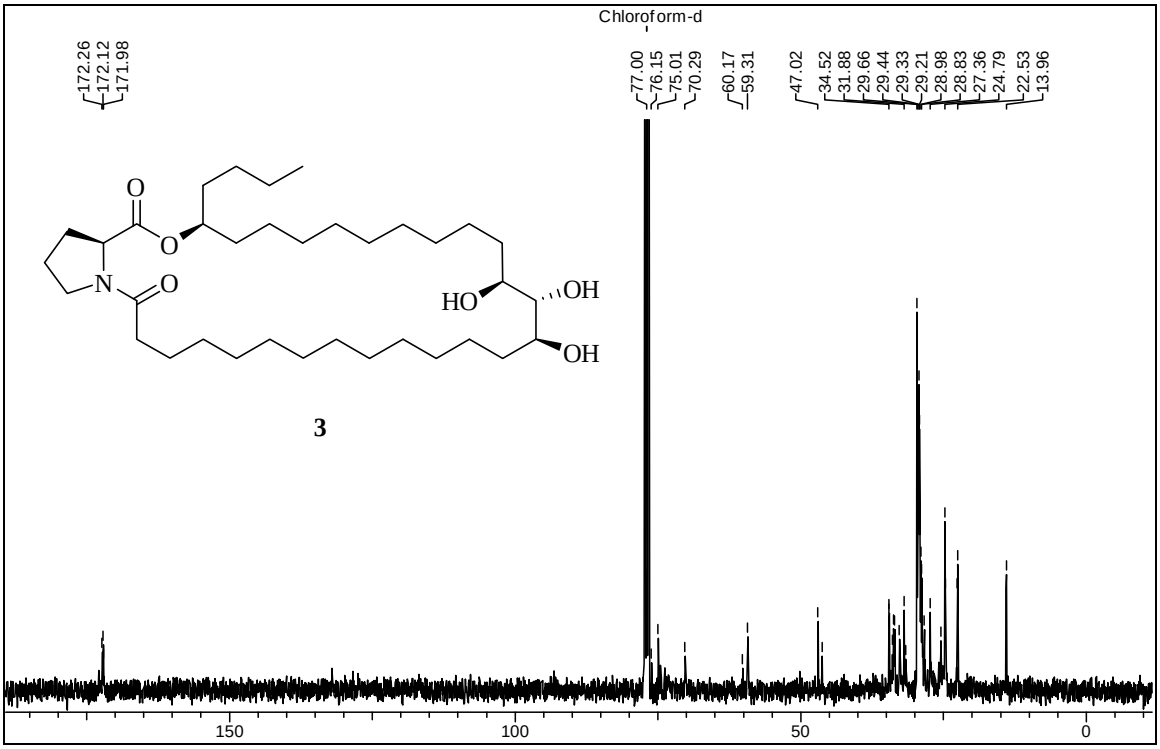


^{13}C NMR spectrum of compound 90 in $CDCl_3$



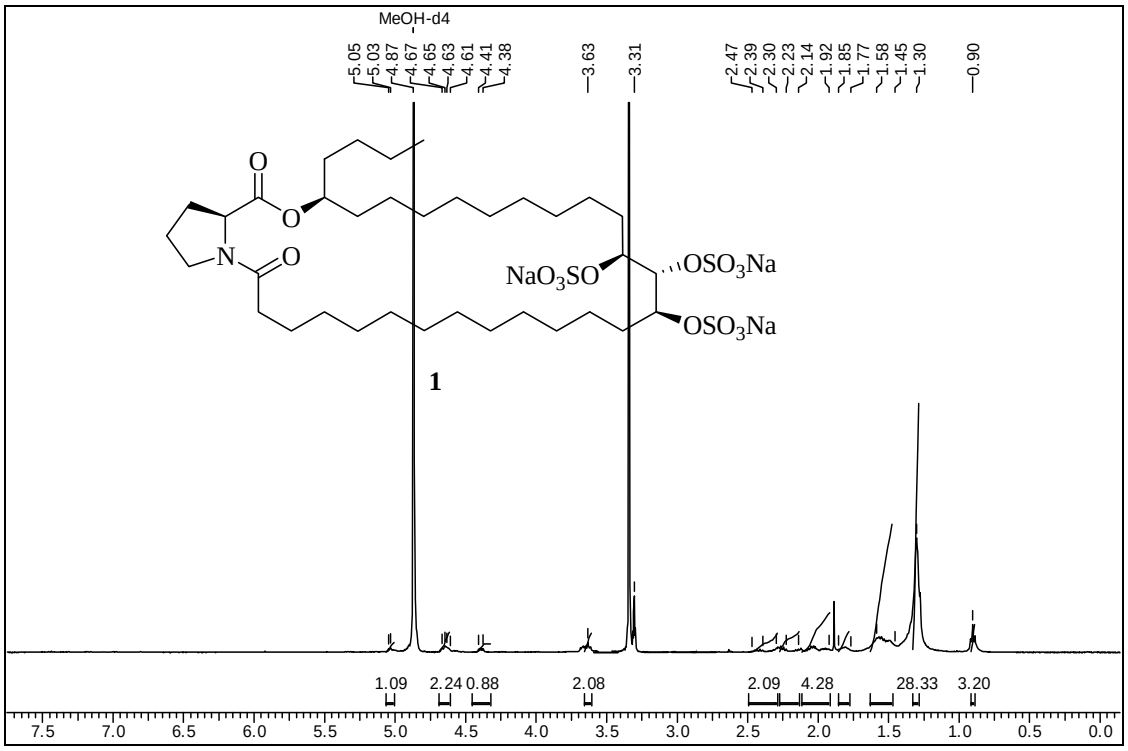
3

^{1}H NMR spectrum of compound 3 in $CDCl_3$

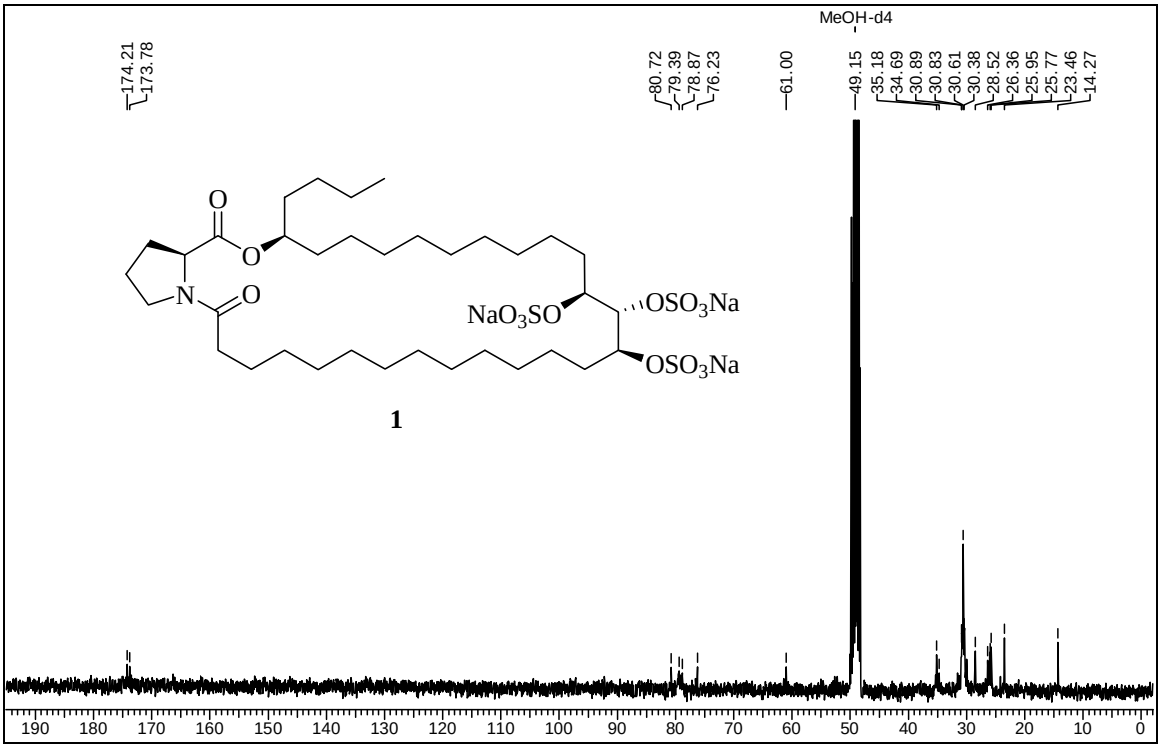


3

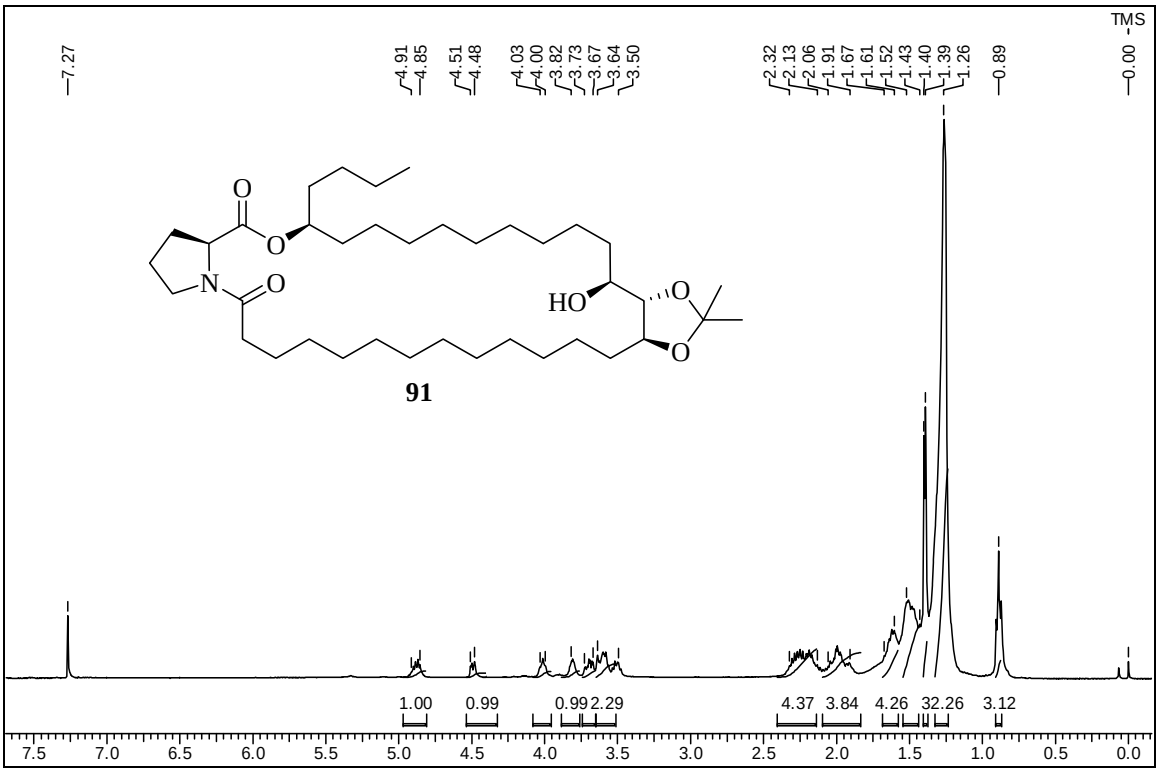
^{13}C NMR spectrum of compound 3 in $CDCl_3$



^{1}H NMR spectrum of compound 1 in CD_3OD

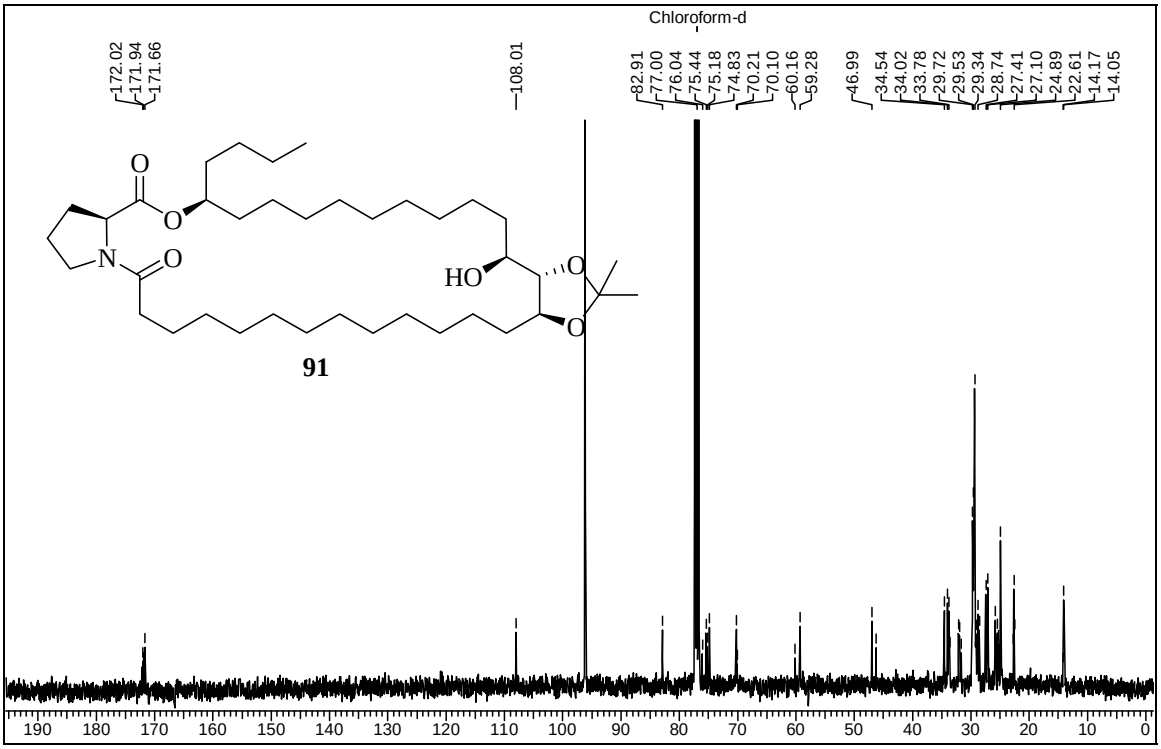


^{13}C NMR spectrum of compound 1 in CD_3OD



91

^{1}H NMR spectrum of compound 91 in $CDCl_3$



91

^{13}C NMR spectrum of compound 91 in $CDCl_3$

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Chapter 3

Studies Toward the Total Syntheses of Schulzeines B and C

PRESENT WORK

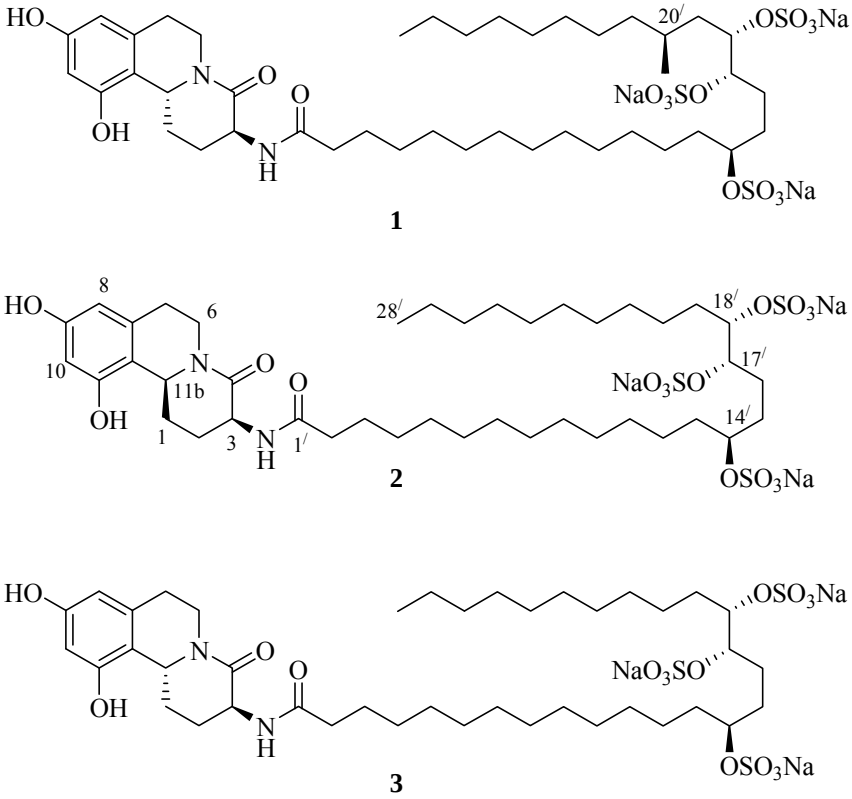
Present work

Sponges have provided more marine natural products than any other phylum, mostly due to their propensity to produce bioactive metabolites. Sponges are the most studied of the marine organisms in marine natural products chemistry and is closely followed by tunicates and coelenterates. It is hard to say whether this is driven by advances in marine biotechnology or by the increasing difficulty in obtaining permits to collect marine invertebrates. There is currently a great interest that is aided by advances in molecular genetics for the possible production of bioactive compounds from marine invertebrates by associated microorganisms.[1] Hence marine natural products continue to be the prime targets for synthesis. However papers reporting partial and formal syntheses outnumber the papers that record total syntheses that is useful for structure elucidation.

The present dissertation will deal with the total syntheses of schulzeines B and C isolated from the marine sponge *Penares schulzei*, which were shown to be α-glucosidase inhibitors. α-glucosidases not only process protein glycosylation that is involved in a wide range of biological processes including promotion of protein folding in the endoplasmic reticulum and stabilization of cell-surface glycoproteins, but also control oligosaccharide metabolism. Thus, inhibitors of α-glucosidases are potential therapeutics for the treatment of diseases such as viral diseases, cancer, and diabetes.[2-4] In fact, imino sugars that are inhibitors of these enzymes show considerable promise in the treatment of type B hepatitis, while a nojirimycin analogue has been approved for the treatment of noninsulin-dependent diabetes. In the course of continuing search for potential drug leads from Japanese marine invertebrates, Fusetani and co-workers isolated three novel tetrahydroisoquinoline alkaloids designated schulzeines A-C (**1**-**3**) in the year 2004 (Figure 1). This was done by a bioassay-guided isolation of hydrophilic extract of marine sponge *Penares schulzei*[5] which inhibit yeast α-glucosidase at concentrations as low as 48-170 nM.[6] It should be noted that desulfated schulzeines A and B still retained activity (IC_{50} values of 2.5 and 1.1 μM, respectively). Thus, the detergent-like nature of the schulzeines may not be important for the activity, although it contributes to the activity to

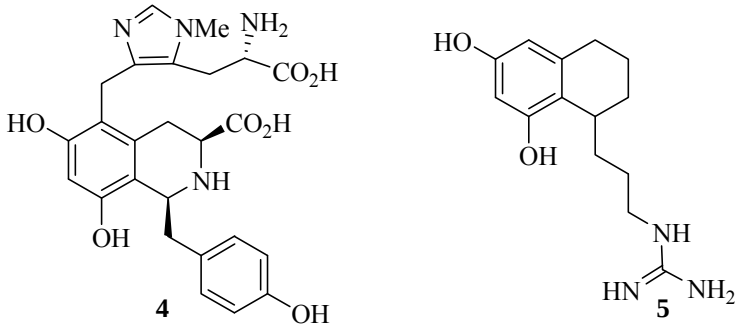
some extent. schulzeines were also inhibitory against viral neuraminidase with IC_{50} values of 60 μM.

Figure 1. *Schulzeines A-C (**1-3**)*.



Schulzeines encompass the 9,11-dihydroxyisoquinoline constellation which is reminiscent of imbricatine (**4**)[7,8] and fuscusine (**5**),[9] both isolated from starfishes (Figure 2).

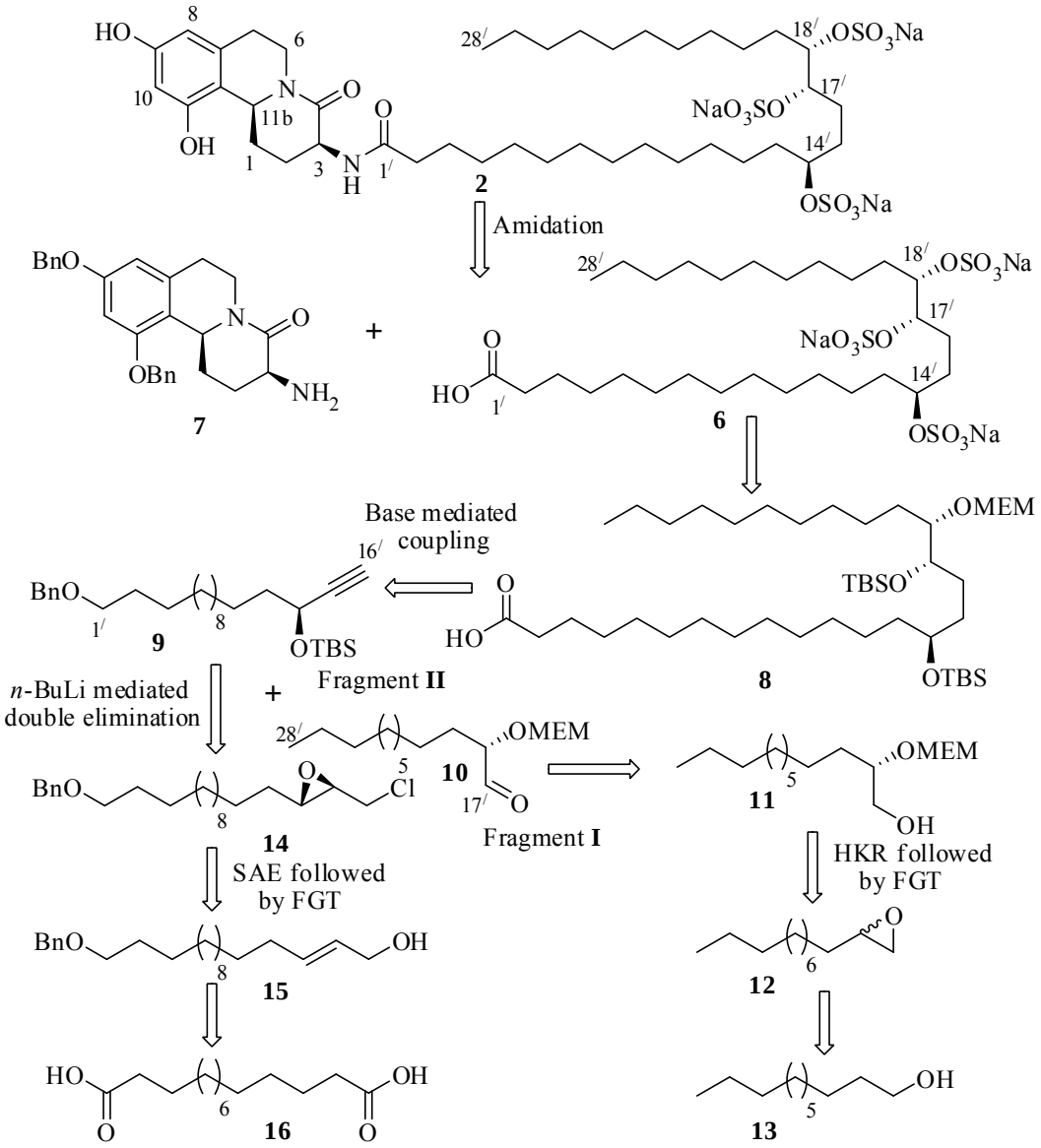
Figure 2



The most notable structural difference of schulzeines from these metabolites is the presence of a long alkyl chain whose central portion was functionalized with three sulfate groups. Therefore, schulzeines are a new class of marine natural products.

The constitution and the relative stereochemistry of schluzeines were elucidated by chemical degradation and by extensive 2D-NMR studies while the absolute configuration was determined by application of Mosher's method.

Scheme 1. *Retrosynthetic strategy*.



Schluzeines encompass the 9,11-tetrahydroisoquinoline constellation and are characterized by a fused δ-lactam ring and a C_{28} sulfated fatty acid side chain linked *via* an amide bond. The tricyclic core **7** bears two stereogenic centers at C_3 and C_{11b} (Figure 1). The stereocenter at C_3 is assigned as '*S'* in all members of this family whereas schulzeines A (**1**) and C (**3**) have C_{11b} '*R'* and schulzeine B (**2**) has C_{11b} '*S'* configuration. The C_{28} fatty acid side chain of schulzeines bear three stereogenic centers at C_{14}, C_{17} and C_{18} as sodium sulfate salts with the configuration assigned as *S*, *S*, *S*. Schulzeine A has an extra stereogenic center at C_{20} bearing a methyl substituent.

The structural complexity and important biological activity of schulzeines A-C drew our attention with regards to their total synthesis. Apart from a recent synthesis[10] of the tetrahydroisoquinoline subunit, no report has yet appeared on the total synthesis of any of these natural products. Herein, we report the first total syntheses of schulzeines B (**2**) and C (**3**) (Figure 1).

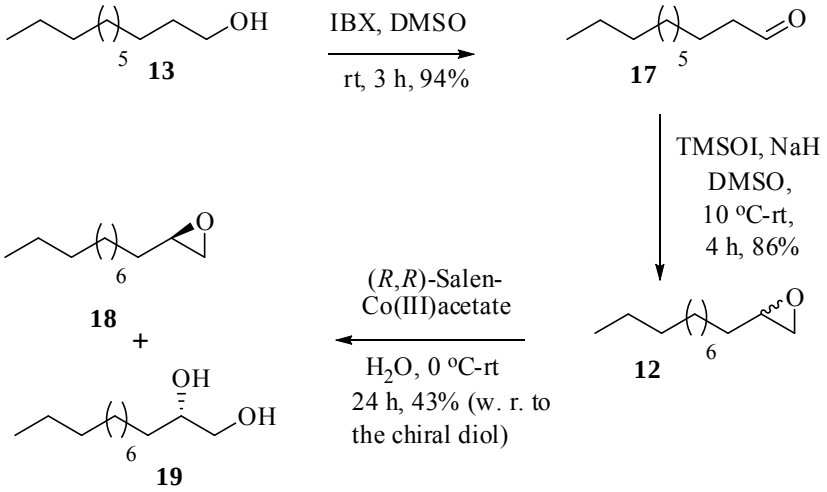
The retrosynthetic analysis for our synthetic endeavor was planned using a 'tactical combination of transforms' putting onus on T-goal approaches, as outlined in Scheme 1. The initial N-C disconnection of tetrahydroisoquinoline moiety appended with C_{28} fatty acid chain would provide the precursor aromatic amine **7** and the trisulfated acid **6**. **8** would be viewed as the synthetic equivalent of **6**, in which all the three hydroxyl groups are suitably protected. Herein, we describe the stereoselective synthesis of the C_{28} fatty acid fragment of schulzeines B and C. The later fragment **8** would, on application of simplifying transform by dissecting C_{28} chain, deliver alkyne synthetic precursor **9** and the aldehyde **10**. This α-substituted aldehyde **10** could be obtained by the application of Jacobsen's hydrolytic kinetic resolution[11] on the racemic epoxide **12** followed by simple functional group manipulations thereafter. The second and key operation using heteroatom ring disconnective transform would reveal the hydroxy alkyne intermediate **9**. In the synthetic direction, the feasibility of this synthetic step (**14** to **9**) was more appealing, since the outcome of the reaction through internal S_N2 displacement in a pre organised substrate would be completely stereospecific. The protected propargyl alcohol **9** on the leftern side was envisaged to arise from epoxymethanol fragment through base-mediated double elimination of epoxymethyl chloride after simple FGT. The allyl alcohol

15 was thought to be the unambiguous retron for the epoxymethanol under the application of stereoflexible and sterocontrolled transform. C=C Wittig disconnection would imply the aldehyde that can be judiciously protected for further refinement. **16** was the requisite starting material for all these relevant chemical transformations.

Synthesis of fragment I

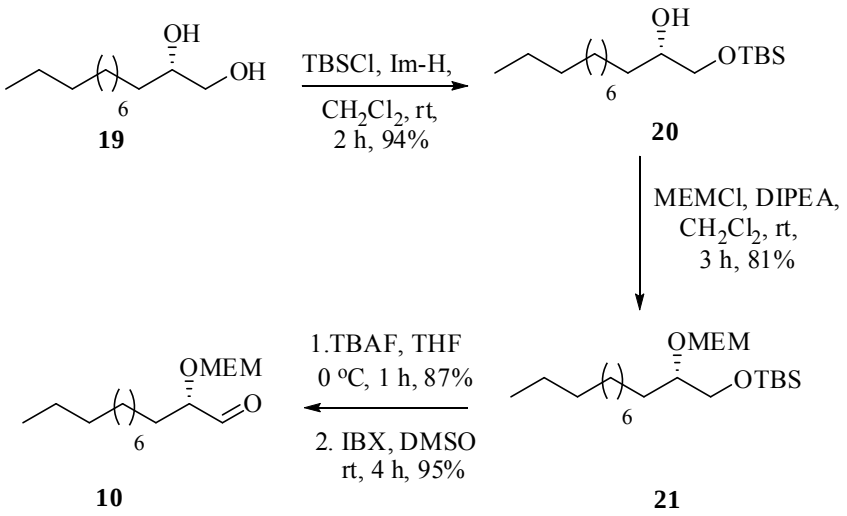
Our synthesis towards the aldehyde **10** commenced with commercially available 1-undecanol (**13**) that was oxidized to the corresponding aldehyde **17** using IBX[12] in DMSO in 94% yield (Scheme 2). Aldehyde **17** was transformed to the racemic epoxide **12** by using trimethylsulfoxonium iodide[13] and sodium hydride in 86% yield. **12** on treatment with H_2O (0.55 eqv) and (*R*,*R*)-Co(III)-Salen acetate complex (Jacobsen's hydrolytic kinetic resolution) produced the resolved epoxide **18** and (*S*)-(−)-1,2-dodecane diol (**19**). Separation of the resolved epoxide **18** and the diol (**19)** was done by silicagel column chromatography. The diol (**19)** was obtained as a white solid and the enantiomeric purity of the diol was determined by comparing optical rotation value from the literature.[11b] In the ^{1}H NMR spectrum of **19** the appearance of the C_2 methine signal at δ 3.42 ppm (m, 1H) and a broad singlet integrating for two protons at δ 3.08 ppm clearly confirmed the formation of the diol **19**. Furthermore in the IR spectrum, a strong peak at 3391 cm^{-1}(characteristic of O-H stretching) was observed. ^{13}C NMR, mass spectra and elemental analysis were in complete conformity of the assigned structure.

Scheme 2



Selective protection of the primary hydroxyl group present in compound **19** as the TBS ether was conveniently achieved with TBSCl and Im-H in anhydrous CH_2Cl_2 to furnish **20** in 94% yield (Scheme 3). The product was confirmed by the presence of additional peaks in the ^{1}H NMR spectrum due to the TBS group. A multiplet at δ 0.91 ppm integrating for nine protons and six protons as a singlet at δ 0.08 ppm was observed.

Scheme 3



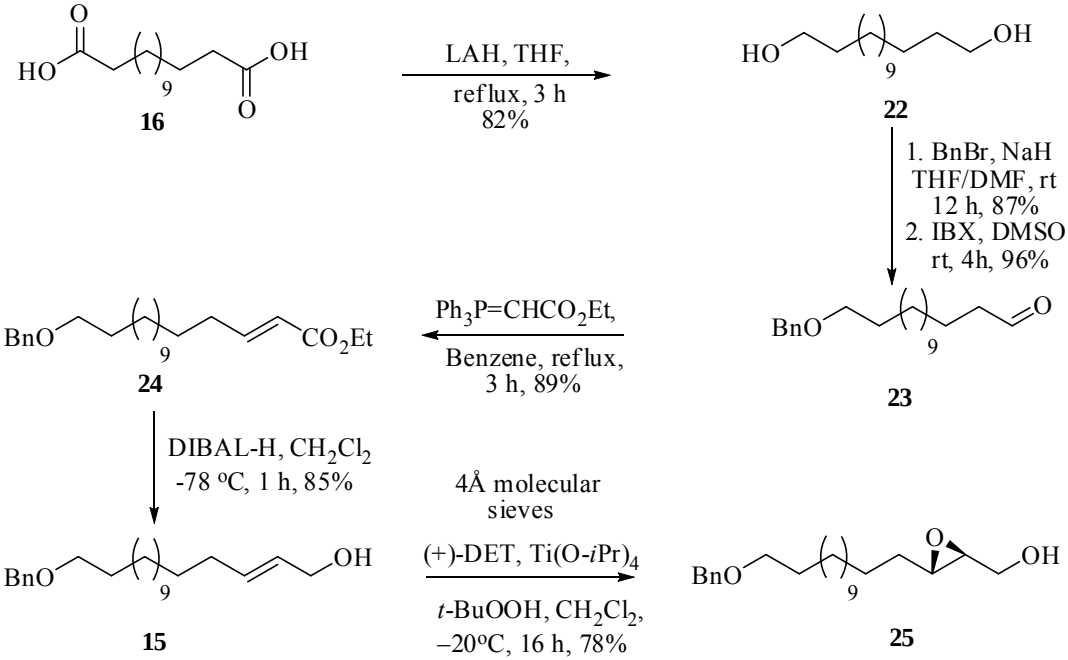
The MEM derivative **21** was derived from **20** in 81% yield on exposure to MEMCl and DIPEA in CH_2Cl_2 solvent for 2 h. The product was readily confirmed by the ^{1}H NMR spectrum together with substantial information from ^{13}C NMR, IR and mass spectra. Treatment of the MEM derivative **21** with TBAF in THF followed by oxidation with IBX in DMSO furnished the α-substituted aldehyde **10** in 82% yield over two steps. The structural feature was unambiguously corroborated from the combined spectral data from ^{1}H NMR, ^{13}C NMR, IR and ESI mass spectra. The peaks owing to TBS group disappeared in the ^{1}H NMR spectrum. New peak at δ 9.61 ppm characteristic of aldehyde proton was observed. The ESI mass spectrum gave a molecular ion peak at (*m/z*) 311.37 for $[M+Na]^+$ that confirmed the formation of **10**.

Synthesis of Fragment II

Synthesis of fragment **II** was started from commercially available 1,12-dodecanedicarboxylic acid (**16**). **16** on reduction with LAH[14] in THF produced the corresponding diol **22** which was converted selectively as the monobenzyl ether by

treating with BnBr[15] and sodium hydride in a solvent system of THF:DMF (7:3) in 87% yield (Scheme 4). This monobenzylated alcohol on exposure to IBX in DMSO furnished the corresponding monoprotected aldehyde **23.** The presence of aldehyde proton at δ 9.75 ppm as a triplet and methylene protons adjacent to aldehyde group at δ 2.41 ppm were the indication of **23** in the ^{1}H NMR spectrum. This was supported by a molecular ion peak at (*m/z*) 341.57 for $[M+Na]^+$ in the ESI mass spectrum. The aldehyde **23** was quickly exposed to (ethoxycarbonylmethylene)-triphenylphosphorane[16] in benzene under reflux to provide the corresponding α,β-unsaturated ester as a predominant *E*-isomer **24** in 89% yield. The ^{1}H NMR spectrum of the α,β-unsaturated ester displayed characteristic coupling constant (J = 15.7 Hz) for olefinic protons. In the IR spectrum, the carbonyl stretching at 1710 cm^{-1} characteristic of α,β-unsaturated ester was observed whereas the ESI mass spectrum showed the highest molecular ion peak at (*m/z*) 411.57 for $[M+Na]^+$. Reductive chemistry was next undertaken with DIBAL-H[17] to provide the corresponding allyl alcohol **15** in 85% yield.

Scheme 4

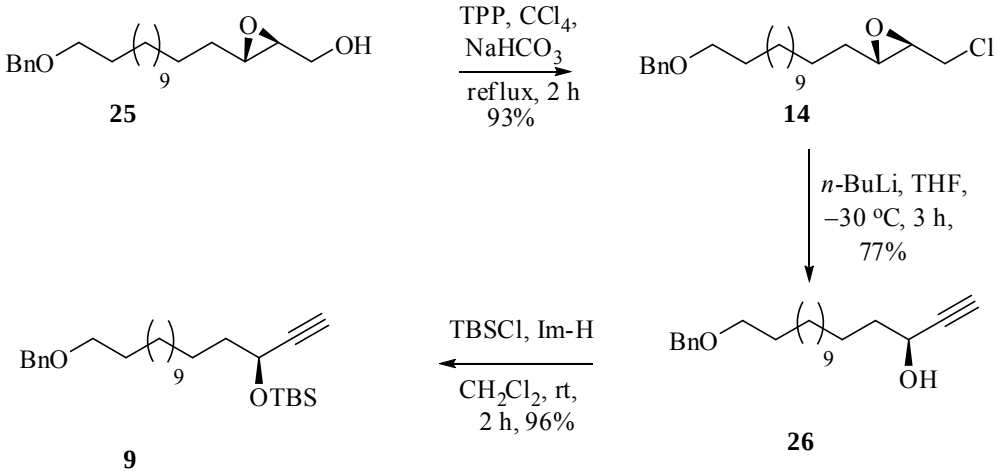


The structure was elucidated on the basis of ^{1}H NMR, IR and ESI mass spectral analysis. In the ^{1}H NMR spectrum, the resonances due to olefinic protons moved upfield

and were observed between δ 5.70-5.57 ppm while the CH_2 group of allyl alcohol was localized at δ 4.05 ppm. The highest molecular ion peak at (*m/z*) 369.29 for $[M+Na]^+$ was recorded in the ESI mass spectrum. The next phase of the endeavor was Sharpless asymmetric epoxidation (SAE)[18] of the allyl alcohol **15**. The epoxidation was performed with Ti(O-*i*Pr)$_4$/(+)-DET as the chiral complex and *t*-butyl hydroperoxide as the oxidant (Scheme 4). The product **25** was obtained after column chromatography in 78% yield. The spectral information from ^{1}H NMR, ^{13}C NMR, IR, ESI mass spectra studies proved the structure of **25** beyond doubt. The multiplet between δ 2.93-2.87 ppm revealed the identity of the epoxy protons, whereas the two olefinic protons disappeared in the region of δ 5.70-5.57 ppm. The rest of the protons resonated at the expected chemical shift regions.

Reaction of epoxy methanol **25** with TPP in refluxing CCl_4[19] containing $NaHCO_3$ gave the required epoxymethyl chloride **14** in gratifying 93% yield (Scheme 5). The methylene group (CH_2Cl) moved upfield and resonated as two doublet of doublet at δ 3.57 ppm (*J* = 11.5, 5.8 Hz) and δ 3.49 ppm (*J* = 11.5, 5.8 Hz) in the ^{1}H NMR spectrum. The molecular ion peak at (*m/z*) 403.75 for $[M+Na]^+$ in the ESI spectrum was an additional informatory support. The key transformation was next effected by exposure of **14** to 3 eqv of *n*-BuLi, which resulted in the generation of propargyl alcohol derivative **26** through double elimination.[20]

Scheme 5



This transformation was clearly verified by ^{1}H NMR, IR, ESI mass spectral data of the product. In the ^{1}H NMR spectrum, the acetylenic proton was seen as a doublet at δ 2.43 ppm and the rest of the protons were present at their respective position of the spectrum. Protection of the newly generated hydroxyl center in the alkynol **26** as its TBS ether resulted in the formation of fragment **II** (**9**). The structure of compound **9** was unambiguously assigned on the basis of spectral studies. The appearance of additional peaks at δ 0.90 (m, 9H) and 0.11 (s, 6H) ppm in the ^{1}H NMR clearly concluded the presence of TBS group in the product. The molecular ion peak at (*m/z*) 481.77 for $[M+Na]^+$ in the ESI mass spectrum was an additional support for that observation.

Coupling of two fragments

As the two fragments were in our hand our next strategy was to unite them. Generation of the lithiated alkyne under various basic conditions to couple with the aldehyde **10** was attempted as mentioned below in Table 1.[21-23] But none of them could succeed in the required coupling to happen. We had also tried zinc triflate[24] mediated coupling of the alkyne with the aldehyde but that attempt was also turned in vain (Scheme 6).

Scheme 6

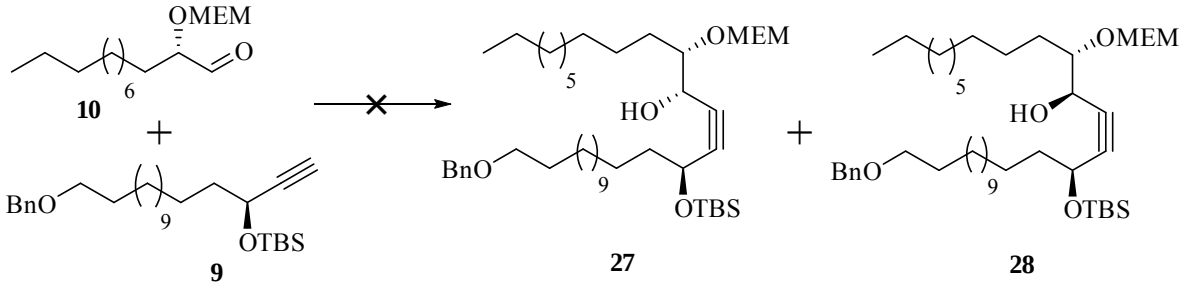
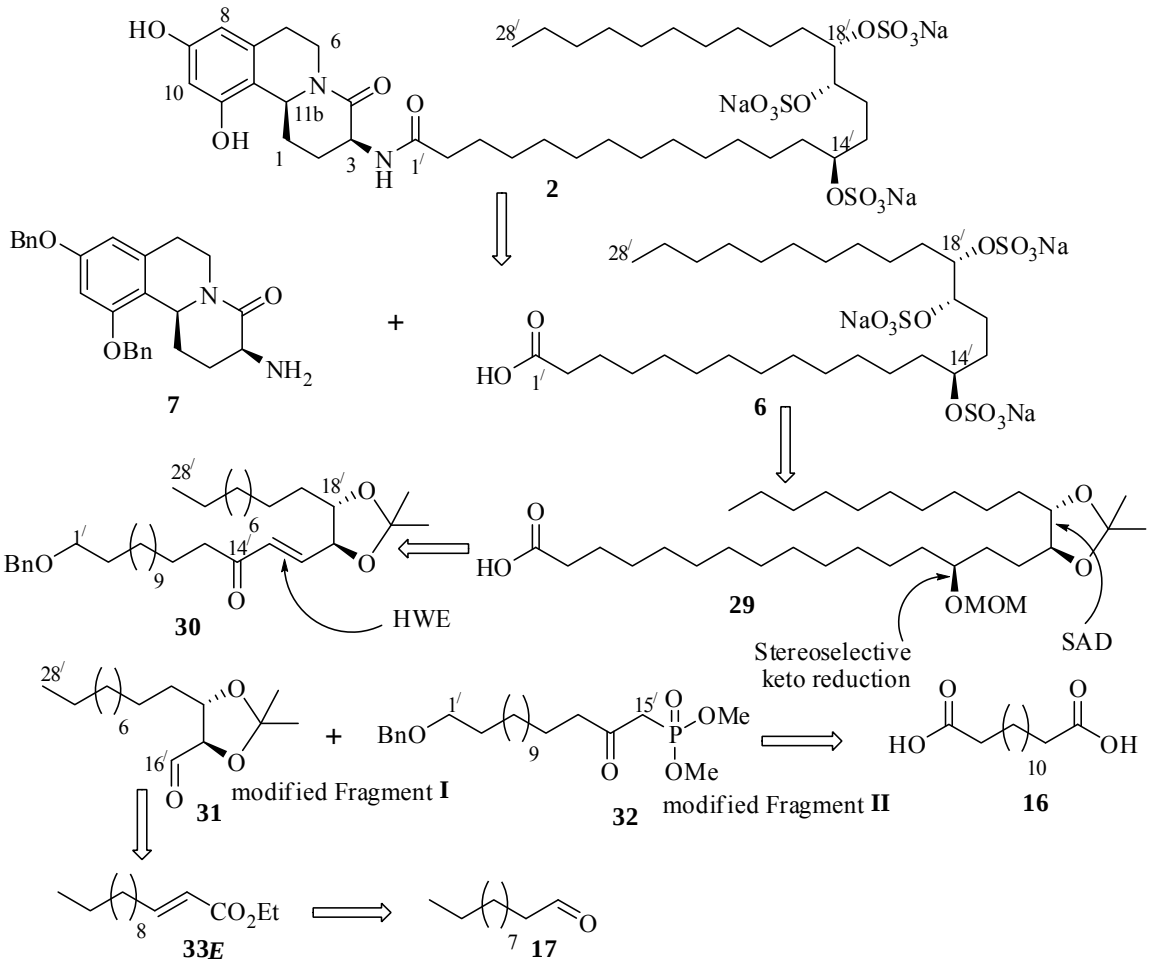


Table 1

Conditions employed	Observation
1. *n*-BuLi, THF, –78 ^{o}C, 1 h.	No reaction. Starting alkyne **9** recovered.
2. *n*-BuLi, THF: HMPA (10:1), –78 ^{o}C, 1 h.	No reaction. Both the Starting material decomposed.
3. *s*-BuLi, TMEDA, THF, –78 ^{o}C, 1 h.	No reaction. Both the Starting material decomposed.
4. LDA, THF, –78 ^{o}C, 1 h.	No reaction. Starting alkyne **9** recovered.
5. $Zn(OTf)_2$, Et_3N, rt, 12 h.	No reaction. Starting alkyne **9** recovered.

After this failure, an alternative yet simplified approach to reach the target was planned. A convergent strategy towards the suitably protected C_{28} fatty acid **29** was envisaged.

Scheme 7. *Modified retrosynthetic Strategy*.



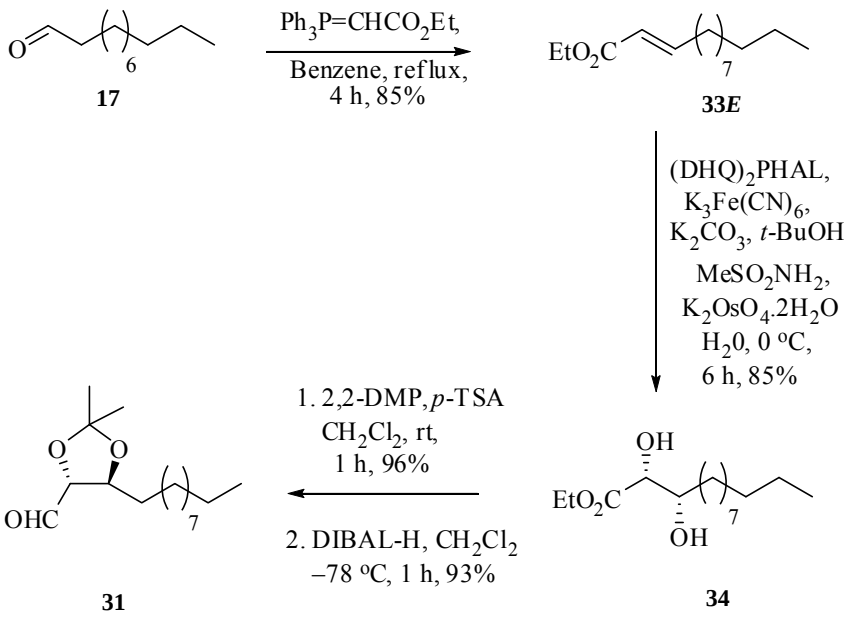
Initial C-C disconnection involved the separation of C_1'-C_{15}' fragment (**32**) from the C_{16}'-C_{28}' fragment (**31**) (Scheme 7). From the synthetic point of view these two building blocks (**31** and **32**) can be united *via* a Horner-Wadsworth-Emmons reaction.[25] The resulting enone *en route* should additionally provide access to the C_{14}'-OH group by employing face selective keto reduction with chiral reducing agent. Our plan for the synthesis of C_{16}'-C_{28}' subunit is founded upon the Sharpless asymmetric dihydroxylation[26] on the α,β-unsaturated ester **33*E*** that can be elaborated from the commercially available 1-undecanal (**17**) by simple two carbon Wittig homologation.

Simple functional group manipulations on 1,12-dodecane dicarboxylic acid (**16**) would lead to the formation of the achiral building block **32**.

Synthesis of modified fragment I

The journey toward the synthesis of aldehyde **31** began with commercially available 1-undecanal (**17**). The treatment of **17** with (ethoxycarbonylmethylene)-triphenylphosphorane in benzene at 80 ^{o}C provided the α,β-unsaturated ester as a geometric mixture (9:1 by TLC) (Scheme 8). The minor (*Z*)-isomer was eliminated through column chromatography. The predominant (*E*)-isomer **33*E*** obtained in 85% yield showed characteristic coupling constant (J = 15.7 Hz) for olefinic protons in the ^{1}H NMR spectrum. The relevant resonances due to alkene (a doublet at δ 5.80 ppm and a doublet of triplet at δ 6.96 ppm) and ester group $CO_2CH_2CH_3$ (δ 1.29 and 4.18 ppm) were observed in the ^{1}H NMR spectrum.

Scheme 8



The next task to generate stereocenters at C_2 and C_3 was carried out by employing Sharpless asymmetric dihydroxylation procedure. Thus, compound **33*E*** was treated with ligand $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$ and $K_2OsO_4.2H_2O$ in *t*-BuOH-H_2O (1:1) at 0 ^{o}C for 6 h to afford the diol **34** in 85% yield. The formation of this product was confirmed after thorough investigation of the ^{1}H NMR, ^{13}C NMR spectra and

elemental analysis. In the ^{1}H NMR spectrum, the H-2 and H-3 protons resonated as doublet and doublet of triplet at δ 4.06 and 3.86 ppm respectively. In the ^{13}C NMR spectrum, peaks at 73.2 and 72.5 ppm correspond to C_2 and C_3 of compound **34**. In the ESI mass spectrum the presence of molecular ion peak at (*m/z*) 297.20 for $[M+Na]^+$ confirmed that observation. The enantiomeric purity of **34** was estimated to be 98.5% *ee* by HPLC analysis of the corresponding dibenzoate using a chiracel OD column (0.8% *i*-Propanol/*n*-hexane, flow rate 0.5mL/min, λ = 225 nm).

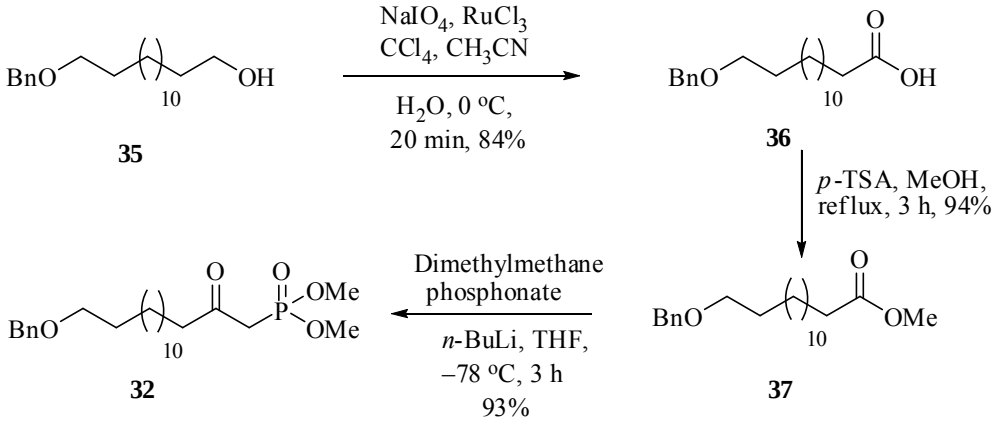
The diol **34** was ketalized under acidic condition using 2,2-dimethoxy propane[30] in CH_2Cl_2 in the presence of catalytic *p*-TSA to furnish **34-acetonide** in 96% yield. Controlled reduction of carboxylate group of **34-acetonide** was performed by using DIBAL-H in anhydrous CH_2Cl_2 at −78 ^{o}C to obtain the requisite aldehyde **31** (Scheme 8). The structure of compound **31** was assigned after thorough investigation of its ^{1}H NMR, ^{13}C NMR, IR and ESI mass spectra. In the ^{1}H NMR spectrum, the absence of signals at δ 4.24 and 1.29 ppm with the concomitant appearance of new peak at δ 9.72 ppm as a clear doublet confirmed the formation of **31**. Appearance of signal at δ 200.9 ppm in the ^{13}C NMR spectrum was also proved to be confirmatory in favor of **31**.

Synthesis of modified Fragment II

The next task was to synthesise the β–keto phosphonate **32** starting from the monobenzyl protected alcohol **35** (synthesized previously in Scheme 4). $NaIO_4$-cat.$RuCl_3$[27] mediated controlled oxidation of **35** in a solvent system of CCl_4-CH_3CN-H_2O (1:1:2) for 20 min furnished the carboxylic acid **36** in 84% yield (Scheme 9). Treatment of the acid **36** with methanol in presence of catalytic *p*-TSA under refluxing condition produced the corresponding methyl ester **37** in 94% yield. The methyl ester **37** gave satisfactory spectral data. The ^{1}H NMR spectrum carried peaks at δ 3.66 ppm integrating for three protons as a singlet, characteristic of O-CH_3 protons. The benzylic methylene protons resonated at δ 4.49 ppm, while the aromatic protons appeared at the region of δ 7.33-7.27 ppm, whereas the other peaks resonated at their expected chemical shifts. This methyl ester **37** was the suitable substrate to produce the crucial phosphonate intermediate **32**. Dimethylmethane phosphonate[28] on reaction with *n*-BuLi at −78 ^{o}C

produced the corresponding lithiated phosphonate ylide, which on reaction with **37** furnished the β-keto phosphonate **32** in 93% yield.

Scheme 9



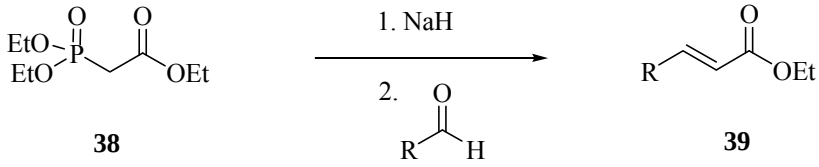
The structure of compound **32** was adequately substantiated by spectral studies. In the ^{1}H NMR spectrum, the activated methylene protons flanked by carbonyl and dimethyl phosphate groups appeared at δ 3.07 ppm as a doublet having coupling constant J = 22.7 Hz. This higher J value can be attributed to the coupling of methylene protons with the adjacent phosphorus atom. The other peaks resonated at their expected chemical shift values. The molecular ion peak at (*m/z*) 463.25 for $[M+Na]^+$ in the ESI mass spectrum was an additional support for that observation.

After the formation of both the coupling partners **31** and **32** our next goal was to furnish the coupling reaction by the modified Wittig-Horner protocol (known as Horner-Wadsworth-Emmons reaction).

A brief overview on Horner-Wadswoth-Emmons reaction

The Horner-Wadsworth-Emmons reaction (or HWE reaction) is the chemical reaction of stabilized phosphonate carbanions with aldehydes (or ketones) to produce predominantly E-alkenes (Scheme 10).

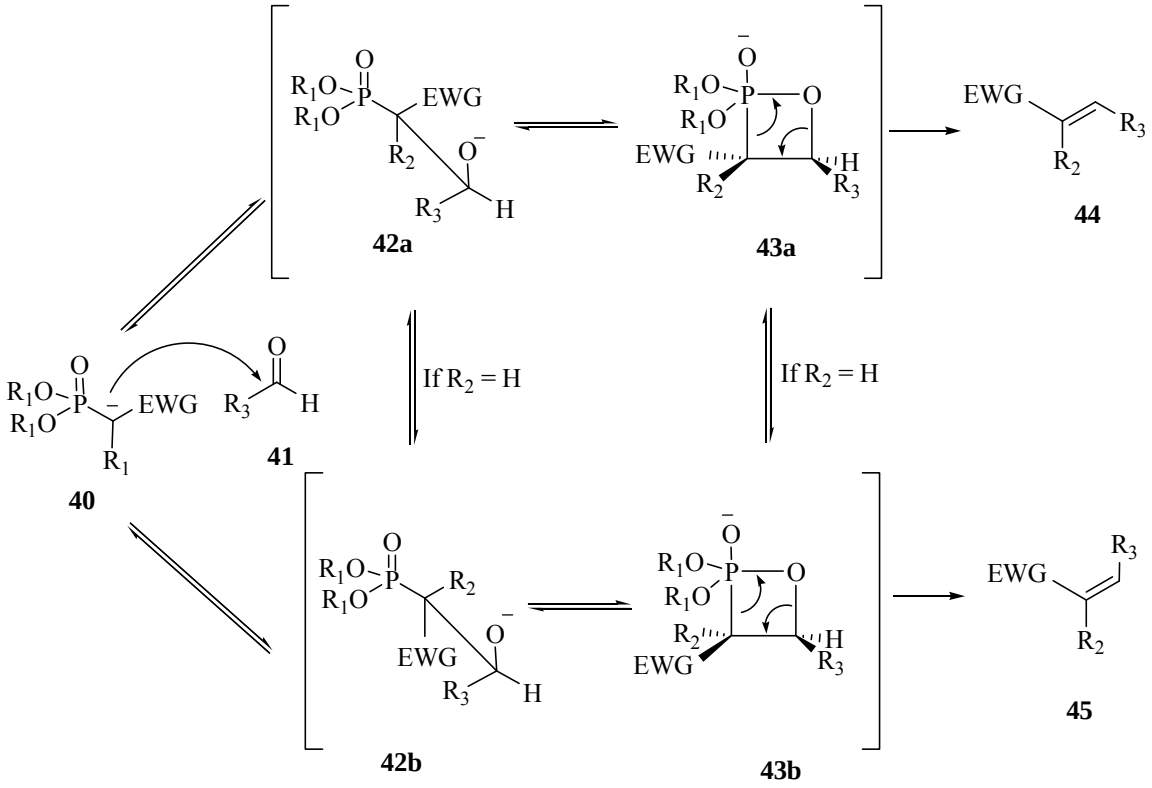
Scheme 10



38 **39**

In 1958, Leopold Horner published a modified Wittig reaction using phosphonate-stabilized carbanions.[29,30] William S. Wadsworth and William D. Emmons further developed the reaction. [31,32] In contrast to phosphonium ylides used in the Wittig reaction, phosphonate-stabilized carbanions are more nucleophilic and more basic. Likewise, phosphonate-stabilized carbanions can be alkylated, unlike phosphonium ylides. The dialkylphosphate salt byproduct is easily removed by aqueous extraction.

Scheme 11*. Reaction mechanism.*



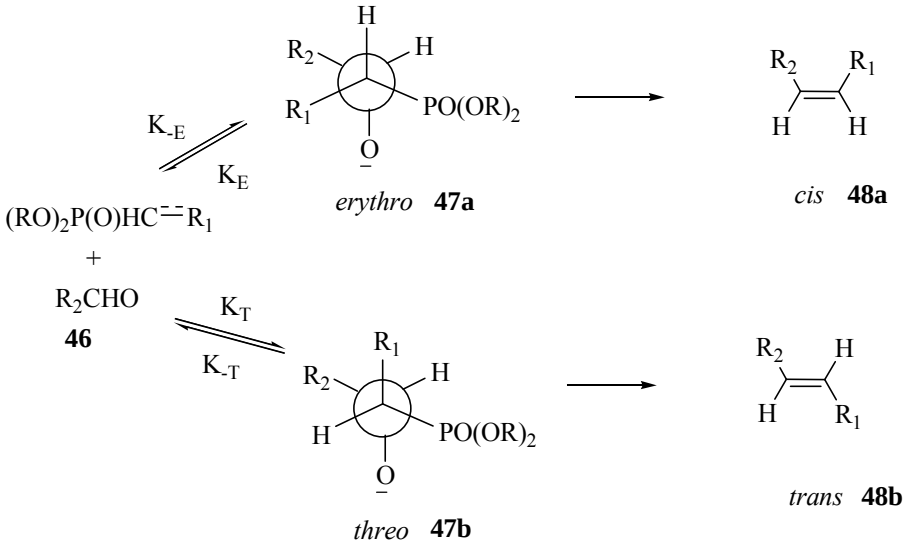
*The Horner-Wadsworth-Emmons reaction begins with the deprotonation of the phosphonate to give the phosphonate carbanion **40** (Scheme 11). Nucleophilic addition of the carbanion onto the aldehyde **41** (or ketone) producing **42a** or **42b** is the rate-limiting step.[33] If R_2=H, then intermediates **42a** and **43a** can interconvert with intermediates **42b***

and ***43b****.*[34] *The final elimination of* ***43a*** *and* ***43b*** *would yield E-alkene* ***44*** *and Z-alkene* ***45****. The ratio of alkene isomers* ***44*** *and* ***45*** *is dependent upon the stereochemical outcome of the initial carbanion addition and upon the ability of the intermediates to equilibrate. The electron-withdrawing group (EWG) α to the phosphonate is necessary for the final elimination to occur. In the absence of an electron-withdrawing group, the final product is the α-hydroxyphosphonate* ***42a*** *and* ***42b****.*[35] *However, these α-hydroxyphosphonates can be transformed to alkenes by reaction with diisopropylcarbodiimide.*[36]

Stereoselectivity

The Horner-Wadsworth-Emmons reaction favours the formation of E-alkenes. In general, the more equilibration occurs amongst intermediates, the higher the selectivity for E-alkene formation. It appears that the stereochemical course of the reaction (Scheme 12)[37] *is governed by the same steric effects at the intermediate level as that of the conventional Wittig reaction.*

Scheme 12*. Proposed stereochemical course of the phosphonate modification of the Wittig reaction showing formation of cis and trans isomers.*



The intermediate oxyanions, formed reversibly by reaction of the phosphonate carbanion and the aldehyde ***46****, can exist as two diastereoisomers, where the erythro betaine* ***47a*** *is the precursor of the cis olefin* ***48a*** *via a cis elimination. Similarly the threo*

betaine ***47b*** *leads to the trans product* ***48b.*** *The ratio of isomeric olefins would then be expected to be determined by the degree of reversibility of the formation of the two oxyanions* ***47a*** *and* ***47b*** *if they do not interconvert directly, and of the rates of their decomposition into olefins* ***48a*** *and* ***48b.*** *Because the stereochemistry of the reaction generally favors the trans olefin, it can be supposed that the formation and decomposition of the threo betaine* ***47b*** *is more rapid than that of the erythro betaine* ***47a.*** *This would be expected on steric grounds since the erythro betaine* ***47a,*** *which is more sterically hindered in the eclipsed conformation, will be formed at a slower rate than the threo betaine* ***47b.*** *Similarly the rate of decomposition of the threo betaine* ***47b*** *to the trans olefin* ***48b*** *is usually greater than that of the erythro betaine* ***47a*** *to the cis olefin* ***48a*** *because the threo betaine is less sterically hindered and provides better conjugative stabilization of the incipient double bond in the transition state. Such conjugation should be more difficult in the transition state from the erythro betaine since the* R_1 *and* R_2 *groups could not become coplanar with the incipient double bond.*

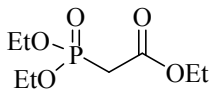
Disubstituted alkenes

Thompson and Heathcock have performed a systematic study of the reaction of trimethyl phosphonoacetate with various aldehydes.[38] *While each effect was small, they had a cumulative effect making it possible to modify the stereochemical outcome without modifying the structure of the phosphonate. They found greater E-stereoselectivity with the following conditions: 1. increasing steric bulk of the aldehyde. 2. Higher reaction temperatures (23* ^oC *over –78* ^oC*). 3. Li>Na>K salts. 4. Using the solvent DME over THF. In a separate study, it was found that bulky phosphonate and bulky electron-withdrawing groups enhance E-alkene selectivity.*

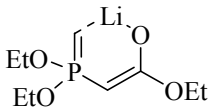
Base sensitive substrates

Since many substrates are not stable to sodium hydride, several procedures have been developed using milder bases. Masamune and Roush have developed mild conditions using lithium chloride and DBU.[39]

Figure 3



49

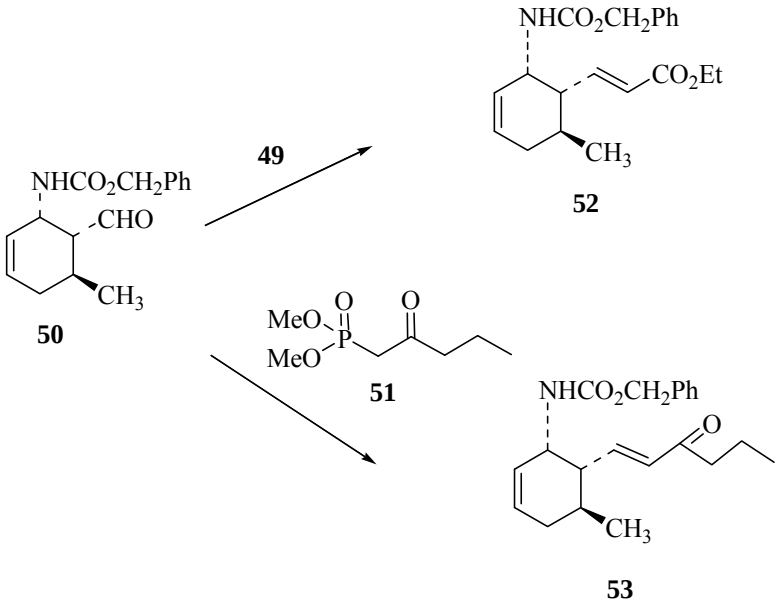


49a

Lithium cations affect the course of the Wittig reaction and its modified version, the Horner-Wadsworth-Emmons (HWE) reaction, in many important ways.[40] *For instance, as contrasted with other metal cations, Li^+ most likely forms a tight complex with the carbanion derived from phosphonate* ***49*** *as shown in* ***49a*** *(Figure 3), thereby enhancing the acidity of* ***49****.*[41] *The pKa values of* ***49*** *in diglyme (Li^+) and in dimethylsulfoxide (K^+), relative to 9-phenylfluorene,*[42] *were reported to be 12.2 and 19.2 respectively.*[43]

These results immediately suggested the possibility that in the presence of a lithium salt related phosphonates could be easily deprotonated with an amine like, DBU (pKa 11.6)[44] *or diisopropylethyl amine (DIPEA, pKa 10.5)*[44] *to generate reactive species under simple, mild conditions. In fact, this reaction protocol has been used to achieve successful olefinations of a base-sensitive substrate or reagent. Conventional methods, for instance using NaH in THF or K_2CO_3 in toluene,*[45] *may cause complications in such cases.*

Scheme 13



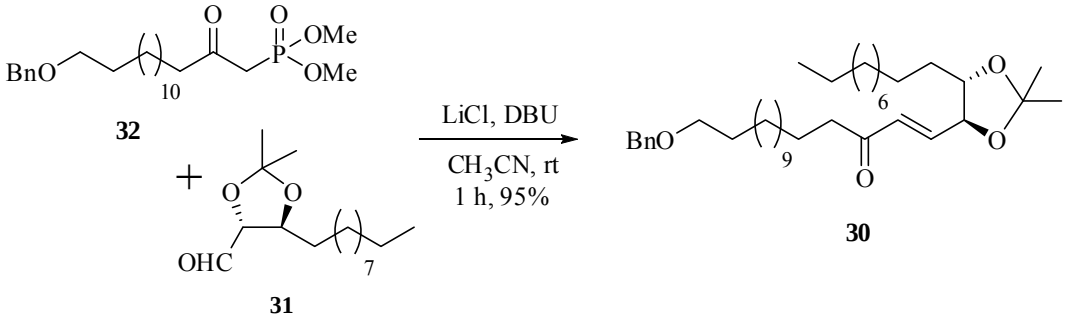
The mild conditions used in this protocol become critically important in certain cases. Thus olefination of the base labile ***50****,*[46] *with the phosphonate* ***49*** *or* ***51****, using the standard procedure with DIPEA as the base proceeded smoothly (Scheme 13). In contrast Overmann and co-workers had noted that the conventional means of*

*deprotonating **49** and **51** with NaH apparently resulted in varying degrees of the epimerization of the aldehyde prior to the olefination.*[47]

The advantages of using phosphonate carbanions in olefin synthesis over the conventional Wittig reaction have resulted in their increasing application in the synthesis of a wide range of compounds. Particular advantage has been made of the fact that the steric requirements at the intermediate stage of the reaction often permit the reaction to proceed stereoselectively to produce predominantly the trans olefin. Syntheses involving natural products illustrate this point.

After exploring a variety of bases (K_2CO_3, NaH and *n*-BuLi), we concluded that the key HWE-reaction between **32** and **31** can be successfully carried out using DBU-LiCl. Thus, compound **32** was treated with LiCl, DBU in acetonitrile and finally the aldehyde **31** was added to it to produce α,β-unsaturated ketone **30** in 95% yield having exclusive *E*-configuration (Scheme 14).

Scheme 14

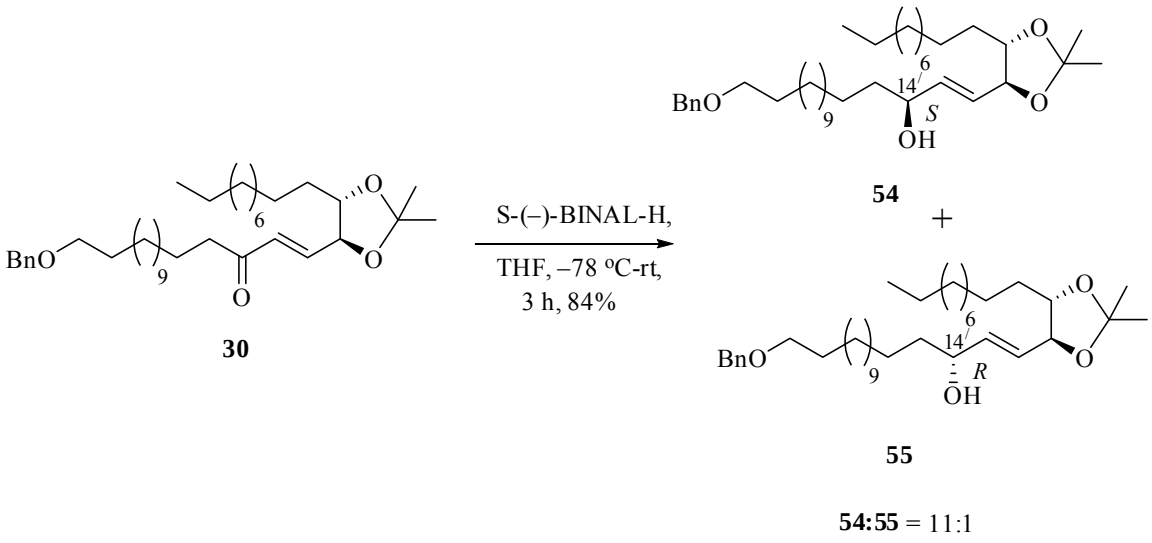


In the IR spectrum, the α,β-unsaturated carbonyl stretching was observed at 1697 cm^{-1} with concomitant absence of the aldehyde stretching at 1736 cm^{-1}. In the ^1H NMR spectrum, the two olefinic protons resonated at δ 6.70 ppm (dd, *J* = 15.8, 5.7 Hz, 1H) and 6.36 ppm (dd, *J* = 15.8, 1.3 Hz, 1H). Coupling constant value of the olefinic protons ($J_{15,16}$ = 15.7 Hz) confirmed the assigned *E*-configuration. The terminal methyl proton appeared at δ 0.88 ppm (t, *J* = 6.7 Hz, 3H). NMR signals from both the coupling partners in the product confirmed structure **30**. In the ^{13}C NMR, resonances due to both the α,β-unsaturated carbonyl and the terminal methyl carbons at δ 199.8 and 14.1 ppm

respectively, further confirmed in favor of facile coupling. In the ESI mass spectrum the highest molecular ion peak of **30** at (*m/z*) 607.03 for $[M+Na]^+$ supported that observation.

In the next step we tried several reaction conditions (Table 2) to tune the asymmetric reduction of enone **30**; the enone **30** was reduced with (*S*)-(−)-BINAL-H[48] in THF at −78 °C to afford **54** and its (14′*R*)-isomer **55** in 11:1 ratio (Scheme 15).

Scheme 15



In order to avoid the use of (*S*)-(−)-BINAL-H, which is required in stoichiometric quantities, the reduction of enone **30** was attempted under Luche's conditions[49] to afford a 2:3 mixture of **54** and its epimer **55**. Interestingly, when the aforementioned ketone reduction was attempted with K-Selectride,[50] the diastereoselectivity was reversed, and the undesired diastereomer **55** was obtained as the major product. The structure of compound **54** was assigned on the basis of spectral and analytical studies. In the ^{13}C NMR, absence of carbonyl signal at δ 199.8 ppm and concomitant appearance of a new signal at δ 81.9 ppm for the hydroxyl bearing methine carbon clearly indicated the formation **54**. O-H stretching at 3446 cm^{-1} in the IR spectrum was seen. In the ESI mass spectrum molecular ion peak of **54** at (*m/z*) 609.47 for $[M+Na]^+$ was further supported that observation.

Table 2

Hydride reducing agents used	Ratio of the diastereomers 54 : 55	
$NaBH_4$	1	1
$NaBH_4.CeCl_3$	2	3
K-selectride	1	4
L-selectride	1	4
$Zn(BH_4)_2$	1	1
S-(–)-BINAL-H	11	1

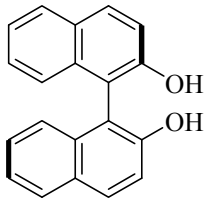
A brief overview on the BINAL-H mediated asymmetric reduction of the ketones

Over the last 20 years an explosive growth of research in the field of asymmetric synthesis has occurred.[51-59] *The aim of enantioselective synthesis or catalysis is to produce chiral products (a single enantiomer as the ultimate goal) starting from achiral substrates by exploiting the presence of chiral reagents. The role of chiral reagents is to generate diastereomeric transition states leading to the two enantiomers so that one of them is preferentially formed over the other. In such a schematic representation only two competitive pathways are present; one leading to the R enantiomer and the other giving rise to the S one. However in most cases the situation can be more complex. For instance, both the substrate and the reagent can exist as a mixture of conformational isomers where several conformations can be significantly populated. They can also exist in different states of aggregation or solvation with each of these species showing its own reactivity. The final result is a weighted average depending on the distribution and reactivity of the species involved and a low stereoselectivity is generally obtained. A rational approach to the control of stereoselectivity is based on the use of molecules possessing only symmetry elements of pure rotation and belonging to the C_n or D_n*

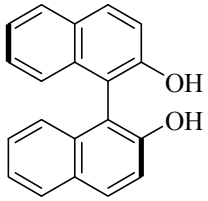
symmetry groups. This allows the prediction of the enantioselectivity due to the presence of only a single defined reactive species in solution. Under these assumptions, interest in the applications of chiral atropoisomers, especially binaphthalene systems has blossomed.[60,61] Since 1990 the enantiomeric atropoisomers of 1,1′- binaphthyl-2,2′-diol (BINOL) have become among the most widely used ligands for both stoichiometric and catalytic asymmetric reactions.

*2,2′-Disubstituted derivatives of 1,1′-binaphthyl have been widely used in organic synthesis. The stability of the enantiomers with barriers of rotation ranging from 23.8 kcal/mol for 1,1′-binaphthyl to more than 46 kcal/mol for 2,2′-diiodo-1,1′-binaphthyl enables their use as chirality inducers in asymmetric reactions. The most important compound of this type is 1,1′-binaphthyl-2,2′-diol (BINOL, $C_{20}H_{14}O_2$, mp 215-217 °C). The chiral atropoisomers (R)-**56** ($[\alpha]^{20}_D$ +35.5 (THF, c = 1), mp 205-211 °C) and (S)-**56** ($[\alpha]^{20}_D$ -34.5 (THF, c = 1), mp 205-211 °C) of which are stable at high temperature[62] and allow numerous asymmetric reactions under various experimental conditions (Figure 4). BINOL **56** is the best known representative of axially chiral molecules[63] and was first prepared as a racemate in 1873 by Von Richter.[64]*

Figure 4



(*R*)-(+)-BINOL **56**



(*S*)-(–)-BINOL **56**

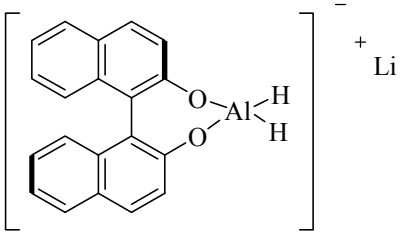
Reduction of Ketones

Among a wide variety of asymmetric reactions, enantioselective reduction of prochiral carbonyl compounds is one of the most extensively studied transformations.[65]

A standard method to this end stems from the use of complex metal hydride reagents bearing chiral alkoxyl or amino ligands. In this area a number of reagents have been developed by modification of lithium aluminum hydride ($LiAlH_4$) with alkaloids and

sugars among the things. Nevertheless, the general difficulty in obtaining a high level of stereoselectivity was attributed to the presence of multiple reactive species that are placed in different chemical and chiral environments. In this context, only Al reagents bearing a ligand with a C_2 axis (such as BINOL ***56****) led to high enantiomeric excesses in the enantioselective reduction of aromatic ketones. A reducing agent called (R)-BINAL-H* ***57*** *was prepared by mixing $LiAlH_4$ and an equimolar amount of enantiomerically pure BINOL* ***56*** *in THF (Figure 5).*[66-70] *However, this initial attempt failed to reduce prochiral acetophenone in significant enantiomeric excess (2% ee). This result prompted Noyori et al. to examine a further modification of the reagent by adding a second simple alcohol*

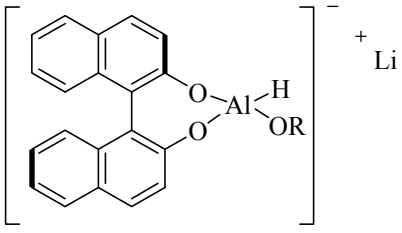
Figure 5



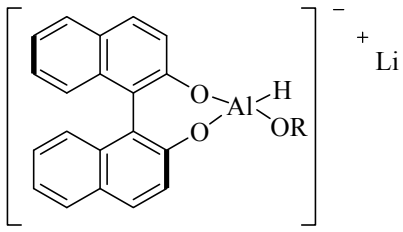
(R)-(+)-**57**

(EtOH): replacement of either hydrogen by an EtO moiety produces an identical single aluminum hydride reagent (Figure 6).[71]

Figure 6



(R)-(+)-**58**

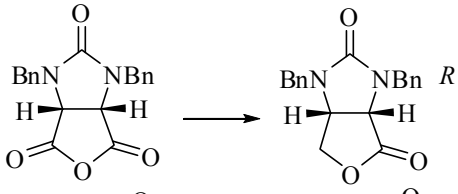
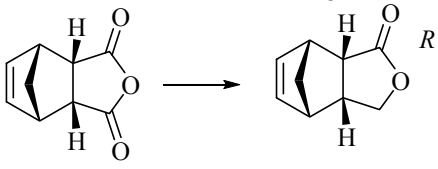


(S)-(–)-**58**

*A series of prochiral alkyl phenyl ketones when reduced with 3 eqv of (R)-****58*** *or (S)-****58*** *at low temperature (–100 to –78 °C) gave the corresponding carbinols in high enantiomeric excess together with good enantioface differentiation as shown in Table 3(entries 10 and 11). This methodology was recently applied to the synthesis of chiral*

lactones through enantioselective reduction of a carbonyl group in meso-1,2-dicarboxylic anhydrides.[72,73]

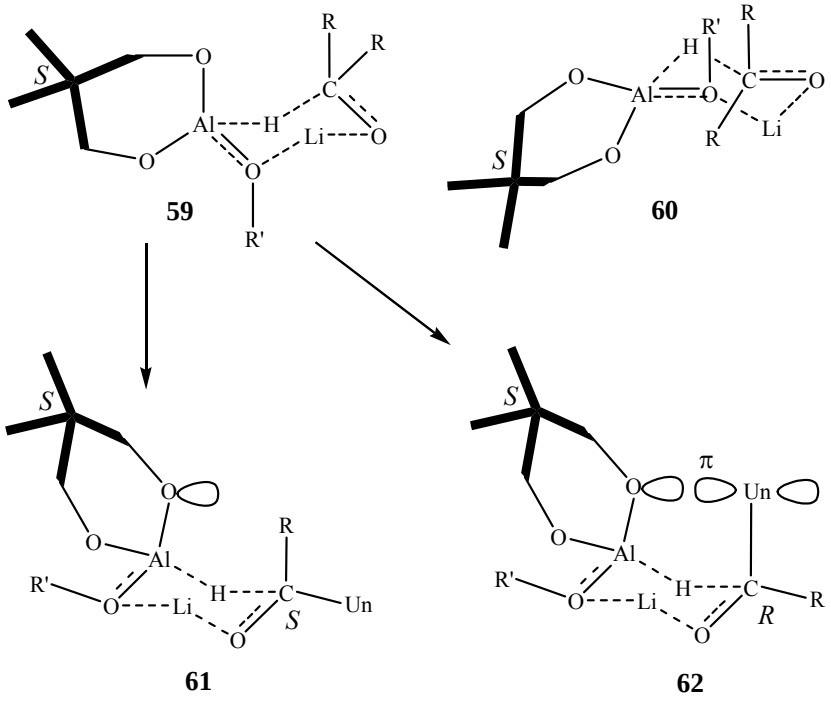
Table 3

Entry	Ketone	BINOL confign. in 58	yield(%)	*ee* (%)
1	$C_6H_5COCH_3$	*R*	61	95(*R*)
2	$C_6H_5COC_2H_5$	*S*	62	98(*S*)
3	C_6H_5CO-*n*-C_3H_7	*S*	92	>99(*S*)
4	C_6H_5CO-*n*-C_4H_9	*S*	64	>99(*S*)
5	$C_6H_5COCH(CH_3)_2$	*S*	68	71(*S*)
6	$C_6H_5COC(CH_3)_3$	*R*	80	44(*R*)
7	α-tetralone	*R*	91	74(*R*)
8	$C_6H_5COCH_2Br$	*R*	97	95(*S*)
9	(*E*)-*n*-C_4H_9CH=$CHCOCH_3$	*R*	47	79(*R*)
10	(*E*)-*n*-C_4H_9CH=$CHCO$-*n*-C_5H_{11}	*R*	91	91(*R*)
11	(*E*)-cyclo-C_5H_9CH=$CHCO$-*n*-C_5H_{11}	*R*	91	92(*R*)
12		*R*	76	90
13		*R*	69	84

Reactivity of the carbonyl substrates toward BINAL-H reduction seems to be greatly influenced by steric and various electronic factors like LUMO level, electron

density at the carbonyl carbon, flexibility of the molecule, etc. Thus, the early or late nature of the transition state (energy, shape, tightness, atomic distances, etc.) varies subtly from reaction to reaction. Although it is not easy to present a unifying view, the stereochemistry of carbonyl group reduction may be rationalized as proceeding through the pathway depicted in Scheme 16.[74]

Scheme 16



The reaction is initiated by the complexation of the Li^+ cation to the oxygen atom of the C=O group which is thus activated. The product-determining hydride transfer then occurs from Al to the carbonyl carbon by way of a six-membered ring transition state (Zimmerman-Traxler). In this case the two binaphthoxy oxygens of (S)-BINAL-H ***58*** *are diastereotopic, and therefore, two types of chairlike transition states,* ***59*** *and* ***60****, are possible. When a prochiral unsaturated ketone (UnCOR, for example) is reacted with* ***59****, there emerge two diastereomeric transition states,* ***61*** *and* ***62****. A series of (S)-BINAL-H reductions giving S products selectively indicates that transition state* ***61*** *is generally favored over the R-generating transition state* ***62****. This* ***61*** *versus* ***62*** *relative stability would be controlled primarily by interactions between the axially located groups. Thus transition state* ***62*** *possessing axial-Un and equatorial R groups is destabilized by the*

substantial n/π-type electronic repulsion between the axially oriented binaphthoxyl oxygen and the unsaturated moiety.

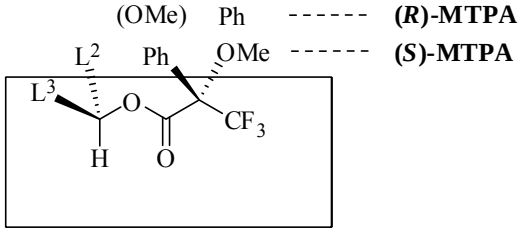
Although the gross structure of **54** was revealed by its spectral studies, the absolute stereochemistry at the newly formed chiral center at $C_{14'}$ of the aliphatic chain could not be ascertained based on spectral studies. Hence, we have opted for modified Mosher's method[75] to establish the absolute stereochemistry.

A brief overview on modified Mosher's ester method

Determination of the absolute stereochemistry of organic compounds has become an important aspect for natural product chemists as well as synthetic chemists. The limitations involved in physical methods such as exciton chirality method and X-ray crystallography forced synthetic chemists for a more reliable alternative. Since NMR spectroscopy has been available to chemists, there have been numerous studies on the applications of this technique. One of these methods use the difference in the chemical shift (i.e. the distance between the peaks) of two diastereomers.[76] It was reasoned that if a mixture of enantiomers could be converted into a mixture of diastereomers then it would be possible to distinguish them using NMR. As a result Harry S. Mosher, et al. came up with the reagent MTPA (α-methoxy-α-(trifluoromethyl)phenylacetic acid also known as Mosher's acid). The corresponding acid chloride, also known as Mosher's acid chloride, and the resultant diastereomeric esters are known as Mosher's esters. Mosher's acid or acid chloride reacts easily with alcohols and amines to give esters and amides respectively. This method is able to determine the configuration of simple chiral amines and alcohols.[77] The reason racemization does not occur is because there is no α-hydrogen near the carboxyl group (therefore it cannot form an enol). This allows it to react with alcohols or amines to form an MPTA ester or amide respectively. Although there are several chemical methods used to predict the absolute configuration of organic substances, Mosher's method using MTPA esters has been most frequently used.

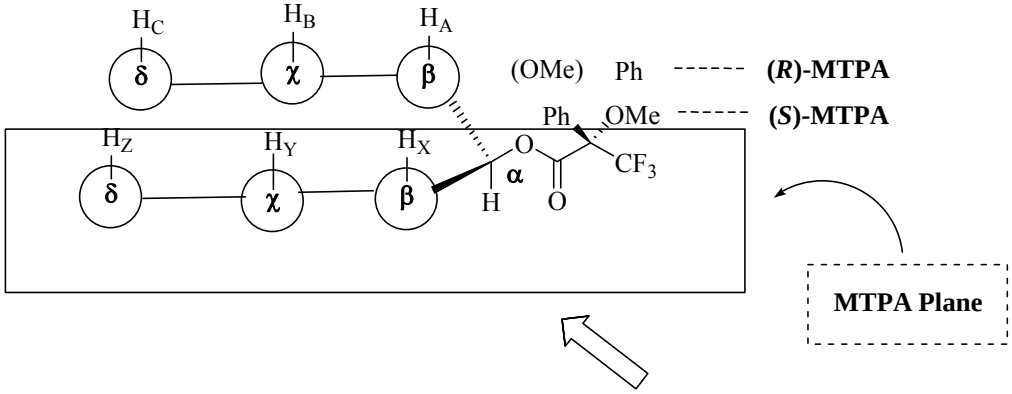
Mosher proposed that in solution the carbinyl proton, ester carbonyl and trifluoromethyl group of the MTPA moiety lie in the same plane (Figure 7).[78]

***Figure 7**. Configurational correlation model for (R)-MTPA and (S)-MTPA derivatives proposed by Mosher.*



When the MTPA group is in the hypothesized conformation, Mosher pointed out that the ^{1}H NMR signal of L^2 of the (R)-MTPA ester will appear upfield relative to that of the (S)-MTPA ester due to the diamagnetic effect of the benzene ring. The lack of reliability associated with Mosher's ^{19}F method using ^{19}F NMR motivated Kakisawa et al. to elaborate this concept for more accuracy.[79] The modified Mosher's ester method (^{1}H) is one of the simple and efficient ways to determine the absolute stereochemistry of the secondary alcohols and amine stereo centers in organic molecules.

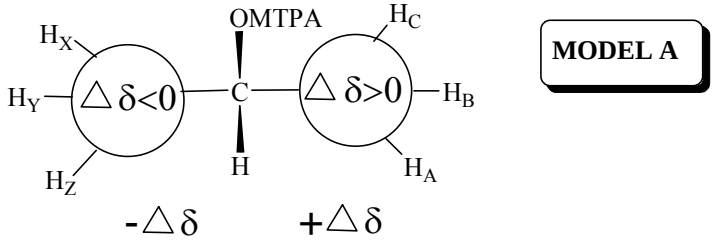
***Figure 8**. MTPA plane of an MTPA ester is shown. $H_{A,B,C}$ and $H_{X,Y,Z}$ are on the right and left sides of the plane respectively.*



The basic concept of the modified Mosher's ester method is essentially the same as Mosher proposed. The idealized conformation is depicted in Figure 8. The plane and the conformation of MTPA group will be called as the MTPA plane and ideal conformation respectively. Due to the diamagnetic effect of the benzene ring, the $H_{A,B,C....}$ NMR signals of (R)-MTPA ester should appear upfield to those of the (S)-MTPA ester. The reverse should hold true for $H_{X,Y,Z....}$. Therefore, when $\Delta\delta = (\delta_S - \delta_R) \times 1000$ protons

on the right side of the MTPA plane must have positive values (Δδ > 0), and the protons on the left side of the MTPA plane must have negative values (Δδ < 0). This is illustrated in model A (Figure 9).

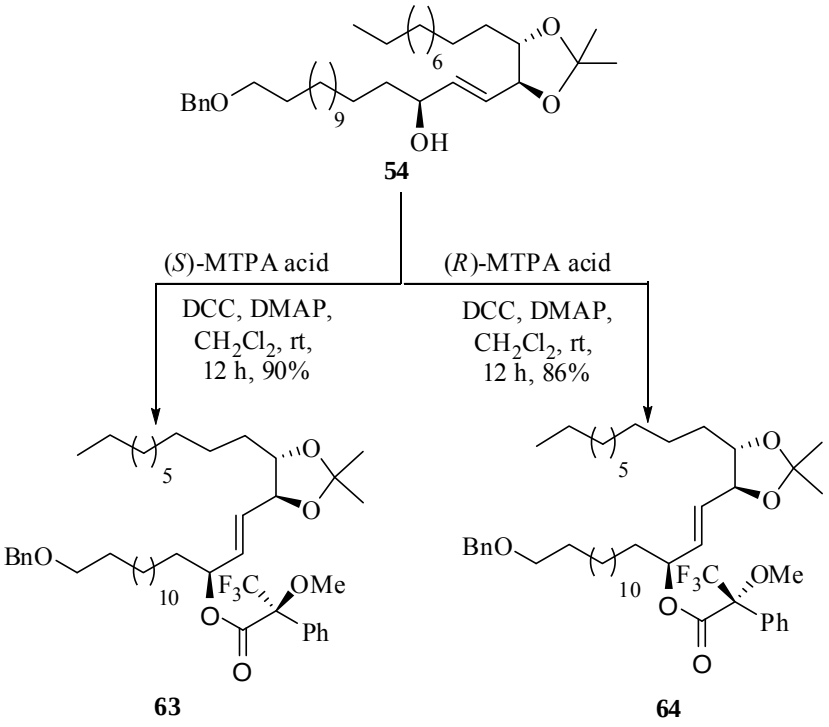
***Figure 9**. A view of MTPA ester drawn in Figure 8 from the direction indicated by the outlined arrow to determine the absolute configuration of secondary alcohol.*



According to Kakisawa and co-workers, the Mosher's method can be extended as follows: (i) assign as many proton signals as possible with respect to each of the (R)- and (S)-MTPA esters (ii) obtain Δδ values for the protons (iii) arrange the protons with positive Δδ values right side and those with negative Δδ values on the left side of the model (iv) construct a molecular model of the compound in question and confirm that all the assigned protons with positive and negative Δδ values are actually found on the right and left sides of the MTPA plane respectively. The absolute values of Δδ must be proportional to the distance from the MTPA moiety. When these conditions are all satisfied, model A will represent the correct absolute configuration of the compound.

In order to assign the absolute stereochemistry of the side chain at $C_{14'}$ in compound **54**, the (*S*)-MTPA ester **63** and (*R*)-MTPA ester **64** were independently prepared from compound **54** by using corresponding (*S*)-MTPA acid and (*R*)-MTPA acid in presence of coupling agent DCC and DMAP (cat.) in anhydrous CH_2Cl_2 at room temperature (Scheme 17).

Scheme 17

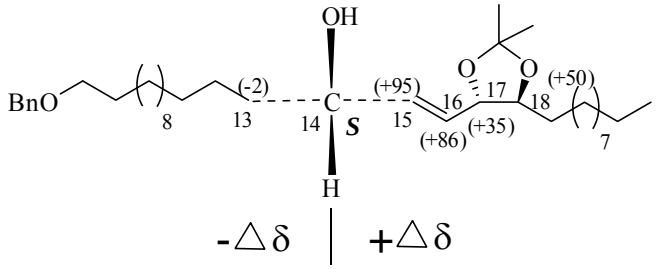


The $\Delta\delta = (\delta_S - \delta_R)$ x 1000 values were calculated for as many protons as possible from the ^{1}H NMR spectrum of (*S*)-MTPA ester **63** and (*R*)-MTPA ester **64** (Table 4). Then, a molecular model of the compound was constructed and the $\Delta\delta = (\delta_S - \delta_R)$ x 1000 values were uniformly arranged as shown in Figure 10. On the basis of the model (Figure 10) we have assigned the absolute stereochemistry of side chain at $C_{14'}$ of **54** as (*S*)-configuration.

Table 4

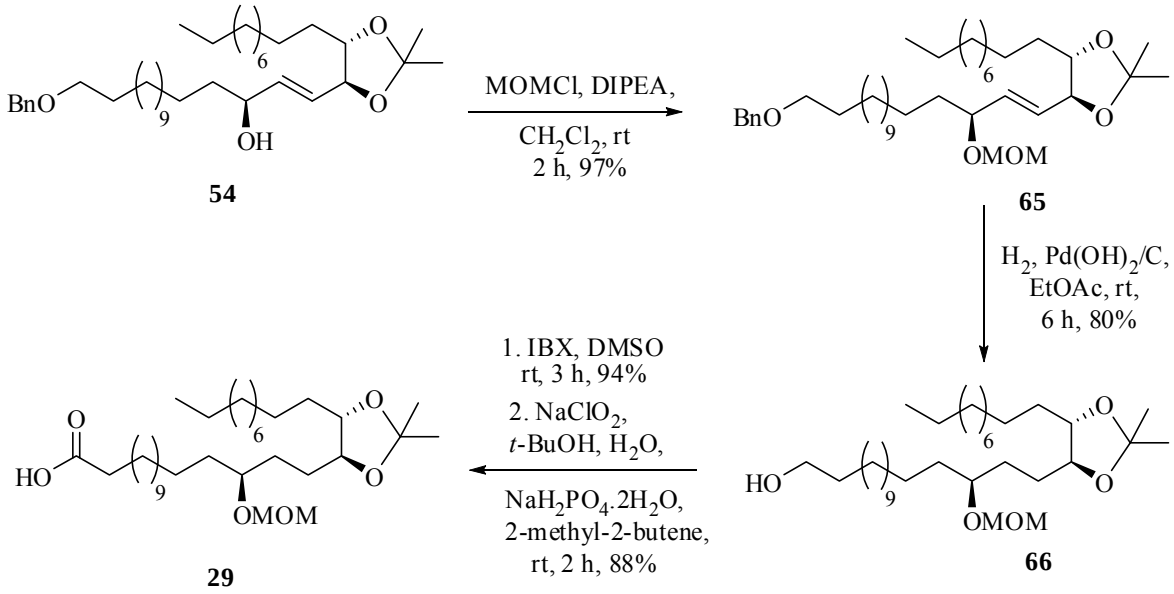
Position	^{1}H Chemical shift (δ)		△ δ
	(*S*)-MTPA	(*R*)-MTPA	$(\delta_S-\delta_R)$x 1000
H-13	1.618	1.620	–2
H-15	5.755	5.66	+95
H-16	5.784	5.68	+86
H-17	3.95	3.915	+35
H-18	3.625	3.575	+50

Figure 10



The secondary hydroxyl group present in compound **54** was protected as methoxymethyl ether by using MOM-Cl[80] and DIPEA in anhydrous CH_2Cl_2 at room temperature for 2 h to afford **65** in 97% yield (Scheme 18). The structure of product **65** was confirmed by ^1H and ^{13}C NMR spectra. In the ^1H NMR spectrum, the appearances of two doublets at δ 4.64 and 4.51 ppm integrating for one proton each (O-CH_2-O), a singlet at δ 3.35 ppm for –OCH_3 of MOM-group confirmed the presence of MOM group.

Scheme 18



The peaks at δ 93.7 and 55.4 ppm, in the ^{13}C NMR spectrum were in support of **65**. The next task ahead was to deprotect benzyl group with simultaneous reduction of the double bond present in **65.** Hydrogenolysis of **65** with $Pd(OH)_2/C$[81] as the catalyst furnished the penultimate alcohol **66** in 80% yield. The absence of peaks due to benzyl group (in the ^1H NMR spectrum peaks at δ 7.33-7.26 ppm and in the ^{13}C NMR resonances at δ 138.7, 134.9, 130.1, 128.3, 127.6 and 127.4 ppm) was evident for the

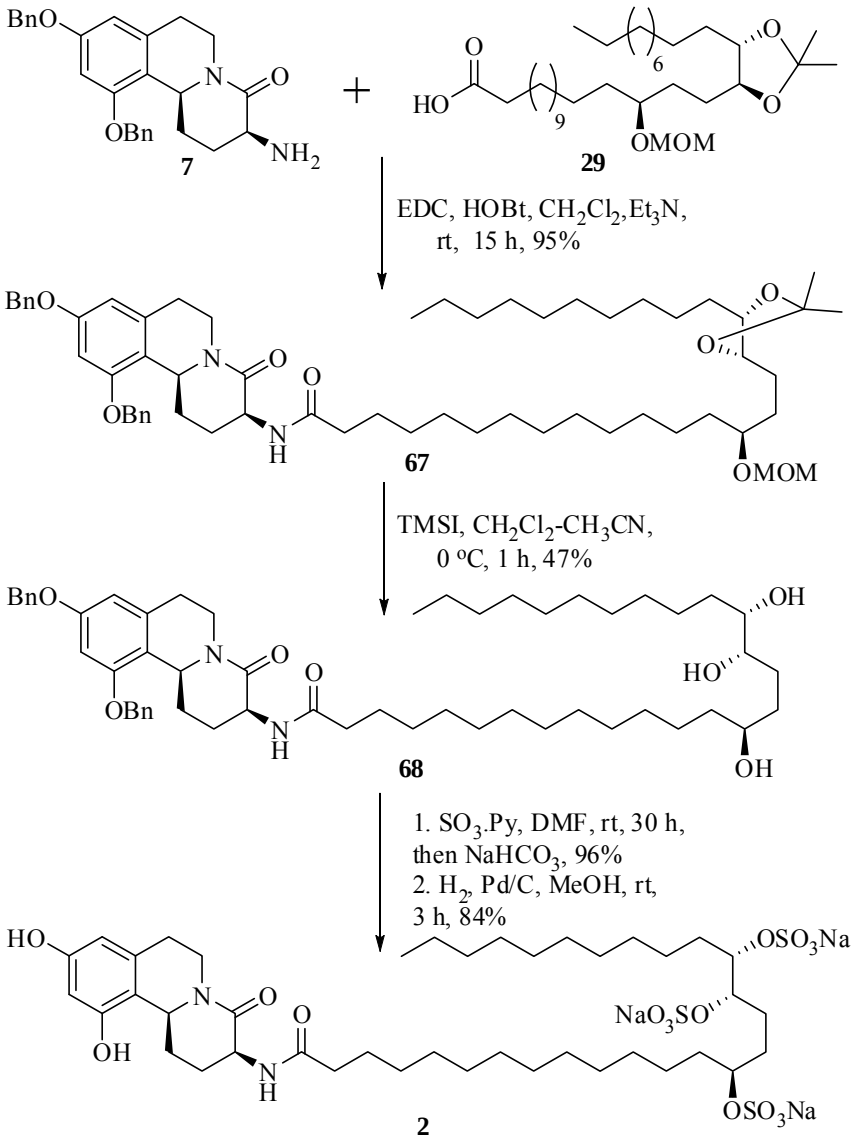
successful removal of the protecting group. Furthermore the absence of olefinic signals at δ 5.62-5.60 ppm confirmed the successful reduction of the double bond as well. The structure was further supported by the IR spectrum with absorption corresponding to free hydroxyl at 3425 cm^{-1} and elemental analysis.

Compound **66** was then oxidized to the corresponding acid by using two step process of oxidation.[82] For that alcohol **66** was treated with Iodoxybenzoic acid in DMSO to produce the corresponding aldehyde. This was then treated with sodium chlorite in a solvent system of *t*-BuOH: H_2O (3:1) in the presence of $NaH_2PO_4.2H_2O$ as the buffer and 2-methyl-2-butene as the chlorine quencher to produce desired carboxylic acid **29** in 88% yield. In the IR spectrum the O-H stretching was observed at 3012 cm^{-1} and the C=O stretching at 1710 cm^{-1}. In the ^1H NMR spectrum, the protons adjacent to the carboxyl group appeared at upfield δ 2.34 ppm (t, J = 7.3 Hz, 2H) in comparison with compound **66**. The carbonyl carbon was observed at δ 179.3 ppm in the ^{13}C NMR spectrum. Other analytical data such as the mass spectrum, and elemental analysis of **29** were in accordance with the proposed structure.

Coupling of acid 29 with amine 7

The next and the final task remained in our hand was to couple the acid **29** with the amine **7** (prepared by one of the colleague in our research group). This was done successfully by using EDC[83] and HOBt to afford the coupled product **67** in an excellent yield (Scheme 19). TMSI[84] mediated deprotection of the acetonide and MOM-protecting groups in **67** gave the triol **68** in 47% yield. Finally, persulfation[85] of triol **68** using SO_3.Py in DMF followed by debenzylation afforded schulzeine B (**2**) in 80% yield over two steps. Similarly, starting with C_{11b} epimer of **7** and coupling it with the acid **29** and following the same sequence of reactions (deprotection, sulfation and debenzylation), the synthesis of schulzeine C (**3**) was accomplished.

Scheme 19



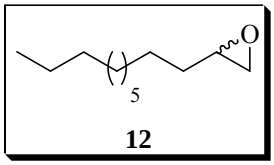
Conclusion

In summary, the first total syntheses of schulzeines B and C are documented.[82] For the synthesis of the key C_{28} fatty acid segment, Sharpless asymmetric dihydroxylation, Horner-Wadsworth-Emmons reaction and BINAL-H mediated asymmetric reduction of the enone were employed as the key reactions. The reported synthetic sequence gave sufficient amount of natural compound which might be useful for further biological investigations.

EXPERIMENTAL

Experimental

2-Decyloxirane (12)

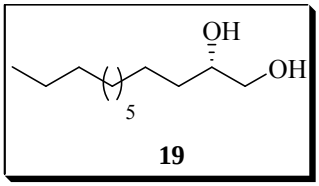


12

To a suspension of NaH (4.83 g, 60% dispersion in oil, 120.8 mmol), trimethylsulfoxonium iodide (26.58 g, 120.8 mmol) in DMSO (100 mL) under argon at 10 ^{o}C was added undecanal (**17**) (13.7 g, 80.5 mmol) in DMSO (50 mL) over a period of 30 min. The reaction mixture was allowed to come to room temperature and stirred for 3 h. After the completion of the reaction (as monitored by TLC) it was quenched with ice-cold water and extracted with ethyl acetate (3x 100 mL). The combined organic layer was washed with water (200 mL), brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on silica gel using light petroleum and ethyl acetate (9:1) to afford compound **12** (12.8 g, 86%) as a yellow oil.

Mol. Formula	: $C_{12}H_{24}O$
IR ($CHCl_3$) υ	: 2927, 1596, 1466, 1216 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$)	: δ 2.89-2.85 (m, 1H), 2.71 (dd, *J* = 4.8, 4.1 Hz, 1H), 2.43 (dd, *J* = 5.0, 2.8 Hz, 1H), 1.52-1.49 (m, 2H), 1.46-1.41 (m, 2H), 1.34-1.25 (m, 14H), 0.87 (t, *J* = 6.7 Hz, 3H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	: δ 52.2, 46.9, 32.5, 31.9, 29.6, 29.5, 29.3, 26.0, 22.7, 14.1 ppm.
ESI-MS (*m/z*)	: 207.38 $[M+Na]^+$.
Elemental Analysis	: Calcd.: C, 78.20; H, 13.12%. Found: C, 78.11; H, 12.97%.

(*S*)-Dodecane-1,2-diol (19)



19

(*R, R*)-Salen-Co(III) catalyst (194 mg, 0.3 mmol) was added to (*R/S)* epoxide **12** (10.81 g, 58.7 mmol), followed by dropwise addition of water (0.58 mL, 32.3 mmol) over 1 h at 0 ^{o}C. The reaction mixture was allowed to come to room temperature and stirred for 24 h. The reaction mixture was filtered and the filtrate concentrated. The residue was purified by silica gel column chromatography eluting with light petroleum and ethyl acetate (1:1) to afford compound **19** (5.1 g, 43%) as a white solid.

Mol. Formula : $C_{12}H_{26}O_2$

M. P. : 68 ^{o}C [Lit. M. P. 69-72 ^{o}C]

$[\alpha]_D^{25}$: –11.2 (*c* = 2.5, EtOH). [Lit. $[\alpha]_D^{25}$ –13.0 (*c* = 2.5, EtOH)].

IR ($CHCl_3$) υ : 3391, 2927, 1466, 1216 cm^{-1}.

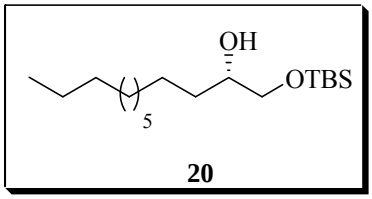
^{1}H NMR (400 MHz, $CDCl_3$) : δ 3.67 (m, 2H), 3.42 (m, 1H), 3.08 (br.s, 2H), 1.42 (m, 4H), 1.26 (m, 14H), 0.88 (t, *J* = 6.7 Hz, 3H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 72.3, 66.7, 33.2, 31.9, 29.8, 29.7, 29.4, 25.7, 22.7, 14.1 ppm.

ESI-MS (*m/z*) : 225.35 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 71.23; H, 12.95%.
Found: C, 71.20; H, 12.99%.

(*S*)-1-(*tert*-Butyldimethylsilyloxy)-dodecan-2-ol (20)



20

To a solution of compound **19** (4.63 g, 22.9 mmol) and imidazole (1.87 g, 27.5 mmol) in CH_2Cl_2 (60 mL) was added TBSCl (3.8 g, 25.2 mmol) in portions and the resulting mixture was stirred at room temperature for 2 h. After completion of the reaction (monitored by TLC), the reaction mixture was poured on ice, diluted with water and extracted with ethyl acetate (3x 75 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on silica gel by using light petroleum and ethyl acetate (9:1) to furnish compound **20** (6.81 g, 94%) as a colorless oil.

Mol. Formula : $C_{18}H_{40}O_2Si$

$[\alpha]_D^{25}$: +3.4 (*c* = 1.2, $CHCl_3$).

IR ($CHCl_3$) υ : 3437, 2929, 1464, 1251, 1216 cm^{-1}.

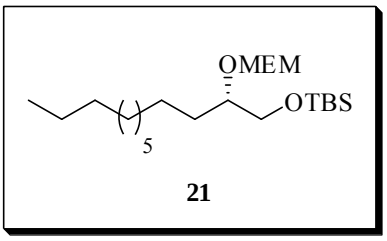
^{1}H NMR (200 MHz, $CDCl_3$) : δ 3.66-3.59 (m, 2H), 3.38 (dd, *J* = 10.5, 8.3 Hz, 1H), 2.05 (br.s, 1H), 1.42-1.34 (m, 4H), 1.27 (m, 14H), 0.91 (m, 9H), 0.90 (t, *J* = 6.7 Hz, 3H), 0.08 (s, 6H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 71.8, 67.3, 32.8, 31.9, 29.8, 29.6 (2C), 29.4, 25.9, 25.6, 22.7, 18.3, 14.2, –5.3, –5.4 ppm.

ESI-MS (*m/z*) : 339.52 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 68.29; H, 12.73%.
Found: C, 68.37; H, 12.59%.

(*S*)-8-Decyl-11,11,12,12-tetramethyl-2,5,7,10-tetraoxa-11-silatridecane (21)



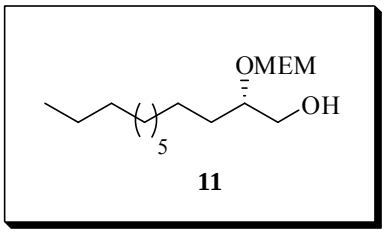
21

To a solution of alcohol **20** (5.7 g, 18.0 mmol) and diisopropylethyl amine (3.77 mL, 21.6 mmol) at 0 °C in CH_2Cl_2 (35 mL), MEMCl (2.26 mL, 19.8 mmol) in CH_2Cl_2 (15 mL) was added dropwise. The reaction mixture was stirred for 2 h, washed

successively with aqueous sodium bicarbonate and water, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on silica gel using light petroleum and ethyl acetate (9:1) to afford the MEM-derivative **21** (5.90 g, 81%) as a yellow oil.

Mol. Formula	: $C_{22}H_{48}O_4Si$
$[\alpha]_D^{25}$	: –18.3 (*c* = 1.2, $CHCl_3$).
IR ($CHCl_3$) υ	: 2856, 1463, 1388, 1254, 1216 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$)	: δ 4.83 (d, *J* = 6.8 Hz, 1H), 4.73 (d, *J* = 6.8 Hz, 1H), 3.72-3.67 (m, 2H), 3.60-3.58 (m, 2H), 3.56-3.52 (m, 3H), 3.37 (s, 3H), 1.53-1.39 (m, 4H), 1.25 (m, 14H), 0.87 (m, 9H), 0.86 (t, *J* = 6.7 Hz, 3H), 0.03 (s, 6H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	: δ 95.1, 78.2, 71.8, 66.9, 65.8, 59.0, 31.9, 31.7, 29.8, 29.6 (2C), 29.3, 25.9, 25.4, 22.7, 18.3, 14.1, –5.4 (2C) ppm.
ESI-MS (*m/z*)	: 427.44 $[M+Na]^+$.
Elemental Analysis	: Calcd.: C, 65.29; H, 11.95%. Found: C, 65.37; H, 11.84%.

(*S*)-2-((2-Methoxyethoxy)-methoxy)-dodecan-1-ol (11)



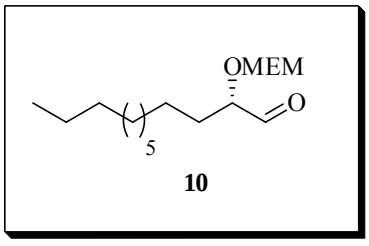
11

To a stirred solution of compound **21** (4.34 g, 10.7 mmol) in THF (20 mL), TBAF (13.95 mL) (1.0 M in THF) was added dropwise. The reaction mixture was then stirred for 1 h, by which time the reaction was complete (as monitored by TLC). The reaction was then quenched by the addition of water and the reaction mixture was concentrated under reduced pressure. The crude mass was taken up in water and extracted with ethyl acetate (3x 50 mL), washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude residue was then purified by silica gel column chromatography

eluting with light petroleum and ethyl acetate (7:3) to furnish compound **11** (2.71 g, 87%) as a light yellow oil.

Mol. Formula	: $C_{16}H_{34}O_4$
$[\alpha]_D^{25}$	: +34.1 (*c* = 1.7, $CHCl_3$).
IR ($CHCl_3$) υ	: 3436, 2854, 1594, 1458, 1042 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$)	: δ 4.81 (d, *J* = 7.3 Hz, 1H), 4.73 (d, *J* = 7.3 Hz, 1H), 3.86-3.81 (m, 1H), 3.68-3.59 (m, 2H), 3.56-3.44 (m, 4H), 3.37 (s, 3H), 1.51-1.34 (m, 4H), 1.25 (m, 14H), 0.87 (t, *J* = 6.7 Hz, 3H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	: δ 95.7, 82.5, 71.7, 67.4, 65.4, 58.9, 31.9, 31.7, 29.7, 29.6, 29.5, 29.3, 25.6, 22.7, 14.1 ppm.
ESI-MS (*m/z*)	: 313.24 $[M+Na]^+$.
Elemental Analysis	: Calcd.: C, 66.17; H, 11.80%. Found: C, 65.98; H, 12.01%.

(*S*)-2-((2-Methoxyethoxy)-methoxy)-dodecanal (10)



10

Iodoxybenzoic acid (IBX) (2.72 g, 9.7 mmol) in DMSO (35 mL) was stirred at room temperature for 30 min till it become a clear solution. Compound **11** (2.35 g, 8.1 mmol) in THF (25 mL) was added to the clear solution and stirred for 4 h at room temperature. The reaction mixture was then diluted with water (50 mL) and filtered. The filtrate was extracted with diethyl ether (3x 50 mL), washed with $NaHCO_3$, water, brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on silica gel eluting with light petroleum and ethyl acetate (9:1) to afford compound **10** (2.22 g, 95%) as a yellow oil.

Mol. Formula : $C_{16}H_{32}O_4$

$[\alpha]_D^{25}$: +2.0 (*c* = 1.0, $CHCl_3$).

IR ($CHCl_3$) υ : 2855, 1734, 1466, 1378, 1282 cm^{-1}.

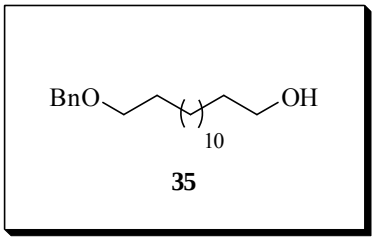
^{1}H NMR (400 MHz, $CDCl_3$) : δ 9.61 (d, *J* = 1.5 Hz, 1H), 4.82 (d, *J* = 7.0 Hz, 1H), 4.77 (d, *J* = 7.0 Hz, 1H), 3.92 (ddd, *J* = 6.9, 5.8, 1.5 Hz, 1H), 3.81-3.68 (m, 2H), 3.52 (t, *J* = 4.5 Hz, 2H), 3.37 (s, 3H), 1.68-1.62 (m, 2H), 1.42-1.37 (m, 2H), 1.25 (m, 14H), 0.87 (t, *J* = 6.7 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) : δ 202.6, 95.6, 82.3, 71.6, 67.6, 59.0, 31.9, 30.0, 29.7, 29.6, 29.5, 29.4, 29.3, 24.8, 22.7, 14.1 ppm.

ESI-MS (*m/z*) : 311.37 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 66.63; H, 11.18%.
Found: C, 66.78; H, 11.26%.

14-(Benzyloxy)-tetradecan-1-ol (35)



35

To a stirred solution of 1,14-tetradecane diol (**22**) (12.34 g, 53.6 mmol) in a mixed solvent of THF/DMF (7:3) (100 mL) at 0 ^oC, NaH (2.36 g, 59.0 mmol) was added portionwise followed by the addition of BnBr (6.36 mL, 53.6 mmol). After 1 h the reaction mixture was allowed to attain room temperature and stirred for another 12 h. After the completion of the reaction (monitored by TLC), the reaction mixture was quenched by the addition of ice cold water (75 mL) and the reaction mixture was concentrated under reduced pressure. The residue thus obtained was diluted with water and extracted with ethyl acetate (3x 75 mL). The combined organic fraction was washed with water (100 mL), brine, dried over anhydrous Na_2SO_4 and evaporated. The residue was purified on silica gel eluting with light petroleum and ethyl acetate (4:1) to afford compound **35** (14.94 g, 87%) as colorless crystals.

Mol. Formula : $C_{21}H_{36}O_2$

M. P. : 40 ^oC [Lit. M. P. 41 ^oC]

IR ($CHCl_3$) υ : 3432, 2853, 1454, 1362, 1102 cm^{-1}.

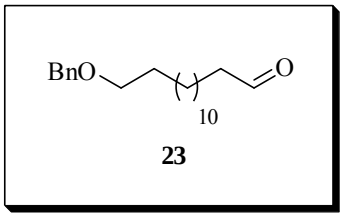
^1H NMR (200 MHz, $CDCl_3$) : δ 7.34-7.28 (m, 5H), 4.49 (s, 2H), 3.62 (t, *J* = 6.6 Hz, 2H), 3.45 (t, *J* = 6.6 Hz, 2H), 1.64-1.49 (m, 6H), 1.26 (m, 18H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 138.5, 128.2, 127.5, 127.3, 72.7, 70.3, 62.5, 32.6, 29.6 (2C), 29.5, 29.4, 26.1, 25.7 ppm.

ESI-MS (*m/z*) : 343.37 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 78.69; H, 11.32%.
Found: C, 78.71; H, 11.29%.

14-(Benzyloxy)-tetradecanal (23)



23

Iodoxybenzoic acid (IBX) (11.52 g, 41.1 mmol) in DMSO (100 mL) was stirred at room temperature for 30 min till it become a clear solution. Compound **35** (10.98 g, 34.3 mmol) in THF (80 mL) was added to the clear solution and stirred for 4 h at room temperature. The reaction mixture was then diluted with water (200 mL) and filtered. The filtrate was extracted with diethyl ether (3x 75 mL), washed with $NaHCO_3$, water, brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on silica gel eluting with light petroleum and ethyl acetate (9:1) to afford compound **23** (10.47 g, 96%) as a yellow oil.

Mol. Formula : $C_{21}H_{34}O_2$

IR ($CHCl_3$) υ : 2854, 1726, 1603, 1454, 1102 cm^{-1}.

^1H NMR : δ 9.75 (t, *J* = 1.8 Hz, 1H), 7.34-7.28 (m, 5H), 4.49 (s, 2H), 3.45

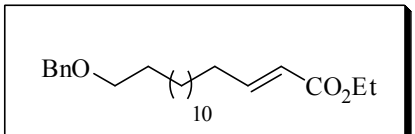
(200 MHz, $CDCl_3$) (t, *J* = 6.7 Hz, 2H), 2.41 (dt, *J* = 7.2, 1.8 Hz, 2H), 1.64-1.54 (m, 4H), 1.25 (m, 18H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 202.5, 138.7, 128.3, 127.6, 127.4, 72.8, 70.5, 43.9, 29.8, 29.6, 29.5, 29.4 (2C), 29.2, 26.2, 22.1 ppm.

ESI-MS (*m/z*) : 341.57 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 79.19; H, 10.76%.
Found: C, 79.06; H, 10.63%.

(*E*)-Ethyl-16-(benzyloxy)-hexadec-2-enoate (24)



24

(Ethoxycarbonylmethylene)-triphenylphosphorane (11.30 g, 32.5 mmol) was heated in toluene (100 mL) at 80 ^oC, till it become a clear solution. Compound **23** (8.61 g, 27.1 mmol) was then added to the reaction mixture at once and the reaction mixture was heated under reflux for 3 h. After the completion of the reaction (monitored by TLC) the reaction mixture was concentrated under reduced pressure. The crude residue thus obtained was purified by silica gel column chromatography eluting with light petroleum and ethyl acetate (9:1) to furnish compound **24** (9.35 g, 89%) as a light yellow oil.

Mol. Formula : $C_{25}H_{40}O_3$

IR ($CHCl_3$) υ : 2928, 1710, 1454, 1275, 1215 cm^{-1}.

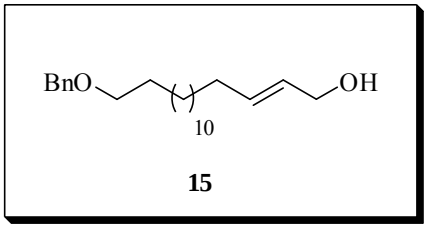
^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.33-7.28 (m, 5H), 6.95 (dt, *J* = 15.7, 6.9 Hz, 1H), 5.79 (d, *J* = 15.7 Hz, 1H), 4.49 (s, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.45 (t, *J* = 6.6 Hz, 2H), 2.19 (q, *J* = 6.9 Hz, 2H), 1.72-1.48 (m, 4H), 1.41-1.32 (m, 4H), 1.28 (s, 3H), 1.25 (m, 14H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 166.6, 149.3, 138.7, 128.2, 127.5, 127.4, 121.2, 72.8, 70.4, 60.0, 32.2, 29.8, 29.6, 29.5 (2C), 29.4, 29.1, 28.0, 26.2, 14.3 ppm.

ESI-MS (*m/z*) : 411.57 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 77.27; H, 10.38%.
Found: C, 77.46; H, 10.67%.

(*E*)-16-(Benzyloxy)-hexadec-2-en-1-ol (15)



15

To a solution of compound **24** (7.57 g, 19.5 mmol) in CH_2Cl_2 (100 mL) at –78 ^oC was added DIBAL-H (1.5 M solution in toluene, 25.97 mL, 39.0 mmol). After 2 h, excess of DIBAL-H was quenched with saturated solution of sodium potassium tartrate. The solid was filtered, the filtrate concentrated to give a residue which was purified on silica gel by eluting with light petroleum and ethyl acetate (4:1) to give compound **15** (5.74 g, 85%) as a colorless oil.

Mol. Formula : $C_{23}H_{38}O_2$

IR ($CHCl_3$) υ : 3392, 2853, 1495, 1454, 1097 cm^{-1}.

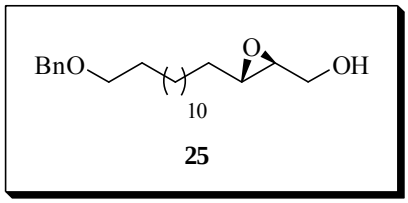
^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.33-7.28 (m, 5H), 5.70-5.57 (m, 2H), 4.49 (s, 2H), 4.05 (d, *J* = 5.3 Hz, 2H), 3.45 (t, *J* = 6.7 Hz, 2H), 2.03 (q, *J* = 6.9 Hz, 2H), 1.80 (s, 1H), 1.61 (quint, *J* = 7.0 Hz, 2H), 1.37-1.34 (m, 2H), 1.26 (m, 18H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) : δ 138.6, 133.2, 128.9, 128.2, 127.5, 127.4, 72.8, 70.4, 63.6, 32.2, 29.7, 29.6 (2C), 29.5, 29.2, 29.1, 26.2 ppm.

ESI-MS (*m/z*) : 369.29 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 79.71; H, 11.05%.
Found: C, 79.60; H, 11.15%.

((2*R*,3*R*)-3-(13-(Benzyloxy)-tridecyl)-oxiran-2-yl)-methanol (25)



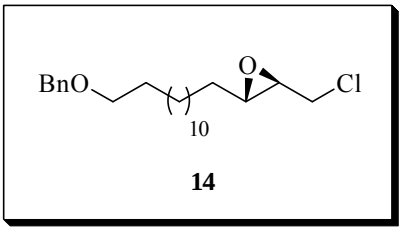
25

To a solution of titanium tetrakis(isopropoxide) (4.25 mL, 14.4 mmol) and (+)-DET (2.95 mL, 17.3 mmol) in CH_2Cl_2 (75 mL) carrying activated molecular sieves (4 Å, 5.0 g) at –20 °C, was added *t*-butylhydroperoxide (2.7 M in toluene) (10.64 mL, 28.7 mmol) dropwise. After 15 min, a solution of allylic alcohol **15** (4.98 g, 14.4 mmol) in CH_2Cl_2 (50 mL) was added dropwise. The reaction mixture was kept at that temperature for 12 h; aqueous tartaric acid (10%) was added followed by stirring for 1 h. The reaction mixture was filtered and the filtrate was extracted with CH_2Cl_2 (3x 75 mL). The combined CH_2Cl_2 extract was concentrated under reduced pressure and was taken up in diethyl ether (75 mL) and treated with 1M NaOH solution (40 mL) and stirred for another 1 h and then extracted with diethyl ether (3x 50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified on silica gel (230-400 mesh) by using light petroleum and ethyl acetate (3:1) to afford the epoxy alcohol **25** (4.06 g, 78%) as colorless oil.

Mol. Formula	: $C_{23}H_{38}O_3$
$[\alpha]_D^{25}$	: –2.7 (*c* = 2.2, $CHCl_3$).
IR ($CHCl_3$) υ	: 3401, 2853, 1595, 1454, 1363 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$)	: δ 7.34-7.28 (m, 5H), 4.49 (s, 2H), 3.86 (d, *J* = 12.6 Hz, 1H), 3.58 (d, *J* = 12.6 Hz, 1H), 3.45 (t, *J* = 6.7 Hz, 2H), 2.93-2.87 (m, 2H), 2.34 (br.s, 1H), 1.61 (quint, *J* = 7.0 Hz, 2H), 1.55 (q, *J* = 6.9 Hz, 2H), 1.47-1.34 (m, 4H), 1.27 (m, 16H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	: δ 138.6, 128.4, 128.3, 127.6, 127.4, 126.9, 72.8, 70.4, 61.7, 58.5, 56.0, 31.5, 29.7, 29.6, 29.5 (2C), 29.4, 26.2, 25.9 ppm.
ESI-MS (*m/z*)	: 385.32 $[M+Na]^+$.
Elemental Analysis	: Calcd.: C, 76.20; H, 10.56%.

Found: C, 76.45; H, 10.51%.

(2*R*,3*S*)-2-(13-(Benzyloxy)-tridecyl)-3-(chloromethyl)-oxirane (14)

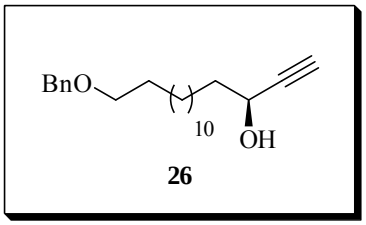


14

A solution of compound **25** (3.62 g, 10.0 mmol) and triphenylphosphine (3.14 g, 12.0 mmol) containing sodium bicarbonate (1.0 g) was refluxed in CCl_4 (70 mL) for 2 h. Removal of solvent and residue purification by silica gel column chromatography using light petroleum and ethyl acetate (9.5:0.5) gave compound **14** (3.53 g, 93%) as a colorless oil.

Mol. Formula	: $C_{23}H_{37}ClO_2$
$[\alpha]_D^{25}$	: –1.7 (*c* = 1.2, $CHCl_3$).
IR ($CHCl_3$) υ	: 2853, 1495, 1466, 1362, 1216 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$)	: δ 7.33-7.28 (m, 5H), 4.49 (s, 2H), 3.57 (dd, *J* = 11.5, 5.8 Hz, 1H), 3.49 (dd, *J* = 11.5, 5.8 Hz, 1H), 3.45 (t, *J* = 6.7 Hz, 2H), 2.98 (dt, *J* = 5.8, 2.0 Hz, 1H), 2.85 (dt, *J* = 5.8, 2.0 Hz, 1H), 1.64-1.53 (m, 4H), 1.47-1.40 (m, 2H), 1.38-1.31 (m, 4H), 1.25 (m, 14H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	: δ 138.7, 128.3, 127.6, 127.4, 72.8, 70.5, 59.1, 57.1, 44.8, 31.4, 29.7 (2C), 29.6, 29.5, 29.3, 26.2, 25.8 ppm.
ESI-MS (*m/z*)	: 403.75 $[M+Na]^+$.
Elemental Analysis	: Calcd.: C, 72.51; H, 9.79%. Found: C, 72.23; H, 9.85%.

(*S*)-16-(Benzyloxy)-hexadec-1-yn-3-ol (26)

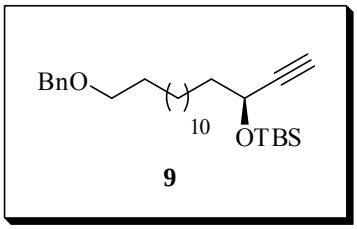


26

n-Butyllithium (14.50 mL, 23.2 mmol, 1.6 M solution in hexane) was added dropwise to a solution of compound **14** (2.94 g, 7.7 mmol) in dry THF (40 mL) at –30 °C under nitrogen atm. After stirring for 1 h at –30 °C, the reaction mixture was gradually warmed to room temperature over a period of 1 h, quenched with aqueous NH_4Cl solution (25 mL), and concentrated. The residue was taken in ethyl acetate, washed with water and brine, dried over anhydrous Na_2SO_4 and evaporated. The residue was purified on silica gel by using light petroleum and ethyl acetate (4:1) to afford compound **26** (2.05 g, 77%) as colorless oil.

Mol. Formula	: $C_{23}H_{36}O_2$
$[\alpha]_D^{25}$	: +1.3 (*c* = 1.5, $CHCl_3$).
IR ($CHCl_3$) υ	: 3402, 3310, 2853, 1495, 1454, 1363, 1099 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$)	: δ 7.33-7.28 (m, 5H), 4.49(s, 2H), 4.33 (dt, *J* = 6.8, 1.8 Hz, 1H), 3.45 (t, *J* = 6.7 Hz, 2H), 2.43 (d, *J* = 1.8 Hz, 1H), 1.91 (br.s, 1H), 1.73-1.67 (m, 2H), 1.64-1.57 (m, 2H), 1.46-1.41 (m, 2H), 1.34-1.29 (m, 6H), 1.26 (m, 12H) ppm.
^{13}C NMR ($CDCl_3$)	: δ 138.7, 128.3, 127.6, 127.4, 85.1, 72.8 (2C), 70.5, 62.3, 37.7, 29.8, 29.6 (2C), 29.5 (2C), 29.3, 26.2, 25.0 ppm.
ESI-MS (*m/z*)	: 367.44 $[M+Na]^+$.
Elemental Analysis	: Calcd.: C, 80.18; H, 10.53%. Found: C, 79.98; H, 10.39%.

(*S*)-(16-(Benzyloxy)-hexadec-1-yn-3-yloxy)-(*tert*-butyl)-dimethylsilane (9)

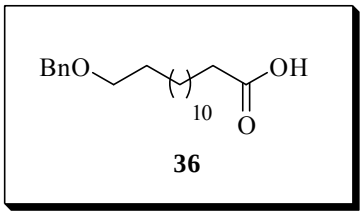


9

To a solution of compound **26** (1.64 g, 4.8 mmol) and imidazole (389 mg, 5.7 mmol) in CH_2Cl_2 (20 mL) was added TBSCl (790 mg, 5.2 mmol) in portions and the resulting mixture was stirred at room temperature for 2 h. After completion of the reaction (monitored by TLC), the reaction mixture was poured on ice, diluted with water and extracted with ethyl acetate (3x 50 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on silica gel by using light petroleum and ethyl acetate (9:1) to furnish compound **9** (2.10 g, 96%) as a colorless oil.

Mol. Formula	: $C_{29}H_{50}O_2Si$
$[\alpha]_D^{25}$	: –4.0 (*c* = 2.0, $CHCl_3$).
IR ($CHCl_3$) υ	: 3310, 2855, 1598, 1463, 1361, 1251 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$)	: δ 7.33-7.28 (m, 5H), 4.49 (s, 2H), 4.32 (dt, *J* = 6.5, 2.0 Hz, 1H), 3.45 (t, *J* = 6.7 Hz, 2H), 2.34 (d, *J* = 2.0 Hz, 1H), 1.68-1.57 (m, 4H), 1.44-1.34 (m, 4H), 1.26 (m, 16H), 0.90 (m, 9H), 0.13 (s, 3H), 0.11 (s, 3H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	: δ 138.8, 128.3, 127.6, 127.4, 85.8, 72.9, 71.9, 70.5, 62.8, 38.6, 29.8, 29.7 (3C), 29.6 (3C), 29.3, 26.3, 25.9, 25.2, 18.3, –4.5, –5.0 ppm.
ESI-MS (*m/z*)	: 481.77 $[M+Na]^+$.
Elemental Analysis	: Calcd.: C, 75.92; H, 10.98%. Found: C, 75.97; H, 11.07%.

14-(Benzyloxy)-tetradecanoic acid (36)

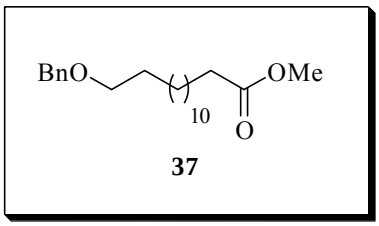


36

To a stirred solution of compound **35** (5.9 g, 18.4 mmol) in a solvent system of CCl_4:CH_3CN:H_2O (1:1:2) (60 mL), $NaIO_4$ (7.87 g, 36.8 mmol) and $RuCl_3$ (191 mg, 0.9 mmol) were added and the reaction mixture was stirred vigorously for 20 min. After the completion of the reaction (as monitored by TLC), the reaction mixture was extracted with ethyl acetate (3x 50 mL), washed with water, brine, dried over anhydrous Na_2SO_4 and evaporated. The crude residue was purified on silica gel by using light petroleum and ethyl acetate (7:3) to furnish compound **36** (5.17 g, 84%) as colorless crystals.

Mol. Formula	: $C_{21}H_{34}O_3$
M. P.	: 47 ^oC [Lit. M. P. 49 ^oC]
IR ($CHCl_3$) υ	: 3420, 2857, 1716, 1463, 1215 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	: δ 7.33-7.25 (m, 5H), 4.49 (s, 2H), 3.45 (t, *J* = 6.6 Hz, 2H), 2.33 (t, *J* = 7.3 Hz, 2H), 1.63-1.57 (m, 4H), 1.26 (m, 18H) ppm.
^{13}C NMR (50 MHz, $CDCl_3$)	: δ 180.0, 138.6, 128.3, 127.6, 127.4, 72.8, 70.4, 34.1, 29.8, 29.6, 29.5, 29.4, 29.3, 29.1, 26.2, 24.7 ppm.
ESI-MS (*m/z*)	: 357.35 $[M+Na]^+$.
Elemental Analysis	: Calcd.: C, 75.41; H, 10.25%. Found: C, 75.53; H, 10.31%.

Methyl-14-(benzyloxy)-tetradecanoate (37)

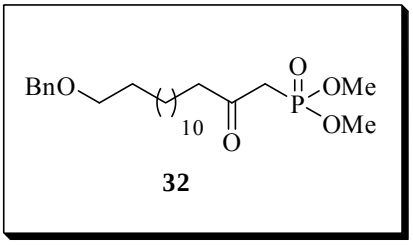


37

Compound **36** (4.6 g, 13.8 mmol), methanol (50 mL) and *p*-TSA (50 mg) were heated under reflux for 3 h and concentrated. The residue was taken up in water and extracted with ethyl acetate (3x 50 mL), washed with water, brine, dried over anhydrous Na_2SO_4 and evaporated. The residue was purified on silica gel eluting with light petroleum and ethyl acetate (9.5:0.5) to afford compound **37** (4.51 g, 94%) as colorless oil.

Mol. Formula	: $C_{22}H_{36}O_3$
IR ($CHCl_3$) υ	: 2927, 2854, 1738, 1602, 1495, 1363 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	: δ 7.33-7.27 (m, 5H), 4.49 (s, 2H), 3.66 (s, 3H), 3.45 (t, *J* = 6.6 Hz, 2H), 2.29 (t, *J* = 7.3 Hz, 2H), 1.64-1.54 (m, 4H), 1.25 (m, 18H) ppm.
^{13}C NMR (50 MHz, $CDCl_3$)	: δ 174.1, 138.7, 128.3, 127.5, 127.4, 72.8, 70.4, 51.3, 34.1, 29.8, 29.6, 29.5 (2C), 29.3, 29.2, 26.2, 24.9 ppm.
ESI-MS (*m/z*)	: 371.26 $[M+Na]^+$.
Elemental Analysis	: Calcd.: C, 75.82; H, 10.41%. Found: C, 75.62; H, 10.62%.

Dimethyl-15-(benzyloxy)-2-oxopentadecylphosphonate (32)



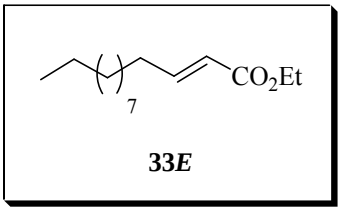
32

To a stirred solution of dimethyl-methanephosphonate (3.2 g, 25.9 mmol) in THF (30 mL) at −78 °C, *n*-BuLi (13.4 mL, 1.6 M in hexane, 21.5 mmol) was added. After 0.5 h, compound **37** (3.0 g, 8.6 mmol) in THF (10 mL) was introduced and stirring was continued for further 2.5 h. Then 10% Na_2HPO_4 solution (20 mL) was added and layers separated. The organic layer was washed with water and the combined aqueous phase was extracted with diethyl ether (3x 50 mL). The combined organic layer was dried over

anhydrous Na_2SO_4 and evaporated. The residue was purified on silica gel by eluting with light petroleum and ethyl acetate (2:3) to afford compound **32** (3.53 g, 93%) as a yellow oil.

Mol. Formula	: $C_{24}H_{41}O_5P$
IR ($CHCl_3$) υ	: 2927, 2855, 1715, 1602, 1454, 1365 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	: δ 7.33-7.25 (m, 5H), 4.49 (s, 2H), 3.81 (s, 3H), 3.76 (s, 3H), 3.45 (t, *J* = 6.6 Hz, 2H), 3.07 (d, *J* = 22.7 Hz, 2H), 2.60 (t, *J* = 7.3 Hz, 2H), 1.67-1.54 (m, 4H), 1.25 (m, 18H) ppm.
^{13}C NMR (50 MHz, $CDCl_3$)	: δ 201.7, 201.6, 138.6, 128.2, 127.4, 127.3, 72.7, 70.3, 52.9, 44.0, 42.4, 39.9, 29.7, 29.5, 29.4, 29.3, 28.8, 26.1, 23.2 ppm.
ESI-MS (*m/z*)	: 463.25 $[M+Na]^+$.
Elemental Analysis	: Calcd.: C, 65.43; H, 9.38%. Found: C, 65.26; H, 9.42%.

(*E*)-Ethyl-tridec-2-enoate (33*E*)



33*E*

(Ethoxycarbonylmethylene)-triphenylphosphorane (17.74 g, 50.9 mmol) was heated in benzene (125 mL) at 80 ^oC, till it become a clear solution. Compound **17** (5.78 g, 33.9 mmol) in toluene (30 mL) was then added to the reaction mixture at once and the reaction mixture was heated under reflux for 4 h. After the completion of the reaction (monitored by TLC) the reaction mixture was concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography eluting with light petroleum and ethyl acetate (9:1) to furnish compound **33*E*** (6.94 g, 85%) as a light yellow oil.

Mol. Formula : $C_{15}H_{28}O_2$

IR ($CHCl_3$) υ : 2926, 1728, 1436, 1395 cm^{-1}.

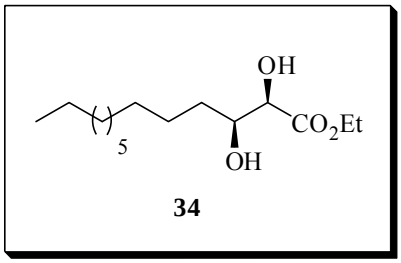
^{1}H NMR (200 MHz, $CDCl_3$) : δ 6.96 (dt, *J* = 15.7, 7.0 Hz, 1H), 5.80 (d, *J* = 15.7 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.19 (q, *J* = 7.1 Hz, 2H), 1.49-1.42 (m, 2H), 1.38-1.32 (m, 2H), 1.29 (s, 3H), 1.26 (m, 12H), 0.88 (t, *J* = 6.7 Hz, 3H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 166.4, 149.1, 121.2, 59.9, 31.8, 29.5 (2C), 29.4, 29.3, 29.1, 28.0, 22.6, 14.0 ppm.

ESI-MS (*m/z*) : 263.41 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 74.95; H, 11.74%.
Found: C, 74.83; H, 11.97%.

(2*R*,3*S*)-Ethyl-2,3-dihydroxytridecanoate (34)



34

To a vigorously stirring mixture of $K_3[Fe(CN)_6]$ (20.6 g, 62.5 mmol), K_2CO_3 (8.64 g, 62.5 mmol), $(DHQ)_2PHAL$ (160 mg, 0.2 mmol), $MeSO_2NH_2$ (1.98 g, 20.8 mmol) and $K_2OsO_4.2H_2O$ (40 mg, 0.1 mmol) in (1:1) *t*-BuOH: H_2O (200 mL) at 0 °C was added compound **33*E*** (5.0 g, 20.8 mmol). After 6 h, sodium sulphite (10 g) was added, *t*-BuOH was evaporated and the aqueous phase was extracted with ethyl acetate (3x 50 mL), washed with 2N KOH solution, water, brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on silica gel by eluting with light petroleum and ethyl acetate (4:1) to afford compound **34** (4.85 g, 85%) as a white solid.

Mol. Formula : $C_{15}H_{30}O_4$

M. P. : 62 ^oC

$[\alpha]_D^{25}$: –10.6 (*c* = 1.0, $CHCl_3$).

IR ($CHCl_3$) υ : 3456, 3018, 2927, 1734, 1466, 1370 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 4.29 (q, *J* = 7.l Hz, 2H), 4.06 (d, *J* = 1.8 Hz, 1H), 3.86 (dt, *J* = 6.3, 1.8 Hz, 1H), 3.25 (br.s, 1H), 2.25 (br.s, 1H), 1.62-1.55 (m, 2H), 1.36-1.27 (m, 19H), 0.88 (t, *J* = 6.7 Hz, 3H) ppm.

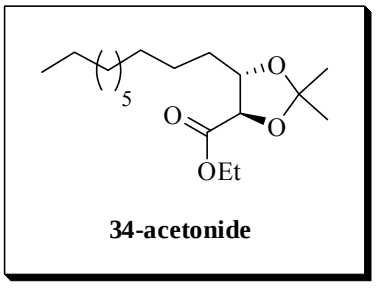
^{13}C NMR (50 MHz, $CDCl_3$) : δ 173.6, 73.2, 72.5, 61.6, 33.5, 31.8, 29.5, 29.3, 25.7, 22.6, 14.0 ppm.

ESI-MS (*m/z*) : 297.20 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 65.66; H, 11.02%.
Found: C, 65.79; H, 11.07%.

Enantiomeric purity of compound **34** was estimated (98.5% *ee*) by HPLC analysis of its dibenzoate derivative using a chiracel OD-H column (0.8% *i*-propanol/*n*-hexane, flow rate 0.5 mL/min, λ = 225 nm).

(4*R*,5*S*)-Ethyl 5-decyl-2,2-dimethyl-1,3-dioxolane-4-carboxylate (34-acetonide)



34-acetonide

A solution of compound **34** (3.0 g, 10.9 mmol), 2,2-dimethoxypropane (1.6 mL, 13.1 mmol) and catalytic *p*-TSA in CH_2Cl_2 (30 mL) was stirred at room temperature for 1 h. After the completion of the reaction (monitored by TLC), the reaction mixture was washed with $NaHCO_3$, water, brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on silica gel by using light petroleum and ethyl acetate (9.5:0.5) to afford the acetonide derivative **34-acetonide** (3.27 g, 96%) as colorless oil.

Mol. Formula : $C_{18}H_{34}O_4$

$[\alpha]_D^{25}$: –15.4 (*c* = 1.0, $CHCl_3$).

IR ($CHCl_3$) υ : 2926, 2855, 1761, 1380 cm^{-1}.

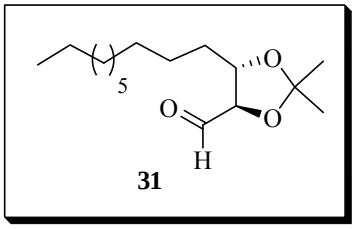
^{1}H NMR (200 MHz, $CDCl_3$) : δ 4.24 (q, *J* = 7.1 Hz, 2H), 4.11-4.07 (m, 2H), 1.77-1.65 (m, 2H), 1.46 (s, 3H), 1.43 (s, 3H), 1.34-1.27 (m, 19H), 0.88 (t, *J* = 6.7 Hz, 3H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 170.8, 110.6, 79.1, 61.0, 33.5, 31.8, 29.4, 29.3, 27.1, 25.6, 22.6, 14.0 ppm.

ESI-MS (*m/z*) : 337.24 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 68.75; H, 10.90%.
Found: C, 68.64; H, 10.75%.

(4*R*,5*S*)-5-Decyl-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (31)



31

To a solution of the acetonide derivative **34-acetonide** (2.5 g, 7.9 mmol) in CH_2Cl_2 (30 mL) at –78 ^oC was added DIBAL-H (1.3 M solution in toluene, 7.30 mL, 9.5 mmol). After 1 h, excess of DIBAL-H was quenched with saturated solution of sodium potassium tartrate. The solid was filtered, the filtrate was concentrated to give a residue which was purified on silica gel by eluting with light petroleum and ethyl acetate (9:1) to give compound **31** (2.0 g, 93%) as a colorless oil.

Mol. Formula : $C_{16}H_{30}O_3$

$[\alpha]_D^{25}$: +3.2 (*c* = 4.2, $CHCl_3$).

IR ($CHCl_3$) υ : 2855, 1736, 1496, 1465, 1243 cm^{-1}.

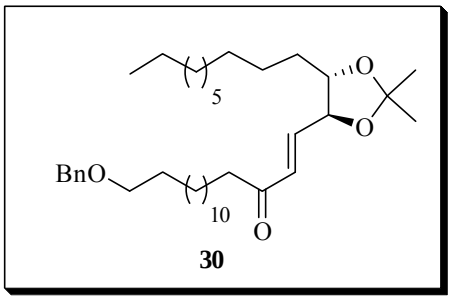
^{1}H NMR (200 MHz, $CDCl_3$) : δ 9.72 (d, *J* = 2.4 Hz, 1H), 4.04 (dd, *J* = 7.7, 5.9 Hz, 1H), 3.94 (dt, *J* = 7.7, 2.4 Hz, 1H), 1.72-1.58 (m, 2H), 1.47 (s, 3H), 1.42 (s, 3H), 1.26 (m, 16H), 0.88 (t, *J* = 6.7 Hz, 3H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 200.9, 110.8, 84.8, 77.0, 33.4, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 27.1, 26.2, 25.6, 22.7, 14.1 ppm.

ESI-MS (*m/z*) : 293.34 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 71.07; H, 11.78%.
Found: C, 70.94; H, 11.87%.

(*E*)-16-(Benzyloxy)-1-((4*S*,5*S*)-5-decyl-2,2-dimethyl-1,3-dioxolan-4-yl)-hexadec-1-en-3-one (30)



30

To a stirred solution of compound **32** (1.95 g, 4.4 mmol), DBU (560 mg, 3.7 mmol) and LiCl (190 mg, 4.4 mmol) in dry CH_3CN (15 mL) under nitrogen at room temperature was added compound **31** (1.0 g, 3.69 mmol). After 1 h, saturated NH_4Cl solution was added, extracted with ether (3 x 15 mL), washed with brine, dried over anhydrous Na_2SO_4 and evaporated. The residue was purified on silica gel by eluting with light petroleum and ethyl acetate (9.5:0.5) to afford compound **30** (2.05 g, 95%) as a yellow oil.

Mol. Formula : $C_{38}H_{64}O_4$

$[\alpha]_D^{25}$: –6.1 (*c* = 1.3, $CHCl_3$).

IR ($CHCl_3$) υ : 2855, 2928, 1697, 1676, 1495, 1371 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.34-7.26 (m, 5H), 6.70 (dd, *J* = 15.8, 5.7 Hz, 1H), 6.36 (dd, *J* = 15.8, 1.3 Hz, 1H), 4.49 (s, 2H), 4.17-4.09 (m, 1H), 3.76-3.66 (m, 1H), 3.45 (t, *J* = 6.6 Hz, 2H), 2.55 (t, *J* = 7.2 Hz, 2H), 1.64-1.51 (m, 8H), 1.43 (s, 3H), 1.38 (s, 3H), 1.26 (m, 32H), 0.88 (t, *J* = 6.7 Hz, 3H) ppm.

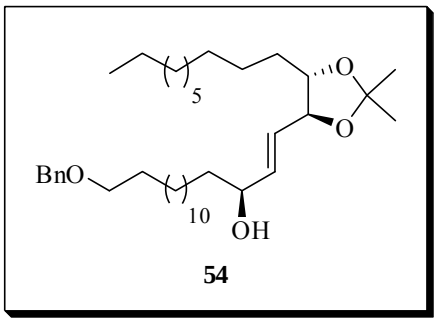
^{13}C NMR : δ 199.8, 141.5, 138.6, 130.3, 128.2, 127.5, 127.4, 109.2, 80.6,

(50 MHz, $CDCl_3$) 80.5, 72.8, 70.4, 40.9, 32.1, 31.9, 29.7, 29.6, 29.5, 29.3, 29.2, 27.3, 26.7, 26.2, 26.0, 23.9, 22.6, 14.1 ppm.

ESI-MS (*m/z*) : 607.03 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 78.03; H, 11.03%.
Found: C, 77.93; H, 11.09%.

(*S*,*E*)-16-(Benzyloxy)-1-((4*S*,5*S*)-5-decyl-2,2-dimethyl-1,3-dioxolan-4-yl)-hexadec-1-en-3-ol (54)



54

The (*S*)-(–)-BINAL-H reagent was prepared by stirring LAH (1.6 M THF solution, 3.2 mL, 5.1 mmol), ethanol (2.0 M THF solution, 2.55 mL, 5.1 mmol) and (–)-binapthol (1.46 g, 5.1 mmol) in THF (15 mL) for 30 min at room temperature. It was then cooled to −78 ^oC, compound **30** (1.0 g, 1.7 mmol) in THF (3 mL) was added drop wise over a period of 15 min. After 2.5 h, methanol (2 mL) was introduced and the reaction mixture was allowed to attain room temperature. After the addition of 2N HCl (1.5 mL), it was extracted with ether (3x 25 mL). The ether layer was washed with saturated sodium bicarbonate solution, water, dried over anhydrous Na_2SO_4 and evaporated. The residue was purified on silica gel (230-400 mesh) by eluting with light petroleum and ethyl acetate (9:1) to afford compound **54** (770 mg, 77%) as a colorless oil.

Mol. Formula : $C_{38}H_{66}O_4$

$[\alpha]_D^{25}$: –0.8 (*c* = 1.5, $CHCl_3$).

IR ($CHCl_3$) υ : 3446, 3012, 2988, 2855, 1647, 1495, 1380 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.33-7.26 (m, 5H), 5.83 (dd, *J* = 15.6, 5.7 Hz, 1H), 5.63 (dd, *J* = 15.6, 7.3 Hz, 1H), 4.49 (s, 2H), 4.13 (q, *J* = 6.0 Hz, 1H), 3.97 (t,

J = 7.8 Hz, 1H), 3.65 (ddd, *J* = 8.3, 6.0, 5.7 Hz, 1H), 3.45 (t, *J* = 6.6 Hz, 2H), 1.64-1.59 (m, 2H), 1.54-1.49 (m, 4H), 1.40 (s, 3H), 1.39 (s, 3H), 1.26 (m, 36H), 0.88 (t, *J* = 6.7 Hz, 3H) ppm.

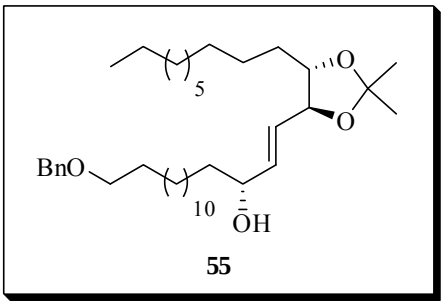
^{13}C NMR (100 MHz, $CDCl_3$) : δ 138.7, 137.9, 128.3, 127.6, 127.4, 127.3, 108.4, 81.9, 80.9, 72.8, 71.8, 70.5, 37.2, 31.9, 29.8 (2C), 29.7, 29.6 (2C), 29.5 (2C), 29.4, 27.3, 27.0, 26.2, 26.1, 25.3, 22.7, 14.1 ppm.

ESI-MS (*m/z*) : 609.47 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 77.76; H, 11.33%.
Found: C, 77.52; H, 11.10%.

Further elution gave compound **55** (70 mg, 7%) as a colorless oil.

(*R*,*E*)-16-(Benzyloxy)-1-((4*S*,5*S*)-5-decyl-2,2-dimethyl-1,3-dioxolan-4-yl)-hexadec-1-en-3-ol (55)



55

Mol. Formula : $C_{38}H_{66}O_4$

$[\alpha]_D^{25}$: –7.7 (*c* = 1.3, $CHCl_3$).

IR ($CHCl_3$) υ : 3446, 3012, 2988, 2855, 1647, 1495, 1380 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.34-7.26 (m, 5H), 5.81 (dd, *J* = 15.3, 6.0 Hz, 1H), 5.61 (dd, *J* = 15.3, 7.2 Hz, 1H), 4.49 (s, 2H), 4.14-4.06 (m, 1H), 4.01-3.93 (m, 1H), 3.68-3.59 (m, 1H), 3.45 (t, *J* = 6.6 Hz, 2H), 1.67-1.50 (m, 8H), 1.40 (s, 6H), 1.26 (m, 34H), 0.88 (t, *J* = 6.7 Hz, 3H) ppm.

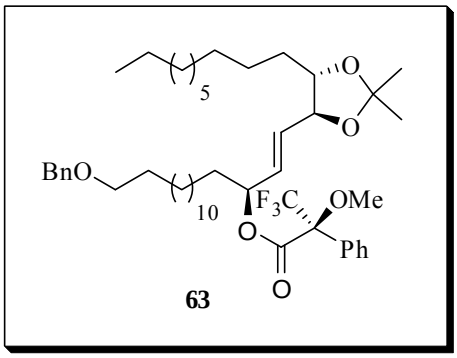
^{13}C NMR : δ 138.7, 138.0, 128.3, 127.5, 127.4, 108.4, 81.9, 80.7, 72.8, 72.1,

(50 MHz, $CDCl_3$) 70.4, 37.1, 31.9, 29.7, 29.6, 29.5, 29.4, 27.3, 27.0, 26.2, 26.1, 25.4, 22.7, 14.1 ppm.

ESI-MS (*m/z*) : 609.47 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 77.76; H, 11.33%.
Found: C, 77.50; H, 11.33%.

(2*S*)-(*S*,*E*)-16-(Benzyloxy)-1-((4*S*,5*S*)-5-decyl-2,2-dimethyl-1,3-dioxolan-4-yl)-hexadec-1-en-3-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (63)



63

To a solution of compound **54** (57 mg, 0.1 mmol) in anhydrous CH_2Cl_2 (4 mL) were added (*S*)-(–)-α-methoxy-α-trifluoromethylphenylacetic acid (*S*-MTPA) (36 mg, 0.15 mmol), DCC (45 mg, 0.2 mmol) and DMAP (4 mg, 0.03 mmol), and stirred for 12 h at room temperature. The reaction mixture was diluted with water, extracted with CH_2Cl_2, washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography eluting with light petroleum and ethyl acetate (9:1) to afford compound **63** (70 mg, 90%) as a yellow oil.

Mol. Formula : $C_{48}H_{73}F_3O_6$

$[\alpha]_D^{25}$: –27.2 (*c* = 2.3, $CHCl_3$).

IR ($CHCl_3$) υ : 2854, 1748, 1603, 1496, 1454, 1240, 1186 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.52-7.26 (m, 10H), 5.78-5.76 (m, 2H), 5.50-5.45 (m, 1H), 4.49 (s, 2H), 3.97-3.93 (m, 1H), 3.65-3.60 (m, 1H), 3.53 (s, 3H), 3.45 (t, *J* = 6.7 Hz, 2H), 1.75-1.64 (m, 2H), 1.61 (t, *J* = 7.2 Hz, 2H), 1.54-1.46 (m, 4H), 1.40 (s, 3H), 1.38 (s, 3H), 1.25-1.20 (m,

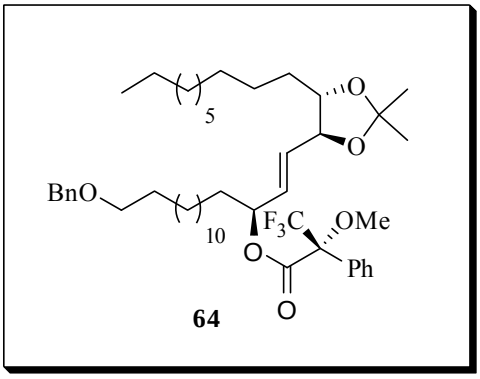
34H), 0.88 (t, J = 6.7 Hz, 3H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 165.8, 138.7, 132.4, 131.1, 129.5, 128.3, 127.6, 127.4, 127.3, 108.7, 81.4, 80.7, 72.9, 70.5, 55.4, 34.0, 31.9 (2C), 29.8 (2C), 29.6, 29.5 (2C), 29.4 (2C), 29.2, 27.3, 26.9, 26.3, 26.1, 24.7, 22.7, 14.2 ppm.

ESI-MS (*m/z*) : 825.74 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 71.79; H, 9.16%.
Found: C, 71.87; H, 9.31%.

(2*R*)-(*S*,*E*)-16-(Benzyloxy)-1-((4*S*,5*S*)-5-decyl-2,2-dimethyl-1,3-dioxolan-4-yl)-hexadec-1-en-3-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (64)



64

The reaction was carried out as described earlier using compound **54** (52 mg, 0.09 mmol), (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (*R*-MTPA) (31 mg, 0.13 mmol), DCC (37 mg, 0.18 mmol) and DMAP (3 mg, 0.03 mmol), in anhydrous CH_2Cl_2 (4 mL). The residue was purified by silica gel column chromatography eluting with light petroleum and ethyl acetate (9:1) to afford compound **64** (61 mg, 86%) as a light yellow oil.

Mol. Formula : $C_{48}H_{73}F_3O_6$

$[\alpha]_D^{25}$: +8.5 (c = 1.3, $CHCl_3$).

IR ($CHCl_3$) υ : 2927, 1746, 1603, 1496, 1454, 1242, 1170 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.52-7.26 (m, 10H), 5.68-5.66 (m, 2H), 5.48-5.43 (m, 1H), 4.49 (s, 2H), 3.93-3.90 (m, 1H), 3.60-3.55 (m, 1H), 3.53 (s, 3H),

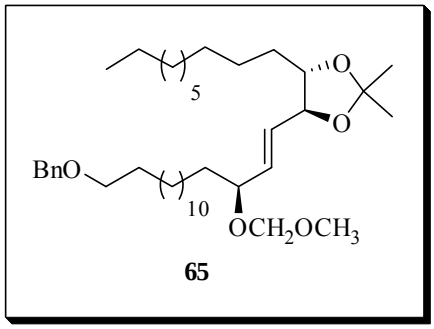
3.45 (t, *J* = 6.7 Hz, 2H), 1.73-1.66 (m, 2H), 1.61 (t, *J* = 7.2 Hz, 2H), 1.53-1.45 (m, 4H), 1.39 (s, 3H), 1.37 (s, 3H), 1.29-1.25 (m, 34H), 0.88 (t, *J* = 6.7 Hz, 3H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 165.7, 138.7, 132.3, 131.9, 131.0, 129.5, 128.3, 127.6, 127.5, 127.4, 108.7, 81.4, 80.7, 72.9, 70.5, 55.4, 34.2, 31.9, 31.8, 29.8 (2C), 29.7 (2C), 29.5 (2C), 29.4, 29.3, 27.3, 26.9, 26.3, 26.1, 25.0, 22.7, 14.2 ppm.

ESI-MS (*m/z*) : 825.74 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 71.79; H, 9.16%.
Found: C, 71.93; H, 9.39%.

(4*S*,5*S*)-4-((*S*,*E*)-16-(Benzyloxy)-3-(methoxymethoxy)-hexadec-1-enyl)-5-decyl-2,2-dimethyl-1,3-dioxolane (65)



65

Compound **54** (500 mg, 0.8 mmol), MOM chloride (0.2 mL, 1.8 mmol) and DIPEA (0.4 mL, 2.2 mmol) in CH_2Cl_2 (4 mL) were stirred at room temperature for 2 h. After the completion of the reaction (monitored by TLC), the reaction mixture was washed with water, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on silica gel (pre treated with Et_3N) using light petroleum and ethyl acetate (9.5:0.5) to furnish the MOM-derivative **65** (520 mg, 97%) as a yellow oil.

Mol. Formula : $C_{40}H_{70}O_5$

$[\alpha]_D^{25}$: –49.8 (*c* = 1.0, $CHCl_3$).

IR ($CHCl_3$) υ : 2928, 2855, 1601, 1495, 1465, 1379 cm^{-1}.

^{1}H NMR : δ 7.33-7.26 (m, 5H), 5.62-5.60 (m, 2H), 4.64 (d, *J* = 6.8 Hz,

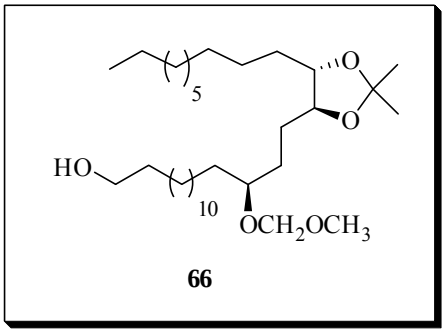
(400 MHz, $CDCl_3$) 1H), 4.51 (d, *J* = 6.8 Hz, 1H), 4.49 (s, 2H), 4.04-3.96 (m, 2H), 3.67-3.62 (m, 1H), 3.45 (t, *J* = 6.6 Hz, 2H), 3.35 (s, 3H), 1.64-1.50 (m, 6H), 1.40 (s, 3H), 1.39 (s, 3H), 1.33-1.26 (m, 36H), 0.88 (t, *J* = 6.7 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) : δ 138.7, 134.9, 130.1, 128.3, 127.6, 127.4, 108.4, 93.7, 81.9, 80.8, 75.9, 72.9, 70.5, 55.4, 35.6, 31.9, 29.8 (2C), 29.5, 29.4, 27.3, 27.0, 26.2, 26.1, 25.4, 22.7, 14.2 ppm.

ESI-MS (*m/z*) : 652.87 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 76.14; H, 11.18%.
Found: C, 75.96; H, 11.10%.

(*S*)-16-((4*S*,5*S*)-5-Decyl-2,2-dimethyl-1,3-dioxolan-4-yl)-14-(methoxymethoxy)-hexadecan-1-ol (66)



66

The MOM-derivative **65** (400 mg, 0.6 mmol), 10% $Pd(OH)_2/C$ (50 mg) in ethyl acetate (4 mL) were hydrogenated at normal temperature and pressure. After 6 h, the reaction mixture was filtered through a pad of Celite and concentrated. The residue was purified on silica gel using light petroleum and ethyl acetate (4:1) to provide compound **66** (270 mg, 80%) as colorless oil.

Mol. Formula : $C_{33}H_{66}O_5$

$[\alpha]_D^{25}$: –13.3 (*c* = 1.9, $CHCl_3$).

IR ($CHCl_3$) υ : 3425, 2927, 2854, 1613, 1465, 1378 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) : δ 4.64 (s, 2H), 3.62 (t, *J* = 6.9 Hz, 2H), 3.58-3.52 (m, 3H), 3.37 (s, 3H), 1.73-1.44 (m, 14H), 1.36 (s, 6H), 1.26 (m, 32H), 0.88 (t, *J*

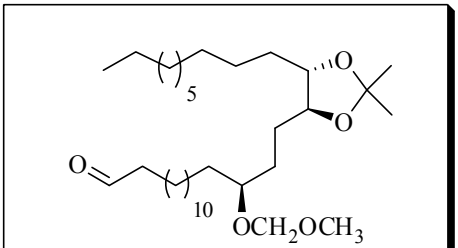
= 6.7 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ 107.8, 95.5, 81.2, 81.0, 77.5, 62.9, 55.5, 34.5, 33.0, 32.8, 31.9, 31.0, 29.8 (2C), 29.6, 29.4, 29.3, 28.8, 27.3, 26.1, 25.8, 25.2, 22.7, 14.1 ppm.

ESI-MS (*m/z*) : 565.73 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 73.01; H, 12.25%.
Found: C, 73.15; H, 12.12%.

(*S*)-16-((4*S*,5*S*)-5-Decyl-2,2-dimethyl-1,3-dioxolan-4-yl)-14-(methoxymethoxy)-hexadecanal (66-ald)



66-ald

Iodoxybenzoic acid (IBX) (163 mg, 0.6 mmol) and compound **66** (243 mg, 0.5 mmol) in DMSO (4 mL) were stirred at room temperature for 3 h, diluted with H_2O (4 mL) and filtered. The filtrate was extracted with diethyl ether (3x 10 mL), washed with $NaHCO_3$, water, brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on silica gel by eluting with light petroleum and ethyl acetate (9:1) to give the corresponding aldehyde **66-ald** (228 mg, 94%) as light yellow oil.

Mol. Formula : $C_{33}H_{64}O_5$

$[\alpha]_D^{25}$: –9.8 (*c* = 0.7, $CHCl_3$).

IR ($CHCl_3$) υ : 2854, 1728, 1459, 1376, 1240, 1218, 1097 cm^{-1}.

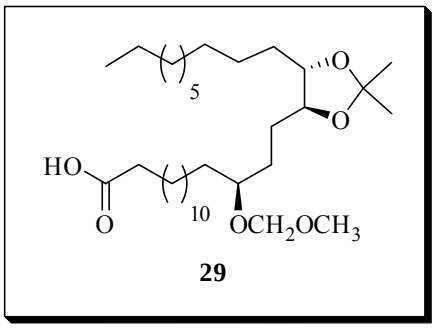
^{1}H NMR (500 MHz, $CDCl_3$) : δ 9.76 (t, *J* = 1.9 Hz, 1H), 4.65 (s, 2H), 3.57 (m, 3H), 3.37 (s, 3H), 2.42 (dt, *J* = 7.3, 1.9 Hz, 2H), 1.75-1.59 (m, 4H), 1.55-1.43 (m, 8H), 1.37 (s, 6H), 1.26 (m, 32H), 0.88 (t, *J* = 6.7 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) : δ 202.4, 107.8, 95.4, 81.2, 81.0, 77.5, 55.5, 43.9, 34.4, 33.0, 31.9, 31.0, 29.8 (2C), 29.7, 29.6, 29.4 (2C), 29.3, 29.2, 28.8, 27.3, 26.2, 25.2, 22.7, 22.1, 14.1 ppm.

ESI-MS (*m/z*) : 563.68 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 73.28; H, 11.93%.
Found: C, 73.17; H, 11.80%.

(*S*)-16-((4*S*,5*S*)-5-Decyl-2,2-dimethyl-1,3-dioxolan-4-yl)-14-(methoxymethoxy)-hexadecanoic acid (29)



29

To the compound **66-ald** (200 mg, 0.4 mmol), *t*-BuOH (2 mL), $NaH_2PO_4.2H_2O$ (190 mg, 1.2 mmol), and 2-methyl-2-butene (0.2 mL), a solution of $NaClO_2$ (110 mg, 1.2 mmol) in water (1 mL) was added drop wise. After 2 h, the reaction mixture was diluted with water, extracted with ethyl acetate, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on silica gel by eluting with light petroleum and ethyl acetate (4:1) to give compound **29** (180 mg, 88%) as a light yellow oil.

Mol. Formula : $C_{33}H_{64}O_6$

$[\alpha]_D^{25}$: –15.1 (*c* = 1.1, $CHCl_3$).

IR ($CHCl_3$) υ : 3012, 2987, 2855, 2928, 1710, 1465, 1379 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 4.65 (s, 2H), 3.62-3.52 (m, 3H), 3.38 (s, 3H), 2.34 (t, *J* = 7.3 Hz, 2H), 1.73-1.48 (m, 10H), 1.37 (s, 6H), 1.26 (m, 34H), 0.88 (t, *J* = 6.7 Hz, 3H) ppm.

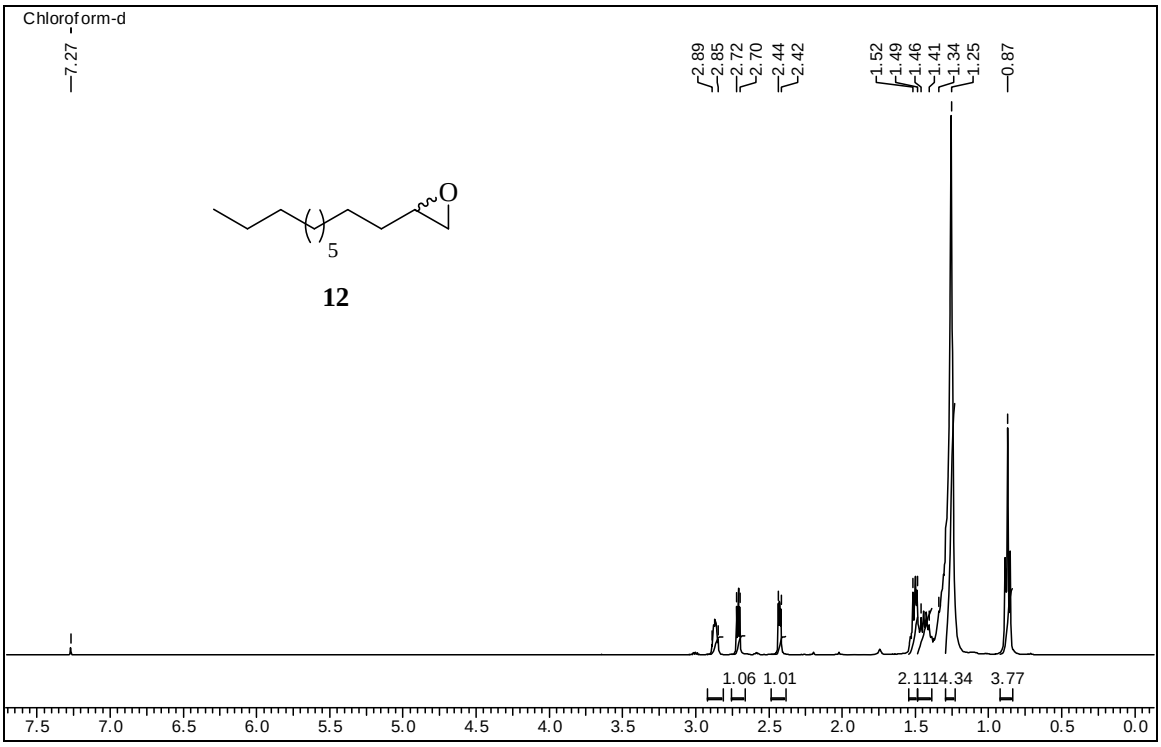
^{13}C NMR (50 MHz, $CDCl_3$) : δ 179.3, 107.8, 95.4, 81.2, 81.0, 77.6, 55.5, 34.4, 34.0, 33.0, 31.9, 29.8 (2C), 29.6 (2C), 29.4, 29.3, 29.2, 29.1, 28.8, 27.3, 26.1,

25.2, 24.7, 22.7, 14.1 ppm.

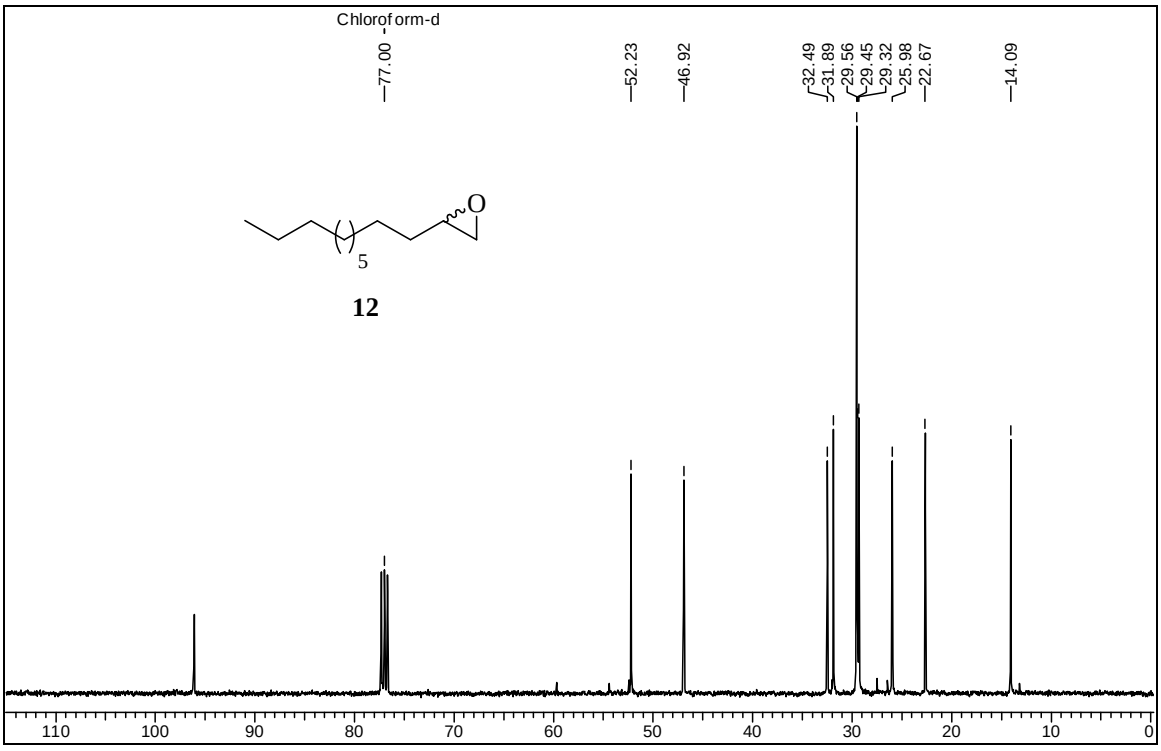
ESI-MS (*m/z*) : 579.19 $[M+Na]^+$.

Elemental Analysis : Calcd.: C, 71.18; H, 11.58%.
Found: C, 71.00; H, 11.75%.

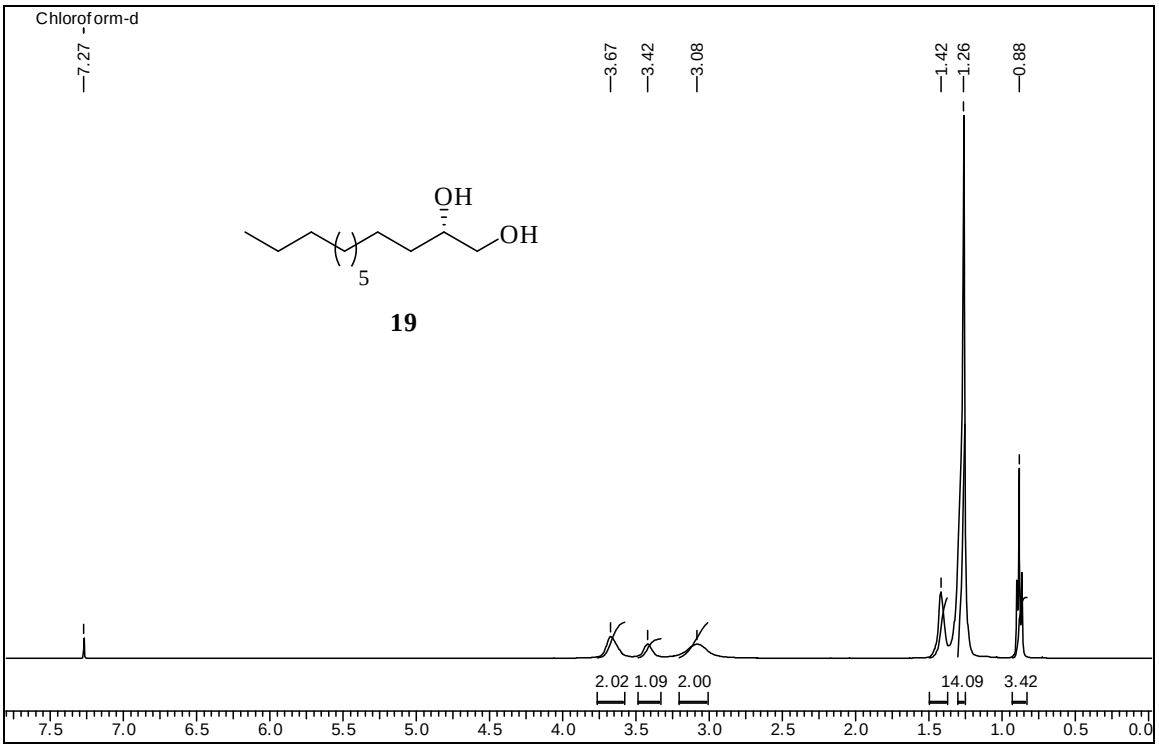
SPECTRA



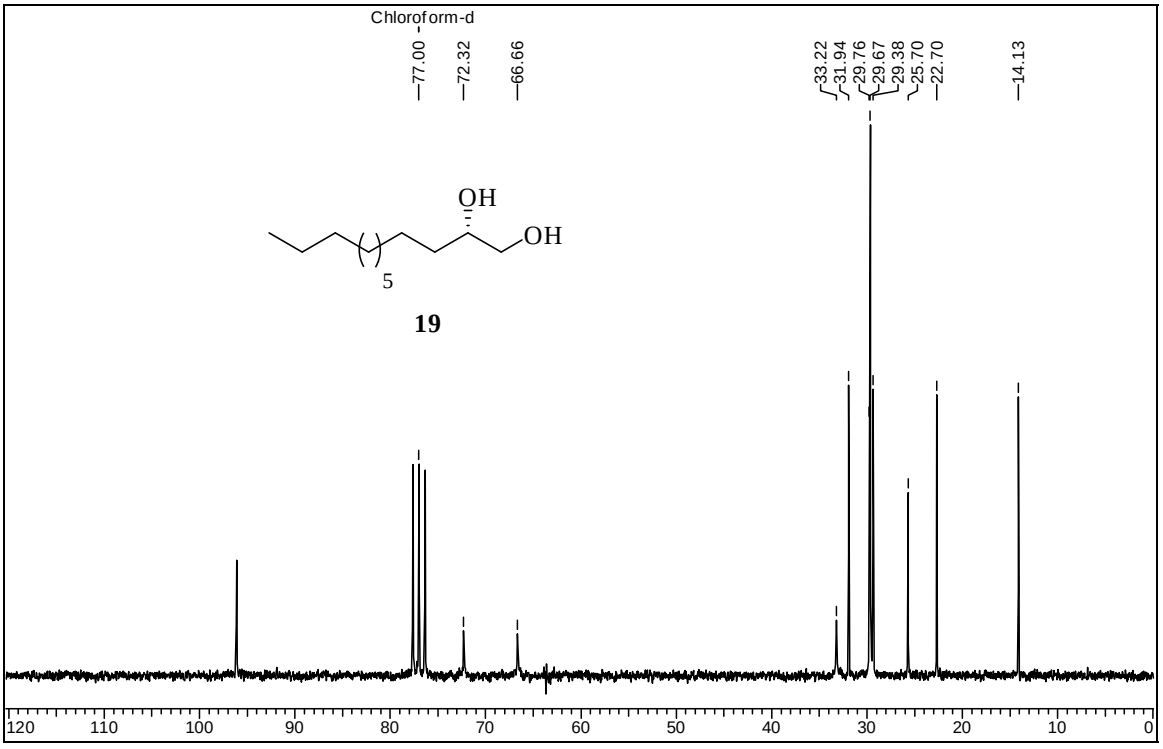
^{1}H NMR spectrum of compound 12 in $CDCl_3$



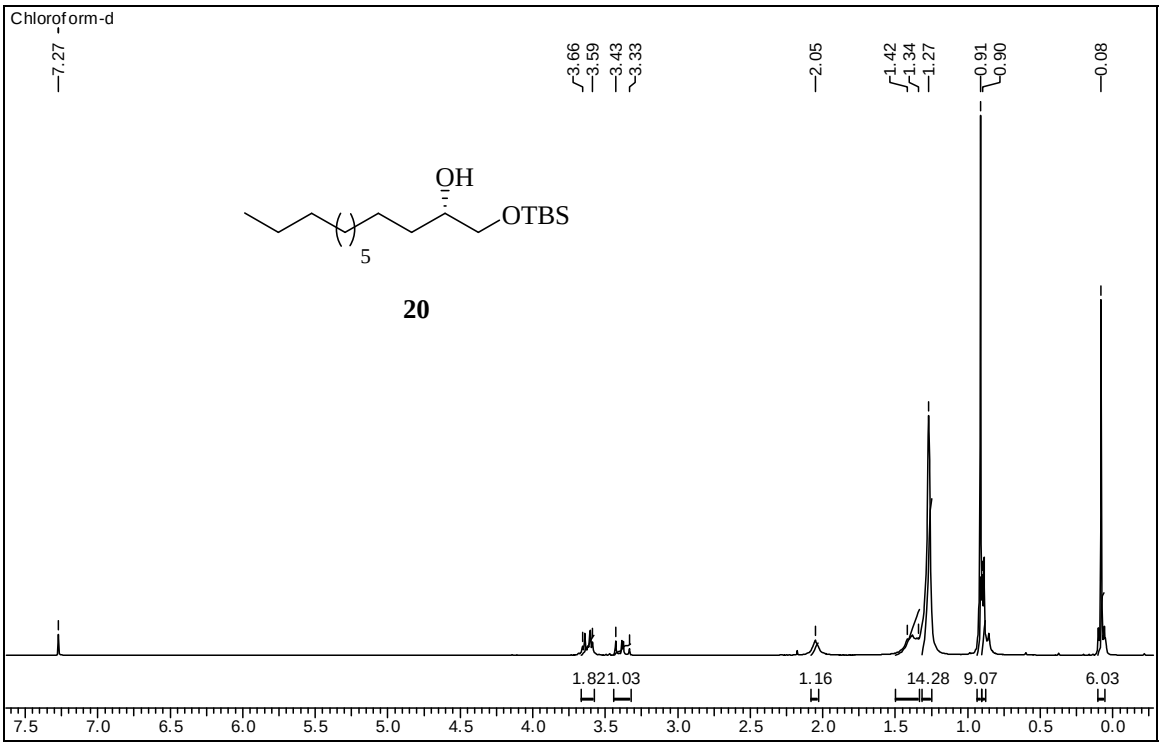
^{13}C NMR spectrum of compound 12 in $CDCl_3$



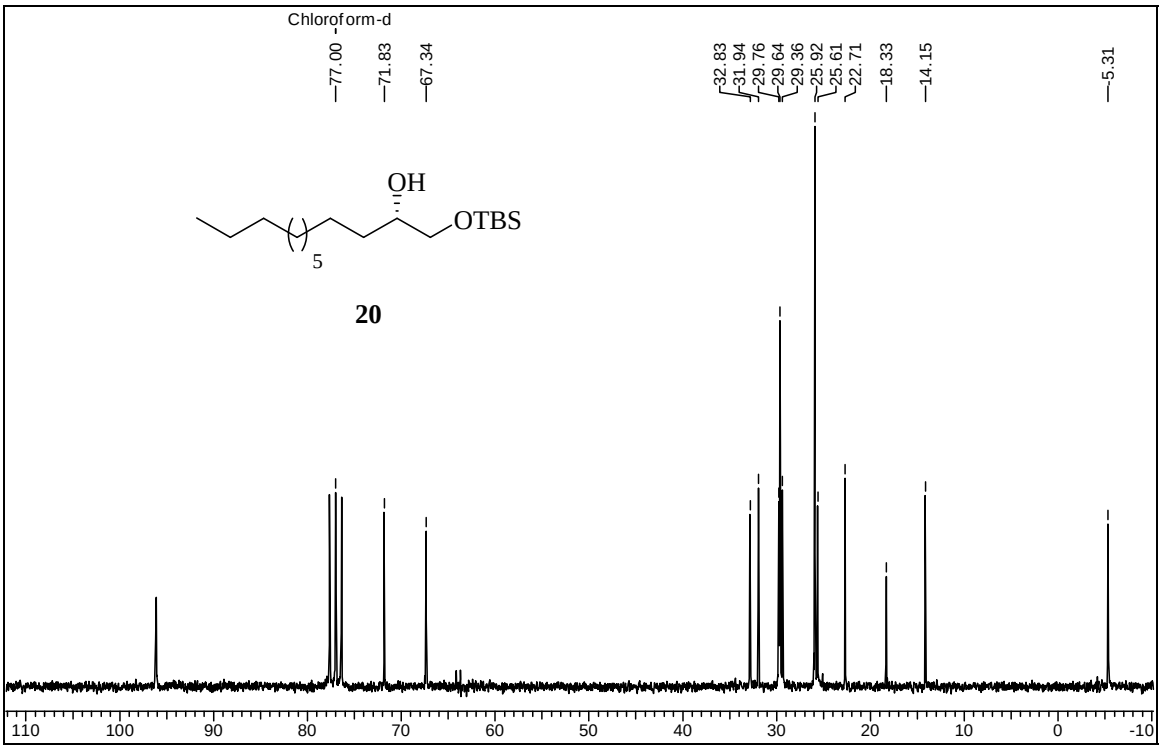
^{1}H NMR spectrum of compound 19 in $CDCl_3$



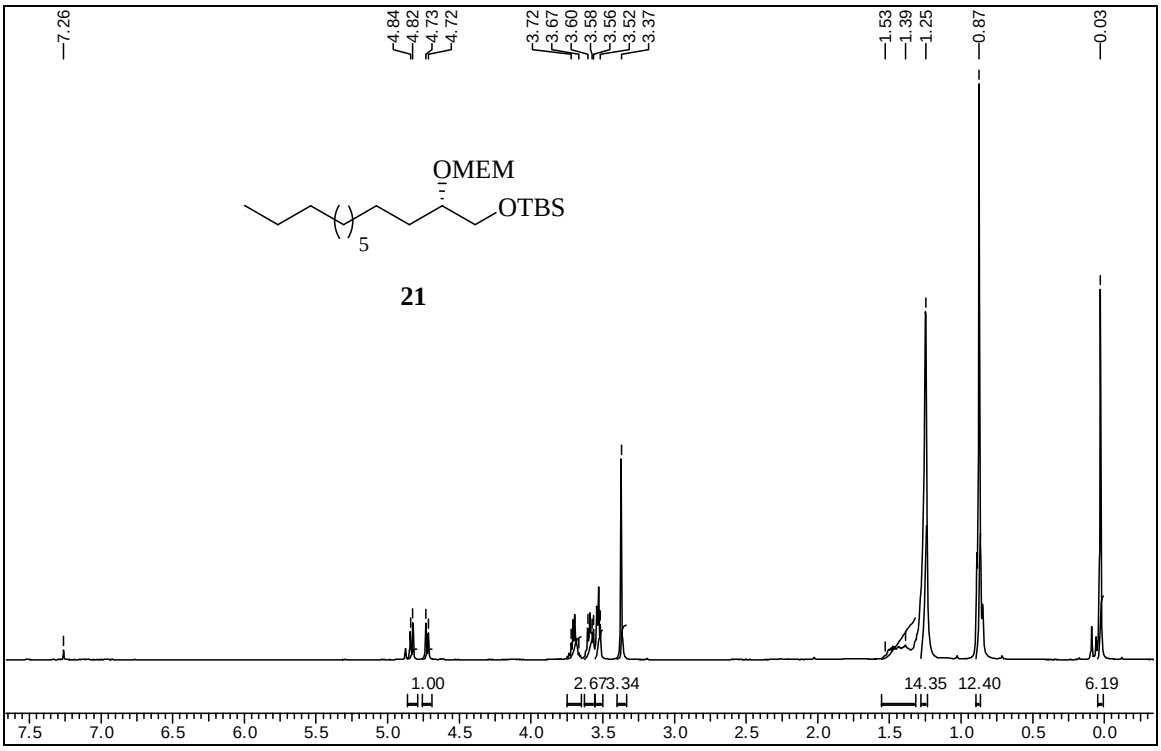
^{13}C NMR spectrum of compound 19 in $CDCl_3$



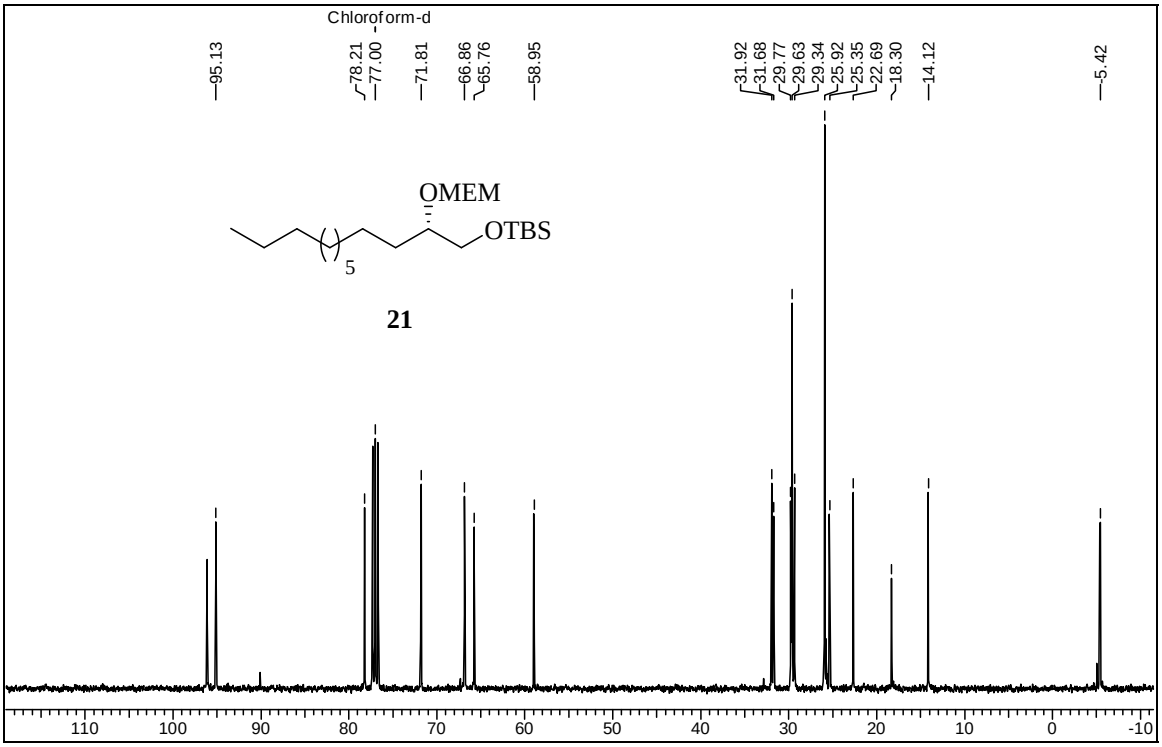
^{1}H NMR spectrum of compound 20 in $CDCl_3$



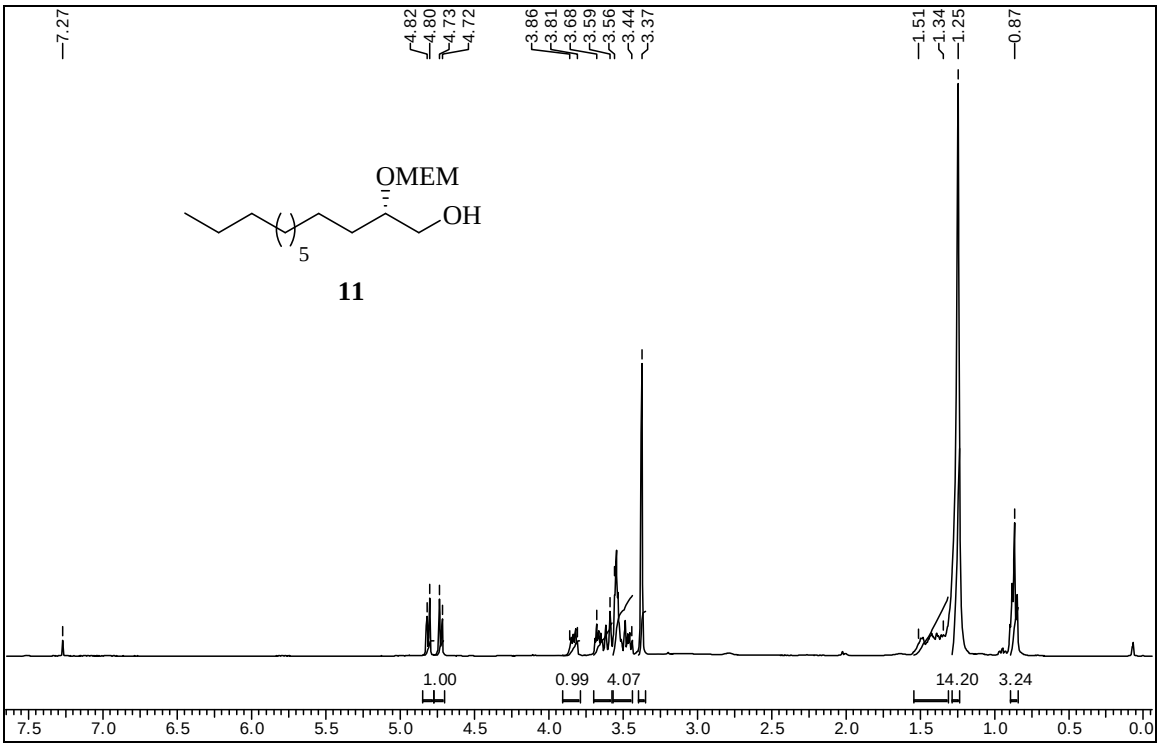
^{13}C NMR spectrum of compound 20 in $CDCl_3$



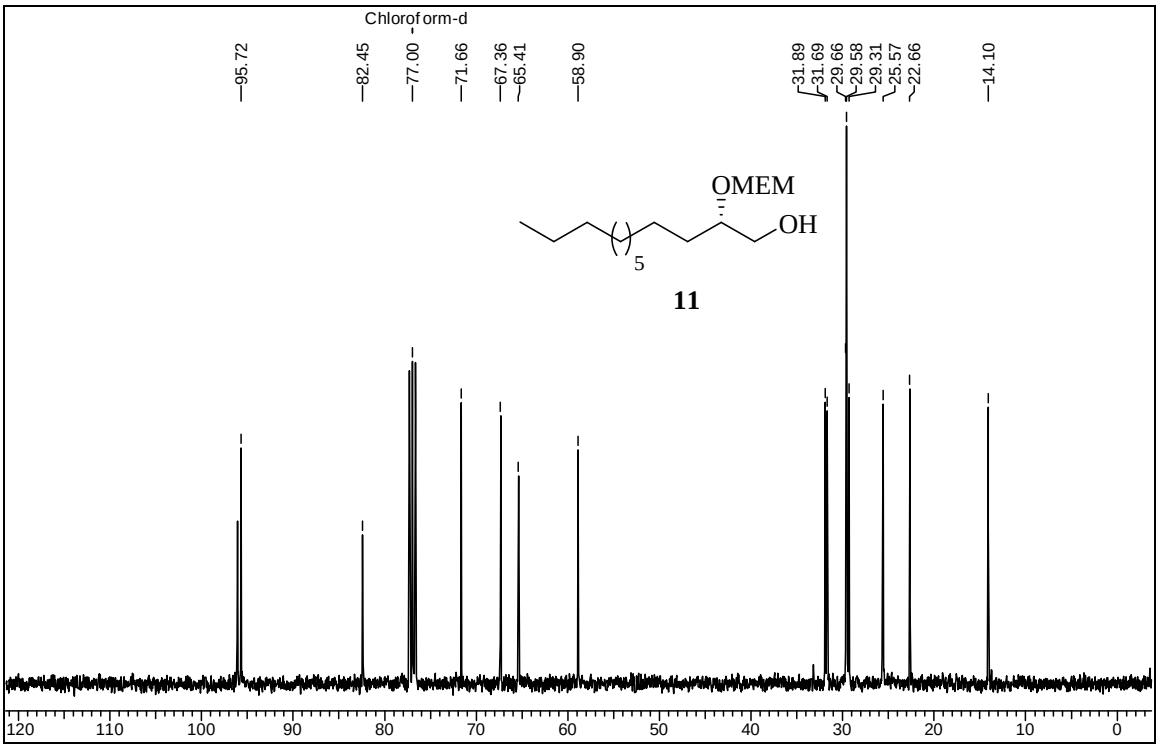
^{1}H NMR spectrum of compound 21 in $CDCl_3$



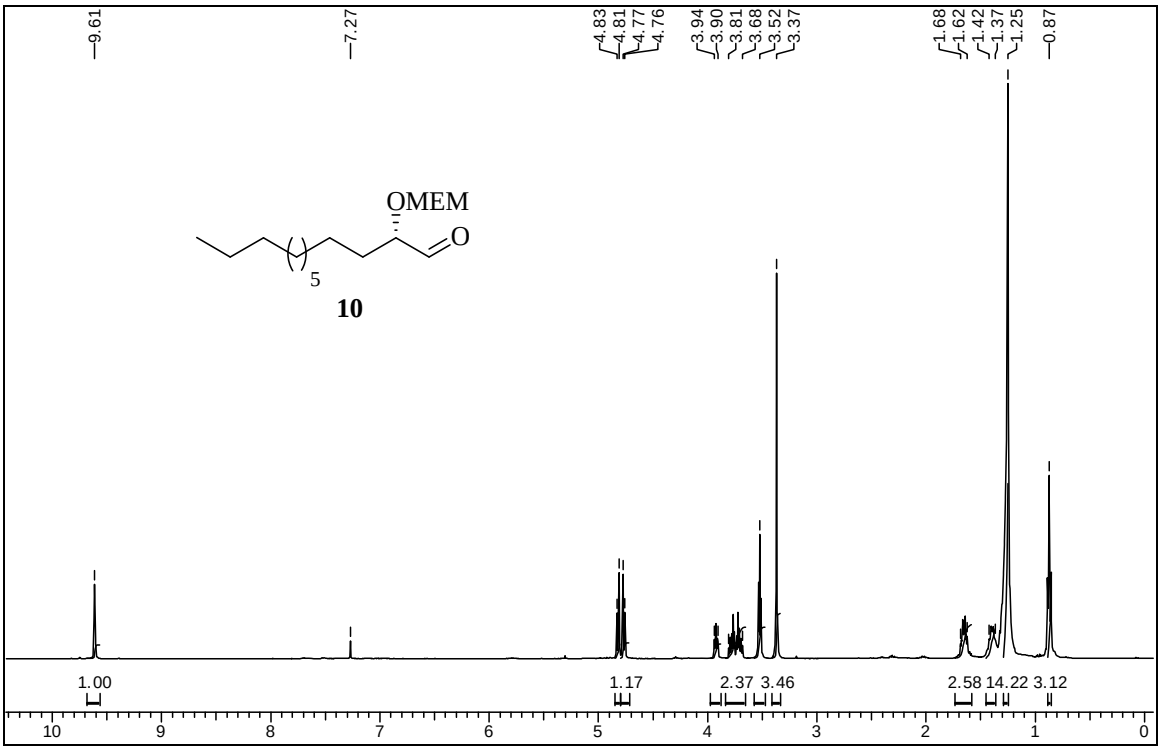
^{13}C NMR spectrum of compound 21 in $CDCl_3$



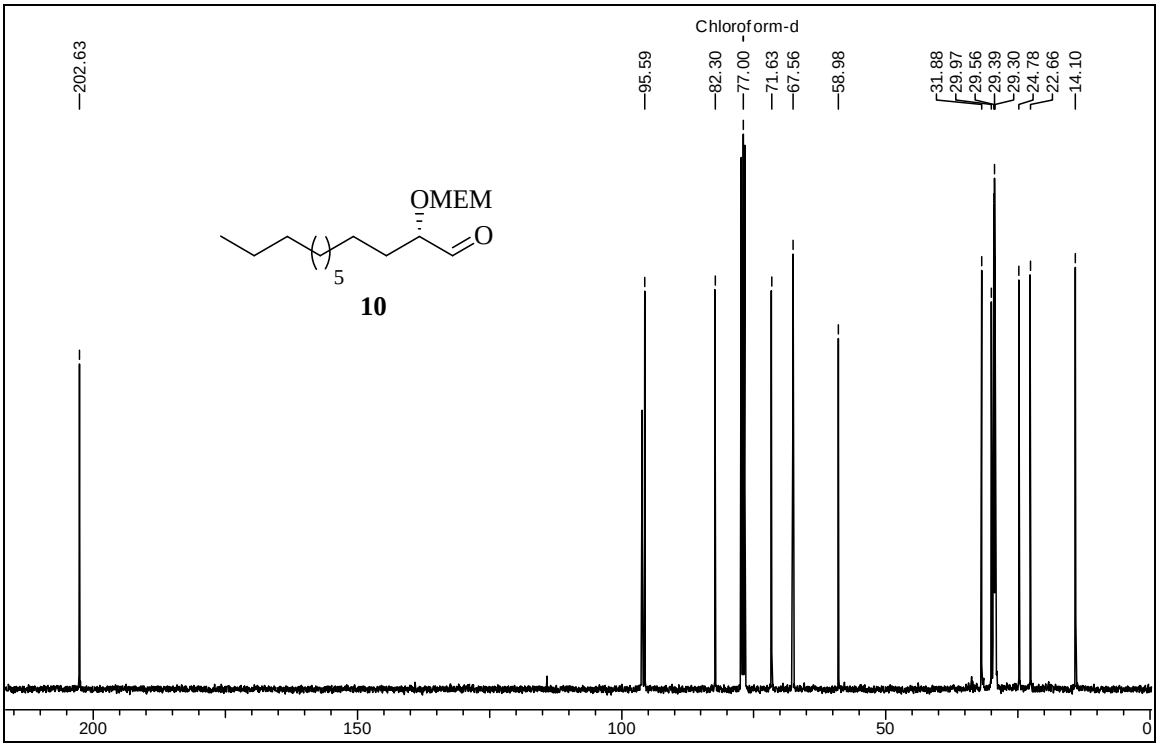
^{1}H NMR spectrum of compound 11 in $CDCl_3$



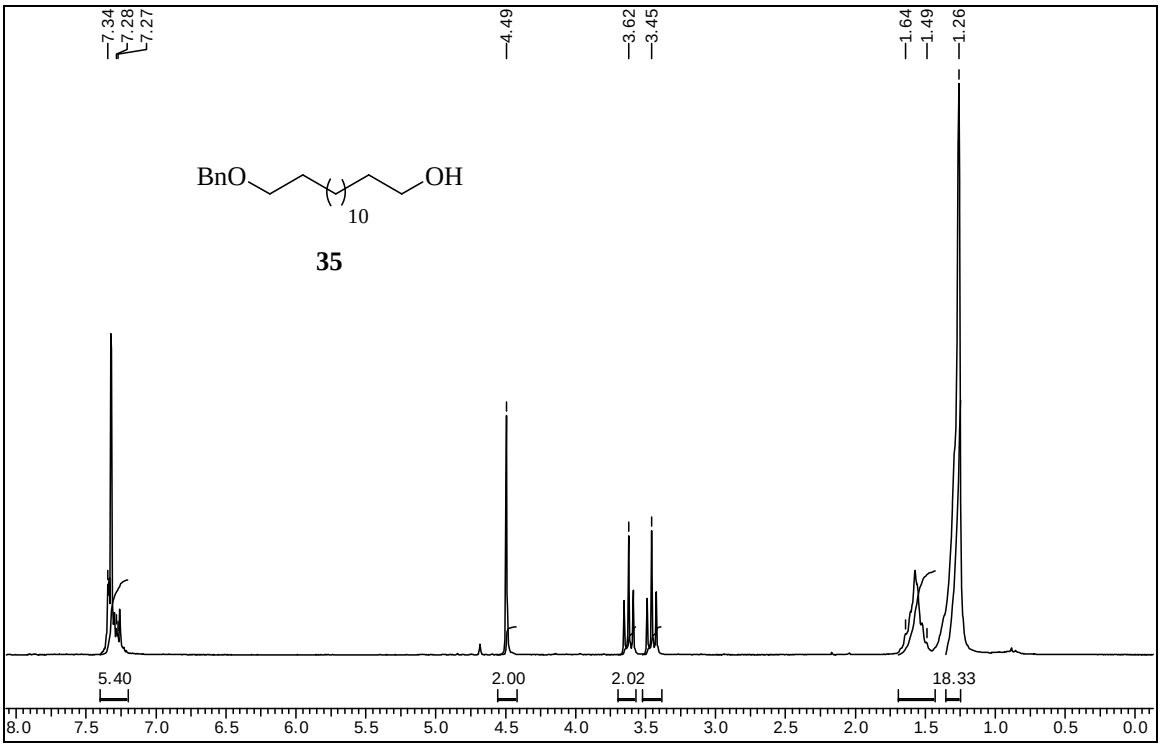
^{13}C NMR spectrum of compound 11 in $CDCl_3$



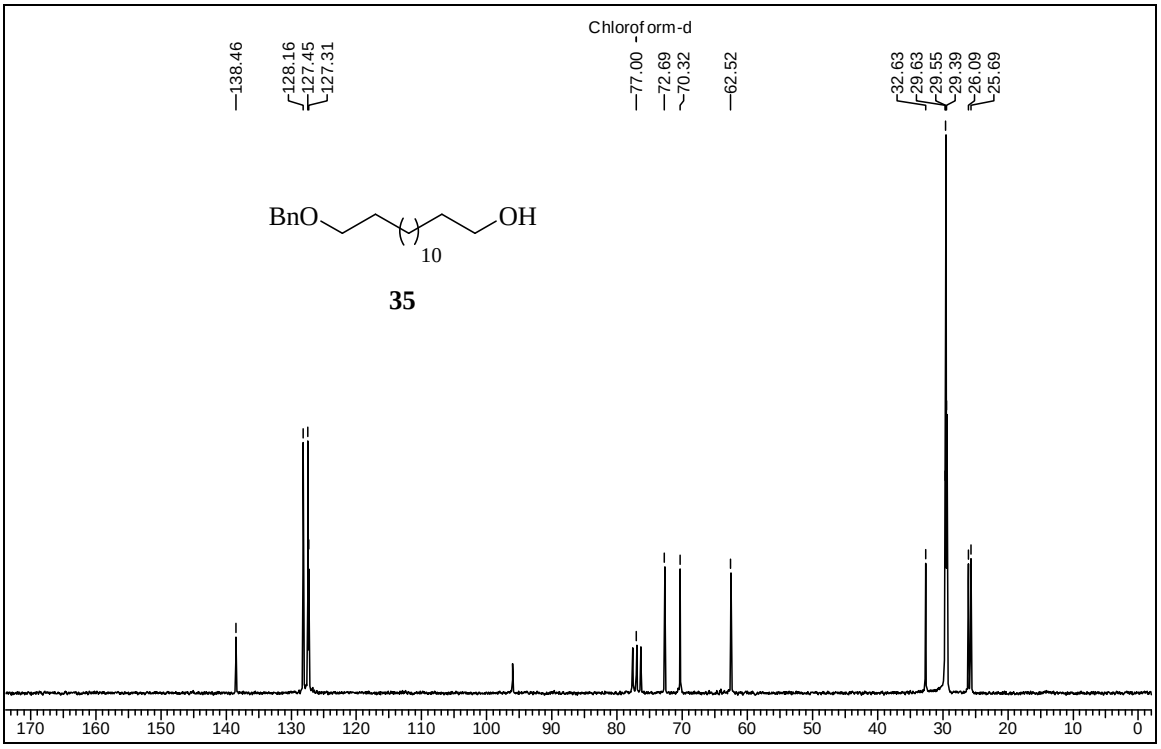
^{1}H NMR spectrum of compound 10 in $CDCl_3$



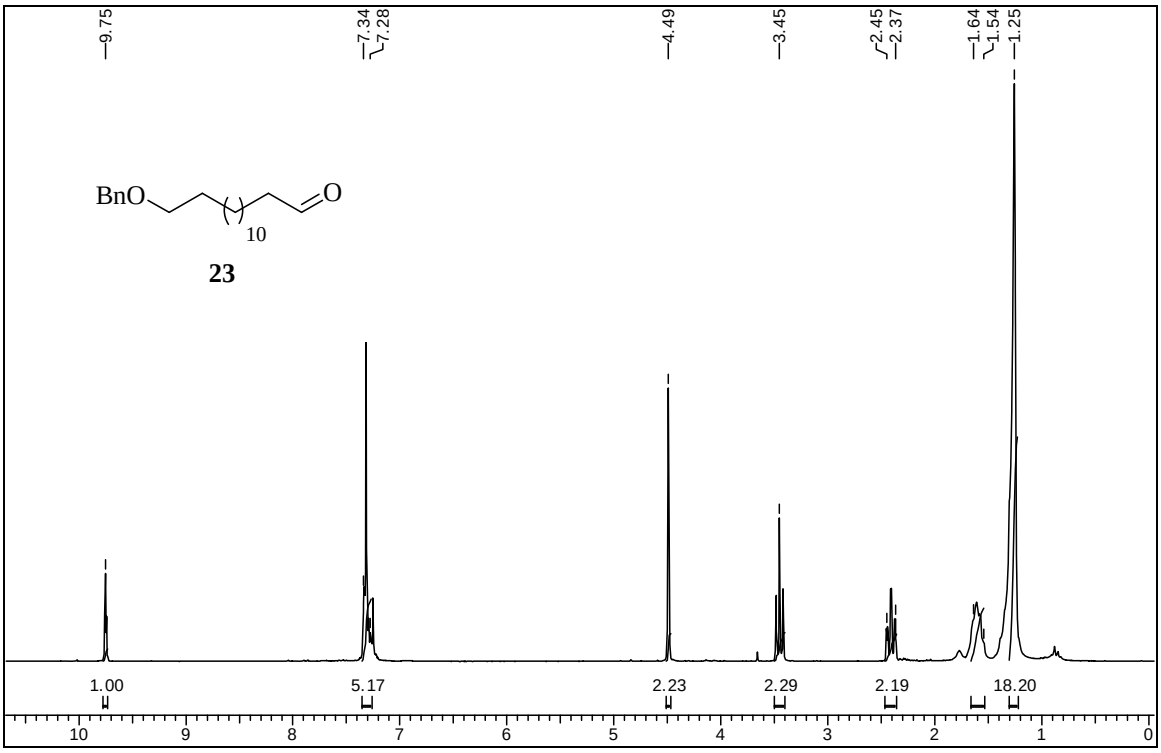
^{13}C NMR spectrum of compound 10 in $CDCl_3$



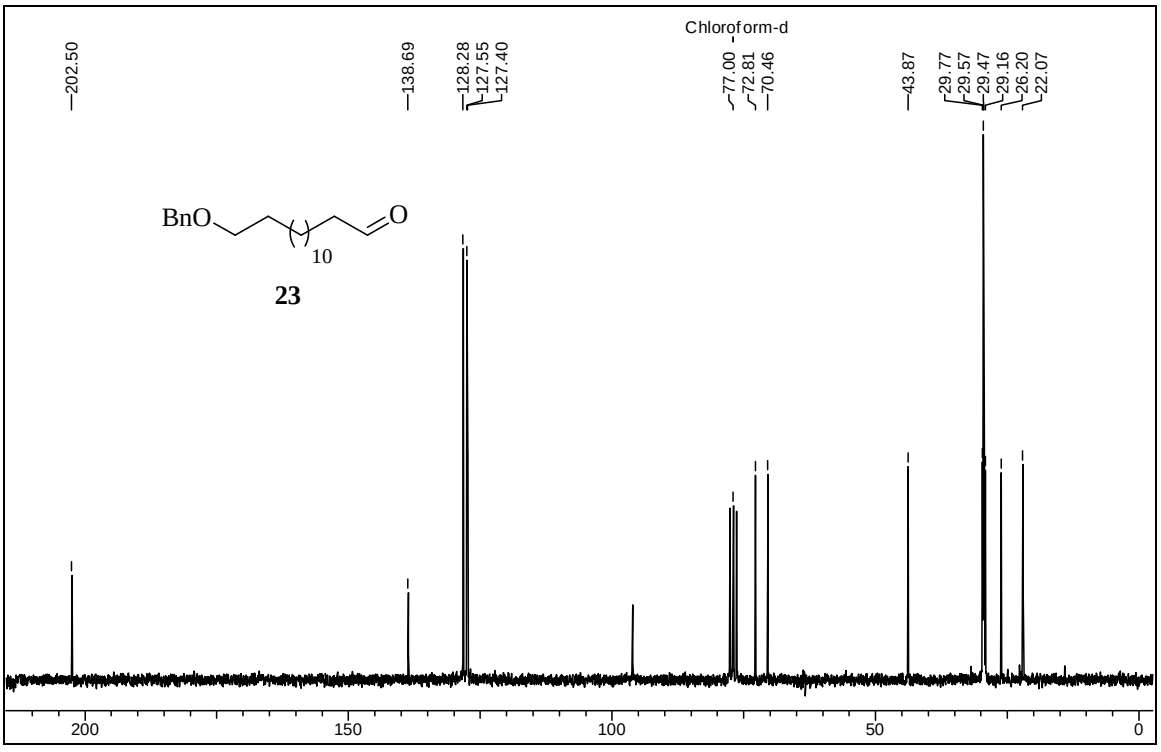
^{1}H NMR spectrum of compound 35 in $CDCl_3$



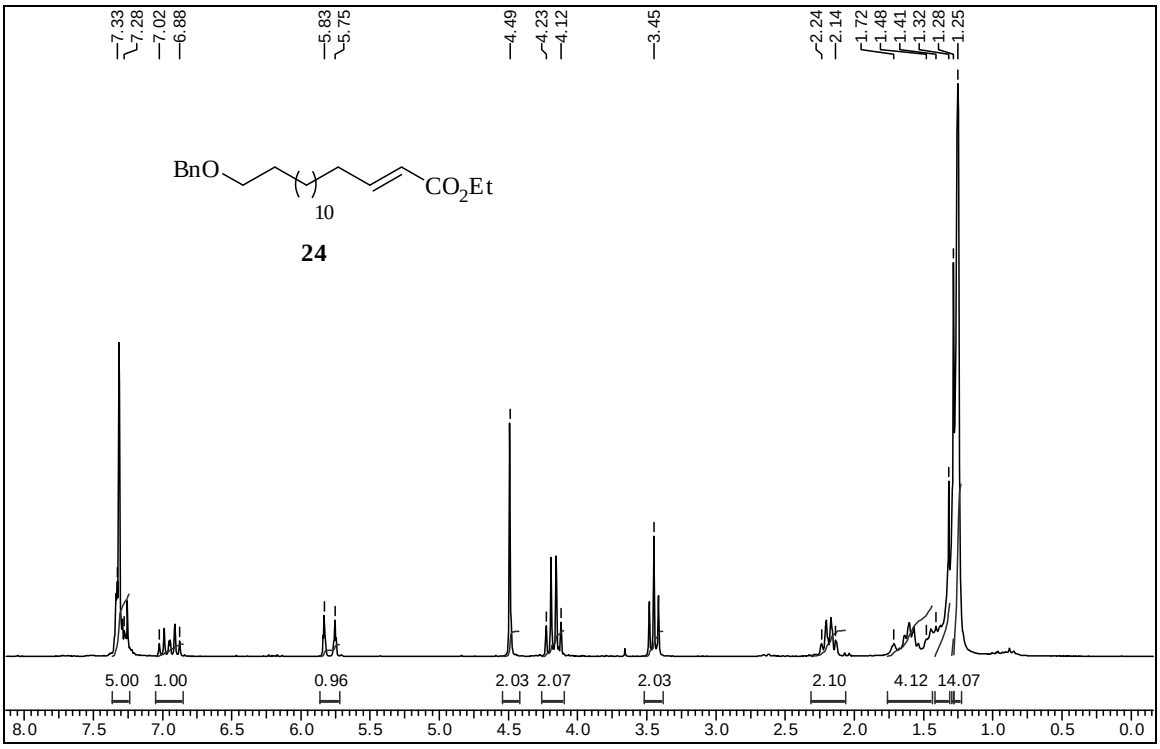
^{13}C NMR spectrum of compound 35 in $CDCl_3$



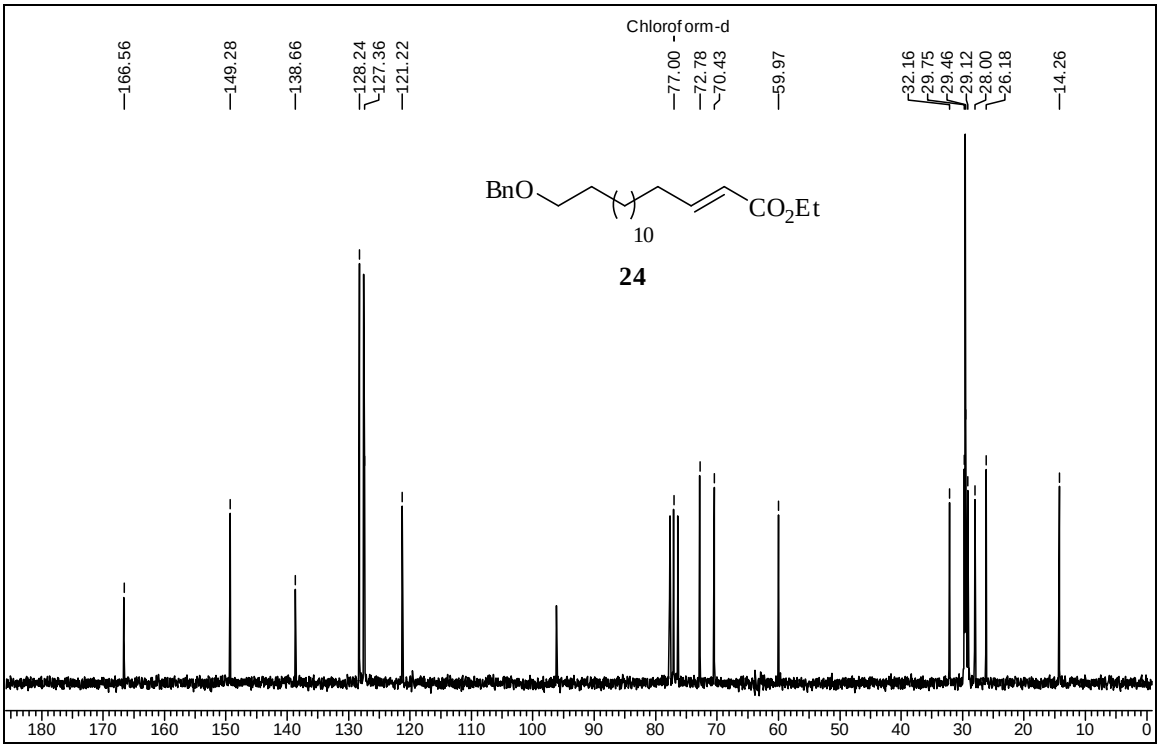
^{1}H NMR spectrum of compound 23 in $CDCl_3$



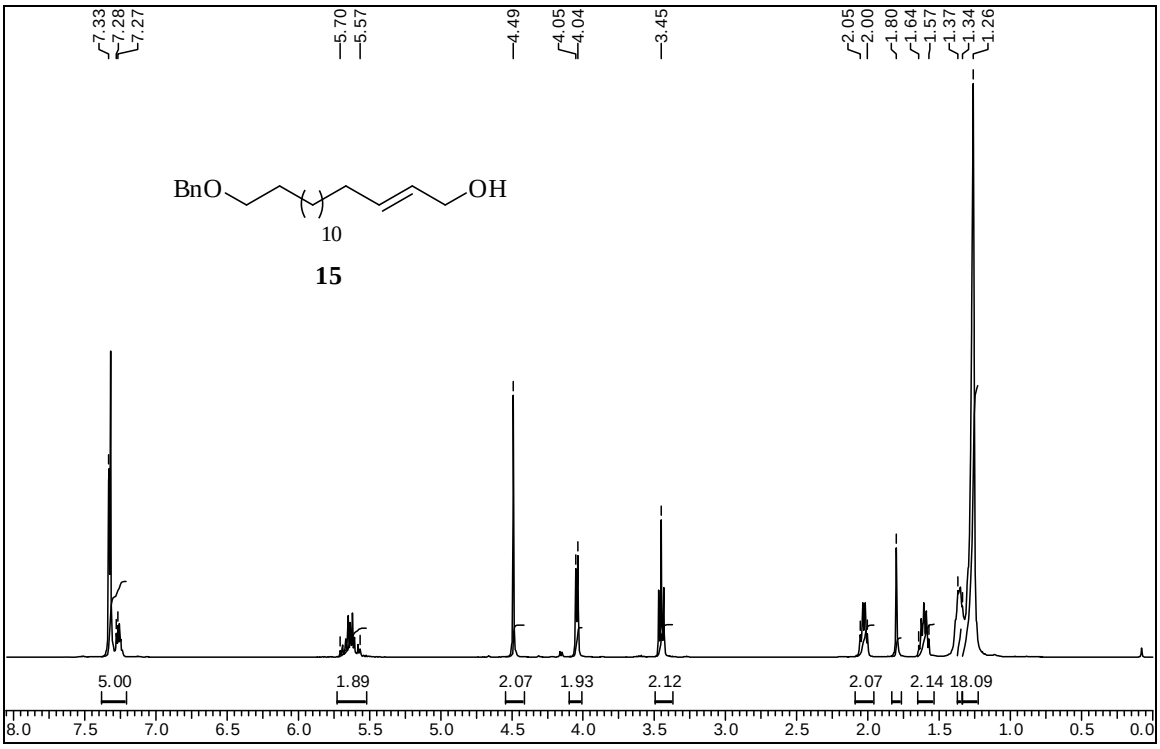
^{13}C NMR spectrum of compound 23 in $CDCl_3$



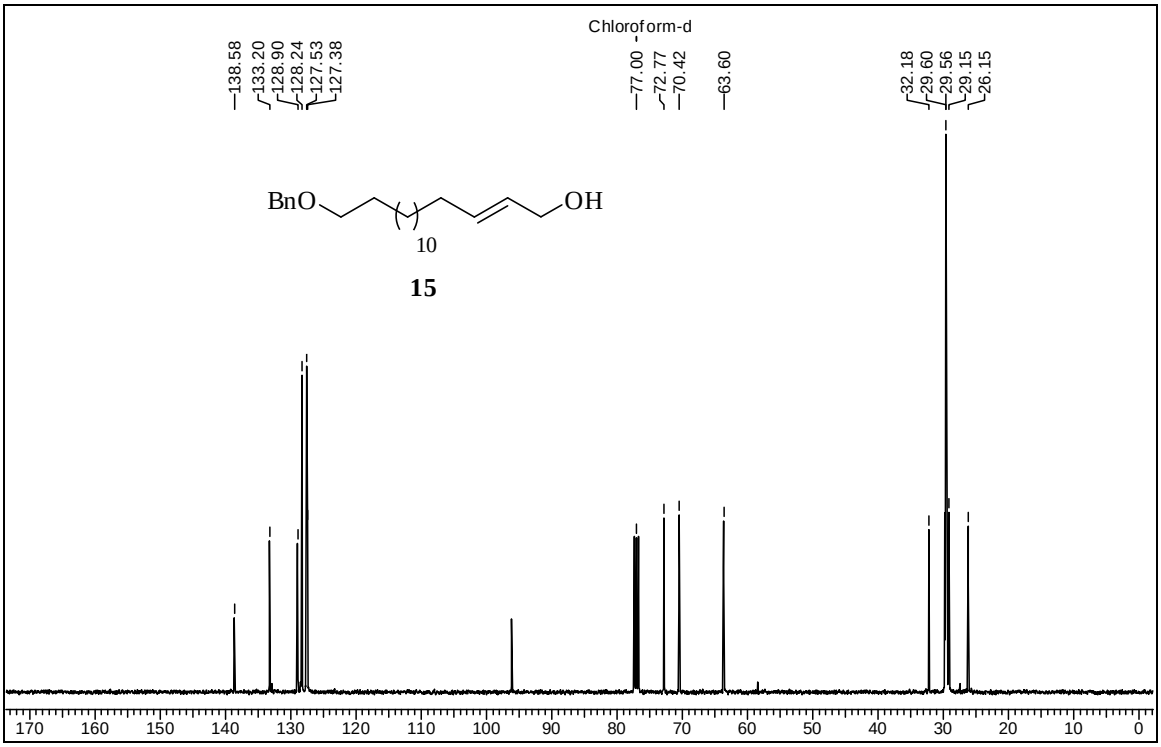
^{1}H NMR spectrum of compound 24 in $CDCl_3$



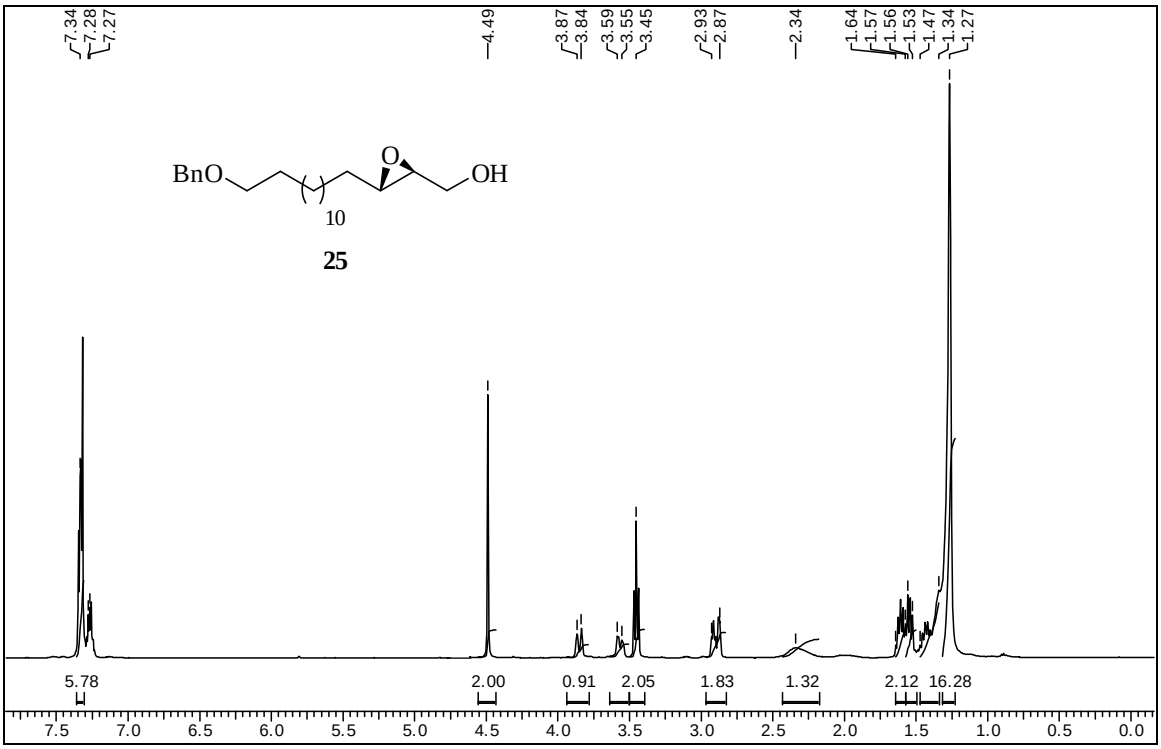
^{13}C NMR spectrum of compound 24 in $CDCl_3$



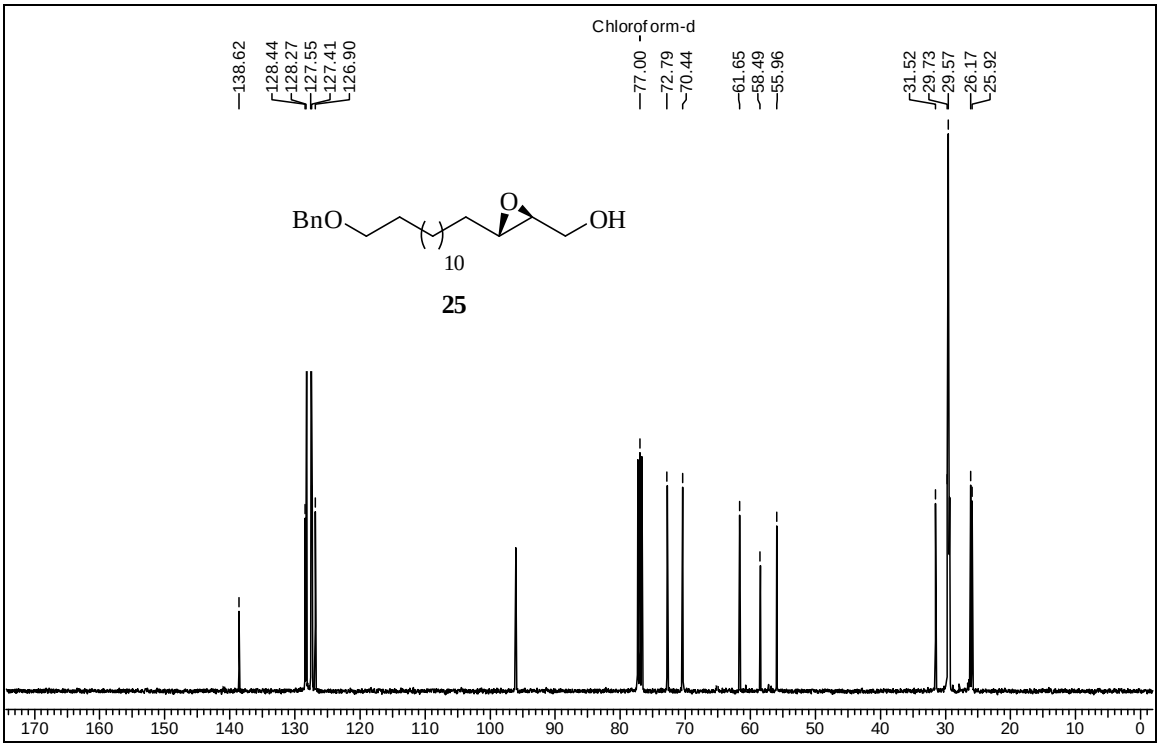
^{1}H NMR spectrum of compound 15 in $CDCl_3$



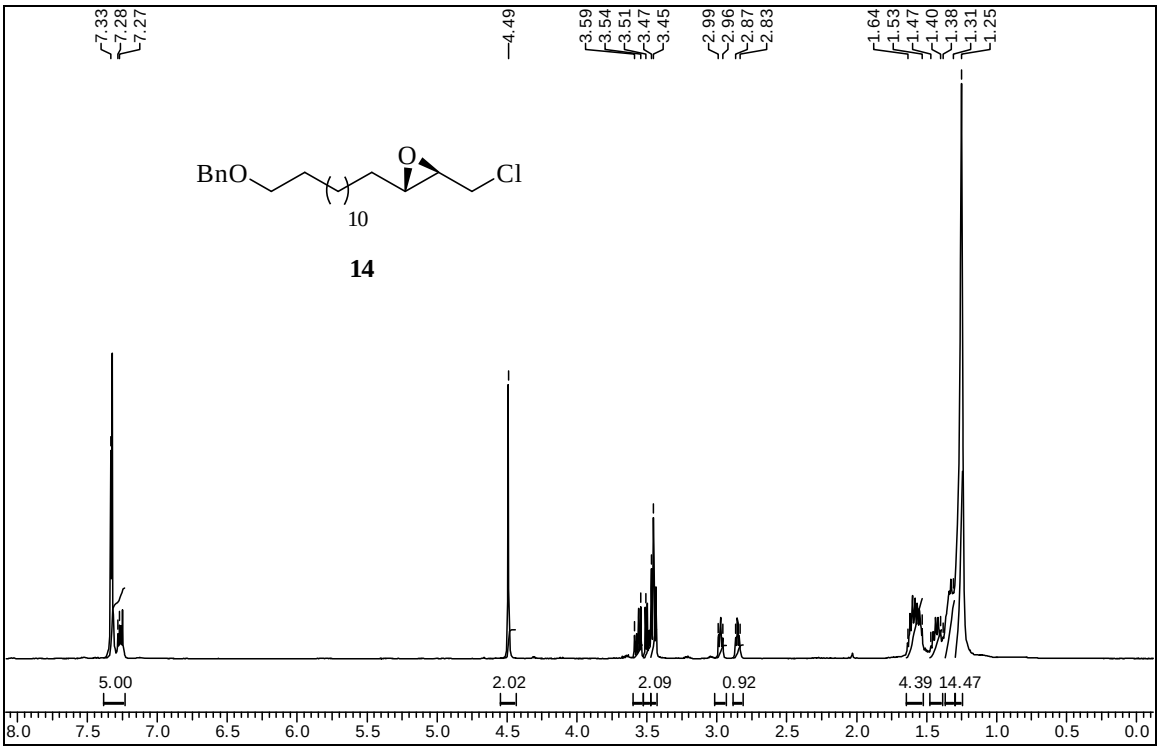
^{13}C NMR spectrum of compound 15 in $CDCl_3$



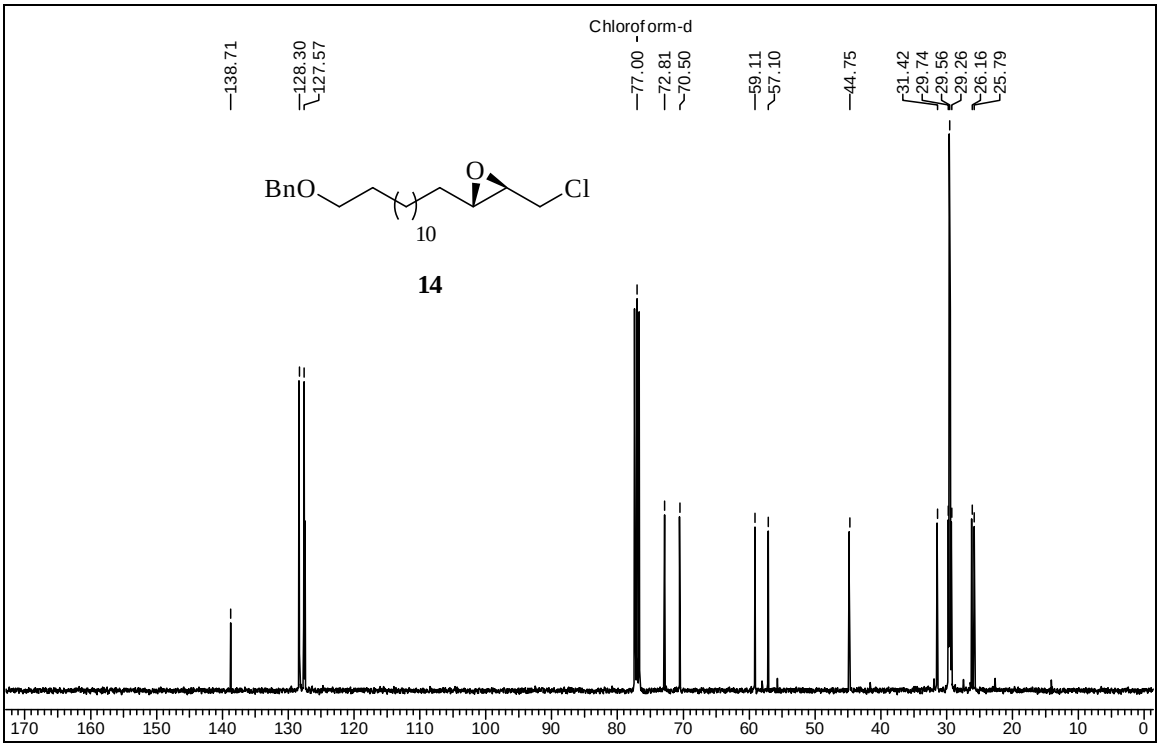
^{1}H NMR spectrum of compound 25 in $CDCl_3$



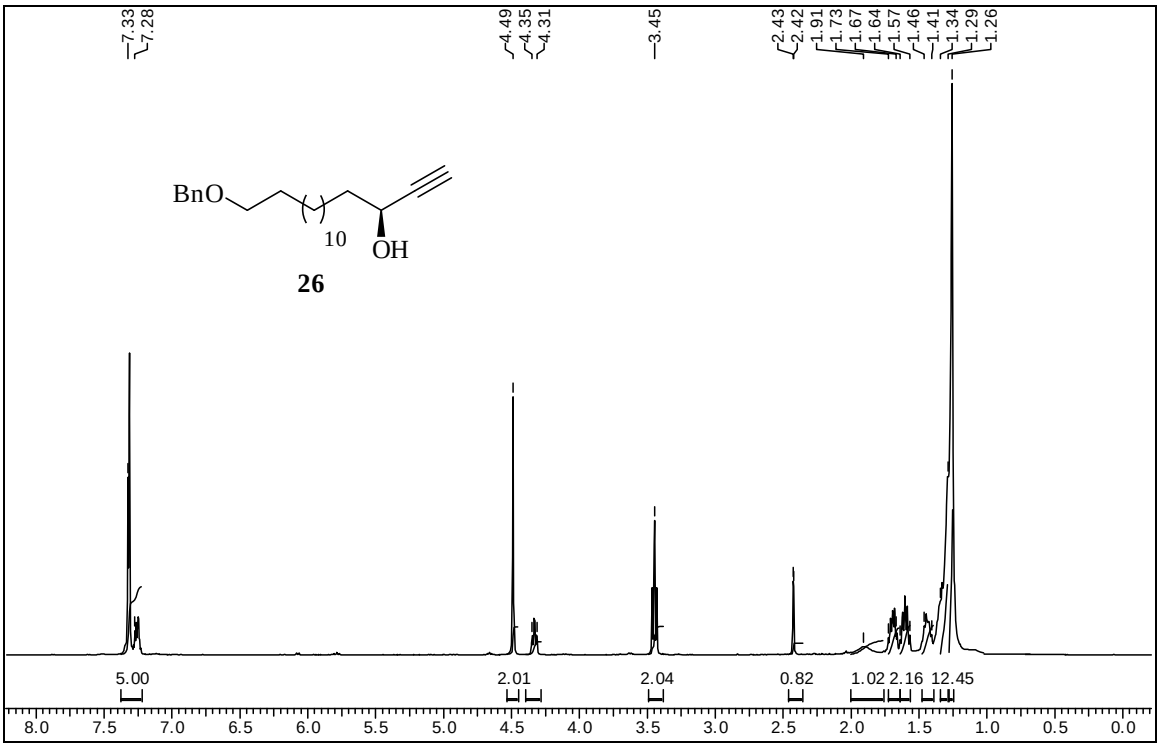
^{13}C NMR spectrum of compound 25 in $CDCl_3$



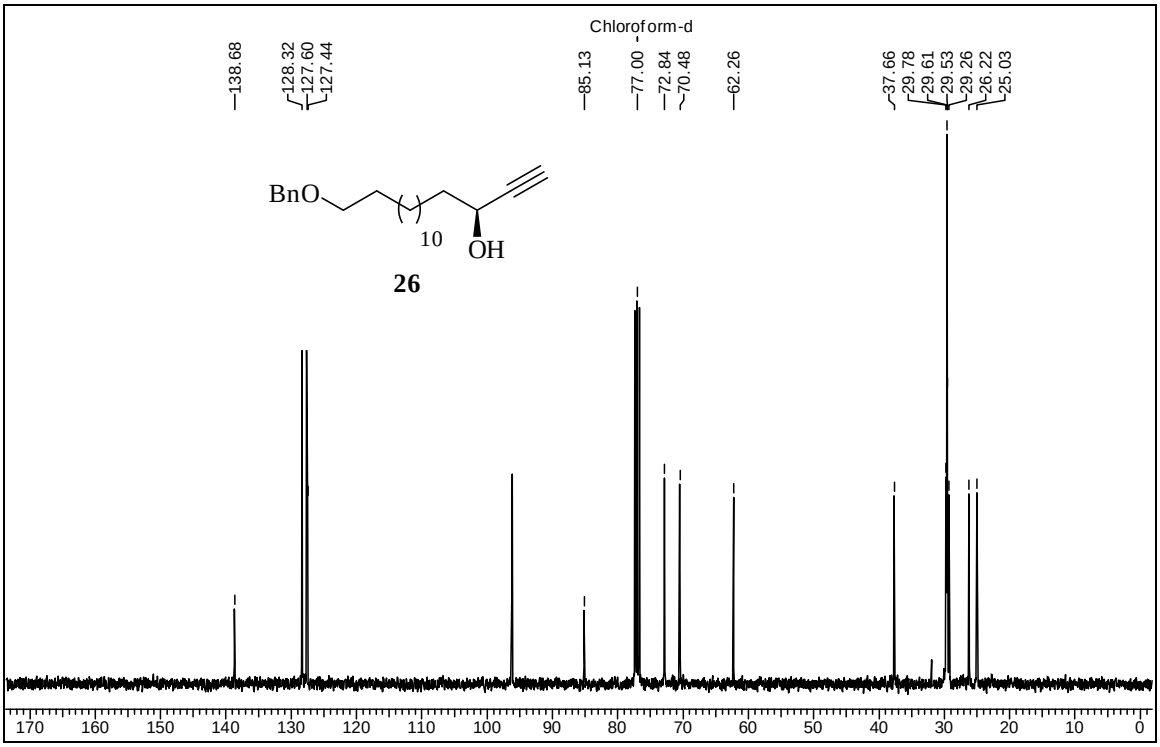
^{1}H NMR spectrum of compound 14 in $CDCl_3$



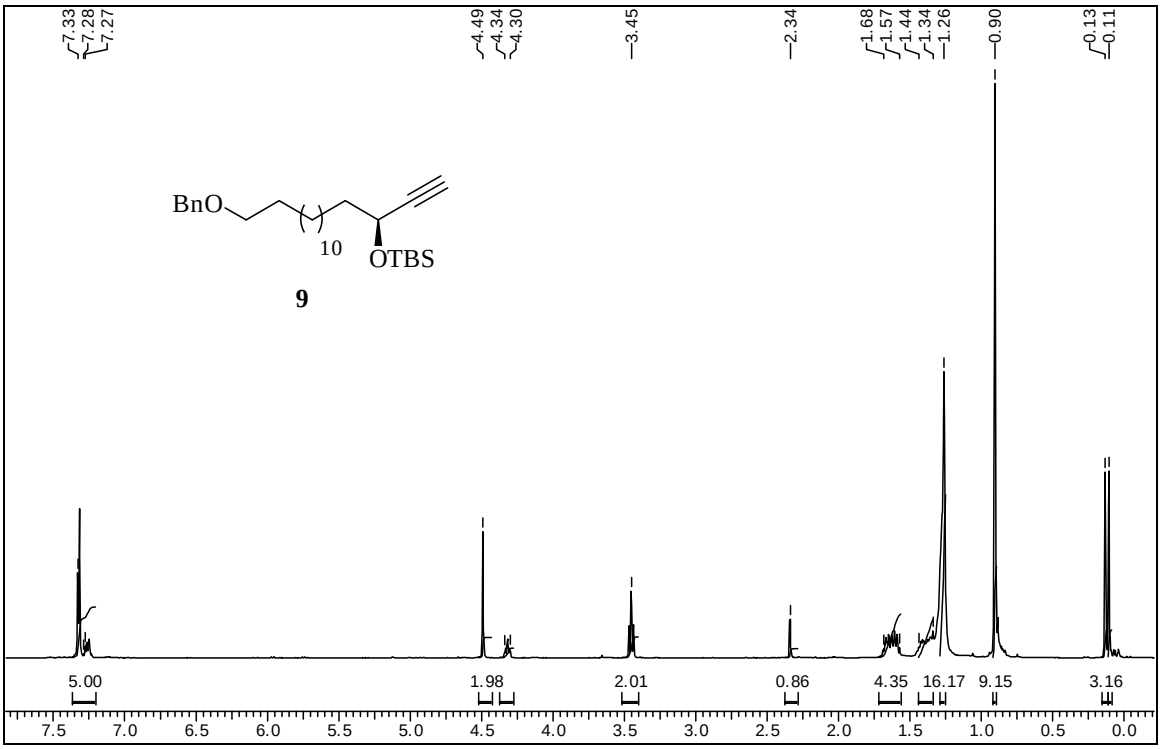
^{13}C NMR spectrum of compound 14 in $CDCl_3$



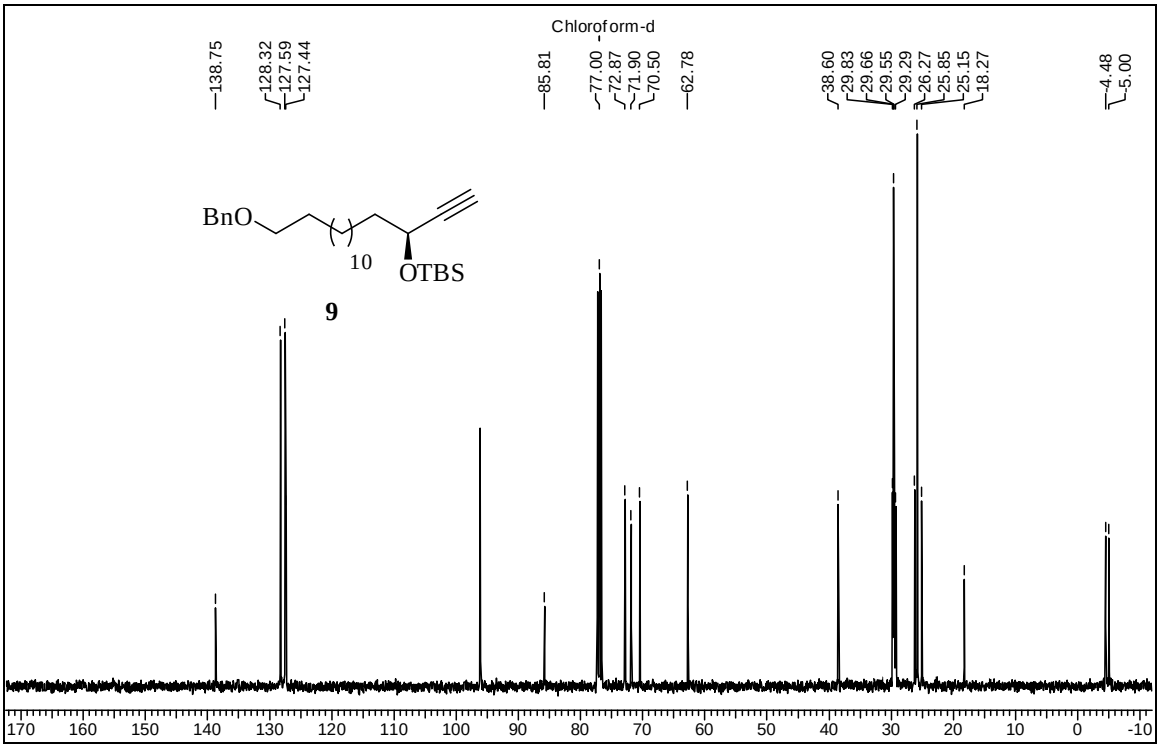
^{1}H NMR spectrum of compound 26 in $CDCl_3$



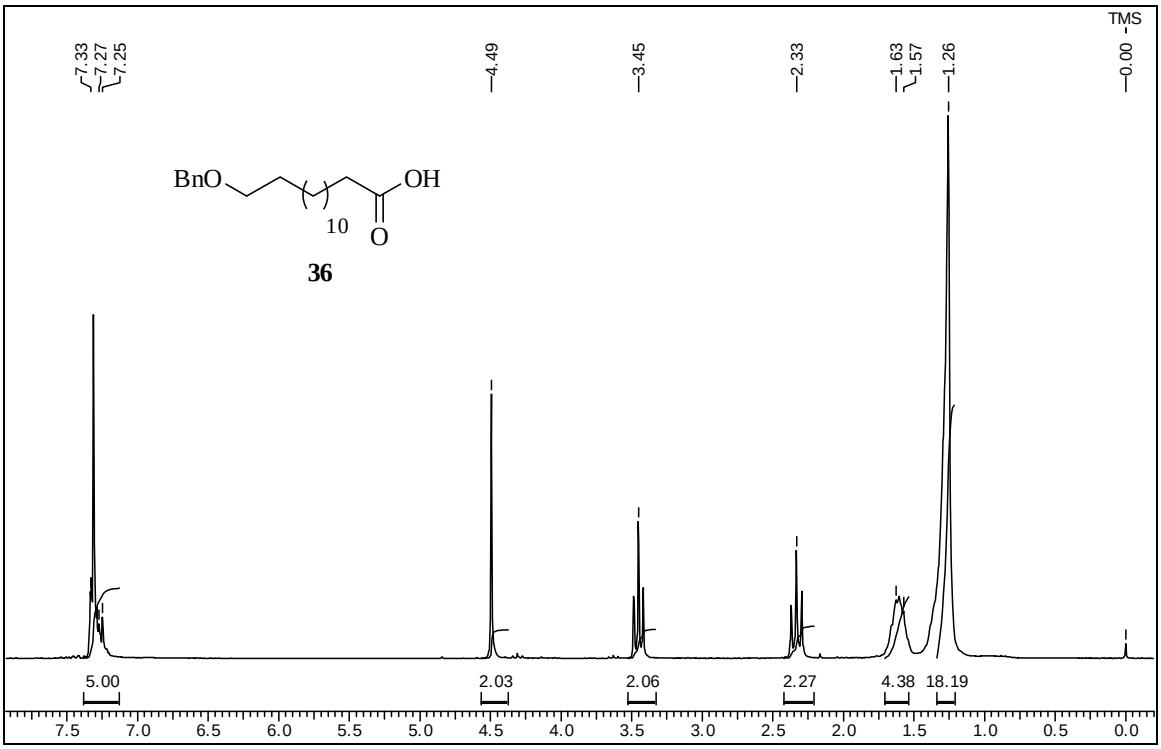
^{13}C NMR spectrum of compound 26 in $CDCl_3$



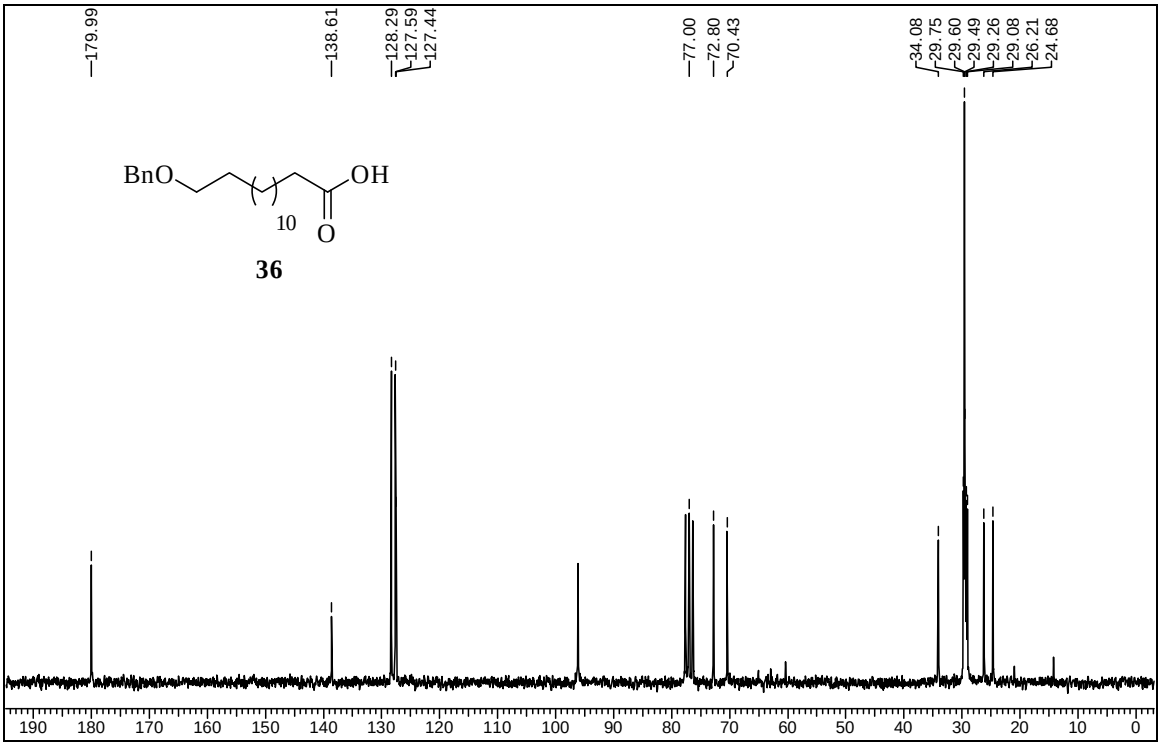
^{1}H NMR spectrum of compound 9 in $CDCl_3$



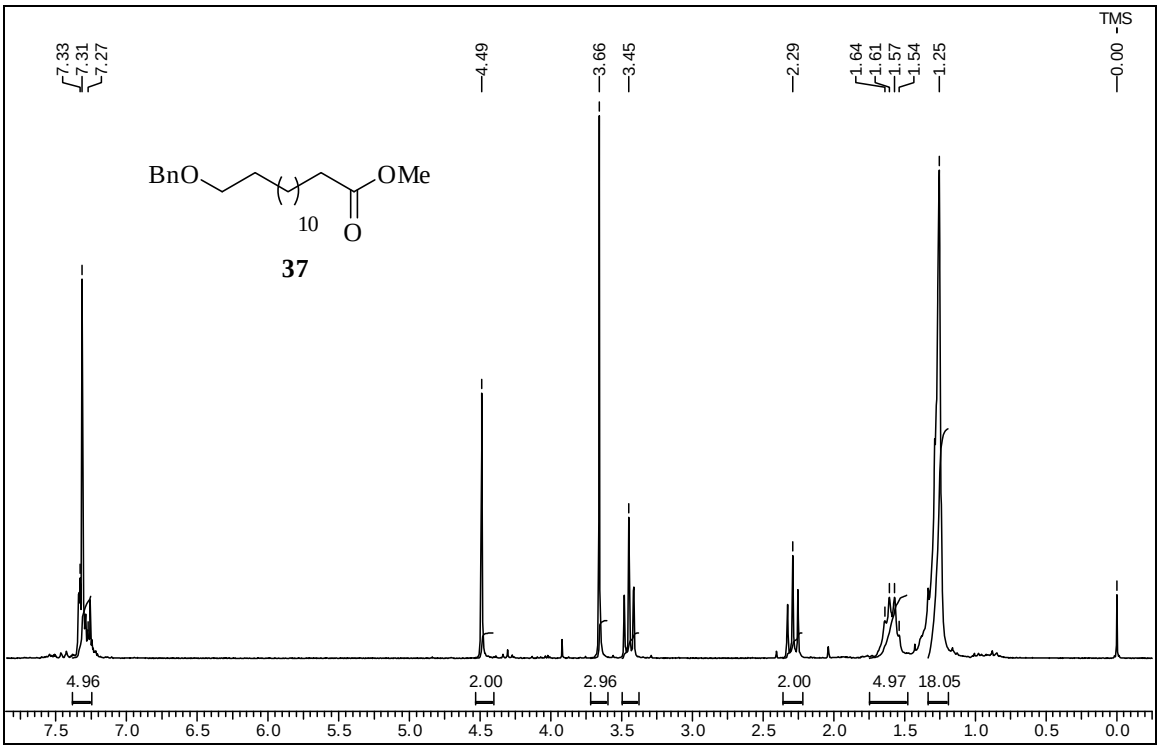
^{13}C NMR spectrum of compound 9 in $CDCl_3$



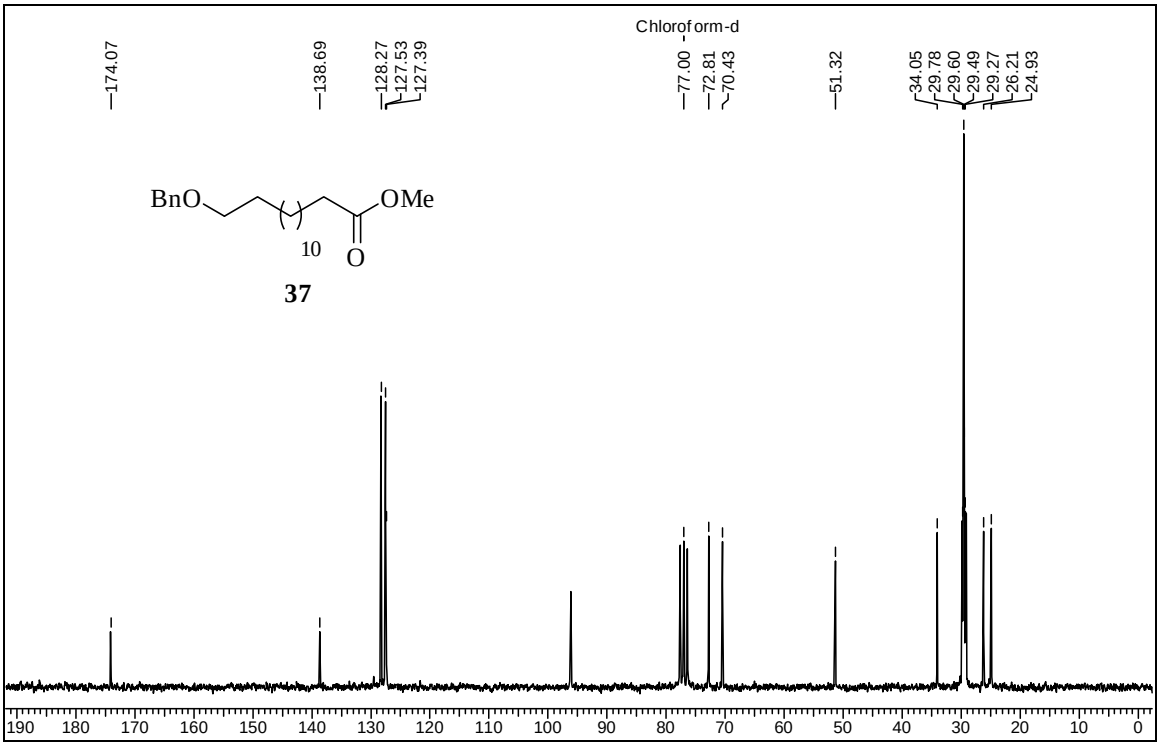
^{1}H NMR spectrum of compound 36 in $CDCl_3$



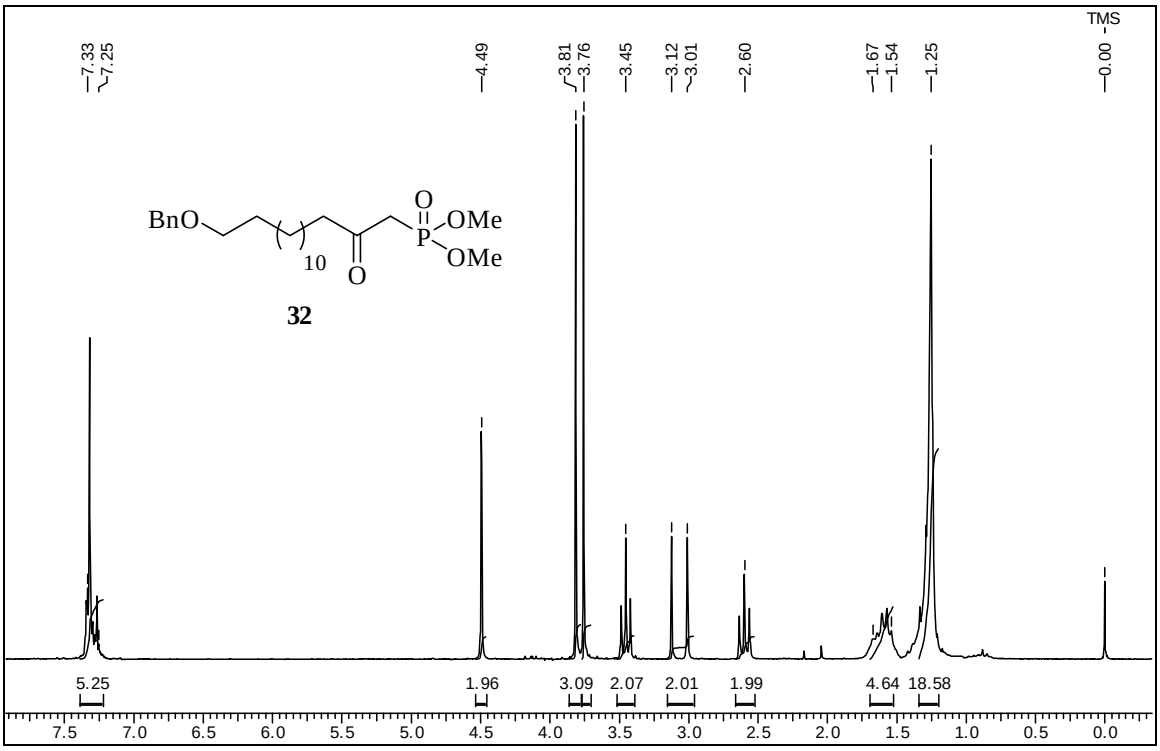
^{13}C NMR spectrum of compound 36 in $CDCl_3$



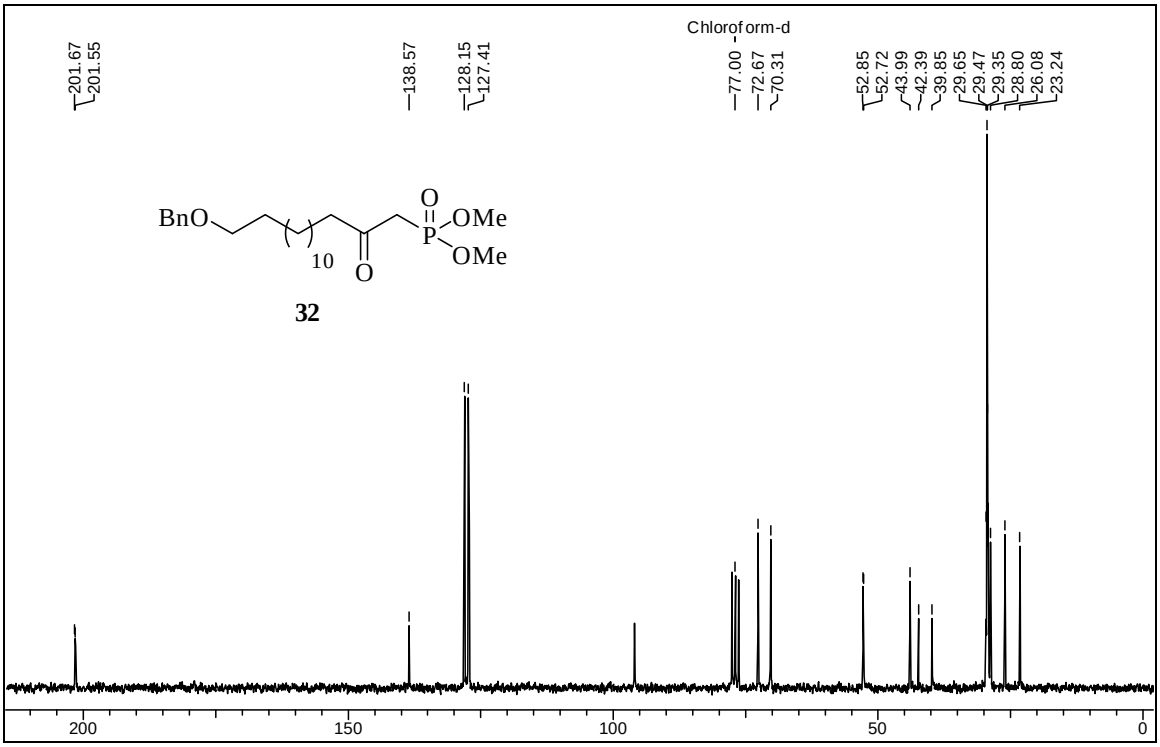
^{1}H NMR spectrum of compound 37 in $CDCl_3$



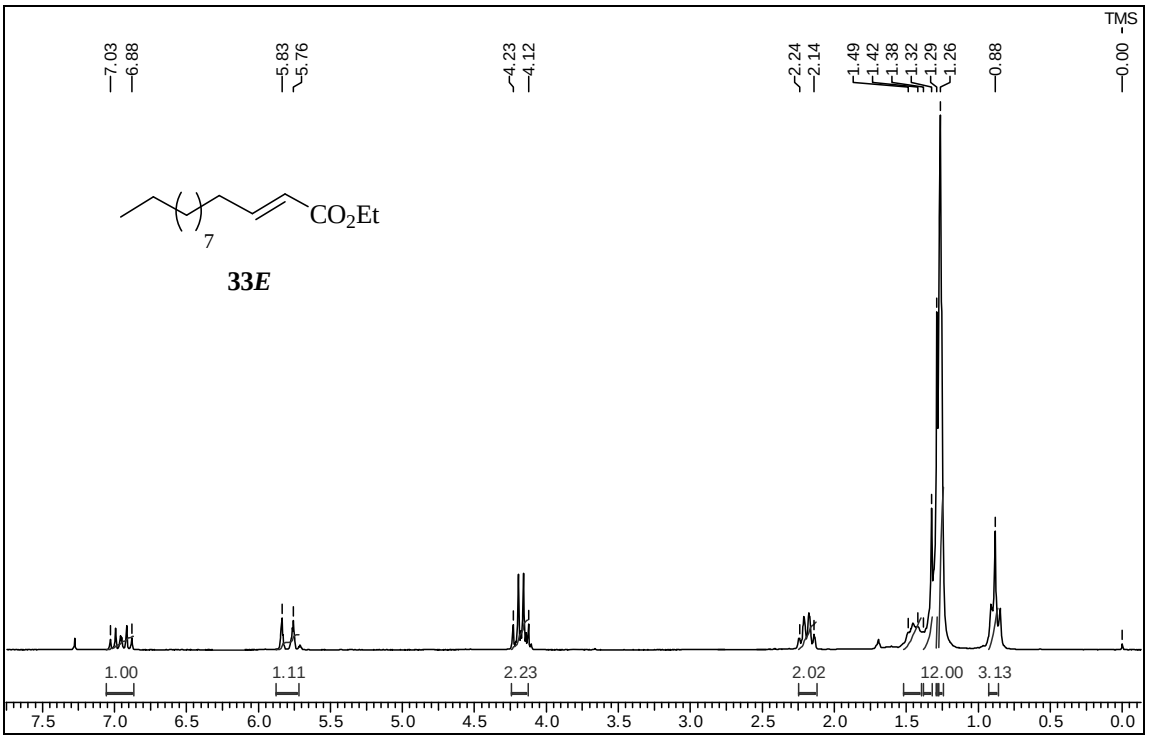
^{13}C NMR spectrum of compound 37 in $CDCl_3$



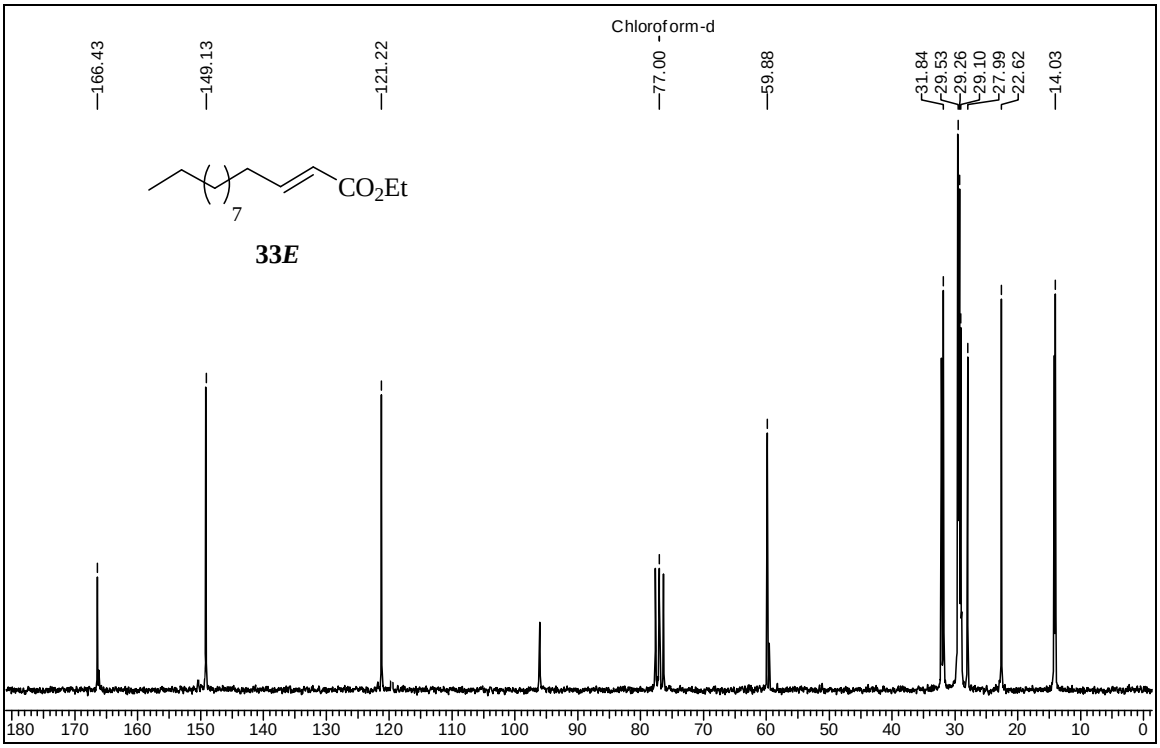
^{1}H NMR spectrum of compound 32 in $CDCl_3$



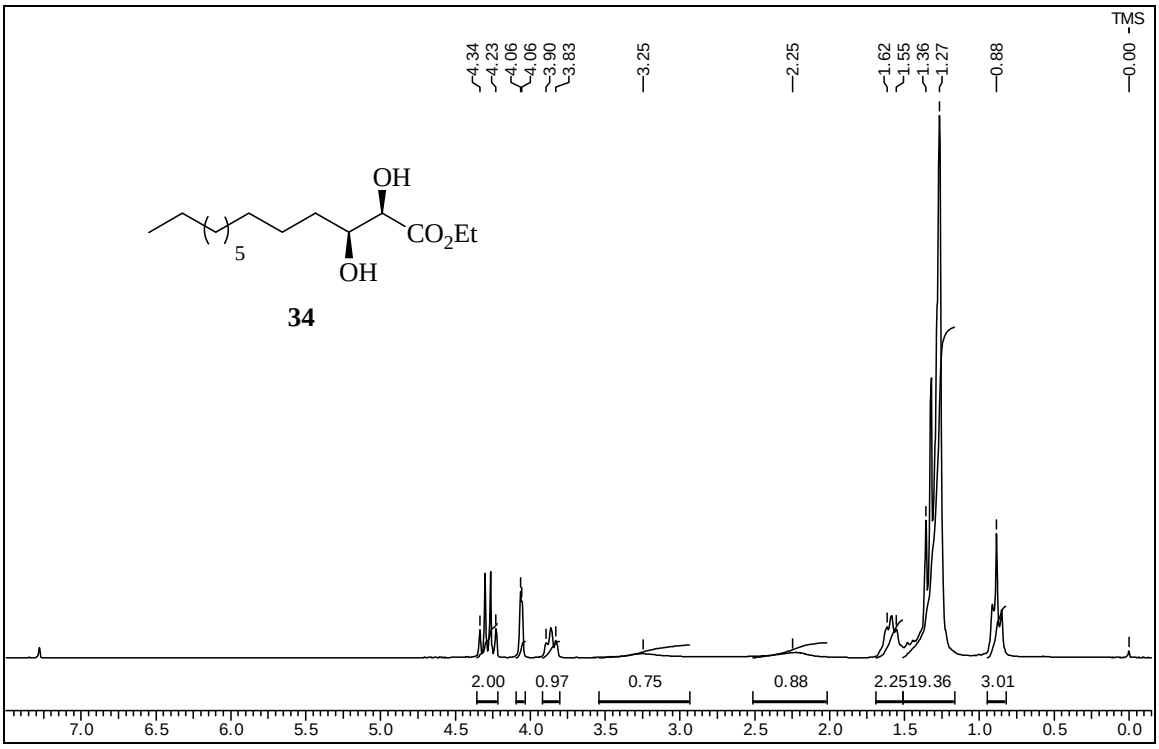
^{13}C NMR spectrum of compound 32 in $CDCl_3$



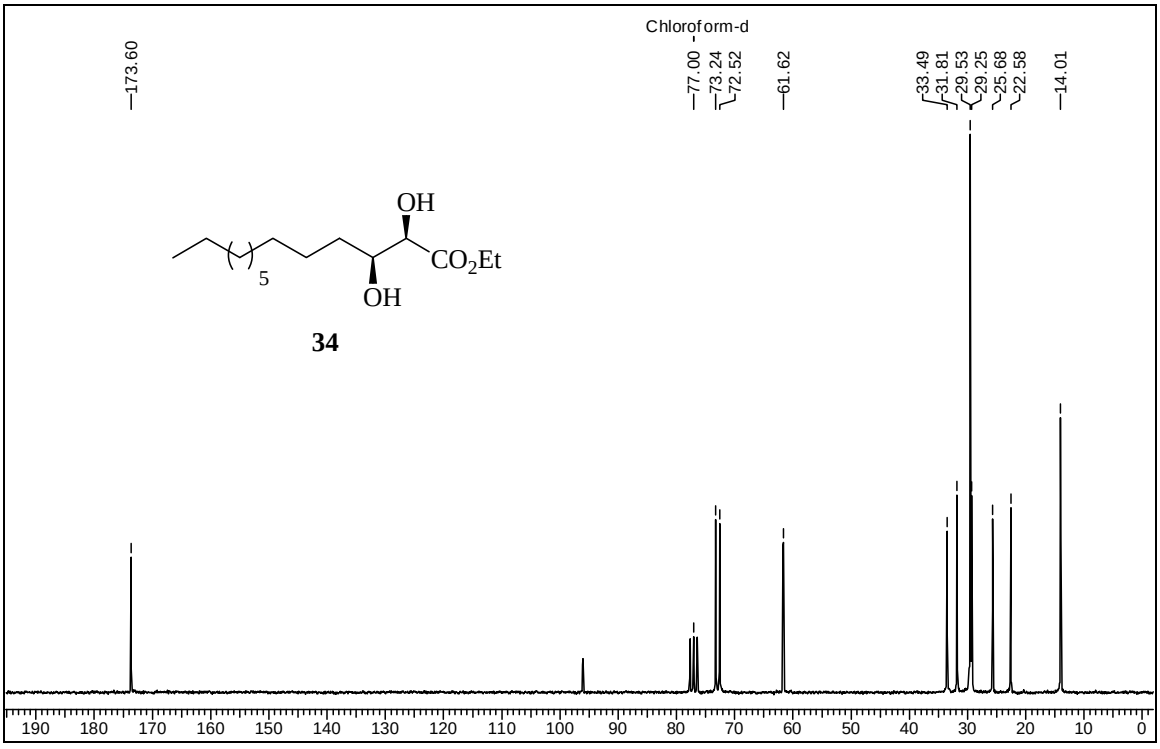
^{1}H NMR spectrum of compound 33*E* in $CDCl_3$



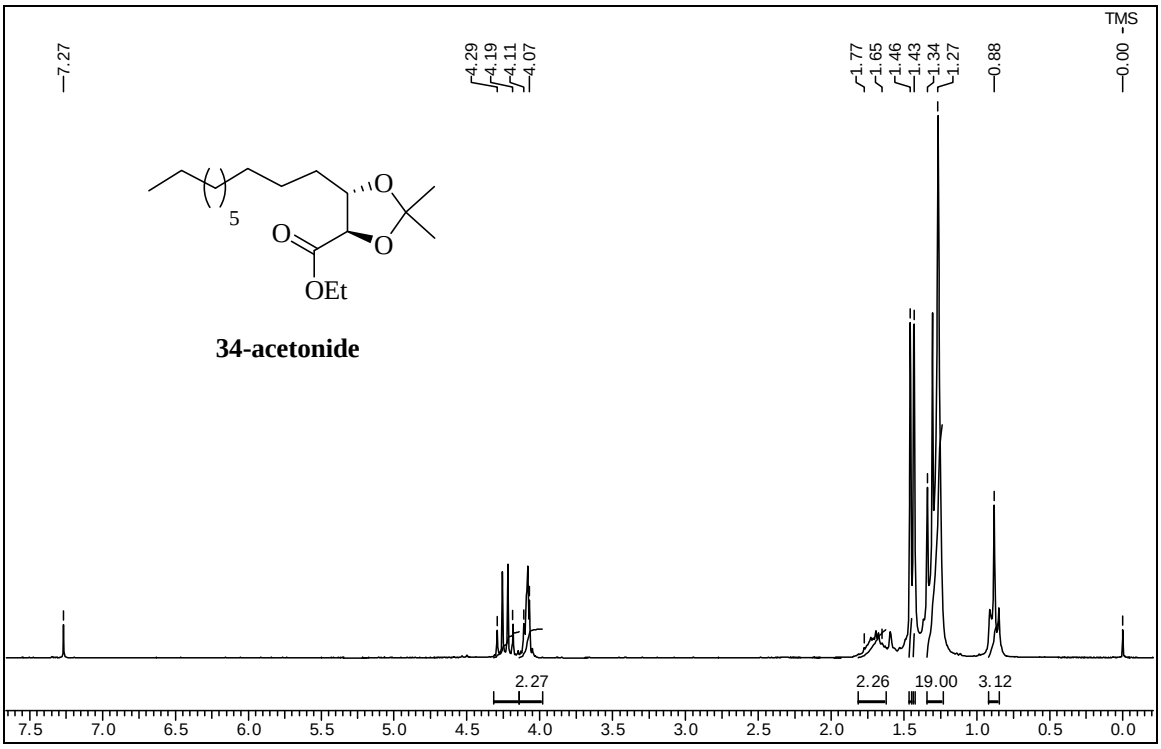
^{13}C NMR spectrum of compound 33*E* in $CDCl_3$



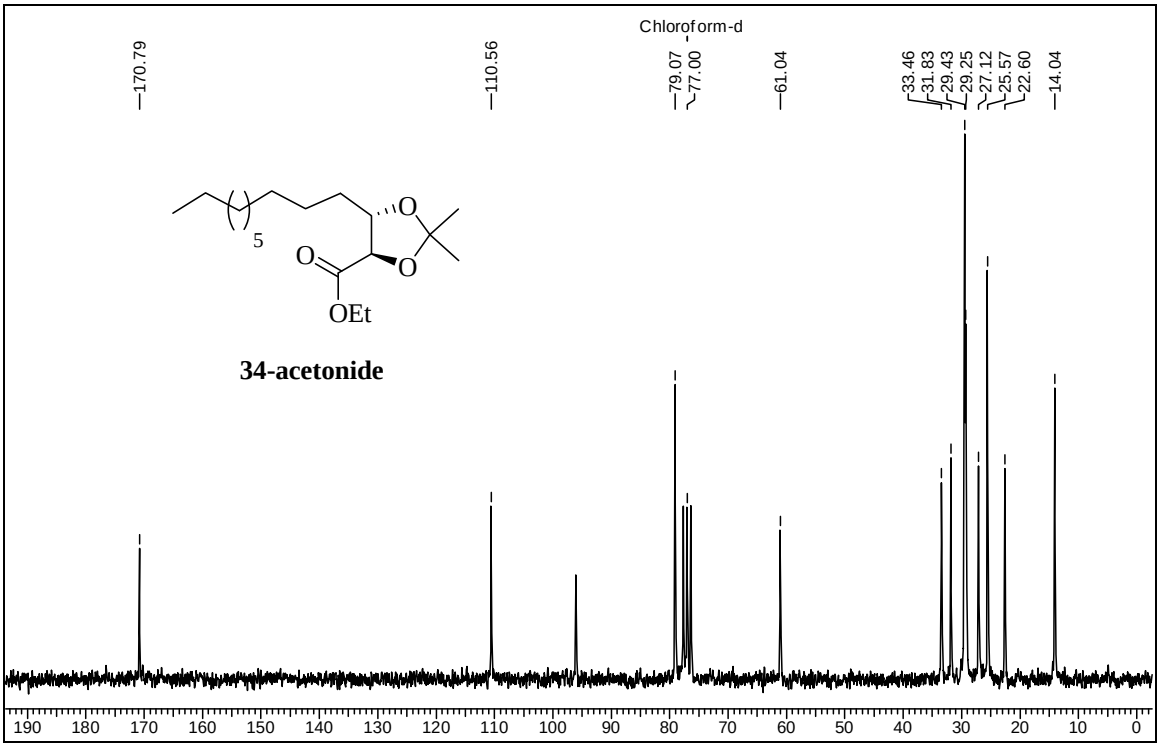
^{1}H NMR spectrum of compound 34 in $CDCl_3$



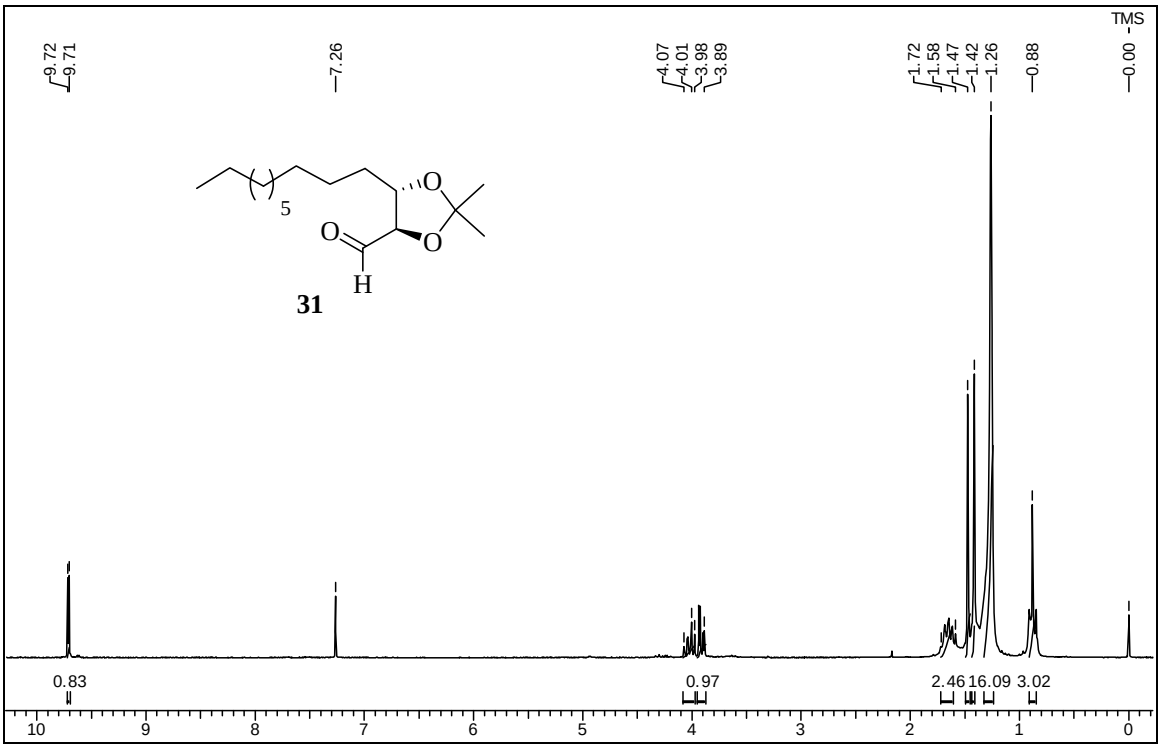
^{13}C NMR spectrum of compound 34 in $CDCl_3$



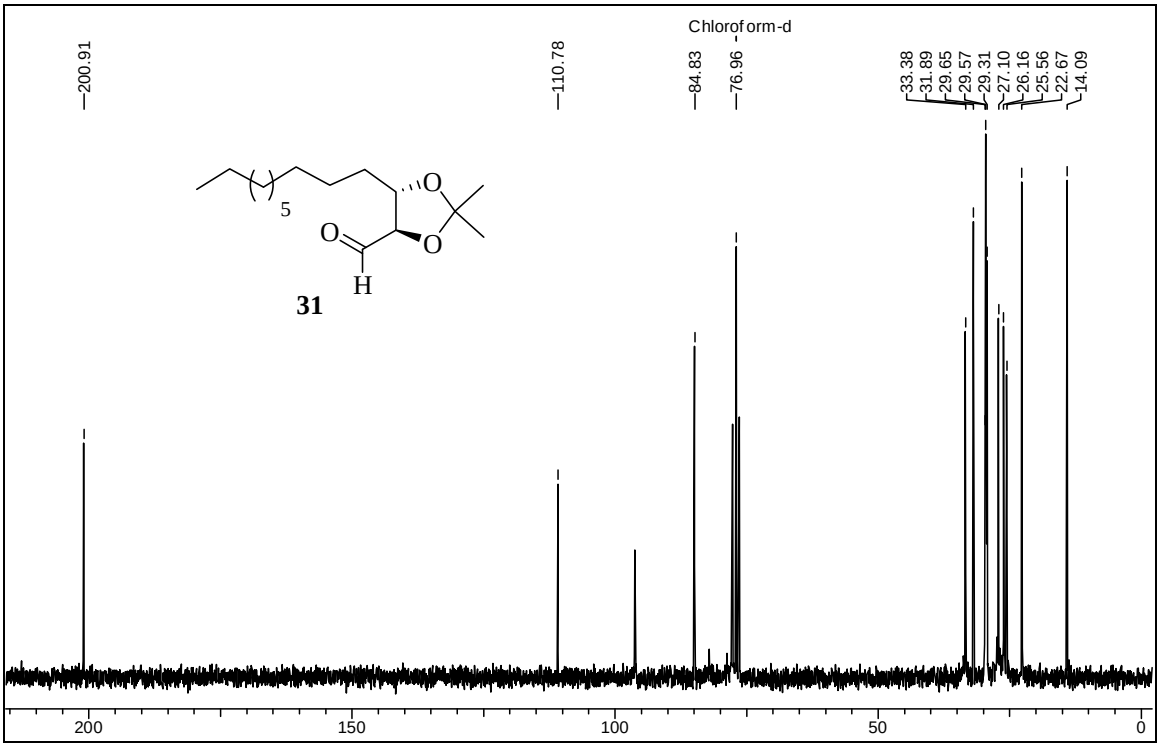
^{1}H NMR spectrum of compound 34-acetonide in $CDCl_3$



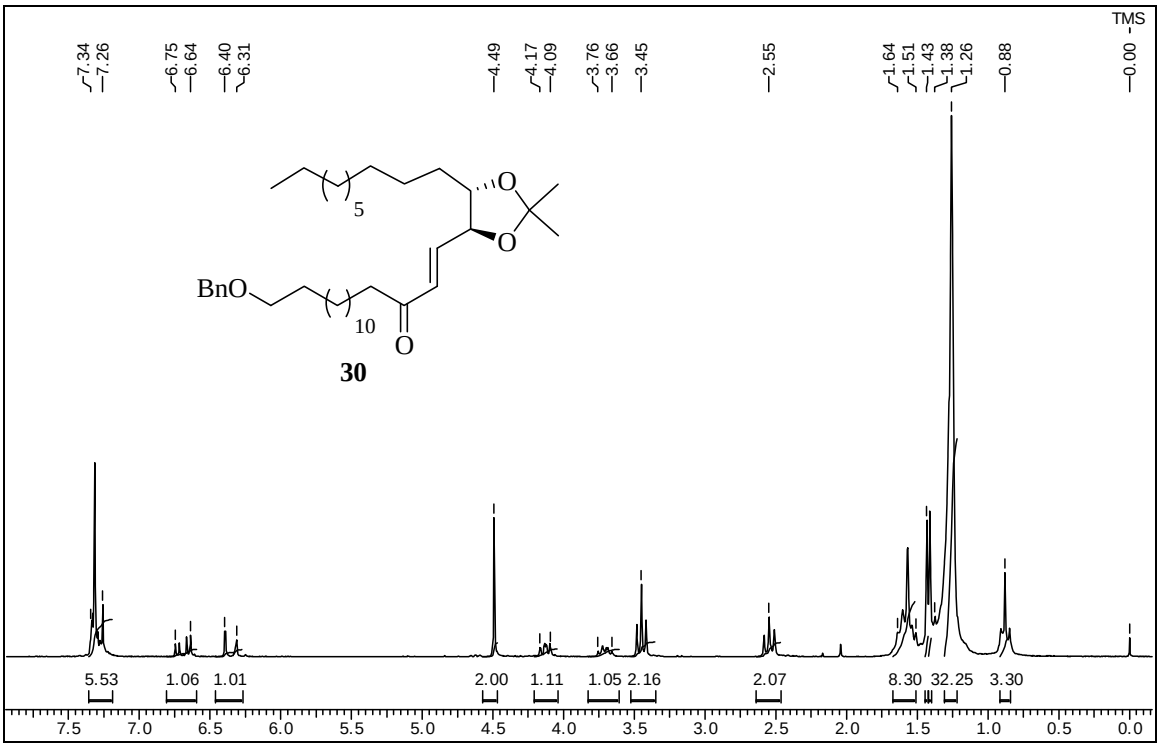
^{13}C NMR spectrum of compound 34-acetonide in $CDCl_3$



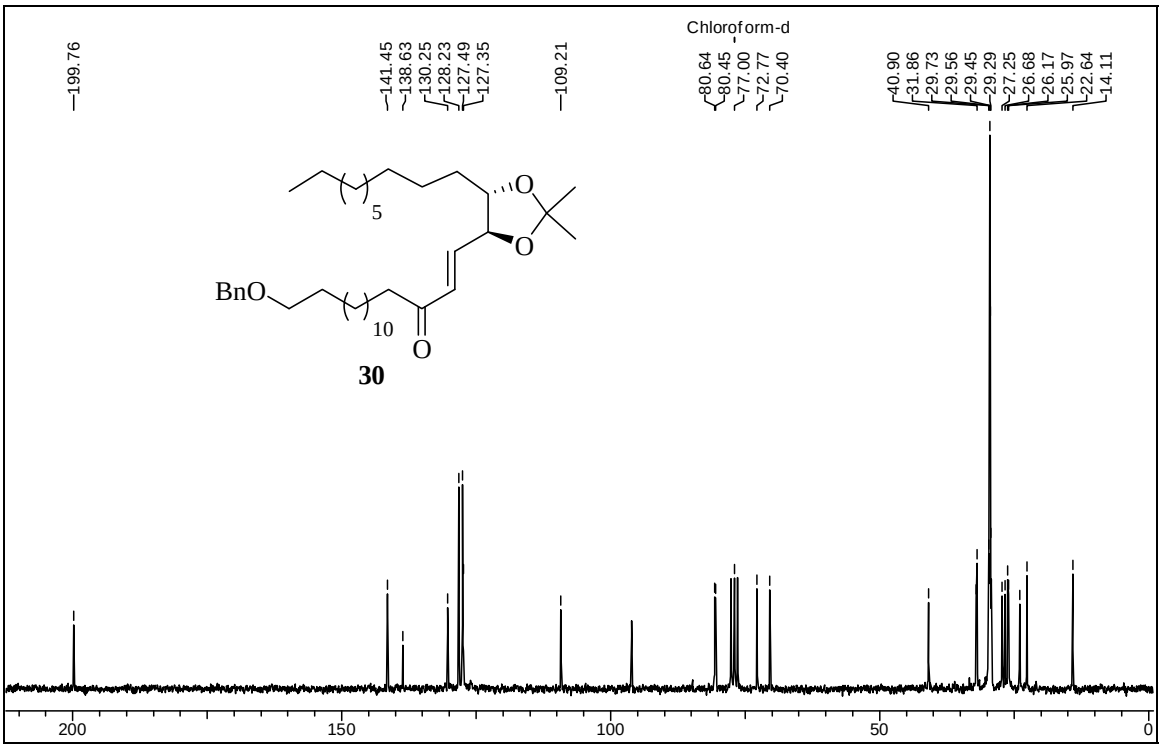
^{1}H NMR spectrum of compound 31 in $CDCl_3$



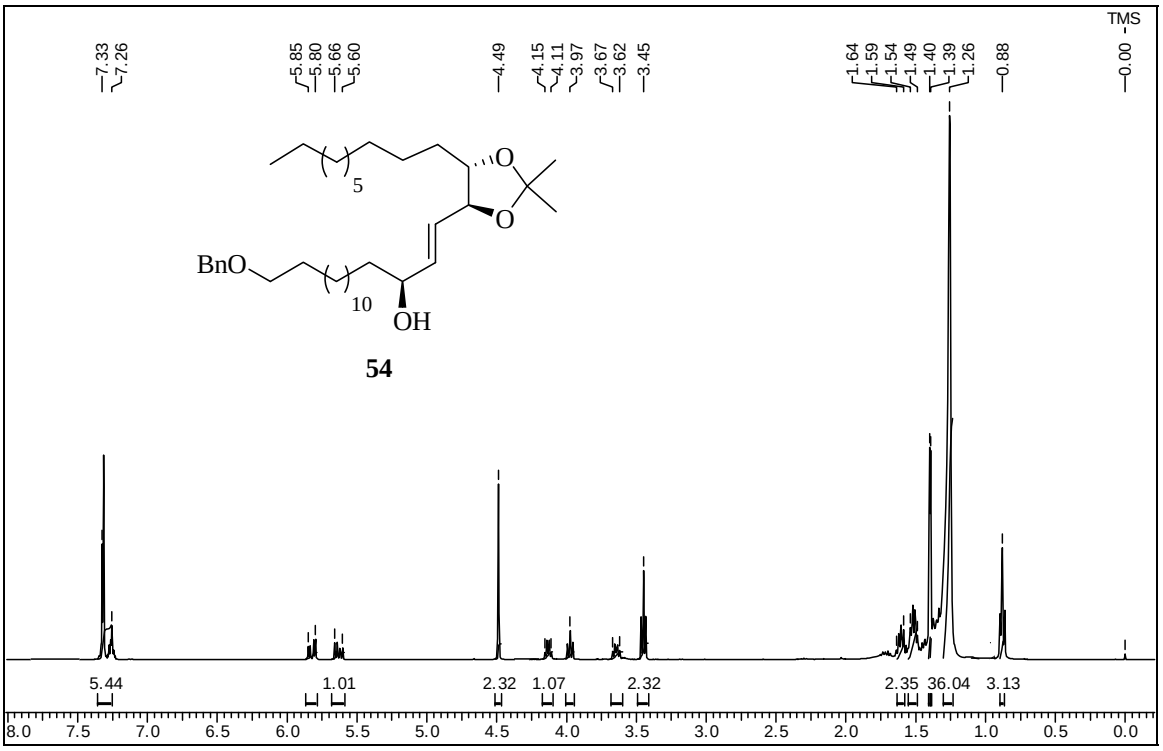
^{13}C NMR spectrum of compound 31 in $CDCl_3$



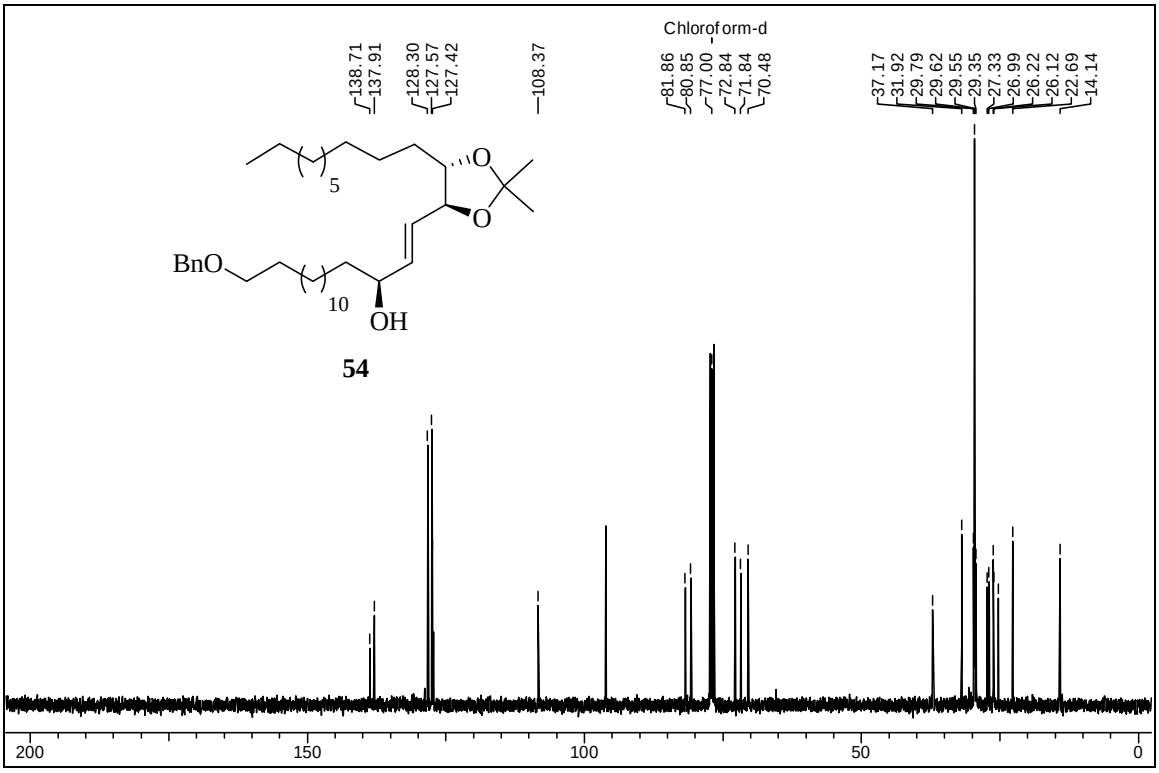
^{1}H NMR spectrum of compound 30 in $CDCl_3$



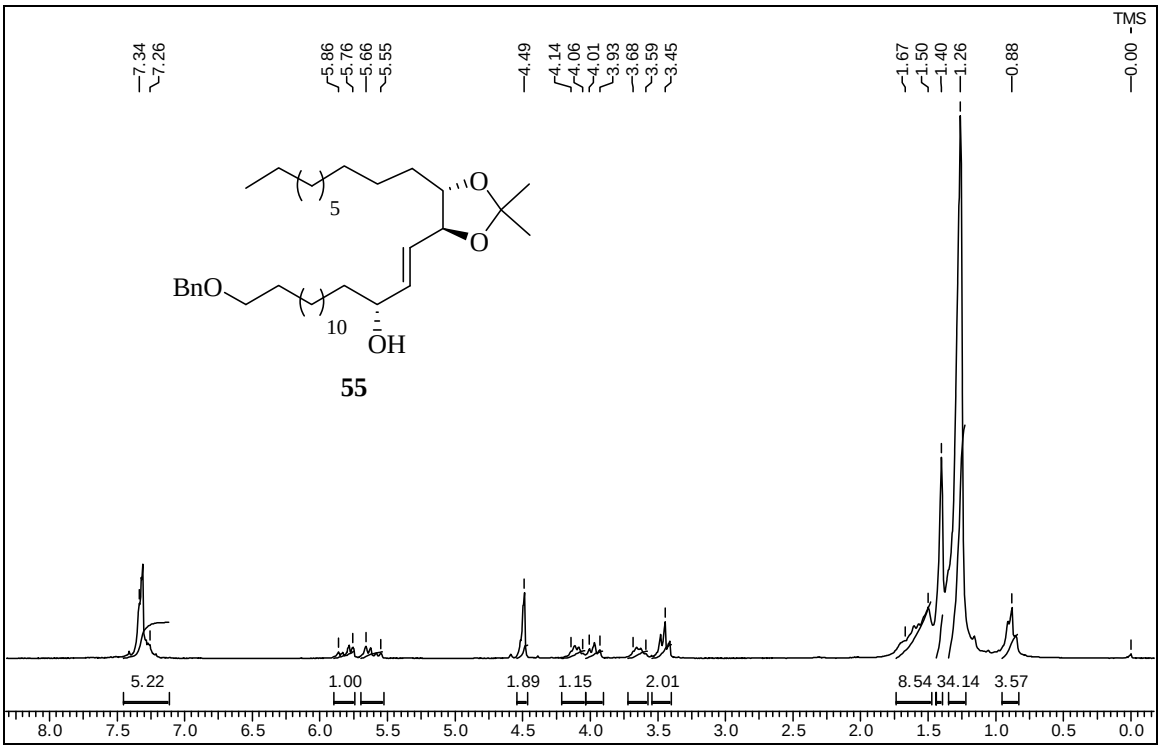
^{13}C NMR spectrum of compound 30 in $CDCl_3$



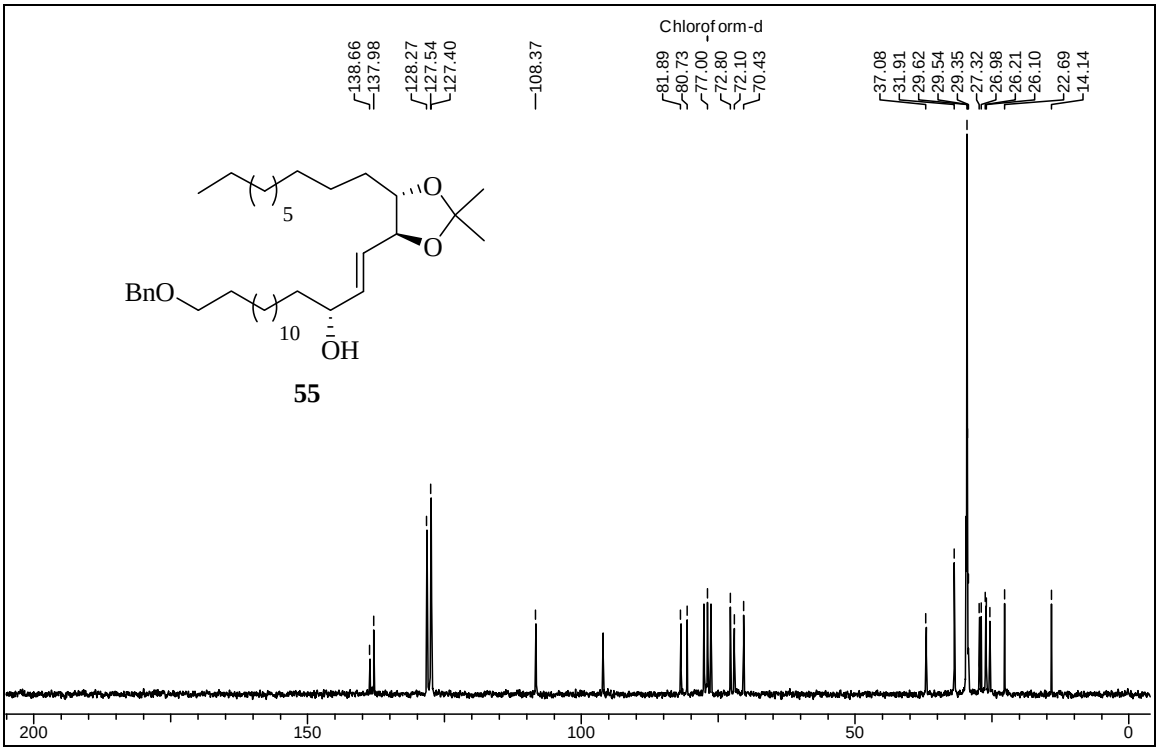
^{1}H NMR spectrum of compound 54 in $CDCl_3$



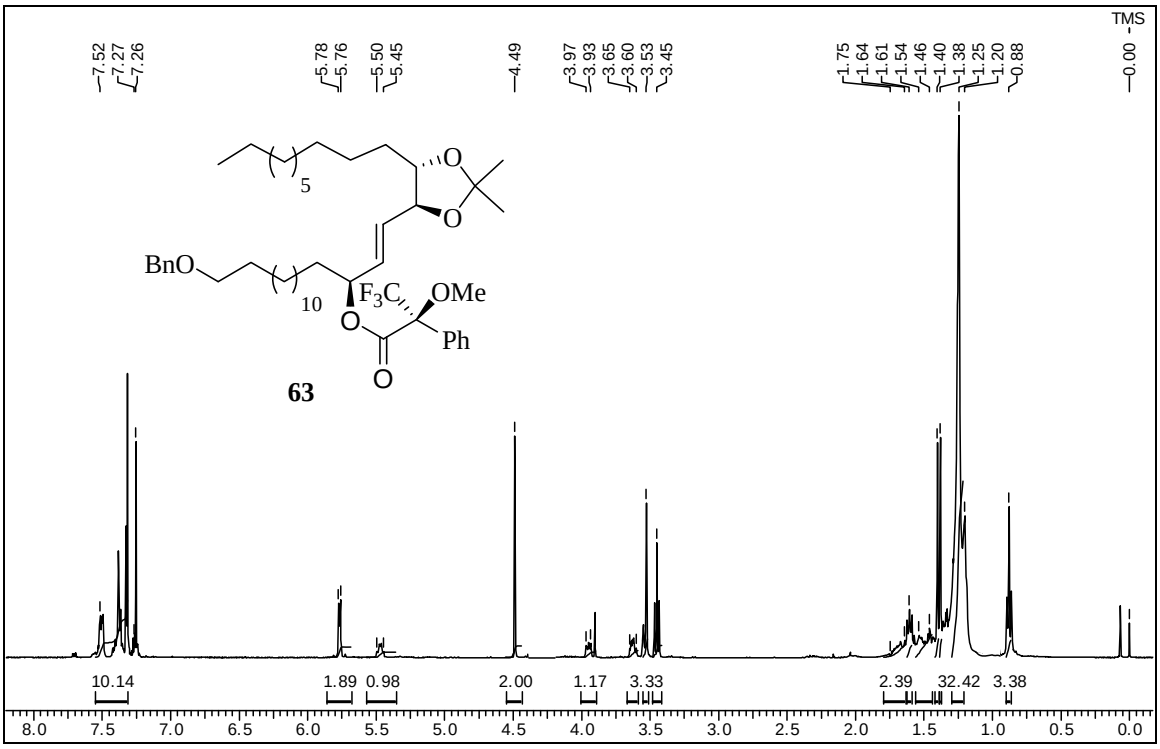
^{13}C NMR spectrum of compound 54 in $CDCl_3$



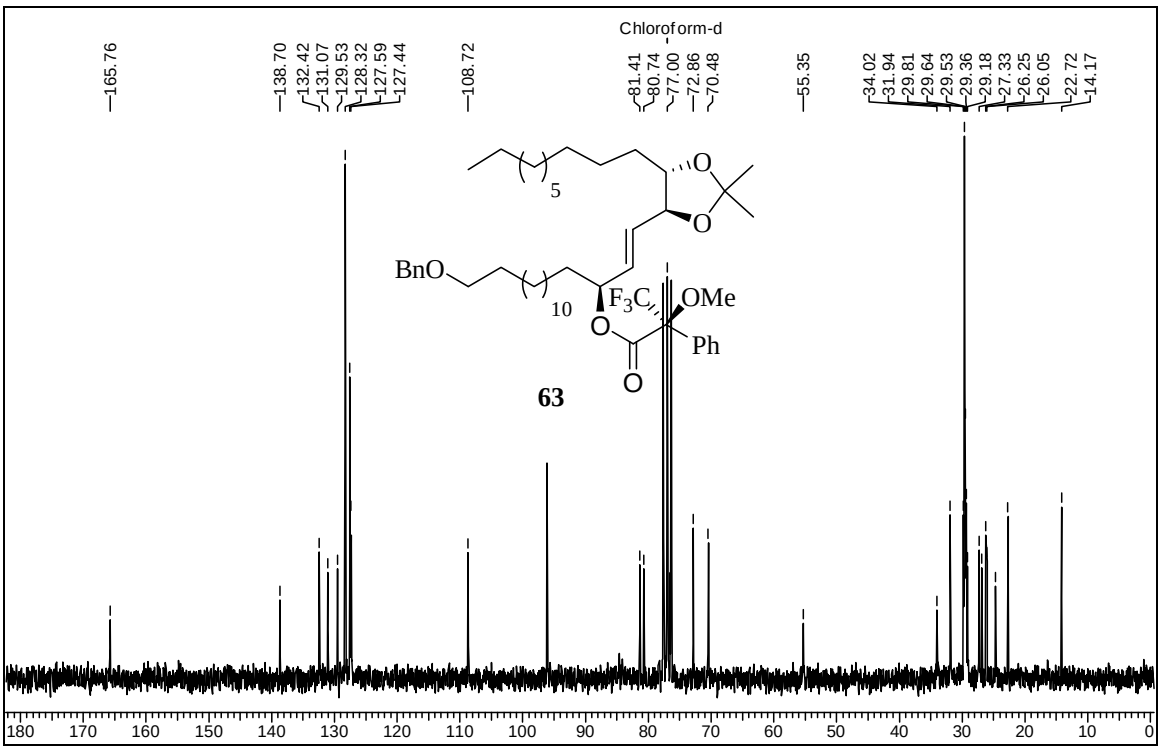
^{1}H NMR spectrum of compound 55 in $CDCl_3$



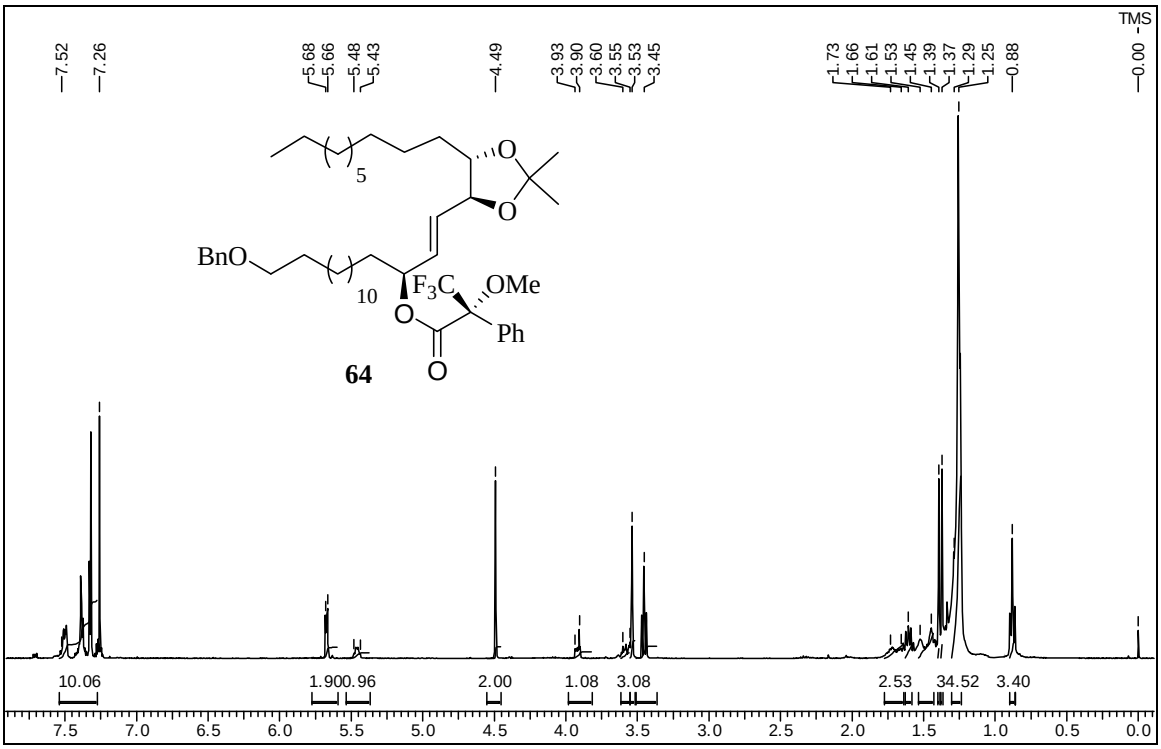
^{13}C NMR spectrum of compound 55 in $CDCl_3$



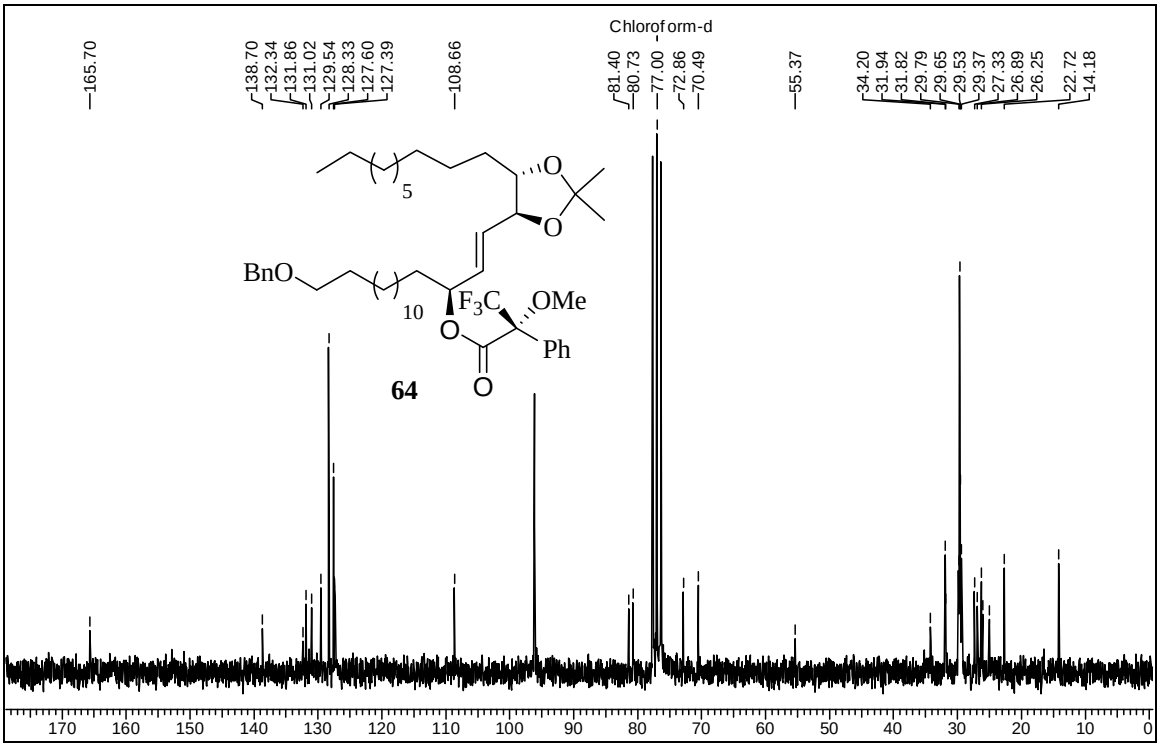
^{1}H NMR spectrum of compound 63 in $CDCl_3$



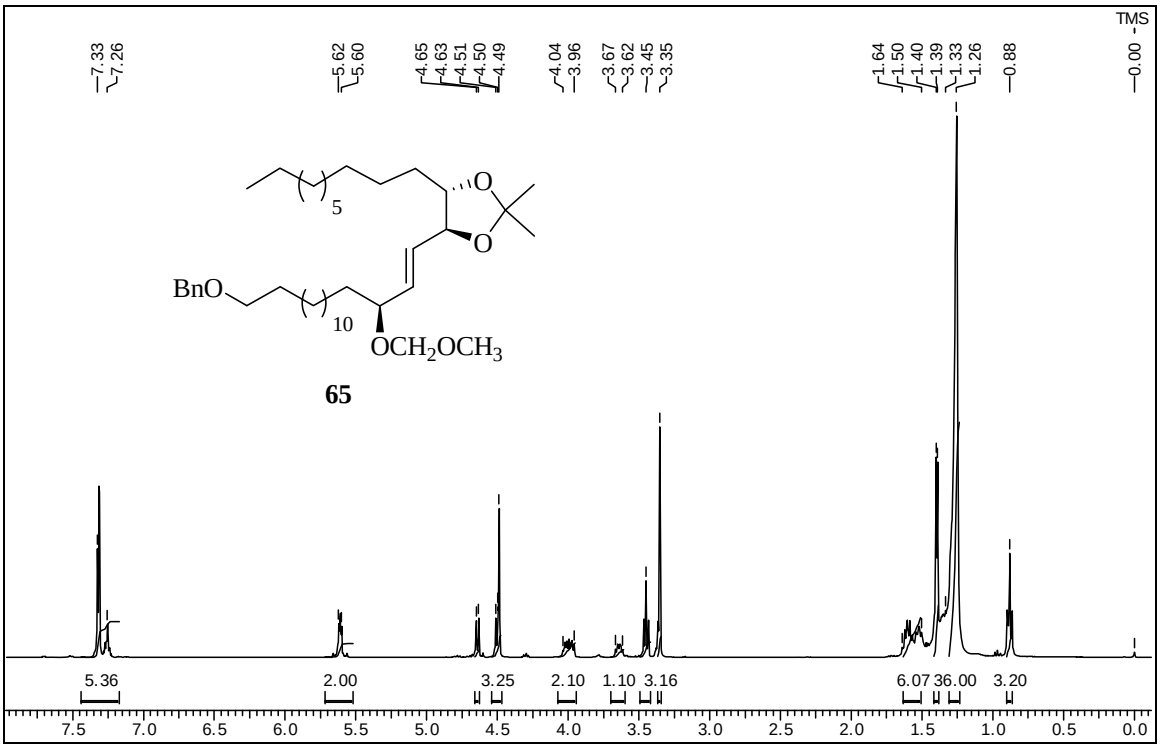
^{13}C NMR spectrum of compound 63 in $CDCl_3$



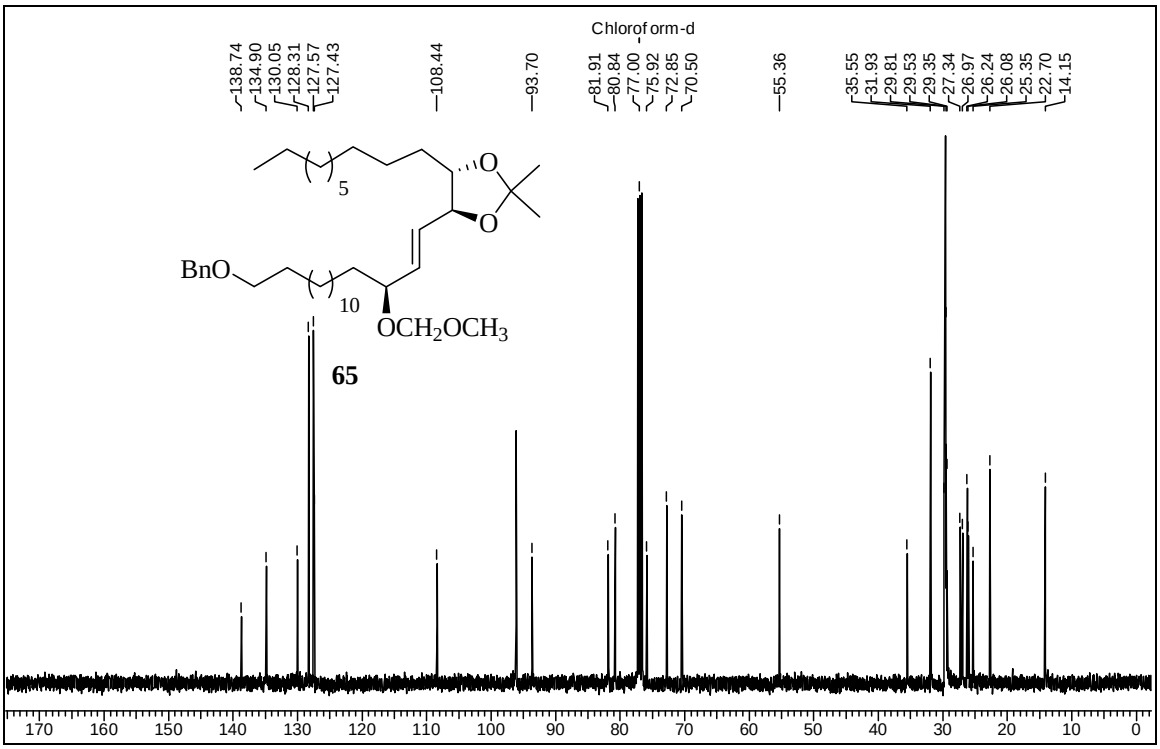
^{1}H NMR spectrum of compound 64 in $CDCl_3$



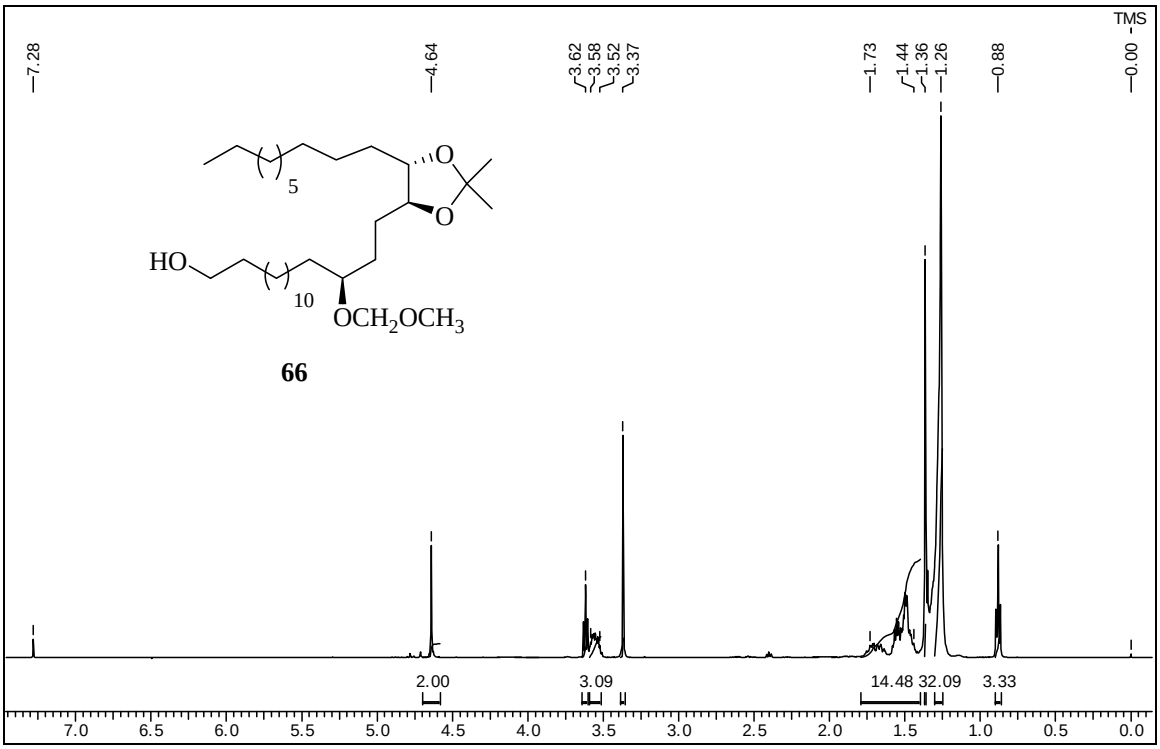
^{13}C NMR spectrum of compound 64 in $CDCl_3$



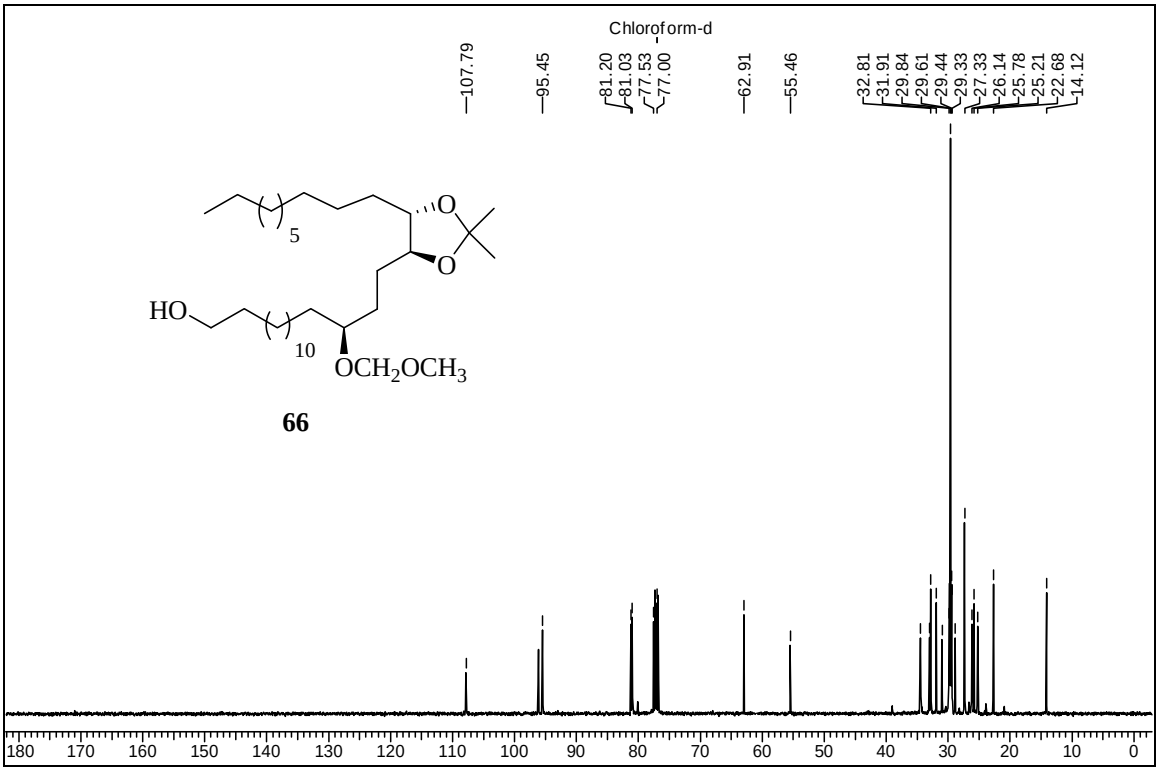
^{1}H NMR spectrum of compound 65 in $CDCl_3$



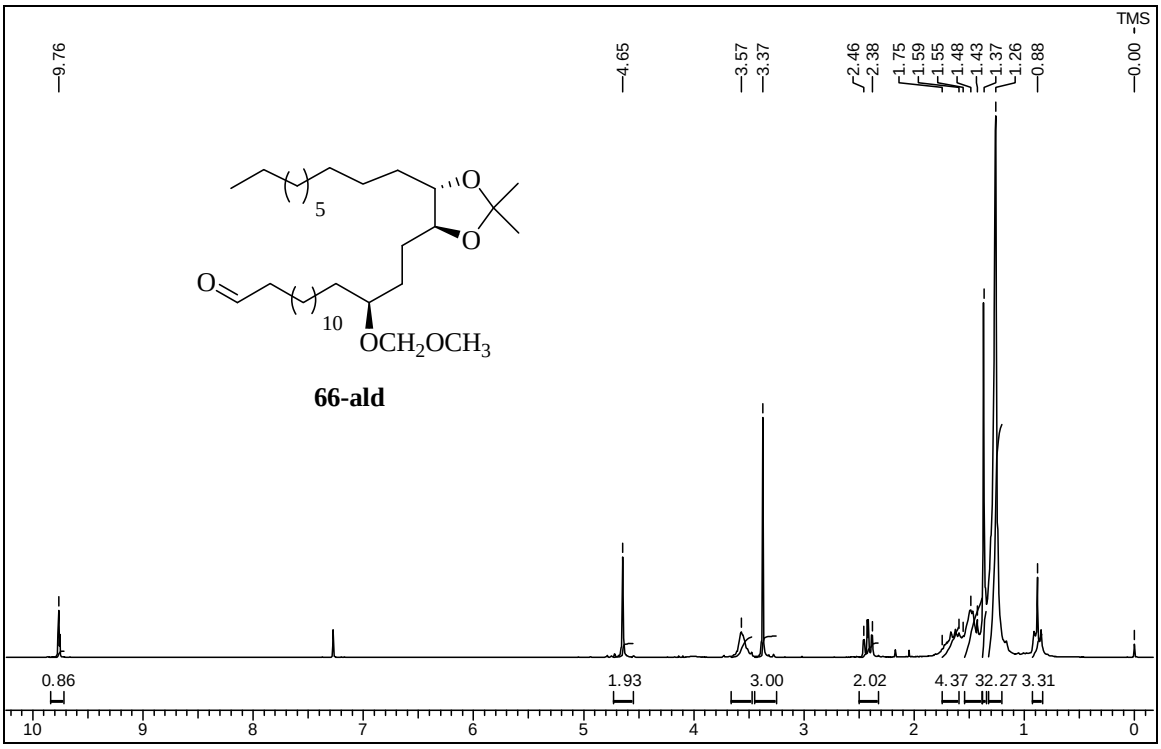
^{13}C NMR spectrum of compound 65 in $CDCl_3$



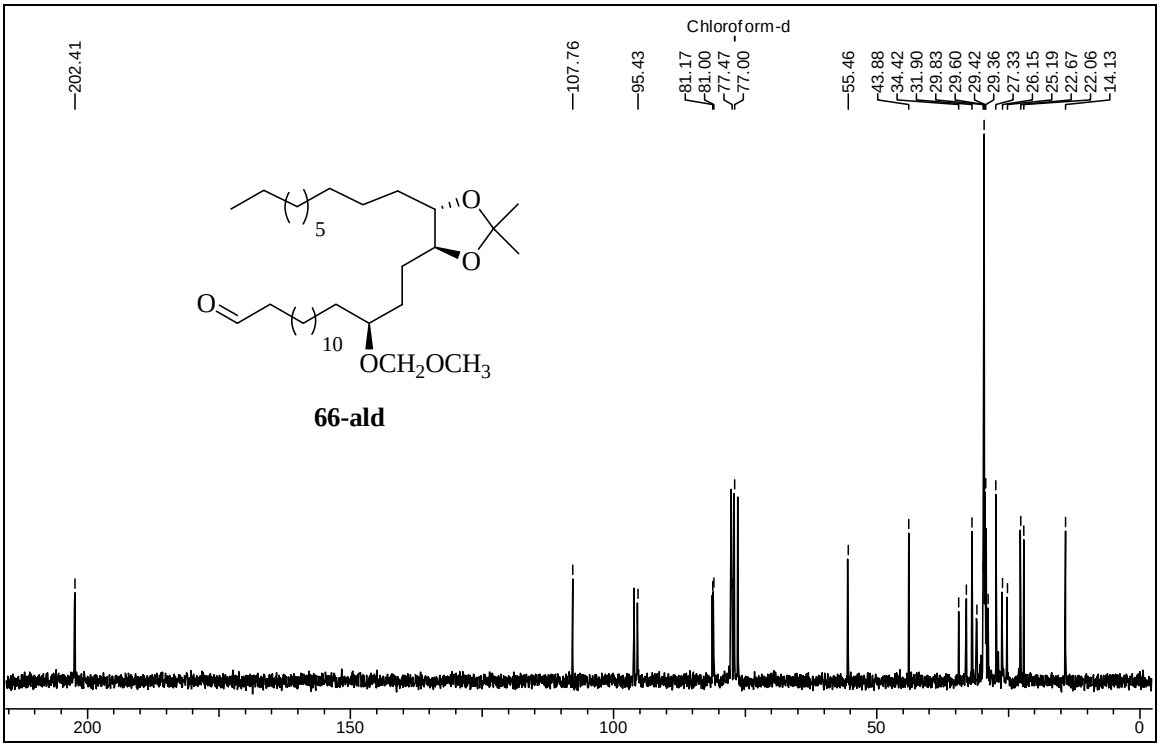
^{1}H NMR spectrum of compound 66 in $CDCl_3$



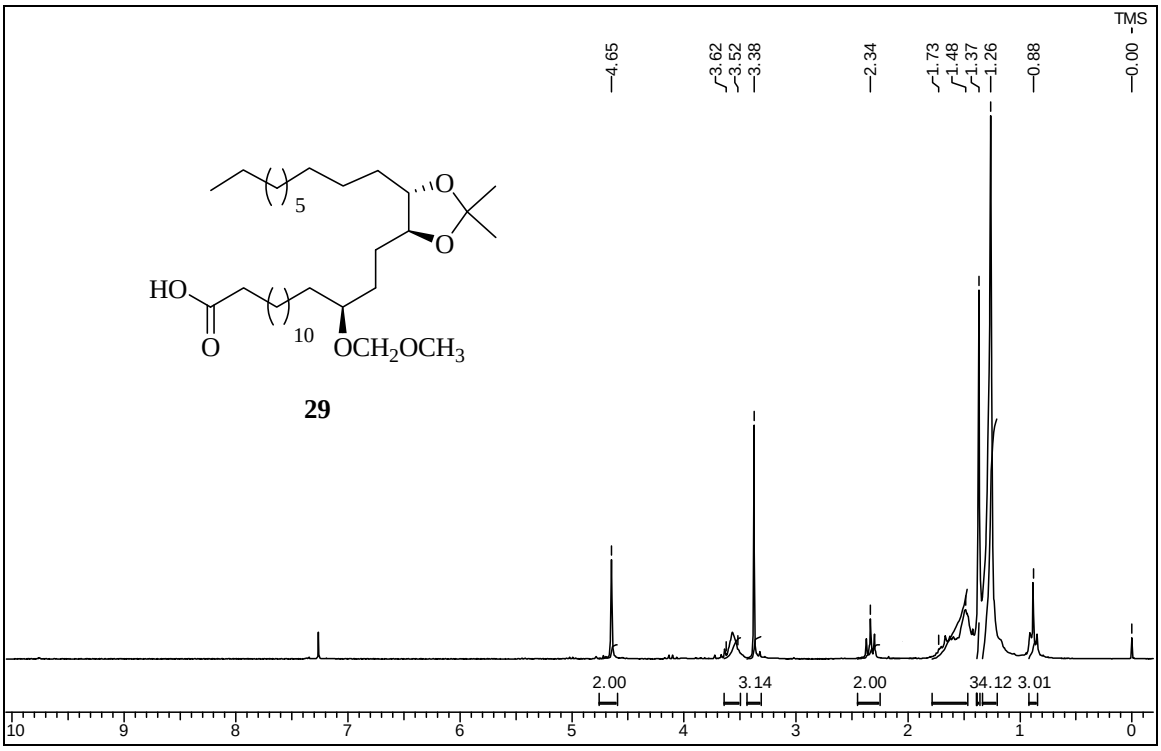
^{13}C NMR spectrum of compound 66 in $CDCl_3$



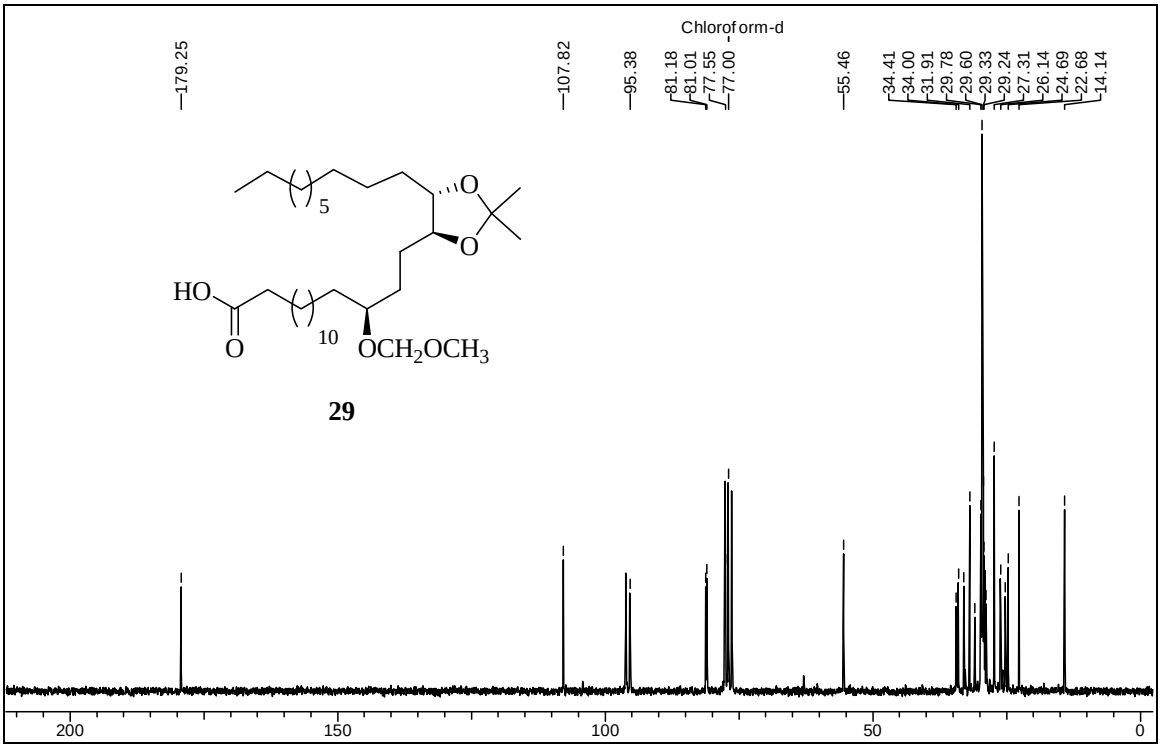
^{1}H NMR spectrum of compound 66-ald in $CDCl_3$



^{13}C NMR spectrum of compound 66-ald in $CDCl_3$



^{1}H NMR spectrum of compound 29 in $CDCl_3$



^{13}C NMR spectrum of compound 29 in $CDCl_3$

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85. See ref. 88a of chapter 2.

List of Publications

1. "Total syntheses of Schulzeines B and C" Mukund K. Gurjar, Chinmoy Pramanik, **Debabrata Bhattasali**, C. V. Ramana and Debendra K. Mohapatra. *J. Org. Chem.* **2007**, *72*, 6591-6594.
2. "Total synthesis of Penarolide sulfate A_1" Debendra K. Mohapatra, **Debabrata Bhattasali**, Mukund K. Gurjar, M. Islam Khan, K. S. Shashidhara. (Communicated).

Erratum