CHAPTER 5

Application of Cetyltrimethylammonium Periodate (CTAPI) in diastereoselective oxidation of (*1S,2S,5R*)-(+) and (*1R,2R,5S*)-(-)-neomenthyl phenyl sulfides to corresponding sulfoxides

5.1 Abstract

This chapter demonstrates the effect of bulky headed oxidant cetyltrimethylammonium periodate (CTAPI) or (hexadecyltrimethylammonium peridoate) in improving diastereomeric ratio of (*Ss*)-(+)/(*Rs*)-(+) and (*Ss*)-(-)/(*Rs*)-(-)-neomenthyl phenyl sulfoxides. These diastereomeric pairs are obtained in stereochemically pure states with improved diastereomeric excess (48 % *de*) as compared to its non-bulky counterpart, sodium metaperiodate (28 % *de*) from respective (+)/(-)-neomenthyl phenyl sulfides. Steric effect involving head group volume of hexadecyltrimethylammonium periodate is found to play role in improving the diastereomeric ratio of the products.

5.2 Introduction

Optically active sulfoxides are often used as chiral auxiliaries and ligands for numerous asymmetric transformations.[1,2] Past two decades have spectatored an extensive use of chiral sulfoxides in asymmetric syntheses, establishing their role as one of the most efficient and versatile chiral controllers.[3,4] Various methods have been developed to carry out asymmetric oxidation of sulfides to optically pure sulfoxides in either diastereoselective or enantioselective mode.[1-4] The diastereoselectivity achieved has been generally accounted for by invoking either steric or neighbouring group participation.[5]

In sulfoxide, sulfur atom is tricoordinated having pyramidal structure; in fact it is a stereogenic center when R_1 and R_2 are not equal (**Figure 5.1**). The oxygen atom donates a lone pair into d-orbital of sulfur (d-π bonding) thus assuming tetrahedral sp^3 hybridzation, with a lone pair of electrons from sulfur in the fourth quadrant.

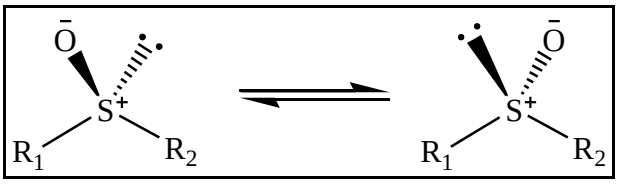
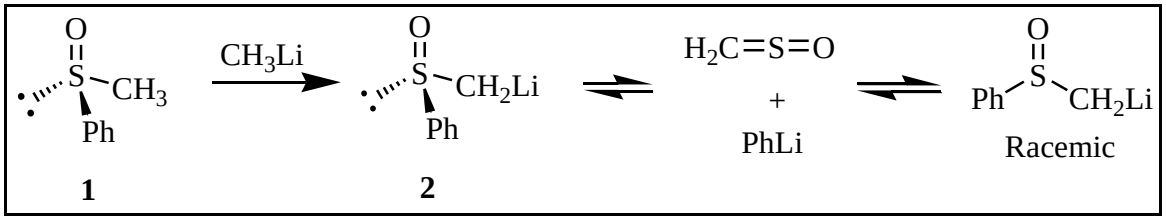


Figure 5.1 Representation of enantiomerically pure sulfoxide

Sulfoxides have good optical stability and they racemize thermally above 200 °C as indicated by the values of the activation parameters of the pyramidal inversion determined for various sulfoxides [from 35 to 42 kcal/mol for $\Delta H^{\#}$, and from -8 to +4 cal/(mol K) for $\Delta S^{\#}$]. However in benzyl and allyl sulfoxides racemization occurs at lower temperatures (130-150 and 50-70 °C, respectively) which are exceptions.[6,7] Apart from the racemization temperature there are other thermal processes which may lead to decomposition of product at lower temperature. (*S*)-Methyl phenyl sulfoxide (**1**) racemizes at room temperature on treatment with methyl lithium[8] (**Scheme 5.1**).



Scheme 5.1 Possible mechanism involved in racemisation of (S)-Methyl phenyl sulfoxide

The first example of an optically active sulfoxide was described in 1926.[9] This discovery was helpful for discussions regarding the nature of the S-O bond and the non-planarity of sulfur. Later, chiral sulfoxides slowly emerged as a class of compounds of interest in asymmetric synthesis.[10-13] Many enantiopure sulfoxides showed biological properties and became important in the pharmaceutical industry. As for example, the world's highest selling anti-ulcer drug in the year 2000, (*S*)-Omeprazole (**3**) (**Figure 5.2**) was the chiral sulfoxide. Consequently, a large number of pharmaceutical companies sought to develop drugs based on the framework of omeprazole (**4**).[14] Other important sulfoxides include the potassium channel activator Aprikalim (**5**),[15] ACAT inhibitor RP 73163 (**6**),[16,17] the calcium channel antagonists (**7**),[18] the anticancer drugs sulforaphane (**8**).[19]

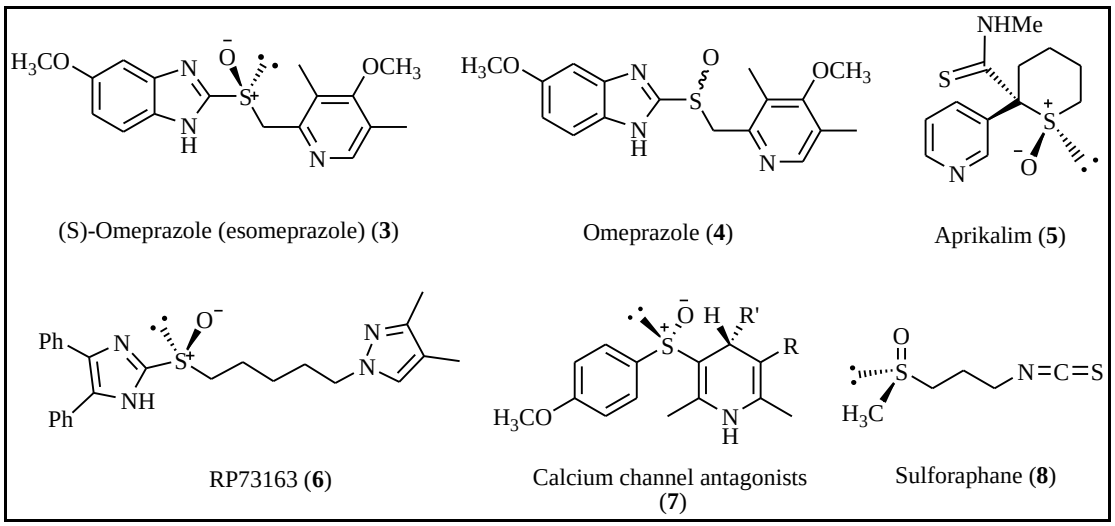
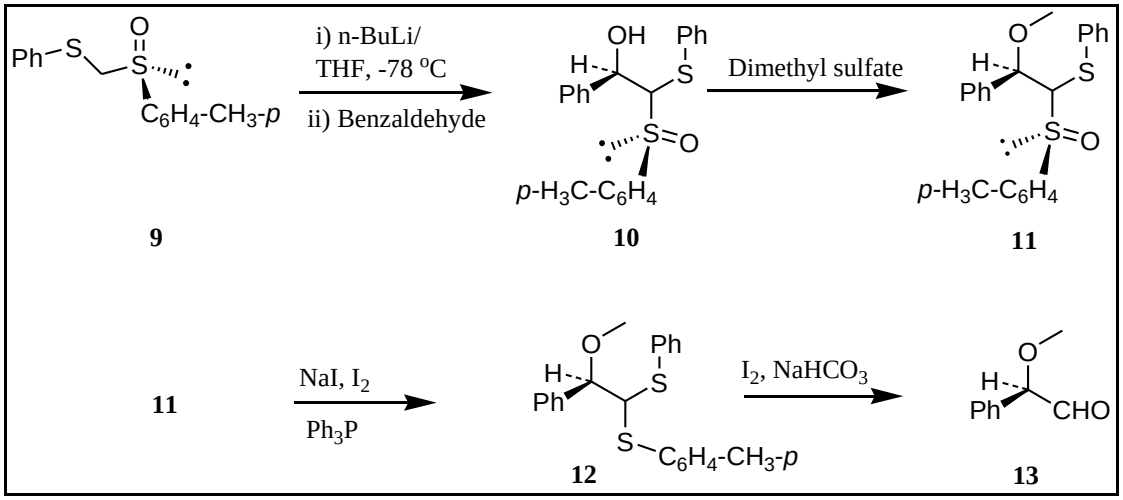


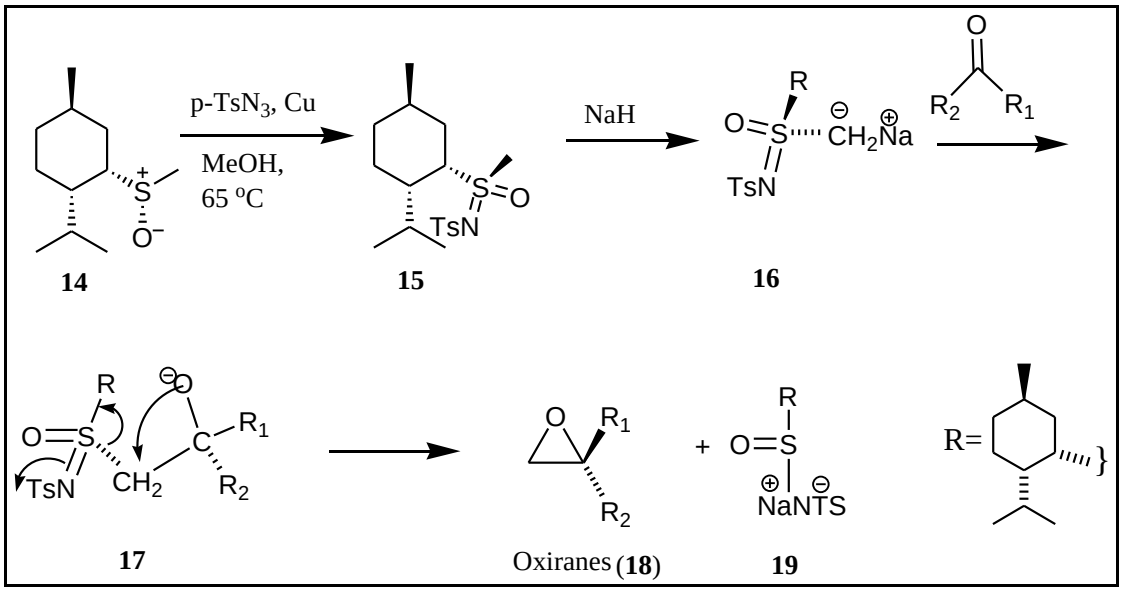
Figure 5.2 Chiral sulfoxides as useful pharmaceutical agents

Carbanions α to a chiral sulfoxide group undergo electrophilic halogenations in highly stereospecific manner.[20] The condensation reaction of anion of chiral

thioacetal monosulfoxide (**9**) with benzaldehyde was used to prepare optically active α-methoxyphenylacetaldehyde (**13**) (**Scheme 5.2**).[21]



Scheme 5.2 Preparation of optically active methoxyphenylacetaldehyde (**13**)



Scheme 5.3 Asymmetric methylene transfer reaction for preparation of chiral oxiranes using chiral sulfoxide as intermediate.

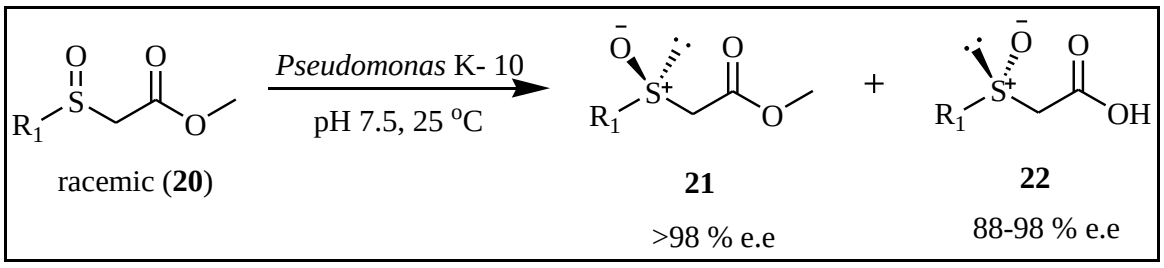
Chiral (+)-methyl neomenthyl sulfoxide (**14**) is often intermediate in the synthesis of chiral oxiranes *via* corresponding sulfoximines in asymmetric methylene transfer reactions (**Scheme 5.3**).[22]

Optically active sulfoxides were used to activate double bonds towards nucleophilic reagents eg the addition of piperidine to optically active α,β-unsaturated sulfoxides occurred with 74 % asymmetric induction.[23] As discussed above chiral sulfoxides are very useful for preparation of pharmaceutical agents and also useful in asymmetric synthesis. Thus many efforts have been devoted to the elaborations of convenient methods for their synthesis. Optically active sulfoxides have been mainly obtained by the methods shown below.

1) Kinetic resolution of sulfoxides
2) Asymmetric oxidation of sulfides.
3) Diastereoselective sulfoxidation

1) Kinetic resolution of sulfoxides

The hydrolysis of some racemic sulfinyl acetates and propionates using *Carynebacterium equi* IF *3730* resulted into the unreacted sulfoxide with 90-97% ee.[24] Burgess used a more readily available biological system *Pseudomonas* K-10 for enzymatic hydrolysis of various arene and alkanesulfinyl acetates which afforded both the unreacted sulfinyl acetate and the acid with excellent e.e (**Scheme 5.4**).[25] To date optical yields are modest, but further improvements are anticipated.

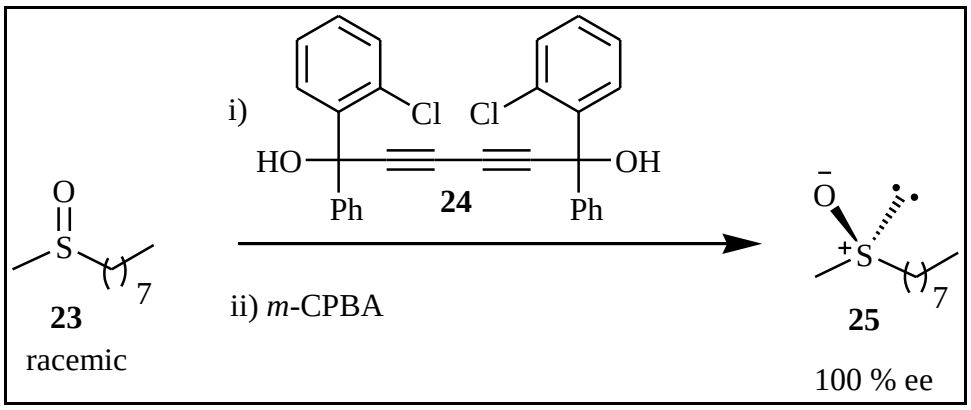


Scheme 5.4 Enzymatic resolution of racemic sulfoxides

Most kinetic resolution methods involve the preferential oxidation of one sulfoxide enantiomer to the sulfone, leaving the remaining sulfoxide enantioenriched. Most of the reported kinetic resolution methods are in fact variations of asymmetric sulfide oxidations, with the principal difference being the substrate used is the sulfoxide rather than the sulfide. While kinetic resolution of racemic sulfoxides is rarely employed as a route to enantioenriched sulfoxides, as the maximum yield is at best 50%, a number of groups engaged in the enantioselective preparation of

sulfoxides have successfully been used asymmetric sulfide oxidation in tandem with kinetic resolution to prepare enantioenriched sulfoxides.

The solid state kinetic resolution of racemic sulfoxide in presence of optically active host compound, (-)-1,6-di(*o*-chlorophenyl)-l,6-diphenylhexa-2,4-diyne-l,6-diol (**24**) is reported by Toda. Racemic sulfoxide (**23**) was mixed with optically active host compound and kept for 24 hr at room temperature. Then achiral oxidizing agent *m*-CPBA was added to it for selective oxidation to sulfone. The optically active host compound selectively binds one sulfoxide enantiomer and the other unbound enantiomer gets oxidized to sulfone thus obtaining enantiomerically rich sulfoxide. The enantioselectivity obtained was excellent in some cases however the yields were low (**Scheme 5.5**).[26]

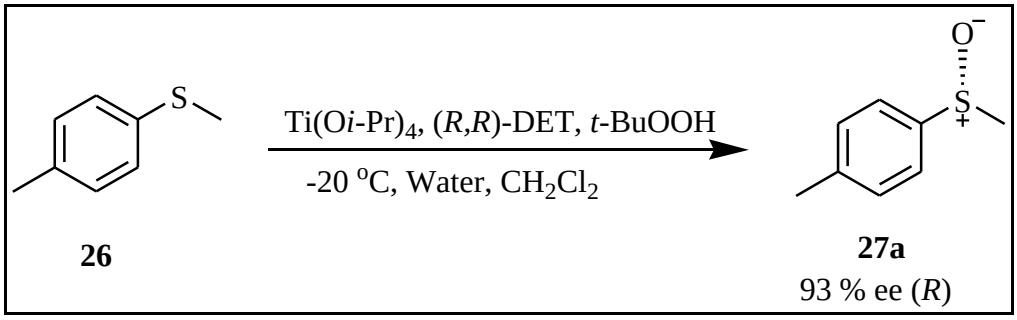


Scheme 5.5 Resolution of racemic sulfoxide (**23**) using (-)-1,6-di(*o*-chlorophenyl)-l,6-diphenylhexa-2,4-diyne-l,6-diol (**24**)

A number of chiral oxidants and enzymes are reported for kinetic resolution of racemic sulfoxides to enantiomerically pure sulfoxides.[27]

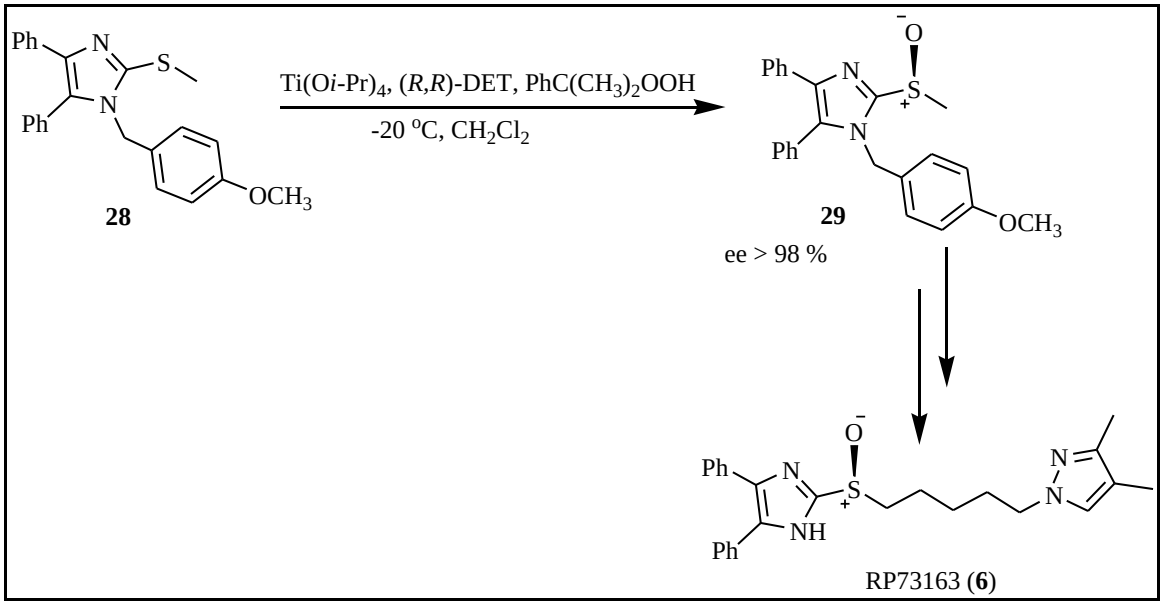
2) Asymmetric oxidation of sulfides

Kagan[28] and Modena[29] were the first to report the asymmetric oxidation of sulfides to sulfoxides independently in 1984 by modifying the Sharpless epoxidation reagent [$Ti(OPr^i)_4$/(+)-DET/ *t*-BuOOH]. The Kagan method used dichloromethane as solvent and addition of water to the oxidation while Modena used dichloroethane as solvent and does not involve addition of water. Kagan method for asymmetric oxidation of sulfides is shown in **scheme 5.6** taking an example of methyl *p*-tolyl sulfide (**26**).



Scheme 5.6 Kagan method for asymmetric oxidation of sulfides

Kagan's method was further developed by replacing *t*-BuOOH by cumene hydroperoxide in order to increase the optical purity of resulting sulfoxides.[30, 31] This procedure was applied for a large-scale asymmetric synthesis of a biologically active sulfoxide RP 73163 (**6**) (**Scheme 5.7**).[32]

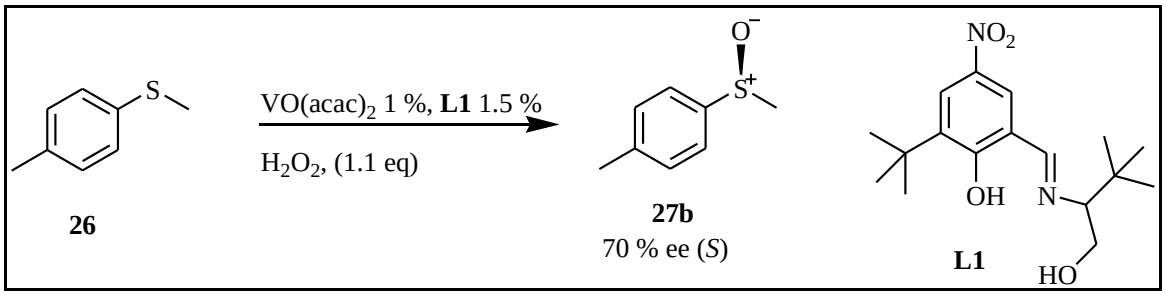


Scheme 5.7 Asymmetric oxidation of biologically active sulfoxide RP 73163 (**6**)

Various chiral ligands were used by replacing optically active diethyl tartrate (+)-(DET) in titanium mediated sulfur oxidation such as binaphthol,[33] hexanediol,[34] camphanediol,[35] mandelic acid,[36] schiff base.[37] While many research groups focused on the use of different hydroperoxides in order to improve the enantiomeric excess of the sulfoxidation.[38-44]

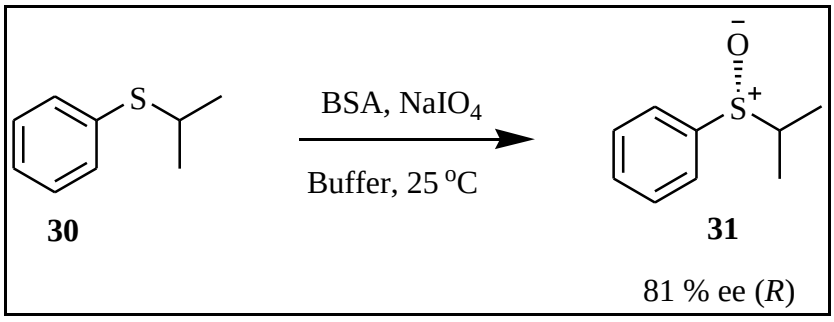
A second major class of metal catalyst used in enantioselective oxidations of sulfides consists of vanadium. Bolm reported the catalyst formed by $VO(acac)_2$ and N-salicylidene amino acid ligands which could achieve good yields and moderate enantioselectivies of aryl alkyl sulfoxides under simple operational conditions using

hydrogen peroxide (**Scheme 5.8**).[45] Thus different metals are used as catalysts for oxidation to obtain optically active sulfoxides which include aluminium, copper, iron, manganese, molybdenum, niobium, osmium, tungsten, zirconium, etc[27]



Scheme 5.8 Vandium catalysed oxidation of methyl *p*-tolyl sulfide (**26**)

Apart from using metals as catalyst for oxidation, many research groups earlier used chiral hydrogen peroxides,[46] oxaziridines,[47,48] iodine based reagents[49-51] for chiral sulfoxidation. Various chiral catalyst along with oxidizing agents were also used such as cyclodextrins[52] and bovine serum albumin (BSA). The latter was used by Sugimoto *et al* for the oxidation of aromatic sulfides. Isopropyl phenyl sulfide (**30**) was oxidized to corresponding sulfoxide (**31**) with optical purity of 81 % using BSA and sodium metaperiodate as oxidant (**Scheme 5.9**).[53]

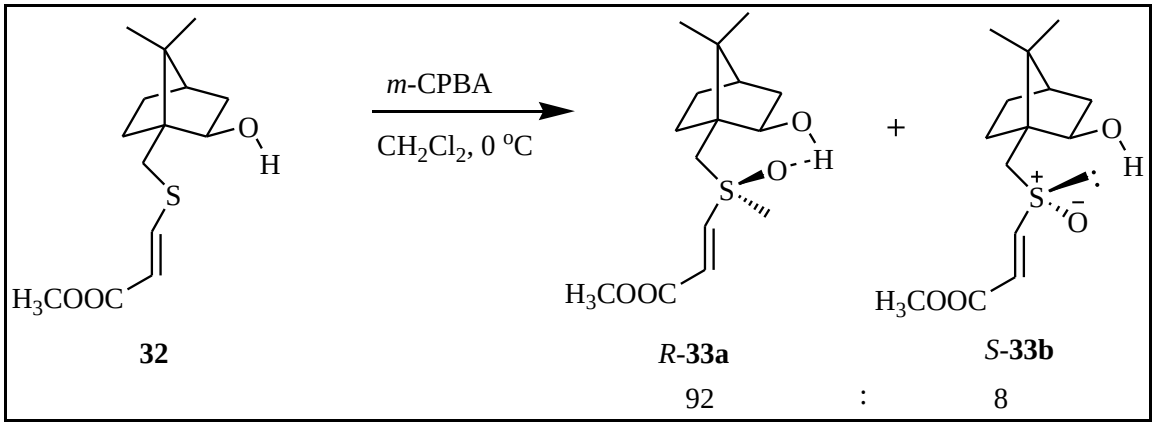


Scheme 5.9 Oxidation of Isopropyl phenyl sulfide (**30**) using BSA and $NaIO_4$ as oxidant

3) Diastereoselective sulfoxidation

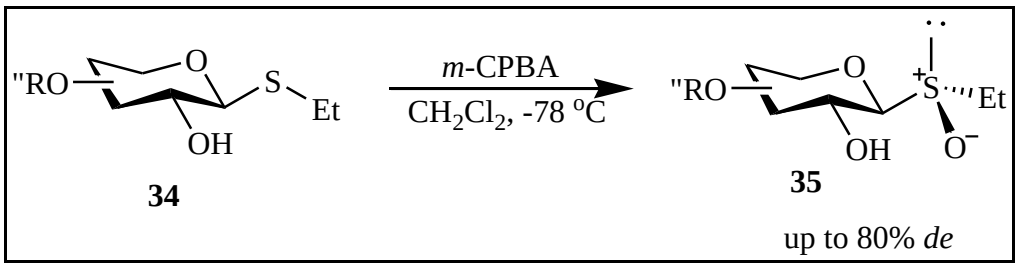
In diastereoselective sulfoxidation the sulfoxide formed acquires stereochemistry by making use of the proximity of a defined chiral center. De Lucchi reported the diastereoselective oxidation of 10-*exo*-hydroxybornyl derivative (**32**) for the synthesis of vinyl sulfoxides (**33a** and **33b**) in 92:8 ratio (**Scheme 5.10**). In this example

hydroxyl group is used as a diastereocontrol bias to deliver the electrophilic oxygen of a peracid to the prochiral sulfide.[54]



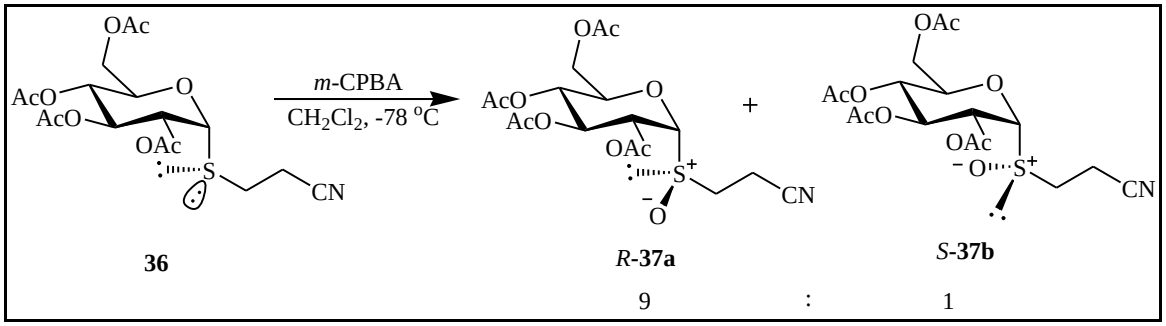
Scheme 5.10 Diastereoselective oxidation of 10-*exo*-hydroxybornyl derivative (**32**)

Khiar reported the oxidation of thioglycoside (**34**) with a free hydroxyl group at C-2 to corresponding *β*- sulfinyl glycosides (**35**) with high disastereoselectivity. The diastereoselectivity observed has been recognized by a hydrogen bonding and the predominance of the *exo*-anomeric conformation of **34** (**Scheme 5.11**).[55]



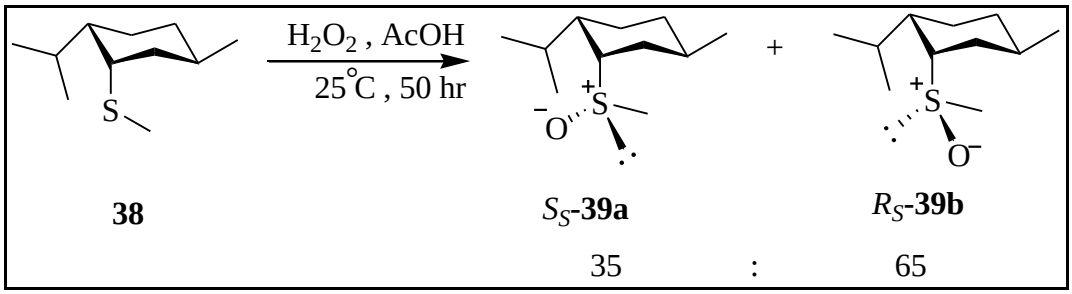
Scheme 5.11 Diastereoselective oxidation of thioglycoside (**34**)

Aversa *et al* have shown the the role of *exo*-anomeric effect in the diastereoselective oxidation of 1- thioglycosides (**36**). In the *exo*-anomeric conformation, only the *pro-R* lone pair of the sulfide is accessible for the peracid, thus affording (R_S)- 1-thio-α-D-glucopyranoside S-oxide (**37**) as a predominating isomer (**Scheme 5.12**).[56]

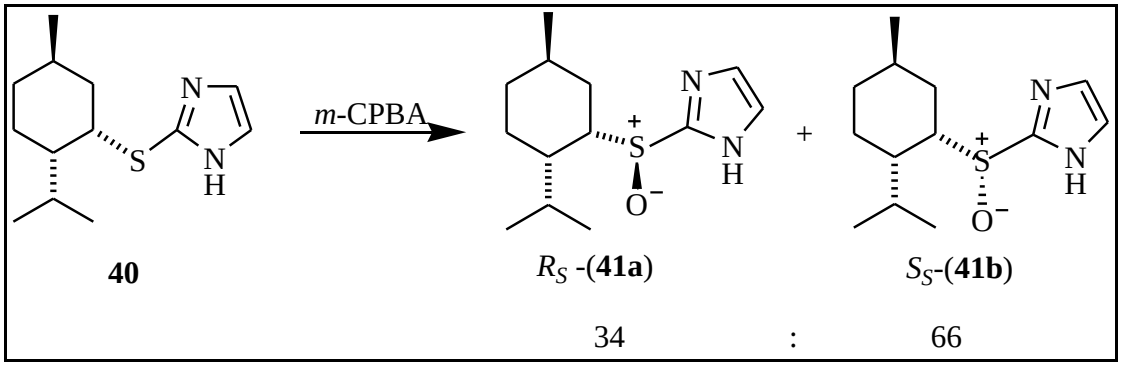


Scheme 5.12 Role of *exo*-anomeric effect in the diastereoselective oxidation of 1-thioglycosides (**36**)

Menthol and its derivatives are amongst the one, to find application as chiral auxiliaries for the preparation of optically active sulfoxides.[57] Oxidation of (*1S,2S,5R*)-(+)-methyl neomenthyl sulfide (**38**) using hydrogen peroxide furnished epimeric sulfoxides (**39a** and **39b)** (**Scheme 5.13**) in the ratio 35:65 with the major isomer (**39b**) having sulfoxide oxygen oriented away from the C-2 isopropyl group. These sulfoxides are further used as intermediates in asymmetric methylene transfer reactions (*vide supra*) (**Scheme 5.3**).[22,58] Similar observations are reported in the literature for the oxidation of different neomenthyl sulfides. Recently Demakova *et al* have reported the oxidation of (*1S,2S,5R*)-(+)-hetaryl neomenthyl sulfides using various reagents to yield two diastereomeric hetaryl neomenthyl sulfoxides in different ratio (**Scheme 5.14**).[59]



Scheme 5.13 Oxidation of (+)-methyl neomenthyl sulfide (**38**) using hydrogen peroxide-acetic acid



Scheme 5.14 Oxidation of 2-((*1S,2S,5R*)-2-isopropyl-5-methylcyclohexylthio)-1*H*-imidazole using *m*-CPBA

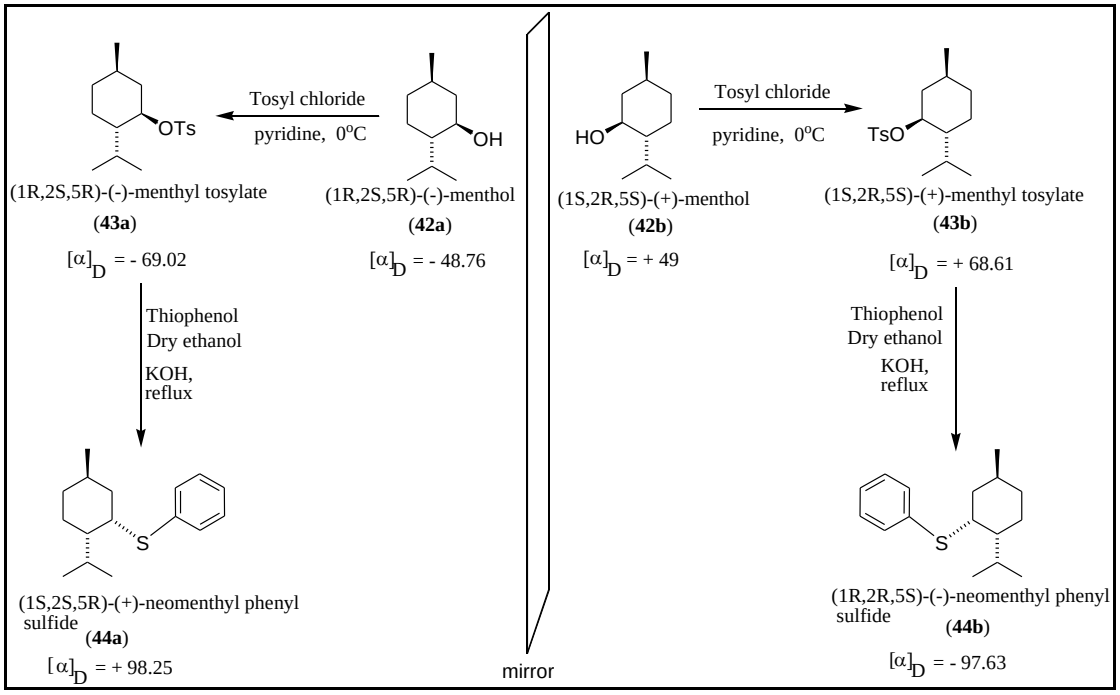
In above examples, skeleton of neomenthyl group behaves as chiral auxiliary with the equatorial isopropyl appendage exerting steric hindrance to the oxidant. However the diastereoselectivity for this sulfoxidation is moderate using oxidant which was achiral.

It was envisaged that better diastereomeric excess of neomenthyl sulfoxides could be achieved using bulkier oxidants which would have limited access to the sulfur center from the more hindered side having isopropyl group. Consequently the oxidation would result *via* approach of the oxidant from less hindered side giving better stereodifferentiation. Our efforts in this direction to employ quaternary ammonium oxidants differing in their head volume achieving stereodifferentation during oxidation of (*1S,2S,5R*)-(+)- and (*1R,2R,5S*)-(-)-neomenthyl phenyl sulfides **44a** and **44b** are presented here under.[60]

5.3 Results and Discussion

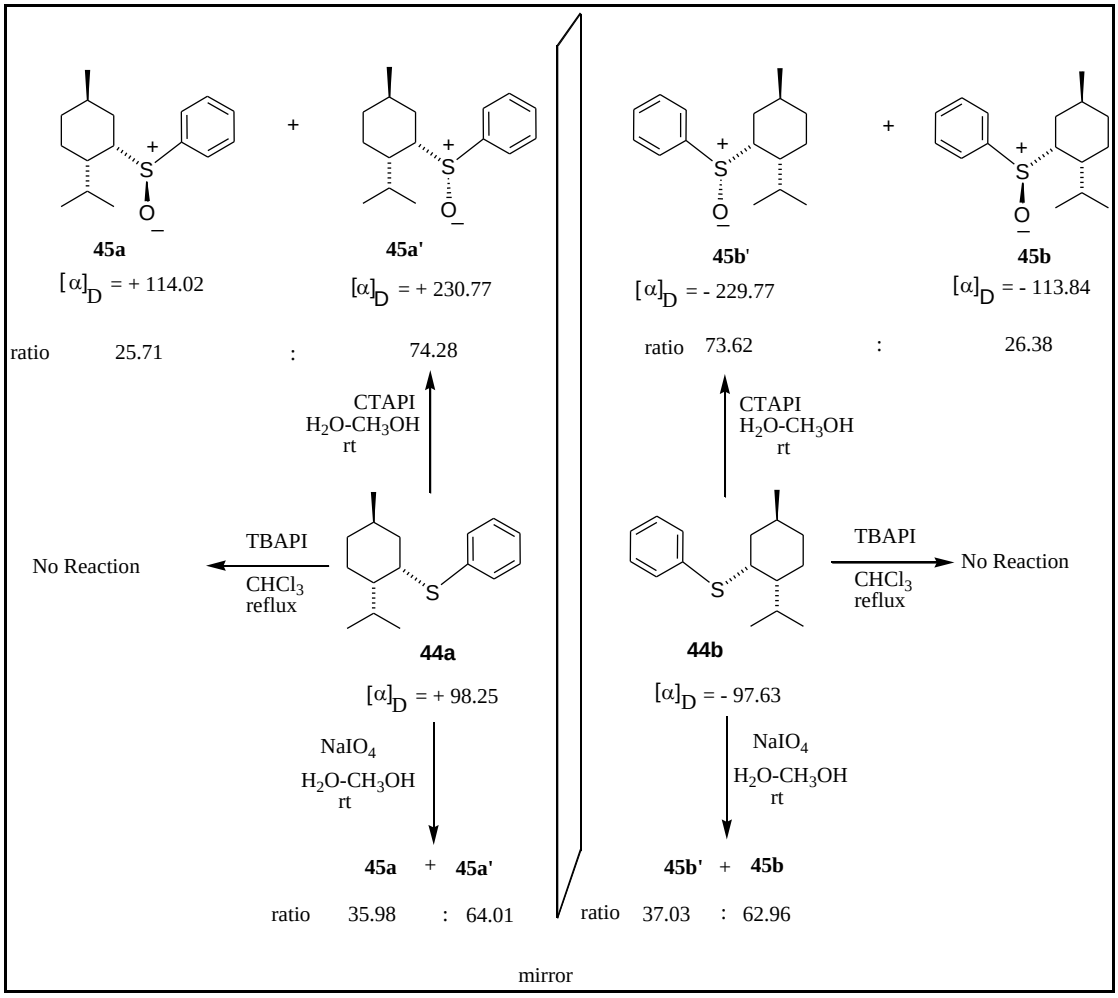
We have reported selective oxidation of structurally different sulfides to corresponding sulfoxides using hexadecyltrimethylammonium periodate (cetyltrimethylammonium periodate, CTAPI)[61] which has a bulky head group. Such unwieldiness is lacking in conventional oxidants like hydrogen peroxide, sodium metaperiodate, *m*-chloroperbenzoic acid etc.

In order to examine our hypothesis (*vide supra*) we quickly prepared (*1S,2S,5R*)-(+)-neomenthyl phenyl sulfide (**44a**) in two steps from (-)-menthol (**42a**) *via* (-)-menthyl tosylate (**43a**).[62] Nucleophilic attack of thiophenol on **43a** in ethanolic potassium hydroxide at 78 °C for 10 h resulted in **44a** (**Scheme 5.15**).



Scheme 5.15 Preparation of (*1S,2S,5R*)-(+) and (*1R,2R,5S*)-(-)-neomenthyl phenyl sulfides (**44a** and **44b**)

(*1S,2S,5R*)-(+)-Neomenthyl phenyl sulfide (**44a**) was initially subjected to oxidation using sodium metaperiodate, by the procedure of Leonard and Johnson[63], which furnished an epimeric pair of sulfoxides (**45a** and **45a′**) in 35.98 : 64.01 (63 %) (**Scheme 5.16**). Oxidation of **44a** using CTAPI in water-methanol (8:2) at 25 °C for 45 h following our own reported procedure,[61] resulted in the formation of diastereomeric sulfoxides (**45a** and **45a′**) in 25.71 : 74.28 (72 %) (**Scheme 5.16**). The observed improvement in the diastereomeric ratio in oxidation using CTAPI might be attributed to the steric hindrance between its bulky head group and the equatorial isopropyl group in **44a**. No oxidation was observed at lower temperature (0-5 ^{o}C) even after 10 h when explored for further improvement in the diastereomeric ratio. It was thought that oxidants bulkier than CTAPI might further improve *de* ratio in favour of **45a′** due to high steric consideration. With this contention, **44a** was subjected to oxidation following the procedure of Santaniello[64] using tetrabutylammonium periodate (TBAPI, head group volume 66.97 Å^3) which has bulkier head group than CTAPI (head group volume 9.02 Å^3). However in contrast to our anticipation it was found that the reaction did not proceed at all even after 12 h under reflux.



Scheme 5.16 Oxidation of **44a** and **44b** using $NaIO_4$, cetyltrimethylammonium periodate (CTAPI) and n-tetrabutylammonium periodate (TBAPI)

This could be due to the excessively large head volume of TBAPI which perhaps completely blocks the oxidant from approaching the sulfur center. The head group volume in case of CTAPI is relatively smaller and hence the oxidation occurs with better diastereoselectivity.

Energy minimized structures of **44a**, **45a**, **45a′**, CTAPI and TBAPI are shown in **Figure 5.3**. An oxidant can approach sulfur center in **44a** *via* two pathways. Equatorial isopropyl group in **44a** poses more steric hindrance to the incoming bulky headed oxidant thus making path-I less favoured as compared to path-II. Therefore in oxidation using CTAPI, sulfoxide **45a** is obtained as a minor diastereomer while **45a′** as major one.

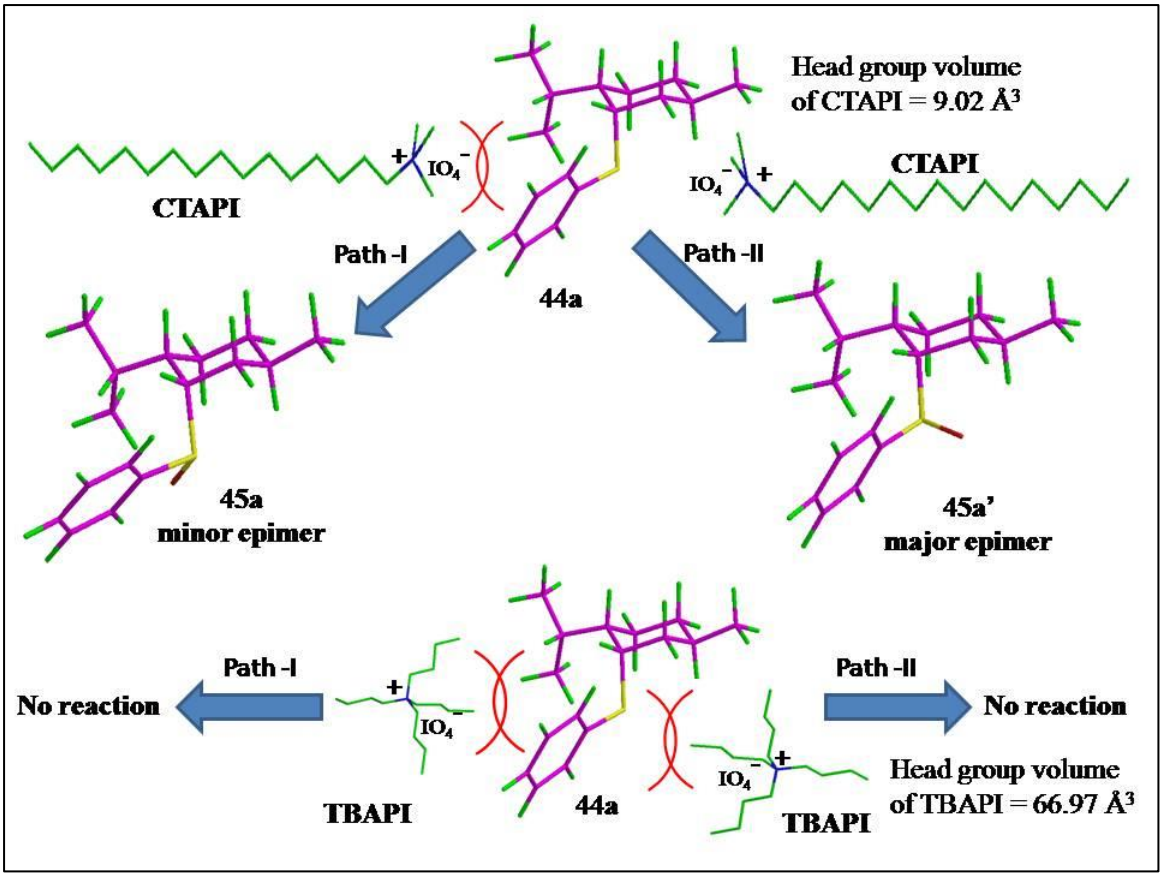


Figure 5.3 Energy minimized structures of **44a**, **45a**, **45a′**, CTAPI and TBAPI

No reaction was observed in case of TBAPI as oxidant as the counter ion IO_4^- responsible for oxidation is unable to access the sulfur center from either path due to long *n*-butyl chains as shown in **Figure 5.3**.

Similar study was also performed on (*1R,2R,5S*)-(-)-neomenthyl phenyl sulfide (**44b**), an enantiomer of **44a** (**Scheme 5.16**) obtained from (*1S,2R,5S*)-(+)-menthol (**42b**) (**Scheme 5.15**) to examine the replicability. The results obtained are in good agreement with those of oxidation of **5a** using three oxidants differing in their size.

The diastereomeric sulfoxides (**45a/a′** and **45b/b′**) obtained from **44a** and **44b** exhibited considerable mobilities during TLC analysis and hence their separation was easily achieved by silica gel column chromatography. Compounds **45a** and **45b** are crystalline in nature while **45a′** and **45b′** are amorphous. All the structures were confirmed by ^1H as well as ^{13}C NMR spectra and HRMS analysis. The absolute configuration at sulfur in sulfoxide **45a** was determined using single crystal X-ray

crystallography and was found to be *Ss* (**Figure 5.4**). Accordingly the epimeric sulfoxide **45a′** was considered *Rs* configuration at sulfur and sulfoxides **45b** and **45b′** being enantiomers of **45a** and **45a′** were assigned *Rs* and *Ss* respectively.

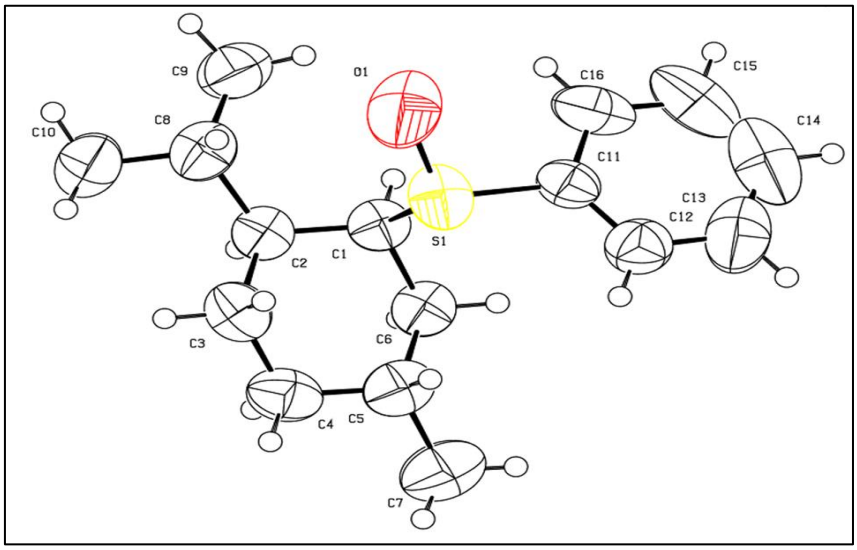


Figure 5.4 ORTEP diagram of **45a**

An examination of the ^{1}H NMR spectra of the sulfoxides **45a** and **45a′** showed that the proton H-1 and three protons of methyl group attached to C-5 of **45a** appear at δ 3.37 and 0.70 ppm. While signals from these protons in **45a′** are observed at δ 2.78 and 0.77 ppm respectively. This difference in chemical shift allows for determination of the diastereomeric purity of the compounds by simple integration of respective proton signals in the ^{1}H NMR spectrum. The oxidation products of **44a** and **44b** were isolated by column chromatography and their diastereomeric excess was determined by means of ^{1}H NMR spectroscopy.

5.4 Experimental

(-)-Menthol (ee: 99 %) and (+)-menthol (ee: 99 %) were purchased from Sigma Aldrich. All solvents were distilled prior to use and stored on oven-dried molecular sieves (4Å). Thin layer chromatography (TLC) analyses were done on glass plates using silica gel G containing 13 % calcium sulphate as binder. The spots were visualized in iodine vapour. Column chromatography was performed using Acme's silica gel (60-120 mesh size) and elution was done using light petroleum (60-80) and ethyl acetate mixtures. Melting points were recorded in open capillary tubes and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker-(400/500) FT-NMR spectrometer (^{1}H NMR 400/500 MHz and ^{13}C NMR at 100 MHz) using $CDCl_3$ as solvent. The chemical shifts, in parts per million (ppm) are either relative to TMS as an internal standard or the residual peak of the solvent. Multiplicities of signals are denoted as doublet (d), doublet of quartet (dq), and multiplet (m). Mass spectra were recorded on a Thermo-Fischer DSQ II GCMS instrument. Mass Spectra (HRMS) were recorded on a Agilent Q-Tof B.05.00 (B5042.0) high resolution MSMS spectrometer using electrospray ionization mode. For crystals of **45a** the intensity data were collected at 293 K on a Nonius Kappa CCD diffractometer system equipped with graphite-monochromated CuKa radiation (λ=1.5418Å). Structure was solved by direct method (SIR97) and refined by a full-matrix least-squares procedure based on F^2. All non-hydrogen atoms were refined anisotropically; hydrogen atoms were located at the calculated positions and were refined by using a riding model with isotropic thermal parameters fixed at 1.2 times the Ueq value of the appropriate carrier atom. CCDC: 1030433. For calculation of head group volume both TBAPI and CTAPI were built in the Schrodinger suite, LLC, New York, NY, 2009. Energy of molecules under study were optimized using Density functional theory (DFT) within the Schrodinger suite, and such optimized structures were used to measure the required dimension of the molecules to calculate head volume of the structures under study. DFT is a quantum mechanical method mainly used to determine the ground state of systems.

Preparation of (-)- and (+)-Menthyl-p-toluenesulfonate (**43a** and **43b**): (-)-**43a** was prepared according to the published procedure[22] as depicted in Scheme 5.15 starting from (1R,2S,5R)-(-)-menthol (**3a**), yield 93%; m.p. 92-94 ^{o}C; $[\alpha]_D$ = -69.02 (c = 2.99, $CHCl_3$) (lit.[65] $[\alpha]_D$ = -69.5 (c = 2.99, $CHCl_3$)) while (+)-**43b** from (1S,2R,5S)-(+)-

menthol (**42b**) following similar procedure, yield 92%; m.p. 90-92 ^{o}C; $[\alpha]_D$ = +68.61 (c = 2.99, $CHCl_3$).

Preparation of (+) and (-)-Neomenthyl phenyl sulfides (**44a** and **44b**): To a stirred solution of thiophenol (2.5 g, 22.7 mmole) in dry ethanol (10 ml) at room temperature was added KOH solution (1.5 g, 27.2 mmole) in dry ethanol (10 ml). The reaction mixture was then heated to 60 ^{o}C, followed by addition of appropriate menthyl tosylate (**43a** or **43b**) (8.5 g, 27.2 mmole) in dry ethanol (30 ml) and was allowed to stir for 12 h. The solvent was evaporated under vacuum and the residue was extracted with ethyl acetate (4 x 25 ml). The combined organic extracts were washed with water (30 ml), brine (20 ml) and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to obtain crude product as a pale yellow liquid, which after chromatography over a column of silica gel using light petroleum afforded pure sulfide **44a** or **44b**

(*1S,2S,5R*)-(+)-2-isopropyl-5-methylcyclohexyl phenyl sulfide (44a): (2.91 g, 52%); $[\alpha]_D$ = + 98.25 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.84 (3H, d, *J* = 6.6 Hz), 0.89-0.93 (7H, m), 1.15-1.30 (3H, m), 1.70-1.80 (3H, m), 1.89 (1H, dq, J_d = 13.5 Hz, J_q = 2.8 Hz), 1.98-2.07 (1H, m), 3.63 (1H, m), 7.10-7.50 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.6, 21.2 (2 x C, -CH($\underline{C}H_3)_2$), 22.2 ($\underline{C}H_3$), 26.2 ($\underline{C}H_2$), 26.5 ($\underline{C}$H), 30.2 (-$\underline{C}$H$(CH_3)_2$), 35.4, 40.5 (2 x C, $\underline{C}H_2$), 48.5 ($\underline{C}$H, to which isopropyl group is attached), 49.7 (-$\underline{C}$HSC_6H_5), 126.1 ($\underline{C}$H, aromatic), 128.8 (2 x $\underline{C}$H, aromatic), 131.0 (2 x $\underline{C}$H, aromatic), 136.8 ($\underline{C}$q, aromatic attached to sulfur). MS m/z 249.25 (M^+ + 1).

(*1R,2R,5S*)-(-)-2-isopropyl-5-methylcyclohexyl phenyl sulfide (**44b):** (2.96 g, 53%); $[\alpha]_D$ = -97.63 (*c* = 1.00, $CHCl_3$) as colourless liquid. R_f 0.82 (light petroleum).

Oxidation of sulfides (44a and 44b) using CTAPI: To stirred solution of sulfides (0.5 g, 2.02 mmole) in aqueous methanol (8:2) (10 ml) at room temperature was added cetyltrimethylammonium periodate (CTAPI) (1.3 g, 7.07 mmole) in portions over a period of 15 min. The mixture was then stirred for 45 hr. The reaction mixture was filtered and the filtrate was extracted with ethyl acetate (5 × 25 ml), dried over anhydrous sodium sulfate and evaporated under reduced pressure to give a mixture of diastereomeric sulfoxides ((**45a** and **45a′**) (0.38 g, 72%)) or (**45b** and **45b′**) (0.37 g, 71%)) depending upon the sulfide used. The ratio of (**45a** and **45a′**) was found to be

25.71 : 74.28 and that of (**45b** and **45b′**) to be 26.38 : 73.62 as determined by ^{1}H NMR of their mixtures. Column chromatography of the product mixture over silica gel with light petroleum/ethyl acetate (80:20) afforded major diastereomeric sulfoxide **45a′**

1-(+)-{(*R)*-[(*1S,2S,5R*)-2-isopropyl-5-methylcyclohexylsulfinyl]}benzene (45a′): White amorphous solid (0.28 g, 53%); R_f 0.52 (25% EtOAc/ light petroleum); mp = 120 ^{o}C; $[\alpha]_D$ = + 230.77 (c = 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.77 (3H, d, J = 6.4 Hz), 0.87-1.01 (3H, m), 1.06 (3H, d, J = 6.4 Hz), 1.09 (3H, d, J = 6.4 Hz), 1.35-1.46 (1H, m), 1.75-1.96 (3H, m), 2.17-2.28 (1H, m), 2-30-2.34 (1H, m), 2.78 (1H, m), 7.48-7.62 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 21.4 (2 x C, -CH($\underline{C}H_3$)$_2$), 22.9 ($\underline{C}H_3$), 26.4 ($\underline{C}H_2$), 27.8 ($\underline{C}$H), 29.6 (-$\underline{C}$H(CH_3)$_2$), 34.3, 35.2 (2 x C, $\underline{C}H_2$), 48.2 ($\underline{C}$H, to which isopropyl group is attached), 62.1 (-$\underline{C}$HSOC_6H_5), 124.5 ($\underline{C}$H, aromatic), 128.9 (2 x $\underline{C}$H, aromatic), 130.2 (2 x $\underline{C}$H, aromatic), 144.2 ($\underline{C}$q, aromatic attached to sulfoxide). HRMS (ESI) *m/z* $[M+Na]^+$ calculated for $C_{16}H_{24}OS$: 287.1446 found: 287.1449.

1-(+)-{(*S)*-[(*1S,2S,5R*)-2-isopropyl-5-methylcyclohexylsulfinyl]}benzene (45a): Further elution of the column with light petroleum /ethyl acetate (70:30) gave minor diastereomeric sulfoxide **45a** as colorless crystal (0.09 g, 17 %); R_f 0.39 (25% EtOAc/ light petroleum); mp = 80 ^{o}C; $[\alpha]_D$ = + 114.02 (c = 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.70 (3H, d, J = 6.2 Hz), 0.98 (3H, d, J = 6.4 Hz), 1.0-1.08 (1H, m), 1.13 (3H, d, J = 6.4 Hz), 1.25-1.46 (3H, m), 1.63-1.72 (1H, m), 1.76-1.87 (1H, m), 1.89-1.95 (1H, m), 2.00-2.03 (1H, m), 2.25-2.34 (1H, m), 3.37 (1H, m), 7.50-7.55 (3H, m) 7.71-7.75 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 22.2 (2 x C, -CH($\underline{C}H_3$)$_2$), 22.3 ($\underline{C}H_3$), 26.0 ($\underline{C}H_2$), 27.9 ($\underline{C}$H), 29.5 (-$\underline{C}$H(CH_3)$_2$), 35.7, 37.7 (2 x C, $\underline{C}H_2$), 50.4 ($\underline{C}$H, to which isopropyl group is attached), 65.7 (-$\underline{C}$HSOC_6H_5), 125.7 ($\underline{C}$H, aromatic), 129.1 (2 x $\underline{C}$H, aromatic), 131.3 (2 x $\underline{C}$H, aromatic), 144.3 ($\underline{C}$q, aromatic attached to sulfoxide). HRMS (ESI) *m/z* $[M+Na]^+$ calculated for $C_{16}H_{24}OS$: 287.1446 found: 287.1440.

5.5 Conclusion

In summary, two new sulfoxides **45a**, **45a′** and their enantiomers **45b**, **45b′** have been prepared and their configurations determined. The present work shows the effect of bulky headed oxidant in improvement of diastereomeric ratio of (+)- and (-)-neomenthyl phenyl sulfoxides (**45a**/**45a′**and **45b**/**45b′**) considering steric aspects. An overall increase of about 20 % in *de* was obtained using CTAPI for oxidation of (*1S,2S,5R*)-(+)- and (*1R,2R,5S*)-(-)-neomenthyl phenyl sulfides **44a** and **44b**. Configurations of **45a**/**45a′**and **45b**/**45b′** were determined as *Ss*, *Rs* and *Rs*, *Ss*.

5.6 References

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5.7 Spectral data of compounds

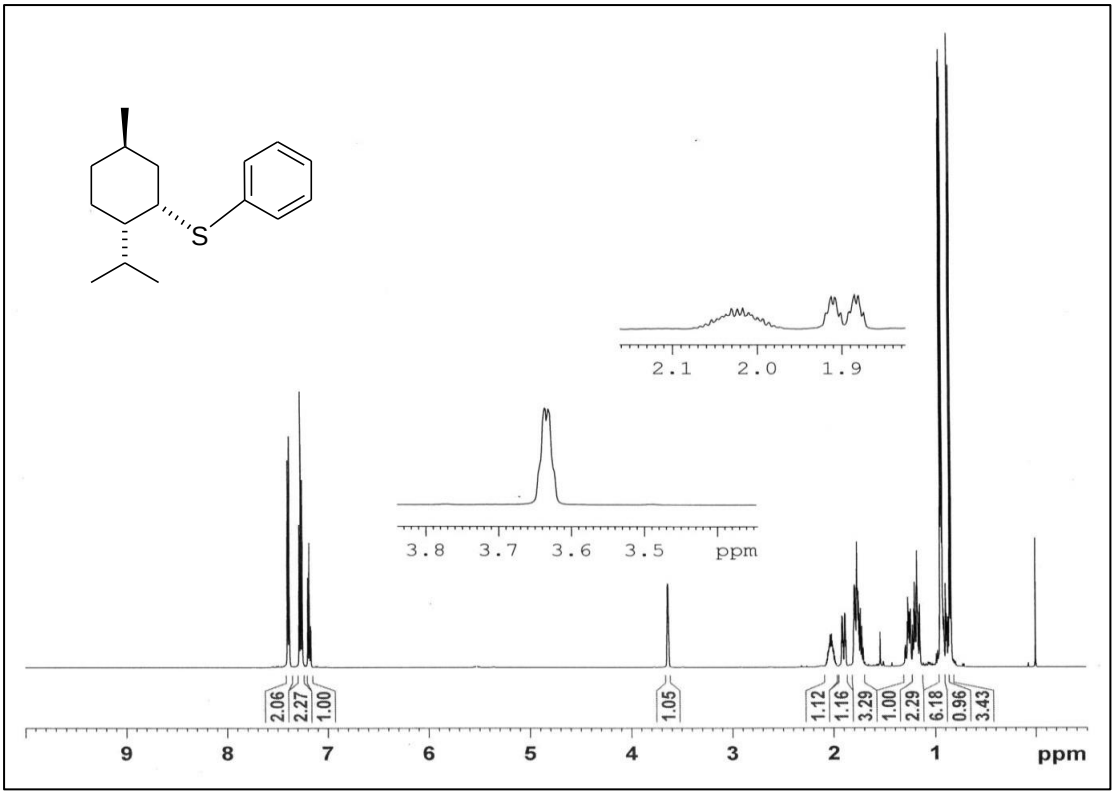

Figure 5.5 ^{1}H NMR of (1S,2S,5R)-(+)-neomenthyl phenyl sulfide (**44a**)

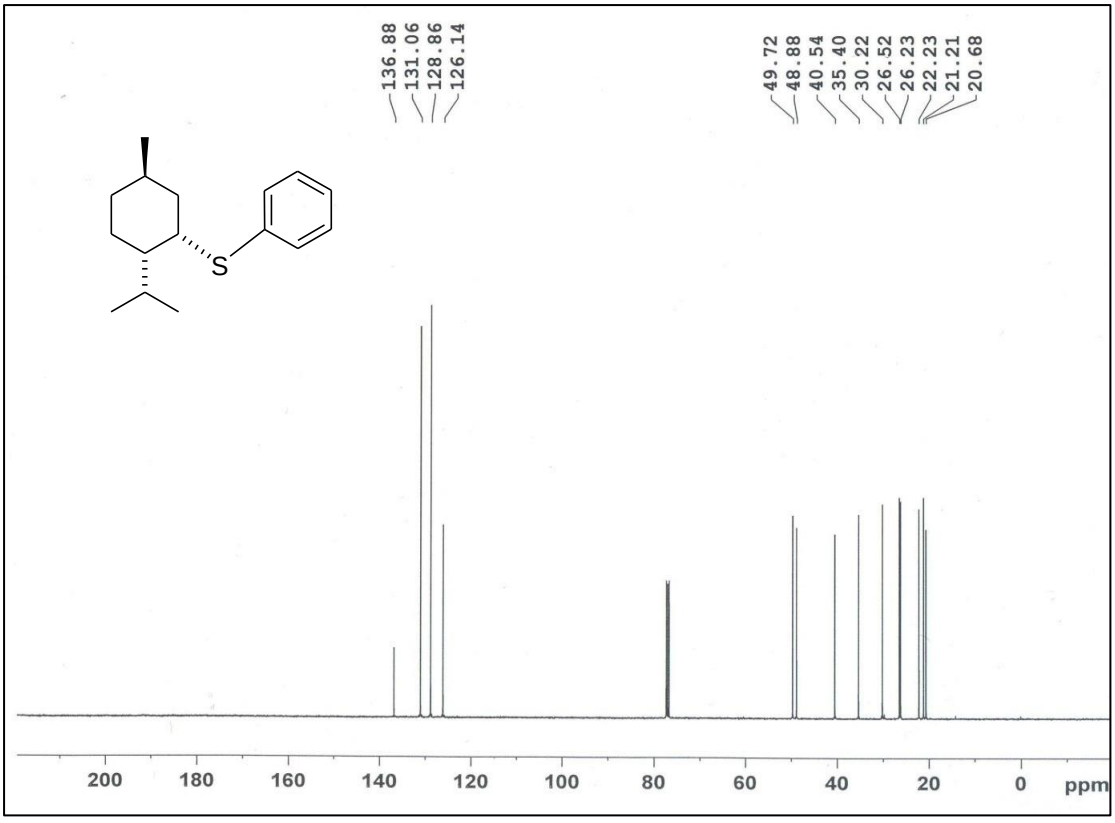

Figure 5.6 ^{13}C NMR of (1S,2S,5R)-(+)-neomenthyl phenyl sulfide (**44a**)

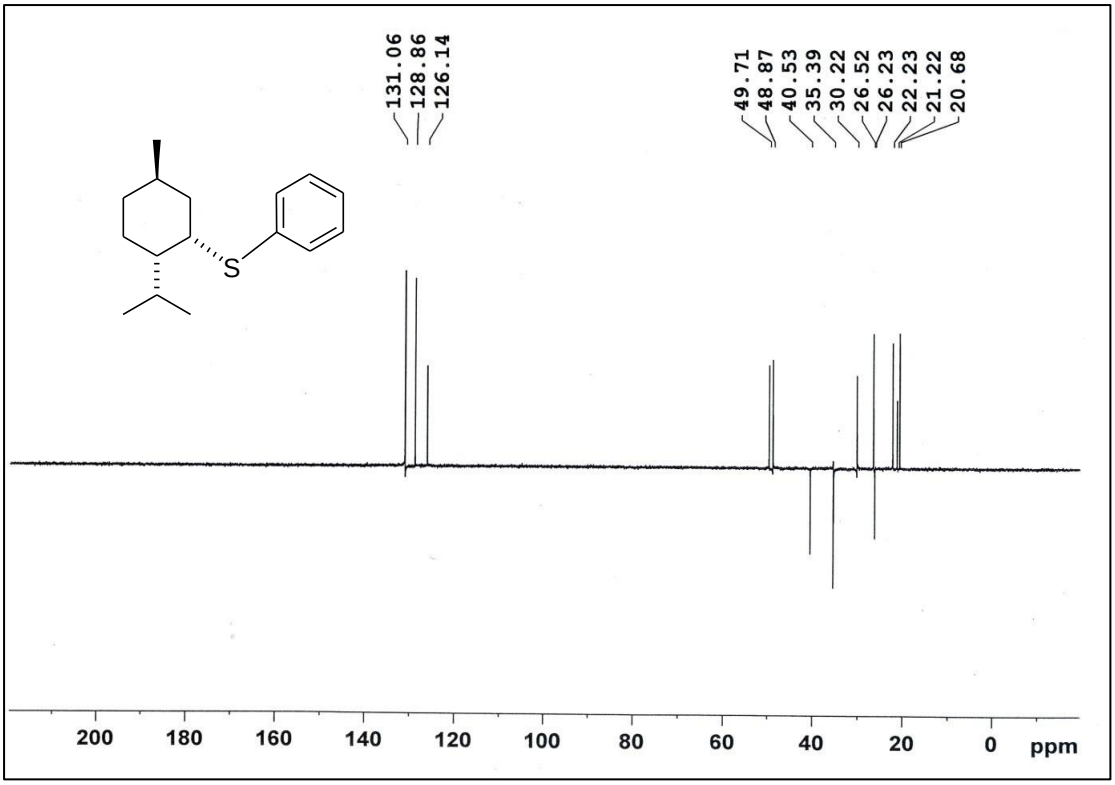

Figure 5.7 DEPT 135 of (1S,2S,5R)-(+)-neomenthyl phenyl sulfide (**44a**)

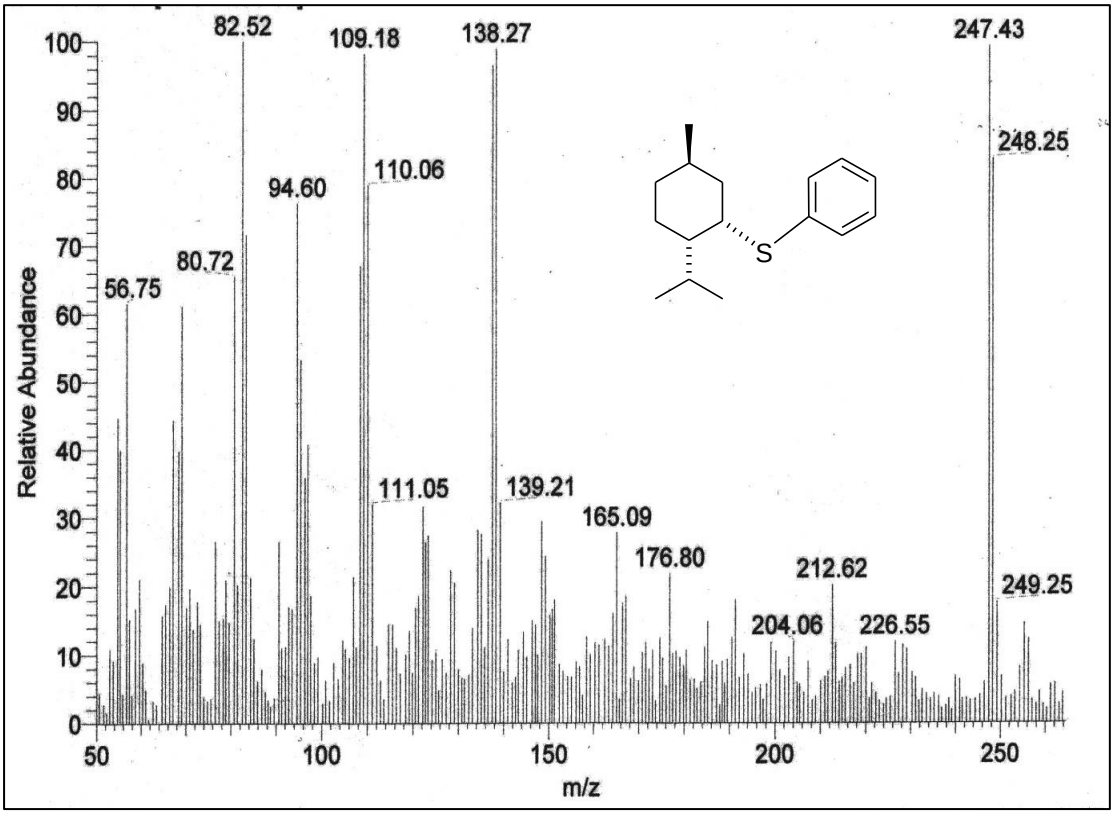

Figure 5.8 Mass spectrum of **44a**

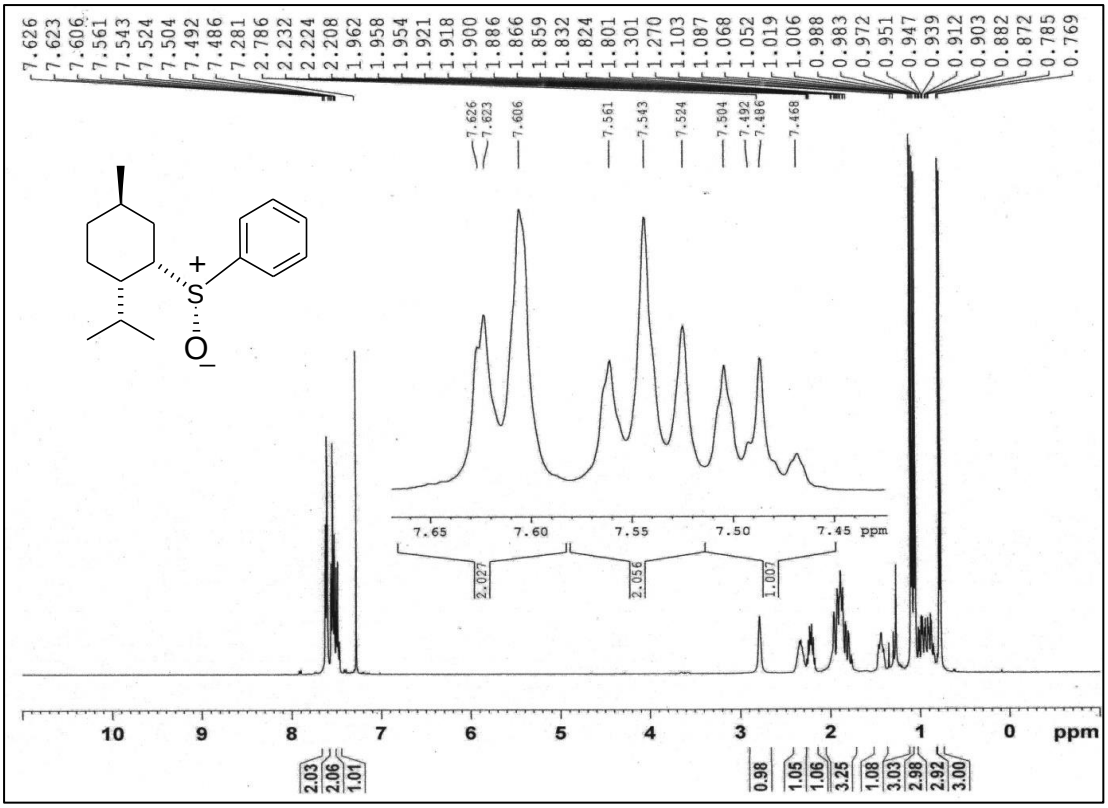

Figure 5.9 ^{1}H NMR of sulfoxide (**45a′**)

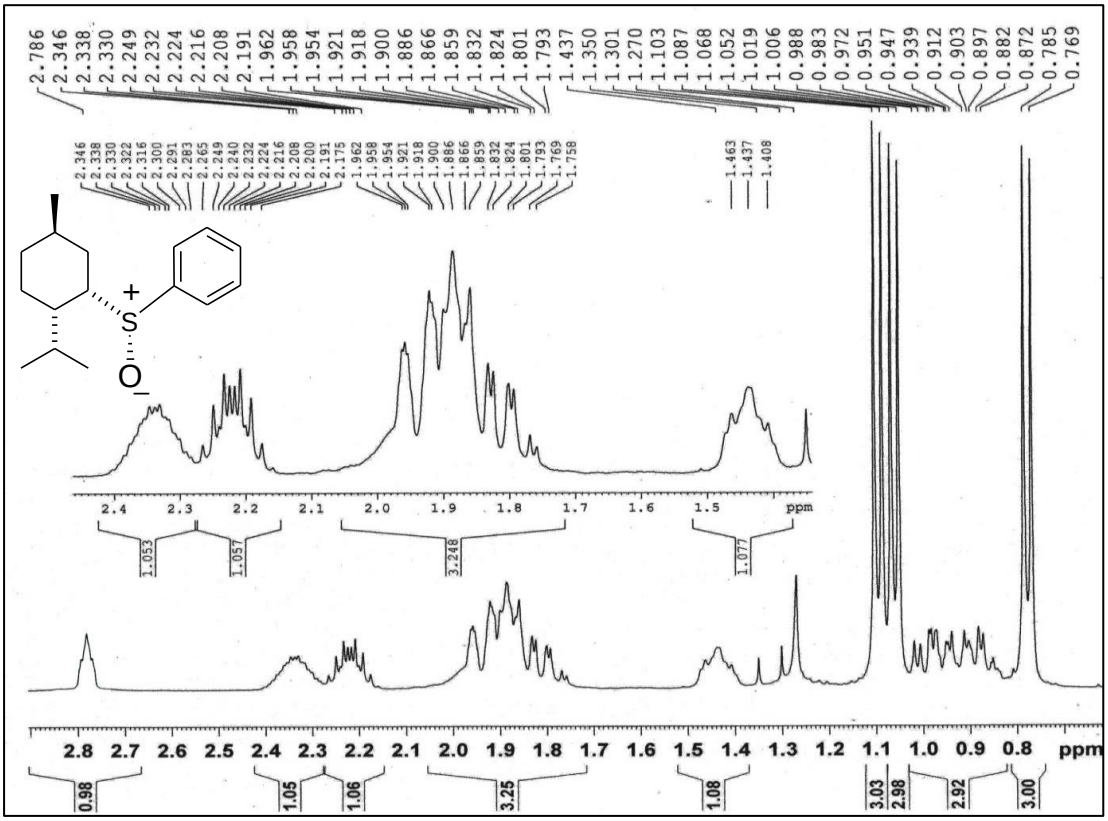

Figure 5.10 Expanded Graph for ^{1}H NMR of sulfoxide (**45a′**)

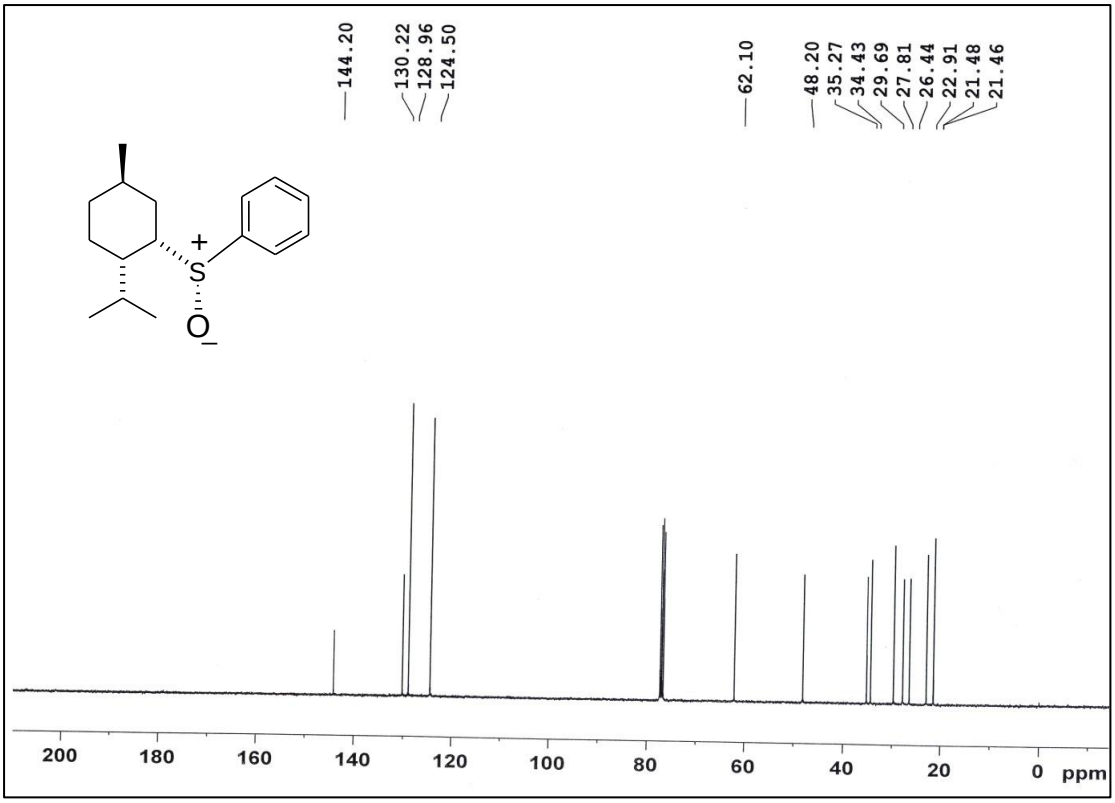

Figure 5.11 ^{13}C NMR of sulfoxide (**45a′**)

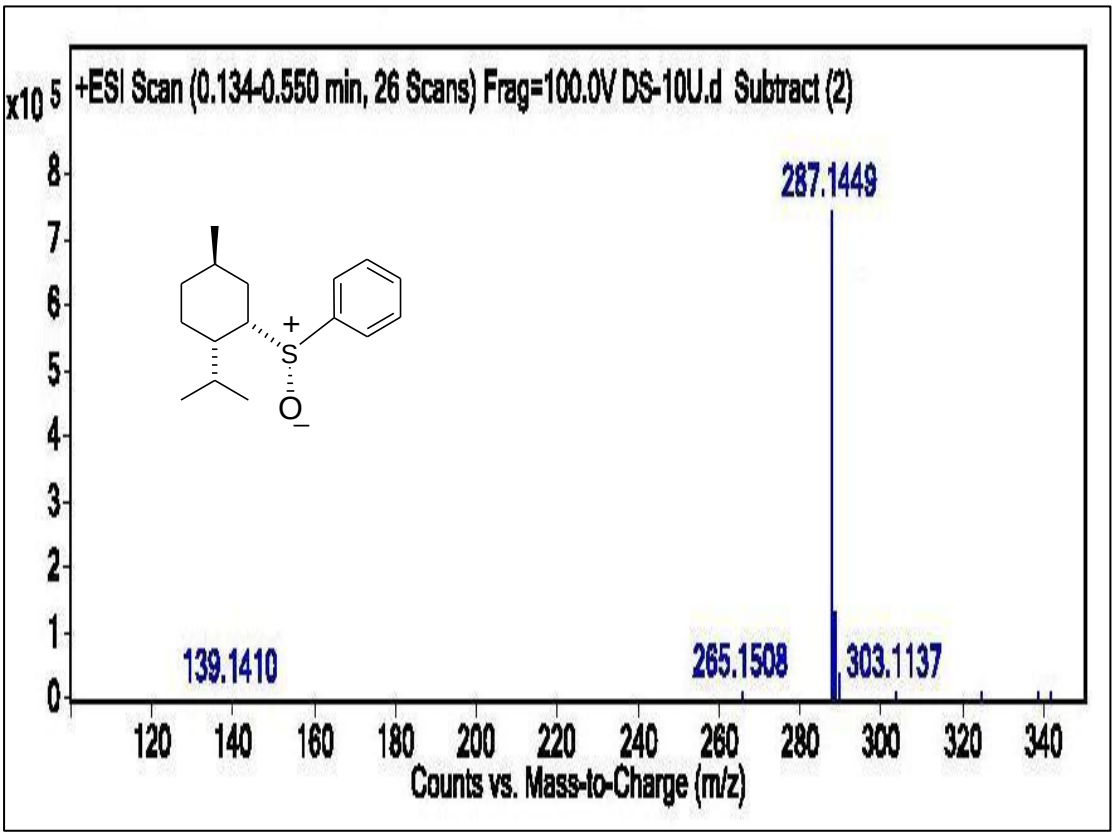

Figure 5.12 HRMS of **45a′**

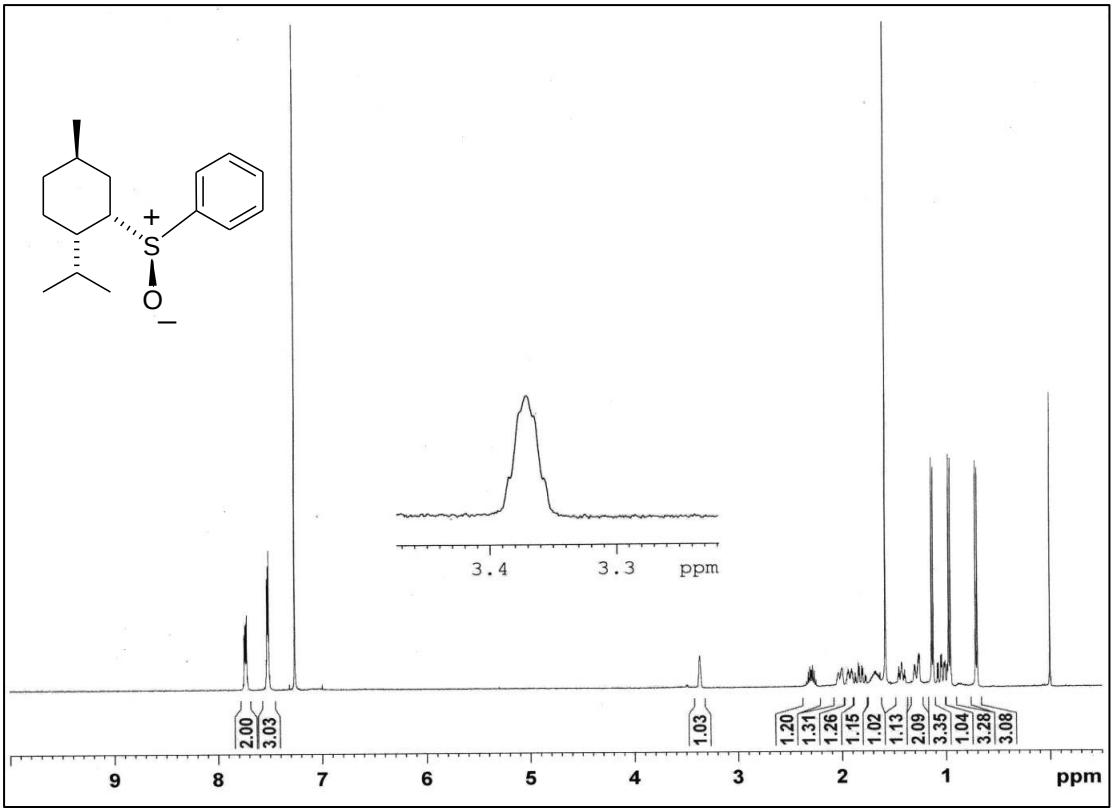

Figure 5.13 ^{1}H NMR of sulfoxide (**45a**)

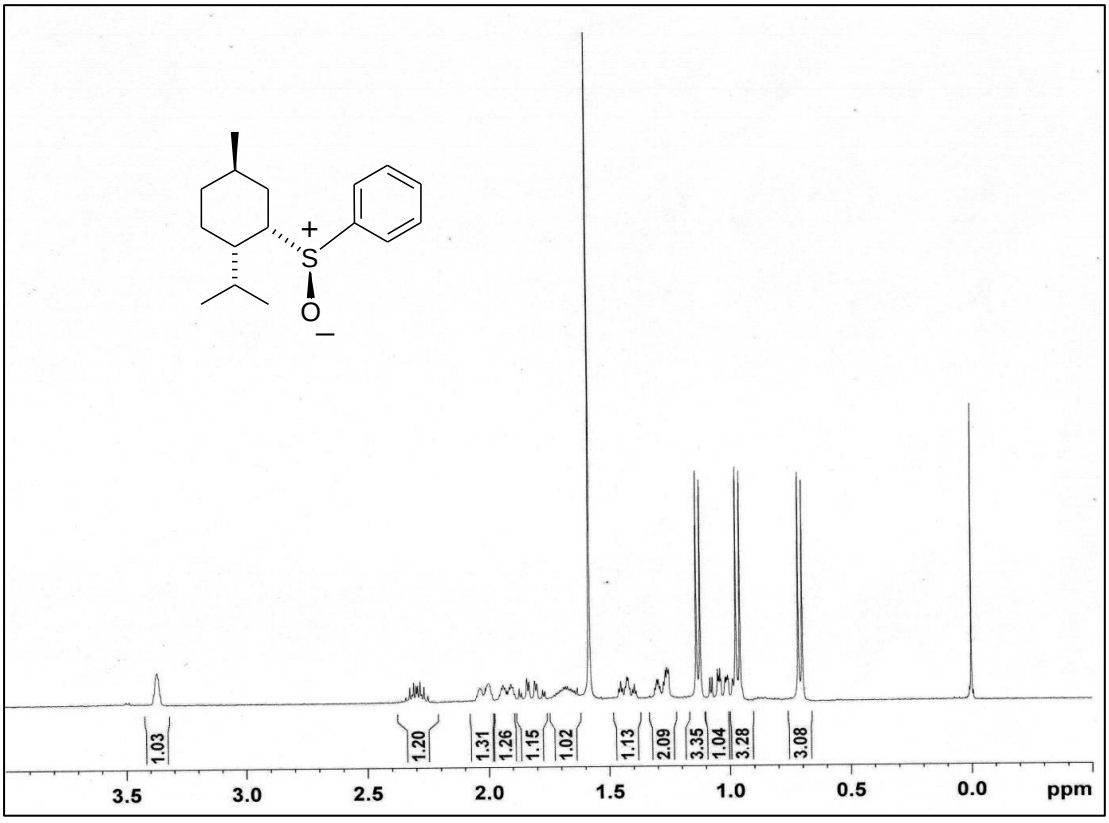

Figure 5.14 Expanded graph for ^{1}H NMR of sulfoxide (**45a**)

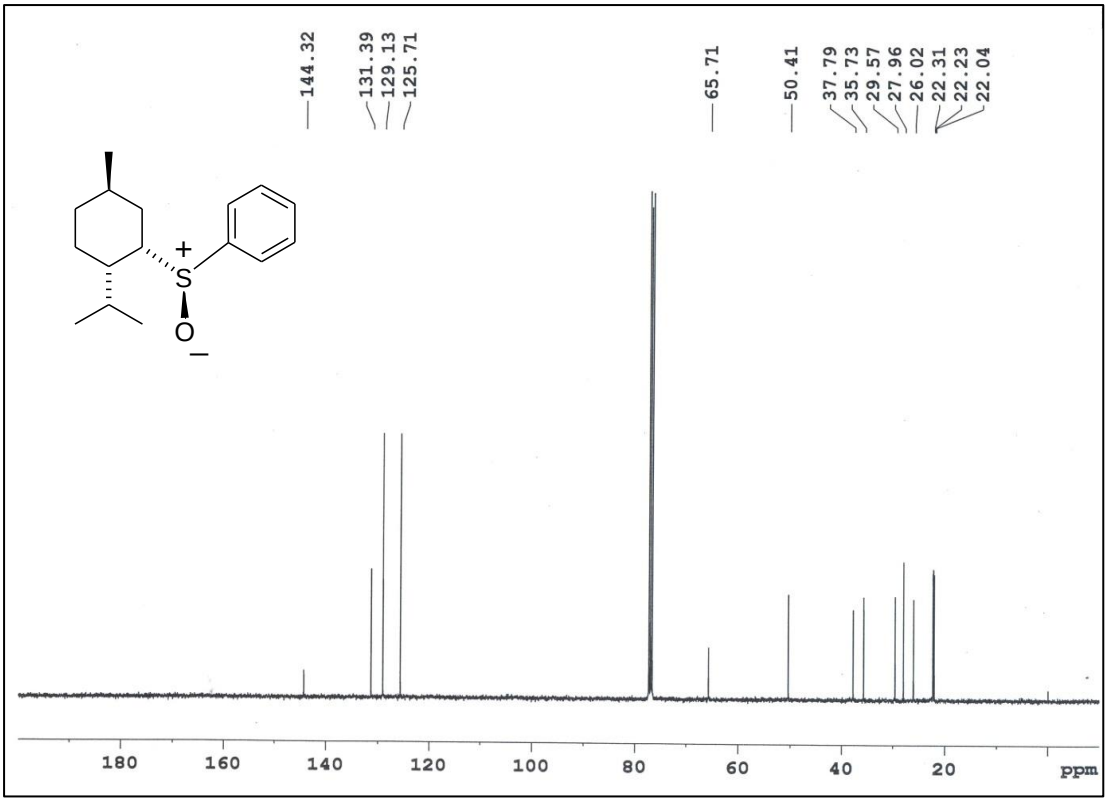

Figure 5.15 ^{13}C NMR of sulfoxide (**45a**)

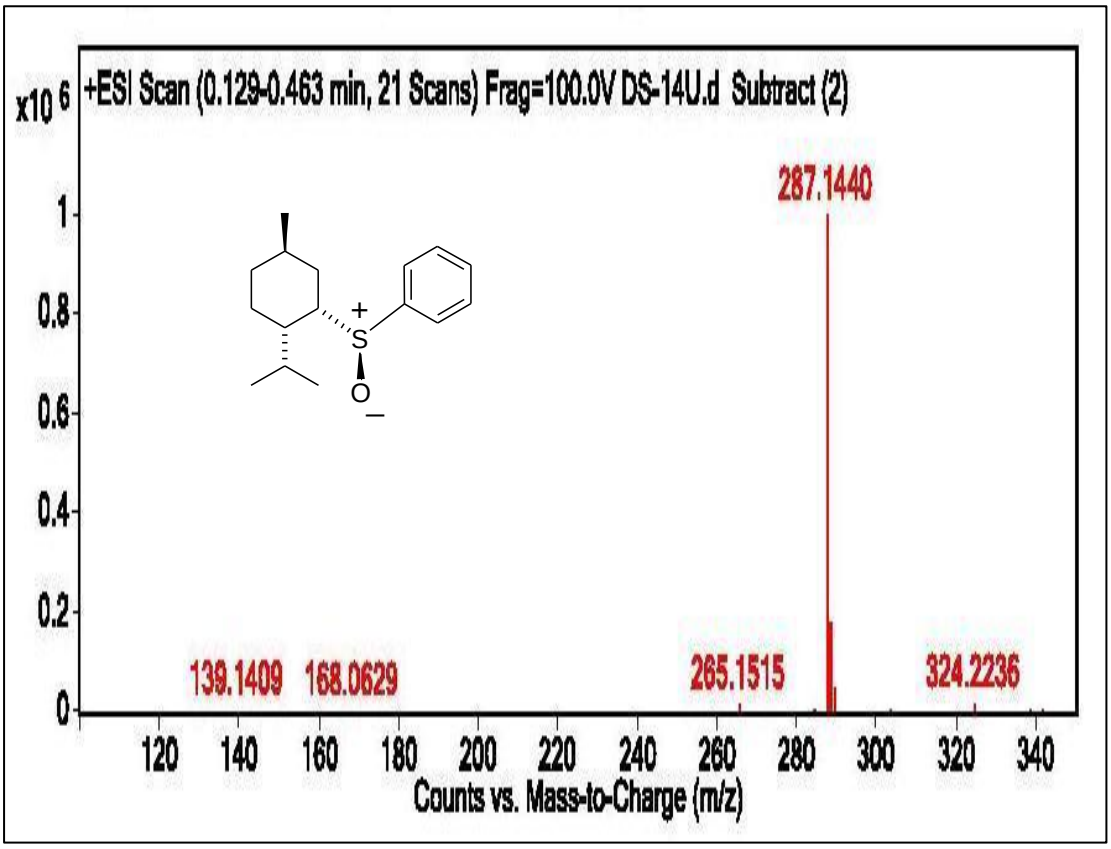

Figure 5.16 HRMS of **45a**

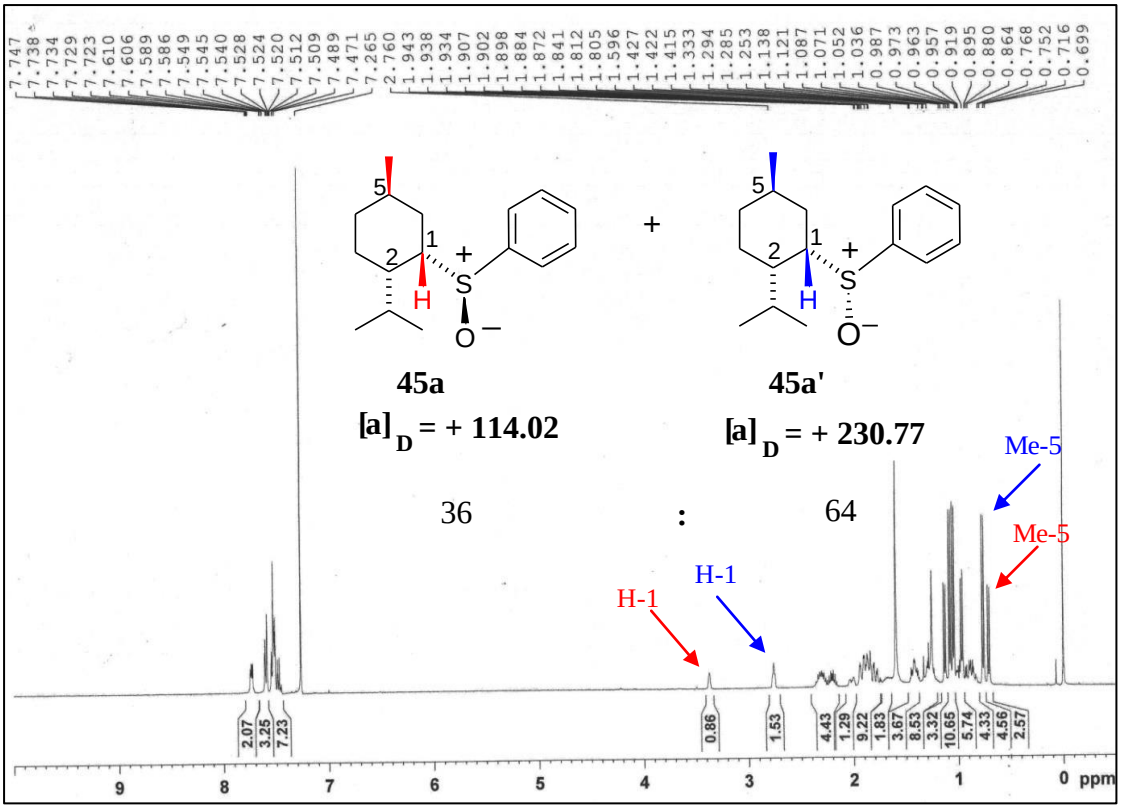

Figure 5.17 ^{1}H NMR of diastereomeric mixture of **45a** and **45a′** obtained using $NaIO_4$

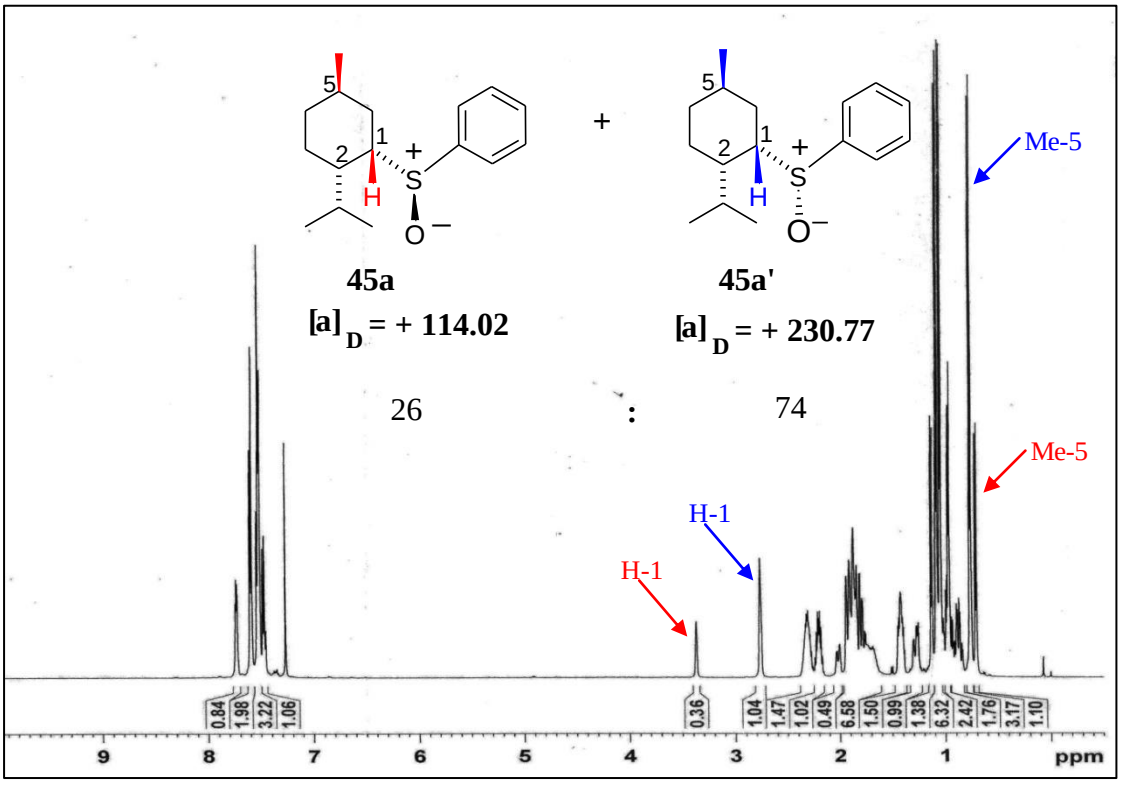

Figure 5.18 ^{1}H NMR of diastereomeric mixture of **45a** and **45a′** obtained using CTAPI

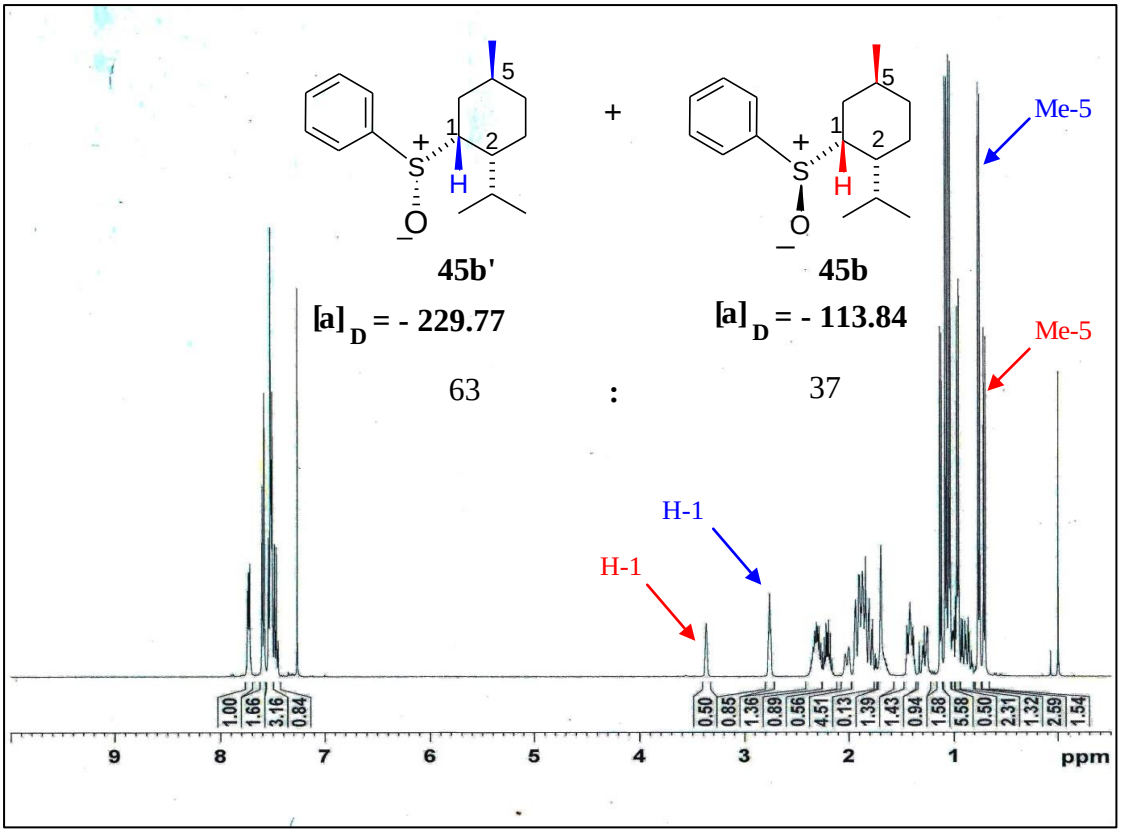

Figure 5.19 ^{1}H NMR of diastereomeric mixture of **45b** and **45b′** obtained using $NaIO_4$

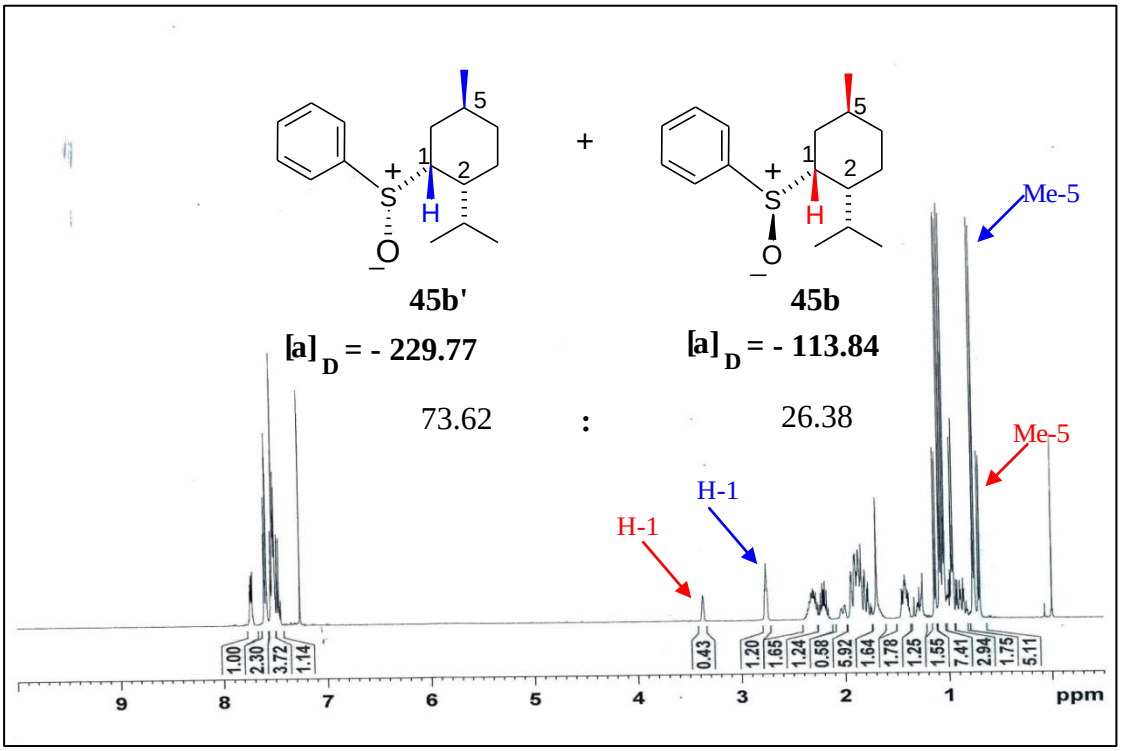

Figure 5.20 ^{1}H NMR of diastereomeric mixture of **45b** and **45b′** obtained using CTAPI

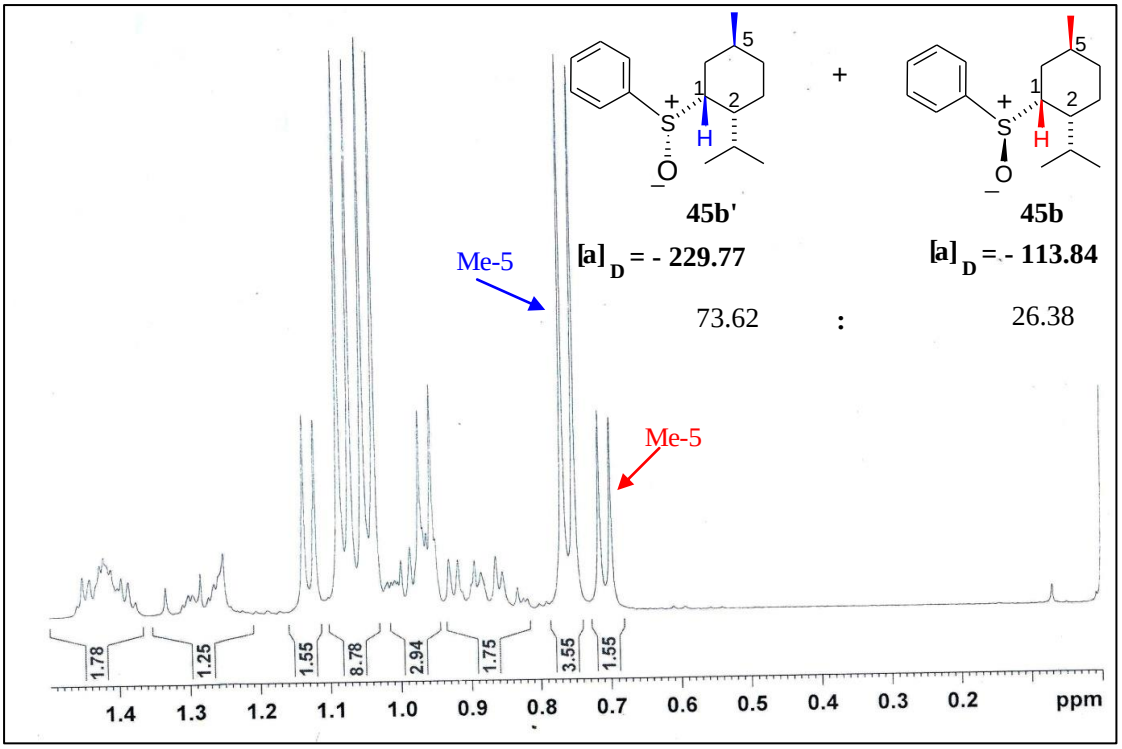

Figure 5.21 Expanded graph for ^{1}H NMR mixture of **45b** and **45b′** obtained using CTAPI