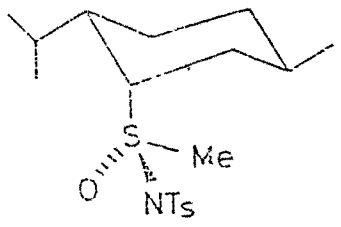
CHAPTER III

ASYMMETRIC SYNTHESIS OF OXIRANES USING CHIRAL (1R,Ss)-(-)-S-METHYL-S-EXO-2-BORNYL-N-TOSYL SULFOXIMINE, 9a, AND ITS EPIMER AT SULFUR (1R,Rs)-(+)-9b

A. INTRODUCTION

In the previous chapter we have shown that chiral neomenthyl group on sulfur in sulfoximines led to an ee of upto 86 % in oxirane synthesis. Assuming that replacement of the monocyclic neomenthyl group on sulfur in sulfoximines 1 and 2 with the bicyclic exo-2-bornyl group should introduce more rigidity in the sulfoximine molecule and more steric crowding around sulfur atom and that this should result in substantially higher enatioselectivity in MT reactions, we prepared a new epimeric pair of (1R,Ss)-(-)-S-methyl-S-exo-2-bornyl-N-tosyl sulfoximine, **9a** and (1R,Rs)-(+)-S-methyl-S-exo-2-bornyl-N-tosyl sulfoximine, **9b** and used them as methylene transfer reagents.



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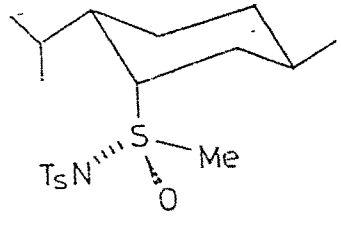

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In this chapter we will present results of our study on the effect of variation in chiral substituent at sulfur on the extent and kind of asymmetric induction in MT reactions.

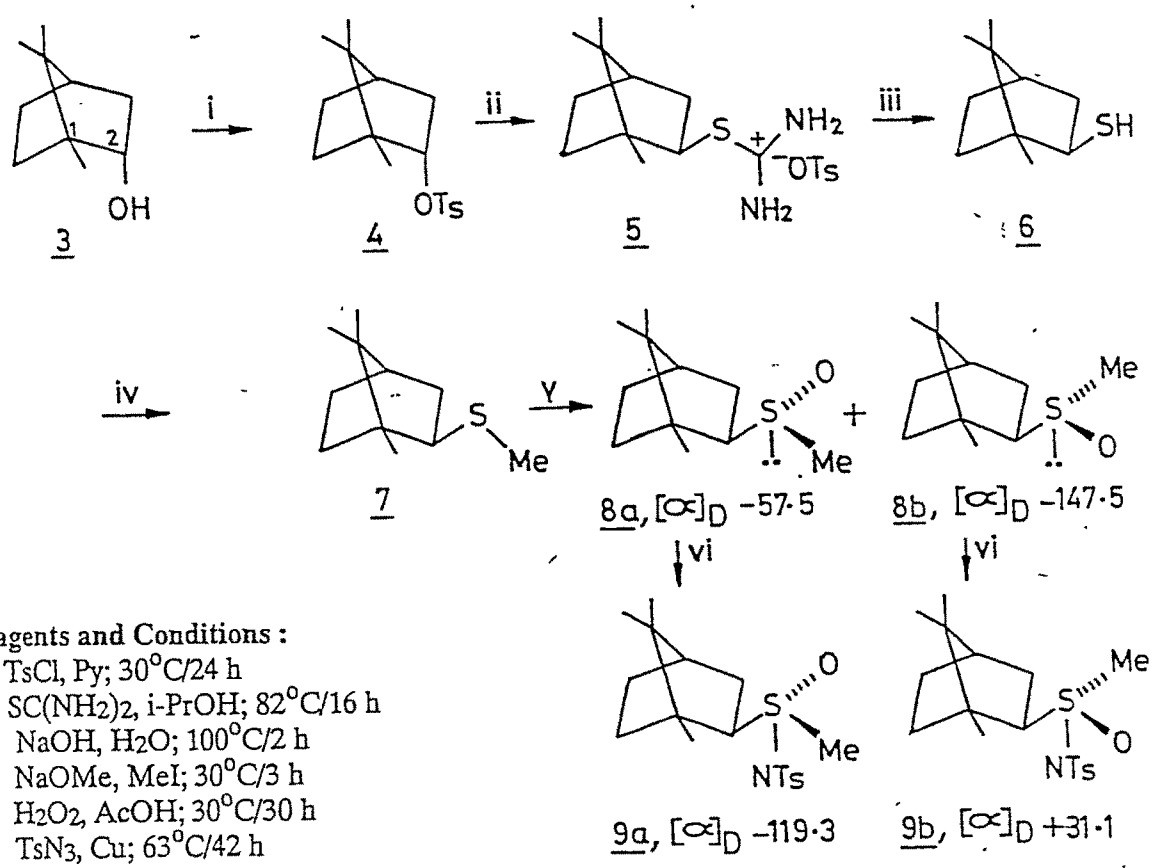
B. RESULTS AND DISCUSSIONS

(1R)-(-)-exo-2-Bornanethiol[1,2], 6 required for the preparation of chiral sulfoximines 9a and 9b was prepared as per known procedure[1] (Scheme 1).

(1R)-(+)-endo-2-borneol, 3 [$[\alpha]_D$ +37.18 (C, 5.05, MeOH)] was treated with pyridine and tosyl chloride at 0^oC to 25^oC to gave (1R)-(+)-endo-2-bornyl tosylate[3], 4 in quantitative yield (97 %). The tosylate 4 was converted into (1R)-(-)-exo-2-bornylisothiouronium p-toluene sulfonate salt[4], 5 [$[\alpha]_D$ -54.19 (c, 2.56, MeOH)] by refluxing 4 with thiourea in isopropanol. This reaction, a typical nucleophilic substitution reaction of SN_2 type is accompanied by an inversion of configuration at C_2. The alkaline hydrolysis of 5 with dilute sodium hydroxide solution gave in good yield the desired (1R)-(-)-exo-2-bornanethiol, 6 of 98.8 % GC purity (6',10 % SE-30 on chromosorb W, 170^oC, FID). The specific rotation of thiol 6 [$[\alpha]_D$ -52.27 (c, 12.11, MeOH)] turned out to be slightly higher in magnitude compared to $[\alpha]_D$ reported[1] for its (+)-isomer [$[\alpha]_D$ +48.3, (c, 11.8, MeOH)].

(1R)-(-)-exo-2-bornanethiol 6 was methylated with methyl iodide into (1R)-(-)-S-methyl-S-exo-2-bornyl sulfide[5], 7 in 90 % yield [$[\alpha]_D$ -78.0 (c, 3.14)]. The sulfide, 7 was oxidised with hydrogen peroxide to an epimeric (at sulfur) pair of sulfoxides

8a and 8b in 45:55 ratio, (GC : epimers resolved very well on cyclodex B capillary column)[6] (Fig. 1). The epimeric mixture shows slightly overlapping spots on TLC plate. The mixture could be separated by repeated column chromatography on silica gel into 99.2 % pure (chiral GC) minor isomer, 8a, $[\alpha]_D$ -57.5 and 99.7 % pure (chiral GC) major isomer, 8b, $[\alpha]_D$ -147.5. The epimer 8b elutes earlier (Relative retention time 1.00) than the epimer 8a (RRT, 1.45). Both 8a and 8b gave satisfactory microanalyses.



3 4 5 6 7 8a, $[\alpha]_D$ -57·5 8b, $[\alpha]_D$ -147·5 9a, $[\alpha]_D$ -119·3 9b, $[\alpha]_D$ +31·1

Reagents and Conditions :
i. TsCl, Py; 30°C/24 h
ii. $SC(NH_2)_2$, i-PrOH; 82°C/16 h
iii. NaOH, H_2O; 100°C/2 h
iv. NaOMe, MeI; 30°C/3 h
v. H_2O_2, AcOH; 30°C/30 h
vi. TsN_3, Cu; 63°C/42 h

Scheme 1

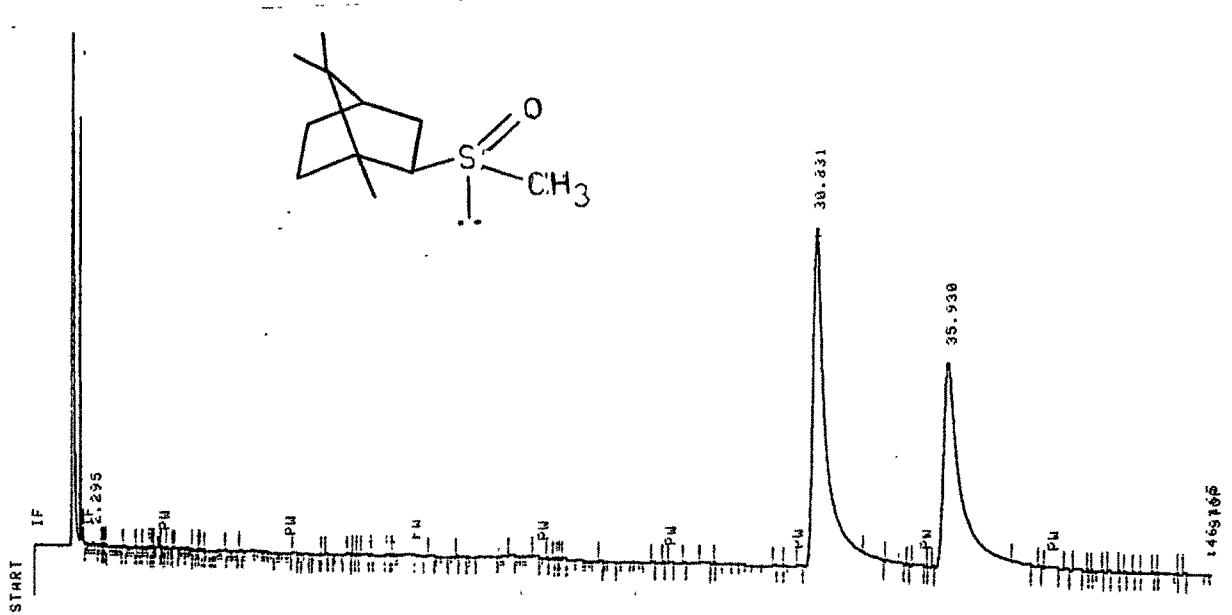


Fig. 1 : Chiral GC Analysis of Epimeric mixture of S-Methyl-S-<u>Exo</u>-2-bornyl Sulfoxide on Cyclodex B Capillary Column

The structures of both epimeric sulfoxides 8a and 8b were characterised by various spectroscopic data. The IR spectra of 8a (Fig.2) and 8b (Fig.3) show characteristic strong bands at 1050 and 1025 Cm^{-1} of S=O stretching vibrations.

The ^{1}H NMR spectra of sulfoxides 8a and 8b differ clearly to further support the chemical and enantiomeric purity. In the case of sulfoxide 8a (Fig.4) the singlets due to one of the three quaternary methyls of the exo-2-bornyl group appears at δ 1.22 whereas in 8b (Fig.5) all the three singlets appear in the region δ 0.86 to 0.98. Also, in 8a, the proton on C_2 (-HC-S-) appear as a triplet at δ 2.62 away from the S-CH_3 singlet (δ2.45) whereas in 8b, (Fig.5) -HC-S-signal appear as a triplet atδ2.51, at the base of the singlet due to -S-CH_3 (δ 2.52).

^{13}C NMR spectra of sulfoxides 8a (Fig.6) and 8b (Fig.7) accounts for all the eleven carbon atoms. The -CH-S carbon of 8a appearing at δ 73.12 and of 8b at δ 71.57 showing a difference of δ 1.55.

Mass spectra of 8a (Fig.8) and 8b (Fig.9) show similar splitting pattern and (M^{+}+1) peak at 201 further support their structures.

S-Methyl-S-exo-2-bornyl sulfoxides were low melting solids and could not be utilized for X-ray structure studies.

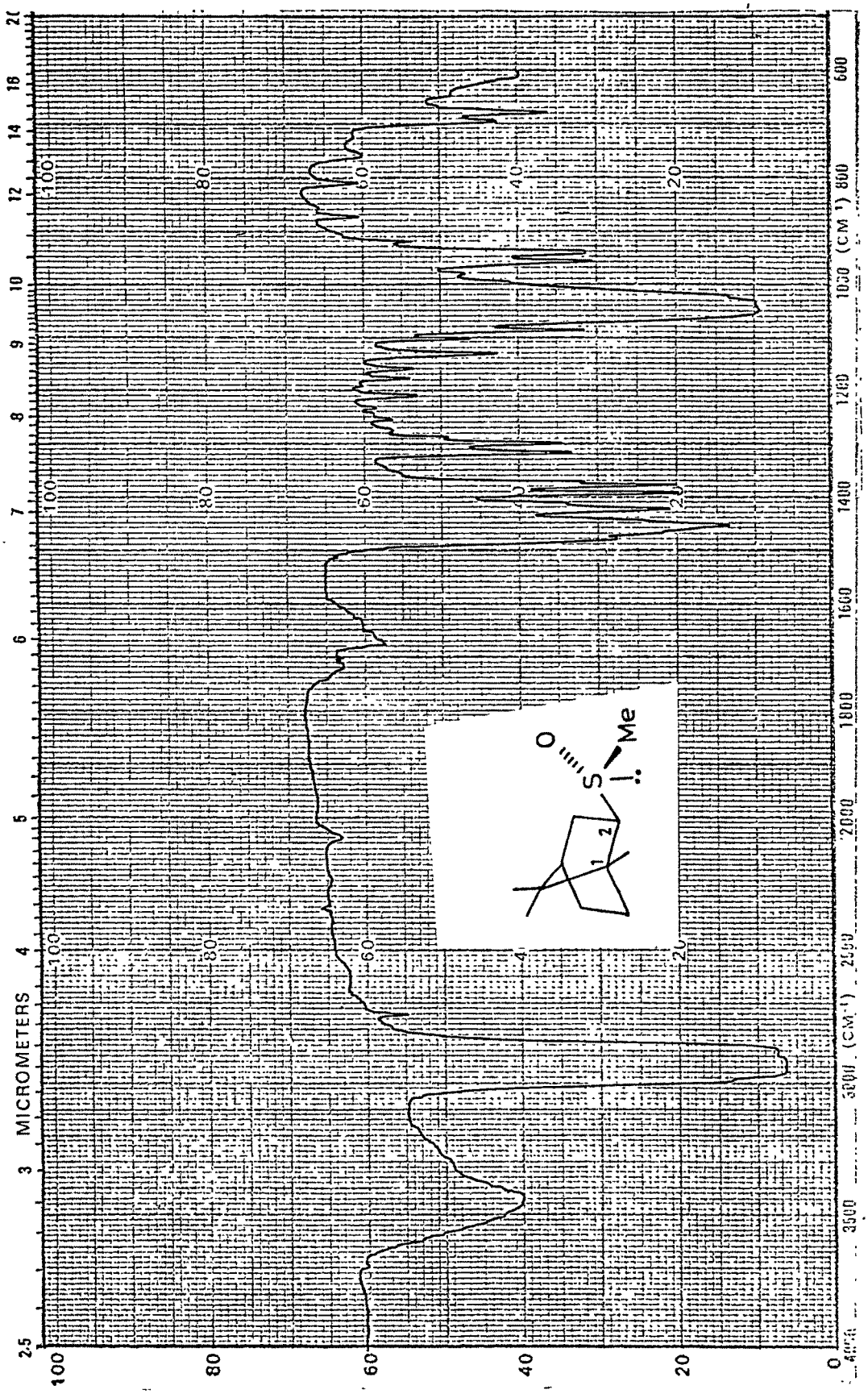


Fig. 2 : IR Spectrum of (1R, S_S)-(-)-S-Methyl-S-exo-2-bornyl Sulfoxide (8a)

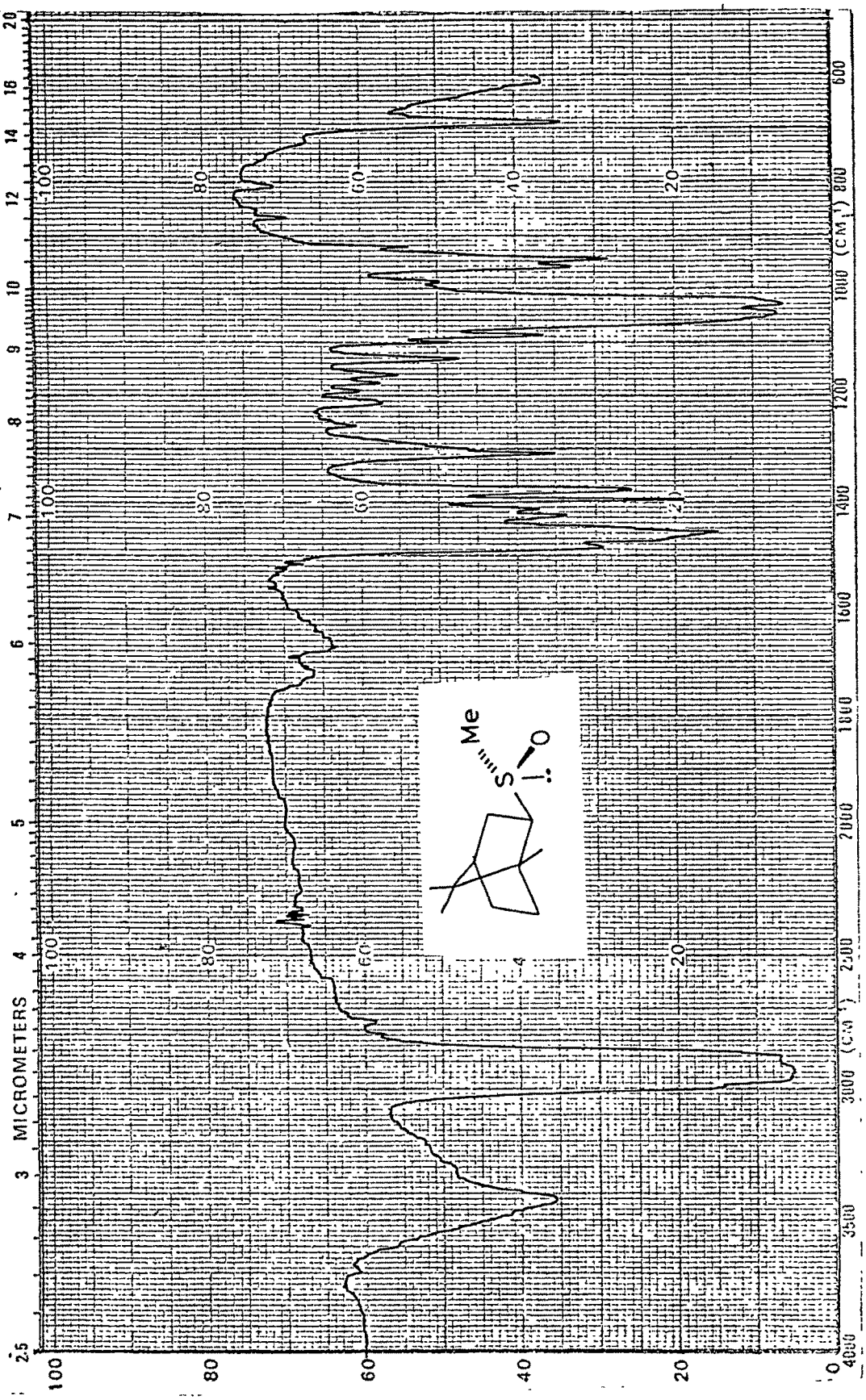


Fig. 3 : IR Spectrum of (1R, R_S)-(-)-S-Methyl-S-exo-2-bornyl Sulfoxide (8b)

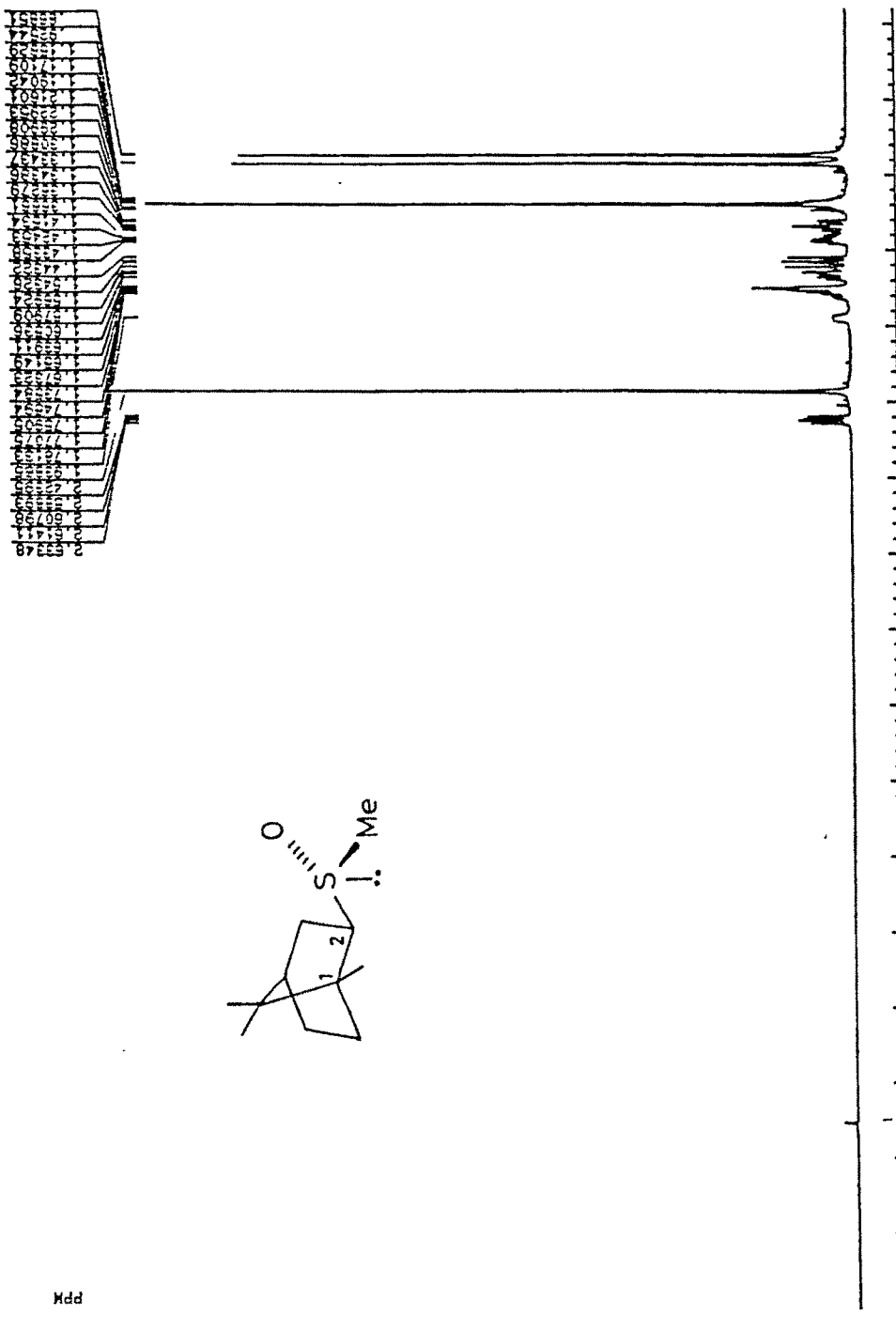


Fig. 4 : ^{1}H NMR Spectrum of (1R, S_s)-(-)-S-Methyl-S-exo-2-bornyl Sulfoxide (8a)

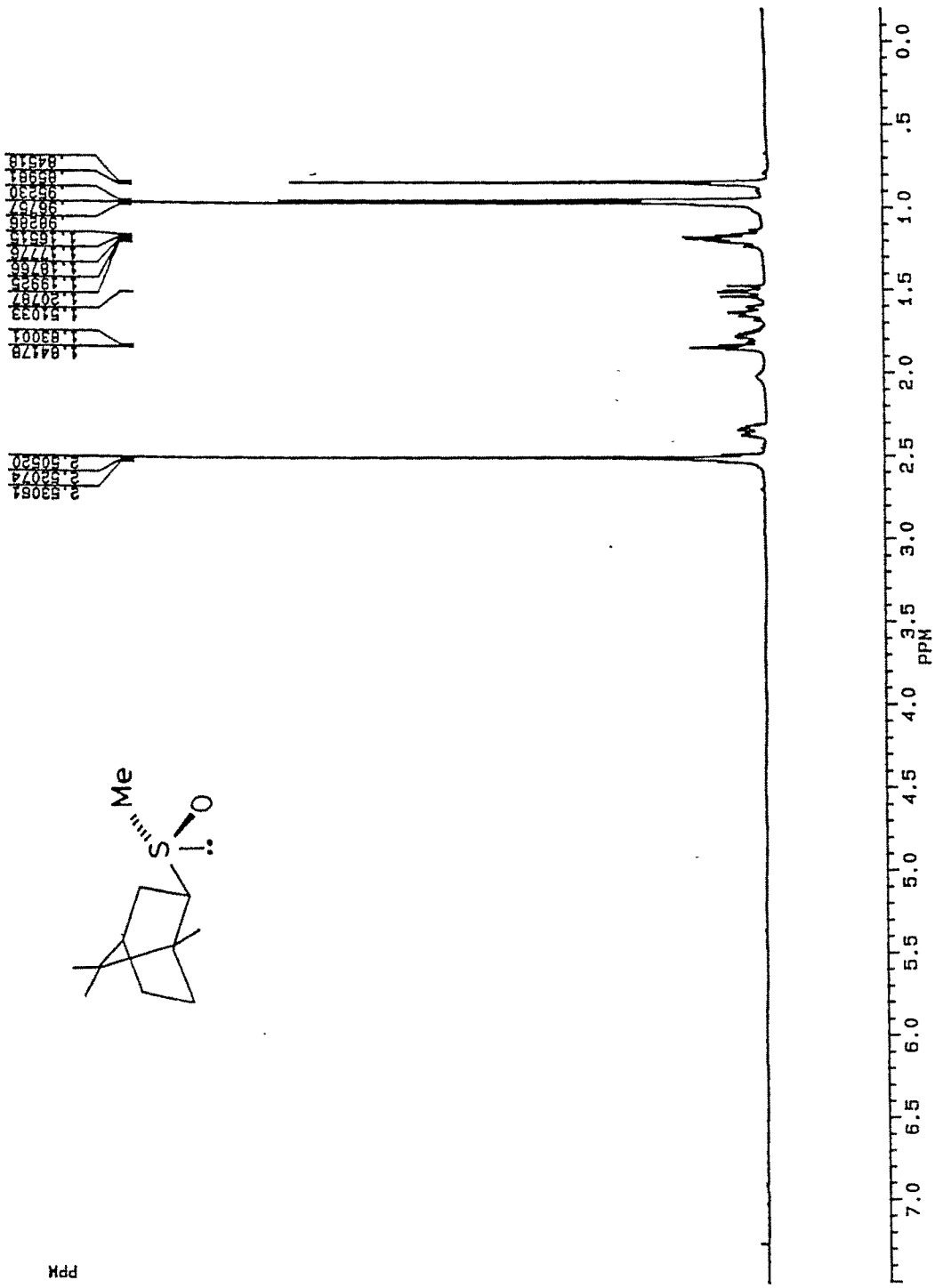


Fig. 5 : ^{1}H NMR Spectrum of (1R, R_S)-(-)-S-Methyl-S-exo-2-bornyl Sulfoxide (8b)

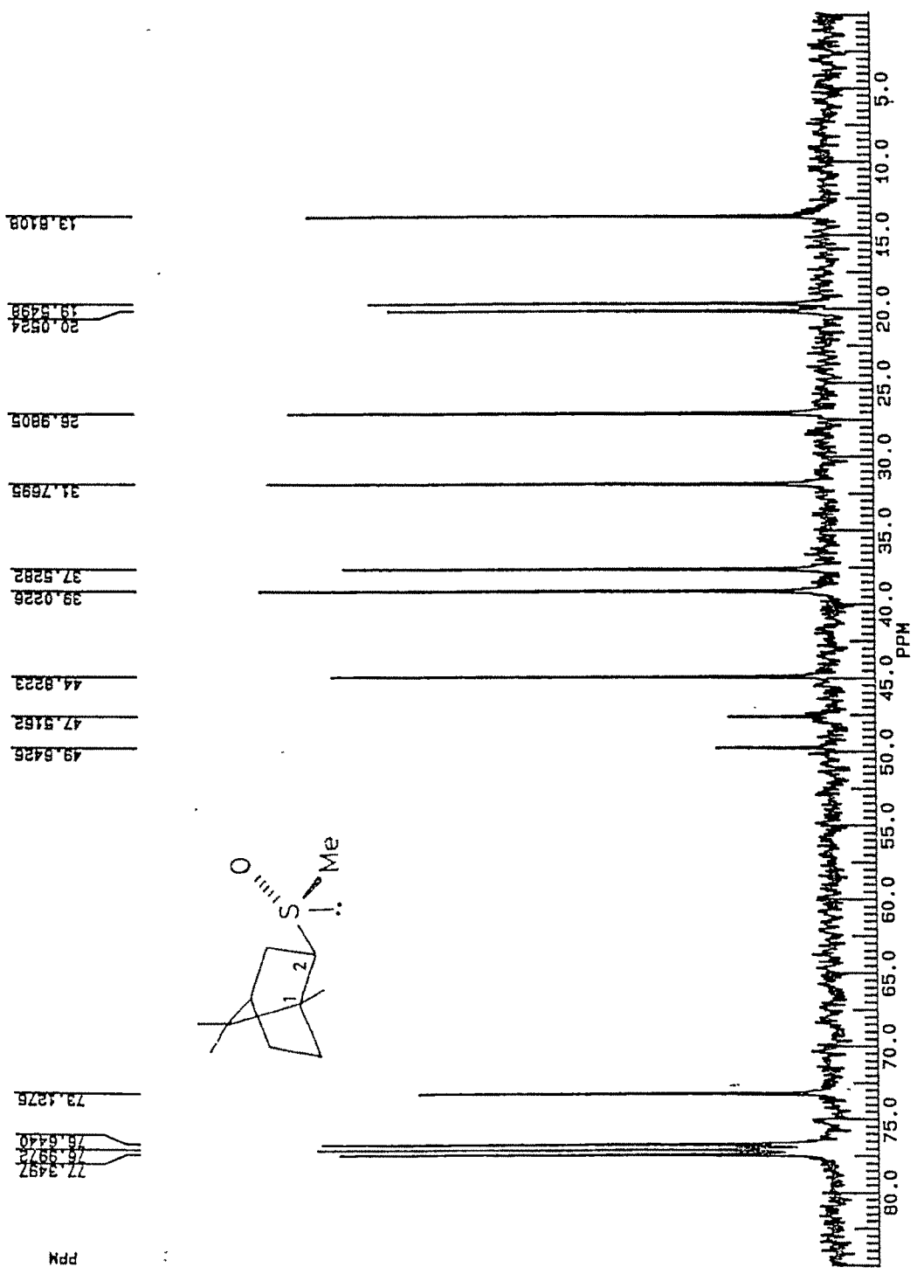


Fig. 6 : ^{13}C NMR Spectrum of (1R, S_S)-(-)-S-Methyl-S-exo-2-bornyl Sulfoxide (8a)

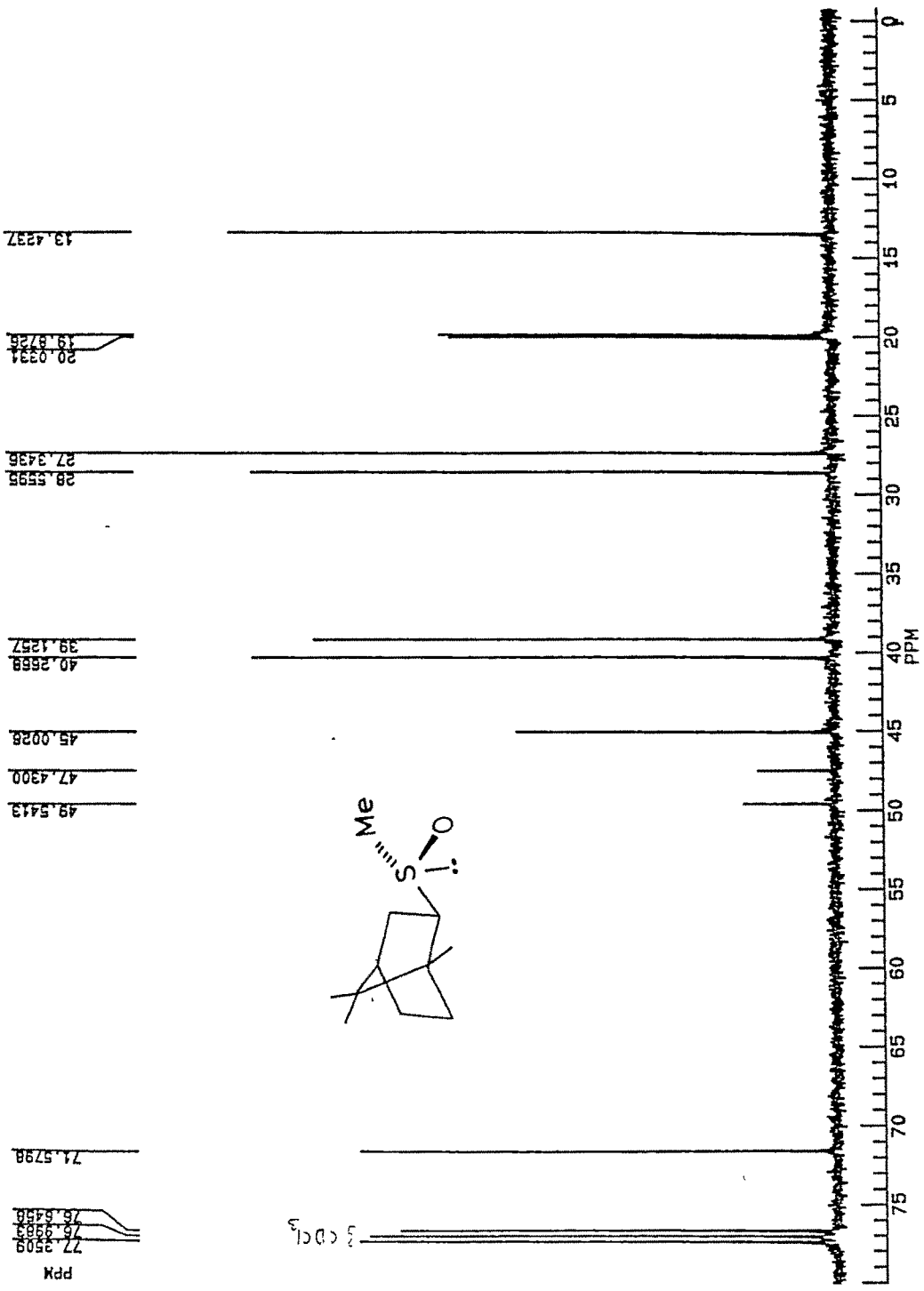


Fig. 7 : ^{13}C NMR Spectrum of (1R, R_S)-(-)-S-Methyl-S-exo-2-bornyl Sulfoxide (8b)

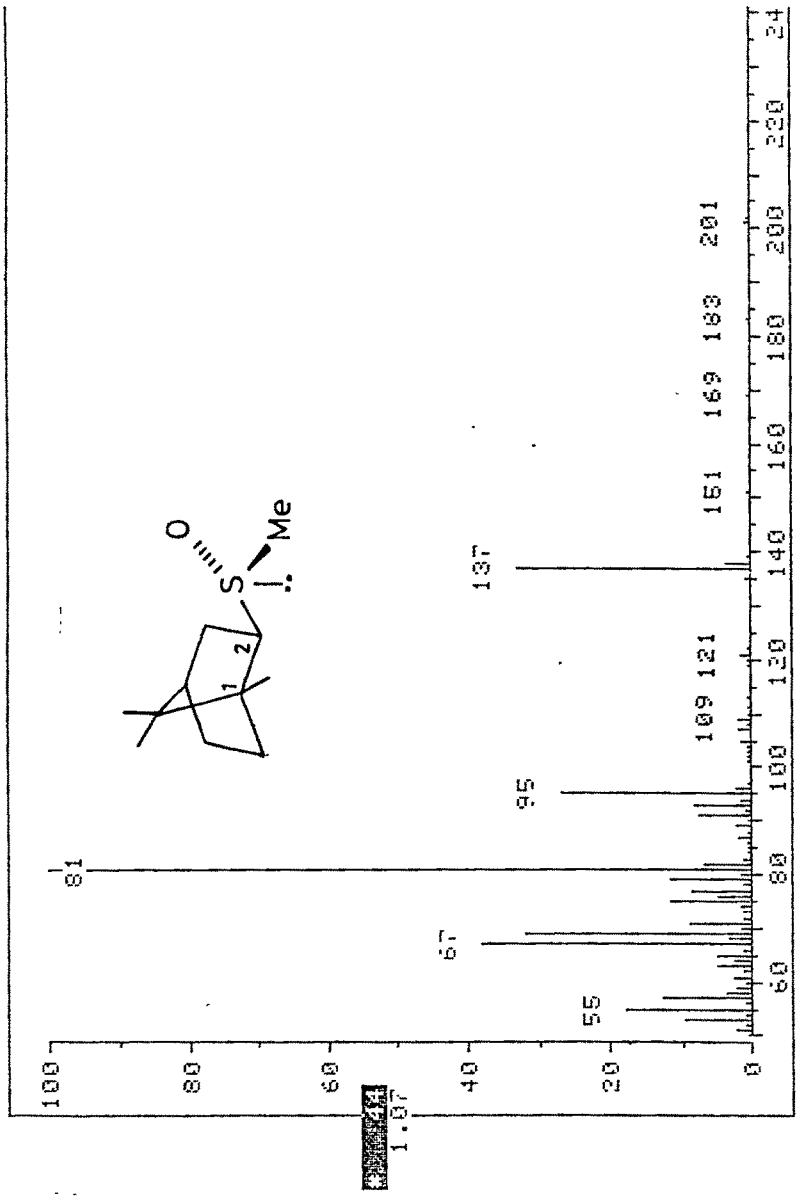


Fig. 8 : Mass Spectrum of (1R, S_S)-(-)-S-Methyl-S-exo-2-bornyl Sulfoxide (8a)

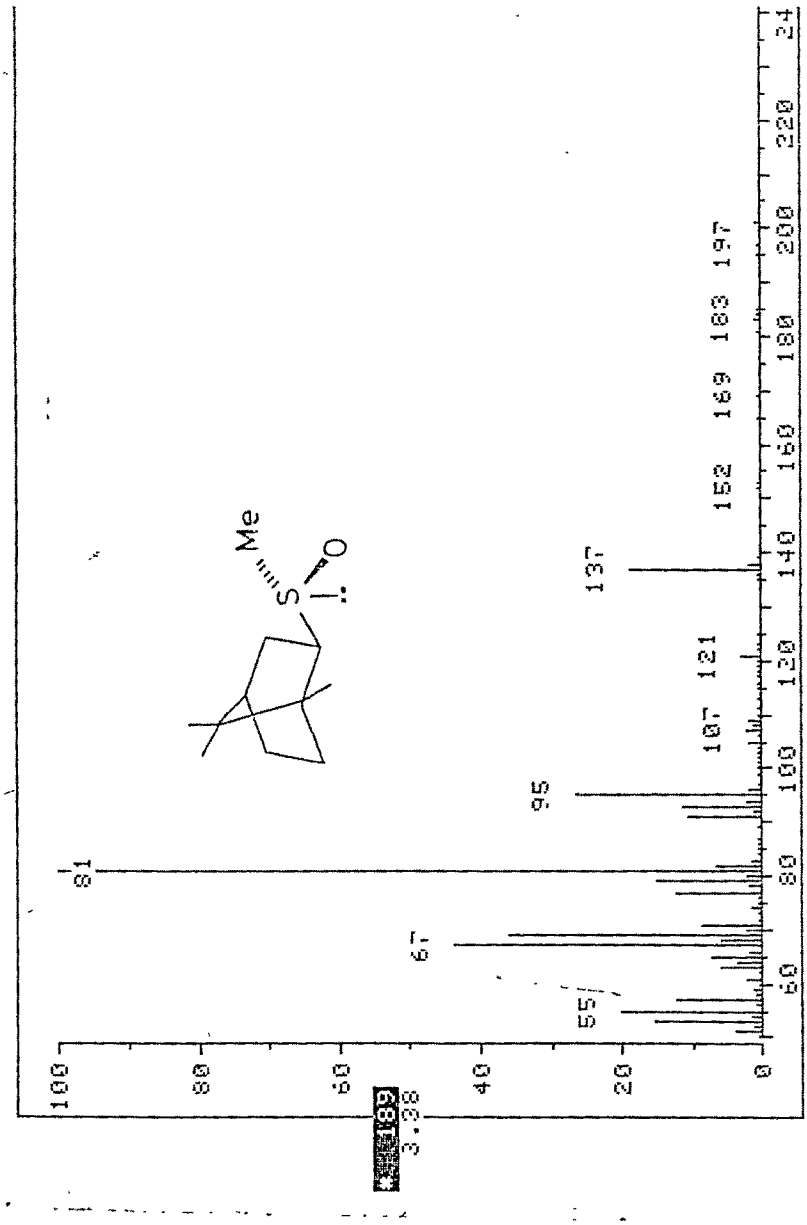


Fig.9 : Mass Spectrum of (1R, R_S)-(-)-S-Methyl-S-exo-2-bornyl Sulfoxide (8b)

The sulfoxide 8a on treatment with p-toluene sulfonyl azide and copper powder in methanol followed by chromatographic purification gave pure (1R,Ss)-(-)S-methyl-S-exo-2-bornyl-N-tosyl sulfoximine, 9a, $[\alpha]_D$ -119.3 (c, 2.49) in 53.4 % yield based on consumed sulfoxide. The column pure product was recrystallised thrice from different solvent systems, viz.; absolute ethanol, acetone:n-hexane (20:80) and acetonitrile : water (85:15). After each crystallization optical rotation remained unaltered.

Similarly, sulfoxide 8b on treatment with p-toluene sulfonyl azide and copper powder in methanol gave corresponding optically pure (1R,Rs)-(+)-S-methyl-S-exo-2-bornyl-N-tosyl sulfoximine 9b, $[\alpha]_D$ +31.3 in 82 % yield based on consumed sulfoxide. The column pure product was recrystallized from hexane:acetone (80:20), absolute ethanol and acetonitrile : water (85:15) into beautiful crystals of 9b.

Both the epimeric sulfoximines 9a and 9b gave satisfactory microanalyses and HRMS.

High resolution ^1H NMR came in handy to clearly establish the chemical and enantiomeric homogeneity of 9a and 9b. In sulfoximine 9b (Fig. 10), the protons of S-CH_3 appear as a singlet at δ 3.31 and -HC-S signal as a triplet, downfield centred at δ 3.42. The corresponding signals of 9a (Fig.11) appear at δ 3.46 (3H,s) and at δ 3.29 (1H, t) respectively.

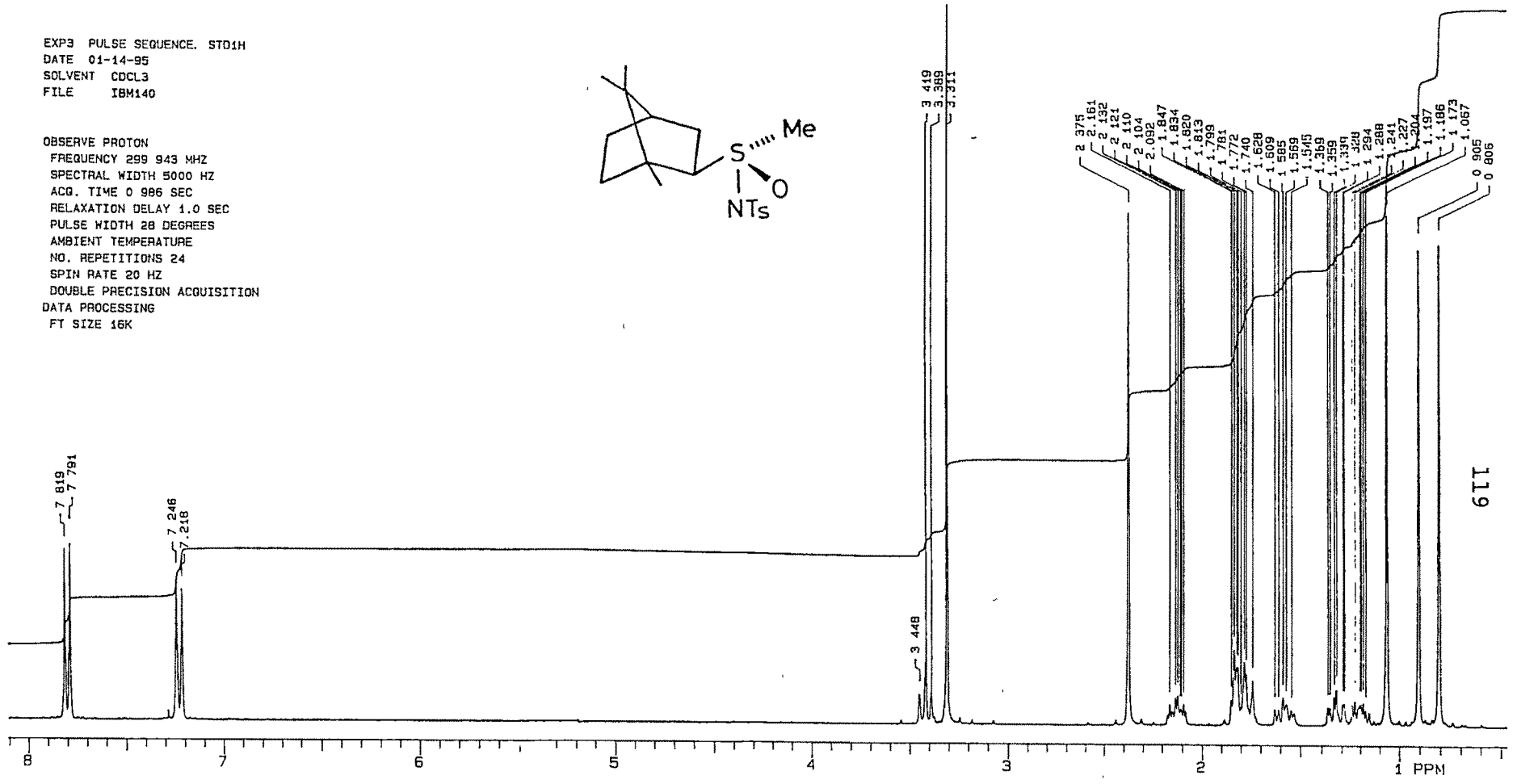


Fig. 10 : ^{1}H NMR Spectrum (300 MHz) of (1R, R_S)-(+)-S-Methyl-S-exo-2-bornyl-N-tosyl Sulfoximine (9b)

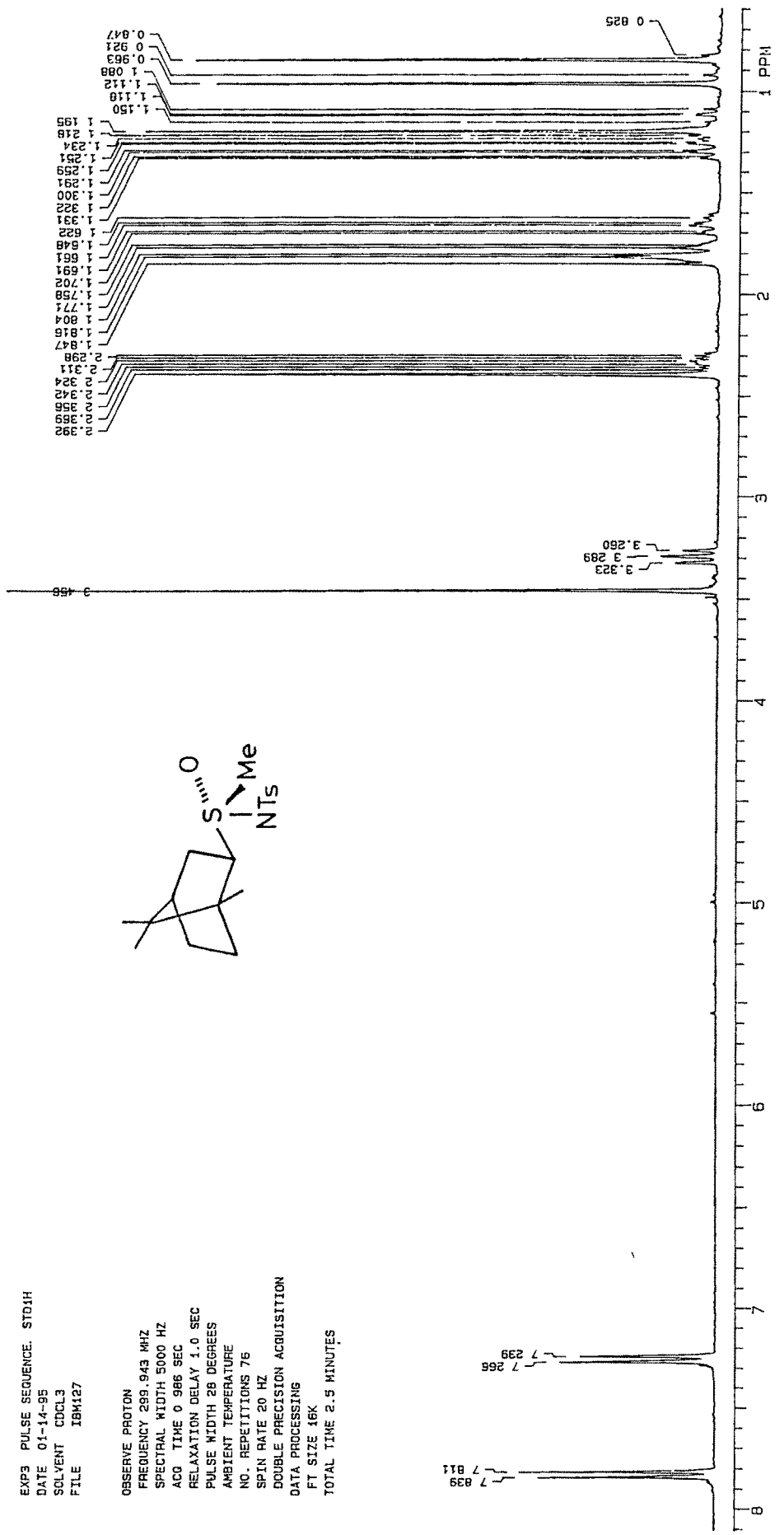


Fig. 11 : ^1H NMR Spectrum (300MHz) of (1R, S_s)-(-)-S-Methyl-S-exo-2-bornyl-N-tosyl Sulfoximine (9a)

Also, one of the three -C-$\underline{CH_3}$ singlets due to quaternary methyl groups in 9a appears at δ 1.195 and in 9b at δ 1.067 respectively.

IR spectra of 9a (Fig.12) and in 9b (Fig.13) show characteristic strong bands due to S=O stretching vibrations at 1040 cm^{-1} and N=S=O stretching vibration at 1222 cm^{-1}.

^{13}C NMR spectra of both the epimers 9a and 9b perfectly account for all the 18 carbon atoms. The four similar Ar-$\underline{C}$H carbon peaks overlaps each other and appear as two peaks only as in the case of neomenthyl sulfoximines 1 and 2. The -$\underline{C}$H-S- carbon peak in 9a (Fig.14) appear at δ 73.87 and in 9b (Fig.15) at δ 71.69.

The high resolution mass spectrum of 9a further support its structure. The exact mass found for (M^++H) is 370.1506 and for (M^+-H)is 368.1367. The corresponding excat mass calculated for $C_{18}H_{28}NO_3S_2$ is 370.1511 and for $C_{18}H_{26}NO_3S_2$ is 368.1354 (Fig.16 to 18).

The structure of sulfoximine 9b was established by single crystal X-ray structure analysis (For details, see Experimental). The absolute configuration at chiral sulfur atom was found to be (R) (ORTEP, Fig.19). This established that sulfoxide 8b then should have (R) configuration and that sulfoxide 8a and sulfoximine 9a should have (S) configuration at sulfur.

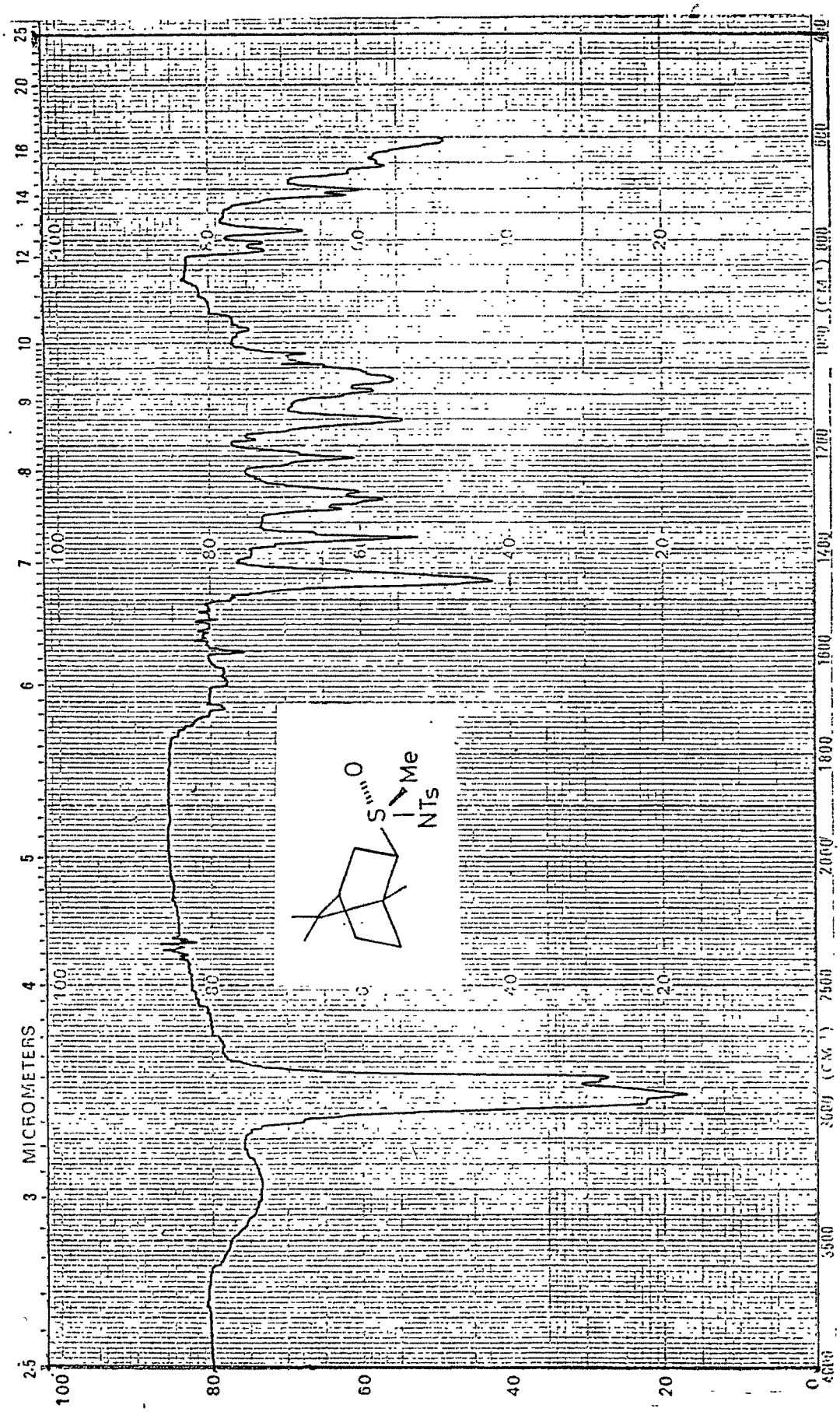


Fig. 12 : IR Spectrum of (1R, S_s)-(-)-S-Methyl-S-exo-2-bornyl-N-tosyl Sulfoximine (9a)

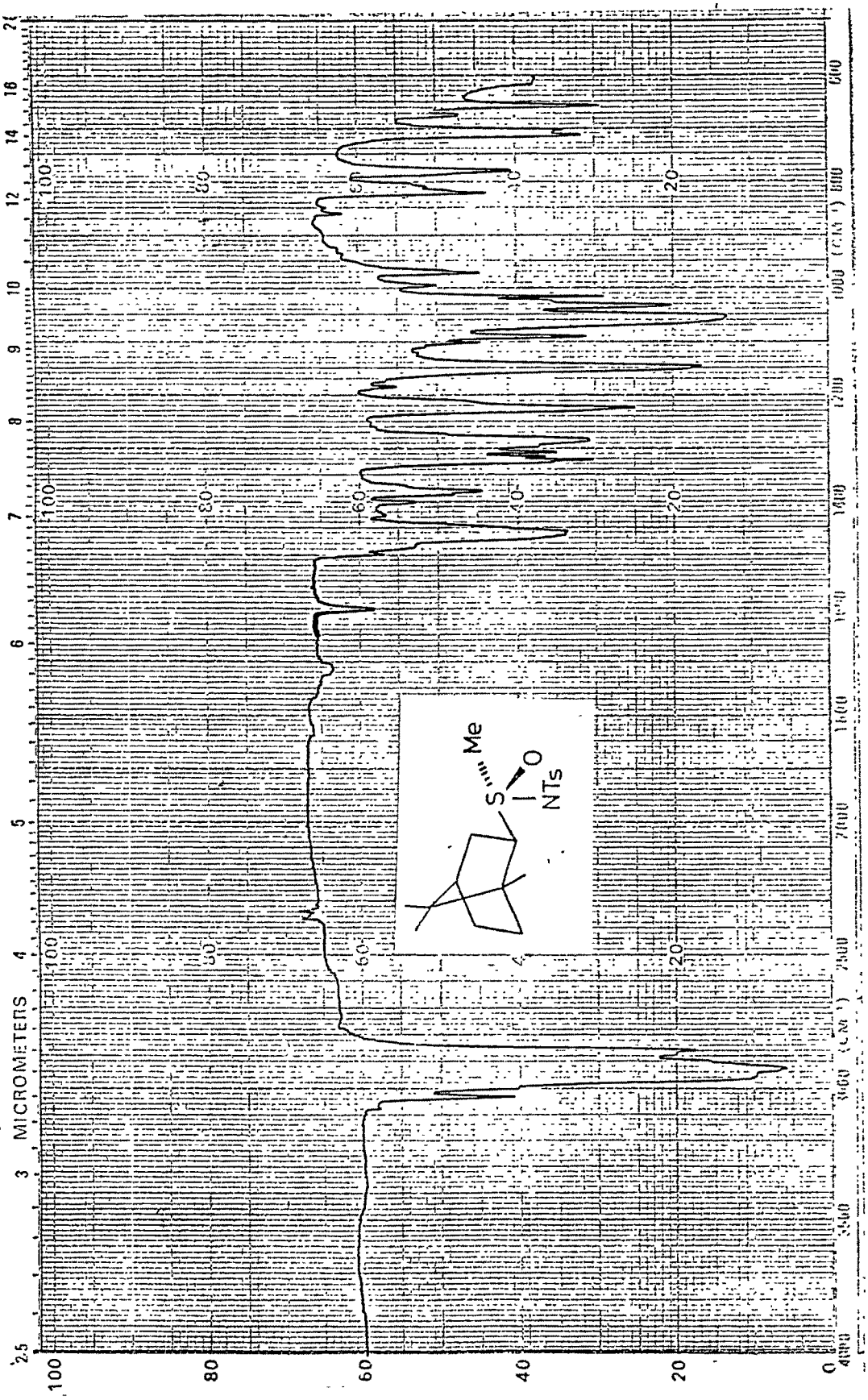


Fig. 13 : IR Spectrum of (1R, R_S)-(+)-S-Methyl-S-exo-2-bornyl-N-tosyl Sulfoximine (9b)

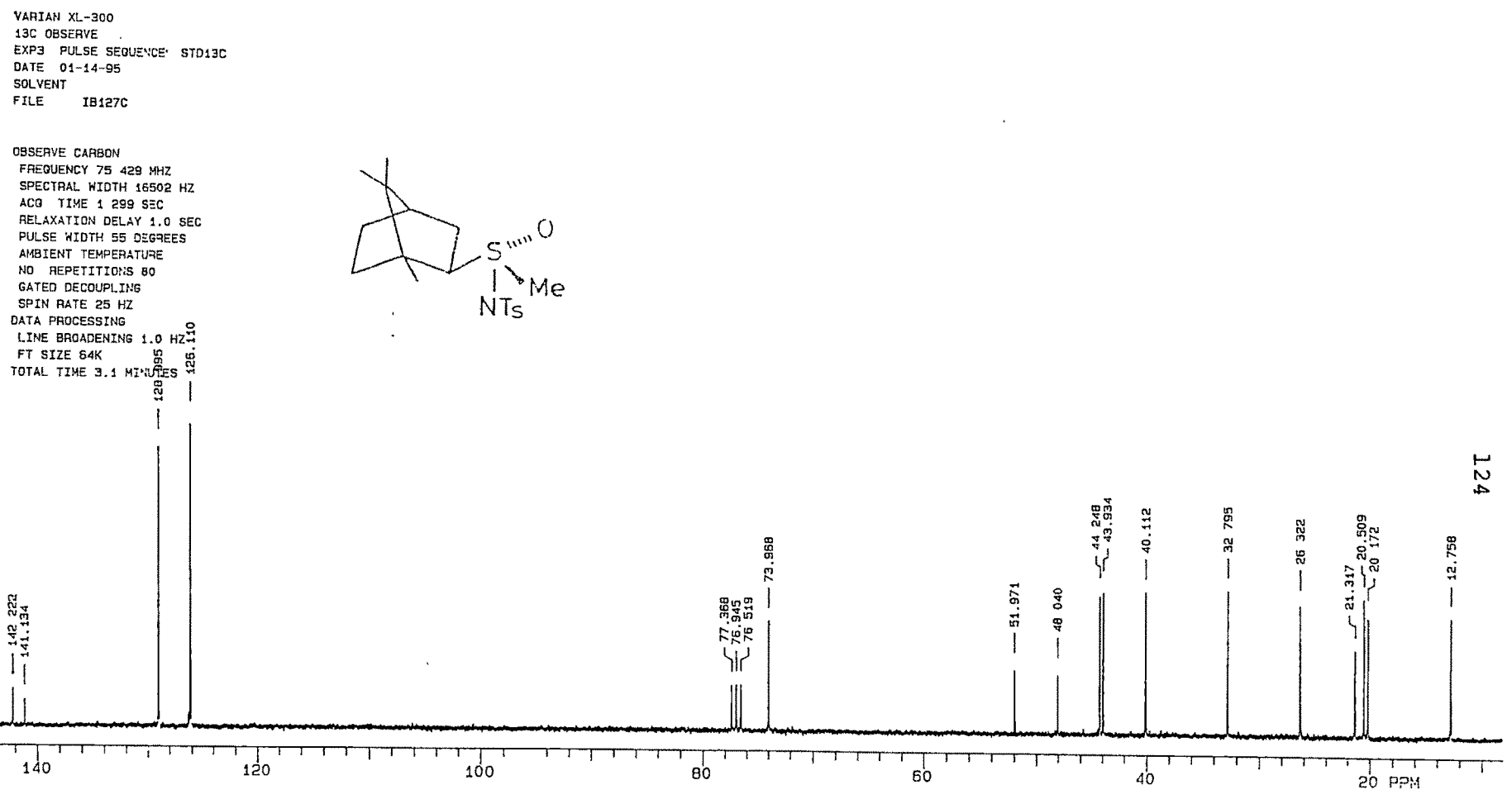


Fig. 14 : ^{13}C NMR Spectrum of (1R, S_s)-(-)-S-Methyl-S-exo-2-bornyl-N-tosyl Sulfoximine (9a)

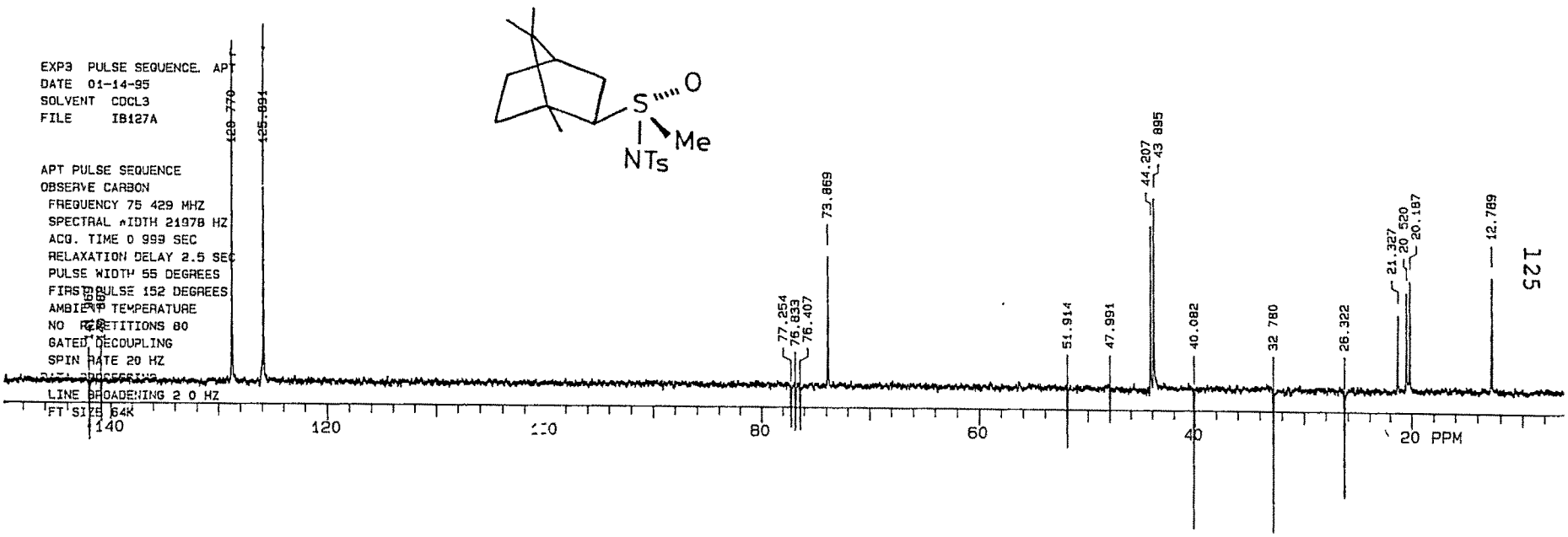


Fig. 14 : ^{13}C NMR Spectrum (APT) of (1R,S_S)-(-)-S-Methyl-S-exo-2-bornyl-N-tosyl Sulfoximine (9a)

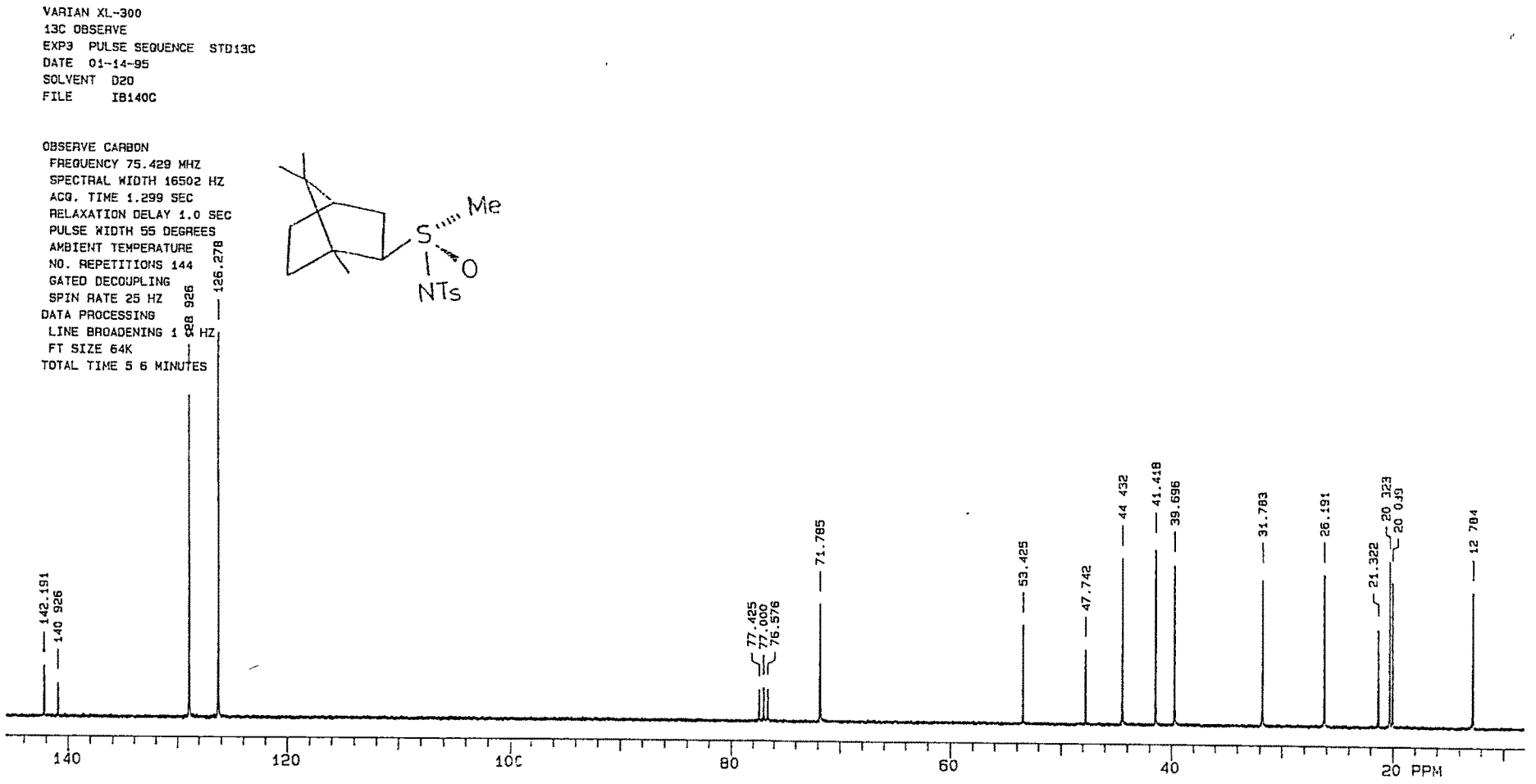


Fig. 15 : ^{13}C NMR Spectrum of (1R,R_S)-(+)-S-Methyl-S-exo-2-bornyl-N-tosyl Sulfoximine (9b)

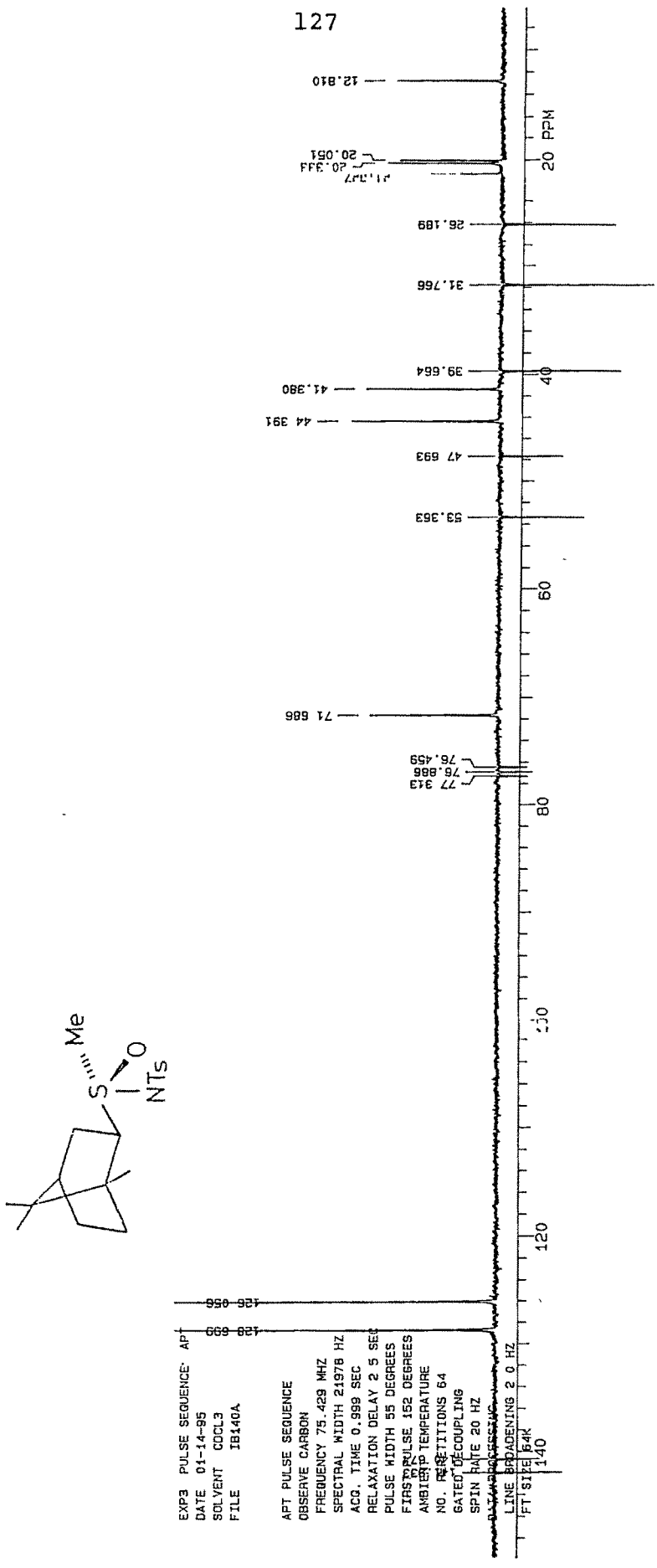
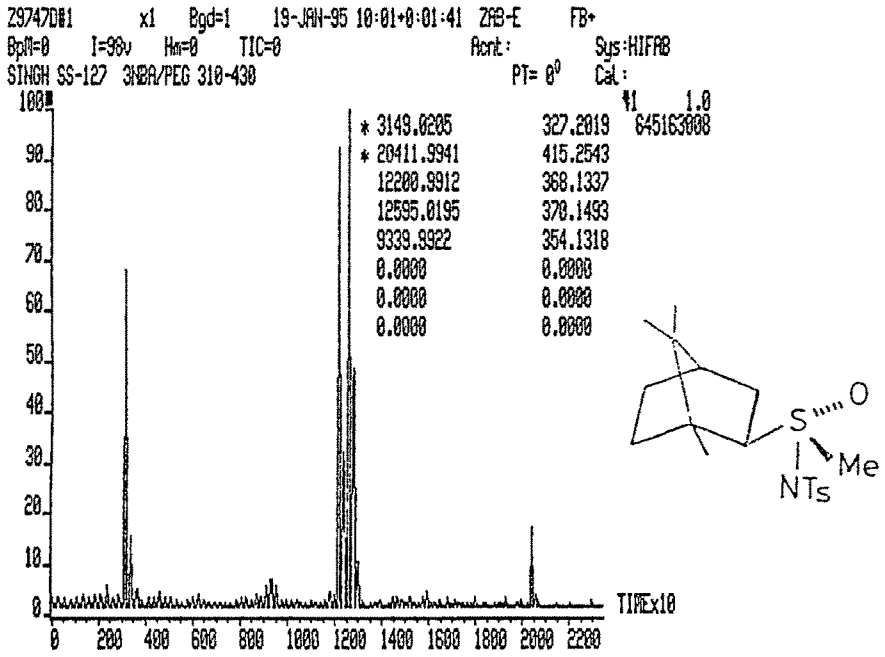


Fig. 15 : ^{13}C NMR Spectrum (APT) of (1R,R_S)-(+)-S-Methyl-S-exo-2-bornyl-N-tosyl Sulfoximine (9b)



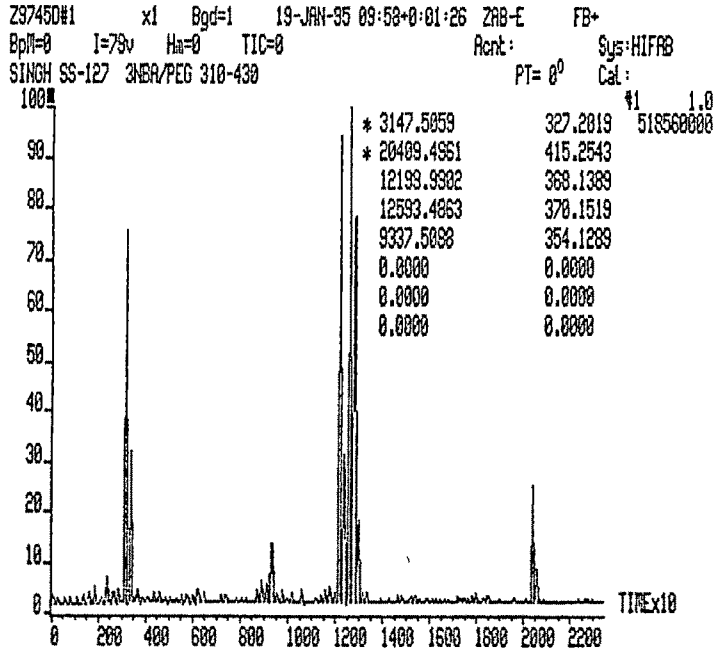


Fig. 16 : HRMS of (1R,S_S)-(-)-S-Methyl-S-exo-2-bornyl-N-tosyl Sulfoximine (9a)

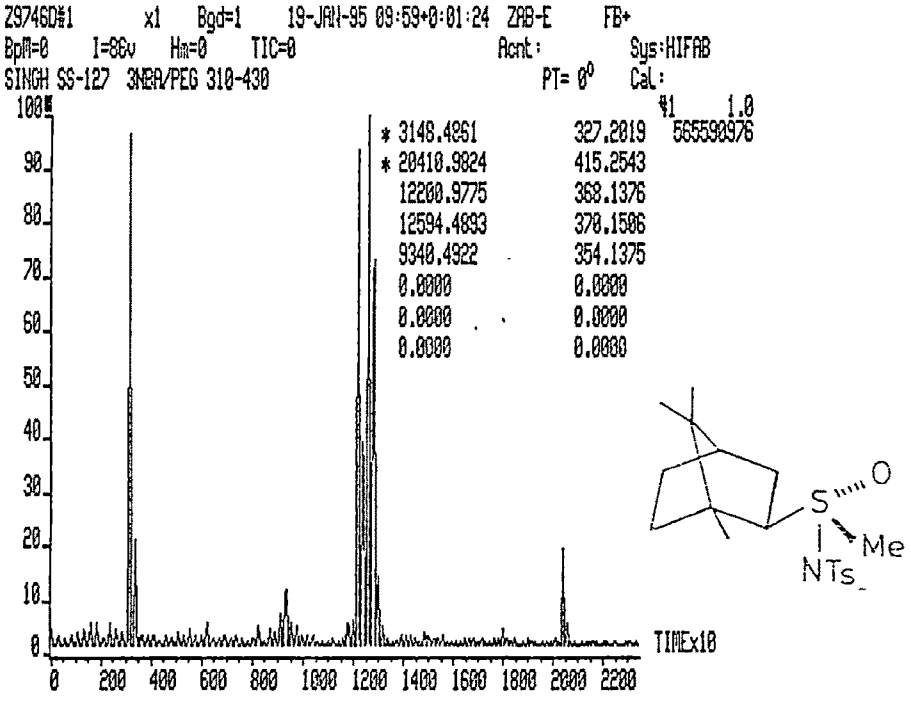
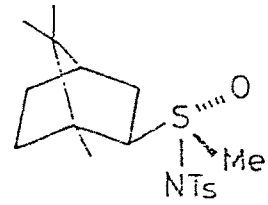


Fig. 17 : HRMS of (1R,S_S)-(-)-S-Methyl-S-exo-2-bornyl-N-tosyl Sulfoximine (9a)



Single Mass Input Page 1-1

M/E	C 12	H	N	O	S	MMU	DBE	OBS.MASS
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	21	22	1	3	1	-4.7	11.5	
✓	18	26	1	3	2	-1.3	6 5	
	15	30	1	3	3	2.1	1.5	

Single Mass Input Page: 1-1

M/E	C 12	H	N	O	S	PPM	DBE	ACC.MASS
368	22	24	0	3	1	-21.5	11.0	368.1446167
	21	22	1	3	1	12.7	11 5	368.1320406
✓	18	26	1	3	2	3.5	6.5	368.1354126
	15	30	1	3	3	-5.7	1.5	368 1387845

Single Mass Input Page. 1-1

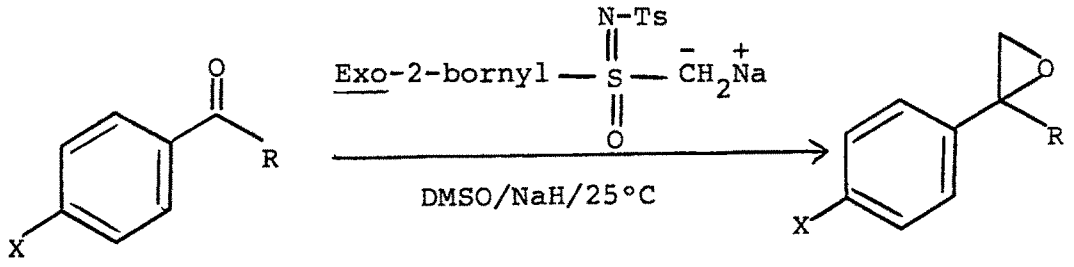
M/E	C 12	H	N	O	S	MMU	DBE	OBS.MASS
370	21	24	1	3	1	-2 9	10 5	370.1506000
✓	18	28	1	3	2	0.5	5 5	
	15	32	1	3	3	3 8	0 5	

Single Mass Input Page 1-1

M/E	C 12	H	N	O	S	PPM	DBE	ACC MASS
370	21	24	1	3	1	7 9	10 5	370.1476907
✓	18	28	1	3	2	-1 2	5 5	370 1510626
	15	32	1	3	3	-10 4	0 5	370 1544346

Fig. 18 : HRMS of (1R,S_S)-(-)-S-Methyl-S-exo-2-bornyl-N-tosyl Sulfoximine (9a)

Four carbonyl compounds, 10 - 13 were used as substrate for the synthesis of chiral oxiranes 14 - 17 using sulfoximines 9a and 9b as MT reagents (Scheme 2).



10-13 14-17

			X	R
Where,	10,	14	H	H
	11	15	Cl	H
	12	16	H	Me
	13	17	Cl	i-Pr

Scheme 2

The asymmetric induction achieved* in oxirane synthesis with sulfoximine 9a is given in Table 1 and with 9b is given in Table 2.

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* The results of these studies has been published in 1995[7].

Table 1 : Asymmetric Induction in Oxirane Synthesis Using Sulfoximine (Ss)-9a

Sr. No.	Carbonyl Substrate	Product Oxirane		
		Identity	Yield (%)	ee(%)GC*
1.	10	(S)-(-)-Phenyloxirane 14	25.0	28.6 (b)
2.	11	(S)-(-)-(4-Chlorophenyl) oxirane 15	23.0	21.7 (b)
3.	12	(-)-2-Methyl-2-phenyl-oxirane 16	-	a > b**
4.	13	(-)-2-(4-Chlorophenyl)-2-isopropyl oxirane 17	52.3	58.1 (b)

* Cyclodex B capillary column 25M x 0.25 m.m.

'a' denotes the fast eluting enantiomer in excess and

'b' denotes the slow eluting enantiomer in excess

** Reaction sluggish, unconverted acetophenone interferes in GC

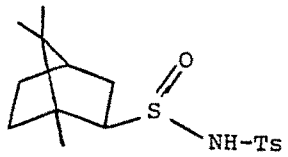
Table 2 : Asymmetric Induction in Oxirane Synthesis Using Sulfoximine (Rs)-9b

Sr. No.	Carbonyl Substrate	Product Oxirane		
		Identity	Yield (%)	ee(%)GC*
1.	10	(S)-(-)-Phenyloxirane 14	40.1	28.5 (b)
2.	11	(S)-(-)-(4-Chlorophenyl) oxirane 15	55.3	18.6 (b)
3.	12	(+)-2-Methyl-2-phenyl-oxirane 16	65.1	56.9 (b)
4.	13	(+)-2-(4-Chlorophenyl)-2-isopropyl oxirane 17	70.2	68.2 (a)

* Same footnote as in Table 1.

It was observed that reactions of S-exo-2-bornyl sulfoximines with prochiral carbonyl compounds giving non-racemic oxiranes are comparatively slower than those of S-neomenthyl sulfoximines 1 and 2 under the same conditions. The yields of oxiranes also were generally lower.

It came as a surprise to us that changing the neomenthyl moiety on sulfur to a more rigid bicyclic chiral auxiliary such as exo-2-bornyl group resulted actually in lower ee (19-68 %) in oxiranes synthesised. Not only that, both (Ss) and (Rs) sulfoximine **9a** and **9b** gave same (S)-oxiranes when the substrates were benzaldehydes, though when phenyl ketones were used as substrate, each sulfoximine gave different enantiomer of oxirane (as in the case of S-neomenthyl sulfoximines). It may be possible that in the transition state, besides configuration at sulfur and neighbouring carbon atom C_2, other factors like steric bulk may also play a role in deciding the direction of asymmetric induction.



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The aqueous-DMSO layer after work up was acidified and extracted with solvent ether to give N-exo-2-bornyl sulfinyl-p-toluene sulfonamide, 18, which has been characterised by ^1H NMR and IR spectra. The ^1H NMR spectra showing total disapperance of S-C<u>H</u>$_3$ peak.

C. ABSOLUTE CONFIGURATION AT CHIRAL SULFUR*

As shown in Scheme 1, in the conversion of (1R)-<u>endo</u>-2-borneol 3 into sulfoximine 9a and 9b, the stereogenic centers on bornyl moiety remains unaltered except in step (ii) when inversion of configuration takes place at C-2 carbon atom. When (1R)-(-)-S-methyl-S-<u>exo</u>-2-bornyl sulfide 7 was oxidised to sulfoxide 8a and 8b, a new stereogenic center is created at sulfur atom. Epimer 8a and 8b differ from each other only in difference in configuration on sulfur. They could be separated into pure epimers by repeated column chromatography on silica gel. Optically pure 8a and 8b on reaction with tosyl azide get converted into optically pure sulfoximines 9a and 9b with retention of configuration at sulfur. The structure of 9b has been established by single crystal X-ray structure analysis.

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* We are thankful to Prof. Gary M. Newton of University of Georgia, Athenes, U.S.A. for the single crystal X-ray analysis of compound 9b.

Crystals of sulfoximine 9b consisted of two independent molecule in one unit cell (ORTEP, Fig.19), which has (R) configuration at sulfur. This establishes that sulfoxide 8b should have (R) configuration and that sulfoxide 8a and sulfoximine 9a should have (S) configuration at sulfur.

D. CONCLUSION

From our study of asymmetric methylene transfer reaction using chiral sulfoximines 1, 2, 9a and 9b, we concluded that chirality on sulfur alone does not lead to significant ee in oxirane synthesis[8]. A chiral substituent on chiral sulfur of sulfoximines leads to fairly high ee in oxiranes produced. Out of the two chiral substituents on sulfur we investigated, neomentyl group is clearly superior to exo-2-bornyl group in both chemcial yields as well as ee of oxiranes in MT reactions.

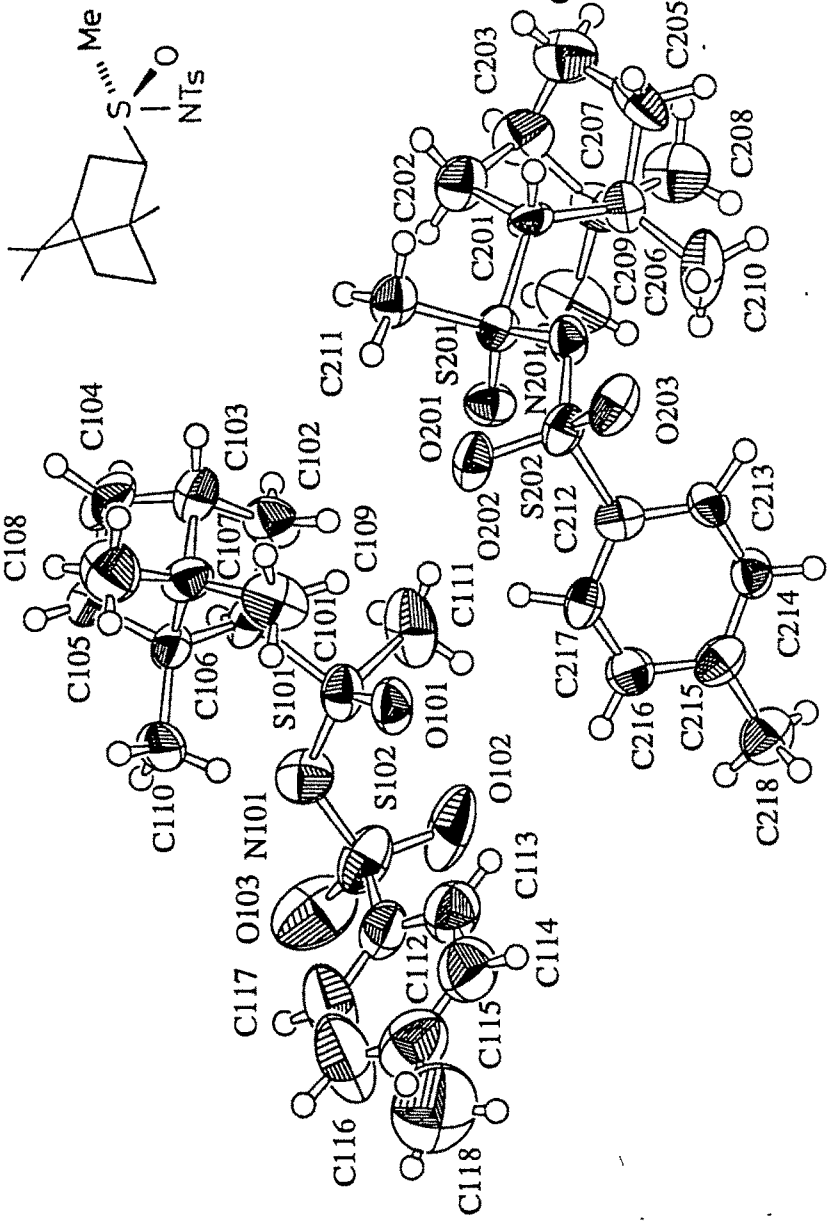

Fig. 19 : ORTEP Diagram of (1R,R_S)-(+)-S-Methyl-S-exo-2-bornyl-N-tosyl Sulfoximine (9b)

E. EXPERIMENTAL

General : All m.p.s. and b.p.s. are uncorrected. Optical rotations were measured at 25°C in chloroform (unless otherwise stated) on a JASCO model DIP-370 digital polrimeter.

Chiral GC analyses, IR and low resolution ^{1}H NMR are same as in Chapter II.

High field ^{1}H NMR : Varian XL-300

^{13}C NMR : Varian XL-300

HRMS : VG - ZAB - E mass spectrometer.

(1R)-(+)-endo-2-bornyl p-toluene sulfonate, (4)[1]

Treatment of (1R)-(+)-endo-2-borneol [$[\alpha]_D$ +37.18 (c, 5.05, MeOH)] (3; 27.77 g, 0.18 mol) in dry pyridine (180 mL) at 0°C with p-toluene sulfonyl chloride (55.3g, 0.29 mol) and the mixture stirred 24h at room temperature. Pyridine was neutralised with dilute HCl (273 mL diluted with 750 mL water) and the mixture was extracted with hexane (80 mLx4). The combined organic layer was washed with water, 10 % sodium bicarbonate solution and water to neutral PH, dried over sodium sulfate and solvent stripped off to give crude product (4; 53.8 g, 97 % yield). It was dissolved in hexane (25 mL) and cooled in refrigerator overnight. The crystals (49 g) were collected by filtration.

$[\alpha]_D$ +15.44 (c, 6.34, MeOH)

Reported[9] $[\alpha]_D$ +15.5 (EtOH) and $[\alpha]_D$ -15.1 (c, 5.5, MeOH)

(1R)-(-)-exo-2-bornylisothiouronium p-toluenesulfonate, (5)[1]

A mixture of 4 (49.4 g, 0.16 mol) and thiourea (25 g, 0.33 mol) in isopropanol (140 mL) was refluxed for 14 h. Reaction was monitored by TLC (disappearance of tosylate). The solvent was removed in vacuo and the solid was dispersed in cold water (170 mL). Solids were collected by filtration and washed with acetone (50 mL).

A small amount of crude product was recrystallized from boiling water into nice crystals for analytical sample

$[\alpha]_D$ -54.19 (c, 2.56, MeOH)

Reported $[\alpha]_D$ +54.4 (c, 2.4, MeOH)[1] (Starting from (1S)-(-)-Borneol)

(1R)-(-)-exo-2-Bornanethiol, (6)[1]

A mixture of crude salt (5; 65 g, 172 mmol) and 0.4 N NaOH solution (473 mL) was heated and allowed water to distil off alongwith thiol, 6. Fresh water was continuously added into the reaction flask from a dropping funnel to replace water distilled out. The distillate (about 700 mL) was extracted with diethyl ether, dried (Sodium sulfate) and distilled off solvent to give white, waxy solid (6, 21.1 g).

$[\alpha]_D$ -52.27 (c, 12.11, MeOH)

Reported $[\alpha]_D$ +48.3 (c, 11.8, MeOH)[1]

(1R)-(-)-S-exo-2-Bornyl-S-methyl sulfide, (7)[5]

(1R)-(-)-exo-2-Bornanethiol, (6; 21.0 g, 123 mmol)was added to a solution of sodium methoxide (7.32 g, 136 mmol) in dry methanol (110 mL), the mixture stirred at 25°C for 1 h and to this was added methyl iodide (19.3 g, 136 mmol). The alkylation was complete in 3 h (GC : 6', 10 % SE-30 on chromosorb W, 170°C, FID). Methanol was distilled off from the reaction mixture. The residue was taken up in diethyl ether (125 mL), washed with water (25 mLx3), dried (on anhydrous sodium sulfate), freed from solvent and distilled under reduced pressure (95°C/5 m.m.) to give S-methyl-S-exo-2-bornyl sulfide (7 ; 20.38 g, 90 % yield).

$[\alpha]_D$ -78.0 (c, 3.14)

IR (Thin film) : 1390, 1375, 1312, 1280, 1130, 1085, 1030, 932, 800 cm^{-1}

^1H NMR (90 MHZ, CCl_4) : (δ), 0.83, 1.00, 1.02 (3H each, s, -C-CH_3), 2.12(3H, s, -S-CH_3), 2.60(1H, t, J=8HZ ; HC-S-Me)

S-Methyl-S-exo-2-bornyl sulfoxides, (8a) and (8b)

To the sulfide (7 ; 53 g, 0.29 mol) in acetic acid (16.6 mL) was added hydrogen peroxide (30 % v/v ; 29.6 mL) and the mixture stirred at 25-30°C for 30h (monitoring by TLC). The reaction mixture was taken up in chloroform (120 mL), washed with water (20 mLx2), potassium carbonate (5 % solution, 40 mL) and water

(40 mL), dried (Na_2SO_4) and freed from solvent to give crude product (56.5 g, 98 % recovery). The crude product was a mixture of epimeric sulfoxides 8a and 8b (diastereomeric ratio, 8b:8a, 55:45; GC : chiral cyclodex B capillary column, RRT:1.00:1.15) (Fig 1).

The epimers were separated into pure components 8a and 8b by repeated column chromatography over silica gel (eluent, n-hexane : acetone, 60:40) and were distilled, b.p. 120°C (bath)/ 0.5 m.m.

(1R,Rs)-(-)-S-Methyl-S-exo-2-bornyl sulfoxide, (8b) :

Elutes first from the column.

Yield : 27.2 g (47 %)

m.p. 38-39°C

$[\alpha]_D$ -147.52 (c, 2.30)

Chiral GC : 99.8 %

IR (Nujol) : 1395, 1375, 1310, 1050, 1025, 945, 690 cm^{-1} (Fig 3)

^1H NMR ($CDCl_3$) : (δ), 0.86, 0.96, 0.98 (3H each, s, All -C-CH_3), 2.52(3H, s, -S-CH_3), 2.51(1H; t, J=7HZ; -HC-S) (Fig 5)

^{13}C NMR ($CDCl_3$) : (δ), 13.42, 19.87, 20.03 (all -C-CH_3), 27.34, 28.56, 39.12, 40.27, 45.00 (-S-CH_3), 47.43, 49.54 (all -C-), 71.58 (-HC-S-) (Fig 7)

EIMS, M/Z (%) : 201(M^++H,1), 137(18), 95(25), 81(100), 67(43), 55(20) (Fig 9)

Microanalysis : $C_{11}H_{20}OS$ Requirers : C, 65.95 % ; H, 10.06 %

Found : C, 65.7 % ; H, 10.33 %

(1R,Ss)-(-)-S-Methyl-S-exo-2-bornyl sulfoxide, (8a) :

Elutes later from the column.

yield : 19.72 g (34 %)

m.p. : 51-52°C

$[\alpha]_D$: -57.5 (c,2.25)

Chiral GC : 99.5 %

IR (Nujol) : 1390, 1375, 1317, 1300, 1130, 1050, 960, 942, 680 cm^{-1} (Fig 2)

^1H NMR ($CDCl_3$) : (δ), 0.89, 0.95, 1.22 (3H each, s, All -C-CH_3), 2.45(3H, s, S-CH_3), 2.62(1H, t; J= 8HZ, -CH-S-) (Fig.4)

^{13}C NMR ($CDCl_3$) :δ13.61, 19.55, 20.05(all -C-CH_3), 26.98, 31.77, 37.53, 39.02, 44.82, (-S-CH_3), 47.52, 49.64 (All -C-) 73.13 (-HC-S-) (Fig.6)

EIMS, M/Z(%) : 201(M^++H,1), 137(32), 95(25), 81(100), 67(38), 55(18) (Fig.8)

Microanalysis : $C_{11}H_{20}OS$ Requires : C, 65.95 % ; H, 10.06 %

Found : C, 65.83 % ; H, 10.23 %

(1R,Rs)-(+)-S-Methyl-S-exo-2-bornyl-N-tosyl sulfoximine, (9b)

A mixture of (1R,Rs)-(-)-S-Methyl-S-exo-2-bornyl sulfoxide (8b; 5.16g, 26 mmol), tosyl azide (10.8 g, 55 mmol) copper powder (1.10g) and dry methanol (30 mL) was heated at 55°C for 42 h (Reaction was monitored by TLC and ^{1}H NMR). After distilling off methanol, the residue was stirred with a saturated solution of Na_2EDTA (80 mL) for 30 minutes. The reaction mixture was extracted with chloroform (120 mL). The chloroform solution was treated with charcoal (3g), filtered, washed with sodium hydroxide solution (10 %, 50 mLx2 ; to remove the by product p-toluene sulfonamide) and water (40 mLx2), dried (Na_2SO_4) and freed from solvent. The residue (11.25 g) was purified by column chromatography over silica gel (eluent, n-hexane:acetone, 80:20) to give pure sulfoximine (9b ; 7.8 g, 82 % yield). The column pure product was recrystallised thrice from hexane:acetone (80:20), absolute ethanol and acetonitrile : water (85:15) into nice crystals.

m.p. : 141-142°C (Decomposed)

$[\alpha]_D$ +31.07 (c, 2.73)

IR (Nujol) : 1600, 1380, 1320, 1285, 1220, 1148, 1055, 1030, 820, 780, 710, 660 cm^{-1} (Fig 13)

^{1}H NMR (300 MHZ, $CDCl_3$) : (δ), 0.81, 0.91, 1.07 (3H each, s, total 9H; All -C-CH_3), 2.38(3H, s, Ar-CH_3), 3.3

(3H, s, -S-C$\underline{H}_3$), 3.42(1H, t; J=9HZ : -$\underline{H}$C-S
7.23, 7.80(2H each, d, J=8.4 HZ; Ar-C$\underline{H}$)
(Fig 10)

^{13}C NMR ($CDCl_3$) :δ12.78, 20.04, 20.32, 21.32 (All -C-C$\underline{H}_3$), 44.43 (-S-C$\underline{H}_3$), 26.19, 31.78, 39.70(All -C-C$\underline{H}_2$), 41.42 (C-C$\underline{H}$), 71.79(-C$\underline{H}$-S-), 47.74, 53.43(-C-),126.28, 128.93(4C, all Ar-C$\underline{H}$), 140.93, 142.19(All Ar-C-)
(Fig 15)

EIMS, M/Z (%) : 369 (M^+,1), 234(7), 155(34), 137(78), 121(28), 107(15), 93(53), 91(100), 81(85), 67(17)

Microanalysis : $C_{18}H_{27}NO_3S_2$ Requires : C, 58.5 % ; H, 7.36 % ; N, 3.77 %
Found : C, 58.21 % ; H, 7.32 % ; N, 3.52 %

X-ray structure analysis : The structure of the sulfoximine 9b was established by single crystal X-ray structure analysis (ORTEP, Fig. 19). The absolute configuration at chiral sulfur was found to be (R). Details are furnished later in this section.

(1R,Ss)-(-)-S-Methyl-S-exo-2-bornyl-N-tosyl sulfoximine, (9a)

A mixture of (1R,Ss)-(-)-S-Methyl-S-exo-2-bornyl sulfoxide (8a; 4.77 g, 23.9 mmol), tosyl azide (14.1 g, 71.6 mmol), copper powder (1.9 g) and dry methanol (30 mL) was heated at 55^{o}C for

60h. After work up as described earlier, crude product (8.3g) was purified by column chromatography over silica gel (Eluent, n-hexane:acetone, 80:20) to give pure sulfoximine, (9a; 2.65g, 53.4 % yield based on consumed sulfoxide) and unreacted sulfoxide (8a, 2.08g). The column pure product was recrystallized from absolute ethanol and acetonitrile : water (85:15) into nice crystalline product.

m.p. : 126 - 127°C

$[\alpha]_D$ -119.27 (c, 2.49)

IR (Nujol) : 1600, 1380, 1305, 1225, 1150, 1075, 780, 700 cm^{-1} (Fig 12)

^1H NMR ($CDCl_3$) : (δ), 0.85, 0.96, 1.20 (3H each, s, total 9H, All -C-C<u>H</u>$_3$), 2.39 (3H, s, Ar-C<u>H</u>$_3$), 3.29 (1H; t, J=9HZ, -C<u>H</u>-S-), 3.46(3H, s, -S-C<u>H</u>$_3$), 7.25, 7.82 (2H each; d, J=8.2 HZ; 4 Ar-C<u>H</u>)(Fig 11)

^{13}C NMR ($CDCl_3$) : (δ), 12.79, 20.19, 20.52, 21.33 (All -C-C<u>H</u>$_3$), 43.90 (-S-C<u>H</u>$_3$), 26.32, 32.78, 40.08(All -C-C<u>H</u>$_2$), 44.21 (-C-C<u>H</u>-), 73.87(-HC-S-), 47.99, 51.91 (All-C-), 125.89, 128.77 (Four Ar-CH), 140.88, 141.97 (Quat Ar-C-) (Fig 14)

EIMS, M/Z (%) : 370 (M^++H, 11), 368(M^+-H, 12), 354(2), 296(4), 234(100), 216(31), 202(5), 187(4), 172(4), 149(3), 131(4)

HRMS : Exact mass, (M^++1) : 370.1506

$C_{18}H_{28}NO_3S_2$ Requires : 370.1511

Exact mass, (M^+-1) : 368.1367

$C_{18}H_{26}NO_3S_2$ Requires : 368.1354

(Fig 16 to 18)

General procedure for the preparation of oxiranes using 9a and 9b

To a mixture of sodium hydride (0.12 g, 50 % oil dispersion, 2.4 mmol, washed thrice with dry n-hexane) in dry DMSO (10 mL) under dry nitrogen atmosphere was added optically pure S-methyl-S-exo-2-bornyl-N-tosyl sulfoximine, 9a or 9b (0.82 g, 2.2 mmol) in dry DMSO (10 mL) and the mixture stirred at 30-40^{o}C for 4 to 7 h. To the sodium methylide solution in DMSO was added the required carbonyl compounds (10 - 13) in dry DMSO (2 mL) and the mixture stirred at 30-40^{o}C for 2 to 22 h. The reaction was as usual monitored by GC (disappearance of starting material). The reaction mixture was cooled to 10^{o}C, diluted with water (25 mL), extracted with hexane (10 mLx5), the combined organic layer washed with water (20 mLx2), dried (anhydrous sodium sulfate) freed from solvent and the residue distilled under reduced pressure. The products were identified by spectroscopic methods (^{1}H NMR, IR). The enantiomeric excesses were determined by GC on chiral cyclodex B capillary column.

The yields of the product oxiranes and ee achieved using 9a is given in Table 1 and 9b is given in Table 2.

Asymmetric synthesis of oxiranes using (1R,Rs)-(+)-S-methyl-S-exo-2-bornyl-N-tosyl sulfoximine, (9b)

(i) (S)-(-)-Phenyloxirane (14) : A mixture of sodium hydride (0.12 g, 50 % oil dispersion, 2.4 mmol) in DMSO and sulfoximine was stirred at room temperature for 4.5h. Freshly distilled benzaldehyde (0.21g, 2 mmol) in DMSO (2 mL) was added and stirred for 1h at room temperature. After work up as above gave pure (S)-(-)-phenyl oxirane (14; 0.09g, 40 % yield).

Chiral GC : Peak No.1 : (R)-(+)-isomer = 35.75 %
Peak No.2 : (S)-(-)-isomer = 64.25 %
ee = 28.5 %

(ii) (S)-(-)-(4-Chlorophenyl) oxirane, (15) : Follow exactly the same procedure as in (i) using P-chlorobenzaldehyde 11 as the substrate. After work up obtained pure oxirane (15 ; 0.15 g, 55 % yield)

Chiral GC : Peak No.1 : (R)-(+)-isomer = 40.8 %
Peak No.2 : (S)-(-)-isomer = 59.2 %
ee = 18.6 %

(iii) (+)-2-Methyl-2-phenyloxirane, (16) : Acetophenone (0.24g, 2mmol) was treated with sodium salt of 9b (2.2 mmol) and stirred at 30-35^{o}C for 20 h. After work up as above gave desired product (16; 0.17 g, 65 % yield).

Chiral GC : Peak No.1 : (+)-isomer = 78.5 %

Peak No.2 : (-)-isomer = 21.5 %

ee = 57.0 %

(iv) (+)-2-(4-Chlorophenyl)-2-isopropyl oxirane, (17) : The carbanion of 9b and P-chloroisobutyrophenone 13 stirred at room temperature for 18h. work up as above gave pure product (17; 0.275 g, 70 % yield).

Chiral GC : Peak No.1 : (+)-isomer = 84.1 %

Peak No.2 : (-)-isomer = 15.9 %

ee = 68.2 %

Asymmetric synthesis of oxiranes using (1R,Ss)-(-)-S-methyl-S-exo-2-bornyl-N-tosyl sulfoximine, (9a)

Reactions of carbonyl compounds with carbanion of 9a were generally slower compare to S-neomenthyl sulfoximines. The isolated yields of oxiranes were also comparatively lower.

(i) (S)-(-)-Phenyloxirane (14) : A mixture of sodium hydride (2.4 mmol, 0.12g) and 9a (2.2 mmol) in dry DMSO (10 mL) was stirred at 40^{o}C for 6h. Freshly distilled benzaldehyde (0.21 g, 2 mmol) was added at room temperature and stirred at 40^{o}C for 5h. Work up as usual gave desired product (14 ; 0.06g, 25 % yeild).

Chiral GC : Peak No.1 : (R)-(+)-isomer = 35.69 %

Peak No.2 : (S)-(-)-isomer = 64.31 %

ee = 28.62 %

(ii) (S)-(-)-(4-Chlorophenyl) oxirane, (15) : Followed exactly the same procedure as in (i) above. Yield : 23 %

Chiral GC : Peak No.1 : (R)-(+)-isomer = 39.15 %

Peak No.2 : (S)-(-)-isomer = 60.85 %

ee = 21.70 %

(iii) (-)-2-Methyl-2-phenyloxirane, (16) : Reaction of 9a with acetophenone remain sluggish. The reaction was repeated three times, but all the time reaction was not completed and unreacted acetophenone was interfering in chiral GC analysis (A third peak of acetophenone near second isomer of 16).

(iv) (-)-2-(4-Chlorophenyl)-2-isopropyl oxirane, (17) : Sodium methylide of 9a treated with p-chloroisobutyrophenone at 35-40^{o}C for 22h. After usual work up gave desired product (17; 0.28, 52.3 % yield).

Chiral GC : Peak No.1 : (+)-isomer = 20.92 %

Peak No.2 : (-)-isomer = 79.07 %

ee = 58.2 %

(1R,Rs)-(+)-S-Methyl-S-exo-2-bornyl-N-Tosyl Sulfoximine (9b)

Experimental

Singal Crystal X-ray Structural analysis*

Data Collection

A colorless needle crystal of $C_{18}H_{27}NO_3S_2$ having approximate dimensions of 0.10 x 0.10 x 0.80 mm was mounted on a glass fiber. All measurements were made on an Enraf-Nonius CAD4 diffractometer with graphite monochromated Cu-Kα radiation.

Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 25 carefully centered reflections in the range $10.00 < 2\theta < 40.00°$ corresponded to a primitive monoclinic cell with dimensions:

a = 15.2781(9) Å
b = 7.635(1) Å β = 110.958(4)°
c = 17.764(1) Å
V = 1935.1(3) Å^3

For Z = 4 and F.W. = 369.54, the calculated density is 1.27 g/cm^3. Based on the systematic absences of:

0k0: k ≠ 2n

packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be:

$P2_1$ (#4)

The data were collected at a temperature of 23 ± 1°C using the ω-2θ scan technique to a maximum 2θ value of 149.8°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.30° with a take-off angle of 2.8°. Scans of (0.65 + 0.14 tan θ)° were made at a speed of 16.5°/min (in omega). The weak reflections ($I < 3.0\sigma(I)$) were rescanned (maximum of 1 scans) and the counts were accumulated to ensure good counting statistics. Moving-crystal moving counter background measurements were made by scanning an additional 25% above and below the scan range. The counter aperture consisted of a variable horizontal slit with a width ranging from 2.0 to 2.5 mm and a vertical slit set to 2.0 mm. The diameter of the incident beam collimator was 0.7 mm and the crystal to detector distance was 17.3 cm. For intense reflections an attenuator was automatically inserted in front of the detector.

Data Reduction

Of the 4287 reflections which were collected, 4217 were unique (R_{int} = 0.014). The intensities of three representative reflection were measured after every 120 minutes of X-ray exposure time. No decay correction was applied.

The linear absorption coefficient, μ, for Cu-Kα radiation is 29.4 cm^{-1}. Azimuthal scans of several reflections indicated no need for an absorption correction. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient = 9.94157e-07).

* See Notes on Page No. 154

Structure Solution and Refinement

The structure was solved by direct methods[1] and expanded using Fourier techniques[2]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement[3] was based on 1833 observed reflections ($I > 3.00\sigma(I)$) and 432 variable parameters and converged (largest parameter shift was 0.01 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma||Fo| - |Fc||/\Sigma|Fo| = 0.050$$

$$R_w = \sqrt{(\Sigma w(|Fo| - |Fc|)^2/\Sigma wFo^2)} = 0.053$$

The standard deviation of an observation of unit weight[4] was 2.64. The weighting scheme was based on counting statistics and included a factor (p = 0.010) to downweight the intense reflections. Plots of $\Sigma w(|Fo| - |Fc|)^2$ versus $|Fo|$, reflection order in data collection, $\sin\theta/\lambda$ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.34 and -0.33 $e^-/\AA^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[5] . Anomalous dispersion effects were included in Fcalc[6]; the values for Δf' and Δf" were those of Creagh and McAuley[7]. The values for the mass attenuation coefficients are those of Creagh and Hubbel[8]. All calculations were performed using the teXsan[9] crystallographic software package of Molecular Structure Corporation.

References

(1) SIR92: Altomare, A., Burla, M.C., Camalli, M., Cascarano, M., Giacovazzo, C., Guagliardi, A., Polidori, G. (1994). J. Appl. Cryst., in preparation.

(2) DIRDIF92: Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., Garcia-Granda, S., Gould, R.O., Smits, J.M.M. and Smykalla, C. (1992). The DIRDIF program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

(3) Least-Squares:

Function minimized: $\Sigma w(|Fo| - |Fc|)^2$

where w = $\frac{1}{\sigma^2(Fo)} = \frac{4Fo^2}{\sigma^2(Fo^2)}$

$\sigma^2(Fo^2) = \frac{S^2(C+R^2B)+(pFo^2)^2}{Lp^2}$

S = Scan rate

C = Total integrated peak count

R = Ratio of scan rime to background counting time

B = Total background count

Lp = Lorentz-polarization factor

p = p-factor

(4) Standard deviation of an observation of unit weight:

$$\sqrt{\Sigma w(|Fo| - |Fc|)^2/(No - Nv)}$$

where: No = number of observations

Nv = number of variables

(5) Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

(6) Ibers, J. A. & Hamilton, W. C.; Acta Crystallogr., 17, 781 (1964).

(7) Creagh, D. C. & McAuley, W J .; "International Tables for Crystallography", Vol C. (A.J.C. Wilson. ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, pages 219-222 (1992).

(8) Creagh, D. C. & Hubbell, J.H..; "International Tables for Crystallography", Vol C. (A.J.C. Wilson ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).

(9) teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992).

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{18}H_{27}NO_3S_2$
Formula Weight	369.54
Crystal Color, Habit	colorless, needle
Crystal Dimensions	0.10 X 0.10 X 0.80 mm
Crystal System	monoclinic
Lattice Type	Primitive
No. of Reflections Used for Unit Cell Determination (2θ range)	25 (10.0 - 40.0°)
Omega Scan Peak Width at Half-height	0.30°
Lattice Parameters	a = 15.2781(9)Å b = 7.635(1) Å c = 17.764(1) Å β = 110.958(4)° V = 1935.1(3) Å^3
Space Group	$P2_1$ (#4)
Z value	~~4.00~~ 4
D_{calc}	~~1.427~~ g/cm^3 ~~1.27~~ 1.27 g/cm^3
F_{000}	891.00
μ(CuKα)	29.44 cm^{-1}

B. Intensity Measurements

Diffractometer	CAD4
Radiation	CuKα (λ = 1.54178 Å) graphite monochromated
Attenuator	Ni foil (factor = 26.00)
Take-off Angle	2.8°
Detector Aperture	2.0 - 2.5 mm horizontal 2.0 mm vertical
Crystal to Detector Distance	17.3 mm
Temperature	23.0°C
Scan Type	ω-2θ
Scan Rate	16.5°/min (in ω)
Scan Width	(0.65 + 0.14 tan θ)°
$2\theta_{max}$	149.8°
No. of Reflections Measured	Total: 4287 Unique: 4217 (R_{int} = 0.014)
Corrections	Lorentz-polarization Secondary Extinction (coefficient: 9.94157e-07)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma u(\|Fo\| - \|Fc\|)^2$
Least Squares Weights	$\frac{1}{\sigma^2(Fo)} = \frac{4Fo^2}{\sigma^2(Fo^2)}$
p-factor	0.010
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	1833
No. Variables	432
Reflection/Parameter Ratio	4.24

Residuals: R; Rw	0.050 ; 0.053
Goodness of Fit Indicator	2.64
Max Shift/Error in Final Cycle	0.01
Maximum peak in Final Diff. Map	0.34 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.33 $e^-/Å^3$

Notes :

(1) All X-ray analysis work has been done by Professor G.M. Newton of University of Georgia, Athenes, USA.

(2) All atomic Coordinates, e.s.ds, bond lenghts, bond angles and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre.

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