CHAPTER IV

ASYMMETRIC SYNTHESIS OF OXIRANES

USING (1R,3S,4S,1'S,Rs)-(+)-S-METHYL-

S-NEOMENTHYL-N-(CAMPHOR-10-SULFONYL)

SULFOXIMINE,3b AND ITS EPIMER AT SULFUR

(1R,3S,4S,1'S,Ss)-(+)-3a

A. INTRODUCTION

With the two pairs of sulfoximines we have studied so for (Chapter II and III), we have seen that for significant ee in oxirane synthesis, not only that the sulfur atom should be chiral but also that the sulfur atom should carry ligands having asymmetric carbons. In the case, where the ligand is a neomenthyl group, the absolute configuration on sulfur determines the absolute configuration of oxirane synthesised, the (Rs) and (Ss) sulfoximines leading to oxiranes having different absolute configuration. In the case, where exo-2-bornyl group was the ligand on sulfur, much against our expectations (Chapter III), the ee achieved was lower (compared to neomenthyl group). Not only that, this ligand played a role in directing the absolute configuration of the oxirane synthesised, both (Rs) and (Ss) sulfoximines giving oxiranes of same absolute configuration from benzaldehydes and of different absolute configuration from phenyl ketones.

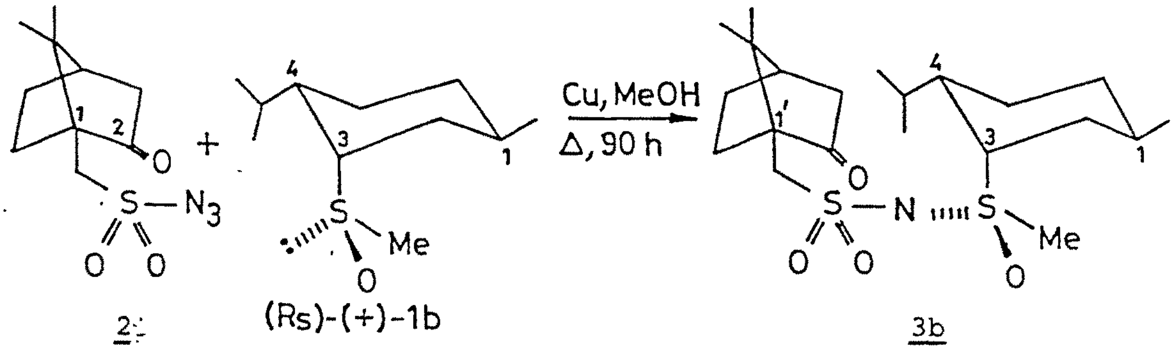
In all cases studied, the substituent on nitrogen remained the same, viz., p-toluene sulfonyl group ; an achiral substituent. In view of the results obtained so far, we decided to investigate whether a chiral auxiliary on nitrogen in addition to that on sulfur would enhance the asymmetric induction in these MT reactions. D-Camphorsulfonic acid, an easily available and much used optically active chemical appeared to us as the first choice as a chiral replacement for p-toluenesulfonic acid in the preparation of sulfoximines.

Accordingly, we prepared a new epimeric pair of sulfoximines, viz., (1R,3S,4S,1'S,Rs)-(+)-S-methyl-S-neomenthyl-N-(camphor-10-sulfonyl) sulfoximine, 3b and its epimer at sulfur, (1R,3S,4S,1'S,Ss)-(+)-3a from (1S)-(+)-camphor-10-sulfonyl azide, 2 and optically pure (1R,3S,4S,Rs)-(+)-S-methyl-S-neomenthyl sulfoxide 1b and its epimer at sulfur, (1R,3S,4S,Ss)-(+)-1a respectively.

B. RESULTS AND DISCUSSIONS

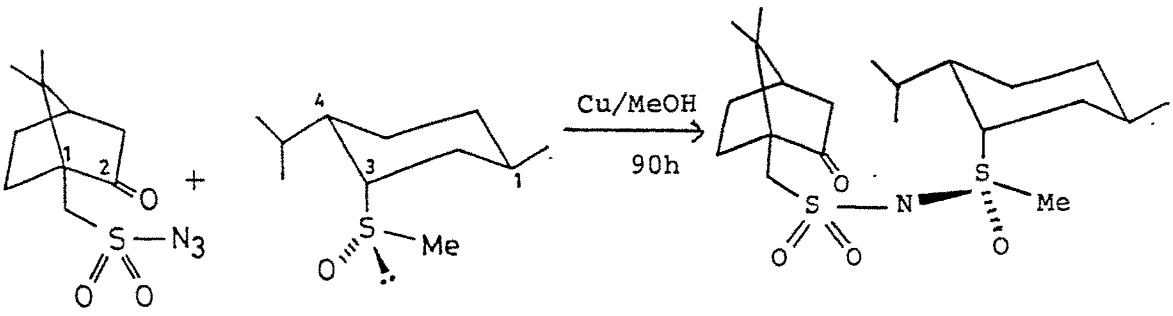
Pure D-camphorsulfonic acid on refluxing with freshly distilled thionyl chloride as per known method[1] gave, after crystallization, pure (1S)-(+)-camphor-10-sulfonyl chloride, m.p. 65-67^{o}C, $[\alpha]_D$ +32.75 (c,1.16) [Reported[2], m.p. 65-67^{o}C, $[\alpha]_D$ +33 (c,1.00)]. The latter on treatment with sodium azide in 1,4-dioxan at 0^{o}C gave optically pure (1S)-(+)-camphor-10-sulfonyl azide[1], 2, $[\alpha]_D$ +47.68 (c,4.14).

The (1R,3S,4S,Rs)-(+)-S-methyl-S-neomenthyl sulfoxide, 1b (liquid epimer) was heated at 60^{o}C with 2 in presence of copper powder and dry methanol for 90h. After chromatographic purification followed by repeated crystallization from two different solvent systems viz., chloroform : hexane (20:80) and ethyl acetate gave beautiful, transparent, bold crystals of (1R,3S,4S,1'S,Rs)-(+)-S-methyl-S-neomenthyl-N-(camphor-10-sulfonyl) sulfoximine, 3b, $[\alpha]_D$ +82.7 (c,1.92). The optical rotation during the final crystallization remained unaltered (Scheme 1).



Scheme 1

Similarly, (1R,3S,4S,Ss)-(+)-S-methyl-S-neomenthyl sulfoxide (crystalline epimer), 1a on treatment with (1S)-(+)-camphor-10-sulfonyl azide 2 in presence of copper and methanol followed by chromatographic purification gave (1R,3S,4S,1'S,Ss)-(+)-S-methyl-S-neomenthyl-N-(camphor-10-sulfonyl) sulfoximine, 3a, $[\alpha]_D$ +28.57 (c,2.03) (Scheme 2).



2 1a 3a

Scheme 2

The reaction of sulfoxide 1a and 1b with 2 in presence of copper powder was found to be very slow. The mechanism[3] of the reaction involves the decomposition of organic azides in presence of copper powder to nitrene intermediate (Scheme 3) which is being trapped by sulfoxides to give the desired sulfoximine. The main competitive reaction is the reaction of nitrene intermediate with solvent methanol to give a by product sulfonamide* and liberating formaldehyde. It is to take care of

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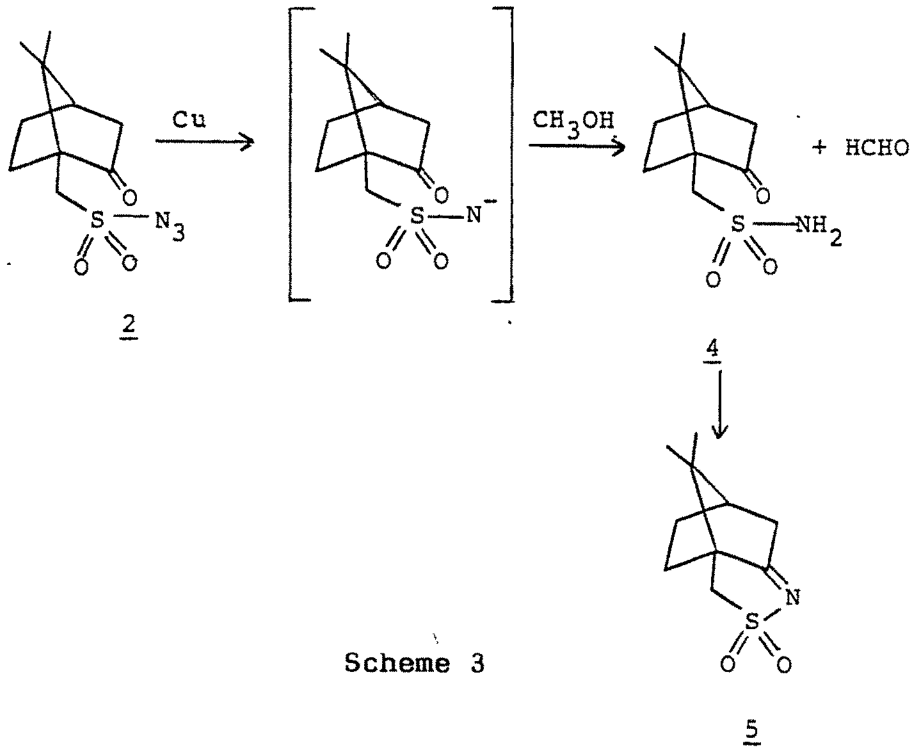
* The crude reaction product on keeping, deposits large quantities of crystals with a m.p. of 222°-225°C. Camphor-10- sulfonamide is reported[1] to have a m.p. 134-35°C and expected to have been removed during washing with 10% sodium hydroxide solution. The crystalline by product that we got has a m.p. 222-25°C and its IR spectrum showed a peak at 1650 cm^{-1} characteristic of -C=N bond. It has been reported that camphor-10-sulfonamide[4] is prone to undergo dehydration leading to the anhydroamide, 5. It is possible that this anhydroamide is the by product that we isolated.



Scheme 3

this side reaction that excess (2-4 molar equivalent) of azide is taken.

Both, the epimeric sulfoximines 3b and 3a were well characterised by its IR, ^{1}H NMR, ^{13}C NMR and mass spectra.

IR spectra of 3b (Fig.1) and 3a (Fig.2) showing a strong band at 1745 cm^{-1} characteristic of carbonyl group present in bornyl moiety. There is a band in the range of 1200-1210 cm^{-1} corresponding to N-S=O stretching.

In ^{1}H NMR spectra, 3a and 3b are differentiated at one point. The -C$\underline{H}$-S proton in 3a (Fig.3) appears as quartet centered at δ 3.83 away from the doublet of SO_2-C$\underline{H}_2$ proton, whereas in 3b (Fig.4) this proton appears as a distorted quartet at δ 3.65, partially mixed with the doublet of one of the -SO_2C$\underline{H}_2$ protons. The S-C$\underline{H}_3$ singlet in both the cases appears at δ 3.49. In 3b, two singlets corresponding to gem dimethyl group of bornyl group (-C-C$\underline{H}_3$) appear at δ 0.9 and 1.16; all the three methyl groups of neomenthyl group is appear as 3 pairs of doublets. In case of 3a all the three methyl groups appear as three pairs of doublets between δ 0.93 and δ 1.13.

^{13}C NMR spectra of both 3a (Fig.5) and 3b (Fig.6) account for all the 21 carbon atoms each. APT of these spectra clearly distinguishes required numbers of -CH_3, -CH_2, -CH and -C carbon atoms. The carbonyl carbon appears at very low field (δ 215.52).

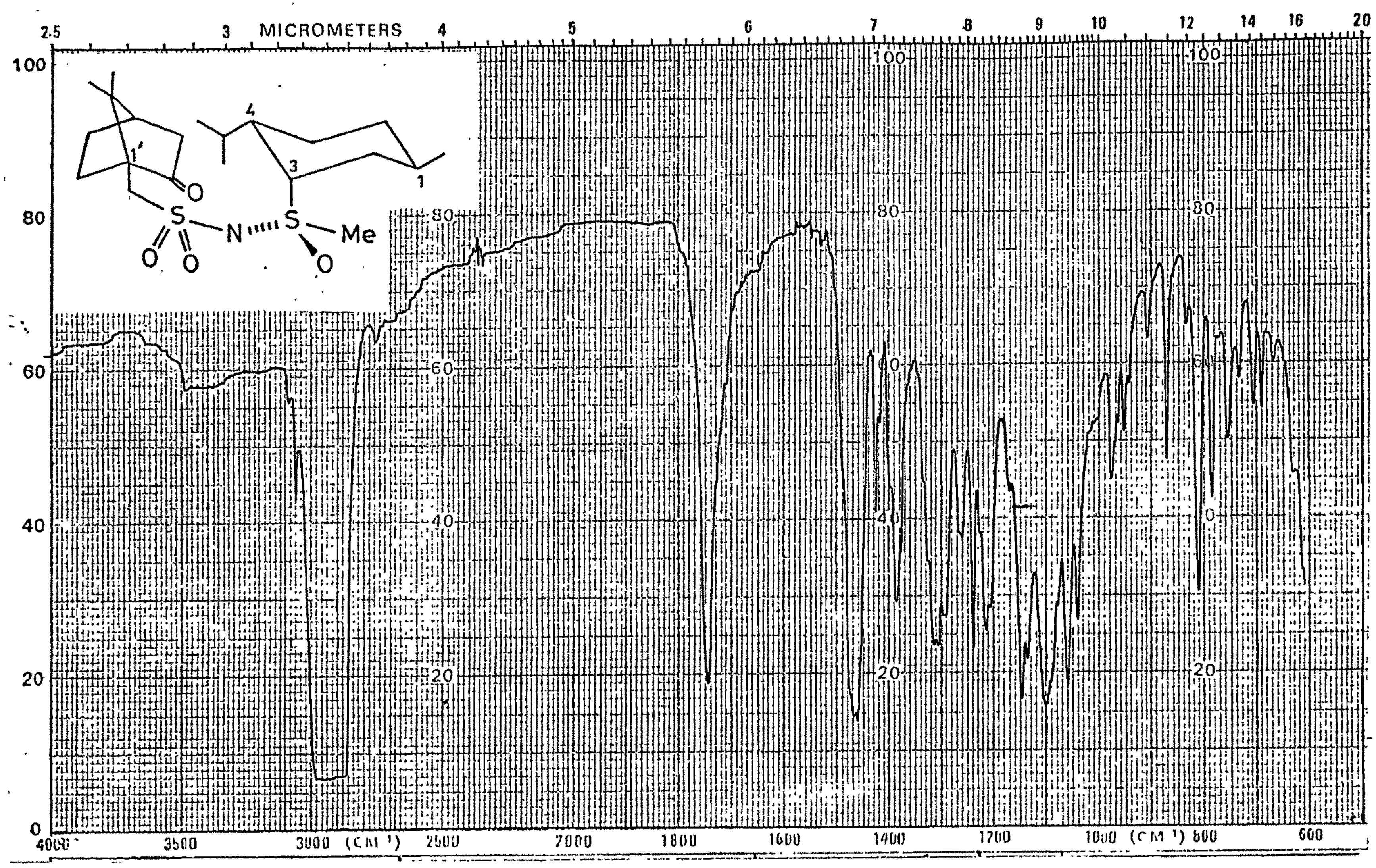


Fig. 1 : IR Spectrum of (1R,3S,4S,1'S,R_S)-(+)-S-Methyl-S-neomenthyl-N-(camphor-10-sulfonyl) Sulfoximine (3b)

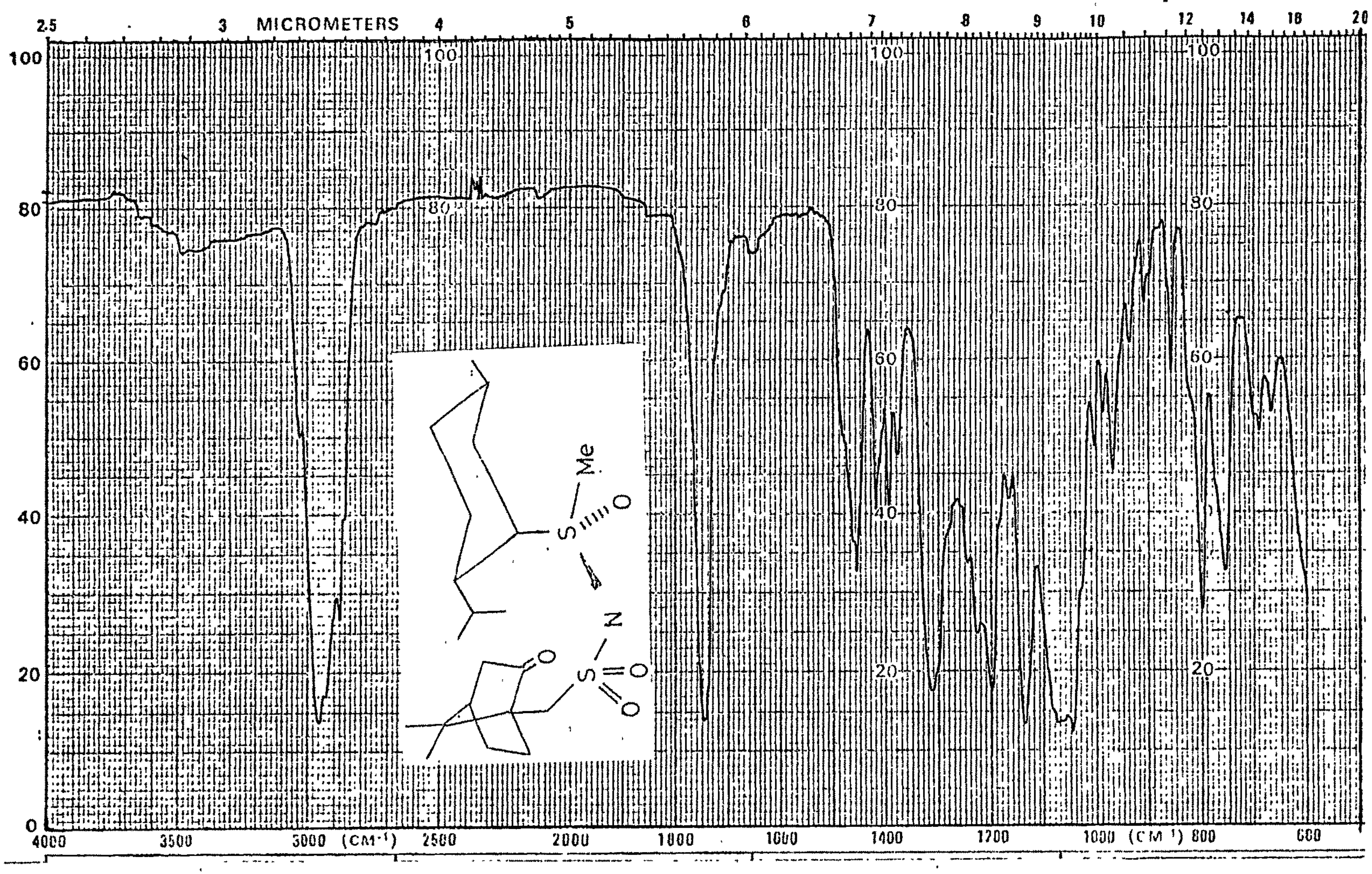


Fig. 2 : IR Spectrum of (1R,3S,4S,1'S,S_S)-(+)-S-Methyl-S-neomenthyl-N-(camphor-10-sulfonyl) Sulfoximine (3a)

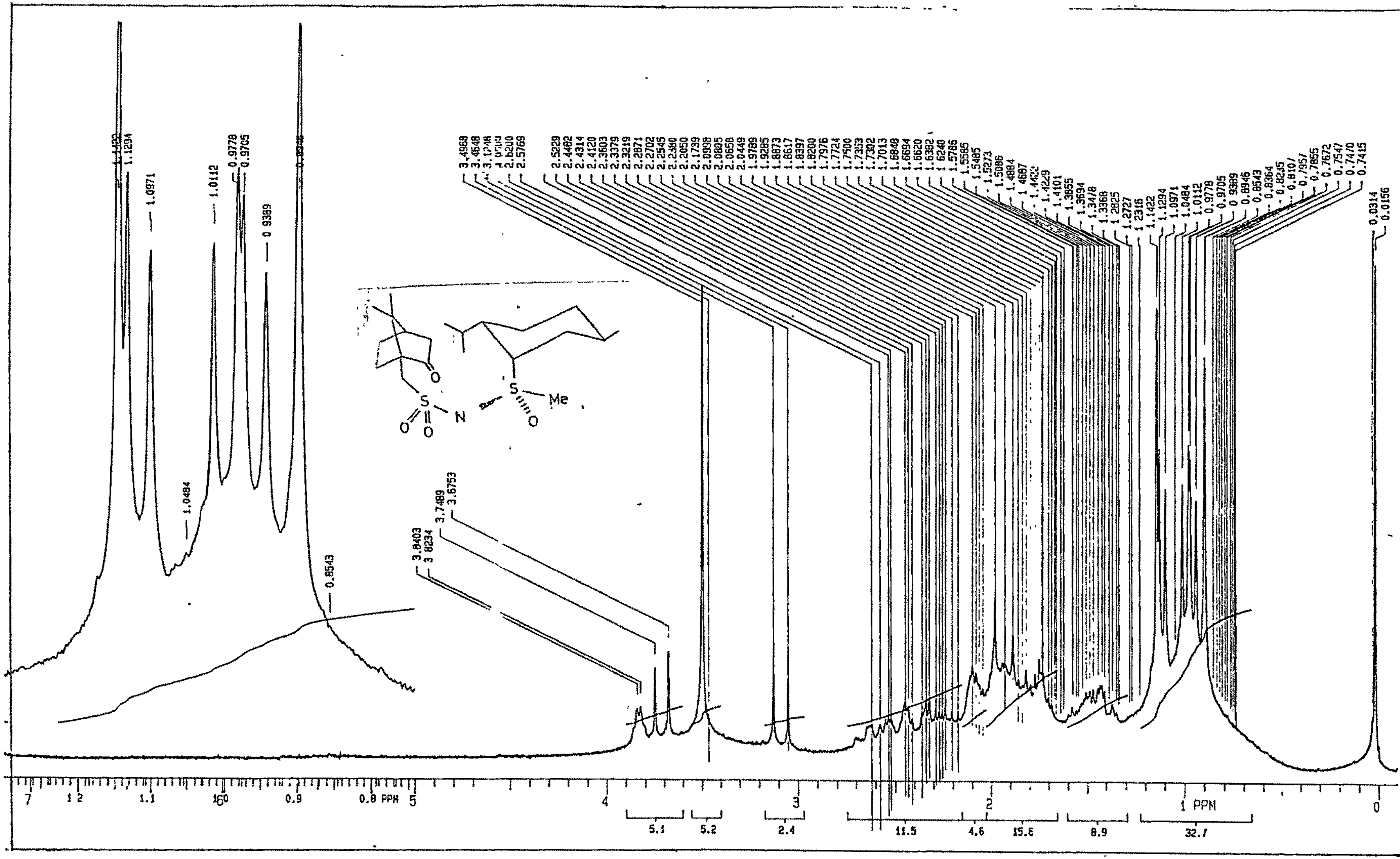


Fig. 3 : ^{1}H NMR Spectrum (200 MHz.) of (1R,3S,4S,1'S,S_S)-(+)-S-Methyl-S-neomenthyl-N-(camphor-10-sulfonyl) Sulfoximine (3a)

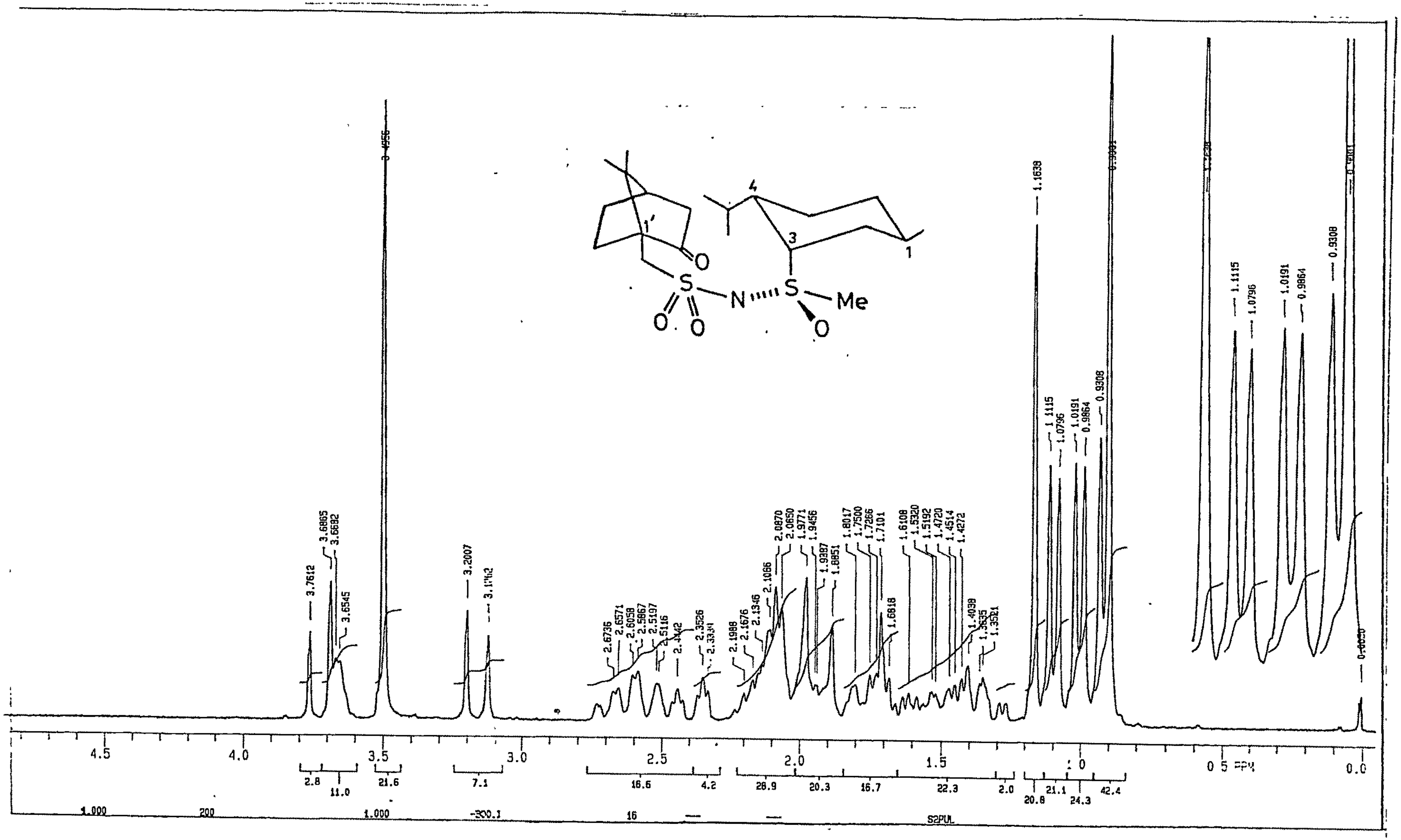


Fig. 4 : ^{1}H NMR Spectrum (200 MH_Z) of (1R,3S,4S,1'S,R_S)-(+)-S-Methyl-S-neomenthyl-N-(camphor-10-sulfonyl) Sulfoximine (3b)

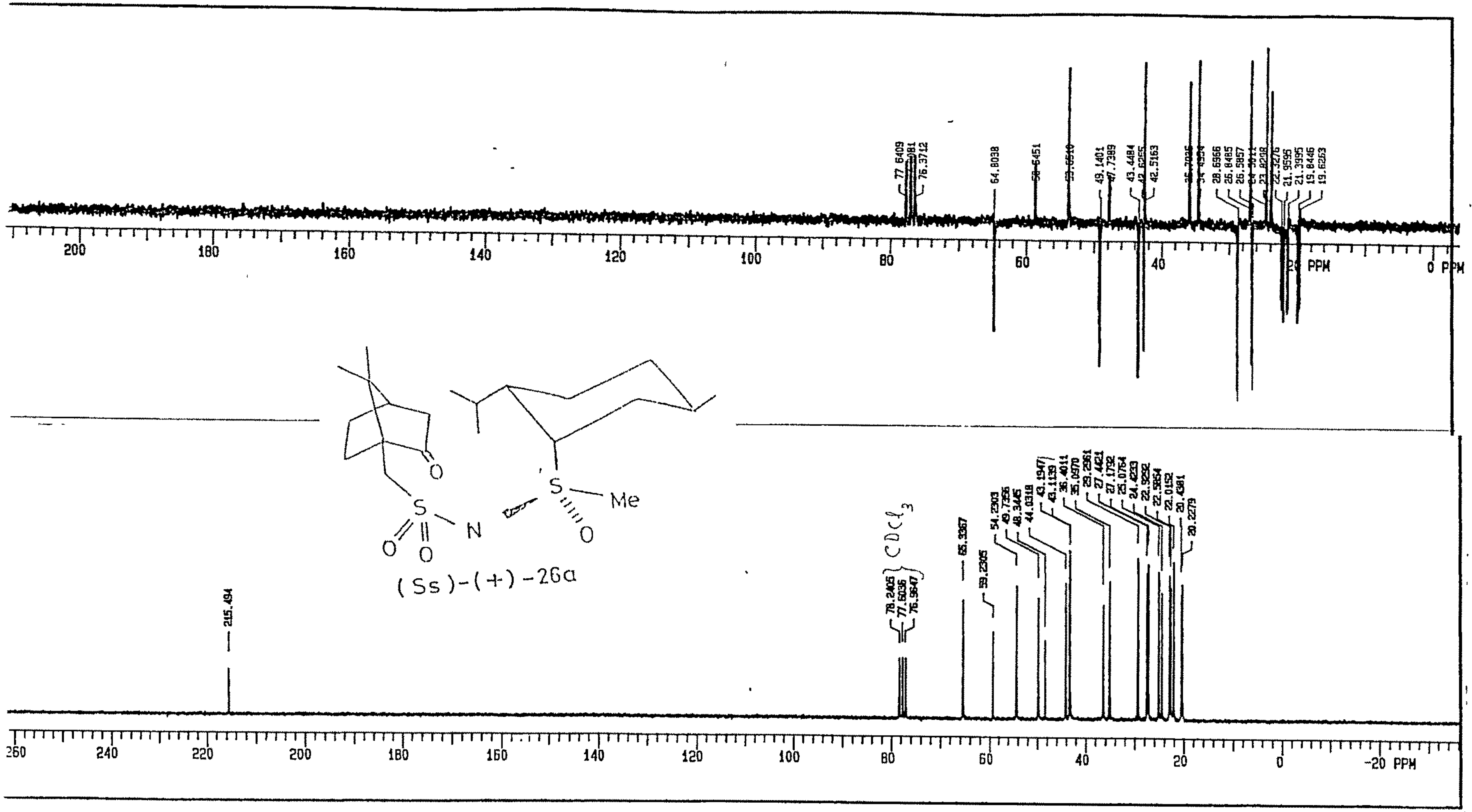


Fig. 5 : ^{13}C NMR Spectrum of (1R,3S,4S,1'S,S_S)-(+)-S-Methyl-S-neomenthyl-N-(camphor-10-Sulfonyl) Sulfoximine (3a)

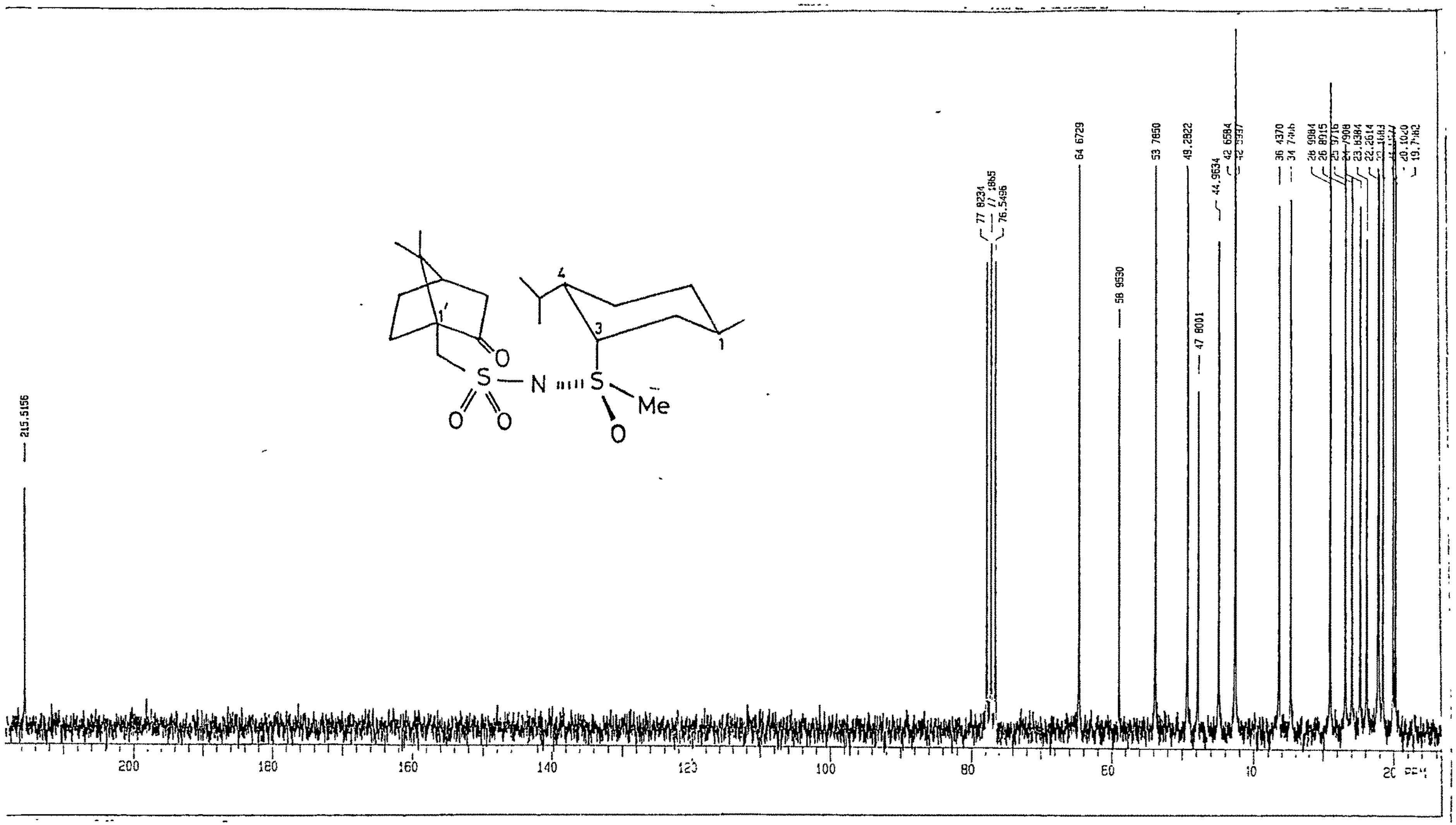
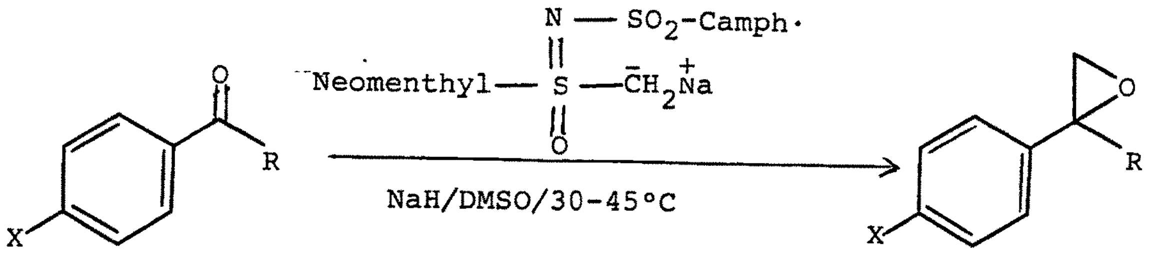


Fig. 6 : ^{13}C NMR Spectrum of (1R,3S,4S,1'S,R_S)-(+)-S-Methyl-S-neomenthyl-N-

Mass spectrum of 3b (Fig.7) shows molecular ion peak at 431 confirming its molecular weight.

The methylene transfer reactions were carried out on four selected carbonyl compounds 6 to 9 using optically pure sulfoximines, 3a and 3b. The general reaction is depicted in Scheme 4.



6-9

10-13

Where,

	X	R
6, 10	H	H
7, 11	Cl	H
8, 12	H	CH_3
9, 13	Cl	i-pr

Scheme 4

Sulfoximines 3a and 3b were treated with sodium hydride in dry DMSO. To the carbanion solution of sulfoximine was added carbonyl compound and stirred at 30-40^{o}C for a fixed time period. The crude product was distilled under reduced pressure.

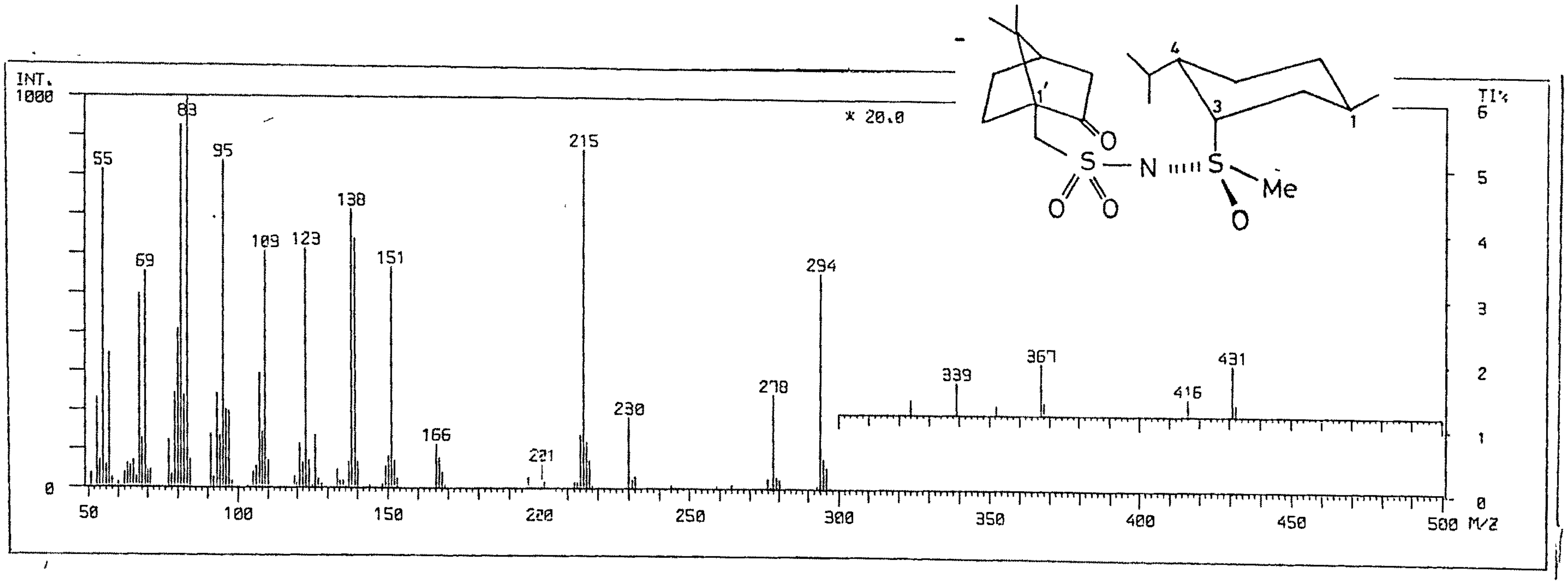
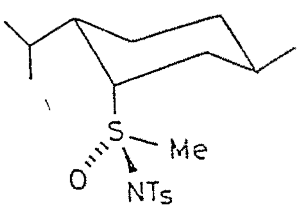


Fig. 7 : Mass Spectrum of (1R,3S,4S,1'S,R_S)-(+)-S-Methyl-S-neomenthyl-N-(camphor-10-sulfonyl) Sulfoximine (3b)

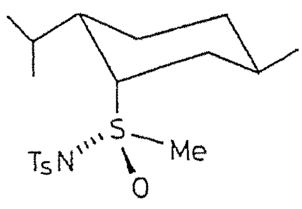
Reactions of carbonyl compounds with sulfoximine 3a and 3b were found to be generally slower compared to corresponding N-tosyl sulfoximines. The yields of oxiranes were also comparatively low. Asymmetric methylene transfer reactions using 3a and 3b required comparatively higher temperature to complete. In the case of N-tosyl sulfoximines, the abstraction of a proton from the -S-CH_3 group is facilitated by the electronegative p-toluene sulfonyl group on nitrogen. Whereas, in 3a and 3b the camphor-10-sulfonyl group may be less electronegative leading to more reaction times and poorer yields in MT reactions. Reaction of acetophenone with 3a was repeated three times with all the possible precautions but all the time reaction never reached to completion.

The asymmetric induction achieved in oxiranes preparation with sulfoximine 3b is given in Table 1 and with sulfoximine 3a is given in Table 2.

The chemical yields of oxiranes obtained using sulfoximines 3a and 3b are poorer compare to the yields obtained from corresponding N-tosyl sulfoximine, 14a and 14b.



14a



14b

Table 1 : Asymmetric Induction in Oxirane Synthesis with Sulfoximine 3b**

Sr. No.	Carbonyl	Reaction Conditions		Product Oxiranes		
		Temp. (^{0}C)	Time (h)	Identity	ee(%)GC*	Yield (%)
1.	6	30	1	(S)-(-)-Phenyloxirane 10	61.0(b)	20.0
2.	7	35	2	(S)-(-)-(4-Chlorophenyl) oxirane, 11	49.9(b)	23.0
3.	8	30-45	22	(+)-2-Methyl-2-phenyloxirane, 12	86.1(b)	32.0
4.	9	30-40	20	(+)-2-(4-Chlorophenyl)-2-isopropyl-oxirane, 13	81.2(a)	47.0

* Cyclodex B capillary column 25M x 0.22 m.m.
"a" denotes fast eluting enantiomer in excess.
"b" denotes slow eluting enantiomer in excess.

It is apparent from data presented in Table 1 and 2, that replacement of the achiral tosyl group with a chiral auxiliary such as (1S)-(+)-camphor sulfonyl on nitrogen in S-methyl-S-neomenthyl sulfoximine has no significant additive effect on the extent of asymmetric induction in MT reactions. On the contrary, such substitution results in lowering in chemical yields.

** This work has been published[5] in 1995.

Table 2 : Asymmetric Induction in Oxirane Synthesis with Sulfoximine, 3a

Sr. No.	Carbonyl	Reaction Conditions		Product Oxiranes		
		Temp. (^{0}C)	Time (h)	Identity	ee(%)GC*	Yield (%)
1.	6	30	1	(R)-(+)-Phenyloxirane 10	56.2(a)	20.0
2.	7	35	2	(R)-(+)-(4-Chlorophenyl) oxirane, 11	36.6(a)	25.0
3.	8	45	32	(-)-2-Methyl-2-phenyloxirane, 12	a > b**	
4.	9	30-40	20	(-)-2-(4-Chlorophenyl)-2-isopropyl-oxirane, 13	84.0(b)	45.0

* Same as footnote in Table 1

** Reaction sluggish ; unconverted acetophenone interferes in GC.

There is a complete similarity between 3a, 3b and 14a, 14b regarding the kind and extent of asymmetric induction as MT reagents. The kind and magnitude of enantiomeric excess with 3a and 3b are comparable with that of 14a and 14b. Sulfoximines 3a and 14a (both originated from same sulfoxide, 1a) having (Ss) configuration at sulfur react with benzaldehyde 6 and p-chlorobenzaldehyde 7 to give corresponding oxiranes 10 and 11 with (R)-(+)-enantiomer in excess and with ketones 8 and 9 to give corresponding oxiranes 12 and 13 with (-)-isomers in excess. Similarly, sulfoximines 3b and 14b (both originated from the same sulfoxide, 1b) having (Rs) configuration at sulfur reacts with benzaldehydes, 6 and 7 to give oxiranes 10 and 11 with (S)-(-)-enantiomer in excess and with ketones 8 and 9 to give oxiranes 12 and 13 with (+)-enantiomer in excess.

In conclusion, we may say that a chiral substituent on nitrogen does not contribute to any extent in inducing asymmetry in oxiranes. The studies so for carried out by us indicate that a chiral ligand on sulfur in sulfoximines is an essential requirement for achieving significant ee in oxirane synthesis by MT reactions. Also, this ligand has a role in determining the absolute configuration of the oxiranes. Substituent on nitrogen, whether they contain a chiral centre or not, do not influence the asymmetric induction to any extent in oxirane synthesis.

C. EXPERIMENTAL

General : Same as in Chapter I. Optical rotations were measured at 25°C in chloroform (unless otherwise stated) on a JASCO model DIP-370 digital polarimeter.

The following instruments were used for various spectra.

^{1}H NMR : GEM - 200 (200 MHZ)

^{13}C NMR : GEM - 200 ; varian - 200 (200 MHZ)

(1S)-(+)-Camphor-10-sulfonyl azide, (2)[1]

A mixture of (1S)-(+)-camphor-10-sulfonic acid (11.6g, 50 mmol) and freshly distilled thionyl chloride (20.8g, 175 mmol) was refluxed for 4.5h. The homogenous solution was cooled to 20°C and added gradually in ice water (100g). The crude acid chloride was collected by filtration and washed with water. The air dried product (13.3g) was crystallized from hexane (40 mL) gave optically pure (1S)-(+)-camphor-10-sulfonyl chloride (8.1g) (yield = 65%) ; m.p. 65°C (Reported[2] 65-67°C).

$[\alpha]_D$ +32.75 (c, 1.16)

Reported[2], $[\alpha]_D$ +33 (c, 1.00)

A solution of (1S)-(+)-camphor-10-sulfonyl chloride (7.2g, 28.7 mmol) in dioxan (42 mL) was added to a solution of sodium azide (3.92g, 60.2 mmol) in water (42 mL) at 0°C. The mixture was kept at 0°C for overnight. Solvents were removed at rotavapor under vacuum and residue was dissolved in water (25 mL). The mixture was extracted with chloroform (25 mLx3). The organic layer dried on Na_2SO_4 and solvent removed under vacuo to give, pale yellow, viscous liquid (2 ; 8.1g).

$[\alpha]_D$ +47.67 (c, 4.14).

(1R,3S,4S,1'S,Rs)-(+)-S-Methyl-S-neomenthyl-N-(camphor-10-sulfonyl) sulfoximine, (3b)

(1R,3S,4S,Rs)-(+)-S-Methyl-S-neomenthyl sulfoxide[6], 1b (6.0g, 30 mmol), (1S)-(+)-camphor-10-sulfonyl azide, 2 (24.1g, 97 mmol), freshly precipitated copper powder (3.1g) and dry methanol (40 mL) were refluxed for 90h (TLC : sulfoxide spot too faint). Methanol was distilled out and the crude product stirred with saturated aqueous solution of Na_2EDTA (120 mL). The mixture was extracted with chloroform (150 mL). The organic layer were stirred with activated charcoal (4g) for 2h, filtered, washed with 10% aqueous NaOH solution (50 mLx2) and water (70 mLx2), dried (Na_2SO_4) and freed from solvent to give crude product (17.38g). Successive trituration of this crude product with n-hexane (20 mLx3) and with n-hexane : chloroform (90:10) (25 mLx4) followed by solvent removal from each extract gave unchanged sulfoxide, 1b (1.5g) and sulfoximine, 3b, (8.9g) respectively. [The undissolved, crystalline solids may be possibly camphor-10-sulfonamide and its anhydro amide, 5 (5.7g)].

The hexane-chloroform extract (8.9g) was purified by column chromatography (SiO_2, 300g, eluent, hexane : ethylacetate, 2:1). Crystallization of the eluate from ethyl acetate gave pure, crystalline sulfoximine, 3b (7.31g, yield based on consumed sulfoxide = 76%).

m.p. : 137-138^{o}C

$[\alpha]_D$ +82.7 (c,1.92)

IR (Nujol) : 1745,1310,1300,1285,1235,1210,1140,1095,1055, 805, 780 cm^{-1} (Fig.1)

^{1}H NMR ($CDCl_3$) : (δ), 0.90,1.16 (3H each, s, -C-C$\underline{H}_3$), 0.92,1.00, 1.10 (3H each ; d, J=6HZ ; -HC-C$\underline{H}_3$), 3.50 (3H, s, -S-C$\underline{H}_3$), 3.16,3.72 (1H each ;d, J=14HZ ; -SO_2-C$\underline{H}_2$), 3.66 (1H; q, J=2.7 HZ ; -C$\underline{H}$-S) (Fig.4)

^{13}C NMR ($CDCl_3$) : (δ), 19.76, 20.10, 21.56, 22.17, 22.26 (All -C-$\underline{C}H_3$), 44.96,(-S-$\underline{C}H_3$), 23.84, 24.79, 25.97, 26.89, 29.00, 34.75, 36.44, 42.60, 42.66, 47.80, 49.28, 53.79, 58.95, 64.67 (-$\underline{C}$H-S-), 215.52 (-$\underline{C}$=O) (Fig.6)

EIMS, M/Z (%) : 431 (M^+, 1), 294(55), 278(24), 230(18), 215(86), 151(56), 139(64), 138(71), 123(62), 109(60), 95(83), 83(100) (Fig.7)

Microanalysis : $C_{21}H_{37}NO_4S_2$ Requires : C, 58.43% ; H, 8.64% ; N, 3.24%

Found : C, 58.25% ; H, 8.94% ; N, 3.12%

(1R,3S,4S,1'S,Ss)-(+)-S-Methyl-S-neomenthyl-N-(camphor-10-sulfonyl) Sulfoximine, (3a)

(1R,3S,4S,Ss)-(+)-S-Methyl-S-neomenthyl sulfoxide[6],1a (6.0g, 30 mmol), (1S)-(+)-camphor-10-sulfonyl azide, 2 (23.3g, 90.6 mmol), freshly precipitated copper powder (3.1g) and dry methanol (40 mL) were heated at 55^{o}C for 75h. The reaction was monitored by TLC whereby sulfoxide spot was too faint. Methanol was distilled off and the crude product was stirred with saturated aqueous solution of Na_2EDTA (120 mL). The organics were stirred with activated charcoal (4g) for 2h, filtered, washed with 10% NaOH solution (50 mLx2) and water (70 mLx2), dried (anhydrous Na_2SO_4) and freed from solvent to give crude product (18.23g). Successive trituration of crude product with n-hexane (20 mLx3) and with n-hexane : chloroform (90:10) (25 mLx4) followed by solvent removal from each extract gave unchanged sulfoxide, 1a (1.4g) and sulfoximine, 3a (10.7g) respectively. The undissolved, crystalline solids (6.0g) may be possibly camphor-10-anhydro sulfonamide, 5 [m.p. 224^{o}C, $[\alpha]_D$ -32.48 (c, 1.46, Acetone)]. The hexane-chloroform extract (10.7g) was purified by column chromatography (silica gel, 300g, eluent, hexane : ethyl acetate

2:1) to give pure product, 3a (8.38g, 85.4% yield based on consumed sulfoxide).

$[\alpha]_D$ +28.57 (c, 2.03)

IR (Neat, Thin film) : 2980, 1745, 1460, 1420, 1395, 1310, 1200, 1140, 1068, 970, 850, 800, 755, cm^{-1} (Fig.2)

^1H NMR ($CDCl_3$) : (δ), 0.89, 1.14 (3H each, s, -C-C$\underline{H}_3$), 0.95, 0.99, 1.11 (3H each ; d, J=6.3 HZ ; All -CH-C$\underline{H}_3$), 3.50 (3H, s, -S-C$\underline{H}_3$), 3.08, 3.71 (1H each ; d, J=14.7HZ ; -SO_2-C$\underline{H}_2$), 3.83 (1H ; q, J=3.4 HZ ; -C$\underline{H}$-S) (Fig.3)

^{13}C NMR ($CDCl_3$) : (δ), 20.23, 20.44, 22.01, 22.59, 22.93 (All -C-$\underline{C}H_3$), 44.03,(-S-$\underline{C}H_3$), 24.42, 25.08, 27.18, 27.44, 29.30, 35.15, 36.40, 43.11, 43.19, 48.34, 49.74, 54.23, 59.23 65.34 (-$\underline{C}$H-S-), 215.50 (-$\underline{C}$=O) (Fig.5)

General procedure for the preparation of oxiranes using sulfoximines 3a and 3b

To a mixture of sodium hydride (0.12g, 50% dispersion in oil, 2.4 mmol, washed three times with dry n-hexane) and dry DMSO (10 mL) under dry nitrogen atmosphere was added a solution of optically pure sulfoximine, 3a or 3b (0.95g, 2.2 mmol) in dry

DMSO (10 mL) and the mixture stirred at 30-45^{o}C for 5h. To the sodium methylide solution formed was added the carbonyl compound (2 mmol) in DMSO (2 mL) and the contents were stirred at 30-40^{o}C. The reaction could be completed in 2 to 22h depending on the substrate. The reaction was monitored by GC (disappearance of carbonyl peak). The reaction mixture was cooled to 10^{o}C, diluted with cold water (25 mL), extracted with n-hexane (10 mLx5), dried (Na_2SO_4), freed from solvent and the residue distilled under reduced pressure (bulb to bulb distillation, 2-20 m.m. vacuum). The enantiomeric excess was determined by GC on chiral cyclodex B capillary column. The asymmetric induction achieved during oxirane preparation using sulfoximine, 3b is given in Table 1 and with sulfoximine, 3a is given in Table 2.

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