CHAPTER II

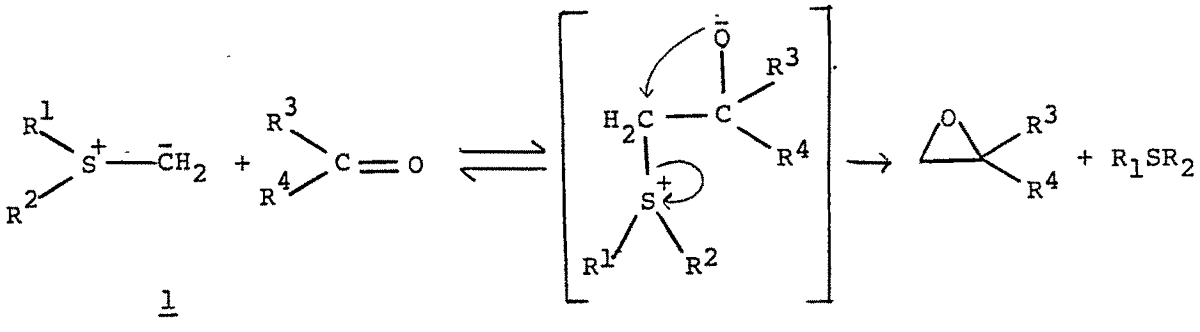
ASYMMETRIC SYNTHESIS OF OXIRANES USING CHIRAL (1R,3S,4S,Ss)-(-)-S-METHYL-S-NEOMENTHYL-N-TOSYL SULFOXIMINE, 10a, AND ITS EPIMER AT SULFUR (1R,3S,4S,Rs)-(+)-10b

A. INTRODUCTION

It is evident from the previous discussion (Chapter I) that asymmetric synthesis of oxiranes is an active and challenging field of research. It has been remarked that "the value of epoxides as synthetic intermediates as well as an end in themselves emphasizes the need and desirability of obtaining these compounds in a high state of enantiomeric purity[1]". With this motivation, we decided to synthesize chiral oxiranes using chiral sulfur compounds.

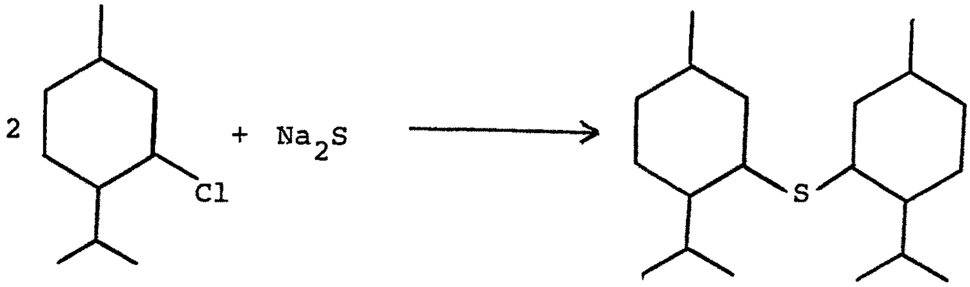
B. STRATEGY

The synthesis of oxiranes by methylene transfer reaction from dimethyl sulfonium methylide and related reagents to carbonyl compounds has been known for over 30 years[2]. The general reaction can be depicted as in Scheme 1.



Scheme 1

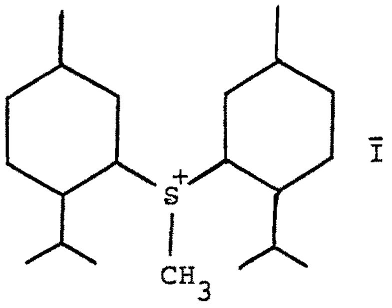
It is apparent from this reaction that transfer of methylene group from sulfur ylide to carbonyl group would lead to the formation of racemic oxirane. We felt that if R1 and R2 in 1 were to be chiral groups, this might influence in inducing asymmetry in the resulting oxiranes. With this in view our initial efforts were directed towards utilising dimenthyl methyl sulfonium iodide 3 and dimenthyl methyl oxosulfonium iodide 4 for the methylene transfer reaction. Although sulfur in these compounds is not stereogenic, we felt that the two menthyl group might help in the stereoselectivity of the reaction to give non-racemic oxiranes. However, our efforts to prepare dimenthyl sulfide 2 from neomenthyl chloride and sodium sulfide (Scheme 2) were not successful as the major product under various reaction conditions was a mixture of p-2-menthene and p-3-menthene.



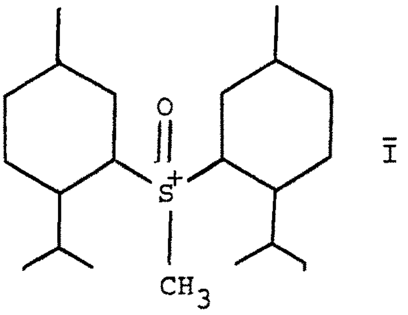
2

Scheme 2

Sulfoximines are another class of methylene transfer reagents used for the synthesis of oxiranes. Attempts at the



3



4

asymmetric synthesis of oxiranes using sulfoximines having stereogenic sulfur have not been very successful[3] (ee, $<$ 40 %). We felt that sulfoximine with suitable chiral ligands could be exploited for the synthesis of chiral oxiranes. In this chapter we present the results of our studies on the enantioselective synthesis of oxiranes in fairly good enantiomeric excess using chiral sulfoximines possessing stereogenicity both on sulfur atom and on carbon atoms of the substituent groups.

There are several favourable features for use of such sulfoximines for asymmetric methylene transfer reactions.

(i) The sulfur atom in the sulfoximine is chiral which may help in inducing asymmetry in oxirane molecule.

(ii) This asymmetric induction power of chiral sulfur atom is further boosted by having suitable chiral ligands on it.

(iii) N-Substituted sulfoximines are stable molecules having long shelf life.

(iv) Presence of tosyl group on nitrogen make the α-hydrogen atom more acidic and upon treatment with a strong base easily furnishes carbanions which form the basis of methylene transfer reaction.

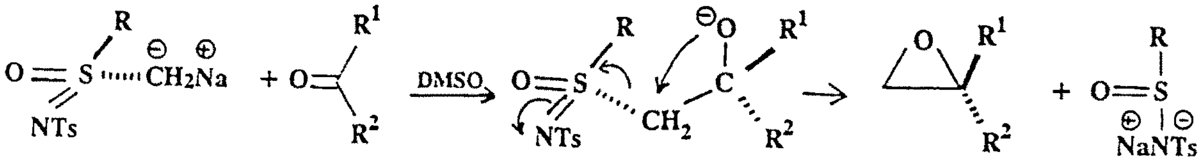
(v) Presence of sulfur and nitrogen atom provide sites for structural variations. This feature of the sulfoximine forms the basis of our work reported in chapter III and IV.

(vi) Optically pure sulfoximine can be easily prepared from optically pure sulfoxide by Kwart-Kahn method[4] with complete retention of configuration at sulfur.

(vii) The configuration on sulfur in sulfoximine is stable. They do not undergo racemization as in the case of chiral sulfonium salts and sulfur ylides.

C. RESULTS AND DISCUSSIONS

As mentioned above, when sulfoximines having chirality only on sulfur were used for the MT reaction, asymmetric induction achieved[3] was less than moderate (ee, $<$ 40 %). The methylene transfer from a S-methyl sulfoximine to carbonyl substrate leading to the formation of an oxirane can be represented as in Scheme 3.



Scheme 3

The stereochemical outcome will be influenced by the stereochemistry of the transition state which in turn will be dependent on the stereochemistry of the reactant sulfoximine. As earlier work[3] has shown that chirality on sulfur of the sulfoximine does have some effect on the chirality of product oxirane, we felt that this effect could be enhanced significantly by having suitable chiral ligands on sulfur. Initially we focussed our attention on the use of (-)-menthol, 5, to provide the menthyl group possessing three stereogenic centers as a ligand on sulfur. Accordingly, we prepared an epimeric pair of new sulfoximines viz., (1R,3S,4S,Ss)-(-)-S-methyl-S-neomenthyl-N-tosyl sulfoximine, 11a, and its epimer at sulfur (1R,3S,4S,Rs)-(+)-S-methyl-S-neomenthyl-N-tosyl sulfoximine, 11b from corresponding sulfoxides 10a and 10b.

The epimeric pair of sulfoxides 10a and 10b were prepared using a published procedure[5]. (1R,3R,4S)-(-)- menthol, 5 was treated with pyridine and tosyl chloride at 0°C to give (1R,3R,4S)-(-)-menthyl tosylate, 6 with retention of configuration at C_3 in 91 % chemical yield (Scheme 4). The tosylate 6, on treatment with potassium thioacetate in dry dimethyl sulfoxide was converted into (1R,3S,4S)-(+)-neomenthyl thioacetate, 7. This reaction, a typical nucleophilic substitution reaction of SN_2 type, was accompanied by inversion of configuration at C_3. The thioacetate, 7, appeared thermolabile as it decomposed slightly at boiling temperature to give p-menthenes as byproducts. On careful distillation it gave product with 98 % GC purity (6',10% SE-30 column, 170^{o}C). The thioacetate 7 on reduction with lithium aluminium hydride gave (1R,3S,4S)-(+)-neomenthanethiol, 8 in 92 % yield with retention of configuration at C_3. The optically active thiol, 8 was converted into (1R,3S,4S)-(+)-S-methyl-S-neomenthyl sulfide, 9 in 94 % yield by reacting it with methyl iodide (GC purity 98 % , 6 ft, 10 % SE-30, 170^{o}C). The sulfide, 9 was subjected to oxidation with hydrogen peroxide to give an epimeric (at sulfur) pair of sulfoxide **10a** and **10b** in 35:65 ratio (GC: cyclodex B capillary column) **(Scheme** 4). One of the epimer 10a could be isolated from the mixture by crystallization from chloroform : petether (5:95) and by repeated crystallization purified to 100 % enantiomeric purity (Chiral GC), $[\alpha]_D$ +140.06. By repeated chilling and separation of the solids by filtration, the mother liquer could be freed from the solid epimer, and enriched to 99 % enantiomeric purity of the second epimer 10b, $[\alpha]_D$ +23.75.

The enantiomeric purity of each epimer 10a and 10b is more then 99 % as revealed from its GC on chiral cyclodex B capillary column. The epimers were separating base to base on this column. The epimer 10a elutes earlier than 10b (Relative retention time (RRT), 10a:10b, 0.98:1).

The most significant difference in the ^{1}H NMR spectra of these epimeric sulfoxides is that the C_3 proton of the crystalline isomer 10a (Fig.1) appears at δ 2.80 whereas in the liquid isomer 10b (Fig.2), it appears at δ 3.28. Both the epimers were well characterised by its ^{13}C NMR spectra. All the eleven carbon atoms, were accounted for. The $\underline{C}H$-S and S-$\underline{C}H_3$ carbon peaks in 10a (Fig. 3 and 4) appearing at δ 59.55 and 47.69 and in 10b (Fig.5) at δ 63.56 and 49.95 respectively. IR spectra of 10a (Fig.6) and 10b (Fig.7) were characterised by a strong band at 1020 and 1035 $cm.^{-1}$ respectively due to S=0 streching vibrations.

The absolute configuration at sulfur of crystalline sulfoxide 10a was established to be (S) by single crystal X-ray structure analysis (For details see experimental). This automatically establishes (R) configuration at sulfur in sulfoxide 10b. The details are discussed in next section D.

The solid sulfoxide 10a on heating with p-toluene sulfonyl azide and freshly precipitated copper powder in dry methanol followed by chromatographic purification and crystallization gave optically pure sulfoximine 11a, $[\alpha]_D$ -60.9. The liquid diastereomer 10b on similar treatment gave corresponding optically pure sulfoximine 11b, $[\alpha]_D$ +101.9.

The sulfoximine 11a after column chromatography was crystallized thrice from different solvent systems, viz., chloroform:hexane (20:80), absolute ethanol and acetonitrile: water (85:15) into beautiful needles of constant m.p.. The

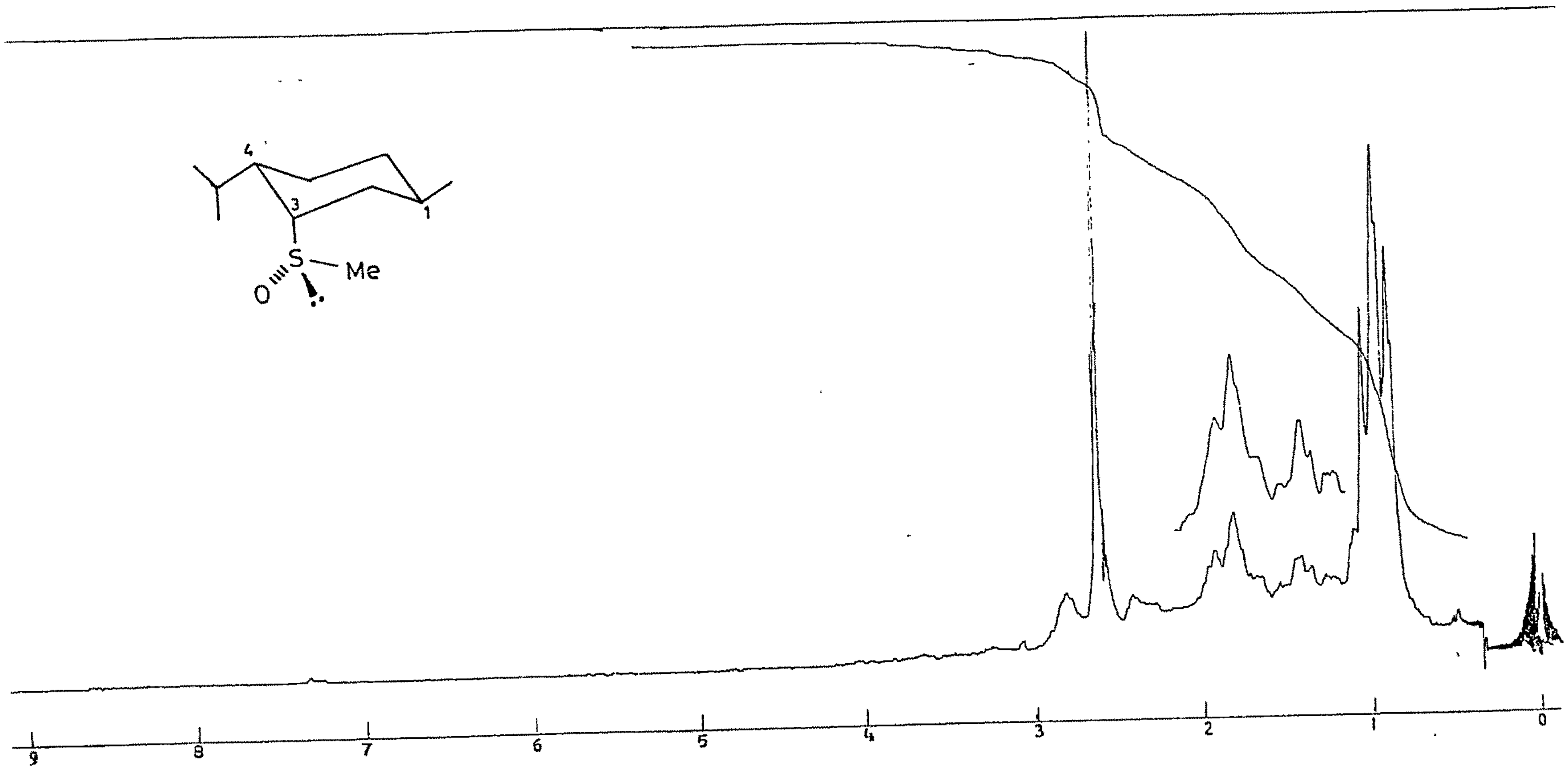


Fig. 1 : ^{1}HNMR Spectrum (90 MHz) of (1R,3S,4S,S_S)-(+)-S-Methyl-S-neomenthyl Sulfoxide (10a)

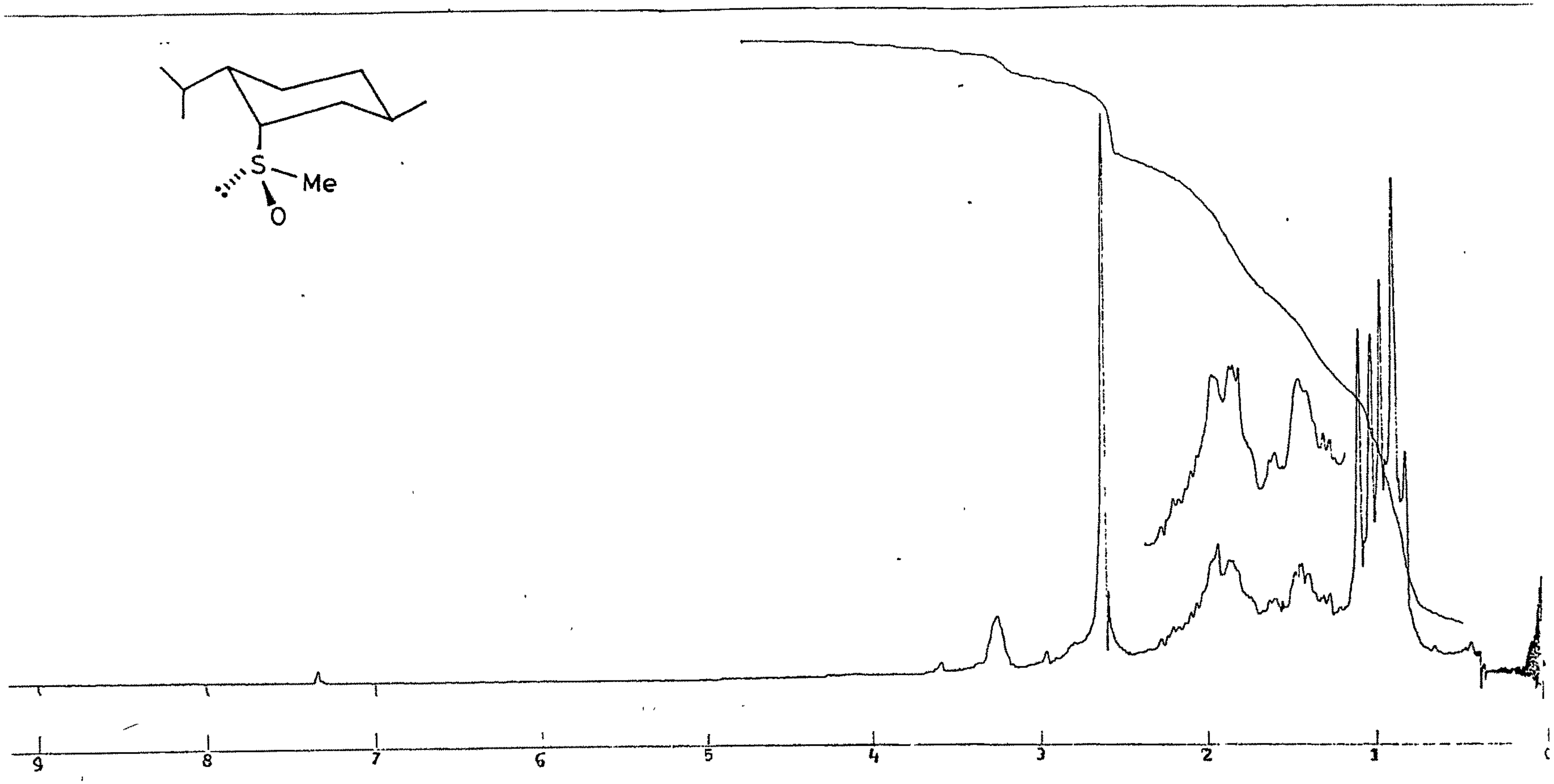


Fig. 2 : ^{1}H NMR Spectrum (90MHz) of (1R,3S,4S,R_S)-(+)-S-Methyl-S-neomenthyl Sulfoxide (10b)

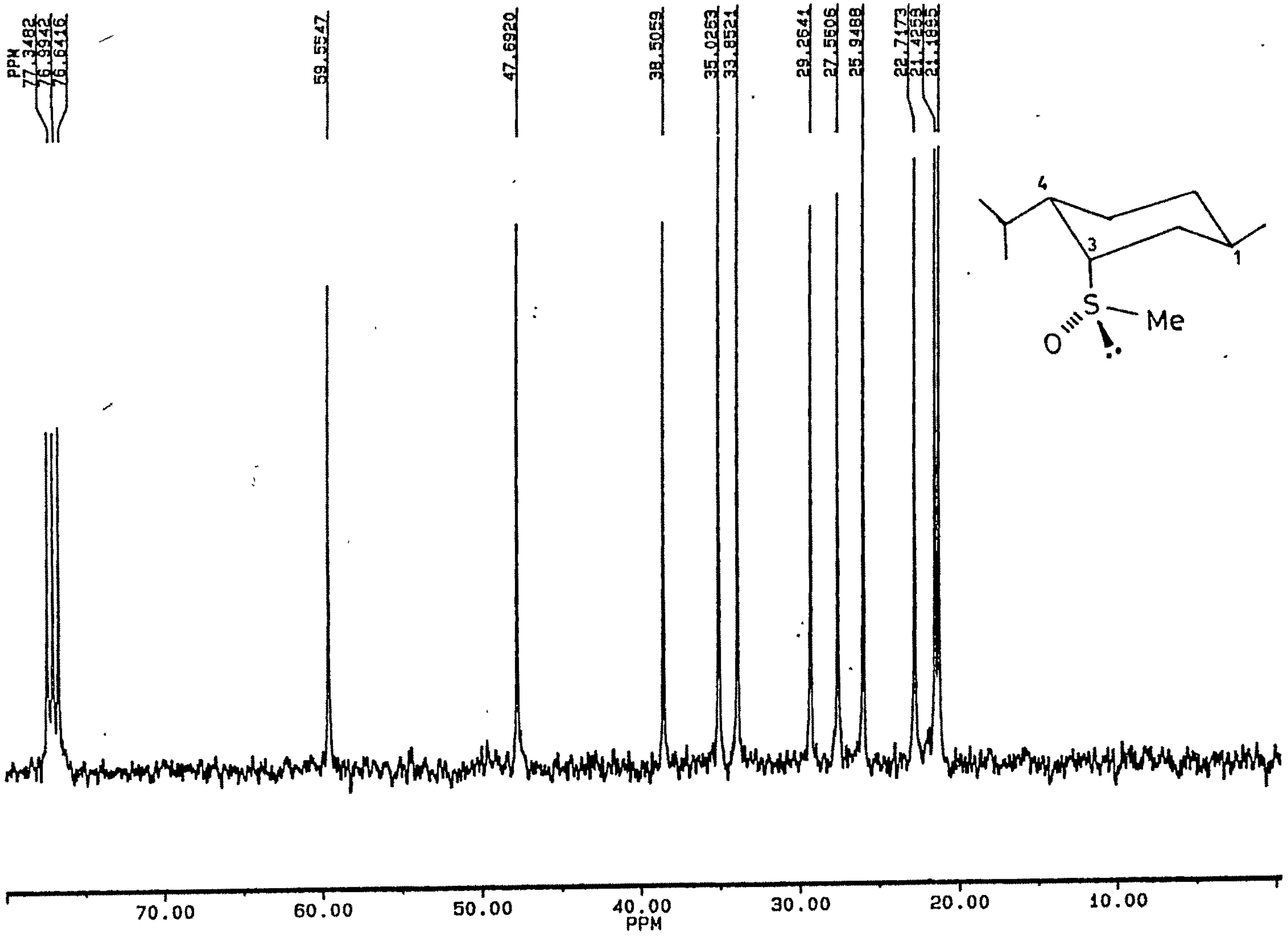


Fig. 3 : ^{13}C NMR Spectrum of (1R,3S,4S,S_S)-(+)-S-Methyl-S-neomenthyl Sulfoxide (10a)

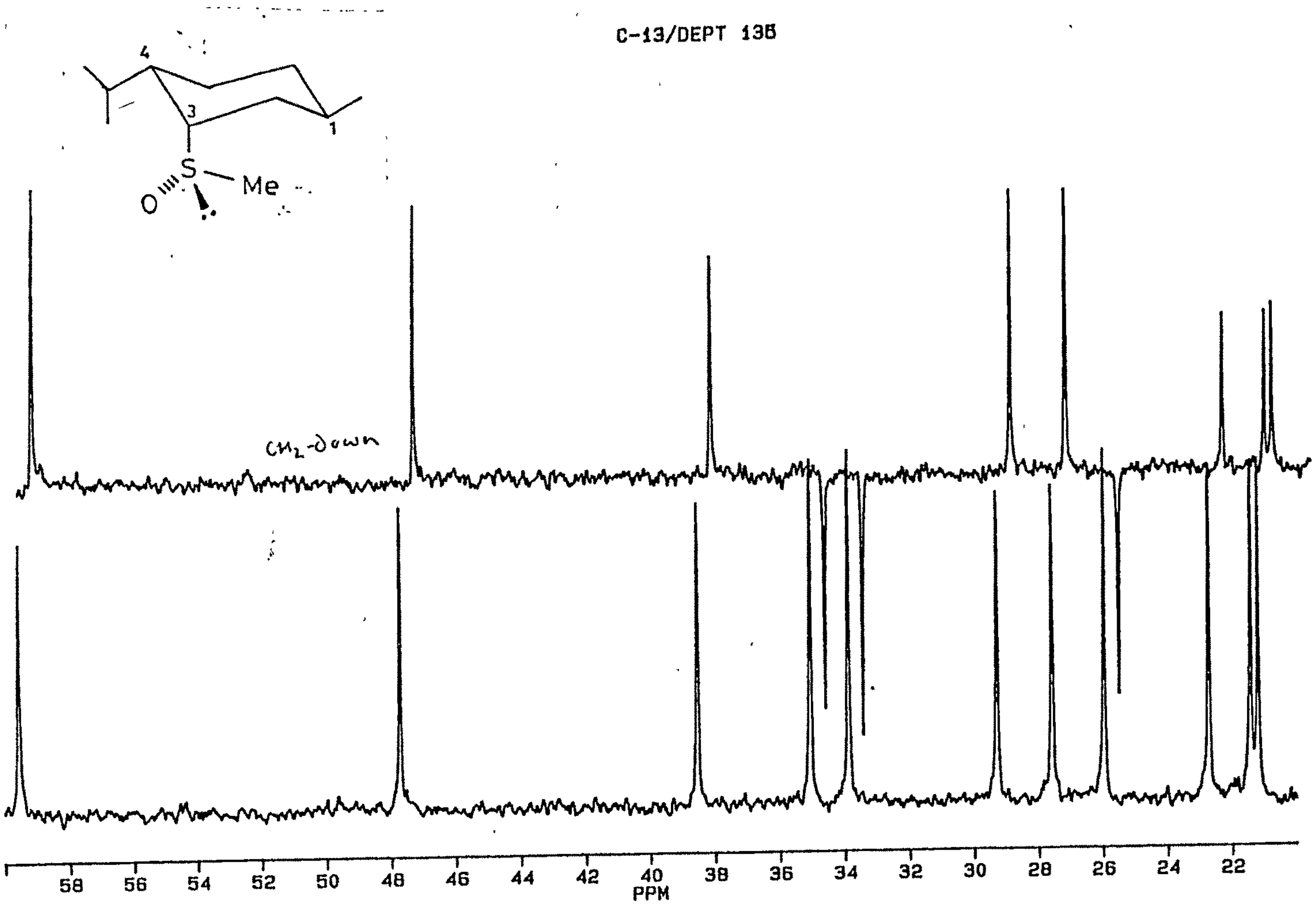


Fig. 4 : ^{13}C NMR Spectrum (DEPT) of (1R,3S,4S,S_S)-(+)-S-Methyl-S-neomenthyl Sulfoxide (10a)

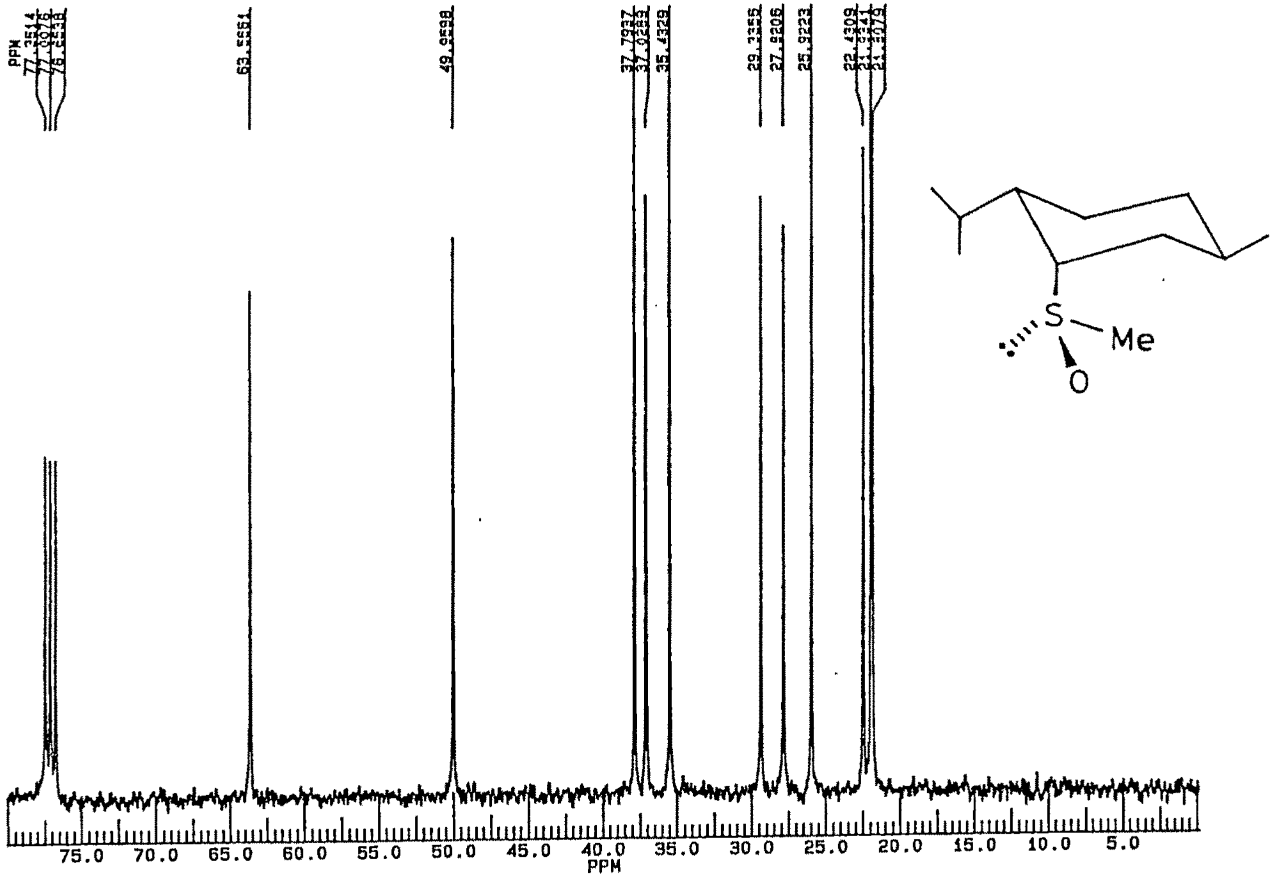


Fig. 5 : ^{13}C NMR Spectrum of (1R,3S,4S,R_S)-(+)-S-Methyl-S-neomenthyl Sulfoxide (10b)

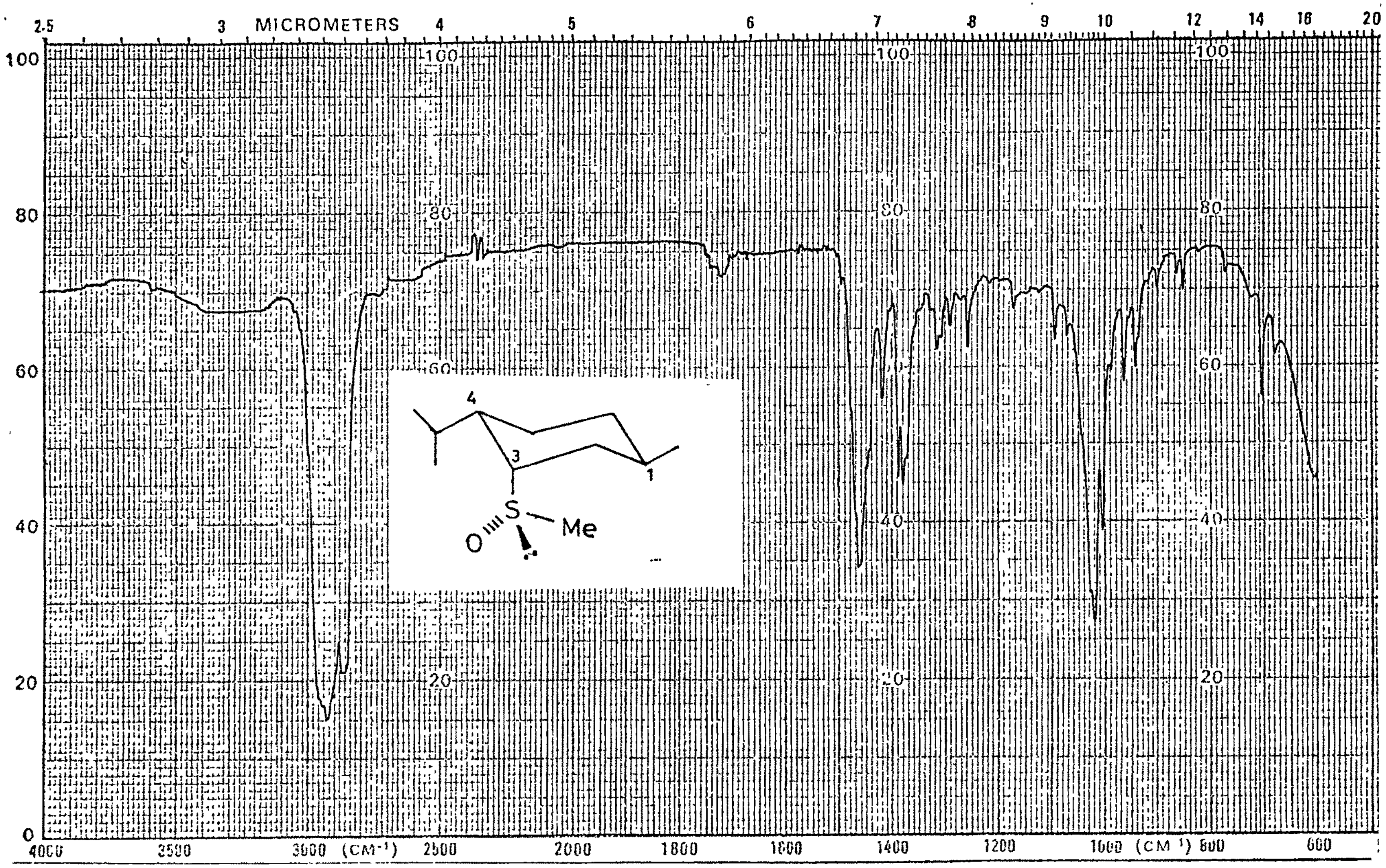


Fig. 6 : IR Spectrum of (1R,3S,4S,S_S)-(+)- -Methyl-S-neomenthyl Sulfoxide (10a)

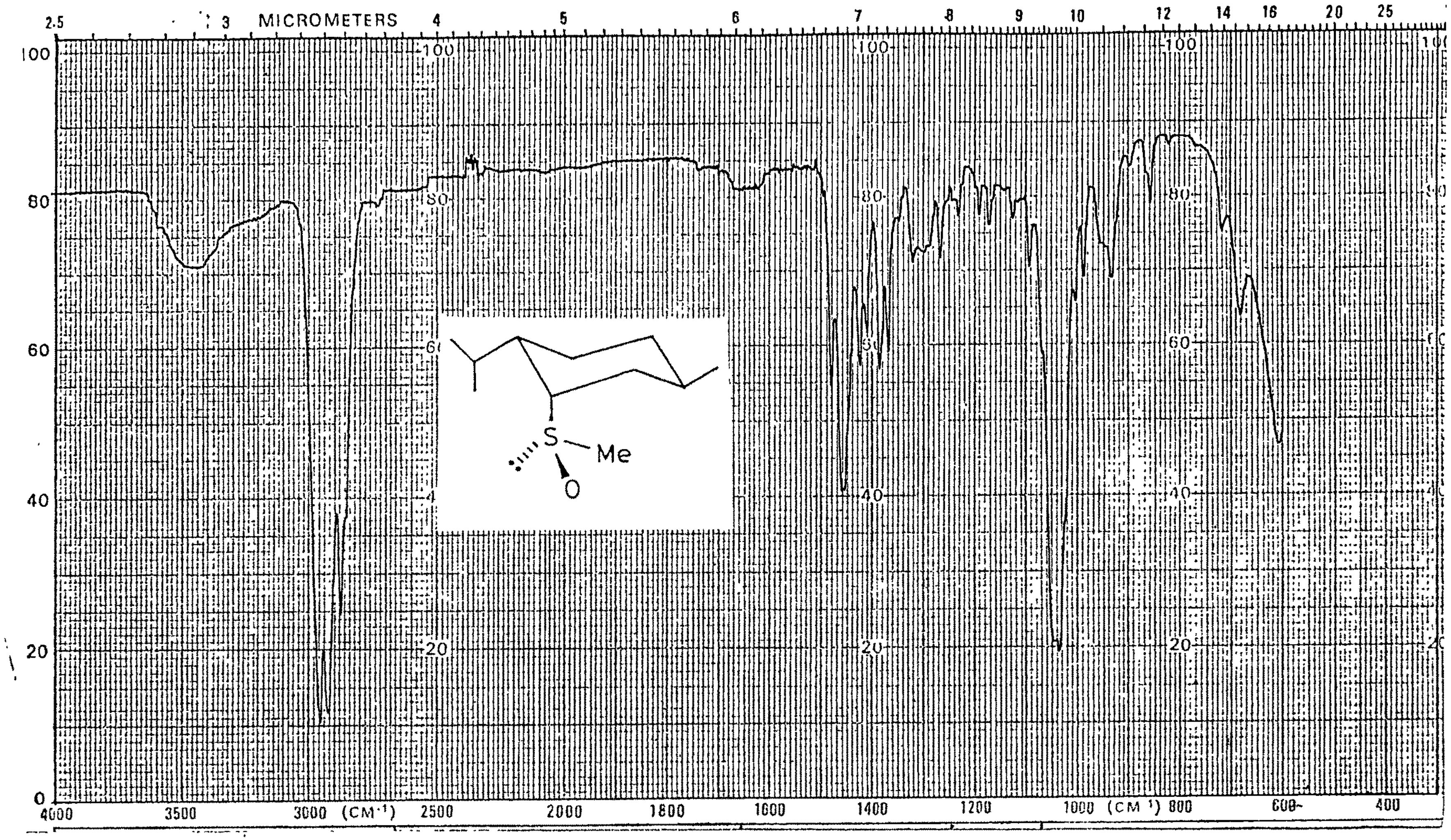
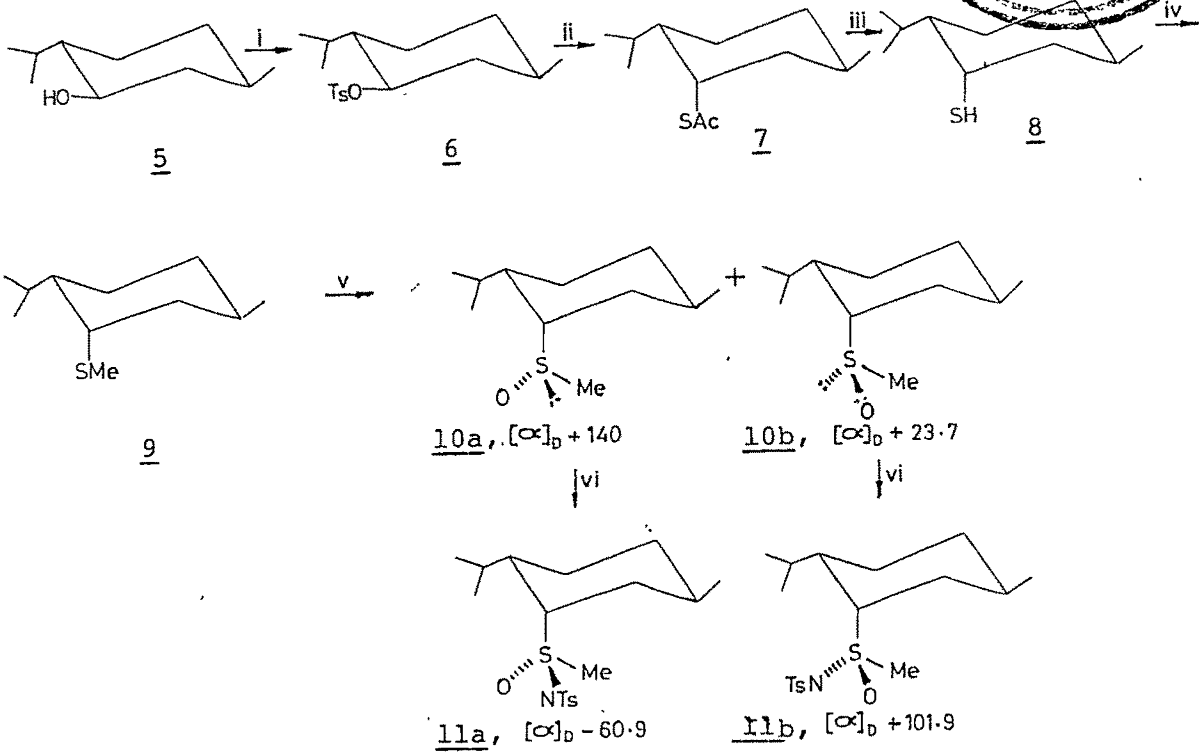


Fig. 7 : IR Spectrum of (1R,3S,4S,R_S)-(+)-S-Methyl-S-neomenthyl Sulfoxide (10b)

optical rotations after each crystallisation remained unaltered



Reagents : i. TsCl/py, 10^{0}C/12h ; ii. KSAc/DMSO, 45^{0}C/44h ; iii. LAH/Et$_2$O, 35^{0}C/6h ; iv. MeONa/MeOH/MeI, 30^{0}C/10h : V. H$_2$O$_2$/AcOH, 25^{0}C/50h ; VI. P-TsN$_3$/Cu/MeOH, 65^{0}C/ 64h

Scheme 4

further confirming the optical purity of the diastereomer. Similarly sulfoximine 11b was recrystallized from relatively dilute solution of chloroform : hexane (8:92) and acetone : petether (6:94) into beautiful tetragonal blocks. The optical rotations after each crystallization remained unaltered proofing its optical purity. The crystal structure of 11b was established by X-ray diffraction method (for details, see experimental) and the absolute configuration at sulfur was found to be (R). This automatically establishes (S) configuration at sulfur in sulfoximine 11a.

The diastereomeric purities of both the sulfoximines 11a and 11b were above 99 % as easily judged from their high resolution ^1H NMR spectra. In 11a, the S-C$\underline{H}_3$ protons appear as a sharp singlet at δ 3.45 and $\underline{H}$C-S proton as a quartet centred at δ 3.78 (Fig.8). The corresponding signals in 11b are seen at δ 3.50 and δ 3.57 respectively (Fig.9 and 10)*. The ^1H NMR spectra of the new compounds 11a and 11b are perfactly matching with its structure[6]. The increased acidity of α - methyl protons of 11a and 11b (S-C$\underline{H}_3$) (Compared to that of sulfoxide 10a and 10b) is reflected in small downfield shift (δ3.45 and 3.50 respectively). The sulfoximine group thus appeared to be slightly more electron withdrawing than the corresponding sulfones and considerably more so than sulfoxide[7]. The C$\underline{H}_3$ protons of tosyl group appear as a

---

* There is a shift of 0.1 PPM (instrumental) towards high field in Fig.9, which is corrected in Fig.10

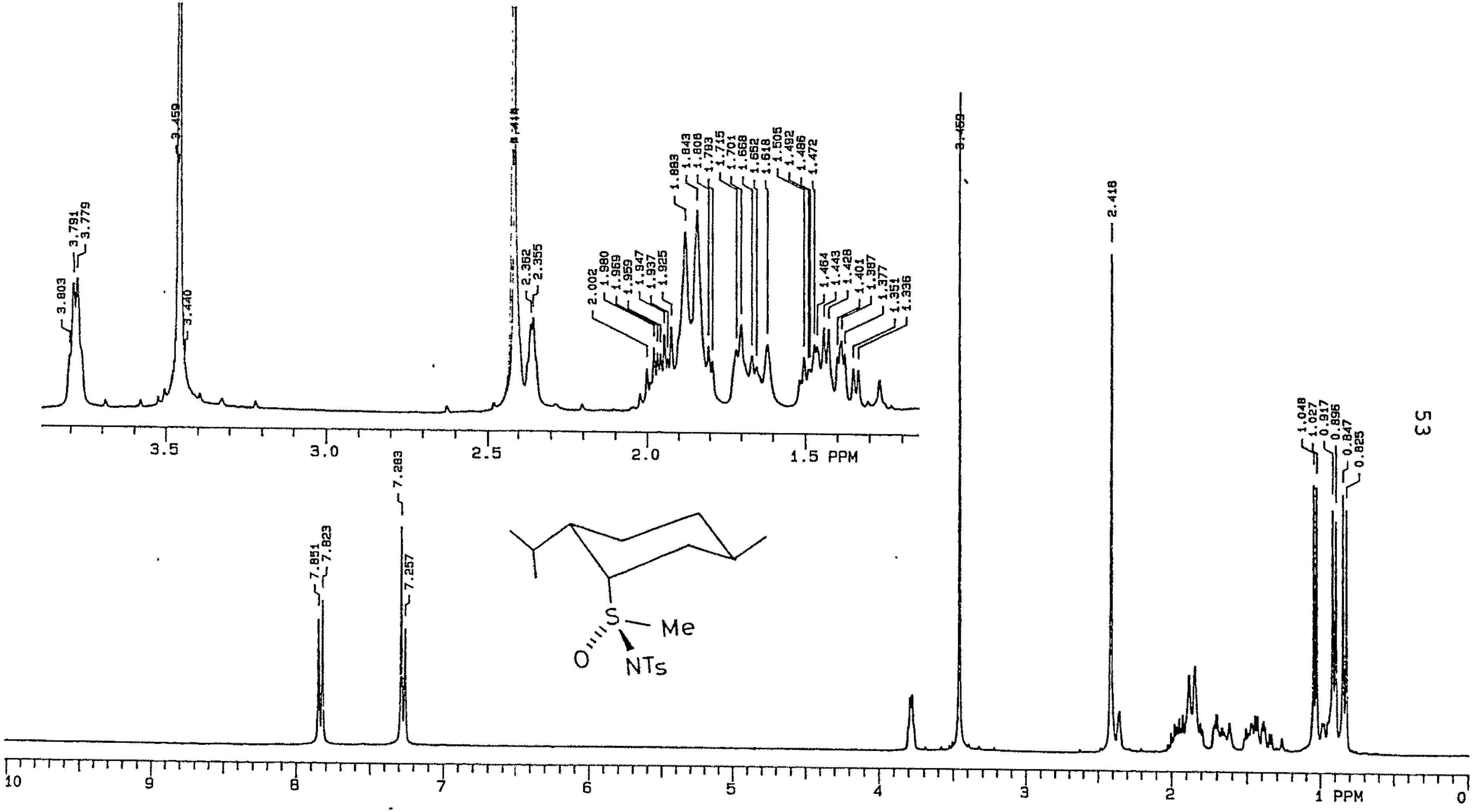


Fig. 8 : ^{1}H NMR Spectrum (300 MHz) of (1R,3S,4S,S_S)-(-)-S-Methyl-S-neomenthyl-N-tosyl Sulfoximine (11a)

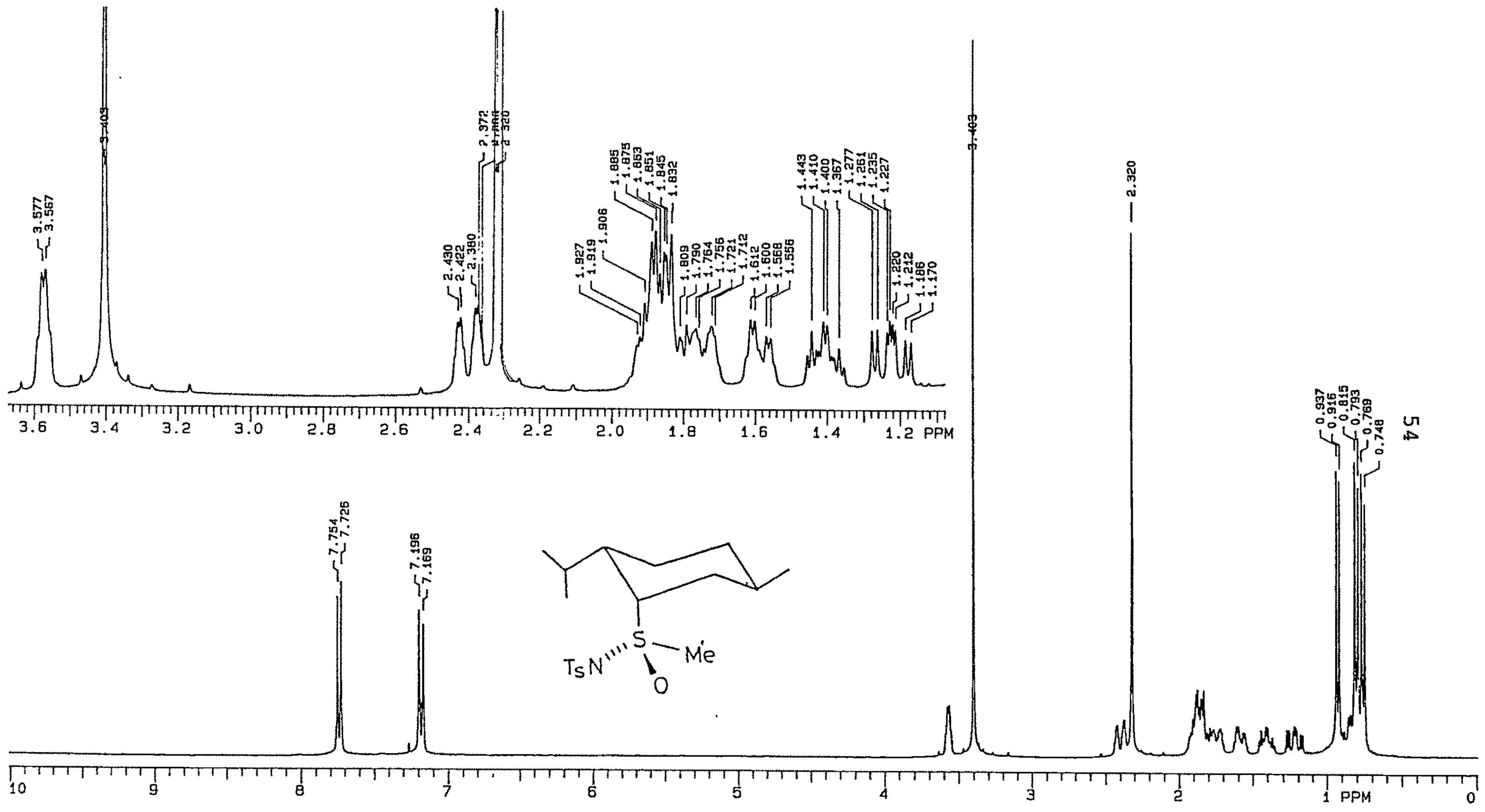
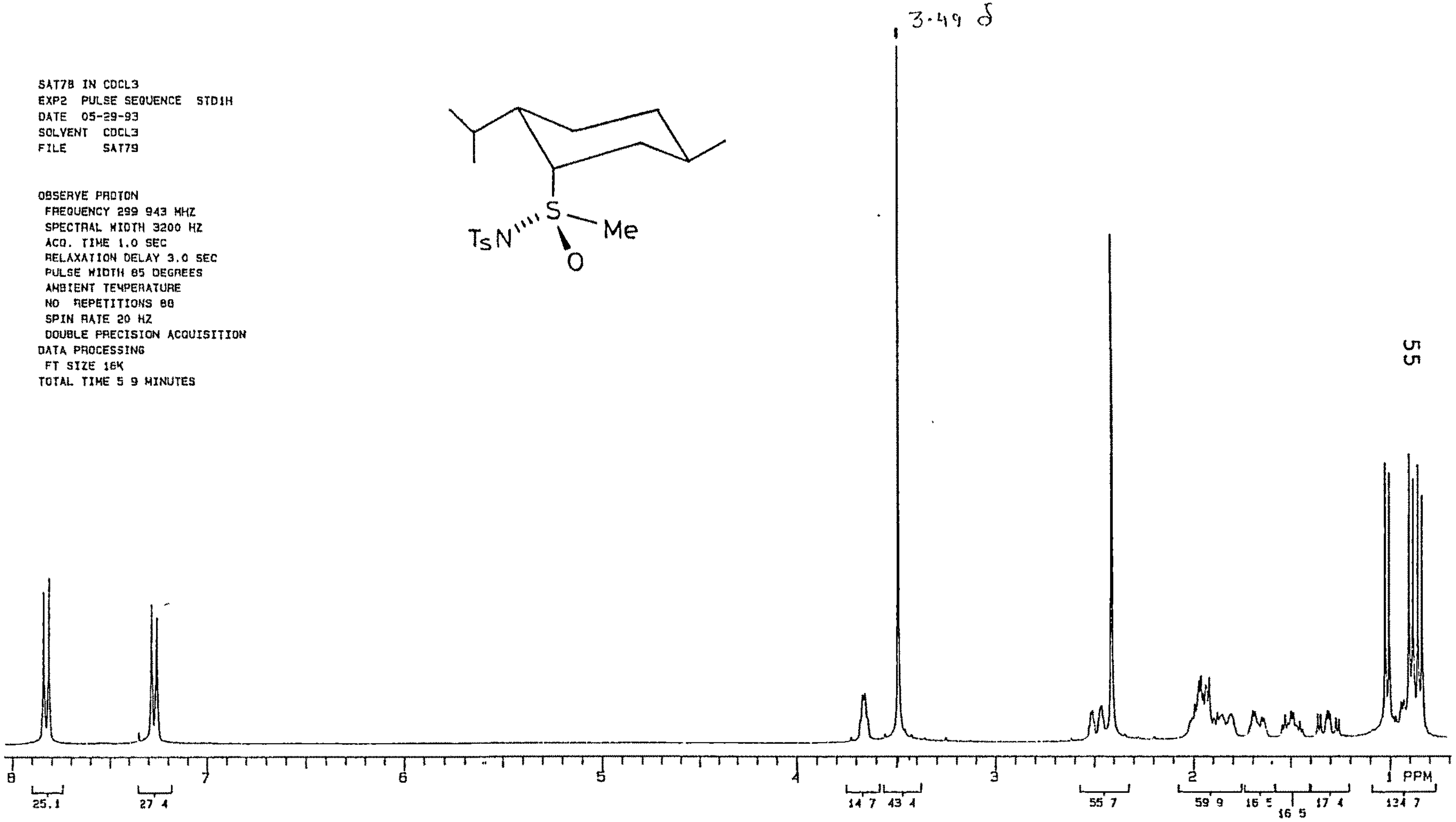


Fig. 9 : ^{1}H NMR Spectrum (300 MHz) of (1R,3S,4S,R_S)-(+)-S-Methyl-S-neomenthyl-N-tosyl Sulfoximine (11b)



```
SAT78 IN CDCL3
EXP2  PULSE SEQUENCE  STD1H
DATE  05-29-93
SOLVENT  CDCL3
FILE     SAT79

OBSERVE PROTON
 FREQUENCY 299 943 MHZ
 SPECTRAL WIDTH 3200 HZ
 ACQ. TIME 1.0 SEC
 RELAXATION DELAY 3.0 SEC
 PULSE WIDTH 85 DEGREES
 AMBIENT TEMPERATURE
 NO  REPETITIONS 88
 SPIN RATE 20 HZ
 DOUBLE PRECISION ACQUISITION
DATA PROCESSING
 FT SIZE 16K
TOTAL TIME 5 9 MINUTES
```

Fig. 10 : ^{1}H NMR Spectrum (300 MHz) of (1R,3S,4S,R_S)-(+)-S-Methyl-S-neomenthyl-N-tosyl Sulfoximine (11b)

sharp singlet at δ 2.42 and δ 2.32 respectively in 11a and 11b[8]. The four aromatic protons of tosyl group splits into double doublet, appearing at δ 7.27 and 7.84 in 11a and δ 7.18 and 7.74 in 11b.

The IR spectra of 11a (Fig.11) and 11b (Fig. 12) show strong bands at 1205 cm^{-1} characteristic of N-S=O streching vibrations[9].

^{13}C NMR spectra of 11a (Fig.13) and 11b (Fig.14 and 15) are perfactly in accordance with its structures. The peak of four aromatic carbon atoms overlapping and appearing as two peaks only. All the eighteen carbon atoms are accounted for. APT experiments could clearly locate all the $-CH_3$, $-CH_2$, -CH and -C- carbon atoms.

The structure of 11a was further supported by its mass spectrum (Fig.16) showing molecular ion peak at 371 confirming its molecular weight. The sulfoximine 11b was characterised by high resolution mass spectrum (Fig 17 & 18). The computer calculated exact mass $(M^{+}+1)$ for $C_{18}H_{30}NO_3S_2$ is 372.1667 and actually observed $(M^{+}+1)$ is 372.1644.

As substrates for this study of asymmetric methylene transfer reactions, we chose phenyl ketones (and benzaldehydes) believing that the resulting chiral oxiranes could be excellent intermediates for preparing a large number of chiral 2 -aryl propionic acids (via the corresponding aldehydes)[10] which in turn

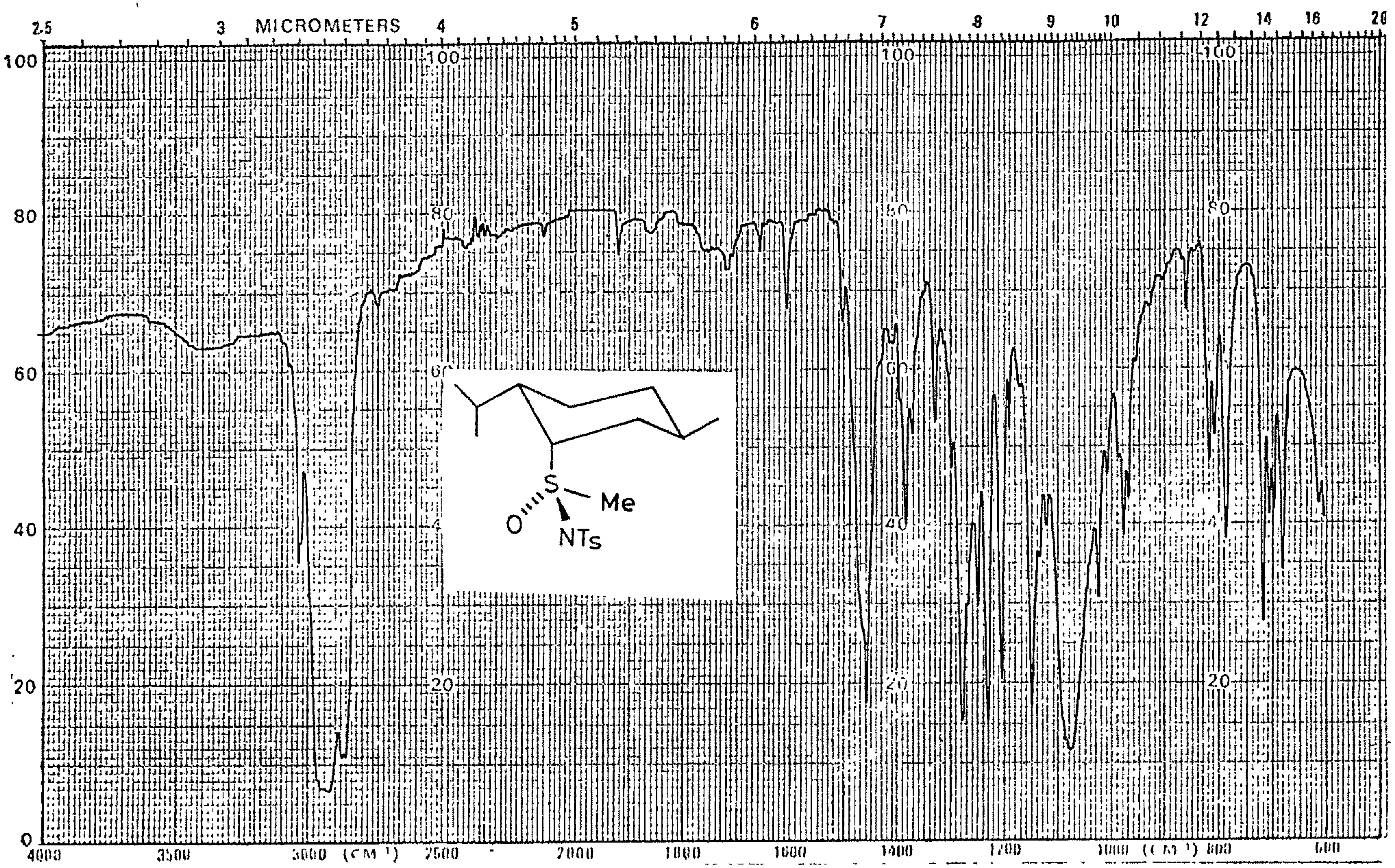


Fig. 11 : IR Spectrum of (1R,3S,4S,S_S)-(-)-S-Methyl-S-neomenthyl-N-tosyl Sulfoximine (11a)

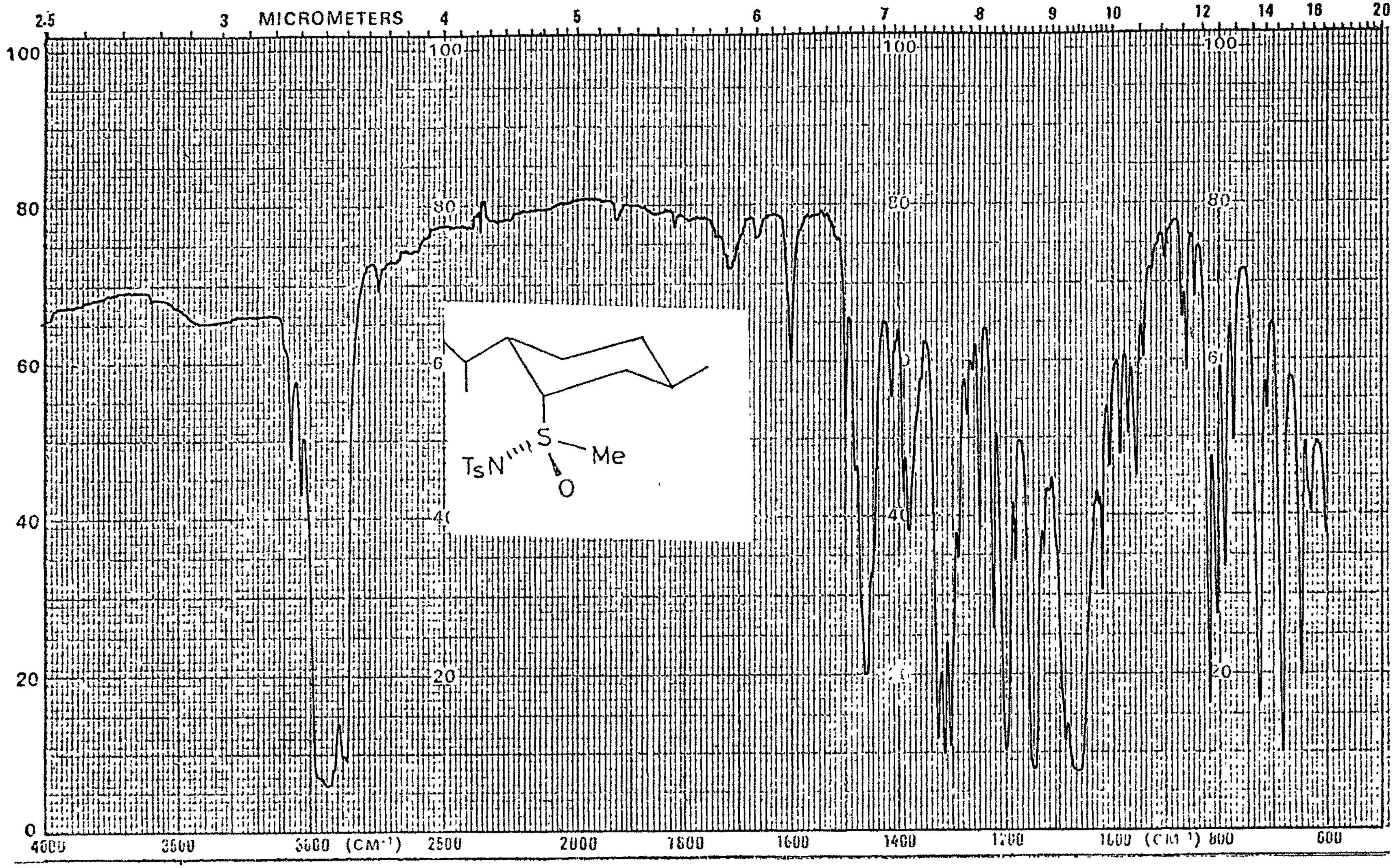


Fig. 12 : IR Spectrum of (1R,3S,4S,R_S)-(+)-S-Methyl-S-neomenthyl-N-tosyl Sulfoximine (11b)

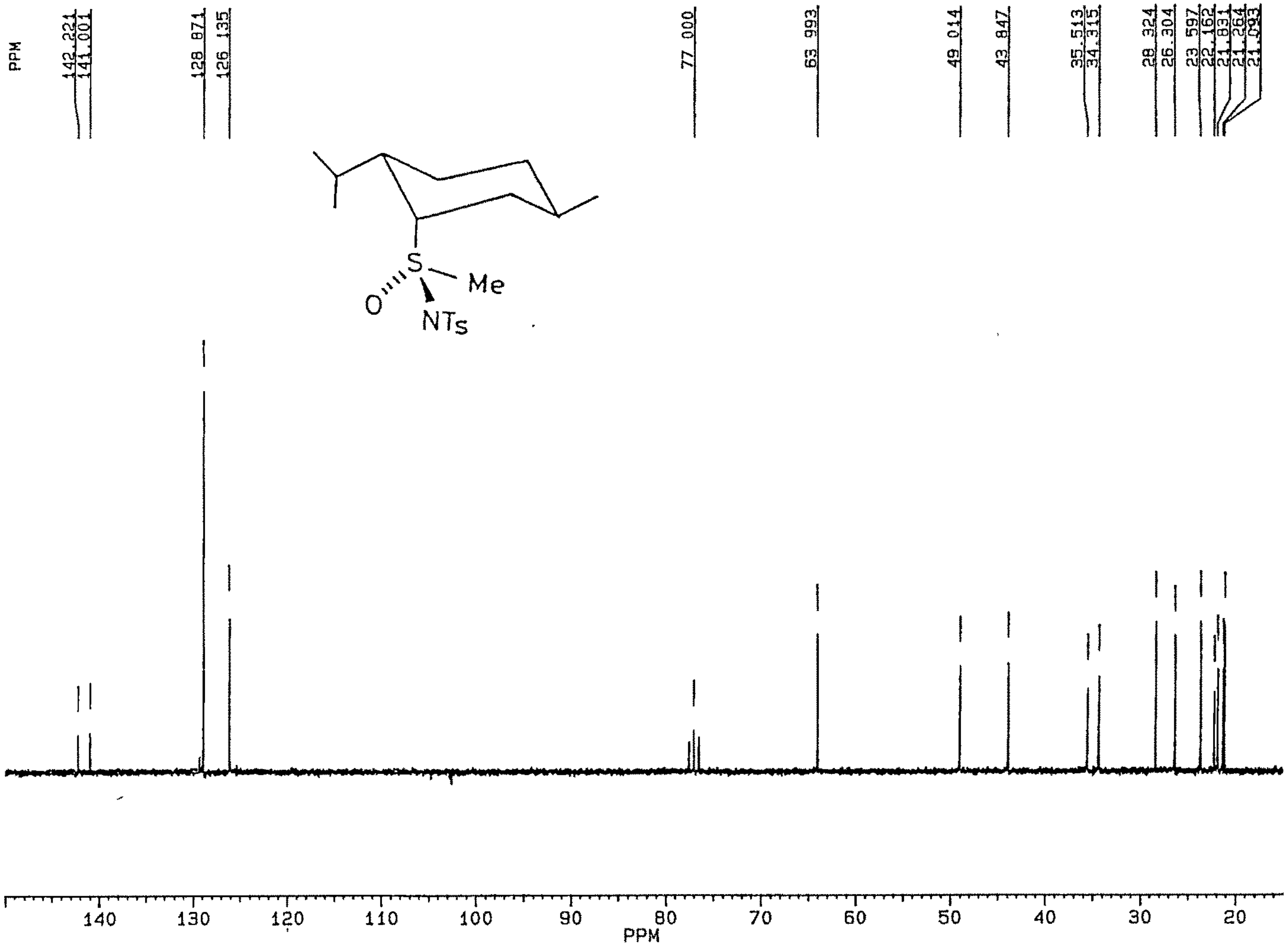
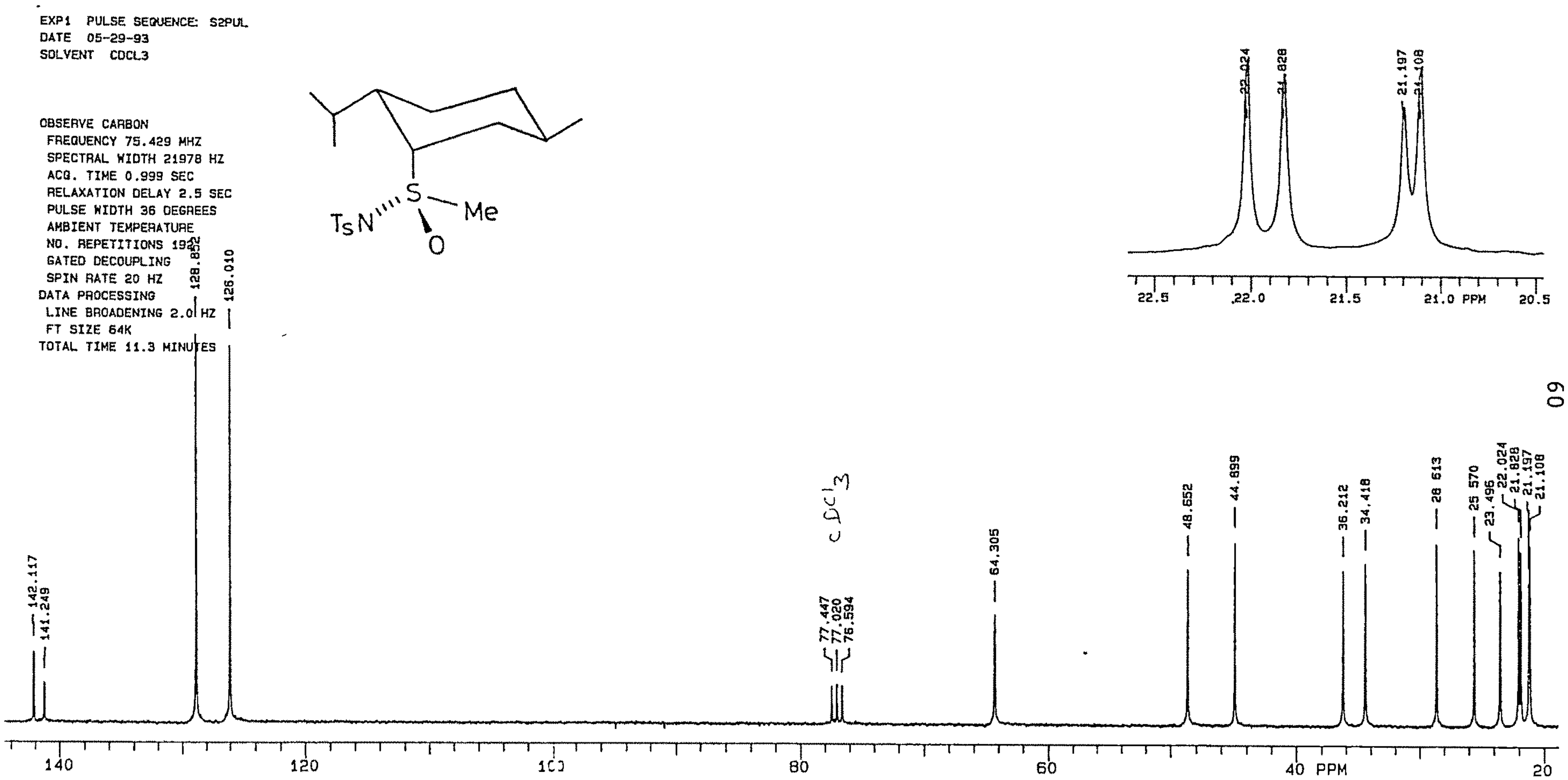


Fig. 13 : ^{13}C NMR Spectrum of (1R,3S,4S,S_S)-(-)-S-Methyl-S-neomenthyl-N-tosyl Sulfoximine (11a)



```
EXP1  PULSE SEQUENCE: S2PUL
DATE  05-29-93
SOLVENT  CDCL3

OBSERVE CARBON
 FREQUENCY 75.429 MHZ
 SPECTRAL WIDTH 21978 HZ
 ACQ. TIME 0.999 SEC
 RELAXATION DELAY 2.5 SEC
 PULSE WIDTH 36 DEGREES
 AMBIENT TEMPERATURE
 NO. REPETITIONS 192
 GATED DECOUPLING
 SPIN RATE 20 HZ
DATA PROCESSING
 LINE BROADENING 2.0 HZ
 FT SIZE 64K
TOTAL TIME 11.3 MINUTES
```

Fig. 14 : ^{13}C NMR Spectrum of (1R,3S,4S,R$_S$)-(+)-S-Methyl-S-neomenthyl-N-tosylSulfoximine (11b)

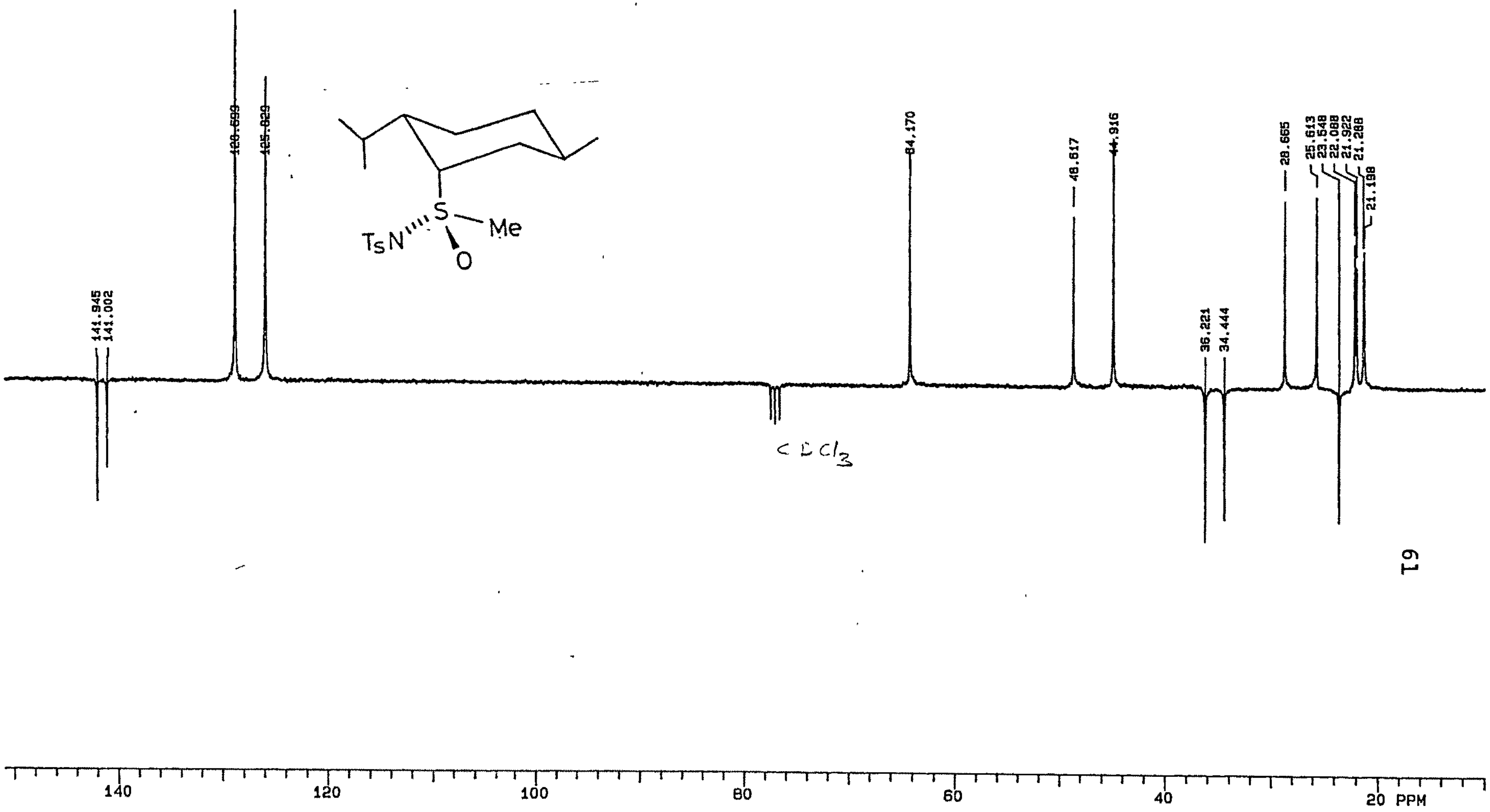


Fig. 15 : ^{13}C NMR Spectrum (APT) of (1R,3S,4S,R_S)-(+)-S-Methyl-S-neomenthyl-N-tosyl Sulfoximine (11b)

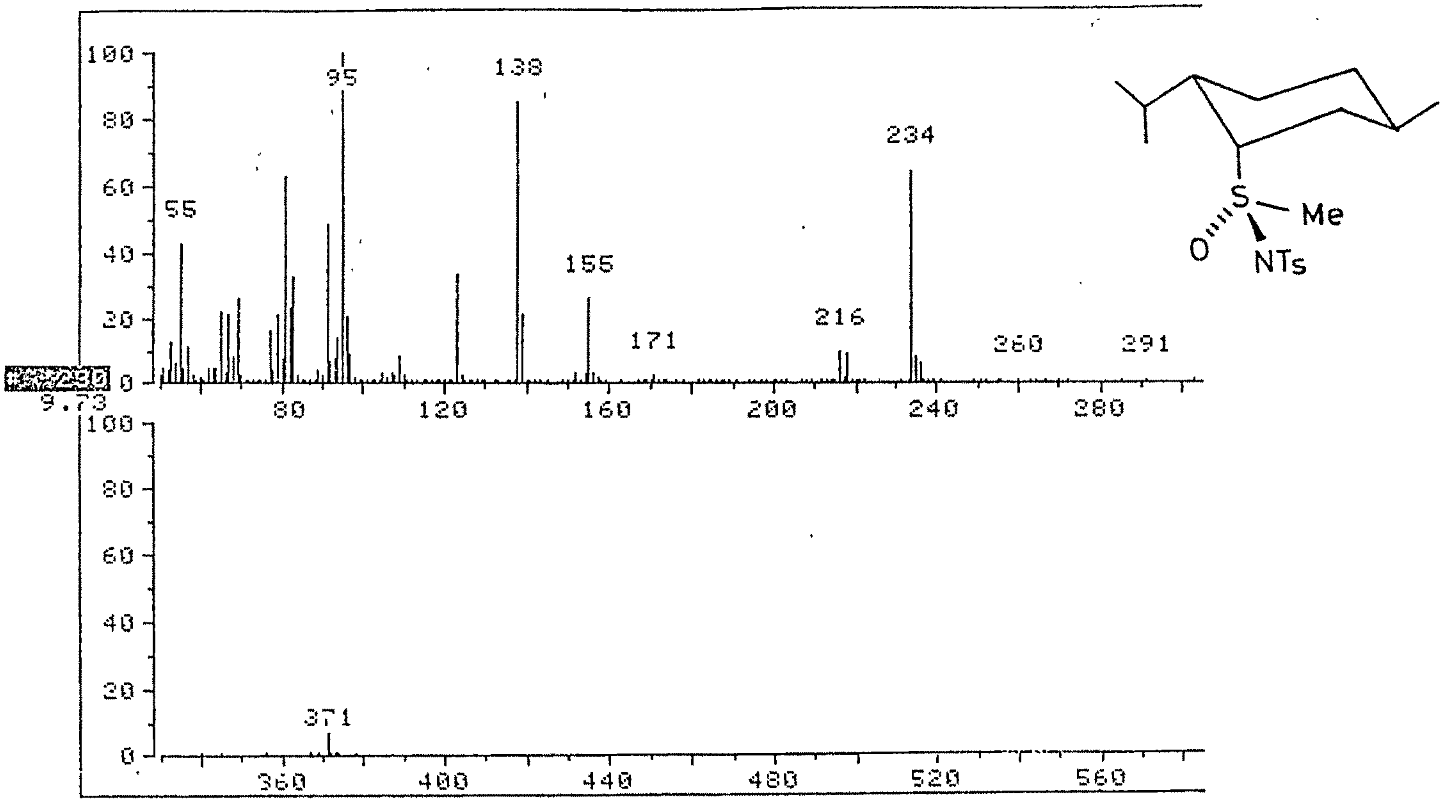
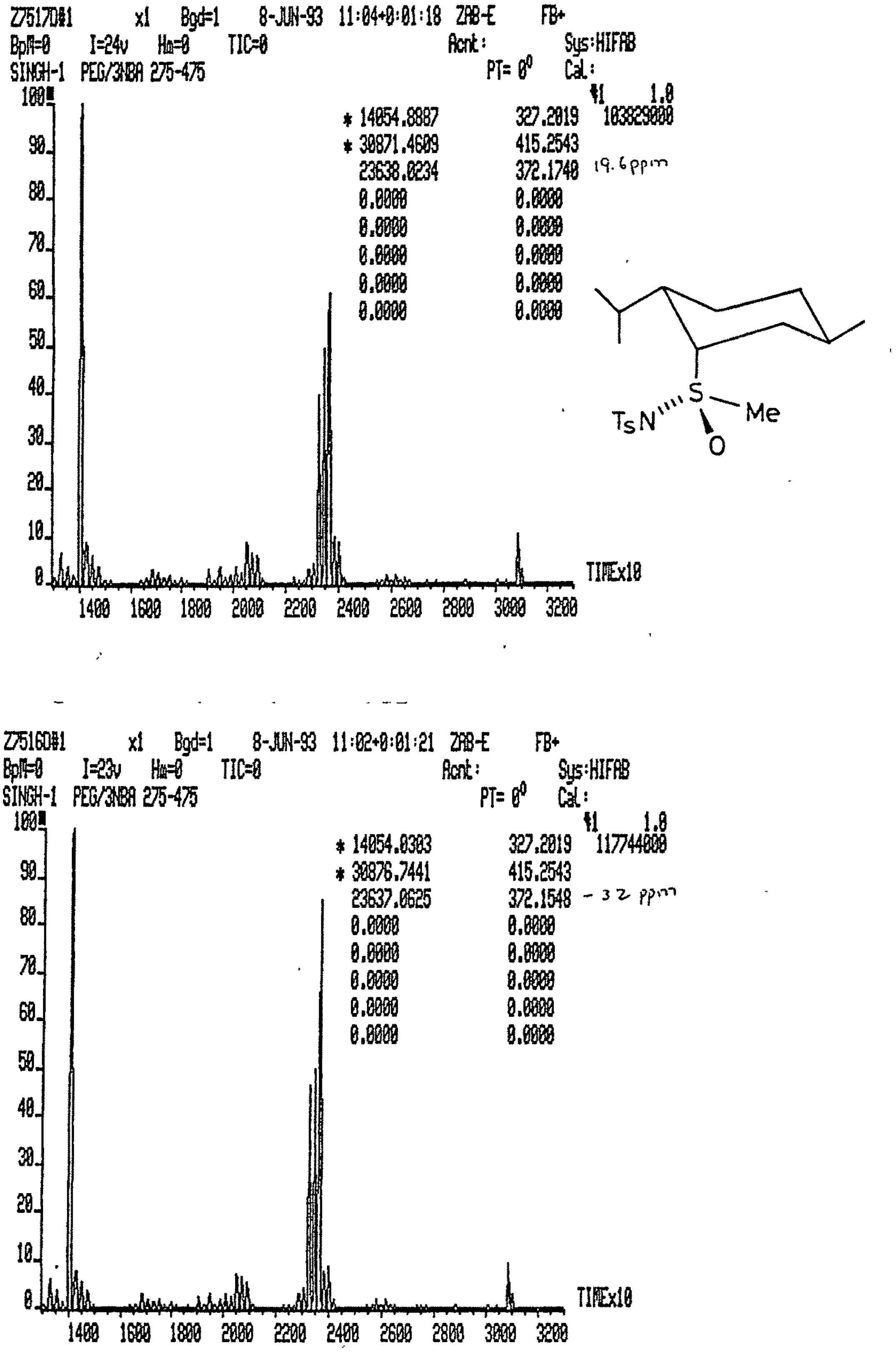


Fig. 16 : Mass Spectrum of (1R,3S,4S,S_S)-(-)-S-Methyl-S-neomenthyl-N-tosyl Sulfoximine (11a)

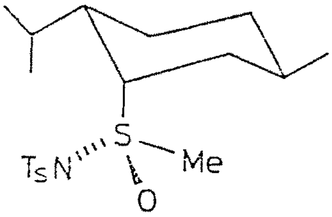


```
Z7517D#1        x1    Bgd=1    8-JUN-93  11:04+0:01:18  ZAB-E      FB+
BpM=0     I=24v    Hm=0     TIC=0                 Acnt:          Sys:HIFAB
SINGH-1  PEG/3NBA 275-475                            PT= 0⁰     Cal:
                                                                 ¶1      1.0
                           * 14054.8887          327.2019   103829000
                           * 30871.4609          415.2543
                             23638.0234          372.1740  19.6ppm
                             0.0000              0.0000
                             0.0000              0.0000
                             0.0000              0.0000
                             0.0000              0.0000
                             0.0000              0.0000
```

```
Z7516D#1        x1    Bgd=1    8-JUN-93  11:02+0:01:21  ZAB-E      FB+
BpM=0     I=23v    Hm=0     TIC=0                 Acnt:          Sys:HIFAB
SINGH-1  PEG/3NBA 275-475                            PT= 0⁰     Cal:
                                                                 ¶1      1.0
                           * 14054.0303          327.2019   117744000
                           * 30876.7441          415.2543
                             23637.0625          372.1548  - 32 ppm
                             0.0000              0.0000
                             0.0000              0.0000
                             0.0000              0.0000
                             0.0000              0.0000
                             0.0000              0.0000
```

Fig. 17 : HRMS of (1R,3S,4S,R_S)-(+)-S-Methyl-S-neomenthyl-N-tosyl Sulfoximine (11b)

```
Single Mass Input        Page:   1-1


M/E     C    H   N   O   S      MMU      DBE       OBS.MASS
       12

372    22   28   0   3   1     11.5      9.0     372.1644000
       19   32   0   3   2     14.9      4 0
       16   36   0   3   3     18.3     -1.0
       15   32   0   4   3    -18.1      0.0
       21   26   1   3   1     -1.1      9.5
       18   30   1   3   2      2.3*     4.5
       15   34   1   3   3      5.7     -0.5
       20   24   2   3   1    -13.6     10 0
       17   28   2   3   2    -10.3      5.0
       14   32   2   3   3     -6.9      0.0
```

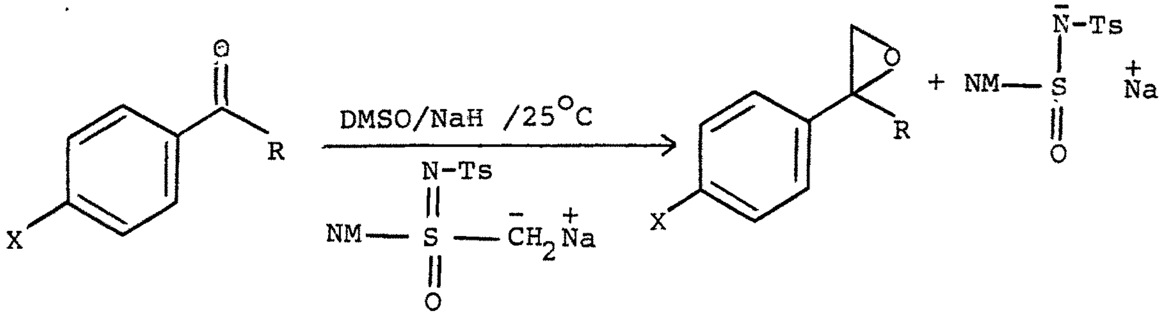


```
Single Mass Input        Page:   1-1


M/E     C    H   N   O   S      PPM      DBE       ACC.MASS
       12

372    22   28   0   3   1    -30.9      9.0     372.1759168
       19   32   0   3   2    -40.0      4.0     372.1792888
       16   36   0   3   3    -49.1     -1.0     372.1826608
       15   32   0   4   3     48.7      0.0     372.1462752
       21   26   1   3   1      2.8      9.5     372.1633408
      ✓18   30   1   3   2     -6.2*     4.5     372.1667127
       15   34   1   3   3    -15.3     -0.5     372.1700847
       20   24   2   3   1     36.6     10.0     372.1507647
       17   28   2   3   2     27.6      5.0     372.1541367
       14   32   2   3   3     18.5      0.0     372.1575086
```

Fig. 18 : HRMS of (1R,3S,4S,R_S)-(+)-S-Methyl-S-neomenthyl-N-tosyl Sulfoximine (11b)

are the most sought after chirons for the synthesis of a variety of commercially important pesticides such as (S)-fenvalerate and drugs such as (S)-ibuprofen, (S)-naproxen etc.

The methylene transfer reactions were carried out on four selected carbonyl compounds 12 - 15 using chiral sulfoximines 11a and 11b. The general reaction can be depicted in Scheme 5.



12-15

16-19

Where,

	X	R
12, 16	H	H
13, 17	Cl	H
14, 18	H	CH_3
15, 19	Cl	i-pr

Scheme 5

The sulfoximine (Ss)-11a on treatment with sodium hydride in dry DMSO gave sodium methylide of S-neomenthyl-N-tosyl sulfoximine with the evolution of hydrogen gas. To the carbanion solution of sulfoximine was added required carbonyl compound at ambient temperature (30-32^{o}C) and stirred for a fixed time. After work up, the crude oxirane was distilled under reduced pressure. The enantiomeric excess achieved for different oxiranes ranged from 56 to 86%* and is summarized in Table 1.

Table 1 : Asymmetric Induction in Oxirane Synthesis using Sulfoximine (Ss)-11a

Sr. No.	Carbonyl Substrate	Product Oxirane			
		Identity	Yield(%)	$[\alpha]_D$	ee(%)GC#
1.	12	(R)-(+)-Phenyl oxirane 16	42	+28.57 (c,1.85;Bz)	66.2(a) (Fig.19)
2.	13	(R)-(+)-(4-Chlorophenyl)oxirane 17	55	+12.27 (c,1.30;Bz)	55.8(a)
3.	14	(-)-2-Methyl-2-phenyl oxirane 18	65	-11.3 (c,0.70;Ac)	82.3(a)
4.	15	(-)-2-(4-Chlorophenyl)-2-isopropyl) oxirane 19	80	-31.22 (c,3.78,Chf)	86.0(b)

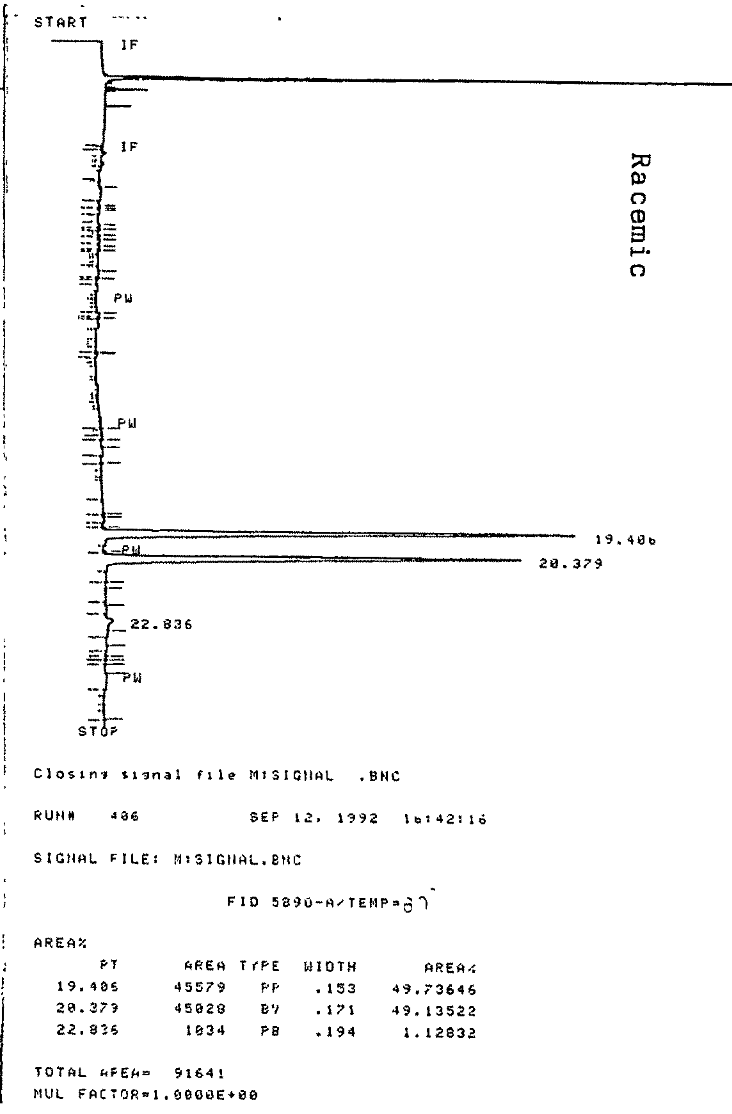
\# Cyclodextrin B capillary column, 25 M x 0.25 m.m

"a" denotes the fast eluting enantiomer in excess

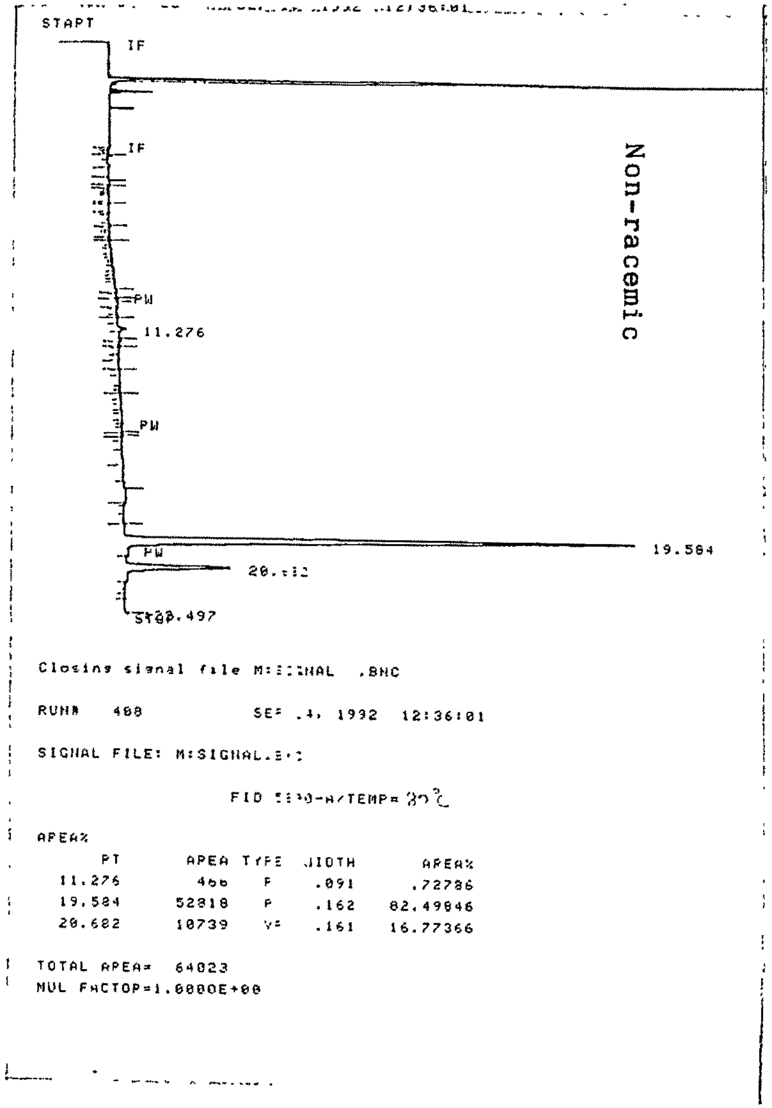
"b" denotes the slow eluting enantiomer in excess

---

* The results of these studies has been published in 1994[11]



```
Closing signal file M:SIGNAL  .BNC

RUN#   406            SEP 12, 1992  16:42:16

SIGNAL FILE: M:SIGNAL.BNC

                    FID 5890-A/TEMP=80

AREA%
      RT        AREA TYPE  WIDTH        AREA%
   19.406      45579   PP   .153   49.73646
   20.379      45028   BV   .171   49.13522
   22.836       1034   PB   .194    1.12832

TOTAL AREA=  91641
MUL FACTOR=1.0000E+00
```



```
Closing signal file M:[illegible]NAL  .BNC

RUN#   408            SEP [illegible]4, 1992  12:36:01

SIGNAL FILE: M:SIGNAL.[illegible]

                    FID [illegible]0-A/TEMP= 80°C

AREA%
      RT        AREA TYPE  WIDTH        AREA%
   11.276        466   P    .091      .72786
   19.584      52818   P    .162   82.49846
   20.682      10739   V[illegible]   .161   16.77366

TOTAL AREA=  64023
MUL FACTOR=1.0000E+00
```

Fig. 19 : Chiral GC Analysis of R-(+)-Styrene oxide (16) on Cyclodex B Capillary Column

Similarly, when sulfoximine (Rs)-11b was used in the preparation of oxiranes 16 to 19, the enantiomeric ratio (a:b by chiral GC) of the products were found to be reversed and the optical rotations were approximately equal in magnitude but opposite in sign to those of oxiranes prepared with sulfoximine 11a. The asymmetric induction achieved# using sulfoximine 11b is summarized in Table 2.

Table 2 : Asymmetric Induction in Oxirane Synthesis using Sulfoximine (Rs)-11b

Sr. No.	Carbonyl Substrate	Product Oxirane			
		Identity	Yield(%)	$[\alpha]_D$	ee(%)G
1.	12	(S)-(-)-Phenyl oxirane 16	38	-26.33 (c,2.16;Bz)	61.0(b)
2.	13	(S)-(-)-(4-Chlorophenyl) oxirane 17	55	-10.77 (c,2.37;Bz)	49.3(b)
3.	14	(+)-2-Methyl-2-phenyloxirane 18	59	-	71.1(b)
4.	15	(+)-2-(4-Chlorophenyl)- 2- isopropyl oxirane 19	81	+29.04 (c,4.0;Chf)	82.4(a)

* Same as footnote in Table 1

The major enantiomer of oxiranes 16 and 17 resulting from the reaction of benzaldehydes 12 and 13 with sulfoximine (Ss)-11a had (R) configuration, whereas sulfoximine (Rs)-11b gave (S) oxiranes. Phenyl ketones 14 and 15 when reacted similarly with

---

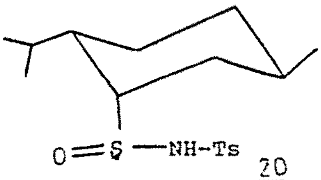
\# The results of these studies has been published in 1994[11].

(Ss)-11a to give oxiranes (-)-18 and (-)-19 (Absolute configuration of these oxiranes not established)[12], while sulfoximine (Rs)-11b reacted with phenyl ketones 14 and 15 to give oxiranes (+)-18 and (+)-19. Thus in all these cases, ee of oxiranes obtained with (Ss) sulfoximine was different from that of the oxiranes obtained with (Rs) sulfoximine.

Other carbonyl compounds like heliotropin and p-anisaldehyde etc. were also reacted with these sulfoximines under identical reaction conditions. The enantiomers of the resulting oxiranes were not separating on chiral GC column and therefore the extent of asymmetric induction achieved could not be found out.

Attempts to extend the applicability of this reaction to aliphatic carbonyl compounds such as n-heptanal, 2-octanone and phenoxyacetaldehyde etc. have not met with success (very poor yield, 10 % under the same condition as for 12 - 14, other side products).

The aqueous layer after work up, during MT reaction contains sodium salt of N-neomenthyl sulfinyl-p-toluene-sulfonamide. Acidification of aqueous layer with quantitative amount of dilute hydrochloric acid followed by extraction of precipitated solid with solvent ether gave N-neomenthyl sulfinyl-p-toluenesulfonamide 20 which has been characterised by ^{1}H NMR and IR. The NMR spectrum shows the disappearance of $S\text{-}CH_3$ singlet at δ 3.45.



20

D. ABSOLUTE CONFIGURATION AT SULFUR[*]

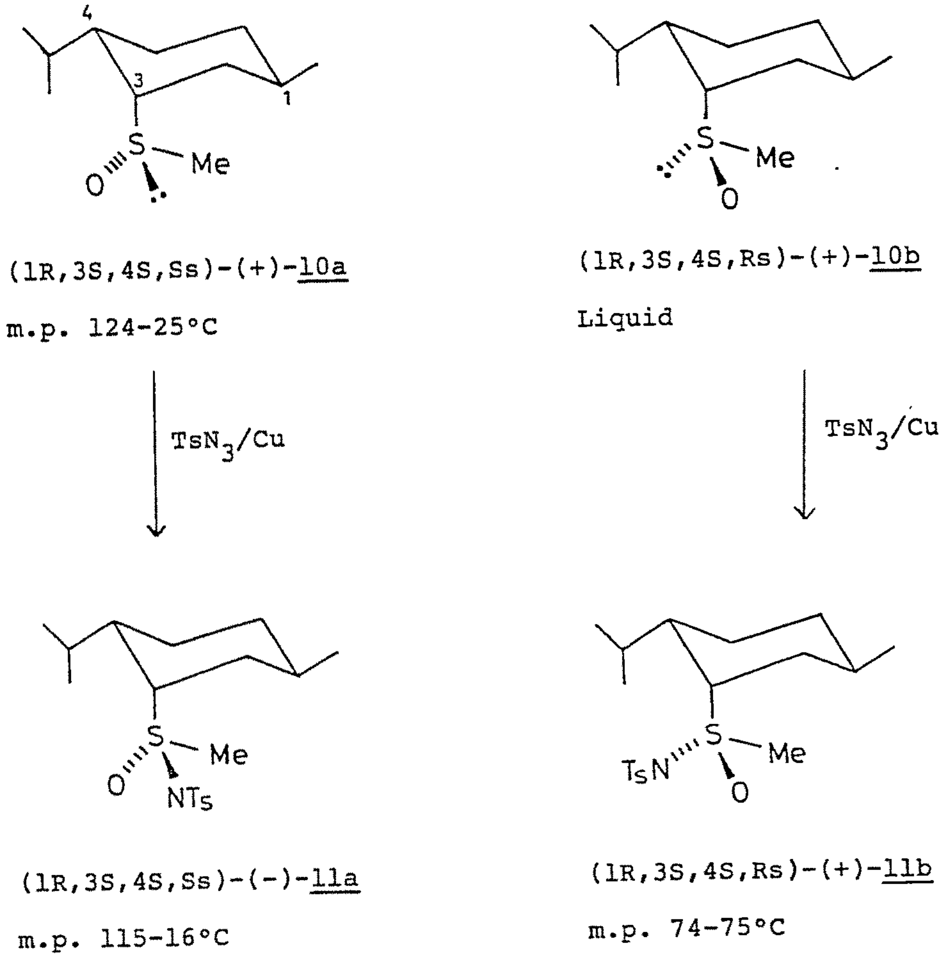
As shown in Scheme 4, (1R,3R,4S)-(-)-menthol possessing three stereogenic centers was the starting material. During the preparation of 11a and 11b (see Scheme 4), in step (ii) inversion of configuration at C_3 takes place. In the remaining steps the configuration of neomenthyl moiety remain (1R,3S,4S) unchanged because they are not directly involved in the reaction.

When neomenthyl methyl sulfide 9 is converted into neomenthyl methyl sulfoxide, a new stereogenic center is created at sulfur atom. As well documented in the literature[13], sulfoxides exhibits pyramidal bonding and can be resolved to its enantiomers. The epimeric pair of sulfoxides 10a and 10b differ only in the configuration at sulfur atom. The epimers of sulfoxides 10a and 10b could be completely separated by repeated fractional crystallization into pure epimers. Absolute configuration at sulfur of (1R,3S,4S)-(+)-S-methyl-S-neomenthyl sulfoxide, 10a (m.p. 124-25°C) has been found to be (S) based on single crystal X-ray structural analysis. (OTREP DIAGRAM, Fig.20). Optically pure sulfoxides having stereogenic sulfur

---

[*] We are thankful to Prof. G. Newton of University of Georgia, Athenes, U.S.A. for single crystal X-ray analysis of compounds 10a and 11b.

react with tosyl azide in presence of copper powder (Kwart-Kahn method)[4] to give corresponding sulfoximines with retention of configuration at sulfur[14]. Accordingly, sulfoximine 11a derived from sulfoxide 10a should have (S) configuration at sulfur **(Scheme 6)**. The epimeric sulfoxide 10b (liquid) and sulfoximine 11b derived from 10b then should have (R) configuration at sulfur[15].



(1R,3S,4S,Ss)-(+)-<u>10a</u>
m.p. 124-25°C

(1R,3S,4S,Rs)-(+)-<u>10b</u>
Liquid

(1R,3S,4S,Ss)-(-)-<u>11a</u>
m.p. 115-16°C

(1R,3S,4S,Rs)-(+)-<u>11b</u>
m.p. 74-75°C

Scheme 6

This has been confirmed by single crystal X-ray structural analysis of sulfoximine 11b (ORTEP DIAGRAM, Fig. 21) showing the configuration at sulfur to be (R).

The determination of absolute configuration at sulfur atom of sulfoxides and sulfoximines in this study once again proved that conversion of optically pure sulfoxides to sulfoximine under Kwart-Kahn condition proceeds with retention of configuration at sulfur.

E. CONCLUSION

We have presented a very useful method, with good scope for further improvement, for the synthesis of non-racemic oxiranes in fairly high enantiomeric excess (56-86%) by the reaction of prochiral carbonyl compounds with chiral sulfoximines. As anticipated at the outset, the chirality of the ligand on sulfur did influence the extent of ee achieved in methylene transfer reaction. The absolute configuration at sulfur appears to be the guiding factor in deciding the absolute configuration of the oxiranes formed. Absolute configuration of crystalline sulfoxide and sulfoximines have been confirmed by X-ray diffraction analysis. Determination of absolute configuration at sulfur of sulfoxides and sulfoximines once again proved conclusively that Kwart-Kahn reaction proceeds with retention of configuration at sulfur.

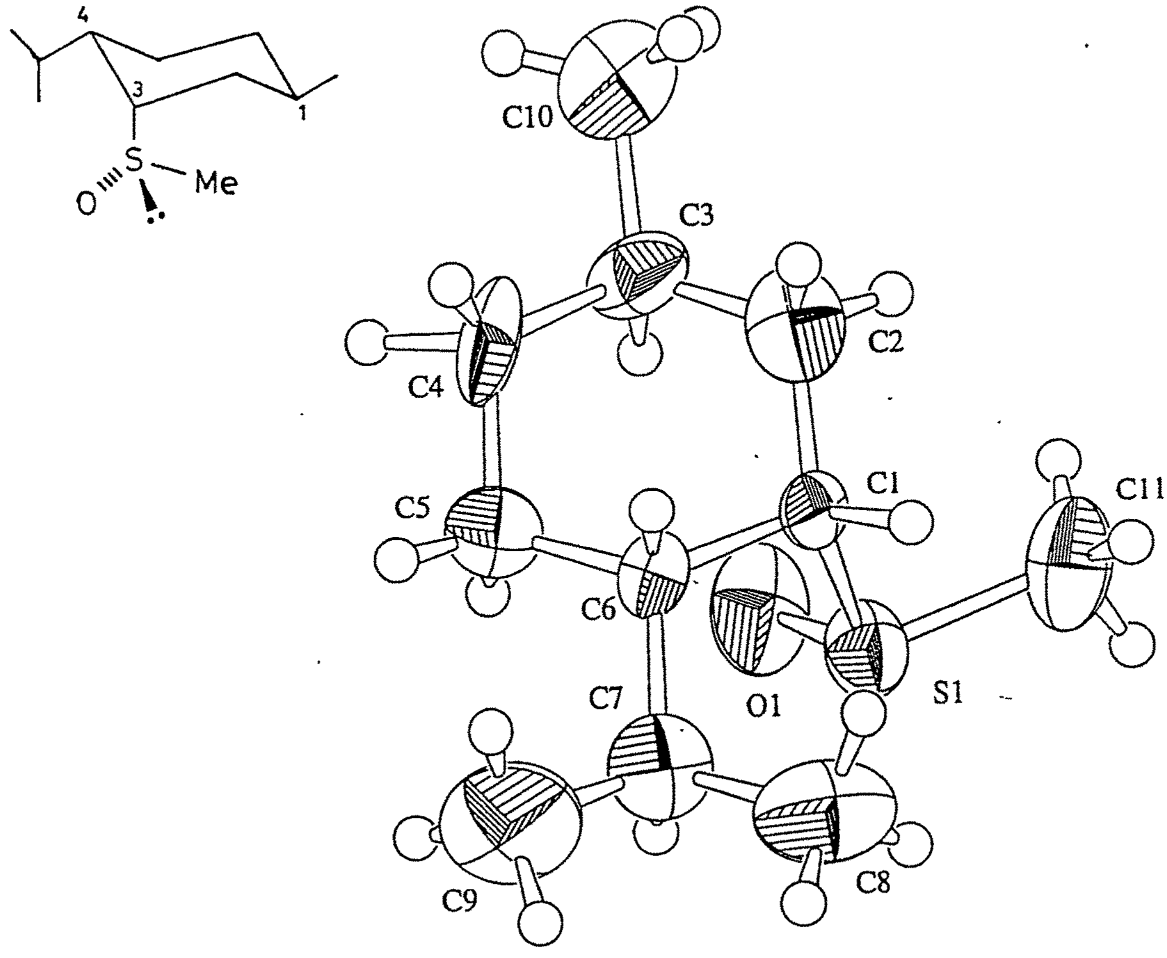


Fig. 20 : ORTEP Diagram of (1R,3S,4S,S_S)-(+)-S-Methyl-S-neomenthyl Sulfoxide (10a)

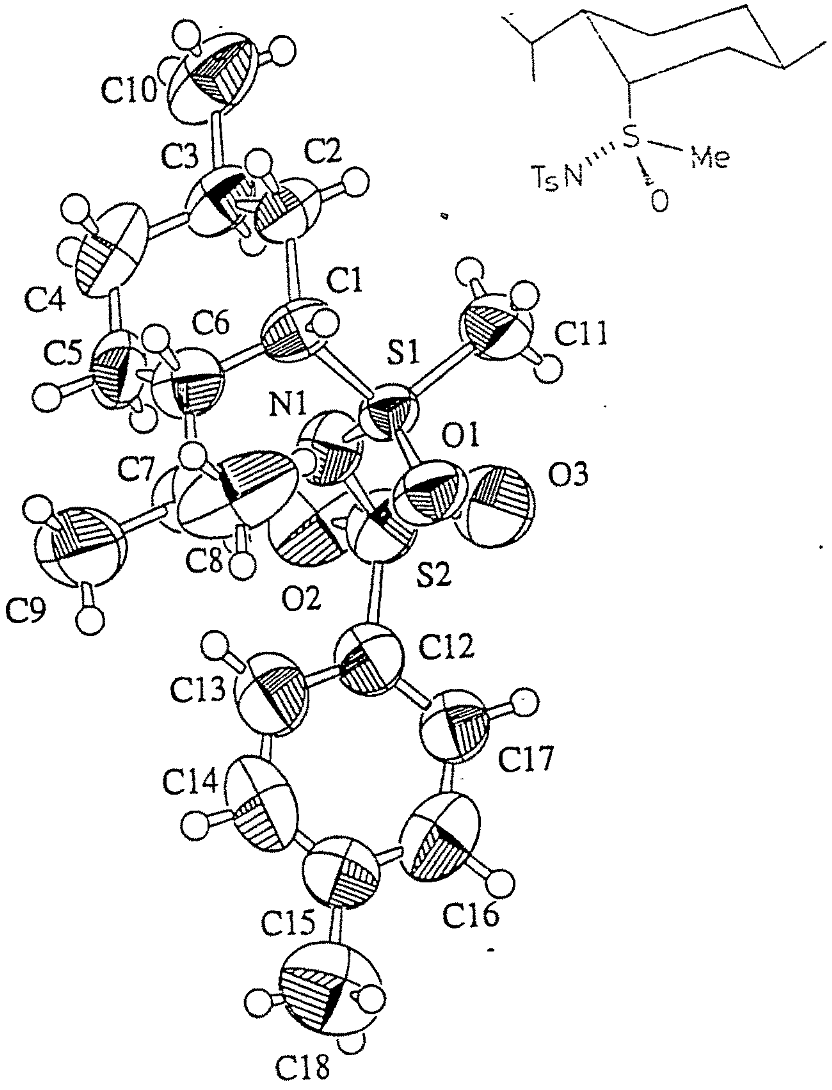


Fig. 21 : ORTEP Diagram of (1R,3S,4S,R_S)-(+)-S-Methyl-S-neomenthyl-N-tosyl Sulfoximine (11b)

F. EXPERIMENTAL

General : All melting points and boiling points are uncorrected. Optical rotations were measured at 25°C in chloroform (unless otherwise stated) on a JASCO model DIP-370 digital polarimeter. Chiral GC analysis were done on a cyclodex B capillary column, 25 M x o.25 m.m. (J & W Scientific) using a Hewlett-Packard model 5890 gas chromatograph and model HP 3396A electronic integrator. The various spectra were obtained using following instruments.

IR Spectra : Perkin Elmer Model 781
UV Spectra : Perkin Elmer Model 402
^{1}H NMR Spectra : Perkin elmer R-32 (90 MHZ)
High resolution ^{1}H NMR : Varian XL-300 spectrometer (300 MHZ)
Bruker AC (250 MHZ).
^{13}C NMR Spectra : Varian XL-300 (75 MHZ)
Bruker AC-250 (63 MHZ)
Mass Spectra : TRIO-1 GC MS and Finnigan Mat - 1020
HRMS : VG ZAB-E mass spectrometer (Manchaster, UK)

Single-crystal X-ray Diffraction Analysis : All X-ray data were collected at room temperature on an Enarf-Nonious CAD-4 diffractometer using Cu-Kα radiation with a graphite monochromator. Structures were solved using direct methods (SIR - 92) and refined by full matrix least square methods in the teXsan program suite.

Solvents and Reagents : Pyridine was dried over calcium hydride and kept over KOH pellets. (-)-Menthol used was of natural origin with 99 + % optical purity. p-Toluene sulfonyl chloride was from Fluka-AG. Dimethyl sulfoxide (DMSO) was dried over calcium hydride and stored over 4^{o}A molecular seives. Diethyl ether was dried on lithium aluminium hydride.

Column chromatography was performed on Acme's silica gel (100-200 mesh size) Thin layer chromatography (TLC) was performed on glass plates (7.8 x 2.5 cm.)using Acme's silica gel containing 13 % calcium sulfate as binder. The spots were visulized in iodine vapour.

(1R,3R,4S)-(-)-Menthyl p-Toluene sulfonate (6)[5]

Treatment of (1R,3R,4S)-(-)-menthol, [$[\alpha]_D$ -49.5; (c,2.2, EtOH)] (5; 81 g, 0.52 mol) in dry pyridine (780 mL) at 0^{o}C with p-toluene sulfonyl chloride (199 g, 1.04 mol) overnight followed by usual work up[16] and crystallization from pet-ether 60-80^{o}C gave beautiful crystals of desired product 6. Yield, 147 g (91%).

Observed $[\alpha]_D$ -67.63 (c,3.12)

Reported[5] $[\alpha]_D$ -69.5 (c,2.99)

(1R,3S,4S)-(+)-Neomenthyl Thioacetate (7)[5]

(-)-Menthyl p-toluene sulfonate (6 ; 110g, 0.35 mol) was added to a solution of potassium thioacetate (125 g, 1.1 mol) in dry DMSO (325 mL) and the mixture stirred vigorously at 45-50°C for 40h (Monitored by TLC). Water (350 mL) was added to the cooled reaction mixture and the product extracted with chloroform (100 x 6mL). The combined organic layer was dried (Na_2SO_4) and the crude product (76g) fractionated via a 25 cm. long vigreux column (b.p.99°C/2 m.m.) to get 7 of 94 % GC purity (6',10% SE-30 on Chromosorb W, oven temperature 170°C, FID). This material was passed though a silica gel column to get single spot (TLC) product, 7. GC - 99.15%, yield, 47g (62%) [Reported yield, 50%][5].

$[\alpha]_D$ +76.4 (c, 2.73)

Reported[5], $[\alpha]_D$ +64.0 (c, 2.66)

(1R,3S,4S)-(+)-Neomenthanethiol (8)[5]

To a stirred suspension of lithium aluminium hydride (6.7g, 0.17 mol) in dry diethyl ether (150 mL), a solution of pure (+)-neomenthyl thioacetate (7; 35.2g, 0.16 mol) in dry ether (70 mL) was added at 25°C under dry nitrogen atmosphere. After completion of addition (1h), the mixture was refluxed for 4h. The reaction was monitored by GC (6', 10% SE-30, 170°C, FID) showing complete disappearance of thioacetate peak and appearance of a new peak at relatively lower retetion time (RRT, 7:8 = 1:0.47) corresponding to thiol. The mixture was cooled in ice water and treated slowly with water (75 mL). The gelatinous ppt was dissolved in aqueous 10% H_2SO_4 (200 mL). The organic layer separated and the aqueous layer re-extracted with solvent ether (60x3 mL). The combined ether extracts dried (Na_2SO_4), ether distilled off and the product (28.9 g) distilled under reduced pressure (b.p. 92°C/7mm) to get pure (+)-neomenthanethiol (8 ; 23g, 92 % yield).

GC (6',10% SE-30 on chromosorb W, 170°C, FID) - 98 % pure.

$[\alpha]_D$ +53.09 (c,1.94)

Reported[5], $[\alpha]_D$ +53.9 (c,1.85)

(1R,3S,4S)-(+)-S-Methyl-S-neomenthyl sulfide (9)[5]

In a dried glass assembly was taken dry methanol (300 mL), under positive pressure of dry nitrogen and pieces of sodium metal (7.4g, 0.32 mol) were added in small lots in about 30 minutes duration. The resulting sodium methoxide solution was cooled to 30°C and (+)-neomenthanethiol (8 ; 50.2g, 0.29 mol) was added in about 15 minutes time. The mixture was stirred at room temperature for about 1h. Methyl iodide (45.3g, 20 mL, 0.32 mol) was added and stirred for 3h. The reaction was monitored by GC (6',10 % SE-30, 170°C, FID) showing complete disappearance of thiol peak and appearance of a relatively higher retention time peak corresponding to sulfide (RRT, 8:9 = 1:1.21). Methanol was distilled out under vacuum, the residue is dissolved in chloroform (200 mL), washed with water (50x2 mL) and dried (Na_2SO_4). Removal of solvent affords the pure product (9 ; 50.7g, 94 % yield). GC (6',10 % SE-30 on Chromosorb W, 170°C, FID) -98 %

$[\alpha]_D$ +95.794 (c,3.85)

Reported[5] $[\alpha]_D$ +90.3 (c,3.52)

(1R,3S,4S)-(+)-S-Methyl-S-neomenthyl sulfoxide (1oa and 10b)[5]

To a solution of (+)-S-methyl-S-neomenthyl sulfide (9 ; 10.13g, 54.5 mmol) in glacial acetic acid (3.2 mL) was added aqueous hydrogen peroxide solution (30 % W/V, 6.2 mL, 54.7 mmol) in 1h at 18°C and the mixture stirred at 20-30°C until the oxidation was complete (50h, monitoring by TLC and ^{1}H NMR). The product was taken up in chloroform (50 mL) washed with water (50 mL), aqueous potassium carbonate solution (5%, 15x2 mL), finally with water (20 mL), dried (Na_2SO_4) and freed from solvent. The residue (10.61g,, 96.5 % yield, $[\alpha]_D$ + 78.08 (c,1.46) was found to be a mixture of epimeric sulfoxides 10a and 10b (35:65; chiral GC, cyclodex B capillary column, 150°C). Crystallization of the product mixture from n-hexane-chloroform (97:3; 20 mL) gave a solid which after recrystallisation to constant m.p. weighed 3.1g, (10a, m.p. 125-26°C). The mother liquor was freed from solid epimer by repeated chilling and filtration. Distillation at 120°C (bath)/0.5 m.m. gave a colourless liquid, (10b ; 6.6g, epimeric ratio, 1:99, chiral GC).

Solid sulfoxide 10a : (1R,3S,4S,Ss)-(+)-S-Methyl-S- neomenthyl sulfoxide

m.p. 125-26°C

$[\alpha]_D$ +140.06 (c,1.48)

Reported[5] $[\alpha]_D$ +136.7 (c,1.35)

IR (Nujol) : 1390, 1380, 1320, 1260, 1020, 1005, 965, 940, 700 cm^{-1} (Fig.6)

^1H NMR (90 MHZ, $CDCl_3$) : (δ), 0.7-1.2 (9H, m, all -C-$\underline{H}_3$), 2.58 (3H, s, -S-C$\underline{H}_3$), 2.81 (1H,t, $\underline{H}$C-S) (Fig.1)

^{13}C NMR ($CDCl_3$) : (δ), 21.18, 21.42, 22.71 (all -C-$\underline{C}H_3$), 47.69 (-S-$\underline{C}H_3$), 25.94, 33.85, 35.02 (all -C-$\underline{C}H_2$), 27.56, 29.26, 38.50 (all -C-$\underline{C}$H), 59.55 ($\underline{C}$H-S) (Fig.3 and 4)

Chiral GC : Cyclodex B capillary column, 25 M x 0.25 m.m. oven temperature -155°C, Retention time 19.6 mins., purity 100 %.

X-ray structural analysis : Slow crystallization from acetonitrile:water (85:15) gave bold crystals of 10a. The structure was confirmed by X-ray structural analysis and absolute configuration at sulfur was established to be (S). (ORTEP DIAGRAM, Fig.20)

Liquid sulfoxide 10b : (1R,3S,4S,Rs)-(+)-S-Methyl-S-neomenthyl sulfoxide

$[\alpha]_D$ +23.75 (c,2.1) Refractive index 1.4950 (25°C)

IR (neat, Thin film) : 2960, 2920, 2880, 1480, 1455, 1425, 1385, 1370, 1035, 930, 680, cm^{-1} (Fig.7)

^{1}H NMR (90MHZ, $CDCl_3$) : (δ), 0.7-1.2 (9H,m, all -C-C$\underline{H}_3$), 2.60 (3H,s, S-C$\underline{H}_3$), 3.28 (1H, broad s, $\underline{H}$C-S) (Fig.2)

^{13}C NMR ($CDCl_3$) : (δ), 21.80, 21.93, 22.43 (all -C-$\underline{C}H_3$), 49.95 (S-$\underline{C}H_3$), 25.92, 35.43, 37.02 (all-C-$\underline{C}H_2$), 27.82, 29.33, 37.79 (all-C-$\underline{C}$H), 63.56 ($\underline{C}$H-S) (Fig.5)

Chiral G C : Cyclodex B capillary column 25 M X0.25 m.m.
oven temperature - 155°C.
Later eluted epimer, Retention time 20.0 mins.
optical purity 99.7 %

(1R,3S,4S,Ss)-(-)-S-Methyl-S-neomenthyl-N-tosyl sulfoximine (11a)

A mixture of solid sulfoxide 10a (7.07g, 35 mmol), p-toluene sulfonyl azide[17] (13.74g, 74 mmol), freshly precipitated copper powder[18] (1.85g) and anhydrous methanol (50 mL) was refluxed gently for 64 h (about 80 % conversion, ^{1}H NMR). Methanol was distilled off on rotavapor and the residue was stirred (30 minutes) with a saturated solution of Na_2EDTA (125 mL). The reaction mixture was extracted with chloroform (50x5 mL), organic layer treated with activated charcoal (2g), filtered (using filter aid) and the filtrate washed with dilute aqueous sodium hydroxide solution (5%, 20x2 mL) (To remove p-toluene sulfonamide being formed as the side product by the reaction of nitrene intermediate generated from tosyl azide with methanol) and water (40x3 mL), dried (Na_2SO_4) and was freed from solvent. The residue (12.1g) was subjected to column chromatography on silica gel (500g) and eluted with n-hexane-acetone (80:20) to give pure sulfoximine (11a ; 8.4g, eluted first) and unreacted sulfoxide (10a ; 1.0g, eluted later). The yield of sulfoximine based on consumed sulfoxide was 75.4 %. The product was recrystallized thrice from different solvent systems viz., chloroform : hexane (20:80), absolute ethanol and acetonitrile : water (85:15) to give beautiful needle shaped crystals. The optical rotations after each crystallization remaims unaltered.

m.p. : 115-16°C

$[\alpha]_D$ -60.9 (c, 2.54)

IR (Nujol) : 1330, 1278, 1232, 1205, 1150, 1080, 1022, 785, 718, 680, cm^{-1} (Fig 11)

UV (EtOH), max (ε) : 237 (3900), 257 (680), 263 (760), 268 (640), and 274(550) nm

^{1}H NMR (300 MHZ, $CDCl_3$): (δ), 0.84,0.91,1.04, (3H each, d ; total 9H, J = 6.6, 6.3, 6.3 HZ respectively ; HC-C$\underline{H}_3$), 2.42 (3H,s, Ar-CH_3), 3.46 (3H, s, S-CH_3), 3.78 (1H,q, J = 3.6 HZ HC-S), 7.27 (2H, d; J = 7.8HZ, Ar-CH), 7.84 (2H,d ; J = 8.4 HZ, Ar-CH) (Fig 8)

^{13}C NMR (75 MHZ; $CDCl_3$): (δ), 21.09, 21.26, 21.83, 22.16 All -C-CH_3), 43.84, (S-CH_3), 23.59, 34.31, 35.51, (All -C-CH_2), 26.30, 28.32, 49.01 (All-C-CH), 63.99 (CH-S), 126.13, 128.87 (All four Ar-CH), 141.00, 142.22 (All Ar-C-) (Fig.13)

EIMS, M/Z (%) : 371 (m^+,7) 234(65), 216(15), 155(28), 138(87), 123(35), 95(100), 91(49), 55(43) (Fig 16)

Microanalysis :

$C_{18}H_{29}NO_3S_2$ Requires : C, 58.18 % ; H, 7.87 % ; N, 3.77 %
Found : C, 58.04 % ; H, 8.21 % ; N, 3.56 %

Absolute configuration at sulfur : Since its epimer 11b has (R) configuration at sufur (See below), this sulfoximine 11a must have (S) configuration at sulfur. Besides, the fact that it has been synthesized from a sulfoxide having (S) configuration at sulfur provides support for this conclusion.

(1R,3S,4S,Rs)-(+)-S-Methyl-S-neomenthyl-N-tosyl sulfoximine (11b)

The liquid sulfoxide 10b (9.1g, 45 mmol), p-toluene sulfonyl azide (17.7g, 90 mmol) freshly precipitated copper powder (2.31g) and anhydrous methanol (55 mL) were refluxed for 46h (about 90 % conversion, ^{1}H NMR). The reaction mixture was worked up exactly as in the case of 11a. The column eluted product (13.5g, 80.5 % yield) was crystalized from two different solvent systems viz., n-hexane : acetone (94:6) and n-hexane : chloroform (92:8) into beautiful tetragonal blocks of crystals which was found to be suitable for X-ray structural analysis. The optical rotations after each crystallization remained unaltered. The epimeric purity of sulfoxinine 11b was 100 % (^{1}H NMR : no detectable signals due to 10a)

m.p. 74 -75°C

$[\alpha]_D$ +101.9 (c, 3.88)

IR (Nujol) : 1602, 1330, 1320, 1305, 1240, 1225, 1200, 1150, 1070, 820, 805, 790, 732, 680, 650 cm^{-1} (Fig.12)

UV (EtOH), max (ε) : 238(3770), 257(680), 263(750), 268(640), 274(550) nm

^{1}H NMR (CDCl$_3$) : (δ), 0.76, 0.80, 0.92 (3H each, d ; Total 9H, J = 6.3, 6.4, 6.3 HZ respectively ;-C-C$\underline{H}_3$), 2.32 (3H, s, Ar-C$\underline{H}_3$), 3.50* (3H, s, S-C$\underline{H}_3$), 3.57 (1H ; q, J = 3.0 HZ, $\underline{H}$C-S) 7.18 (2H, d ; J = 8.1HZ, Ar-C$\underline{H}$), 7.74 (2H, d, J = 8.4 HZ; Ar-C$\underline{H}$) (Fig. 9 and 10)

---

* There is a Shift of 0.1 ppm (instrumental) towards high field which is corrected in Fig.10.

^{13}C NMR (75 MHZ, $CDCl_3$) : (δ) 21.19, 21.28, 21.92, 22.08
(All -C-$\underline{C}H_3$), 44.91, (-S-$\underline{C}H_3$)
23.54, 34.44, 36.22 (All -C-$\underline{C}H_2$)
25.61, 28.66, 48.61 (All -C-$\underline{C}H$)
64.17 ($\underline{C}H$ -S)
125.82, 128.69 (4C, Ar-$\underline{C}H$)
141.00, 141.94 (2C, -$\underline{C}$-)
(Fig. 14 and 15)

EIMS, M/Z, (%) : 372(M^++1, 33), 370(M^+-1, 29), 236(54), 235(50), 234(100), 218(25), 217(20), 216(100), 159(19), 152(21), 139(31), 105(25)

HRMS : Exact mass, (M^++1), Found : 372.1644
$C_{18}H_{30}NO_3S_2$ Requires : 372.1667 **(Fig.17 and 18)**

Absolute configuration at sulfur : Structure of sulfoximine 11b was established by single crystal X-ray structural analysis (ORTEP DIAGRAM, **Fig.21**). The absolute configuration at sulfur was found to be (R).

General procedure for the preparation of oxiranes (16-19) from carbonyl compound (12-15) using sulfoximine 11a and 11b

To a solution of sodium hydride (0.12g, 50% dispersion in oil, 2.4 mmol, washed three times with dry n-hexane) in dry dimethyl sulfoxide (10 mL) under dry nitrogen atmosphere was added corresponding optically pure S-methyl S-neomenthyl-N-tosyl sulfoximine, 11a or 11b (0.82 g, 2.2 mmol) in dry DMSO (10mL) and the mixture stirred at ambient temperature (30-32°C) for 4h. To the sodium methylide solution in DMSO was added the corresponding individual carbonyl compound (2 mmol) in DMSO (2 mL) and the reaction mixture stirred at room temperature. The reaction takes about 2-18 h to complete (GC, disappearance of carbonyl compound). The reaction mixture was cooled to 10°C, diluted with water (25 mL), extracted with n-hexane (10x5 mL), the combined organic layer washed with water (20x2 mL), dried (Na_2SO_4), freed from solvent and the residue distilled under reduced pressure (2-20 m.m., small bulb to bulb distillation). The products were identified by spectroscopic methods (IR, ^1H NMR). The enantiomeric excess were determined by GC on chiral cyclodex B, capillary column.

The yields of the product oxiranes, their specific rotations and enantioneric excess obtained are summarised in Table 1 for sulfoximine 11a and in Table 2 for sulfoximine 11b.

Asymmetric synthesis of oxiranes using (1R,3S,4S,Ss)-(-)-S-methyl-S-neomenthyl-N--tosyl sulfoximine, 11a

(i) (R)-(+)-Phenyloxirane,(16) : The sodium salt of 11a (0.82g, 2.2 mmol) in DMSO was treated with freshly distilled benzaldehyde, 12 (0.21g, 2 mmol) and stirred at room temperature for 30 minutes. The work up of reaction mixture as above gave (R)-(+)-Phenyloxirane, 16 (0.1g, 42% yield).

The product was characterised by ^1H NMR and IR.

$[\alpha]_D$ +28.57 (c,1.85, Benzene)

Reported[19] $[\alpha]_D$ +44.4 (c,1.05, Benzene)

Chiral GC : Cyclodex B capillary column, oven temperature, 80°C (isothermal). The enantiomers were separated base to base Peak No.1 : (R)-(+)-isomer = 83.0 %

Peak No.2 : (S)-(-)-isomer = 16.8 %

% ee = 66.2% (Fig.19)

The racemic oxirane (prepared as per reported method)[10] was separated base to base exactly at the same position with 50:50 composition. (Fig.19)

(ii) **(R)-(+)-(4-Chlorophenyl)oxirane (17)** : Following exactly the same method as in (i) using p-chlorobenzaldehyde, 13 to gave 17 in 55% yield.

$[\alpha]_D$ +12.27 (c, 1.3, Benzene) The $[\alpha]_D$ of pure oxirane not reported.

Chiral GC : Oven temperature 100°C. Enantiomers separating base to base.

Peak No.1 : (R)-(+)-(4-chlorophenyl) oxirane = 77.91 %

Peak No.2 : (S)-(-)-(4-chlorophenyl) oxirane = 22.09 %

% ee = 55.82 %

(iii) (-)-2-Methyl-2-Phenyloxirane, (18) : The sodium salt of 11a (2.2 mmol) in dry DMSO was treated with distilled acetophenone 14 (0.24g, 2 mmol) and stirred at room temperature for 18h, work up as usual furnished pure 18 (0.17g, 65% yield)

$[\alpha]_D$ -11.3 (c,0.7, Acetone)

Chiral GC : Oven temperature 80°C

Peak No.1 : (-)-18 = 91.12 %

Peak No.2 : (+)-18 = 8.88 %

% ee = 82.24 %

(iv) (-)-2-(4-Chlorophenyl)-2-isopropyl oxirane, (19) : 1-(4-Chlorophenyl)-2-methyl-propan-1-one, 15 was treated similarly as in (iii) and stirred 18h followed by work up furnished oxirane, 19 (0.31g, 80 % yield)

$[\alpha]_D$ -31.22 (c,3.78, $CHCl_3$) The $[\alpha]_D$ of pure oxirane not reported

Chiral GC : Oven temperature - Programming from 80°C to 110°C (Rate - 1°C/minute)

Peak No.1 : (+)-19 = 6.93 %

Peak No.2 : (-)-19 = 92.02 %

% ee = 85.1 %

Asymmetric synthesis of oxiranes using (1R,3S,4S,Rs)-(+)-S-methyl-S-neomenthyl-N-tosyl sulfoximine, (11b)

The method of preparation is same as described in 11a

(i) (S)-(-) Phenyloxirane, (16) :

Yield - 38 %

$[\alpha]_D$ -26.33 (c, 2.16, Benzene)

Reported[19] $[\alpha]_D$ -44.4 (c,1.5, Benzene)

Chiral GC : Peak No.1 : (R)-(+)-Phenyloxirane = 19.5 %
Peak No.2 : (S)-(-)-Phenyloxirane = 80.2 %
ee = 60.8 %

(ii) (S)-(-)-(4-Chlorophenyl) oxirane, (17)

$[\alpha]_D$ -10.77 (c, 2.3, Benzene)

Chiral GC : Peak No.1 : (R)-(+)-isomer = 25.4 %
Peak No.2 : (S)-(-)-isomer = 74.6 %
ee = 49.2 %

(iii) (+)-2-Methyl-2-Phenyloxirane, (18) :

Chiral GC : Peak No.1 : (-)-18 = 14.5 %
Peak No.2 : (+)-18 = 85.5 %
ee = 71.0 %

(iv) (+)-2-(4-Chlorophenyl)-2-isopropyl oxirane, (19)

$[\alpha]_D$ +29.04 (c,4.0 Chloroform)

Chiral GC : Peak No.1 : (+)-19 = 91.18 %
Peak No.2 : (-)-19 = 8.81 %
ee = 82.37 %

(1R,3S,4S,Ss)-(+)-S-Methyl-S-neomenthyl Sulfoxide (10a)

Experimental

Singal Crystal X-ray Structural analysis*

Data Collection

A colorless needle crystal of $C_{11}H_{22}OS$ having approximate dimensions of 0.30 x 0.40 x 0.70 mm was mounted in a glass capillary. 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 orthorhombic cell with dimensions:

$a = 5.3742(3)\ \AA$

$b = 11.154(3)\ \AA$

$c = 20.785(3)\ \AA$

$V = 1246.0(3)\ \AA^3$

For Z = ~~8~~ 4 and F.W. = 202.35, the calculated density is ~~1.48~~ 1.08 g/cm^3. The systematic absences of:

h00: $h \neq 2n$

0k0: $k \neq 2n$

00l: $l \neq 2n$

uniquely determine the space group to be:

$P2_12_12_1$ (#19)

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 $(0.65 + 0.14 \tan \theta)°$ 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

A total of 1485 reflections was collected. 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 27.7 cm^{-1}. Azimuthal scans of several reflections indicated no need for an absorption correction. The data were corrected for Lorentz and polarization

---

* See Notes on Page No. 95

effects.

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 387 observed reflections ($I > 3.00\sigma(I)$) and 118 variable parameters and converged (largest parameter shift was 0.06 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma||Fo| - |Fc||/\Sigma|Fo| = 0.038$$

$$R_w = \sqrt{(\Sigma w(|Fo| - |Fc|)^2/\Sigma w Fo^2)]} = 0.041$$

The standard deviation of an observation of unit weight[4] was 1.78. The weighting scheme was based on counting statistics and included a factor ($p = 0.021$) 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 0.13 and -0.13 $e^-/\text{Å}^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[5] . Anomalous dispersion effects were included in Fcalc[6]; the values for $\Delta f'$ and $\Delta f''$ 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	$C_{11}H_{22}OS$
Formula Weight	202.35
Crystal Color, Habit	colorless, needle
Crystal Dimensions	0.30 X 0.40 X 0.70 mm
Crystal System	orthorhombic
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 = 5.3742(3)Å
	b = 11.154(3) Å
	c = 20.785(3) Å
	V = 1246.0(3) $Å^3$
Space Group	$P2_12_12_1$ (#19)
Z value	~~5.50~~ 4
D_{calc}	~~1.483~~ g/cm^3 . 1.08 g/cm^3
F_{000}	616.00
$\mu(CuK\alpha)$	27.70 cm^{-1}

B. Intensity Measurements

Diffractometer	CAD4
Radiation	CuKα ($\lambda = 1.54178$ 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	$(0.65 + 0.14 \tan\theta)°$
$2\theta_{max}$	149.8°
No. of Reflections Measured	Total: 1485
Corrections	Lorentz-polarization

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma w(\lvert Fo\rvert - \lvert Fc\rvert)^2$
Least Squares Weights	$\frac{1}{\sigma^2(Fo)} = \frac{4Fo^2}{\sigma^2(Fo^2)}$
p-factor	0.021
Anomalous Dispersion	All non-hydrogen atoms
No. Observations ($I>3.00\sigma(I)$)	387
No. Variables	118
Reflection/Parameter Ratio	3.28
Residuals: R; Rw	0.038 ; 0.041
Goodness of Fit Indicator	1.78

Max Shift/Error in Final Cycle	0.06
Maximum peak in Final Diff. Map	0.13 $e^-/\AA^3$
Minimum peak in Final Diff. Map	-0.13 $e^-/\AA^3$

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 lengths, bond angles and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre.

(1R,3S,4S,Rs)-(+)-S-Methyl-S-neomenthyl-N-tosyl sulfoximine(11b)

Experimental

Singal Crystal X-ray Structural analysis*

Data Collection

A colorless random crystal of $C_{18}H_{29}NO_3S_2$ having approximate dimensions of 0.20 x 0.40 x 0.50 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 tetragonal cell (laue class: 4/mmm) with dimensions:

$a = 10.630(1)$ Å

$c = 36.027(3)$ Å

$V = 4071.2(5)$ Å^3

For Z = 8 and F.W. = 371.55, the calculated density is 1.21 g/cm^3. Based on the systematic absences of:

h00: $h \neq 2n$

00l: $l \neq 4n$

and the successful solution and refinement of the structure, the space group was determined to be:

$P4_12_12$(#92) $P4_12_12$

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 $(0.65 + 0.14 \tan \theta)°$ 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 4745 reflections which were collected, 2698 were unique ($R_{int} = 0.053$). 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 24.9 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 = 1.77991e-07).

* See Notes on Page No. 101

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 925 observed reflections ($I > 3.00\sigma(I)$) and 241 variable parameters and converged (largest parameter shift was 0.04 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma||Fo| - |Fc||/\Sigma|Fo| = 0.034$$

$$R_w = \sqrt{(\Sigma w(|Fo| - |Fc|)^2/\Sigma w Fo^2)]} = 0.036$$

The standard deviation of an observation of unit weight[4] was 1.76. The weighting scheme was based on counting statistics and included a factor (p = 0.014) to downweight the intense reflections. Plots of $\Sigma w(|Fo| - |Fc|)^2$ versus $|Fo|$, reflection order in data collection, sin θ/λ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.20 and -0.18 $e^-/\AA^3$, 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	$C_{18}H_{29}NO_3S_2$
Formula Weight	371.55
Crystal Color, Habit	colorless, ~~rock~~ block
Crystal Dimensions	0.20 X 0.40 X 0.50 mm
Crystal System	tetragonal
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 = 10.630(1)Å c = 36.027(3) Å V = 4071.2(5) $Å^3$
Space Group	$P4_12_12$(#92) $P4_12_12$
Z value	8
D_{calc}	1.212 g/cm^3
F_{000}	1600.00
μ(CuKα)	24.88 cm^{-1}

B. Intensity Measurements

Diffractometer	CAD4

Radiation	CuKα ($\lambda = 1.54178$ 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	$(0.65 + 0.14 \tan \theta)°$
$2\theta_{max}$	149.8°
No. of Reflections Measured	Total: 4745 Unique: 2698 ($R_{int} = 0.053$)
Corrections	Lorentz-polarization Secondary Extinction (coefficient: 1.77991e-07)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma w(\lvert Fo\rvert - \lvert Fc\rvert)^2$
Least Squares Weights	$\frac{1}{\sigma^2(Fo)} = \frac{4Fo^2}{\sigma^2(Fo^2)}$
p-factor	0.014
Anomalous Dispersion	All non-hydrogen atoms
No. Observations ($I>3.00\sigma(I)$)	925
No. Variables	241
Reflection/Parameter Ratio	3.84
Residuals: R; Rw	0.034 ; 0.036

Goodness of Fit Indicator	1.76
Max Shift/Error in Final Cycle	0.04
Maximum peak in Final Diff. Map	0.20 $e^-/\AA^3$
Minimum peak in Final Diff. Map	-0.18 $e^-/\AA^3$

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.

REFERENCES

1. Scott, J.M. in "Asymmetric Synthesis"; Morrison, J.D.; Ed., Academic Press, New York, 1984 vol. 4, PP 1- 226.

2. Review : Gololobov , Y.G. ; Neseyanov, A.N.; Lysenko, V.P.; Boldeskul, I.E. Tetrahedron Report No. 219, Tetrahedron 1987, 43, 2607.

3. a) Johnson, C.R.; Schroeck, C.W.; Shanklin, J.R. J. Am. Chem. Soc. 1973, 95, 7418. b) Johnson, C.R., Kirchhoff, R.A. ; Reischer, R.J.; Katekar, G.F. J. Am. Chem. Soc. 1973, 95, 4287.

4. Kwart, H. ; Kahn, A.A. J. Am. Chem. Soc. 1967, 89, 1950.

5. Mikolojczyk, M. ; Pertikowsska, W.; Omelanczuk, J. Synthesis, 1987, 1009.

6. Furukawa, N. ; Tsujihara, K. ; Oae, S. Chem. Ind. 1969, 266.

7. Kennewell, P.D.; Taylor J.B. Chem. Soc. Rev. 1975, 4, 189.

8. Johnson, C.R. in "Comprehensive Organic Chemistry", Jones, D.N., Ed., vol.3, chapter 11, pp 224, pergamon press, Oxford, 1979.

9. Oae, S.; Harada, K.; Tsufihara, k.; Furukawa, N. Internat. J. Sulfur Chem. (A) 1972, 2, 49.

10. Bhan, P.; Sharma, C.S.; Rajaram,J.; Chawla, H.P.S.; Sukh Dev, Indian Patent No. 155 639 (Nov. 6, 1982); Chem. Abstr. 1986, 105, 78660

11. Taj, S.S.; Soman, R. Tetrahedron : Asymmetry 1994, 5, 1513.

12. Although (-)-16 is sometimes shown as having (S)-configuration, this is not substantiated. see a) Ref 3b. b) Pyne, S.G. Sulfur Reports, 1992, 12, 57.

13. Review : Walker, A.J. Tetrahedron : Asymmetry Report No.10, Tetrahedron : Asymmetry 1992, 3, 961 and refs. cited theirin

14. a) Rayner, D.R. ; Von Schritz, D.M. ; Day, J. ; Cram, D.J. J. Am. Chem. Soc. 1968, 90, 2721. b) Cram, D.J. ; Day, J. ; Rayner, D.R. ; Von Schriltz, D.M. ; Duchamp, D.J. ; Garwood, D.C. J. Am. Chem. Soc. 1970, 92, 7369. c) Truce, W.E. ; Klingler, T.C.; Brand, W.W. in "Organic Chemistry of Sulfur" Oae, S. ; Ed. ; Plenum Press, New York, 1977, P P 590.

15. There is no commenly adopted system of representing stereogenic sulfur. In this thesis, the unshared electron pair at sulfur, S-C single bonds , S=N and S=O double bonds are all represented by single lines giving tetrahedral form to stereogenic sulfur in sulfoxides and sulfoximines. a) Ref. 12b. b) Pyne, S.G.; Dong, Z.; Skelton, B.W. ; White. A.H. J. Chem. Soc. Perkin Trans I 1994, 2607. c) Bailey P.L.; Clegg, W.; Jackson, R.F. W. ; Meth - Cohn, O. J. Chem.

Soc. Perkin Trans I 1993, 343. d) Briggs, A.D. ; Jackson, R.F.W.; Clegg, W. ; Elsegood, M.R.J. ; Kelly J. ; Brown, P.A. Tetrahedron Lett. 1994, 35, 6945. e) Gais, H.J. ; Scommoda, M. ; Lenz, D. Tetrahedron Lett. 1994, 35, 7361. f) Marino, J.P. ; Laborde, E;.; Deering, C.F. ; Paley, R.S. ; Ventura, M.P. J. Org. Chem. 1994, 59, 3139.

16. Tipson, R.S. ; Clapp, H. J. Org. Chem. 1947, 12, 133.

17. Regitz, M.; Hocker, J. ; Liedhagner, A. in "Organic Syntheses" Coll. vol.5, Banmgarten, H.E., Ed., John Wiley, New Work, 1973, P. 179.

18. Vogel's Textbook of Practical Organic Chemistry, 5th edition, ELBS, Longman, UK, 1989., P 426.

19 a) Berti, G. ; Bottari, F. ; Ferrarini, P.L. ; Macchia, B. J. Org. Chem. 1965, 30, 4091. b) Rosenberger, M. ; Jackson, W. ; Saucy, G. Helv. Chim. Acta. 1980, 63, 1665.