Short Communication

Steric Considerations on Improving the Diastereomeric Ratio of (+)- and (−)-Neomenthyl Phenyl Sulfoxides Using Bulky-Headed Oxidant Hexadecyltrimethylammonium Periodate and Assignment of Their Configuration

UMESH V. CHAUDHARI,[1] DEEPAK SINGH,[1] PRADEEP T. DEOTA,[1]* AND ASHUTOSH V. BEDEKAR[2]

[1]*Applied Chemistry Department, Faculty of Technology & Engineering, The M. S. University of Baroda, Vadodara, Gujarat, India*
[2]*Department of Chemistry, Faculty of Science, The M. S. University of Baroda, Vadodara, Gujarat, India*

ABSTRACT The bulky-headed oxidant hexadecyltrimethylammonium periodate affords the diastereomeric pairs, (*Ss*)-(+)/(*Rs*)-(+) and (*Ss*)-(−)/(*Rs*)-(−)-neomenthyl phenyl sulfoxides in stereochemically pure states with improved diastereomeric excess (48% diastereomeric excess [de]) as compared to its nonbulky counterpart, sodium metaperiodate (28% de) from respective (+)/(−)-neomenthyl phenyl sulfides. Steric effects involving the head group volume of hexadecyltrimethylammonium periodate is found to play a role in improving the diastereomeric ratio of the products. The two diastereomers can be readily separated by column chromatography. Absolute configuration at the sulfur center in (+)-neomenthyl phenyl sulfoxide was determined by single-crystal X-ray crystallography and found to be *Ss*. Relative configurations of other sulfoxides were assigned based on the configuration of (+)-neomenthyl phenyl sulfoxide. *Chirality 27:370–374, 2015.*

KEY WORDS: diastereoselective; hexadecyltrimethylammonium periodate; steric hindrance; neomenthyl phenyl sulfoxides

Optically active sulfoxides are often used as chiral auxiliaries and ligands for numerous asymmetric transformations.[1,2] The past two decades have seen an extensive use of chiral sulfoxides in asymmetric synthesis, 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 neighboring group participation.[5]

Menthol and its derivatives are among those that have found application as chiral auxiliaries for the preparation of optically active sulfoxides.[6] Chiral (+)-methyl neomenthyl sulfoxides (**2a** and **2b**) are often intermediates in the synthesis of chiral oxiranes via corresponding sulfoximines in asymmetric methylene transfer reactions. Oxidation of (*1S*,*2S*,*5R*)-(+)-methyl neomenthyl sulfide (**1**) using hydrogen peroxide furnished the epimeric sulfoxides (**2a** and **2b**) (Scheme 1) in a ratio of 35:65, with the major isomer (**2b**) having sulfoxide oxygen oriented away from the C-2 isopropyl group.[7,8]

Similar observations are reported in the literature for the oxidation of different neomenthyl sulfides. Recently, Demakova et al. reported the oxidation of (*1S*,*2S*,*5R*)-(+)-hetaryl neomenthyl sulfides using various reagents to yield two diastereomeric hetaryl neomenthyl sulfoxides in different ratios.[9]

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

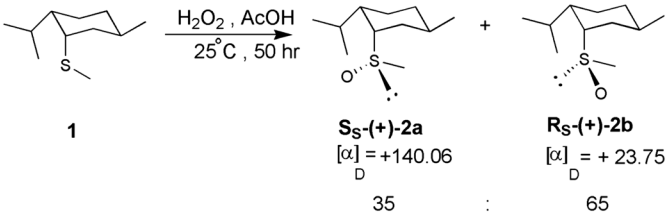
It was envisaged that a better diastereomeric excess of neomenthyl sulfoxides could be achieved using bulkier oxidants, which would have limited access to the sulfur center from the more hindered side having isopropyl group. Consequently, the oxidation would result via the approach of the oxidant from a less hindered side, giving better stereodifferentiation.

EXPERIMENTAL

General Methods

(−)-Menthol (enantiomeric excess [ee]: 99%) and (+)-menthol (ee: 99%) were purchased from Sigma Aldrich (St. Louis, MO). 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 sulfate as binder. The spots were visualized in iodine vapor. 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 (Billerica, MA) (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 tetramethylsilane (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-Fisher (Waltham, MA) DSQ II

*Correspondence to: P.T. Deota, Applied Chemistry Department, Faculty of Technology & Engineering, The Maharaja Sayajirao University of Baroda, Post Box No. 51, Kalabhavan, Vadodara 390 001, Gujarat, India. E-mail: deotapt@yahoo.com
Received for publication 27 December 2014; Accepted 25 March 2015
DOI: 10.1002/chir.22454
Published online 7 May 2015 in Wiley Online Library (wileyonlinelibrary.com).



Scheme 1. Oxidation of (+)-methyl neomenthyl sulfide (**1**) using hydrogen peroxide-acetic acid.

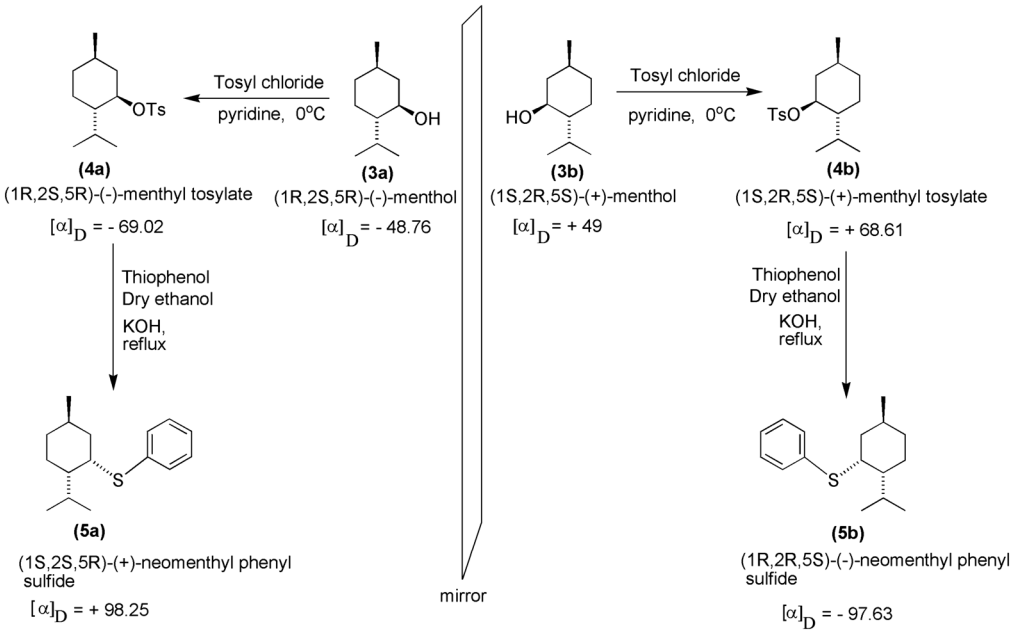
GCMS instrument. Mass Spectra (HRMS) were recorded on an Agilent (Palo Alto, CA) Q-Tof B.05.00 (B5042.0) high-resolution MSMS spectrometer using electrospray ionization mode. For crystals of **6a** the intensity data were collected at 293K on a Nonius Kappa CCD diffractometer system equipped with graphite-monochromated CuKa radiation (λ = 1.5418Å). The structure was solved by a direct method (SIR97) and refined by a full-matrix least-squares procedure based on F^2. All nonhydrogen 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 (New York, NY). 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.

(−)-*and* (+)-*menthyl-p-toluenesulfonate* (**4a** and **4b**). (−)-**4a** was prepared according to the published procedure[8] as depicted in Scheme 2 starting from (1R,2S,5R)-(−)-menthol (**3a**), yield 93%; mp 92–94°C; $[\alpha]_D$ = −69.02 (c = 2.99, $CHCl_3$) (lit.[10] $[\alpha]_D$ = −69.5 (c = 2.99, $CHCl_3$)) while (+)-**4b** from (1S,2R,5S)-(+)-menthol (**3b**) following a similar procedure, yield 92%; mp 90–92°C; $[\alpha]_D$ = +68.61 (c = 2.99, $CHCl_3$).

(+) *and* (−)-*neomenthyl phenyl sulfides* (**5a** and **5b**). To a stirred solution of thiophenol (2.5 g, 22.7 mmol) in dry ethanol (10 ml) at room temperature was added KOH solution (1.5 g, 27.2 mmol) in dry ethanol (10 ml). The reaction mixture was then heated to 60°C, followed by addition of the appropriate menthyl tosylate (**4a** or **4b**) (8.5 g, 27.2 mmol) 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 sulfate. The solvent was removed under reduced pressure to obtain the crude product as a pale yellow liquid, which after chromatography over a column of silica gel using light petroleum afforded pure sulfide **5a** (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). (−)-*neomenthyl phenyl sulfide* (**5b**) (2.96 g, 53%); $[\alpha]_D$ = −97.63 (*c* = 1.00, $CHCl_3$) as colorless liquid. R_f 0.82 (light petroleum).

Oxidation of sulfides* (5a and 5b) *using CTAPI. To stirred solution of sulfides (0.5 g, 2.02 mmol) in aqueous methanol (8:2) (10 ml) at room temperature was added cetyltrimethylammonium periodate (CTAPI) (1.3 g, 7.07 mmol) in portions over a period of 15 min. The mixture was then stirred for 45 h. 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 ((**6a** and **6a'**) (0.38 g, 72%)) or (**6b** and **6b'**) (0.37 g, 71%)) depending on the sulfide used. The ratio of (**6a** and **6a'**) was found to be



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

25.71:74.28 and that of (**6b** and **6b'**) 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 **6a'** as a white amorphous solid (0.28 g, 53%); R_f 0.52 (25% EtOAc/ light petroleum); mp = 120°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.

Further elution of the column with light petroleum / ethyl acetate (70:30) gave the minor diastereomeric sulfoxide **6a** as **a** colorless crystal (0.09 g, 17%); R_f 0.39 (25% EtOAc/ light petroleum); mp = 80°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.

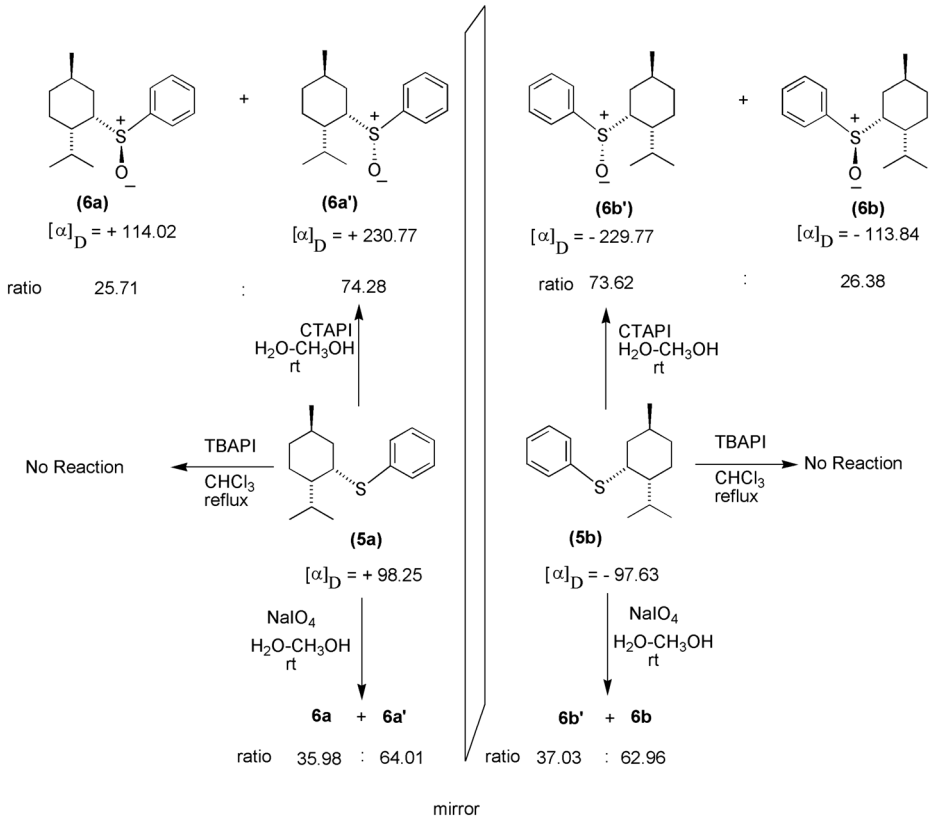
RESULTS AND DISCUSSION

We recently reported selective oxidation of structurally different sulfides to corresponding sulfoxides using hexadecyltrimethylammonium periodate (cetyltrimethylammonium periodate, CTAPI),[11] 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 (**5a**) in two steps from (−)-menthol (**3a**) via (−)-menthyl tosylate (**4a**).[12] Nucleophilic attack of thiophenol on **4a** in ethanolic potassium hydroxide at 78°C for 10 h resulted in **5a** (Scheme 2).

(*1S,2S,5R*)-(+)-Neomenthyl phenyl sulfide (**5a**) was initially subjected to oxidation using sodium metaperiodate, by the procedure of Leonard and Johnson,[13] which furnished an epimeric pair of sulfoxides (**6a** and **6a'**) in 35.98:64.01 (63%) (Scheme 3).

Oxidation of **5a** using CTAPI in water–methanol (8:2) at 25°C for 45 h following our reported procedure[11] resulted in the formation of diastereomeric sulfoxides (**6a** and **6a'**) in 25.71:74.28 (72%) (Scheme 3). 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 **5a**. No oxidation



Scheme 3. Oxidation of **5a** and **5b** using $NaIO_4$, cetyltrimethylammonium periodate (CTAPI) and n-tetrabutylammonium periodate (TBAPI).

was observed at lower temperature (0-5°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 a *de* ratio in favor of **6a**' due to high steric consideration. With this contention, **5a** was subjected to oxidation following the procedure of Santaniello et al.[14] using tetrabutylammonium periodate (TBAPI, head group volume 66.97 Å^3) which has a 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. 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 the case of CTAPI is relatively smaller, and hence the oxidation occurs with better diastereoselectivity. Energy minimized structures of **5a**, **6a**, **6a**', CTAPI, and TBAPI are shown in Figure 1. An oxidant can approach the sulfur center in **5a** via two pathways. Equatorial isopropyl group in **5a** poses more steric hindrance to the incoming bulky headed oxidant, thus making path-I less favored as compared to path-II. Therefore, in oxidation using CTAPI, sulfoxide **6a** is obtained as a minor diastereomer, while **6a**' as major one. No reaction was observed in the case of TBAPI as oxidant, as the counterion 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 1.

A similar study was also performed on (*1R,2R,5S*)-(−)-neomenthyl phenyl sulfide (**5b**), an enantiomer of **5a**

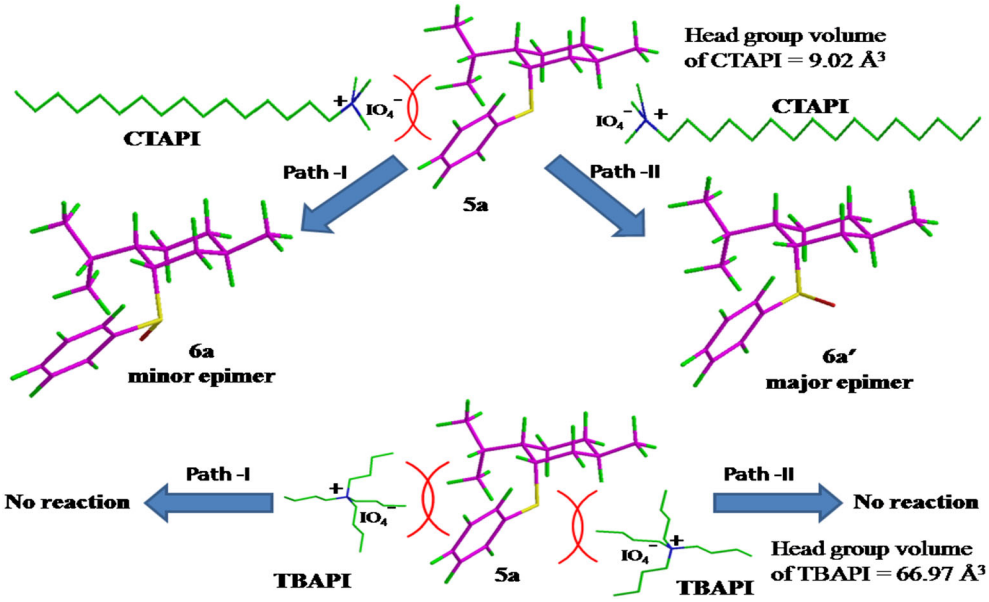


Fig. 1. Energy minimized structures of **5a**, **6a**, **6a**', CTAPI and TBAPI.

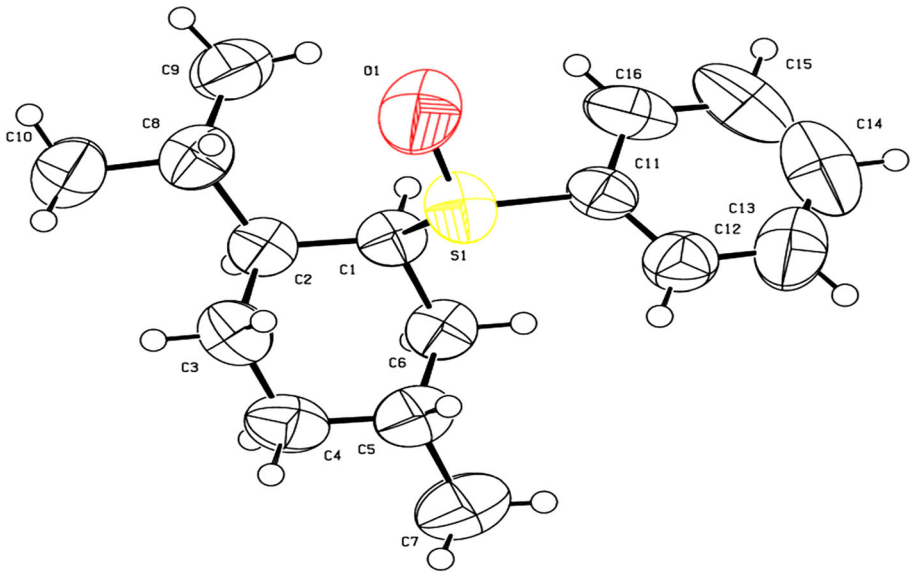


Fig. 2. ORTEP diagram of **6a**.

(Scheme 3) obtained from (*1S,2R,5S*)-(+)-menthol (**3b**) (Scheme 2) 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 (**6a/a'** and **6b/b'**) obtained from **5a** and **5b** exhibited considerable mobilities during TLC analysis and hence their separation was easily achieved by silica gel column chromatography. Compounds **6a** and **6b** are crystalline in nature, while **6a'** and **6b'** are amorphous. All the structures were confirmed by ^{1}H as well as ^{13}C NMR spectra and HRMS analysis. The absolute configuration at sulfur in sulfoxide **6a** was determined using single crystal X-ray crystallography and was found to be *Ss* (Figure 2). Accordingly, the epimeric sulfoxide **6a'** was considered *Rs* configuration at sulfur and sulfoxides **6b** and **6b'** being enantiomers of **6a** and **6a'** were assigned *Rs* and *Ss*, respectively.

An examination of the ^{1}H NMR spectra of the sulfoxides **6a** and **6a'** showed that the proton H-1 and three protons of methyl group attached to C-5 of **6a** appear at δ 3.37 and 0.70 ppm, while signals from these protons in **6a'** 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 the respective proton signals in the ^{1}H NMR spectrum. The oxidation products of **5a** and **5b** were isolated by column chromatography and their diastereomeric excess was determined by means of ^{1}H NMR spectroscopy.

CONCLUSION

In summary, two new sulfoxides, **6a**, **6a'**, and their enantiomers, **6b**, **6b'**, 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 (**6a/6a'**and **6b/6b'**) considering steric aspects. An overall increase of about 20% in *de* was achieved using CTAPI for oxidation of (1S,2S,5R)-(+)- and (1R,2R,5S)-(−)-neomenthyl phenyl sulfides **5a** and **5b**. A study to explore the effect of the head volume of less bulkier quaternary ammonium oxidants than TBAPI on the diastereoselectivity of neomenthyl sulfoxides is currently under way. Further, the protocol presented here can in principle be used for other oxidations intended for achieving diastereodifferentiation.

ACKNOWLEDGEMENTS

We thank the Head, Chemistry Department, Faculty of Science, Dr. Ashok Vishwakarma, Mr. Sanjay Verma and Mr. Hemant Mande, The M.S. University of Baroda, for their help in single crystal X-ray analysis. We also thank Prof. M. R. Yadav and Mr. Ashish Kanhed, Pharmacy Department, The M.S. University of Baroda, for their help in head volume of oxidants.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.

LITERATURE CITED

1. Fernandez I, Khiar N. Recent developments in the synthesis and utilization of chiral sulfoxides. Chem Rev 2003; 103: 3651–3706.
2. Carreno MC. Application of sulfoxides to asymmetric synthesis of biologically active compounds. Chem Rev 1995; 95: 1717–1760.
3. Walker AJ. Asymmetric carbon-carbon bond formation using sulfoxide-stabilized carbanions. Tetrahedron: Asymmetry 1992; 3: 961–998.
4. Pellissier H. Chiral sulfur containing ligands for asymmetric catalysis. Tetrahedron 2007; 63: 1297–1330.
5. Hoveyda AH, Evans DA, Fu G. Substrate directable chemical reaction. Chem Rev 1993; 93: 1307–1370.
6. Oertling H, Reckziegel A, Surburg H, Bertram HJ. Applications of menthol in synthetic chemistry. Chem Rev 2007; 107: 2136–2164.
7. Taj SS, Soman R. Asymmetric methylene transfer reactions I: Asymmetric synthesis of oxiranes from carbonyl compounds by methylene transfer reaction using chiral S-methyl-S-neomenthyl-N-tosyl sulfoximines. Tetraheron: Asymmetry 1994; 5: 1513–1518.
8. Taj SS, Shah AC, Lee D, Newton G, Soman R. Asymmetric methylene transfer reactions II: Asymmetric synthesis of oxiranes from carbonyl compounds by methylene transfer reaction using chiral S-neomenthyl and S-exo-2-bornyl sulfoximines. Tetraheron: Asymmetry 1995; 6: 1731–1740.
9. Demakova MY, Sudarikov DV, Rubtsova SA, Slepukhin PA, Kutchin AV. Asymmetric oxidation of hetaryl neomenthyl sulfides. Russ J Org Chem 2012; 48: 113–118.
10. Mikolojczyk M, Perlikowsska W, Omelanczuk J. Synthesis of (+)-neomenthanethiol and some of its derivatives. A new example of asymmetric induction in the sulfoxide synthesis. Synthesis 1987; 1009–1012.
11. Chaudhari UV, Deota PT. Selective oxidation of sulfides to sulfoxides with cetyltrimethylammonium periodate. Org Prep Proceed Int 2012; 44: 381–365.
12. Blanco JM, Caamaiio O, Femandez F, Gomez G, Lopez C. A useful synthesis of chiral sulfonyl cyanides: (*1S,2S,5R*)-2-isopropyl-5-methylcyclohexanesulfonyl cyanide. Tetrahedron: Asymmetry 1992; 3: 749–752.
13. Leonard NJ, Johnson CR. Periodate oxidation of sulfides to sulfoxides. J Org Chem 1962; 27: 282–284.
14. Santaniello E, Manzocchi A, Farachi C. Tetrabutylammonium periodate; an selective and versatile oxidant for organic substrate. Synthesis 1980; 563–365.