Heterofunctionalization of olefins by a pendant sulfoxide: Application to the Synthesis of (2*R*,3*R*)-HFA-12, (-)-Allosedamine, *xylo*-(2*R*,3*S*,4*S*), *lyxo*-(2*R*,3*R*,4*R*)-Phytosphingosines and Synthesis of a Novel Safety-Catch Linker

A THESIS
SUBMITTED FOR THE DEGREE OF
Doctor of Philosophy

A. RAJENDER

School of Chemistry
University of Hyderabad
Hyderabad - 500 046
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Indian Institute of
Chemical Technology
Hyderabad - 500 007, INDIA

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Director

निदेशक

CERTIFICATE

This is to certify that the research work presented in the thesis entitled "**Heterofunctionalization of olefins by a pendant sulfoxide: Application to the Synthesis of (2*R*,3*R*)-HPA-12, (-)-Allosedamine, *xylo*-(2*R*,3*S*,4*S*), *lyxo*-(2*R*,3*R*,4*R*)-Phytosphingosines and Synthesis of a Novel Safety-Catch Linker**", has been carried out under my supervision and is a bonafide work of **Mr. A. Rajender**. This work is original and has not been submitted for any other degree or diploma to this or any other University.

E D Jemmis
13-1-2004

Dean
School of Chemistry
University of Hyderabad
Hyderabad-500 046, India

[J.S. YADAV]
Research Guide

DECLARATION

I hereby declare that the work presented in the thesis entitled "**Heterofunctionalization of olefins by a pendant sulfoxide: Application to the Synthesis of (2*R*,3*R*)-HPA-12, (-)-Allosedamine, *xylo*-(2*R*,3*S*,4*S*), *lyxo*-(2*R*,3*R*,4*R*)-Phytosphingosines and Synthesis of a Novel Safety-Catch Linker**" is entirely original and was carried out by me independently at Indian Institute of Chemical Technology, Hyderabad under the supervision of **Dr. J. S. Yadav**, Director, Indian Institute of Chemical Technology. I declare that this thesis has not formed the basis for the award of any degree or diploma, fellowship or associateship or similar title of any university or institution.

(A. Rajender)

Date : 8th Jan., 2004

Division of Organic Chemistry-I
Indian Institute of Chemical Technology
Hyderabad - 500 007.

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Raju

Glossary of abbreviations

Ac	:	Acetyl
AIBN	:	Azobisisobutyronitrile
Ar	:	Aryl
$BF_3.Et_2O$	:	Boran trifluride diethylether
Bn	:	Benzyl
Boc	:	*tert*-Butoxycarbonyl
Bu	:	Butyl
^{t}Bu	:	*tert*-Butyl
CD	:	Circular dichroism
CDI	:	N,N′-Carbonyldiimidazole
CSA	:	Camphor-10-sulfonic acid
DBU	:	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	:	N,N′-Dicyclohexylcarbodiimide
DCM	:	Dichloromethane
DEAD	:	Diethylazodicarboxylate
DIBAL	:	Diisobutylaluminum hydride
DMAP	:	4-(Dimethylamino)pyridine
DME	:	Dimethoxyethane
DMF	:	Dimethyl formamide
DMP	:	2,2-Dimethoxypropane
DMSO	:	Dimethyl sulfoxide
Et	:	Ethyl
g	:	Gram
h	:	Hour
HMPA	:	Hexamethylphosphoramide
HOBt	:	1-Hydroxybenzotriazole
Hz	:	Hertz
IBX	:	2-Iodoxybenzoic acid
IR	:	Infra red
KHMDS	:	Potassium bis(trimethylsilyl)amide
LDA	:	Lithiumdi*iso*propylamine

LAH	:	Lithium aluminium hydride
*m*CPBA	:	*meta*-Chloroperbenzoic acid
Me	:	Methyl
min	:	Minute
mL	:	Milliliter
Moc	:	Methoxycarbonyl
mp	:	Melting point
Ms	:	Methane sulfonyl
NBS	:	*N*-Bromosuccinimide
NMR	:	Nuclear magnetic resonance
Ns	:	Nosyl
OMe	:	O-Methyl ether
Ph	:	Phenyl
PMR	:	Proton magnetic resonance
*p*TSA	:	*para*-Toluenesulfonic acid
Py	:	Pyridine
r.t.	:	Room temperature
TBS, TBDMS	:	*tert*-Butyldimethylsilyl
TBDPS	:	*tert*-Butyldiphenylsilyl
TEA	:	Triethylamine
Tf	:	Trifluoromethanesulfonyl
TFA	:	Trifluoroacetic acid
TFAA	:	Trifluoroacetic anhydride
THF	:	Tetrahydrofuran
TLC	:	Thin layer chromatography
TMS	:	Trimethylsilyl
Tol	:	Tolyl
TPP	:	Triphenylphosphine
Ts	:	Tosyl

GENERAL REMARKS

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

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CHAPTER-I

Regio- and stereoselective bromohydrin formation from β-protectedamino-γ,δ- unsaturated sulfoxides mediated by a pendant sulfoxide

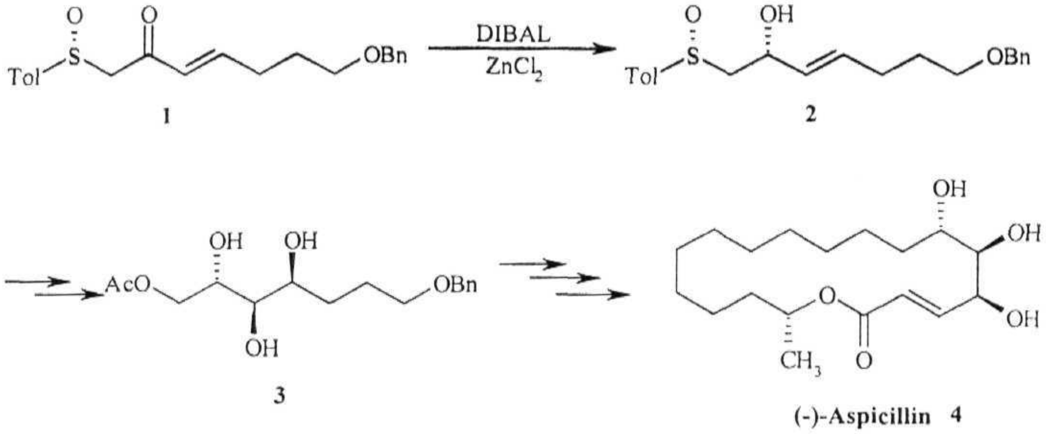
A brief account of the application of sulfoxides in asymmetric synthesis

The use of sulfoxides as chiral synthons in asymmetric synthesis is now a well-established and reliable strategy, and has been the subject of several excellent reviews.[1] The efficiency of the sulfoxide in diastereoselective auxiliary-induced reactions is mainly due to the steric and stereoelectronic differences existing between the substituents of the stereogenic sulfur atom: a lone pair of electron, an oxygen, and two different carbon ligands. Besides the configurational stability of the sulfinyl group,[2] the existence of several efficient methods to obtain homochiral sulfoxides[3] as well as their synthetic versatility has led to a substantial growth of the use of these chiral starting materials in the synthesis of biologically active compounds. Some examples wherein sulfoxides are used for the stereoselective generation of new stereogenic centers are illustrated below.

1) Reduction of β-ketosulfoxides

The stereoselectivity of the reduction of β-ketosulfoxides was first investigated by Annunziata and Cinquini[4] with $NaBH_4$ and LAH. This reaction was further investigated and extended to other reducing agents by Solladie.[5] The best results were obtained with DIBAL, which gave mainly, or exclusively one diastereomer. The opposite absolute configuration at the new stereogenic hydroxy bearing carbon was achieved using DIBAL/$ZnCl_2$ system. The strategy was employed in the elaboration of the vicinal triol **3** moiety present in aspicillin **4** (Scheme 1).[6]

Scheme 1

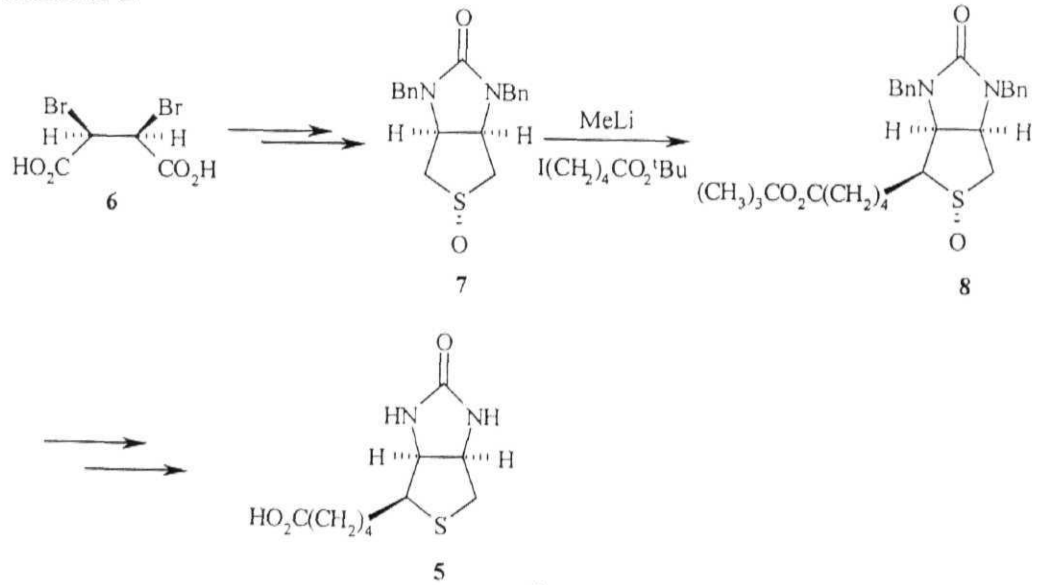


2) Reactions of sulfoxide stabilized carbanions

a) 1,2-Asymmetric induction

The first successful application of the alkylation strategy was reported by Marquet and co-workers in the total synthesis of *dl*-biotin **5**.[7] The bicyclic sulfoxide **6**, prepared from *meso*-dibromosuccinic acid **6**, was alkylated in the presence of diglyme/HMPA to afford the advanced intermediate **8** with complete stereocontrol (Scheme 2).

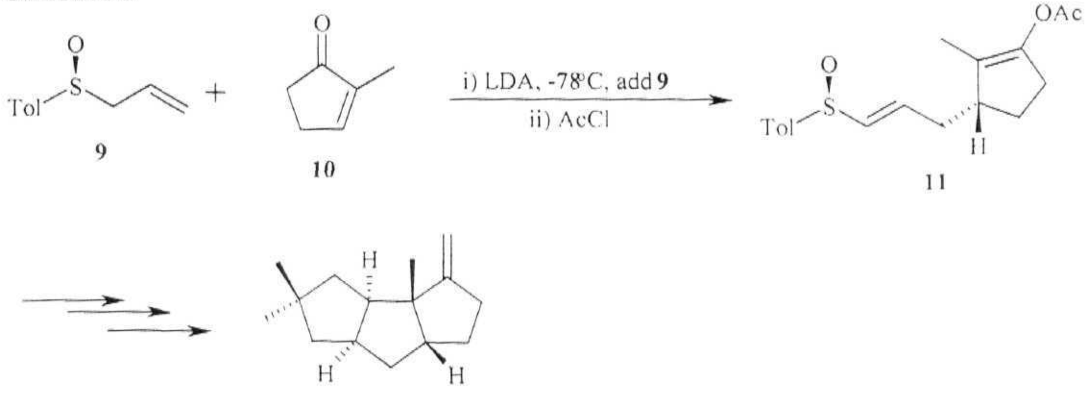
Scheme 2



b) Addition to α,β-unsaturated compounds

The application of the addition of sulfoxide stabilized carbanions to α,β-unsaturated compounds in the asymmetric synthesis of natural products were mainly due to Hua. The highly diastereoselective addition of the anion, resulting from the treatment of (*S*)-allyl *p*-tolyl sulfoxide **9** with LDA, to 2-methylcyclopentenone **10** was the key step in the total synthesis of the sesquiterpene hirsutene[8] **12** (Scheme 3).

Scheme 3

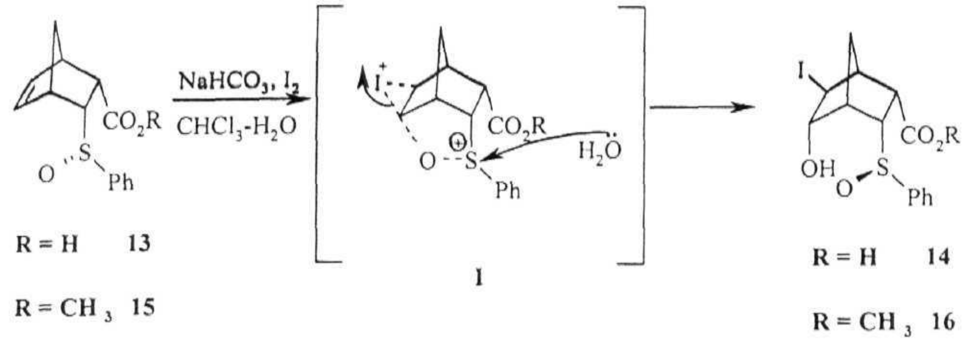


(+)-Hirsutene 12

Neighbouring group participation by sulfinyl oxygen

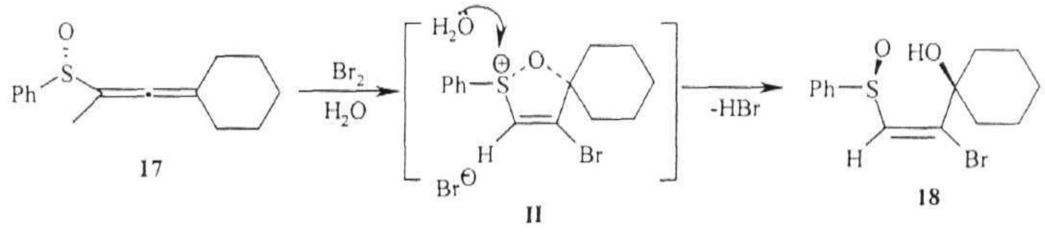
The participation by the sulfinyl-oxygen as a neighboring group was first demonstrated in the iodolactonisation of *syn*-3-*endo*-phenysulfinylbicyclo[2,2-1]hept-5-ene-2-*endo*-carboxylic acid **13** using iodine and sodium hydrogen carbonate in $CHCl_3$-water.[9] This acid afforded 35% of the iodohydrin **14** together with the expected iodolactone, while the corresponding sulfide and sulfone, afforded only iodolactones. The iodohydrin **16** was the only product from the *syn* ester **15** (Scheme 4). Using ^{18}O labeled water it was shown that the reaction proceeded through an inversion of sulfur configuration.[10] The ^{18}O label was observed in the sulfinyl group of the iodohydrin and none at the hydroxy group. The experimental results suggested the existence of a sulfoxonium salt **I**, resulting from neighbouring group participation by the sulfinyl oxygen, followed by nucleophilic attack by water at sulfur resulting in Walden inversion.

Scheme 4



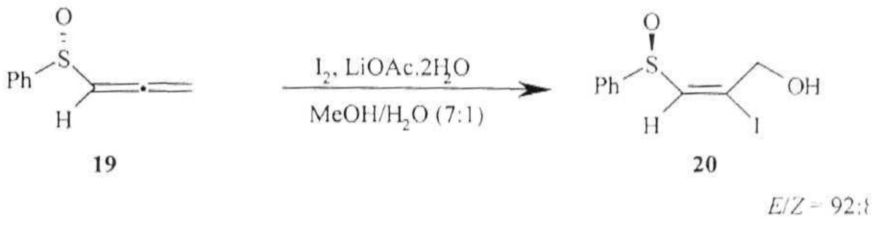
Neighbouring group participation by sulfinyl oxygen was also demonstrated by Binder *et al.*,[11] in the stereoselective bromohydration of 1,2-allenylsulfoxides **17** with Br_2 and H_2O (Scheme 5).

Scheme 5



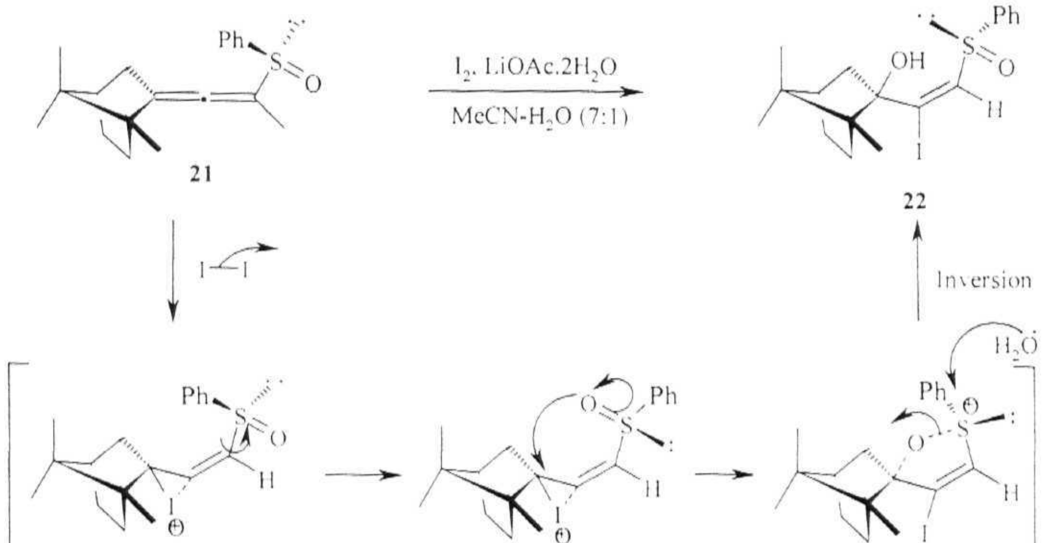
More recently neighbouring group participation by sulfinyl oxygen was demonstrated by Ma *et al.*,[12] in the highly regio- and stereoselective iodohydroxylation reaction of 1,2-allenylsulfoxides with I^+ and H_2O. The iodohydroxylation reaction of 1,2-allenyl phenylsulfoxide **19** with I_2 and H_2O was carried out in MeCN/H_2O (7:1) to afford *E*-2-iodo-3-(phenylsulfinyl)-2-propen-1-ol **20** with good selectivity (Scheme 6).

Scheme 6



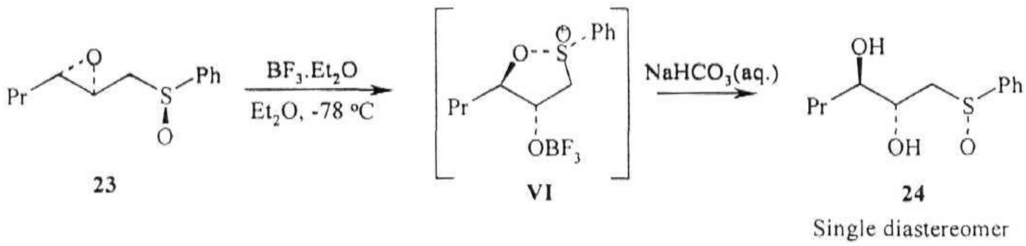
Based on the result, a mechanism involving the participation of the sulfinyl group was proposed. First, the iodonium ion (I^+) reacts with the electron rich carbon-carbon double bond to form the intermediate **III**. Intramolecular attack by the sulfinyl oxygen at the C3 position would afford the five membered cyclic intermediate **V**. Subsequent hydrolysis of **V** would afford the product **22** stereospecifically (Scheme 7).

Scheme 7



Rayner *et al.*[13] demonstrated the potential of the sulfoxide group as an intramolecular nucleophile in the opening of 2,3-epoxysulfoxides with high degree of regiocontrol (Scheme 8).

Scheme 8



Present work

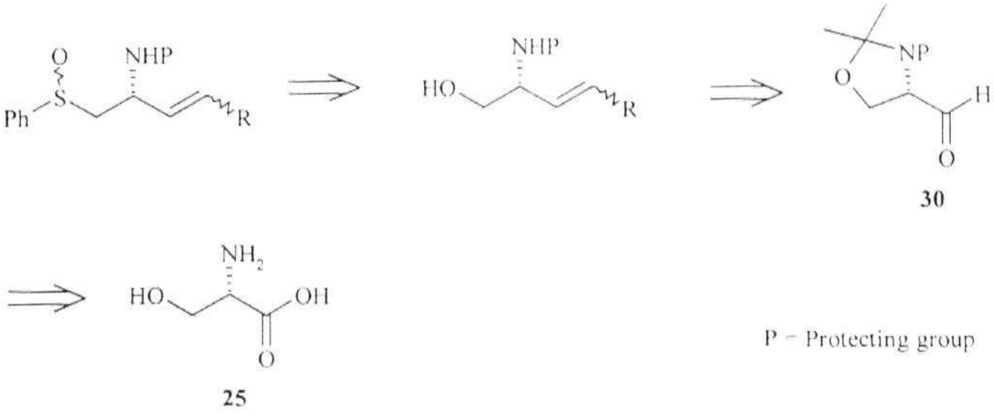
1,3-Aminoalcohols are structural units present in many synthetic[14] and natural products[15] possessing potent biological activity. Their potential as chiral auxiliaries and ligands in asymmetric synthesis is also well recognized.[16] Not surprisingly, 1,3-aminoalcohols have attracted the attention of synthetic chemists and a number of different strategies have been devised for their construction.[17] 1,2-/1,3-Stereocontrol, in the reaction of acyclic allylic and homoallylically substituted olefins with electrophiles, by asymmetric induction, constitutes a valuable synthetic tactic.[18]

As pointed out in the foregoing discussion the sulfoxide group participates in halohydrin formation from cyclic, simple acyclic olefins and allenes. Its potential to produce functionalized products with stereocontrol at two adjacent centers in substituted acyclic systems remains unexplored. The regio- and stereoselective synthesis of 1,3-aminoalcohol derivatives from allylamine derivatives via internal sulfinyl group participation is disclosed in this chapter.

1. Preparation of β-protectedamino-γ,δ-unsaturated sulfoxides

The β-protectedamino-γ,δ-unsaturated sulfoxides were envisaged to be derived from L-serine (Scheme 9, retro synthetic analysis).

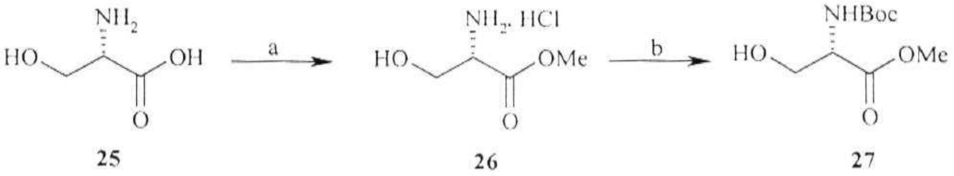
Scheme 9

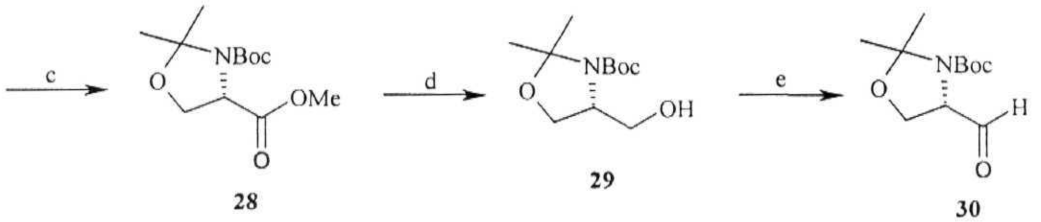


P = Protecting group

Aldehyde **30** was readily elaborated from L-serine **25** following the literature procedure.[19] Thus, esterification of **25** with methanol and acetyl chloride afforded **26**. The salt **26** on treatment with $(Boc)_2O$ in the presence of excess Et_3N afforded the carbamate **27**. Isopropylidene protection of **27** was effected in acetone with 2,2-DMP in the presence of $BF_3.Et_2O$ to furnish **28**. Compound **28** on treatment with $LiBH_4$ in absolute ethanol[20] afforded the alcohol **29**, which was oxidized to the aldehyde **30** under Swern conditions using diisopropylethylamine as the base to minimize racemization[21] (Scheme 10).

Scheme 10

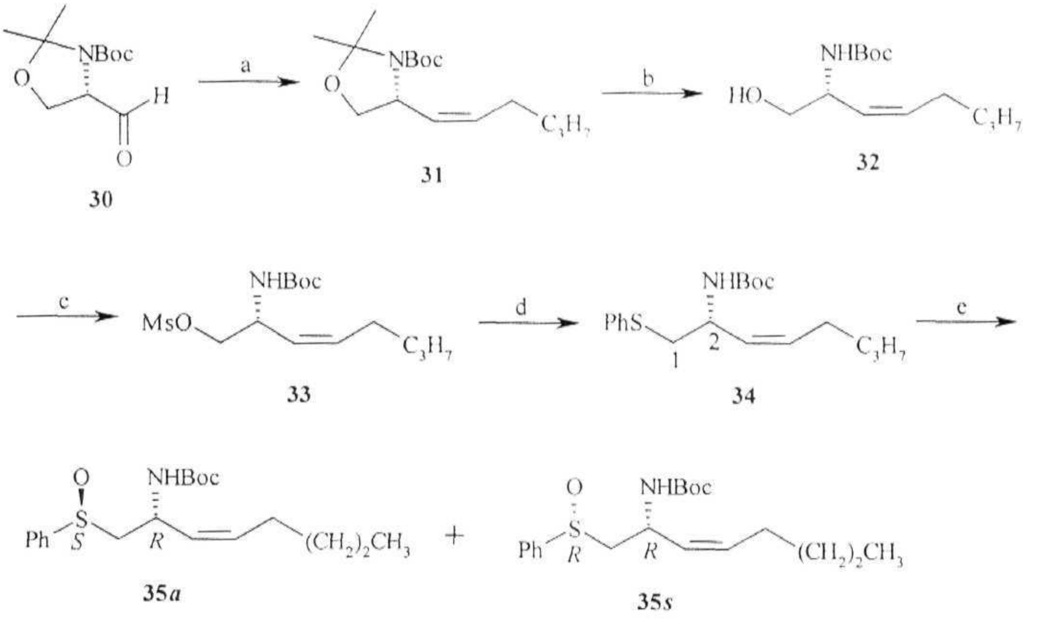




Reagents and conditions: (a) AcCl, MeOH, reflux, 6 h, 100%; (b) $(Boc)_2O$, Et_3N, THF, r.t., 6 h, 91%; (c) 2,2-DMP, acetone, $BF_3.Et_2O$, r.t.,1 h, 92%; (d) $NaBH_4$, LiCl, abs. ethanol, r.t., 16 h, 93%; (e) $(COCl)_2$, DMSO, *N,N*-diisopropylethyl amine, DCM, -78 °C, 78%.

Reaction of aldehyde **30** with the ylide, generated in*situ* from *n*-pentyltriphenylphosphoniumbromide and *n*-BuLi[22] afforded the Z-alkene **31** as the only product. Deprotection of the acetonide group in **31** by treatment with catalytic amounts of camphor-10-sulfonic acid and methanol yielded the amino alcohol **32**, which showed signals at δ 5.57 (dt) and δ 5.25 (dd) for the olefinic protons with $J_{CH=CH}$ = 10.9 Hz in its PMR spectrum suggesting the *Z*-geometry. The signals for the *gem*-dimethyl groups of the acetonide were absent in the PMR spectrum. Compound **32** was converted into the sulfide **34** following a two-step protocol. Reaction of **32** with methanesulfonyl chloride in the presence of Et_3N and catalytic amounts of DMAP[23] furnished the mesylate **33**. The PMR spectrum of **33** revealed a signal at δ 2.99 (s) for the SO_2CH_3. Compound **33** was transformed into the sulfide **34** by treatment with thiophenol in the presence of DBU (Scheme 11).[24] The PMR spectrum of the sulfide **34** showed signals at δ 7.50-7.12 (m) integrating for five aromatic protons, δ 3.18 (dd) and δ 2.95 (dd) for the C1 methylene protons. Treatment of the sulfide **34** with aqueous NaIO4[25] afforded an equimolar mixture of sulfoxides **35*a*** and **35*s***.

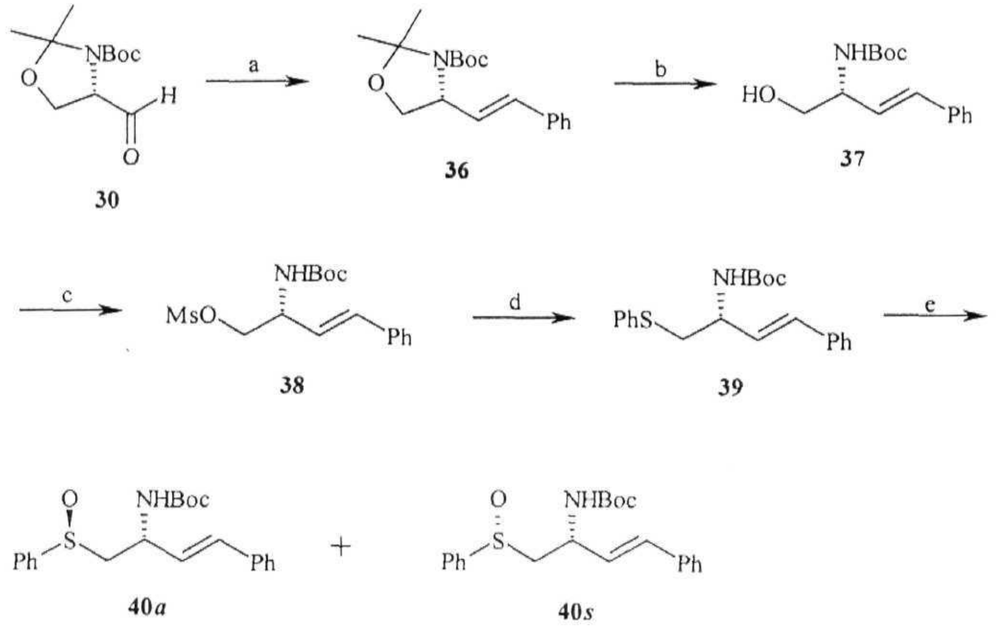
Scheme 11



Reagents and conditions: (a) $Ph_3PCH_2C_4H_9Br$, *n*-BuLi, -78 °C, THF, 30 min, 0 °C, 1 h, add **30** at -78 °C, r.t. 4 h, 62%; (b) CSA, MeOH, r.t., 16 h, 72%; (c) MsCl, Et_3N, DMAP, DCM, 0 °C, 10 min, 95%; (d) PhSH, DBU, benzene, r.t., 30 min, 91%; (e) aq. $NaIO_4$, MeOH, 0 °C-r.t., 16 h, 94%.

Reaction of the aldehyde **30** with the ylide generated from benzyltriphenylphosphonium bromide and *n*-BuLi[22] at -78 °C afforded a mixture of **36** along with the *cis* isomer (*trans*:*cis* = 4:1). The mixture without purification was subjected to isomerization following the protocol devised by Schwarz *et al.*[26] Thus, refluxing the mixture of olefins in benzene with catalytic amounts of PhSH and AIBN for 16 h furnished the *trans* isomer **36** exclusively. The PMR spectrum showed signals at δ 6.49 (d) and δ 5.68 (dd) for the double bond protons with a coupling constant $J_{CH=CH}$ = 12.2 Hz suggesting an *E*-geometry for the olefin. Following the same sequence of reactions as outlined for the olefin **31**, compound **36** was transformed into the epimeric mixture of sulfoxides **40*a*** and **40*s*** (Scheme 12).

Scheme 12

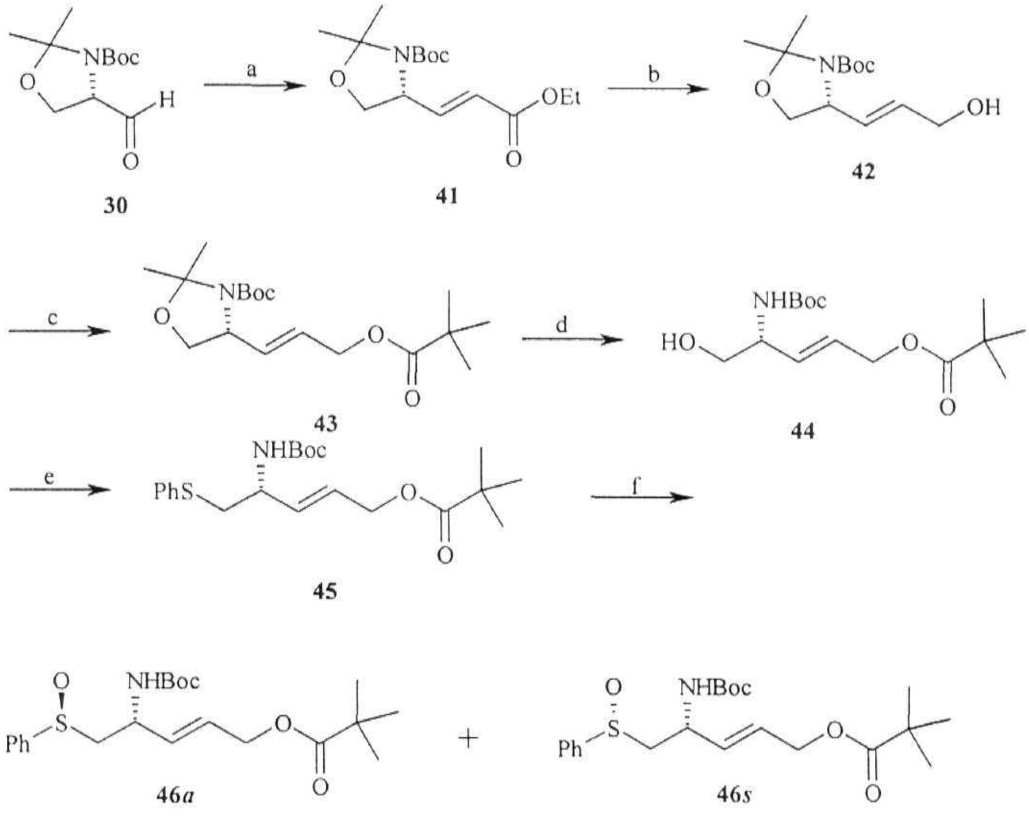


Reagents and conditions: (a) i) Ph_3PCH_2PhBr, *n*-BuLi, -78 °C, THF, 30 min then 0 °C 1 h, add 30 at -78 °C, r.t., 4 h; (ii) PhSH, AIBN, benzene, reflux, 16 h, 66% (for the two steps); (b) CSA, MeOH, r.t., 16 h, 75%; (c) MsCl, Et_3N, DMAP, DCM, 0 °C, 10 min, 98%; (d) PhSH, DBU, benzene, r.t., 30 min, 87%; (e) aq. $NaIO_4$, MeOH, 0 °C-r.t., 16 h, 92%.

Reaction of aldehyde **33** with ethyl(triphenylphosphoranilide)acetate in benzene afforded the *trans* α,β-unsaturated ester **41** as the sole product. The PMR spectrum of **41** showed resonances at δ 6.83 (dd) and δ 5.87 (d) for the olefinic protons with a coupling constant $J_{CH=CH}$ = 15.8 Hz proving the *trans* geometry of the double bond. Following a literature protocol[27] the unsaturated ester was reduced with the ate-complex generated *insitu* from DIBAL and *n*-BuLi to afford the allylalcohol **42**. The PMR spectrum of alcohol **42** showed signals at δ 4.02-3.72 (m) for the *CH_2*OH and at δ 3.90 (bs) for the O*H*. Protection of the hydroxy group as the pivalate ester by treatment with pivaloyl chloride in the presence of Et_3N afforded **43**. The pivalate ester **43** showed a resonance at δ 1.17 (s) integrating to 9H for the *tert*-butyl group. The IR spectrum showed an absorption band at 1706 cm^{-1} for the C=O stretching.

Removal of the acetonide group by treatment with catalytic amounts of CSA in methanol afforded the alcohol **44**. Reaction of the alcohol **44** with the Hata reagent under modified conditions[28] afforded the desired phenyl sulfide **45** (Scheme 13). The PMR spectrum revealed resonances at δ 7.42-7.15 (m) for the aromatic protons, δ 3.12 (dd) and δ 2.98 (dd) for the methylene protons on C1 carbon. Treatment of the sulfide with aqueous $NaIO_4$ afforded an equimolar mixture of sulfoxides **46*a*** and **46*s***.

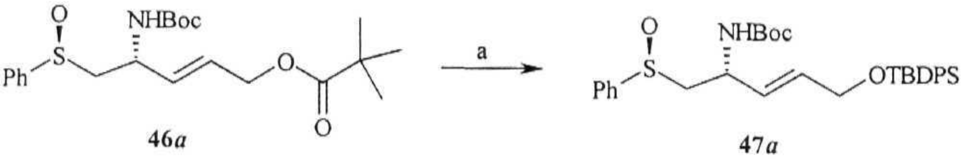
Scheme 13



Reagents and conditions: (a) Ph_3PCHCO_2Et, benzene, r.t., 30 min, 95%; (b) DIBAL, *n*-BuLi, toluene, 30 min, added to **41**, -78 °C, 30 min, 73%; (c) Piv-Cl, Et_3N, DMAP, 0 °C-r.t., 25 min, 83%; (d) CSA, MeOH, r.t., 16 h, 70%; (e) PhSSPh, Bu_3P, THF, 72 °C, 36 h, 63%; (f) aq. $NaIO_4$, MeOH, 0 °C-r.t., 16 h, 90%.

The pivalate group in **46*a*/46*s*** was deprotected individually by saponification using aq. NaOH in methanol to yield the corresponding allylalcohol which was subsequently protected as its silyl ether **47*a*/47*s*** respectively by treating with *tert*-butyldiphenylchlorosilane in the presence of imidazole (Scheme 14, one of the isomer depicted).

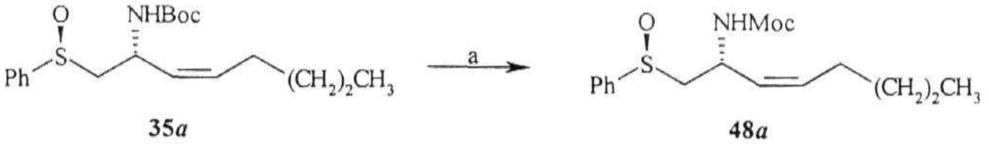
Scheme 14



Reagents and conditions: (a) i) aq. NaOH, MeOH, r.t., 0 °C-r.t., 4 h, 95%; ii) TBDPS-Cl, imidazole, DCM, r.t., 1 h, **47*a***: 76% ; **47*s***: 75%.

The methyl carbamate derivatives **48*a*/48*s*** were prepared individually from **35*a*/35*s*** respectively by treatment with trifluoroacetic acid to yield the ammonium salt, followed by treatment with methyl chloroformate and Et_3N in the same pot (Scheme 15, one of the isomer depicted).

Scheme 15

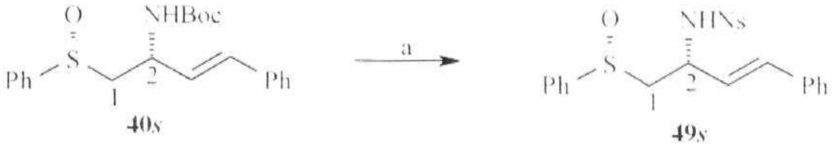


Reagents and conditions: (a) i) TFA, DCM, 0 °C, 30 min; ii) $ClCO_2Me$, Et_3N, 0 °C-r.t., 1 h.

Assignment of configuration to the isomeric β-protectedamino-γ,δ-unsaturated sulfoxides

Suitable crystals were obtained from the *p*-nitrobenzenesulfonamide derivative **49*s***, which was derived from **40*s*** (Scheme 16) by successive deprotection and reprotection. The structure of **49*s*** was deduced by X-ray diffraction (Figure 1). The structure could therefore be assigned to **40s** from which **49s** was derived. The structures were assigned to **35s** and **47s** by comparison of their PMR data with **40s** which revealed similarities. Likewise the PMR spectra of **35*a***, and **47*a*** were similar to the PMR of **40*a***.

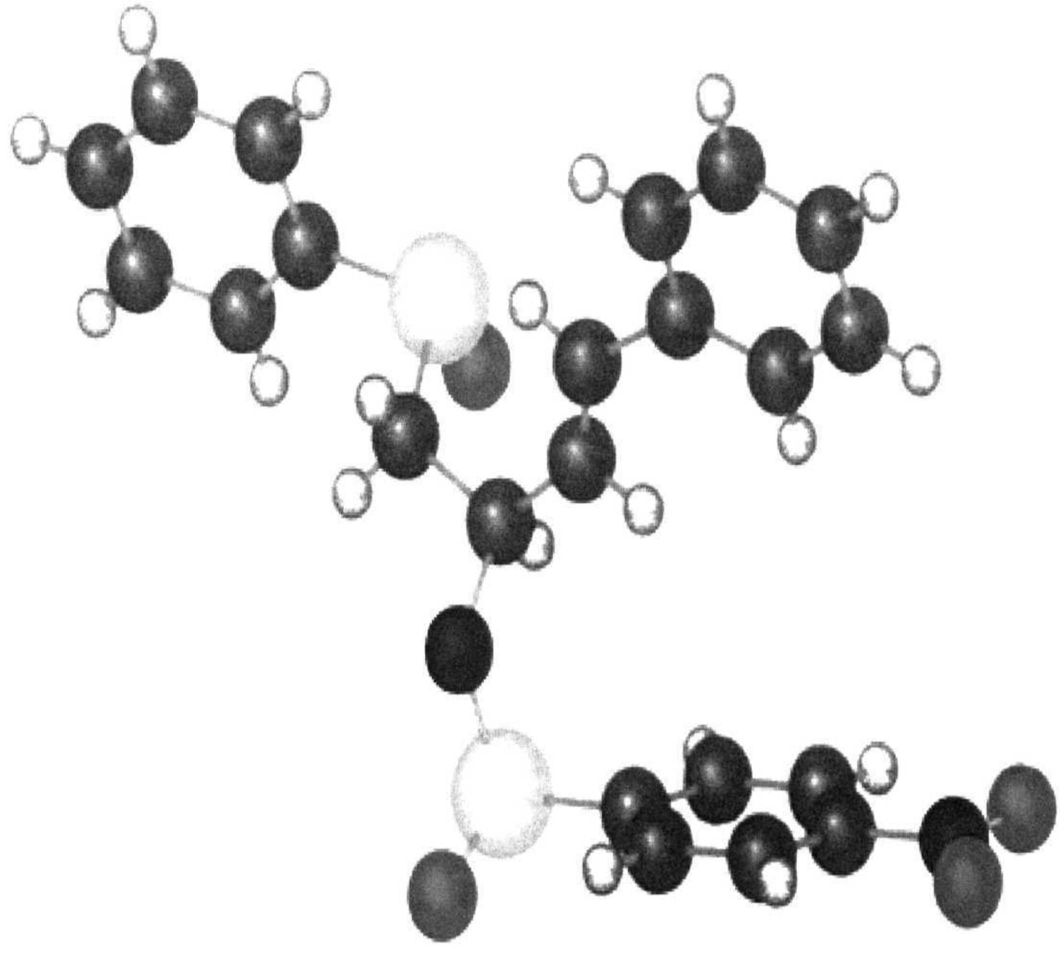
Scheme 16



Ns = 4-nitrobenzenesulfonyl

Reagents and conditions: (a) i) TFA, DCM, 0 °C, 30 min, 90%; ii) *p*-NO_2-C_6H_4-SO_2Cl, Et_3N, DCM, r.t., 1 h, 79%.

Figure 1: X-ray structure of **49*s***



The chemical shift of the methine proton on C2 carbon (C2 H) of the epimeric sulfoxides and their chiroptical properties are diagnostic and help deduce the configuration at sulfur (Table I).[29] Inspection of Table I reveals that C2 H of (S_{S},R_{C}) isomers resonate downfield compared to C2 H of the (R_{S},R_{C}) diastereomers. The (S_{S},R_{C}) diastereomers show negative optical rotation where as (R_{S},R_{C}) diastereomers show positive optical rotation.

Table I: Comparison of the C2 *H* methine proton resonance and Optical rotations.

Compound	C2 H δ ppm	$[\alpha]_D^{25}$	Compound	C2 H δ ppm	$[\alpha]_D^{25}$
35*a*	4.81	-168.0	**35*s***	4.71	+72.4
40*a*	4.74	-167.0	**40*s***	4.63	+13.5
46*a*	4.58	-36.6	**46s**	4.44	+38.3
47*a*	4.83	-276.4	**47*s***	4.75	+89.4

Regio- and stereoselective bromohydrin formation

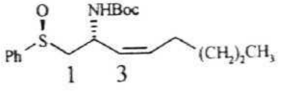
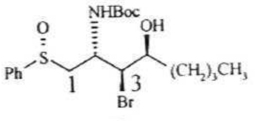
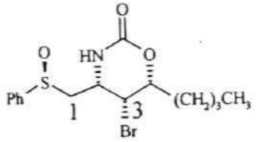
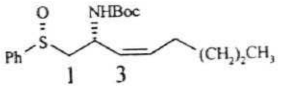
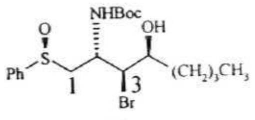
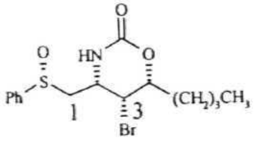
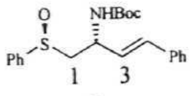
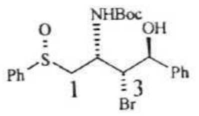
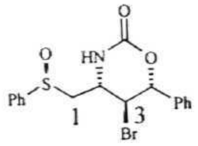
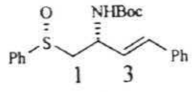
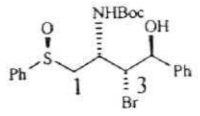
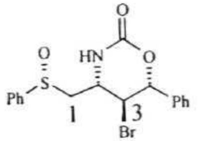
The unsaturated β-protectedamino-γ,δ-unsaturated sulfoxides were reacted with *N*-bromosuccinimide in toluene in the presence of water to afford the bromohydrins regio- and stereoselectively (Table II).

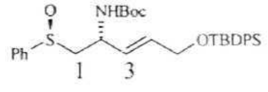
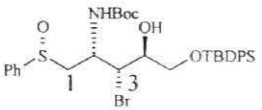
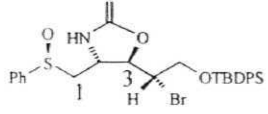
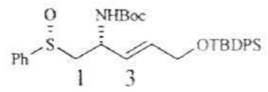
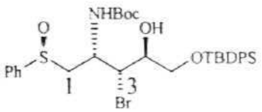
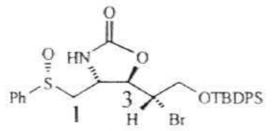
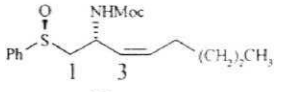
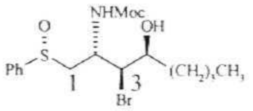
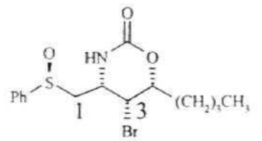
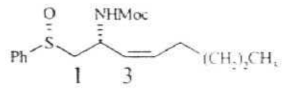
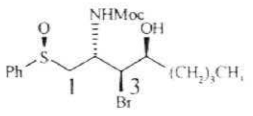
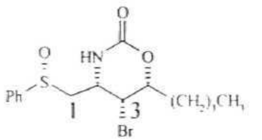
Examination of the Table II reveals the following trends

- ✓ The carbamate group competes with the sulfinyl group as the intramolecular nucleophile. The pathway involving the carbamate moiety is slightly preferred over the sulfinyl moiety.
- ✓ Opposite stereoselectivity is observed in products arising via carbamate and sulfinyl group participation indicating different reaction pathways.
- ✓ The stereoselectivity of the products resulting from carbamate participation is very high.

- ✓ The reaction pathway involving the sulfinyl group is a highly regioselective affording products from a 6-*endo* nucleophilic attack, probably as a consequence of the inductive electron withdrawing nature of the allylic amino substituent, which would destabilize any partial positive charge developing at C3 carbon.
- ✓ The reaction is general for different classes of olefins.

Table II: Regio- and stereoselectivity in formation of bromohydrins

S. No.	Substrate	Product from Sulfinyl group participation	C2/C3 *Anti/Syn*	Product from Carbamate Participation	C2/C3 *Syn/Anti*	Ratio [b]	Yield [a]
1	 **35*a***	 **50*s***	83:17	 **52*a***	>95:<5	3:2	78
2	 **35*s***	 **50*a***	9:1	 **52*s***	>95:<5	1:2	78
3	 **40*a***	 **54*s***	17:83	 **55*a***	<5:>95	1:3	84
4	 **40*s***	 **54*a***	1:9	 **55*s***	<5:>95	2:3	82

5	 **47*a***	 **56*s***	<5:>95	 **58*a***	>95:<5	2:1	81
6	 **47*s***	 **56*a***	<5:>95	 **58*s***	>95:<5	31:19	80
7	 **48*a***	 **59*s***	92:8	 **52*a***	>95:<5	4:1	70
8	 **48*s***	 **60*a***	>95:<5	 **52*s***	>95:<5	17:3	70

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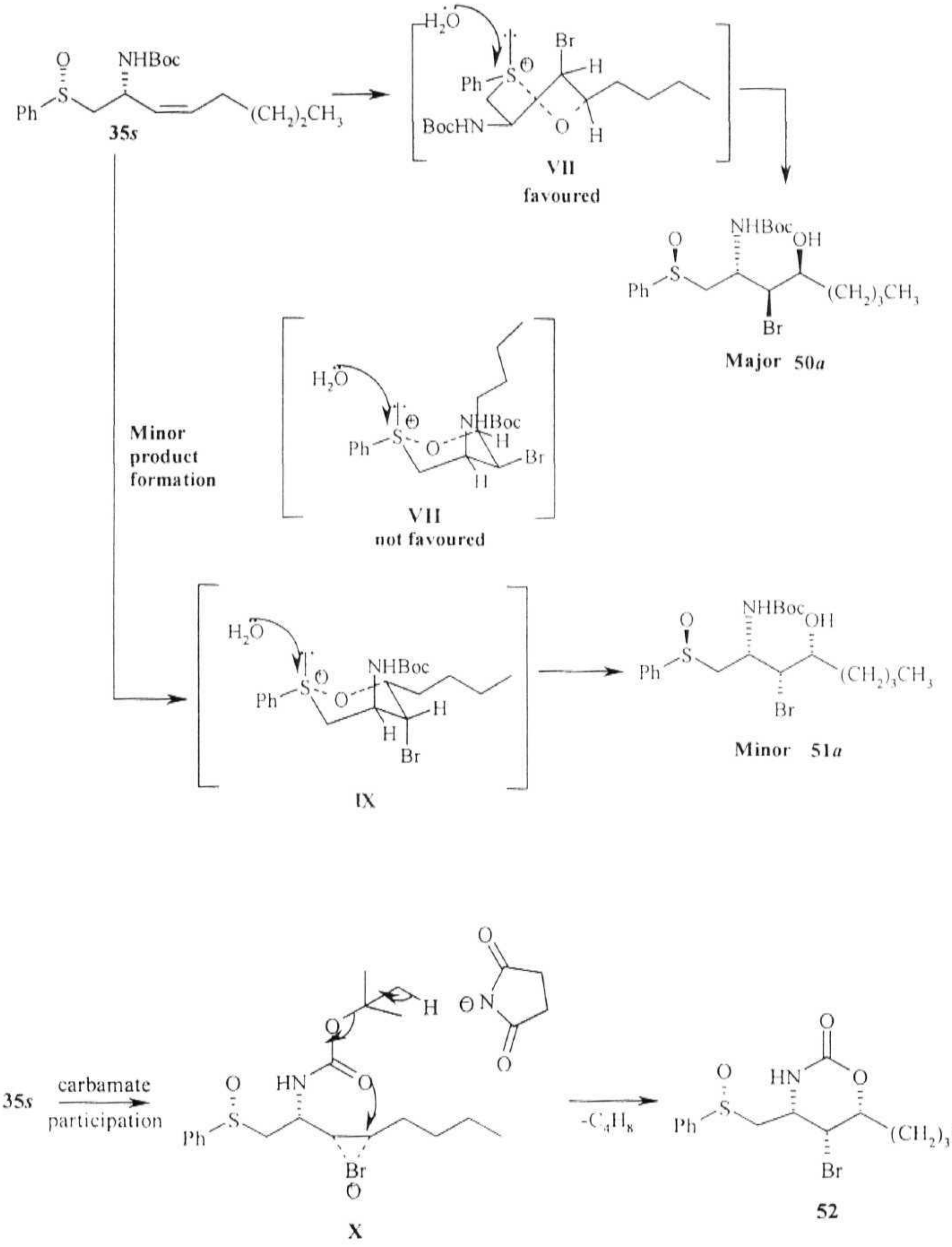
[a] Yield refers to the combined yield of all the products [b]Product ratio between sulfinyl participation and carbamate participation

- ✓ The sulfoxides with a relative *syn* orientation of the sulfinyl and amino substituents react more stereoselectively than sulfoxides with an *anti* disposition.
- ✓ The methyl carbamate moiety is known to be a poorer nucleophile[30e] than the *t*-butyl carbamate group. It is clear from entries 7 and 8 in Table II that the products resulting from the sulfinyl group participation, although not formed exclusively, were now the predominant component of the reaction mixture. The nucleophilicity of the sulfinyl group can therefore be assumed to be in between that of the *t*-butyl and methyl carbamates.

The formation of the bromohydrins regio- and stereoselectively can be rationalized by invoking the intermediacy of sulfoxonium salts, formed by the nucleophilic attack of the internal sulfinyl group on the olefin π complexed to the bromonium ion and subsequent hydrolysis by attack of water at sulfur in a S_N2 fashion resulting in products with net inversion of sulfur configuration.

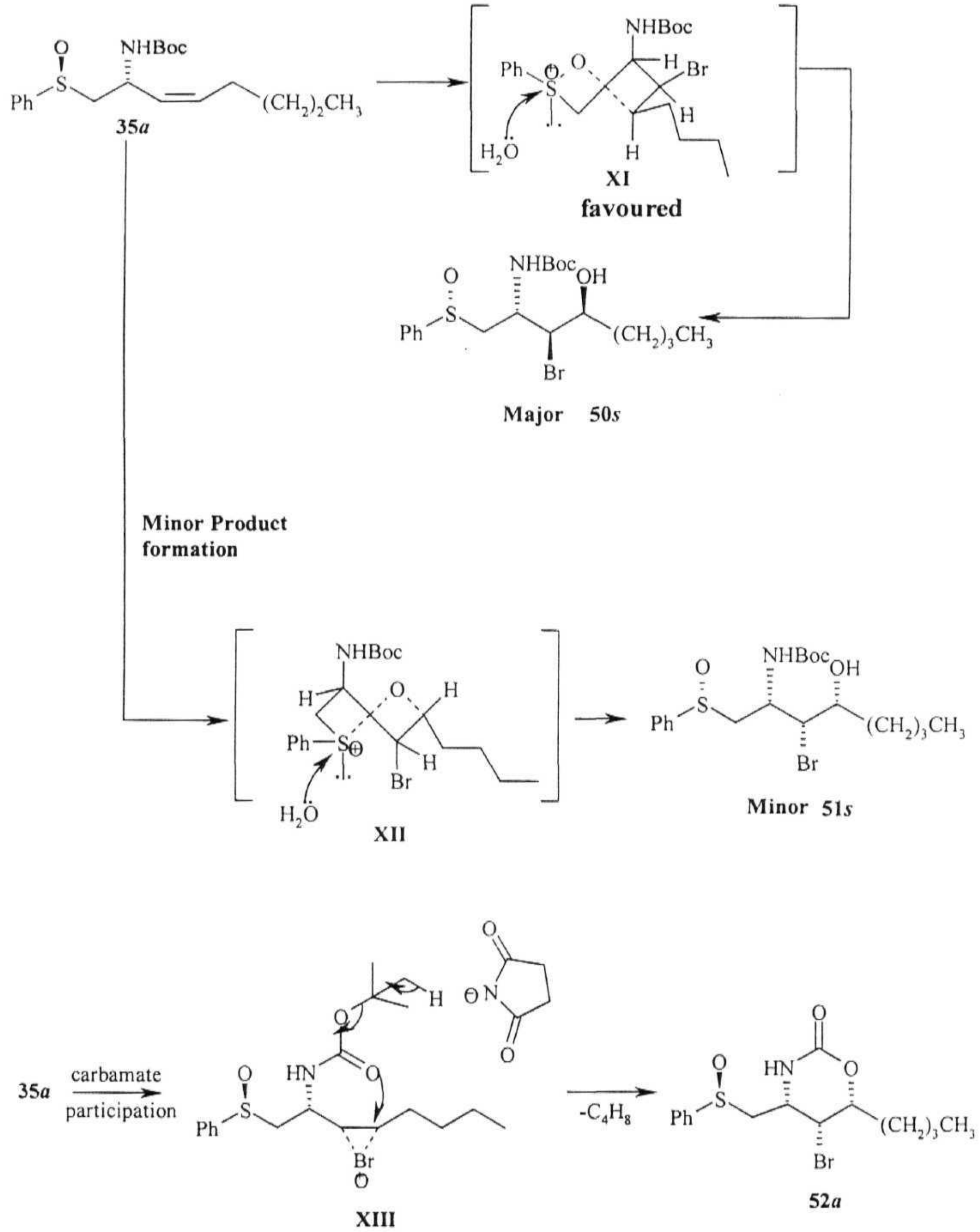
Formation of the predominant product by the sulfinyl group participation from **35*s*** in NBS reaction could be explained by the formation of sulfoxonium salt (**VII**). Though, both **VII** and **VIII** would provide the same product, the latter is destabilized due to repulsion between the amino substituent and alkyl substituent (Scheme 17).

Scheme 17



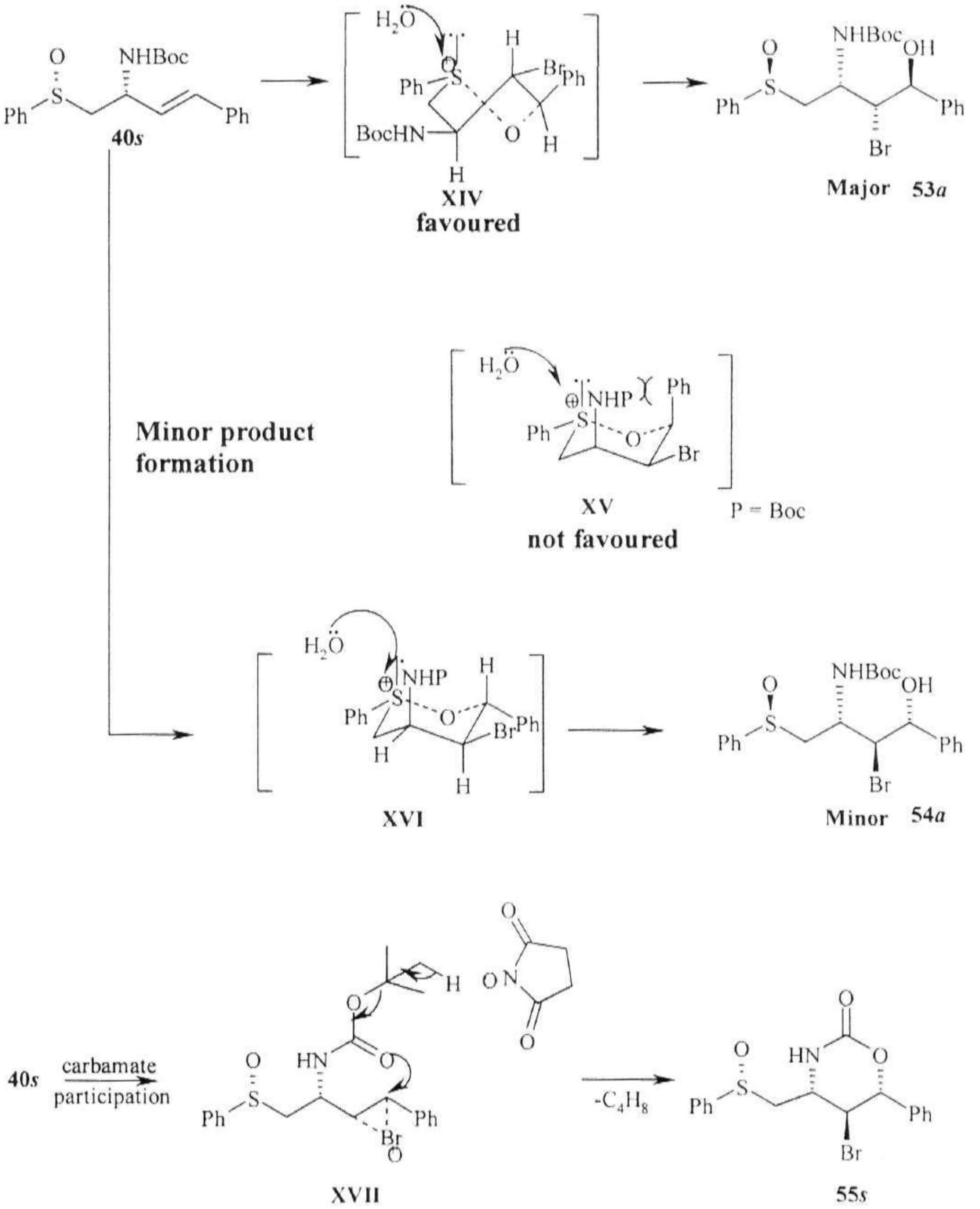
The products resulting from the diastereomer **35a** can be rationalized by the intermediacy of sulfoxonium salts **XI** and **XII** to yield the major and minor products respectively (Scheme 18).

Scheme 18



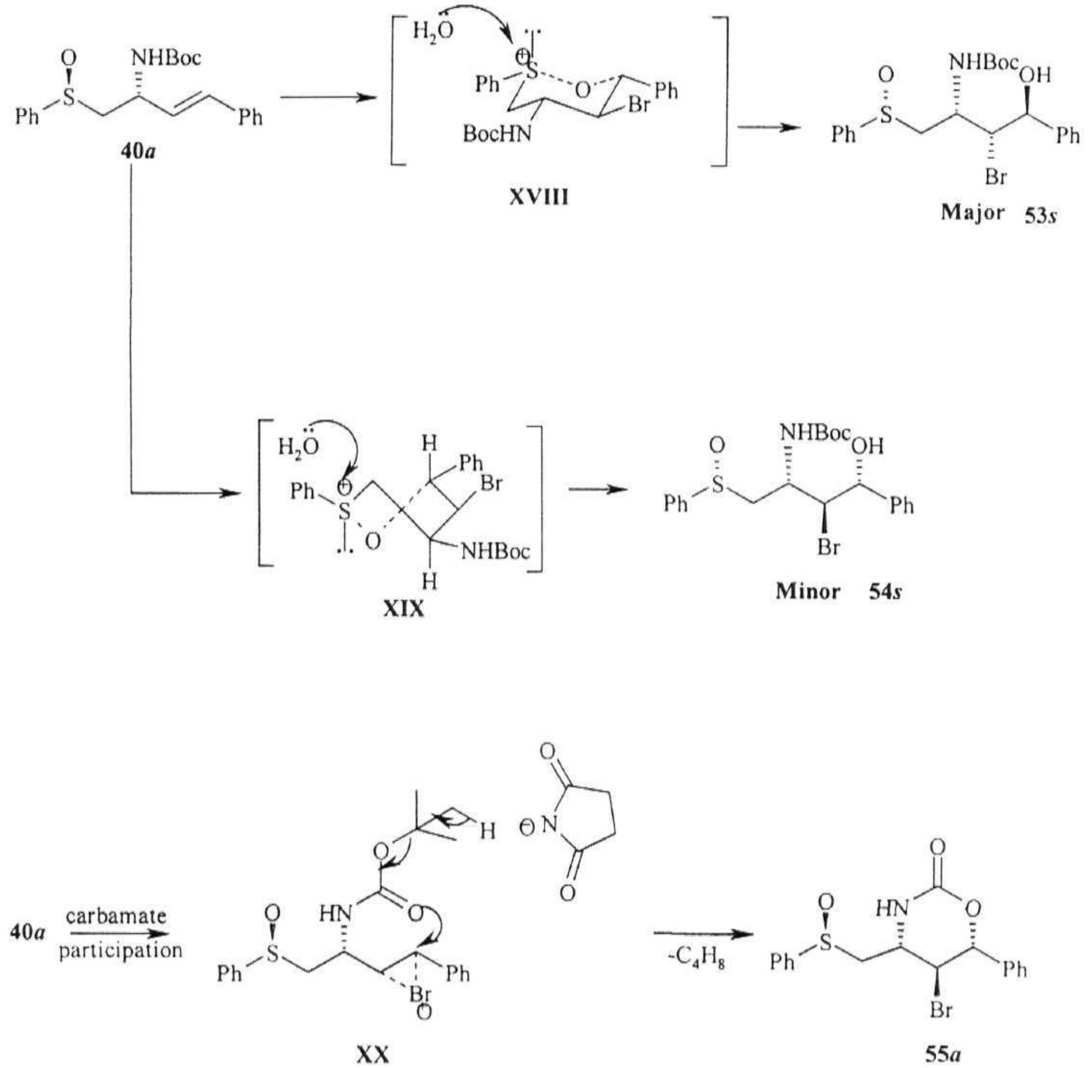
Formation of products from **40s**: The sulfoxonium salt **XIV** in a twist boat confirmation would explain for the formation of the major isomer **53*a***. The intermediate **XV** would suffer from steric repulsion of the amino and the phenyl groups. Sulfoxonium salt **XVI** would explain for the formation of the minor product **54*a*** (Scheme 19).

Scheme 19



In a similar fashion intermediates **XVIII** and **XIV** can be invoked to explain the formation of major and minor products **53*s*** and **54*s*** respectively via sulfinyl group participation from **40*a***.

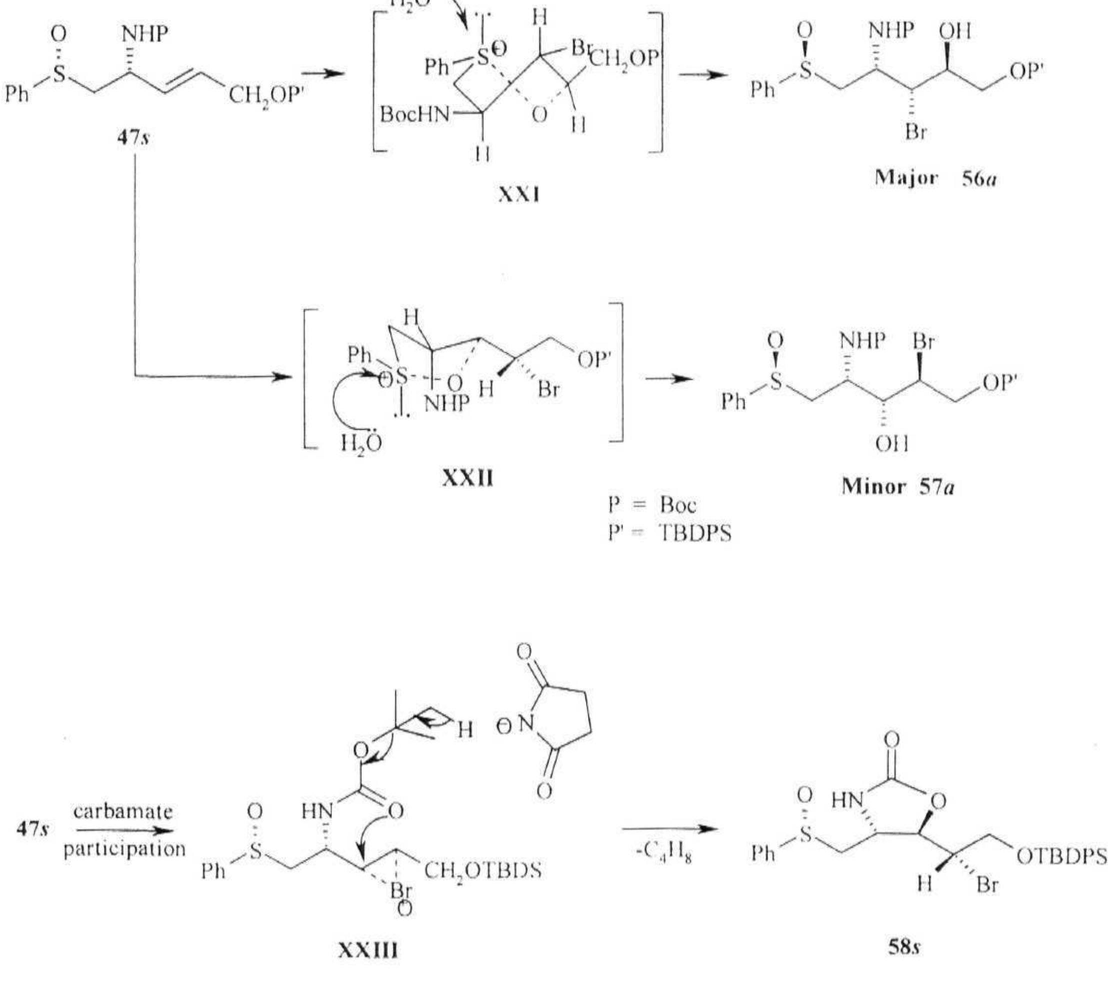
Scheme 20



Probably the relative energies of the different ground state conformations of the starting material are important in determining the facial selectivity of bromonium ion approach and product selectivity in the pathway involving internal carbamate participation.

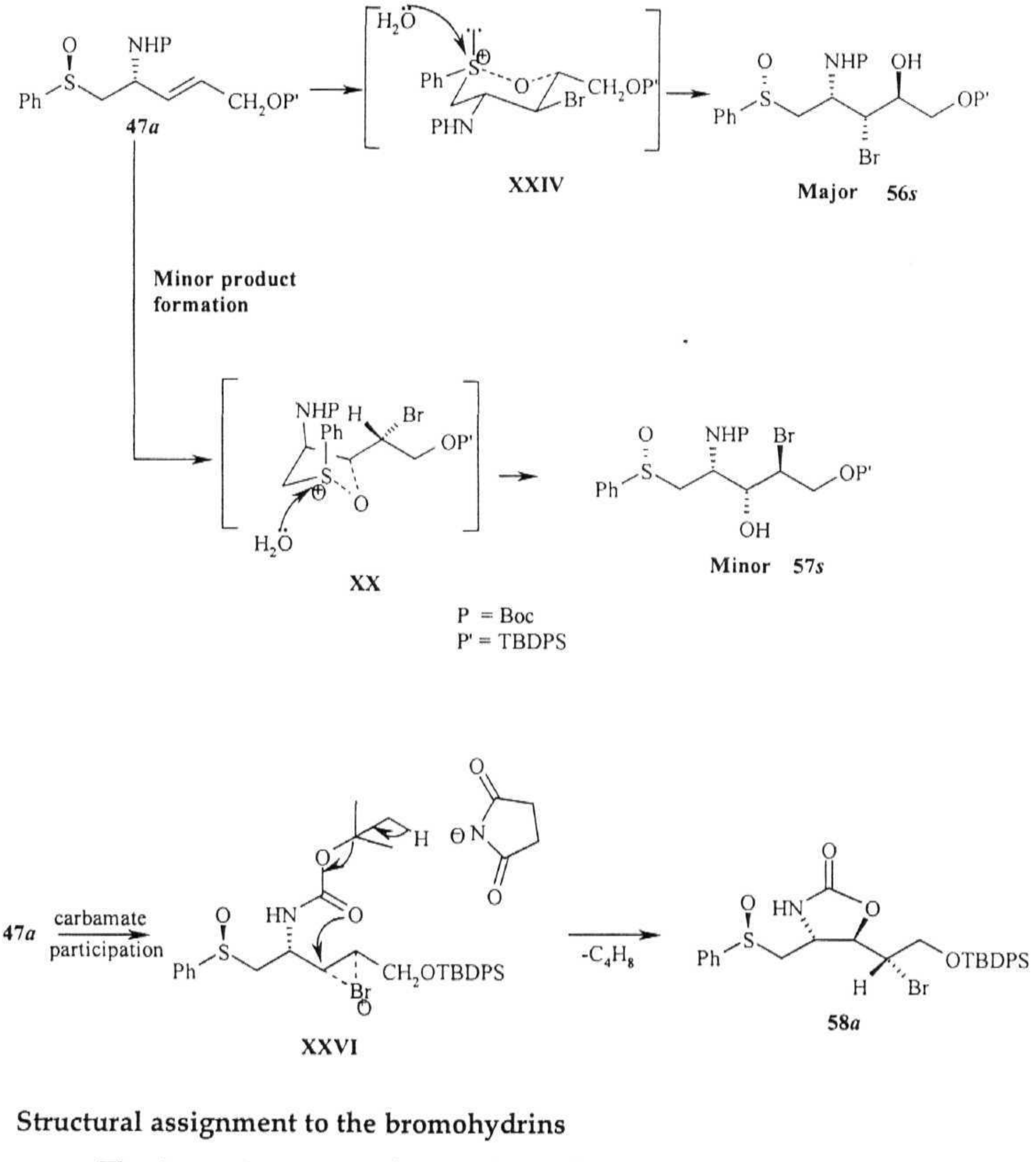
The formation of the major and minor products from sulfinyl group participation from **47*s*** can be rationalized through intermediates **XXI** and **XXII**. The product from carbamate participation can be explained via the intermediacy of **XXIII** (Scheme 21).

Scheme 21



In a similar fashion the intermediate sulfoxonium salts **XXIV** and **XXV** can explain formation of the major and minor products from **47*a***. Product from carbamate participation can be explained by intermediacy of **XXVI** (Scheme 22).

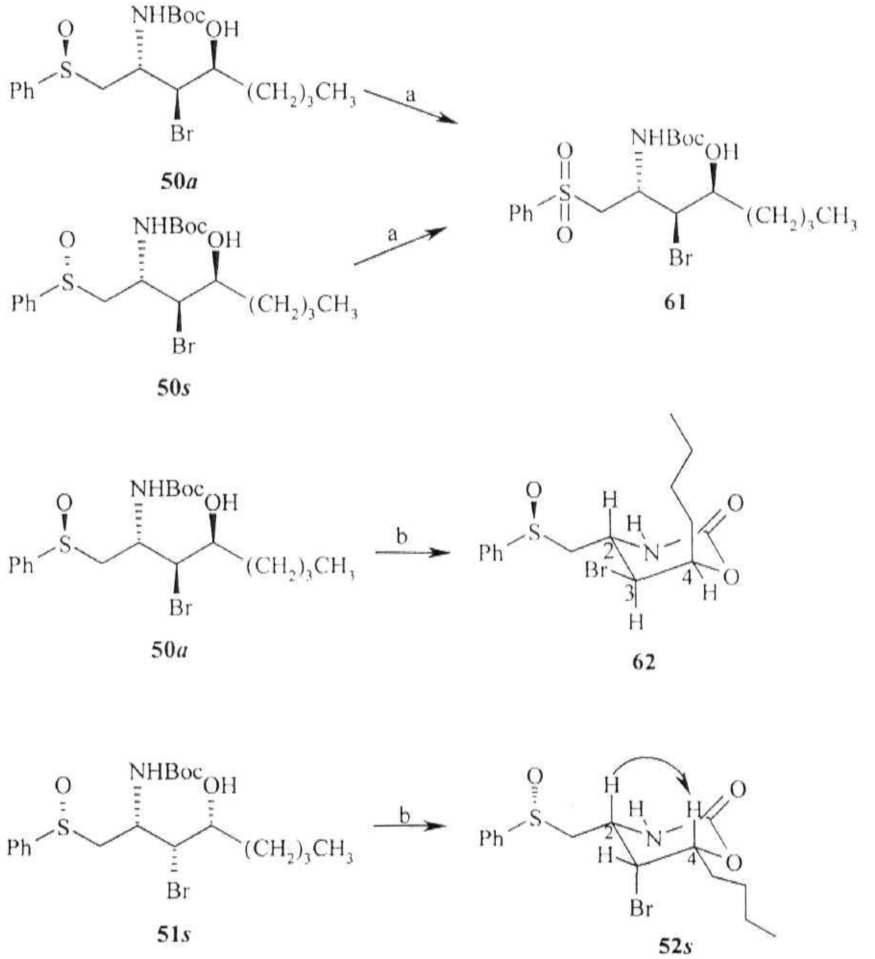
Scheme 22

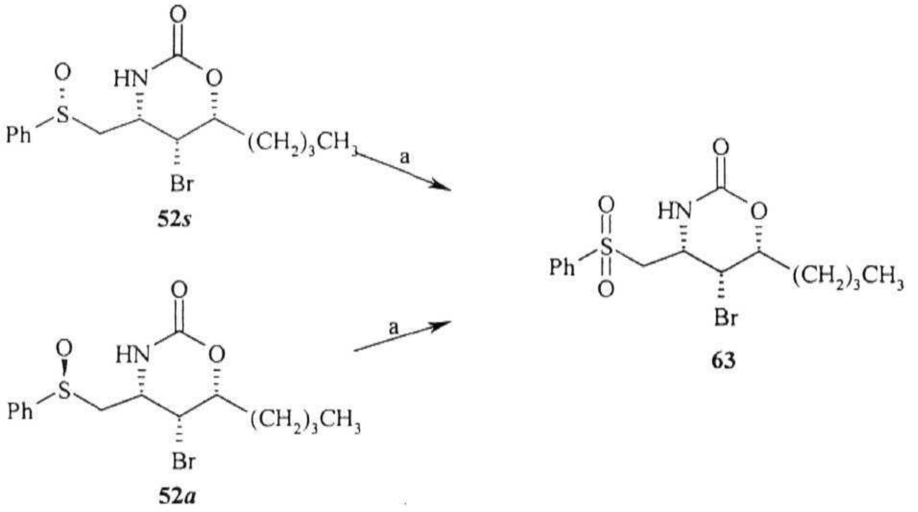


Structural assignment to the bromohydrins

The isomeric nature of major bromohydrins 50*a*/50*s* and 52*a*/52*s* was established by oxidation of the sulfoxides individually to yield identical sulfones. The structure of **50*a***, the major stereoisomer from **35*s***, was assigned by transforming it to the oxazinone **62** by treatment with TFA/CH_2Cl_2 followed by the treatment of the resulting salt with carbonyl di imidazole in the presence of DABCO as the base in THF as the solvent (Scheme 23). The C3 methine proton coupled with C2 and C4 methine protons and the *J* values respectively are 8.7 and 3.6 Hz. Irradiation of C2 H in **52*s*** showed nOe with C4 H confirming the structure assigned to it.

Scheme 23



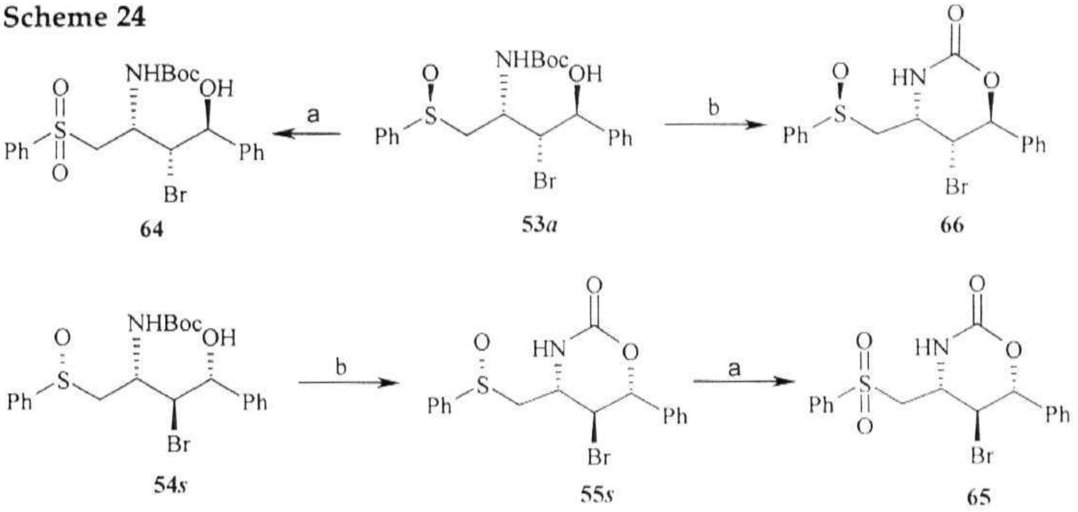


Reagents and conditions: (a) *m*CPBA, $CHCl_3$, 0 °C, 10 min, **61**: 90%; **63**: 87%; (b) i) TFA: DCM, r.t., 30 min; ii) DABCO, CDI, THF, r.t., 24 h.

The minor stereomer **51*s*** from **35*a*** was transformed to the oxazinone which was identical to the product resulting from carbamate participation from **35*s***. This proves that **51*s*** arises via sulfinyl group participation and the sulfur center is inverted in the process. The PMR data of oxazinone **52*a*** supported the structure assigned to it. The *J* values for C3 methine proton coupling with the C2 and C4 methine protons were 3.6 and 2.6 Hz respectively.

Oxidation of the bromohydrins **53*a*** and **53*s*** with *m*-CPBA yielded identical sulfone **64**. Oxidation of the carbamate participation products **55*a*** and **55*s*** individually yielded identical sulfone **65**. The PMR data of the oxazinone **66**, derived from the major bromohydrin **53*a*** arising from **40*s***, unambiguously confirmed the structure assigned to it and the stereochemistry of **53*s***. Oxazinone derived from the minor product **54*s*** arising from **40*a*** was found to be identical to **55*s*** (Scheme 24).

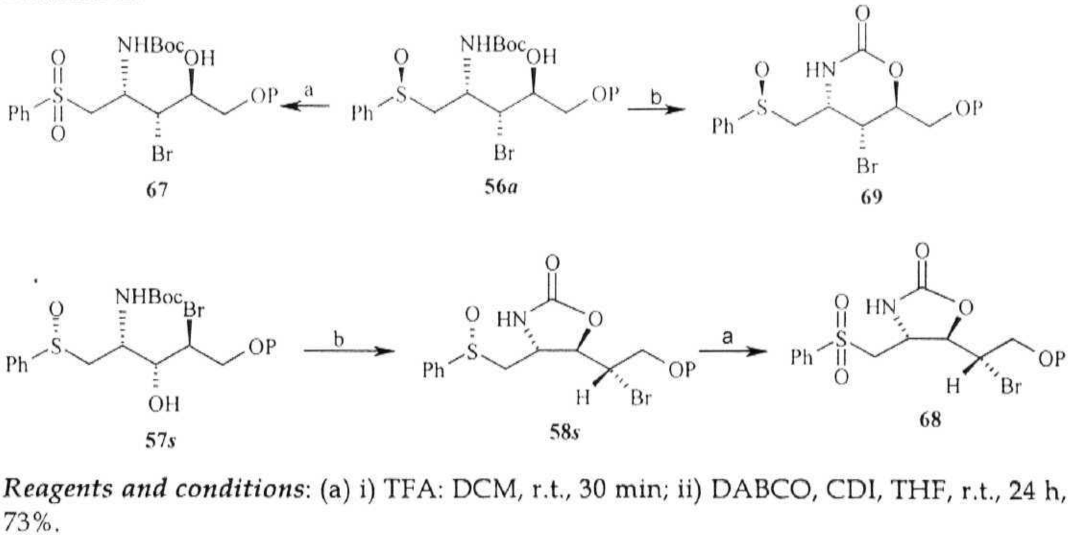
Scheme 24



Reagents and conditions: (a) *m*CPBA, $CHCl_3$, 0 °C, 10 min; (b) i) TFA: DCM, r.t., 30 min; ii) DABCO, CDI, THF, r.t., 24 h, 75%.

The epimeric nature of major bromohydrins **56*a*/56*s*** and products arising from carbamate participation **58*a*/58*s*** was confirmed by transforming into identical sulfones 67 and 68 respectively. Major bromohydrin **56*a*** arising from **47*s*** afforded oxazinone **69** by a two-step reaction sequence. Minor product **60*a*** provided **58*s*** by a two-step protocol (Scheme 25). The PMR spectra of 69 and 58s helped assign the structures to 56a and 57s unambiguously.

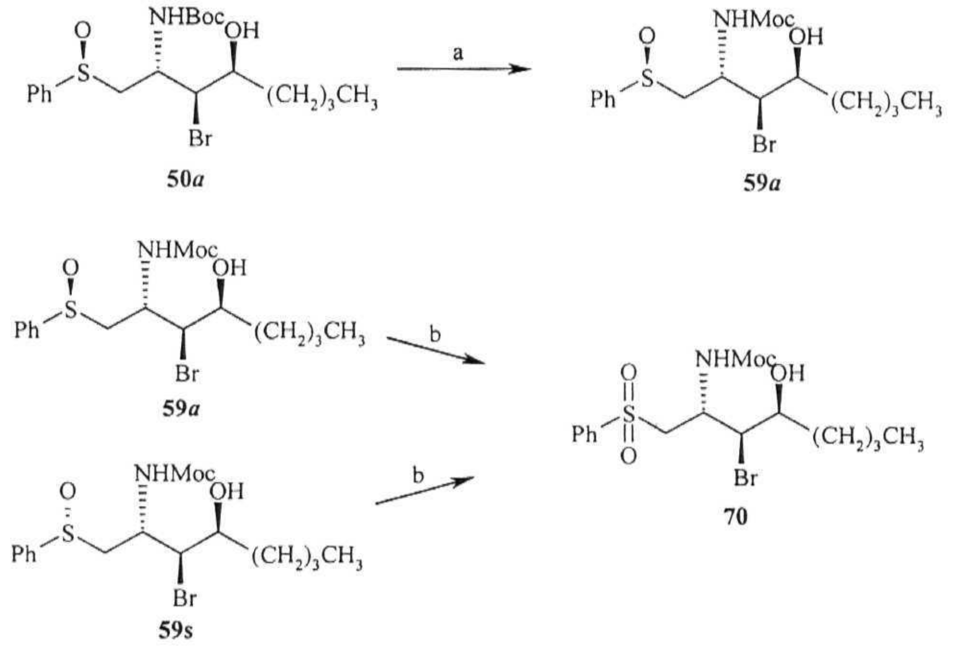
Scheme 25



Reagents and conditions: (a) i) TFA: DCM, r.t., 30 min; ii) DABCO, CDI, THF, r.t., 24 h, 73%.

The PMR spectra of the products **59*a*** and **59*s*** arising from the methyl carbamates **48*a*/48*s*** had PMR data similar to the products arising from *t*-butyl carbamates **35*a*/35*s***. Their structure was confirmed by transforming **50*a*** into **59*a*** by a two-step sequence. Thus, removal of *t*-butyl carbamate group with trifluoroacetic acid and subsequent treatment of the resulting ammonium salt with methylchloro formate in the presence of Et_3N yielded methyl carbamate protected 1,3-amino alcohol derivatives. Again the major products **59*s*** and **59*a*** arising from diastereomeric sulfoxides yielded identical sulfone **70** upon oxidation using *m*CPBA (Scheme 26).

Scheme 26

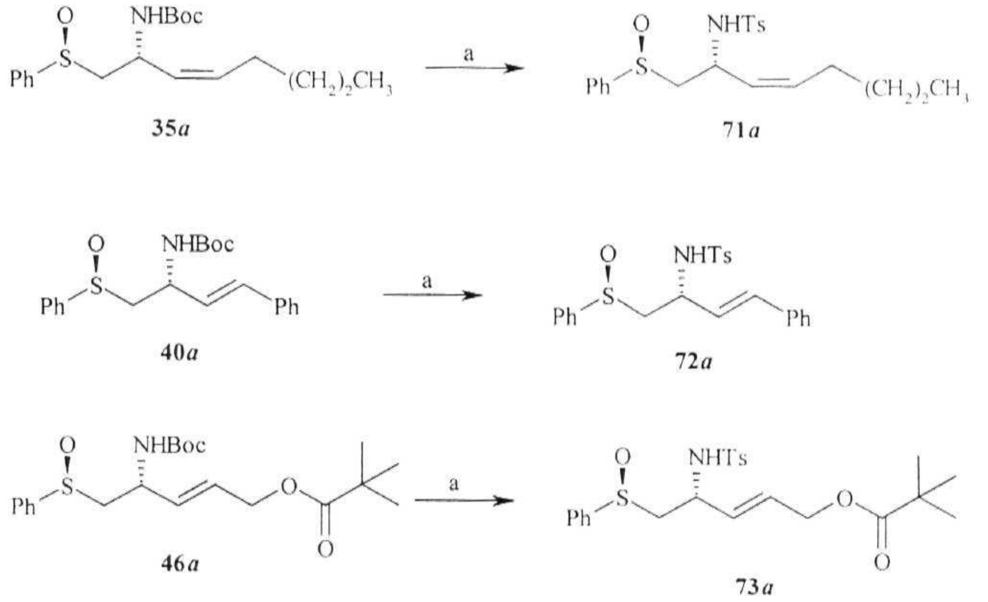


Reagents and conditions: (a) i) TFA: DCM, r.t., 30 min; ii) $ClCO_2Me$, Et_3N, r.t., 1 h, 60%; (b) *m*CPBA, $CHCl_3$, 0 °C, 10 min, 83%.

Preparation of sulfonamide diastereomers

In the search for an amino substituent that would not act as a nucleophile in the reaction, the *p*-toluenesulfonyl group was judiciously selected. Thus, the sulfoxide diastereomers **35, 40** and **46** were individually transformed into sulfonamide derivatives **71**, **72** and **73** respectively by treatment of the individual diastereomers with trifluoroacetic acid followed by *p*-TsCl in the presence of Et_3N and catalytic amounts of DMAP (Scheme 27, one of the isomers illustrated).

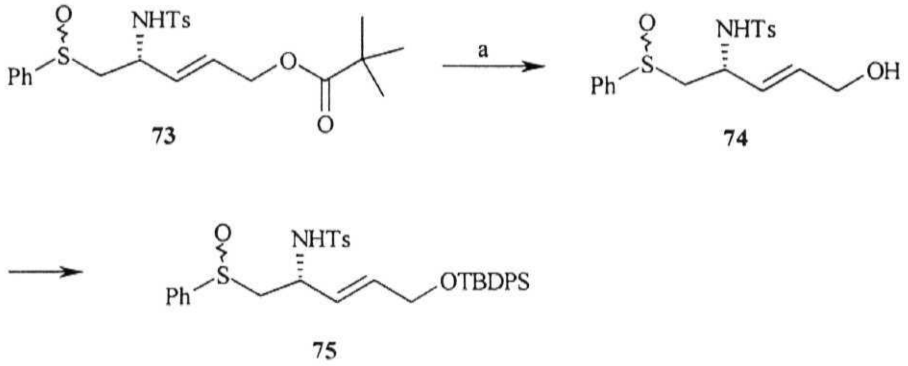
Scheme 27



Reagents and conditions: (a) i) TFA, DCM, 0 °C, 30 min; ii) *p*-TsCl, Et_3N, 0 °C-r.t., 1 h.

The individual pivalate epimers 73*a* and 73*s* upon treatment with aq. NaOH in methanol afforded alcohol 74. Subsequently the alcohol was converted into the silyl derivative 75 (Scheme 28) by treatment with TBDPS-Cl in the presence of imidazole.

Scheme 28



Reagents and conditions: (a) i) aq. NaOH, MeOH, r.t., 0 °C-r.t., 4 h, **74*a***: 73%; **74*s***: 75%; ii) TBDPS-Cl, imidazole, DCM, r.t., 1 h, **75*a***: 83%, **75*s***: 81%.

The diastereomeric *p*-toluenesulfonamides also revealed similarities in their PMR spectra (Table III), optical rotation data (Table IV) with the corresponding Boc protected diastereomers. The C2 H of *anti* diastereomers resonated downfield relative to the *syn* diastereomers.

Table III: Chemical shift for the C1 protons

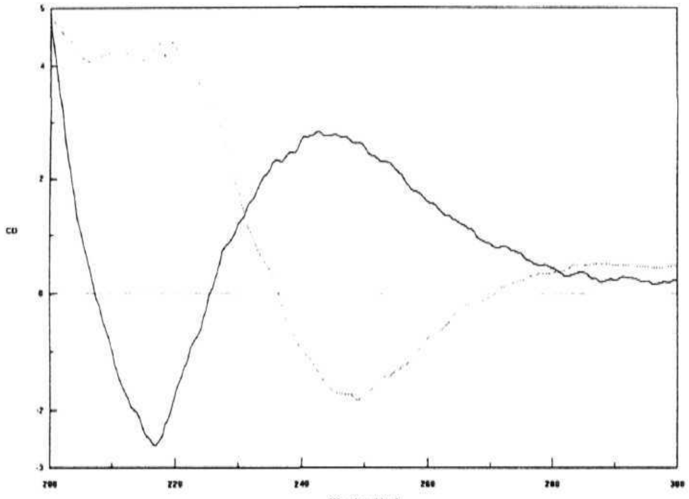
Compound	δ (ppm)	Δ	Compound	δ (ppm)	Δ
71*a*	3.03, 2.69	0.34	71*s*	3.13, 2.75	0.38
72*a*	2.97	0.00	72*s*	3.16, 2.92	0.24
75*a*	2.76	0.00	75*s*	2.98, 2.70	0.28

Table IV: chemical shift for the C2 H proton and optical rotation

Substrate	**C2 H δ ppm**	$[\alpha]_D^{25}$	**Compound**	**C2 H δ ppm**	$[\alpha]_D^{25}$
71*a*	4.45	-118.8	**71*s***	4.38	+168.7
72*a*	4.52	-115.9	**72*s***	4.38	+9.2
73*a*	4.40	-90.1	**73*s***	4.21	+92.3
75*a*	4.34	-75.8	**75*s***	4.15	+64.5

It has been known for decades that a correlation exists between the absolute configuration of sulfoxides and their chiroptical properties.[31] It was expressed in terms of the signs and rotational strengths of the appropriate Cotton effects (CE). The phenylsulfinyl group is an inherently chiral chromophore and the sign of CE is determined solely by the chirality of the chromophore. Its primary UV band (usually at 235-255 nm) is optically active with CE, $\Delta\varepsilon$ ca. 20. Also a shorter wavelength absorption band (ca. 210-220 nm) demonstrates CE of similar amplitude but opposite sign. The CD spectra of **71*s*, 72*s*** and **75*s*** revealed a positive sign for the primary band (235-255 nm) in the cotton effect curve corresponding to the (*R*)-configuration of the sulfinyl group, while sulfoxides **71*a*, 72*a*** and **75*a*** showed a negative sign for the primary band (235-255 nm) in their cotton effect curve corresponding to (*S*)-configuration.

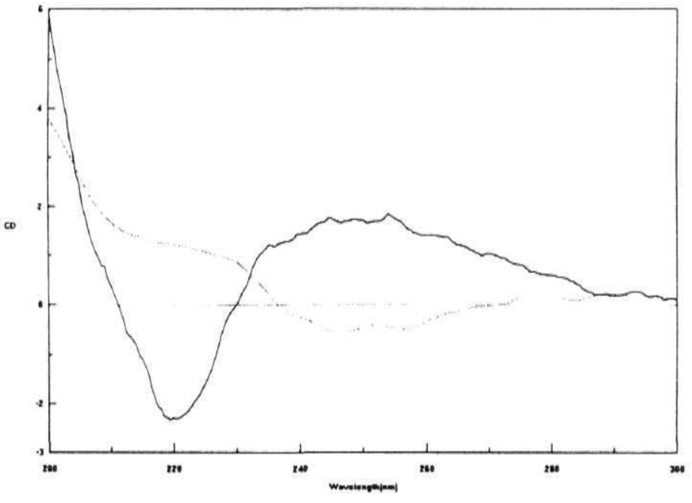
Figure 2: CD spectra



Light line = **71*a***

Dark line = **71*s***

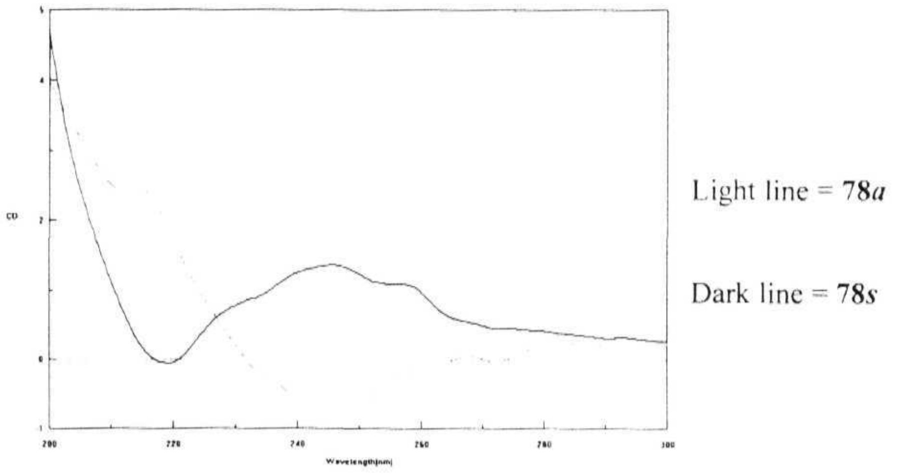
CD-Spectra of **71*a*** and **71*s***



Light line = **72*a***

Dark line = **72*s***

CD-Spectra of **72*a*** and **72*s***



CD-Spectra of **75*a*** and **75*s***

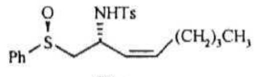
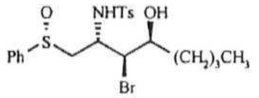
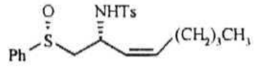
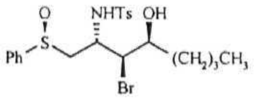
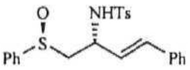
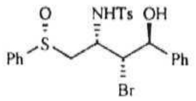
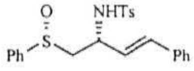
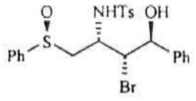
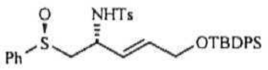
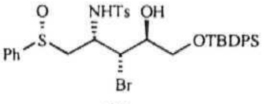
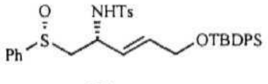
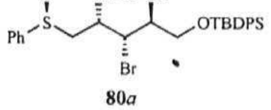
The spectra were recorded in acetonitrile at the concentration range of 10^{-4}-10^{-5}M.

The sulfonamide derivatives **71**,**72** and **75** were reacted with NBS at ambient temperature in toluene in the presence of water to afford amino alcohol derivatives (Table V). An observation of the table reveals the following points.

1. Compounds from sulfinyl group participation were the only products obtained as expected.
2. The product distribution is similar to that observed with Boc and Moc groups indicating that protecting group had little influence on the product stereo- and regioselectivity.

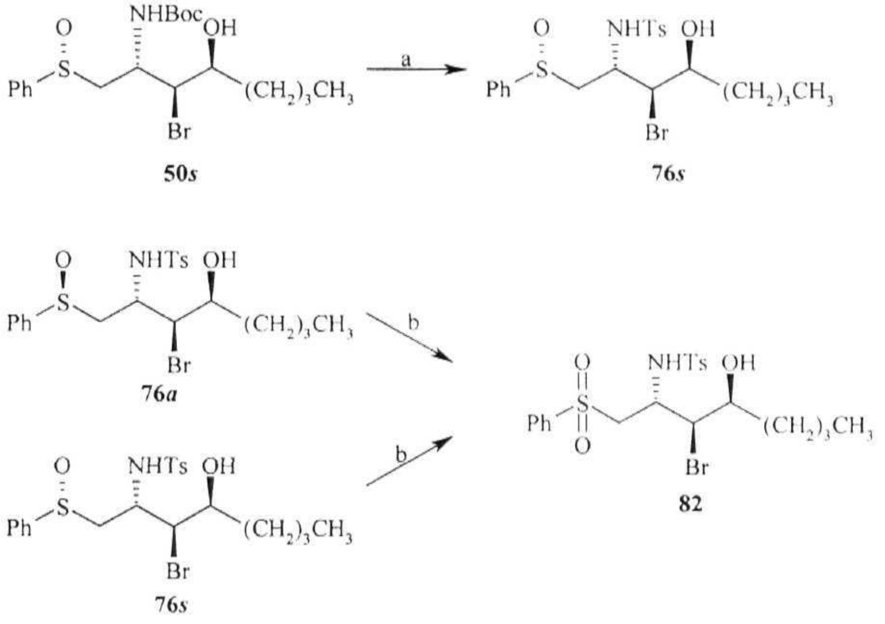
The bromohydrin **50s** upon deprotection of the *t*-butoxycarbonyl group followed by treatment with *p*-TsCl in DCM in the presence of Et_3N afforded **76s**, supporting the structure assigned to **76s**. Bromohydrins **76*a*** and **76*s*** yielded identical sulfone **82** upon treatment with *m*CPBA (Scheme 29).

Table V: Regio- and stereoselectivity in formation of bromohydrins from sulfonamide derivatives

S. No	Sulfoxide	Product	C2/C3 *Anti/Syn*	Yield
1	 71*a*	 76*s*	8.5:1.5	76
2	 71*s*	 76*a*	>95:<5	82
3	 72*a*	 78*s*	1.5:8.5	75
4	 72*s*	 78*a*	<5:>95	80
5	 75*a*	 80*s*	3:7 [a]	70
6	 75*s*	 80*a*	1.5:8.5 [b]	70

[a]Both the major and minor bromohydrins obtained as a mixture of stereomers in 7:3 ratio; [b]Major bromohydrin obtained as a mixture of stereomers in 4:1 ratio.

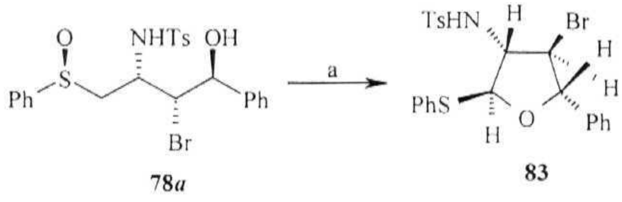
Scheme 29

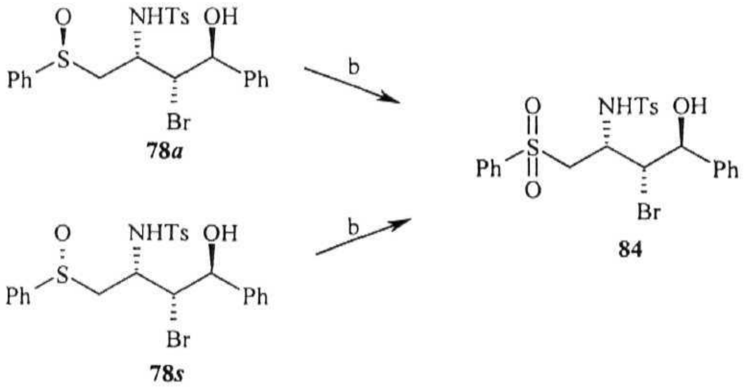


Reagents and conditions: (a) i) TFA, DCM, 0 °C, 30 min; ii) *p*-TsCl, Et_3N, 0 °C-r.t., 1 h; (b) *m*CPBA, $CHCl_3$, 0 °C, 10 min, 82%.

The structure of **78*a*** was proven unambiguously by transforming it into a tetrahydrofuran derivative **83** (mechanisitic aspects and structure confirmation by nOe measurements discussed in section C of Chapter II). Oxidation of the sulfoxides **78*s*** and **78*a*** individually furnished an identical sulfone **84** proving the epimeric nature of the bromonydrins (Scheme 30).

Scheme 30

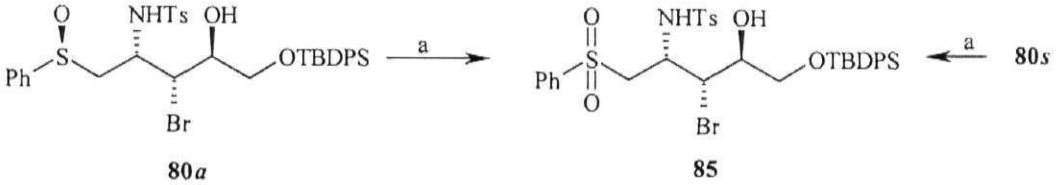




Reagents and conditions: (a) TBDPS-Cl, DMF, r.t., 30 min, 86%; (b) *m*CPBA, $CHCl_3$, 0 °C, 10 min, 90%.

Analogous to the *trans* olefin **72**, the olefin **75** is expected to afford products wherein the amino and bromo substituents would be *syn* disposed. The major bromohydrins **80*a*/80s** furnished identical sulfone **85** upon oxidation with *m*CPBA in chloroform (Scheme 32).

Scheme 32



Reagents and condtions: (a) *m*CPBA, $CHCl_3$, 0 °C, 10 min, 78%.

In conclusion, a methodology for the regio- and stereoselective synthesis of 1,3-aminoalcohols from allylamine derivatives via efficient asymmetric induction and intramolecular nucleophilic participation by the sulfinyl group is disclosed. Highly functionalized products are obtained which can be further elaborated by carbon-carbon and carbon-heteroatom bond formations into bioactive target molecules.

Experimental

Methyl *N*-Boc-serinate, 27.

Acetyl chloride (60 mL) was added dropwise over 10 min to MeOH (400 mL) cooled in ice. The solution was stirred for 5 min then solid (L)-serine **25** (31.0 g, 295 mmol) was added in one portion and the solution slowly heated at reflux. Heating was continued for 2 h, cooling and removal of the solvent by evaporation under reduced pressure gave the crude methyl serinate hydrochloride **26** as a colourless crystalline solid, which was used without further purification. Yield 100%.

Methyl serinate hydrochloride (25 g, 160 mmol) was suspended in THF (500 mL) and Et_3N (35 g, 345 mmol) added. The resulting white suspension was cooled to 0 °C and a solution of $(Boc)_2O$ (35.8 g, 159 mmol) in THF (250 mL) was added dropwise over 30 min. The mixture was allowed to warm to r.t. and stirred for 6 h, and then warmed to 50 °C and stirred further for a period of 2 h. The solvent was removed in vacuo, and the residue partitioned between Et_2O and water. The aqueous phase was extracted with Et_2O and the combined organic phases washed with 3% HCl, 5% $NaHCO_3$ and brine. Evaporation of the solvent afforded **27** as a colourless oil (32.2 g, 22.8 mmol) in 91% yield.

PMR (C_6D_6, 200 MHz) : 5.60 (bs, NH), 4.42-4.37 (m, 1H), 3.83-3.64 (m, 2H), 3.27 (s, 3H), 1.43 (s, 9H).

$[\alpha]^{25}_D$: –18.2 (*c* 5.0, MeOH)

Lit. $[\alpha]^{25}_D$: –18.9 (*c* 5.0, MeOH)

3-(1,1-Dimethylethyl)-4-methyl-(S)-2,2-dimethyloxazolidine-3,4-dicarboxylate, 28.

The ester **27** (30.5 g, 139 mmol) was dissolved in a mixture of acetone (400 mL) and 2,2-DMP (30 mL) to which $BF_3.Et_2O$ (1 mL) was added. The resulting solution was stirred at r.t. for 2 h, after which time TLC showed no unreacted starting material. The solvent was removed in vacuo, the residual oil taken up in DCM and washed with aq. sat. $NaHCO_3$ solution, water, brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure afforded the acetonide **28** (33.1 g, 127.8 mmol) in 92% yield.

Pale yellow oil.

PMR (C_6D_6, 200 MHz) : 4.33-4.21 (m, 1H), 3.83-3.70 (m, 2H), 3.36 (s, 3H), 1.80 (s, 3H), 1.53 (s, 3H), 1.40 (s, 9H).

$[\alpha]^{25}_D$: –55.2 (*c* 1.3, $CHCl_3$)

Lit. $[\alpha]^{25}_D$: –54.0 (*c* 1.3, $CHCl_3$)

***tert*-Butyl 4-hydroxymethyl-2,2-dimethyl-1,3-oxazolane-3-carboxylate, 29.**

To the solution of the acetonide **28** (7.73 g, 30 mmol) in THF (45 mL) under nitrogen, anhydrous LiCl (2.54 g, 60 mmol) and $NaBH_4$ (2.27 g, 60 mmol) were added. After the addition of absolute ethanol (80 mL), the mixture was stirred at room temperature overnight. The reaction mixture was cooled in an ice water bath; adjusted to pH 4 by the gradual addition of 10% citric acid solution, and concentrated in vacuo. Water was added to the residue, which was extracted with DCM and dried over Na_2SO_4. Removal of the solvent gave **29** (6.44 g, 27.9 mmol) in 93% yield, which without further purification was taken to the next step.

PMR ($CDCl_3$, 200 MHz) : 3.73-3.62 (m, 1H), 3.62-3.57 (m, 3H), 3.53-3.48 (m, 1H), 1.57 (s, 3H), 1.45 (s, 3H), 1.39 (s, 9H).

To the solution of $(COCl)_2$ (3.82 g, 30.1 mmol) in DCM (55 mL) cooled at -78 °C was added DMSO (3.92 g, 50.3 mmol) dropwise via syringe. The resulting solution was stirred for 10 min at –78 °C, and then the solution of alcohol **29** (5.8 g, 25.1 mmol) in DCM (55 mL) was added dropwise via syringe. The reaction mixture was stirred for 15 min at –78 °C and then Hunig's base (17.5 mL, 100 mmol) in DCM (5 mL) was added slowly. The cooling bath was removed and the mixture allowed to warm to 0 °C over 30 min. The reaction mixture was transferred into a separating funnel charged with ice-cold 1 N HCl solution. The two phases were separated, the aqueous phase was extracted with DCM and the combined organic layers were washed with phosphate buffer (pH 7), water, brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded the aldehyde **30** (4.48 g, 19.6 mmol) in 78% yield.

Colourless oil.

PMR (C_6D_6, 200 MHz)	: 3.90 (m, 1H), 3.65-3.57 (m, 2H), 1.59 (s, 3H), 1.40 (s, 3H), 1.33 (s, 9H).
$[\alpha]^{25}_D$	: –90.4 (*c* 1.0, $CHCl_3$)
Lit.[19] $[\alpha]^{25}_D$	: –89.0 (*c* 1.0, $CHCl_3$)

tert-Butyl 4-[(Z)-1-hexenyl]-2,2-dimethyl-(4*S*)-1,3-oxazolane-3-carboxylate, 31.

To the suspension of *n*-pentyltriphenylphosphonium bromide (4.45 g, 11 mmol) in dry THF (44 mL) cooled at –78 °C, *n*-BuLi (5 mL, 2M in hexanes, 10 mmol) was added dropwise over 10 min. The mixture was stirred for 30 min gradually allowing the temperature to reach 0 °C and stirred further for a period of 1 h at the same temperature. The dark red solution was cooled to –78 °C and the solution of aldehyde **30** (2.3 g, 10 mmol) in THF (10 mL) was added dropwise over 10 min. The reaction mixture was gradually allowed to attain room temperature over a period of 30 min and stirred for a further period of 4 h at room temperature. Then the reaction mixture was quenched with water and washed successively with aq. 1 N HCl solution, brine and dried over Na_2SO_4. Purification by chromatography on silica gel column using AcOEt/petroleum ether (1:19, v/v) afforded **34** (1.26 g, 6.2 mmol) in 62% yield.

Liquid.

PMR (200 MHz, $CDCl_3$)	: δ 5.52-5.32 (m, 2H), 4.72-4.50 (bs, 1H), 4.02 (dd, *J* = 9.0, 6.7 Hz, 1H), 3.61 (dd, *J* = 9.0, 4.2 Hz, 1H), 2.24-1.98 (m, 2H), 1.56 (s, 3H), 1.54-1.24 (m, 16H), 0.91 (t,

J = 6.7 Hz, 3H).

$[\alpha]^{25}_D$: +55.0 (*c* 0.95, $CHCl_3$)

m/z (EI) : 283 $[M]^+$

IR (neat) cm^{-1} : 2930, 1695, 1375, 1250, 1175, 1090, 1050, 850.

Elemental analysis : Calcd. for $C_{16}H_{29}NO_3$: C, 67.81; H, 10.31; N, 4.94.

Found : C, 67.75; H, 10.13; N, 4.72.

2-(*tert*-Butyloxycarbonylamido)-(2*R*,3*Z*)-3-octen-1-ol, 32.

To the substrate **31** (1.41 g, 5 mmol) in methanol (20 mL) was added camphor-10-sulphonic acid (62.5 mg, 0.25 mmol) at room temperature and stirred for 16 h under N_2 atmosphere. The reaction mixture was quenched by the addition of few drops of Et_3N and the solvent evaporated under reduced pressure. The crude product mixture was chromatographed on a silica gel column using AcOEt/petroleum ether (1:24, v/v) as the eluent to afford the aminoalcohol **32** (874 mg, 3.6 mmol) in 72% yield.

Solid.

mp : 65-66 °C

PMR (200 MHz, $CDCl_3$) : δ 5.57 (dt, *J* = 10.9, 7.4 Hz, 1H), 5.25 (dd, *J* = 10.9, 9.1 Hz, 1H), 4.72-4.53 (bs, NH), 4.52-4.35 (m, 1H), 3.64-3.48 (m, 2H), 2.25-2.05 (m, 2H), 1.45 (s, 9H), 1.45-1.26 (m, 4H), 0.91 (distorted t, 3H).

$[\alpha]^{25}_D$: +29.6 (*c* 1.0, $CHCl_3$)

m/z (EI) : 243 $[M]^+$

IR (neat) cm^{-1} : 3420, 2950, 1701, 1500, 1387, 1258, 1145.

Elemental analysis : Calcd. for $C_{13}H_{25}NO_3$: C, 64.17; H, 10.35; N, 5.76.

Found : C, 64.21; H, 10.28; N, 5.72.

2-(*tert*-Butyloxycarbonylamido)-(Z)-3-octenyl methanesulfonate, 33.

To the solution of **32** (243 mg, 1 mmol) in dichloromethane (2 mL) cooled at 0 °C was added successively Et_3N (131 mg, 1.3 mmol), DMAP (cat.) and methanesulfonyl chloride (115 mg, 1 mmol) and stirred for 10 min. at the same temperature. The reaction mixture was quenched by the addition of water and then extracted into dichloromethane. The organic layer was washed successively with 10% aq. citric acid, aq. $NaHCO_3$, water, brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford **33** (303 mg, 0.95 mmol) in 95% yield which was taken to the next step without further purification.

Viscous liquid.

PMR (200 MHz, $CDCl_3$) : δ 5.63 (dt, *J* = 10.8, 7.4 Hz, 1H), 5.31 (dd, *J* = 10.8, 8.8 Hz, 1H), 4.75-4.54 (m, 1H and NH), 4.23 (dd, *J* = 9.7, 3.7 Hz, 1H), 4.14 (dd, *J* = 9.7, 5.6 Hz, 1H), 2.99 (s, 3H), 2.23-2.02 (m, 2H), 1.54-1.22 (m, 13H), 0.92 (t, *J* = 6.7 Hz, 3H).

1-Phenylsulfanyl-(2*R*,3Z)-3-octen-2-*tert*-butyloxycarbonylamide, 34.

To the solution of **33** (319 mg, 1 mmol) in benzene (2 mL) at room temperature was added successively PhSH (110 mg, 1 mmol) and DBU (228 mg, 1.5 mmol) under N_2 and stirred for 30 min. The reaction mixture was diluted with ether and washed successively with 0.2 N aq. NaOH solution, water, brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure followed by purification on silica gel column using AcOEt/petroleum ether (3:97, v/v) afforded the thioether **34** (305 mg, 0.91 mmol) in 91% yield.

Viscous liquid.

PMR (200 MHz, $CDCl_3$) : δ 7.50-7.12 (m, 5H), 5.51 (dt, *J* = 10.8, 6.7 Hz, 1H), 5.34-5.27 (m, 1H), 4.65-4.45 (m, 1H and NH), 3.18 (dd, *J* = 14.1, 4.7 Hz, 1H), 2.95 (dd, *J* = 14.1, 7.0 Hz, 1H), 2.12-1.96 (m, 2H), 1.43 (s, 9H), 1.36-1.20 (m, 4H), 0.88 (t, *J* = 6.7 Hz, 3H).

$[\alpha]^{25}_D$: –4.0 (*c* 0.75, $CHCl_3$)

m/z (LSIMS) : 336 $[M+H]^+$

IR (neat) cm $^{-1}$: 3312, 2927, 2897, 1698, 1503, 1400, 1245, 1163, 1023.

Elemental analysis : Calcd. for $C_{19}H_{29}NO_2S$: C, 68.02; H, 8.71; N, 4.17; S, 9.56;

Found : C, 67.85; H, 8.43; N, 4.47; S, 9.23.

General procedure for the preparation of sulfoxides from sulfides:

To the solution of the substrate (1 mmol) in methanol (10 mL) was added dropwise a solution of $NaIO_4$ (1 mmol) in water (5 mL) at 0 °C and allowed to attain room temperature during a period of 30 min. After stirring for 16 h, the reaction mixture was filtered and the filtrate was evaporated to remove most of methanol under reduced pressure. The aq. residue was extracted into ethylacetate, dried over Na_2SO_4 and evaporated. The diastereomers were separated by column chromatography using AcOEt/petroleum ether (1:3, v/v) as the eluent. The *anti* isomer eluted initially and then the *syn* isomer.

1-(S_S)-Phenylsulfinyl-(2*R*,3*Z*)-3-octen-2-*tert*-butyloxycarbonylamide, 35*a*.

47%. Solid.

mp : 107-109 °C.

PMR (200 MHz, $CDCl_3$) : δ 7.68-7.58 (m, 2H), 7.56-7.46 (m, 3H), 5.76-5.41 (m, 2H and NH), 4.90-4.70 (m, 1H), 3.17-3.03 (m, 1H), 2.89 (dd, *J* = 13.5, 4.1 Hz, 1H), 2.25-2.01 (m, 2H), 1.60-1.28 (m, 13H), 0.91 (distorted t, 3H).

$[\alpha]^{25}_D$: –168.0 (*c* 1.0, $CHCl_3$)

m/z (LSIMS) : 353 $[M+H]^+$

IR (neat) cm $^{-1}$: 3207, 2972, 2925, 2837, 1703, 1537, 1175, 1044.

Elemental analysis : Calcd. for $C_{19}H_{29}NO_3S$: C, 64.92; H, 8.32; N, 3.98; S, 9.12;

Found : C, 65.13; H, 8.14; N, 3.63; S, 9.34.

1-(*R*$_S$)-Phenylsulfinyl-(2*R*,3*Z*)-3-octen-2-*tert*-butyloxycarbonylamide, 35*s*.

47%. Solid.

mp : 68-69 °C

PMR (200 MHz, $CDCl_3$) : δ 7.76-7.66 (m, 2H), 7.56-7.45 (m, 3H), 5.60-5.36 (m, 2H), 4.95-4.81 (bs, NH), 4.71 (quintet, *J* = 6.9 Hz, 1H), 3.10 (dd, *J* = 13.9, 6.9 Hz, 1H), 2.98-2.85 (m, 1H), 2.11-1.95 (m, 2H), 1.45 (s, 9H), 1.39-1.09 (m, 4H), 0.85 (distorted t, 3H).

$[\alpha]^{25}_D$: +72.4 (*c* 1.0, $CHCl_3$)

m/z (LSIMS) : 353 $[M+H]^+$

IR (neat) cm $^{-1}$: 3243, 2975, 2928, 1700, 1540, 1169.

Elemental analysis : Calcd. for $C_{19}H_{29}NO_3S$: C, 64.92; H, 8.32; N, 3.98; S, 9.12;

Found : C, 64.73; H, 8.47; N, 3.73; S, 9.29.

***tert*-Butyl2,2-dimethyl-4-[2-phenyl-(*E*)-1-ethenyl]-1,3-oxazolane-3-carboxylate, 36.**

Benzyltriphenylphophonium bromide (3.92 g, 11mmol) was suspended in dry THF (44 mL) in a round bottom flask under N_2, cooled at -78 °C and *n*-BuLi (5 mL, 2M in hexanes, 10 mmol) was added dropwise over 10 min. The mixture was stirred for 30 min gradually allowing the temperature to reach 0 °C and stirred further for a period of 1 h at the same temperature. The dark red solution was cooled to -78 °C and the solution of aldehyde **30** (2.3 g, 10 mmol) in THF (10 mL) was added dropwise over 10 min. The reaction mixture was gradually allowed to attain room temperature over a period of 30 min and stirred for a further period of 4 h at room temperature. Then the reaction mixture was quenched with water and washed successively with aq. 1 N HCl solution, brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded the crude product mixture. The PMR of the crude product revealed the presence of *cis* and *trans* olefins in a ratio of 4:1. The product mixture was subjected to isomerisation following the protocol reported by Schwarz et al.[7i] Thus, PhSH (37 mg, 0.33 mmol) and AIBN (54 mg, 0.33 mmol) were added to the olefin mixture (2.0 g, 6.6 mmol) in benzene (25 mL) and refluxed for 16 h. The reaction mixture was diluted with benzene and washed successively with 0.2 N NaOH soln., water, brine and dried over Na_2SO_4. Evaporation of the volatiles under reduced pressure followed by column chromatography using AcOEt/petroleum ether (1:19, v/v) as the eluent afforded **36** (2.0 g, 6.6 mmol) in 66% overall yield for 2 steps.

Liquid.

PMR (200 MHz, $CDCl_3$) : δ 7.35-7.10 (m, 5H), 6.49 (d, *J* = 12.2 Hz, 1H), 5.68 (dd, *J* = 12.2, 9.5 Hz, 1H), 4.91-4.75 (m, 1H), 4.23-4.08 (m, 1H), 3.86-3.72 (m, 1H), 1.62 (s, 3H), 1.49 (s, 3H), 1.42 (s, 9H).

$[\alpha]^{25}_{D}$: –63.6 (*c* 1.0, $CHCl_3$)

m/z (EI) : 304 $[M]^+$

IR (neat) cm^{-1} : 2970, 1700, 1480, 1455, 1380, 1255, 1175, 1100.

Elemental analysis : Calcd. for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62.

Found : C, 70.97; H, 8.13; N, 4.83.

2-(*tert*-Butyloxycarbonylamido)-4-phenyl-(2*R*,3*E*)-3-buten-1-ol, 37.

Following the procedure as detailed for the preparation of **32**, **36** (1.52 g, 5 mmol) on treatment with CSA gave **37** (986 mg, 3.75 mmol) in 75% yield.

Solid.

mp : 95-96 °C

PMR (200 MHz, $CDCl_3$) : δ 7.41-7.17 (m, 5H), 6.60 (d, *J* = 15.8 Hz, 1H), 6.14 (dd, *J* = 15.8, 6.3 Hz, 1H), 4.95-4.82 (bs, NH), 4.47-

4.32 (m, 1H), 3.78 (dd, *J* = 10.2, 4.1 Hz, 1H), 3.73 (dd, *J* = 10.2, 4.9 Hz, 1H), 1.46 (s, 9H).

$[\alpha]^{25}_{D}$: –40.6 (*c* 1.0, $CHCl_3$)

m/z (EI) : 263 $[M]^+$

IR (neat) cm^{-1} : 3400, 3080, 3005, 1700, 1500, 1270, 1170.

Elemental analysis : Calcd. for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32;

Found : C, 68.32; H, 8.17; N, 5.70.

2-(*tert*-Butyloxycarbonylamido)-4-phenyl-(*E*)-3-butenyl methanesulfonate, 38.

Mesylation of **37** (263 mg, 1 mmol) following the procedure detailed for the preparation of **33** yielded **38** (334 mg, 0.98 mmol) in 98% yield.

Liquid.

PMR (200 MHz, $CDCl_3$) : δ 7.38-7.18 (m, 5H), 6.63 (d, *J* = 15.6 Hz, 1H), 6.12 (dd, *J* = 15.6, 6.2 Hz, 1H), 4.92 (d, *J* = 8.6 Hz, NH), 4.60-4.56 (m, 1H), 4.37 (dd, *J* = 9.8, 4.4 Hz, 1H), 4.29 (dd, *J* = 9.8, 5.1 Hz, 1H), 3.02 (s, 3H), 1.47 (s, 9H).

3-Phenyl-1-phenylsulfanylmethyl-(1*R*,2*E*)-2-*tert*-butyloxycarbonylamide, 39.

Following the procedure as detailed for the preparation of **34**, **38** (341 mg, 1 mmol) on treatment with PhSH in the presence of DBU afforded **39** (310 mg, 0.87 mmol) in 87% yield.

Solid.

mp : 64-66 °C

PMR (200 MHz, $CDCl_3$) : δ 7.40-7.10 (m, 4H), 7.33-7.12 (m, 6H), 6.53 (d, *J* = 15.6 Hz, 1H), 6.13 (dd, *J* = 15.6, 5.9 Hz, 1H), 4.90-4.77 (bs, NH), 4.54-4.50 (m, 1H), 3.27 (dd, *J* = 13.4, 5.2 Hz, 1H), 3.12 (dd, *J* = 13.4, 5.9 Hz, 1H), 1.46 (s, 9H).

$[\alpha]^{25}_{D}$: +14.2 (*c* 1.1, $CHCl_3$)

m/z (LSIMS) : 356 $[M+H]^+$

IR (neat) cm $^{-1}$: 3375, 2928, 1696, 1500, 1366, 1247, 1167, 1022, 745.

Elemental analysis : Calcd. for $C_{21}H_{25}NO_2S$: C, 70.95; H, 7.09; N, 3.94; S, 9.02;

Found : C, 70.67; H, 7.19; N, 3.73; S, 9.27.

4-Phenyl-1-(S_S)-phenylsulfinyl-(2*R*,3*E*)-3-buten-2-*tert*-butyloxycarbonylamide, 40*a*:

46%. Solid.

mp : 147-148 °C

PMR (200 MHz, $CDCl_3$) : δ 7.68-7.59 (m, 2H), 7.56-7.46 (m, 3H), 7.41-7.10 (m, 5H), 6.65 (d, *J* = 16.3 Hz, 1H), 6.37 (dd, *J* = 16.3, 5.9 Hz, 1H), 5.90-5.76 (bs, NH), 4.74 (quintet, *J* = 5.9 Hz, 1H), 3.22-3.02 (m, 2H), 1.48 (s, 9H).

$[\alpha]^{25}_D$: –167.0 (*c* 1.04, $CHCl_3$)

m/z (LSIMS) : 372 $[M+H]^+$

IR (neat) cm $^{-1}$: 3290, 2978, 2925, 1709, 1525, 1147, 1040.

Elemental analysis : Calcd. for $C_{21}H_{25}NO_3S$: C, 67.90; H, 6.78; N, 3.77; S, 8.63;

Found : C, 67.45; H, 7.04; N, 3.77; S, 8.53.

4-Phenyl-1-(R_S)-phenylsulfinyl-(2*R*,3*E*)-3-buten-2-*tert*-butyloxycarbonylamide, 40s.

46%. Solid.

mp : 133-134 °C

PMR (200 MHz, $CDCl_3$) : δ 7.72-7.61 (m, 2H), 7.58-7.46 (m, 3H), 7.36-7.15 (m, 5H), 6.55 (d, *J* = 15.2 Hz, 1H), 6.19 (dd, *J* = 15.2, 7.0 Hz, 1H), 5.18-5.04 (bs, NH), 4.63 (quintet, *J* = 7.0 Hz, 1H), 3.16 (d, *J* = 7.0 Hz, 2H), 1.46 (s, 9H).

$[\alpha]^{25}_D$: +13.5 (*c* 0.70, $CHCl_3$)

m/z (LSIMS) : 372 $[M+H]^+$

IR (neat) cm^{-1} : 3284, 2968, 1710, 1523, 1157, 1037.

Elemental analysis : Calcd. for $C_{21}H_{25}NO_3S$: C, 67.90; H, 6.78; N, 3.77; S, 8.63;

Found : C, 67.73; H, 6.64; N, 3.84 S, 8.67.

tert-Butyl 4-[2-ethyloxycarbonyl-(_E_)-1-ethenyl]-2,2-dimethyl-1,3-oxazolane-3-carboxylate, 41.

Ethyl(triphenylphosporanilidine)acetate (8.3 g, 20 mmol) was added portionwise to the solution of aldehyde **30** (4.6 g, 20 mmol) in benzene (60 mL) at room temperature and stirred for 30 min. After evaporation of the solvent under reduced pressure, ether was added to the residue and cooled to 0 °C. Most of the triphenylphosphine oxide formed in the reaction precipitated out and was removed by filtration. The filtrate was concentrated and the residue purified by column chromatography using AcOEt/petroleum ether (1:9, v/v) as the eluent to afford the *trans* unsaturated ester **41** (5.68 g, 19 mmol) in 95% yield.

Liquid.

PMR (200 MHz, $CDCl_3$) : δ 6.83 (dd, *J* = 15.8, 8.7 Hz, 1H), 5.87 (d, *J* = 15.8 Hz, 1H), 4.59-4.34 (m, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 4.12-3.98 (m, 1H), 3.73-3.68 (m, 1H), 1.68-1.39 (m, 15H), 1.25 (t, *J* = 7.0 Hz, 3H).

$[\alpha]^{25}_D$: –63.6 (*c* 1.0, $CHCl_3$)

m/z (LSIMS) : 300 $[M+H]^+$

IR (neat) cm^{-1} : 2928, 1742, 1698, 1390, 1256, 1176.

tert-Butyl-4-[3-hydroxy-(_E_)-1-propenyl]-2,2-dimethyl-1,3-oxazolane-3-carboxylate, 42.

In a dry round bottom flask containing dry toluene (32 mL), diisobutylaluminum hydride (47.5 mmol, 47.5 mL, 1M soln. in toluene) was added followed by *n*-BuLi (47.5 mmol, 23.75 mL, 2M in hexanes) dropwise over a period of 10 min at ambient temperature. The mixture was stirred further for a period of 30 min. The above prepared ate complex was added to the solution of the unsaturated ester **41** (5.68 g, 19 mmol) in toluene (38 mL) cooled at -78 °C, over a period of 10 min. The reaction mixture was stirred for 40 min gradually allowing it to attain r.t. and stirred further for a period of 30 min. The reaction mixture was diluted with ether (100 mL) and small ice pieces were added to quench the reaction. The gel that precipitated out was filtered through a sintered funnel and the gel washed with hot ethyl acetate. Evaporation of the filtrate under reduced pressure and column chromatography of the residue using AcOEt/petroleum ether (3:7, v/v) afforded the allylalcohol **42** (3.55 g, 13.87 mmol) in 73% yield.

Liquid.

PMR (200 MHz, $CDCl_3$)	: δ 5.78-5.60 (m, 2H), 4.40-4.23 (m, 1H), 4.16-4.07 (m, 2H), 4.02-3.72 (m, 2H), 3.90 (bs, OH),1.61-1.42 (m, 15H).
$[\alpha]^{25}_D$	: +23.6 (*c* 0.75, $CHCl_3$)
m/z (EI)	: 258 $[M+H]^+$
IR (neat) cm^{-1}	: 3445, 2980, 1696, 1392, 1255, 1170.

tert-Butyl-4-[3-(_tert_-butylcarbonyloxy)-(_E_)-1-propenyl]-2,2-dimethyl-1,3-oxazolane-3-carboxylate, 43.

To the stirred solution of allylalcohol **42** (3.55 g, 13.9 mmol) in dry dichloromethane (56 mL) was added successively Et_3N (2.10 g, 20.8 mmol) and pivaloyl chloride (1.81 g, 15 mmol) at 0 °C. The reaction mixture was gradually allowed to attain r.t. and stirred further for a period of 25 min. The reaction mixture was diluted with DCM, washed successively with water, 10% aq. citric acid soln., brine, dried over Na_2SO_4. The organic layer was evaporated under reduced pressure, and the crude residue was purified by column chromatography using AcOEt/petroleum ether (1:9, v/v) as the eluent to afford the ester **43** (3.91 g, 11.51 mmol) in 83% yield. (58% overall yield from Garner aldehyde).

Liquid.

PMR (200 MHz, $CDCl_3$) : δ 5.74-5.53 (m, 2H), 4.60-4.47 (m, 2H), 4.30-4.16 (m, 1H), 4.02 (dd, *J* = 8.9, 6.7 Hz, 1H), 3.72 (dd, *J* = 8.9, 2.2 Hz, 1H), 1.59 (s, 3H), 1.51-1.31 (bs, 12H), 1.17 (s, 9H).

$[\alpha]^{25}_D$: +1.6 (*c* 1.0, $CHCl_3$)

m/z (LSIMS) : 342 $[M+H]^+$

IR (neat) cm^{-1} : 3378, 2977, 2877, 1699, 1479, 1383, 1254, 1159, 1097.

Elemental analysis : Calcd. for $C_{18}H_{31}NO_5$: C, 63.32; H, 9.15; N, 4.10.

Found : C, 63.49; H, 9.42; N, 3.87.

4-(*tert*-Butyloxycarbonylamido)-5-hydroxy-(*E*,4*R*)-2-pentenyl pivalate, 44.

Acetonide deprotection with CSA as detailed earlier afforded **44** (1.05 g, 3.50 mmol) from **43** (1.70 g, 5 mmol) in 70% yield.

Liquid.

PMR (200 MHz, $CDCl_3$) : δ 5.82-5.60 (m, 2H), 4.78 (d, *J* = 6.0 Hz, NH), 4.57 (d, *J* = 4.0 Hz, 2H), 4.26-4.22 (m, 1H), 3.72-3.53 (m, 2H), 1.47 (s, 9H), 1.22 (s, 9H).

$[\alpha]^{25}_D$: +3.6 (*c* 1.0, $CHCl_3$)

m/z (LSIMS) : 302 $[M+H]^+$

IR (neat) cm^{-1} : 3369, 2975, 1712, 1699, 1518, 1367, 1284, 1163, 1059.

Elemental analysis : Calcd. for $C_{16}H_{29}NO_3$: C, 59.78; H, 9.03; N, 4.65;

Found : C, 59.66; H, 9.14; N, 4.77.

4-(*tert*-Butyloxycarbonylamido)-5-phenylsulfanyl-(*E*,4*R*)-2-pentenyl pivalate, 45.

A hard glass tube containing the alcohol **44** (2.41 g, 8 mmol), PhSSPh (5.2 g, 24 mmol) and PBu_3 (6.46 g, 32 mmol) in dry THF (32 mL) was sealed at the top at -78° C and after attaining room temperature, heated at 72 °C for 36 h. The reaction mixture was diluted with ethylacetate and washed sequentially with 0.2 N NaOH solution, water, brine and dried over anhydrous Na_2SO_4. After evaporating the solvent on a rotary evaporator the crude product mixture was chromatographed on a silica gel column using AcOEt/petroleum ether (1:9, v/v) as the eluent to afford **45** (1.98 g, 5.04 mmol) in 63% yield.

Low melting solid.

PMR (200 MHz, $CDCl_3$) : δ 7.42-7.15 (m, 5H), 5.79-5.77 (m, 2H), 4.75-4.65 (m, 1H), 4.52 (s, 2H), 4.43-4.32 (m, 1H), 3.12 (dd, *J* = 14.1, 5.8 Hz, 1H), 2.98 (dd, *J* = 14.1, 5.8 Hz, 1H), 1.39 (s, 9H), 1.15 (s, 9H).

$[\alpha]^{25}_D$: +7.8 (*c* 1.0, $CHCl_3$)

m/z (LSIMS) : 394 $[M+H]^+$

IR (neat) cm^{-1} : 3403, 2953, 1714, 1698, 1510, 1365, 1267, 1159, 1039.

Elemental analysis : Calcd. for $C_{21}H_{31}NO_4S$: C, 64.09; H, 7.94; N, 3.56; S, 8.15;

Found : C, 64.35; H, 7.63; N, 3.76; S, 8.53.

4-(*tert*-butyloxycarboxamido)-5-(*S*s)-phenylsulfinyl-(*E*,4*R*)-2-pentenyl pivalate, 46*a*.

45%. Liquid.

PMR (200 MHz, DMSO-d_6): δ 7.68-7.50 (m, 5H), 7.30 (d, *J* = 8.4 Hz, NH), 5.76-5.62 (m, 2H), 4.57-4.32 (m, 3H), 3.0-2.80 (m, 2H), 1.40 (s, 9H), 1.12 (s, 9H).

$[\alpha]^{25}_D$: −93.0 (c 0.75, $CHCl_3$)

m/z (LSIMS) : 410 $[M+H]^+$

IR (neat) cm^{-1} : 3312, 2968, 1725, 1699, 1517, 1360, 1157, 1037.

Elemental analysis : Calcd. for $C_{21}H_{31}NO_5S$: C, 61.59; H, 7.63; N, 3.42; S, 7.83;

Found : C, 61.23; H, 7.54; N, 3.57; S, 7.87.

4-(*tert*-Butyloxycarboxamido)-5-(*R*s)-phenylsulfinyl-(*E*,4*R*)-2-pentenyl pivalate,

46*s*.

45%. Liquid.

PMR (200 MHz, $CDCl_3$) : δ 7.73-7.46 (m, 5H), 5.92-5.75 (m, 2H), 5.10-4.95 (bs, NH), 4.65-4.41 (m, 3H), 3.12-2.96 (m, 2H), 1.46 (s, 9H), 1.22 (s, 9H).

$[\alpha]^{25}_D$: +66.1 (c 0.66, $CHCl_3$)

m/z (LSIMS) : 410 $[M+H]^+$

IR (neat) cm^{-1} : 3310, 2970, 1728, 1695, 1510, 1457, 1245, 1159, 1040.

Elemental analysis : Calcd. for $C_{21}H_{31}NO_5S$: C, 61.59; H, 7.63; N, 3.42; S, 7.83;

Found : C, 61.42; H, 7.64; N, 3.33; S, 7.93.

General procedure for the preparation of the silyl ether from the pivaloyl esters:

To the solution of the pivalate ester **46*a*** (820 mg, 2 mmol) in methanol (15 mL) cooled at 0 °C was added dropwise the solution of 0.2 N aq. NaOH (15 mL). The reaction mixture was allowed to attain r.t gradually and stirred for 4 h. The solvent was removed under reduced pressure and the product alcohol was extracted into ethylacetate. The organic layer was washed with water, brine and dried over Na_2SO_4. Evaporation of the solvent followed by column chromatography using AcOEt/petroleum ether (2:3, v/v) as the eluent afforded the alcohol (722 mg, 1.9 mmol) in 95% yield.

To the solution of the above alcohol (570 mg, 1.5 mmol) in dichloromethane (6 mL) was added imidazole (204 mg, 3 mmol) followed by TBDPS-Cl (453 mg, 1.65 mmol) and stirred at r.t. for 1 h. Dichloromethane (10 mL) was added to the reaction mixture and the organic layer washed with water, brine and dried over Na_2SO_4. Column chromatography using AcOEt/petroleum ether (1:4, v/v) as the eluent afforded the **47*a*** (857 mg, 1.52 mmol) in 80% yield. (76% overall yield for 2 steps).

Following a similar procedure detailed for the conversion of **46*a*** into **47*a***, **46*s*** yielded **47*s*** in 75% overall yield for 2 steps.

1*N*-[4-*tert*-Butyldiphenylsilyloxy-1-(*S*s)-phenylsulfinylmethyl-(1*R*,2*E*)-2-butenyl]-carbamic acid *tert*-butylester, 47*a*.

76%. Viscous liquid.

PMR (200 MHz, $CDCl_3$) : δ 7.71-7.45 (m, 9H), 7.40-7.28 (m, 6H), 5.98-5.62 (m, 2H and NH), 4.65-4.55 (m, 1H), 4.24 (s, 2H), 3.08-2.84 (m, 2H), 1.45 (s, 9H), 1.05 (s, 9H).

$[\alpha]^{25}_D$: −36.6 (*c* 0.61, $CHCl_3$)

m/z (LSIMS) : 564 $[M+H]^+$

IR (neat) cm^{-1} : 3323, 2922, 1699, 1519, 1168, 1020.

Elemental analysis : Calcd. for $C_{32}H_{41}NO_4SSi$: C, 68.17; H, 7.33; N, 2.48; S, 5.69;

Found : C, 68.13; H, 7.14; N, 2.53; S, 5.84.

1*N*-[4-*tert*-Butyldiphenylsilyloxy-1-(*R*s)-phenylsulfinylmethyl-(1*R*,2*E*)-2-butenyl]-carbamic acid *tert*-butylester, 47*s*.

75%. Solid.

mp : 101-103 °C

PMR (200 MHz, $CDCl_3$) : δ 7.72-7.52 (m, 6H), 7.51-7.27 (m, 9H), 5.76-5.58 (m, 2H), 4.96 (d, *J* = 6.7 Hz, NH), 4.52-4.36 (m, 1H), 4.17 (s, 2H), 3.10-2.90 (m, 2H), 1.42 (s, 9H), 1.03 (s, 9H).

$[\alpha]^{25}_D$: +38.3 (*c* 0.61, CHCl$_3$)

m/z LSIMS : 564 [M+H]$^+$

IR (neat) cm^{-1} : 3389, 2925, 2854, 1712, 1465, 1111, 703.

Elemental analysis : Calcd. for C$_{32}$H$_{41}$NO$_4$SSi: C, 68.17; H, 7.33; N, 2.48; S, 5.69;

Found : C, 68.56; H, 7.45; N, 2.49; S, 5.60.

Preparation of the methyl carbamates from the *tert*-butylcarbamates.

To a stirred solution of sulfoxide **35** (0.5 mmol) in dichloromethane (0.5 mL) was added dropwise a solution of trifluoroacetic acid/dichloromethane (1:1, 0.5 mL) at 0 °C and stirred for 30 min. The solvent was evaporated under reduced pressure, dried under vacuum and without further purification the ammonium salt was taken into dichloromethane (2 mL) and treated with triethylamine (101 mg, 1 mmol) followed by methylchloroformate (47 mg, 0.5 mmol) at 0 °C. After stirring for 1 h at room temperature, the reaction mixture was diluted with dichloromethane and washed successively with aq. citric acid, water, brine and dried over Na$_2$SO$_4$. Evaporation of the solvent under reduced pressure followed by purification on a silica gel column using AcOEt/petroleum ether (9:11, v/v) afforded **48.**

1-(S$_S$)-Phenylsulfinyl-(2*R*,3Z)-3-octen-2-methoxycarbonylamide, 48*a*.

43%. Solid.

mp : 115-117 °C

PMR (200 MHz, CDCl$_3$) : δ 7.65-7.58 (m, 2H), 7.54-7.45 (m, 3H), 5.93 (d, *J* = 7.5 Hz, NH), 5.75-5.45 (m, 2H), 4.90-4.74 (m, 1H), 3.67 (s, 3H), 3.20-3.03 (m, 1H), 2.88 (dd, *J* = 12.9, 2.8 Hz, 1H), 2.21-2.00 (m, 2H), 1.42-1.25 (m, 4H), 0.92 (t, *J* = 6.7 Hz, 3H).

$[\alpha]^{25}_{D}$: –276.4 (*c* 1.16, $CHCl_3$)

m/z (LSIMS) : 310 $[M+H]^+$

IR (neat) cm^{-1} : 3262, 2963, 2921, 1726, 1698, 1527, 1252, 1035.

Elemental analysis : Calcd. for $C_{16}H_{23}NO_3S$: C, 62.11; H, 7.49; N, 4.53; S, 10.36.

Found : C, 61.98; H, 7.13; N, 4.43; S, 10.09.

1-(R_S)-Phenylsulfinyl-(2*R*,3*Z*)-3-octen-2-methoxycarbonylamide, 48*s*.

43%. Solid.

mp : 143-146 °C

PMR (200 MHz, $CDCl_3$) : δ 7.72-7.65 (m, 2H), 7.60-7.44 (m, 3H), 5.60-5.39 (m, 2H), 5.26 (d, *J* = 7.1 Hz, NH), 4.75 (quintet, *J* = 7.1 Hz, 1H), 3.64 (s, 3H), 3.12 (dd, *J* = 13.0, 7.1 Hz, 1H), 2.91 (dd, *J* = 13.0, 5.7 Hz, 1H), 2.12-1.91 (m, 2H), 1.41-1.17 (m, 4H), 0.88 (distorted t, 3H).

$[\alpha]^{25}_{D}$: +89.4 (*c* 0.70, $CHCl_3$)

m/z (LSIMS) : 310 $[M+H]^+$

IR (neat) cm^{-1} : 3310, 2970, 2923, 1716, 1520, 1040, 750, 683.

Elemental analysis : Calcd. for $C_{16}H_{23}NO_3S$: C, 62.11; H, 7.49; N, 4.53; S, 10.36;

Found : C, 62.58; H, 7.33; N, 4.59; S, 10.77.

Preparation of the sulfonamides from the *tert*-butylcarbamates.

To a stirred solution of sulfoxide (0.5 mmol) in dichloromethane (0.5 mL) was added dropwise a solution of trifluoroaceticacid/dichloromethane (1:1, 0.5 mL) at 0 °C and stirred for 30 min. The solvent was evaporated under reduced pressure, dried under vacuum and without further purification the ammonium salt was taken into dichloromethane (2 mL) and treated with triethylamine (101 mg, 1 mmol) followed by arylsulfonyl chloride (0.5 mmol) at 0 °C. After stirring for 1 h at room temperature, the reaction mixture was diluted with dichloromethane and washed successively with aq. citric acid, water, brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure followed by purification on a silica gel column using AcOEt/petroleum ether (9:11, v/v) afforded the sulfonamide derivative.

1*N*-[1-Phenylsulfinylmethyl-(*S*S)-(1*R*,2*E*)-2-heptenyl]-4-methyl-1-benzenesulfonamide 71*a*.

82%. Solid.

mp : 112-114 °C

PMR (200 MHz, $CDCl_3$) : δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.55-7.40 (m, 5H), 7.28 (d, *J* = 8.2 Hz, 2H), 6.31 (d, *J* = 5.9 Hz, NH), 5.45-5.30 (m, 2H), 4.49-4.40 (m, 1H), 3.03 (dd, *J* = 13.4, 7.5 Hz, 1H), 2.69 (dd, *J* = 13.4, 3.0 Hz, 1H), 2.44 (s, 3H), 1.81-1.69 (m, 2H), 1.23-1.10 (m, 4H), 0.86 (distorted t, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 21.4, 22.2, 27.0, 31.1, 48.2, 60.4, 123.9, 127.1, 127.4, 129.2, 129.4, 131.2, 133.5, 137.6, 142.6, 143.2.

$[\alpha]_D^{25}$: –118.8 (*c* 1.0, $CHCl_3$)

m/z (LSIMS) : 406 $[M+H]^+$

IR (neat) cm $^{-1}$: 3342, 2928, 2855, 1330, 1159.

Elemental analysis : Calcd. for $C_{21}H_{27}NO_3S_2$: C, 62.19; H, 6.71; N, 3.45; S, 15.81;

Found : C, 61.86; H, 6.97; N, 3.71; S, 16.10.

1*N*-[1-Phenylsulfinylmethyl-(*R*s)-(1*R*,2*E*)-2-heptenyl]-4-methyl-1-benzenesulfonamide, 71*s*.

84%. Solid.

mp : 114-116 °C

PMR (200 MHz, $CDCl_3$) : δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.70-7.45 (m, 5H), 7.28 (d, *J* = 8.2 Hz, 2H), 5.49-5.23 (m, 2H), 4.46-4.33 (m, 1H), 3.13 (dd, *J* = 13.4, 6.7 Hz, 1H), 2.75 (dd, *J* = 13.4, 6.7 Hz, 1H), 2.42 (s, 3H), 1.80-1.60 (m, 2H), 1.28-1.08 (m, 4H), 0.91 (distorted t, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 21.4, 22.2, 27.1, 31.1, 48.0, 62.9, 124.0, 126.4, 127.4, 129.3, 129.5, 131.2, 134.7, 143.4, 143.7.

$[\alpha]_D^{25}$: +168.7 (*c* 1.0, $CHCl_3$)

m/z (LSIMS) : 406 $[M+H]^+$

IR (neat) cm $^{-1}$: 3258, 2924, 2847, 1455, 1327, 1160.

Elemental analysis : Calcd. for $C_{21}H_{27}NO_3S_2$: C, 62.19; H, 6.71; N, 3.45; S, 15.81;

Found : C, 62.56; H, 6.38; N, 3.01; S, 16.13.

1*N*-[3-Phenyl-1-(*S*s)-phenylsulfinylmethyl-(1*R*,2*E*)-2-propenyl]-4-methyl-1-benzenesulfonamide, 72*a*.

80%. Solid.

mp : 177-178 °C

PMR (200 MHz, $CDCl_3$) : δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.62-7.43 (m, 5H), 7.38-7.11 (m, 7H), 6.45-6.40 (m, 1H and NH), 6.04 (dd, *J* = 16.3, 7.4 Hz, 1H), 4.56-4.48 (m, 1H), 2.98-2.92 (d, *J* = 5.2 Hz, 2H), 2.34 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 20.8, 51.4, 62.2, 123.4, 125.9, 127.4, 127.8, 128.9, 130.6, 131.8, 135. 3, 142.5, 143.1.

$[\alpha]_D^{25}$: –115.9 (*c* 0.5, $CHCl_3$)

m/z (LSIMS) : 426 $[M+H]^+$

IR (neat) cm $^{-1}$: 3112, 2929, 1452, 1328, 1157.

Elemental analysis : Calcd. for $C_{23}H_{23}NO_3S_2$: C, 64.92; H, 5.45; N, 3.29; S, 15.07.

Found : C, 64.67; H, 5.66; N, 3.14; S, 14.90.

1*N*-[3-Phenyl-1-(*R*s)phenylsulfinylmethyl-(1*R*,2*E*)-2-propenyl]-4-methyl-1-benzenesulfonamide, 72*s*.

87%. Solid.

mp : 152-153 °C

PMR (200 MHz, $CDCl_3$) : δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.62-7.46 (m, 5H), 7.30-7.08 (m, 7H), 6.35 (d, *J* = 16.3 Hz, 1H), 5.90 (dd, *J* = 16.3, 9.2 Hz, 1H), 4.44-4.32 (m, 1H), 3.16 (dd, *J* = 13.4, 7.4 Hz, 1H), 2.92 (dd, *J* = 13.4, 5.9 Hz, 1H), 2.35 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 21.3, 53.2, 62.3, 124.1, 125.8, 127.4, 129.4, 129.5, 131.4, 133.2, 137.5, 143.2, 143.4.

$[\alpha]_D^{25}$: +9.2 (*c* 0.7, $CHCl_3$)

m/z (LSIMS) : 426 $[M+H]^+$

IR (neat) cm $^{-1}$: 3062, 2927, 1445, 1331, 1159.

Elemental analysis : Calcd. for $C_{23}H_{23}NO_3S_2$: C, 64.92; H, 5.45; N, 3.29; S, 15.07.

Found : C, 65.07; H, 5.26; N, 3.55; S, 15.20.

1*N*-[3-Phenyl-1-(*R*s)phenylsulfinylmethyl-(1*R*,2*E*)-propenyl]-4-nitro-1-benzenesulfonamide, 49*s*.

88%. Solid.

mp : 164-165 °C

PMR (200 MHz, DMSO-d_6): δ 8.05 (d, *J* = 9.1 Hz, 2H), 7.89 (d, *J* = 9.1 Hz, 2H), 7.62-7.38 (m, 5H), 7.18-6.90 (m, 5H), 6.12 (d, *J* = 15.6 Hz, 1H), 5.64 (dd, *J* = 15.6, 8.2 Hz, 1H), 4.48-4.26 (bs, NH), 4.23-4.18 (m, 1H), 3.06 (dd, *J* = 12.6, 6.7 Hz, 1H), 2.83 (dd, *J* = 12.6, 7.4 Hz, 1H).

m/z (LSIMS) : 457 $[M+H]^+$

IR (neat) cm $^{-1}$: 3421, 2927, 1587, 1520, 1327, 1160.

Elemental analysis : Calcd. for $C_{22}H_{20}N_2O_5S_2$: C, 57.88; H, 4.42; N, 6.14; S, 14.05.

Found : C, 57.92; H, 4.57; N, 6.14; S, 14.12.

4-(4-Methylphenylsulfonamido)-5-(S_S)-phenylsulfinyl-(*E*,4*R*)-2-pentenyl pivalate, 73*a*.

79%. Viscous liquid.

PMR (200 MHz, $CDCl_3$) : δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.55-7.44 (m, 5H), 7.26 (d, *J* = 8.2 Hz, 2H), 6.50 (d, *J* = 8.2 Hz, NH), 5.72-5.65 (m, 2H), 4.43-4.38 (m, 3H), 2.94-2.74 (m, 2H), 2.43 (s, 3H), 1.18 (s, 9H).

$[\alpha]_D^{25}$: –90.1 (*c* 0.75, $CHCl_3$)

m/z (LSIMS) : 464 $[M+H]^+$

IR (neat) cm $^{-1}$: 3325, 1732, 1332, 1159.

Elemental analysis : Calcd. for $C_{23}H_{29}NO_5S_2$: C, 59.59; H, 6.30; N, 3.02; S, 13.83.

Found : C, 59.69; H, 5.92; N, 3.27; S, 14.22.

4-(4-Methylphenylsulfonamido)-5-(S_R)-phenylsulfinyl-(*E*,4*R*)-2-pentenyl pivalate, 73*s*.

81%. Viscous liquid.

PMR (200 MHz, $CDCl_3$) : δ 7.73 (d, *J* = 8.2 Hz, 2H), 7.62-7.46 (m, 5H), 7.28 (d, *J* = 8.2 Hz, 2H), 6.03 (d, *J* = 5.9 Hz, NH), 5.62-5.58 (m, 2H), 4.38 (d, *J* = 3.7 Hz, 2H), 4.23-4.20 (m, 1H), 3.03 (dd, *J* = 13.4, 7.4 Hz, 1H), 2.83 (dd, *J* = 13.4, 5.9 Hz, 1H), 2.44 (s, 3H), 1.17 (s, 9H).

$[\alpha]_D^{25}$: +92.3 (*c* 0.25, $CHCl_3$)

m/z (LSIMS) : 464 $[M+H]^+$

IR (neat) cm $^{-1}$: 3250, 1725, 1337, 1161.

Elemental analysis : Calcd. for $C_{23}H_{29}NO_5S_2$: C, 59.59; H, 6.30; N, 3.02; S, 13.83.

Found : C, 59.93; H, 6.08; N, 3.40; S, 13.62.

1*N*-[4-Hydroxy-1-(S_S)-phenylsulfinylmethyl-(1*R*,2*E*)-2-butenyl]-4-methyl-1-benzenesulfonamide, 74*a*.

73%. Solid.

mp : 143-145 °C

PMR (200 MHz, $CDCl_3$) : δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.50-7.44 (m, 5H), 7.28 (d, *J* = 8.2 Hz, 2H), 6.30 (d, *J* = 8.9 Hz, NH), 5.86-5.64 (m, 2H), 4.31-4.29 (m, 1H), 4.08-3.96 (m, 2H), 2.92-2.78 (m, 2H), 2.43 (s, 3H).

$[\alpha]_D^{25}$: –119.8 (*c* 0.25, $CHCl_3$)

m/z (LSIMS) : 380 $[M+H]^+$

IR (neat) cm $^{-1}$: 3270, 1537, 1458, 1328, 1158.

Elemental analysis : Calcd. for $C_{18}H_{21}NO_4S_2$: C, 56.97; H, 5.58; N, 3.69; S, 16.90.

Found : C, 56.69; H, 5.52; N, 3.97; S, 16.85.

1*N*-[4-Hydroxy-1-(S_S)-phenylsulfinylmethyl-(1*R*,2*E*)-2-butenyl]-4-methyl-1-benzenesulfonamide, 74*s*.

75%. Low melting solid.

PMR (200 MHz, $CDCl_3$) : δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.60-7.40 (m, 5H), 7.25 (d, *J* = 8.2 Hz, 2H), 6.66 (d, *J* = 6.7 Hz, NH), 5.75-5.55 (m, 2H), 4.17-4.13 (m, 1H), 3.94-3.91 (m, 2H), 3.06 (dd, *J* = 13.4, 6.7 Hz, 1H), 2.92 (dd, *J* = 13.4, 7.4, 1H), 2.38 (s, 3H).

$[\alpha]_D^{25}$: +112.6 (*c* 1.0, $CHCl_3$)

m/z (LSIMS) : 380 $[M+H]^+$

IR (neat) cm $^{-1}$: 3145, 2926, 1460, 1330, 1159.

Elemental analysis : Calcd. for $C_{18}H_{21}NO_4S_2$: C, 56.97; H, 5.58; N, 3.69; S, 16.90.

Found : C, 57.11; H, 5.72; N, 3.47; S, 16.99.

1*N*-[4-*tert*-Butyldiphenylsilyoxy)-1-(*S*s)-phenylsulfinylmethyl-(1*R*,2*E*)-2-butenyl]-4-methyl-1-benzenesulfonamide, 75*a*.

83%. Solid.

mp : 115-116 °C

PMR (200 MHz, $CDCl_3$) : δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.62-7.54 (m, 4H), 7.48-7.45 (m, 5H), 7.38-7.28 (m, 6H), 7.18 (d, *J* = 8.2 Hz, 2H), 5.80-5.56 (m, 2H), 4.41-4.26 (m, 1H), 4.06 (bs, 2H), 2.76 (d, *J* = 5.2 Hz, 2H), 2.33 (s, 3H), 1.02 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 19.0, 21.2, 26.6, 51.6, 61.8, 63.0, 123.8, 126.1, 127.1, 127.5, 129.2, 129. 3, 129.5, 131.0, 132.4, 133.2, 135.2, 137.9, 142.9.

$[\alpha]_D^{25}$: –75.8 (*c* 0.3, $CHCl_3$)

m/z (LSIMS) : 618 $[M+H]^+$

IR (neat) cm $^{-1}$: 3421, 2927, 1168, 1043.

Elemental analysis : Calcd. for $C_{34}H_{39}NO_4S_2Si$: C, 66.09; H, 6.36; N, 2.27; S, 10.38.

Found : C, 66.29; H, 5.94; N, 2.63; S, 10.62.

1*N*-[4-*tert*-Butyldiphenylsilyoxy-1-(*R*s)-phenylsulfinylmethyl-(1*R*,2*E*)-2-butenyl]-4-methyl-1-benzenesulfonamide, 75*s*.

81%. Low melting solid.

PMR (200 MHz, $CDCl_3$) : δ 7.69 (d, *J* = 8.2 Hz, 2H), 7.60-7.44 (m, 9H), 7.35-7.24 (m, 6H), 7.20 (d, *J* = 8.2 Hz, 2H), 5.58-5.52 (m, 2H), 4.20-4.07 (m, 1H), 4.03 (s, 2H), 2.98 (dd, *J* = 13.4, 7.4 Hz, 1H), 2.70 (dd, *J* = 13.4, 5.9 Hz, 1H), 2.35 (s, 3H), 0.98 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 19.1, 21.4, 26.7, 52.4, 62.4, 63.1, 124.0, 126.3, 127.3, 127.6, 129.3, 129.5, 129.6, 131.3, 133.1, 135.3, 137.3, 143.3.

$[\alpha]_D^{25}$: +64.5 (*c* 0.55, $CHCl_3$)

m/z (LSIMS) : 618 $[M+H]^+$

IR (neat) cm $^{-1}$: 3489, 2925, 2853, 1367, 1157, 1029.

Elemental analysis : Calcd. for $C_{34}H_{39}NO_4S_2Si$: C, 66.09; H, 6.36; N, 2.27; S, 10.38.

Found : C, 65.78; H, 6.77; N, 2.23; S, 10.72.

General procedure for the reaction of the sulfoxides with NBS.

To the solution of the sulfoxide (0.5 mmol) in toluene (2.5 mL) were added water (18 μL, 1 mmol) followed by freshly recrystallized *N*-bromosuccinimide (0.107 g, 0.6 mmol) and stirred at r.t. under nitrogen atmosphere. The progress of the reaction was monitored by TLC. When no starting material could be detected (30 min-6h), the reaction mixture was taken into ethyl acetate (10 mL) and washed with aqueous saturated sodium bicarbonate (10 mL), water (2 x 10 mL) and brine (10 mL). The organic layer was dried over sodium sulfate and evaporated under vacuum to afford the crude product mixture. Purification of the crude product by column chromatography on silica gel using AcOEt/petroleum ether as eluent afforded products in 70-85% combined yield.

Products from 35*a*.

2-(*tert*-Butyloxycarbonylamido)-3-bromo-1-(R_S)-phenylsulfinyl-(2*S*,3*S*,4*S*)-octan-4-ol, 50*s*.

40%. Viscous liquid.

PMR (200 MHz, $CDCl_3$) : δ 7.64-7.54 (m, 2H), 7.50-7.40 (m, 3H), 5.38 (d, *J* = 6.9 Hz, NH), 4.13-3.89 (m, 2H), 3.75-3.63 (m, 1H), 3.40-3.10 (m, 2H), 1.51-1.10 (m, 15H), 0.82 (t, *J* = 6.8 Hz, 3H).

$[\alpha]^{25}_{D}$: +31.7 (*c* 0.8, $CHCl_3$)

m/z LSIMS : 449 $[M+H]^+$

IR (neat) cm $^{-1}$: 3310, 2974, 2923, 1697, 1540, 1030.

Elemental analysis : Calcd. for $C_{19}H_{30}BrNO_4S$: C, 50.89; H, 6.74; N, 3.12; S, 7.15;

Found : C, 50.64; H, 6.99; N, 3.19; S, 6.89.

2-(*tert*-Butyloxycarbonylamido)-3-bromo-1-(*R*$_S$)-phenylsulfinyl-(2*S*,3*R*,4*R*)-octan-4-ol, 51*s*.

8%. Liquid.

PMR (200 MHz, $CDCl_3$) : δ 7.72-7.60 (m, 2H), 7.58-7.45 (m, 3H), 5.12 (d, *J* = 7.2 Hz, NH), 4.41-4.23 (m, 2H), 3.72 (bs, 1H), 3.31-3.06 (m, 2H), 1.62-1.40 (m, 6H), 1.41 (s, 9H), 0.91 (distorted t, 3H).

$[\alpha]^{25}_{D}$: +25.2 (*c* 0.64, $CHCl_3$)

m/z (LSIMS) : 448 $[M+H]^+$

IR (neat) cm $^{-1}$: 3310, 2947, 1696, 1546, 1153, 1029.

Elemental analysis : Calcd. for $C_{19}H_{30}BrNO_4S$: C, 50.89; H, 6.74; N, 3.12; S, 7.15;

Found : C, 51.04; H, 6.39; N, 3.42; S, 7.08.

5-Bromo-6-butyl-4-(*S*s)-phenylsulfinylmethyl-(4*S*,5*R*,6*R*)-1,3-oxazinan-2-one 52*a*.

33%. Solid.

mp : 129-130 °C

PMR (200 MHz, $CDCl_3$) : δ 7.68-7.50 (m, 5H), 6.21-6.15 (bs, NH), 4.43 (dd, *J* = 3.5, 2.5 Hz, 1H), 4.14 (dt, *J* = 9.3, 3.5 Hz, 1H), 4.02 (dt, *J* = 10.4, 2.5 Hz, 1H), 3.35 (dd, *J* = 12.7, 9.3 Hz, 1H), 2.91 (dd, *J* = 12.7, 3.5 Hz, 1H), 1.90-1.18 (m, 6H), 0.90 (t, *J* = 6.9 Hz, 3H).

$[\alpha]^{25}_D$: −164.8 (*c* 1.0, $CHCl_3$)

m/z (LSIMS) : 375 $[M+H]^+$

IR (neat) cm $^{-1}$: 3262, 2960, 2928, 2845, 1757, 1465, 1035.

Elemental analysis : Calcd. for $C_{15}H_{20}BrNO_3S$: C, 48.14; H, 5.39; N, 3.45; S, 8.57;

Found : C, 48.33; H, 5.08; N, 3.49; S, 8.98.

Products from **35s**.

2-(*tert*-Butyloxycarbonylamido)-3-bromo-1-(S_S)-phenylsulfinyl-(2*S*,3*S*,4*S*)-octan-4-ol, 50*a*.

26%. Liquid.

PMR (200 MHz, $CDCl_3$) : δ 7.70-7.59 (m, 2H), 7.57-7.48 (m, 3H), 5.71-5.57 (bs, NH), 4.40-4.27 (m, 1H and OH), 4.07-3.87 (m, 2H), 3.42 (dd, *J* = 13.4, 8.3 Hz, 1H), 3.17 (dd, *J* = 13.4, 2.3 Hz, 1H), 2.08-1.85 (m, 2H), 1.49 (s, 9H), 1.45-1.28 (m, 4H), 0.91 (t, *J* = 6.7 Hz, 3H).

$[\alpha]^{25}_D$: −74.3 (*c* 1.9, $CHCl_3$)

m/z (LSIMS) : 448 $[M+H]^+$

IR (neat) cm $^{-1}$: 3343, 2965, 2855, 1700, 1259, 1043.

Elemental analysis : Calcd. for $C_{19}H_{30}BrNO_4S$: C, 50.89; H, 6.74; N, 3.12; S, 7.15;

Found : C, 51.24; H, 6.42; N, 3.37; S, 7.49.

5-Bromo-6-butyl-4-(*R*s)-phenylsulfinylmethyl-(4*S*,5*R*,6*R*)-1,3-oxazinan-2-one, 52*s*.

52%. Solid.

mp : 147-149 °C

PMR (200 MHz, $CDCl_3$) : δ 7.78-7.54 (m, 5H), 6.08-5.95 (bs, NH), 4.57 (dd, *J* =

3.4, 2.5 Hz, 1H), 4.46 (dt, *J* = 7.6, 2.5 Hz, 1H), 4.26 (dt, *J* = 9.5, 3.4 Hz, 1H), 3.25-3.02 (m, 2H), 2.04-1.86 (m, 2H), 1.79-1.59 (m, 2H), 1.55-1.32 (m, 2H), 0.98 (t, *J* = 6.7 Hz, 3H).

$[\alpha]^{25}_{D}$: +120.0 (*c* 1.0, $CHCl_3$)

m/z (LSIMS) : 375 $[M+H]^+$

IR (neat) cm $^{-1}$: 3257, 2962, 2920, 1749, 1261, 1053.

Elemental analysis : Calcd. for $C_{15}H_{20}BrNO_3S$: C, 48.14; H, 5.39; N, 3.45; S, 8.57.

Found : C, 48.45; H, 5.78; N, 3.48; S, 8.33.

Products from **40*a***.

2-Bromo-3-(*tert*-butoxycarbonylamido)-1-phenyl-4-(*R*s)-phenylsulfinyl-(1*S*,2*R*,3*S*)-butan-1-ol, 54*s*.

16%. Viscous liquid.

PMR (200 MHz, $CDCl_3$) : δ 7.71-7.61 (m, 2H), 7.58-7.48 (m, 3H), 7.44-7.25 (m, 5H), 5.37 (bd, *J* = 8.9 Hz, 1H), 4.87-4.73 (m, 2H), 4.62-4.42 (m, 1H), 3.30 (dd, *J* = 13.5, 3.6 Hz, 1H), 3.10-2.92 (m, 1H), 1.47 (s, 9H).

$[\alpha]^{25}_{D}$: +14.1 (*c* 1.0, $CHCl_3$)

m/z (LSIMS) : 469 $[M+H]^+$

IR (neat) cm $^{-1}$: 3403-3168, 2928, 2837, 1714, 1520, 1471, 1163, 1040.

Elemental analysis : Calcd. for $C_{21}H_{26}BrNO_4S$: C, 53.85; H, 5.59; N, 2.99; S, 6.84.

Found : C, 54.04; H, 5.88; N, 2.78; S, 6.53.

2-Bromo-3-(*tert*-butoxycarbonylamido)-1-phenyl-4-(*R*s)-phenylsulfinyl-(1*R*,2*S*,3*S*)-butan-1-ol, 53*s*.

5%. Liquid.

PMR (200 MHz, $CDCl_3$) : δ 7.72-7.62 (m, 2H), 7.61-7.50 (m, 3H), 7.41-7.24 (m, 5H), 5.08 (d, *J* = 9.5 Hz, 1H), 4.88-4.73 (m, 1H), 4.49 (d, *J* = 10.4 Hz, 1H), 4.04 (d, *J* = 10.4 Hz, 1H), 3.22 (dd, *J* = 13.0, 8.5 Hz, 1H), 3.04 (dd, *J* = 13.0, 5.2 Hz, 1H), 1.51 (s, 9H).

$[\alpha]^{25}_{D}$: +19.6 (*c* 1.0, $CHCl_3$)

m/z (LSIMS) : 469 $[M+H]^+$

IR (neat) cm $^{-1}$: 3498, 2970, 1716, 1456, 1351, 1156, 1041.

Elemental analysis : Calcd. for $C_{21}H_{26}BrNO_4S$: C, 53.85; H, 5.59; N, 2.99; S, 6.84.

Found : C, 53.64; H, 5.28; N, 3.19; S, 6.99.

5-Bromo-6-phenyl-4-(*S*s)-phenylsulfinylmethyl-(4*S*,5*S*,6*R*)-1,3-oxazinan-2-one, 55*a*.

63%. Solid.

PMR (200 MHz, $CDCl_3$) : δ 7.76-7.55 (m, 5H), 7.45-7.30 (m, 5H), 5.27 (d, *J* = 9.4 Hz, 1H), 4.32 (t, *J* = 9.4 Hz, 1H), 4.03 (dt, *J* = 9.4, 1.2 Hz, 1H), 3.40 (dd, *J* = 13.4, 9.4 Hz, 1H), 3.15 (dd, *J* = 13.4, 1.2 Hz, 1H).

$[\alpha]^{25}_{D}$: -140.7 (*c* 1.0, THF)

m/z (LSIMS) : 395 $[M+H]^+$

IR (neat) cm $^{-1}$: 3281, 2925, 1714, 1447, 1399, 1085, 1031.

Elemental analysis : Calcd. for $C_{17}H_{16}BrNO_3S$: C, 51.79; H, 4.09; N, 3.55; S, 8.13.

Found : C, 52.01; H, 4.38; N, 3.76; S, 8.45.

Products from **40*s*.**

2-Bromo-3-(*tert*-butoxycarbonylamido)-1-phenyl-4-(*S*s)-phenylsulfinyl-(1*R*,2*S*,3*S*)-butan-1-ol, 53*a*. 4%.

27%. Liquid.

PMR (200 MHz, $CDCl_3$) : δ 7.72-7.62 (m, 2H), 7.58-7.48 (m, 3H), 7.42-7.24 (m, 5H), 5.30 (bs, 1H), 4.85-4.74 (m, 2H), 4.61-4.43 (m, 1H), 3.31 (dd, *J* = 12.8, 1.2 Hz, 1H), 3.13-2.95 (m, 1H), 1.47 (s, 9H).

$[\alpha]^{25}_D$: -27.4 (*c* 0.32, CH_2Cl_3)

m/z (LSIMS) : 469 $[M+H]^+$

IR (neat) cm^{-1} : 3445, 2970, 1710, 1435, 1351, 1159, 1043.

Elemental analysis : Calcd. for $C_{21}H_{26}BrNO_4S$: C, 53.85; H, 5.59; N, 2.99; S, 6.84.

Found : C, 54.10; H, 5.96; N, 3.08; S, 7.04.

2-Bromo-3-(*tert*-butoxycarbonylamido)-1-phenyl-4-(*S*s)-phenylsulfinyl-(1*S*,2*R*,3*S*)-butan-1-ol, 54*a*.

Liquid.

PMR (200 MHz, $CDCl_3$) : δ 7.71-7.62 (m, 2H), 7.60-7.48 (m, 3H), 7.38-7.24 (m, 5H), 5.13 (d, *J* = 8.3 Hz, 1H), 5.0-4.84 (m, 1H), 4.49 (d, *J* = 9.5 Hz, 1H), 3.99 (d, *J* = 9.5 Hz, 1H), 3.11-2.90 (m, 2H), 1.53 (s, 9H).

$[\alpha]^{25}_D$: -53.0 (*c* 1.0, CH_2Cl_2)

m/z (LSIMS) : 469 $[M+H]^+$

IR (neat) cm^{-1} : 3467, 2974, 1711, 1157, 1041.

Elemental analysis : Calcd. for $C_{21}H_{26}BrNO_4S$: C, 53.85; H, 5.59; N, 2.99; S, 6.84.

Found : C, 53.74; H, 5.69; N, 3.17; S, 6.65.

5-Bromo-6-phenyl-4-(*R*s)-phenylsulfinylmethyl-(4*S*,5*S*,6*R*)-1,3-oxazinan-2-one, 55*s*.

52%. Viscous liquid.

PMR (200 MHz, $CDCl_3$) : δ 7.68-7.60 (m, 2H), 7.58-7.46 (m, 3H), 7.43-7.25 (m, 5H), 7.0 (s, 1H), 5.26 (d, *J* = 10.5 Hz, 1H), 4.47 (dt, *J*

= 10.5, 1.2 Hz, 1H), 3.93 (t, *J* = 10.5 Hz, 1H), 3.25 (dd, *J* = 12.8, 1.2 Hz, 1H), 2.94 (dd, *J* = 12.8, 10.5 Hz, 1H)

$[\alpha]^{25}_D$:+25.4 (*c* 0.8, $CHCl_3$)

m/z (LSIMS) : 395 $[M+H]^+$

IR (neat) cm^{-1} : 3298, 2927, 1718, 1456, 1390, 1097, 1040.

Elemental analysis : Calcd. for $C_{17}H_{16}BrNO_3S$: C, 51.79; H, 4.09; N, 3.55; S, 8.13.

Found : C, 51.46; H, 4.23; N, 3.65; S, 7.95.

<u>Products from **47*a***.</u>

1*N*-[3-Bromo-4-(*tert*-butyldiphenylsilyloxy)-2-hydroxy-1-(*R*s)-phenylsulfinylmethyl-(1*R*,2*R*,3*S*)-butyl]-*tert*-butylcarbamate, 57*s*.

7%. Viscous liquid.

PMR (200 MHz, $CDCl_3$) : δ 7.72-7.48 (m, 9H), 7.43-7.31 (m, 6H), 5.30 (bs, NH), 4.64-4.47 (m, 1H), 4.20-4.06 (m, 2H), 4.05-3.89 (m, 2H), 3.36 (dd, *J* = 13.2, 5.1 Hz, 1H), 3.05 (dd, *J* = 13.2, 2.5 Hz, 1H), 1.42 (s, 9H), 1.07 (s, 9H).

$[\alpha]^{25}_D$: +30.5 (*c* 0.19, $CHCl_3$)

m/z (LSIMS) : 661 $[M+H]^+$

IR (neat) cm^{-1} : 3424, 2968, 2864, 1697, 1505, 1373, 1158, 1042.

1*N*-[2-Bromo-4-(tert-butyldiphenylsilyloxy)-3-hydroxy-1-(*R*s)-phenylsulfinylmethyl-(1*S*,2*R*,3*S*)-butyl]-*tert*-butylcarbamate, 56*s*.

24%. Liquid.

PMR (200 MHz, $CDCl_3$) : δ 7.74-7.50 (m, 9H), 7.43-7.31 (m, 6H), 5.03 (d, *J* = 8.5 Hz, NH), 4.73-4.59 (m, 1H), 4.26 (d, *J* = 9.4 Hz, 1H), 3.94 (d, *J* = 2.4 Hz, 2H), 3.63 (dt, *J* = 9.4, 2.4 Hz, 1H), 3.23 (dd, *J* = 12.9, 9.4 Hz, 1H), 3.04 (dd, *J* = 12.9, 4.7 Hz, 1H), 1.48 (s, 9H), 1.07 (s, 9H).

$[\alpha]^{25}_{D}$: +53.9 (*c* 0.86, $CHCl_3$)

m/z (LSIMS) : 661 $[M+H]^+$

IR (neat) cm^{-1} : 3443, 2910, 2841, 1694, 1453, 1160, 1041.

5-[1-Bromo-2-(*tert*-butyldiphenylsilyloxy)-(1*S*)-ethyl]-4-(*S*s)-phenylsulfinylmethyl-(4*R*,5*S*)-1,3-oxazolan-2-one, 58*a*. 50%.

Liquid.

PMR (200 MHz, $CDCl_3$) : δ 7.64-7.53 (m, 8H), 7.48-7.37 (m, 7H), 6.28 (s, NH), 4.54 (dd, *J* = 8.6, 5.5 Hz, 1H), 4.0-3.95 (m, 2H), 3.90 (ddd, *J* = 8.6, 4.4, 4.2 Hz, 1H), 3.65 (dd, *J* = 11.6, 4.2 Hz, 1H), 3.48 (dd, *J* = 13.8, 10.6 Hz, 1H), 3.13 (dd, *J* = 13.8, 1.5 Hz, 1H), 1.04 (s, 9H).

$[\alpha]^{25}_{D}$: -69.0 (*c* 0.47, $CHCl_3$)

m/z (LSIMS) : 587 $[M+H]^+$

IR (neat) cm^{-1} : 3260, 2959, 2843, 1773, 1495, 1157.

Products from **47*s*.**

1*N*-[3-bromo-4-(*tert*-butyldiphenylsilyloxy)-2-hydroxy-1-(*S*s)-phenylsulfinylmethyl-(1*R*,2*R*,3*S*)-butyl]-*tert*-butylcarbamate, 57*a*.

4%. Viscous liquid.

PMR (200 MHz, $CDCl_3$) : δ 7.74-7.45 (m, 9H), 7.45-7.29 (m, 6H), 5.31 (d, *J* = 7.1 Hz, 1H), 4.91 (d, *J* = 6.2 Hz, 1H), 4.55-4.41 (m, 1H), 4.25-4.13 (m, 1H), 4.12-3.83 (m, 2H), 3.40 (dd, *J* = 13.2, 9.5 Hz, 1H), 3.01 (dd, *J* = 13.2, 4.7 Hz, 1H), 1.43 (s, 9H), 1.06 (s, 9H).

$[\alpha]^{25}_{D}$: -23.6 (*c* 0.39, $CHCl_3$)

m/z (LSIMS) : 661 $[M+H]^+$

IR (neat) cm^{-1} : 3429, 2962, 2842, 1718, 1471, 1158, 1043.

1*N*-[2-bromo-4-(*tert*-butyldiphenylsilyloxy)-3-hydroxy-1-(*S*s)-phenylsulfinylmethyl-(1*S*,2*R*,3*S*)-butyl]-*tert*-butylcarbamate, 56*a*.

24%. Viscous liquid.

PMR (200 MHz, $CDCl_3$) : δ 7.78-7.48 (m, 9H), 7.48-7.29 (m, 6H), 5.09 (d, *J* = 9.4 Hz, NH), 4.83-4.67 (m, 1H), 4.30 (d, *J* = 9.4 Hz, 1H), 3.94 (bs, 2H), 3.15-3.07 (m, 1H), 3.10-2.95 (m, 2H), 1.48 (s, 9H), 1.06 (s, 9H).

$[\alpha]^{25}_D$: -59.7 (*c* 0.73, $CHCl_3$)

m/z (LSIMS) : 661 $[M+H]^+$

IR (neat) cm^{-1} : 3313, 2957, 2849, 1709, 1497, 1149, 1039.

5-[1-bromo-2-(*tert*-butyldiphenylsilyloxy)-(1*S*)-ethyl]-4-(*R*s)-phenylsulfinylmethyl-(4*R*,5*S*)-1,3-oxazolan-2-one, 58*s*.

50%. Liquid.

PMR (200 MHz, $CDCl_3$) : δ 7.74-7.49 (m, 9H), 7.47-7.28 (m, 6H), 6.93 (s, 1H), 4.46-4.28 (m, 2H), 4.27-3.89 (m, 3H), 3.30 (d, *J* = 13.2 Hz, 1H), 2.98 (dd, *J* = 13.2, 9.4 Hz, 1H), 1.05 (s, 9H).

$[\alpha]^{25}_D$: +18.7 (*c* 0.42, $CHCl_3$)

m/z (LSIMS) : 587 $[M+H]^+$

IR (neat) cm^{-1} : 3398, 2959, 2845, 1765, 1501, 1158.

Products from **48*a*.**

2-(Methoxycarbonylamido)-3-bromo-1-(*R*s)-phenylsulfinyl-(2*S*,3*S*,4*S*)-octan-4-ol, 59*s*.

52%. Liquid.

PMR (200 MHz, $CDCl_3$) : δ 7.70-7.60 (m, 2H), 7.59-7.49 (m, 3H), 5.55 (d, *J* = 7.6 Hz, NH), 4.22-4.05 (m, 2H), 3.86-3.60 (m, 4H), 3.40-3.20 (m, 2H), 2.05-1.70 (m, 2H), 1.60-1.24 (m, 4H), 0.90 (t, *J* = 6.7 Hz, 3H).

$[\alpha]^{25}_{D}$: +47.3 (*c* 0.47, $CHCl_3$)

m/z (LSIMS) : 407 $[M+H]^+$

IR (neat) cm^{-1} : 3334, 2924, 2360, 1700, 1444, 1528, 1027.

Elemental analysis : Calcd. for $C_{16}H_{24}BrNO_4S$: C, 47.30; H, 5.95; N, 3.45; S, 7.89;

Found : C, 47.65; H, 6.08; N, 3.79; S, 7.96.

2-(Methoxycarbonylamido)-3-bromo-1-(R_S)-phenylsulfinyl-(2*S*,3*R*,4*R*)-octan-4-ol, 60*s*.

4%. Liquid.

PMR (200 MHz, $CDCl_3$) : δ 7.75-7.45 (m, 5H), 5.21 (d, *J* = 8.9 Hz, NH), 4.84-4.65 (m, 1H), 3.85-3.61 (m, 4H), 3.60-3.44 (m, 1H), 3.29 (dd, *J* = 13.4, 8.9 Hz, 1H), 2.97 (dd, *J* = 13.4, 5.1 Hz, 1H), 2.10-1.80 (m, 1H), 1.70-1.18 (m, 5H), 0.92 (distorted t, 3H).

$[\alpha]^{25}_{D}$: +28.4 (*c* 0.31, $CHCl_3$)

m/z (LSIMS) : 407 $[M+H]^+$

IR (neat) cm^{-1} : 3289, 2927, 1708, 1465, 1524, 1032.

Elemental analysis : Calcd. for $C_{16}H_{24}BrNO_4S$: C, 47.30; H, 5.95; N, 3.45; S, 7.89;

Found : C, 47.13 H, 5.88; N, 3.09; S, 8.16.

Products from **48*s*.**

2-(Methoxycarbonylamido)-3-bromo-1-(S_S)-phenylsulfinyl-(2*S*,3*S*,4*S*)-octan-4-ol, 59*a*.

59%. Viscous liquid.

PMR (200 MHz, $CDCl_3$) : δ 7.73-7.60 (m, 2H), 7.59-7.48 (m, 3H), 6.03 (d, *J* = 7.3 Hz, NH), 4.50-4.25 (m, 1H and OH), 4.20-3.83 (m, 2H), 3.72 (s, 3H), 3.47-3.10 (m, 2H), 2.10-1.83 (m, 2H), 1.70-1.25 (m, 4H), 0.96 (t, *J* = 6.8 Hz, 3H).

$[\alpha]^{25}_{D}$: –72.0 (*c* 0.55, $CHCl_3$)

m/z LSIMS : 407 $[M+H]^+$

IR (neat) cm^{-1} : 3355, 2964, 2922, 2843, 1709, 1259, 1037.

Elemental analysis : Calcd. for $C_{16}H_{24}BrNO_4S$: C, 47.30; H, 5.95; N, 3.45; S, 7.89;

Found : C, 47.65; H, 6.28; N, 3.07; S, 7.54.

Products from **71*a*.**

1*N*-[2-Bromo-3-hydroxy-3-phenyl-1-(*R*s)-phenylmethylsulfinyl-(1*S*,2*S*,3*S*)-heptyl]-4-methyl-1-benzenesulfonamide, 76*s*: 65%.

Solid.

mp : 94-96 °C

PMR (200 MHz, $CDCl_3$) : δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.69-7.47 (m, 5H), 7.29 (d, *J* = 8.2 Hz, 2H), 6.62 (d, *J* = 7.4 Hz, NH), 4.08-3.88 (m, 1H and OH), 3.79-3.61 (m, 2H), 3.47 (dd, *J* = 13.4, 2.2 Hz, 1H), 3.02 (dd, *J* = 13.4, 5.2 Hz, 1H), 2.45 (s, 3H), 1.98-1.74 (m, 1H), 1.74-1.53 (m, 1H), 1.40-1.03 (m, 4H), 0.82 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 13.7, 21.4, 21.7, 29.6, 35.5, 54.3, 59.4, 60.0, 73.5, 124.1, 127.1, 129. 3, 129.7, 131.4, 137. 3, 141.9, 143.7

$[\alpha]_{D}^{25}$ + : 109.7 (*c* 0.3, $CHCl_3$)

m/z (LSIMS) : 502 $[M+H]^+$

IR (neat) cm^{-1} : 3368, 2928, 1331, 1159.

Elemental analysis : Calcd. for $C_{21}H_{28}BrNO_4S_2$: C, 50.20; H, 5.62; N, 2.79; S, 12.76.

Found : C, 50.53; H, 5.22; N, 2.73; S, 12.52.

1*N*-[2-Bromo-3-hydroxy-3-phenyl-1-(*R*s)-phenylmethylsulfinyl-(1*S*,2*R*,3*R*)-heptyl]-4-methyl-1-benzenesulfonamide, 77*s*.

11%. Liquid.

PMR (200 MHz, CDCl$_3$) : δ 7.64 (d, *J* = 8.2 Hz, 2H), 7.56-7.44 (m, 5H), 7.28 (d, *J* = 8.2 Hz, 2H), 6.16-6.07 (bs, NH), 4.60-4.55 (m, 1H), 3.77-3.68 (m, 1H), 3.50-3.44 (m, 1H), 3.34 (dd, *J* = 14.1, 7.0 Hz, 1H), 3.20 (dd, *J* = 14.0, 5.9 Hz, 1H), 2.42 (s, 3H), 2.04-1.80 (m, 2H), 1.44-1.10 (m, 4H), 0.88 (t, *J* = 6.7 Hz, 3H).

$[\alpha]_D^{25}$: +78.4 (*c* 0.2, CHCl$_3$)

m/z (LSIMS) : 502 [M+H]$^+$

IR (neat) cm^{-1} : 3281, 2925, 1367, 1158.

Elemental analysis : Calcd. for $C_{21}H_{28}BrNO_4S_2$: C, 50.20; H, 5.62; N, 2.79; S, 12.76.

Found : C, 50.43; H, 5.98; N, 2.43; S, 12.99.

Product from 71*s*.

1*N*-[2-Bromo-3-hydroxy-3-phenyl-1-(*S*s)-phenylmethylsulfinyl-(1*S*,2*S*,3*S*)-heptyl]-4-methyl-1-benzenesulfonamide, 76*a*.

82%. Solid.

mp : 93-95 °C

PMR (200 MHz, CDCl$_3$+D$_2$O) : δ 7.83 (d, *J* = 8.2 Hz, 2H), 7.56-7.44 (m, 5H), 7.30 (d, *J* = 8.2 Hz, 2H), 4.46-4.37 (m, 1H), 3.99-3.83 (m, 1H), 3.82 (d, *J* = 8.2 Hz, 1H), 2.96 (dd, *J* = 13.4, 5.2 Hz, 1H), 2.65 (dd, *J* = 13.4, 2.3 Hz, 1H), 2.42 (s, 3H), 2.08-1.73 (m, 2H), 1.60-1.23 (m, 4H), 0.91 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 13.8, 21.4, 21.9, 29.6, 35.6, 54.5, 56.9, 61.0, 74.0, 123.7, 127.2, 129.3, 129.7, 131.3, 137.8, 143.2, 143.6

$[\alpha]_D^{25}$: –89.6 (*c* 0.3, CHCl$_3$)

m/z (LSIMS) : 502 [M+H]$^+$

IR (neat) cm^{-1} : 3262, 2926, 1328, 1157.

Elemental analysis : Calcd. for $C_{21}H_{28}BrNO_4S_2$: C, 50.20; H, 5.62; N, 2.79; S, 12.76.

Found : C, 50.03; H, 5.87; N, 2.59; S, 12.53.

Products from 72*a*.

1*N*-[2-Bromo-3-hydroxy-3-phenyl-1-(*R*s)-phenylmethylsulfinyl-(1*S*)-propyl]-4-methyl-1-benzenesulfonamide, 78*s*.

64%. Solid.

mp : 184-186 °C

PMR (200 MHz, $CDCl_3$) : δ 7.60 (d, *J* = 8.2 Hz, 2H), 7.53-7.40 (m, 5H), 7.32-7.20 (m, 7H), 5.27 (d, *J* = 8.9 Hz, NH), 4.84 (d, *J* = 8.9 Hz, 1H), 4.56 (d, *J* = 8.9 Hz, 1H), 4.24-4.13 (m, 1H), 3.26 (dd, *J* = 14.1, 9.7 Hz, 1H), 2.78 (dd, *J* = 14.1, 4.5 Hz, 1H), 2.44 (s, 3H).

m/z (LSIMS) : 523 $[M+H]^+$

IR (neat) cm $^{-1}$: 3321, 2927, 1541, 1159.

Elemental analysis : Calcd. for $C_{23}H_{24}BrNO_4S_2$: C, 52.87; H, 4.63; N, 2.68; S, 12.27.

Found : C, 53.03; H, 4.92; N, 2.63; S, 12.52.

Product from 72*s*.

1*N*-[2-Bromo-3-hydroxy-3-phenyl-1-(*S*s)-phenylmethylsulfinyl-(1*S*,2*S*,3*R*)-propyl]-4-methyl-1-benzenesulfonamide, 78*a*.

80%. Solid.

mp : 172-174 °C

PMR (200 MHz, $CDCl_3$) : δ 7.78 (d, *J* = 8.2 Hz, 2H), 7.56-7.46 (m, 5H), 7.38-7.14 (m, 7H), 5.40 (d, *J* = 10.4 Hz, NH), 4.84 (d, *J* = 9.7 Hz, 1H), 4.71-4.61 (m, 1H), 4.11 (d, *J* = 9.7 Hz, 1H), 2.99 (dd, *J* = 13.4, 5.2 Hz, 1H), 2.73 (dd, *J* = 13.4, 6.7 Hz, 1H), 2.41 (s, 3H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 21.1, 49.9, 62.0, 62.5, 73.5, 123.7, 127.0, 127.5, 127.8, 128.0, 129.5, 129.7, 131.2, 138.6, 142.6, 143.1, 144.2.

$[\alpha]_D^{25}$: –48.4 (*c* 1.0, CHCl$_3$)

m/z (LSIMS) : 523 [M+H]$^+$

IR (neat) cm $^{-1}$: 3291, 2925, 1455, 1157.

Elemental analysis : Calcd. for $C_{23}H_{24}BrNO_4S_2$: C, 52.87; H, 4.63; N, 2.68; S, 12.27.

Found : C, 52.63; H, 4.33; N, 2.93; S, 12.42.

Products from **75*a*.**

1*N*-[2-Bromo-4-(*tert*-butyldiphenylsilyloxy)-3-hydroxy-1-(*R*s)-phenylsulfinylmethyl-(1*S*,2*R*,3*S*)-butyl]-4-methyl-1-benzenesulfonamide, 79*s*.

42%. Liquid.

PMR (300MHz, CDCl$_3$) : δ 7.73-7.42 (m, 11H), 7.40-7.16 (m, 8H), 5.10 (d, *J* = 11.7 Hz, NH), 4.46-4.42 (m, 1H), 4.28-4.10 (m, 1H), 3.82 (dd, *J* = 12.4, 1.7 Hz, 1H), 3.76-3.43 (m, 2H), 3.16 (d, *J* = 13.4, 8.2 Hz, 1H), 2.83 (dd, *J* = 13.4, 2.7 Hz, 1H), 2.35 (s, 3H), 1.01 (bs, 9H).

m/z (LSIMS) : 714 [M+H]$^+$

IR (neat) cm $^{-1}$: 3267, 2924, 2865, 1587, 1156, 1039.

Elemental analysis : Calcd. for $C_{34}H_{40}BrNO_5S_2Si$: C, 59.47; H, 5.87; N, 2.04; S, 9.34.

Found : C, 59.81; H, 5.62; N, 1.93; S, 9.45.

1*N*-[3-Bromo-4-(*tert*-butyldiphenylsilyoxy)-2-hydroxy-1-(*R*s)-phenylsulfinylmethyl-(1*R*,2*R*,3*S*)-butyl]-4-methyl-1-benzenesulfonamide, 80*s*.

15%. Liquid.

PMR (200 MHz, CDCl$_3$) : δ 7.82-7.41 (m, 11H), 7.40-7.20 (m, 8H), 5.32 (d, *J* =

8.2 Hz, NH), 4.60-4.51 (m, 1H), 4.37-4.10 (m, 1H) 4.04-3.80 (m, 2H), 3.70-3.58 (m, 1H), 3.24 (dd, *J* 13.4, 8.7 Hz, 1H), 2.88 (dd, *J* = 13.4, 3.3 Hz, 1H), 2.41 (s, 3H), 1.08 (bs, 9H).

m/z (LSIMS) : 714 [M+H]$^+$

IR (neat) cm^{-1} : 3262, 2927, 2834, 1568, 1455, 1158, 1043.

Products from **75*s***.

1*N*-[2-Bromo-4-(*tert*-butyldiphenylsilyloxy)-3-hydroxy-1-(*S*s)-phenylsulfinylmethyl-(1*S*,2*R*,3*S*)-butyl]-4-methyl-1-benzenesulfonamide, 79*a*.

51%. Solid.

mp : 173-175 °C.

PMR (300 MHz, CDCl$_3$) : δ 7.87-7.51 (m, 11H), 7.56-7.20 (m, 8H), 5.38 (d, *J* = 11.7 Hz, NH), 4.57-4.40 (m, 1H), 4.34-4.15 (m, 1H), 3.97-3.70 (m, 3H), 3.12 (dd, *J* = 13.4, 3.0 Hz, 1H), 2.80-2.60 (m, 1H), 2.42 (s, 3H), 1.11 (bs, 9H).

m/z (LSIMS) : 714 [M+H]$^+$

IR (neat) cm^{-1} : 3298, 2920, 1375, 1158, 1036.

Elemental analysis : Calcd. for $C_{34}H_{40}BrNO_5S_2Si$: C, 59.47; H, 5.87; N, 2.04; S, 9.34.

Found : C, 59.11; H, 6.20; N, 1.93; S, 9.45.

1*N*-[3-[illegible]-(*tert*-butyldiphenylsilyoxy)-2-hydroxy-1-(*S*s)-p[illegible]inylmethyl-(1*R*,2*R*,3*S*)-butyl]-4-methyl-1-benzenesulfonamide,

10%. Liquid.

PMR (300 MHz, CDCl$_3$) : δ 7.68-7.40 (m, 11H), 7.38-7.18 (m, 8H), 5.18 (d, *J* = 9.5 Hz, NH), 4.30-4.20 (m, 1H), 4.16-4.12 (m, 1H), 3.97 (dd, *J* = 11.6, 2.0 Hz, 1H), 3.84 (dd, *J* = 11.6, 4.1

Hz, 1H), 3.77-3.69 (m, 1H), 3.06 (dd, *J* = 13.4, 8.2 Hz, 1H), 2.86 (dd, *J* = 13.4, 2.7 Hz, 1H), 2.32 (s, 3H), 0.98 (s, 9H).

$[\alpha]_D^{25}$: –28.4 (*c* 0.3, $CHCl_3$)
m/z (LSIMS) : 714 $[M+H]^+$
IR (neat) cm $^{-1}$: 3305, 2926, 1569, 1378, 1157, 1038.
Elemental analysis : Calcd. for $C_{34}H_{40}BrNO_5S_2Si$: C, 59.47; H, 5.87; N, 2.04; S, 9.34.
Found : C, 59.84; H, 6.04; N, 2.23; S, 9.65.

General procedure for the conversion of bromohydrins to oxazinones.

To a cooled –15 °C solution of the bromohydrin (0.1 mmol) in dichloromethane (0.5 mL) was added trifluoroacetic acid (0.5 mL) dropwise and the mixture stirred gradually allowing to attain r.t. and stirred further for a period of 30 min. at the same temperature. The volatiles were removed and the residue taken into THF (0.5 mL). DABCO (0.3 mmol) and CDI (0.2 mmol) were added and the reaction mixture stirred at r.t under nitrogen atmosphere for 24 h. The reaction mixture was concentrated under vacuum and the residue was taken into ethyl acetate (15 mL). The organic layer was washed successively with water (5 mL), brine (5 mL) and dried over sodium sulfate. Evaporation of the solvent afforded the crude product which on purification by chromatography on silica gel using AcOEt/petroleum ether (1:1, v/v) as eluent afforded the oxazinone.

5-Bromo-6-butyl-4-(*S*s)-phenylsulfinylmethyl-(4*S*,5*S*,6*S*)-1,3-oxazinan-2-one, 62.

70%. Viscous liquid.

PMR (400 MHz, $CDCl_3$) : δ 7.66-7.52 (m, 5H), 6.27-6.23 (bs, NH), 4.58 (dd, *J* = 8.7, 3.6 Hz, 1H), 4.32-4.29 (m, 1H), 3.90 (dt, *J* = 10.3, 3.6 Hz, 1H), 3.78 (dd, *J* = 13.4, 10.3 Hz, 1H), 2.84

(dd, *J* = 13.4, 2.0 Hz, 1H), 2.33-2.29 (m, 1H), 2.05-1.45 (m, 5H), 0.93 (distorted t, 3H).

$[\alpha]_D^{25}$: +138.4 (*c* 0.5, CHCl$_3$)

m/z (LSIMS) : 375 [M+H]$^+$

IR (neat) cm^{-1} : 3456, 1745, 1457, 1276, 1120.

Elemental analysis : Calcd. for C$_{15}$H$_{20}$BrNO$_3$S: C, 48.14; H, 5.39; N, 3.45; S, 8.57;

Found : C, 48.43; H, 5.08; N, 3.49; S, 8.78.

5-Bromo-6-phenyl-4-(*S*s)-phenylsulfinylmethyl-(4*S*,5*R*,6*S*)-1,3-oxazinan-2-one, 66.

75%. Viscous liquid.

PMR (200 MHz, CDCl$_3$) : δ 7.51-7.39 (m, 5H), 7.38-7.27 (m, 3H), 7.22-7.13 (m, 2H), 6.72 (bs, 1H), 5.50 (d, *J* = 2.3 Hz, 1H), 4.21-4.15 (bs, 1H), 3.69 (dt, *J* = 10.2, 2.3 Hz, 1H), 3.28 (d, *J* = 14.0, 10.2 Hz, 1H), 2.69 (d, *J* = 14.0, 2.3 Hz, 1H)

$[\alpha]^{25}_D$: –63.07 (*c* 0.26, CHCl$_3$)

m/z (LSIMS) : 395 [M+H]$^+$

IR (neat) cm^{-1} : 3222, 2926, 2855, 1718, 1530, 1472, 1159.

5-[1-Bromo-2-(*tert*-butyldiphenylsilyoxy)-(1*S*)-ethyl]-4-phenylsulfinylmethyl-(4*R*,5*R*)-1,3-oxazolan-2-one, 69.

73%. Viscous oil.

PMR (400 MHz, CDCl$_3$) : δ 7.65-7.53 (m, 9H), 7.47-7.37 (m, 6H), 6.42 (s, 1H), 4.55-4.45 (m, 2H), 4.24-4.16 (m, 1H), 3.81 (dd, *J* = 10.3, 3.9 Hz, 1H), 3.76 (dd, *J* = 10.3, 5.3 Hz, 1H), 3.32 (dd, *J* = 13.8, 9.6 Hz, 1H), 2.93 (dd, *J* = 13.8, 2.3 Hz, 1H), 1.00 (s, 9H).

$[\alpha]^{25}_D$: –81.7 (*c* 0.7, CHCl$_3$)

m/z (LSIMS) : 587 [M+H]$^+$

IR (neat) cm^{-1} : 3392, 2973, 2843, 1728, 1356, 1280, 1120.

Preparation of sulfones from predominant sulfoxides formed during bromohydration:

To a solution of sulfoxide (0.05 mmol) in $CHCl_3$ (0.2 mL) was added *m*-CPBA (12 mg, 0.05 mmol) at 0 °C and allowed to stir for 10 min. The reaction mixture was diluted with ether and washed successively with aq. Sodiumbisulfite solution, aq. $NaHCO_3$ solution, water, brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure followed by column chromatography using AcOEt/petroleum ether afforded the sulfone.

2-(*tert*-Butyloxycarbonylamido)-3-bromo-1-(S_S)-phenylsulfonyl-(2*S*,3*S*,4*S*)-octan-4-ol, 61.

90%. Liquid.

PMR (200 MHz, $CDCl_3$) : δ 7.92 (d, *J* = 8.2 Hz, 2H), 7.75-7.50 (m, 3H), 5.20 (bs, NH), 4.43-3.65 (m, 4H), 3.55-3.41 (m, 1H and OH), 2.08-1.78 (m, 2H), 1.70-1.13 (m, 13H), 0.90 (t, *J* = 6.7 Hz, 3H).

m/z (LSIMS) : 465 $[M+H]^+$

IR (neat) cm^{-1} : 3189, 2970, 2925, 1701, 1158, 1043.

Elemental analysis : Calcd. for $C_{19}H_{30}BrNO_5S$: C, 49.14; H, 6.51; N, 3.02; S, 6.90.

Found : C, 49.41; H, 6.24; N, 3.34; S, 6.76.

2-(Methoxycarbonylamido)-3-bromo-1-(R_S)-phenylsulfonyl-(2*S*,3*S*,4*S*)-octan-4-ol, 70.

83%. Liquid.

PMR (200 MHz, $CDCl_3$) : δ 7.91 (d, *J* = 8.2 Hz, 2H), 7.71-7.47 (m, 3H), 5.43 (d, *J* = 9.4 Hz, NH), 4.48-4.32 (m, 1H), 4.23 (ddd, *J* = 11.2, 3.7, 1.1 Hz, 1H), 4.13-3.94 (m, 1H), 3.89-3.45 (m, 5H and OH), 2.08-1.75 (m, 2H), 1.70-1.04 (m, 4H), 0.90 (t, *J* = 6.7 Hz, 3H).

m/z (LSIMS) : 423 [M+H]$^+$

IR (neat) cm^{-1} : 3289, 2955, 1699, 1543, 1034.

Elemental analysis : Calcd. for $C_{16}H_{24}BrNO_5S$: C, 45.50; H, 5.73; N, 3.32; S, 7.59.

Found : C, 45.69, 5.98, 3.22, 7.89.

5-bromo-6-butyl-4-phenylsulfonylmethyl-(4*S*,5*R*,6*R*)-1,3-oxazinan-2-one, 63.

87%. Solid.

mp : 132-134 °C

PMR (200 MHz, $CDCl_3$) : δ 7.95 (d, *J* = 8.6 Hz, 2H), 7.80-7.69 (m, 3H), 6.01 (bs, NH), 4.48 (dd, *J* = 5.9, 3.2 Hz, 1H), 4.34 (q, *J* = 5.9 Hz, 1H), 4.12 (dt, *J* = 10.2, 3.2 Hz, 1H), 3.40 (d, *J* = 5.9 Hz, 2H), 2.06-1.21 (m, 6H), 0.93 (t, *J* = 6.7 Hz, 3H).

m/z (LSIMS) : 391 [M+H]$^+$

IR (neat) cm^{-1} : 3357, 2962, 2923, 2870, 1764, 1292, 1149.

Elemental analysis : Calcd. for $C_{15}H_{20}BrNO_4S$: C, 46.16; H, 5.16; N, 3.59; S, 8.21.

Found : C, 46.31; H, 5.04; N, 3.78; S, 8.60.

2-(*tert*-Butyloxycarbonylamido)-3-bromo-1-(R_S)-phenylsulfonyl-(2*S*,3*R*,4*R*)-octan-4-ol, 64.

85%. Viscous oil.

PMR (200 MHz, $CDCl_3$) : δ 7.94 (d, *J* = 8.4 Hz, 2H), 7.72-7.55 (m, 3H), 7.36-7.26 (bs, 5H), 4.92 (d, *J* = 9.7 Hz, NH), 4.87-4.75 (m, 1H), 4.48 (d, *J* = 9.7 Hz, 1H), 4.02 (d, *J* = 9.7 Hz, 1H), 3.49 (dd, *J* = 14.4, 8.6 Hz, 1H), 3.32 (dd, *J* = 14.4, 4.1 Hz, 1H).

m/z (LSIMS) : 395 [M+H]$^+$

1*N*-[2-bromo-4-(*tert*-butyldiphenylsilyloxy)-3-hydroxy-1-phenylsulfonylmethyl-(1*S*,2*R*,3*S*)-butyl]-*tert*-butyl carbamate, 67.

83%. Liquid.

PMR (200 MHz, $CDCl_3$) : δ 7.94 (d, *J* = 8.4 Hz, 2H), 7.72-7.45 (m, 8H), 7.45-7.28 (m. 5H), 4.85 (d, *J* = 9.0 Hz, NH), 4.80-4.52 (m, 1H), 4.28 (d, *J* = 10.4 Hz, 1H), 3.93 (s, 2H), 3.57 (bd, *J* = 10.4 Hz, 1H), 3.50-3.27 (m, 2H), 1.44 (s, 9H), 1.07 (s, 9H).

m/z (LSIMS) : 678 $[M+H]^+$

1*N*-[2-bromo-3-hydroxy-3-phenyl-1-phenylmethylsulfonyl-(1*S*,2*S*,3*S*)-heptyl]-4-methyl-1-benzenesulfonamide, 82.

82%. Solid.

mp : 128-129 °C

PMR (200 MHz, $CDCl_3$) : δ 7.87-7.54 (m, 7H), 7.36 (d, *J* = 8.2 Hz, 2H), 5.86 (d, *J* = 10.5 Hz, NH), 4.24-4.01 (m, 2H), 3.85 (d, *J* = 9.7 Hz, 1H), 3.58 (dd, *J* = 14.1, 3.7 Hz, 1H), 3.21 (dd, *J* = 14.1, 3.7 Hz, 1H), 2.46 (s, 3H), 2.18-1.73 (m, 2H), 1.62-1.24 (m, 4H), 0.93 (t, *J* = 6.7 Hz, 3H).

m/z (LSIMS) : 518 $[M+H]^+$

IR (neat) cm^{-1} : 3499, 3288, 2929, 1304, 1157.

Elemental analysis : Calcd. for $C_{21}H_{28}BrNO_5S_2$: C, 48.65; H, 5.44; N, 2.70; S, 12.37.

Found : C, 48.91; H, 5.34; N, 2.73; S, 12.65.

1*N*-[2-bromo-3-hydroxy-3-phenyl-1-phenylmethylsulfonyl-(1*S*,2*S*,3*R*)-propyl]-4-methyl-1-benzenesulfonamide, 84.

90%. Solid.

mp : 70-72 °C

PMR (200 MHz, $CDCl_3$) : δ 7.73-7.40 (m, 7H), 7.37-7.13 (m, 7H), 5.27 (bs, NH), 4.82 (d, *J* = 8.6 Hz, 1H), 4.62 (d, *J* = 8.6 Hz, 1H), 4.16-4.09 (m, 1H), 3.54 (dd, *J* = 14.1, 10.2 Hz, 1H), 3.20 (d, *J* = 14.1 Hz, 1H), 2.48 (s, 3H).

m/z (LSIMS) : 539 $[M+H]^+$

IR (neat) cm^{-1} : 3475, 3282, 2928, 1442, 1310, 1175.

Elemental analysis : Calcd. for $C_{23}H_{24}BrNO_5S_2$: C, 51.30; H, 4.49; N, 2.60; S, 11.91.

Found : C, 51.47; H, 4.34; N, 2.93; S, 12.23.

1*N*-[2-bromo-4-(*tert*-butyldiphenylsilyoxy)-3-hydroxy-1-phenylsulfonylmethyl-(1*S*,2*R*,3*S*)-butyl]-4-methyl-1-benzenesulfonamide, 85.

78%. Solid.

mp : 173-175 °C

PMR (200 MHz, $CDCl_3$) : δ 7.89-7.48 (m, 11H), 7.47-7.17 (m, 8H), 4.73 (d, *J* = 10.4 Hz, NH), 4.31-4.18 (m, 1H), 3.82 (bs, 2H), 3.65-3.26 (m, 2H), 3.28-2.99 (m, 2H), 2.40 (s, 3H), 1.08 (s, 9H).

m/z (LSIMS) : 730 $[M+H]^+$

Elemental analysis : Calcd. for $C_{34}H_{40}BrNO_6S_2Si$: C, 58.11; H, 5.74; N, 1.99; S, 9.12.

Found : C, 58.34; H, 5.44; N, 1.93; S, 9.43.

4-Bromo-3-(4-methylphenylsulfonamido)-5-phenyl-2-phenylsulfanyl-(2*S*,3*S*,4*R*,5*S*)-tetrahydrofuran, 87.

To the bromohydrin **81s** (52mg, 0.1 mmol) in dry DMF (0.1 mL) were added imidazole (13 mg, 0.2 mmol) followed by TBDPS-Cl (27 mg, 0.1 mmol) at room temperature under N_2 atmosphere. The reaction mixture was stirred at r.t. until TLC revealed complete consumption of the starting material. The reaction mixture was diluted with ether and washed successively with water, brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product mixture. Purification by column chromatography using EtOAc/petroleum ether (1:24) afforded **16** (43 mg, 0.086 mmol) in 86% yield.

Viscous liquid.

PMR (200 MHz, $CDCl_3$) : δ 7.82 (d, *J* = 8.2 Hz, 2H), 7.38-7.13 (m, 12H), 6.07 (d, *J* = 8.2 Hz, NH), 5.30 (d, *J* = 4.6 Hz, 1H), 5.06 (d, *J* = 8.9 Hz, 1H), 4.05 (ddd, *J* = 8.2, 6.7, 4.6 Hz, 1H), 3.69 (dd, *J* = 8.9, 6.7 Hz, 1H), 2.36 (s, 3H).

m/z (LSIMS) : 382 [M-STol]$^+$

Elemental analysis : Calcd. for $C_{23}H_{22}BrNO_3S_2$: C, 54.76; H, 4.40; N, 2.78; S, 12.71.

Found : C, 54.63; H, 4.52; N, 2.87; S, 12.62.

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SPECTRA

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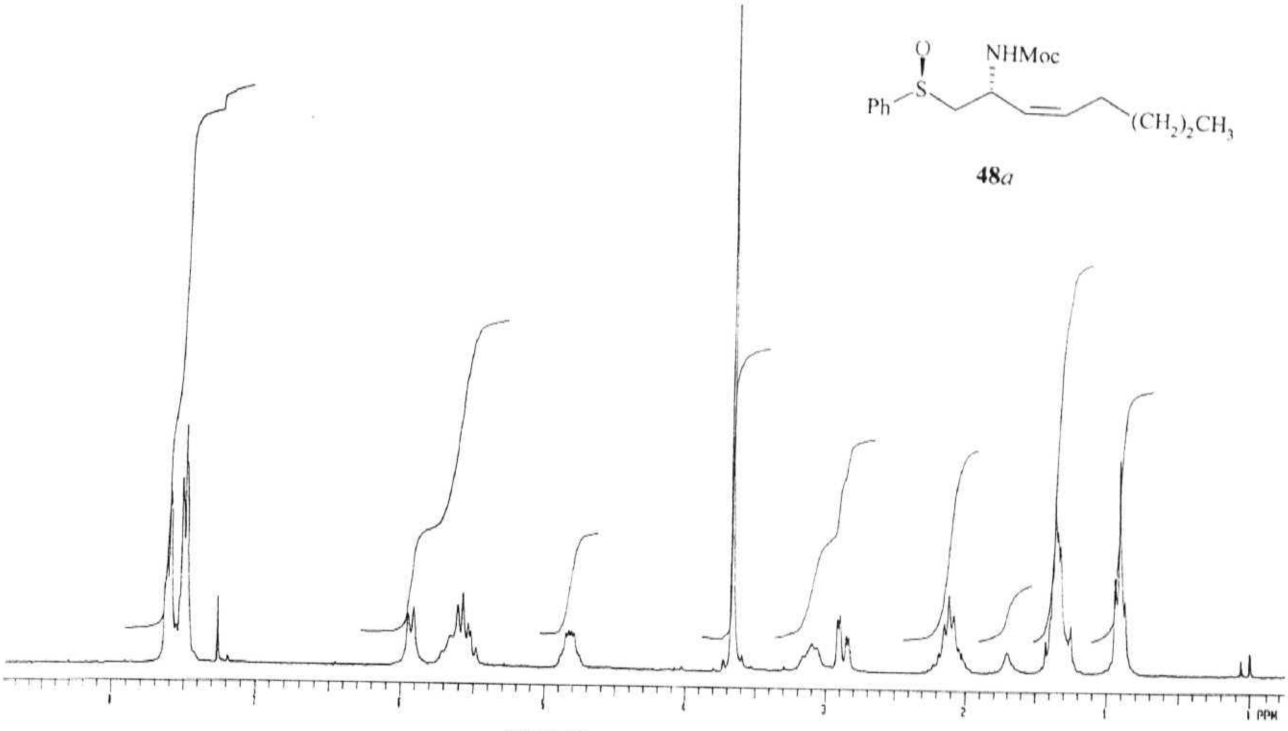
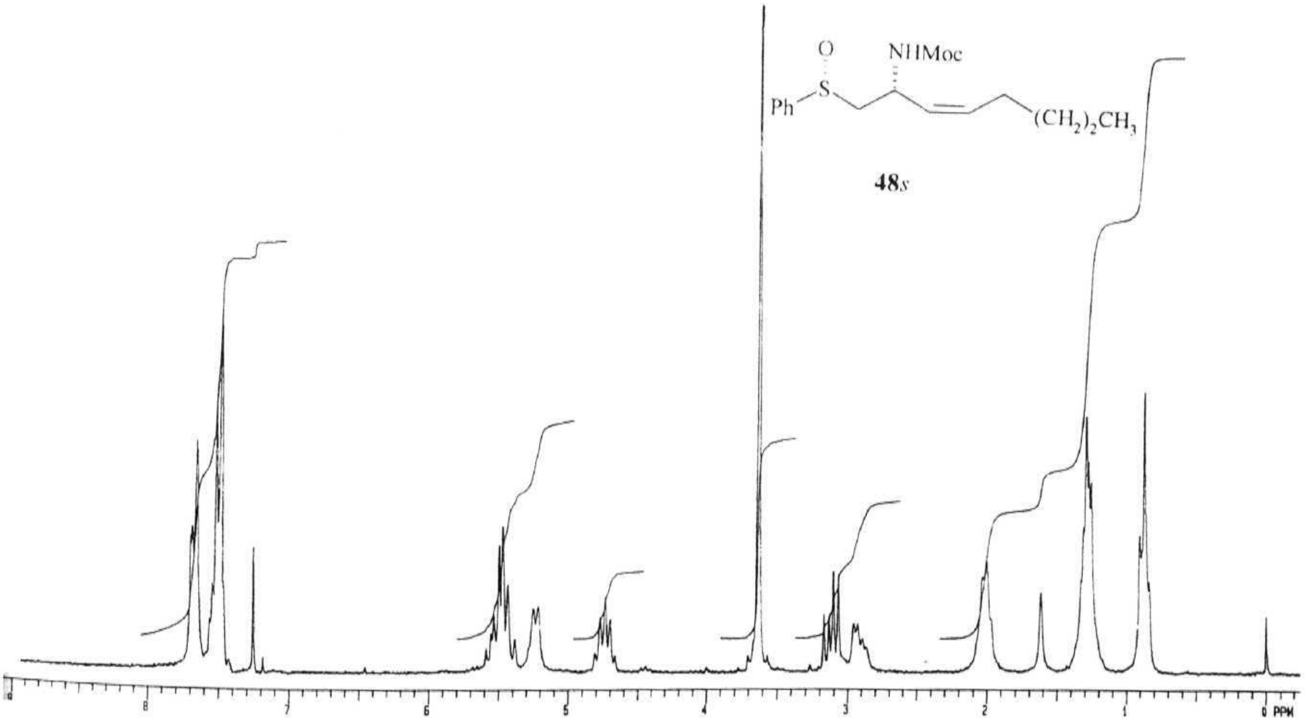
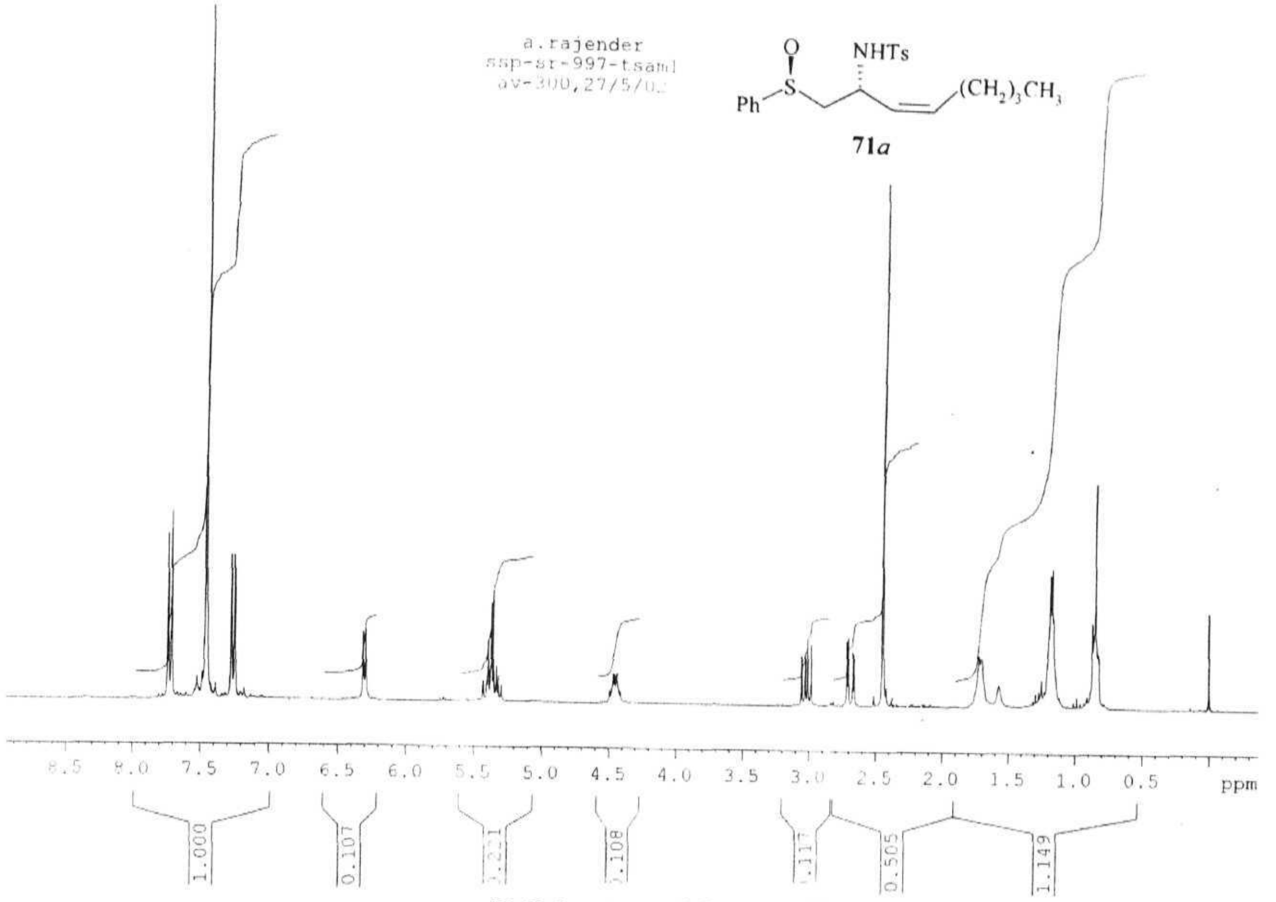


PMR Spectrum of Compound 48*a*



PMR Spectrum of Compound 48*s*



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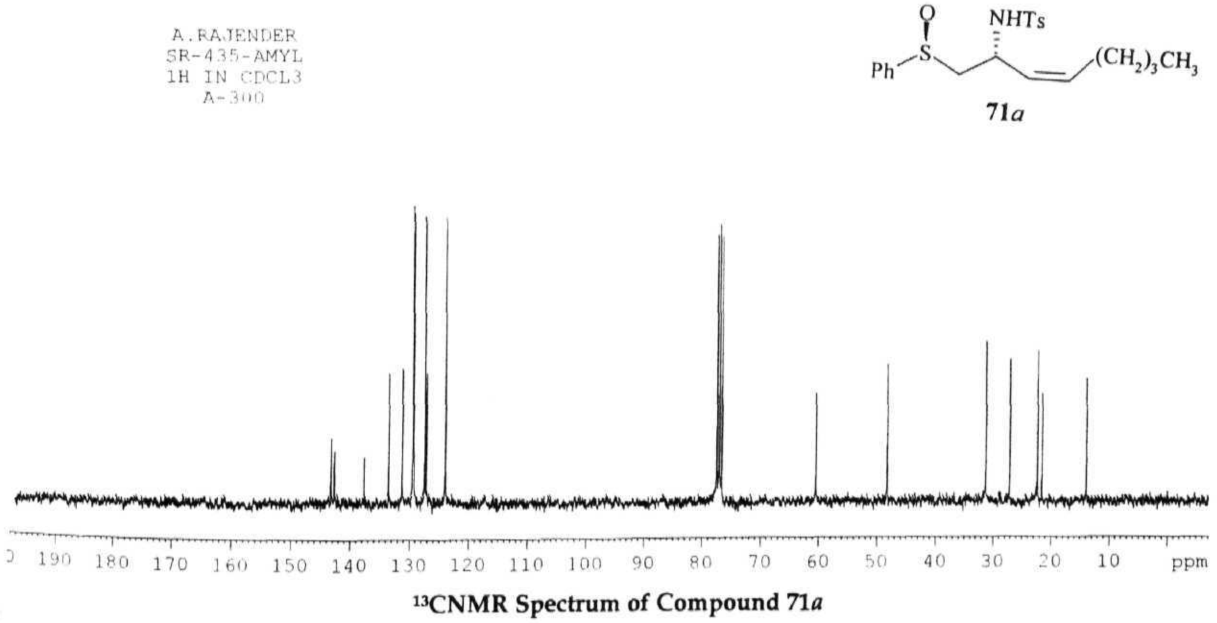
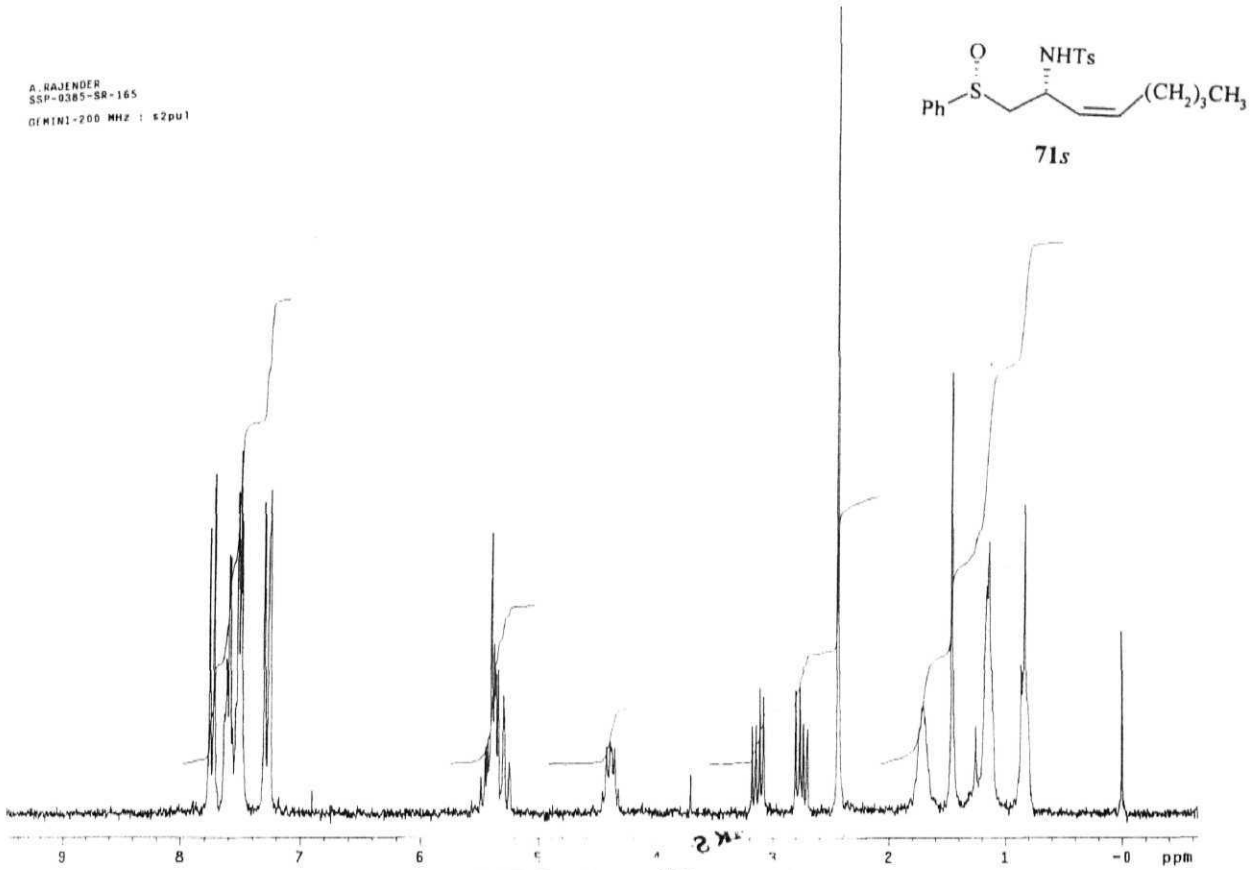


^{13}CNMR Spectrum of Compound 71*a*



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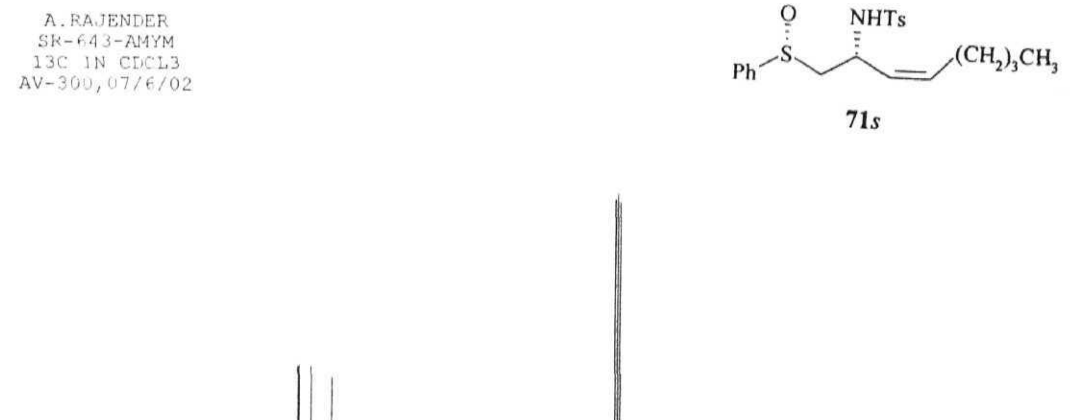

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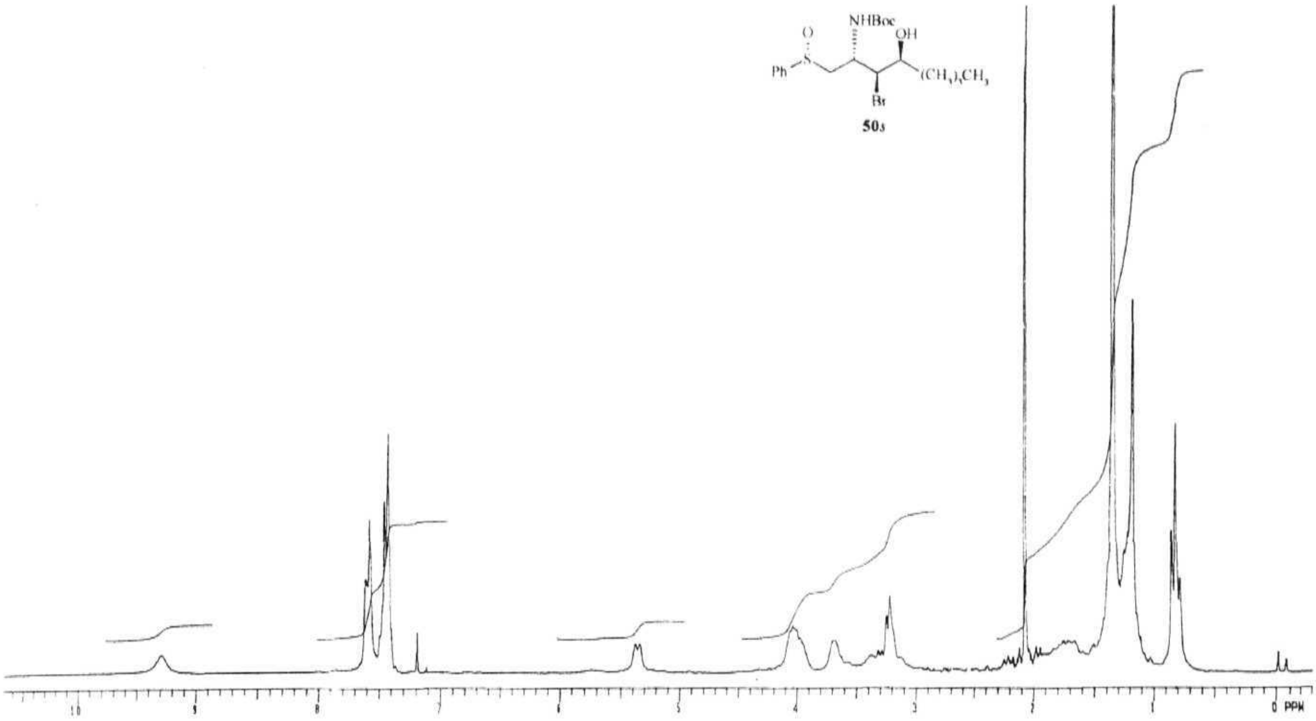

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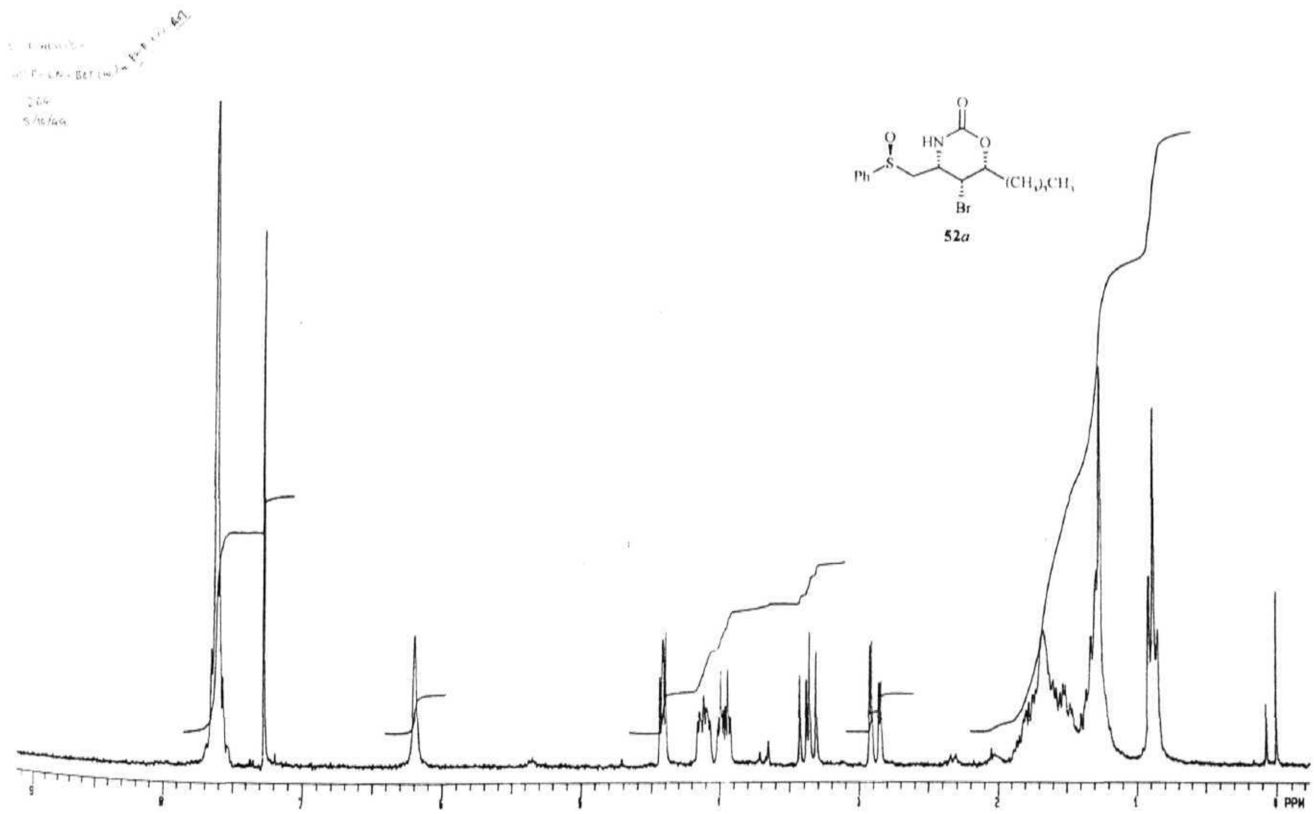
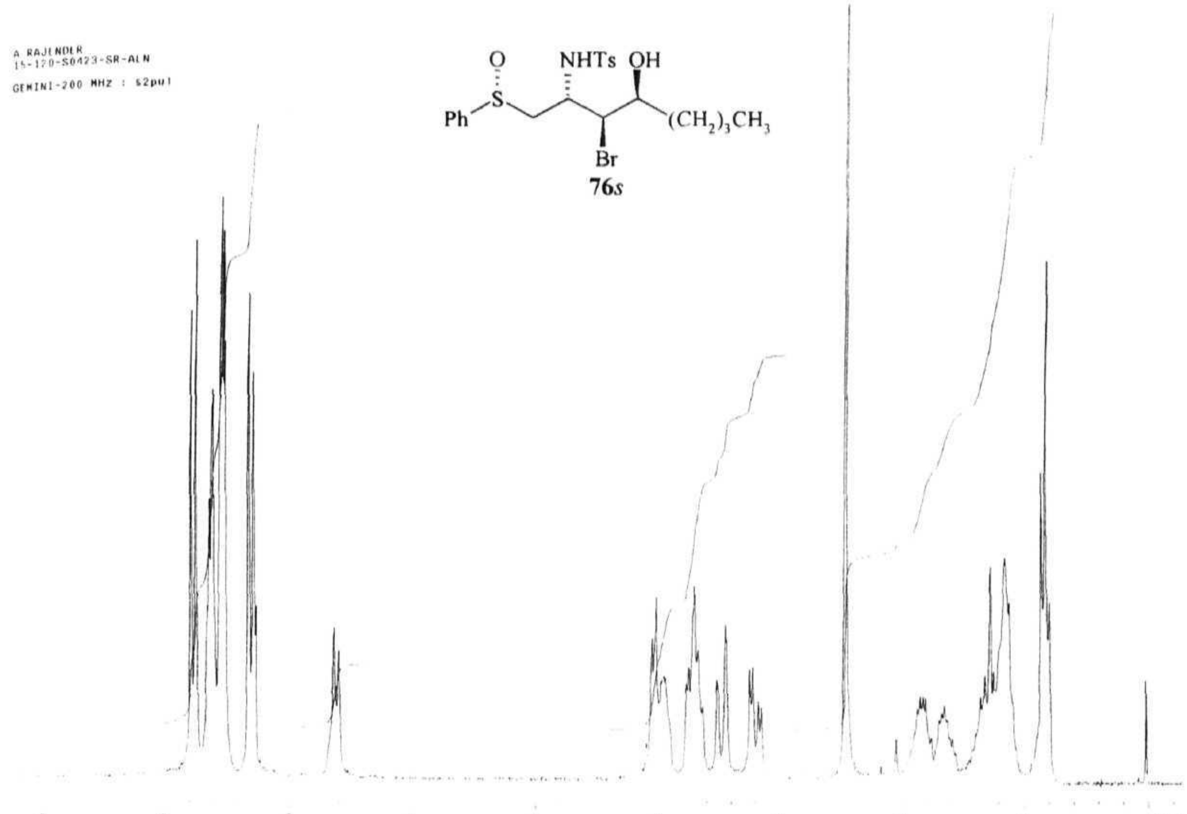
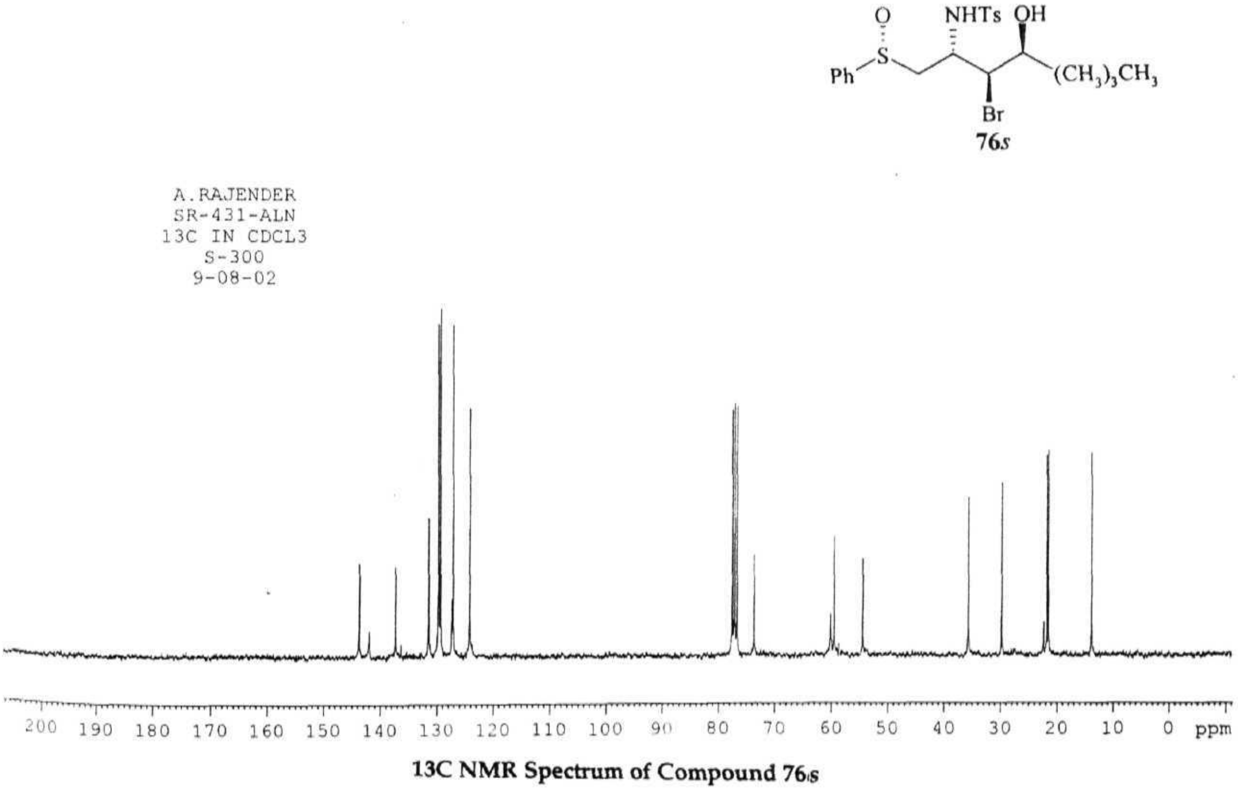


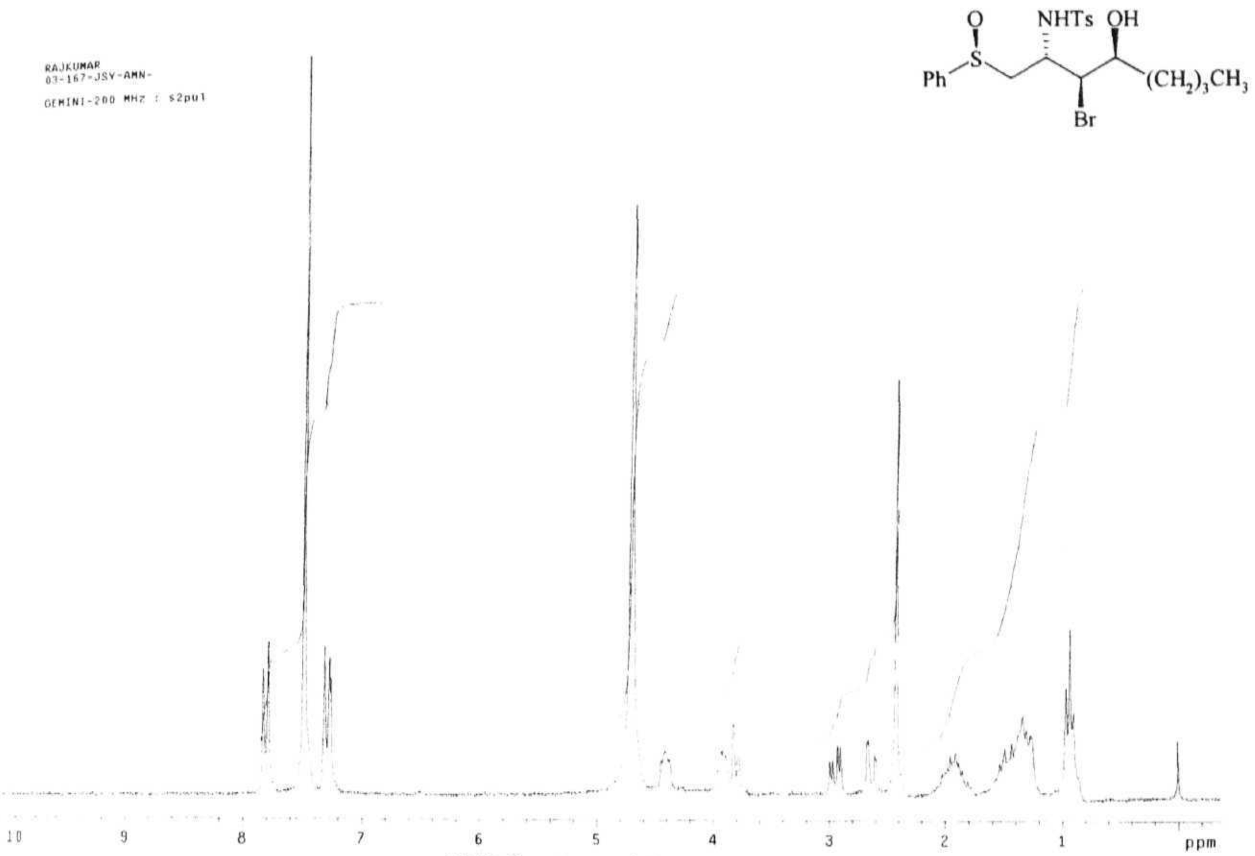
PMR Spectrum of Compound 52*a*



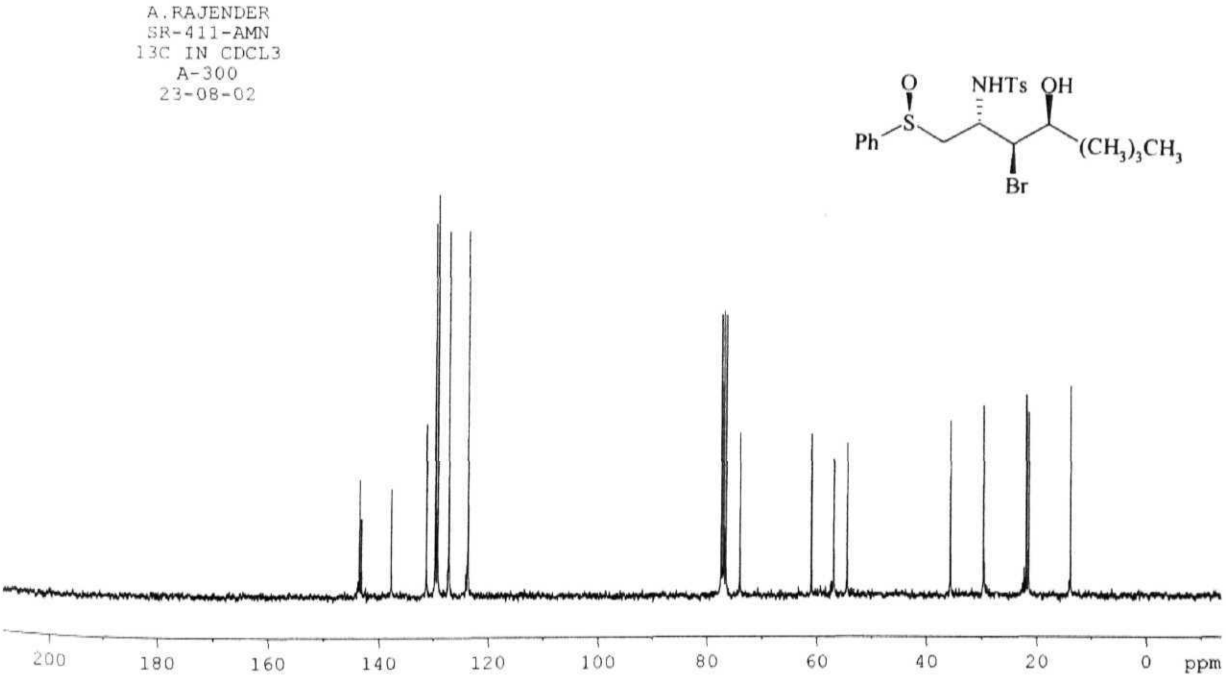
PMR Spectrum of Compound 76*s*



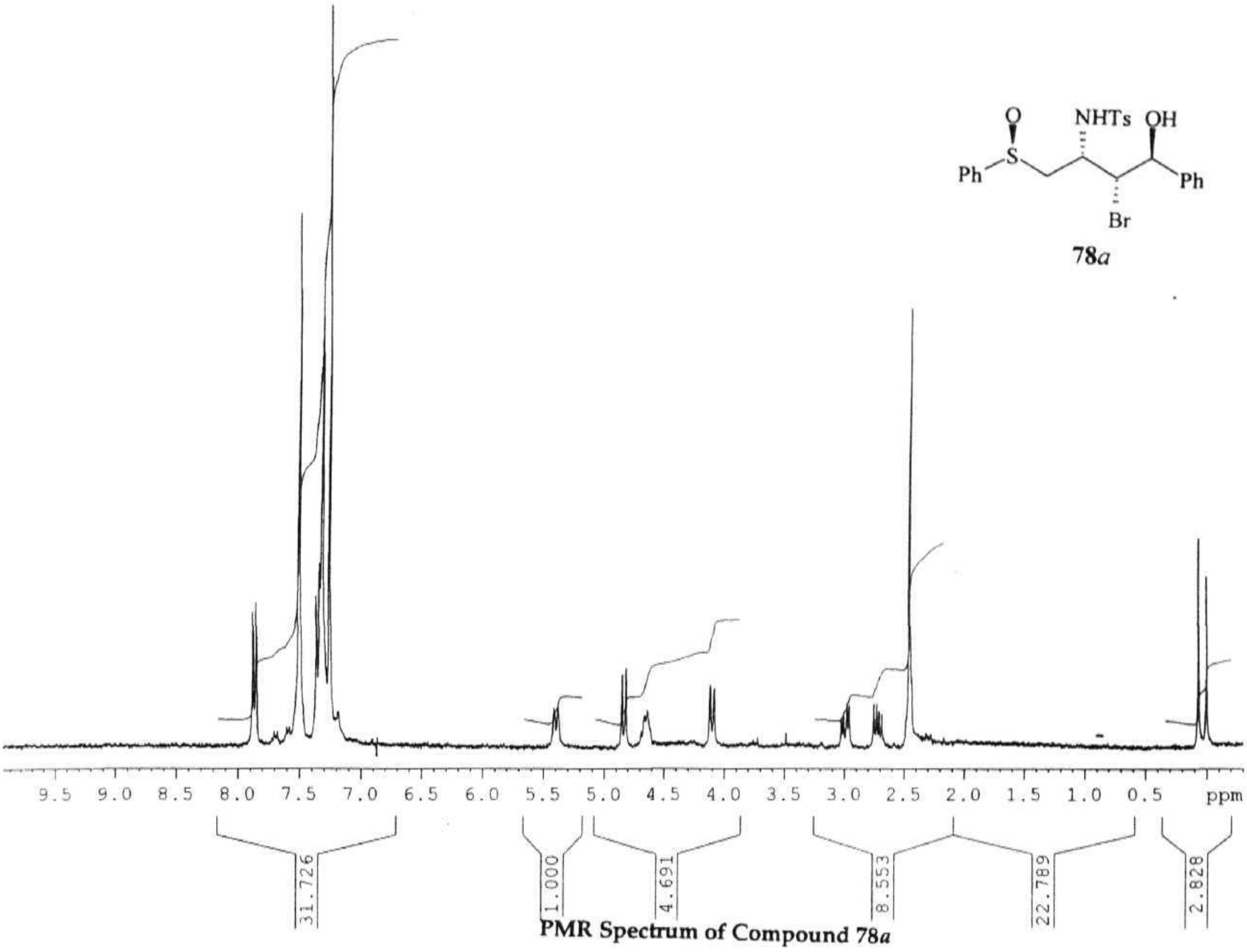
13C NMR Spectrum of Compound 76*s*



PMR Spectrum of Compound 76*a*

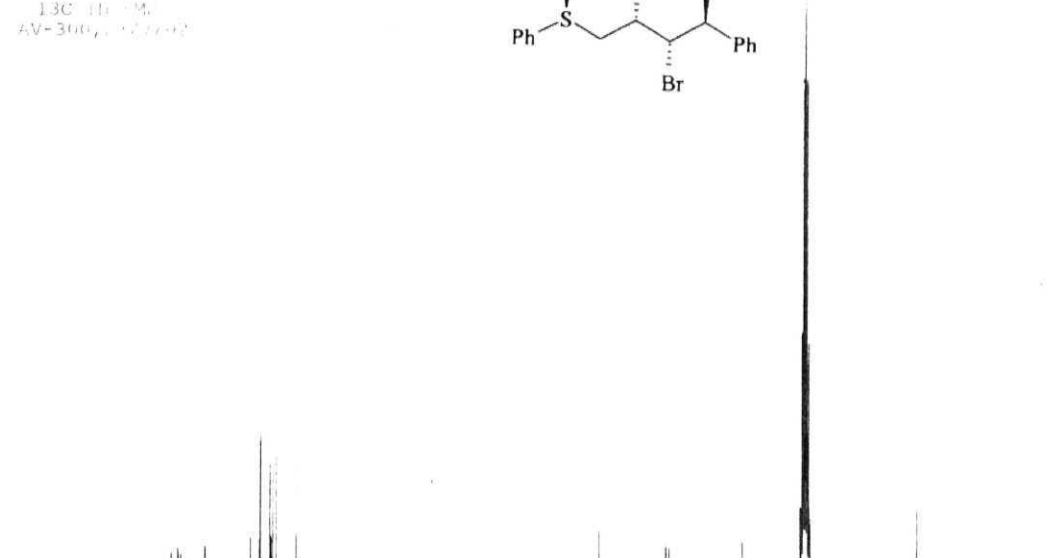


13C NMR Spectrum of Compound 76*a*

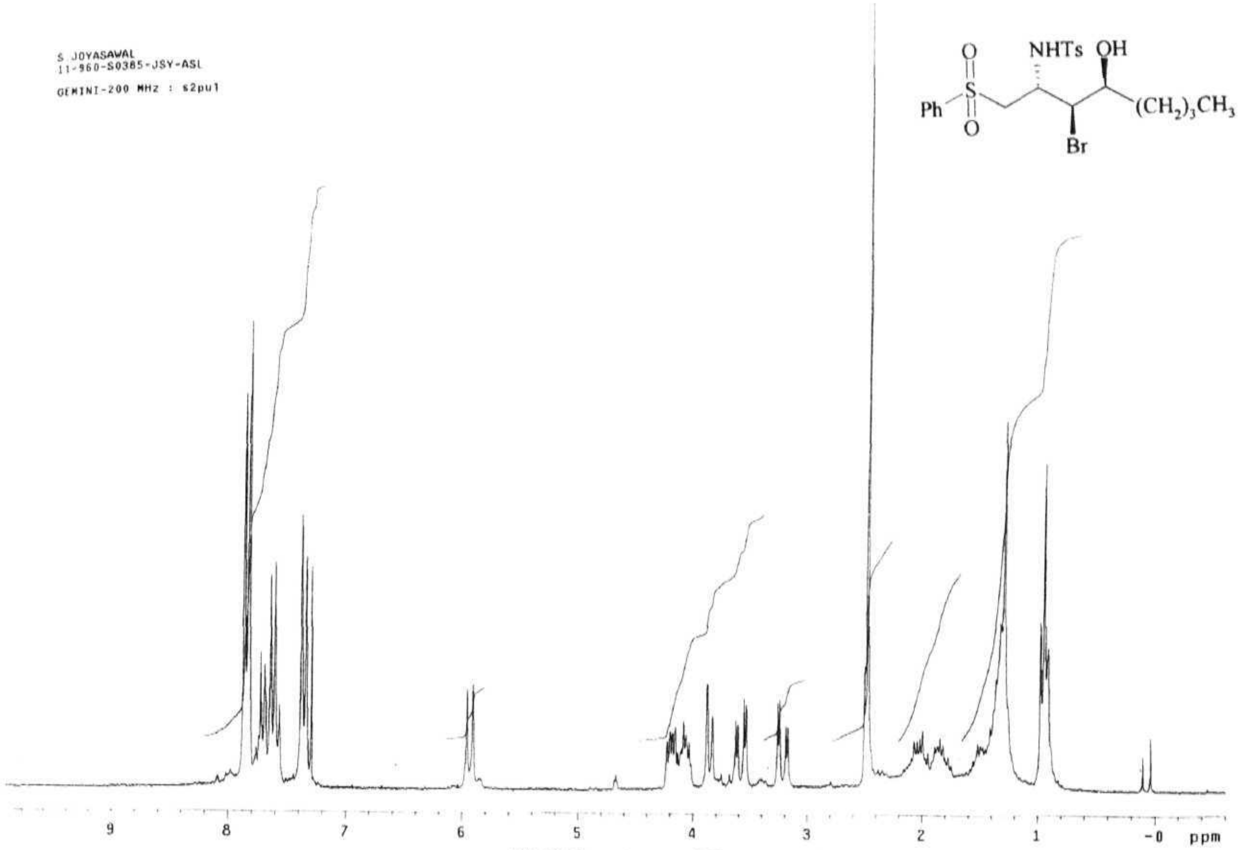


78*a*

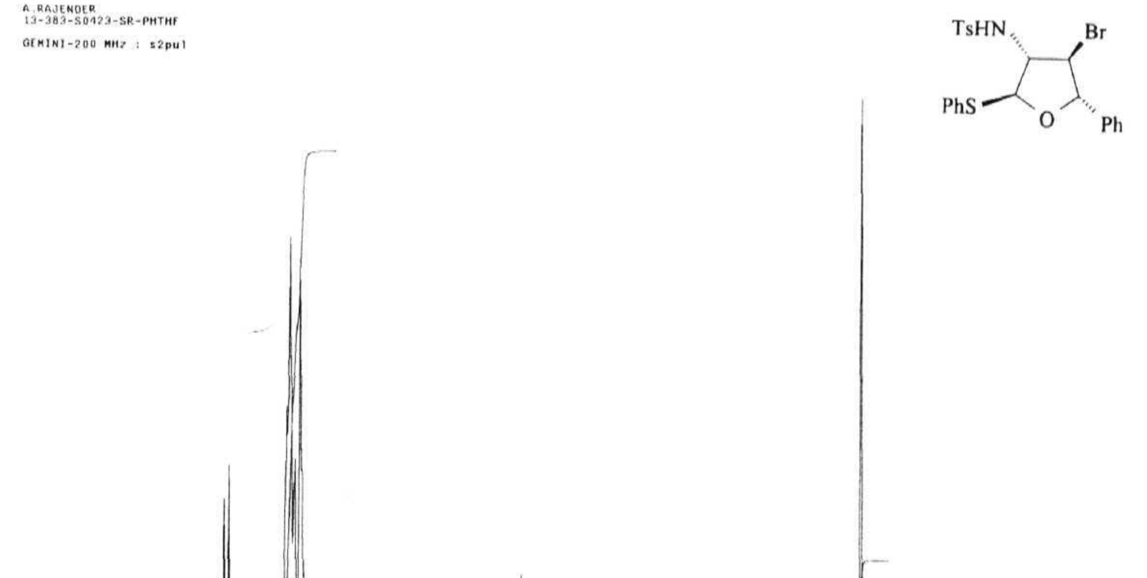
PMR Spectrum of Compound 78*a*



13C NMR Spectrum of Compound 78*a*



PMR Spectrum of Compound 82



PMR Spectrum of Compound 83

CHAPTER-II

Stereoselective synthesis of (1*R*,3*R*)-HPA-12, (-)-allosedamine and functionalized tetrahydrofurans

Section-A

Stereoselective synthesis of (1*R*,3*R*)-*N*-(3-hydroxy-1-hydroxymethyl-3-phenylpropyl)-dodecanamide (HPA-12)

&

Section-B

Stereoselective synthesis of (-)-allosedamine

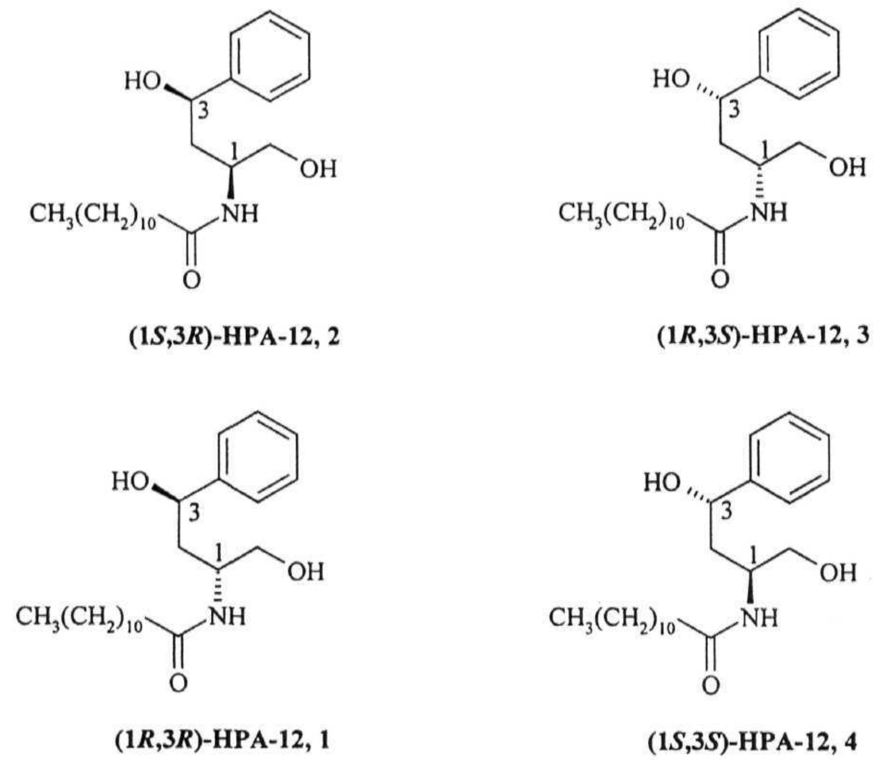
Introduction

Sphingolipids are ubiquitous constituents of membrane lipids in mammalian cells and play important roles in cell growth, differentiation, and apoptosis.[1] Moreover, together with cholesterol, sphingolipids in plasma membrane constitute detergent-resistant micro domains termed lipids rafts, which are involved in membrane trafficking and cell signaling.[2] *De novo* biosynthesis of sphingolipids in mammalian cells proceeds as follows.[3] The first step is the condensation of L-serine and palmitoyl-CoA, a reaction catalyzed by serine *palmitoyl transferase*, to generate 3-ketodihydrosphingosine, which is reduced to dihydrosphingosine. Dihydrosphingosine undergoes *N*-acylation followed by desaturation to generate ceramide. These reactions to produce ceramide occur at the cytosolic surface of the endoplasmic reticulum. Then, ceramide is delivered to the luminal side of the Golgi apparatus and converted to sphingomyelin by *sphingomyelin synthase* catalyzing the transfer of phosphocholine from phosphatidylcholine to ceramide.

Various natural and chemically synthesized compounds have been found to be highly selective, even if not strictly specific, inhibitors of sphingolipid synthesis. For example, sphingofungins and ISP-1 appear to be specific and potent inhibitors of serine palmitoyl transferase.[5] Fumonisins seem to inhibit (dihydro)sphingosine-*N*-acyltransferase specifically.[6] D-*threo*-1-Phenyl-2-decanoylamino-3-morpholino-1-propanol and some of its derivatives selectively inhibit GlcCer synthase.[7]

N-(3-Hydroxy-1-hydroxymethyl-3-phenylpropyl)dodecanamide (HPA-12), a novel analog of ceramide was found to be a specific inhibitor for sphingomyelin synthesis[8] in mammalian cells. Till date, no drug has been discovered that inhibits intracellular trafficking of sphingolipids, except for broad-spectrum inhibitors such as brefeldin A and energy poisons. HPA-12 inhibits ATP-dependent transport of ceramide from the endoplasmic reticulum to the site of sphingomyelin synthesis without inhibition of protein trafficking, thereby inhibiting conversion of ceramide to sphingomyelin, but not to GlcCer. HPA-12 can exist in four stereoisomeric forms (Scheme 1).

Scheme 1



(1*S*,3*R*)-HPA-12, 2

(1*R*,3*S*)-HPA-12, 3

(1*R*,3*R*)-HPA-12, 1

(1*S*,3*S*)-HPA-12, 4

Initial experiments with the mixture of *anti* isomers (2&3) and mixture of *syn* isomers (1&4) revealed that, only the former subgroup inhibited the *de novo* sphingomyelin synthesis. Examination of (1*R*,3*R*)-isomer and (1*S*,3*S*) individually showed that (1*R*,3*R*)-type inhibited *de novo* synthesis of sphingomyelin strongly, whereas (1*S*,3*S*)-type did so moderately. (1*R*,3*R*)-HPA-12 was also effective against HeLa cells, a human cervical carcinoma cell line, and HuH7 cells, a human hepatoma cell line.[1]

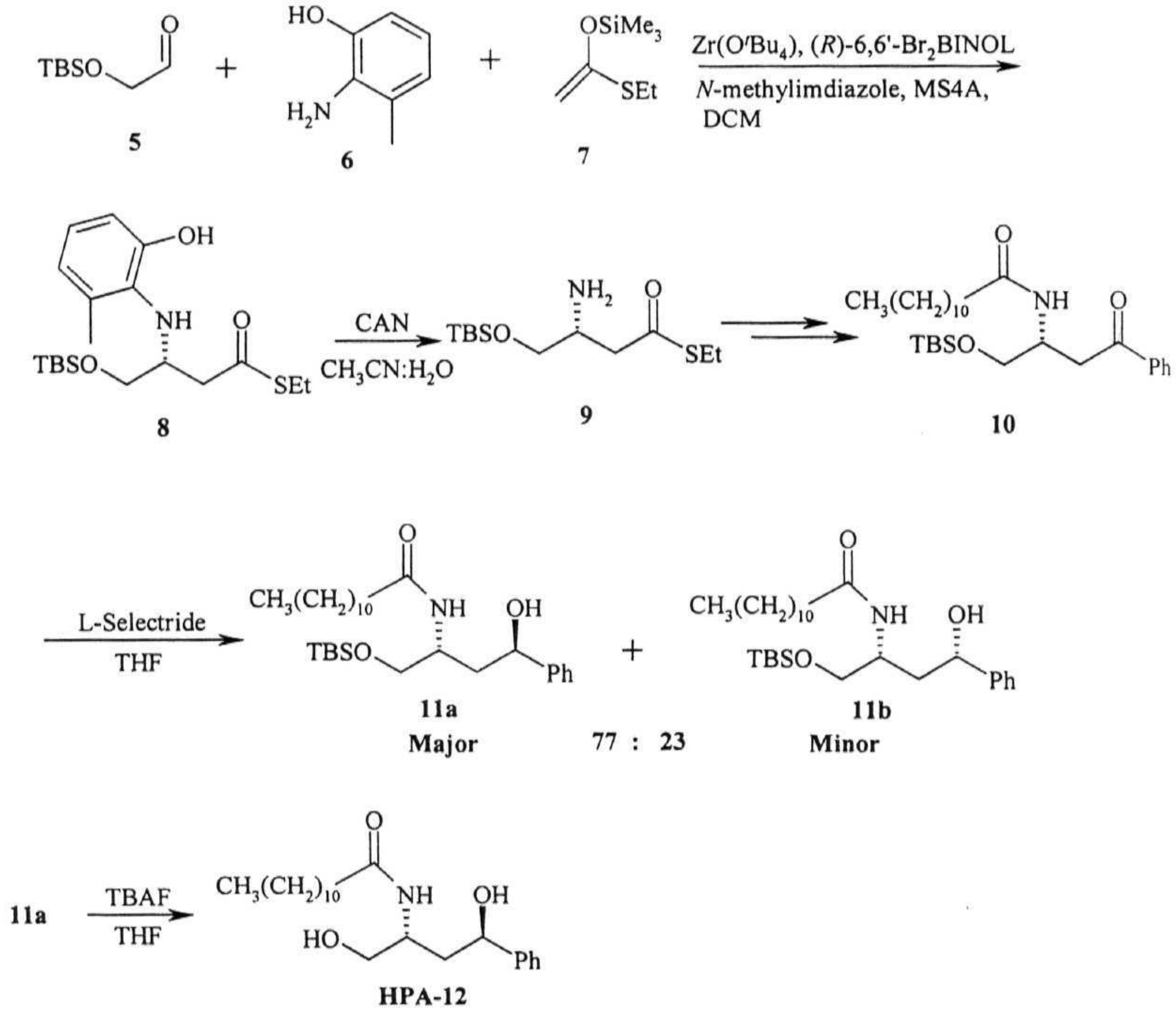
Earlier approaches to the synthesis of (1*R*,3*R*)-HPA-12

Three syntheses of (1*R*,3*R*)-HPA-12 are reported till date. Kobayashi and co-workers reported all of these. Asymmetric Mannich-type reaction was used as the key step.

First approach[9]:

Kobayashi *et al.* reported the first total synthesis of (1*R*,3*R*)-HPA-12 in 2001. This approach includes a chiral zirconium-catalyzed enantioselective Mannich-type reaction as the key step. A three component condensation of α-*tert*-butyldimethylsilyloxy acetalaldehyde **5**, 2-amino-3-methylphenol **6**, and 1-ethylthio-1-trimethylsiloxyethene **7** in the presence of a catalytic amount of a chiral zirconium complex afforded the adduct **8** in 47% yield in 80% ee. The compound **8** on treatment with cericammoniumnitrate afforded amino compound **9**. Acetylation of **9** under standard reaction conditions followed by treatment with diphenylcopper lithium in THF afforded the ketone **10** in 37% yield with 55% recovery of starting material. The *anti*-selective reduction of the ketone **10** using L-selectride proceeded in 54% de (Scheme 2). Removal of the silyl protection in major diastereomer **11a** furnished (1*R*,3*R*)-HPA-12.

Scheme 2

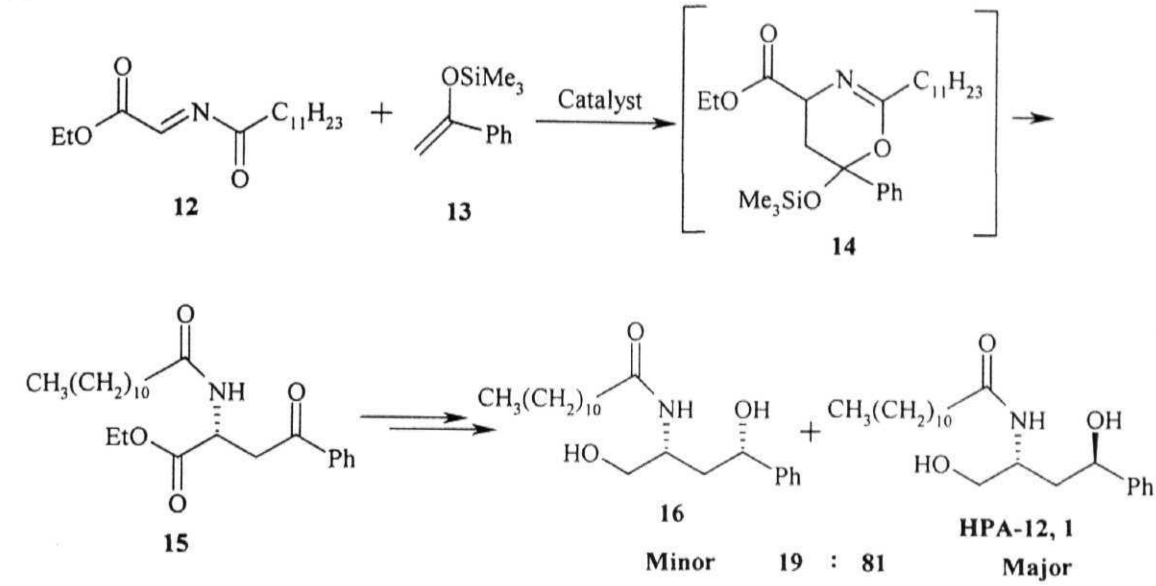


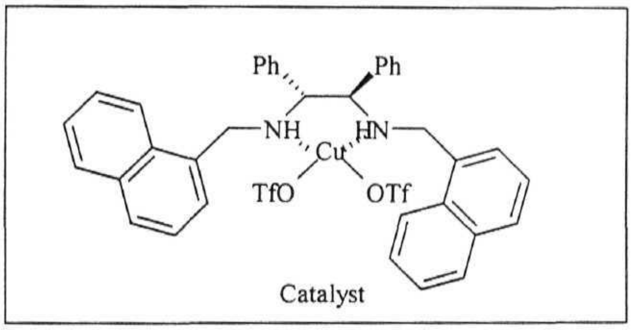
Second approach[10]:

The second approach to (1*R*,3*R*)-HPA-12 reported in 2002, was achieved by enantioselective Mannich-type reaction catalyzed by a chiral copper catalyst.

Mannich-type reaction of the *N*-acyliminoester **12,** prepared from the corresponding α-chloroglycine derivative, with the silyl enol ether **13,** derived from acetophenone, in the presence of catalyst 'C' afforded the adduct **15** in 94% ee. The Mannich-type adduct was treated with K-Selectride and then $LiBEt_3H$ to afford (1*R*,3*R*)-HPA-12 in 62% de.

Scheme 3



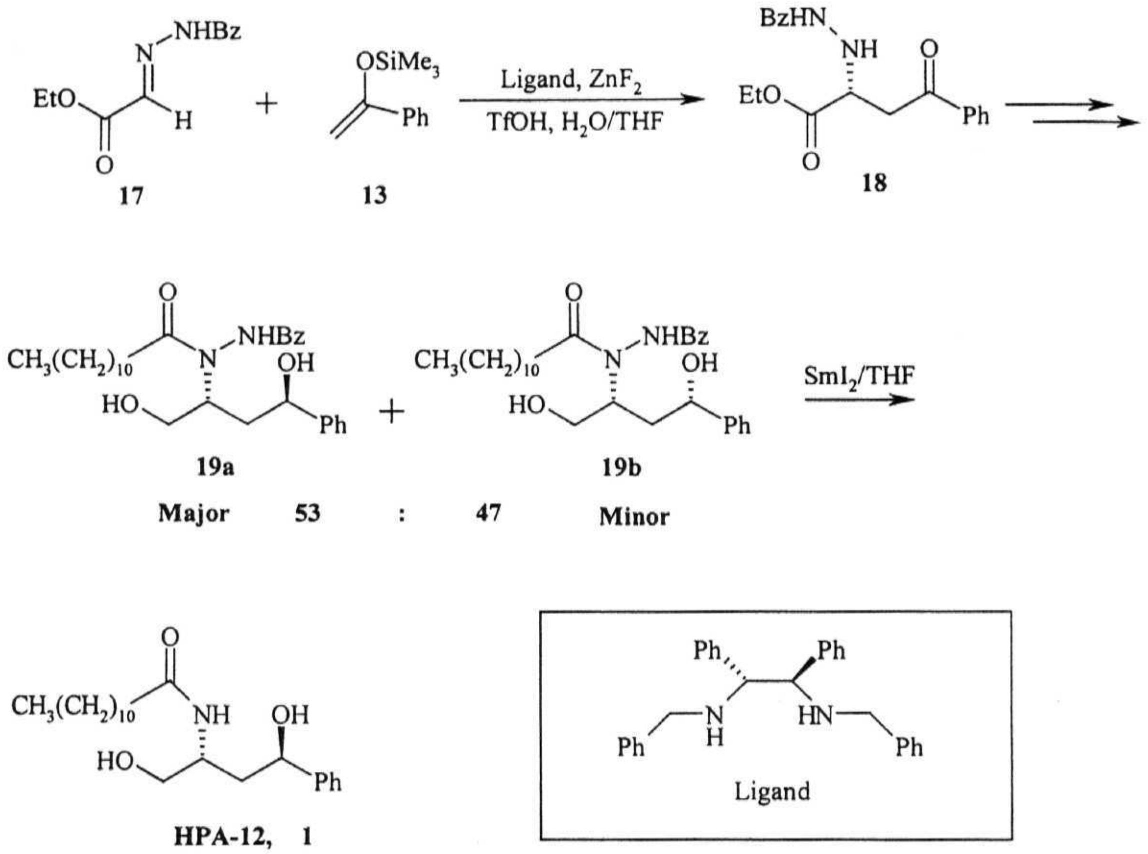


Catalyst

Third approach[11]:

Kobayashi *et al.* reported yet another synthesis of (1*R*,3*R*)-HPA-12 in 2002 employing the asymmetric Mannich-type reaction as the key step. The reaction between ester **17** and silyl enol ether **13** in the presence of ligand L and ZnF_2 afforded the adduct **18** in 94% ee. Mannich adduct **18** was *N*-acylated and the keto and ester groups were reduced by $NaBH_4$ in ethanol to afford the diols **19a** and **19b** in 47:53 ratio. Cleavage of N-N bond in *anti* diol **19a** using SmI_2 afforded (1*R*,3*R*)-HPA-12 (Scheme 4).

Scheme 4

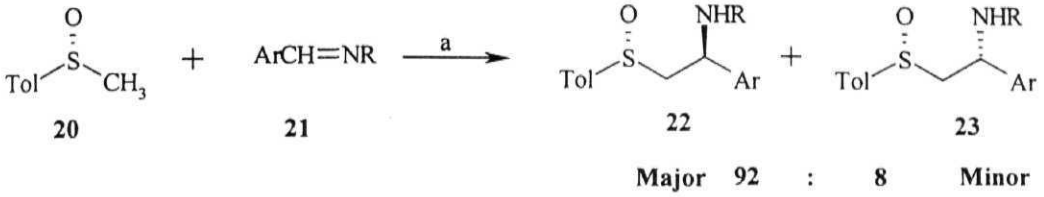


Diastereoselective additions of sulfoxide anion to imines:

The use of chiral sulfoxide-stabilized carbanions for asymmetric carbon-carbon bond formation, *via* alkylation or addition reactions to C=O and activated C=C double bonds, is the most synthetically powerful application of this chiral auxiliary and has been studied extensively.[12] However, the addition of chiral sulfoxide anions to the C=N bond of an achiral imine has received much less attention.[13]

In 1973, Tsuchihashi[13a] reported that the addition of the lithium carbanion of (*R*)-(+)-methyl *p*-tolyl sulfoxide to *N*-benzylidine aniline at 0 °C to -20 °C was a highly diastereoselective process. The generality of this method, however, was not demonstrated. Kagan[14] reported the diastereoselective addition of the lithium carbanion of **20** to **21** and *N*-benzylidenealkylamines. Employing the optimal conditions (0 °C for carbanion generation and -78 °C for addition of imine), diastereomeric sulfoxides **22** and **23** were obtained in a ratio of 92:8 (Scheme 4).

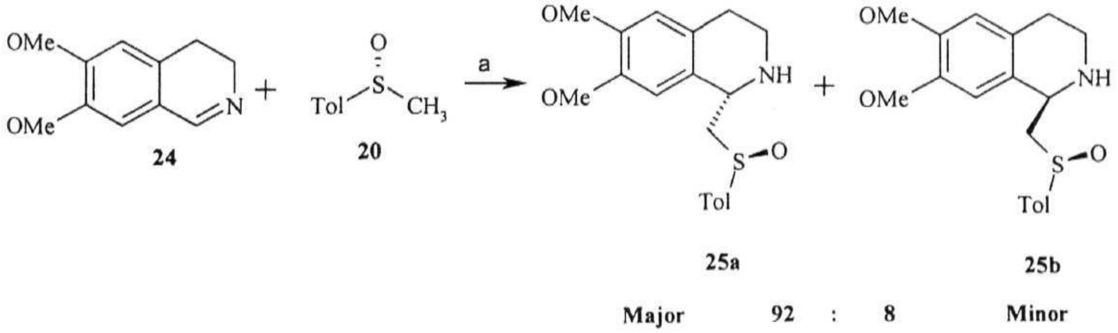
Scheme 4



Reagents and conditions: (a) LDA, THF, 0 °C, add **21** at -78 °C, 10 min.

Pyne and co-workers[15] reported the synthesis of (*R*)-(+)-tetrahydropalmitate via diastereoselective addition of anion derived from **20** to **24**. Generation of the carbanion and addition of the imine at -78 °C followed by stirring at 0 °C for 12 h afforded the diastereomers **25a** and **25b** in 92:8 ratio (Scheme 5).

Scheme 5

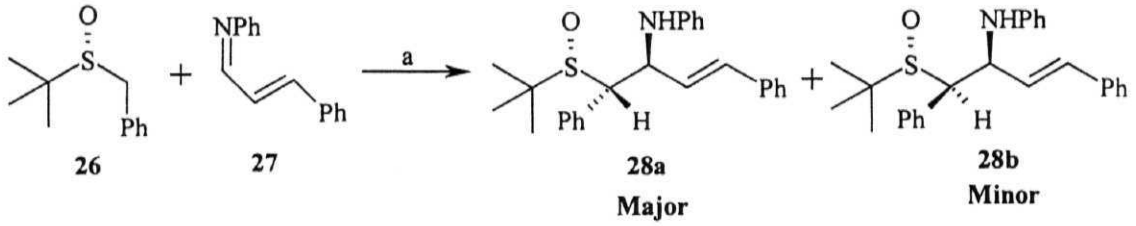


Reagents and conditions: (a) LDA, THF, -78 °C, add **20**, 1 h, then add **24**, 1 h, warm to 0 °C, 12 h.

A single report by Pyne and co-workers[16] detailed the addition of the carbanion from **26** to α,β-unsaturated imines. Generation of the carbanion from **26** and addition of the imine **27** to the resulting anion at -78 °C followed by stirring at

-78 °C for 5 h afforded the *anti* product in a highly diastereoselective fashion (>95% de) (Scheme 6).

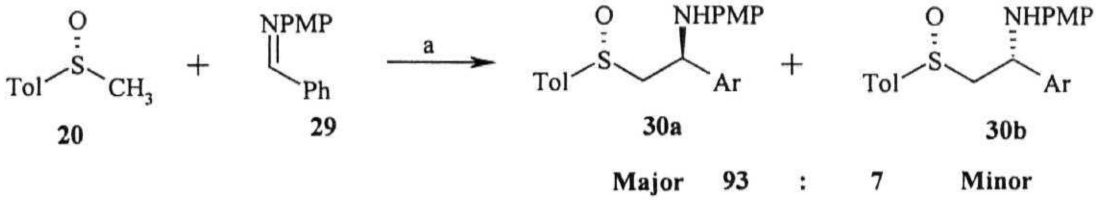
Scheme 6



Reagents and conditions: (a) *n*-BuLi, THF, -78 °C, $ZnCl_2$, 10 min, add **27**, -78 °C, 5 h.

Bravo *et al.*[13h] reported the asymmetric synthesis of arylglycinols via addition of lithium anion of **20** to *N*-(PMP)arylaldimines. Generation of the carbanion at 0 °C and addition of the imine to the anion at –70 °C followed by stirring at –70 °C for 15 min afforded the diastereomers **30a** and **30b** in 93:7 ratio (Scheme 7).

Scheme 7



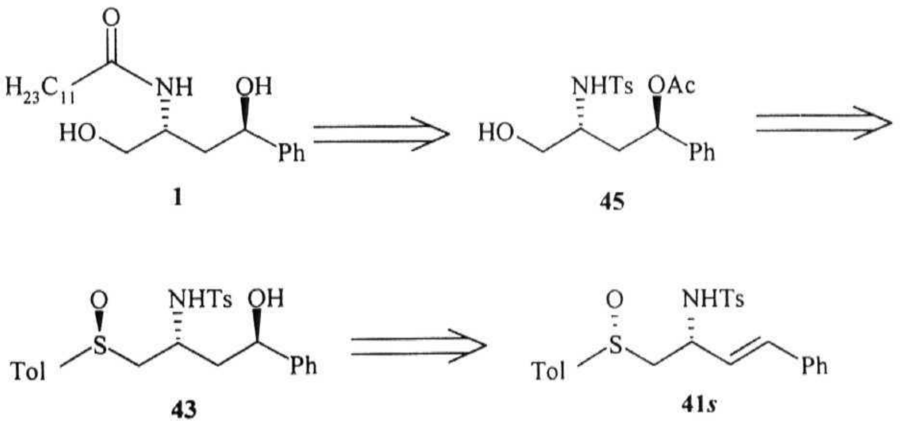
Reaction conditions: (a) LDA, THF, -0 °C, add **20**, 15 min, cool to -70 °C then add **29**, 15 min.

Present work

As disclosed earlier in this section, three asymmetric routes to (1*R*,3*R*)-HPA-12 were reported by Kobayashi *et al.* All the approaches used asymmetric Mannich-type reaction as the key step and proceeded with moderate selectivity particularly while attempting to introduce the chiral center bearing the hydroxy group. This section deals with the stereo- and regioselective synthesis of (1*R*,3*R*)-HPA-12 by a route that exploits the potential of the sulfinyl moiety as an intramolecular nucleophile to heterofunctionalize olefins.

By a retrosynthetic analysis (Scheme 7), (1*R*,3*R*)-HPA-12 was envisioned to be derived from the hydroxy acetate **45**, which in turn can be obtained from the alcohol **43**. The compound **43** can be readily obtained from the β-aminosulfoxide **41*s***.

Scheme 7

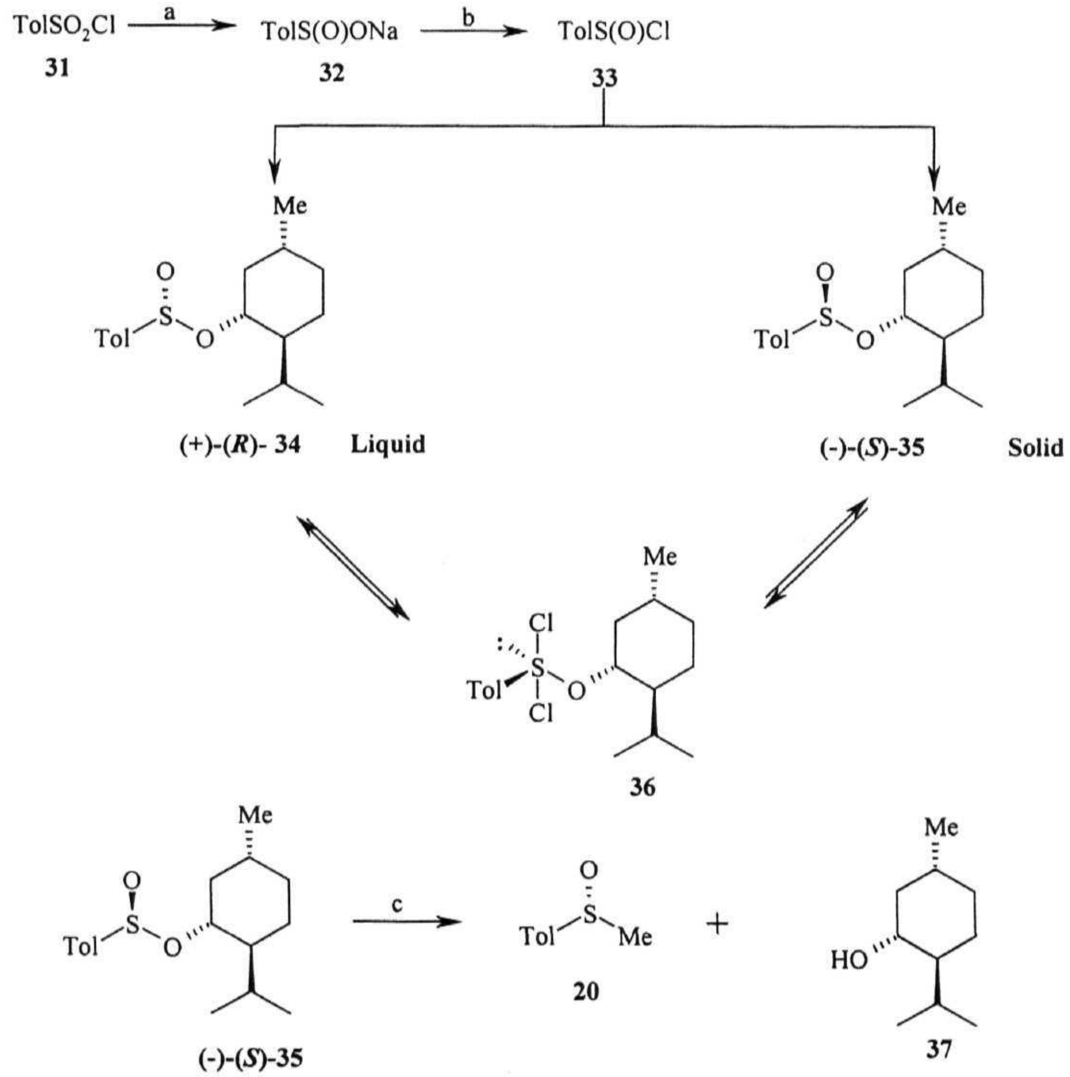


Preparation of (*R*)-(+)-Methyl *p*-tolylsulfoxide

(*R*)-(+)-Methyl *p*-tolylsulfoxide **20** was prepared by Andersen's protocol[18] by the nucleophilic addition of MeMgI to diastereomerically pure (S_S)-menthyl *p*-toluenesulfinate which proceeds with inversion of the configuration at sulfur.

Treatment of *p*-tolylsulfinyl chloride **33** with (-)-menthol afforded a mixture of diastereomeric menthyl *p*-tolylsulfinates **34** and **35**. Equilibration of the epimers by treatment with catalytic hydrochloric acid in acetone led to the displacement of the equilibrium by precipitation of the (S_S) diastereomer to afford **35** in 80% yield[19] (Scheme 8).

Scheme 8



Reagents and conditions: (a) Na_2SO_3, $NaHCO_3$, H_2O, 80 °C, 3 h, 90%; (b) $SOCl_2$, benzene, 0 °C to r.t., 2 h, add (-)-menthol, pyridine, ether, r.t., 1 h, recrystallization in acetone, HCl, –20 °C, 80%; (c) CH_3MgI, benzene, 0 °C, r.t., 2 h, 80%.

The first objective in the synthesis was the preparation of the β-protectedaminosulfoxide **41*s*** with good diastereoselectivity via addition of the lithium anion generated from (*R*)-(+)-methyl *p*-tolylsulfoxide **20** to imine **40**. The imine **40** was synthesized by following the protocol reported by Proctor *et al.*[20] Thus, condensation of cinnamaldehyde **38** with *p*-toluenesulfonamide **39** in the presence of $BF_3.Et_2O$ afforded imine **40**. The PMR spectrum of **40** showed resonances at δ 8.75 (d) for C*H*NTs proton, δ 7.82-7.32 (m) for the aromatic protons and one of the olefinic proton. The other olefinic proton resonated at δ 6.97 (dd) and the methyl group appeared as a singlet at δ 2.45 (s). As already noted by Kagan *et al.*[14] the stereoselectivity in the condensation reaction is influenced by the reaction conditions which includes the temperatures of anion generation, temperature of condensation and duration of the reaction. Therefore preparation of β-toluenesulfonamido sulfoxides (**41*a*** and **41*s***) was investigated by varying the temperature of a) the anion generation and b) the condensation of the resulting anion with the imine. Addition of the anion derived from **20** (1.0 eq.), using LDA to the imine **40** (1.1 eq.) cooled at –43 °C, proceeded with 62% conversion in 30 min (entry 1), to yield a mixture of the diastereomers **41*s*** and **41*a*** in a ratio of 58/42, respectively. Next, a series of reactions were performed varying the temperature of deprotonation of the starting sulfoxide and addition of imine. Thus, addition of lithium anion of **20**, prepared at -30 °C, to the imine at -78 °C gave a mixture of **41*s*** and **41*a*** in 70/30 ratio (entry 2). Under the same reaction conditions, addition of 1 eq. of $BF_3.Et_2O$ to the imine did not improve the ratio of formation of **41*s*** isomer (entry 3). The reaction of lithium anion of **20**, prepared at -70 °C, with the imine **40** at -70 °C gave **41*s*** and **41*a*** in a ratio of 75/25 (entry 4). Addition of the anion prepared at -70 °C, to the imine at -70 °C followed by stirring 0 °C for 1.5 h afforded almost a 1:1 mixture of diastereomers (entry 5).

Table I: Addition reactions between imine 40 and lithium (*R*)-methyl *p*-tolyl sulfoxide 20

Entry	T1[a] °C	T2[b] °C	Time min	Yield (%)	Ratio[c] (2*R*,*R*$_S$)	 (2*S*,*R*$_S$)
1	-43 °C	-43 °C	30	62[e]	58	42
2	-30 °C	-78 °C	15	82	70	30
3	-30 °C	-78 °C	15	78	68	32
4	-70 °C	-70 °C	15	81	77	23
5	-70 °C	-70-0 °C	90	71	55	45

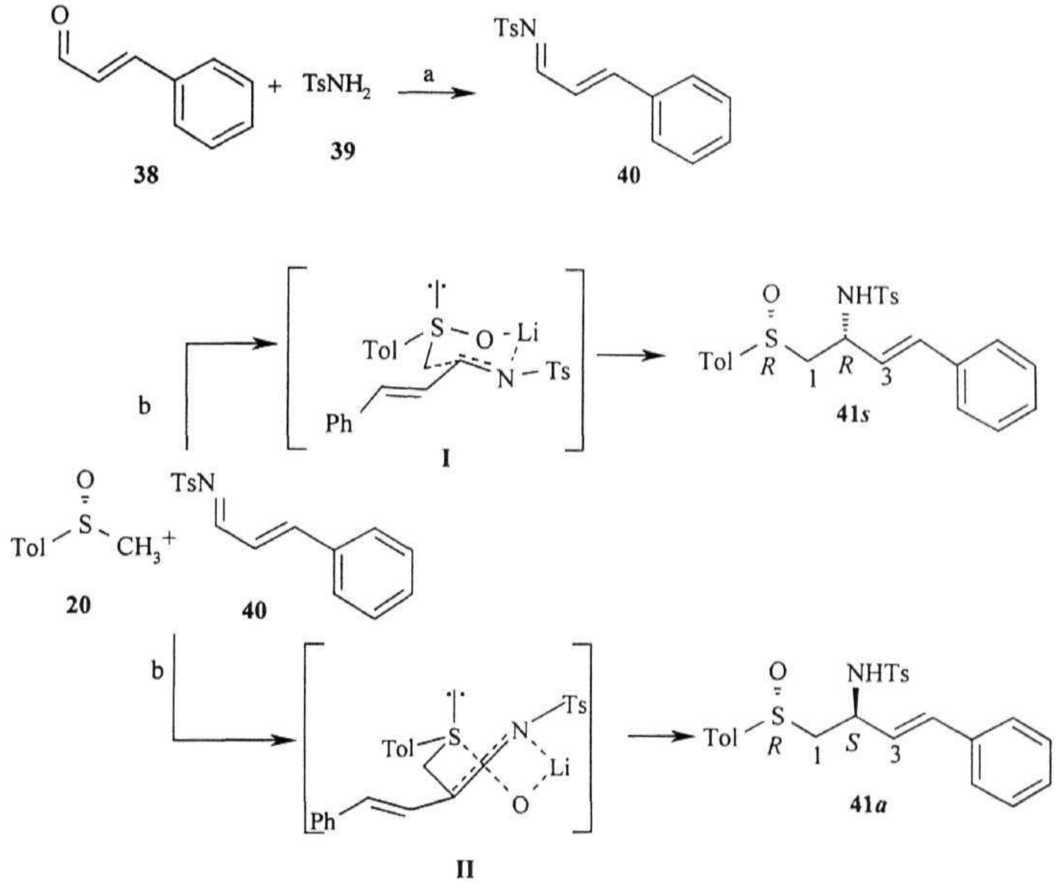
[a] Temperature at which lithium (*R*)-methyl *p*-tolyl sulfoxide was formed using LDA; [b] Temperature at which the anion condensed with the imine; [c] Ratios were determined by PMR analysis of the crude reaction mixture; [d] 1 eq. of $BF_3.Et_2O$ was added along with imine; [e] Some unreacted imine also observed.

Observation of the table reveals the following characteristics.

- The reactions proceeds under kinetic control at –78 °C. -70 °C show kinetic control.
- Equilibration of the diastereomers occurs at higher temperatures and is completed in 1.5-2 h time at 0 °C temperature (entry 5) affording almost equal amounts of the diastereomers.
- The reaction conducted in the presence of $BF_3.Et_2O$ did not improve the diastereomeric ratio.

The approach of the α-sulfinyl carbanion to the *si* face and *re* face of the imine group would furnish the diastereomers **41*s*** and **41*a*** respectively (Scheme 9). The sulfoxides were separated by column chromatography and the configuration assigned by comparing the chemical shift for the C2 H proton with the diastereomers **40*s*** and **40*a*** reported in Chapter I, Table I.

Scheme 9

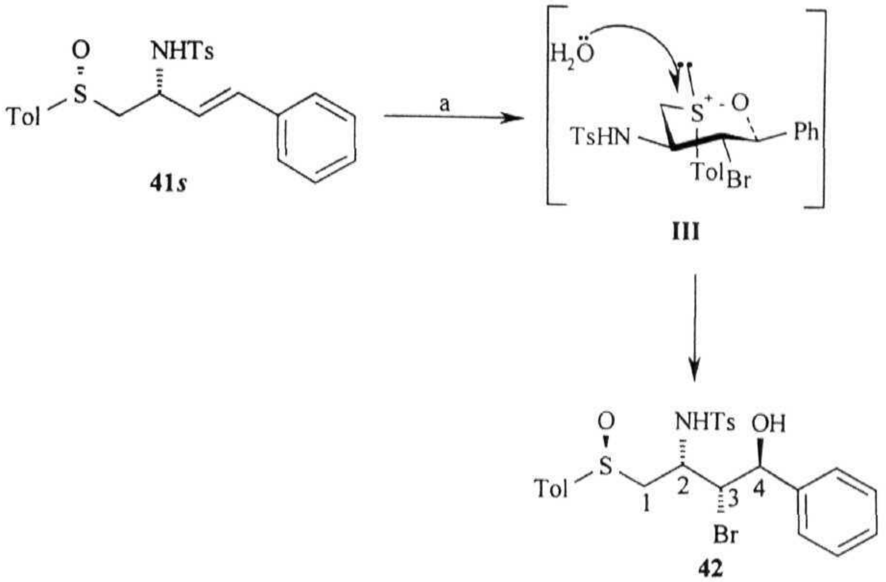


Reagents and conditions: (a) BF$_3$.Et$_2$O, benzene, reflux (Dean and Stark apparatus), 2 h, 73%; (b) LDA, THF, -78 ºC, add **20**, 20 min, then add **40**, 15 min, 81%.

The (R_S,R_C) diastereomer showed resonances at δ 6.30 (d) for C*H*Ph, δ 6.09 (d) for the N*H*, δ 5.88 (dd) for C3 *H*, δ 4.43-4.26 (m) for the C*H*NTs, δ 3.11 (dd) and 2.89 (dd) for C*H*$_2$SO in its PMR spectrum. The (R_S,S_C) diastereomer showed resonances at δ 6.48 (d) for the N*H*, δ 6.41 (d) for C*H*Ph, 6.03 (dd) for C3 *H* proton, δ 4.58-4.42 for the C*H*NTs proton, δ 2.94-2.85 for C*H*$_2$SO. The C*H*N proton of **40***s* also appears upfield at δ 4.38 relative to the C*H*N of **40***a* which resonates at δ 4.52.

Upon subjecting **41***s* to treatment with NBS in toluene in the presence of water at ambient temperature, the bromohydrin **42** was obtained regio- and stereoselectively. The structure assigned to it was supported by its PMR spectrum, which showed resonances at δ 7.86 (d) for the aromatic protons *ortho* to the sulfoxide group, δ 4.85 (dd) for the benzylic proton, δ 4.70-4.56 (m) for C*H*NTs, δ 4.06 (d) for C*H*Br and the absence of signals for the olefinic protons. The structure assigned to **42** was further supported by its mass spectrum which showed *m/z* 536 $[M+H]^+$ and 538 $[M+2+H]^+$ peaks. The observed regio- and stereoselectivity can be explained through the intermediacy of a sulfoxonium salt (**III**) formed by the 6-*endo* nucleophilic attack by the sulfinyl group onto the olefin π-complexed to the bromonium ion, followed by the attack of water on sulfur in a S_N2 fashion resulting in inversion of configuration at sulfur (Scheme 10).[22] The orientation as indicated for the hydroxy group and bromine at C-3 and C-4 respectively is expected from an overall *trans* addition of the electrophile and nucleophile across the double bond.[23] A coupling constant of J = 9.7 Hz for the C3 methine proton with C4 methine proton further supported the geometry of the substituents at C3 and C4 carbon. The regioselective 6-*endo* attack by the internal sulfinyl nucleophile could be attributed to the stabilization of the partial positive charge at the C4 (benzylic) carbon by the phenyl group.

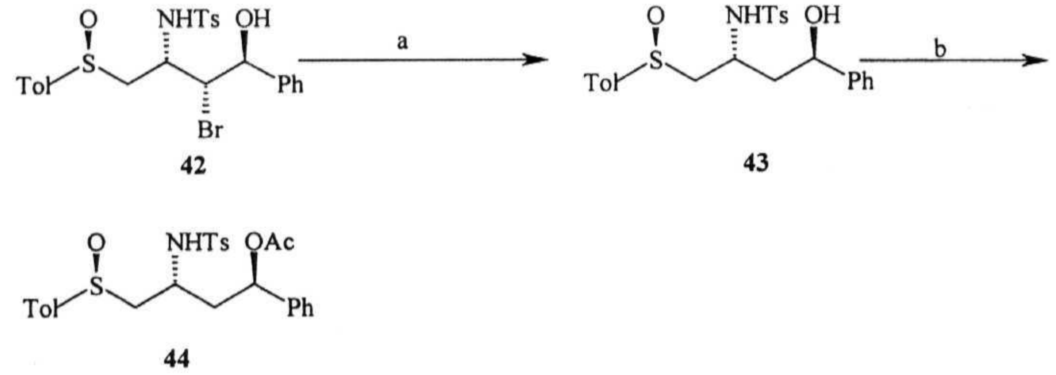
Scheme 10



Reagents and conditions: (a) NBS, H_2O, toluene: $CHCl_3$, r.t., 1 h, 84%.

The bromine atom in **42** was removed by treatment with *n*-Bu_3SnH in the presence of catalytic amounts of AIBN in benzene. The PMR spectrum of the compound **43** showed resonances at δ 4.87 (d) for the benzylic proton, δ 4.58-4.52 (m) for C*H*NTs, C3 methylene protons appeared at δ 2.12-1.96 (m) and δ 1.91-1.75 (m) and the signal for C*H*Br was absent. Acetylation of the benzylic hydroxy group in **43** by treatment with acetic anhydride in the presence of pyridine yielded **44**. The benzylic proton appeared downfield at δ 5.71 (dd) and the methyl of the acetyl group appeared at δ 2.02 (s) in the PMR spectrum of compound **44** (Scheme 11).

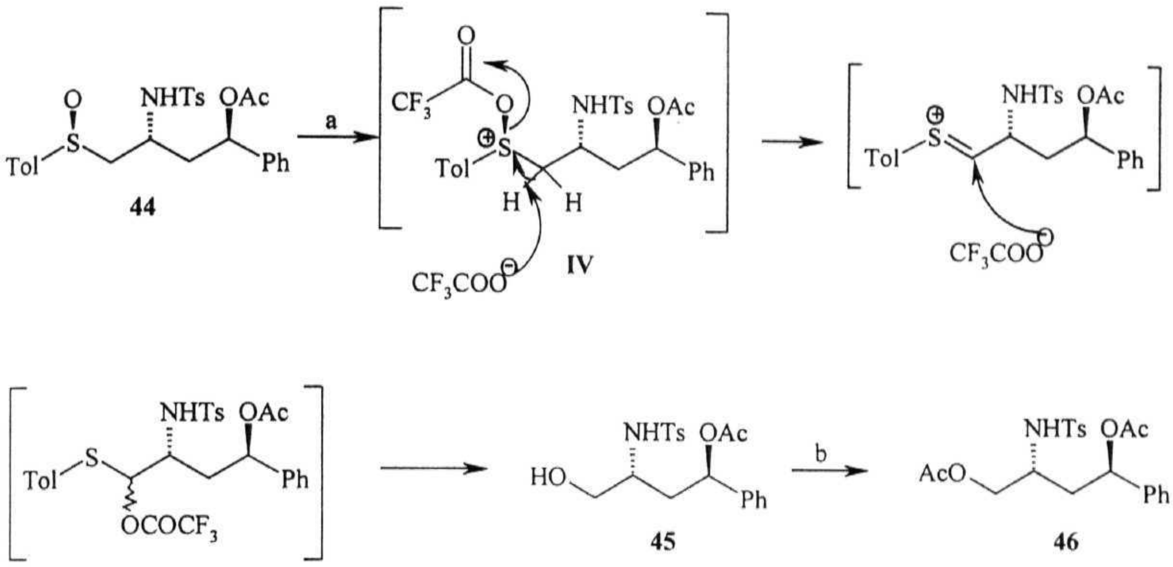
Scheme 11



Reagents and conditions: (a) *n*-Bu_3SnH, AIBN (cat.), benzene, reflux, 1.5 h, 76%; (b) Ac_2O, pyridine, r.t., 1 h, 96%.

The next step in the synthesis warranted the transformation of the toluenesulfinyl moiety to a hydroxy group. This was achieved by subjecting **44** to Pummerer reaction[24] conditions. Thus, **44** on treatment with TFAA and 2,6-lutidine in acetonitrile afforded the intermediate (IV) which without isolation was subjected to treatment with aqueous K_2CO_3 solution followed by $NaBH_4$ to afford alcohol **45**. The structure assigned to the compound **45** was confirmed by its PMR spectrum, which showed signals at δ 5.60 (dd) for the benzylic proton, δ 4.13-4.04 (m) for C*H*NTs, δ 3.38-3.16 (m) for C*H*$_2$OH and absence of the signals corresponding to the C*H*$_2$SO. Alcohol **45** was acetylated by treatment with acetic anhydride in the presence of pyridine to yield the diacetate **46** (Scheme 12), which revealed resonances for C*H*$_2$O at δ 4.0-3.84 (m) and presence of the two-acetyl methyl groups in its PMR spectrum.

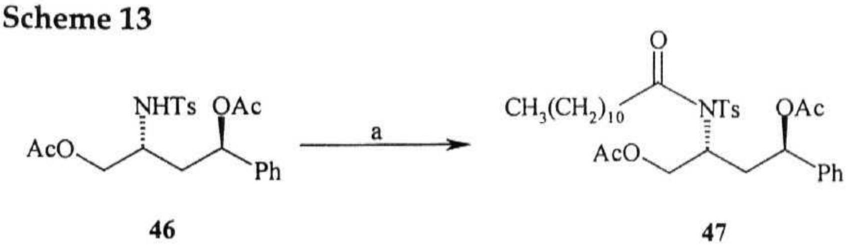
Scheme 12



Reagents and conditions: (a) TFAA, 2,6-lutidine, 5 min, K_2CO_3, $NaBH_4$, CH_3CN, 0 °C, 15 min, 78%; (b) Ac_2O, pyridine, r.t., 2 h, 97%.

Acylation of **46** with lauryl chloride in the presence of Et_3N and catalytic amounts of DMAP afforded the amide **47** (Scheme 13). The C*H*N signal appeared downfield at δ 4.73-4.58 (m), and the C*H*$_2$O resonated downfield at δ 4.50-4.32 (m) relative to **46**. The PMR spectrum also clearly revealed the protons corresponding to the long alkyl chain.

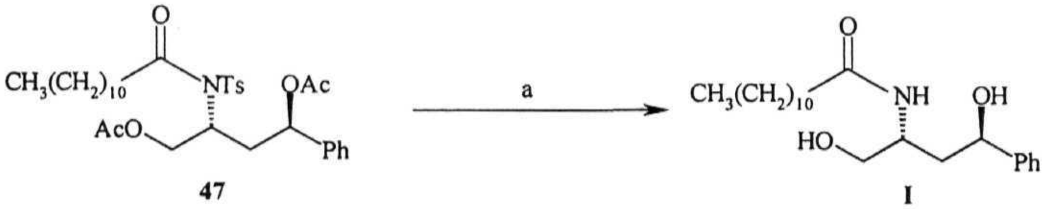
Scheme 13



Reagents and conditions: (a) $C_{11}H_{23}COCl$, Et_3N, DMAP, 0 °C to r.t., 30 min, 91%.

Finally the synthesis of (1*R*,3*R*)-HPA-12, was achieved by reductive removal of the *p*-toluenesulfonyl protection on nitrogen with concomitant deacetylation under the workup conditions. Thus, diacetate **47** was reacted with freshly prepared sodium naphthanilide[25] in dimethoxyethane to afford (1*R*,3*R*)-HPA-12 (Scheme 14), which had physical characteristics in full agreement to that reported in the literature.

Scheme 14



Reagents and conditions: (a) Na-Naphthalinide, DME, -23 °C, 2 min, K_2CO_3, 24 h, 55%.

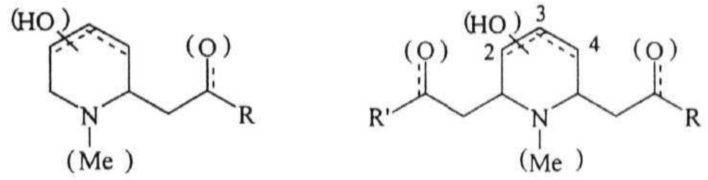
In summary, a stereoselective synthesis of *N*-(3-hydroxy-1-hydroxymethyl-3-phenylpropyl)dodecanamide (HPA-12) is detailed in this section. The key transformations include, diastereoselective addition of carbanion derived from 20 to imine the **40**, regio- and stereospecific bromohydrin formation via intramolecular nucleophilic participation of the sulfinyl group.

Stereoselective Synthesis of (-)-Allosedamine

Introduction

A large numbers of alkaloids have been isolated from various *Sedum* and *Lobelia* species. Both one-armed and two-armed derivatives, containing every combination of C=O or CHOH functionality, *cis/trans* geometry and chirality exist, combined with a variety of terminal R groups, both similar and different, and occasionally bearing extra OH or unsaturated features in the region of the 3, 4, 5-carbons. The group includes both *N*H and *N*Me analogues (Scheme 1).

Scheme 1

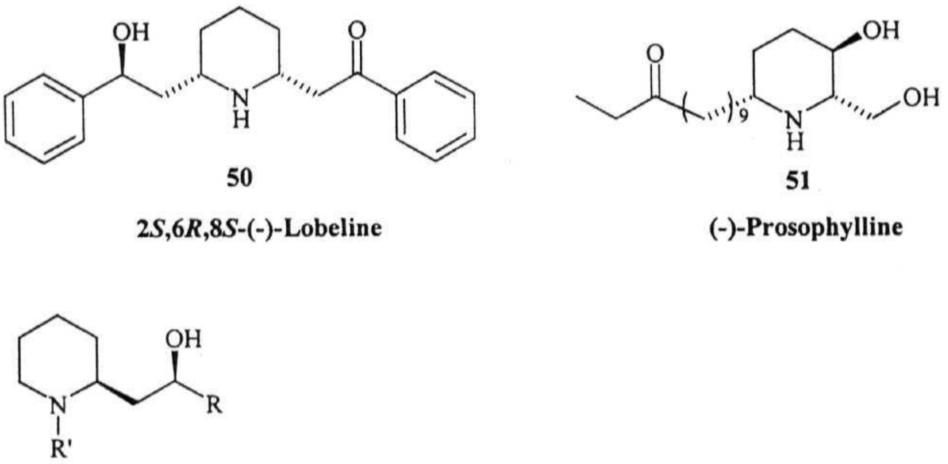


48 **49**

Summary of various types of alkaloids found in Sedum and Lobelia species

Piperidine alkaloids constitute a large family of compounds, many of which exhibit a wide range of physiological activities.[26] As a result, intense attention has been devoted to the isolation and structure determination of bases of this class and to the development of general routes for their synthesis (Scheme 2).[27]

Scheme 2



50

2*S*,6*R*,8*S*-(-)-Lobeline

51

(-)-Prosophylline

R' = Me, R = Phenyl **Allosedamine, 52**

R' = H, R = Methyl **Sedridine, 53**

Representative piperidine alkaloids

(-)-Allosedamine is a piperidine alkaloidal constituent[28] of *Lobelia inflata*, which is also known as *Rapuntium inflatum*, Indian weed, puke weed, asthma weed, gagroot, vomitwort, bladderpod, eyebright, and Indian tobacco. The herb was named after Matthias de Lobel, a famous French botanist. The name "Indian tobacco" could have been derived from the tobacco-like sensation imparted to the tongue and stomach upon chewing the plant leaves, or from the fact that the American Indians smoked the dried leaves to obtain the CNS effects of the alkaloids in the plant. Schoepf noted application of *L. inflata* as an emetic and for sore eyes in 1787. In 1813, *L. inflata* was introduced to the medical profession by Reverend D. Cutler as a valuable remedy for asthma.[29] The first documentation of the pharmacological actions of the plant was obtained from a liquid alkaloid extract, first prepared by Proctor in 1838. Extract of *L. inflata* were used as an expectorant, emetic, anti-asthmatic, anti-spasmodic, respiratory stimulant, general muscular relaxant, diaphoretic, diuretic, and stimulant and also to treat narcotic overdose. Allosedamine was also isolated from many *Sedum acre* species, ex:

Sedum oryzifolium.[30] In the study of interactions of *Pea Seedlings Amine Oxidase* (PSAO, EC 1.4.3.6) with sedamine derivatives,[31] all compounds exhibited a competitive inhibition with the inhibition constants in the range 0.03-1.0 mM. The inhibitory potential is as follows.

Allosedamine < Sedamine < Norallosedamine < Norsedamine

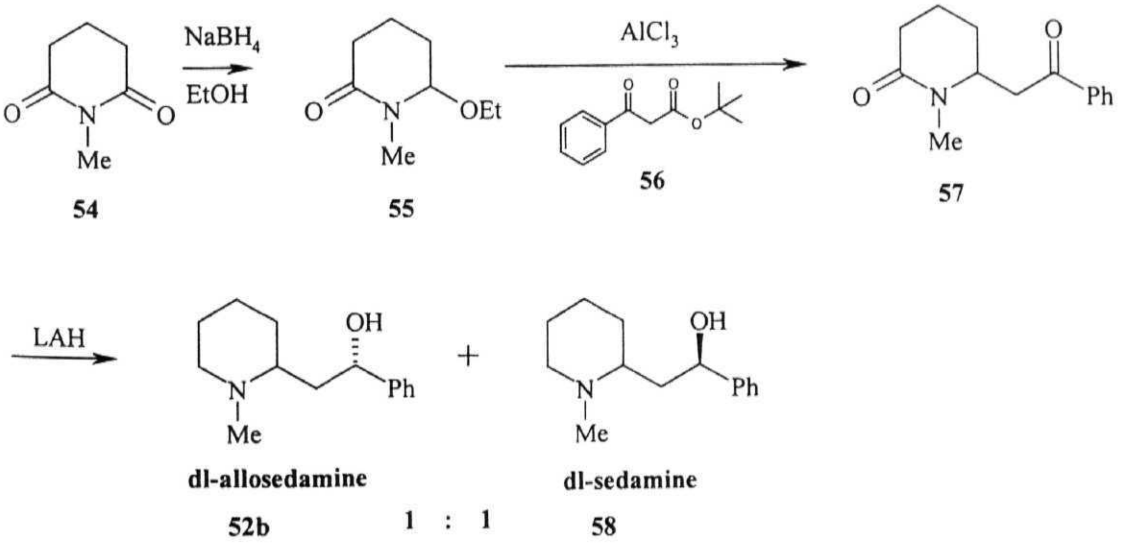
The nor derivatives were found to be five fold stronger compared to the normal. Interestingly, (-) diastereomer of the sedamines were found to be considerably strong inhibitors than the (+)-antipodes.

Earlier approaches toward the synthesis of allosedamine:

Ozawa' s approach[32]:

Ozawa *et al.*, reported the synthesis of racemic sedamine and allosedamine in 1991. Reduction of *N*-methyl glutaramide **54** with $NaBH_4$ and subsequent treatment with ethanol under acid catalyzed conditions afforded the piperidone **55**. Reactions of **55** with **56** in the presence of $AlCl_3$ afforded **57**. Reduction with LAH afforded 1:1 mixture of dl-sedamine **58** and dl-allosedamine **52 b** (Scheme 3).

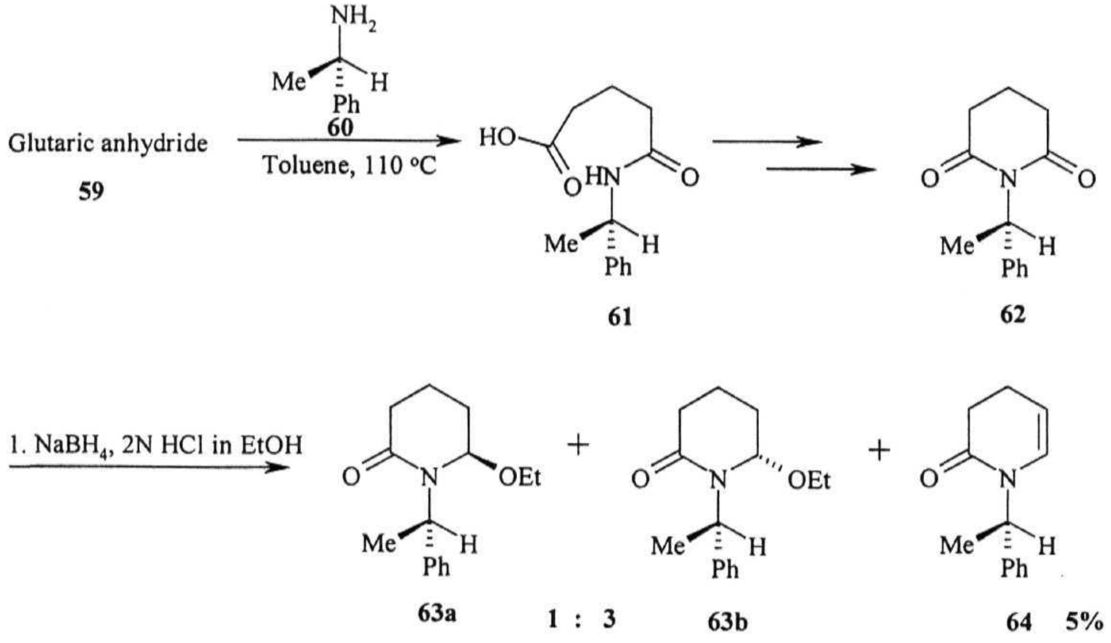
Scheme 3

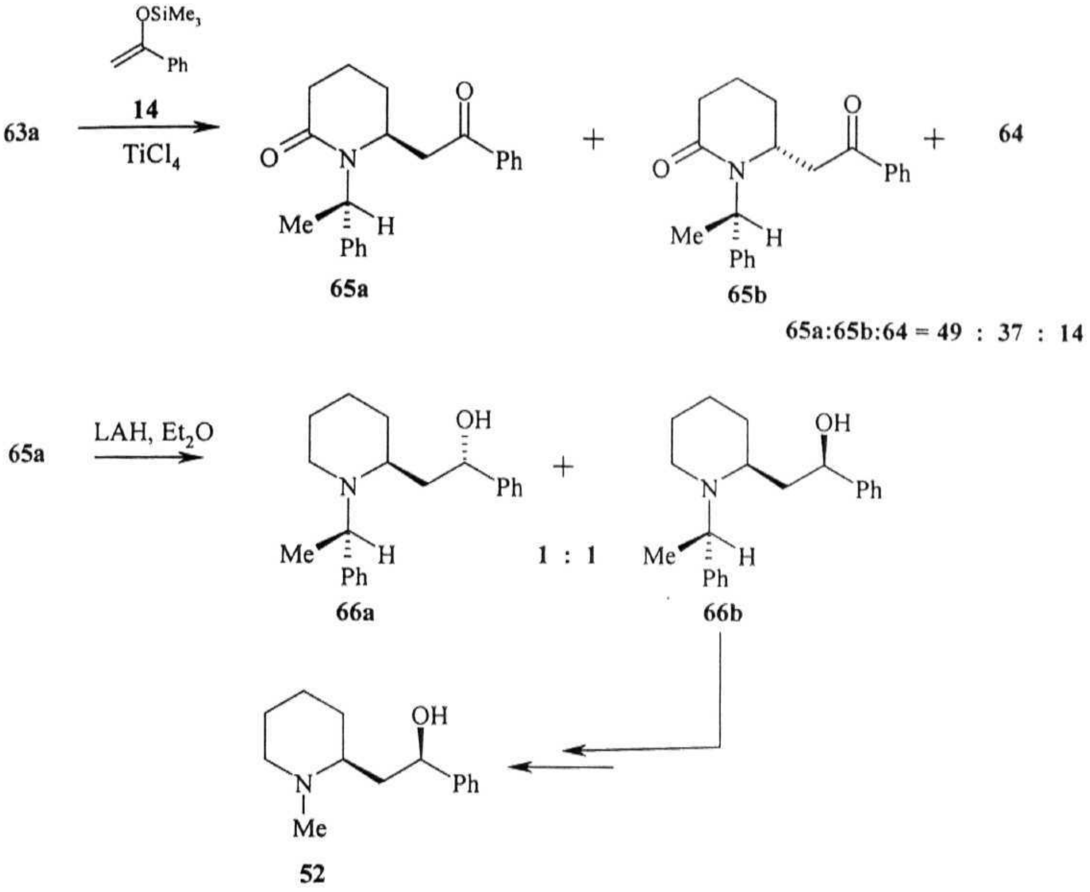


Naito's approach[33]**:**

Naito *et al.*, reported the synthesis of (+)- and (-)-coniine, (-)-sedamine and (-)-allosedamine via the diastereoselective alkylation reaction of the chiral 6-ethoxy-piperidinone **63a**. The reduction of the imide **62** with $NaBH_4$ followed by treatment with 2N HCl in ethanol afforded the lactams **63a** and **63b** in a 1:3 ratio along with 5% of enamide **64**. Treatment of **63a** with silyl enol ether **14** in the presence of titanium (IV) chloride gave three products **65a, 65b** and **64** in 49, 37, and 14% yield respectively after column chromatography. The major product **65a** was reduced with LAH to give a 1:1 mixture of the amines **66a** and **66b**. Carbamoylation with trichloroethyl chloroformate followed by lithium aluminum hydride reduction afforded allosedamine (Scheme 4).

Scheme 4

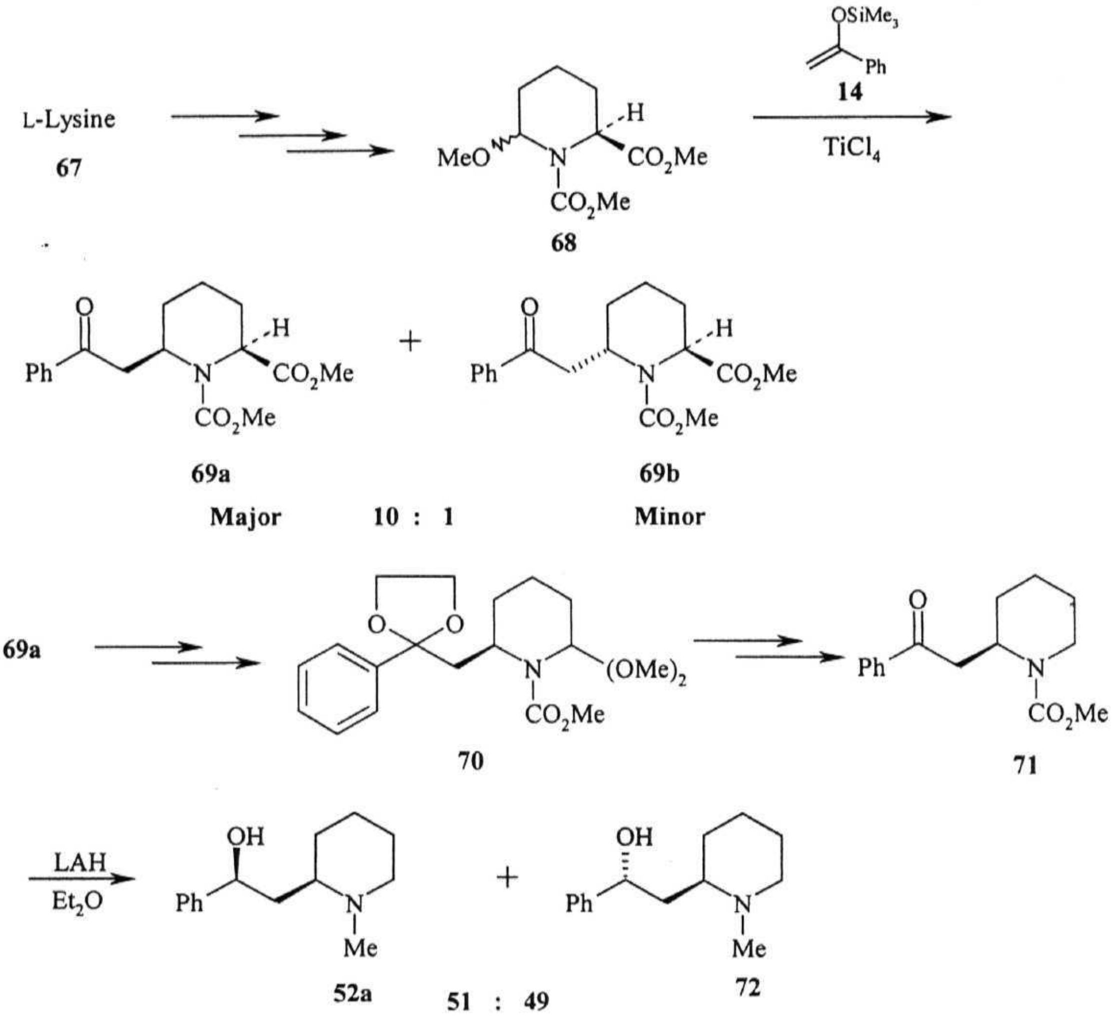




Tanaka's approach[34]:

Tanaka *et al.*, reported the synthesis of (+)-sedamine and (+)-allosedamine in 1985 starting from L-lysine **67**. Condensation of **68** with silyl enol ether **14** afforded the pipecolates **69a** and **69b** in a ratio of 10:1 respectively. Following a standard reaction sequence, **69a** was transformed into the keto-carbamate **71.** The keto-carbamate **71** was further reduced with LAH to give two epimeric alcohols sedamine and allosedamine, **72** and **52a**, in a 49:51 ratio (Scheme 5).

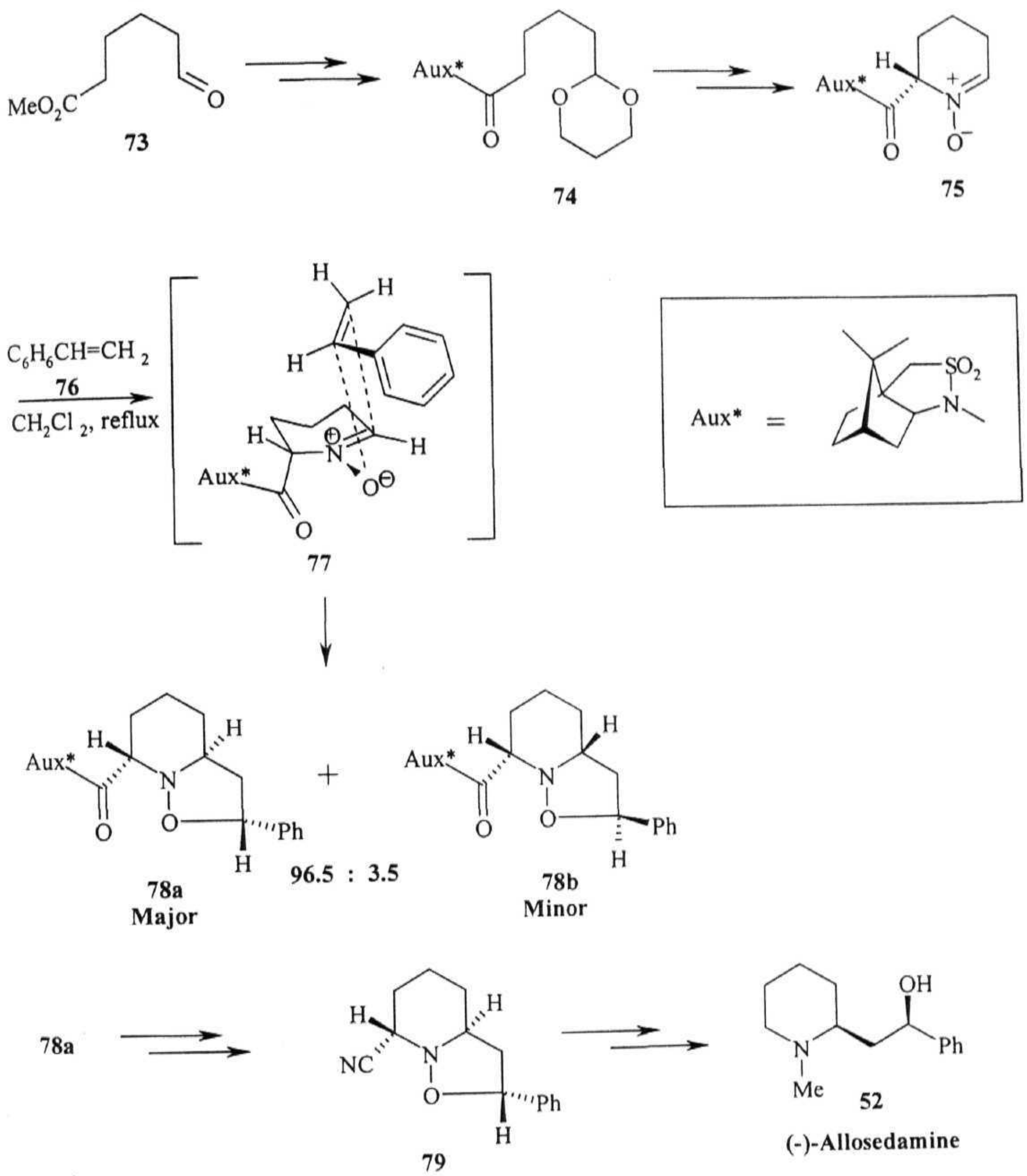
Scheme 5



Oppolzer's approach[35]:

The first diastereo- and enantiocontrolled synthesis of (-)-allosedamine was reported by Oppolzer and co-workers starting from formyl-ester **73** in nine steps. *Exo*-selective 1,3-dipolar addition of nitrone **75** with styrene **76** afforded the cycloadducts **78a** and **78b** in a ratio of 96.5:3.5 via the transition state **77**. Following a standard reaction sequence, the compound **79** was elaborated from **78a** in 66% yield. Compound **79** was further transformed into (-)-allosedamine (Scheme 6).

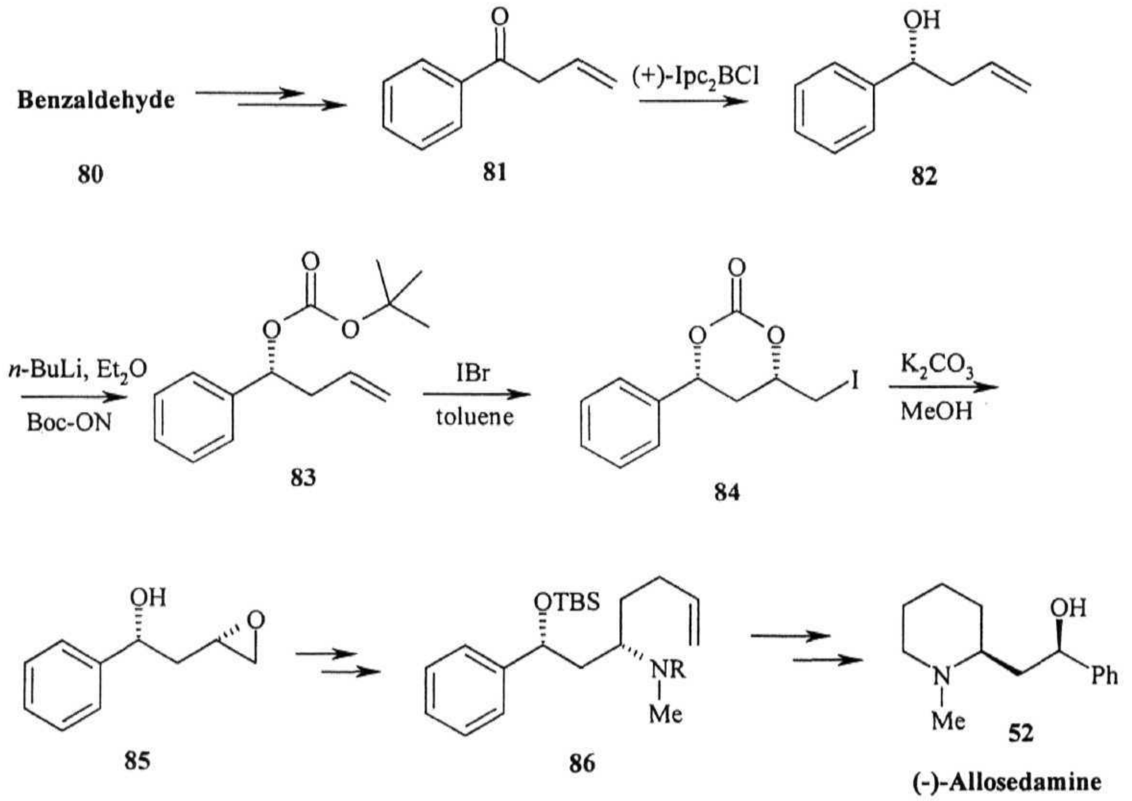
Scheme 6


MeO$_2$C
O
73
Aux*
O
O
O
74
Aux*
H
N
+
O$^-$
O
75
C$_6$H$_6$CH=CH$_2$
76
CH$_2$Cl$_2$, reflux
H
H
H
H
N
H
Aux*
O
O
77
Aux* =
SO$_2$
N
Aux*
H
H
N
O
O
Ph
H
78a
Major
+
96.5 : 3.5
Aux*
H
H
N
O
O
Ph
H
78b
Minor
78a
H
H
NC
N
O
Ph
H
79
OH
N
Me
Ph
52
(-)-Allosedamine

Lebreton's approach[36]:

Lebreton *et al.*, reported a synthesis of (-)-allosedamine in 2002, in 14 steps with an overall yield of 29% starting from benzaldehyde **80**. The enantioselective reduction of the β,γ-unsaturated ketone **81** with (+)-Ipc_2BCl proceeded with >99% ee to afford **82**. Diastereoselective iodine-induced electrophilic cyclization of the homoallylic *tert*-butyl carbonate **83** with IBr furnished the iodocarbonate **84** as a single diastereomer, which under basic conditions led to the epoxide **85**. Epoxide **85** was transformed into olefin **86** by a standard reaction sequence. Olefin **86** was transformed into (-)-allosedamine following a straightforward reaction sequence (Scheme 7).

Scheme 7

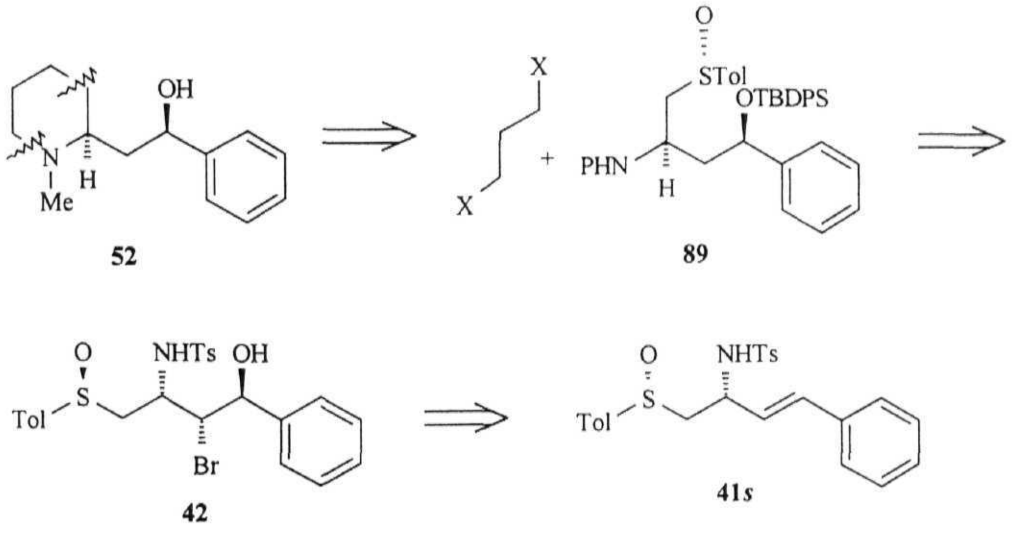


Present work

As outlined in the foregoing discussion, several syntheses of racemic allosedamine have been reported. Only Oppolzer *et al.* and Lebreton *et al.* reported a stereoselective asymmetric synthesis of (-)-allosedamine. The potential of the internal sulfinyl moiety to functionalize an olefin is exploited to device a stereoselective synthesis of (-)-allosedamine. The details are presented hereunder.

Retrosynthetically (Scheme 8), (-)-allosedamine **52** was envisaged to be derived by a dialkylation[37] reaction of the dianion derived from silyl ether **89** with a 1,3-dielectrophile. The silyl ether itself was envisaged to be derived from the bromohydrin **42**, which in turn can be obtained from the β-aminosulfoxide **41*s***.

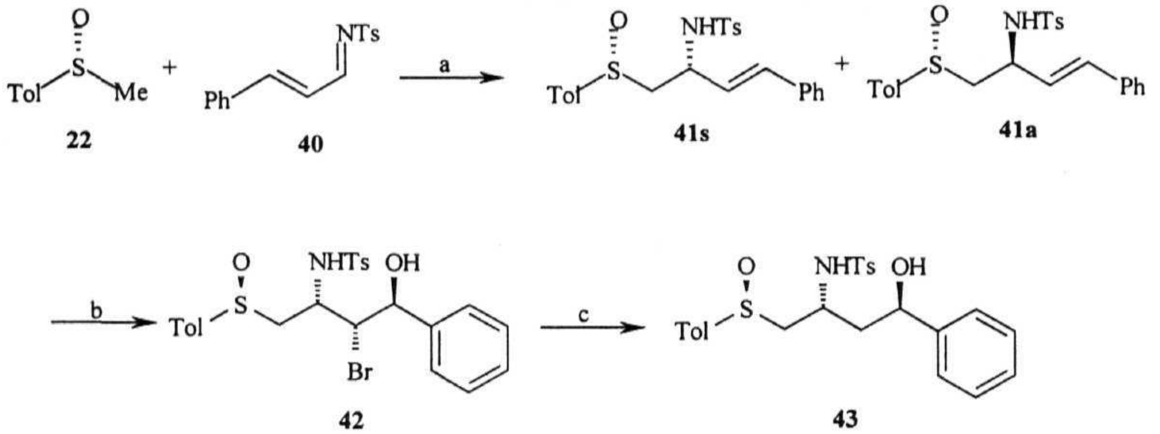
Scheme 8



X = Leaving group

As detailed in the previous section, the diastereoselective preparation of β-aminosulfoxide **41*s*** was achieved via addition of the anion derived from (*R*)-(+)-methyl *p*-tolylsulfoxide **20** to the imine **40**. Upon subjecting **41*s*** to treatment with NBS in toluene at ambient temperature in the presence of water, bromohydrin **42** was obtained regio- and stereoselectively. The bromine atom in **42** was removed by treatment with *n*-Bu_3SnH in the presence of cat. amount of AIBN in benzene to furnish **43** (Scheme 9).

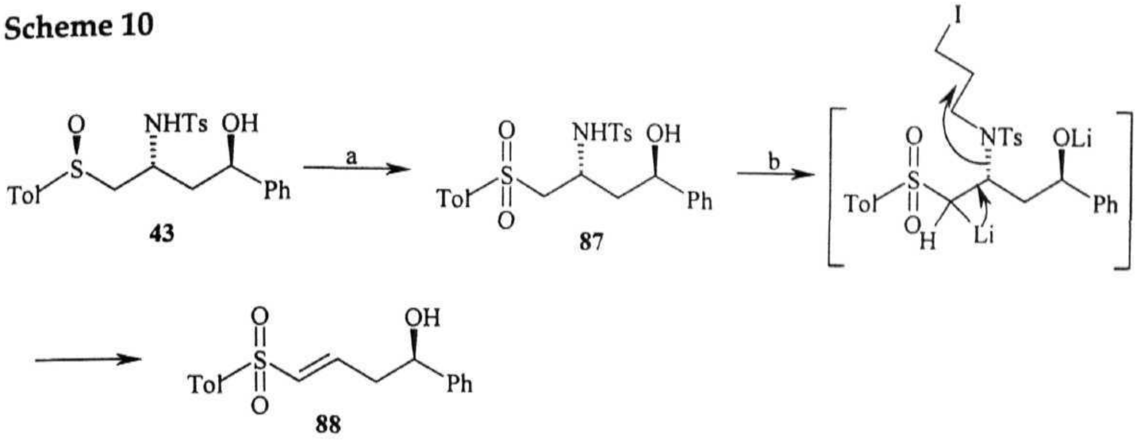
Scheme 9



Reagents and conditions: (a) LDA, THF, add **20**, -78 °C, then add **40**, 15 min, 81%; (b) NBS, H_2O, toluene: $CHCl_3$, r.t., 30 min, 84%; (c) TBTH, AIBN, benzene, reflux, 1.5 h, 76%.

The sulfoxide **43** was oxidized to sulfone **87** by treatment with *m*-chloroperbenzoic acid in chloroform. The PMR spectrum of the compound 87 showed signals at δ 3.45 (dd) and at δ 3.26 (dd) for the methylene protons at C1, a downfield shift compared to signals for the same protons in sulfoxide **43**. Attempted alkylation of the trianion derived from **87** by treatment with *n*-BuLi, using 1,3-diiodopropane[37] as the dielectrophile to construct the piperidine ring led to the isolation of only the β-eliminated product **88** as the major product without any trace of the desired product (Scheme 10). The structure assigned to the product was confirmed by the presence of the olefinic signals at δ 6.71 (dt) and at δ 5.97 (d), CH_2CHOH signal at δ 2.50-2.40 (m) and the disappearance of the protons corresponding to the *N*-Ts group in its PMR spectrum. The product is probably formed via an initial *N*-alkylation followed by β-elimination.

Scheme 10

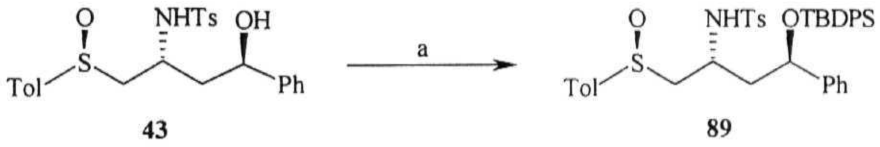


43 87 88

Reagents and conditions: (a) *m*-CPBA, CHCl$_3$, r.t., 10 min, 80%; (b) *n*-BuLi, I(CH$_2$)$_3$I, THF, -78 °C, 2 h.

The hydroxy group in **43** was protected as its silyl ether **89** by treatment with *tert*-butyldiphenylsilyl chloride and imidazole in dichloromethane (Scheme 11). The PMR spectrum of **89** revealed signals for the aromatic protons of the silyl ether and also a signal at δ 1.06 (s) for the *tert*-butyl group.

Scheme 11

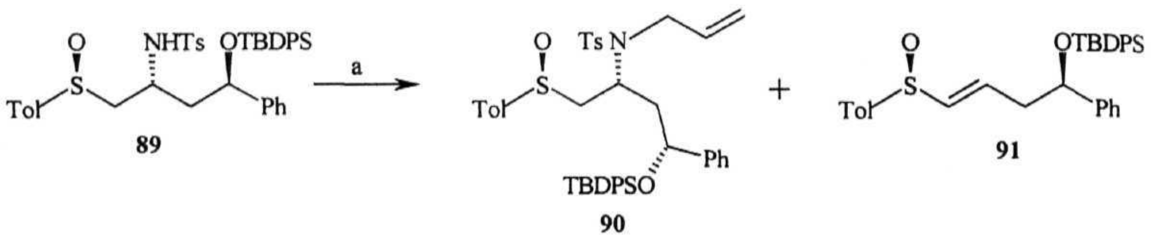


43 89

Reagents and conditions: (a) TBDPS-Cl, imidazole, DCM, r.t., 2 h, 80%.

Attempted alkylation of the dianion derived from the silyl ether **89**, by treatment with *n*-BuLi, with 1,3-diidopropane afforded the *N*-allylated product **90** as the major component and none of the desired product. Also the use of other bases like LDA, *n*-BuLi and KHMDS for the generation of the dianion and in the presence/absence of HMPA proved unsuccessful. The β-elimination product **91** or the *N*-allylation product **90** were obtained in varying yields without any trace of the desired product (Scheme 12).

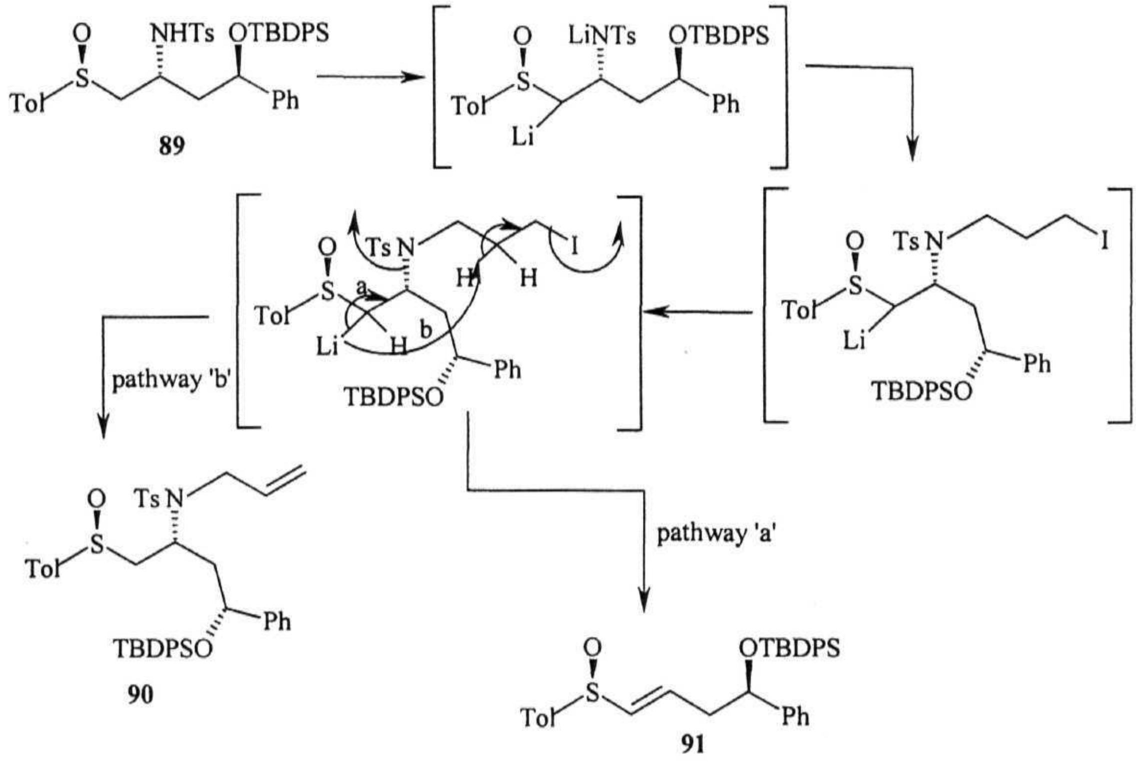
Scheme 12



Reagents and conditions: (a) *n*-BuLi (2 eq.), HMPA, I(CH$_2$)$_3$I, -78 °C-20 °C, THF, 2 h.

The formation of the products **90** and **91** may be rationalized by the mechanism depicted in Scheme 13.

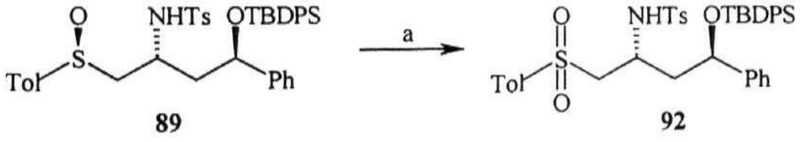
Scheme 13



The dialkylation reaction was also investigated employing 1,3-dibromopropane and 1,3-propane di triflate, derived from 1,3-propanediol by treatment with trifluoromethanesulfonic anhydride in the presence of pyridine in dichloromethane,[38] as the dielectrophile. The reaction did not proceed with these dielectrophiles too to afford any piperidine derivative but instead *N*-allylation or β-elimination products only were isolated in varying yields. Najera *et al.*[39] observed formation of *N*-allylated product as a by-product in the study of lithiated β-aminoalkyl sulfones as mono and dinucleophiles in the preparation of nitrogen heterocycles. The PMR spectrum of the *N*-allylated compound **90** showed resonances at δ 5.56-5.42 (m), δ 4.82 (d) and at δ 4.57 (d) for the olefinic protons, at δ 4.27 (dd) for the benzylic proton, at δ 3.58 (dd) and at δ 3.51 (dd) for the NCH_2CHCH_2 protons, at δ 3.32 (dd) and δ 2.78 (dd) for the CH_2SO protons and δ 0.98 (s) for the *tert*-butyl group. The structure assigned to the β-elimination product **91** was confirmed by the presence of resonances at δ 6.27 (dt) for CHCHSO, δ 5.93 (d) for CHSO, δ 4.71 (dd) for CHOTBDPS and at δ 0.98 (s) for the *tert*-butyl group and the absence of the peaks corresponding to the *N*-Ts group in its PMR spectrum.

The reactions were next attempted on the β-aminosulfone derivative **92** obtained by mCPBA oxidation of sulfoxide **89** (Scheme 14). The PMR spectrum of the sulfone **92** showed resonances at δ 4.80 (t) for CHOTBDPS, at δ 3.63 (dd) and δ 2.77 (dd) for CH_2SO_2, and at δ 0.97 (s) for the *tert*-butyl group.

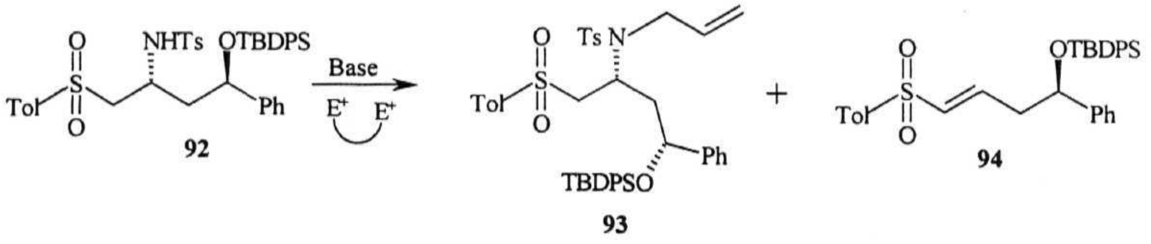
Scheme 14



Reagents and conditions: (a) *m*-CPBA, chloroform, 0 °C-r.t., 10 min, 93%.

Again alkylation reactions using different bases, like LDA, *n*-BuLi for the generation of the dianion in the presence/absence of HMPA (in stoichiometric ratio or as a co-solvent), led to the isolation of only the *N*-allylated product **93** or the β-eliminated product **94** in varying amounts without any trace of the desired product (Scheme 15). Change of nucleofuge did not alter the results (Table II). The structure assigned to the *N*-allylated compound **93** was confirmed by the presence of signals at δ 5.49-5.28 (m), δ 4.75 (d) and δ 4.59 (d) for the olefinic protons, δ 4.24 (dd) for CHOTBDPS, δ 3.56-3.50 (m) and δ 3.42 (dd) for *N*-CH_2 protons, δ 3.21 (dd) and δ 2.62 (dd) for CH_2SO_2, 0.97 (s) for the *tert*-butyl group in its PMR spectrum. The PMR spectrum of the β-elimination product **94** showed signals at δ 6.27 (dt) for $CHCHSO_2$, δ 5.93 (d) for $CHSO_2$, δ 2.37-2.04 (m) for the CH_2CHOTBDPS and δ 0.98 (s) for the *tert*-butyl group.

Scheme 15



Employing a different strategy the piperidine ring was envisaged to be constructed by an intramolecular Pummerer reaction[40] (Scheme 16).

Scheme 16

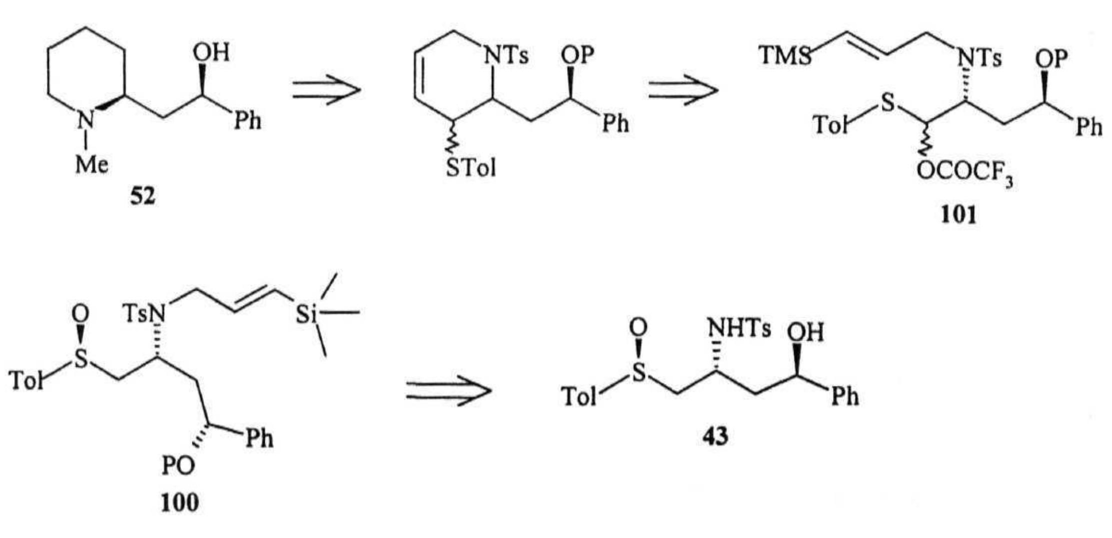


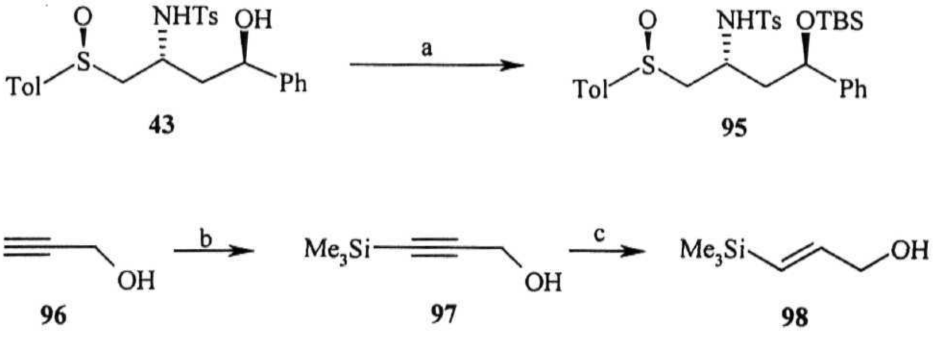
Table II: Alkylation reactions with dielectrophiles

Entry	Sub.	Dielectrophile	Base	T °C[a]	Time (h)	Pro.[b]
1	**87**	$I(CH_2)_3I$	*n*-BuLi	-78	4	**88**
2	**87**	$TfO(CH_2)_3OTf$	*n*-BuLi/HMPA	-78	3	**88**
3	**87**	$I(CH_2)_3I$	LDA	-60	3	**88**
4	**89**	$I(CH_2)_3I$	*n*-BuLi	-20	2	**90**
5	**89**	$TfO(CH_2)_3OTf$	*n*-BuLi	-40	2	**91**
6	**89**	$Br(CH_2)_3Br$	*n*-BuLi	r.t.	32	**91**
7	**89**	$I(CH_2)_3I$	*n*-BuLi/HMPA	-20	2	**90**
8	**89**	$I(CH_2)_3I$	KHMDS	-20	2	**mix.**[f]
9	**92**	$I(CH_2)_3I$	*n*-BuLi	-20	6	**93**
10	**92**	$I(CH_2)_3I$	LDA/HMPA[c]	-20	3	**94**
11	**92**	$TfO(CH_2)_3OTf$[d]	LDA/HMPA	-20	16	**94**
12	**92**	$I(CH_2)_3I$[d]	LDA/HMPA	-20	1	**93**
13	**92**	$I(CH_2)_3I$	KHMDS	-20	2	**mix.**[f]
14	**92**	$I(CH_2)_3I$	LDA	-10	3	**93**
15	**92**	$TfO(CH_2)_3OTf$[e]	*n*-BuLi/HMPA	-10	4	**mix.**[f]
16	**92**	$TfO(CH_2)_3OTf$	*n*-BuLi	-20	3	**94**

[a] Anion was generated at -78 °C and warmed gradually to the temperature indicated in the table after adding the electrophile; [b] predominant product mentioned; [c] HMPA used as a co-solvent; [d] 5eq. of dielectrophile was added; [e] 1.5eq. of dielectrophile was added; [f] complex mixture of products observed.

Towards this end alcohol **43** was protected as its *tert*-butyldimethylsilyl ether **95** by treatment with *tert*-butyldimethylsilyl chloride in the presence of imidazole in dichloromethane. The PMR spectrum of **95** showed signals at δ 4.97 (t) for the benzylic proton, δ 0.90 (s) for the *tert*-butyl group, δ 0.11 (s) and δ -0.21 (s) for the two methyl groups confirming the structure assigned to it. The sulfoxide **95** on treatment with allylbromide **99** in the presence of K_2CO_3 in acetonitrile furnished the *N*-allylated product **100**. Vinylsilane **99** was readily elaborated from propargyl alcohol **96**. Thus, treatment of **96** with excess ethyl magnesium bromide, followed by with the trimethylsilyl chloride and acidolysis with aq. hydrogen chloride afforded the alcohol **97**. The PMR spectrum of **97** showed signals at δ 0.02 (s) integrating for 9 protons of the trimethyl silyl group. Reduction of **97** with LAH in diethylether afforded the allyl alcohol **98**. The PMR spectrum of **98** showed signals corresponding to the olefinic protons at δ 6.17 (dt) and δ 5.88 (d) and δ 4.13 (d) for CH_2OH protons. The allyl alcohol **98** upon treatment with PBr_3 in ether furnished allylbromide **99**. The PMR spectrum of **99** showed resonances at δ 6.12 (dt) and δ 5.90 (d) for the olefinic protons and δ 3.91 (d) for CH_2Br (Scheme 17).

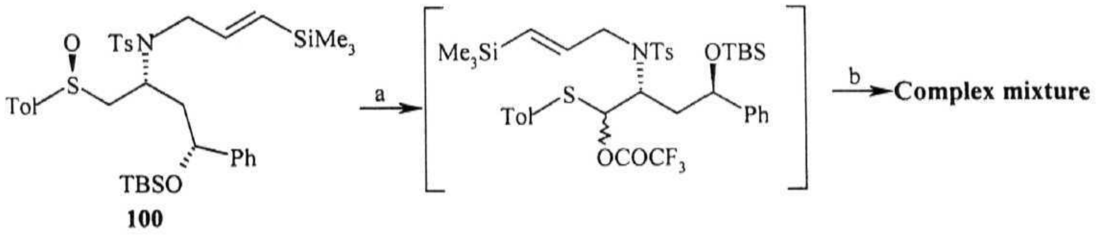
Scheme 17



Reagents and conditions: (a) TBS-Cl, imidazole, DCM, r.t., 2 h, 85%; (b) EtMgBr, TMS-Cl, 6N HCl, Et_2O, 0 °C-r.t., 85%; (c) LAH, Et_2O, reflux, 6 h, 92%; (d) PBr_3, Et_2O, reflux, 1.5 h, 93%; (e) K_2CO_3, acetonitrile, reflux, 3 h, 67%.

The structure assigned to **100** was confirmed by the presence of signals at δ 6.23 (dt) and δ 6.0 (d) for the olefinic protons, at δ 4.20-3.95 (m) for CH_2N at δ 0.27 (s) integrating for the 9 protons for the trimethylsilyl group, in its PMR spectrum. Compound **100** on subjecting to Pummerer reaction conditions[41] afforded the intermediate **101**, which without isolation was treated with $SnCl_4$ to afford a complex mixture of products without any trace of the desired product (Scheme 18). Pummerer ene reaction done in the presence of Et_3N again afforded a complex mixture of products.

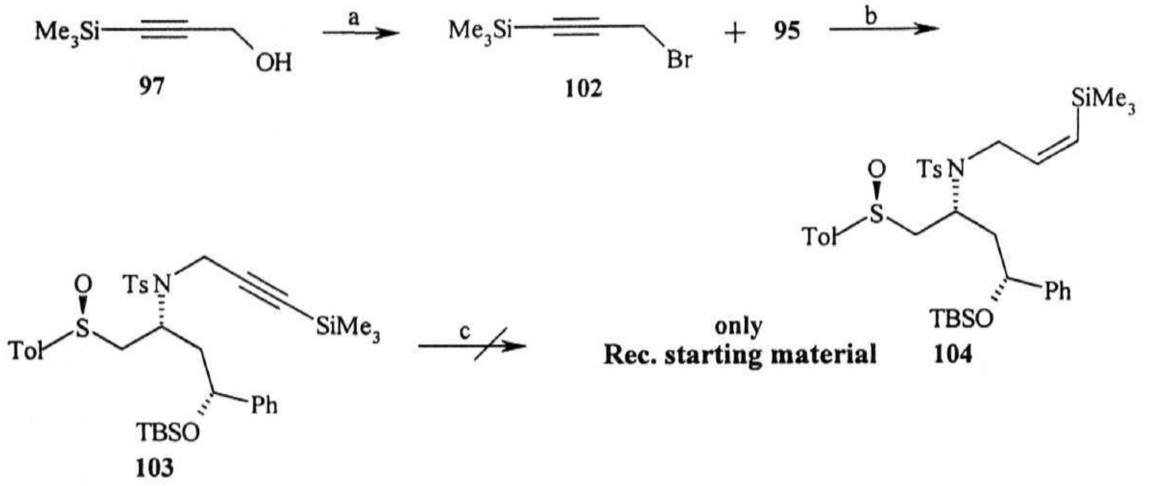
Scheme 18



Reagents and conditions: (a) TFAA, DCM, 0 °C, 50 min; (b) $SnCl_4$, 0 °C, 5 min.

Attempted elaboration of the *cis* vinyl silane **104**, to try the Pummerer ene reaction, from the acetylenic compound **103** met with failure (Scheme 19). Sulfoxide **95** on treatment with propargyl bromide **102** afforded **103**.

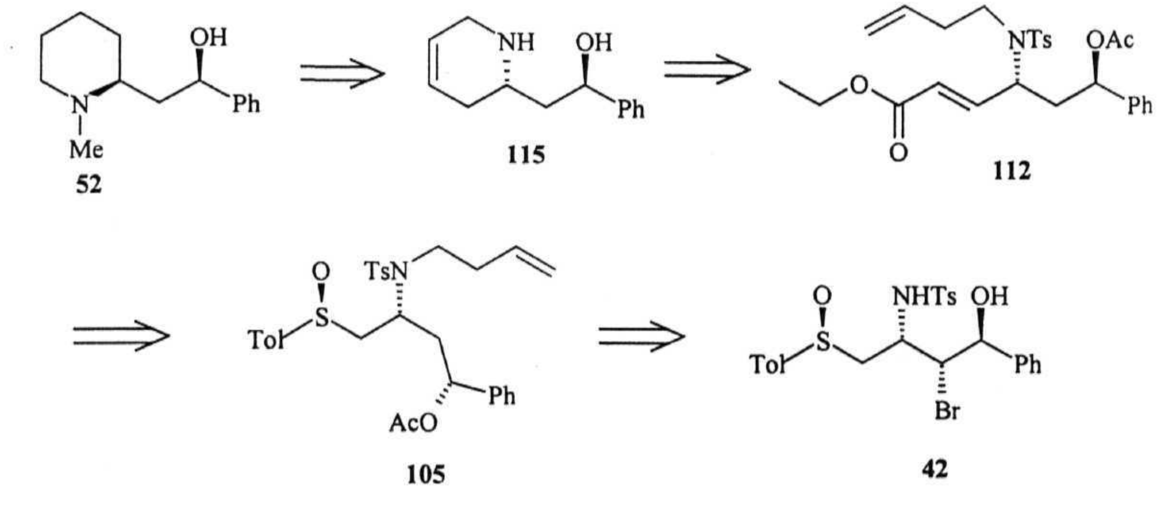
Scheme 19



Reagents and conditions: (a) PBr_3, pyridine, ether, 0 °C-reflux, 1.5 h, 85%; (b) K_2CO_3, CH_3CN, reflux, 2 h, 68%; (c) Pd/$BaSO_4$, quinoline (cat.), ethanol, H_2, 6 h.

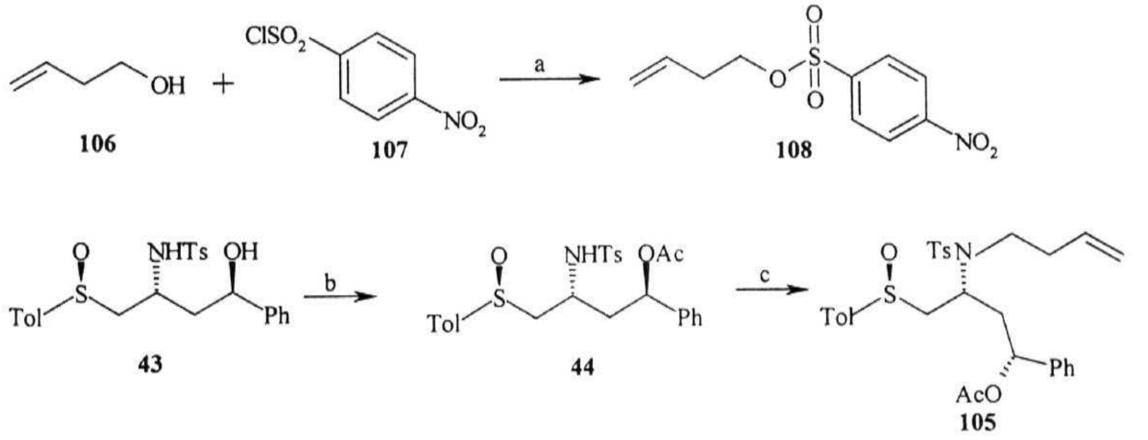
The synthesis of (-)-allosedamine was finally achieved by a strategy that included a ring-closing metathesis reaction (Scheme 20, retrosynthetic analysis). (-)-Allosedamine can be obtained from the allylamine **115**, which in turn can be readily elaborated from ester **112** via RCM reaction. Compound **112** can be derived from *N*-alkylated compound **105**, which can be derived from bromohydrin **42**.

Scheme 20



Treatment of **43** with acetic anhydride and pyridine in DCM afforded acetate **44**. The PMR spectrum of the acetate **44** exhibited a downfield shift for the benzylic proton from δ 4.87 (d) in **43** to δ 5.71 (dd), and a signal at δ 2.02 (s) for the acetyl group. The IR spectrum showed a strong absorption band at 1741 cm^{-1} for C=O stretching of the acetyl group, a broad band at 3249 cm^{-1} for N-H stretching and the absence of a broad band at 3540 cm^{-1} corresponding to the hydroxy group. *N*-homoallylation on **44** was achieved by treatment of **44** with nosylate **108** in acetonitrile in the presence of K_2CO_3 under reflux temperature to yield **105**. The nosylate **108** was prepared from 3-butene-1-ol **106** by treatment with *p*-nitro benzene sulfonyl chloride **107** in the presence of Et_3N and catalytic amount of DMAP (Scheme 21). The nosylate **108** showed signals at δ 8.41 (d) for the protons *ortho* to nitro group, δ 8.08 (d) for the protons *ortho* to sulfonyl group, δ 5.78-5.67 (m) and δ 5.18-5.04 (m) for the olefinic protons in its PMR spectrum. Olefin **105** revealed resonances at δ 5.68-5.48 (m) integrating for two protons (CH_2=C*H* and C*H*OAc), δ 5.04-4.90 (m) for C*H*$_2$=CH protons, δ 3.28 (dd) and at δ 3.14 (dd) for C*H*$_2$N protons, δ 2.36-2.10 (m) integrating for 4 protons (C*H*$_2$CH$_2$N and C*H*$_2$CHOAc).

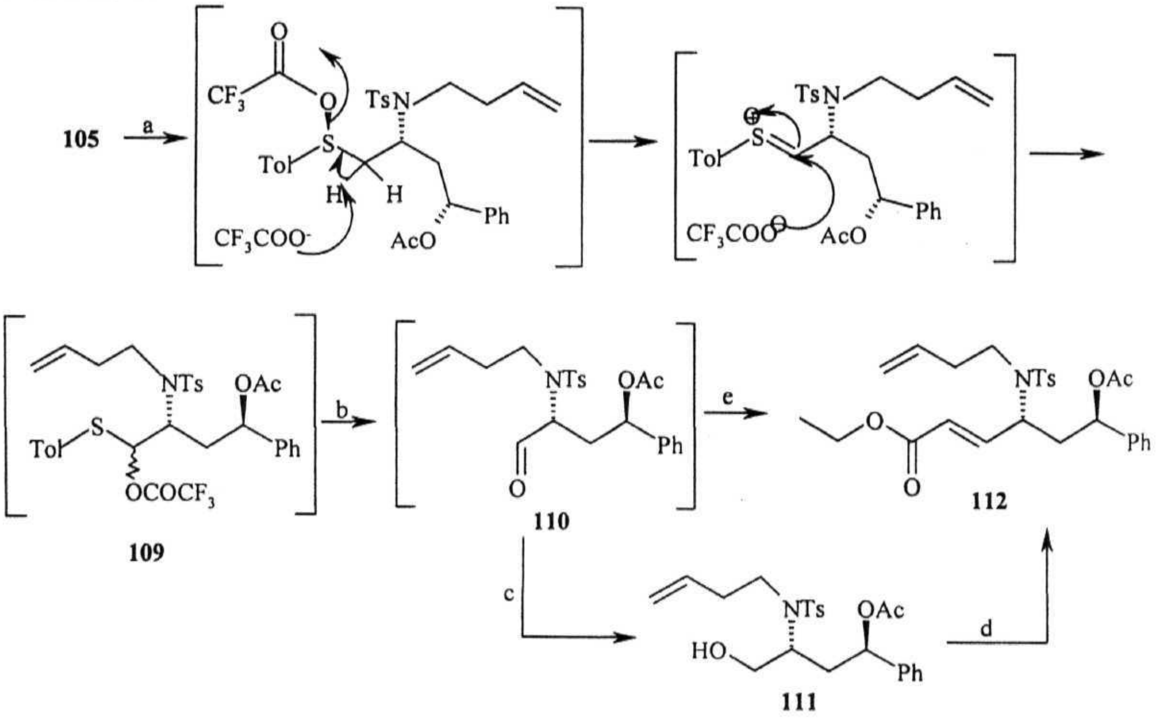
Scheme 21



Reagents and conditions: (a) Et_3N, DMAP (cat.), DCM, r.t., 4 h, 80%; (b) Ac_2O, Pyridine, 0 °C-r.t., 1 h, 96%; (c) K_2CO_3, **108**, acetonitrile, reflux, 2 h, 90%.

The next objective was the elaboration of a suitable diene as the substrate for the metathesis reaction. Thus, compound **105** on treatment with TFAA in the presence of Et_3N in acetonitrile[41] afforded the intermediate **109**, which without isolation was subjected to hydrolysis with aq. $NaHCO_3$ solution to give the aldehyde **110** and subsequently reduced with $NaBH_4$ to afford the alcohol **111** in one pot operation. A one-pot oxidation-Wittig olefination of alcohol **111** with Dess-Martin periodinane[42] and ethyl(triphenylphosphoranylidene)acetate yielded the *trans* ester **112** exclusively. The *trans* olefin could be obtained also by Wittig olefination of the aldehyde **110**, obtained by hydrolysis of the intermediate 109 (Scheme 22). The structure assigned for the ester **112** was confirmed by the presence of signals at δ 6.54 (dd) for -*C*HCHCO$_2$Et, δ 5.76-5.56 (m) integrating for three protons (-CH=*C*HCO$_2$Et, CH$_2$=*C*HCH$_2$- and the benzylic proton), δ 4.12 (q) for -CO$_2$C*H*$_2$CH$_3$ protons. The mass spectrum indicated the presence of $[M+H]^+$ peak at *m/z* 500.

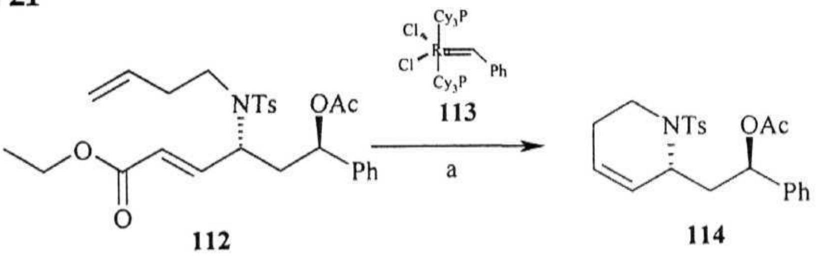
Scheme 22



Reagents and conditions: (a) Et_3N, TFAA, CH_3CN, 0 °C, 50 min; (b) aq. $NaHCO_3$, 0°C, 20 min.; (c) $NaBH_4$ (excess), 0 °C, 1 h, 85% for the two steps; (d) Dess-Martin periodinane, C_6H_5COOH, $Ph_3PCH_2CO_2Et$, DMSO, DCM, r.t., 3 h, 88%; (e) $Ph_3PCH_2CO_2Et$, benzene, r.t., 30 min, 75% for the two steps.

The advent of well-defined catalysts for olefin metathesis that combine high activity, durability and excellent tolerance towards polar functional groups has revolutionized the field. The success of this development is witnessed by a plethora of elegant applications to the synthesis of natural and nonnatural products.[43] Olefin metathesis of ester **112**, which consists a terminal double bond and an α,β-unsaturated system,[44] was effected in toluene with bis(tricyclohexylphophine)benzylideneruthenium(IV)dichloride. The reaction afforded the allylamine **114** without any event (Scheme 23). The PMR spectrum of compound **114** showed signals at δ 5.74 (dd) for the benzylic proton and δ 5.66-5.54 (m) olefinic protons integrating for two. The IR spectrum showed an absorption band at 1744 cm $^{-1}$ for the C=O stretching of the acetyl group. The structure was further supported by mass spectrum, which showed a peak at *m/z* 400 $[M+H]^+$.

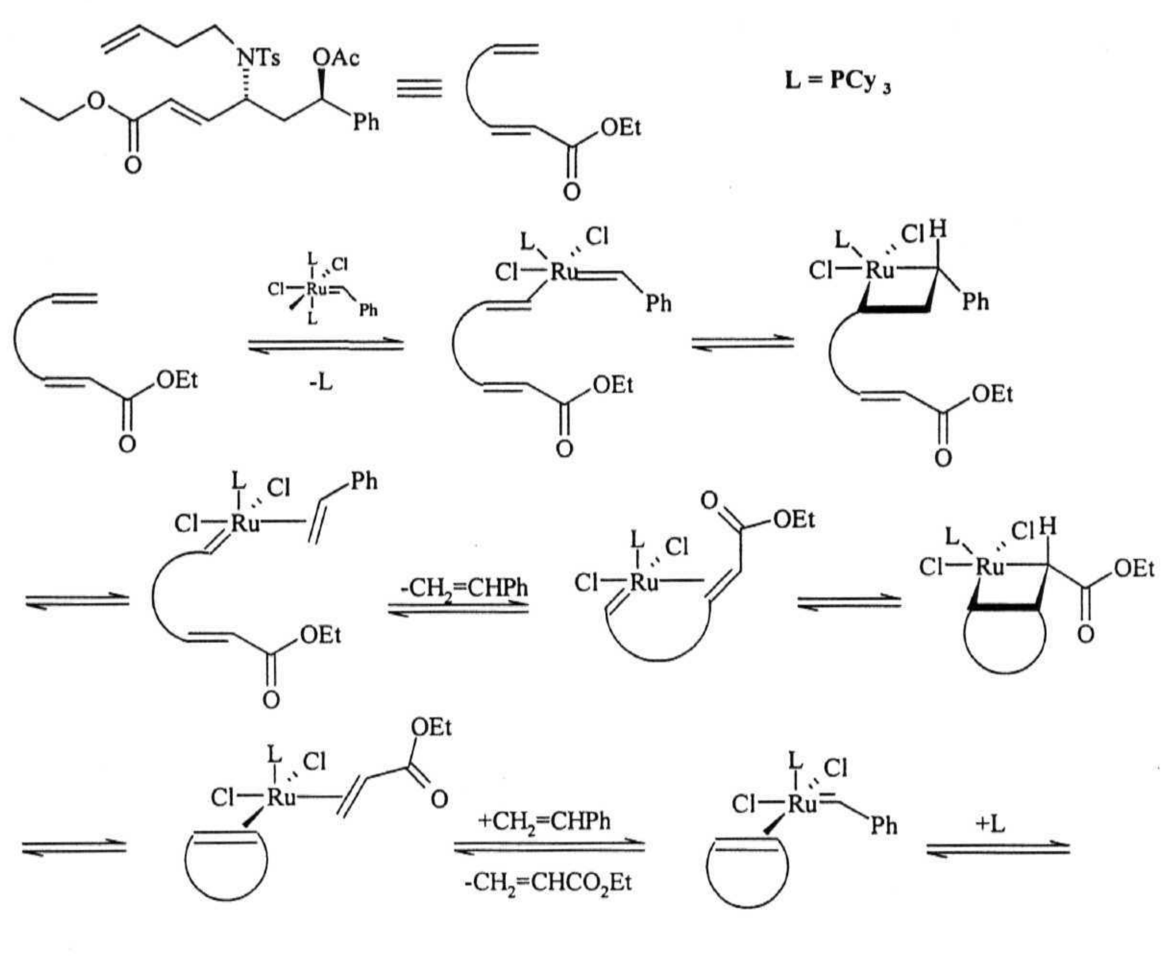
Scheme 21



Reagents and conditions: (a) **113**, toluene, 110 °C, 16 h, 80%.

The formation of the product can be explained by a mechanism where in all individual steps involved and, as a consequence, the overall transformation, are reversible (Scheme 22). Once the substrate is depleted, the active species is recaptured by CH_2=CHPh, and precatalyst **113** is, there by, regenerated.

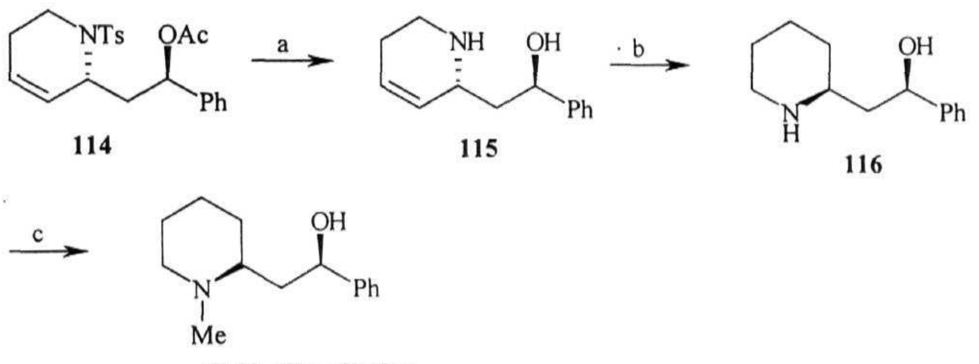
Scheme 22



114 + **113**

(-)-Allosedamine was elaborated from **114** employing a straightforward reaction sequence depicted in Scheme 23. Thus, reductive removal of *p*-toluene sulfonyl group on nitrogen was effected in anhydrous methanol with Na-Hg, bufferd with disodium hydrogen phosphate.[45] The reaction proceeded with concomitant deacetylation, yielding the alcohol **115**. The assigned structure was confirmed with the aid of PMR spectrum, which revealed resonances at δ 5.12-4.96 (d) for the benzylic proton, resonances corresponding to *N*-Ts group were absent. The IR spectrum showed a strong absorption at 3500-3250 cm^{-1} corresponding to the amino and hydroxy group. The double bond in **115** was reduced by treatment over Pt/C in ethylacetate[46] under an atmosphere of hydrogen affording piperidine **116**. Compound **116** revealed absence of signals for the olefinic protons in its PMR spectrum and a peak at *m/z* 206 $[M+H]^+$ in its mass spectrum. Compound **116** was transformed into (-)-allosedamine **52**, by reductive alkylation[47] with formaldehyde in the presence of sodium cyanoborohydride in acetonitrile (Scheme 23). (-)-Allosedamine synthesized above had physical characteristics such as PMR and optical rotation in full agreement to that reported in the literature.[35]

Scheme 23



52 (-)-Allosedamine

Reagents and conditions: (a) Na-Hg, Na_2HPO_4, MeOH, rt -reflux, 6 h, 78%; (b) Pt/C, H_2 (1 atm.), AcOEt, 3 h, 90%; (c) 37% aq. HCHO, $NaCNBH_3$, AcOH, CH_3CN, r.t., 4 h, 70%.

In conclusion, a stereoselective route to (-)-allosedamine **52** from β-aminosulfoxide ***41s*** is described in this section. The key steps include, stereospecific bromohydrin **42** formation by internal sulfinyl group participation with an efficient 1,2-induction and a olefin metathesis of the α,β-unsaturated ester **112**.

Experimental

R-(+)-Methyl *p*-tolyl sulfoxide, 22.

To the suspension of Na_2SO_3 (71.22 g, 562.2 mmol) and $NaHCO_3$ (53 g, 630 mmol) in H_2O (1.5 L) heated to a temperature of 80 °C was added, portionwise, tosyl chloride (60 g, 315 mmol) and stirred for 3 h at the same temperature. When the addition was completed the reaction mixture was heated and stirred at 80 °C for a longer period of time until the volume of water was The reaction mixture was then removed from the hot plate and allowed to stand for 5 h. The solid *p*-toluene sulfinate which precipitated was collected by filtration. The residue was dried overnight in a heating oven to remove any traces of water to afford anhydrous sodium salt of *p*-toluene sulfinic acid **32** (50.4 g, 283.5 mmol) in 90% yield.

Powdered sodium salt of *p*-toluenesulfinic acid **32** (50 g, 0.281 mol) was added in small portions to a solution of thionyl chloride (100 mL, 1.4 mol) in benzene (500 mL) at 0 °C. Then the mixture was allowed to reach room temperature over a period of 30 min. The solution was concentrated to 1/4th of its volume by distilling off benzene and excess of thionyl chloride. The residue was diluted with anhydrous ether (500 mL) and cooled at 0 °C. A solution of (-)-menthol (48.3 g, 0.309 mol) in pyridine (50 mL) was then added dropwise. After the addition, the mixture was stirred for 1 h at room temperature and hydrolyzed with water (200 mL). The organic layer was washed with 10% hydrochloric acid (200 mL), brine, dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was dissolved in acetone (200 mL) and few drops of conc. HCl were added. The solution was allowed to crystallize at –20 °C. After filtration of the first crop of crystals, the mother liquor was concentrated, a drop of conc. HCl added and the solution allowed to crystallize again at -20°C. This operation was repeated 4 times. Finally the product was recrystallized once from hot acetone. Yield 66 g (80%).
White crystals

mp : 109 °C
Lit.,[18b] : 105-107 °C
$[\alpha]_D^{25}$: -203.4 (*c* 2, acetone)
Lit.,[18a] : -201 (*c* 2, acetone)

A solution of methylmagnesium iodide (2 M in ether, 143 mL, 286 mmol) was slowly added to a solution of (-)-menthyl (*S*)-*p*-toluenesulfinate (*S*-**35**) 60 g, 204 mmol) in anhydrous benzene (200 mL) between 0 °C and 10 °C. After the addition, the mixture was stirred at room temperature for 2 h and then hydrolyzed with saturated aqueous solution of ammonium chloride (200 mL). The aqueous solution was extracted with ether and the combined organic layer washed with brine, dried over anhydrous Na_2SO_4 and evaporated to dryness. The oily residue was mixed with hot hexane till formation of a light white cloudy precipitate. Crystals were obtained on cooling to –15 °C for 16 h. The white crystals were dissolved in minimum amount of hot hexane and cooled to –15 °C. The crystals formed were filtered and the mother liquor concentrated and submitted to the same treatment. Yield 25 g (80%).

White crystals

mp : 74°C
Lit.[18b] : 73-74°C
$[\alpha]_D^{25}$: +145 (*c* 2, acetone)
Lit.[18a] : +146 (*c* 2, acetone)
m/z EI : 154 $[M^+]$
PMR ($CDCl_3$, 200 MHz) : δ 7.62-7.54 (d, *J* = 8.0 Hz, 2H), 7.40-7.34 (d, *J* = 8.0 Hz, 2H), 2.76 (s, 3H), 2.42 (s, 3H).

1*N*-[3-Phenyl-(2*E*)-2-propenylidine]-4-methyl-1-benzenesulfonamide, 40.

To the solution of cinnamaldehyde (1.32 g, 10 mmol) and *p*-toluenesulfonamide (1.71 g, 10 mmol) in dry benzene (60 mL) under reflux in a Dean Stark apparatus was added $BF_3.Et_2O$ (50 mg, 0.4 mmol). The reflux was continued for 2 h and the solution was cooled to 0 °C. The reaction mixture was diluted with ethylacetate and washed with cold 1 N NaOH solution. The organic layer was washed with water, brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded a solid that was crystallized from chloroform-petroleum ether to afford the imine **40** (2.08 g, 7.3 mmol) as colourless crystals in 73% yield.

Solid.

mp : 202-204 °C

PMR (300 MHz, $CDCl_3$) : δ 8.75 (d, *J* = 9.4 Hz, 1H), 7.82 (d, *J* = 8.3 Hz, 2H), 7.57-7.38 (m, 6H), 7.32 (d, *J* = 8.3 Hz, 2H), 6.97 (dd, *J* = 15.9, 9.4 Hz, 1H), 2.45 (s, 3H).

Experimental procedure for the condensation of sulfoxide 20 with imine 40.

Diisopropylamine (2.4 mL, 18 mmol) in dry THF (27 mL) was cooled at 0 °C and *n*-BuLi (9 mL, 2.0 M, 18 mmol) was added dropwise over 10 min. The reaction mixture was allowed to stir for 10 min. at 0 °C and then cooled to -78 °C. Methyl *p*-tolylsulfoxide **20** (1.85 gm, 12 mmol) in dry THF (18 mL) was added dropwise via a syringe and stirred for 20 min. at this temperature. A solution of the imine **40** (2.65 gm, 12 mmol) in dry THF (12 mL) was added dropwise over a period of 5 min. After being stirred for 15 min. at -78 °C, the reaction mixture was quenched by the addition of aq. saturated NH_4Cl solution. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The diastereomeric sulfonamide **41*s*** and **41*a*** were separated by column chromatography using

AcOEt/chloroform (23:2, v/v) as the eluent. The diastereomer **41*a*** eluted first followed by **41s** in 20% and 61% yields respectively (combined yield 81%).

4-Methyl-1-[2-(R_S)-(4-methylphenylsulfonamido)-4-phenyl-(2*R*,3*E*)-3-butenylsulfinyl]benzene, 41*s*.

Solid.

mp : 187-188 °C

$[\alpha]_D^{25}$: + 75.0 (*c* 0.7, $CHCl_3$)

PMR (200 MHz, DMSO-d_6): δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.49 (d, *J* = 8.2 Hz, 2H), 7.36-7.04 (m, 9H), 6.30 (d, *J* = 15.6 Hz, 1H), 6.09 (d, *J* = 5.9 Hz, NH), 5.88 (dd, *J* = 15.6, 7.4 Hz, 1H), 4.43-4.26 (m, 1H), 3.11 (dd, *J* = 13.4, 7.4 Hz, 1H), 2.89 (dd, *J* = 13.4, 6.7 Hz, 1H), 2.40 (s, 3H), 2.32 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 20.8, 20.9, 51.7, 62.2, 124.0,125.6, 126.3, 126.5, 126.7, 127.8, 128.4, 129.2, 129.8, 131.9, 141.1, 141.4, 141.8, 142.6.

m/z (LSIMS) : 440 [M^++H]

IR (neat) cm^{-1} : 3453, 1597, 14.93, 1365, 1338, 1158.

Elemental analysis : Calcd. for $C_{24}H_{25}NO_3S_2$: C, 65.58; H, 5.73; N, 3.19; S, 14.59.

Found : C, 65.43; H, 5.65; N, 3.12; S, 14.51.

4-Methyl-1-[2-(R_S)(4-methylphenylsulfonamido)-4-phenyl-(2*R*,3*E*)-3-butenylsulfinyl]benzene, 41*a*.

Solid.

mp : 208 °C

$[\alpha]_D^{25}$: + 91.8 (*c* 1.5, $CHCl_3$)

m/z (LSIMS) : 440 [M^++H]

PMR (200 MHz, $CDCl_3$) : δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.36-7.10 (m, 9H), 6.48 (d, *J* = 6.7 Hz, NH), 6.41 (d, *J* = 15.6 Hz, 1H), 6.03 (dd, *J* = 15.6, 6.7 Hz, 1H), 4.58-4.42 (m, 1H), 2.94-2.85 (m, 2H), 2.43 (s, 3H), 2.33 (s, 3H).

1*N*-[2-Bromo-3-hydroxy-1-(S_S)(4-methylphenylsulfinylmethyl)-3-phenyl-(1*S*,2*R*)-propyl]-4-methyl-1-benzenesulfonamide, 42.

To the solution of sulfoxide **41*s*** (3.07 g, 7 mmol) in toluene/chloroform (2:1, 35 mL) was added water (210 μL, 11.7 mmol) followed by *N*-bromosuccinimide (1.58 g, 8.4 mmol) and the reaction mixture stirred at room temperature for 1 h. Then the reaction mixture was quenched by the addition of aqueous saturated NaHCO$_3$ solution. The mixture was diluted with chloroform and the organic layer was washed with water, brine and dried over Na$_2$SO$_4$. Evaporation of the solvent afforded the crude bromohydrin, which was purified by column chromatography using AcOEt/petroleum ether (7:13, v/v) as the eluent to yield bromohydrin (3.15 g, 5.88 mmol) in 84% yield.

Solid.

mp : 180-182 °C

$[\alpha]_D^{25}$: -38.8 (*c* 1, Acetone)

PMR (200 MHz, CDCl$_3$) : δ 7.86 (d, *J* = 8.2 Hz, 2H), 7.48-7.24 (m, 11H), 5.32 (d, *J* = 10.4 Hz, NH), 4.85 (dd, *J* = 9.7, 5.2 Hz, 1H), 4.70-4.56 (m, 1H), 4.06 (d, *J* = 9.7 Hz, 1H), 3.84 (d, *J* = 5.2 Hz, OH), 3.01 (dd, *J* = 13.4, 6.0 Hz, 1H), 2.68 (dd, *J* = 13.4, 7.4 Hz, 1H), 2.47 (s, 3H), 2.43 (s, 3H).

^{13}C NMR (75 MHz, DMSO-d$_6$) : δ 21.0, 21.2, 49.9, 61.9, 62.6, 73.6, 123.8, 127.0, 127.5, 127.9, 128.1, 129.8, 130.1, 138.6, 140.8, 141.4, 142.6, 143.2.

m/z (LSIMS) : 536 [M+H]$^+$

Elemental Analysis : Calcd. for $C_{24}H_{26}BrNO_4S_2$ C, 53.73; H, 4.88; N, 2.61; S, 11.95.

Found : C, 53.69; H, 4.84; N, 2.62; S, 11.95.

1*N*-[3-Hydroxy-1-(S_S)(4-methylphenylsulfinylmethyl)-3-phenyl-(1*R*)-propyl]-4-methyl-1-benzenesulfonamide, 43.

To the stirred solution of bromohydrin (2.68 g, 5 mmol) in dry benzene (30 mL) were added successively at room temperature TBTH (1.53 g, 5.25 mmol) and AIBN (41 mg, 0.25mmol). The solution was refluxed for 90 min when TLC examination revealed complete consumption of starting material. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column using AcOEt/petroleum ether (2:3, v/v) as the eluent to afford the product (1.73 g, 3.8 mmol) in 76% yield.

White solid.

mp : 55-56 °C

$[\alpha]_D^{25}$: -63.7 (*c* 1, Acetone)

PMR (200 MHz, $CDCl_3$) : δ 7.77 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.26-7.11 (m, 9H), 6.86 (d, *J* = 8.9 Hz, NH), 4.87 (d, *J* = 8.9 Hz, 1H), 4.58-4.52 (m, 1H), 3.75 (bs, OH), 2.79-2.67 (m, 2H), 2.39 (s, 6H), 2.12-1.96 (m, 1H), 1.91-1.75 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 21.3, 21.4, 43.4, 49.0, 60.9, 70.0, 123.9, 125.5, 127.2, 127.3, 128.3, 129.7, 130.2, 137.6, 139.8, 142.0, 143.4, 143.8.

m/z (LSIMS) : 458 $[M+H]^+$

IR (neat) cm^{-1} : 3540, 3272, 1598, 1494, 1398, 1327, and 1159.

Elemental Analysis : Calcd. for $C_{24}H_{27}NO_4S_2$ C, 62.99; H, 5.95; N, 3.06; S, 14.07.

Found : C, 63.03; H, 5.91; N, 3.05; S, 14.06.

4-(S_S)(4-Methylphenylsulfinyl)-3-(4-methylphenylsulfonamido)-1-phenyl-(1*R*,3*R*)-butylacetate, 44.

To the stirred solution of **43** (1.37 g, 3 mmol) in dry dichloromethane (12 mL) were added pyridine (474 mg, 6 mmol) followed by acetic anhydride (331 mg, 3.25 mmol). The reaction mixture was stirred for 1 h and then diluted with dichloromethane. The organic layer was washed successively with aqueous saturated $CuSO_4$ solution, water, 5% aq. $NaHCO_3$ solution, water, brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure followed by column chromatography using AcOEt/petroleum ether (1:1, v/v) as the eluent afforded the acetate **44** (1.44 g, 2.88 mmol) in 96% yield as a white solid.

mp : 70-72 °C

$[\alpha]_D^{25}$: -71.8 (*c* 0.75, Chloroform)

PMR (200 MHz, $CDCl_3$) : δ 7.72 (d, J = 8.2 Hz, 2H), 7.36-7.13 (m, 11H), 6.16 (d, J = 8.2 Hz, NH), 5.71 (dd, J = 8.9, 4.5 Hz, 1H), 3.98-3.81 (m, 1H), 2.78 (d, J = 5.2 Hz, 2H), 2.45 (s, 3H), 2.42 (s, 3H), 2.41-2.14 (m, 2H), 2.02 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 21.0, 21.3, 21.4, 41.2, 48.3, 60.1, 72.4, 123.9, 126.1, 127.2, 128.0, 128.5, 129.7, 130.0, 137.9, 139.8, 139.9, 142.0, 143.3, 169.9.

m/z (LSIMS) : 500 $[M+H]^+$

IR (neat) cm^{-1} : 3249, 1741, 1596, 1493, 1371, 1327 and 1152.

Elemental analysis : Calcd. for $C_{26}H_{29}NO_5S_2$: C, 62.50; H, 5.85; N, 2.80; S, 12.83.

Found : C, 62.43; H, 5.91; N, 2.84; S, 12.80.

4-Hydroxy-3-(4-methylphenylsulfonamido)-1-phenyl-(1*R*,3*R*)-butylacetate, 45.

To the stirred solution of **44** (1.05 g, 2.1 mmol) and dry 2,6-lutidine (674 mg, 6.3 mmol) in acetonitrile (15 mL) under a nitrogen atmosphere at 0 ^{o}C, neat trifluoroacetic anhydride (1.5 mL, 10.5 mmol) was added dropwise. The reaction mixture was stirred at 0 ^{o}C for 5 min. Aq. 20% K_2CO_3 solution was added to adjust pH to 7. Then $NaBH_4$ (400 mg, 10.5 mmol) was added portionwise and the reaction mixture allowed to attain room temperature. After 15 min the reaction was quenched with an aqueous saturated ammonium chloride solution. The reaction mixture was extracted with ethylacetate and the combined organic layers dried over anhydrous sodium sulfate. Evaporation of the solvent followed by purification on a silica gel column using acetone/petroleum ether (1:4, v/v) afforded the β-amino alcohol **45** (617 mg, 1.64 mmol) in 78% yield.

Solid.

mp : 159-161^{o}C

$[\alpha]_D^{25}$: +13.6 (*c* 0.6, Acetone)

PMR (200 MHz, $CDCl_3$) : δ 7.69 (d, *J* = 8.2 Hz, 2H), 7.34-7.12 (m, 7H), 7.01 (d, *J* = 8.2 Hz, NH), 5.60 (dd, *J* = 10.4, 4.4 Hz, 1H), 4.13-4.04 (m, 1H), 3.38-3.16 (m, 2H and 1-OH), 2.44 (s, 3H), 2.09-1.72 (m, 5H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 20.8, 21.1, 38.1, 51.7, 63.7, 72.1, 125.6, 126.4, 127.5, 128.5, 129.7, 138.9, 141.6, 142.6, 169.3.

m/z (LSIMS) : 378 $[M+H]^+$

Elemental analysis : Calcd. for $C_{21}H_{25}NO_6S$: C, 60.46; H, 6.14; N, 3.71; S, 8.49.

Found : C, 60.48; H, 6.03; N, 3.79; S, 8.33.

4-Methylcarbonyloxy-2-(4-methylphenylsulfonamido)-4-phenyl-(2*R*)-butylacetate, 46.

To the stirred solution of **45** (377 mg, 1 mmol) in dichloromethane (4 mL) was added successively pyridine (158 mg, 2 mmol) and acetic anhydride (122 mg, 1.1 mmol) at room temperature under N_2. The reaction mixture was stirred for a period of 2 h at room temperature. The reaction mixture was then diluted with dichloromethane and washed sequentially with aq. saturated $CuSO_4$ solution, water, aq. 5% $NaHCO_3$ solution, water, brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure followed by purification using AcOEt/petroleum ether (1:3, v/v) as the eluent afforded the diacetate (406 mg, 0.97 mmol) in 97% yield.

Viscous liquid.

$[\alpha]_D^{25}$	: +11.4 (*c* 0.75, Chloroform).
PMR (200 MHz, $CDCl_3$)	: δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.48-7.12 (m, 7H), 5.68 (dd, *J* = 9.7, 4.5 Hz, 1H), 5.58 (d, *J* = 8.9 Hz, NH), 4.0-3.84 (m, 2H), 3.76-3.52 (m, 1H), 2.44 (s, 3H), 2.12-1.80 (m, 8H).
^{13}C NMR (75 MHz, $CDCl_3$):	δ 20.6, 21.0, 21.5, 39.2, 49.8, 65.7, 72.6, 126.2, 127.0, 128.1, 128.6, 129.8, 137.7, 140.0, 143.6, 169.8, 170.7.
m/z (LSIMS)	: 420 $[M+H]^+$
Elemental analysis	: Calcd. for $C_{21}H_{25}NO_6S$: C, 60.13; H, 6.01; N, 3.34; S, 7.64.
Found	: C, 60.43; H, 5.91; N, 2.94; S, 7.80.

2-Dodecanoyl(4-methylphenyl)sulfonamido-4-methylcarbonyloxy-4-phenyl-(2*R*)-butyl acetate, 47.

The solution of lauryl chloride (110 mg, 0.5 mmol) in dichloromethane (0.25 mL) was added dropwise to the mixture of the diacetate **46** (210 mg, 0.5 mmol), Et_3N (101 mg, 1 mmol) and DMAP (cat.) in dichloromethane (1.5 mL) at 0 °C under N_2. The reaction mixture was gradually allowed to attain room temperature and stirred further for a period of 30 min. The reaction mixture was diluted with dichloromethane and washed successively with water, 10% aq. citric acid solution, brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel with AcOEt/petroleum ether (1:9, v/v) to afford the amide **47** (274 mg, 0.46 mmol) in 91% yield.

Liquid.

$[\alpha]_D^{25}$	: +9.7 (*c* 2.0, acetone)
PMR (200 MHz, $CDCl_3$)	: δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.40-7.22 (m, 7H), 5.57 (dd, *J* = 9.7, 4.5 Hz, 1H), 4.73-4.58 (m, 1H), 4.50-4.32 (m, 2H), 2.60-2.16 (m, 7H), 2.11 (s, 3H), 2.0 (s, 3H), 1.71-1.11 (m, 18H), 0.88 (t, *J* = 6.7 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$)	: δ 14.1, 20.8, 21.2, 21.6, 22.6, 24.7, 28.9, 29.0, 29.2, 29.4, 29.6, 31.9, 38.3, 56.0, 64.2, 73.4, 126.3, 127.7, 128.1, 128.6, 129.9, 137.2, 140.2, 144.9, 170.2, 170.5, 174.1.
m/z (LSIMS)	: 542 $[M-OAc]^+$
Elemental analysis	: Calcd. for $C_{33}H_{47}NO_7S$: C, 65.86; H, 7.87; N, 2.33; S, 5.33.
Found	: C, 65.66; H, 7.42; N, 2.13; S, 5.47.

1*N*-[3-Hydroxy-1-hydroxymethyl-3-phenyl-(1*R*)-propyl]dodecanamide, 1.

To the substrate **47** (30 mg, 0.05 mmol) in dry dimethoxyethane (0.5 mL) was added freshly prepared Na-Naphthanilide in dimethoxyethane (the solution of sodium naphthanilide in dimethoxyethane was prepared by adding dimethoxy ethane (10 mL) to a mixture of Na (300 mg, 13 mmol) and naphthalene (2.05 g, 16 mmol) and stirring the mixture at r.t. for 2 h) at –20 °C under nitrogen atmosphere until light green colour persisted (ca. 2 min). The reaction mixture was quenched by the addition of water. Solid K_2CO_3 (140 mg) was added and the reaction mixture stirred at room temperature for 24 h. The solvent was evaporated under reduced pressure and the residue was extracted into ethylacetate. Column chromatography using hexane/isopropylalcohol (4:1, v/v) afforded the product 1 (10 mg, 0.27 mmol) in 55% yield.

Solid.

mp : 76-78 °C

Lit.[8] : 75.5-77 °C

$[\alpha]_D^{25}$: –36.6 (*c* 0.56, $CHCl_3$)

Lit.[8] : -35.1 (*c* 0.8, $CHCl_3$)

PMR (200 MHz, $CDCl_3$) : 7.40-7.12 (m, 5H), 6.19 (d, *J* = 5.9 Hz, NH), 4.62 (bd, *J* = 7.5 Hz, 1H), 4.08-4.19 (m, 1H), 3.62-3.77 (m, 2H), 2.31-2.13 (m, 2H), 1.68-1.45 (m, 2H), 1.42-1.20 (m, 18H), 0.86 (t, *J* = 6.7 Hz, 3H).

1-[4-Hydroxy-2-(4-methylphenylsulfonamido)-4-phenyl-(2*R*)-butylsulfonyl]-4-methylbenzene, 87.

To the solution of sulfoxide **43** (228 mg, 0.5 mmol) in chloroform (2 mL), *m*-CPBA (123 mg, 0.5 mmol, 60%) was added at 0 °C and the reaction mixture was stirred at 0 °C for 10 min. The reaction mixture was diluted with chloroform and washed successively with 10% aq. sodium bi sulfite solution, 10% aq. sodium bi carbonate solution, water and brine. The reaction mixture was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford the crude product. Column chromatography using AcOEt/petroleum ether (1:4, v/v) afforded **87** (189 mg, 0.4 mmol) in 80% yield.

Viscous oil.

PMR (200 MHz, $CDCl_3$) : δ 7.74-7.50 (m, 4H), 7.45-7.05 (m, 9H), 6.2 (d, *J* = 7.4 Hz, NH), 4.95 (dd, *J* = 9.6, 2.7 Hz, 1H), 3.84-3.78 (m, 1H), 3.45 (dd, *J* = 13.4, 3.7 Hz, 1H), 3.26 (dd, *J* = 13.4, 7.4 Hz, 1H), 2.52 (s, 3H), 2.44 (s, 3H), 2.20-1.90 (m, 2H).

m/z (LSIMS) : 474 $[M+H]^+$

4-(4-Methylphenylsulfonyl)-1-phenyl-(1*R*,3*E*)-3-buten-1-ol, 88.

To the solution of **87** (47 mg, 0.1 mmol) in THF (1.6 mL) was added dropwise *n*-BuLi (0.48 mL, 0.3 mmol, 1.6M) at -78 °C. After being stirred for 30 min at the same temperature, a solution of 1,3-di iodopropane (66 mg, 0.22 mmol) in THF (0.8 mL) was added dropwise, and stirring was continued for 2 h at -78 °C. The reaction was quenched by the addition of saturated aq. NH_4Cl solution. The solvent was removed and the residue was extracted into ether. The ether extracts were washed with brine, dried and evaporated. Column chromatography on silica gel using AcOEt/petroleum ether (1:9, v/v) as the eluent afforded the product **88.**

Solid.

mp : 89-91 °C

PMR (200 MHz, $CDCl_3$) : δ 7.62 (d, *J* = 8.2 Hz, 2H), 7.45-7.10 (m, 7H), 6.71 (dt, *J* = 15.7, 7.8 Hz, 1H), 5.97 (d, *J* = 15.7 Hz, 1H), 4.80 (t, *J* = 5.7 Hz, 1H), 2.50-2.40 (m, 4H), 2.05 (m, 1H).

m/z (LSIMS) : 303 $[M+H]^+$

1-[4-*tert*-Butyldiphenylsilyloxy-2-(4-methylphenylsulfonamido)-4-phenyl-(2*R*)-butyl-(S_S)-sulfinyl]-4-methylbenzene, 89.

To the solution of the sulfoxide **43** (457 mg, 1 mmol) in dichlormethane (4 mL) was added imidazole (136 mg, 2 mmol) and TBDPS-Cl (275 mg, 1 mmol) at ambient temperature. The reaction mixture was stirred for 2 h at room temperature and solvent was removed under reduced pressure. The residue was diluted with ether and washed with water, brine, dried and evaporated to afford the crude product mixture. Purification on silica gel column using AcOEt/petroleum ether (3:17, v/v) as the eluent afforded the silyl ether **89** (557 mg, 0.8 mmol) in 80% yield.

Viscous oil.

PMR (200 MHz, $CDCl_3$) : δ 7.72-7.60 (m, 4H), 7.57-6.97 (m, 17H), 6.79 (d, *J* = 8.2 Hz, 2H), 5.94 (bs, NH), 4.70 (t, *J* = 4.7 Hz, 1H), 3.32-3.26 (m, 1H), 2.92-2.85 (m, 2H), 2.47 (s, 3H), 2.45-2.42 (m, 4H), 2.25-2.18 (m, 1H), 1.06 (s, 9H).

m/z (LSIMS) : 696 $[M+H]^+$

Typical experiment for the dialkylation of sulfoxide:

To a solution of sulfoxide **89** (36 mg, 0.05 mmol) in THF (0.5 mL) was added *n*-BuLi (0.1 mL, 0.1 mmol, 1M) dropwise at –78 °C. After stirring for 30 min at this temperature, a solution of di iodopropane (33 mg, 0.11 mmol) in THF (0.1 mL) was added dropwise, and stirring was continued at the temperature indicated in the Table I. After stirring for appropriate time indicated in the Table I, the reaction mixture was quenched by addition of saturated aq. NH_4Cl solution and extracted with ether. The ether extracts were washed with brine, dried and evaporated. Column chromatography on silica gel eluting with AcOEt/petroleum ether (1:9, v/v) afforded the products.

1-[2-Allyl(4-methylphenyl)sulfonamido-4-(*tert*-butyldiphenylsilyloxy)-4-phenyl-(2*R*)-butyl-(S_S)-sulfinyl]-4-methylbenzene, 90.

Low melting solid.

PMR (200 MHz, CDCl$_3$) : δ 7.62-7.57 (m, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.40-7.08 (m, 19H), 5.56-5.42 (m, 1H), 4.82 (d, *J* = 9.8 Hz, 1H), 4.57 (d, *J* = 16.9 Hz, 1H), 4.27 (dd, *J* = 9.8, 3.7 Hz, 1H), 3.86-3.73 (m, 1H), 3.58 (dd, *J* = 15.4, 6.4 Hz, 1H), 3.51 (dd, *J* = 15.4, 6.4 Hz, 1H), 3.32 (dd, *J* = 15.1, 6.4 Hz, 1H), 2.78 (dd, *J* = 15.1, 11.7 Hz, 1H), 2.49 (s, 3H), 2.43 (s, 3H), 2.12-1.96 (m, 2H), 0.98 (s, 9H).

m/z (LSIMS) : 758 $[M+Na]^+$

4-(*tert*-Butyldiphenylsilyloxy)-1-(S_S)(4-methylphenylsulfinyl)-4-phenyl-(*E*)-1-butene sulfoxide, 91.

Viscous oil.

PMR (200 MHz, CDCl$_3$) : δ 7.73-7.62 (m, 2H), 7.47-7.18 (m, 17H), 6.27 (dt, *J* = 15.8, 8.2 Hz, 1H), 5.93 (d, *J* = 15.8 Hz, 1H), 4.71 (dd, *J* = 7.6, 3.8 Hz, 1H), 2.40 (s, 3H), 2.37-2.04 (m, 5H), 0.98 (s, 9H).

m/z (LSIMS) : 524 $[M+H]^+$

1-[4-(*tert*-Butyldiphenylsilyloxy)-2-(4-methylphenylsulfonamido)-4-phenyl-(2*R*)-butylsulfonyl]-4-methylbenzene, 92.

To the solution of sulfoxide **89** (350 mg, 0.5 mmol) in chloroform (2 mL), *m*-CPBA (123 mg, 0.5 mmol, 60%) was added at 0 °C and the reaction mixture was stirred at 0 °C for 10 min. The reaction mixture was diluted with chloroform and washed successively with 10% aq. sodium bi sulfite solution, 10% aq. sodium bi carbonate solution, water and brine. The reaction mixture was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford crude product. Column chromatography using AcOEt/petroleum ether (1:4, v/v) afforded sulfone **92** (330 mg, 0.47 mmol) in 93% yield.

Viscous oil.

PMR (200 MHz, $CDCl_3$) : δ 7.77-7.65 (m, 2H), 7.54-7.28 (m, 9H), 7.27-6.97 (m, 10H), 6.76 (d, *J* = 8.2 Hz, 2H), 5.72 (d, *J* = 5.9 Hz, NH), 4.80 (t, *J* = 4.6 Hz, 1H), 3.63 (dd, *J* = 13.4, 3.1 Hz, 1H), 3.24-3.13 (m, 1H), 2.77 (dd, *J* = 13.4, 8.9 Hz, 1H), 2.48 (s, 6H), 2.46-2.40 (m, 1H), 2.14-2.07 (m, 1H), 0.97 (s, 9H).

m/z (LSIMS) : 712 $[M+H]^+$

1-[2-Allyl(4-methylphenyl)sulfonamido-4-(*tert*-butyldiphenylsilyloxy)-4-phenyl-(2*R*)-butylsulfonyl]-4-methylbenzene, 93.

Low melting solid.

PMR (200 MHz, $CDCl_3$) : δ 7.78-7.60 (m, 4H), 7.54-7.13 (m, 19H), 5.49-5.28 (m, 1H), 4.75 (d, *J* = 10.2 Hz, 1H), 4.59 (d, *J* = 16.5 Hz, 1H), 4.24 (dd, *J* = 7.9, 4.9 Hz, 1H), 3.90-3.72 (m, 1H), 3.56-3.50 (m, 1H), 3.42 (dd, *J* = 15.4, 6.8 Hz, 1H), 3.21 (dd, *J* = 15.1, 6.8 Hz, 1H), 2.62 (dd, *J* = 15.1, 4.5 Hz, 1H), 2.46 (s, 3H), 2.41 (s, 3H), 2.35-2.26 (m, 1H), 2.10-2.01 (m, 1H), 0.97 (s, 9H).

m/z (LSIMS) : 775 $[M+Na]^+$

4-(2,2-Dimethyl-1,1-diphenylpropoxy)-1-(4-methylphenylsulfonyl)-4-phenyl-(*E*)-1-butene, 94.

Viscous oil.

PMR (200 MHz, $CDCl_3$) : δ 7.73-7.62 (m, 2H), 7.47-7.18 (m, 17H), 6.27 (dt, *J* = 15.7, 7.9 Hz, 1H), 5.93 (d, *J* = 15.7 Hz, 1H), 4.79 (t, *J* =

6.3 Hz, 1H), 2.47 (s, 3H), 2.37-2.04 (m, 2H), 0.98 (s, 9H).

m/z (LSIMS) : 541 [M+H]$^+$

1-[4-(*tert*-Btyldimethylsilyloxy)-2-(4-methylphenylsulfonamido)-4-phenyl-(2*R*)-butylsulfinyl]-4-methylbenzene, 95.

To the solution of the sulfoxide **43** (228 mg, 0.5 mmol) in dichlormethane (2 mL) was added imidazole (68 mg, 1 mmol) and TBDMS-Cl (75 mg, 0.5 mmol) at ambient temperature. The reaction mixture was stirred for 2 h at room temperature and solvent was removed under reduced pressure. The residue was diluted with ether and washed with water, brine, dried and evaporated to afford the crude product mixture. Purification on silica gel column using AcOEt/petroleum ether (3:17, v/v) as the eluent afforded the silyl ether **95** (243 mg, 0.42 mmol) in 85% yield.

Viscous oil.

PMR (200 MHz, $CDCl_3$) : δ 7.73 (d, *J* = 8.2 Hz, 2H), 7.32-7.10 (m, 11H), 6.36 (d, *J* = 6.7 Hz, NH), 4.97 (t, *J* = 6.0 Hz, 1H), 3.91 (q, *J* = 6.0 Hz, 1H), 2.81 (dd, *J* = 13.4, 5.2 Hz, 1H), 2.69 (dd, *J* = 13.4, 6.0 Hz, 1H), 2.47 (s, 3H), 2.43 (s, 3H), 2.13 (t, *J* = 6.0 Hz, 2H), 0.90 (s, 9H), 0.11 (s, 3H), -0.21 (s, 3H).

m/z (LSIMS) : 572 [M+ H]$^+$

3-Trimethylsilyl-2-pentyne-1-ol, 97.

A 3-necked round bottom flask was fitted with a pressure equalizing funnel, reflux condenser and a N_2 inlet. The flask was flushed with N_2 and charged with 3-butyn-1-ol **96** (2.51 g, 44.8 mmol) and 90 mL of dry THF. The stirred solution was cooled to 0 °C under N_2 and to it was added over 20 min a solution of EtMgBr in THF (50 mL, 2 M in THF). The resulting heterogeneous mixture was rapidly stirred at 0 °C for 1 h, allowed to warm to room temperature and stirred for 1 h and then recooled to 0 °C. To this mixture was slowly added over 30 min with rapid stirring freshly distilled TMS-Cl (10.7 g, 98.6 mmol). The reaction mixture was stirred at 0 °C for 1 h and allowed to attain room temperature. At this temperature, the reaction mixture was stirred for 2 h. The reaction mixture was then poured slowly with rapid stirring into a 1 L conical flask containing ice-cold 3 M HCl and stirred for an additional 2 h. The organic phase was separated and aq. phase was extracted with ether. The combined organic layers were washed with water, 10% aq. $NaHCO_3$ solution, water, brine, dried and evaporated to afford 97 (4.93 g, 38.5 mmol) in 85% yield.

Viscous oil.

PMR (400 MHz, $CDCl_3$) : δ 4.23 (d, *J* = 6.2 Hz, 2H), 1.44 (bs, OH), 0.02 (s, 9H).

3-Trimethylsilyl-(*E*)-2-penten-1-ol, 98.

To a stirred suspension of LAH (1.12 g, 29.6 mmol) in dry THF (20 mL) was added the acetylenic compound **97** (1.89 g, 14.8 mmol) in dry THF (20 mL) under nitrogen atmosphere at 0 °C. The reaction mixture was allowed to warm to room temperature and slowly heated to reflux. After being stirred at reflux for 6 h, it was cooled to 0 °C, diluted with ether and quenched with small ice pieces. The resulting white suspension was filtered through a sintered funnel. The residual white cake was washed repeatedly with hot ethylacetate and the filtrate was concentrated in vacuo. The crude product mixture was purified by column chromatography to furnish the *trans*-allylic alcohol **98** (1.77 g, 13.6 mmol) in 92% yield.

Light yellow oil.

PMR (300 MHz, $CDCl_3$) : δ 6.17 (dt, *J* = 16.7, 4.2 Hz, 1H), 5.88 (d, *J* = 16.7 Hz, 1H), 4.13 (d, *J* = 4.2 Hz, 2H), 1.53 (bs, OH), 0.10 (s, 9H).

1-Bromo-3-trimethylsilyl-(*E*)-2-pentene, 99.

To a solution of allylic alcohol **98** (260 g, 2 mmol) in anhydrous ether (2 mL) was added catalytic amount of pyridine. The reaction mixture was cooled to 0 °C and PBr_3 (180 mg, 0.67 mmol) in anhydrous ether (0.67 mL) was added dropwise. The reaction mixture was refluxed for 1.5 h and allowed to return to room temperature. The reaction mixture was poured into ice. The crude product mixture was extracted into ether and washed successively with water, 5% aq. $NaHCO_3$, brine, dried over anhydrous Na_2SO_4 and evaporated. Distillation of the crude product at reduced pressure afforded pure bromide **99** (3.59 g, 1.86 mmol) in 93% yield.

Colourless oil.

PMR (300 MHz, $CDCl_3$) : δ 6.12 (dt, *J* = 17.8, 8.6 Hz, 1H), 5.90 (d, *J* = 17.8 Hz, 1H), 3.91 (d, *J* = 8.6 Hz, 2H), 0.10 (s, 9H).

1-[2-[3-Trimethylsilyl-(*E*)-2-propenyl(4-methylphenyl)sulfonamido]-4-phenyl-4-(*tert*-butyldimethylsilyloxy)butyl-(S_S)sulfinyl]-4-methylbenzene, 100.

To the mixture of **95** (572 mg, 1 mmol), K_2CO_3 (166 mg, 1.2 mmol) in dry acetonitrile (4 mL) was added **99** (193 mg, 1 mmol) at room temperature and slowly heated to reflux. After being stirred at reflux for 2 h, the reaction mixture was allowed to return to room temperature and water was added. The organic layer was separated. The aq. layer was extracted with ethylacetate and combined organic layers were washed with water, brine, dried over Na_2SO_4 and evaporated under reduced pressure. Column chromatography using AcOEt/petroleum ether (1:4, v/v) as the eluent afforded **100** (458 mg, 0.67 mmol) in 67% yield.

Viscous oil.

PMR (200 MHz, $CDCl_3$) : δ 7.93 (d, *J* = 8.2 Hz, 2H), 7.80-7.43 (m, 11H), 6.23 (dt, *J* = 18.6, 6.1 Hz, 1H), 6.0 (d, *J* = 18.6 Hz, 1H), 4.97 (dd, *J* = 8.7, 4.6 Hz, 1H), 4.78-4.51 (m, 1H), 4.20-3.95 (m, 2H), 3.37-3.22 (m, 2H), 2.74 (s, 6H), 2.58-2.20 (m, 2H), 1.12 (s, 9H), 0.40 (s, 3H), 0.27 (s, 9H), 0.0 (s, 3H).

m/z (LSIMS) : 681 $[M+H]^+$

1-Bromo-3-trimethylsilyl-prop-2-yne, 102.

To a solution of alcohol **97** (1.28 g, 10 mmol) in anhydrous ether (10 mL) was added catalytic amount of pyridine. The reaction mixture was cooled to 0 °C and PBr_3 (900 mg, 3.35 mmol) in anhydrous ether (4 mL) was added dropwise. The reaction mixture was refluxed for 1.5 h and allowed to return to room temperature. The reaction mixture was poured into ice. The crude product mixture was extracted into ether and washed successively with water, 5% aq. $NaHCO_3$, brine, dried over anhydrous Na_2SO_4 and evaporated. Distillation of the crude product at reduced pressure afforded pure bromide **102** (1.62 g, 8.5 mmol) in 85% yield.

PMR (200 MHz, $CDCl_3$) : δ 3.75 (s, 2H), 0.0 (s, 9H).

1-[2-[3-Trimethylsilyl-2-propynyl(4-methylphenyl)sulfonamido]-4-phenyl-4-(*tert*-butyldimethylsilyloxy)butyl-(S_S)-sulfinyl]-4-methylbenzene, 103.

To the mixture of **95** (286 mg, 0.5 mmol), K_2CO_3 (83 mg, 0.6 mmol) in dry acetonitrile (2 mL) was added **102** (95 mg, 0.5 mmol) at room temperature and slowly heated to reflux. After being stirred at reflux for 2 h, the reaction mixture was allowed to return to room temperature and water was added. The organic layer was separated. The aq. layer was extracted with ethylacetate and combined organic layers were washed with water, brine, dried over Na_2SO_4 and evaporated under reduced pressure. Column chromatography using AcOEt/petroleum ether (1:4, v/v) as the eluent afforded **103** (232 mg, 0.34 mmol) in 68% yield.

Viscous oil.

PMR (200 MHz, $CDCl_3$) : δ 7.68 (d, *J* = 9.0 Hz, 2H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.37-7.18 (m, 9H), 4.72 (dd, *J* = 8.5, 4.6 Hz, 1H), 4.67-4.44

(m, 1H), 4.32-3.90 (m, 2H), 3.10 (dd, *J* = 13.4, 6.3 Hz, 1H), 2.96 (dd, *J* = 13.4, 4.9 Hz, 1H), 2.40 (s, 6H), 2.38-2.0 (m, 2H), 0.83 (s, 9H), 0.08 (s, 3H), -0.06 (s, 9H), -0.32 (s, 3H).

m/z (LSIMS) : 682 $[M+H]^+$

4-(*S*s)(4-Methylphenylsulfinyl)-3-(4-methylphenylsulfonamido)-1-phenyl-(1*R*,3*R*)-butylacetate, 44.

To a stirred solution of **43** (1.37 g, 3 mmol) in dichloromethane (12 mL) were added pyridine (474 mg, 6 mmol) and acetic anhydride (331 mg, 3.25 mmol). The reaction mixture was stirred at room temperature for 1 h and then diluted with dichlormethane. The organic layer was washed successively with aqueous saturated $CuSO_4$ solution, water, 5% aq. $NaHCO_3$ solution, water, brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure followed by column chromatography using AcOEt/petroleum ether (1:1) as the eluent afforded the acetate (1.44 g, 2.88 mmol) in 96% yield.

White solid.

mp : 70-72 °C

$[\alpha]_D^{25}$: -71.8 (*c* 0.75, $CHCl_3$)

PMR (200 MHz, $CDCl_3$) : δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.36-7.13 (m, 11H), 6.16 (d, *J* = 8.2 Hz, NH), 5.71 (dd, *J* = 8.9, 4.5 Hz, 1H), 3.98-3.81 (m, 1H), 2.78 (d, *J* = 5.2 Hz, 2H), 2.45 (s, 3H), 2.42 (s, 3H), 2.41-2.14 (m, 2H), 2.02 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 21.0, 21.3, 21.4, 41.2, 48.3, 60.1, 72.4, 123.9, 126.1, 127.2, 128.0, 128.5, 129.7, 130.0, 137.9, 139.8, 139.9, 142.0, 143.3, 169.9.

m/z (LSIMS) : 500 $[M+H]^+$

IR (neat) cm^{-1} : 3249, 1741, 1596, 1493, 1371, 1327, 1152.

Elemental analysis : Calcd. for $C_{26}H_{29}NO_5S_2$: C, 62.50; H, 5.85; N, 2.80; S, 12.83.

Found : C, 62.43; H, 5.91; N, 2.84; S, 12.80.

3-Butenyl 4-nitro-1-benzenesulfonate, 108.

To the solution of 3-butene-1-ol (360 mg, 5mmol) in dry dichloromethane (20 mL) was added successively Et_3N (10 mmol), DMAP (cat.) and *p*-nitrobenzenesulfonyl chloride (5 mmol) at room temperature under N_2. The reaction mixture was stirred for a period of 4 h. The reaction mixture was washed with water, brine and evaporated to dryness under reduced pressure. The crude product mixture was chromatographed on silica gel using AcoEt/petroleum ether (1:4, v/v) as the eluent to afford the nosylate **17** (1.03 g, 4 mmol) in 80% yield.
Solid.

mp : 122 °C

PMR (200 MHz, $CDCl_3$) : 8.42 (d, *J* = 8.8 Hz, 2H), 8.19 (d, *J* = 8.8 Hz, 2H), 5.78-5.55 (m, 1H), 5.18-5.05 (m, 2H), 4.21-4.11 (m, 2H), 2.51-2.36 (m, 2H).

m/z (LSIMS) : 258 $[M^{+}+H]$

3-[3-Butenyl(4-methylphenylsulfonamido)-4-(S_S)(4-methylphenylsulfinyl)-1-phenyl-(1*R*,3*R*)-butylacetate, 105.

Homoallynosylate **108** (566 mg, 2.2 mmol) was added to a stirred mixture of acetate **44** (1.1 g, 2.2 mmol) and K_2CO_3 (456 mg, 3.3 mmol) in dry acetonitrile (8.8 mL) and the reaction mixture was allowed to reflux for 2 h. The reaction mixture was diluted with ethylacetate and washed with water followed by brine solution. After drying over Na_2SO_4, column chromatography using AcOEt/petroleum ether (3:7, v/v) as the eluent afforded the *N*-alkylated product (1.1 g, 1.98 mmol) in 90% yield.

Viscous oil.

$[\alpha]_D^{25}$: -45.5 (*c* 2.2, $CHCl_3$)

PMR (200 MHz, $CDCl_3$) : δ 7.67 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.2 Hz, 2H), 7.36-7.11 (m, 9H), 5.68-5.48 (m, 2H), 5.04-4.90 (m, 2H), 4.21-4.04 (m, 1H), 3.28 (dd, *J* = 15.6, 8.2 Hz, 1H), 3.14 (dd, *J* = 15.6, 7.4 Hz, 1H), 2.94 (dd, *J* = 13.4, 7.4 Hz, 1H), 2.79 (dd, *J* = 13.4, 6.7 Hz, 1H), 2.42 (s, 6H), 2.36-2.10 (m, 4H), 2.02 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 21.0, 21.4, 21.5, 34.1, 40.9, 47.1, 52.1, 62.5, 72.8, 117.2, 123.9, 126.3, 127.5, 128.1, 128.5, 129.8, 130.0, 134.2, 137.5, 139.8, 140.4, 141.7, 143.7, 169.8.

m/z (LSIMS) : 554 $[M^{+}+H]$

IR (neat) cm^{-1} : 2977, 1752, 1595, 1488, 1449, 1337, 1142, 1083.

Elemental analysis : Calcd. for $C_{30}H_{35}NO_5S_2$: C, 65.07; H, 6.37; N, 2.53; S, 11.58.

Found : C, 65.43; H, 5.75; N, 2.21; S, 12.01.

Ethyl-4-[3-butenyl(4-methylphenyl)sulfonamido]-6-methylcarbonyloxy-6-phenyl-(*E*,4*R*)-2-hexenoate, 112.

To the solution of the *N*-homoallyl compound (664 mg, 1.2 mmol) in acetonitrile (6 mL) cooled at 0 °C was added triethylamine (364 mg, 3.6 mmol) followed by trifluoroacetic anhydride (1.26 g, 6 mmol) and the mixture stirred for 50 min. An aq. 5% $NaHCO_3$ solution (2 mL) was added at 0 °C and stirred for another 20 min. The reaction mixture was then extracted into benzene (10 mL) and washed successively with water, brine and dried over Na_2SO_4. The benzene solution of the aldehyde was directly taken ahead to the next step and reacted with ethyl(triphenylphosporanilidine)acetate (498 mg, 1.2 mmol). The reaction was stirred at r.t. for 30 min. The solvent was removed under reduced pressure to afford a residue which was purified by column chromatography using EtOAc/petroleum ether (1:9) as the eluent to afford the α,β-unsaturated ester (449 mg, 0.9 mmol) in 75% yield (for the two steps).

Solid.

mp : 59-61 °C

$[\alpha]_D^{25}$: +58.7 (*c* 2.25, Chloroform)

PMR (200 MHz, $CDCl_3$) : δ 7.63 (d, *J* = 8.2 Hz, 2H), 7.39-7.20 (m, 7H), 6.54 (dd, *J* = 15.6, 5.2 Hz, 1H), 5.76-5.56 (m, 3H), 5.08-4.93 (m, 2H), 4.64-4.47 (m, 1H), 4.12 (q, *J* = 6.7 Hz, 2H), 3.18 (ddd, *J* = 15.6, 11.1, 5.9 Hz, 1H), 2.92 (ddd, *J* = 15.6, 10.4, 5.9 Hz, 1H), 2.56-2.16 (m, 6H), 2.06-1.91 (m, 4H), 1.24 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 14.6, 21.5, 21.9, 36.0, 39.5, 45.2, 55.8, 61.0, 73.0, 117.7, 124.3, 126.8, 127.7, 128.7, 129.1, 130.2, 134.8, 137.5, 140.1, 144.0, 144.7, 165.9, 170.3.

m/z (LSIMS) : 500 $[M^{+}+H]$

Elemental analysis : Calcd. for $C_{27}H_{36}NO_6S$: C, 64.91; H, 6.66; N, 2.80; S, 6.42.

Found : C, 65.08; H, 6.85; N, 2.71; S, 6.46.

2-[1-(4-Methylphenylsulfonyl)-(6*R*)-2,3-dihydro-6-pyridinyl]-1-phenyl-(1*R*)-ethylacetate, 114.

Bis(tricyclohexylphophine)benzylideneruthenium(IV)dichloride (10 mg, 0.013 mmol) was added to a solution of diene **112** (324 mg, 0.65 mmol) in toluene and refluxed for 16 h., when TLC revealed the complete consumption of the starting material. The solvent was removed under reduced pressure. Column chromatography using AcOEt/petroleum ether (1:4, v/v) as the eluent afforded the product (207 mg, 0.52 mmol) in 80% yield.

Solid.

mp : 75-76 °C

$[\alpha]_D^{25}$: -119.0 (*c* 0.75, Chloroform)

PMR (200 MHz, $CDCl_3$) : δ 7.67 (d, *J* = 8.9 Hz, 2H), 7.36-7.16 (m, 7H), 5.74 (dd, *J* = 9.7, 4.5 Hz, 1H), 5.66-5.54 (m, 2H), 4.54-4.41 (m, 1H), 3.77 (dd, *J* = 14.9, 5.2 Hz, 1H), 3.08 (ddd, *J* = 14.9, 11.9, 5.2 Hz, 1H), 2.42 (s, 3H), 2.20-1.60 (m, 7H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 21.2, 21.5, 29.7, 38.0, 41.4, 50.2, 72.7, 125.5, 126.5, 127.2, 127.3, 128.0, 128.5, 129.5, 138.1, 140.5, 143.2, 170.1.

m/z (LSIMS) : 400 $[M+H]^+$

IR (neat) cm^{-1} : 3032, 2925, 2853, 1744, 1598, 1494, 1374, 1345, 1159, 1096.

Elemental analysis : Calcd. for $C_{27}H_{25}NO_4S$: C, 66.14; H, 6.31; N, 3.51; S, 8.02.

Found : C, 66.03; H, 6.55; N, 3.41; S, 8.07.

2-[(6*R*)-2,3-Dihydro-6-pyridinyl]-1-phenyl-(1*R*)-ethan-1-ol, 115.

Freshly prepared Na-Hg (6%, 150 mg) was added to a well-stirred mixture of **114** (179 mg, 0.45 mmol), anhydrous Na_2HPO_4 (319 mg, 2.25 mmol) in methanol (9 mL) at room temperature and allowed to reflux for 6 h. The reaction mixture was quenched with water and extracted into ethylacetate. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was chromatographed on a small pad of silica gel using CH_2Cl_2: MeOH (50:1 then 1:10, v/v) as the eluent to afford **115** (71 mg, 0.35 mmol) in 78% yield.

Viscous liquid.

$[\alpha]_D^{25}$: -39.1 (*c* 0.8, $CHCl_3$)

PMR (200 MHz, $CDCl_3$) : δ 7.40-7.12 (m, 5H), 5.97-5.82 (m, 1H), 5.58-5.44 (m, 1H), 5.12-4.96 (m, 1H), 4.04-3.88 (m, 1H), 3.43-3.24 (m, 1H), 3.03-2.83 (m, 1H), 2.56-1.85 (m ,4H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 29.6, 40.3, 41.3, 51.1, 69.4, 125.4, 126.3, 127.1, 128.3, 144.0.

m/z (LSIMS) : 204 $[M^{+}+H]$

Elemental analysis : Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89.

Found : C, 76.57; H, 8.15; N, 6.66.

1-Phenyl-2-[(6*S*)-tetrahydro-6-pyridinyl]-(1*R*)-ethan-1-ol, 116.

To a solution of **115** (15 mg, 0.075 mmol) in ethylacetate (1.5 mL) was added Pt/C (5 mg, 10% wt/wt) and the reaction mixture was allowed to stir under H_2 atmosphere for 3 h. The reaction mixture was filtered through celite and evaporated to dryness under reduced pressure to afford **115** (14 mg, 0.068 mmol) in 90% yield.

$[\alpha]_D^{25}$: -28.1 (*c* 0.2, Methanol)

PMR (200 MHz, $CDCl_3$) : δ 7.42-7.18 (m, 5H), 5.22 (bd, *J* = 7.4 Hz, 1H), 3.44 (bd, *J* = 11.7 Hz, 1H), 3.36-3.21 (m, 1H), 2.91-2.71 (m, 1H), 2.42-2.22 (m, 1H), 2.04- 1.66 (m, 6H), 1.51-1.32 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 22.0, 22.5, 29.6, 42.1, 44.9, 54.4, 68.4, 125.5, 127.2, 128.4, 143.6.

m/z EI : 206 $[M^{+}+H]$

Elemental analysis : Calcd. for $C_{13}H_{19}NO$, C, 76.06; H, 9.33; N, 6.82.

Found : C, 76.57; H, 9.15; N, 6.66.

2-[1-Methyl-(6*S*)-tetrahydro-6-pyridinyl]-1-phenyl-(1*R*)-ethan-1-ol, 52.

To a solution of the substrate **115** (12mg, 0.06 mmol) in acetonitrile (0.9 mL) was added 37% aq. HCHO (0.28 mL), AcOH (20 μL) and $NaCNBH_3$ (19 mg). The resulting reaction mixture was stirred at r.t. for 4 h and then concentrated under reduced pressure. The residue was extracted into dichloromethane and the solvent was evaporated under reduced pressure. Column chromatography using MeOH: DCM (first with 1:10 v/v then methanol alone) as the eluent afforded the product in 70% yield as a solid.

mp : 78-80 °C

Lit.[35] : 80-81 °C

$[\alpha]_D^{25}$: -27.8 (*c* 0.4, Methanol)

Lit.[35] $[\alpha]_D^{25}$: -29.8 (*c* 0.2, Methanol)

PMR (200 MHz, $CDCl_3$) : δ 7.40-7.21 (m, 5H), 5.10 (dd, *J* = 10.4, 3.4 Hz, 1H), 3.02 (d, *J* = 10.4 Hz, 1H), 2.46 (s, 3H), 2.45-3.32 (m, 1H), 2.17 (ddd, *J* = 14.9, 10.9, 4.3 Hz, 1H), 1.96-1.53 (m, 6H), 1.32-1.20 (m, 2H).

m/z (LSIMS) : 220 $[M+H]^+$

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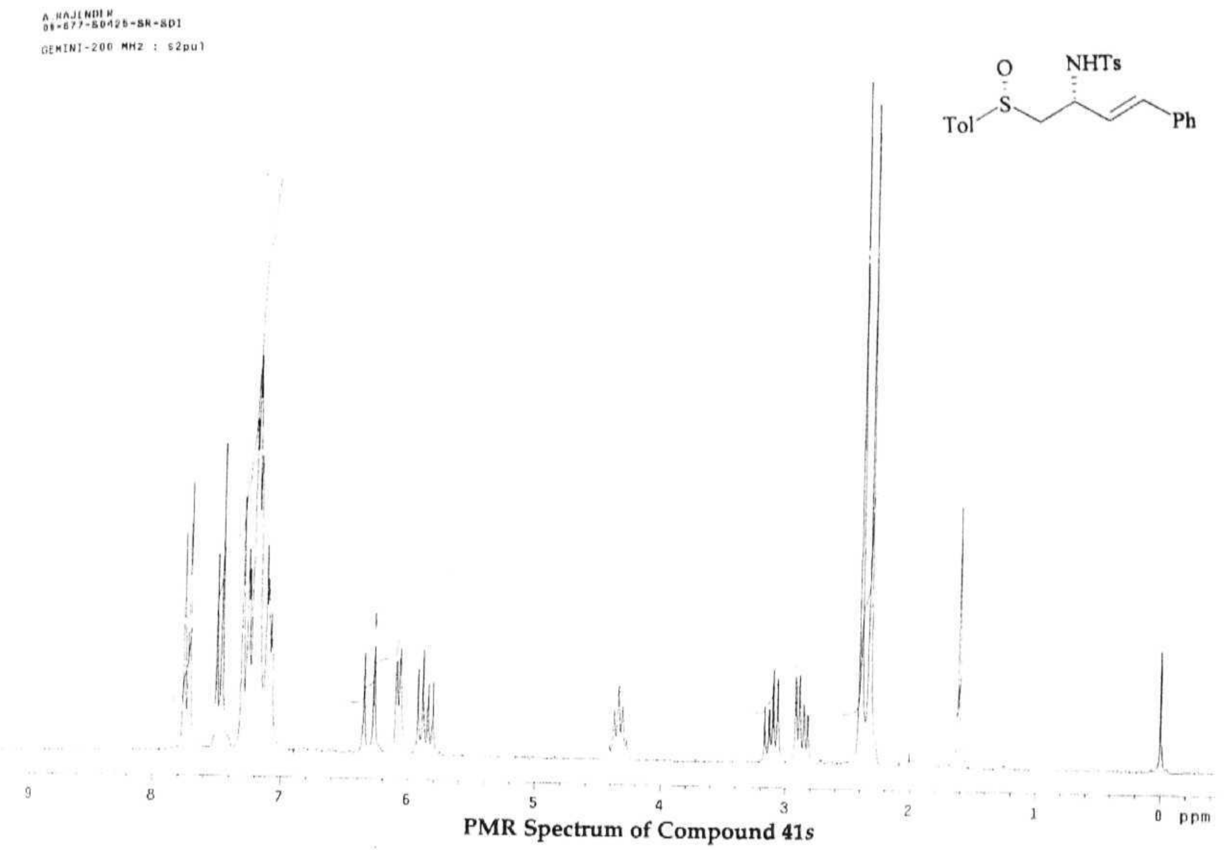
SPECTRA



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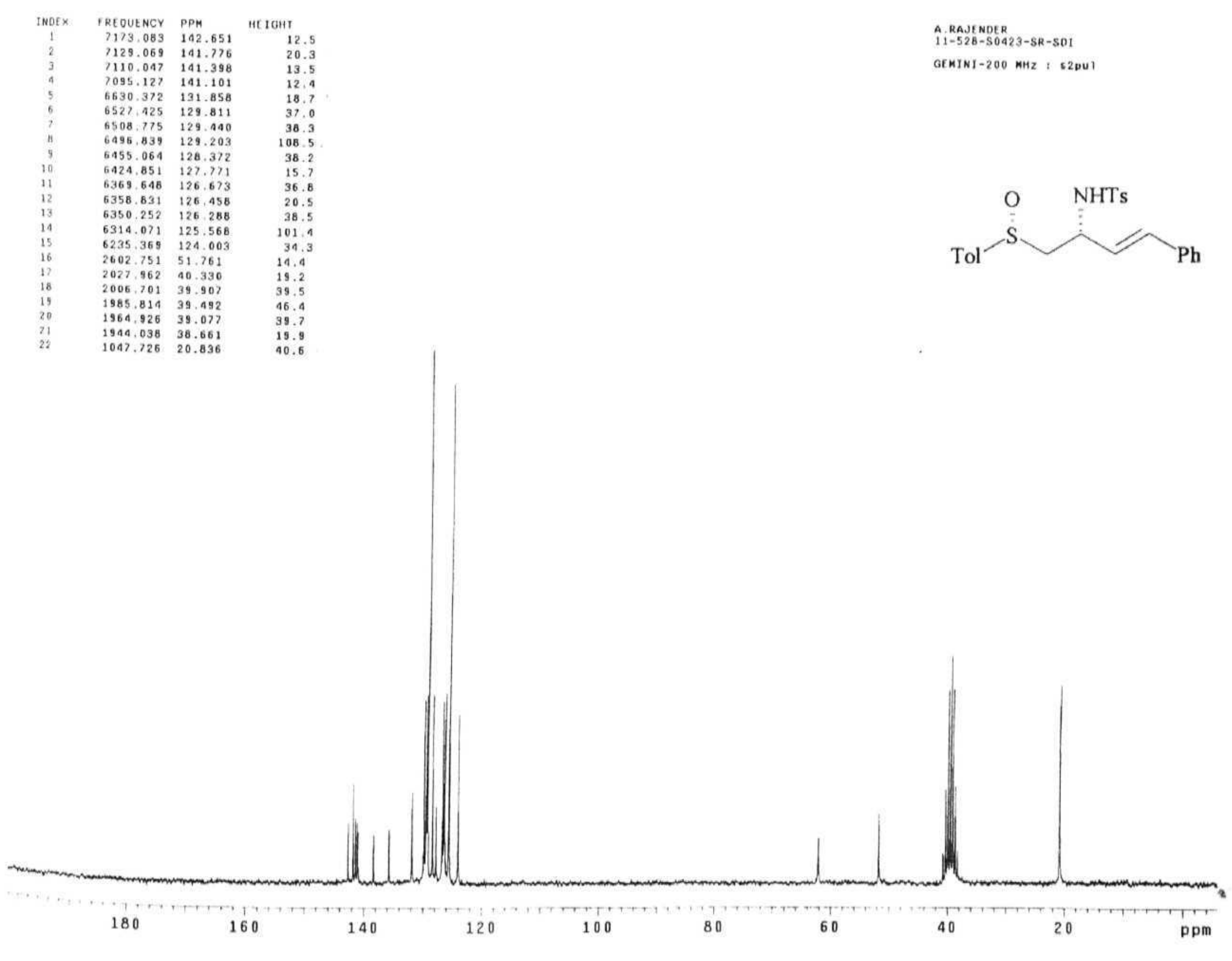

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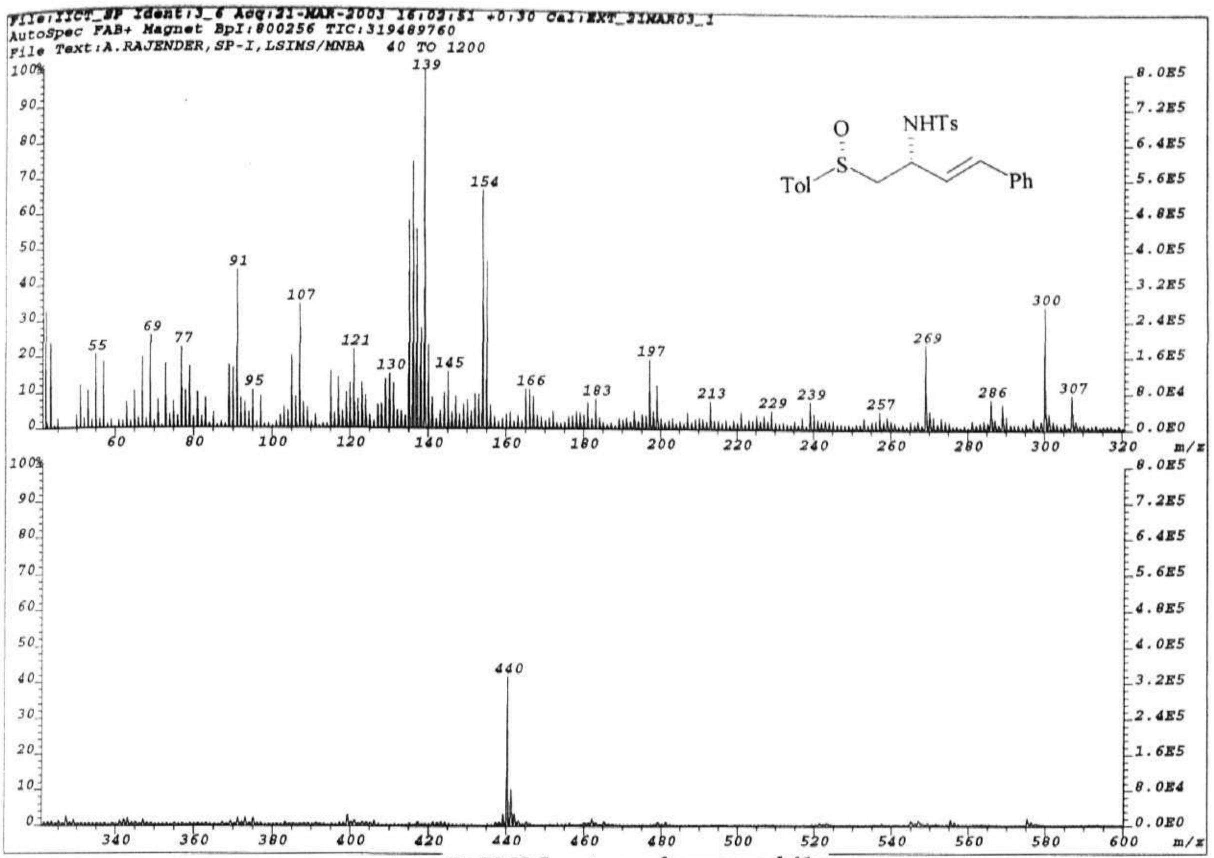

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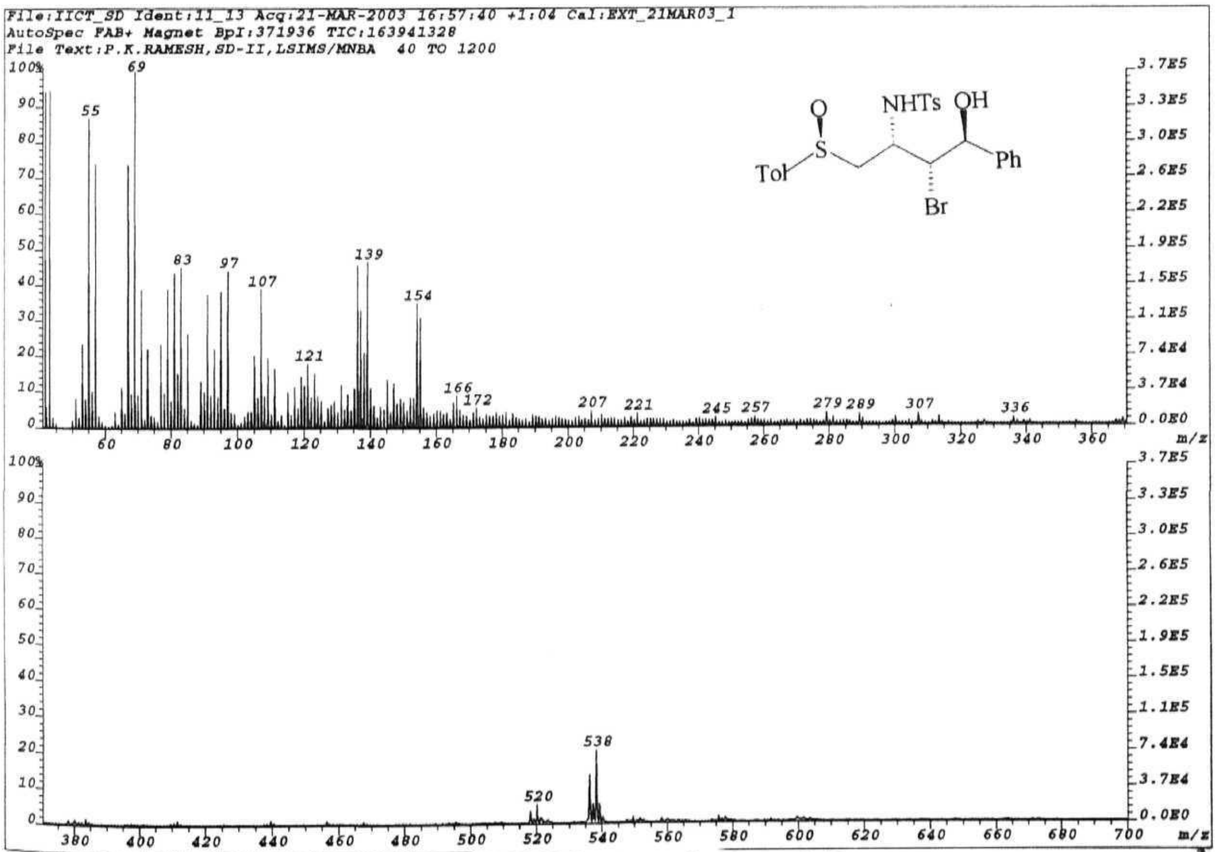

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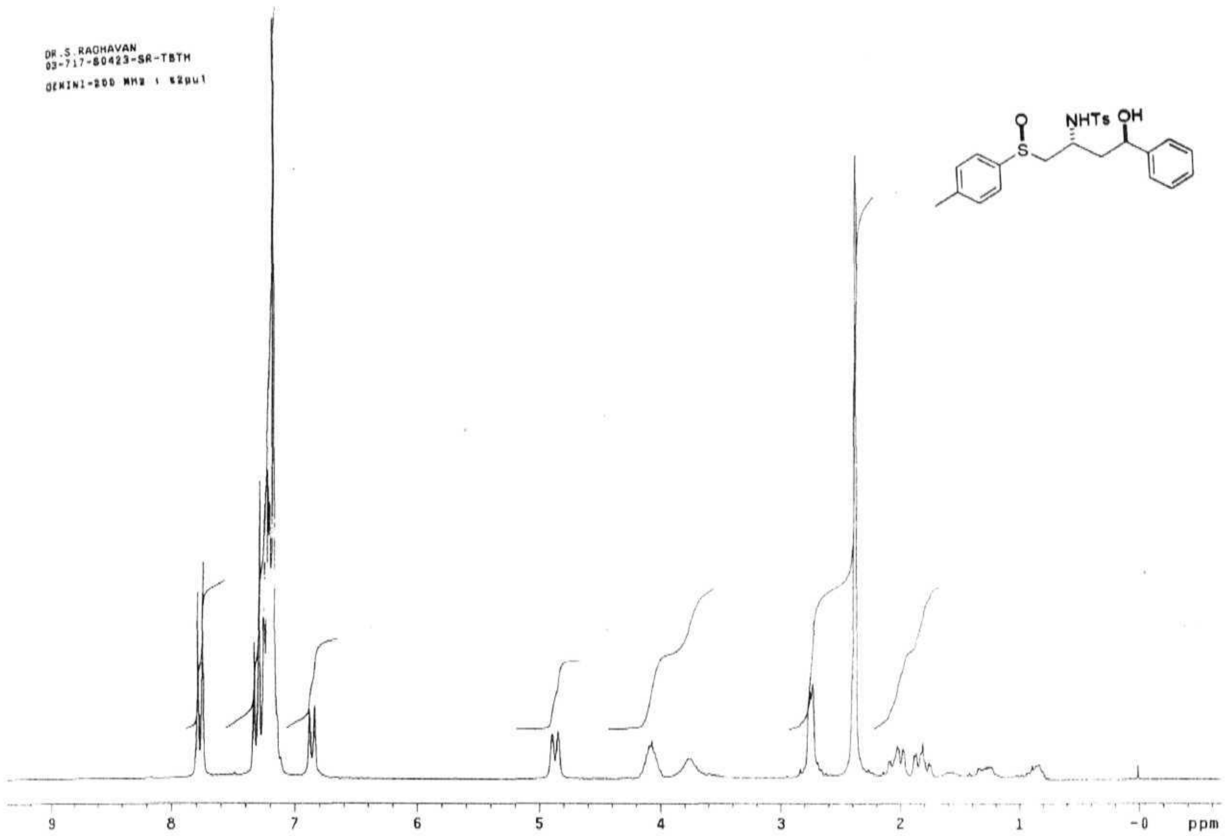

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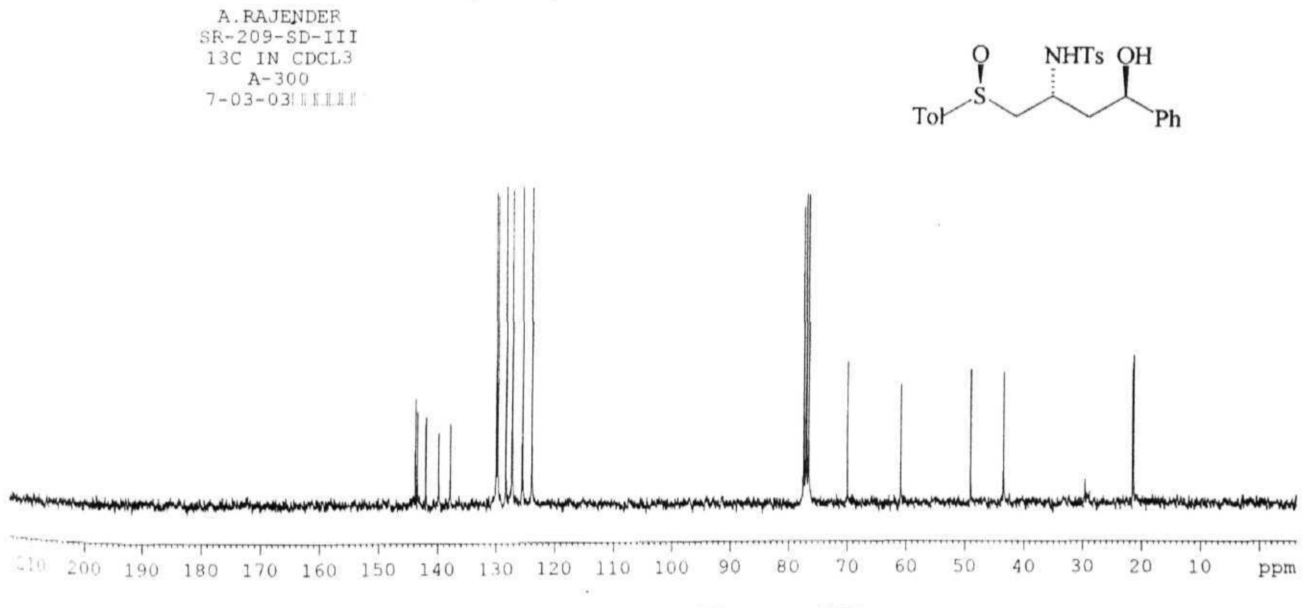

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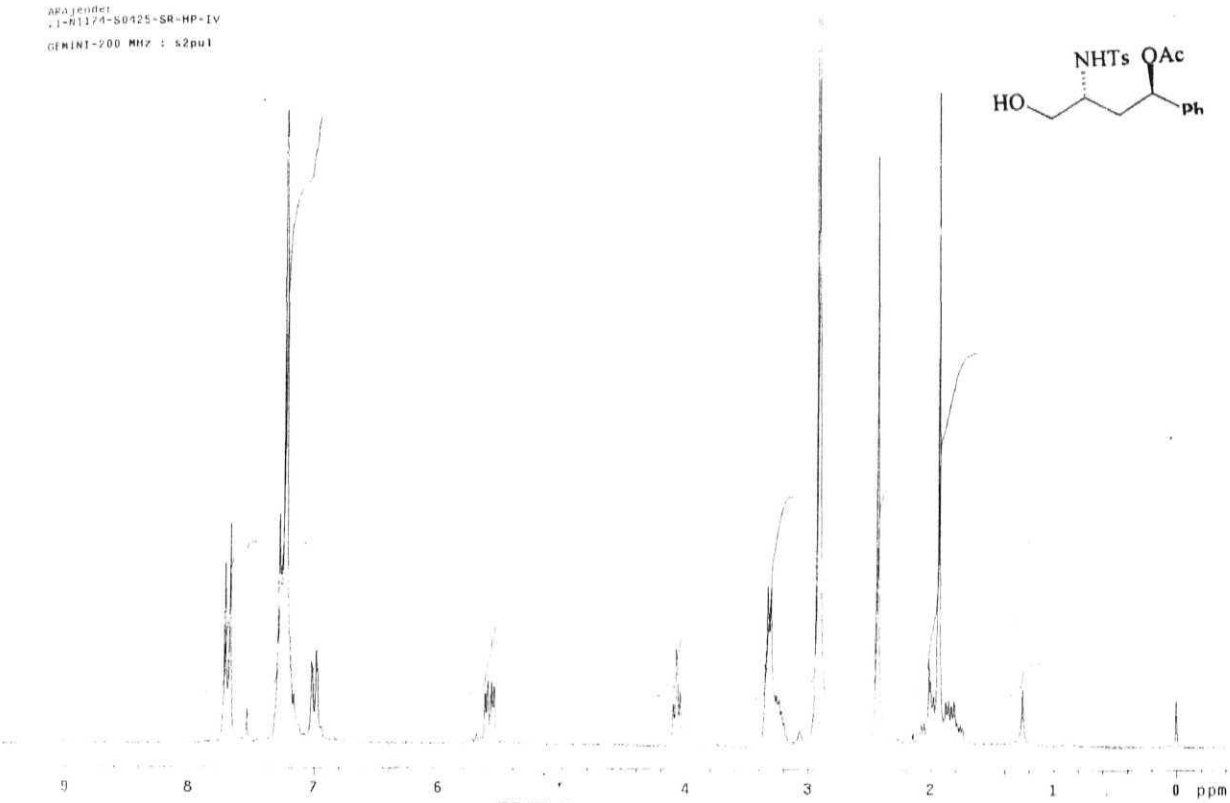

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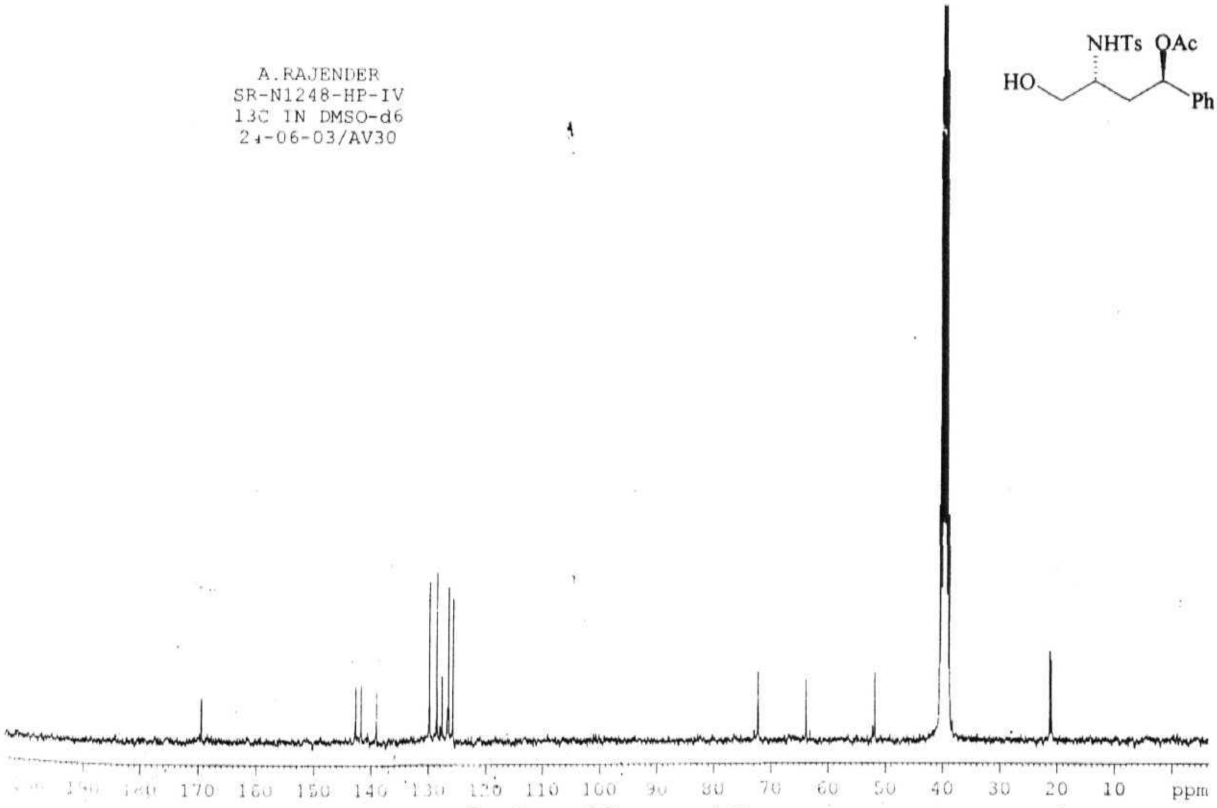

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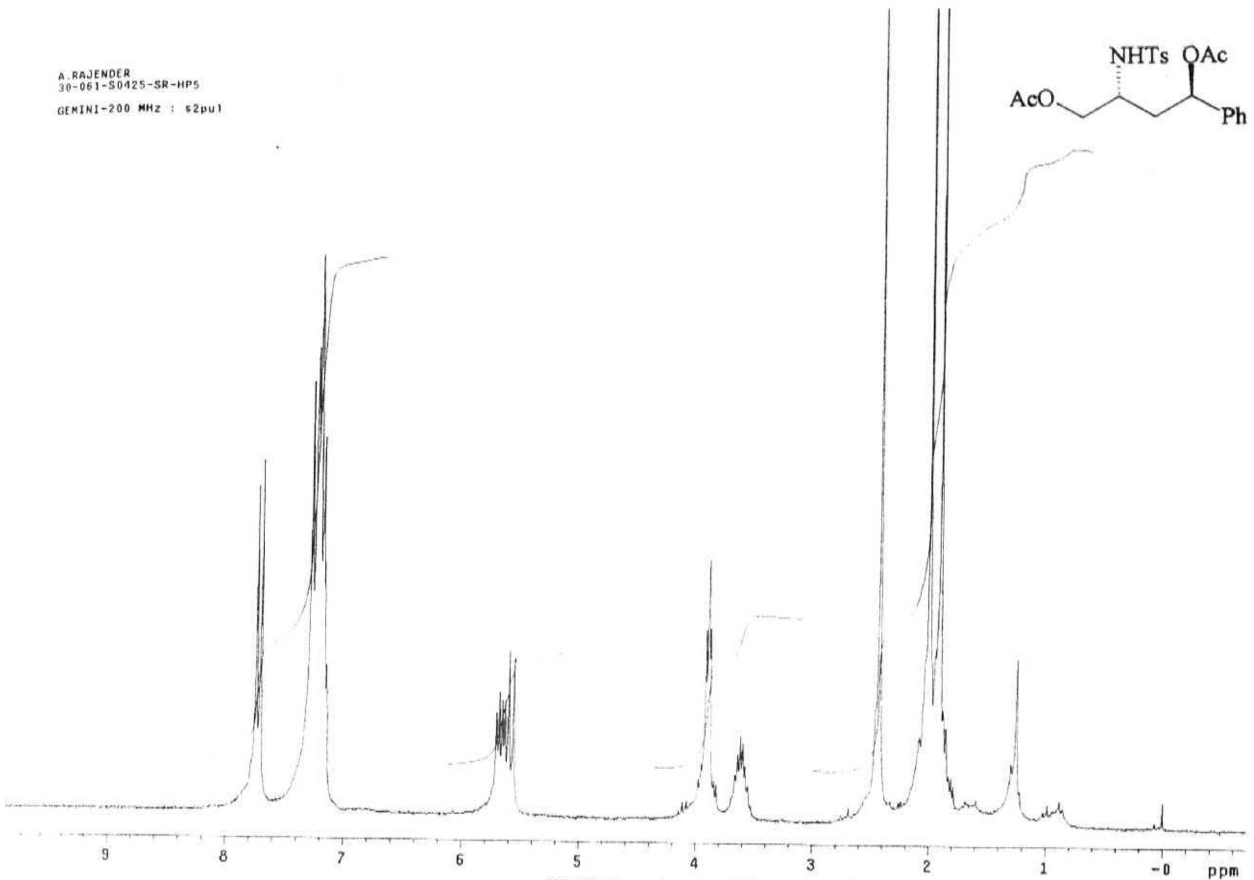

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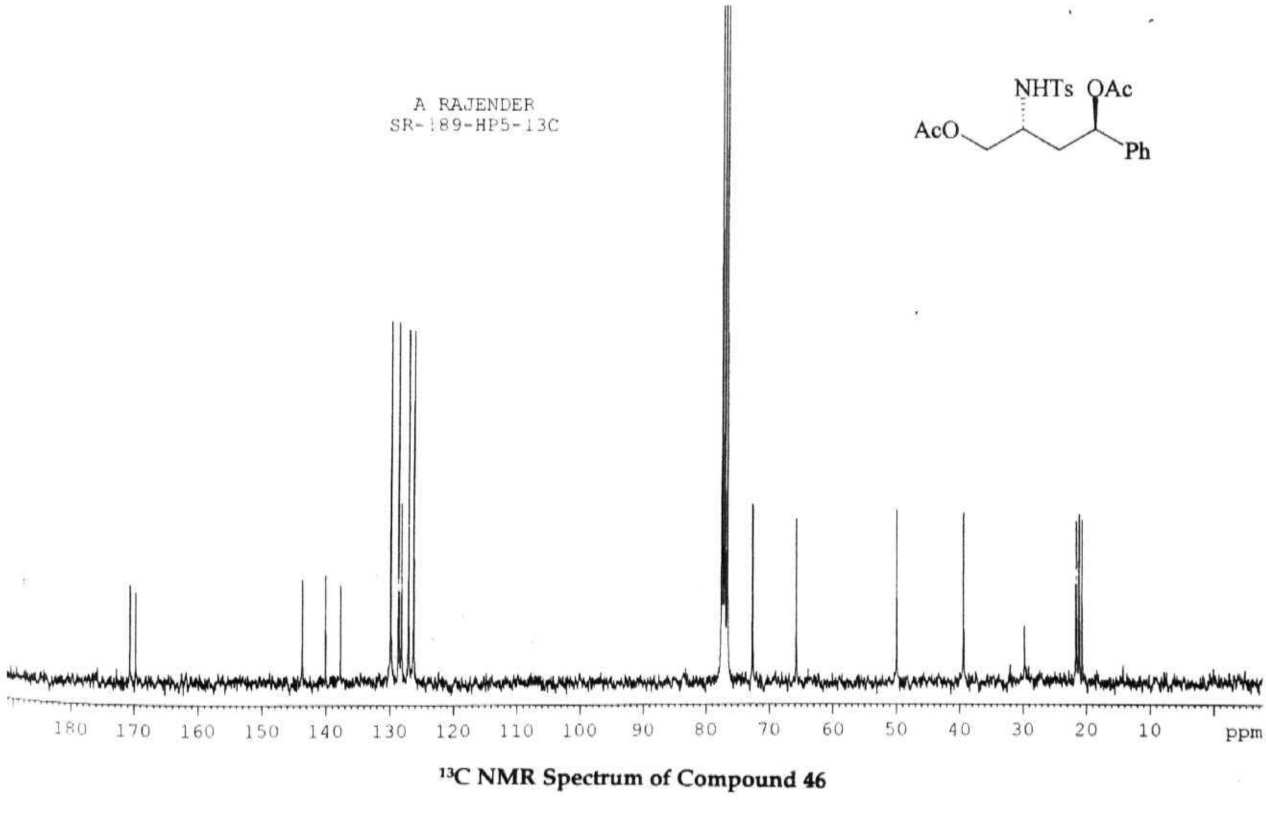
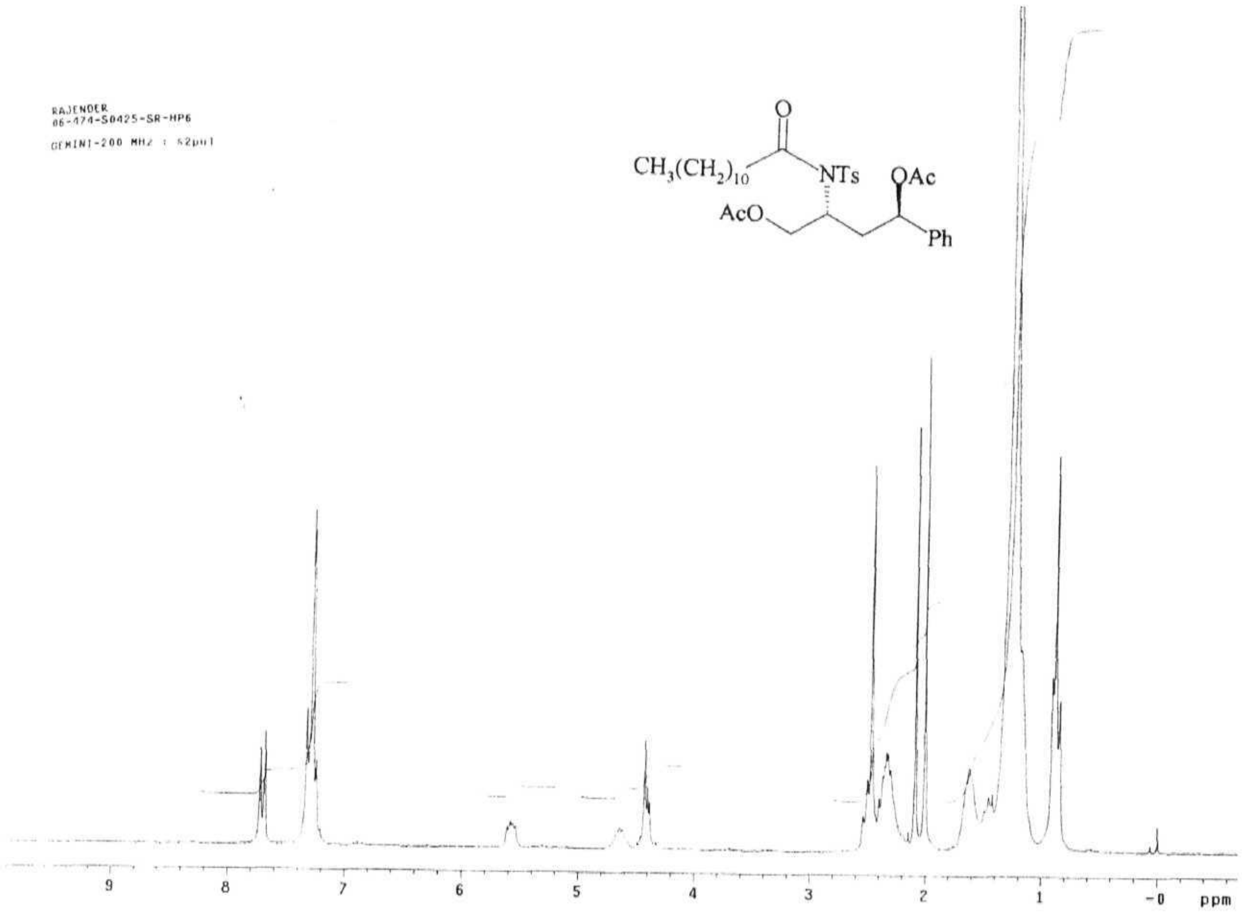
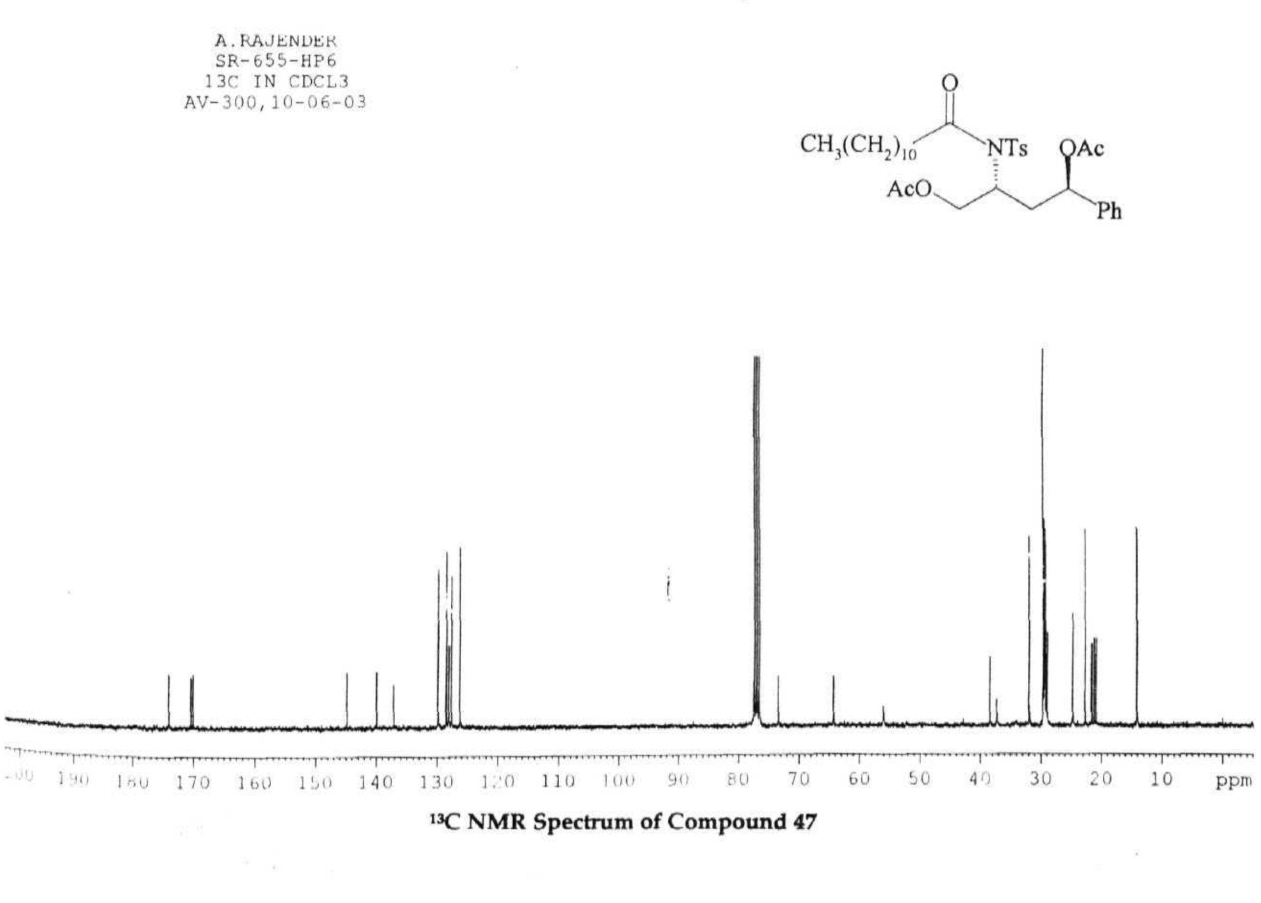


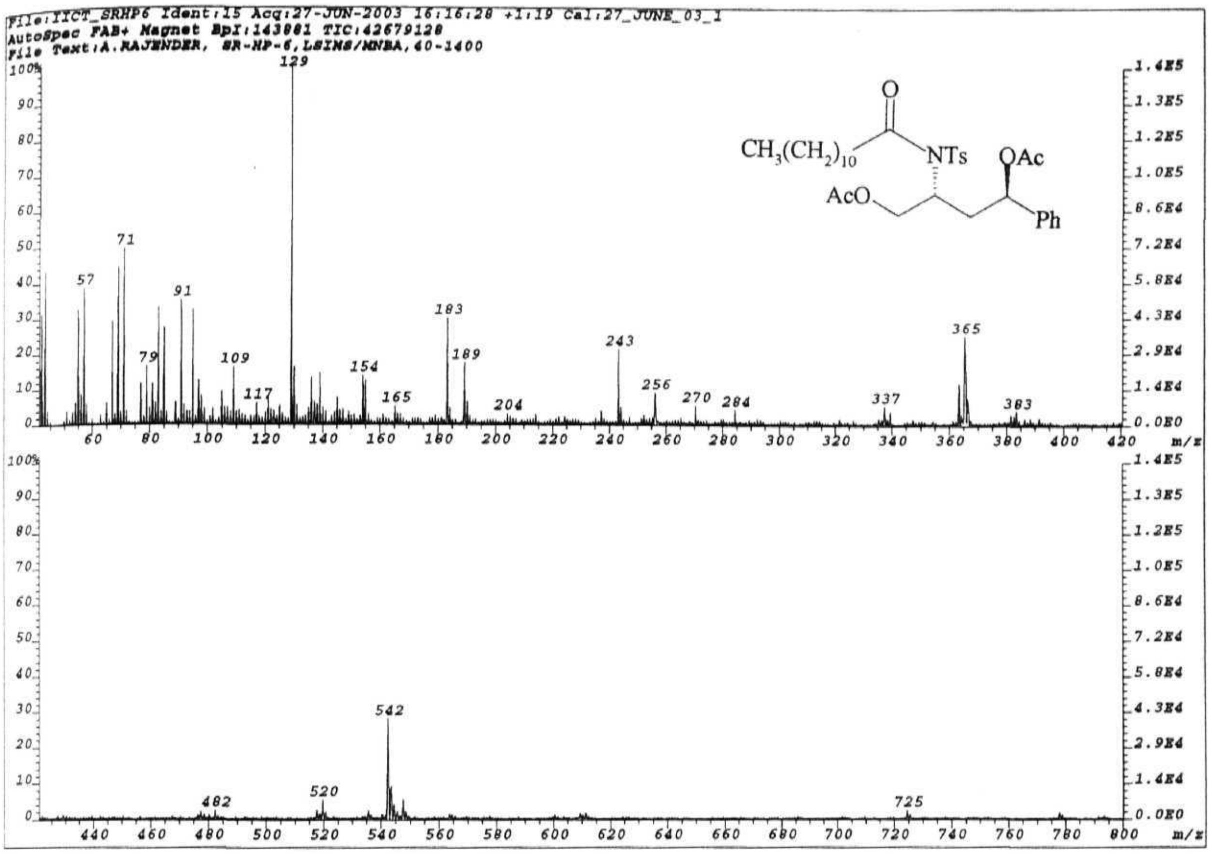
^{13}C NMR Spectrum of Compound 46

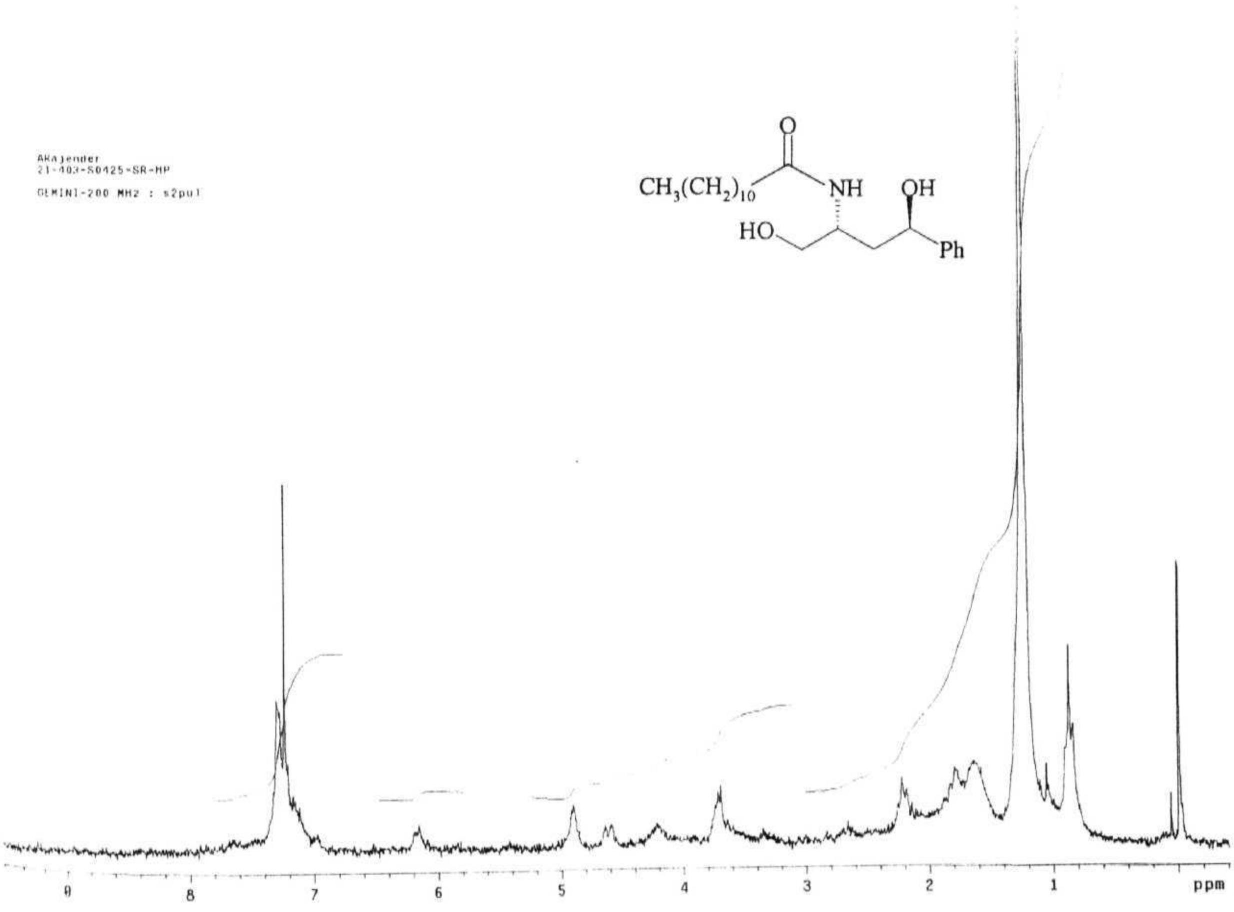


PMR Spectrum of Compound 47

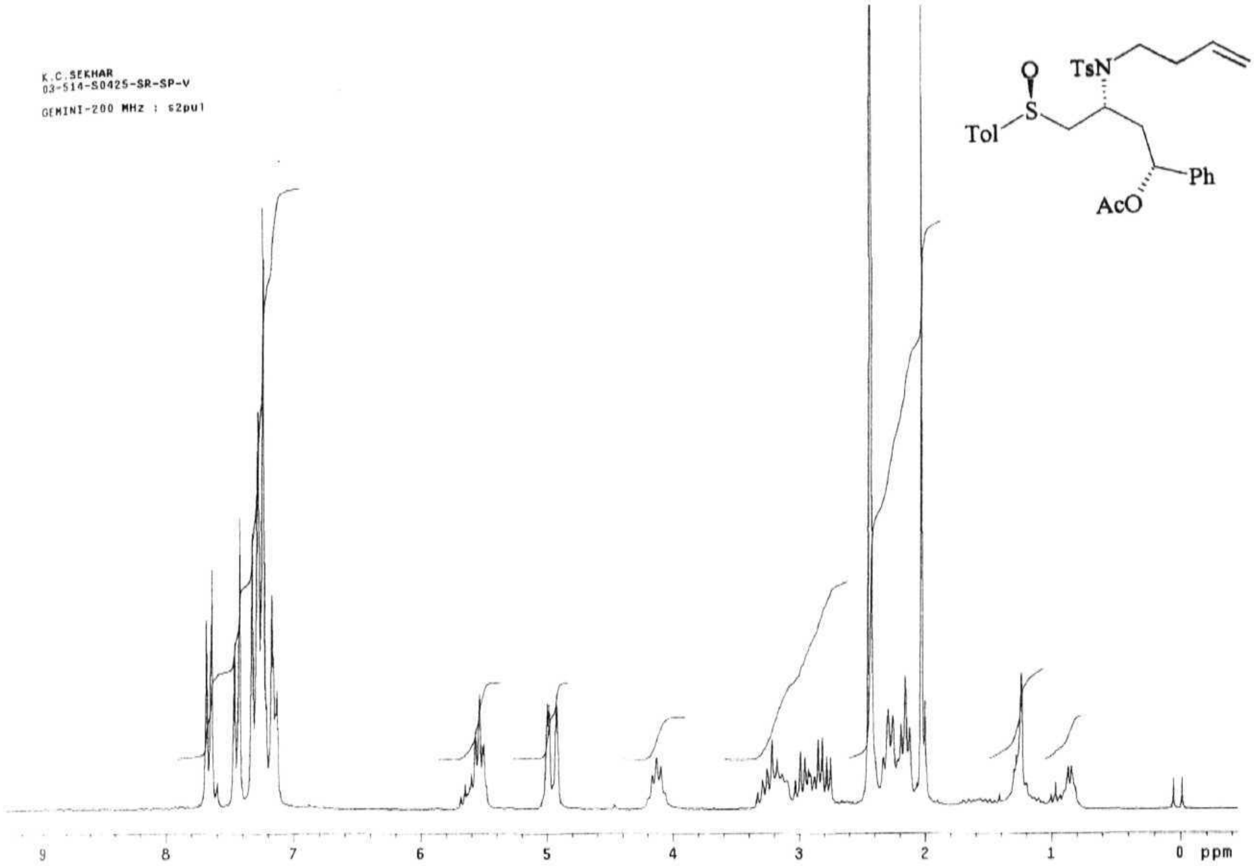


^{13}C NMR Spectrum of Compound 47

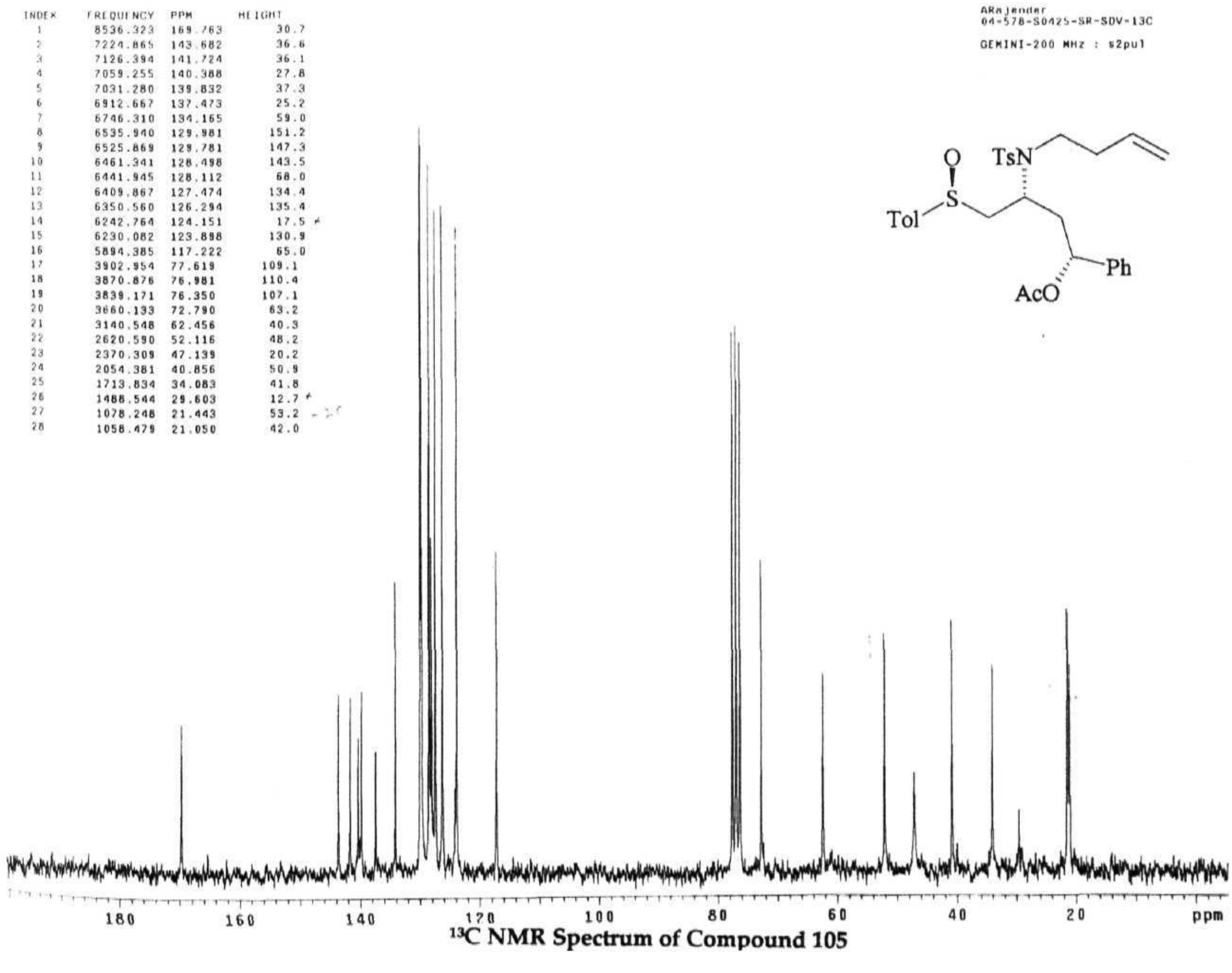




PMR Spectrum of Compound 1



PMR Spectrum of Compound 105



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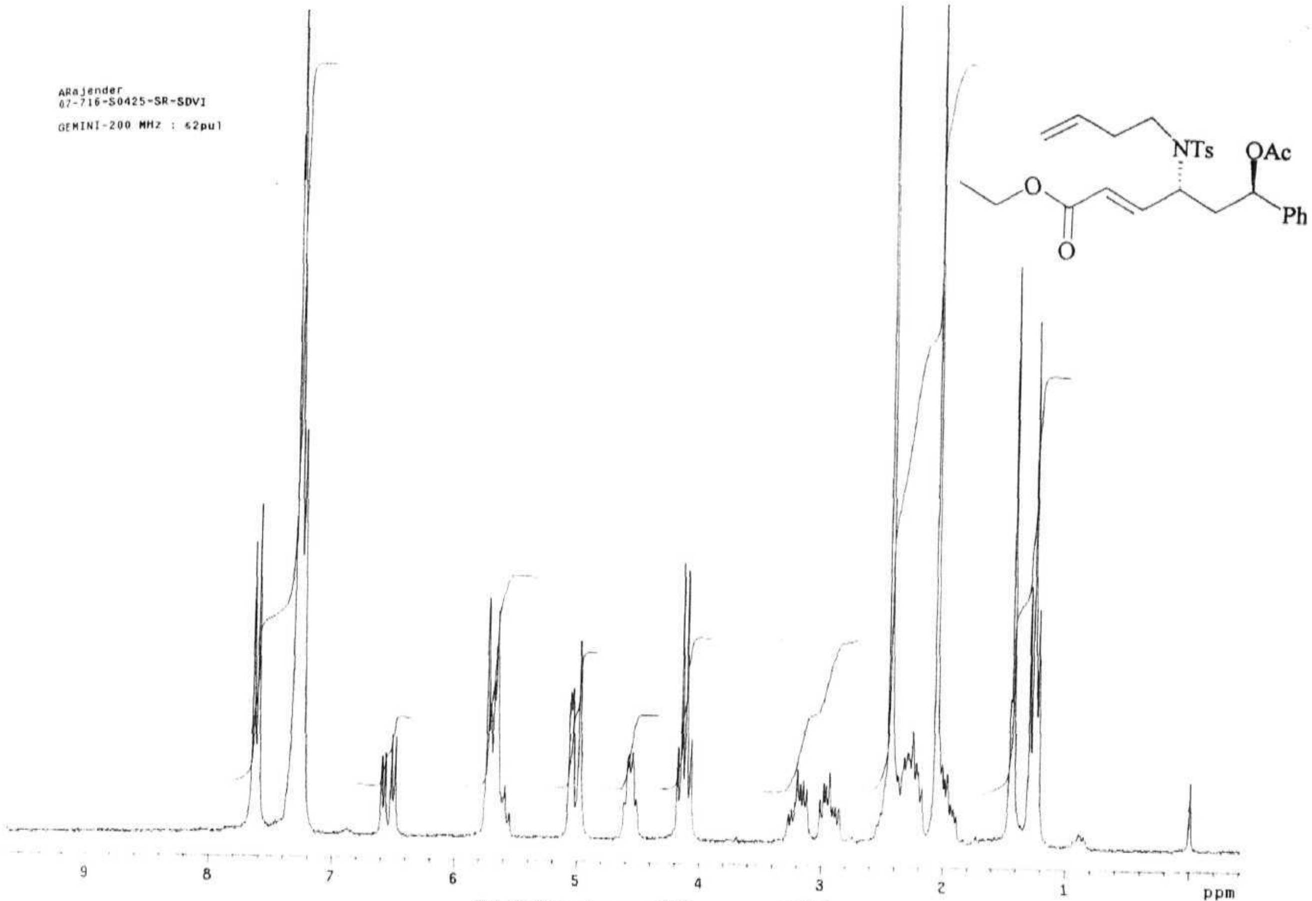
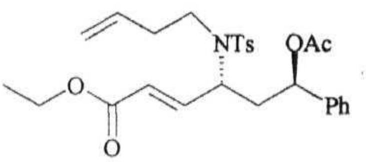
INDEX   FREQUENCY   PPM       HEIGHT
  1     8536.323    169.763     30.7
  2     7224.865    143.682     36.6
  3     7126.394    141.724     36.1
  4     7059.255    140.388     27.8
  5     7031.280    139.832     37.3
  6     6912.667    137.473     25.2
  7     6746.310    134.165     59.0
  8     6535.940    129.981    151.2
  9     6525.869    129.781    147.3
 10     6461.341    128.498    143.5
 11     6441.945    128.112     68.0
 12     6409.867    127.474    134.4
 13     6350.560    126.294    135.4
 14     6242.764    124.151     17.5
 15     6230.082    123.898    130.9
 16     5894.385    117.222     65.0
 17     3902.954    77.619     109.1
 18     3870.876    76.981     110.4
 19     3839.171    76.350     107.1
 20     3660.133    72.790      63.2
 21     3140.548    62.456      40.3
 22     2620.590    52.116      48.2
 23     2370.309    47.139      20.2
 24     2054.381    40.856      50.9
 25     1713.834    34.083      41.8
 26     1488.544    29.603      12.7
 27     1078.248    21.443      53.2
 28     1058.479    21.050      42.0
```

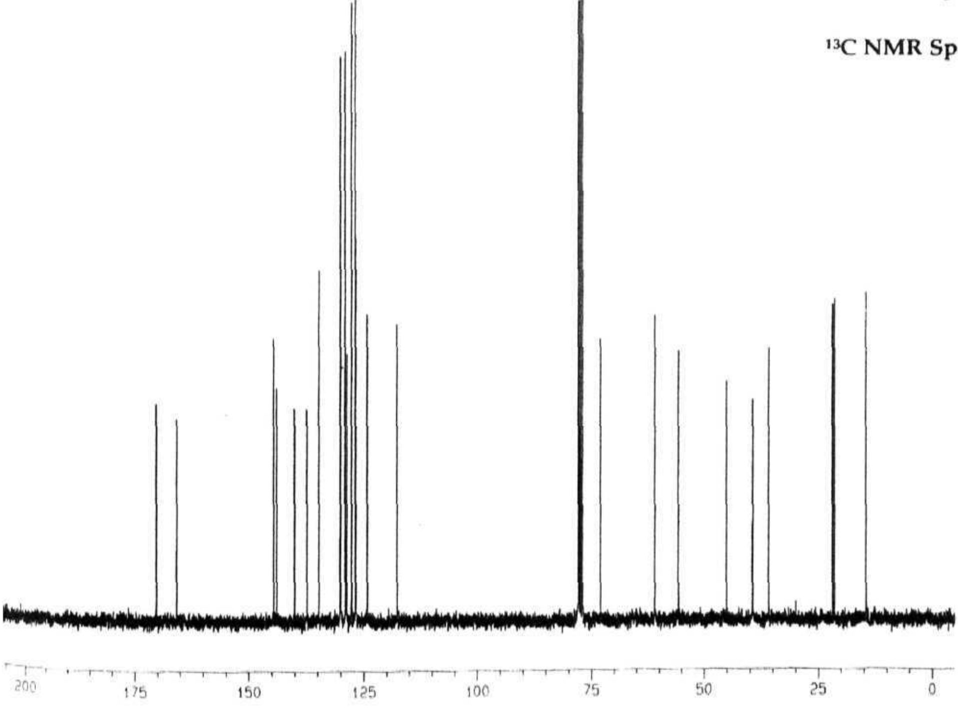
^{13}C NMR Spectrum of Compound 105



PMR Spectrum of Compound 112

sr-752-sd-v1
C13CPD CDCl3 D:/u routine 1





^{13}C NMR Spectrum of Compound 112

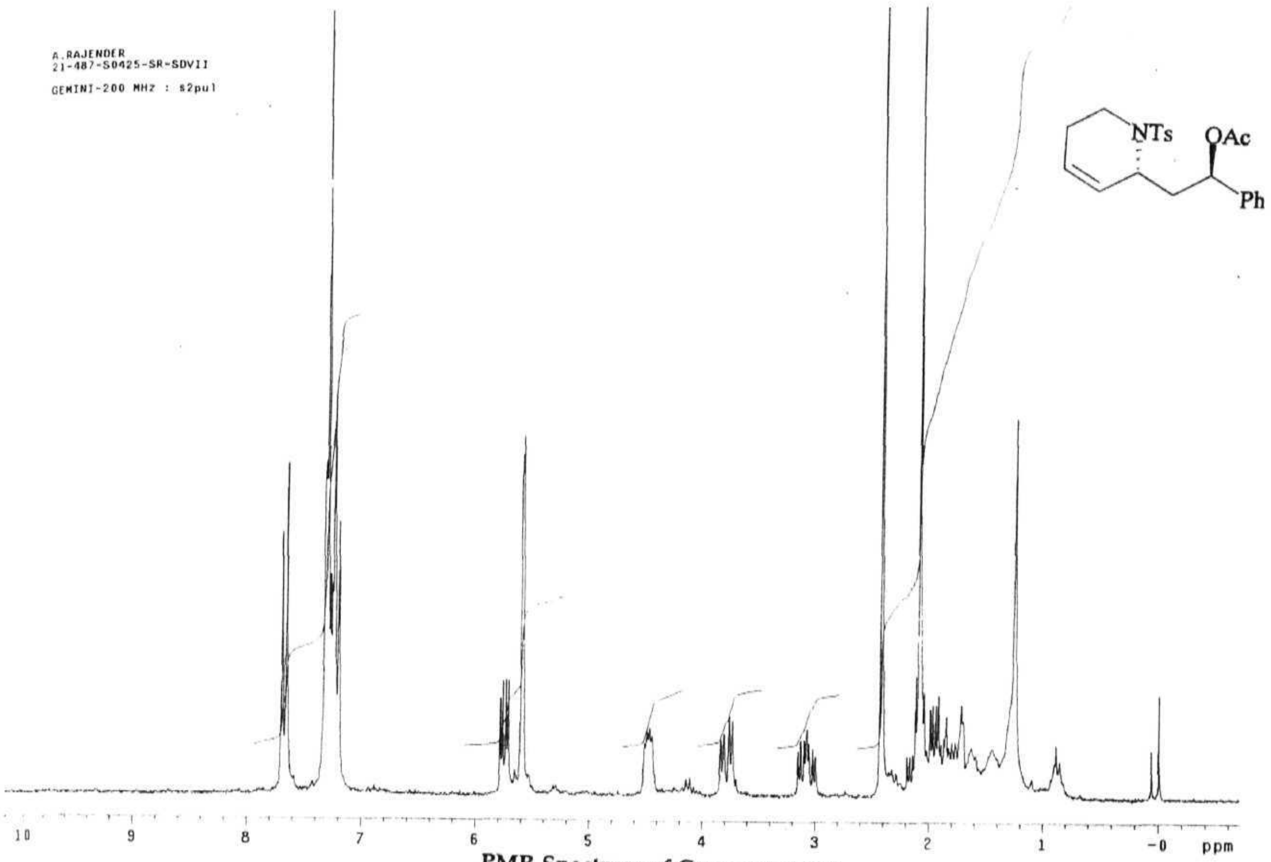
```
FIDRES          0 274439 Hz
AQ            1 8219786 sec
RG                645 1
DW               27 800 usec
DE                 6.00 usec
TE                300 0 K
D1           2 00000000 sec
d11          0 03000000 sec
d12          0 00002000 sec

======== CHANNEL f1 ========
NUC1                13C
P1                 5 25 usec
PL1               -6.00 dB
SFO1        75 4752653 MHz

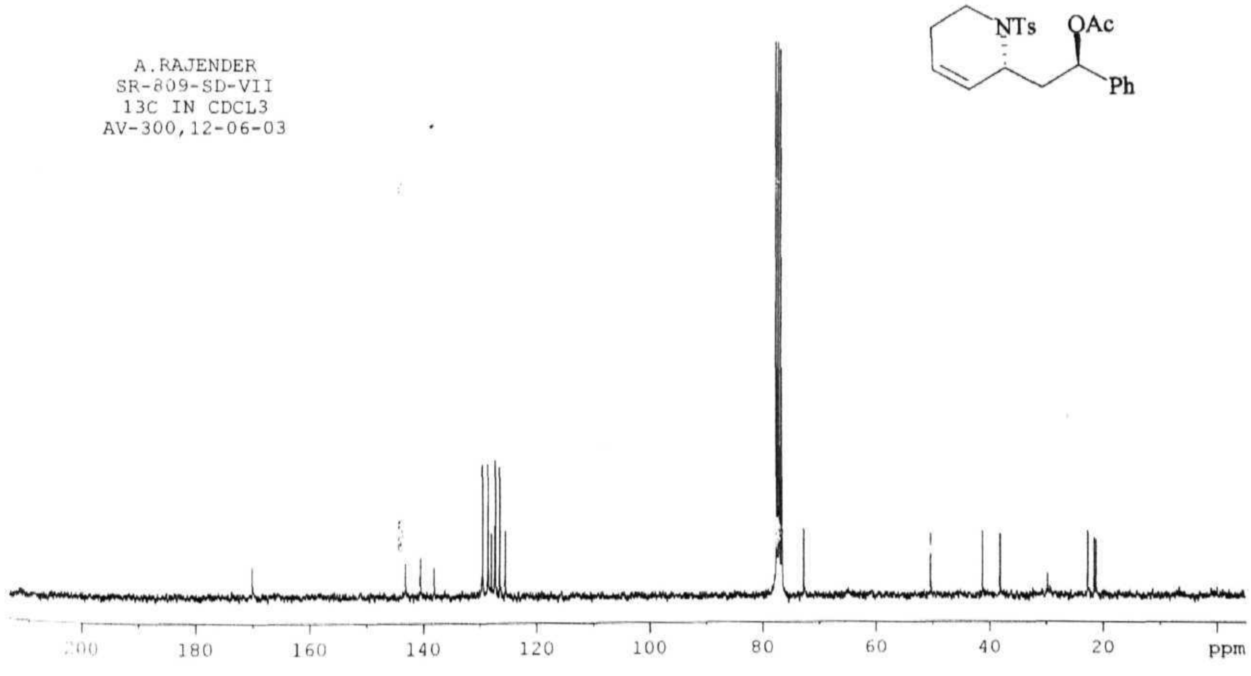
======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                 1H
PCPD2             80.00 usec
PL2               -2.00 dB
PL12              16.00 dB
PL13              16 00 dB
SFO2       300 1312005 MHz

F2 - Processing parameters
SI                32768
SF          75 4677190 MHz
WDW                  EM
SSB                   0
LB                 1 00 Hz
GB                    0
PC                 1.40

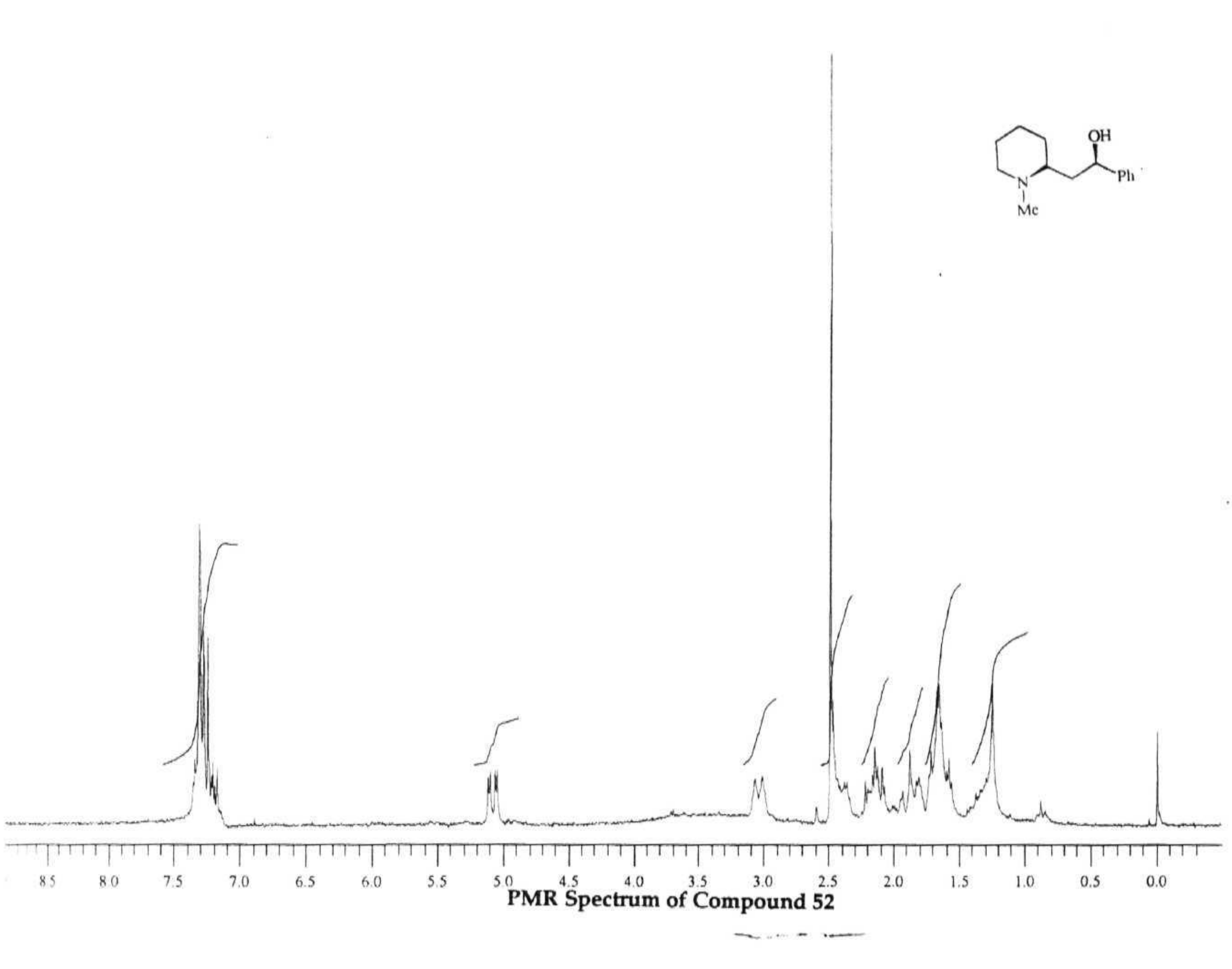
1D NMR plot parameters
CX                20 00 cm
CY                12 50 cm
F1P             215 000 ppm
F1             16225 56 Hz
F2P              -5.000 ppm
F2              -377.34 Hz
PPMCM       11.00000 ppm/cm
HZCM        830 14490 Hz/cm
```



PMR Spectrum of Compound 114



^{13}C NMR Spectrum of Compound 114



PMR Spectrum of Compound 52

Section-C

Synthesis of highly functionalized tetrahydrofurans via silicon promoted Pummerer type reaction.

Introduction

The tetrahydrofuran ring system is widely distributed in nature and has attracted the attention of the synthetic community relating to the total synthesis of natural products.[1] The stereocontrolled construction of substituted tetrahydrofurans is challenging, prompting the development of new methodologies for its efficient elaboration.[2]

The well-known Pummerer rearrangement of sulfoxides, is of significant interest from both synthetic and mechanistic point of view, because it would provide means for the synthesis of enantiomerically pure α-substituted sulfides.[3] The Pummerer reaction has been initiated with a variety of electrophilic reagents.[4] The most commonly used Pummerer reaction conditions require sodium acetate in refluxing acetic anhydride as the activating agent for the sulfoxide. In case of thermally sensitive sulfoxides, trifluoroacetic anhydride (TFAA), another sulfoxide activating agent, promotes almost spontaneously a mild Pummerer reaction at low temperature. Intramolecular Pummerer type cyclization was reported for the first time and independently by Allenmark[5] and Oae[6] with a chirality transfer from sulfur to the adjacent carbon atom. Further examples showed induction with 10-30% enantiomeric excess when acetic anhydride was used to effect this rearrangement.[7] In one case, although the stereoselectivity was improved up to 70% ee by the addition of 1,3-dicyclohexyldicarbodiimide (DCC) as an efficient scavenger of acetic acid, the chemical yield decreased to 10%.[8] Later, Marino *et al.*[9] reported the first example under Pummerer conditions of an intramolecular cycloaddition between a vinyl sulfoxide and dichloroketene. The stereochemistry was dependent on the *E* or *Z* configuration of the vinylic component. β-Lactams were also obtained by ring closure of β-amidosulfoxides under Pummerer conditions with either TMSOTf or O-silylated ketene acetals.[10] In most of the cases, the observed enantioselectivity for these cycloadditions was moderate (30 to 85%).

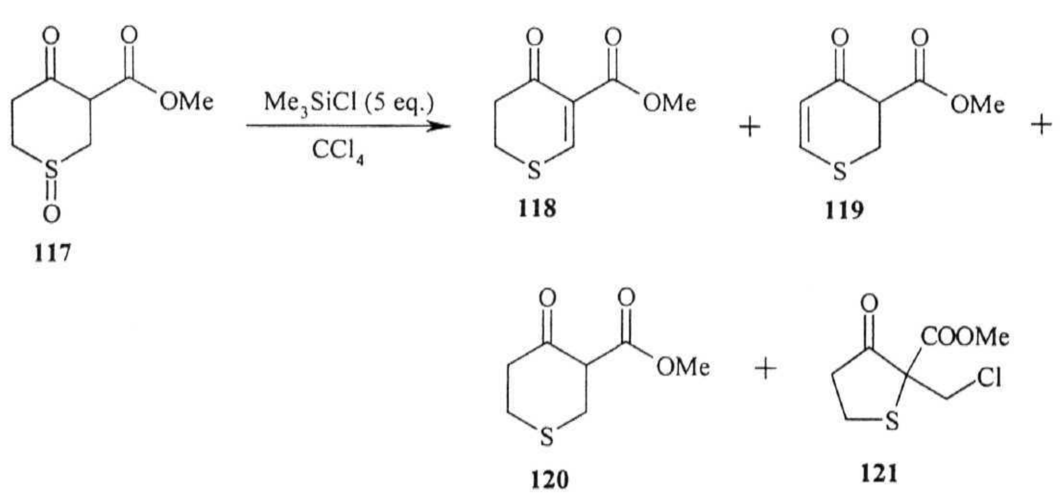
A very highly enantioselective Pummerer type reaction was reported by Bravo *et al.*[11] Solladie *et al.* reported the stereoselective synthesis of β-hydroxy-γ-sulfenyl-γ-butyrolactone by asymmetric Pummerer type cyclization.

Earlier contributions: Ketene methyl *t*-butyldimethylsilyl acetal, chlorotrimethyl silane, t-butyldimethylsilyl triflate, trimethylsilyl triflate and TFAA in the presence of sodiumtrifluoroacetates are the some of the reagents used as the activating reagents in the preparation of the heterocycles via intramolecular Pummerer rearrangement. Few Pummerer type reactions reported in the literature are detailed below.

Taylor's contribution[12]:

Taylor *et al.* reported chlorotrimethylsilane as the activating agent in the Pummerer type reaction for the conversion of sulfoxides into α,β-unsaturated sulfides in the absence of base (Scheme 1). Saturated sulfides were also formed in the reaction. Treatment of ketosulfoxide **117** with Me_3SiCl in CCl_4 afforded the unsaturated sulfides **118** and **119** in 72% and 16% yields respectively. Saturated sulfides **120** and **121** were also isolated in 7% combined yield.

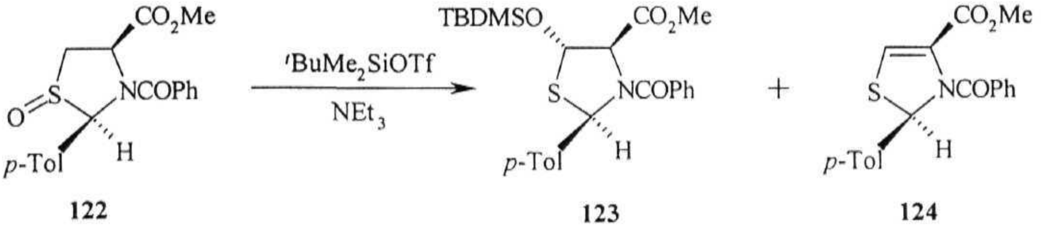
Scheme 1



Ando's contribution[13]:

Ando *et al.* reported a stereospecific formation of α-silyloxy sulfides from optically active thiozolidine S-oxides using trialkylsilyl triflate in the Pummerer reaction. Thus, treatment of **122** with *tert*-butyldimethylsilyl triflate in the presence of Et_3N afforded the desired α-silyloxy sulfide **123** in 27% yield along with 50% of α,β-unsaturated sulfide **124** (Scheme 2).

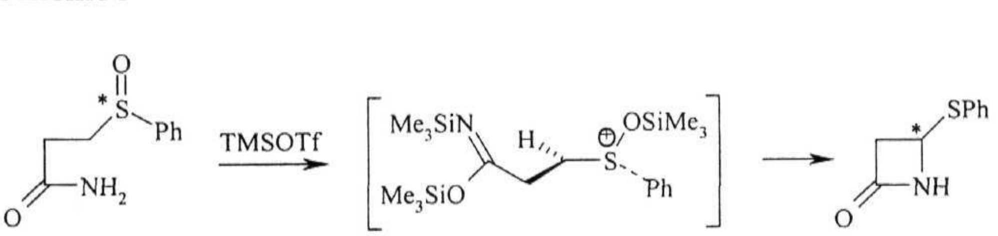
Scheme 2



Kaneko's contribution[14]:

Kaneko *et al.*, reported the preparation of optically active β-lactams via Pummerer type cyclization reaction. Treatment of the sulfoxide **125** with excess trimethylsilyl triflate in the presence of Hunig's base afforded the β-lactam **126** in 74% yield and in 67% de (Scheme 3).

Scheme 3

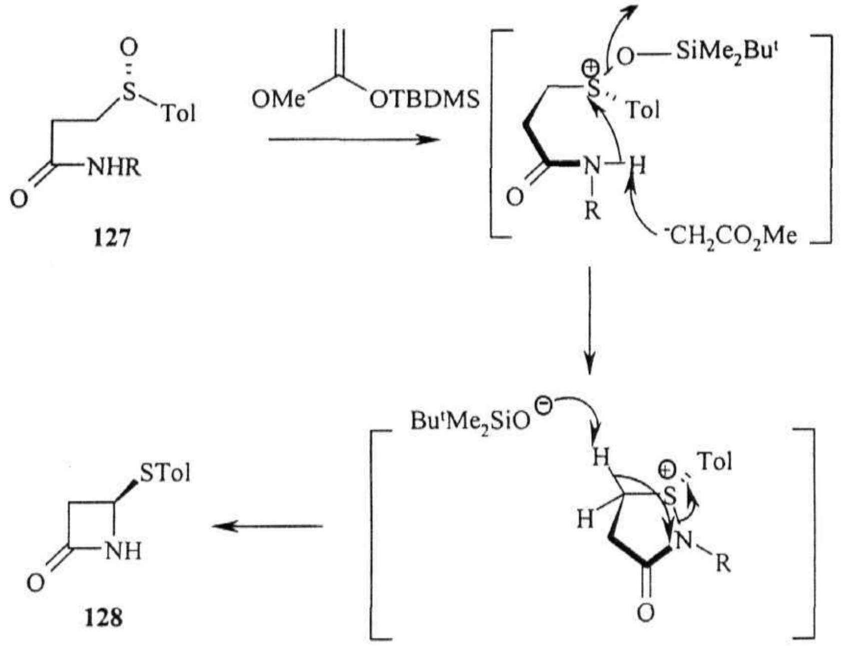


Kita's contribution[15]:

Optically pure *S*-sulfoxides **127** were transformed into *R*-β-lactams **128** under silicon promoted Pummerer type reaction. Upon treatment with *tert*-

butyldimethylsilyl acetal, sulfoxide with a chiral amido group **127a** afforded β-lactam **128a** in 60% de. Sulfoxides with an achiral amido group provided β-lactams in >80% de (Scheme 4).

Scheme 4

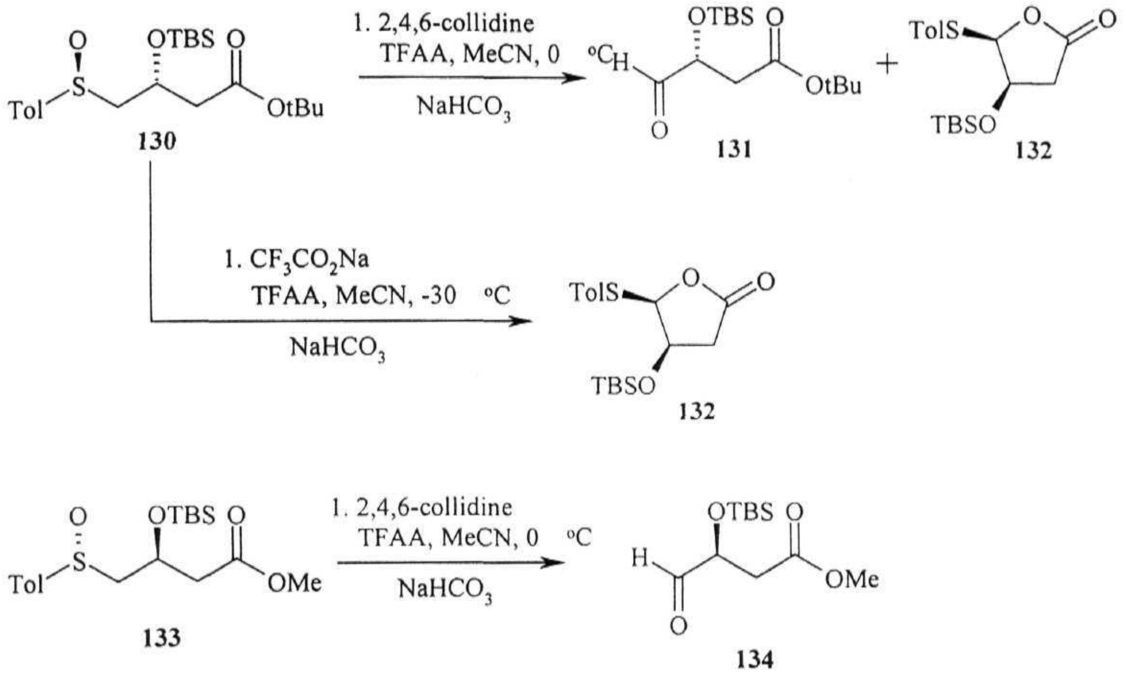


Alkyl group		de
R = CH(Me)Ph	**127a**	60
R = CH$_2$Ph	**127b**	82
R = CHPh$_2$	**127c**	83

Solladie's contribution[16]:

Synthesis of β-hydroxy-γ-sulfenyl-γ-butyrolactone by asymmetric Pummerer type cyclization was reported. Treatment of sulfoxide **130** with TFAA in the presence of *sym*-collidine in acetonitrile followed by treatment with aq. $NaHCO_3$ afforded the aldehyde **131** and the lactone **132** in almost equal amounts. When sodium trifluoroacetate used as the base, only lactone **132** was formed. Under the similar conditions methyl ester **133** yielded the aldehyde **134** as the only product (Scheme 5). This methodology is limited to *tert*-butyl esters only.

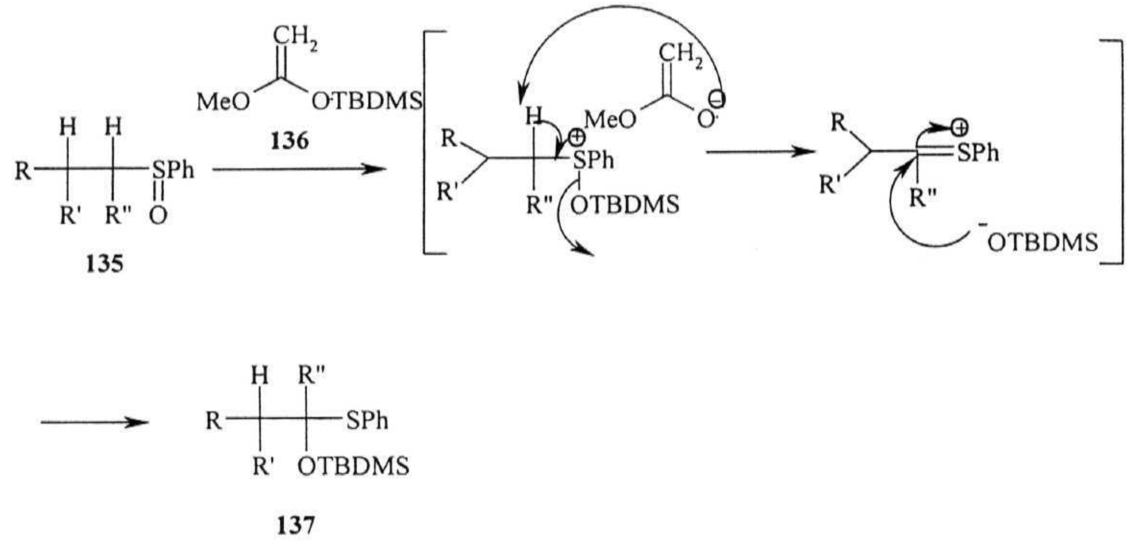
Scheme 5



Kita's contribution[17]:

Kita and co-workers reported the synthesis of α-silyloxy sulfides by Pummerer type reaction. Ketene methyl *t*-butyldimethylsilyl acetal was used as the activating agent (Scheme 6).

Scheme 6

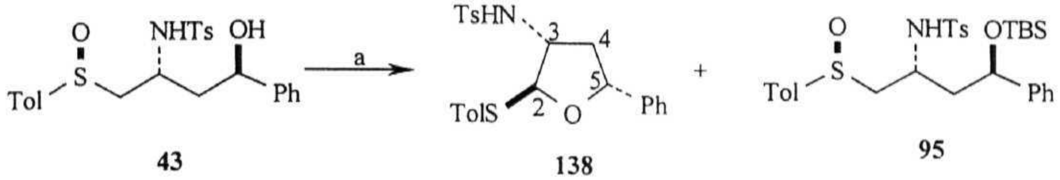


Present work

In this section, a novel methodology leading to α-sulfenyl tetrahydrofurans from the δ-hydroxy sulfoxides by silicon promoted Pummerer reaction is discussed.

In the course of the synthesis of *dl*-allosedamine, the hydroxy group in **43** required to be protected as its silyl ether. Thus, compound **43** was treated with *tert*-butyldimethylchlorosilane in DMF in the presence of imidazole.[18] Surprisingly, two products were observed, the major product (60%) was not the expected silyl ether, but the tetrahydrofuran **137**; the minor product (30%) turned out to be the silyl ether **95** (Scheme 7). The cyclized product showed resonances at δ 5.17 (d) for anomeric C*H*S, δ 4.76 (d) for the benzylic proton, δ 3.96-3.90 (m) for C*H*N, δ 2.72 (dt) for one of the C4 *H* protons and at δ 1.71 (ddd) for the other C4 *H* proton.

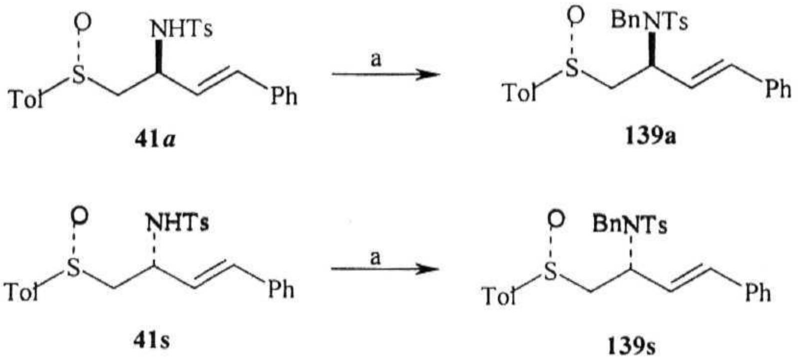
Scheme 7



Reagents and conditions: (a) TBS-Cl, imidazole, DMF (0.33 M), r.t., 2 h, 70% (combined yield of two products).

The encouraging result gave the impetus to explore the generality of this simple, rapid and convenient cyclization of δ-hydroxysulfoxides into tetrahydrofurans, using a mild reagent. In an effort to optimize the reaction conditions to afford the substituted tetrahydrofurans as the only product, the bulky *tert*-butyldiphenylchlorosilane was employed at higher concentration of the solvent. Thus, compound **43** was treated with *tert*-butyldiphenylchlorosilane in the presence of imidazole in DMF (1 M). The reaction proceeded smoothly to afford **138** as the only product. The generality of the reaction was investigated on other δ-hydroxy sulfoxides. To this end, the substrates **139a** and **139s** were prepared by *N*-benzylation of **41*a*** and **41*s*** (racemic samples) respectively. Thus, treatment of the sulfoxides individually with benzyl bromide, K_2CO_3 in the presence of tetrabutylammonium iodide in acetonitrile afforded **139a** and **139s** (Scheme 8). The PMR spectrum of **139a** revealed signals at δ 6.24 (d) for C4 *H*, δ 6.02 (dd) for C3 *H*, 4.61 (q) for C*H*N, δ 4.46 (d) and 4.33 (d) for -NCH_2. The PMR spectrum of **139s** showed resonances at δ 6.24 (d) for C4 *H* proton, δ 6.04 (dd) for C3 *H* proton, δ 4.69 (m) for C*H*N, δ 4.47 (d) and δ 4.30 (d) for NCH_2.

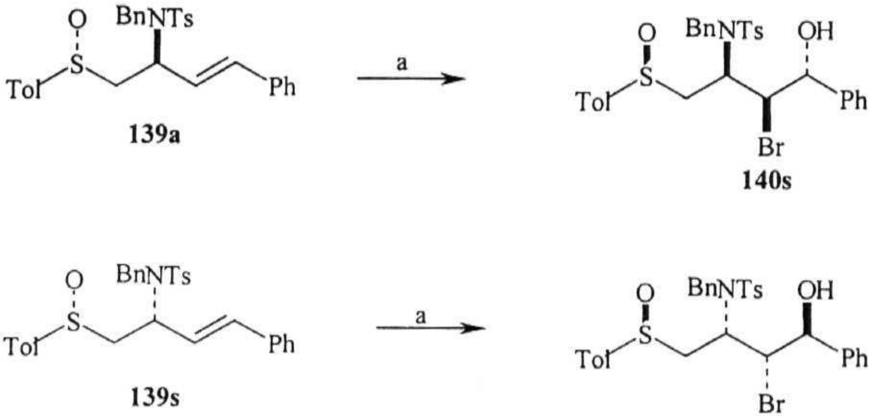
Scheme 8



Reagents and conditions: (a) BnBr, TBAI, K_2CO_3, CH_3CN, reflux, 1 h, 90%.

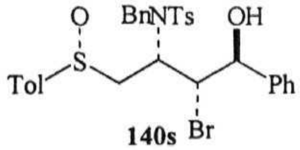
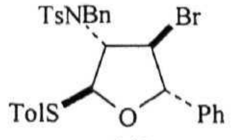
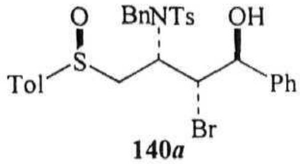
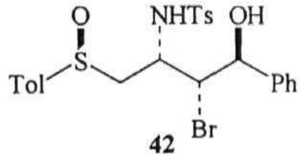
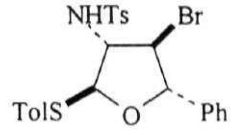
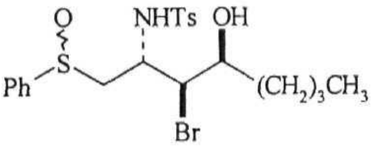
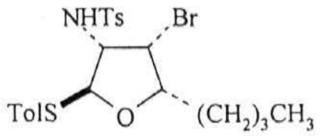
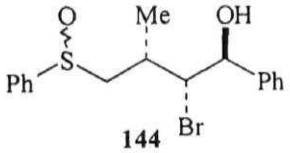
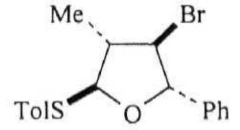
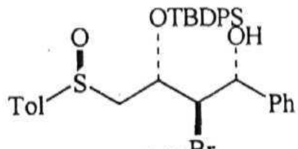
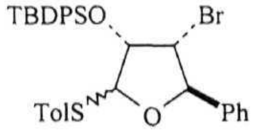
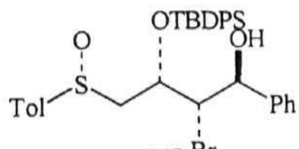
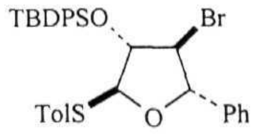
Upon subjecting **139*a*** and **139*s*** to treatment with NBS in toluene in the presence of water at ambient temperature afforded bromohydrins **140*s*** and **140*a*** respectively as the only products (Scheme 9).

Scheme 9



Reagents and conditions: (a) NBS, toluene, water, r.t., 30 min, **140*s***: 80%; **140*a***: 76%.

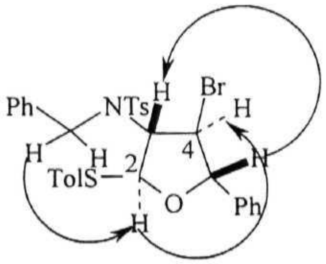
[a]Table 1: Formation of tetrahydrofurans.

Entry	Hydroxysulfoxide	Tetrahydrofuran	Yield[b] %
1	 140s	 141	90%
2	 140a	141	90%
3	 42	 142	86%
4		 143	90%
5	 144	 145	93%
6	 146	 147	82%
7	 148	 149	90%

a) All reactions were done on racemic substrates on 0.2 mmol scale in the presence of 1 eq. of *t*-butyldiphenylchlorosilane and 2 eq. of imidazole in DMF as the solvent. b) Yield refers to the isolated yield.

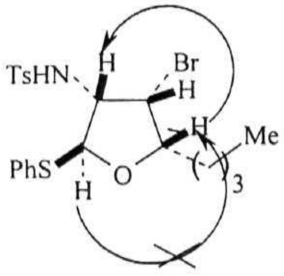
The structure of **141** and **143** was tentatively established by nOe experiments. Thus irradiation of the methine proton at C2 in **141** revealed nOe with the *N*-benzyl protons and C4 methine proton. Irradiation of the C5 methine proton revealed nOe with C3 methine proton (Figure 1).

Figure 1



141

Figure 2

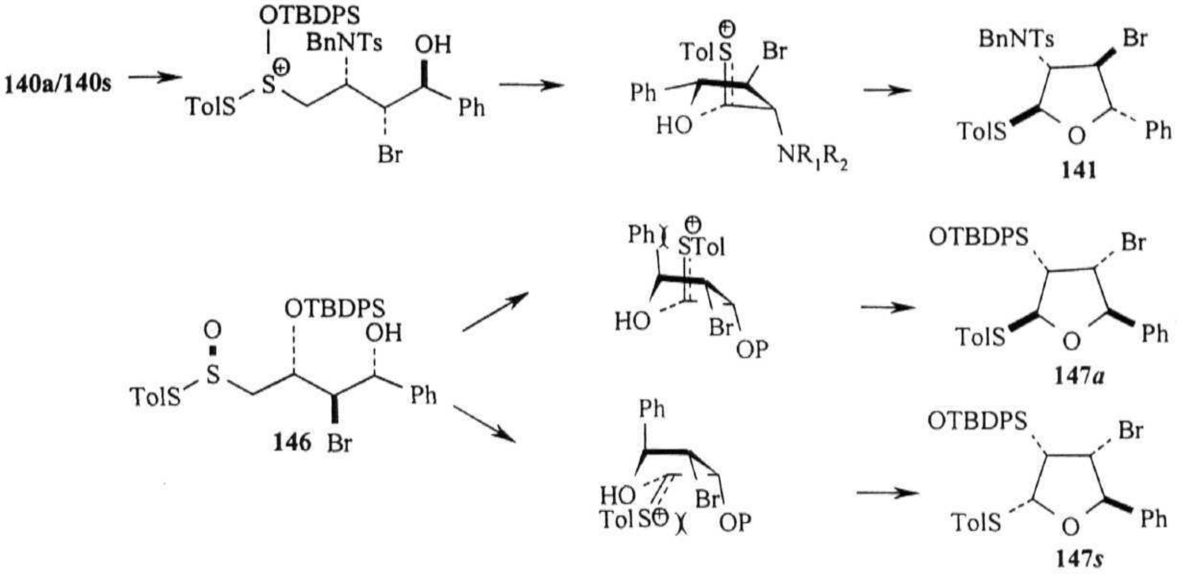


143

The PMR spectrum of **143** showed resonances at δ 4.99 (d) for C5 methine proton, δ 4.24 (dd) for C3 methine proton, δ 3.85 (ddd) for C4 methine proton and δ 3.74 (dt) for C2 methine proton. Structure of **143** was confirmed by nOe studies. Thus, irradiation of C2 methine proton revealed nOe with C4 methine proton. Irradiation of C5 methine proton did not reveal nOe with C2 methine and C3 methine protons (Figure 1). The structures of the other tetrahydrofurans (entry no 3, 5, 6 and7) were assigned by comparison of their PMR spectra with **141**.

The formation of tetrahydrofuran can be rationalized by coordination of the sulfoxide oxygen to silicon to afford the sulfoxonium salt, which on elimination of *t*-butyldiphenylsilyloxy group (OTBDPS) would yield the sulfonium ion which would then be attacked intramolecularly by the hydroxy group. The substituent at C3 would direct the sulfenyl moiety away from itself, to minimize steric interactions, and afford the observed product. The intermediate from **146** would experience unfavorable steric interactions between the phenyl ring and sulfenyl moiety while the latter is oriented *anti* to the C3 OTBDPS substituent, which would probably explain for the obtention of a mixture of sulfides in this case (Scheme 9).

Scheme 9



The intermediacy of the sulfonium ion was confirmed by the fact that the same product is obtained from reactions done individually on diastereomeric sulfoxides **138*a*** and **138*s***.

In summary a highly stereoselective route for the elaboration of tetrahydrofurans from δ-hydroxy sulfoxides under very mild conditions in a Pummerer like reaction is disclosed. It is worthwhile to note that the sulfenyl group provides a suitable handle for further elaboration into more complex molecules.[19]

Experimental

Procedure for the preparation of 139*a* and 139*s*.

To a solution of acetonitrile (2 mL) containing **41*a*/41*s*** (215 mg, 0.5 mmol), K_2CO_3 (138 mg, 1 mmol) and tetrabutylammonium iodide (10 mg, 0.05 mmol) was added neat BnBr (78 mg, 0.5 mmol). The reaction mixture was heated at reflux for 1 h and then gradually allowed to attain room temperature. After evaporation of the solvent under reduced pressure, the residue was taken into ethylacetate and washed with water, brine and dried over anhydrous Na_2SO_4. Ethylacetate was removed under reduced pressure and the residue chromatographed on silica gel using AcOEt/petroleum ether (1:4, v/v) as the eluent to afford **139*a*/139*s*** in 90% yield.

1*N*-Benzyl-1*N*-[3-phenyl-1-phenylsulfinylmethyl-(1*S*,2*E*)-2-propenyl]-4-methyl-1-benzenesulfonamide, 139*a*.

90%. Solid.

mp : 155-157 °C

PMR (200 MHz, $CDCl_3$) : δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.45-7.07 (m, 16H), 6.24 (d, *J* = 16.7 Hz, 1H), 6.04 (dd, *J* = 16.7, 6.9 Hz, 1H), 4.61 (q, *J* = 6.9 Hz, 1H), 4.46 (d, *J* = 16.2 Hz, 1H), 4.33 (d, *J* = 16.2 Hz, 1H), 3.08-2.85 (m, 2H), 2.42 (bs, 6H).

m/z (LSIMS) : 516 $[M + H]^+$

1*N*-Benzyl-1*N*-[3-phenyl-1-phenylsulfinylmethyl-(1*R*,2*E*)-2-propenyl]-4-methyl-1-benzenesulfonamide, 139*s*.

90%. Solid.

mp : 168-169 °C

PMR (200 MHz, $CDCl_3$) : δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.40-7.01 (m, 16H), 6.11 (d, *J* = 17.2 Hz, 1H), 5.95 (dd, *J* = 17.2, 7.0 Hz,1H), 4.79-4.65

(m, 1H), 4.61 (d, *J* = 16.3 Hz, 1H), 4.32 (d, *J* = 16.3 Hz, 1H), 3.23 (dd, *J* = 13.4, 8.9 Hz, 1H), 2.77 (dd, *J* = 13.4, 6.7 Hz, 1H), 2.43 (s, 3H), 2.37 (s, 3H).

m/z (LSIMS) : 516 $[M + H]^+$

1*N*-Benzyl-1*N*-[2-bromo-3-hydroxy-3-phenyl-1-(R_S)-phenylsulfinylmethyl-(1*S*,2*R*)-propyl]-4-methyl-1-benzenesulfonamide, 140*a*.

74%. Solid.

mp : 196-198 °C

PMR (200 MHz, $CDCl_3$) : δ 7.83 (d, *J* = 8.2 Hz, 2H), 7.46-7.21 (m, 16H), 5.16 (d, *J* = 10.8 Hz, 1H), 5.04 (dd, *J* = 9.6, 4.8 Hz, 1H), 4.68 (d, *J* = 4.8 Hz, OH), 4.51 (d, *J* = 16.2 Hz, 1H), 4.35 (d, *J* = 9.6 Hz, 1H), 4.09 (d, *J* = 16.2 Hz,1H), 3.08 (dd, *J* = 13.4, 10.8 Hz, 1H), 2.49 (s, 3H), 2.41 (s, 3H), 2.08 (d, *J* = 13.4 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4, 21.6, 49.7, 53.1, 58.9, 59.7, 73.5, 123.7, 127.4, 128.1, 128.2, 128.3, 130.1, 130.3, 134.3, 137.5, 140.2, 140.6, 142.3, 144.6.

m/z (LSIMS) : 612 $[M+ H]^+$

1*N*-Benzyl-1*N*-[2-bromo-3-hydroxy-3-phenyl-1-(R_S)-phenylsulfinylmethyl-(1*R*,2*R*)-propyl]-4-methyl-1-benzenesulfonamide, 140*s*.

83%. Solid.

mp : 75-76 °C

PMR (200 MHz, $CDCl_3$) : δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.37-7.13 (m, 16H), 5.14-5.06 (m, 1H), 4.96 (dd, *J* = 8.9, 4.5 Hz, 1H), 4.71 (d, *J* = 4.5 Hz, 1H), 4.62 (d, *J* = 16.2 Hz, 1H), 4.05 (d, *J* = 16.2 Hz, 1H), 3.98 (bs, OH), 3.22 (dd, *J* = 13.4, 7.4 Hz, 1H), 2.55 (dd, *J* = 13.4, 4.5 Hz, 1H), 2.47 (s, 3H), 2.42 (s, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) : δ 21.4, 21.6, 50.4, 53.8, 59.1, 61.0, 74.2, 123.9, 127.3, 127.6, 128.0, 128.1, 128.4, 130.0, 135.5, 137.1, 139.3, 140.8, 142.2, 144.4.

m/z (LSIMS) : 612 [M + H]$^+$

2-Bromo-3-methyl-1-phenyl-4-(S_S)-phenylsulfinyl-(1*S*,2*R*,3*S*)-butan-1-ol, 144*s*.

Solid.

mp : 160-162 °C

PMR (200 MHz, CDCl$_3$) : δ 7.58-7.45 (m, 5H), 7.34 (bs, 5H), 4.80 (d, *J* = 8.9 Hz, 1H), 4.25 (dd, *J* = 8.9, 2.0 Hz, 1H), 3.13-3.01 (m, 1H), 2.89 (dd, *J* = 13.2, 3.8 Hz, 1H), 2.61 (dd, *J* = 13.2 8.9 Hz, 1H), 1.33 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (50 MHz, CDCl$_3$) : δ 14.3, 30.0, 65.3, 66.0, 76.0, 124.0, 127.0, 128.4, 128.5, 129.3, 131.1, 141.6, 144.0.

m/z (LSIMS) : 367 [M + H]$^+$

2-Bromo-3-methyl-1-phenyl-4-(R_S)-phenylsulfinyl-(1*S*,2*R*,3*S*)-butan-1-ol, 144*a*.

Liquid.

PMR (200 MHz, CDCl$_3$) : δ 7.60-7.31 (m, 10H), 4.82 (d, *J* = 8.1 Hz, 1H), 4.72 (d, *J* = 8.1 Hz, 1H), 3.07 (m, 2H), 2.77 (dd, *J* = 10.1, 8.0 Hz, 1H), 1.18 (s, *J* = 6.3 Hz, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) : δ 15.4, 29.7, 64.1, 64.2, 76.0, 123.9, 127.0, 128.5, 128.6, 129.4, 131.1, 141.5, 143.7.

m/z (LSIMS) : 367 [M+H]$^+$

2-Bromo-3-(*tert*-butyldiphenylsilyloxy)-1-phenyl-4-(S_S)-phenylsulfinyl-(1*R*,2*R*,3*S*)-butan-1-ol, 146.

Liquid.

PMR (300 MHz, CDCl$_3$) : δ 7.68-7.65 (m, 4H), 7.48-7.2 (m, 13H), 7.08-7.03 (m, 2H), 4.96-4.91 (m, 1H), 4.52 (d, *J* = 9.1 Hz, 1H), 4.14-4.09 (m, 1H), 3.24 (dd, *J* = 13.6, 3.0 Hz, 1H), 2.88 (dd, *J* = 13.6, 6.8 Hz, 1H), 2.43 (s, 3H), 1.13 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 19.5, 21.4, 27.0, 64.4, 64.8, 67.5, 75.1, 123.8, 127.0, 127.9, 128.1, 128.2, 130.1, 132.8, 133.1, 136.0, 140.2, 140.6, 141.8.

m/z (LSIMS) : 621 $[M + H]^+$

2-bromo-3-(*tert*-butyldiphenylsilyloxy)-1-phenyl-4-(*R*$_S$)-phenylsulfinyl-(1*S*,2*S*,3*S*)-butan-1-ol, 148.

Liquid.

PMR (200 MHz, $CDCl_3$) : δ 7.80-7.63 (m, 4H), 7.54-7.21 (m, 13H), 7.17-7.04 (m, 2H), 4.84 (d, *J* = 9.7 Hz, 1H), 4.69-4.61 (m, 1H), 4.52 (dd, *J* = 9.7, 1.5 Hz, 1H), 3.27 (dd, *J* = 13.4, 9.7 Hz, 1H), 2.86 (dd, *J* = 13.4, 3.0 Hz, 1H), 2.38 (s, 3H), 1.09 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 19.6, 21.4, 26.9, 60.2, 62.4, 67.1, 74.9, 124.0, 127.1, 127.8, 127.9, 128.2, 128.3, 129.9, 130.1, 130.2, 132.4, 133.2, 135.9, 136.0, 139.3, 141.3, 141.6.

m/z (LSIMS) : 621 $[M + H]^+$

General procedure for the cyclization:

To the substrate (0.2 mmol) in dry DMF (0.2 mL) were added imidazole (27 mg, 0.4 mmol) followed by TBDPS-Cl (55 mg 0.2 mmol) at room temperature under N_2 atmosphere. The reaction mixture was stirred at room temperature until TLC revealed complete consumption of the starting material. The reaction mixture was diluted with ether and washed successively with water, brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product mixture. Purification by column chromatography using AcOEt/hexane (1:24, v/v) afforded the pure product.

2-(4-Methylphenylsulfanyl)-3-(4-methylphenylsulfonamido)-5-phenyl-(2*S*,3*R*,5*R*)-tetrahydrofuran, 138.

74%. Solid.

mp : 153-154 °C

PMR (300 MHz, $CDCl_3$) : δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.30-7.20 (m, 9H), 7.03 (d, *J* = 8.2 Hz, 2H), 5.17 (d, *J* = 6.5 Hz, 1H), 4.76 (d, *J* = 8.7 Hz, 1H), 3.98-3.89 (m, 1H), 2.72 (dt, *J* = 14.0, 7.6 Hz, 1H), 2.42 (s, 3H), 2.32 (s, 3H), 1.71 (ddd, *J* = 14.0, 8.7, 5.4 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 21.0, 21.5, 40.9, 59.6, 78.6, 92.1, 125.9, 127.3, 127.9, 128.5, 129.6, 129.8, 132.9, 134.7, 137.0, 137.8, 139.9, 143.7.

m/z (LSIMS) : 316 $[M^+ -STol]$

1-[4-(*tert*-Butylsilyloxy)-2-(4-methylphenylsulfonamido)-4-phenyl-(2*R*)-butylsulfinyl]-4-methylbenzene, 95.

Viscous liquid.

PMR (200 MHz, $CDCl_3$) : δ 7.73 (d, *J* = 8.2 Hz, 2H), 7.32-7.10 (m, 11H), 6.36 (d, *J* = 6.7 Hz, NH), 4.97 (t, *J* = 6.0 Hz, 1H), 3.91 (q, *J* = 6.0 Hz, 1H), 2.81 (dd, *J* = 13.4, 5.2 Hz, 1H), 2.69 (dd, *J* = 13.4, 6.0 Hz, 1H), 2.47 (s, 3H), 2.43 (s, 3H), 2.13 (t, *J* = 6.0 Hz, 2H), 0.9 (s, 9H), 0.11 (s, 3H), -0.21 (s, 3H).

m/z (LSIMS) : 572 $[M + H]^+$

3-Benzyl(4-methylphenyl)sulfonamido-4-bromo-2-(4-methylphenylsulfanyl)-5-phenyl-(2*S*,3*S*,4*R*,5*S*)-tetrahydrofuran, 141.

90%. Solid.

mp : 107-108 °C

PMR (200 MHz, $CDCl_3$) : δ 7.84 (d, *J* = 8.2 Hz, 2H), 7.32-7.20 (m, 14H), 7.04 (d, *J* = 8.2 Hz, 2H), 5.48 (d, *J* = 6.0 Hz, 1H), 4.96 (d, *J* = 9.7 Hz, 1H), 4.50 (dd, *J* = 8.2, 5.2 Hz, 1H), 4.55 (d, *J* = 15.6 Hz, 1H), 4.36 (d, *J* = 15.6 Hz, 1H), 4.13 (dd, *J* = 9.7, 8.2 Hz, 1H), 2.44 (s, 3H), 2.32 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 21.1, 21.5, 50.2, 51.0, 72.5, 83.4, 88.3, 127.0, 128.1, 128.2, 128.4, 128.7, 128.9, 129.6, 129.7, 130.0, 132.7, 135.7, 136.0, 136.9, 138.1, 143.9.

m/z (LSIMS) : 484 [M^+ -STol]

4-Bromo-2-(4-methylphenylsulfanyl)-3-(4-methylphenylsulfonamido)-5-phenyl-(2*S*,3*S*,4*R*,5*S*)-tetrahydrofuran, 142.

86%. Viscous liquid.

PMR (300 MHz, $CDCl_3$) : δ 7.81 (d, *J* = 8.2 Hz, 2H), 7.36-7.22 (m, 9H), 7.02 (d, *J* = 8.2 Hz, 2H), 5.34 (d, *J* = 4.3 Hz, 1H), 5.24 (d, *J* = 7.6 Hz, 1H), 5.16 (d, *J* = 8.7 Hz, 1H), 4.04 (ddd, *J* = 7.6, 6.5, 4.3 Hz, 1H), 3.69 (dd, *J* = 8.7, 6.5 Hz, 1H), 2.43 (s, 3H), 2.32 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 20.9, 21.3, 53.3, 68.2, 84.0, 91.1, 126.6, 127.3, 128.4, 128.8, 129.5, 129.6, 132.7, 135.6, 136.9, 137.9, 143.8.

m/z (LSIMS) : 394 [M^+ -STol]

4-Bromo-5-butyl-3-(4-methylphenylsulfonamido)-2-phenylsulfanyl-(2*S*,3*S*,4*S*,5*S*)-tetrahydrofuran, 143.

90%. Low melting solid.

PMR (300 MHz, $CDCl_3$) : δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.36-7.19 (m, 7H), 5.14 (d, *J* = 10.5 Hz, 1H), 4.99 (d, *J* = 8.2 Hz, 1H), 4.24 (dd, *J* = 4.8, 2.2 Hz, 1H), 3.85 (ddd, *J* = 10.5, 8.2, 4.8 Hz, 1H), 3.74 (td, *J* = 6.7, 2.2 Hz, 1H), 2.48 (s, 3H), 1.80-1.50 (m, 2H), 1.36-1.24 (m, 4H), 0.90 (t, *J* = 6.7 Hz, 3H).

m/z (LSIMS) : 375 [M^+ -STol]

3-Bromo-4-methyl-2-phenyl-5-phenylsulfanyl-(2*S*,3*R*,4*S*,5*S*)-tetrahydrofuran, 145.

93%. Solid.

mp : 53-54 °C

PMR (200 MHz, $CDCl_3$) : δ 7.56-7.22 (m, 10H), 5.25 (d, *J* = 7.4 Hz, 1H), 5.02 (d, *J* = 9.7 Hz, 1H), 3.5 (dd, *J* = 9.7, 8.9 Hz, 1H), 2.54-2.47 (m, 1H), 1.36 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 15.1, 50.5, 56.6, 85.4, 92.2, 126.8, 127.4, 128.4, 128.7, 128.9, 131.7, 134.6, 137.1.

m/z (LSIMS) : 239 [M^+ -STol]

3-Bromo-4-(*tert*-butyldiphenylsilyloxy)-2-phenyl-5-(4-methylphenylsulfanyl)-(2*R*,3*R*,4*S*)-tetrahydrofuran, 147 (Anomeric mixture).

82%. Viscous liquid.

PMR (200 MHz, $CDCl_3$) : δ 7.88-7.62 (m, 12H), 7.52-6.97 (m, 26H), 5.62 (d, *J* = 5.9 Hz, 1H), 5.41 (d, *J* = 2.9 Hz, 1H), 5.34 (d, *J* = 5.9 Hz, 1H), 5.11 (d, *J* = 8.9 Hz, 1H), 4.55-4.43 (m, 2H), 4.06-3.86 (m, 2H), 2.33 (s, 6H), 1.12 (s, 9H), 1.04 (s, 9H).

m/z (LSIMS) : 479 [M^+ -STol]

3-Bromo-5-(4-methylphenylsulfanyl)-4-(*tert*-butyldiphenylsilyloxy)-2-phenyl-(2*S*,3*S*,4*S*,5*S*)-tetrahydrofuran, 149.

90%. Liquid.

PMR (200 MHz, $CDCl_3$) : δ 7.76-7.59 (m, 4H), 7.50-7.28 (m, 11H), 7.14 (d, *J* = 8.2 Hz, 2H), 6.98 (d, *J* = 7.4 Hz, 2H), 5.38 (d, *J* = 3.0 Hz, 1H), 5.10 (d, *J* = 8.9 Hz, 1H), 4.48 (dd, *J* = 5.2, 3.0 Hz, 1H), 3.92 (dd, *J* = 8.9, 5.2 Hz, 1H), 2.32 (s, 3H), 1.09 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 19.1, 21.1, 26.9, 57.0, 85.1, 86.0, 93.6, 126.8, 127.7, 127.7, 128.5, 128.6, 129.5, 130.0, 130.3, 132.4, 132.6, 136.0, 137.0, 137.7.

m/z (LSIMS) : 479 [M^+ -STol]

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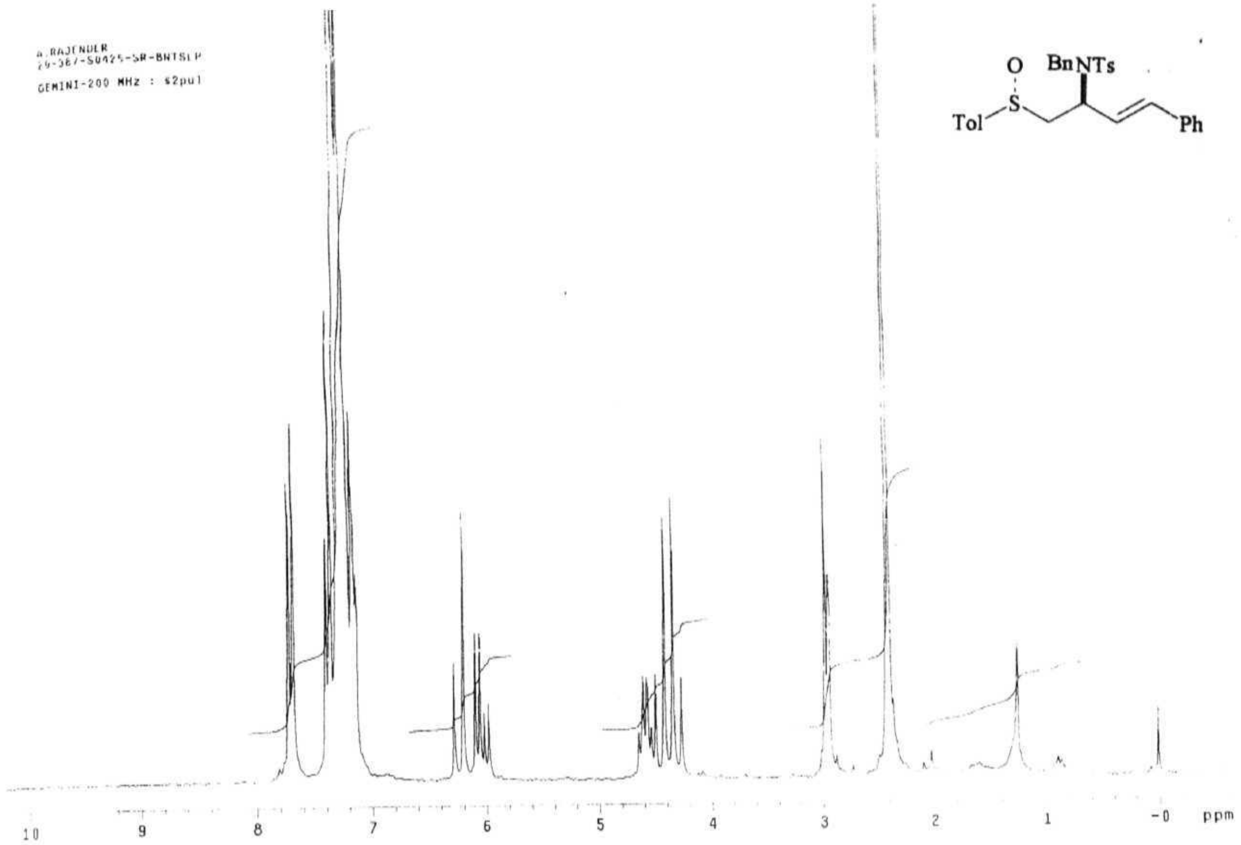
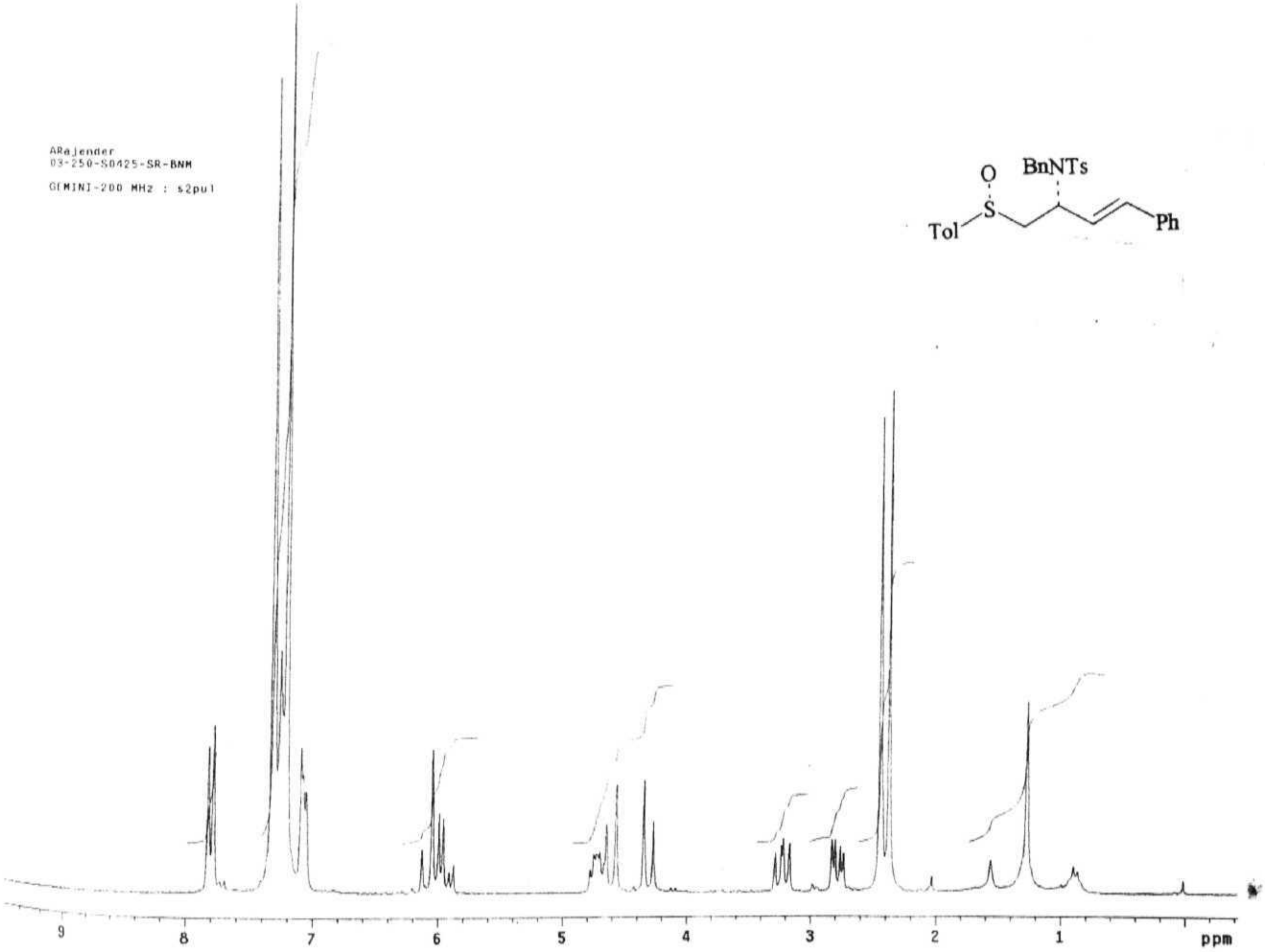
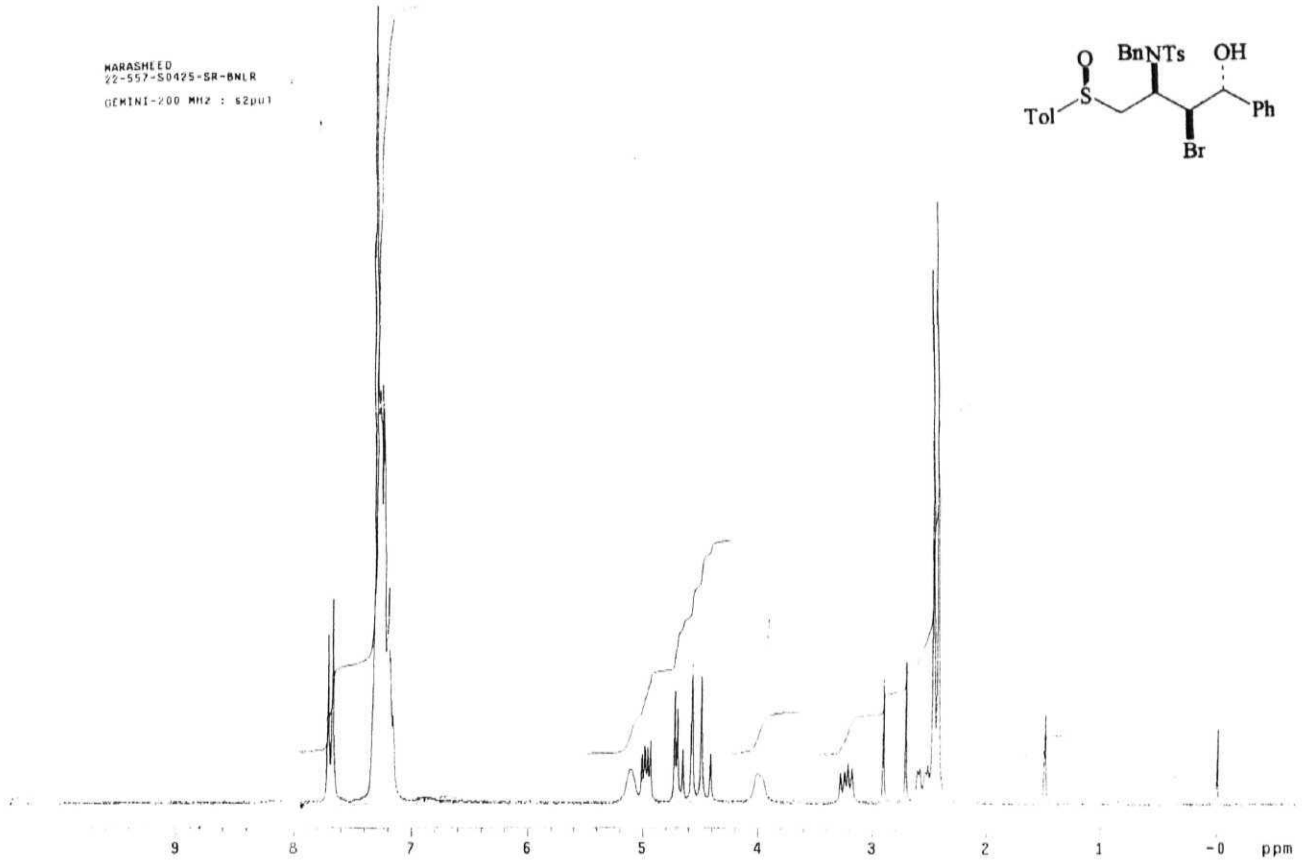
SPECTRA



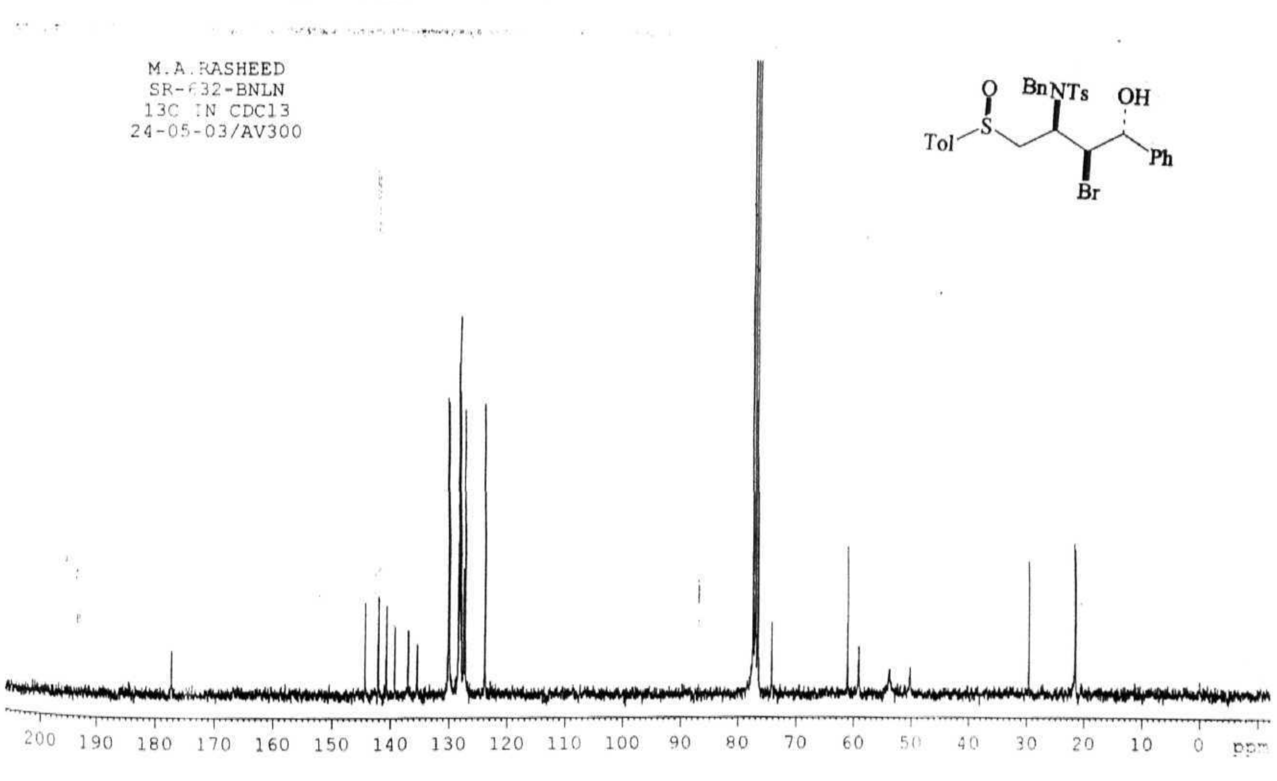
PMR Spectrum of Compound 139*a*



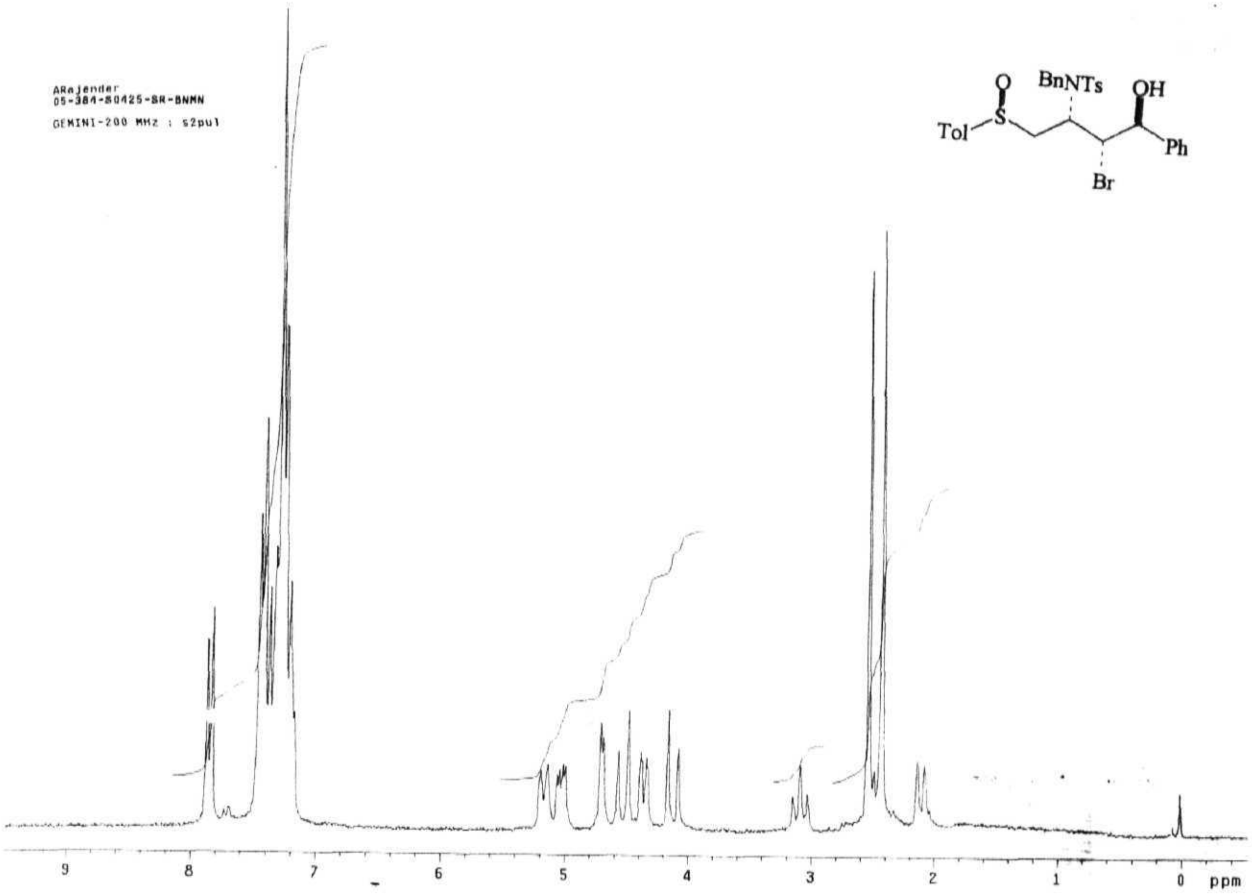
PMR Spectrum of Compound 139*s*



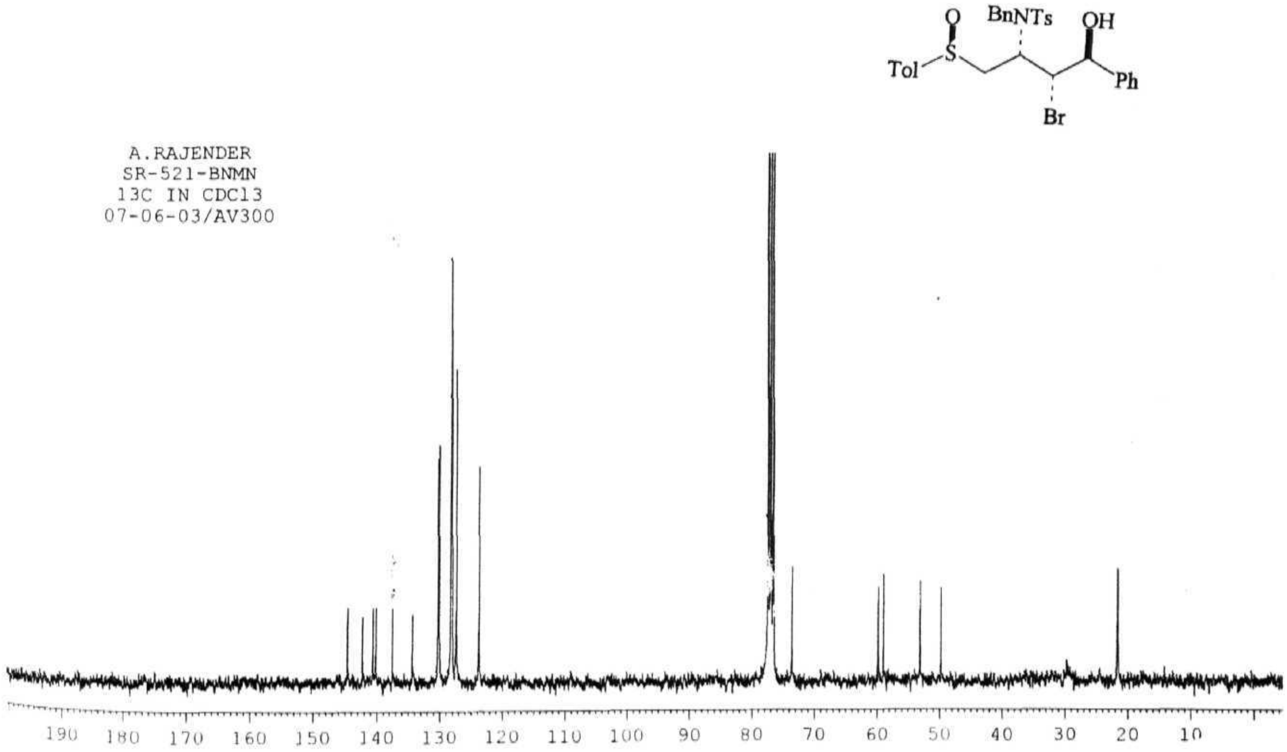
PMR Spectrum of Compound 140s



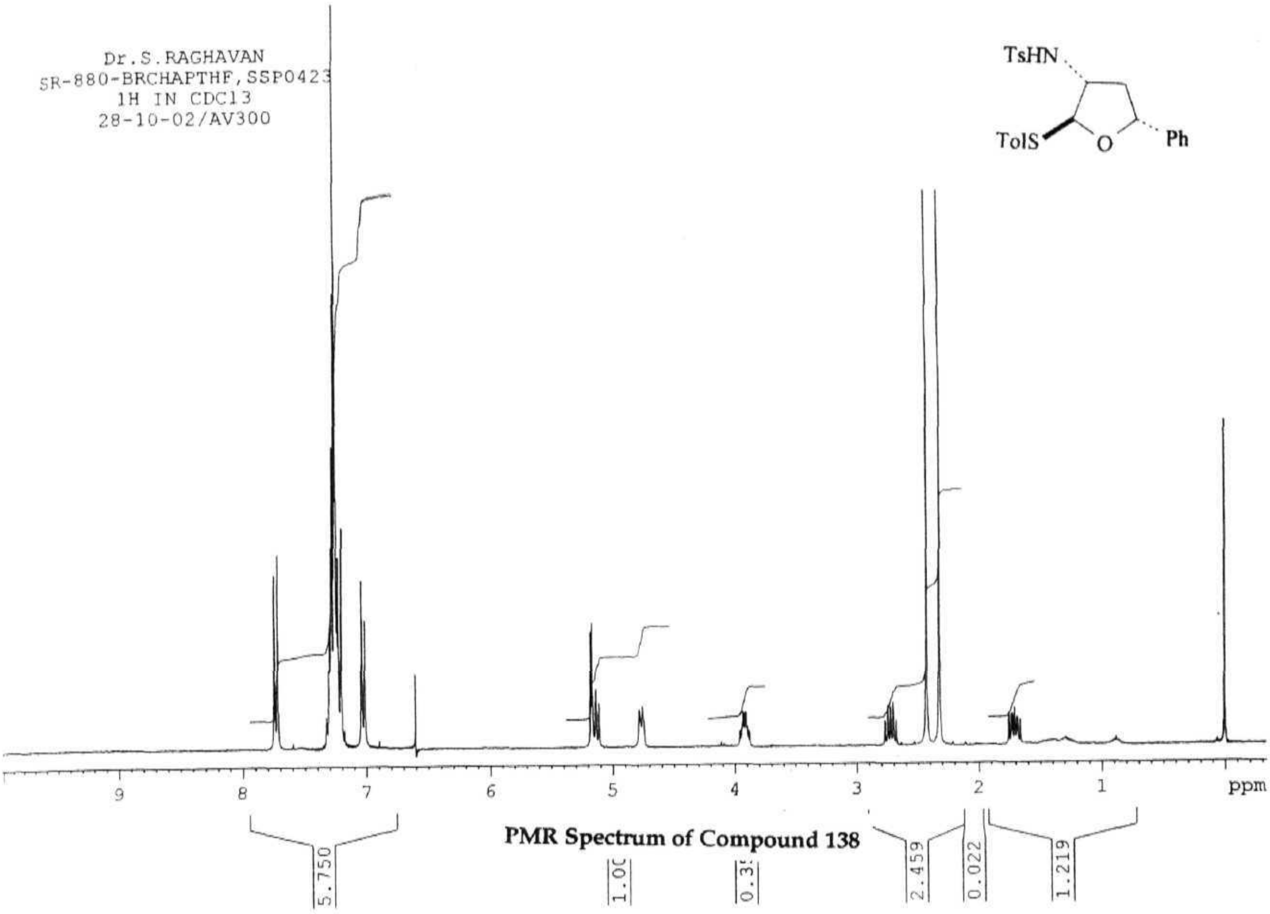
^{13}C Spectrum of Compound 140s



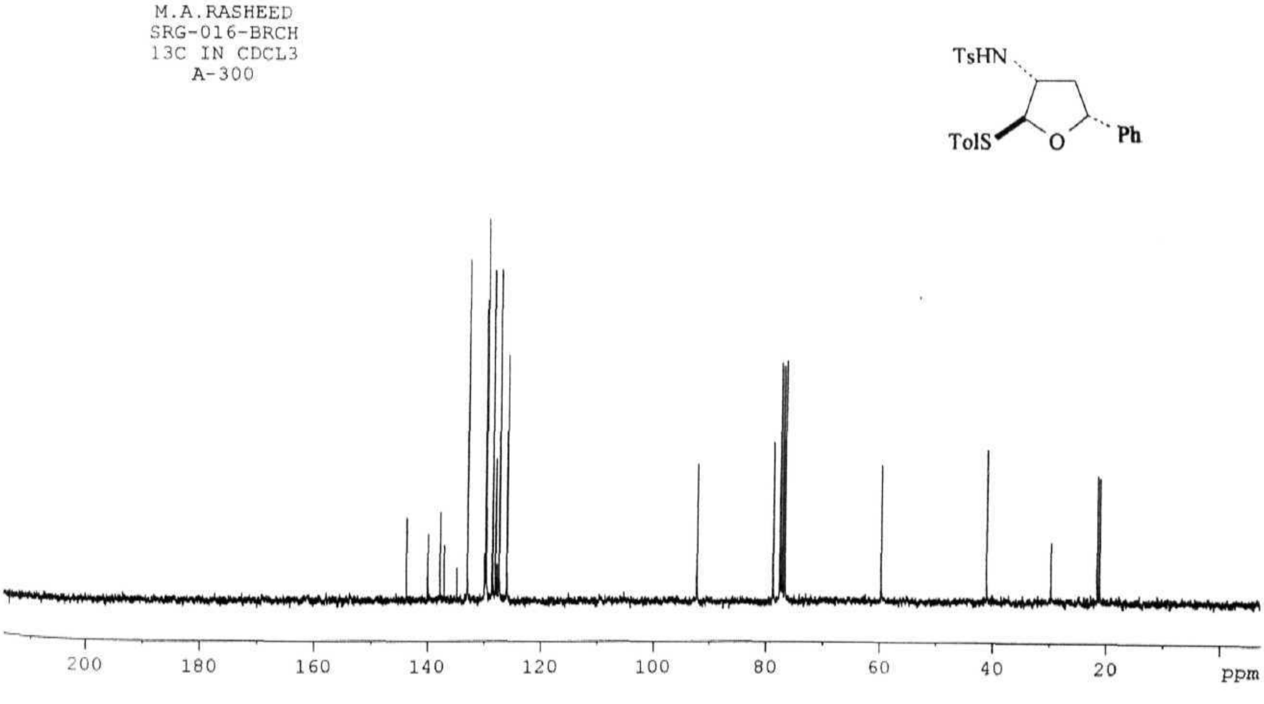
PMR Spectrum of Compound 140*a*



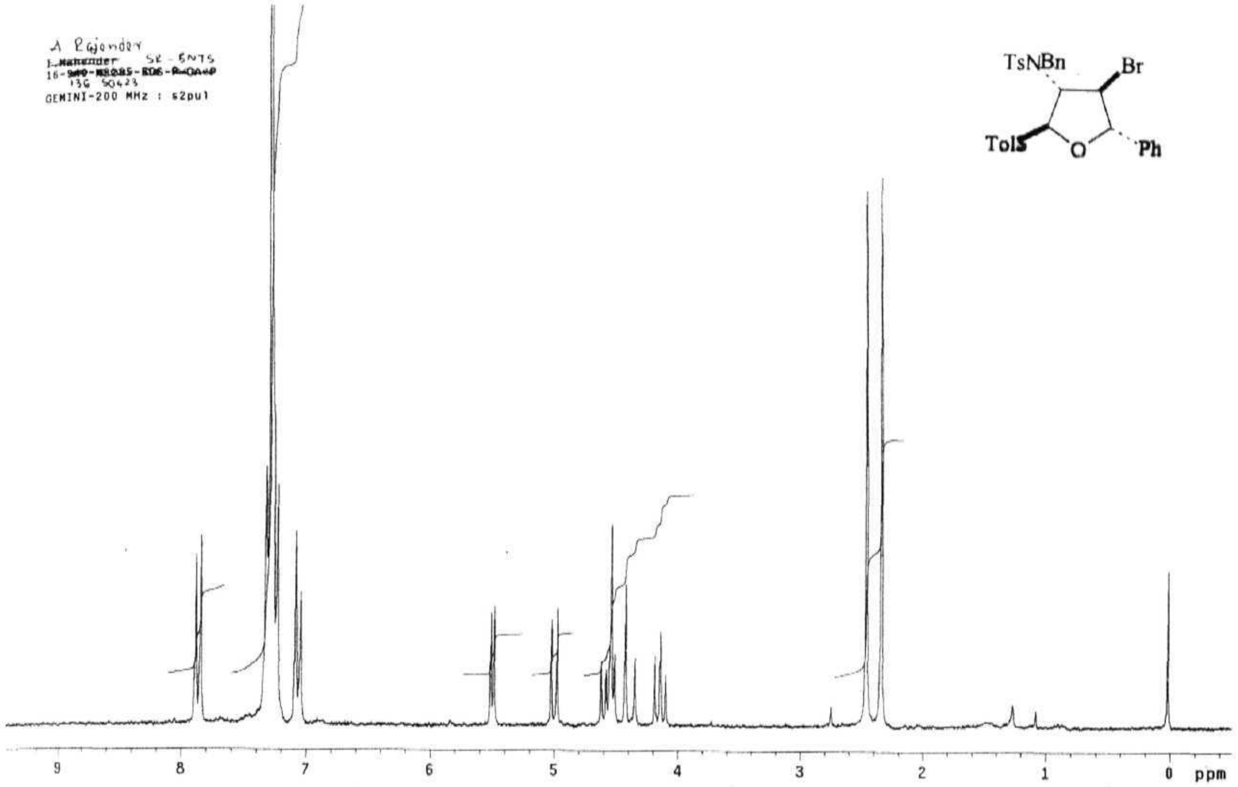
^{13}C Spectrum of Compound 140*a*



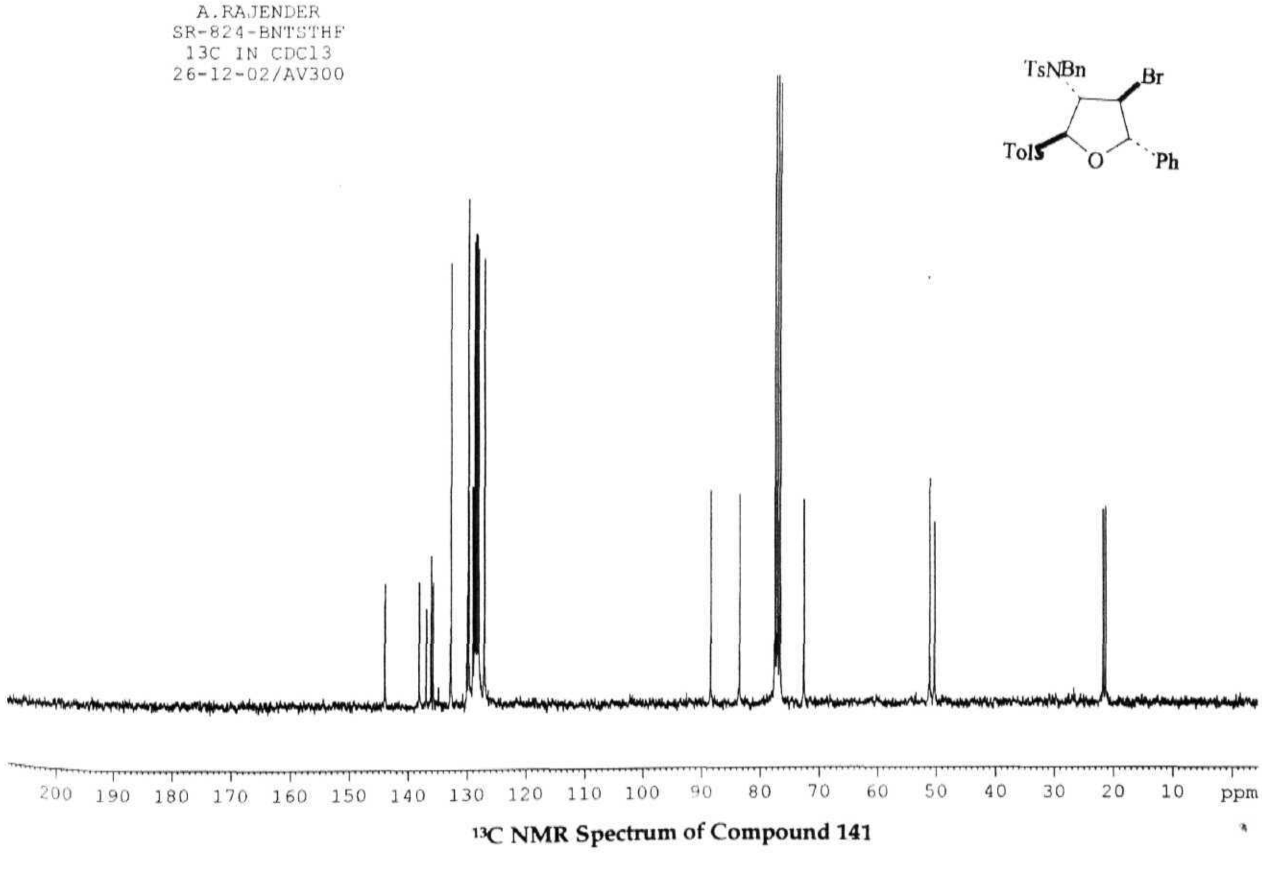
PMR Spectrum of Compound 138



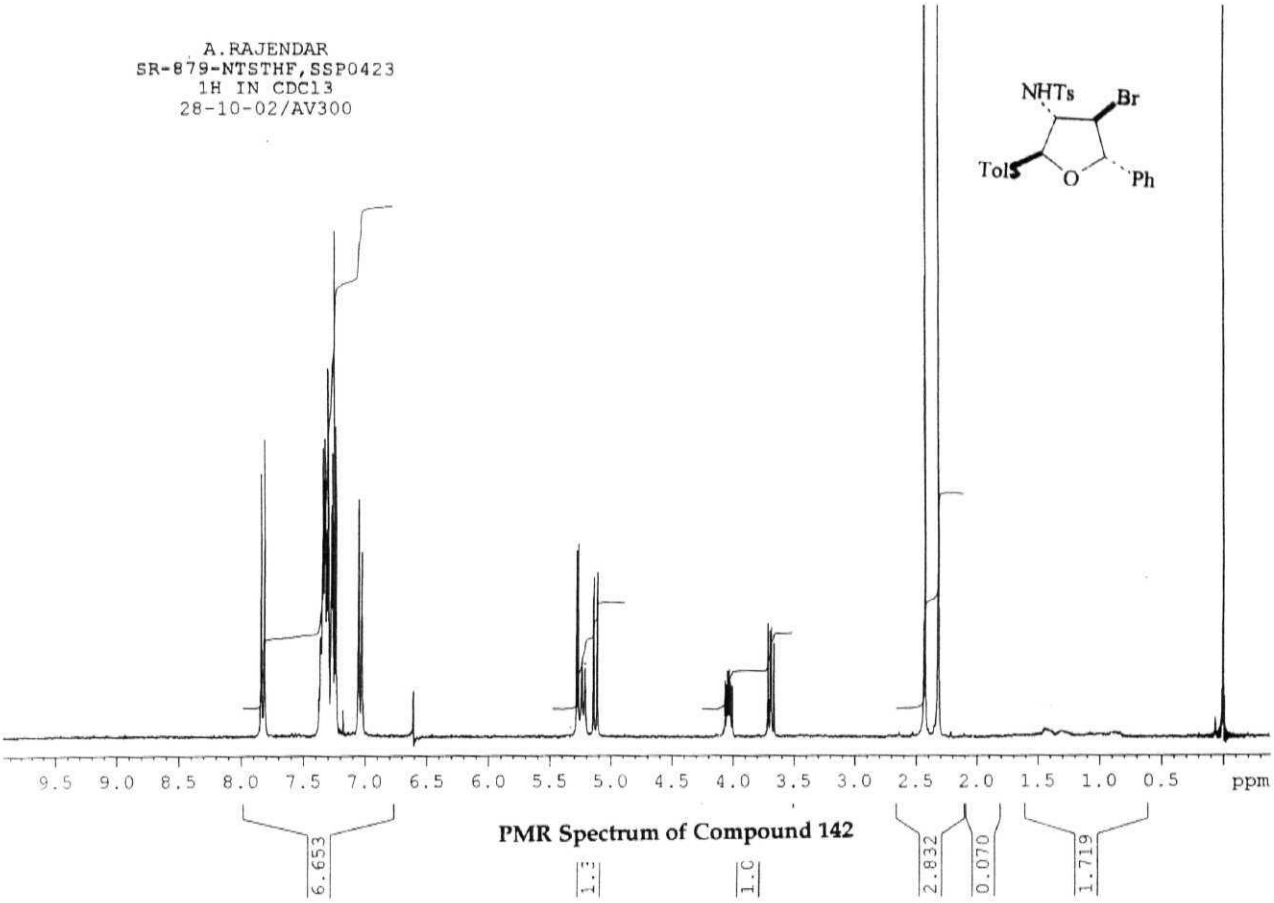
^{13}C NMR Spectrum of Compound 138



PMR Spectrum of Compound 141



^{13}C NMR Spectrum of Compound 141


A.RAJENDAR
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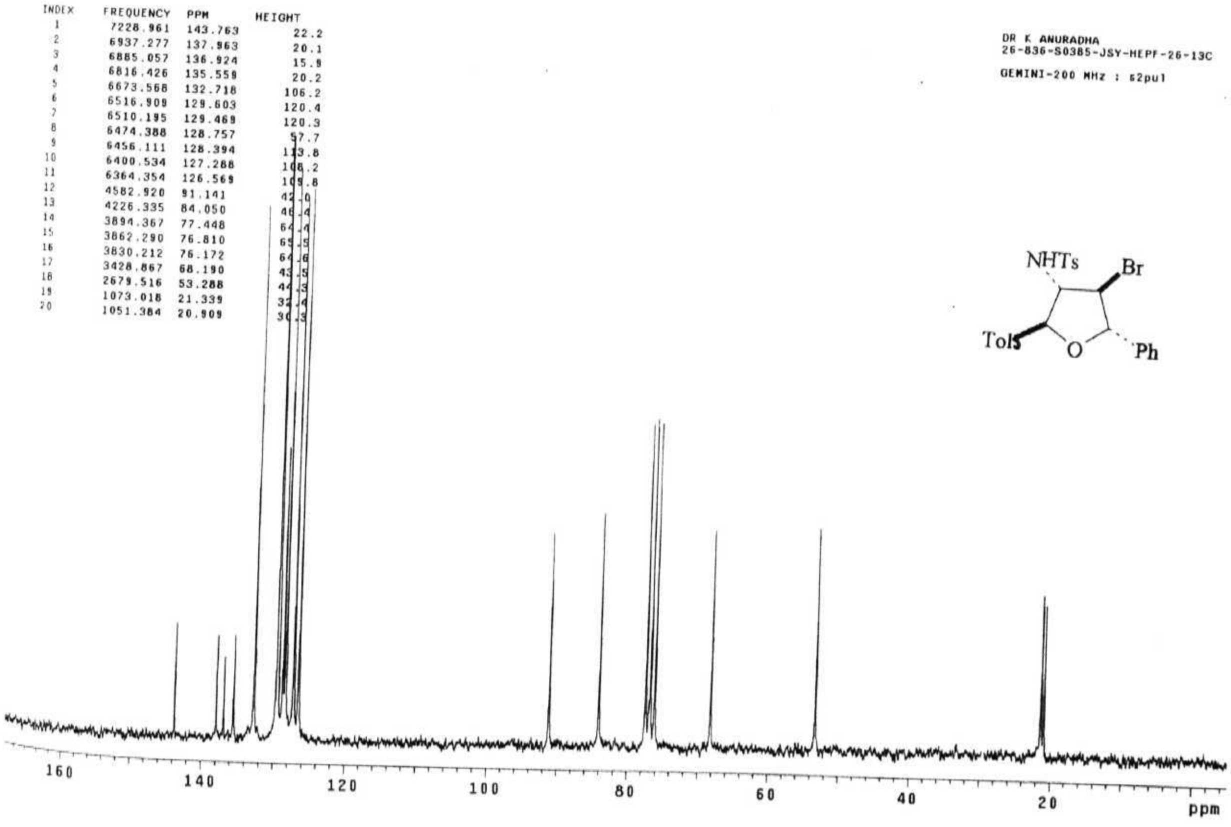
28-10-02/AV300

PMR Spectrum of Compound 142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  5      6673.568   132.718     106.2
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  7      6510.195   129.469     120.3
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  9      6456.111   128.394     113.8
 10      6400.534   127.288     108.2
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 12      4582.920    91.141      42.0
 13      4226.335    84.050      46.4
 14      3894.367    77.448      64.4
 15      3862.290    76.810      65.5
 16      3830.212    76.172      64.6
 17      3428.867    68.190      43.5
 18      2679.516    53.288      44.3
 19      1073.018    21.339      32.4
 20      1051.384    20.909      30.3
```
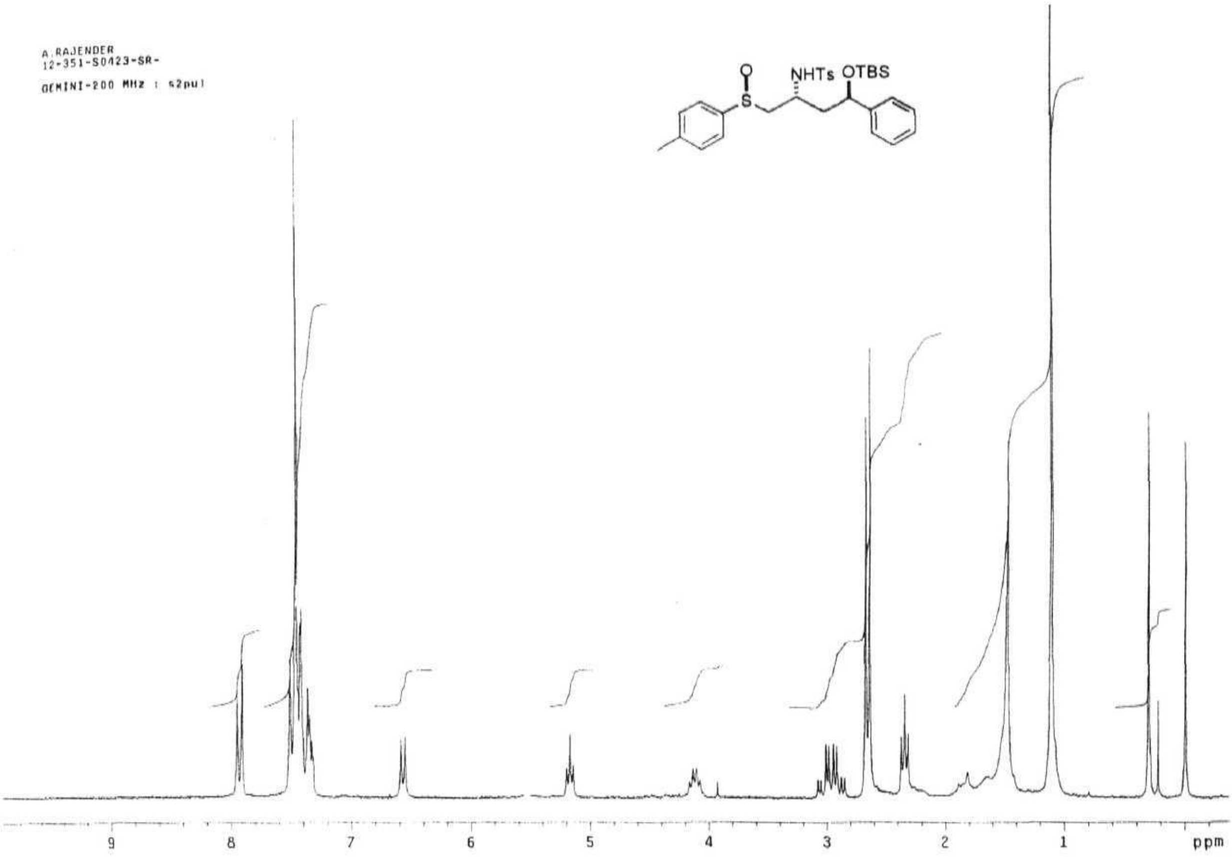
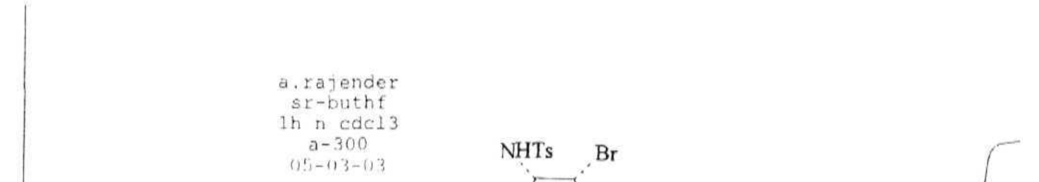
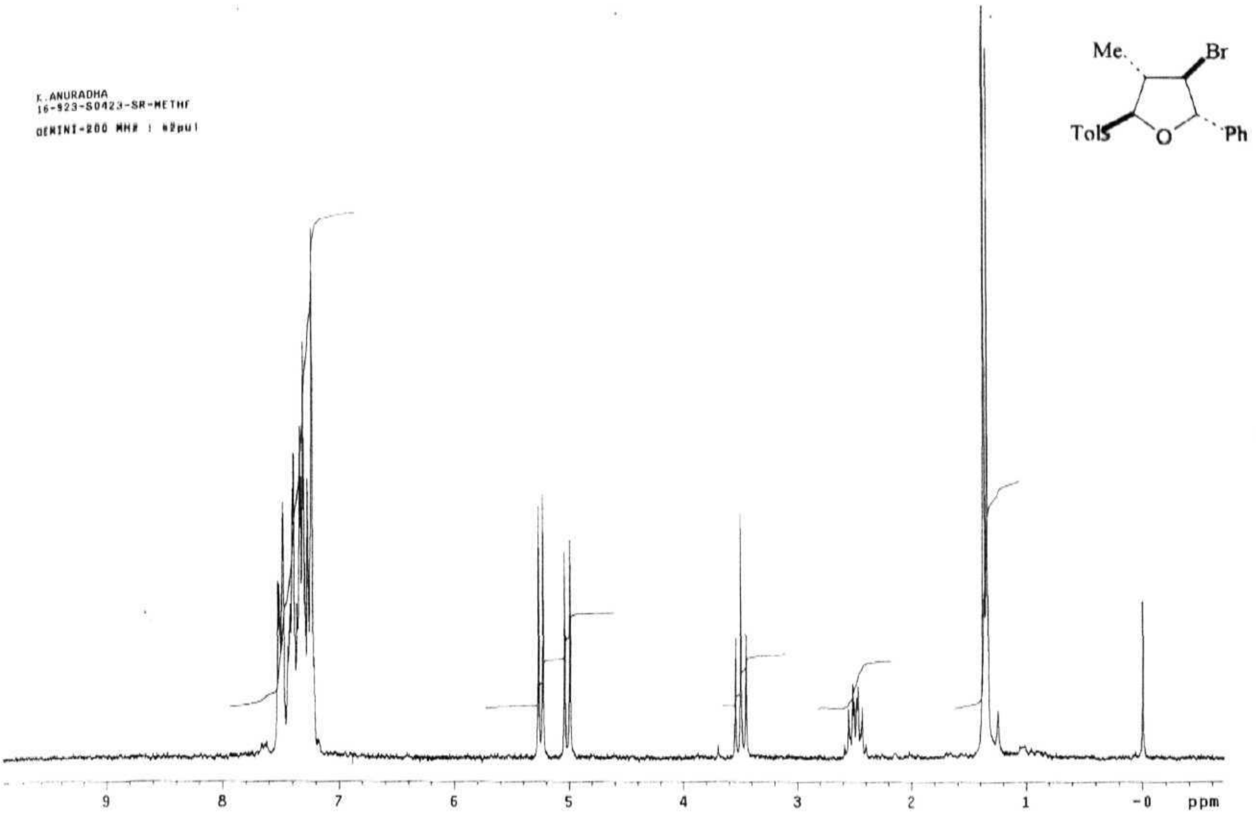

DR K ANURADHA
26-836-S0385-JSY-HEPF-26-13C
GEMINI-200 MHz : s2pul

^{13}C NMR Spectrum of Compound 142

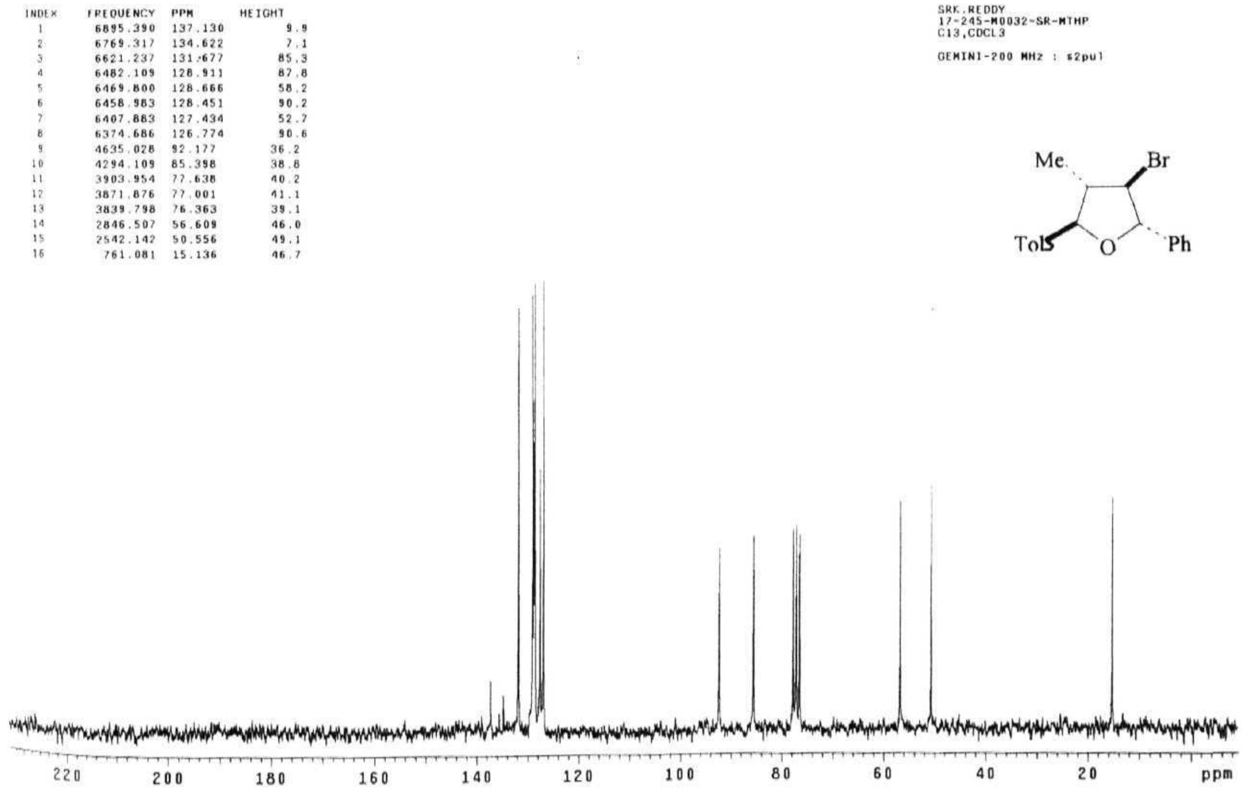




PMR Spectrum of Compound 143



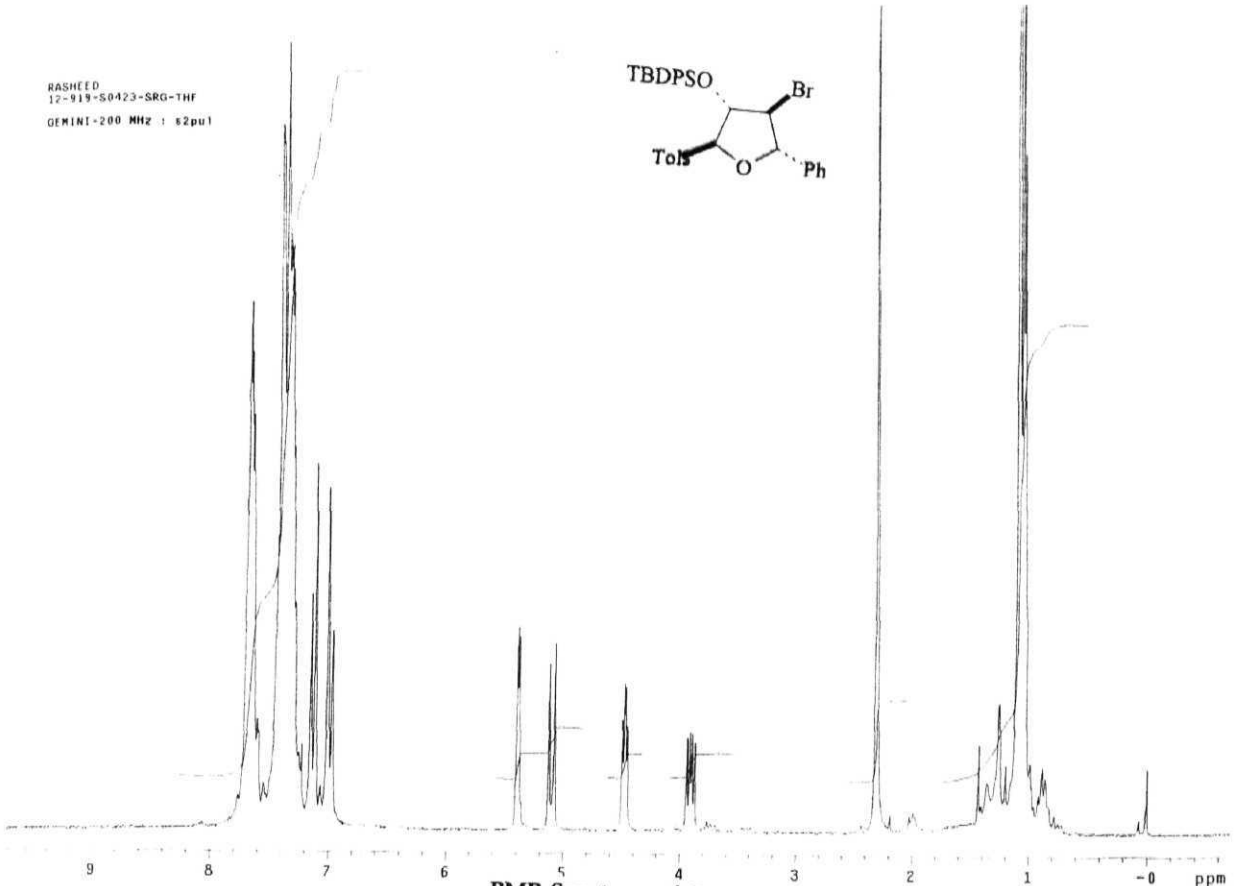
PMR Spectrum of Compound 145



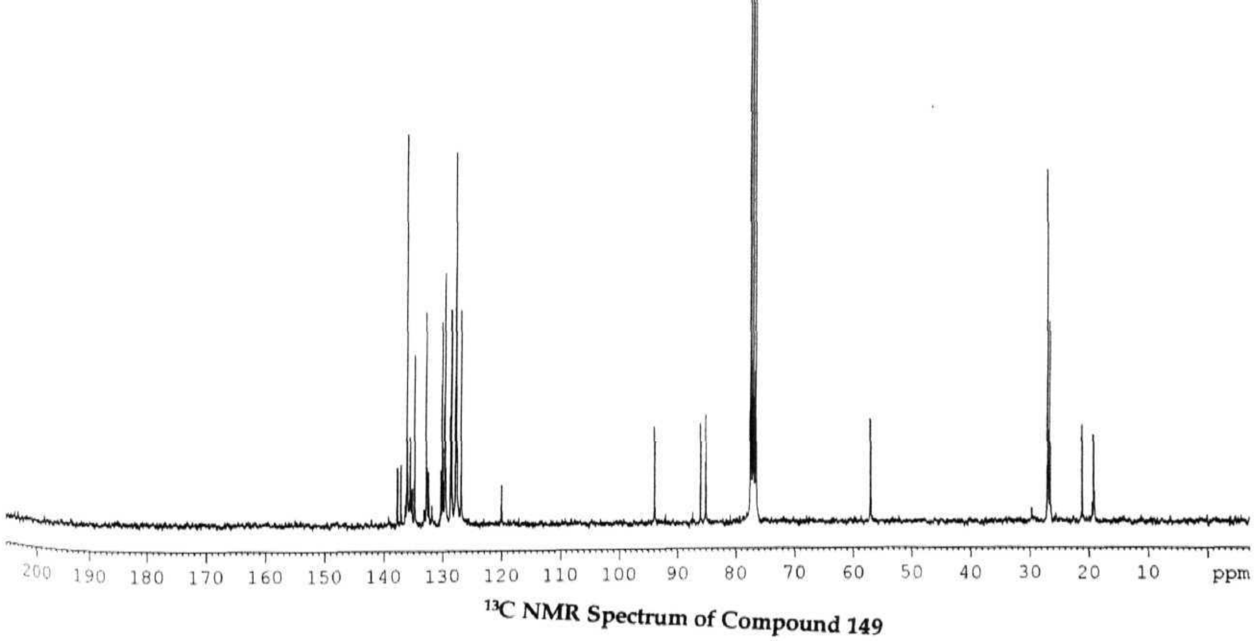
```
INDEX   FREQUENCY  PPM      HEIGHT
  1     6895.390   137.130     9.9
  2     6769.317   134.622     7.1
  3     6621.237   131.677    85.3
  4     6482.109   128.911    87.8
  5     6469.800   128.666    58.2
  6     6458.983   128.451    90.2
  7     6407.883   127.434    52.7
  8     6374.686   126.774    90.6
  9     4635.028   92.177     36.2
 10     4294.109   85.398     38.8
 11     3903.954   77.638     40.2
 12     3871.876   77.001     41.1
 13     3839.798   76.363     39.1
 14     2846.507   56.609     46.0
 15     2542.142   50.556     49.1
 16      761.081   15.136     46.7
```

```
SRK.REDDY
17-245-M0032-SR-MTHP
C13,CDCL3

GEMINI-200 MHz : s2pul
```

^{13}C NMR Spectrum of Compound 145



PMR Spectrum of Compound 149



^{13}C NMR Spectrum of Compound 149

CHAPTER-III

Stereospecific synthesis of phytosphingosines and sphingosines

Section-A

Stereospecific synthesis of *xylo*-(2*R*,3*S*,4*S*)-phytosphingosine and *threo*-(2*R*,3*R*)-sphingosine

&

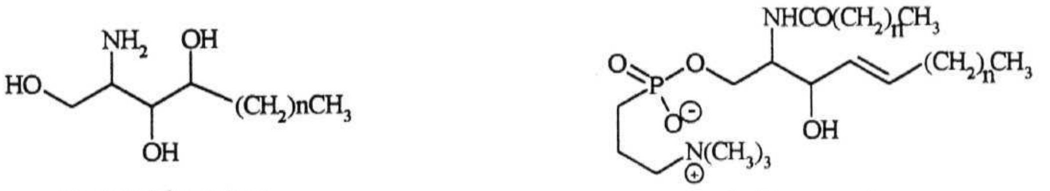
Section-B

Efficient and Stereospecific synthesis of *lyxo*-(2*R*,3*R*,4*R*)-phytosphingosine and *erythro*-(2*R*,3*S*)-sphingosine

General introduction

Sphingolipid is a derivative of sphingosine, a long chain unsaturated amino alcohol. It has a polar head group as well as two hydrophobic hydrocarbon chains, one is the sphingosine chain and the other is the fatty acid chain. Sphingolipids are ubiquitous membrane components of essentially all eukaryotic cells and are abundantly located in all plasma membranes as well as in some intracellular organelles (endoplasmic reticulum, Golgi complex and mitochondria).[1] Sphingolipids (Figure 1) have been implicated in a vast variety of physiological functions but are not readily obtained from natural sources in homogenous form. They have also been shown to play critical roles as secondary messengers in cell signaling. Interest in glycosphingolipids has increased in recent years due to the recognition that they modulate immune responses.

Figure 1



Phytosphingosines

Sphingomyelins

Sphingosines

R = H	**Ceramides**
R = Sugar	**Cerebrosides**
R = Sugar with salicilic acid residue	**Gangliosides**

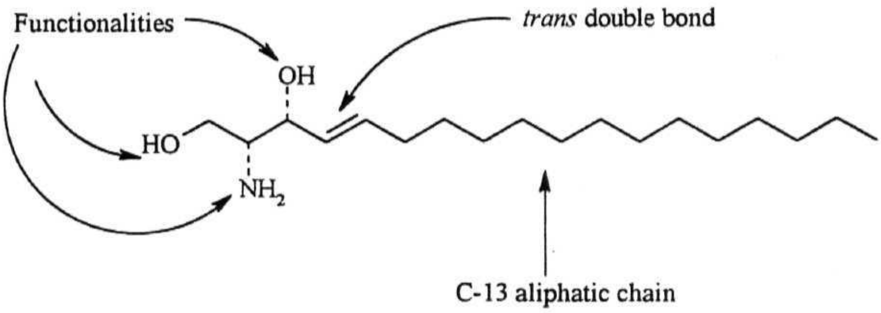
Sphingolipids

Sphingosines:

There are currently over 300 known sphingolipids with distinct head groups all containing the sphingoid baseback bone.[2] The discovery of the sphingomyelin cycle has stimulated numerous studies on sphingolipids as potential mediators of signaling pathways.[1b]

The word sphingosine is derived from the Greek word "sphingein" meaning to bind tightly, implying that these are bound tightly to tissues, particularly in the brain.

Figure 2



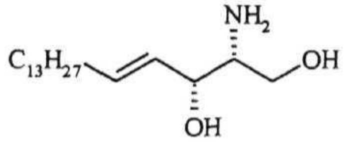
Key structural features of sphingosine

Sphingosine was first isolated in 1884 by Thudicum[3] as a waxy unstable substance obtained from the hydrolysate of a lipid fraction of the brain tissue. In the early decades of this century investigators recognized it as "dihydroxyaminooctadecane". Apart from being the backbone component of the cerebrosides, reports have also established[4] sphingosines to be potent inhibitors of protein kinase C *in vitro* and *in vivo*. Sphingosines also block cellular responses to agonist that are thought to act via this enzyme. To date, many syntheses of sphingosines have been reported. Many of them used naturally occurring chiral substrates such as D-galactose, D-glucose and D-xylose as starting material. The carbohydrates mentioned above possess the D-*threo*-diol sub-structure and therefore at some stage the nitrogen atom was introduced with inversion of configuration to obtain the natural sphingosine geometry. Likewise, D-tartaric acid an unnatural substrate possessing the D-

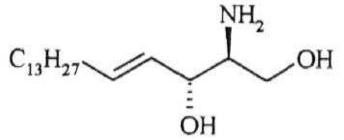
threo-diol structure has also been employed. Chiral auxiliaries such as Evans oxazolidinone and Enders' SAMP hydrazone have been used for the synthesis of sphingosines. There are few reports based on chemoenzymatic approaches for the synthesis of sphingosine.[5]

The sphingosine has two asymmetric centers and exists in four stereoisomeric forms (Figure 3). Comparison of the four stereoisomers showed that all had approximately the same potency as the inhibitors of PKC.

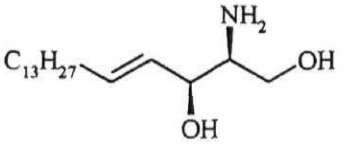
Figure 3



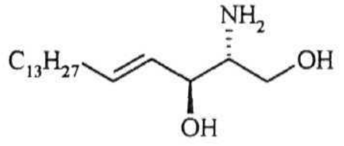
threo-(2*R*,3*R*)-sphingosine 1



erythro-(2*S*,3*R*)-sphingosine 2



threo-(2*S*,3*S*)-sphingosine 3



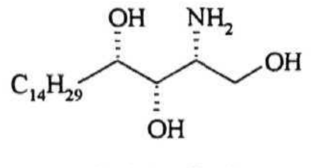
erythro-(2*R*,3*S*)-sphingosine 4

Phytosphingosines

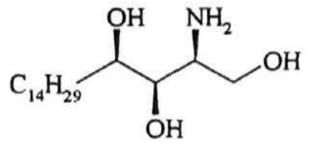
Phytosphingosines are found in various glycosphingolipids such as cerebrosides and gangliosides.[6] The first phytosphingosine was isolated from the mushroom *Amanita muscaria* in 1911 by Zellner[7] as a nitrogen-containing "fungus cerebrin" and subsequently from higher plants,[8] yeast,[9] fungi,[10] marine organisms[11] and mammalian tissues[12] such as kidney, liver, uterus, intestine, skin, blood plasma and thymocytes. Structure of the "cerebrin base" was established as 2-amino-1,3,4-trihydroxyoctadecane in 1952. Because of its plant origin and structural similarity to sphingosine, the term "phytosphingosine" was proposed for this base. Phytosphingosines have also been found in human kidney cerebrosides and some cancer cell types.

The first synthesis of all the four racemic phytosphingosines was reported in 1970,[13] while optically active *ribo, arabino, xylo* and *lyxo*-phytosphingosines were synthesized in 1990.[14] Phytosphingosines can exist in eight stereoisomeric forms depicted below (Figure 3).

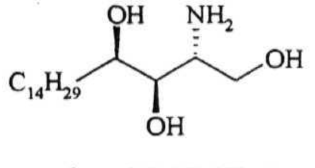
Figure 3



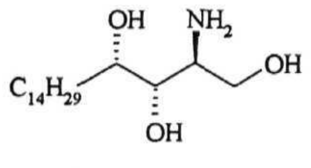
xylo-(2*R*,3*S*,4*S*) 5



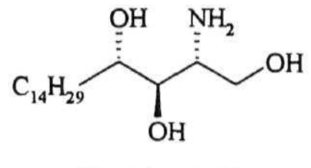
xylo-(2*S*,3*R*,4*R*) 6



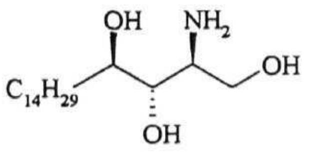
lyxo-(2*R*,3*R*,4*R*) 7



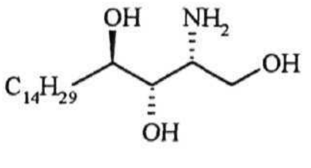
lyxo-(2*S*,3*S*,4*S*) 8



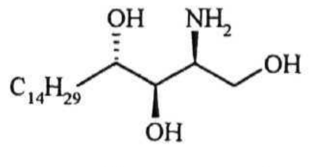
ribo-(2*R*,3*R*,4*S*) 9



ribo-(2*S*,3*S*,4*R*) 10



arabino-(2*R*,3*S*,4*R*) 11



arabino-(2*S*,3*R*,4*S*) 12

Due to subtle biostereoselectivities of the individual sphingosines and phytosphingosines,[15] a great deal of effort has been devoted towards the synthesis of the individual phytosphingosines and sphingosines. Synthetic efforts have been primarily focused on the preparation of *arabino*- and *ribo*-phytosphingosines starting from compounds of the chiral pool[16] or by asymmetric induction.[17] In contrast, the *xylo*- and *lyxo*-phytosphingosines have attracted less attention from the synthetic community.[18]

Since differences in the various phytosphingosines and sphingosine occur mainly in the aliphatic substituent, any synthesis of phytosphingosine or sphingosine has to take into consideration the establishment of chiral centers and chain elongation.

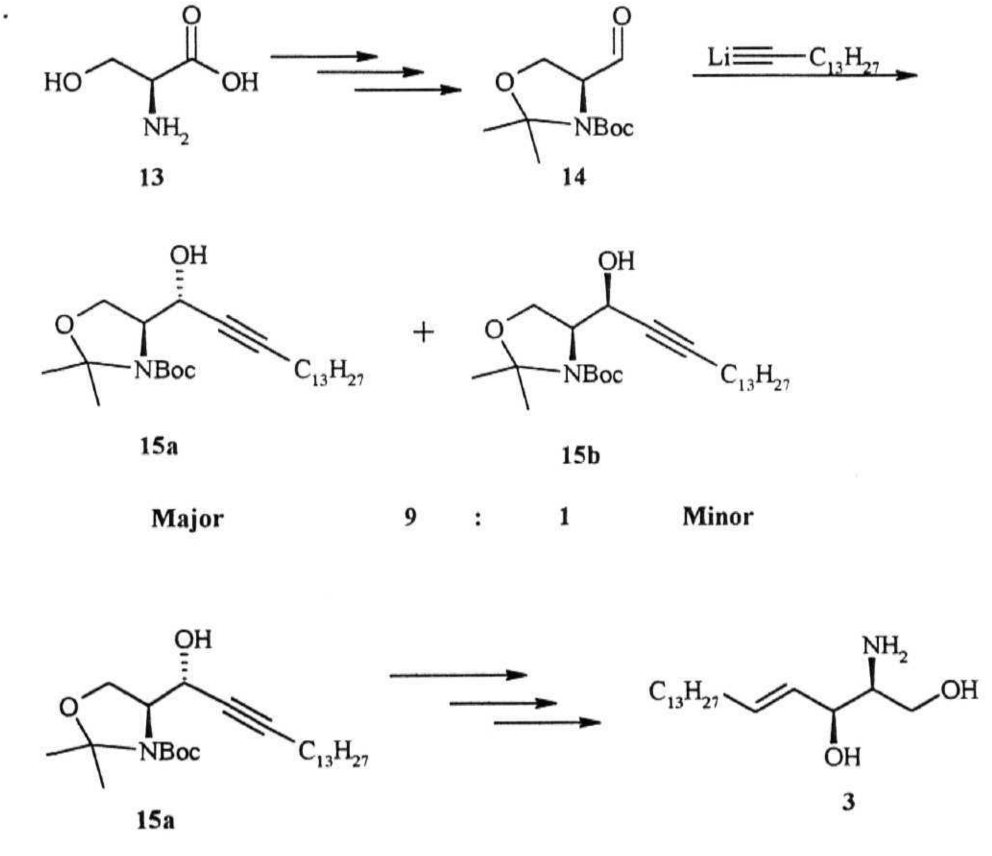
Previous approaches to the synthesis of sphingosines:

Few earlier approaches to sphingosines reported in the literature[5] are detailed below.

Nimkar's approach[19]:

Nimkar *et al.*, reported the synthesis of D-*erythro*- and L-*threo*-sphingosine starting from L-serine **13**. Thus, chelation controlled addition of lithiated pentadecyne provided a 9:1 diastereomeric mixture of alcohols **15a** and **15b** respectively. Alcohol **15a** was transformed using routine steps into L-*threo*-sphingosine (Scheme 1).

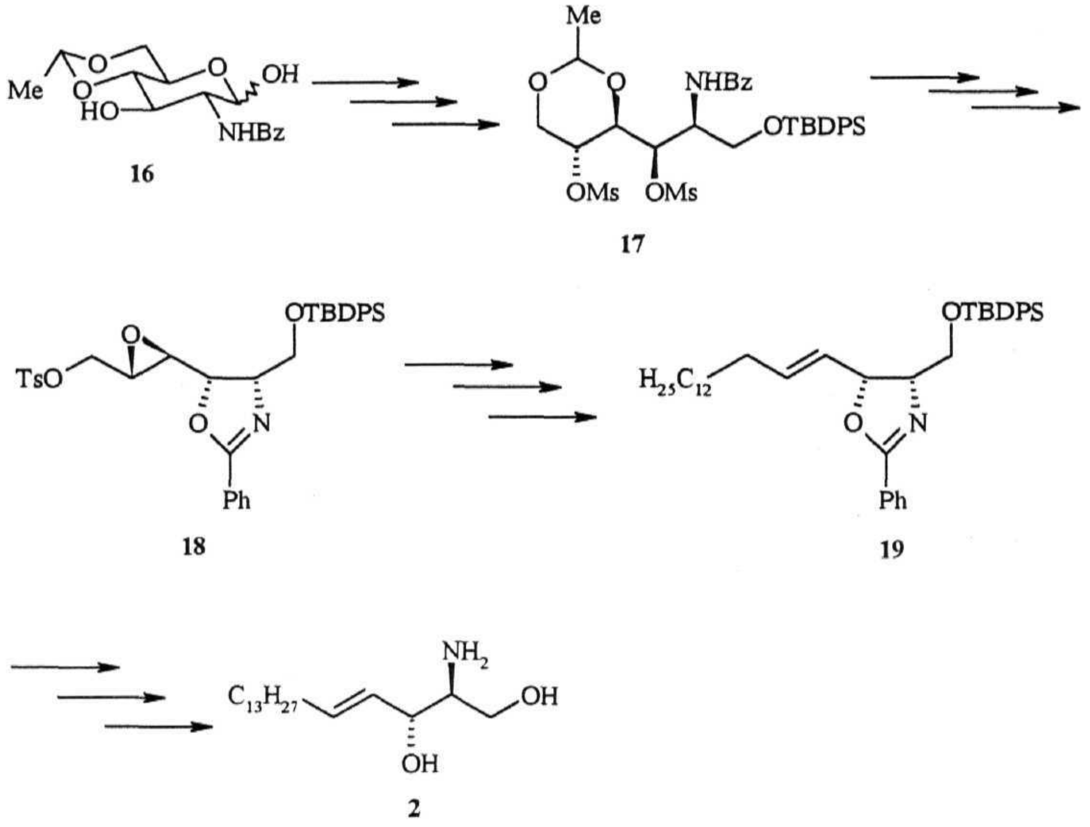
Scheme 1



Murakami's approach[20]:

Murakami *et al.*, disclosed the synthesis of D-*erythro*-sphingosine starting from D-glucosamine **16**. D-Glucosamine was transformed into the tosyloxy derivative **18**, which was then substituted by dodecyl chain to afford **19**. This was further elaborated to the target molecule using a series of reactions (Scheme 2).

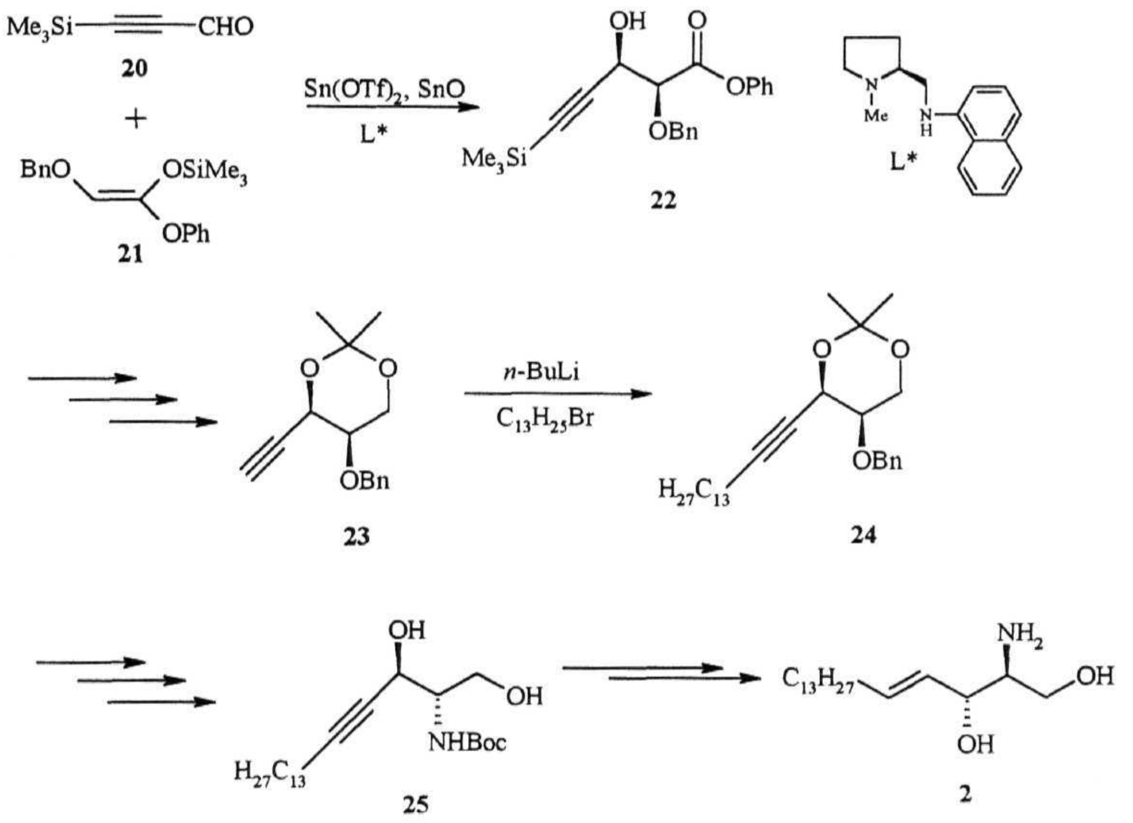
Scheme 2



Kobayashi's approach[21]:

Kobayashi *et al.*, chose the chiral tin (II)-catalyzed asymmetric aldol reaction for the synthesis of *erythro*-sphingosine. Reaction between trimethylsilylpropynal **20** and α-benzyloxyacetate derived ketenesilyl acetal **21** was carried out in the presence of tin (II) triflate and the diamine ligand L* to afford the adduct **22** in 94% de and 91% ee. The alkyl chain was introduced by alkylation of alkyne **23** to yield **24**, which was transformed into *erythro*-sphingosine using standard reactions (Scheme 3).

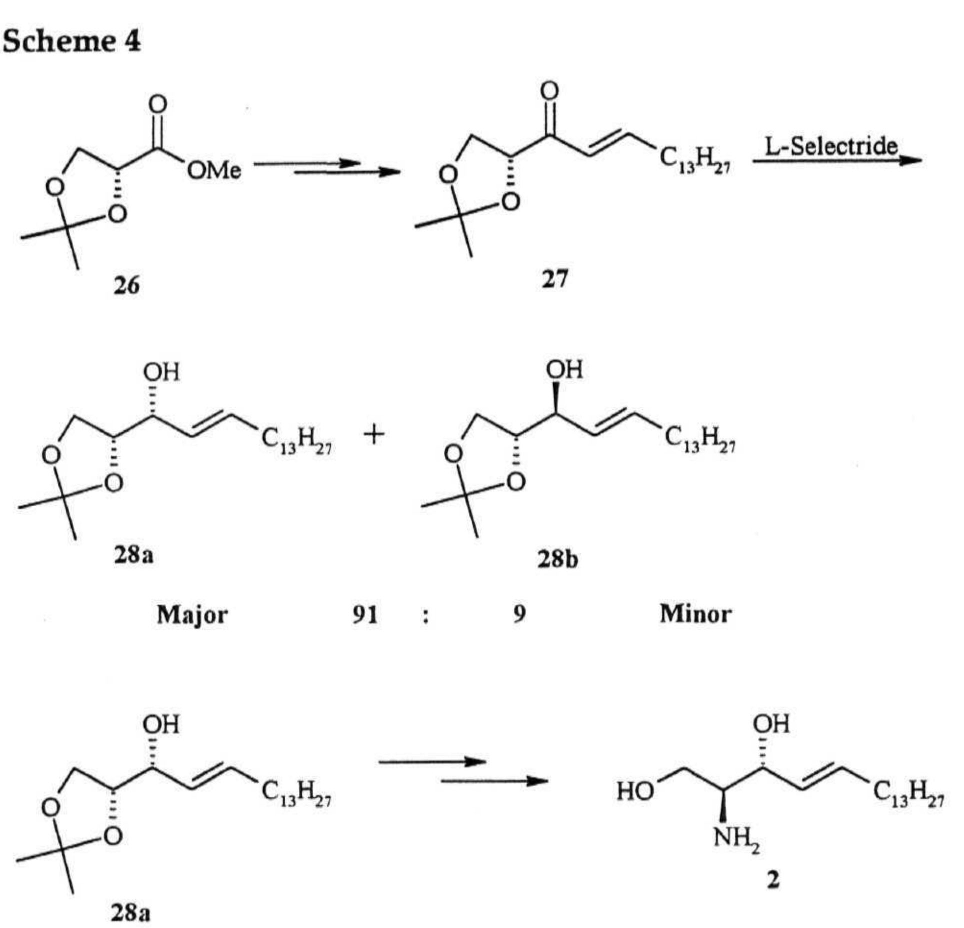
Scheme 3



Yamanoi's approach[22]:

Yamanoi *et al.*, reported the synthesis of *erythro*-sphingosine relying on *E*-selective modified Horner-Wadsworth-Emmons chemistry. Reaction between the tetradecanal and β-ketophosphonate derived from methyl 2,3-*O*-isopropylidene-D-glycerate **26** yielded enone **27**. Diastereoselective reduction of **27** with L-selectride furnished diastereomeric alcohols **28a** and **28b** in 82% de. Alcohol **28a** was further transformed into *erythro*-sphingosine (Scheme 4).

Scheme 4

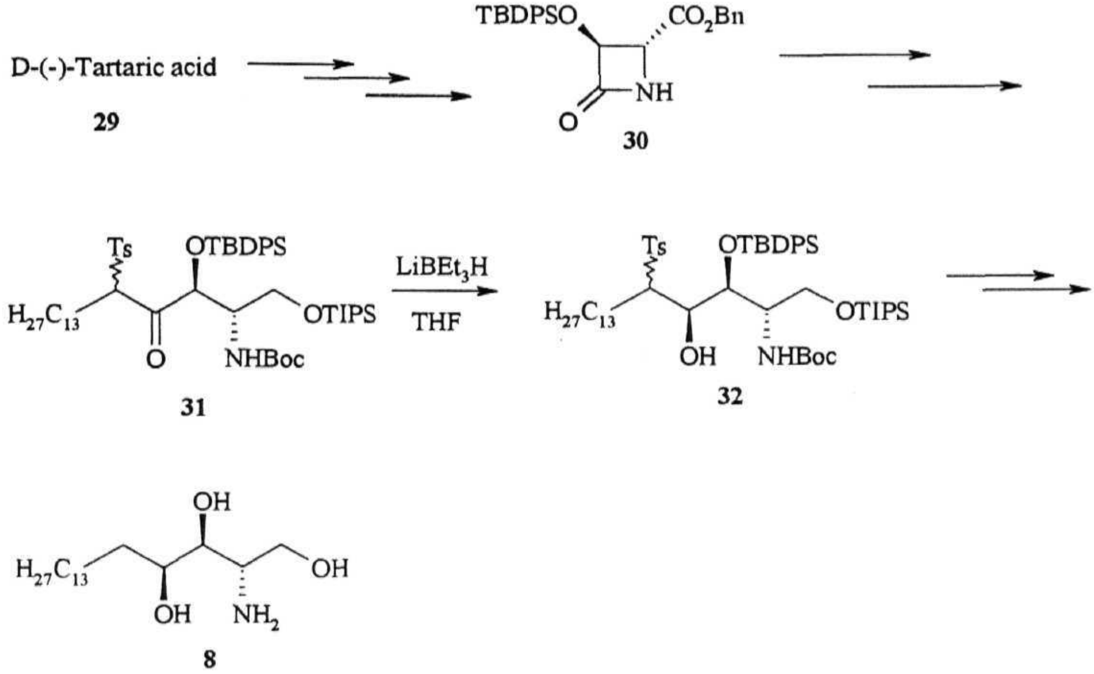


Previous approaches to the synthesis of *xylo*-phytosphingosine and *lyxo*-phytosphingosine.

Nakamura's approach[23]:

Nakamura *et al.,* reported the synthesis of *lyxo*-(2*S*,3*S*,4*S*)-phytosphingosine starting from chiral β-lactam **30** obtained in 9 steps from commercially available D-(-)-tartaric acid **29**. The tetradecyl chain was introduced by reacting with *n*-tetradecyl *p*-toluenesulfone in the presence of *n*-BuLi to afford **31**. The reduction of ketone **31** with lithium triethylborohydride in THF afforded the alcohol **32** as the only product, which was subsequently transformed following a straightforward sequence of reactions into *lyxo*-(2*S*,3*S*,4*S*)-phytosphingosine (Scheme 5).

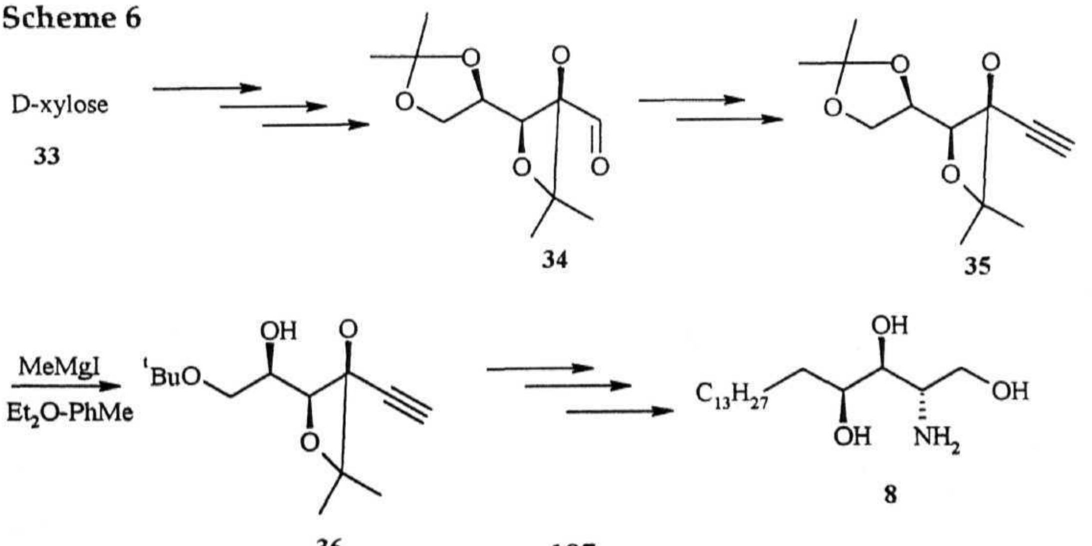
Scheme 5



Wu's approach[24]:

Wu *et al.,* reported the synthesis of *lyxo*-(2*S*,3*S*,4*S*)-phytosphingosine starting from D-xylose **33** in an overall 8% yield. D-Xylose was transformed into the alkyne **35** via diacetonide **34** by treatment with CBr_4-PPh_3-Zn followed by debromination. Regioselective transformation of the terminal acetonide **35** into the *tert*-butyl ether **35** proceeded in moderate yield. Alkyne **36** was subsequently transformed by a sequence of routine reactions into *lyxo*-(2*S*,3*S*,4*S*)-phytosphingosine (Scheme 6).

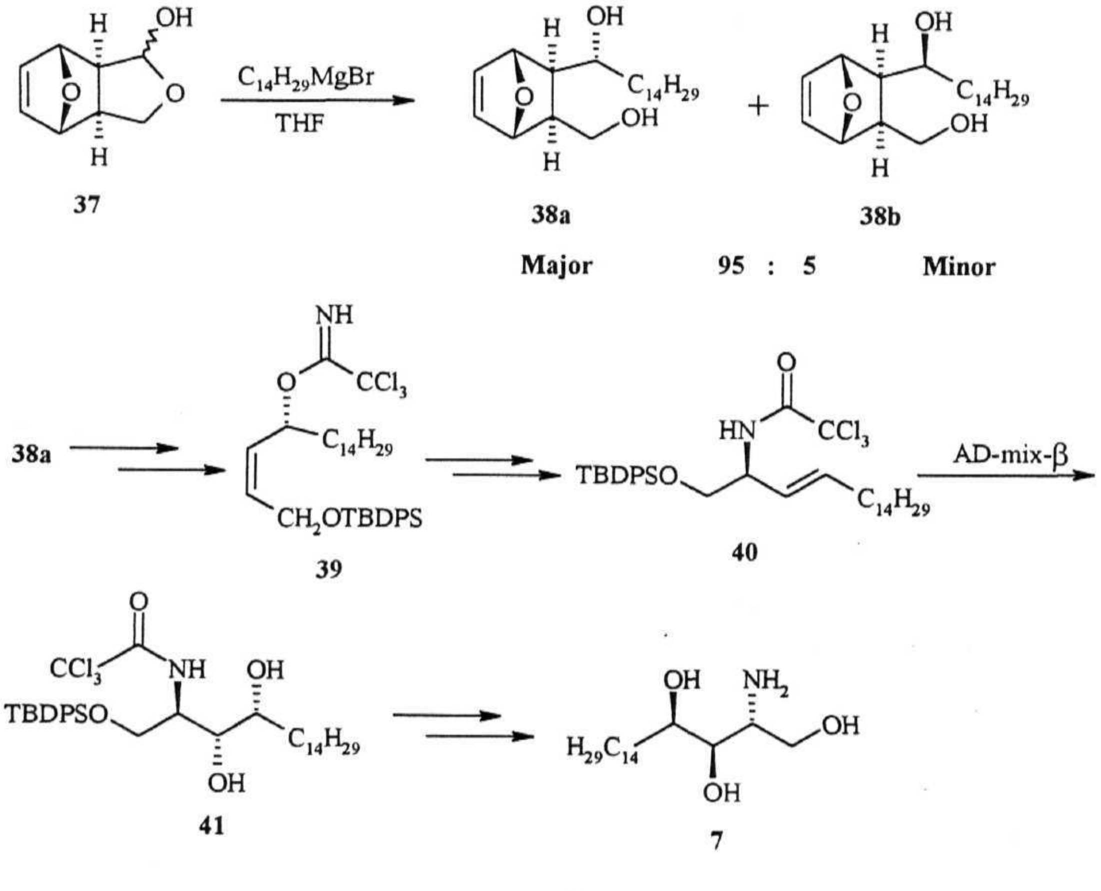
Scheme 6



Bloch's approach[25]:

Bloch *et al.*, reported an enantioselective synthesis of *lyxo*-(2*R*,3*R*,4*R*)-phytosphingosine starting from the chiral lactol **37**. Grignard reaction of **37** with tetradecylmagnesium bromide afforded **38** in 90% de. Protection of the hydroxy group in **38a** as its silyl ether, retro Diels-Alder reaction followed by reaction with trichloroacetonitrile furnished **39**. (*Z*)-Alkene **39** was transformed into (*E*)-allylic trichloroacetamide **40** by Overman rearrangement in 93% ee. *Cis*-dihydroxylation of **40** furnished the diol **41** in 94% de. Trichloroacetamide **41** was further transformed into *lyxo*-(2*R*,3*R*,4*R*)-phytosphingosine (Scheme 7).

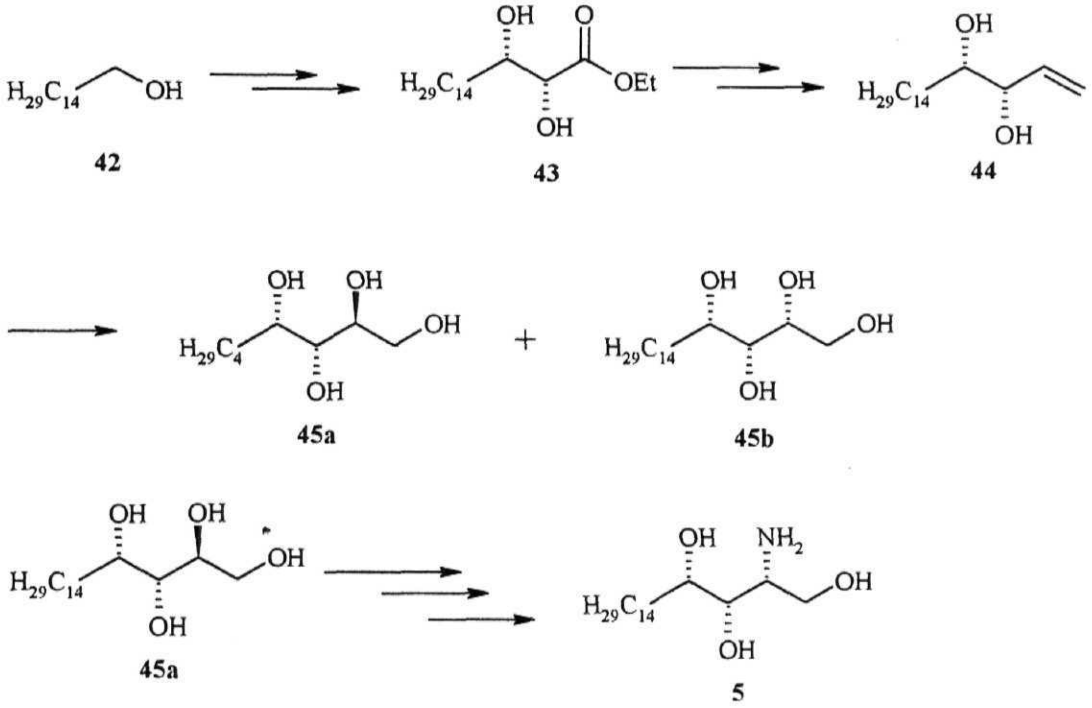
Scheme 7



Pradeep Kumar's approach[26]:

Pradeep Kumar *et al.*, reported the synthesis of *xylo*-(2*R*,3*S*,4*S*)-phytosphingosine starting from pentadecanol in 13 steps. The olefin **44** was obtained from pentadecanol in 7 steps. Double diastereoselective dihydroxylation of enantiomerically enriched terminal olefin **44** using (DHQD)2-PHAL ligand afforded the diastereomeric polyols **45a** and **45b** in 66% de. The major diastereomer **45a** was transformed into *xylo*-(2*R*,3*S*,4*S*)-phytosphingosine (Scheme 8).

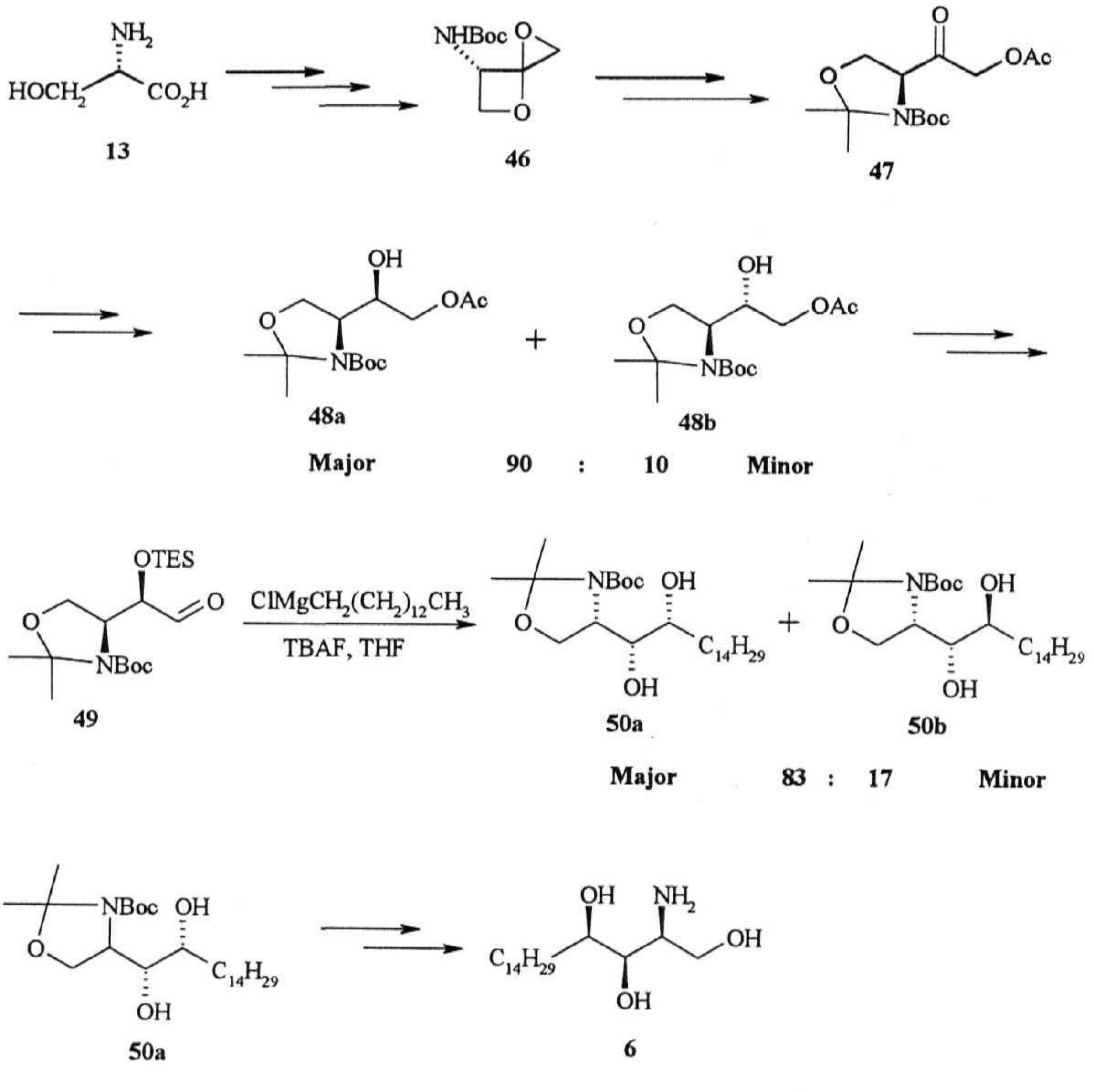
Scheme 8



Howell's approach[27]**:**

Howell *et al.*, reported the synthesis of *xylo*-(2*S*,3*R*,4*R*)-phytosphingosine in 13 steps using serine-derived 1,5-dioxaspiro[3,2]hexane template as the precursor . Dioxaspirohexane **46** was prepared from L-serine **13** in four steps in 33% yield. Stereoselective reduction of the ketoacetonide **47** with $NaBH_4$ afforded the diastereomeric alcohols **48a** and **48b** in 80% de. Protection of the hydroxy group in **48a**, selective deprotection of the acetyl group followed by oxidation of the resulting primary alcohol afforded the aldehyde **49**. Nucleophilic addition of tetradecylmagnesium chloride to **49** followed by deprotection of the silyl ether provided the diols **50a** and **50b** in 66% de (Scheme 9). The major diastereomer **50a** was transformed into the target molecule.

Scheme 9

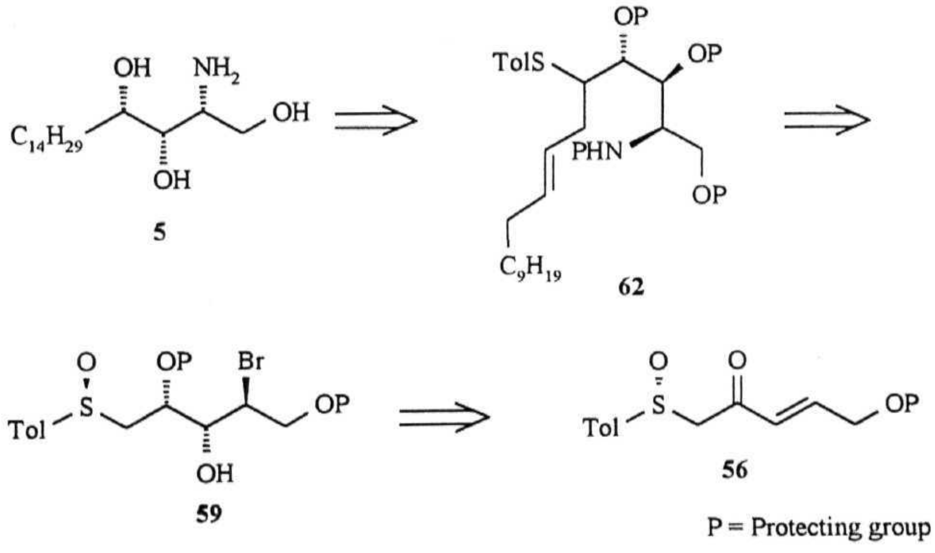

NH₂
HOCH₂
CO₂H
13
NHBoc
46
O
OAc
NBoc
47
OH
48a
Major
90 : 10
48b
Minor
OTES
49
ClMgCH₂(CH₂)₁₂CH₃
TBAF, THF
C₁₄H₂₉
50a
50b
Major
83 : 17
Minor
NH₂
6

Section A: Efficient and stereospecific synthesis of *xylo*-(2*R*,3*S*,4*S*)-phytosphingosine and *threo*-(2*R*,3*R*)-sphingosine

As it is clear from the foregoing discussion sphingolipid constituents have attracted the attention of synthetic chemists and a number of strategies have been devised for their synthesis. Synthetic efforts have primarily focused on the preparation of *arabino*- and *ribo*- phytosphingosines starting from compounds of the chiral pool or by asymmetric induction. In contrast, the *xylo*- and *lyxo*- phytosphingosines have attracted less attention from the synthetic community. Therefore, there is a need for the development of a practical approach to the synthesis of *xylo*- and *lyxo*-phytosphingosines. In this section, the elaboration of *xylo*-(2*R*,3*S*,4*S*)-phytosphingosine and *threo*-(2*R*,3*R*)-sphingosine from a common intermediate is disclosed. The key step in the reaction sequence involves stereo- and regiospecific functionalization of an olefin by intramolecular nucleophilic sulfinyl group participation.

By retrosynthetic analysis (Scheme 10), *xylo*-(2*R*,3*S*,4*S*)-phytosphingosine was envisaged to be synthesized from the sulfide **62**, which in turn can be obtained from bromohydrin **59**. The bromohydrin **59** can be readily elaborated from the β-ketosulfoxide **56**.

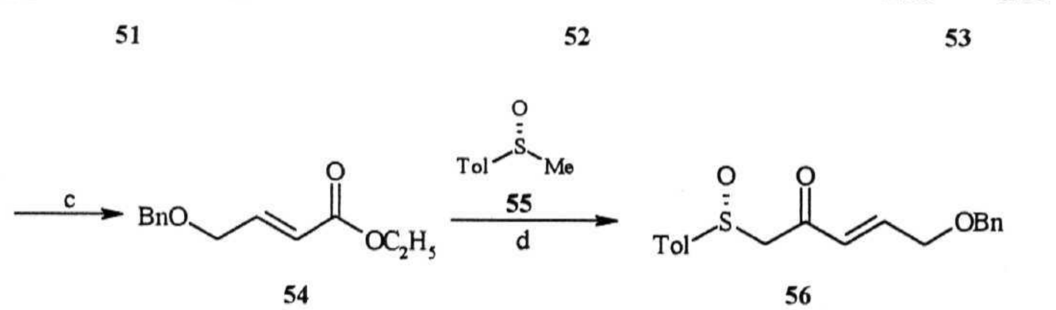
Scheme 10



P = Protecting group

The synthesis commenced with the condensation of the lithium anion derived from (*R*)-(+)-methyl *p*-tolylsulfoxide **55** with the ester **54** following the protocol devised by Solladie *et al.*, to afford the β-ketosulfoxide[28] **56** (Scheme 11). The identity of **56** was confirmed by its PMR spectrum, which showed resonances at δ 6.81 (dt) and 6.38 (dd) for the olefinic protons, and at δ 4.19 (d) and 3.98 (d) for the methylene protons of β-ketosulfoxide group. The ester **54** was readily elaborated from *cis*-but-2-en-1,4-diol **51**. Thus, the diol **51** on treatment with sodium hydride followed by an excess of benzyl bromide afforded the dibenzylated ether **52**. The PMR spectrum of **52** showed resonances at δ 4.51 (s) for the benzylic protons and at δ 5.78 (t) for the olefinic protons. The compound **52** on ozonolysis in dichloromethane at -78 °C followed by treatment with dimethylsulfide afforded the aldehyde **53**, which without purification was used in the next step. Treatment of **53** with ethyl(triphenylphosphoranylidene)acetate in benzene as the solvent at r.t., afforded the *trans* ester **54** as the only product. The PMR spectrum of **54** exhibited resonances at δ 6.94 (dt) and 6.10 (d) corresponding to the olefinic protons with a coupling of 14.6 Hz between the olefinic protons, confirming the (*E*)-geometry.

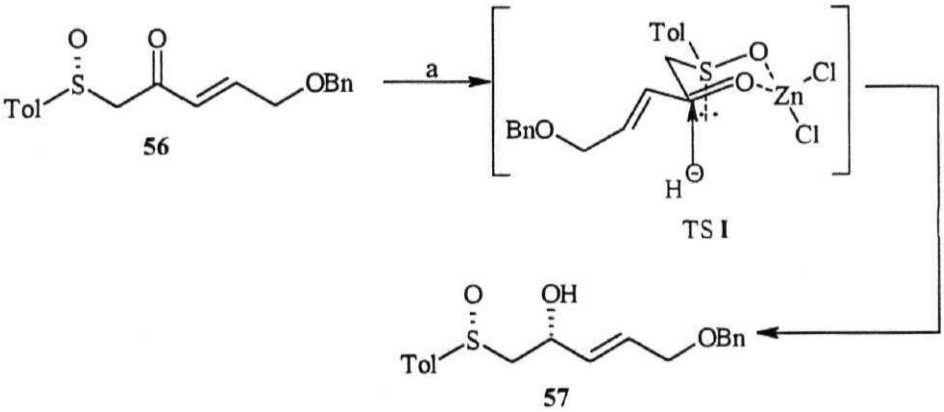
Scheme 11



Reagents and conditions: (a) NaH, *n*-Bu_4NI, 0 °C, 30 min, then BnBr, 0 °C to r.t., 4 h, 88%; (b) O_3, CH_2Cl_2, -78 °C, 30 min then Me_2S, -78 °C - r.t., 8 h; (c) Ph_3PCHCO_2Et, PhH, r.t., 30 min, 82% (for two steps); (d) LDA, THF, -40 °C, 30 min then add **54** at 0 °C, 1 h, 60%.

Diastereoselective reduction[29] of **56** with diisobutylaluminum hydride (DIBAL) in the presence of anhydrous zinc chloride yielded **57** as a single diastereomer, the structure of which, was confirmed by its PMR spectrum which showed resonances at δ 5.87 (dt) and 5.72 (dd) corresponding to the olefinic protons and at δ 4.82-4.69 (m) corresponding to the -C*H*(OH) proton. The methylene protons at C1 appeared as two sets of doublet of doublet at δ 2.94 and 2.76. The β-hydroxysulfoxide **57** had physical characteristics that were in full agreement to that reported in the literature.[29] The high stereoselectivity observed in the reduction using DIBAL/$ZnCl_2$ can be explained by the formation of a chelated intermediate (TS I) formed between the ketosulfoxide and $ZnCl_2$ followed by transfer of hydride ion intermolecularly from the less hindered side of the half chair conformation adopted by the chelated species (Scheme 11).

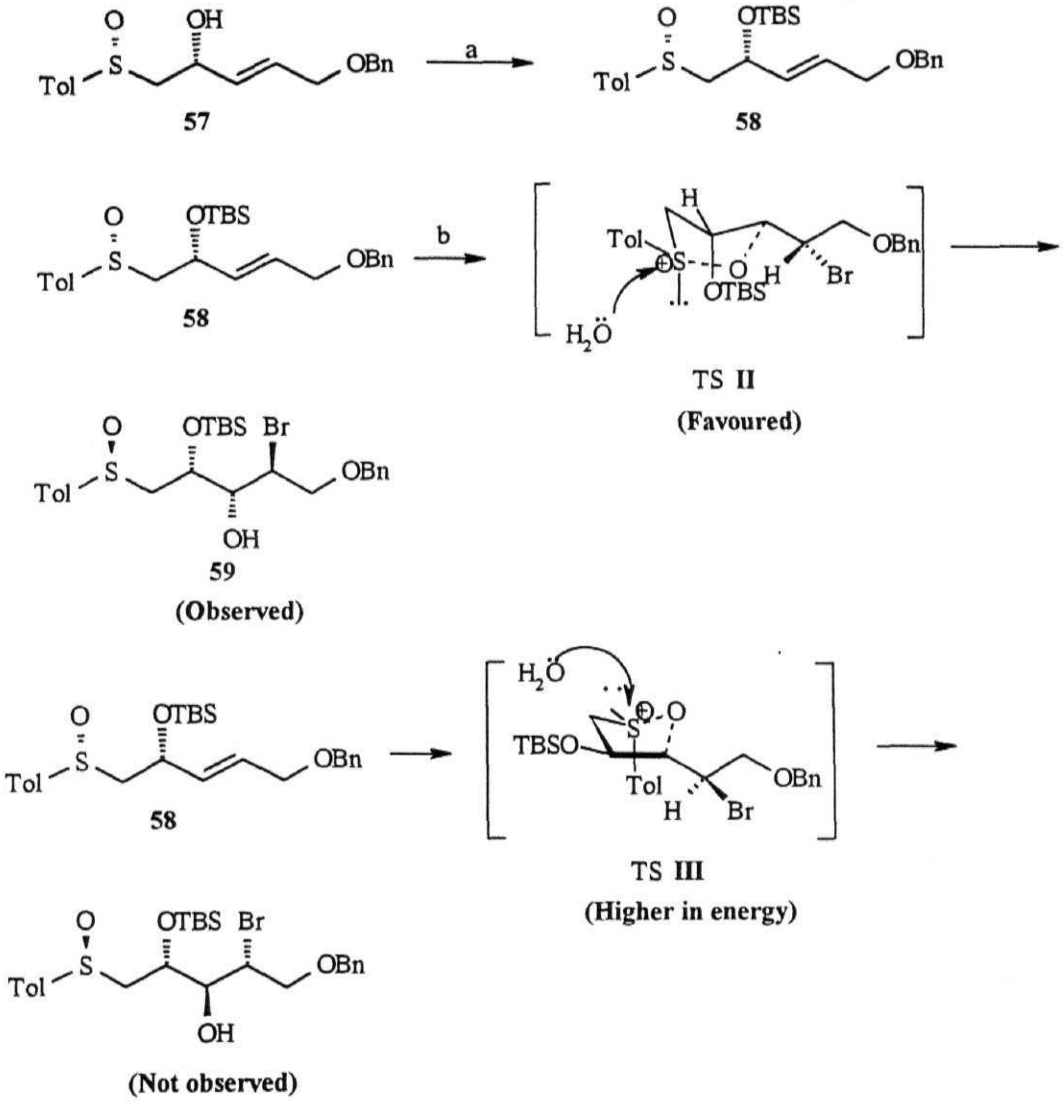
Scheme 11



Reagents and conditions: (a) DIBAL, $ZnCl_2$, THF, -78 °C, 2 h, 91%.

The hydroxy group in **57** was protected as its silyl ether by treatment with *tert*-butyldimethylsilyl chloride in the presence of imidazole in dichloromethane. The PMR spectrum of the silyl ether **58** revealed signals at δ 5.59 (dt) and at δ 5.45 (dd) for the olefinic protons, δ 4.56-4.48 (m) for the C*H*OTBDMS, δ 0.74 (s) for the *tert*-butyl group and two singlets for the methyl groups on silicon at δ 0.0 and δ -0.11. Subjecting silyl ether **58** to treatment with NBS in toluene at ambient temperature afforded bromohydrin **59** regio- and stereospecifically.[30] The structure of **59** was confirmed by its PMR spectrum which revealed a signal at δ 3.92-3.80 (m) integrating for four protons i.e., C3 *H*, C4 *H* and C5 H_2 and the disappearance of olefinic peaks in its PMR spectrum. The observed stereo- and regioselectivity can be rationalized through the intermediacy of the sulfoxonium salt (II) (Scheme 12). The 5-*exo* nucleophilic attack by the sulfinyl group onto the olefin π-complexed to the bromonium ion would result in the formation of the sulfoxonium salt, which upon hydrolysis by attack of water on sulfur in a S_N2 fashion would yield the bromohydrin **59**, with inversion of sulfur configuration. The orientation as indicated for the hydroxy group and bromine at C3 and C4 respectively is expected from an overall *trans* addition of the electrophile and nucleophile across the double bond.[31] It has been reported that the electron withdrawing substituent at the allylic position has a significant stereodirecting effect on electrophilic additions to double bonds.[32] Onium intermediates formed by the addition of electrophiles to the double bonds are generally freely reversible, hence the relative energies of the diastereomeric transition states is important in determining product stereoselectivity.[32f] Having an electron withdrawing allylic substituent in an orthogonal position (axial as in TS II) with respect to the π-system would make TS II lower in energy due to stereoelectronic effects as compared to the TS III in which the allylic substituent is oriented parallel to the π-system although both would afford the same product. An electron withdrawing allylic substituent at the equatorial position (TS III) is better aligned to maximize conjugation of the $\sigma^*_{C\text{-}O}$ orbital with the π-system, which results in the increasing its energy, thereby decreasing the rate of product formation.

Scheme 12

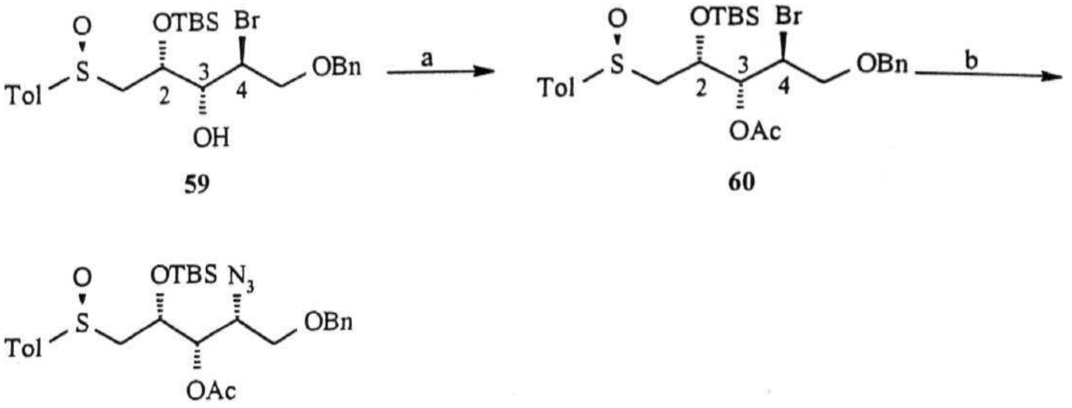


Reagents and conditions: (a) TBS-Cl, imidazole, DCM, rt, 1 h, 97%; (b) NBS, H_2O, toluene, 30 min, 80%.

Submitting the resulting bromohydrin **59** to treatment with acetic anhydride in dichloromethane in the presence of Et_3N and catalytic amounts of DMAP furnished acetate **60**. The structure of acetate was confirmed by its PMR spectrum, which revealed a downfield shift for the C3 *H* from δ 4.56-4.52 (m) to δ 5.42 (dd) and a singlet at δ 1.89 corresponding to $-OCOCH_3$. The C3 methine proton showed a coupling of 8.9 Hz with the C4 methine proton and coupling of 2.9 Hz with the C2 methine proton. The S_N2 displacement of the bromide with azide was achieved by treatment of **60** with excess NaN_3 in DMF (Scheme

13). The structure assigned to the azidoacetate **61** was confirmed by its PMR spectrum, which revealed signals at δ 5.28 (dd) for the C*H*OAc and at δ 3.96-3.88 (m) for the C*H*N$_3$. The presence of azido functionality in **61** was further confirmed by its IR spectrum, which revealed an absorption band at 2103 cm^{-1}.

Scheme 13



59

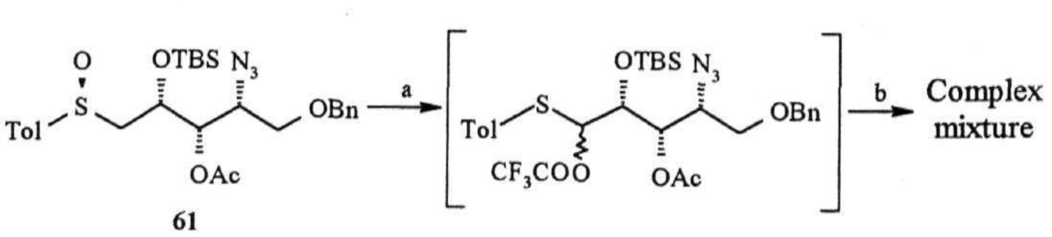
60

61

Reagents and conditions: (a) Ac$_2$O, Et$_3$N, DMAP, r.t., 1 h, 96%; (b) NaN$_3$, DMF, 80 °C, 6 h, 65%.

The elaboration of the alkyl chain onto the azidoacetate **61** was envisaged to be achieved via the Pummerer ene[33] reaction. Thus, compound **61** was subjected to treatment with TFAA to afford the intermediate **62**. Ene reaction on the Pummerer intermediate with 1-tridecene in the presence of SnCl$_4$ afforded a complex mixture of products from which the desired product could not be isolated (Scheme 14).

Scheme 14

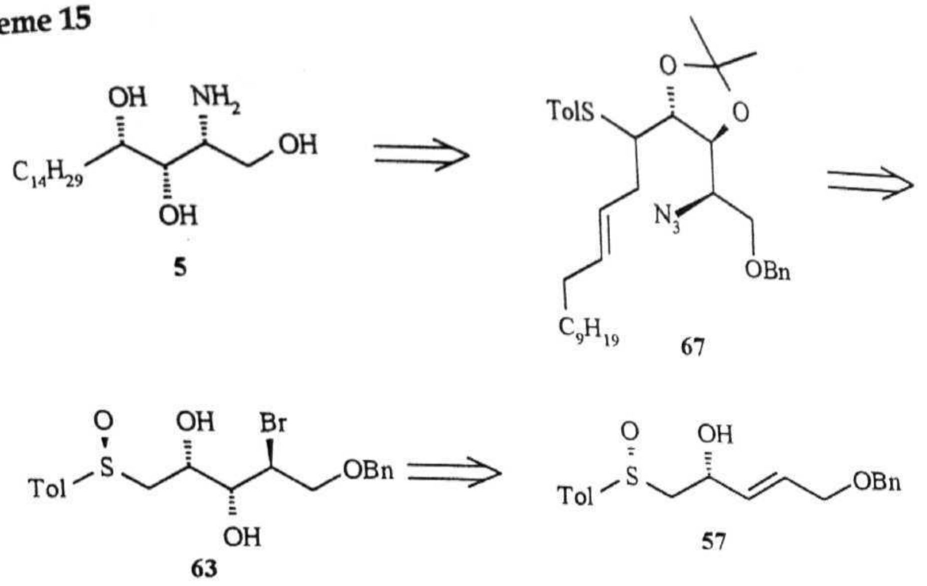


61

Reagents and conditions: (a) TFAA, DCM, 0 °C, 50 min; (b) C$_{13}$H$_{26}$, SnCl$_4$, 0 °C, 5 min.

In the next approach, the acetonide **67** derived from the bromohydrin **63**, was envisaged as the substrate for attempting the Pummerer ene reaction. Retrosynthesis (Scheme 15) is depicted below.

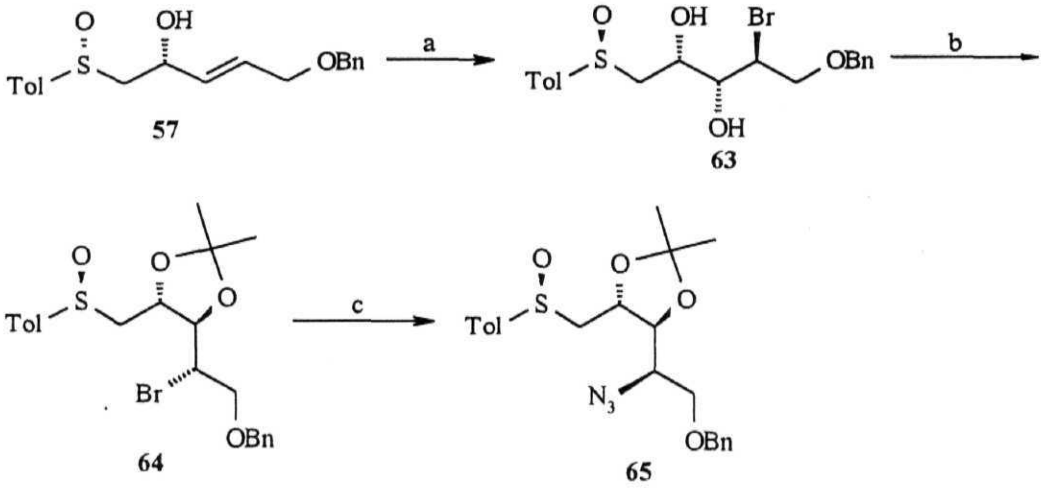
Scheme 15



Subjecting the allylalcohol **57** to treatment with NBS in toluene at ambient temperature in the presence of water, afforded bromohydrin **63** regio- and stereospecifically. The structure of **63** was confirmed by its PMR spectrum which revealed a double doublet at δ 3.98 corresponding to the -C*H*(OH) at C3, a doublet of triplet (dt) at δ 3.61 corresponding to the -C*H*(Br) and the disappearance of signals for the olefinic protons in its PMR spectrum. The bromodiol **63** was transformed into the acetonide **64**, by reaction with 2,2-dimethoxypropane catalyzed by CSA, which showed a singlet at δ 1.40 in the PMR spectrum corresponding to the *gem*-dimethyl group. The ^{13}C spectrum of **64** revealed signals for the methyl groups of the acetonide at δ 27.0, 27.4 and for the quaternary ketal carbon at δ 110.5 proving beyond doubt the *syn* disposition[34] of the hydroxy groups in **63**. The acetonide **64** was then converted into the azido acetonide **65** by treatment with excess sodium azide in DMSO (Scheme 16). The structure of **65** was confirmed by its PMR spectrum which showed a resonance at δ 3.74-3.61 (m) corresponding to the -C*H*(N_3) proton. The IR spectrum showed a strong absorption band at 2100 cm^{-1} corresponding to N-

N stretching of the azido group. The azido acetonide **65** has all the three stereogenic centers disposed as in target molecule, both in a relative and an absolute sense.

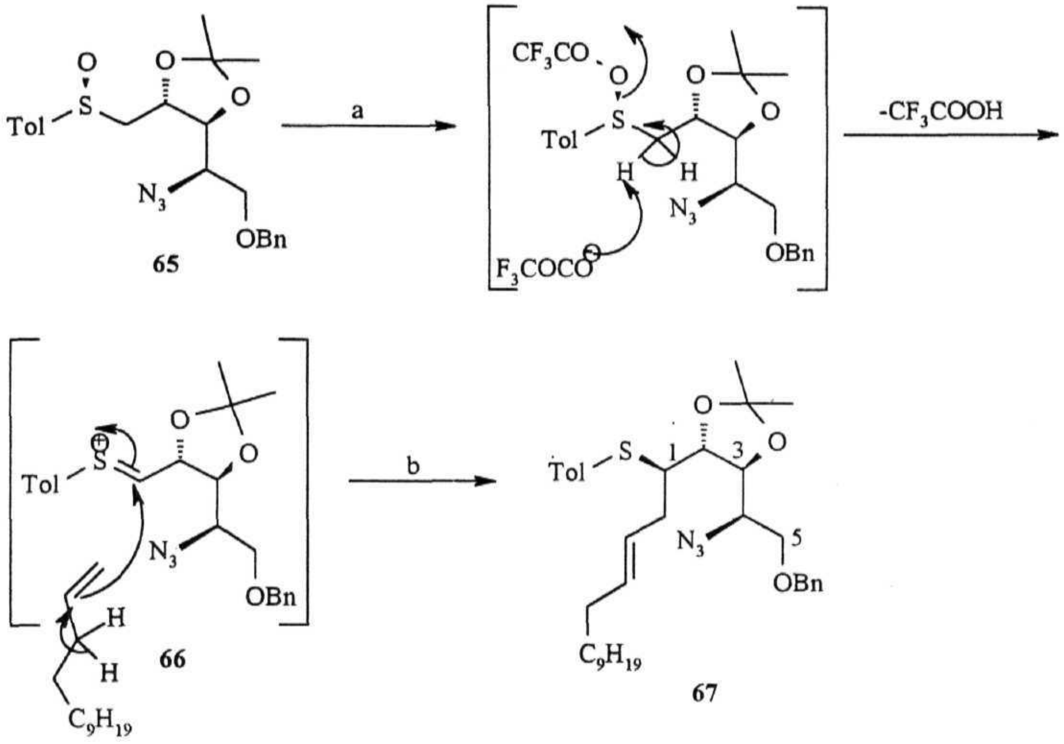
Scheme 16



Reagents and conditions: (a) NBS, H_2O, toluene, r.t., 15 min, 88%; (b) 2,2-DMP, CSA, acetone, r.t., 2 h, 86%; (c) NaN_3, DMSO, 85 °C, 8 h, 75%.

The next step in the proposed synthetic sequence was to introduce C_{13} hydrocarbon chain. This was achieved by the Pummerer ene reaction on **65**. Thus, azidoacetonide **65** was treated with TFAA in dichloromethane to afford the intermediate **66**, which was reacted in the same vessel with 1-tridecene and $SnCl_4$ to yield the sulfide **67** as the sole product (Scheme 17). The PMR and ^{13}C NMR spectrum of **67** revealed the presence of only one isomer although four isomers are theoretically expected; two that differ due to the configuration at the newly created stereogenic center and two geometrical isomers. The structure of the sulfide was not rigorously established since the tolylthio group on the newly created center had to be removed eventually. The structure assigned to the sulfide was discerned with the aid of its PMR spectrum, which showed resonance at δ 6.95 (d) for the protons *ortho* to the sulfanyl group, δ 5.50-5.20 (m) integrating for two olefinc protons, δ 2.90 (td) for the C*H*STol and the presence of aliphatic chain. The ^{13}C spectrum of **67** showed resonances at δ 126.4 and 132.4 for the olefinic carbons and an upfield shift for the C 1 carbon from δ 141.7 to δ 137.0.

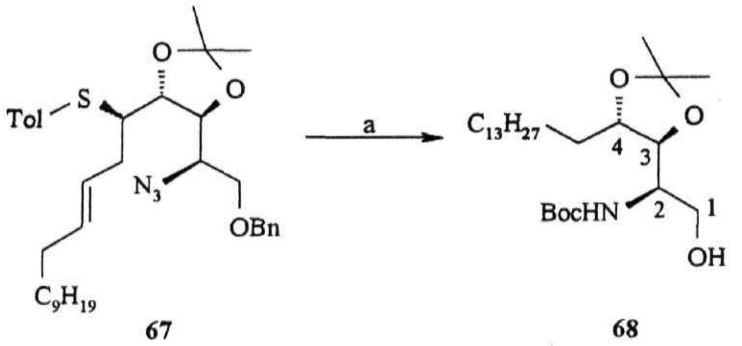
Scheme 17



Reagents and conditions: (a) TFAA, DCM, 0 °C, 1 h; (b) $C_{13}H_{26}$, $SnCl_4$, 0 °C, 65% for the two steps.

Five transformations were effected in a one-pot operation, by treatment of the sulfide **67** with Ra-Ni in methanol in the presence of di-*tert*-butyl dicarbonate under an atmosphere of hydrogen to yield the acetonide **68** (Scheme 18). The azido group was reduced and transformed into a urethane, the double bond reduced and the toluenethio group and the benzyl ether was hydrogenolysed under the reaction conditions. The structure assigned to urethane **68** was confirmed by its PMR spectrum, which revealed signals at δ 5.04 (d) for N*H* proton, δ 3.82-3.55 (m) integrating for five protons i.e., methylene protons on C1 carbon, C2 *H*, C3 *H* and C4 *H*. The signals corresponding to the *tert*-butyl group and aliphatic chain were also observed.

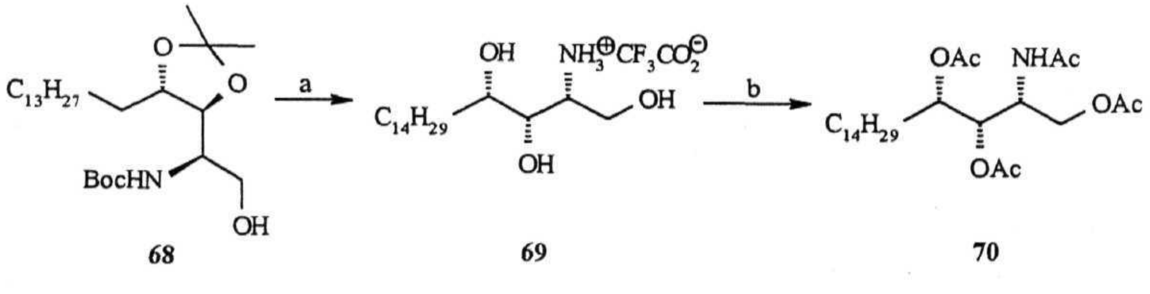
Scheme 18



Reagents and conditions: (a) Ra-Ni, $(Boc)_2O$, H_2, MeOH, r.t. to reflux, 68%.

The acetonide hydrolysis and removal of *tert*-butoxycarbonyl group on nitrogen was effected by treatment of the urethane **68** with trifluoroacetic acid and water to afford ammonium salt **69**, which was subsequently acetylated by treatment with acetic anhydride in the presence of pyridine and catalytic amount of DMAP[35] to afford the tetraacetate **70** (Scheme 19) which had physical characteristics similar[18b] (except for the sign of rotation) to that reported in the literature.

Scheme 19

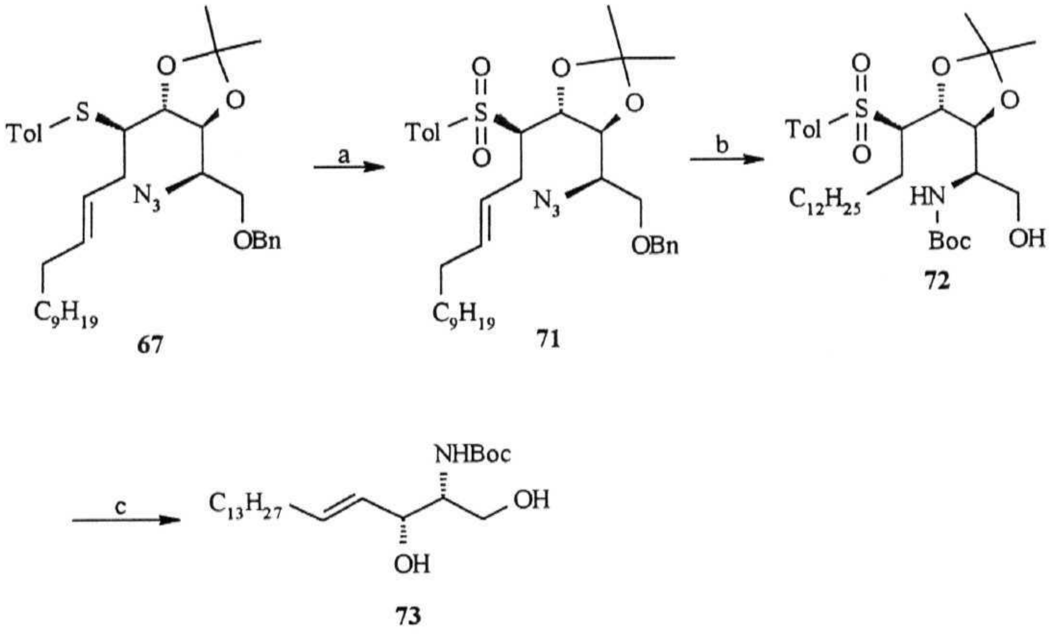


Reagents and conditions: (a) TFA:H_2O, 0 °C, 3 h; (b) Ac_2O, DMAP (cat.), pyridine, r.t., 16 h, 78%.

Synthesis of *threo*-(2*R*,3*R*)-sphingosine

The Pummerer ene product **67** served as the key intermediate for the synthesis of *threo*-sphingosine. Thus, the sulfide **67**, on treatment with oxone[36] in a solvent mixture of THF, MeOH and water afforded the sulfone **71**, which showed a downfield resonance for the protons *ortho* to sulfonyl moiety from δ 6.95 to δ 7.74 (d) and a down field shift for the -C*H*S from δ 2.90 to δ 3.28 in its PMR spectrum confirming the structure assigned to it. One-pot four-step transformation of sulfone **71** to the urethane **72** was effected in ethanol with $Pd(OH)_2$ in the presence of di-*tert*-butyl dicarbonate under an atmosphere of H_2. The absence of olefinic protons, benzyl ether protons and the presence of *tert*-butyl group in its PMR spectrum confirmed the structure. Finally, submission of urethane **72** to treatment with Na-Hg in the presence of Na_2HPO_4 in methanol[37] afforded the sphingosine derivative **73** (Scheme 20), which possessed physical characteristics similar to that reported in the literature.[38]

Scheme 20



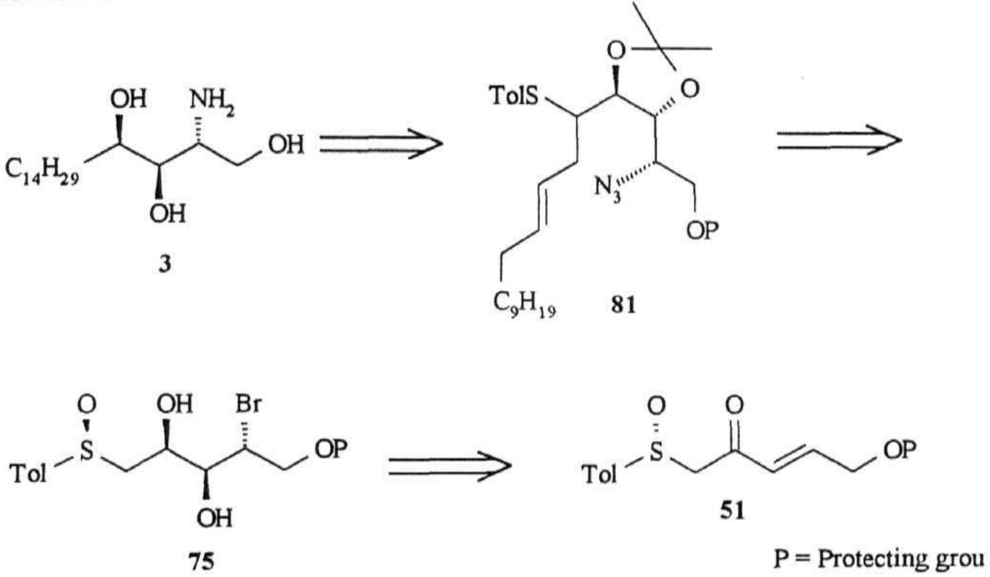
Reagents and conditions: (a) $2KHSO_5.KHSO_4.K_2SO_4$, $MeOH:H_2O:THF$, 0 °C to r.t., 4 h, 82%; (b) $Pd(OH)_2/C$, $(Boc)_2O$, H_2 (1 atm.), EtOH, r.t., 16 h, 71%; (c) Na-Hg, Na_2HPO_4, MeOH, −20 °C-r.t., 2 h, 65%.

In conclusion, a flexible (use of different olefins in the Pummerer ene reaction would permit the introduction of variable carbon chains), stereospecific synthesis of *xylo*-(2*R*,3*S*,4*S*)-C_{18}-phytosphingosine and *threo*-(2*R*,3*R*)-C_{18}-sphingosine is disclosed. The key step of the synthesis are i) asymmetric induction from sulfur to C_2 in the transformation of **56** to **57**, ii) asymmetric induction from C_2 to C_3 and C_4 in the transformation of **57** to **63**, iii) ene reaction for the introduction of the hydrocarbon chain, iv) one pot multi step transformation of **67** to **68** and **71** to **72**. It is pertinent to mention that starting from the C_2 diastereomer of alcohol (6), the *xylo*-(2*S*,3*R*,4*R*)-phytosphingosine and *threo*-(2*S*,3*S*)-sphingosine can be synthesized, essentially following an identical reaction sequence.

Section B: Stereospecific synthesis of *lyxo*-(2*R*,3*R*,4*R*)-phytosphingosine and *erythro*-(2*R*,3*S*)-sphingosine.

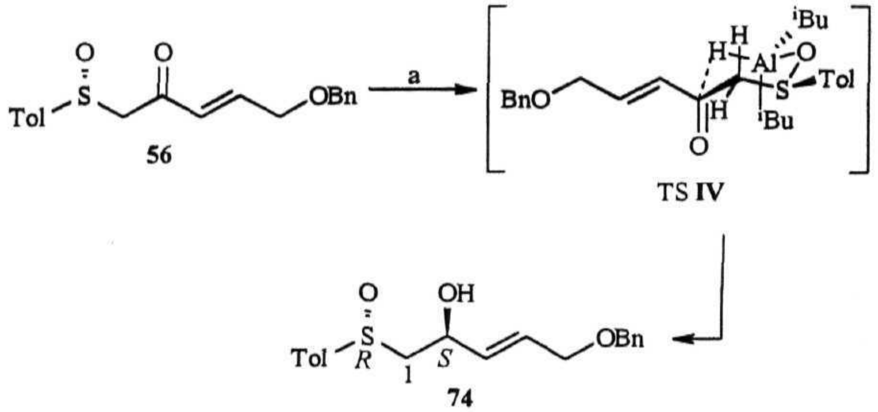
A strategy similar to that detailed for the synthesis of *xylo*-(2*R*,3*S*,4*S*)-C_{18}-phytosphingosine and *threo*-(2*R*,3*R*)-C_{18}-sphingosine was envisaged for the synthesis of the *lyxo*-(2*R*,3*R*,4*R*)-phytosphingosine derivative (Scheme 21, retrosynthetic analysis). *lyxo*-(2*R*,3*R*,4*R*)-Phytosphingosine was envisaged to be synthesized from sulfide **81**, which in turn can be obtained from bromohydrin **75**. The bromohydrin can be readily elaborated from the β-ketosulfoxide **51**.

Scheme 21



The diastereoselective reduction of **56** using diisobutylaluminum hydride[29] (DIBAL) yielded **74** as a single product. The structure of **74** was confirmed by its PMR spectrum which showed resonanaces at δ 5.87 (dt) and 5.70 (dd) corresponding to the olefinic protons and at δ 4.75-4.63 (m) corresponding to the *C*H(OH). The methylene protons at C 1 appeared as two sets of doublet of doublet at δ 3.0 and at 2.68. The high stereoselectivity observed in the reduction can be explained on the basis of the Lewis acidic character of DIBAL, which is able to complex with the Lewis basic sulfinyl oxygen. Intramolecular hydride transfer via stable chair like transition state (TS IV) adopted by the chelated species would yield alcohol **74** (Scheme 22).

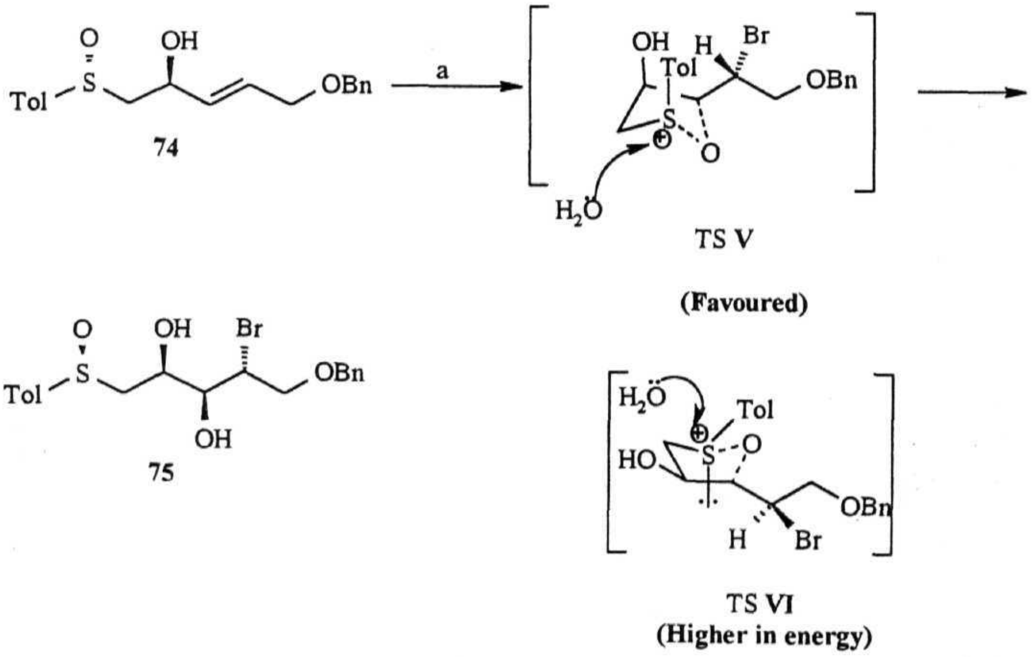
Scheme 22



Reagents and conditions: (a) DIBAL, THF, -78 °C, 15 min, 92%.

Treatment of **74** with *N*-bromosuccinimide in toluene in the presence of water afforded bromohydrin **75** regio- and stereospecifically.[30] The structure of **75** was confirmed by its PMR spectrum, which revealed signals at δ 4.23-4.17 (m) for the C 3 methine proton, δ 4.01-3.81 (m) for the C 5 methylene protons and the C 4 methine proton. The signals due to the olefinic protons were characteristically absent. The observed regio- and stereoselectivity of the reaction can be explained by the intermediacy of the sulfoxonium salt (Scheme 23).

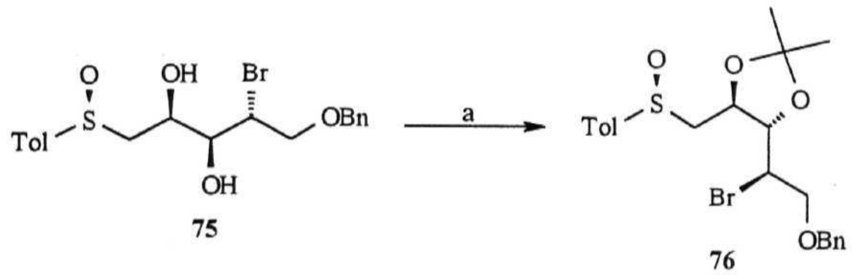
Scheme 23



Reagents and conditions: (a) NBS, H_2O, toluene, 30 min, 88%.

To confirm the relative stereochemistry of the hydroxy groups on the adjacent carbons, the bromodiol **75** was transformed into the acetonide **76** by reaction with 2,2-dimethoxypropane catalyzed by camphor-10-sulfonic acid. The ^{13}C NMR spectrum of compound **76** revealed signal at δ 27.2 and 27.5 for the methyl groups of the acetonide and at δ 110.5 for the ketal carbon proving unequivocally the *syn* disposition of the hydroxy group in **75** (Scheme 24).[34]

Scheme 24

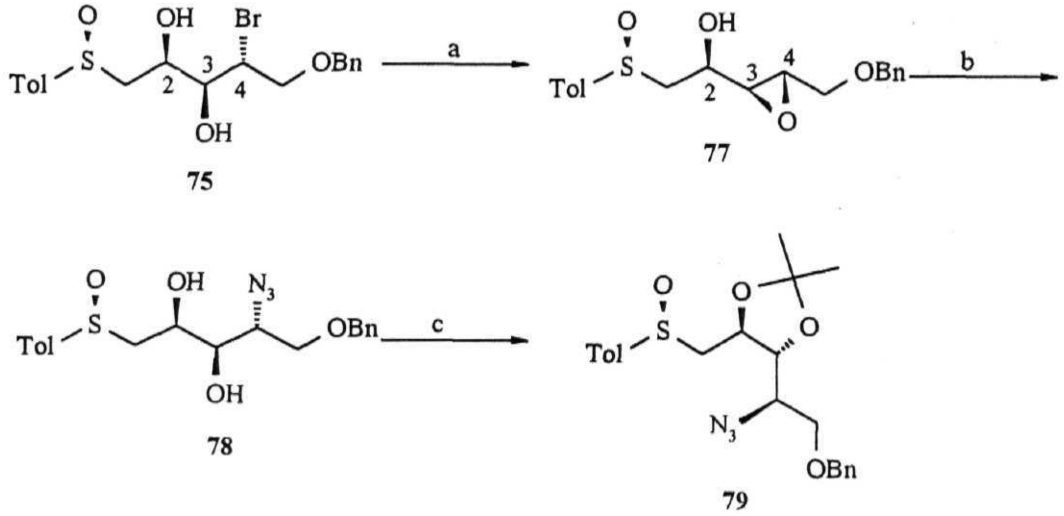


Reagents and conditions: (a) 2,2-DMP, CSA, acetone, r.t., 1 h, 86%.

The next objective was to introduce the amino functionality onto bromodiol **75** with retention of relative stereochemistry. This was achieved by a two-step transformation. Thus, the bromohydrin **75** was converted into the epoxide **77** by treatment with K_2CO_3 in methanol. The structure of the compound **77** was confirmed by the presence of the signals at δ 3.24-3.18 (m) and 3.08 (dd) corresponding to C4 *H* and C3 *H* respectively in its PMR spectrum and signals at δ 54.4 and 57.3 in the ^{13}C spectrum corresponding to C4 and C3 carbon. FAB (HRMS) further supported the structural assignment. The epoxide **77** was regio- and stereoselectively transformed into the azidodiol **78** employing the Sharpless protocol.[39] Thus, compound **77** was treated with excess NaN_3, NH_4Cl in $MeOH/H_2O$ to yield **78**. The structure of **78** was confirmed by the presence of signals at δ 60.1 and 70.5 corresponding to C-4 and C-3 carbons in its ^{13}C spectrum. The IR spectrum showed an absorption band at 2107 cm^{-1} corresponding to the N-N stretching indicating the presence of azide group. Treatment of **78** with 2,2-dimethoxypropane in the presence of catalytic amounts of CSA afforded the acetonide **79**, which showed resonances at δ 1.43

(s) and 1.37 (s) corresponding to the gem-dimethyl groups in the PMR spectrum. The ^{13}C spectrum of the compound showed resonances at δ 26.7 and 26.9 corresponding to the *gem*-dimethyl groups and at δ 110.3 corresponding to the ketal carbon thereby proving unambiguously the *syn* disposition of the two hydroxy groups on the adjacent carbons in **78** (Scheme 25). The epoxide opening by azide nucleophile was therefore regiospecific since the ^{13}C spectrum did not reveal any signals for anti 1,3-acetonide that would be expected from the azide attack at C3.

Scheme 25

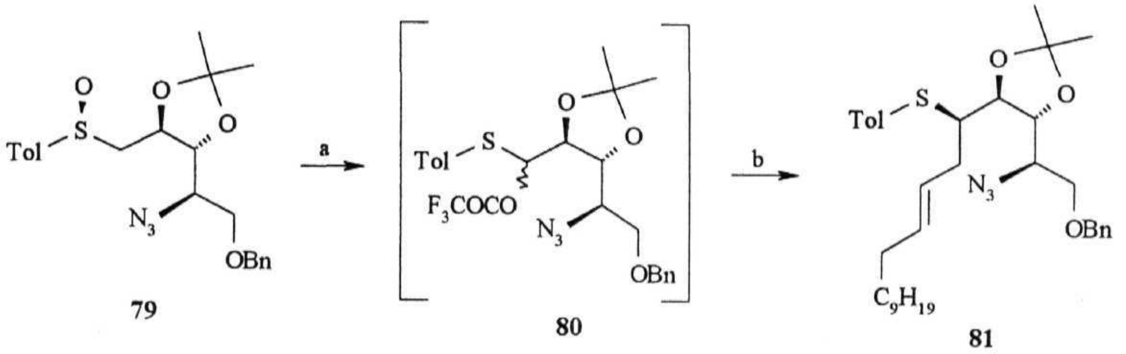


Reagents and conditions: a) K_2CO_3, methanol, r.t., 1 h, 83%; b) NaN_3, NH_4Cl, MeOH: H_2O, reflux, 6 h, 85%; c) 2,2-DMP, CSA (cat.), r.t., 1 h, 87%.

The next step called for the introduction of the aliphatic chain onto the acetonide **79**. This was achieved by the Pummerer ene reaction.[33] Thus, treatment of the acetonide **79** with TFAA in DCM afforded the intermediate **80**, which without isolation was reacted in the same pot with 1-tridecene and $SnCl_4$ to yield the sulfide **81**. The PMR spectrum of the sulfide showed signals at δ 7.02 (d) corresponding to the aromatic protons *ortho* to sulfanyl group, δ 5.47 (dt) and 5.32 (dt) for the olefinic protons, δ 3.14 (m) for *CH*(STol) and the signals for the protons corresponding to the aliphatic chain were also evident. The ^{13}C

NMR spectrum showed peaks at δ 126.6 and 134.0 for the olefinic carbons (Scheme 26).

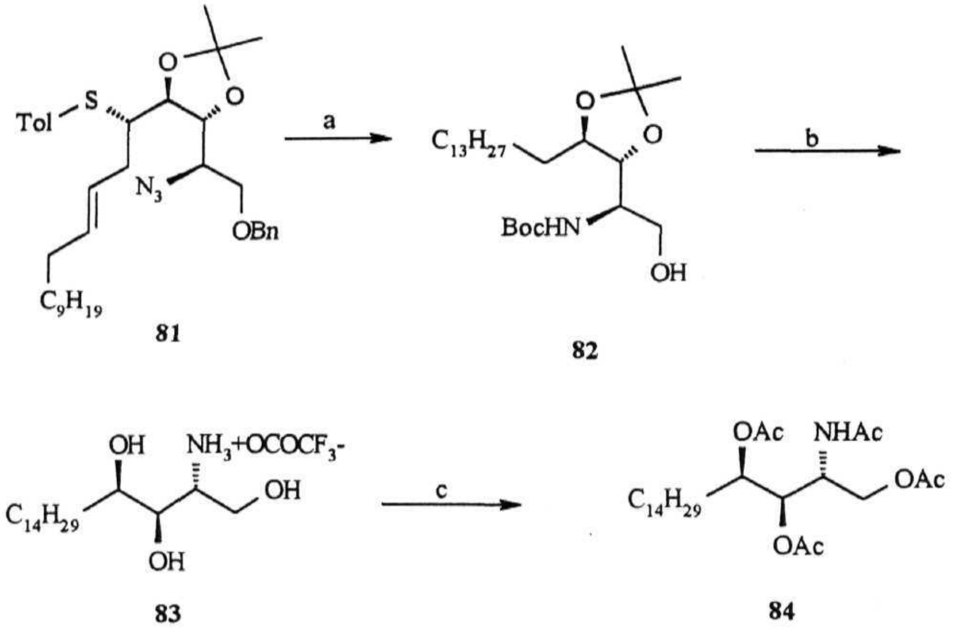
Scheme 26



Reagents and conditions: a) TFAA, DCM, 0 °C; b) $C_{13}H_{26}$, $SnCl_4$, 0 °C, 76% for the two steps.

Treatment of the sulfide **81** with Ra-Ni in methanol in the presence of di-*tert*-butyl dicarbonate under an atmosphere of hydrogen afforded the aminoalcohol **82** in a one-pot five-step transformation. The absence of the olefinic protons, protons corresponding to the benzyl ether and the toluenethio group protons and the presence of the signal at δ 5.05 (d) corresponding to N*H* proton and additional proton count in the aliphatic region (δ 1.51-1.01) corresponding to the *tert*-butoxy group in the PMR spectrum of the compound **82** confirmed the structure assigned to it. Finally, deprotection of the acetonide and the *tert*-butoxycarbonyl group on nitrogen by treatment with a mixture of trifluoroacetic acid and water afforded the ammonium salt **83** which was subsequently converted into the tetraacetate **84** by treatment with acetic anhydride in the presence of pyridine and catalytic amounts of DMAP (Scheme 27). The physical characteristics of **84** such as PMR, ^{13}C NMR, mass and optical rotation (enantiomer) were in full agreement with that reported in the literature.[14b]

Scheme 27

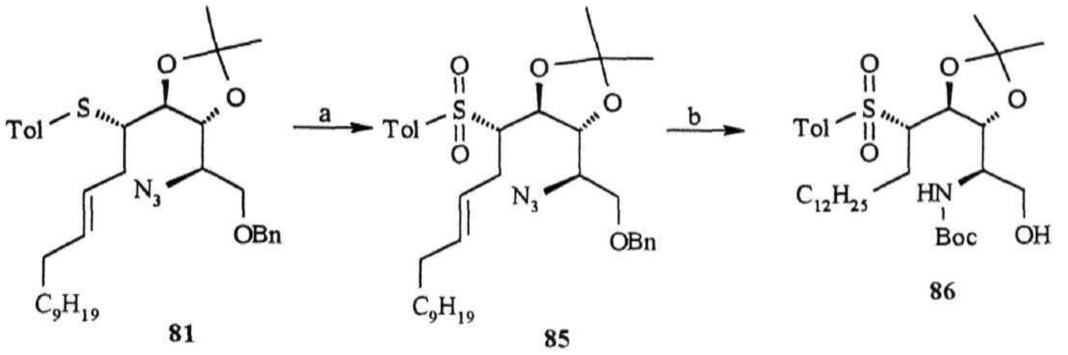


Reagents and conditions: a) Ra-Ni, H_2, $(Boc)_2O$, methanol, r.t. to reflux, 75%; b) TFA:H_2O; c) Ac_2O, DMAP (cat.), pyridine, r.t., 70% for the two steps.

Synthesis of *erythro*-(2*R*,3*S*)-C_{18}-sphingosine

Sulfide **81** was elaborated to *threo*-sphingosine in a straightforward reaction sequence depicted in Scheme 28. Thus, oxidation of the sulfanyl moiety in **81** with Oxone[35] in a mixture of THF: MeOH: H_2O solvent afforded the sulfone **85**. The PMR spectrum of sulfone showed resonances at δ 7.76 (d) for the protons *ortho* to sulfonyl moiety, δ 3.42-3.34 (m) for $C\mathit{H}SO_2$ indicating a downfield shift. All the remaining proton resonances were consistent with the assigned structure. The sulfone **85** was transformed in a one-pot four-step operation into the aminoalcohol **86** by reaction with $Pd(OH)_2/C$ in the presence of $(Boc)_2O$ under an atmosphere of H_2 in ethanol (Scheme 28). The PMR spectrum of urethane revealed signals at δ 7.78 (d) for the protons *ortho* to sulfonyl moiety, δ 7.31 (d) for the protons *meta* to sulfonyl moiety. The signals corresponding to olefinic protons and benzyl ether were characteristically absent.

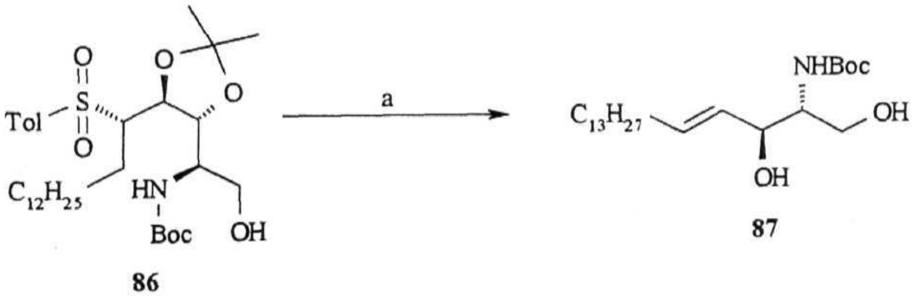
Scheme 28



Reagents and conditions:(a) 2KHSO$_5$.KHSO$_4$.K$_2$SO$_4$, MeOH: H$_2$O: THF, 0 °C to r.t., 82%; (b) Pd(OH)$_2$/C, (Boc)$_2$O, H$_2$ (1 atm.), EtOH, r.t., 71%.

Treatment of sulfone **86** with Na-Hg,[37] buffered with sodiumdihydrogen phosphate in methanol, afforded the sphingosine derivative **87** with concomitant loss of acetone (Scheme 29). Compound **87** had physical characteristics such as PMR and ^{13}C in excellent agreement to that reported in the literature except for the sign of rotation.[38]

Scheme 29



Reagents and conditions: (a) Na-Hg, Na$_2$HPO$_4$, MeOH, −20 °C- r.t., 60%.

In conclusion, an efficient, flexible, atom economical and stereospecific synthesis of *lyxo*-phytosphingosine and *erythro*-sphingosine is described in this section. The key steps include stereoselective bromohydrin formation using the sulfinyl moiety as an intramolecular nucleophile, stereo- and regioselective opening of epoxide, chain extension by Pummerer ene reaction, one pot atom economical five/four step transformations. It is worthwhile to note that starting from the C$_2$ diastereomer of the alcohol (2), the *lyxo*-(2*S*,3*S*,4*S*)-phytosphingosine and *erythro*-(2*S*,3*R*)-sphingosine can be synthesized following an identical reaction sequence as detailed above. Also the strategy is flexible and would permit the synthesis of sphingolipids with different chain lengths (C_{16}/C_{20}) by using olefins of different chain lengths (C_{11}/C_{15}).

EXPERIMENTAL

1,4-Di(benzyloxy)-(Z)-2-butene, 52.

To the suspension of sodium hydride (60% dispersion in nujol, 1 g, 31.5 mmol) in anhydrous THF (15 mL) at 0 °C was added *n*-Bu_4NI (297 mg, 10 mol%, 1.5 mmol) followed by the addition of *cis*-2-butene-1,4-diol (1.32 g, 15 mmol) in THF (15 mL) and stirred at the same temperature for 30 min. This was followed by the dropwise addition of neat benzyl bromide (3.75 mL, 31.5 mmol) over a period of 10 min at 0 °C. The reaction mixture was stirred at r.t., for 4 h and then quenched using saturated aq. NH_4Cl solution (20 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (4 x 35 mL). The combined organic layers were successively washed with water, brine and dried over Na_2SO_4. Evaporation of the solvent afforded the crude product, which was purified by column chromatography using AcOEt/petroleum ether (1:1, v/v) as the eluent to yield dibenzyl ether **47** (3.55 g, 13.2 mmol) in 88% yield.

Viscous oil.

PMR ($CDCl_3$, 200 MHz) : δ 7.38-7.20 (m, 10H), 5.78 (t, *J* = 4.6 Hz, 2H), 4.51 (s, 4H), 3.98 (d, *J* = 4.6 Hz, 4H).

m/z (LSIMS) : 270 $[M+H]^+$

Ethyl-4-benzyloxy-(*E*)-2-butenoate, 54.

Ozone gas was bubbled into the solution of the dibenzylether **52** (2.9 g, 10 mmol) in DCM (20 mL) cooled at –78 °C until the reaction mixture showed a pale blue coloration. Dimethyl sulfide (1.20 g, 20 mmol) was added to the reaction mixture at the same temperature and stirred for 30 min. The reaction mixture was then brought to r.t., and stirred further for a period of 8 h. The reaction mixture was washed with water and the solvent was evaporated to afford the aldehyde **53**, which was taken ahead without further purification. Thus, the aldehyde **53** was taken into benzene (60 mL) and treated with ethyl(triphenylphosphoranylidene)acetate (7.64 g, 20 mmol) and stirred at r.t. for 30 min. The solvent was evaporated and diethylether (100 mL) was added and the reaction mixture was cooled to 0 °C. The precipitated $Ph_3P(O)$ was filtered and the filtrate was evaporated to dryness. The residue on column chromatography using AcOEt/petroleum ether (1:9, v/v) afforded the ester **54** (3.38 g, 16.4 mmol) in 82% (for two steps) yield.

Viscous oil.

PMR ($CDCl_3$, 200 MHz)	:	δ 7.38-7.28 (m, 5H), 6.94 (dt, J = 14.6, 4.3 Hz, 1H), 6.10 (d, J = 14.6 Hz, 1H), 4.55 (s, 2H), 4.25-4.12 (m, 4H), 1.30 (t, J = 6.7 Hz, 3H).
m/z (LSIMS)	:	221 $[M+H]^+$

5-Benzyloxy-(1*R*s)-(4-methylphenylsulfinyl)-(*E*)-3-penten-2-one, 56.

A 1.38 M solution of *n*-BuLi in hexane (11.7 mL, 16.2 mmol) was added to a solution of diisopropylamine (2.37 mL, 16.9 mmol) in dry THF (42 mL) at 0 °C. After 15 min the resulting lithium diisopropylanide solution was cooled to –40 °C and the solution of (*R*)-(+)-methyl *p*-tolylsulfoxide **55** (1.20 g, 7.8 mmol) in 10 mL of dry THF was added dropwise and stirred at the same temperature for 30 min. Then the temperature was allowed to reach 0 °C and the ester **54** (1.59 g, 7.7 mmol) in THF (8 mL) added dropwise. The reaction was stirred further for a period of 1 h at 0 °C. The reaction was quenched by the addition of an aq.

saturated NH_4Cl solution (50 mL) and then the solution adjusted to pH 2 by the addition of 5% aq. H_2SO_4 solution. The two layers were separated and the aqueous phase extracted with ether (2 x 20 mL). The combined organic layer was washed successively with water, brine and dried over Na_2SO_4. Evaporation of the solvent afforded the crude product, which was purified by column chromatography using AcOEt/petroleum ether (2:3, v/v) as the eluent to afford β-ketosulfoxide **50** (1.52 g, 4.62 mmol) in 60% yield.

Viscous oil.

$[\alpha]_D^{25}$: +133 (*c* 3.2, $CHCl_3$)

PMR ($CDCl_3$, 200 MHz) : δ 7.52 (d, *J* = 8.2 Hz, 2H), 7.46-7.21 (m, 7H), 6.81 (dt, *J* = 16.0, 4.0 Hz, 1H), 6.38 (dd, *J* = 16.0, 1.7 Hz, 1H), 4.55 (s, 2H), 4.19 (dd, *J* = 4.0, 1.7 Hz, 2H), 4.08 (d, *J* = 13.6 Hz, 1H), 3.85 (d, *J* = 13.6 Hz, 1H), 2.40 (s, 3H).

m/z (LSIMS) : 329 $[M+H]^+$

5-Benzyloxy-1-(S_R)-(4-methylphenylsulfinyl)-(2*R*,3*E*)-penten-2-ol, 57.

The β-ketosulfoxide **56** (1.56 g, 4.76 mmol) in dry THF (12 mL) was added to a well-stirred solution of $ZnCl_2$ (935 mg, 5.7 mmol) in dry THF (36 mL). The reaction mixture was stirred for 30 min. The reaction mixture was cooled to -78 °C, and DIBAL (2M solution in toluene, 3.6 mL, 7.2 mmol) was added dropwise over a period of 10 min. After being stirred further for a period of 2 h at -78 °C, methanol (48 mL) was added and the reaction mixture allowed to attain room temperature. The solvent was evaporated under reduced pressure. The residue was diluted with 5% aq. HCl solution and extracted into CH_2Cl_2. The organic layer was washed with 5% aq. NaOH solution, brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure afforded the crude product which was purified by column chromatography using

AcOEt/petroleum ether (1:1, v/v) as the eluent to afford the β-hydroxysulfoxide **57** (1.41 g, 4.3 mmol) as a single diastereomer in 91% yield.

Pale yellow liquid.

$[\alpha]_D^{25}$: +118.9 (*c* 0.75, $CHCl_3$)

PMR (200 MHz, $CDCl_3$) : δ 7.53 (d, *J* = 8.2 Hz, 2H), 7.36-7.22 (m, 7H), 5.87 (dt, *J* = 14.9, 5.9 Hz, 1H), 5.72 (dd, *J* = 14.9, 4.6 Hz, 1H), 4.82-4.72 (m, 1H), 4.52 (s, 2H), 4.06 (d, *J* = 4.6 Hz, 2H), 2.94 (dd, *J* = 13.4, 9.6 Hz, 1H), 2.76 (dd, *J* = 13.4, 3.0 Hz, 1H), 2.43 (s, 3H).

m/z (LSIMS) : 331 $[M+H]^+$

5-Benzyloxy-2-(*tert*-butyldimethylsilyloxy)-(2*R*,3*E*)-3-pentenyl4-methylphenyl sulfoxide, 58.

To the solution of **57** (660 mg, 2 mmol) in dry dichloromethane (8 mL) was added imidazole (204 mg, 3 mmol) followed by *tert*-butyldimethylsilyl chloride (300 mg, 2 mmol) at ambient temparature and stirred for 1 h. The reaction mixture was diluted with dichloromethane, washed with water, brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded the crude product mixture. Purification on a silica gel column using EtOAc/petroleum ether (1:9, v/v) as the eluent afforded **58** (861 mg, 1.94 mmol) in 97% yield.

Viscous oil.

PMR (300 MHz, $CDCl_3$) : δ 7.26 (d, *J* = 8.3 Hz, 2H), 7.10-6.97 (m, 7H), 5.59 (dt, *J* = 15.5, 5.3 Hz, 1H), 5.45 (dd, *J* = 15.5, 6.4 Hz, 1H), 4.56-4.48 (m, 1H), 4.23 (s, 2H), 3.70 (d, *J* = 5.3 Hz, 2H), 2.54 (dd, *J* = 12.8, 2.6 Hz, 1H), 2.46 (dd, *J* = 12.8, 10.2 Hz, 1H), 2.18 (s, 3H), 0.74 (s, 9H), 0,0 (s, 3H), - 0.11 (s, 3H).

m/z (LSIMS) : 447 $[M+H]^+$

1-Benzyloxy-2-bromo-5-(4-methylphenylsulfinyl)-4-(*tert*-butyldimethylsilyloxy)-(2*S*,3*R*,4*R*)-pentan-3-ol, 59.

To the solution of the sulfoxide **58** (843 mg, 1.90 mmol) in dry toluene (8 mL) was added water (68 μL, 3.8 mmol) followed by *N*-bromosuccinimide (406 mg, 2.3 mmol) and the reaction mixture stirred at room temperature for 30 min. The reaction was quenched by the addition of an aqueous saturated $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted with ethylacetate. The combined organic layers were successively washed with water, brine and dried over Na_2SO_4. Evaporation of the solvent afforded the crude product, which was purified by column chromatography using AcOEt/hexane (2:3, v/v) as the eluent to yield bromohydrin **59** (822 mg, 1.52 mmol) in 80% yield.

Solid.

mp	: 129-132 °C
PMR (300 MHz, $CDCl_3$)	: δ 7.38 (d, *J* = 8.3 Hz, 2H), 7.24-7.09 (m, 7H), 4.56-4.52 (m, 1H), 4.50 (s, 2H), 3.92-3.80 (m, 4H), 3.04 (dd, *J* = 15.6, 9.4 Hz, 1H), 2.64 (dd, *J* = 15.6, 2.6 Hz, 1H), 2.29 (s, 3H), 0.76 (s, 9H), 0.0 (s, 3H), -0.14 (s, 3H).
m/z (LSIMS)	: 542 $[M+H]^+$

3-Benzyloxy-2-bromo-1-[2-(4-methylphenylsulfinyl)-1-(*tert*-butyldimethylsilyloxy)-(1*R*)-ethyl]-(1*R*,2*S*)-propyl acetate, 60.

To the solution of **59** (649 mg, 1.2 mmol) in dichloromethane (5 mL) were added successively Et_3N (242 mg, 2.4 mmol), DMAP (cat.) and acetic anhydride (122 mg, 1.2 mmol). The reaction mixture was stirred at room temperature for 1 h when TLC examination revealed completion of the reaction. The reaction mixture was diluted with dichloromethane and washed successively with water, 10% aq. citric acid followed by brine. Volatiles were removed under reduced pressure and chromatographed on a silica gel column using

AcOEt/petroleum ether (1:4, v/v) as the eluent to afford acetate **60** (671 mg, 1.15 mmol) in 96% yield.

Viscous oil.

PMR (200 MHz, $CDCl_3$) : δ 7.44 (d, *J* = 8.2 Hz, 2H), 7.32-7.14 (m, 7H), 5.42 (dd, *J* = 8.9, 2.9 Hz, 1H), 4.72-4.62 (m, 1H), 4.51 (d, *J* = 12.6 Hz, 1H), 4.40 (d, *J* = 12.6 Hz, 1H), 4.24 (dt *J* = 8.9, 5.2 Hz, 1H), 3.68 (d, *J* = 5.2 Hz, 2H), 2.74-2.66 (m, 2H), 2.34 (s, 3H), 1.89 (s, 3H), 0.80 (s, 9H), 0.40 (s, 3H), 0.05 (s, 3H).

m/z (LSIMS) : 583 $[M+H]^+$

2-Azido-3-benzyloxy-1-[2-(4-methylphenylsulfinyl)-1-(*tert*-butyldimethylsilyloxy)-(1*R*)-ethyl]-(1*S*,2*R*)-propyl acetate, 61.

To the solution of the acetate **60** (583 mg, 1 mmol) in dimethylformamide (4 mL) was added NaN_3 (325 mg, 5 mmol) and heated at 80 °C for 6 h. The reaction mixture was diluted with ether and washed with water, brine and dried over Na_2SO_4. Solvent was evaporated under reduced pressure to afford the crude product. Purification on a silica gel using AcOEt/petroleum ether (1:4, v/v) as the eluent afforded the azide **61** (354 mg, 0.65 mmol) in 65% yield.

Viscous oil.

PMR (200 MHz, $CDCl_3$) : δ 7.52 (d, *J* = 8.2 Hz, 2H), 7.58-7.28 (m, 7H), 5.28 (dd, *J* = 5.2, 2.9 Hz, 1H), 4.55 (s, 2H), 4.34-4.26 (m, 1H), 3.96-3.88 (m, 1H), 3.72 (dd, *J* = 10.4, 5.2 Hz, 1H), 3.64 (dd, *J* = 10.4, 7.4 Hz, 1H), 3.04 (dd, *J* = 13.4, 6.7 Hz, 1H), 2.94 (dd, *J* = 13.4, 4.6 Hz, 1H), 2.44 (s, 3H), 2.03 (s, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H).

m/z (LSIMS) : 545 $[M+H]^+$

5-Benzyloxy-4-bromo-1-(S_S)-(4-methylphenylsulfinyl)-(2*R*,3*R*,4*S*)-pentane-2,3-diol, 63.

To the solution of the sulfoxide **57** (1.32 g, 4 mmol) in dry toluene (16 mL) was added water (144 mg, 8 mmol) followed by *N*-bromosuccinimide (850 mg, 4.8 mmol) and the reaction mixture stirred at room temperature for 15 min. The reaction mixture was quenched by the addition of aqueous saturated $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted with ethylacetate. The combined organic layers were successively washed with water, brine and dried over Na_2SO_4. Evaporation of the solvent afforded the crude product, which was purified by column chromatography using AcOEt/petroleum ether (2:3, v/v) as the eluent to yield bromohydrin **63** (1.5 g, 3.52 mmol) in 88% yield.

White solid.

mp : 136-137 °C

$[\alpha]_D^{25}$: -129.5 (*c* 1.0, $CHCl_3$)

PMR (300 MHz, $CDCl_3$) : δ 7.53 (d, *J* = 8.2 Hz, 2H), 7.35-7.27 (m, 7H), 4.64-4.56 (m, 3H), 4.17 (dt, *J* = 7.6, 4.8 Hz, 1H), 3.98 (dd, *J* = 10.3, 4.8 Hz, 1H), 3.85 (dd, *J* = 10.3, 4.8 Hz, 1H), 3.65-3.58 (m, 1H), 3.38-3.17 (m, 1H, OH), 2.66 (dd, *J* = 13.4, 1.88 Hz, 1H), 2.43 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.3, 51.2, 61.0, 65.9, 71.6, 73.3, 75.1, 124.0, 127.6, 127.7, 128.4, 130.0, 137.5, 139.6, 141.6.

m/z (LSIMS) : 427 $[M+H]^+$

4-[2-Benzyloxy-1-bromo-(1*S*)-ethyl]-2,2-dimethyl-5-(S_S)-(4-methylphenylsulfinyl-methyl)-(4*R*,5*R*)-1,3-dioxolane, 64.

To a solution of the diol **63** (1.45 g, 3.4 mmol) in a mixture of 2,2-dimethoxypropane and acetone (1:3, 13 mL) was added CSA (32 mg, 0.14 mmol) and the reaction mixture stirred at ambient temperature for 2 h. The organic layer was evaporated under reduced pressure to afford the crude product which was purified by column chromatography using 20% AcOEt/petroleum ether as the eluent to yield acetonide **64** (1.35 g, 2.92 mmol) as a colourless crystalline solid in 86% yield.

Solid.

mp : 147-149 °C

$[\alpha]_D^{25}$: -152.4 (*c* 1.0, $CHCl_3$)

PMR (200 MHz, $CDCl_3$) : δ 7.56 (d, *J* = 8.2 Hz, 2H), 7.37-7.27 (m, 7H), 4.65-4.53 (m, 3H), 4.12-3.96 (m, 2H), 3.80-3.70 (m, 2H), 3.35 (dd, *J* = 13.2, 2.9 Hz, 1H), 2.84 (dd, *J* = 13.2, 10.3 Hz, 1H), 2.41 (s, 3H), 1.40 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 21.3, 27.0, 27.4, 51.9, 63.6, 71.1, 73.3, 74.9, 79.8, 110.5, 123.9, 127.6, 127.7, 128.3, 130.0, 137.6, 141.4, 141.5.

m/z (LSIMS) : 467 $[M+H]^+$

4-[1-Azido-2-benzyloxy-(1*R*)-ethyl]-2,2-dimethyl-5-(S_S)-(4-methylphenylsulfinyl-methyl)-(4*S*,5*R*)-1,3-dioxolane, 65.

To a solution of acetonide **64** (1.33 g, 2.85 mmol) in DMSO (12 mL) was added NaN_3 (925 mg, 14.2 mmol). The reaction mixture was stirred at 85 °C for 8 h. The reaction mixture allowed to attain room temperature and diluted with ether. The organic layer was washed successively with water, brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure followed by purification by column chromatography of the crude product using AcOEt/petroleum ether (1:4, v/v) as the eluent afforded azido acetonide **65** (915 mg, 2.14 mmol) in 75% yield.

White solid.

mp : 82-84 °C

$[\alpha]_D^{25}$: -49.5 (*c* 0.65, $CHCl_3$)

PMR (200 MHz, $CDCl_3$) : δ 7.52 (d, *J* = 8.2 Hz, 2H), 7.33-7.26 (m, 7H), 4.60-4.50 (m, 3H), 3.88 (dd, *J* = 7.4, 4.6 Hz, 1H), 3.74-3.61

(m, 2H), 3.58-3.52 (m, 1H), 2.95 (dd, *J* = 13.4, 3.7 Hz, 1H), 2.81 (dd, *J* = 13.4, 8.2 Hz, 1H), 2.43 (s, 3H), 1.48 (s, 3H), 1.42 (s, 3H) .

^{13}C NMR (50MHz, $CDCl_3$) : δ 21.4, 26.6, 27.2, 60.1, 62.2, 69.6, 72.0, 73.4, 80.0, 110.4, 123.8, 127.7, 127.8, 128.9, 130.0, 137.4, 141.1, 141.7.

m/z (LSIMS) : 430 $[M+H]^+$

2-Azido-2-[2,2-dimethyl-5-[1-(4-methylphenylsulfanyl)-(*E*)-3-tetradecenyl]-(4*S*,5*R*)-1,3-dioxolan-4-yl]ethylbenzylether, 67.

To the mixture of the acetonide **65** (880 mg, 2.05 mmol) and 1-tridecene (560 mg, 3.08 mmol) in dichloromethane (16 mL) cooled at 0° C was added trifluoroacetic anhydride (1.3 g, 6.15 mmol) dropwise over 5min. and stirred for 1 h at the same temperature. $SnCl_4$ (550 mg, 2.05 mmol) was added, and after 10 min. at 0° C, the reaction mixture was quenched by slow addition of aq. saturated Na_2CO_3 solution. Extraction into diethylether followed by purification by column chromatography using AcOEt/petroleum ether (1:49) afforded **67** (790 mg, 1.33 mmol) in 65% yield.

Pale yellow Liquid.

$[\alpha]_D^{25}$: 13.1 (*c* 0.2, $CHCl_3$)

PMR (200 MHz, $CDCl_3$) : δ 7.31-7.16 (m, 7H), 6.95 (d, *J* = 8.2 Hz, 2H), 5.50-5.20 (m, 2H), 4.50 (s, 2H), 4.25-4.10 (m, 2H), 3.70-3.45 (m, 3H), 2.90 (td, *J* = 7.4, 2.2 Hz, 1H), 2.56-2.24 (m, 2H), 2.22 (s, 3H), 1.96-1.82 (m, 2H), 1.36 (s, 3H), 1.32 (s, 3H), 1.24-1.11 (m, 16H), 0.78 (t, *J* = 6.7 Hz, 3H) .

^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 21.0 22.6, 26.7, 27.1, 29.1, 29.3, 29.5, 29.6, 31.9, 32.5, 35.6, 60.8, 70.4, 73.5, 76.7, 77.0, 77.3, 109.7, 126.4, 127.7, 127.8, 128.3, 128.4, 129, 129.7, 132.2, 132.4, 133.0, 137.0.

m/z (LSIMS) : 594 $[M+H]^+$

2N-(*tert*-Butoxycarbonylamido)-2-(2,2-dimethyl-5-tetradecyl(4*S*,5*R*)-1,3-dioxalan-4-yl) -1-ethanol, 68.

To the mixture of **67** (118 mg, 0.2 mmol), $(Boc)_2O$ (87 mg, 1 mmol) in methanol (2 mL) was added Ra-Ni (1 g). The reaction mixture was stirred under H_2 pressure for 2 h at room temperature. Then the reaction mixture was refluxed for 6 h when TLC revealed the completion of reaction. The reaction mixture was allowed to attain room temperature and filtered through a small pad of celite. The celite pad was repeatedly washed with methanol (10 x 5). Evaporation of the solvent under reduced pressure followed by purification by column chromatography using AcOEt/petroleum ether (1:4, v/v) afforded the aminoalcohol **68** (62 mg, 0.14 mmol) in 68% yield.

Pale yellow liquid.

$[\alpha]_D^{25}$: -9.1 (*c* 0.6, $CHCl_3$)

PMR (200 MHz, $CDCl_3$) : δ 5.04 (d, *J* = 6.9 Hz, 1H, NH), 3.82-3.55 (m, 5H), 1.95 (bs, 1H, OH), 1.60-1.43 (m, 2H), 1.41-1.10 (m, 39H), 0.86 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 22.6, 25.6, 26.1, 26.7, 27.2, 28.2, 29.3, 29.6, 30.8, 31.8, 32.4, 33.2, 52.9, 63.0, 71.3, 80.0, 81.2, 108.7, 156.4.

m/z (LSIMS) : 458 $[M+H]^+$

3,4-Di(methylcarbonyloxy)-2-methylcarboxamido-(2*R*,3*S*,4*S*)-octadecylacetate, 70.

To the solution of **68** (40 mg, 0.09 mmol) in dichloromethane (0.1 mL) was added a 20:1 solution of TFA/water (0.4 mL) at 0 °C and stirred for 3 h. The solvent was evaporated under reduced pressure and then azeotroped with benzene. The aminotriol was directly taken to the next step without further purification. Pyridine (0.9 mL), and acetic anhydride (0.1 mL) were added to the reaction vessel and the resulting mixture stirred at r.t. overnight. The reaction mixture was concentrated, and the residue was chromatographed on a silica gel column using EtOAc/petroleum ether (7:3, v/v) system as the eluent to give the tetraacetylderivative **70** (34 mg, 0.07 mmol) in 78% yield.

Viscous liquid.

$[\alpha]_D^{25}$: -6.9 (*c* 0.9, $CHCl_3$)

Lit.[18b] $[\alpha]_D^{21}$: +7.0 (c = 0.86, $CHCl_3$) for the enantiomer

PMR (300 MHz, $CDCl_3$) : δ 5.73 (d, *J* = 9.5 Hz, 1H, NH), 5.11 (dd, *J* = 6.5, 4.3 Hz, 1H), 5.03 (dd, *J* = 12.7, 6.5 Hz, 1H), 4.52-4.46 (m, 1H), 4.03 (dd, *J* = 11.3, 6.0 Hz, 1H), 3.97 (dd, *J* = 11.3, 5.9 Hz, 1H), 2.08 (s, 3H), 2.06 (s, 6H), 2.01 (s, 3H), 1.67-1.51 (m, 2H), 1.39-1.15 (m, 24H), 0.88 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 20.6, 20.7, 20.9, 22.7,23.2, 24.8, 29.2, 29.3, 29.5, 29.6, 30.5, 31.9, 48.0, 62.9, 71.9, 72.2, 169.9.

LSIMS *m/z* : 485 $[M+H]^+$

1-[5-[1-Azido-2-benzyloxy-(1*R*)-ethyl]-2,2-dimethyl-5-[1-(4-methylphenylsulfonyl)-(*E*)-3-tetradecenyl]-(4*S*,5*R*)-1,3-dioxolane,71.

To the solution of the sulfide **67** (296 mg, 0.5 mmol) in a mixture of MeOH:water:tetrahydrofuran (1:1:2, 0.5 mL) was added Oxone® (153 mg, 1.0 mmol) at 0° C and allowed to attain room temperature during 30 min. After complete conversion to the sulfone, which was revealed by TLC examination (*ca.* 4 h), the solvent was evaporated under reduced pressure and the residue extracted into ethylacetate. Column chromatography using AcOEt/petroleum ether (1:6, v/v) afforded sulfone **71** (250 mg, 0.4 mmol) in 82% yield.

Viscous liquid.

$[\alpha]_D^{25}$: -12.7 (*c* 1.6, $CHCl_3$)

PMR (200 MHz, $CDCl_3$) : δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.39-7.22 (m, 7H), 5.35 (dt, *J* = 13.4, 6.7 Hz, 1H), 5.16 (dt, *J* = 13.4, 6.7 Hz, 1H), 4.58 (s, 2H), 4.50 (dd, *J* = 8.2, 3.7 Hz, 1H), 4.28 (dd, *J* = 8.2, 2.2 Hz, 1H), 3.85-3.68 (m, 3H), 3.32-3.24 (m, 1H), 2.60-2.40 (m, 5H), 1.96-1.76 (m, 2H), 1.55-1.15 (m, 22H), 0.88 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 21.6, 22.6, 26.5, 26.9, 28.8, 29.1, 29.2, 29.3, 29.5, 29.6, 31.9, 32.3, 59.6, 65.4, 70.5, 73.3, 74.4, 77.2, 109.5, 124.8, 127.7, 127.8, 128.4, 128.9, 129.5, 134.7, 136.4, 137.7, 144.7, 144.8.

m/z (LSIMS) : 626 $[M+H]^+$

2*N*-(*tert*-Butoxycarbonylamido)-2-{2,2-dimethyl-5-[1-(4-methylphenylsulfonyl)-tetracetyl](4*S*,5*S*)-1,3-dioxalan-4-yl}-1-ethanol, 72.

To the mixture of sulfone **71** (188 mg, 0.3 mmol) and $(Boc)_2O$ (130 mg, 0.60 mmol) in absolute ethanol (0.6 mL) was added $Pd(OH)_2/C$ (20 mg, 0.03 mmol, 10 mol%). After evacuating, the reaction mixture was stirred under H_2 atmosphere for 16 h. The reaction mixture was filtered through a small pad of celite and repeatedly washed with ethanol. Evaporation of the solvent afforded the crude product which was purified by column chromatography using 30% AcOEt/petroleum ether as the eluent to yield **72** (134 mg, 0.22 mmol) in 71%.

Low melting oily solid.

$[\alpha]_D^{25}$: -3.4 (*c* 2.4, $CHCl_3$)

PMR (200 MHz, $CDCl_3$) : δ 7.78 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 5.09 (d, *J* = 8.9 Hz, NH, 1H), 4.70 (d, *J* = 8.3 Hz, 1H), 4.04 (dd, *J* = 8.3, 3.8 Hz, 1H), 3.93 (dd, *J* = 9.7, 4.5 Hz, 1H), 3.86-3.79 (m, 1H), 3.69 (dd, *J* = 11.1, 4.5 Hz, 1H), 3.33-3.26 (m, 1H), 2.45 (s, 3H), 1.76-1.63 (m, 2H), 1.44-1.16 (m, 37H), 0.88 (t, *J* = 6.7 Hz, 3H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2, 21.7, 22.7, 26.8, 28.4, 29.2, 29.4, 29.7, 32.0, 50.1, 65.0, 75.2, 78.7, 79.9, 109.1, 129.1, 129.5, 136.9, 144.4, 155.9.

m/z (LSIMS) : 612 $[M+H]^+$

2-(*N-tert*-butoxycarbonyl)amino-(2*R*,3*R*,4*E*)-4-octadecene-1,3-diol, 73.

6% Na-Hg (250 mg) was added to the solution of **72** (100 mg, 0.16 mmol) and Na_2HPO_4 (29 mg, 0.32 mmol) in methanol (3.2 mL) at –20° C and allowed to attain r.t. during 30 min. After being stirred for 2 h, the reaction mixture was extracted with ethylacetate and the solvent was evaporated under reduced pressure to afford the crude product mixture. Purification by column chromatography using 25% AcOEt/petroleum ether afforded the sphingosine **73** (41 mg, 0.104 mmol) in 65% yield.

Low melting solid.

$[\alpha]_D^{25}$: +0.41 (*c* 0.9, $CHCl_3$)

Lit.[38] $[\alpha]_D^{25}$: -0.41 (c = 1.0, $CHCl_3$) for the enantiomer

PMR (200 MHz, $CDCl_3$) : δ 5.71 (dt, *J* = 15.6, 6.7 Hz, 1H), 5.46 (dd, *J* = 15.6, 6.7 Hz, 1H), 5.1 (bs, 1H, NH), 4.29 (dd, *J* = 5.9, 3.7 Hz, 1H), 3.80-3.71 (m, 2H), 3.58 (m, 1H), 2.08-1.88 (m, 2H, OH), 1.44-1.12 (m, 31H), 0.85 (t, *J* = 6.5 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 22.7, 28.3, 29.1, 29.2, 29.3, 29.5, 29.7, 31.9, 32.3, 55.6, 64.5, 73.6, 79.8, 129.0, 134.2, 156.4.

m/z (LSIMS) : 400 $[M+H]^+$

5-Benzyloxy-1-(4-methylphenylsulfinyl)-(2*S*,3*E*)-penten-2-ol, 74.

To the solution of the β-ketosulfoxide **56** (1.8 g, 5.5 mmol) in dry tetrahydrofuran (27 mL) cooled at –78 °C was added DIBAL (2M solution in toluene, 4.15 mL, 8.3 mmol) dropwise over a period of 20 min. After the addition, the reaction mixture was stirred at –78 °C for another 15 min. Methanol (27 mL) was then added at –78 °C, the reaction mixture was allowed to warm to r.t. and the solvent was evaporated under vacuum. The residue was dissolved in CH_2Cl_2 (50 mL) and treated with 5% H_2SO_4 (15 mL) solution. The organic layer was separated and washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure to afford the crude product. Column chromatography using AcOEt/petroleum ether (3:2, v/v) afforded the alkenol **74** (1.67 g, 5.1 mmol) in 92% yield.

Viscous oil.

$[\alpha]_D^{25}$: **+122.6 (*c* 1.0, $CHCl_3$)**

PMR (200 MHz, $CDCl_3$) : δ 7.51 (d, *J* = 8.2 Hz, 2H), 7.38-7.23 (m, 7H), 5.87 (dt, *J* = 14.9, 5.2 Hz, 1H), 5.70 (dd, *J* = 14.9, 4.5 Hz, 1H), 4.75-4.63 (m, 1H), 4.46 (s, 2H), 3.97 (d, *J* = 5.2 Hz, 2H), 3.0 (dd, *J* = 13.4, 10.4 Hz, 1H), 2.68 (dd, *J* = 13.4, 1.5 Hz, 1H), 2.43 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.2, 62.9, 66.0, 69.6, 72.1, 123.8, 127.4, 127.5, 127.9, 128.1, 128.9, 129.9, 137.9, 139.6, 141.4.

m/z (LSIMS) : 331 $[M+H]^+$

Elemental analysis : Calcd. for $C_{19}H_{22}O_3S$ C, 69.06; H, 6.71; S, 9.70.

Found : C, 69.18; H, 6.93; S, 9.40.

5-Benzyloxy-4-bromo-1-(4-methylphenylsulfinyl)-(2*S*,3*S*,4*R*)-pentane-2,3-diol, 75.

To the solution of the sulfoxide **74** (1.56 g, 4.75 mmol) in dry toluene (19 mL) was added water (171 μL, 9.5 mmol) followed by *N*-bromosuccinimide (1.01 g, 5.7 mmol) and the reaction mixture stirred at room temperature for 15 min. The reaction was quenched by the addition of an aqueous saturated $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted with ethylacetate. The combined organic layers were successively washed with water, brine and dried over Na_2SO_4. Evaporation of the solvent afforded the crude product, which was purified by column chromatography using AcOEt/petroleum ether (2:3, v/v) as the eluent to yield bromohydrin **75** (1.95 g, 4.18 mmol) in 88%.

White solid.

mp : 137-139 °C

$[\alpha]_D^{25}$: -120.0 (*c* 1.0, $CHCl_3$)

PMR (200 MHz, $CDCl_3$) : δ 7.52 (d, *J* = 8.2 Hz, 2H), 7.40-7.25 (m, 7H), 4.72-4.66 (m, 1H), 4.59 (s, 2H), 4.24-4.16 (m, 1H), 4.01-3.81 (m, 3H), 3.10 (dd, *J* = 13.4, 8.2 Hz, 1H), 2.84 (dd, *J* = 13.4, 3.7 Hz, 1H), 2.80-2.50 (bs, 2-OH), 2.44 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4, 51.0, 61.1, 67.9, 71.4, 73.3, 74.7, 124.1, 127.7, 127.8, 128.4, 130.1, 137.4, 139.7, 142.0.

HRMS-FAB (*m/z*)$[M+H]^+$: calcd for $C_{19}H_{22}BrO_4S$ 427.0578, found 427.0573.

4-[2-Benzyloxy-1-bromo-(1*R*)-ethyl]-2,2-dimethyl-5-(4-methylphenylsulfinyl methyl)-(4*S*,5*S*)-1,3-dioxolane, 76.

To the solution of the diol **75** (47 mg, 0.11 mmol) in a mixture of 2,2-dimethoxypropane and dry acetone (1:3, 0.50 mL) was added CSA (1.0 mg, 0.004 mmol) and the reaction mixture was stirred at ambient temperature for 2 h. The organic layer was evaporated under reduced pressure to afford the crude product, which was purified by column chromatography using AcOEt/petroleum ether (1:4, v/v) as the eluent to yield acetonide **76** (44 mg, 0.095 mmol) as a viscous liquid in 86% yield.

Viscous oil.

PMR (200 MHz, $CDCl_3$) : δ 7.56 (d, *J* = 8.2 Hz, 2H), 7.36-7.24 (m, 7H), 4.56 (s, 2H), 4.28-4.20 (m, 1H), 4.04 (dd, *J* = 7.4, 3.7 Hz, 1H), 3.95 (dd, *J* = 8.2, 4.5 Hz, H), 3.80-3.74 (m, 2H), 3.32 (dd, *J* = 13.4, 7.4 Hz, 1H), 3.16 (dd, *J* = 13.4, 3.7 Hz, 1H), 2.44 (s, 3H), 1.46 (s, 3H), 1.36 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 21.5, 27.2, 27.5, 52.3, 61.9, 71.2, 73.3, 75.9, 79.6, 110.5, 124.6, 127.7, 128.4, 129.9, 137.6, 140.9, 141.4.

HRMS-FAB (*m/z*)[M+H]$^+$: calcd for $C_{22}H_{27}BrO_4S$ 467.0880, found 427.0891.

1-[3-Benzyloxymethyl-3(*S*)-oxiran-2-yl]-2-(methylphenylsulfinyl)-1-(*S*)-ethan-1-ol, 77.

To the solution of **76** (1.8 g, 4.05 mmol) in methanol (16 mL) was added K_2CO_3 (615 mg, 4.45 mmol) at 0 °C and the temperature allowed to rise to r.t. during 45 min. After stirring the reaction mixture at r.t. for a further period of 1 h, TLC revealed the complete conversion of starting material. Ether (15 mL) was added to the reaction mixture, and after 10 min. reaction mixture was filtered and the filtrate evaporated to afford the epoxide **77** (1.16 g, 3.35 mmol) in 83% yield. This was taken ahead to the next step without further purification.

Solid.

mp : 104-106 °C

$[\alpha]_D^{25}$: -104.3 (*c* 0.75, $CHCl_3$)

PMR (200 MHz, $CDCl_3$) : δ 7.51 (d, *J* = 8.2 Hz, 2H), 7.36-7.22 (m, 7H), 4.52 (s, 2H), 4.29-4.20 (m, 1H), 3.72 (dd, *J* = 11.2, 3.0 Hz, 1H), 3.48 (dd, *J* = 11.2, 5.2 Hz, 1H), 3.30 (d, *J* = 4.5 Hz, 1H), 3.24-3.18 (m, 1H), 3.08 (dd, *J* = 3.7, 2.2 Hz, 1H), 3.03-2.96 (m, 1H), 2.86 (dd, *J* = 13.4, 4.5 Hz, 1H), 2.43 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 21.4, 54.4, 57.3, 59.7, 66.7, 69.1, 73.3, 124.1, 127.1, 127.7, 128.4, 130.2, 137.7, 140.1, 142.1.

HRMS-FAB (*m/z*)[M+H]$^+$: calcd for $C_{19}H_{27}O_4S$ 347.1317, found 347.1332.

4-Azido-5-benzyloxy-1-(4-methylphenylsulfinyl)-(2*S*,3*R*,4*R*)-pentane-2,3-diol, 78.

To the epoxide **77** (1.04 g, 3.1 mmol) in a solvent mixture of MeOH: H_2O (8:1, 18 mL) was added NH_4Cl (498 mg, 9.3 mmol) followed by NaN_3 (1.21 g, 18.6 mmol) and the mixture heated at reflux for 6 h. The reaction mixture was allowed to attain r.t. and the solvent was evaporated. The residue was extracted with ethylacetate (2 x 30 mL). The crude reaction mixture was purified by column chromatography using AcOEt/petroleum ether (2:3, v/v) to afford the azidodiol **78** (1.03 g, 2.64 mmol) in 85% yield.

White solid.

mp : 95-96 °C

$[\alpha]_D^{25}$: -103.4 (*c* 0.8, $CHCl_3$)

PMR (200 MHz, $CDCl_3$) : δ 7.51 (d, *J* = 8.2 Hz, 2H), 7.38-7.24 (m, 7H), 4.57 (s, 2H), 4.46-4.42 (m, 1H), 3.94-3.86 (m, 1H), 3.76-3.64 (m, 2H), 3.50 (d, *J* = 8.2 Hz, 1H), 3.22 (bs, 2-OH), 3.10 (dd, *J* = 13.4, 6.7 Hz, 1H), 2.90 (dd, *J* = 13.4, 4.5 Hz, 1H), 2.41 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4, 60.1, 62.0, 65.2, 70.5, 73.5, 124.4, 127.5, 127.7, 128.4, 130.1, 137.7, 139.2, 141.9.

HRMS-FAB (*m/z*)$[M+H]^+$: calcd for $C_{19}H_{23}N_3O_4S$ 390.1487, found 390.1478.

4-[1-Azido-2-benzyloxy-(1*R*)-ethyl]-2,2-dimethyl-5-(4-methylphenylsulfinyl methyl)-(4*R*,5*S*)-1,3-dioxolane, 79.

To the solution of the azidodiol **78** (973 mg, 2.5 mmol) in a mixture of 2,2-dimethoxypropane and acetone (1:3, 10 mL) was added CSA (24 mg, 0.1 mmol) and the reaction mixture stirred at ambient temperature for 1 h. The organic layer was evaporated under reduced pressure to afford the crude product which was purified by column chromatography using AcOEt/petroleum ether (1:4, v/v) as the eluent to yield acetonide **79** (925 mg, 2.15 mmol) in 87% yield.

Viscous liquid

$[\alpha]_D^{25}$: -47.5 (*c* 0.6, $CHCl_3$)

PMR (200 MHz, $CDCl_3$) : δ 7.55 (d, *J* = 8.2 Hz, 2H), 7.38-7.25 (m, 7H), 4.52 (s, 2H), 4.02-3.90 (m, 2H), 3.70 (dd, *J* = 9.4, 3.1 Hz, 1H), 3.67-3.54 (m, 1H), 3.54 (dd, *J* = 9.4, 7.3 Hz, 1H), 3.22 (dd, *J* = 13.4, 7.3 Hz, 1H), 3.07 (dd, *J* = 13.4, 3.1 Hz, 1H), 2.42 (s, 3H), 1.43 (s, 3H), 1.37 (s, 3H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 21.4, 26.7, 26.9, 60.7, 62.7, 70.2, 73.4, 74.4, 78.2, 110.3, 124.4, 127.6, 127.8, 128.4, 129.9, 137.3, 140.0, 141.9.

m/z (LSIMS) : 430 [M+H]$^+$

Elemental analysis : Calcd. for $C_{22}H_{27}N_3O_4S$ C, 61.52; H, 6.34; N, 9.78; S, 7.46.

Found : C, 61.39; H, 6.52; N, 9.97; S, 7.49.

2-Azido-2-[2,2-dimethyl-5-[1-(4-methylphenylsulfinyl)-(*E*)-3-tetradecenyl]-(4*R*,5*S*)-1,3-dioxolan-4-yl]-ethylbenzylether, 81.

To the mixture of the acetonide **79** (885 mg, 2.05 mmol) and 1-tridecene (560 mg, 3.08 mmol) in dichloromethane (10 mL) cooled at 0 °C was added trifluoroacetic anhydride (1.3 g, 6.15 mmol) dropwise over 5min. and stirred for 1h at the same temperature. SnCl$_4$ (550 mg, 2.05 mmol) was added and after being stirred for 10 min. at 0 °C, the reaction mixture was quenched by the addition of aq. saturated Na$_2$CO$_3$ solution. Extraction into diethyl ether and usual workup followed by purification by column chromatography using AcOEt/petroleum ether (1:49, v/v) afforded **81** (930 mg, 1.57 mmol) in 76% yield.

Pale yellow liquid.

$[\alpha]_D^{25}$: +15.8 (*c* 1.0, CHCl$_3$).

PMR (200 MHz, CDCl$_3$) : δ 7.34-7.25 (m, 7H), 7.02 (d, *J* = 7.2 Hz, 2H), 5.47 (dt, = 15.3, 6.6 Hz, 1H), 5.32 (dt, *J* = 15.3, 6.8 Hz, 1H), 4.54 (s, 2H), 4.19-4.1 (m, 2H), 3.77 (dd, *J* = 9.7, 3.1 Hz, 1H), 3.66 (td, *J* = 7.5, 3.1 Hz, 1H), 3.54 (dd, *J* = 9.7, 7.5 Hz, 1H), 3.18-3.10 (m, 1H), 2.46-2.41 (m, 2H), 2.32 (s, 3H), 1.97-1.92 (m, 2H), 1.45 (s, 3H), 1.44-1.40 (m, 2H), 1.35 (s, 3H), 1.32-1.2 (m, 17H), 0.88 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 21.0, 22.6, 26.9, 27.0, 29.1, 29.3, 29.5, 29.6, 31.9, 32.5, 37.6, 52.1, 63.8, 70.8, 73.4, 76.6, 80.0, 109.8, 126.6, 127.5, 127.7, 128.4, 129.6, 132.0, 132.3, 134.0, 137.0, 137.6.

m/z (LSIMS) : 593 [M^+]

Elemental analysis : Calcd. for $C_{35}H_{51}N_3O_3S$ C, 70.79; H, 8.66; N, 7.08; S, 5.40.

Found : C, 70.56; H, 8.91; N, 7.12; S, 5.44.

2-(*N-tert*-butyloxycarbonyl)amino-2-[2,2-dimethyl-5-tetradecyl-(4*R*,5*S*)-1,3-dioxalan-4yl]-1-ethanol, 82.

To the mixture of **81** (297 mg, 0.5 mmol), $(Boc)_2O$ (218 mg, 1.0 mmol) in methanol (5 mL) was added Ra-Ni (2.5 g). The reaction mixture was stirred under H_2 pressure for 2 h at room temperature and then refluxed for 6 h when TLC examination revealed completion of the reaction. The reaction mixture was allowed to attain room temperature and filtered through a small pad of celite. Celite pad was repeatedly washed with methanol (25 mL x 5). Evaporation of the solvent under reduced pressure followed by purification of the crude product by column chromatography using AcOEt/petroleum ether (1:4, v/v) afforded the aminoalcohol **82** (169 mg, 0.37 mmol) in 75% yield.

White solid.

mp : 47-49 °C

$[\alpha]_D^{25}$: +12.8 (*c* 2.5, $CHCl_3$)

PMR (200 MHz, $CDCl_3$) : δ 5.05 (bs, NH), 3.88-3.72 (m, 2H), 3.62-3.47 (m, 3H), 1.92 (bs, OH, 1H), 1.51-1.01 (m, 42H), 0.8 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 22.6, 26.2, 27.0, 27.2, 28.3, 29.3, 29.6, 31.9, 33.8, 52.9, 62.6, 79.3, 81.8, 108.7, 156.0.

m/z (LSIMS) : 458 $[M+H]^+$

Elemental analysis : Calcd. for $C_{26}H_{51}NO_5$ C, 68.23; H, 11.23; N, 3.06.

Found	: C, 68.62; H, 11.41; N, 3.09.

3,4-(Dimethylcarbonyloxy)-2-methylcarboxamido-(2*R*,3*R*,4*R*)-octadecylacetate, 84.

To the protected amino alcohol **82** (90 mg, 0.2 mmol) in dichloromethane (0.2 mL) was added a 20:1 solution of TFA/water (0.4 mL) at 0° C and stirred for 3 h. The solvent was evaporated under reduced pressure and then azeotroped with benzene. The aminotriol was taken directly to the next step without further purification. Pyridine (2 mL) was added followed by DMAP (2.5 mg, 0.02 mmol) and finally Ac_2O (0.2 mL). After stirring at rt for 16 h., pyridine was evaporated under vacuum and the reaction mixture extracted into ethylacetate. The organic layer was successively washed with aq. $CuSO_4$ solution, aq. sat. $NaHCO_3$ solution, water, brine and dried over Na_2SO_4. Evaporation of the solvent afforded the crude tetraacetylphytosphingosine. Purification using AcOEt/petroleum ether (1:4, v/v) afforded **84** (69 mg, 0.14 mmol) in 70% yield.

White crystalline solid.

mp	: 58-60 °C
$[\alpha]_D^{25}$	: +3.2 (*c* 1, $CHCl_3$)
lit[18b] $[\alpha]_D^{21}$	: −3.1(*c* 1.1 $CHCl_3$) for the enantiomer
PMR (300 MHz, $CDCl_3$)	: δ 5.75 (d, *J* = 9.8 Hz, 1H, NH), 5.08 (m, 2H), 4.51 (m, 1H) 4.23 (dd, *J* = 11.7, 4.6 Hz, 1H), 3.91 (dd, *J* = 11.7, 3.1 Hz, 1H), 2.12 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H), 1.96 (s, 3H), 1.52-1.38 (m, 2H), 1.33-1.18 (m, 24H), 0.88 (t, *J* = 6.7 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$)	: δ 14.1, 20.7, 20.8, 21.0, 22.7, 23.3, 25.2, 29.3, 29.4, 29.5, 29.7, 30.9, 31.9, 47.5, 63.1, 71.2, 71.8, 169.6, 170.3, 170.6, 170.8.
m/z (LSIMS)	: 486 $[M+H]^+$
Elemental analysis	: Calcd. for $C_{26}H_{47}NO_7$ C, 64.30; H, 9.75; N, 2.88.

Found : C, 64.02; H, 9.93; N, 2.97.

1-[5-[1-Azido-2-benzyloxy-(1*R*)-ethyl]-2,2-dimethyl-5-[1-(4-methylphenylsulfonyl)-(E)-3-tetradecenyl]-(4*R*,5*S*)-1,3-dioxolane, 85.

To the solution of the sulfide **81** (297 mg, 0.5 mmol) in a mixture of MeOH: water: tetrahydrofuran (1:1:2, 2 mL) was added oxone (614 mg, 1.0 mmol) at 0 °C and allowed to attain room temperature during a period of 30 min. After complete conversion to the sulfone as revealed by TLC examination (*ca.* 4h), the solvent was evaporated under reduced pressure and the residue extracted into ethylacetate. Column chromatography using AcOEt/hexane (3:17, v/v) afforded sulfone **85** (257 mg, 0.41 mmol) in 82% yield.

Viscous Liquid.

$[\alpha]_D^{25}$: +11.7 (*c* 0.3, EtOAc)

PMR (300 MHz, $CDCl_3$) : δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.36-7.24 (m, 7H), 5.46 (dt, *J* = 13.6, 6.8 Hz, 1H), 5.14 (dt, *J* = 13.6, 6.8 Hz, 1H), 4.59 (s, 2H), 4.53 (dd, *J* = 7.6, 6.8 Hz, 1H), 4.23 (dd, *J* = 7.6, 3.0 Hz, 1H), 3.84 (m ,1H), 3.71-3.62 (m, 2H), 3.38 (m, 1H), 2.58 (m, 1H), 2.48 (s, 3H), 2.4 (m, 1H), 1.98-1.88 (m, 2H), 1.33-1.22 (m, 22H), 0.88 (t, *J* 6.8 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 21.5, 22.6, 26.8, 26.9, 29.1, 29.2, 29.2, 29.4, 29.5, 30.7, 31.8, 32.4, 63.5, 64.8, 70.5, 76.1, 77.1, 110.1, 124.4, 127.6, 127.7, 128.4, 129.1, 129.3, 136.9, 137.5, 144.3.

m/z (LSIMS) : 626 $[M+H]^+$

Elemental analysis : Calcd. for $C_{35}H_{51}N_3O_5S$ C, 67.17; H, 8.21; N, 6.71; S, 5.12.

Found : C, 67.49; H, 8.48; N, 6.79; S, 5.23.

2-(*N-tert*-butoxycarbonyl)amino-2-{2,2-dimethyl-5-[1-(4-methylphenylsulfonyl)-tetracecyl]-(4*S*, 5*R*)-1,3-dioxalan-4-yl}-1-ethanol, 86.

To the mixture of sulfone **85** (188 mg, 0.30 mmol) and $(Boc)_2O$ (130 mg, 0.60 mmol) in absolute ethanol (0.6 mL) was added $Pd(OH)_2$ (20 mg, 10% by wt.). The reaction mixture was evacuated, subsequently filled with H_2 and stirred for 16 h. The reaction mixture was filtered through a small pad of celite and repeatedly washed with ethanol. Evaporation of the solvent afforded the crude product, which was purified by column chromatography using AcOEt/petroleum ether (3:7, v/v) as the eluent to yield **86** (136 mg, 0.2 mmol) in 71% yield.

Viscous liquid.

$[\alpha]_D^{25}$: +9.5 (*c* 1, $CHCl_3$)

PMR (200 MHz, $CDCl_3$) : δ 7.78 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 5.40 (d, *J* = 8.9 Hz, 1H, NH), 4.52 (m, 1H), 4.31 (dd, *J* = 6.7, 3.7 Hz, 1H), 3.90-3.68 (m, 2H), 3.17 (m, 1H), 2.46 (s, 3H), 1.84-1.68 (m, 2H), 1.46-1.11 (m, 38H), 0.88 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 14.1, 21.6, 22.7, 26.8, 27.2, 27.6, 28.3, 28.4, 29.1, 29.2, 29.3, 29.4, 29.6, 30.9, 31.9, 53.9, 63.0, 66.0, 69.1, 70.2, 79.9, 109.6, 128.9, 129.5, 136.7, 144.5, 155.8.

m/z (LSIMS) : 612 $[M+H]^+$

Elemental analysis : Calcd. for $C_{35}H_{57}NO_7S$ C, 64.78; H, 9.39; N, 2.29; S, 5.24.

Found : C, 64.39; H, 9.72; N, 2.32; S, 5.31.

2-(*N-tert*-butoxycarbonyl)amino-(2*R*,3*S*,4*E*)-4-octadecene-1,3-diol, 88.

6% Na-Hg (250 mg) was added to the solution of **86** (100 mg, 0.16 mmol) and Na_2HPO_4 (58 mg, 0.32 mmol) in methanol (3.2 mL) at –20° C and allowed to attain r.t. during a period of 30 min. After further stirring for 1 h, the reaction mixture was cooled to 0 °C, diluted with water and evaporated under reduced pressure. The residue was extracted with ethylacetate to afford the crude product. After evaporating the solvent, purification by column chromatography using AcOEt/petroleum ether (1:4, v/v) afforded the sphingosine derivative **88** (38 mg, 0.097 mmol) in 60% yield.

Low melting oily solid.

$[\alpha]_D^{25}$: +1.4 (*c* 1, $CHCl_3$)

lit.[38] $[\alpha]_D^{24}$: -1.4 (*c* 1.0 $CHCl_3$) for the enantiomer

PMR (200 MHz, $CDCl_3$) : δ 5.77 (dt, *J* = 15.1, 6.7 Hz, 1H), 5.52 (dd, *J* = 15.1, 6.7 Hz, 1H), 4.33-4.19 (m, 1H), 3.98-3.82 (m, 1H), 3.76-3.61 (m, 1H), 3.60-3.45 (m, 1H), 2.6-2.24 (bs, OH), 2.10-1.88 (m, 2H), 1.44-1.11 (m, 31H), 0.88 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 22.7, 28.4, 29.1, 29.2, 29.3, 29.5, 29.6, 29.7, 31.9, 32.3, 55.5, 62.7, 74.8, 79.9, 128.9, 134.2, 156.2.

m/z (LSIMS) : 400 $[M+H]^+$

Elemental analysis : Calcd. for $C_{23}H_{45}NO_4$ C, 69.13; H, 11.35; N, 3.51.

Found : C, 69.45, H, 11.62, N, 3.59.

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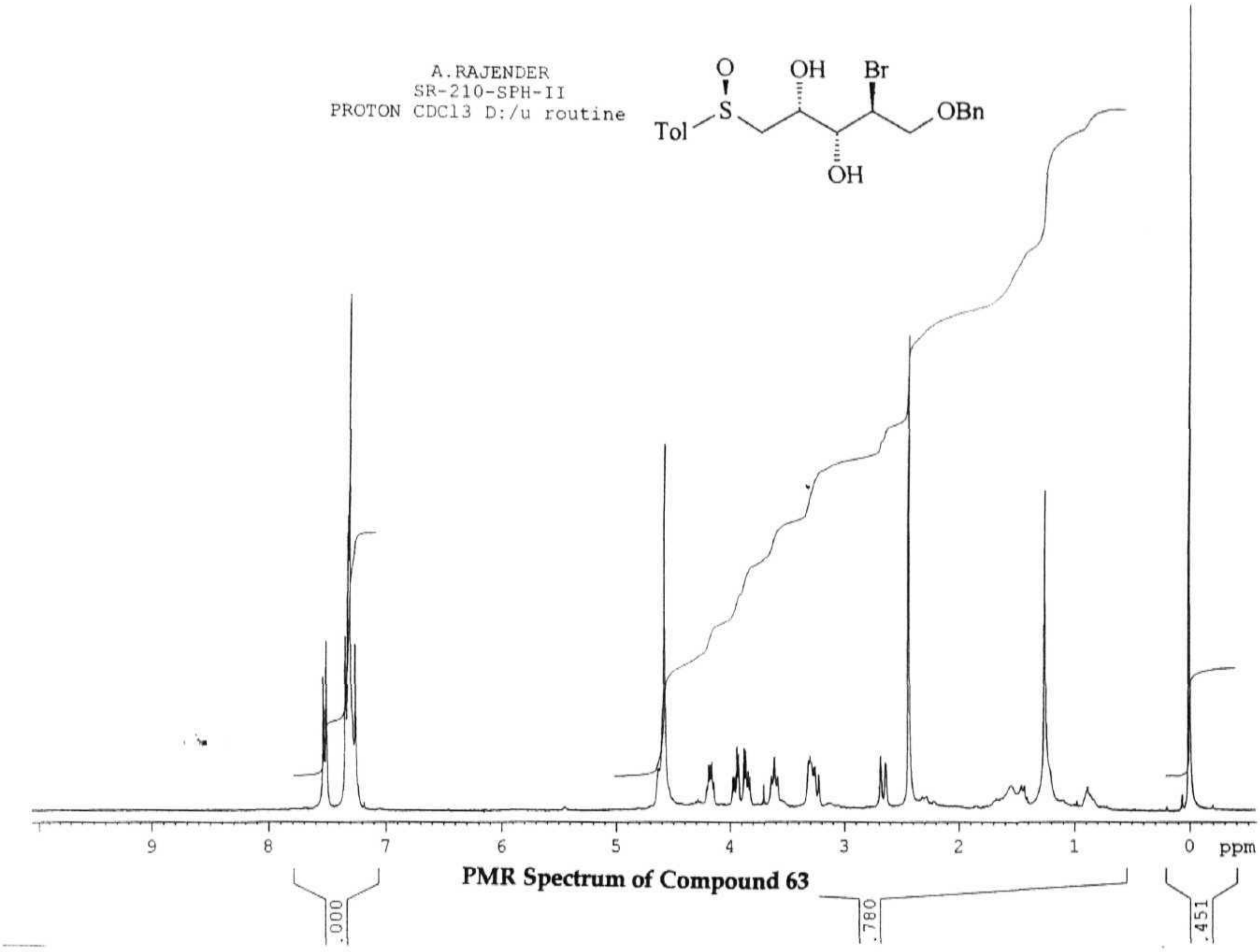
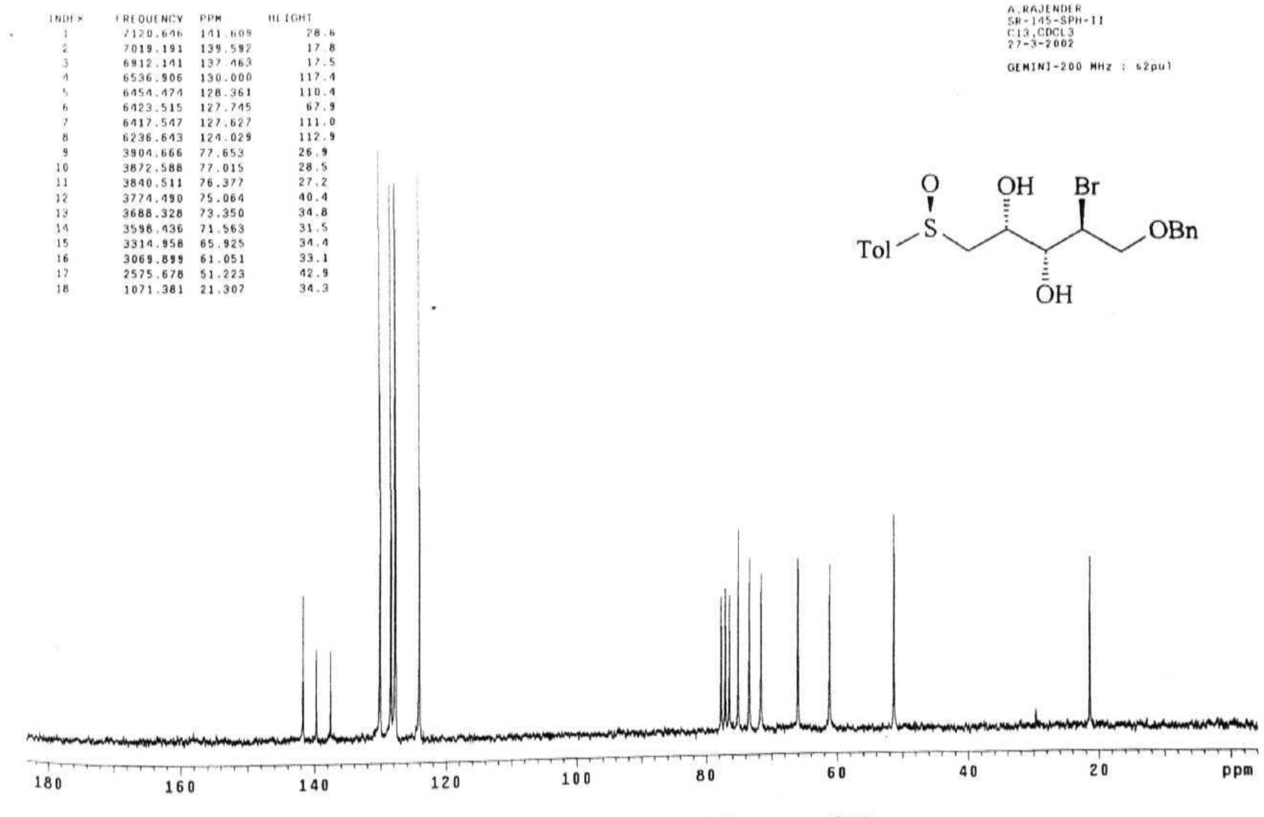
SPECTRA



PMR Spectrum of Compound 63



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INDEX   FREQUENCY   PPM       HEIGHT
  1     7120.646   141.609      28.6
  2     7019.191   139.592      17.8
  3     6912.141   137.463      17.5
  4     6536.906   130.000     117.4
  5     6454.474   128.361     110.4
  6     6423.515   127.745      67.9
  7     6417.547   127.627     111.0
  8     6236.643   124.029     112.9
  9     3904.666    77.653      26.9
 10     3872.588    77.015      28.5
 11     3840.511    76.377      27.2
 12     3774.490    75.064      40.4
 13     3688.328    73.350      34.8
 14     3598.436    71.563      31.5
 15     3314.958    65.925      34.4
 16     3069.899    61.051      33.1
 17     2575.678    51.223      42.9
 18     1071.381    21.307      34.3
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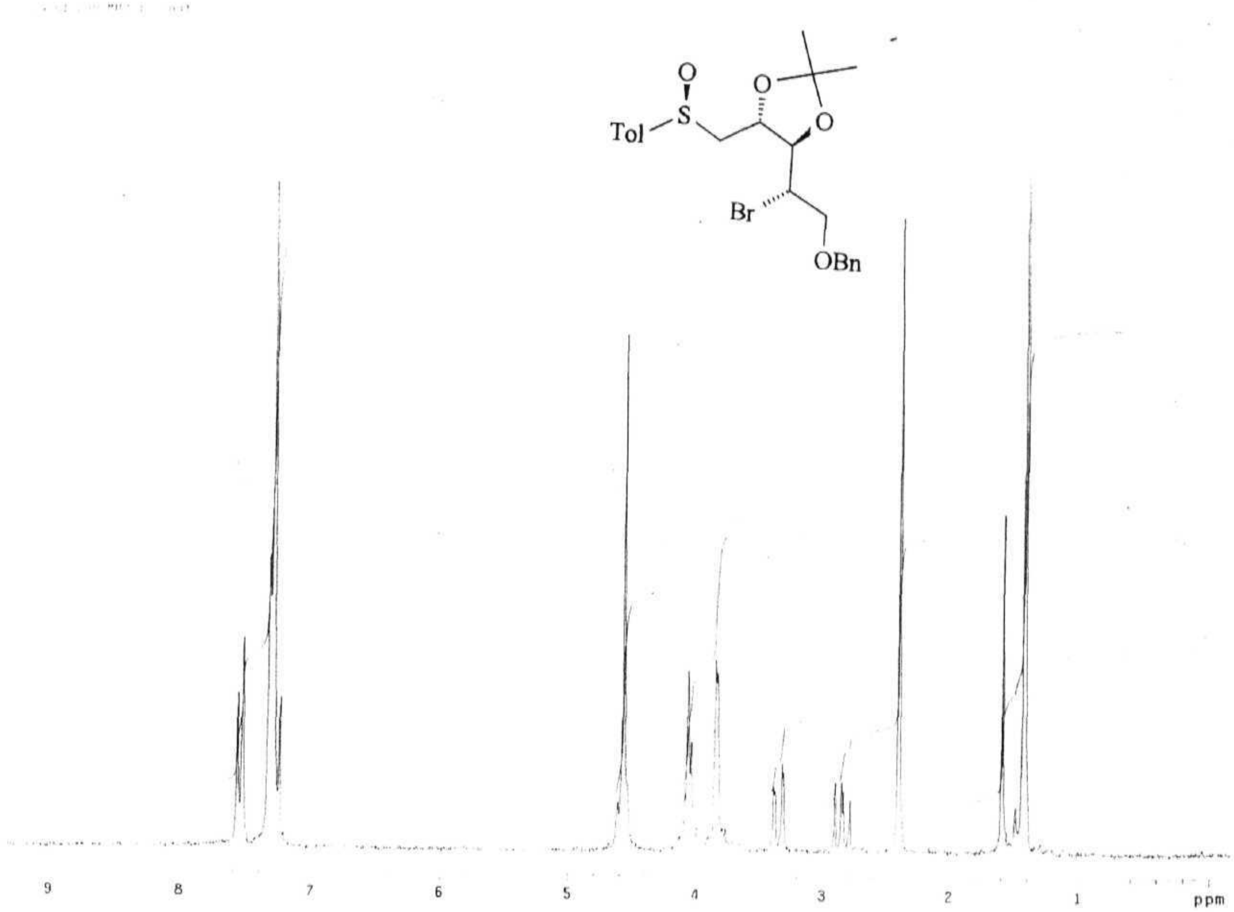
¹³C NMR Spectrum of Compound 63



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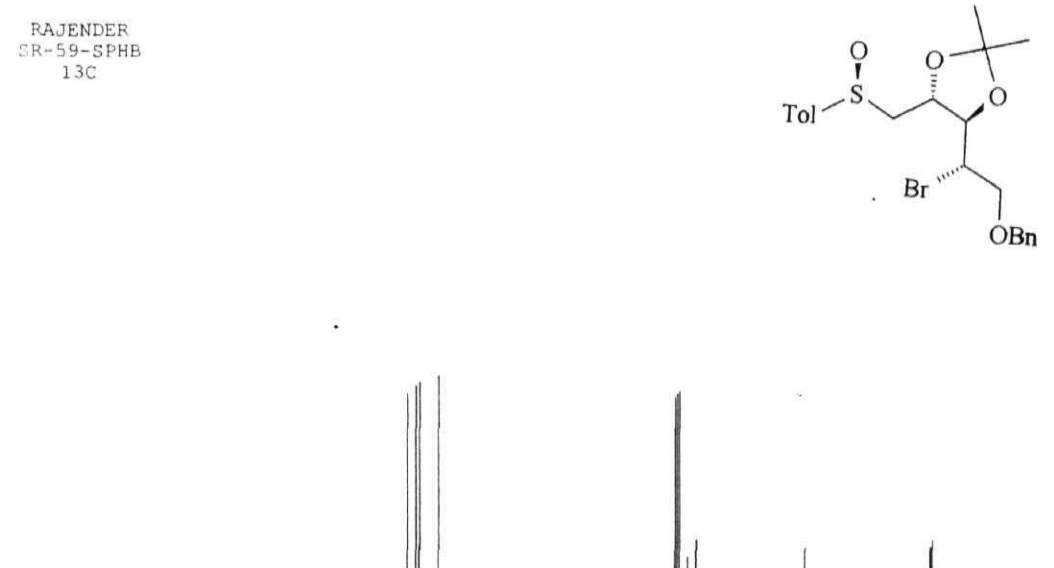

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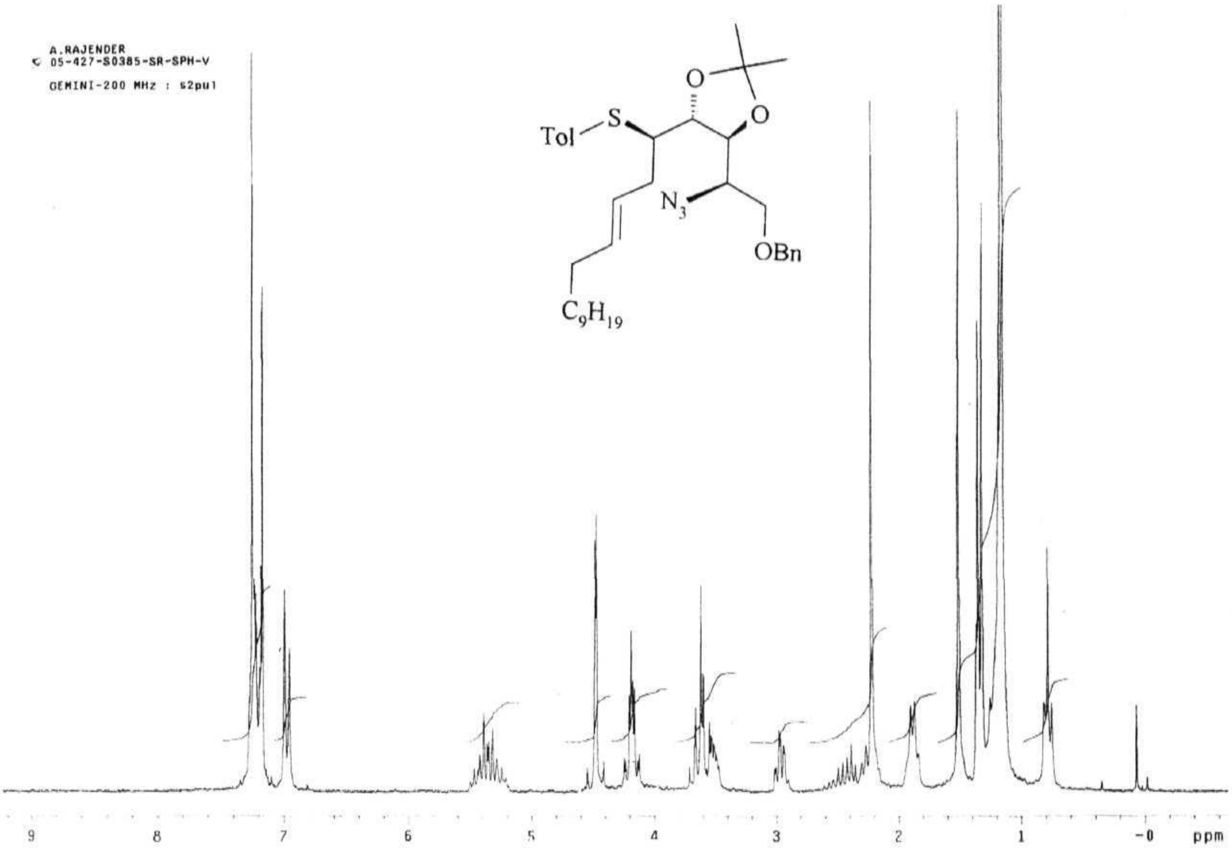

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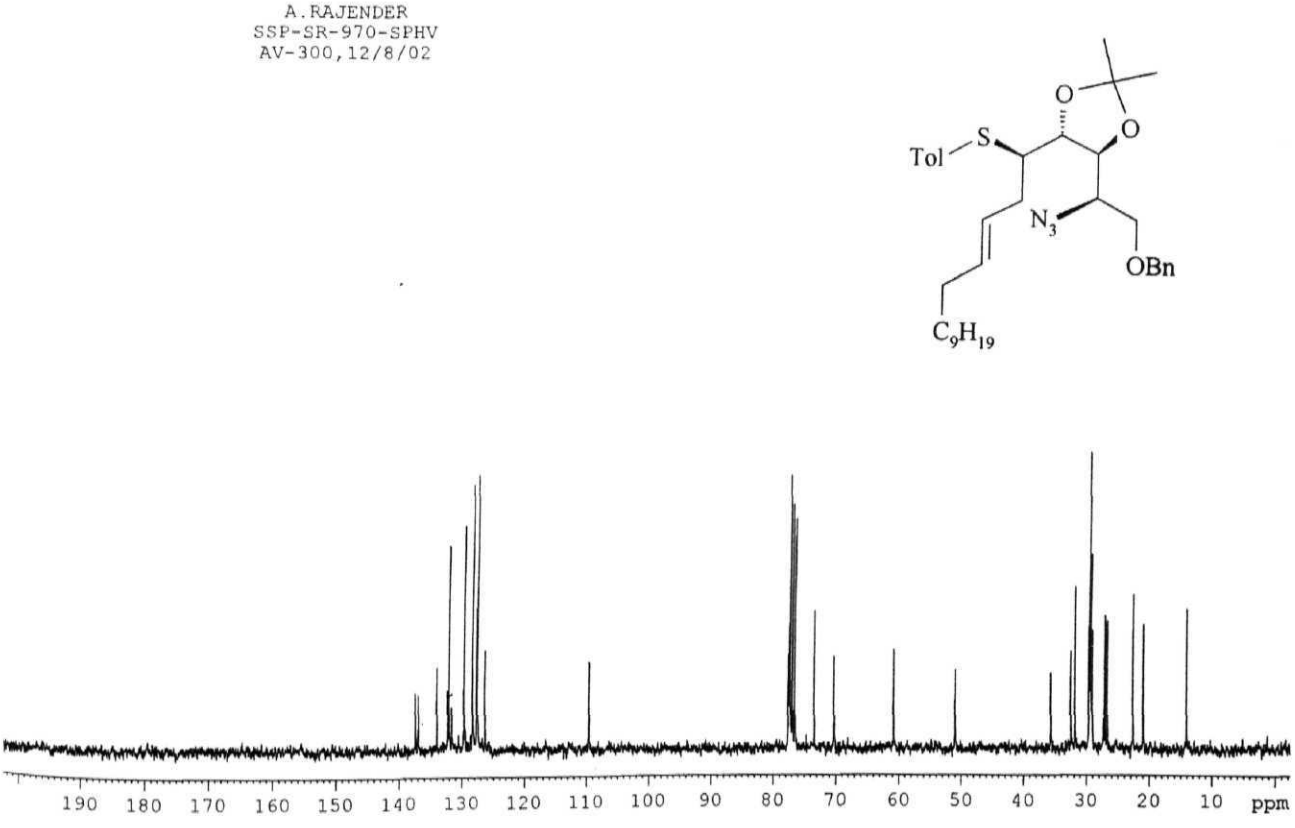
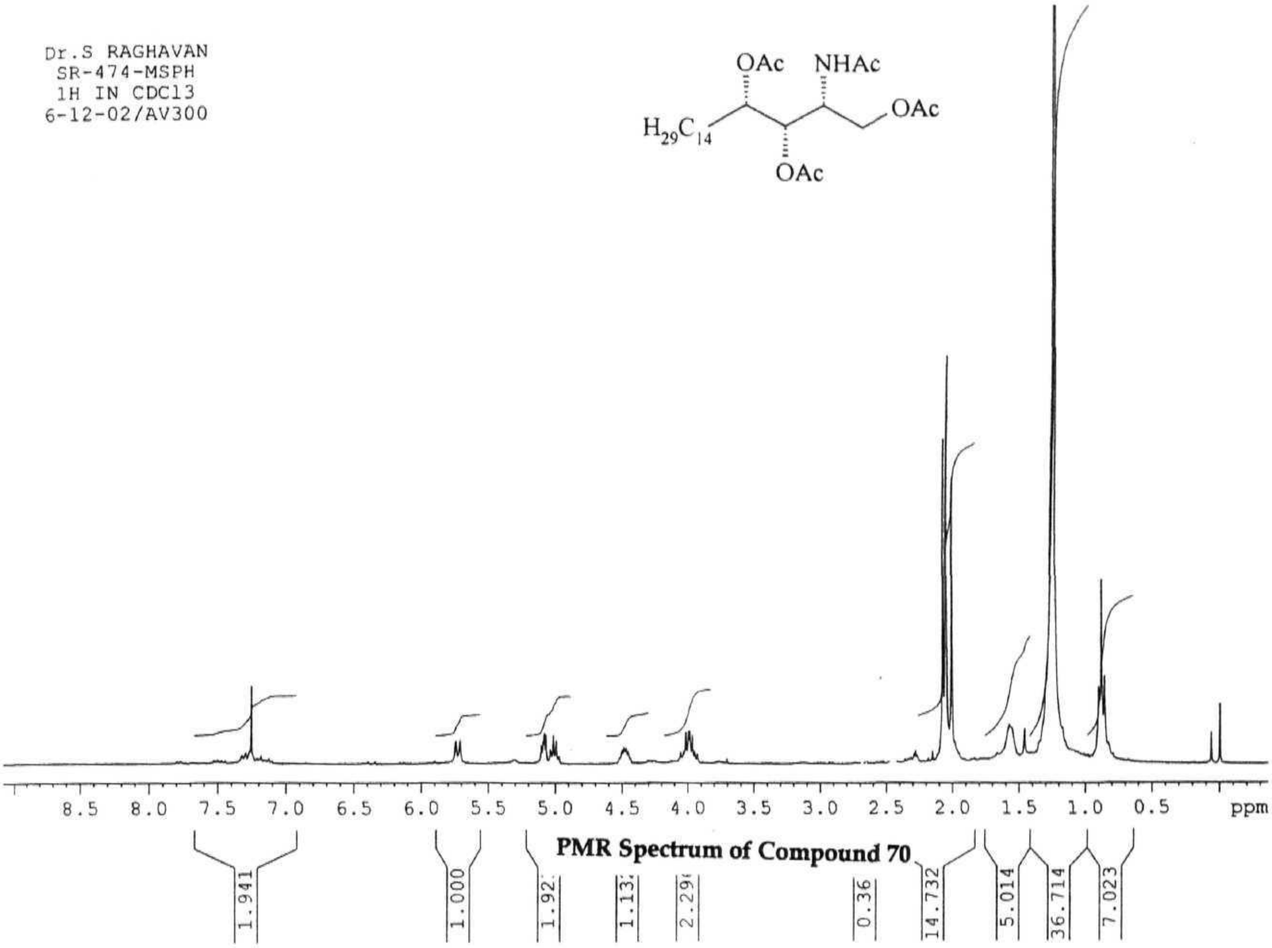
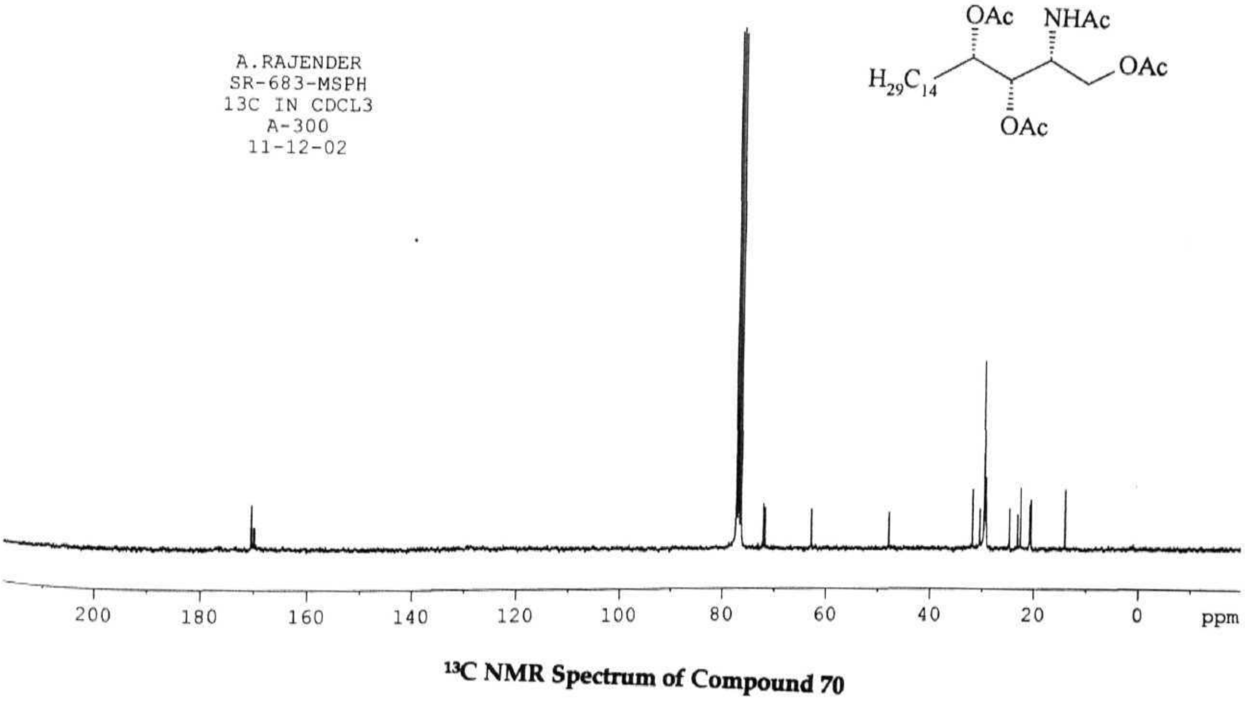


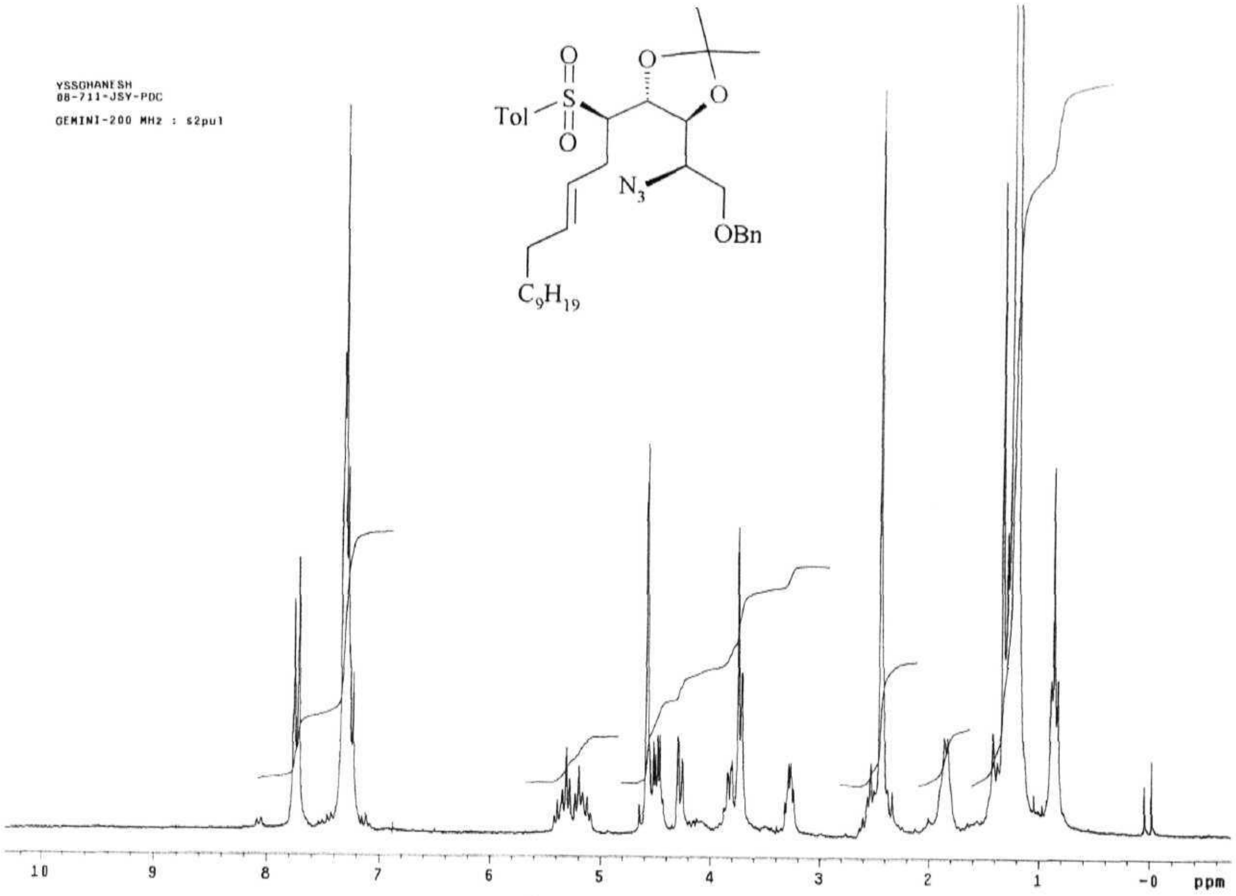
^{13}C NMR Spectrum of Compound 67



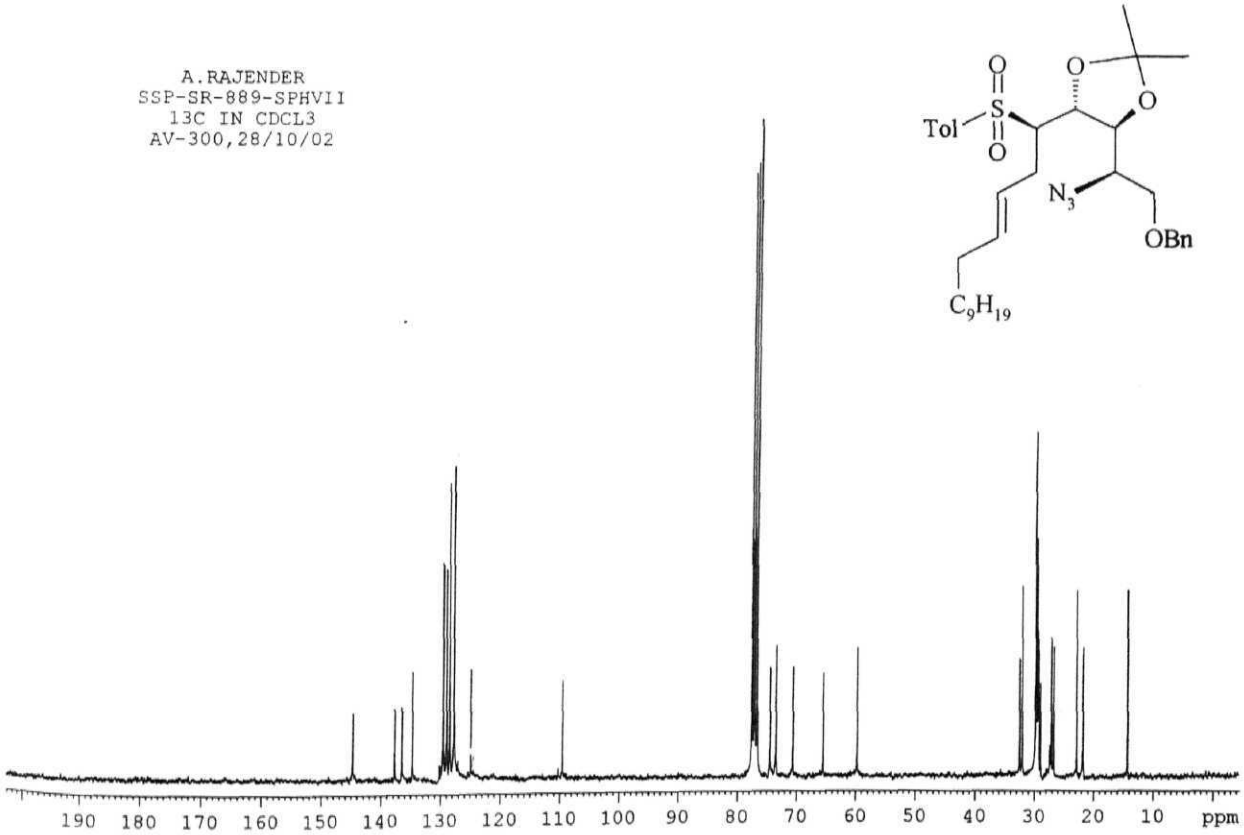
PMR Spectrum of Compound 70



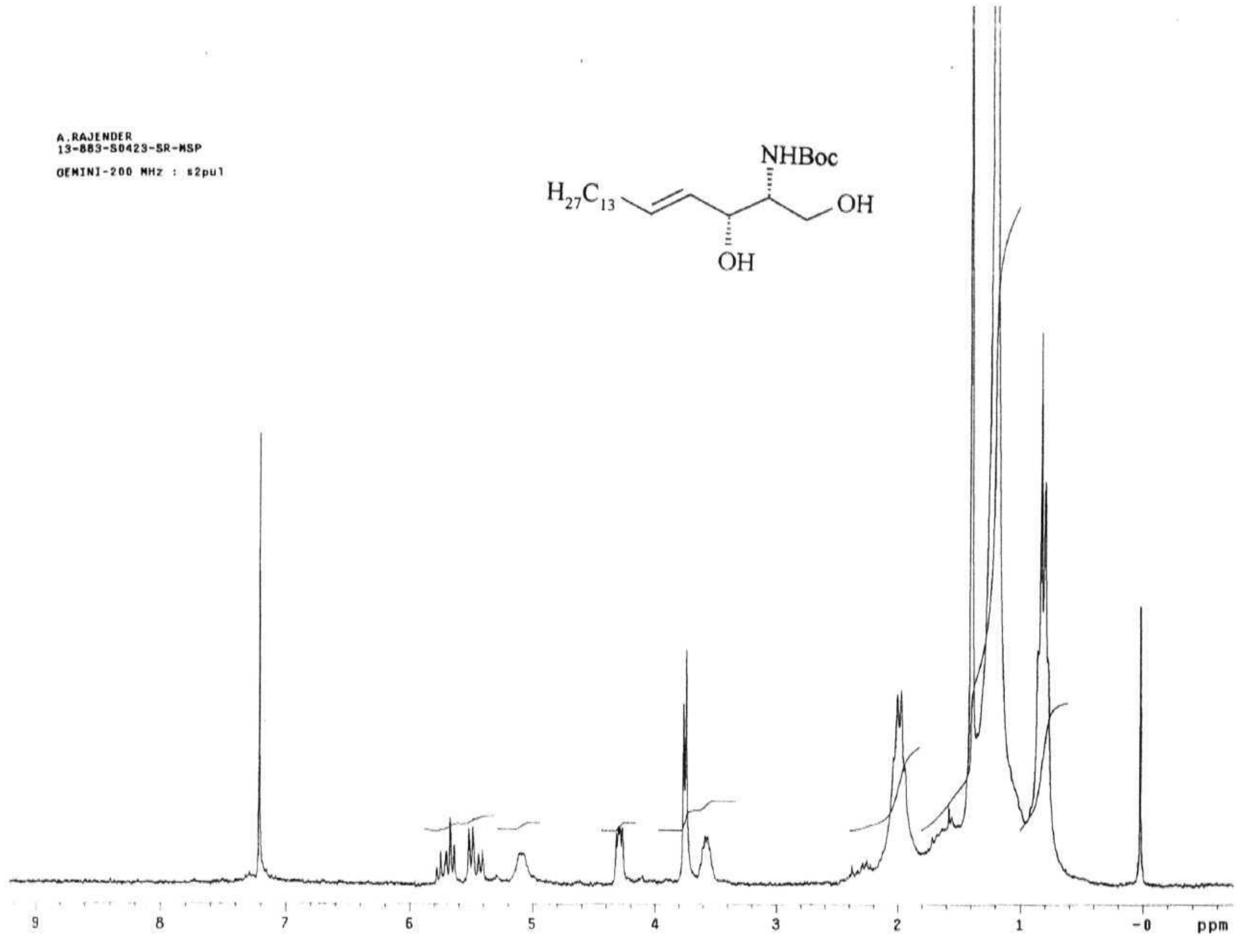
^{13}C NMR Spectrum of Compound 70



PMR Spectrum of Compound 71



^{13}C NMR Spectrum of Compound 71



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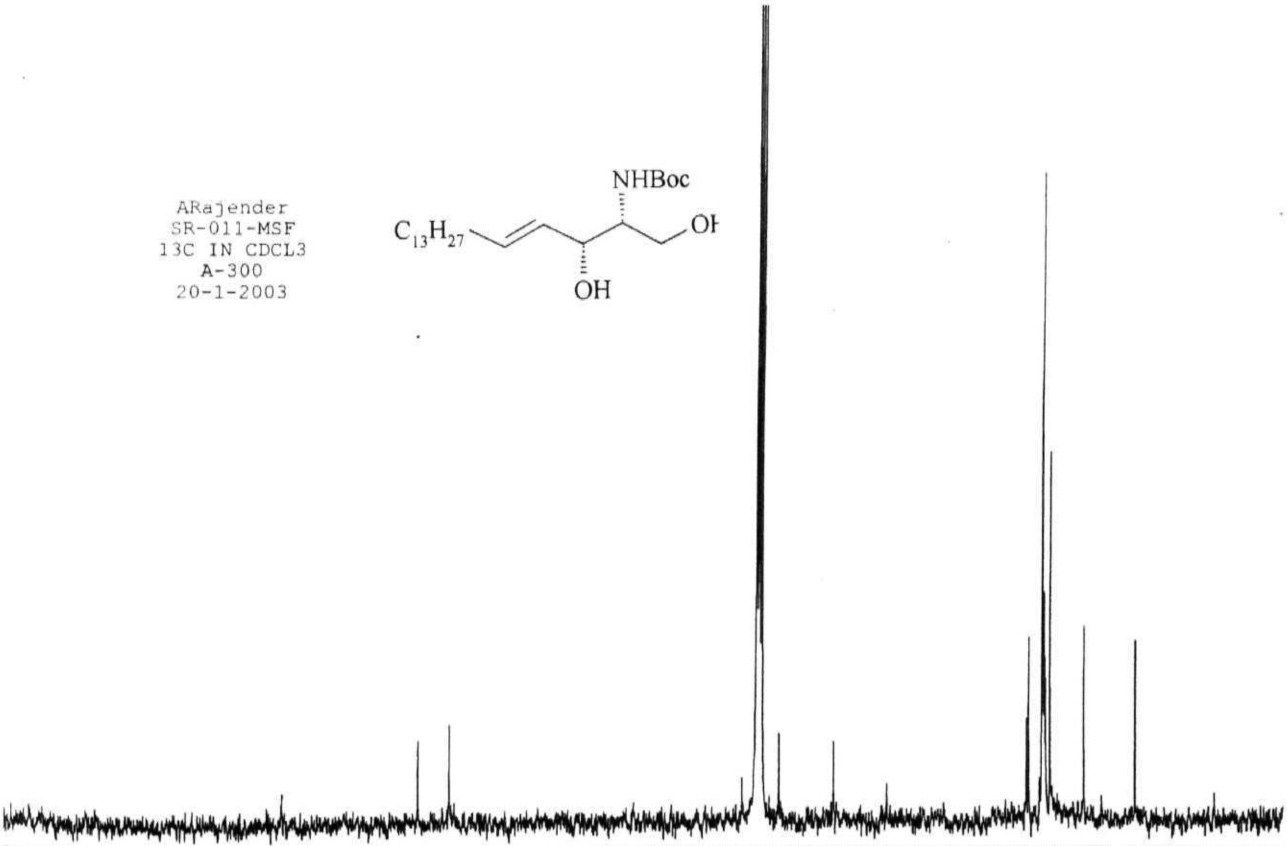
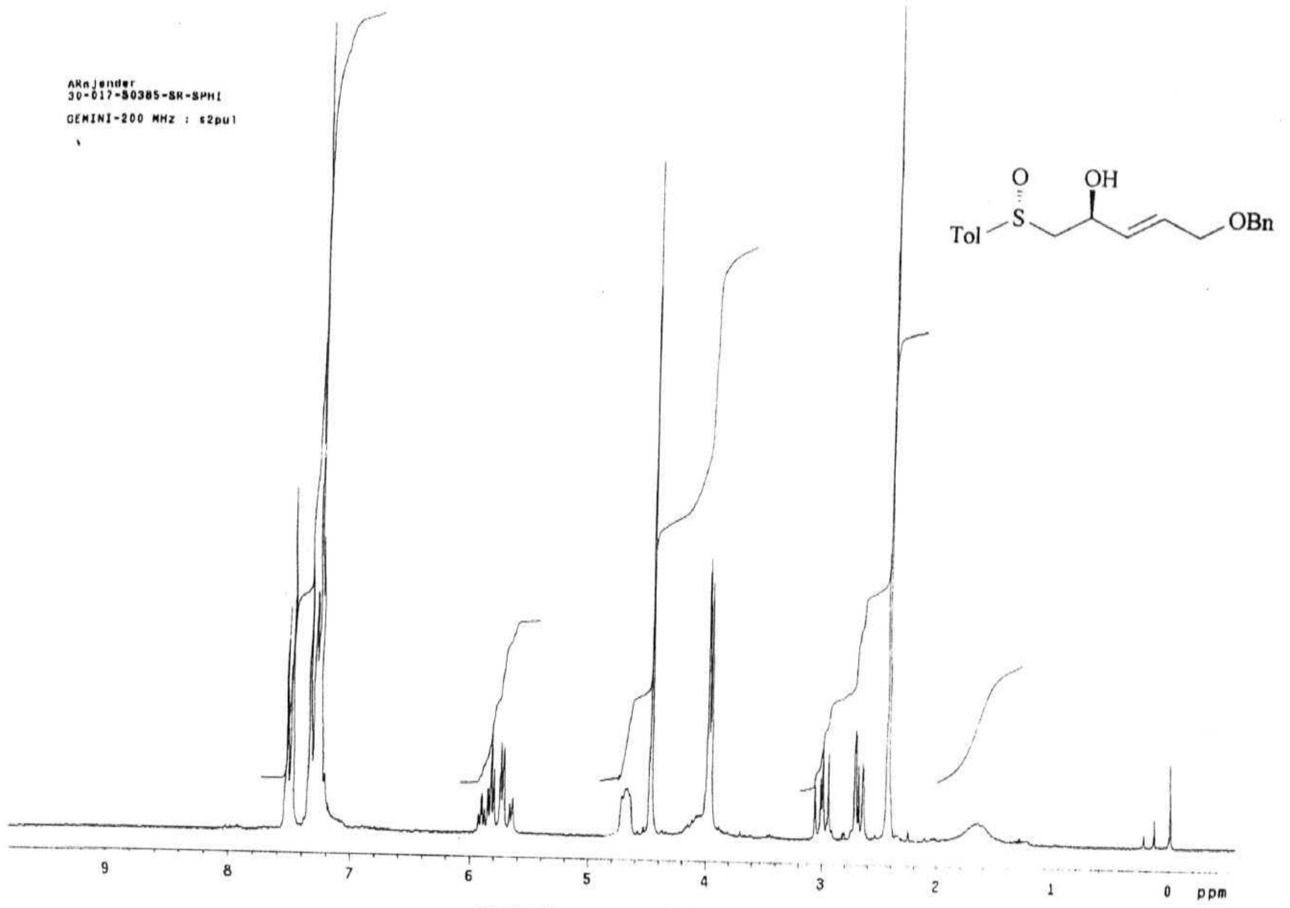
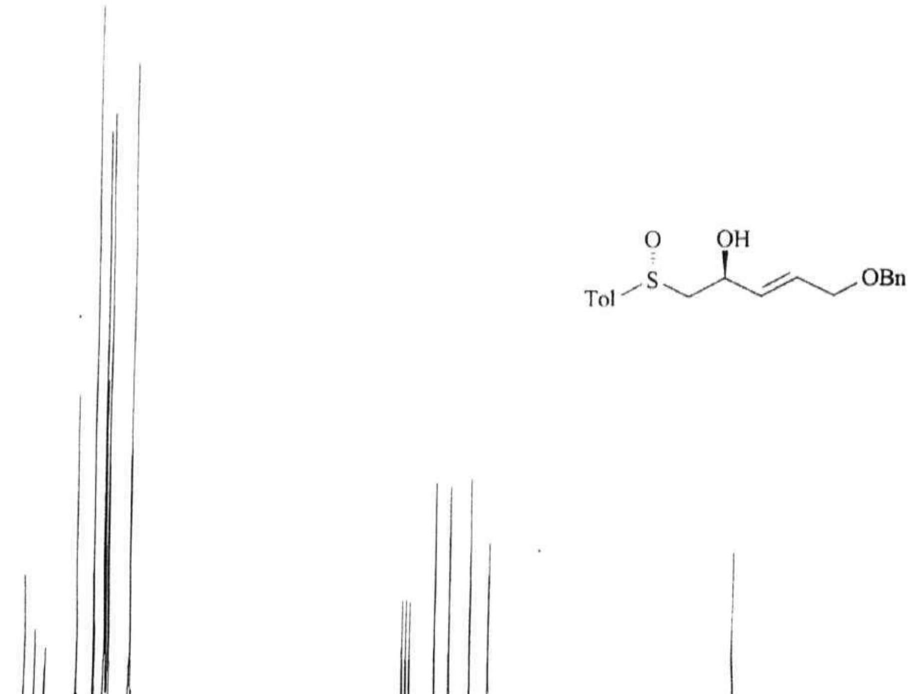


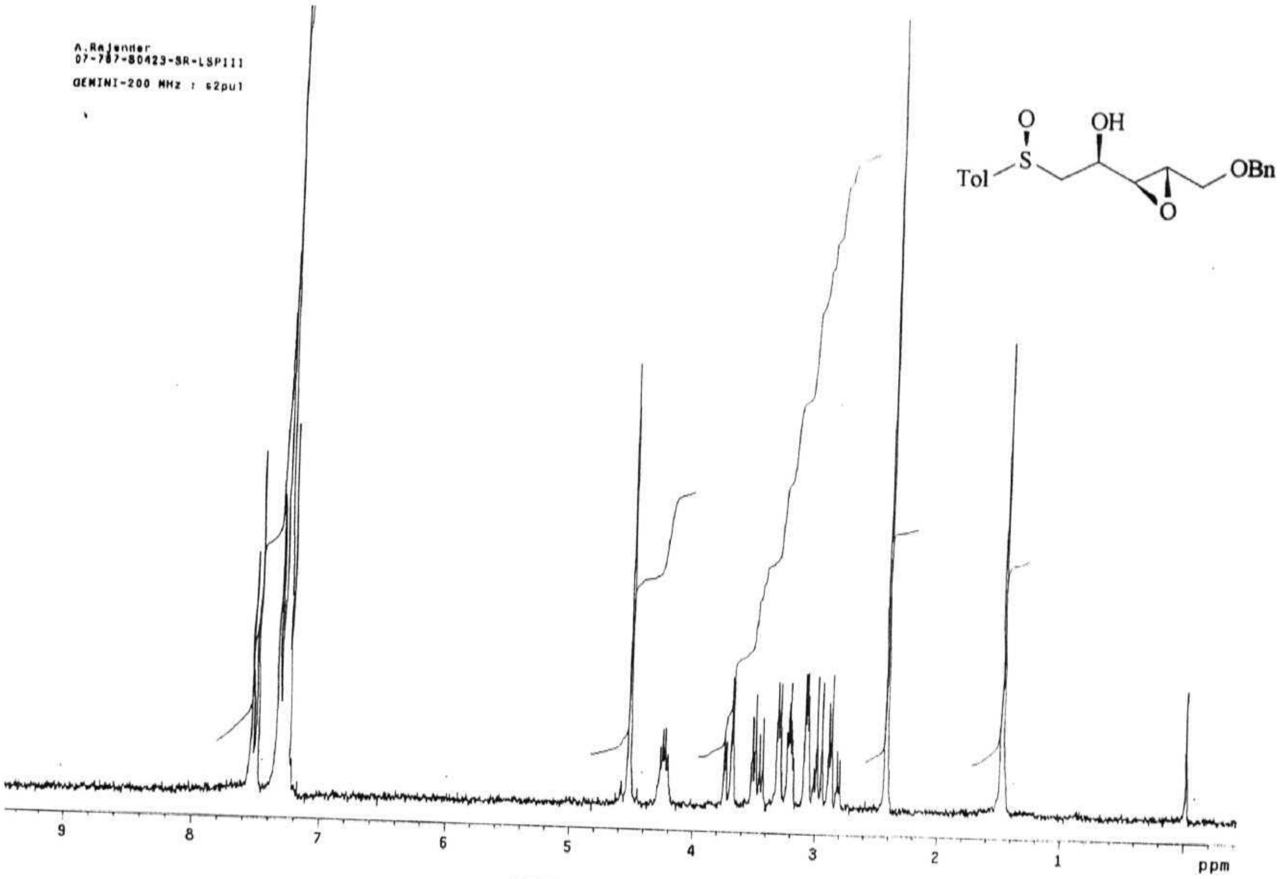
^{13}C NMR Spectrum of Compound 73



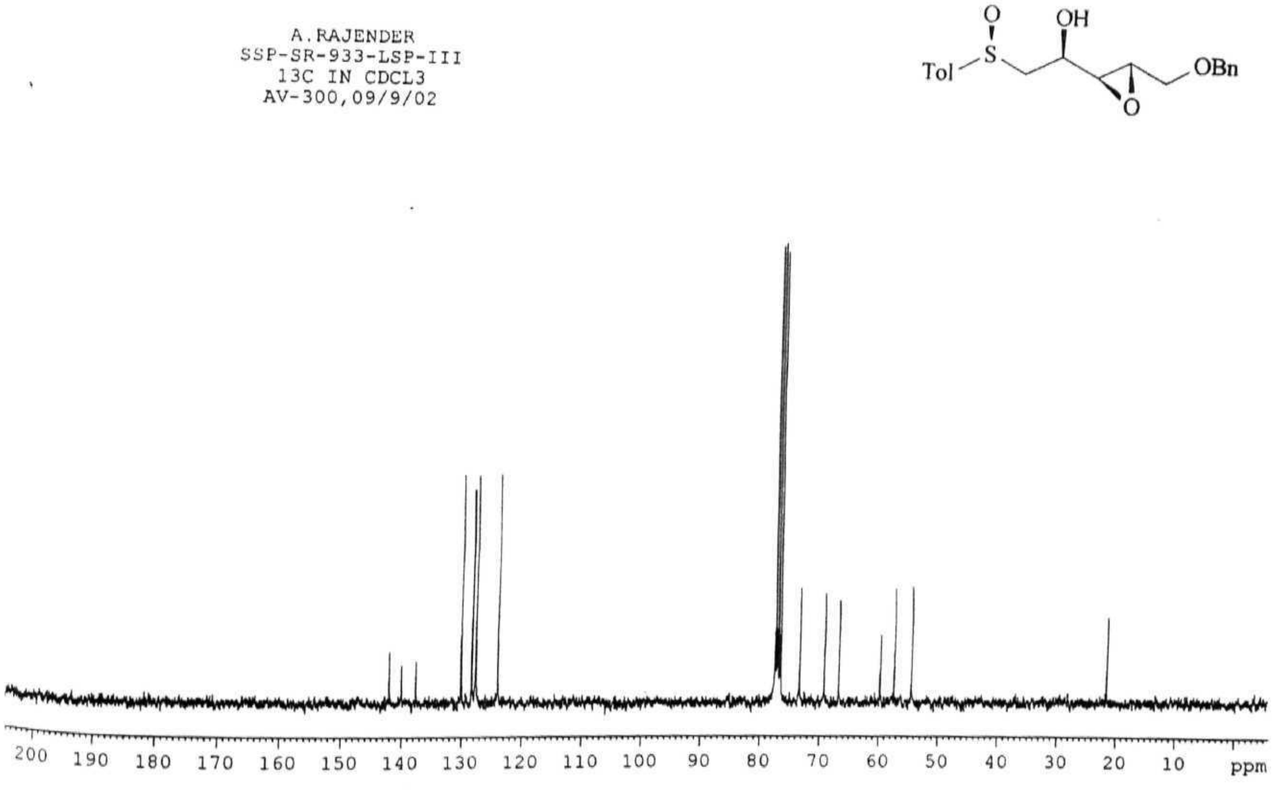
PMR Spectrum of Compound 74



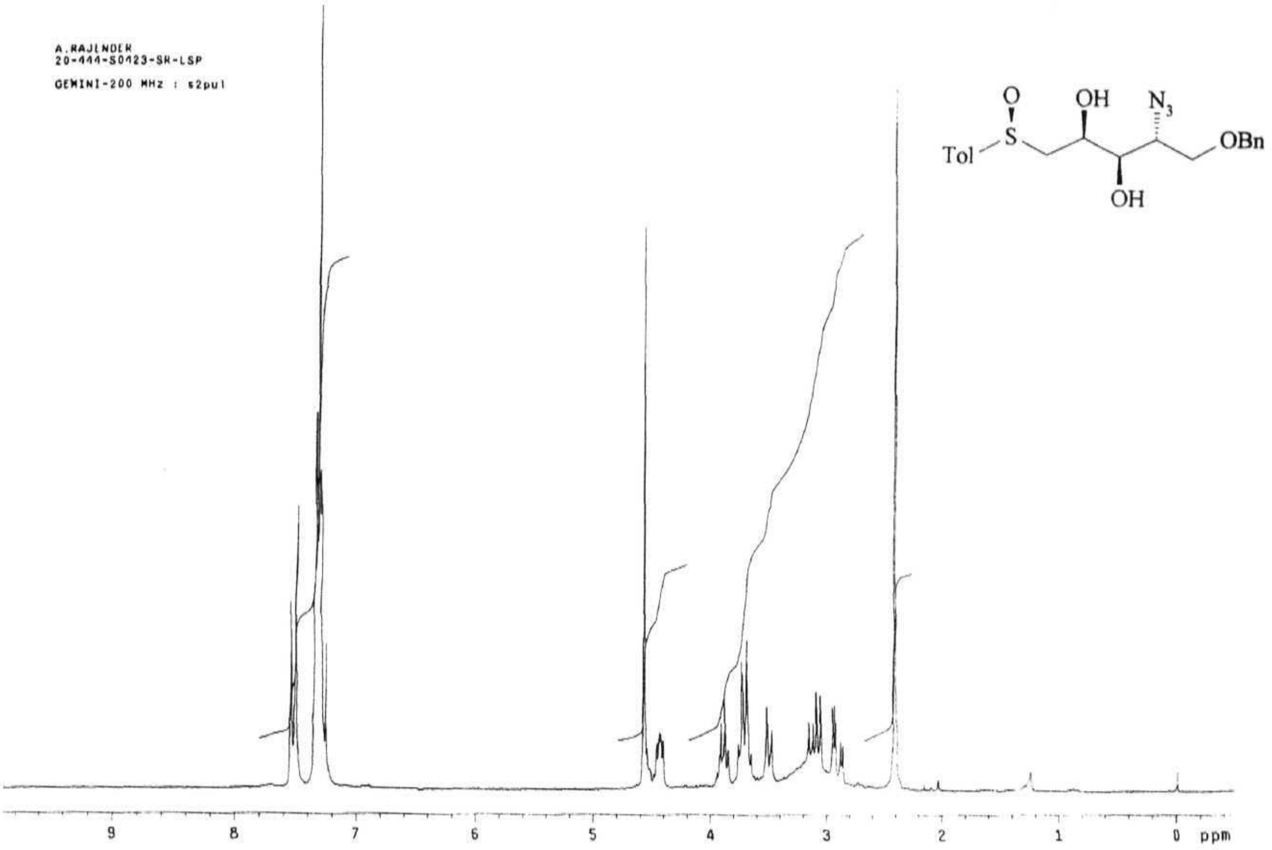
^{13}C NMR Spectrum of Compound 74



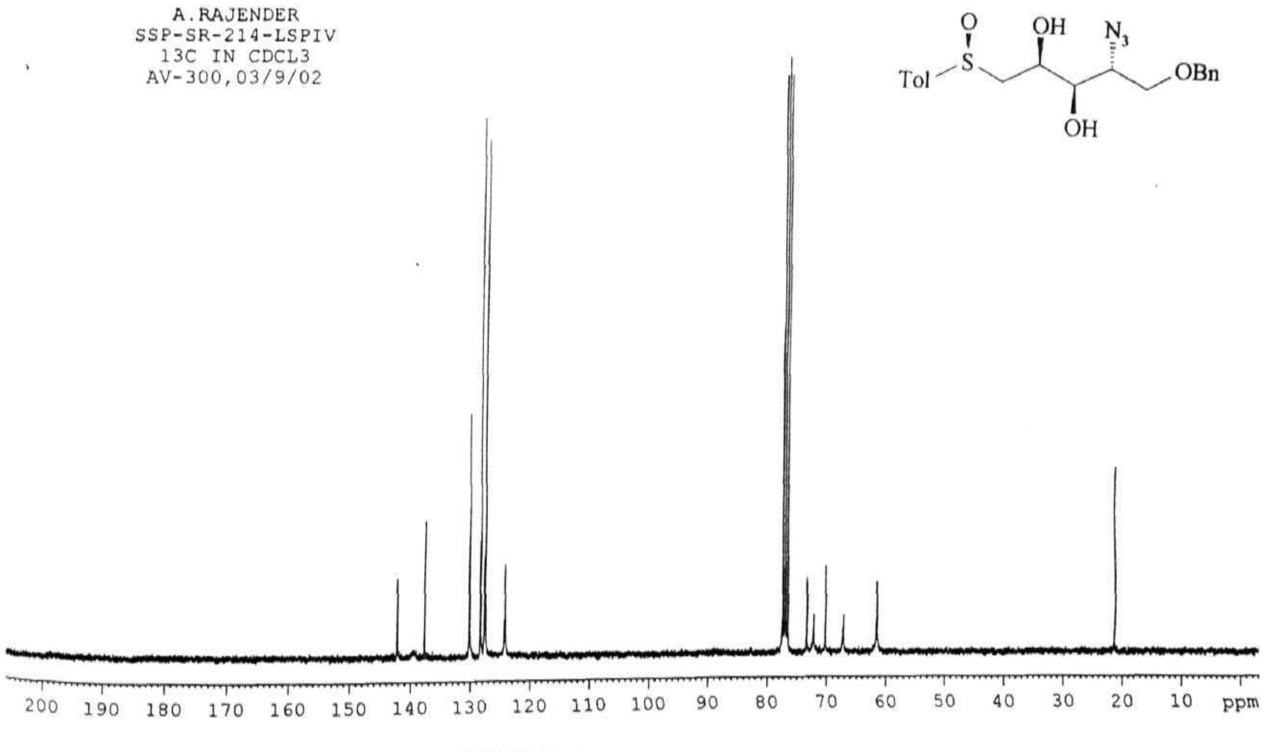
PMR Spectrum of Compound 77



^{13}C NMR Spectrum of Compound 77



PMR Spectrum of Compound 78



^{13}C NMR Spectrum of Compound 78

```
                         Elemental Composition                 Date : 29-APR-2003

File:IICT_HR_LSPIII Ident:4_15 SMO(1,7) PKD(7,3,7,0.50%,0.0,0.00%,F,F)
AutoSpec FAB+ Voltage BpI:2659011 TIC:335131136 Flags:NORM
File Text:A RAJENDER LSP-III FAB HRMS
 Heteroatom Max:    20     Ion:  Both Even and Odd
 Limits:

 347.000      0.0                                  -0.5    0    0    0    0    0
 349.000    100.0            5.0                   20.0   19    1  400    4    1

    Mass      %RA    mDa    PPM   Calc. Mass       DBE    C  13C    H    O    S

 348.136261   2.1   -1.2   -3.4   348.135061       8.5   18    1   23    4    1
 347.133214   3.9   -1.5   -4.3   347.131706       8.5   19        23    4    1

 Statistic calculations

                      mDa  | PPM
                    --------------
 Mean               -1.35  |  -3.89    n = 2
  RMS                1.36  |   3.92
   SD                0.22  |   0.63
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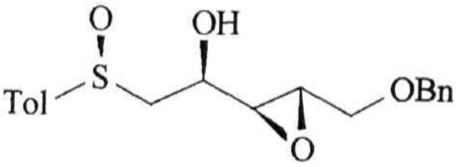

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                         Elemental Composition                 Date : 29-APR-2003

File:IICT_HR_LSPIV Ident:9_18 SMO(1,7) PKD(7,3,7,0.50%,0.0,0.00%,F,F)
AutoSpec FAB+ Voltage BpI:396640 TIC:72530256 Flags:NORM
File Text:A RAJENDER LSP-IV FAB HRMS
 Heteroatom Max:    20     Ion:  Both Even and Odd
 Limits:

 390.000      0.0                                  -0.5    0    0    0    0    0
 391.000    100.0            5.0                   20.0   19   30    3    4    1

    Mass      %RA    mDa    PPM   Calc. Mass       DBE    C    H    N    O    S

 390.147874  16.0    0.9    2.3   390.148753       9.5   19   24    3    4    1

 Statistic calculations

                      mDa  | PPM
                    --------------
 Mean                0.88  |   2.26    n = 1
  RMS                0.88  |   2.26
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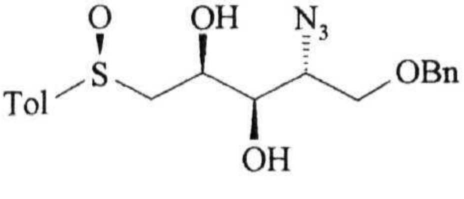
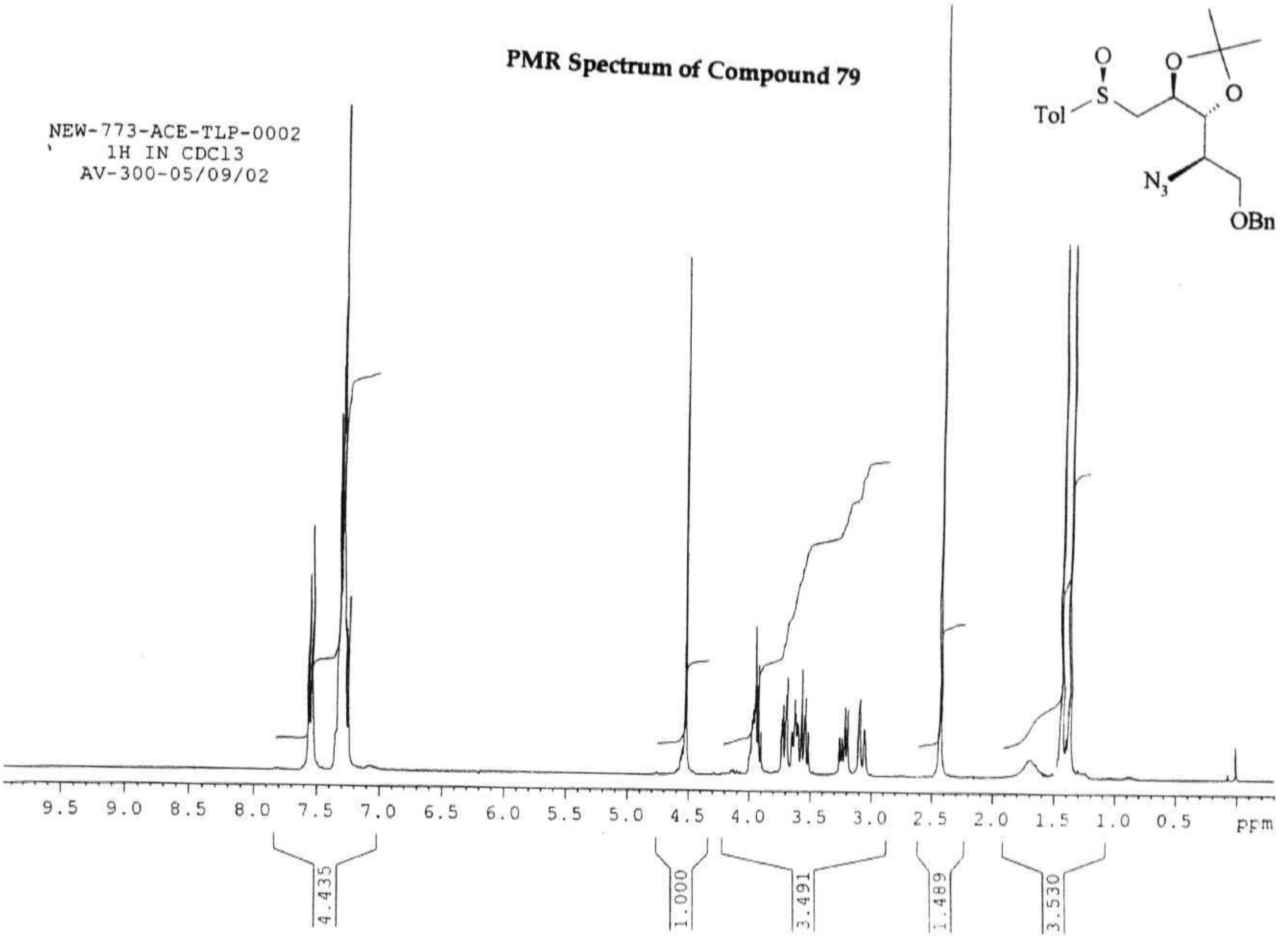
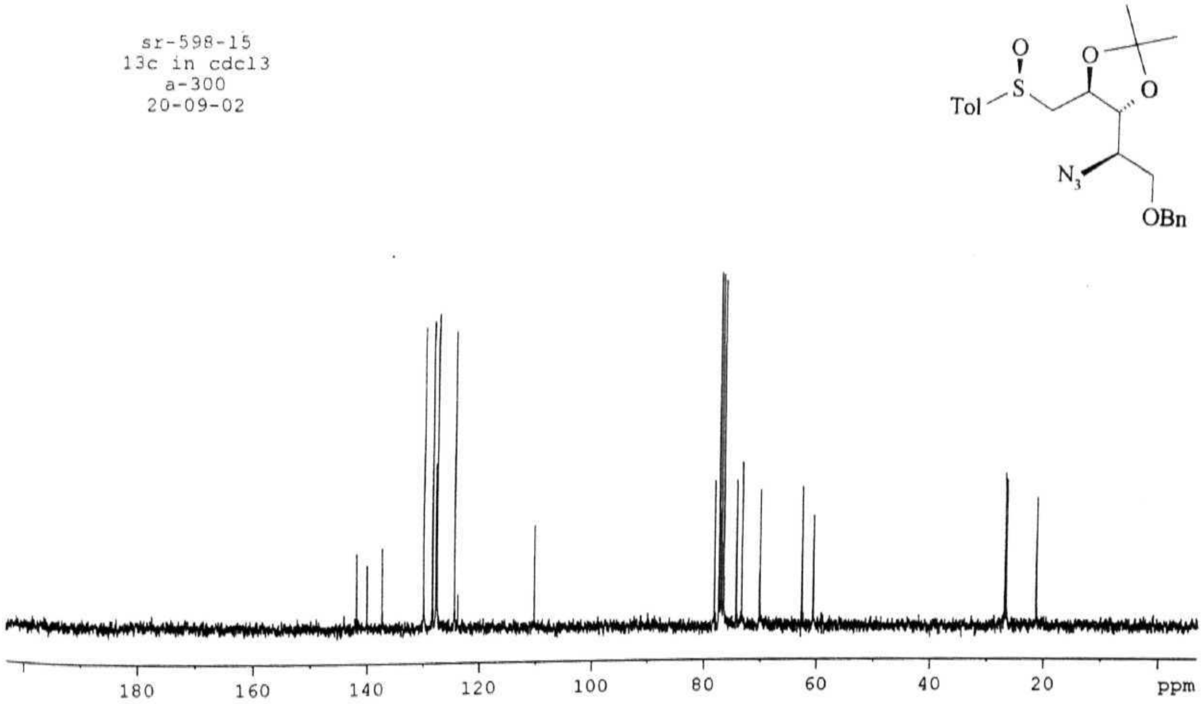
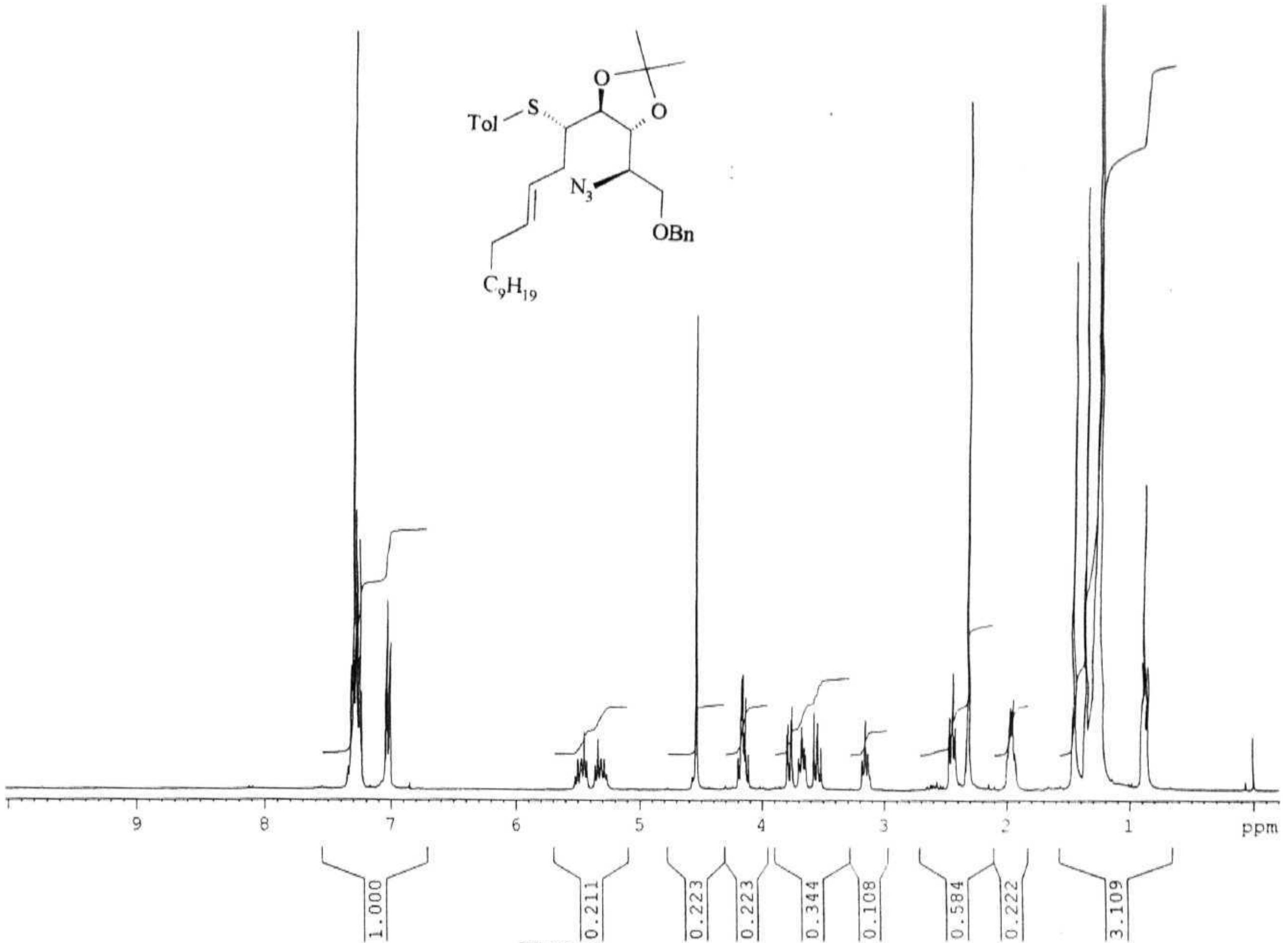


PMR Spectrum of Compound 79

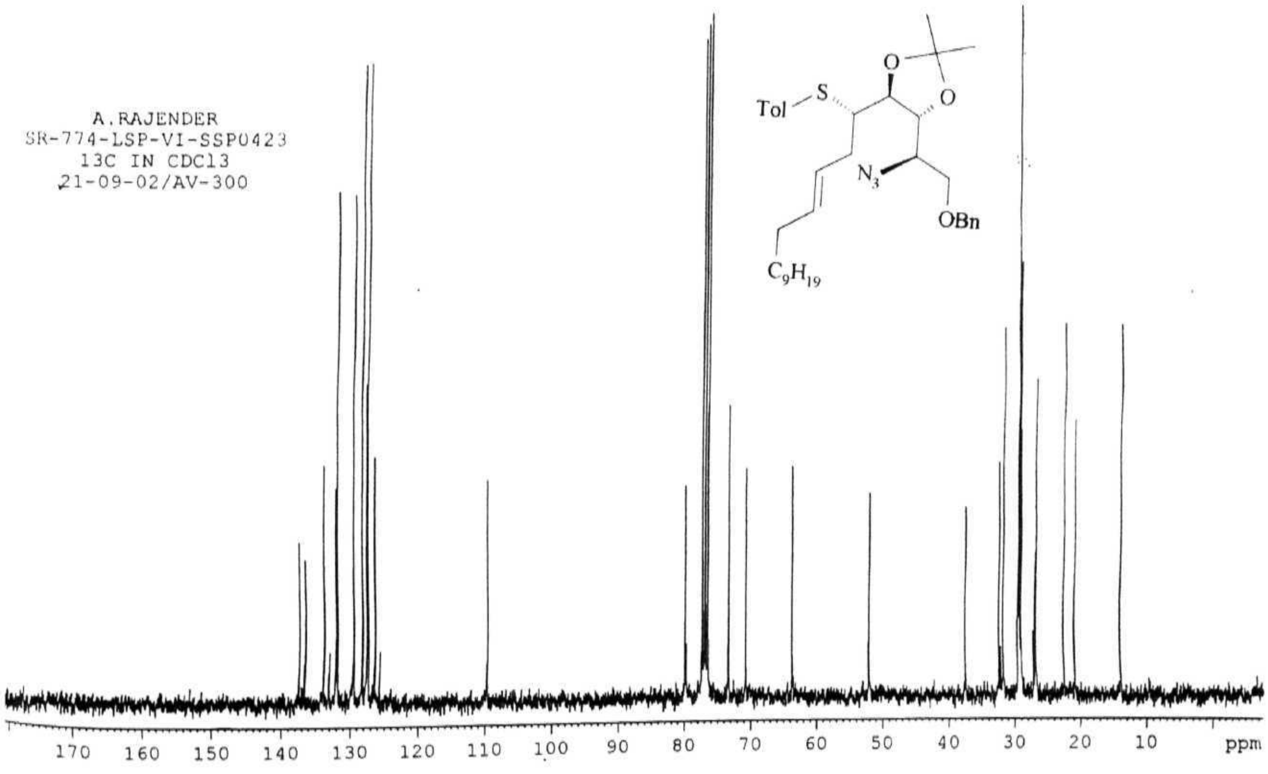




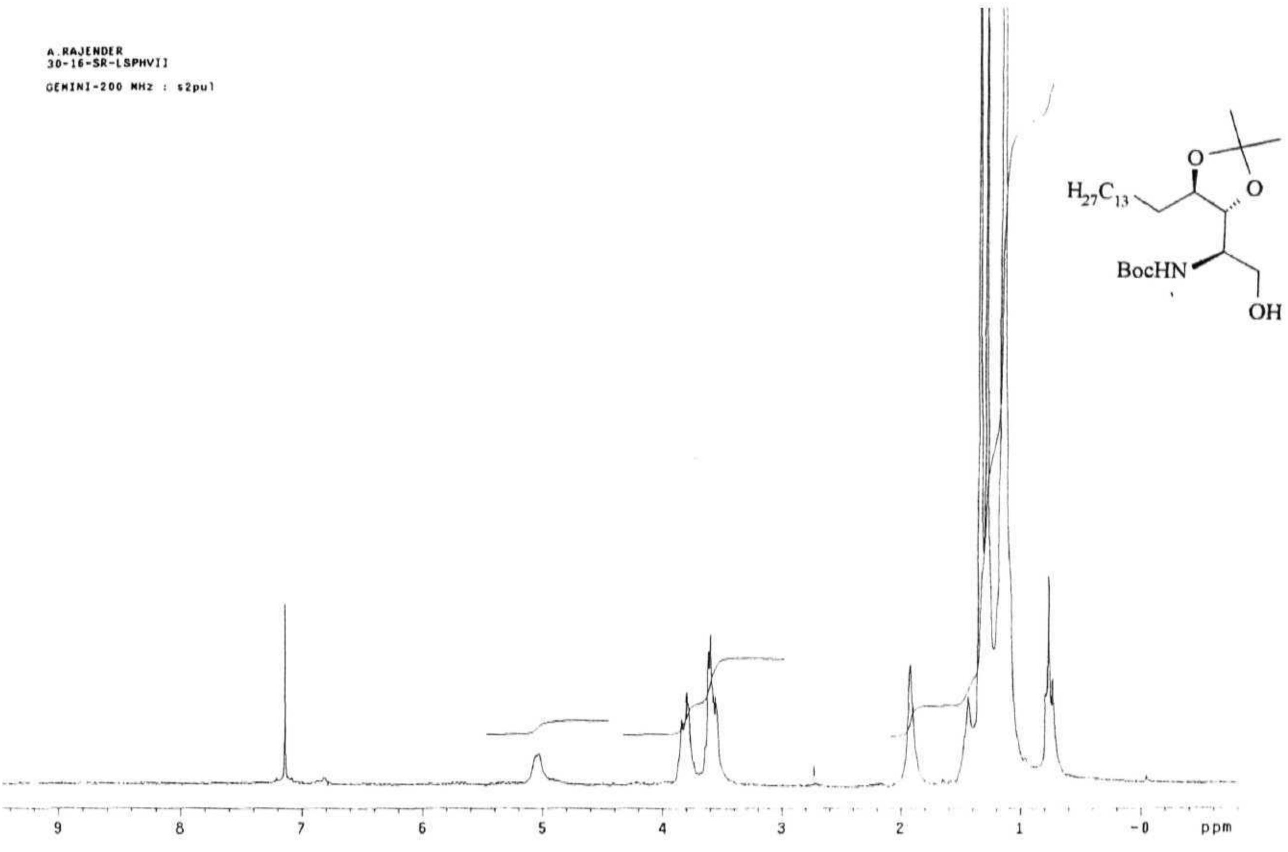
^{13}C NMR Spectrum of Compound 79



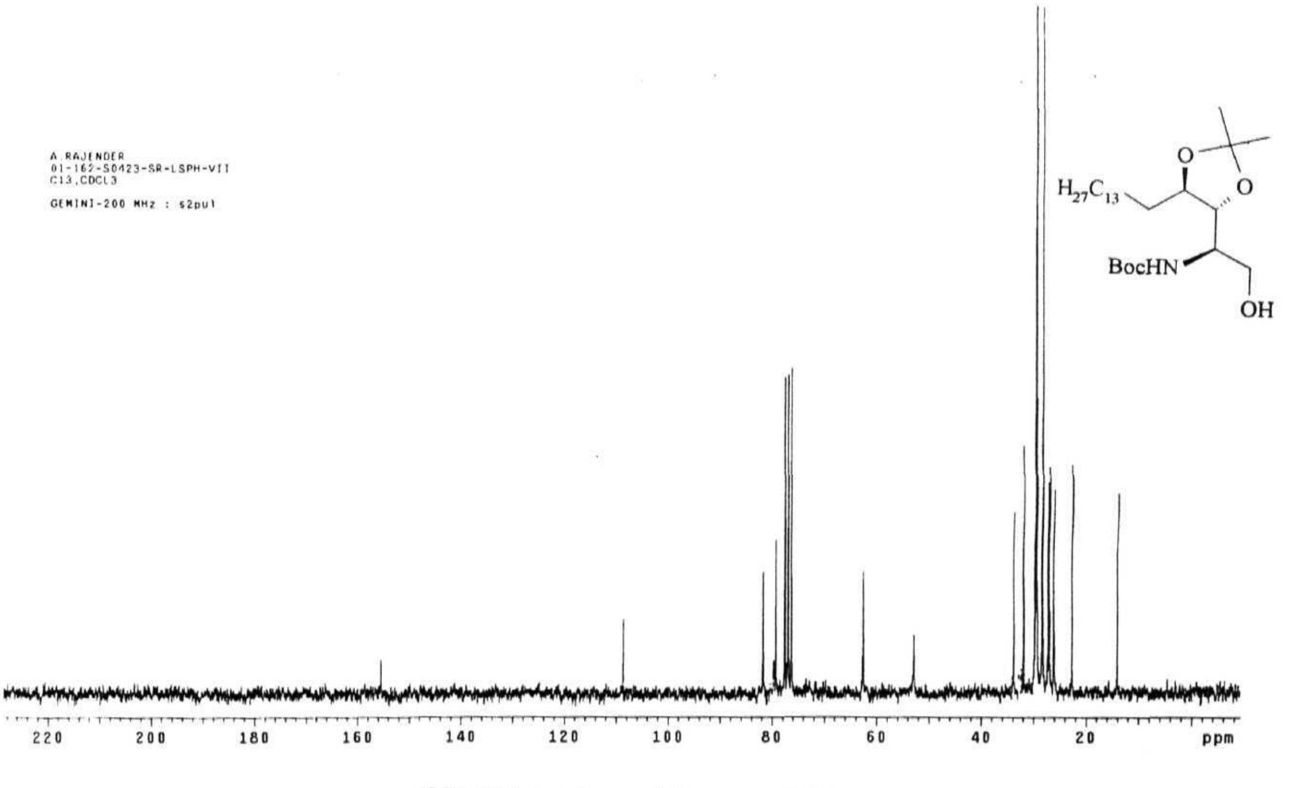
PMR Spectrum of Compound 81



^{13}C NMR Spectrum of Compound 81

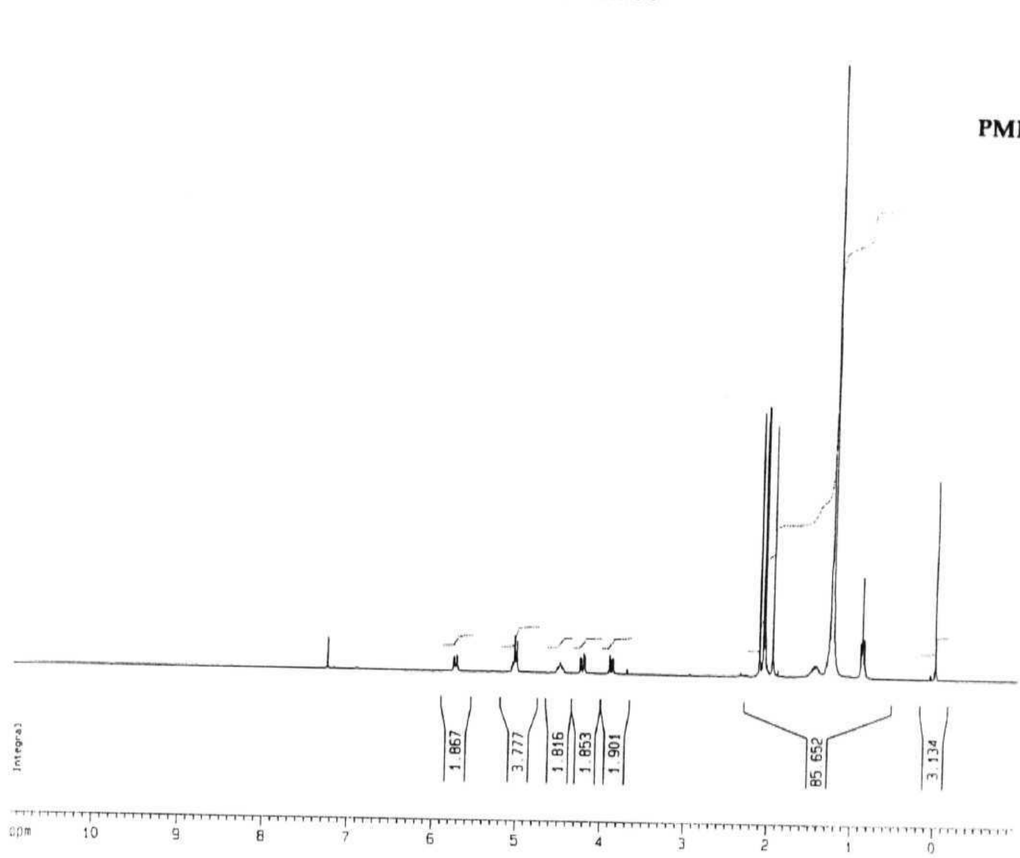


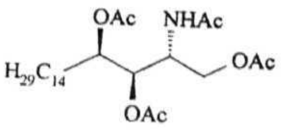
PMR Spectrum of Compound 82



^{13}C NMR Spectrum of Compound 82

a rajender
sr-594 lsph
PROTON CDCl3 {D \u} routine 27





PMR Spectrum of Compound 84

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INSTRUM              av300
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PULPROG               zg30
TD                   32768
SOLVENT              CDCl3
NS                      16
DS                       2
SWH            6188.119 Hz
FIDRES         0.188846 Hz
AQ           2.6477852 sec
RG                     362
DW             80.800 usec
DE               6.00 usec
TE                 300.0 K
D1          1.00000000 sec

******** CHANNEL f1 ********
NUC1                    1H
P1              10.00 usec
PL1               -2.00 dB
SFO1        300.1318534 MHz

F2 - Processing parameters
SI                   32768
SF          300.1300054 MHz
WDW                     EM
SSB                      0
LB                 0.30 Hz
GB                       0
PC                    1.00

1D NMR plot parameters
CX                20.00 cm
CY                12.50 cm
F1P             11.000 ppm
F1              3301.43 Hz
F2P             -1.000 ppm
F2              -300.13 Hz
PPMCM       0.60000 ppm/cm
HZCM       180.07800 Hz/cm
```
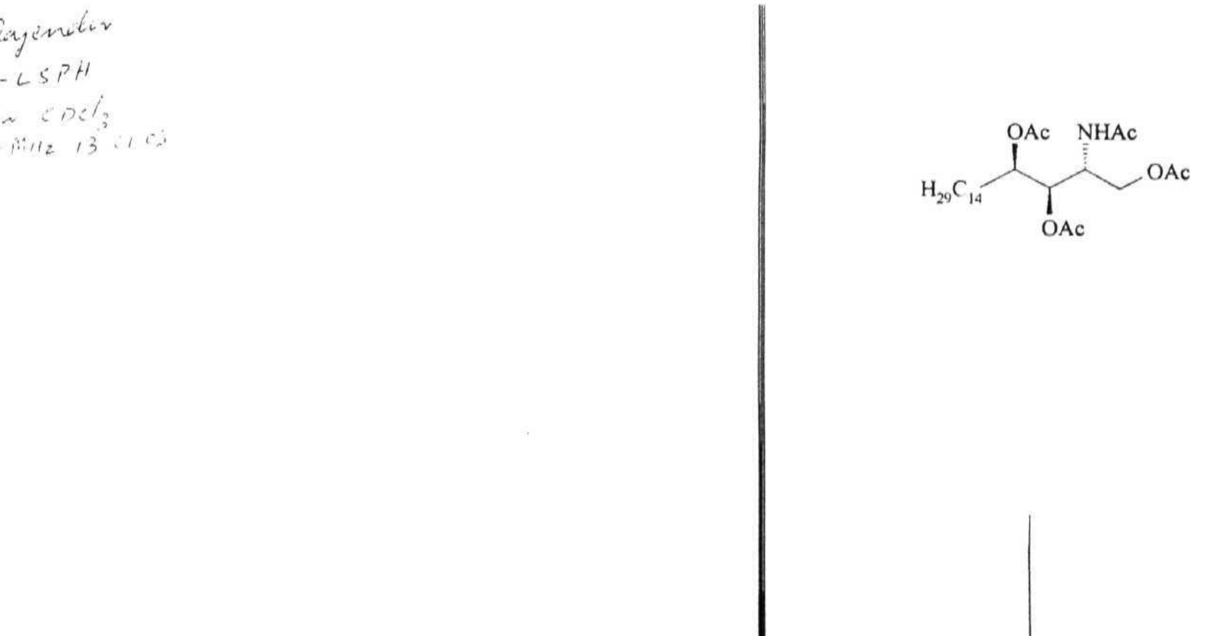
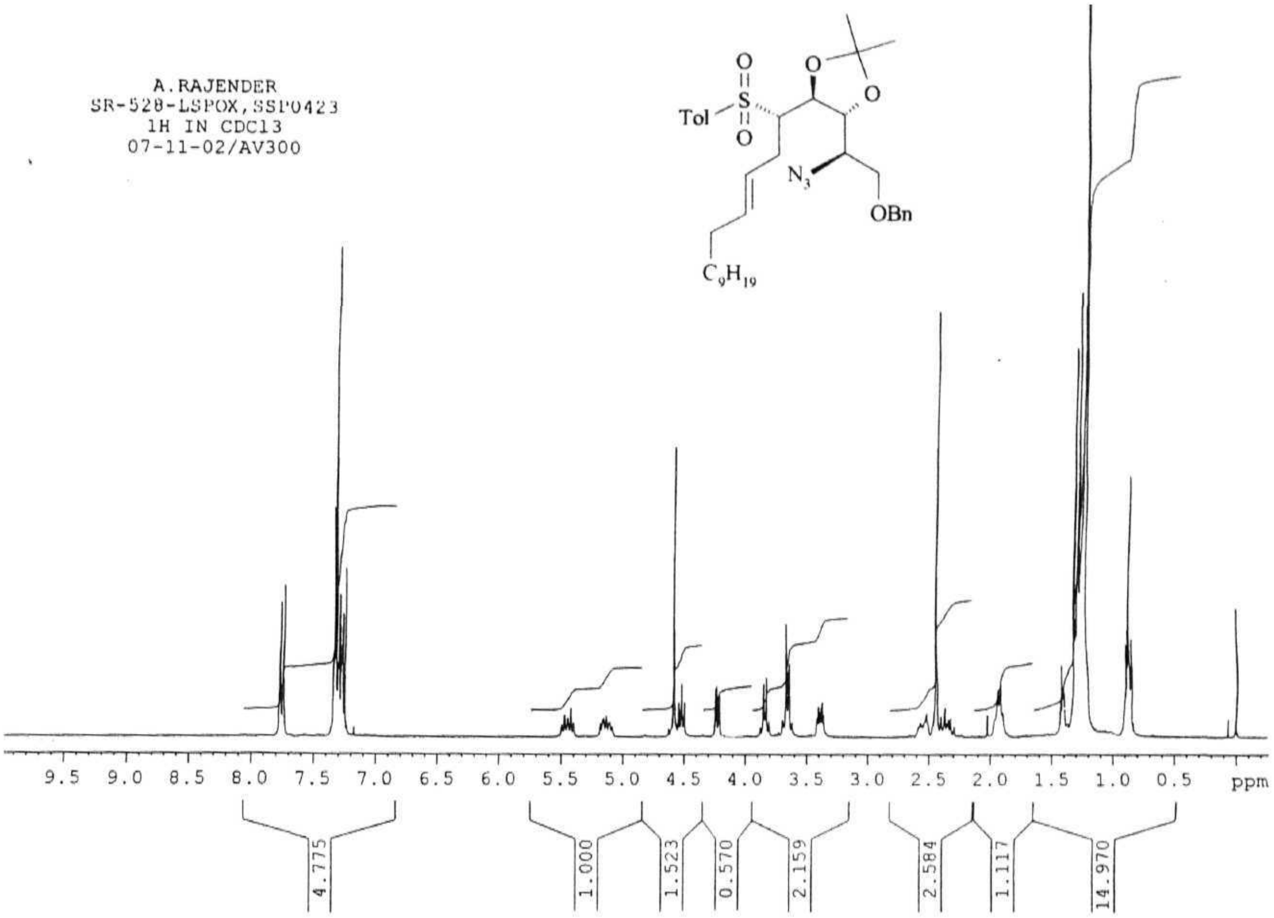
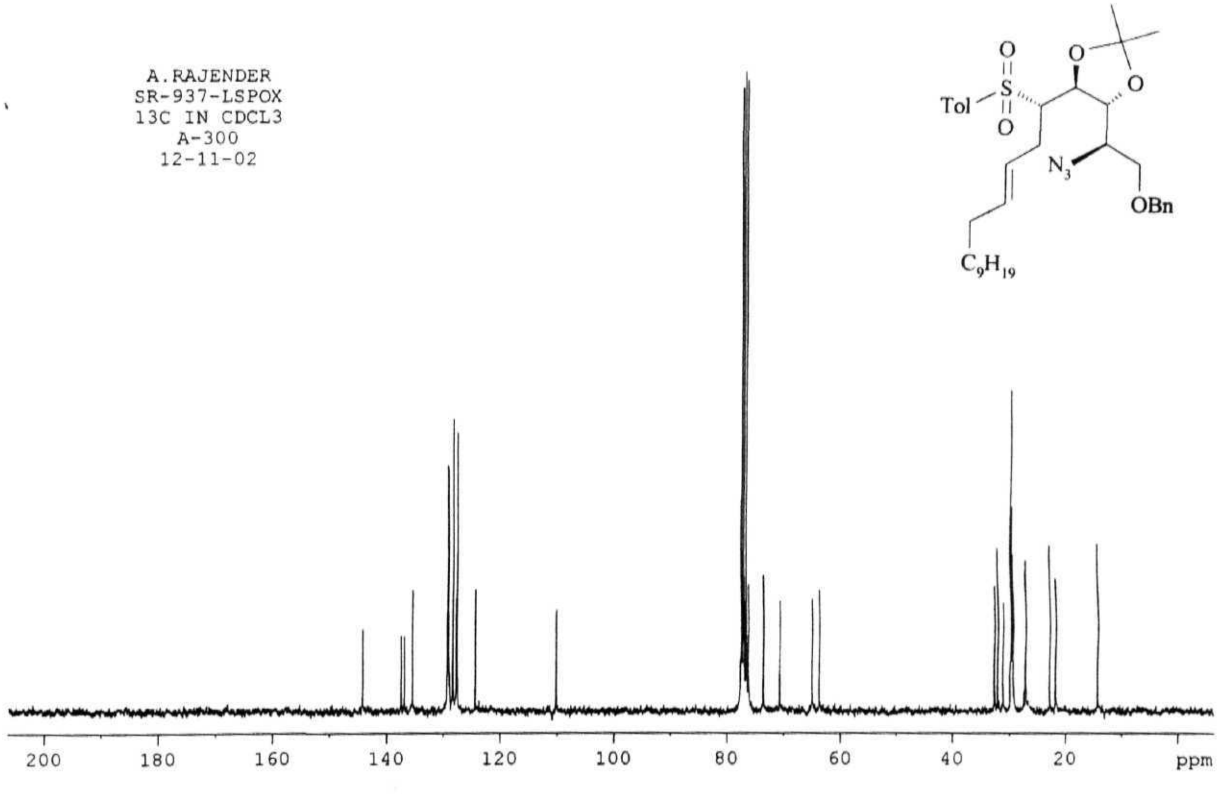

A Rajender
DR-LSPH
S in CDCl3
[illegible] 300 MHz 13 C [illegible]



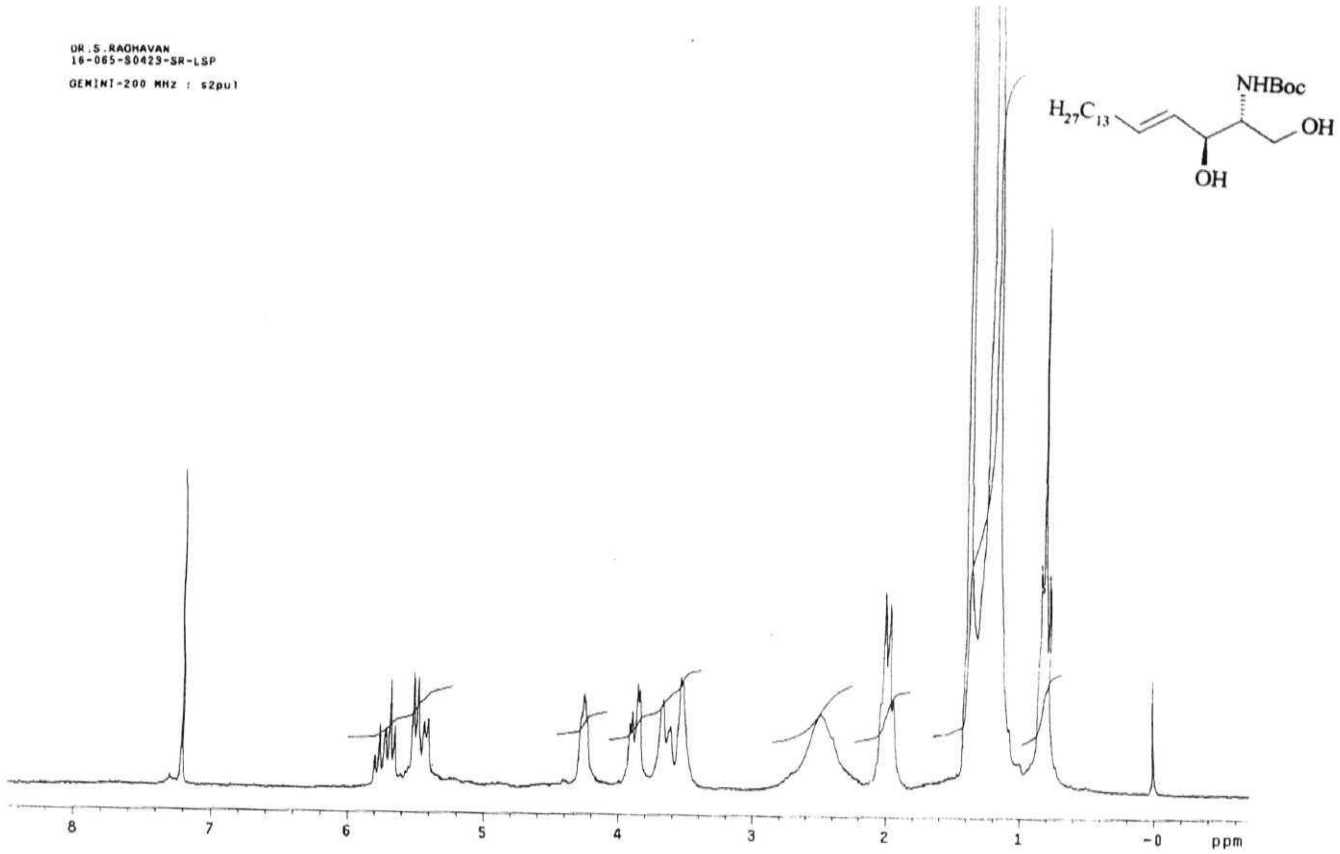
^{13}C NMR Spectrum of Compound 84



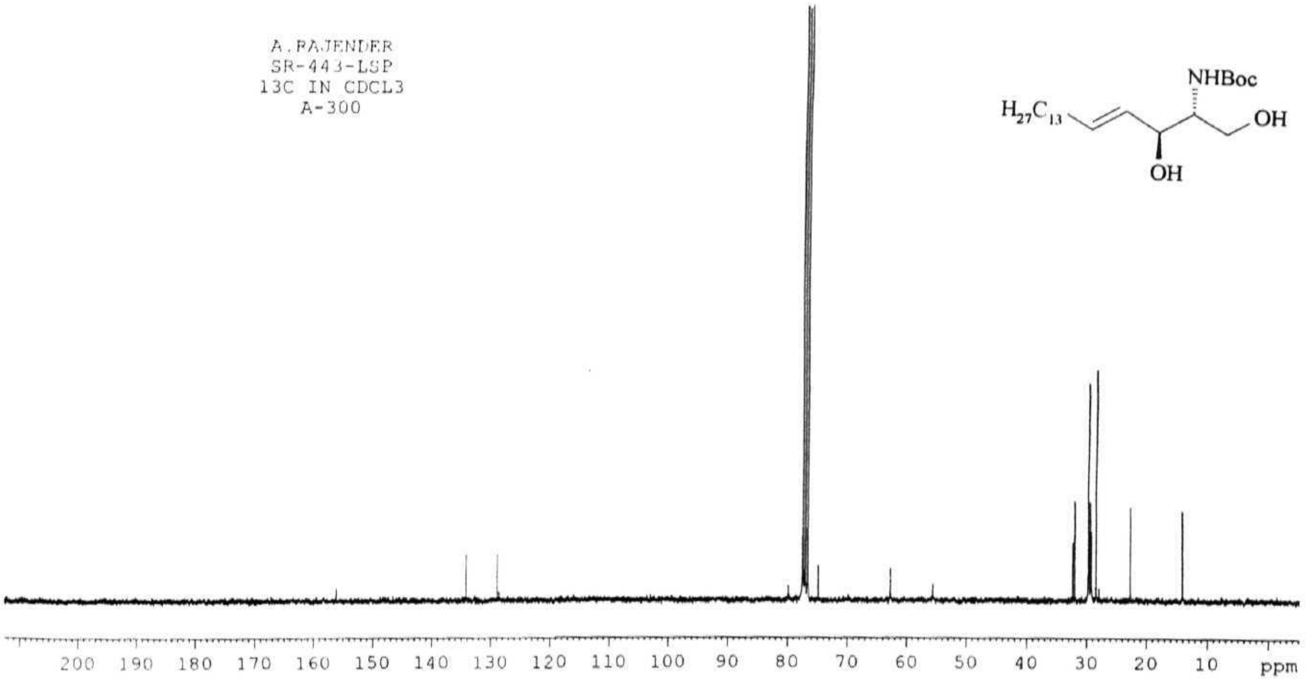
PMR Spectrum of Compound 85



^{13}C NMR Spectrum of Compound 85



PMR Spectrum of Compound 87



^{13}C NMR Spectrum of Compound 87

CHAPTER-IV

The design and synthesis of a novel safety-catch linker

Introduction

Over 30 years, solid phase chemistry has been practiced for the synthesis of molecules, first for peptide, and then nucleotide synthesis.[1] The advent of combinatorial techniques for the small molecule synthesis has brought about a major consciousness in the study of solid-phase organic synthesis.[2] Large numbers of reactions have been translated from solution-phase to solid-phase and more continue to be developed. [3]

Critical to this process is the attachment of the molecule to the solid phase. Solid phase synthesis usually requires the use of a linker[4] to attach the compound of interest to the solid support. A linker has been described as a bifunctional protecting group - it is attached to the molecule being synthesized through a bond labile to the cleavage conditions (e.g. silyl ethers, esters, etc.) and is attached to the solid phase polymer through a more stable bond (alkyl ethers, amides or alkanes). The cleavage may involve a range of techniques and give a range of functional groups. The functional group obtained may be dependent not only on the linker but also on the method of cleavage.

The ideal linker should fulfill a number of important features.

- It should be inexpensive and readily available
- The attachment of starting material would be readily achieved in high yield
- The linker should be stable to the chemistry used in the synthesis
- Cleavage should be efficient under conditions that do not damage the final product
- The cleavage method should involve easy workup conditions to enable preparing libraries of compounds and should not introduce impurities that are difficult to remove.

Many work up procedures add to the number of post-cleavage manipulations. Most cleavage methods use excess reagents to ensure complete cleavage. Many use reagents that are volatile, and excess reagent is removed by evaporation. Other methods use reagents that may be removed by lyophilization, for example, NH_4OH. A number of cleavage methods, though, use reagents that are not readily removed by simple methods, for example cleavage using lithium aluminum hydride. However, new techniques of high throughput purification,[5] the use of disposable short columns and solid phase reagents to remove impurities[6] may make the introduction of impurities in the cleavage step less problematic than it was only a few years ago.

It is not surprising that a wide range of linkers have been reported in recent years given the range of reactions that a linker may have to survive during the synthesis of a molecule, the different types of molecules and functional groups that may have to survive the cleavage conditions, and the wide range of functional groups through which a substrate may be attached to the solid phase.

The choice of base polymer and linker needs careful consideration when planning a reaction sequence on the solid phase because they may affect the outcome of a synthesis. Poor solvation of the base polymer or the presence of the functional groups may interfere with the planned chemistry. Successful attachment of the linker to the solid-phase is one the important aspects to concentrate.

Types of linkers: The following are most commonly used types of linkers, which are categorized according to the method of cleavage.

1. Acid Labile
2. Base Labile
3. Photo Labile
4. Traceless Linkers

5. Safety catch Linkers

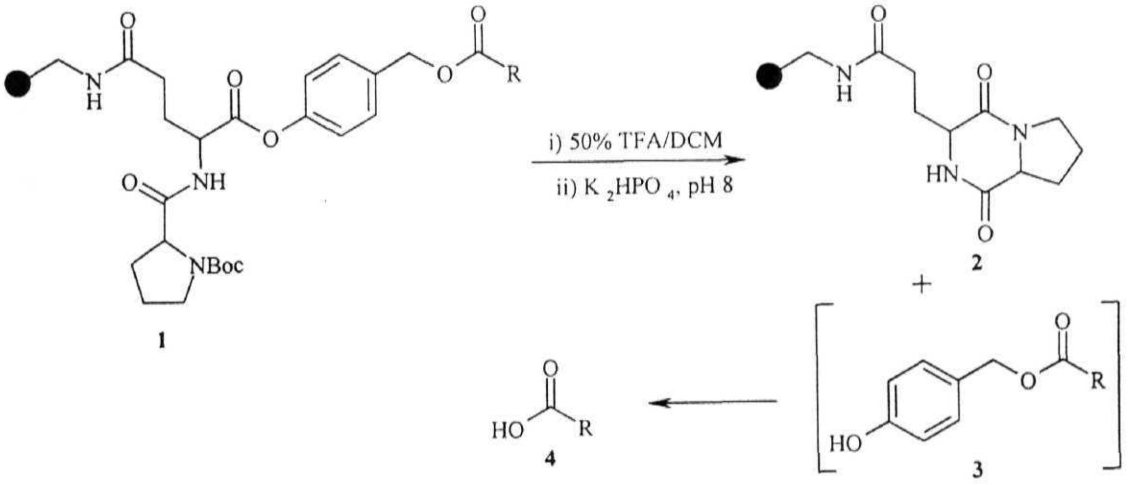
Safety-Catch linkers

Safety catch linkers are those that rely on a two-step cleavage process.[7] The first step involves activation of the linker, the second step involves the actual cleavage. The main advantage of these linkers is that if there is a need to use conditions similar to the cleavage conditions during the synthesis, this can be accommodated, as the linker is stable until activated. However, the product being cleaved must be stable to both the activation and cleavage conditions.

Bradley's contribution[8]:

The linker was designed to cleave acids into the solution and leave the diketopiperazine on the resin. Activation of **1** was achieved by removing the BOC protecting group with TFA, and then cleavage was achieved by neutralization at pH 7-8 to release the phenol **3**, which then underwent elimination to give the acid (Scheme 1). A similar approach has been used with BOC protected imidazoles, which then cyclized cleaving the ester bond after deprotection and neutralization.

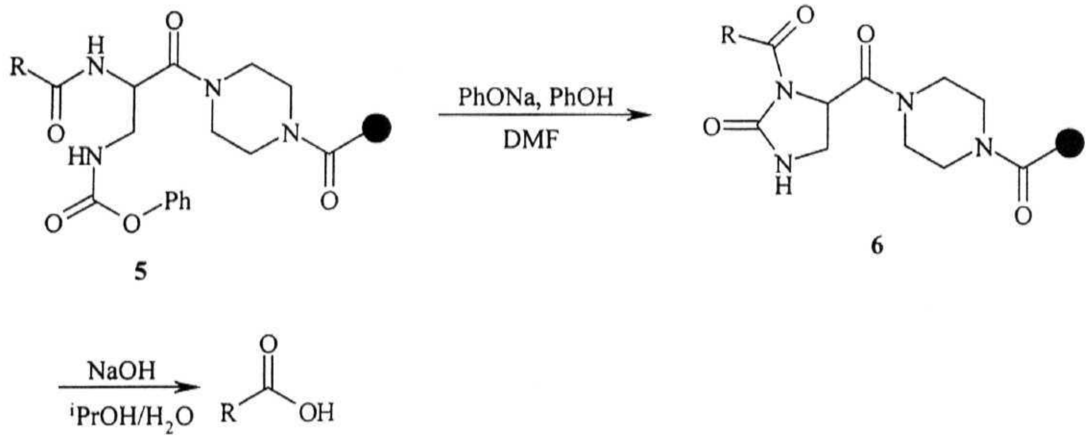
Scheme 1



Pascal's contribution[9]:

Linker **5** was stable to acidic and neutral conditions. It was activated by treatment with sodium phenoxide and formed the cyclic urea **6** via the isocyanate (Scheme 2). The urea **6** was labile to nucleophiles and was cleaved by treatment with NaOH in 70% ^{i}PrOH in water to release the acid.

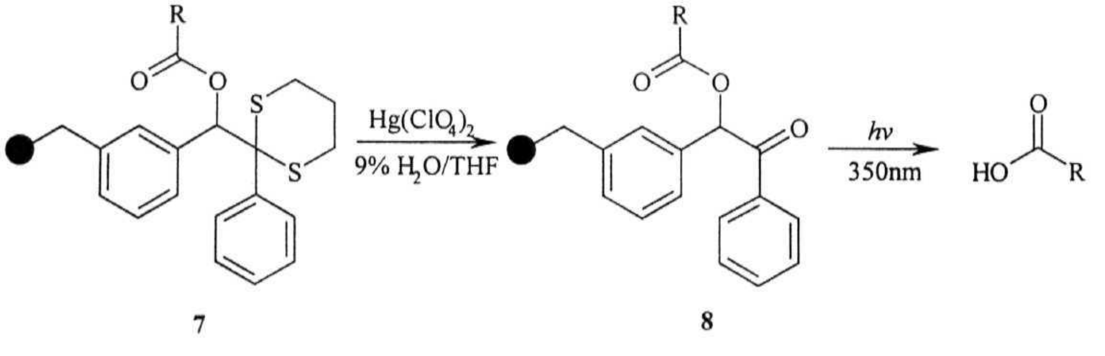
Scheme 2



Balasubramanian's contribution[10]:

Activation of the linker 7 involved removal of the dithioacetal using mercury(II) perchlorate, cleavage of the linker was achieved by irradiation at 350 nm (Scheme 3). The linker was used for attaching carboxylic acids via the ester linkage and alcohols via the carbonate.

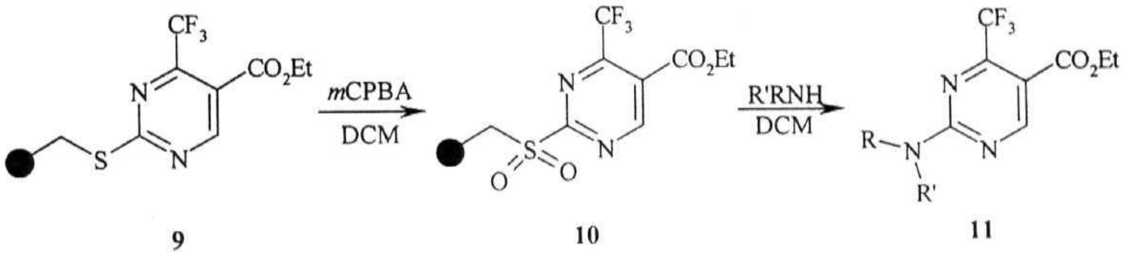
Scheme 3



Suto's contribution[11]:

A sulfide linker **9** has been used for pyrimidines. The sulfide linker was stable to both acidic and basic conditions, however, once oxidized to the sulfone **10** with *m*CPBA, it was cleaved by nucleophilic aromatic substitution by amines to yield substituted pyrimidines (Scheme 4).

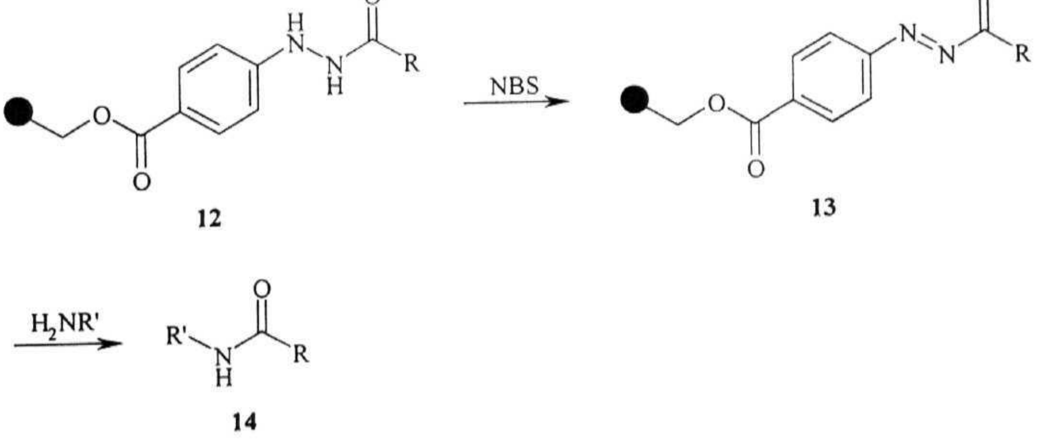
Scheme 4



Wieland's contribution[12]:

The diphenylhydrazide linker **12** was activated by oxidation with NBS (Scheme 5). The resulting product was then base labile and was cleaved by treatment with an amine to release the product as an amide. Oxidation and cleavage was achieved in one step, using copper (II) acetate in the presence of the nucleophile and base by Lowe *et al.*

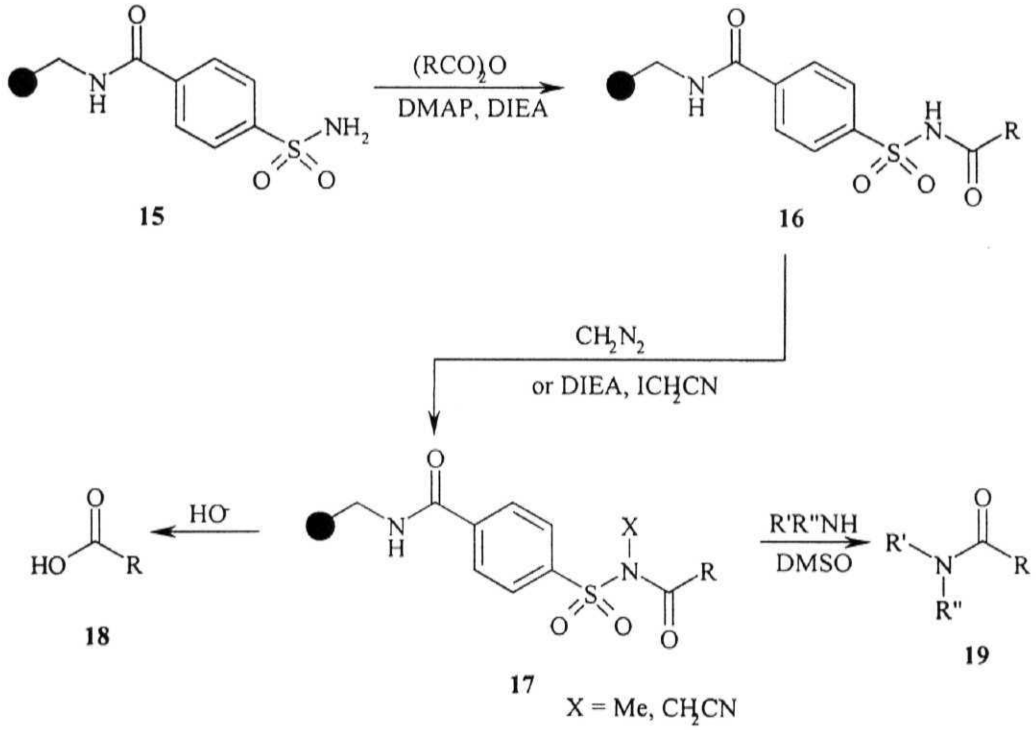
Scheme 5



Kenner's contribution[13]:

The acyl sulfonamide linker developed by Kenner is stable to both acidic and basic conditions prior to activation. Under basic conditions the acidic acyl sulfonamide proton of **15** was removed protecting the acyl group from nucleophilic cleavage. To activate the linker for cleavage the nitrogen was alkylated with either diazomethane, or iodoacetonitrile (Scheme 6). It was then cleaved using nucleophiles, such as hydroxide to afford the carboxylic acid **18**, or amines to yield the corresponding amides **19**.

Scheme 6

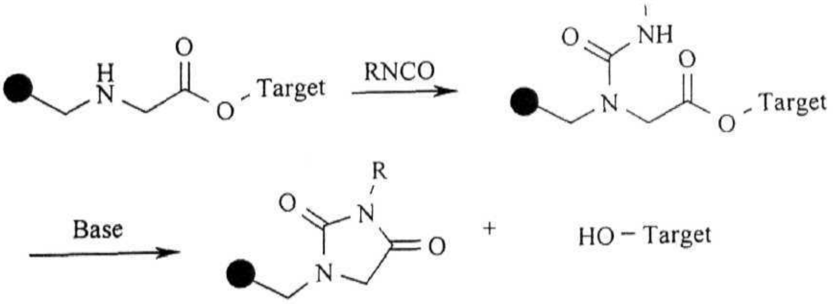


Present work

Paramount to the success of solid-phase organic synthesis approach is the availability of suitable polymers and widely applicable linker groups for the attachment of the desired compounds to the polymeric carrier. Recent research in this field has focused on and achieved the successful transfer of a steadily growing number of reaction types to synthesis on solid supports. The demands on the linker groups concerning their stability under different reaction conditions and selective cleavage have risen accordingly. Therefore, new and broadly applicable linkers which are stable under a variety of reaction conditions, but which at the same time allow release of the synthesized products under the mildest conditions, are of great interest in organic synthesis and combinatorial chemistry. This chapter deals with the development of glycine as a new safety catch linker[14] for solid-phase organic synthesis allowing for the attachment to polymer support and release of the alcohol/phenol under mild conditions.

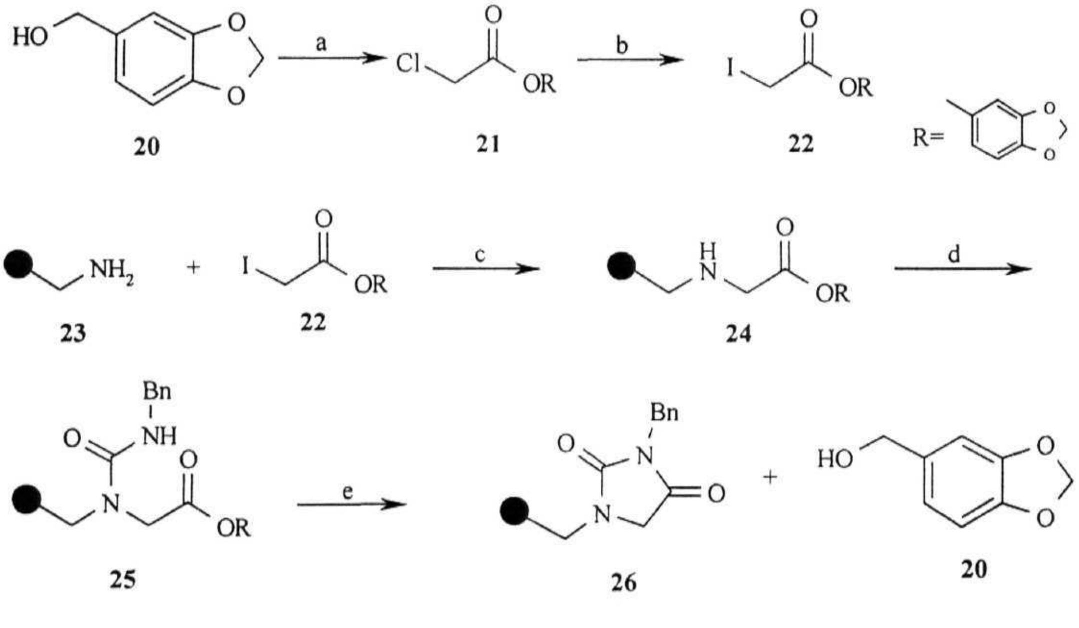
The central idea of the design was product alcohol/phenol release by cyclative cleavage via hydantoin formation on the solid support. Activation of the linker, involves reaction with an isocyanate to afford a urea, which upon treatment with a base would undergo cyclization releasing the target alcohol (Scheme 7).

Scheme 7



The polymer carrier chosen for attachment to the linker was commercially available aminomethylpolystyrene resin **23** with an average loading capacity of 1.2 mmol/g. Piperonyl alcohol **20** was reacted with chloroacetyl chloride in the presence of Et_3N to afford the chloroacetate **21**, which was then subjected under Finkelstein's reaction conditions to yield the iodoacetate **22**. Iodoacetate **22** was attached to aminomethylpolystyrene resin **23** by reacting in DMF at ambient temperature in the presence of Hunig's base. Resin **24** showed a strong absorption at 1734 cm^{-1} corresponding to the C=O stretching in its FTIR spectrum. The linker **24** was activated by treatment with benzyl isocyanate in a mixture of DMF/toluene.[15] Upon treatment with neat diisopropyl amine **25** released piperonyl alcohol **20** via cyclative cleavage (Scheme 8).

Scheme 8



Reagents and conditions: (a) $ClCH_2COCl$, Et_3N, DCM, 0 °C, 20 min, 100%; (b) NaI, acetone, r.t., 4 h, 96%; (c) $^iPr_2NEt$, DMF, r.t., 16 h, 80%; (d) $PhCH_2NCO$, toluene/DMF (1:1), r.t., 8 h; (e) $^iPr_2NH$, r.t., 1 h, 75%.

Fmoc quantitation[16] is commonly used for determining the amount of amine present on solid support. Thus, amino functionality of the resin **24** was protected as its Fmoc derivative by treatment with Fmoc-Cl in the presence of a base. The resulting Fmoc derivative was then treated with piperidine in DMF to afford Fmoc adduct. Submitting the values in equation 1, it was observed that loading was achieved in 80% in the coupling reaction of **23** with **22**.

procedure:

5 mg of resin was weighed into a 10 mL volumetric flask. To the flask were added 0.4 mL Piperidine and 0.4 mL of dichloromethane. The mixture was allowed to cleave for 30 min., at which point MeOH (1.6 mL) and dichloromethane (7.6 mL) were added to bring the total volume to 10 mL. The spectrophotometer was zeroed with a blank solution containing 0.4 mL of piperidine, 1.6 mL of MeOH, and dichloromethane to make 10 mL. The absorbance was measured at 301nm and the loading level was calculated by using the following equation.

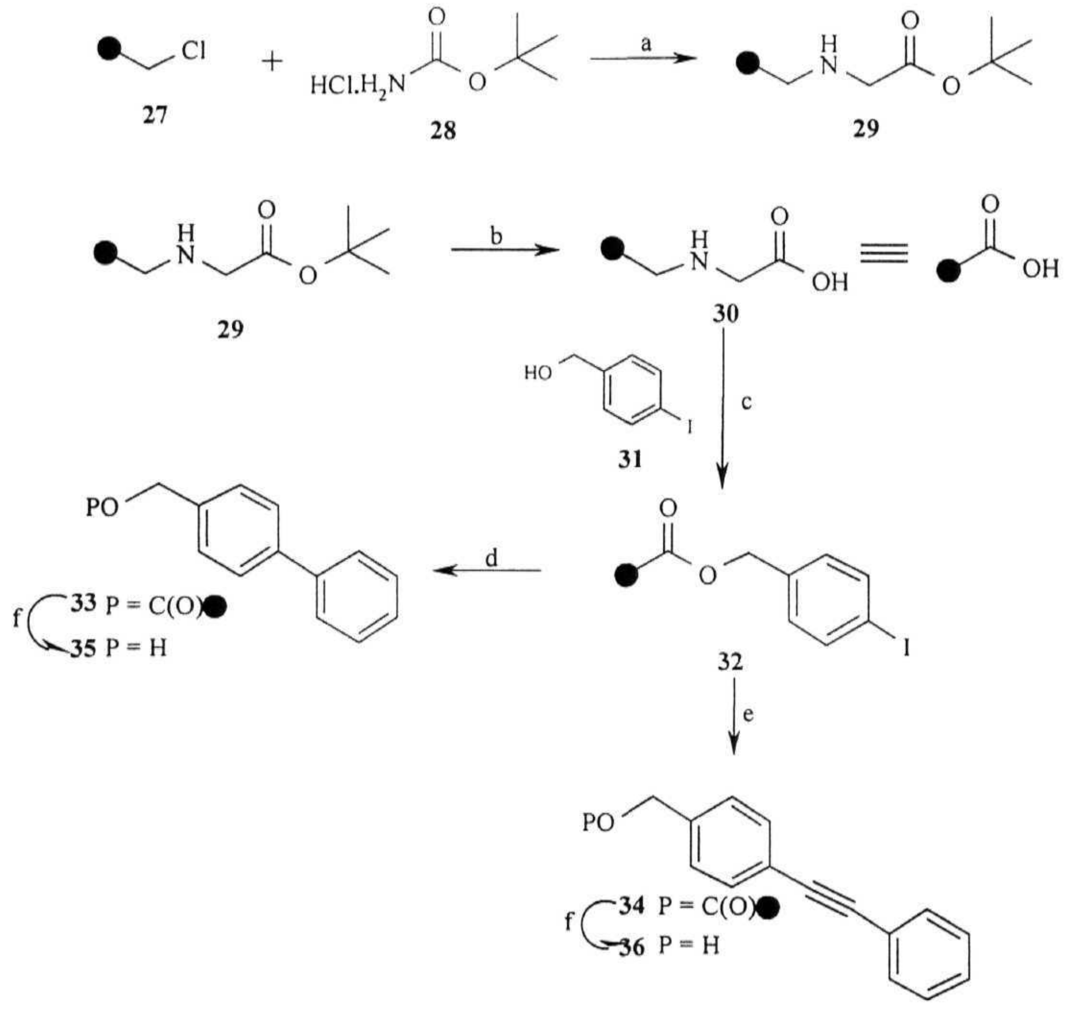
$$\text{Loading (mmol/g)} = \frac{A_{301} \times 10}{7800 \times Wt} \qquad \text{---- Eqn. 1}$$

A = Absorbance measured at 301nm

Wt = weight of the resin taken

In another approach the *tert*-butylglycine ester **28** was attached to Merrifield resin **27** in the presence of Hunig's base and NaI in DMF. *tert*-Butyl ester **29** was deprotected by treating the resin with trifluoroacetic acid in dichloromethane to afford the amine hydrochloride which on treatment with Et_3N yield the free amino acid **30**. The suitability of the polymer-linker-conjugate **30** for solid-phase synthesis was investigated for a variety of synthetic transformations. To this end, first the carboxyl group of the linker **30** was esterified with *p*-iodobenzylalcohol **31** and the polymer bound aryl iodide **32** generated was then further transformed by Suzuki[17] and Sonogoshira[18] reactions to furnish **33** and **34.** Two-step activation and cleavage protocol afforded the products **35** and **36** (Scheme 9).

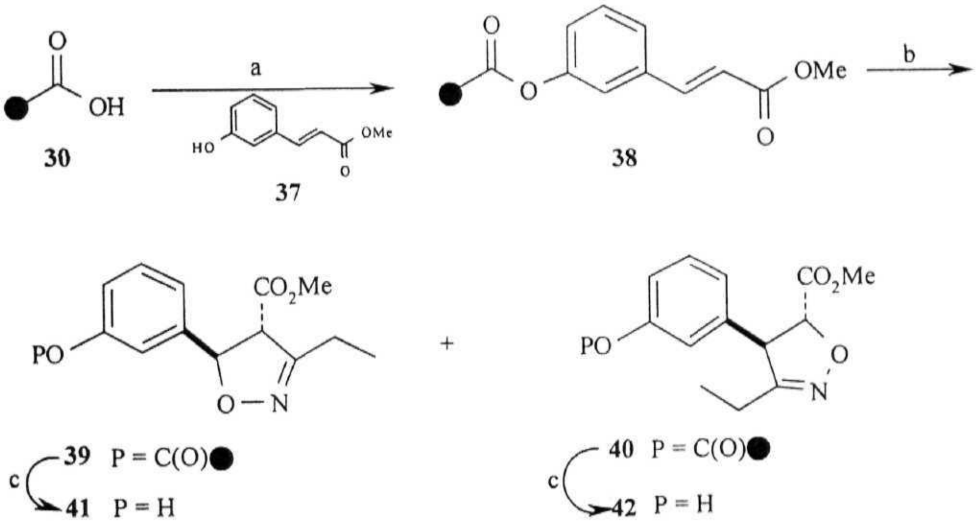
Scheme 9



Reagents and conditions: (a) $^{i}Pr_2NEt$, NaI, DMF, 65 °C, 36 h; (b) TFA/DCM (1:1), r.t., 3h; (c) DCC, HOBt, cat. DMAP, DCM, r.t., 8 h; (d) $Pd(OAc)_2$, $PhB(OH)_2$, K_2CO_3, dioxane/H2O, (7:1), 100 °C, 24 h; (e) $PdCl_2(PPh_3)_2$, CuI, Et_3N, dioxane, r.t., 24 h; (f) i) $PhCH_2NCO$, toluene/DMF (1:1), r.t., 8 h, ii) $^{i}Pr_2NH$, r.t., 1 h.

In a further experiment to test the nitile oxide cycloaddition reaction, the polymer-linker **30** was esterified with methyl-3-hydroxycinnamate **37** resulting polymer bound unsaturated ester **38**. The polymer bound unsaturated ester was then treated with nitropropane, 4-methoxyphenylisocyanate[19] in the presence of catalytic amounts of triethylamine to provide **39** and **40**. Cleavage from solid-support afforded the regioisomeric cycloadducts **41** and **42** in a ratio of 4:1 (Scheme 10).

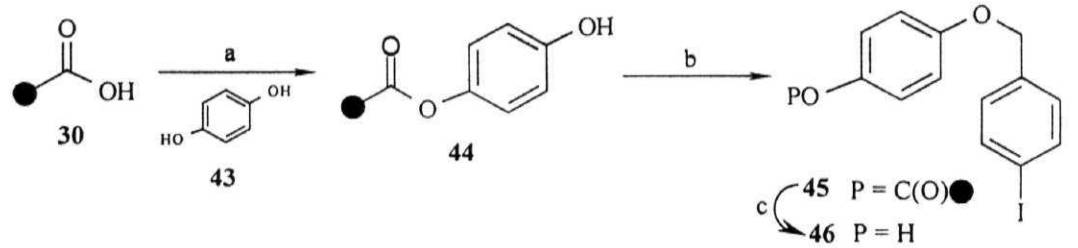
Scheme 10



Reagents and conditions: (a) DCC, HOBt, cat. DMAP, DCM, r.t., 8 h; (b) $PrNO_2$, 4-OMe-PhNCO, cat.Et_3N, benzene, r.t., 16 h; (c) i) $PhCH_2NCO$, toluene/DMF (1:1), r.t., 8 h, ii) $^iPr_2NH$, r.t., 1 h.

In another experiment Mitsunobu esterification[14c] was investigated (Scheme 11). For this reaction, hydroquinone **43** was coupled to linker **30** and the resulting polymer bound phenol **44** was reacted with *p*-iodobenzylalcohol under Mitsunobu reaction conditions to yield the phenyl ether **45**. Subsequent activation and cleavage reactions afforded the alcohol **46**.

Scheme 11



Reagents and conditions: (a) DCC, HOBt, cat. DMAP, DCM, r.t., 8 h; (b) DEAD, PPh3, THF, r.t., 16 h; (c) i) $PhCH_2NCO$, toluene/DMF (1:1), r.t., 8 h, ii) $^{i}Pr_2NH$, r.t., 1 h.

Experimental

benzo[*d*][1,3]dioxol-5-ylmethyl 2-iodoacetate, 22.

To the solution of the piperonyl alcohol **20** (304 mg, 2 mmol) in dichloromethane (8 mL) at 0 °C, triethylamine (0.56 mL, 4 mmol) and chloroacetyl chloride (226 mg, 2 mmol) were added and maintained at the same temperature for 25 min. The reaction mixture was diluted with dichloromethane and washed successively with 10% aq. citric acid solution, water and brine. Drying over sodium sulfate and concentration afforded the chloroacetyl ester **21** in nearly quantitative yield, which was taken ahead to the next step without further purification. PMR ($CDCl_3$, 200 M Hz), δ 6.90-6.78 (m, 3H), 6.0 (s, 2H), 5.12 (s, 2H), 4.04 (s, 2H).

To the above compound in acetone (4 mL), NaI (1.5 g, 10 mmol) was added and stirred at r.t. for 4 h. The solvent was evaporated, the residue taken into ethyl acetate, washed with water and brine. Evaporation of the solvent under reduced pressure afforded the iodoacetyl ester **22** in 96% yield. PMR ($CDCl_3$, 200 M Hz), δ 6.89-6.78 (m, 3H), 6.0 (s, 2H), 5.07 (s, 2H), 3.71 (s, 2H).

Immobilization of iodoacetyl ester 22, by alkylation

Preparation of 24.

To the suspension of the aminomethyl polystyrene resin **23** (500 mg, 0.6 mmol) in DMF (4 mL) was added the solution of iodoacetyl ester **22** (384 mg, 1.2 mmol) in DMF (1 mL) followed by Hunig's base (1.0 mL, 6 mmol). The reaction mixture was shaken at room temperature for 16 h. The resin was filtered and washed sequentially with DMF (2×10 mL), dioxane/water (9:1, 2×10 mL), dioxane (2×10 mL), MeOH (2×10 mL), MeOH/DCM (1:1, 2×10 mL), DCM (3×10 mL) and finally with ether (2×10 mL). The resin **24** was dried under vacuum and weighed 610 mg.

Immobilisation of alcohols/phenols directly to the solid support

Preparation of 29.

To the suspension of Merrifield resin 27 (500 mg, 1 mmol) in dry DMF (4 mL) was added NaI (150 mg, 1 mmol), *t*-butyl glycine.HCl 28 (502 mg, 3 mmol) followed by Hunig's base (1.0 mL, 6 mmol). The reaction mixture was heated at 65 °C for 36 h and cooled to r.t. The resin was filtered, washed as detailed earlier and dried under vacuum to yield 580mg of 29. The loading of glycine ester was found to be 80% by the Fmoc quantitation assay.

Preparation of 30.

The resin 29 (500 mg, 0.69 mmol) was suspended in TFA/DCM (1:1, 5 mL) at 0 °C and allowed to attain r.t. gradually and let stir at the same temperature for a further 3 h period. The resin was washed with Et_3N/DCM (0.5: 9.5, 2×25 mL), DCM (2×25 mL) and dried under vacuum to yield 30 (465 mg).

General procedure for the DCC coupling:

Preparation of 32.

To the suspension of the resin 30 (500mg, 0.67 mmol) in DCM (5 mL), were added HOBt (89 mg, 0.67mmol) and *p*-iodo benzyl alcohol 31 (467 mg, 2.0 mmol). The mixture was cooled to 0 °C, DCC (139 mg, 0.67mmol) was added and allowed to attain r.t. Stirring was continued for another 6 h at r.t. The resin was then washed sequentially with MeOH (5×15 mL), MeOH/DCM (1:1, 3×20 mL), DCM (2×15 mL) and dried under vacuum to yield 601mg of the resin 32.

Preparation of 38.

The above-mentioned procedure was used for the immobilization of *m*-hydroxy methyl cinnamate 37 onto 500 mg of the resin 30 to yield 580 mg of the resin 38.

Preparation of 44.

Following the general procedure hydroquinone was tagged onto the resin 30 (500 mg, 0.67 mmol) to yield 543mg of 44.

General procedure for activation and cleavage from the solid-support:

To the suspension of the resin 24 (500mg, 0.49 mmol) in DMF/Toluene (1:1, 10 mL) was added benzyl isocyanate (0.62 mL, 5 mmol). The mixture was shaken at r.t. for 6 h. The resin was then washed as described earlier and dried. The vacuum dried resin was suspended in dry diisopropyl amine (1 mL) and shaken for 1 h at r.t. The resin was filtered and washed with CH_2Cl_2 (2x10 mL). The combined filtrates were evaporated to afford piperonyl alcohol (56 mg) in 75% yield.

4-phenylphenylmethanol, 35.

To the suspension of the resin 32 (500 mg, 0.39 mmol) in dioxane (5 mL), phenyl boronic acid (475 mg, 3.9 mmol), K_2CO_3 (1.15 g, 8.3 mmol) dissolved in water (2.5 mL) was added and the resulting suspension was degassed for 30 min. $Pd(OAc)_2$ (2mg, 0.01 mmol) was added and the reaction mixture was maintained at 100 °C for 24 h. The reaction mixture was allowed to attain r.t., the resin filtered, washed sequentially with dioxane (6x5 mL), water (6x5 mL), water/EtOH (1:1, 3x5 mL), EtOH (3x5 mL) and ether (3x5 mL). The resin was dried under vacuum and subjected to the same reaction conditions once again. Filtration and drying afforded 481mg of resin 33. The resin was subjected to the same reaction conditions once again. Following the general procedure for cleavage, the crude Suzuki coupling product 35 was obtained. Purification by column chromatography using 12% EtOAc/petroleum ether afforded pure 35 (71 mg) in 70% yield.

PMR (200 MHz, $CDCl_3$) : δ 7.59-7.52 (m, 4H), 7.43-7.20 (m, 5H), 4.71 (s, 2H), 1.66 (bs, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 64.6, 126.9, 127.0, 127.3, 127.7, 128.6, 139.7, 140.3, 140.6.

m/z (EI) : 184 [M^+]

4-(2-Phenyl-1-ethynyl)phenylmethanol, 36.

The mixture of the resin 32 (500 mg, 0.39 mmol), Et_3N (5.15 mL, 38mmol), CuI (14mg, 0.08 mmol) and phenyl acetylene (118 mg, 1.16 mmol) in dioxane (10 mL) was degassed for 30 min. and then $Pd(PPh_3)_2Cl_2$ (27 mg, 0.04 mmol) was added in one portion and shaken at 25 °C for 24 h. The resin was filtered, washed and dried. The resin was subjected to the same reaction conditions once again to afford 490 mg of 34. Following the general cleavage protocol the crude Sonogoshira product 36. Purification by column chromatography using 12% EtOAc/pet. ether afforded pure 36 (58 mg) in 72% yield.

PMR (200 MHz, $CDCl_3$) : δ 7.57-7.49 (m, 4H), 7.38-7.30 (m, 5H), 4.64 (s, 2H), 1.85 (bs, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 64.7, 89.1, 89.4, 122.4, 123.1, 126.8, 128.2, 128.3, 131.5, 131.7, 140.9.

m/z (EI) : 208 [M^+]

Preparation of 40&42:

To the suspension of the resin 38 (500 mg, 0.43 mmol) in benzene (10 mL) were added nitropropane (115 mg, 1.29 mmol), *p*-methoxyphenyl isocyanate (577 mg, 2.58 mmol) and Et_3N (70 μL, 0.5 mmol). The resulting mixture was shaken at r.t. for 24 h. The resin was washed sequentially with MeOH (5×10 mL), MeOH/DCM (1:1, 3×5 mL), DCM (2×5 mL) and finally with ether (2×5 mL). The weight of the resin after drying was 524mg. Cleavage from solid-support afforded the crude product mixture. Purification by column chromatography using 8%

EtOAc/pet. ether as the eluent afforded 40 (50 mg) and 42 (13 mg) in a 4 : 1 ratio in 70% combined yield.

Methyl 3-ethyl-5-(3-hydroxyphenyl)-4,5-dihydro-4-isoxazolecarboxylate, 40.

Viscous liquid.

PMR (200 MHz, $CDCl_3$) : δ 7.21 (t, *J* = 5.71 Hz, 1H), 6.9 (bs, 2H), 6.8 (m, 2H), 5.81 (d, *J* = 8.57 Hz, 1H), 4.01 (d, *J* = 8.57 Hz, 1H), 3.82 (s, 3H), 2.52 (m, 1H), 2.35 (m, 1H), 1.2 (t, *J* = 9.1 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 10.5, 20.7, 53.0, 63.0, 84.6, 112.4, 115.7, 117.3, 130.1, 140.9, 156.7, 156.8, 168.8.

m/z (EI) : 249 [M^+]

Methyl 3-ethyl-4-(3-hydroxyphenyl)-4,5-dihydro-5-isoxazolecarboxylate, 42.

Viscous oil.

PMR (200 MHz, $CDCl_3$) : δ 7.10 (d, *J* = 7.12 Hz, 1H), 6.91-6.66 (m, 4H), 4.85 (d, *J* = 5 Hz, 1H), 4.45 (d, *J* = 5 Hz, 1H), 3.79 (s, 3H), 2.39-2.04 (m, 2H), 1.08 (t, *J* = 6.6 Hz, 3H).

m/z (EI) : 249 [M^+]

4-(4-Iodobenzyloxy)phenol, 46.

To the suspension of the resin 44 (500 mg, 0.43 mmol) in THF (5 mL) were added TPP (282 mg, 1.08 mmol), *p*-iodo benzyl alcohol (251mg, 1.08 mmol) and cooled to 0 °C. DEAD (187 mg, 1.08 mmol) was added, the temperature allowed to rise to r.t and stirred for further 8 h. The resin was filtered and washed successively with dioxane (3x5 mL), MeOH (3x5 mL), MeOH/DCM (1:1, 3x5 mL) and then with DCM (2x5 mL). The resin was dried to afford 45 (565 mg). Cleavage from the solid-support afforded the crude product 46. Purification by column chromatography using 15% EtOAc/petroleum ether as the eluent afforded pure 16 (51mg) in 60% yield.

PMR (200 MHz, $CDCl_3$) : δ 7.68 (d, *J* = 7.59 Hz, 2H), 7.14 (d, *J* = 7.59 Hz, 2H), 6.8-6.63 (m, 5H), 4.92 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 151.0, 150.9, 136.8, 136.7, 128.7, 115.4, 115.3, 69.4.

m/z (EI) : 327 [M^+]

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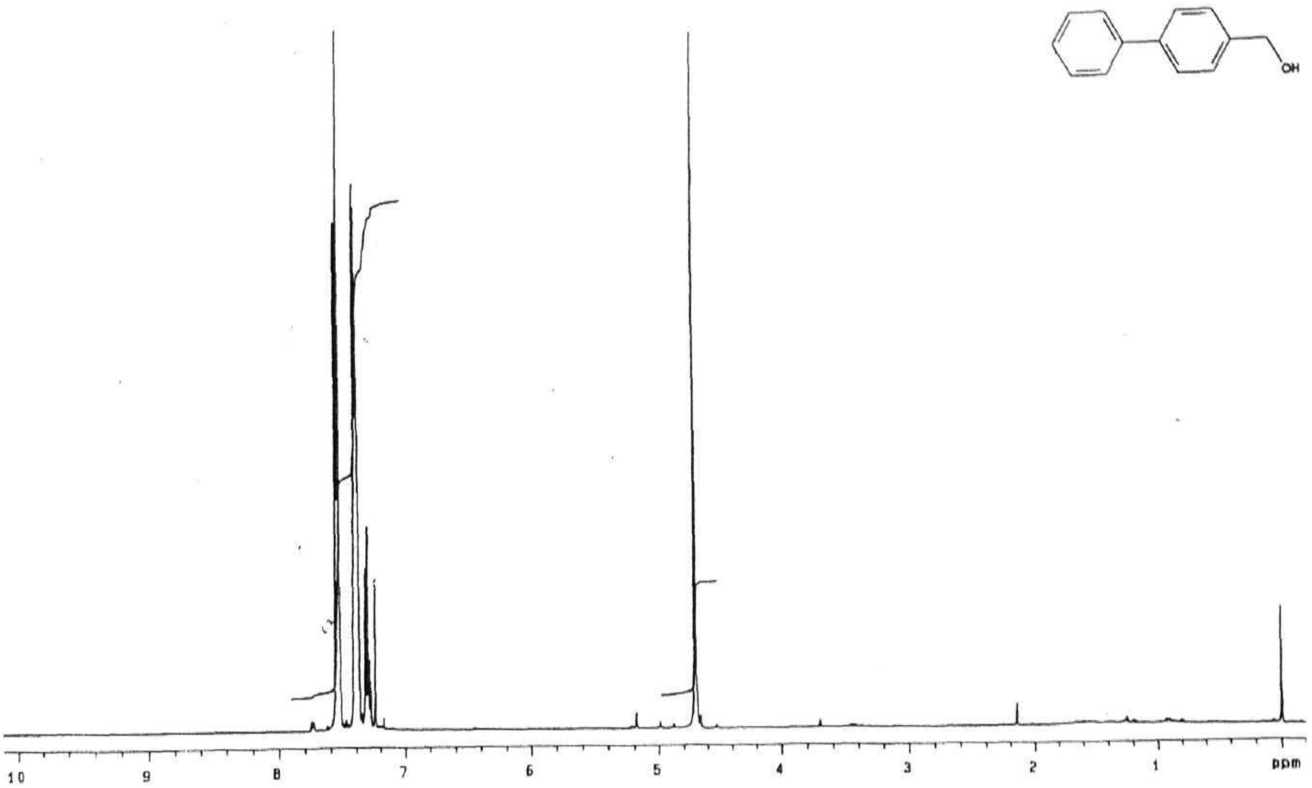
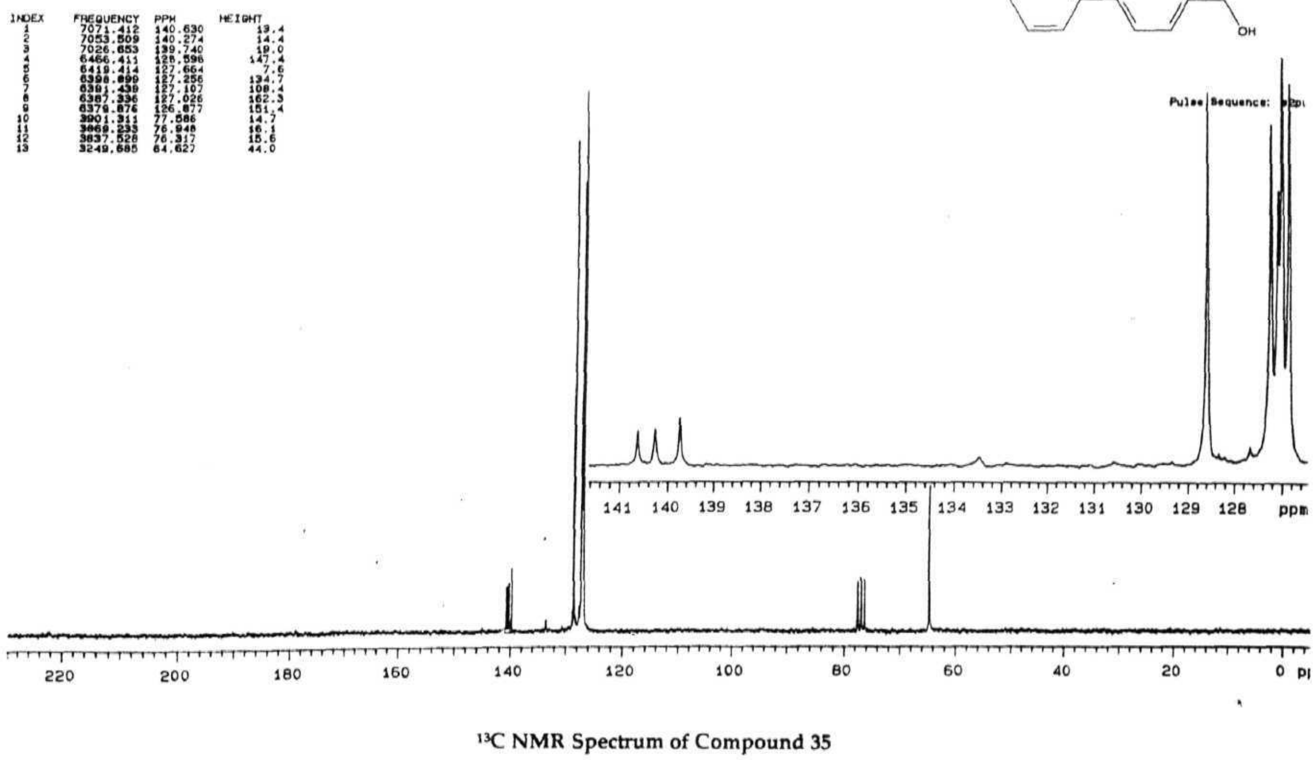
SPECTRA



PMR Spectrum of Compound 35



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INDEX   FREQUENCY  PPM      HEIGHT
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  2     7053.509   140.274    14.4
  3     7026.653   139.740    19.0
  4     6466.411   128.596   147.4
  5     6419.414   127.664     7.6
  6     6398.899   127.256   134.7
  7     6391.439   127.107   108.4
  8     6387.336   127.026   162.3
  9     6379.876   126.877   151.4
 10     3901.311   77.586     14.7
 11     3869.233   76.948     16.1
 12     3837.528   76.317     15.6
 13     3249.685   64.627     44.0
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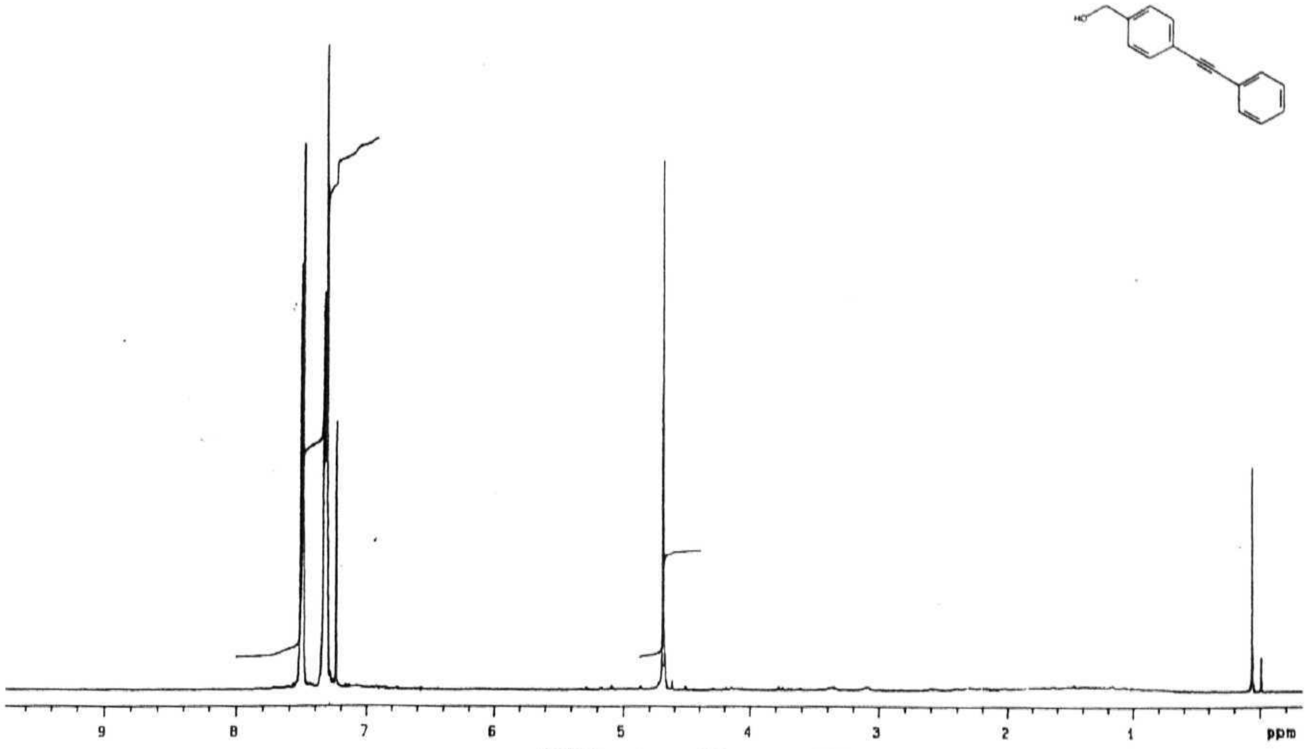
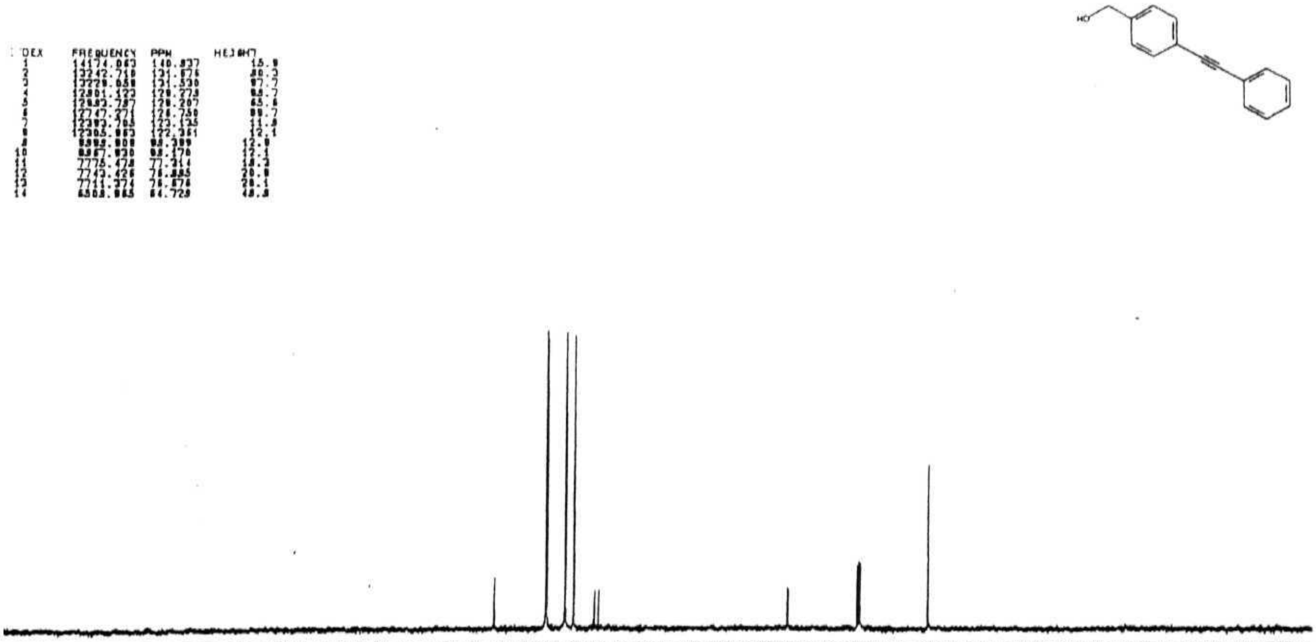
¹³C NMR Spectrum of Compound 35



PMR Spectrum of Compound 36



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I DEX     FREQUENCY   PPM        HEIGHT
   1     14174.063   140.837      15.9
   2     13242.710   131.676      80.3
   3     13228.058   131.530      97.7
   4     12901.123   128.279      88.7
   5     12893.787   128.207      65.6
   6     12747.271   126.750      99.7
   7     12383.705   123.135      11.8
   8     12305.063   122.351      12.1
   9      8994.008    89.399     12.0
  10      8971.030    89.170     12.1
  11      7776.478    77.314     18.3
  12      7743.426    76.985     20.0
  13      7711.374    76.676     28.1
  14      6508.983    64.729     48.8
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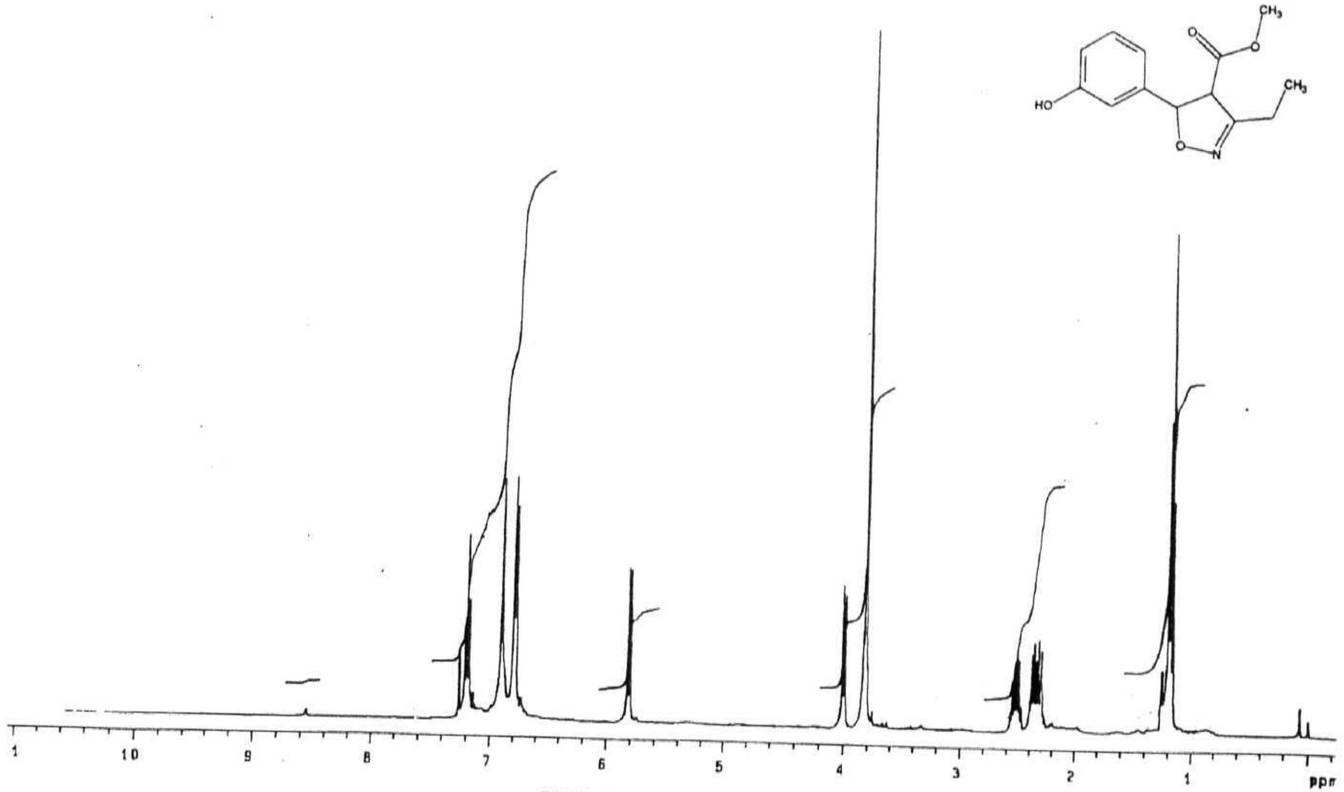
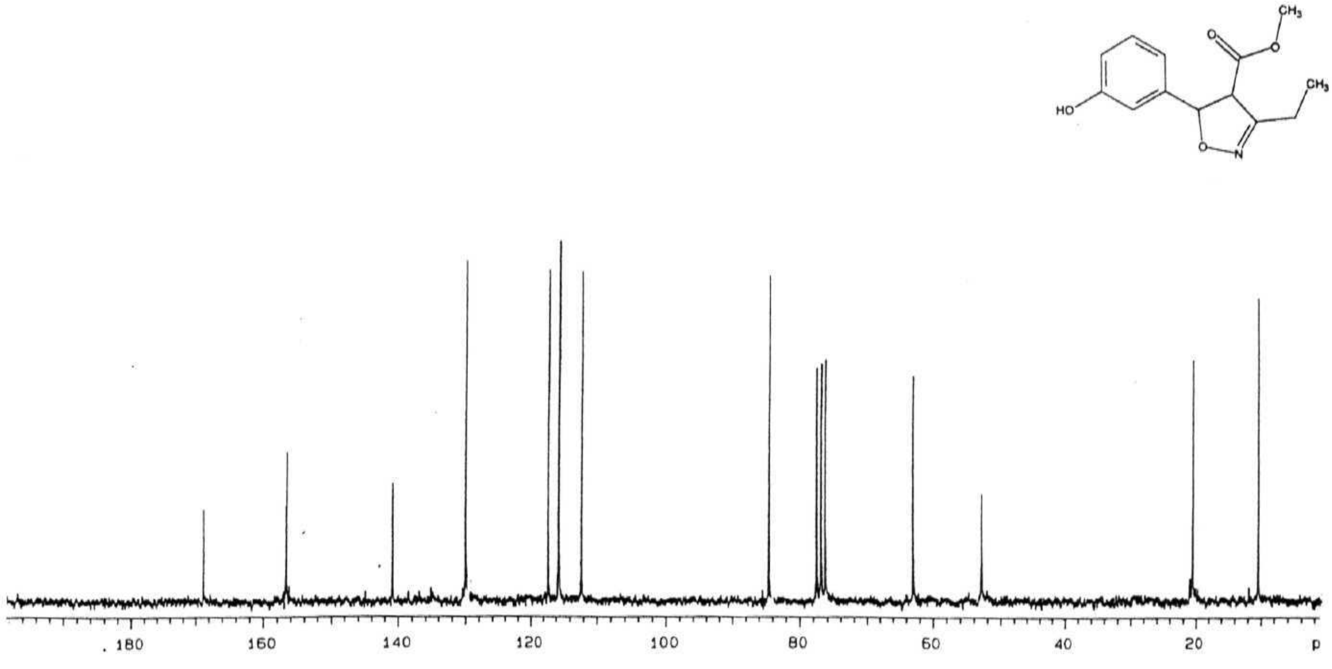
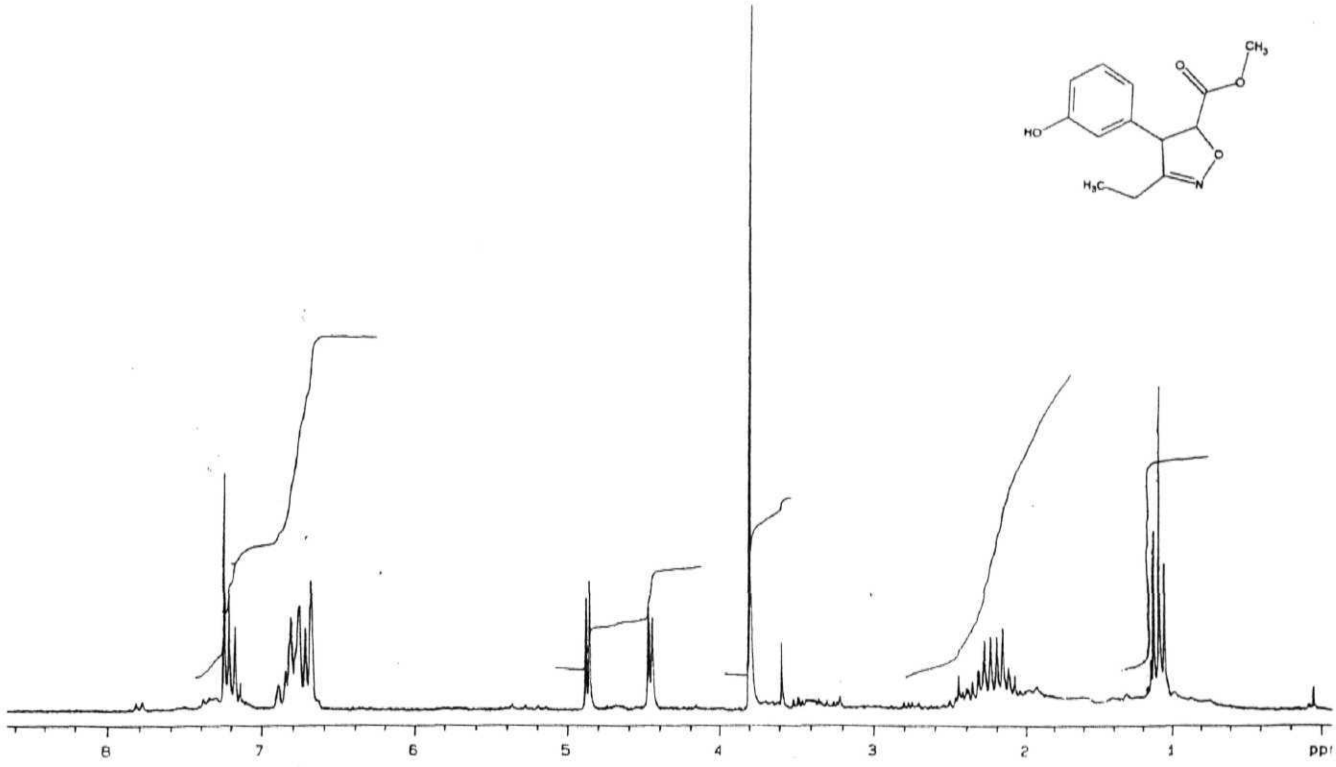
^{13}C NMR Spectrum of Compound 36



PMR Spectrum of Compound **41**



^{13}C NMR Spectrum of Compound **41**



PMR Spectrum of Compound **42**

PMR Spectrum of Compound **46**

List of publications

1) Stereoselective bromohydrin formation from β-hydroxysulfoxides mediated by the pendant sulfoxide group
S. Raghavan, M. Abdul Rasheed, Suju C. Joseph and **A. Rajender**
Chem. Commun., **1999**, 42, 1845.

2) Catalytic Oxidation of Thiols to Disulfides with Vanadyl Acetylacetonate ($VO(acac)_2$)
Sadagopan Raghavan, **A. Rajender**, Suju C. Joseph and M. Abdul Rasheed
Synth. Commun., **2001**, 31, 1477.

3) Target alcohol/phenol release by cyclative cleavage using glycine as a safety-catch linker
Sadagopan Raghavan and **A. Rajender**
Chem. Commun., **2002**, 1572.

4) Novel, Short, Stereospecific Synthesis of *lyxo*-(2*R*,3*R*,4*R*)-phytosphingosine and *erythro*-(2*R*,3*S*)-sphingosine
Sadagopan Raghavan and **A. Rajender**
J. Org. Chem. **2003**, 68, 7094.

5) Novel, Efficient and Stereospecific Synthesis of *xylo*-(2*R*,3*S*,4*S*)-phytosphingosine and *threo*-(2*R*,3*R*)-sphingosine
Sadagopan Raghavan, **A. Rajender** and J. S. Yadav
Tetrahedron Asymmetry, **2003**, 14, 2093.

6) Synthesis of Tetrahydrofurans via Silicon Promoted Pummerer Type Reaction
Sadagopan Raghavan, **A. Rajender**, M. Abdul Rasheed and S. RamakrishnaReddy
Tetrahedron Lett. **2003**, 44, 8253.

7) Regio- and stereoselective synthesis of 1,3-aminoalcohol derivatives from allyamine derivatives via internal sulfinyl group participation
S. Raghavan, **A. Rajender**, Suju C. Joseph and M. Abdul Rasheed
Tetrahedron Asymmetry, **2004**, 15, ASAP.

8) Stereoselective synthesis of (-)-allosedamine
Sadagopan Raghavan and **A. Rajender**
Tetrahedron Lett. **2004**, 45, ASAP.

9) Stereoselective synthesis of (1*R*,3*R*)-HPA-12 via diastereoselective addition of (*R*)-(+)-methyl *p*-tolyl sulfoxide anion to an imine.
Sadagopan Raghavan and **A. Rajender**
(Communicated).

ABOUT THE AUTHOR

A. Rajender was born in Kamareddy, a village in Nizamabad district of Andhra Pradesh, India, in 1974. He received his elementary and secondary school education in Kamareddy. After completion of B.Sc. and M.Sc. degrees from Osmania University, Hyderabad, he joined the School of Chemistry, University of Hyderabad for his Ph.D. degree in 1998.