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UNIVERSITÉ D'OTTAWA
UNIVERSITY OF OTTAWA

To Chantal

and

my Family

"Ce qu'on appelle créer, n'est parfois qu'une
aptitude à révéler ce qui existe secrètement.
Libérer, c'est déjà créer."

P. Marion, *Pensées,*
(1973), p.12

"La liberté est une source inepuisable d'inventions,
et chaque fois qu'on en favorise l'essor
on enrichit le monde."

Simone de Beauvoir,
La Force de l'Age,
(1960) p.153

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Finally, I would like to express my thanks to my colleagues Sagar Raj. Shakya, Shahrokh Esfandiari, Robert N. Ben and Shawna McKinon who in various capacities contributed to a more enjoyable working environment during the completion of these projects.

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ABBREVIATIONS AND SYMBOLS

δ	chemical shift (in ppm)
Δ	heat (reflux)
Ac	acetyl
Ac_2O	acetic anhydride
AcOH	acetic acid
AcCl	acetic chloride
AIBN	azobisisobutylnitrile
Aq	aqueous
Ar	aryl
Bn	benzyl
BTEAC	benzyltriethylammonium chloride
br	broad
°C	degrees Celcius
C.I.	chemical ionization
CCl_4	carbon tetrachloride
d	doublet in ^1H NMR
DEPT	distortionless enhanced polarization transfer
dd	doublet of doublets in ^1H NMR
DMF	dimethylformamide
DMSO	dimethylsulfoxide
ee	enantiomeric excess
E.I.	electron impact
eq.	equivalent(s)

Et_2O	diethyl ether
EtOAc	ethyl acetate
EWG	electron withdrawing group
HMPA	hexamethylphosphoric triamide
HMPT	hexamethylphosphorous triamide
HOMCOR	homonuclear correlation
HRMS	high resolution mass spectrometry
hv	ultraviolet irradiation
Hz	hertz
J	coupling constant
i-Pr	isopropyl
IR	infrared
LDA	lithium di*iso*propylamine
LAH	lithium aluminium hydride
m	multiplet in ^1H NMR
M^+	parent molecular ion
MCPBA	*m*-chloroperoxybenzoic acid
Me	methyl
MeOH	methanol
min	minute
mL	milliliter
mmol	millimole
m.p.	melting point
Ms	mesylate
MS	mass spectrum

m/z	mass to charge ratio
NBS	*N*-bromosuccinimide
NaOH	sodium hydroxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Ph	phenyl
PTC	phase transfer catalysis
Py	pyridine
q	quatet in ^{1}H NMR
s	singlet ^{1}H NMR
t	triplet ^{1}H NMR
TBAC	tetrabutylammonium chloride
t-BuSH	*t*-butylthiol
TEA	triethylamine
THF	tetrahydrofuran
TLC	thin layer chromatography
TsOH	*p*-toluenesulfonic acid

ABSTRACT

Part A:

Several optically active thiolanes were synthesized and converted into sulfonium salts. These were subsequently transformed into the corresponding sulfur ylides which in turn reacted with carbonyl compounds to produce optically active epoxides. *trans*-2,3-Diaryloxiranes have been obtained in up to 83% enantiomeric excess *via* the reaction of S-benzyl ylides prepared from optically active *trans*-2,5-disubstituted thiolanes. The complete stereofacial transfer of a benzylidene group to a substituted benzaldehyde was successfully accomplished using S-benzyl ylide derived from (1R,2S,3R,5S)-2,3-dibenzyl-1,8,8-trimethyl-3-thianiumbicyclo[3.2.1]octane perchlorate 123 (prepared from 1R,3S-(+)-camphoric acid). *trans*-Stilbene oxides were produced with ee's approaching enantiomeric purity. These results represent the first example of the preparation of epoxides in nearly enantiomerically pure form by a sequence which involves both a carbon-carbon and a carbon-oxygen bond rather than only carbon-oxygen bond formation. A rationale for the high chiral induction in the latter case based on the control of facial selectivity at the ylide will be discussed. The facial selectivity at the carbonyl is believed to play a minor role. The design of potentially more efficient chiral sulfide auxiliaries and their use in the synthesis of epoxide is also presented.

Part B:

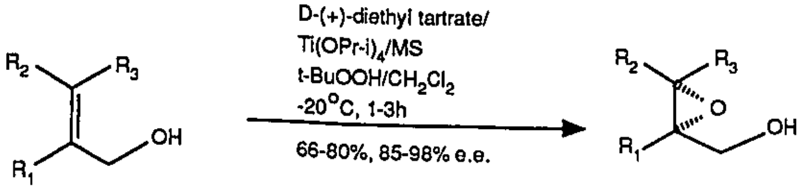
Erythro- and threo-1,2-diphenyl-2-butylsulfinylethanol **154** and **158** were prepared from the condensation of the α-lithio derivative of benzyl-*t*-butyl sulfoxide with benzaldehyde. The reaction of the *erythro*-isomer with sulfuryl chloride gave an unknown substance whose structure was established by X-ray difractometry as (2R*,3S*,4R*,6R*)-3,4-diphenyl-6-(diphenylmethyl)-1,5-dioxa-2-thiane-2-oxide **156**, the first representative of a new heterocyclic ring system. Similar treatment of the *threo*-isomer **158** resulted in the formation of **157**, a stereoisomer of **156**.

PART A: SULFUR YLIDE CHEMISTRY: SYNTHESIS OF OPTICALLY ACTIVE EPOXIDES.

INTRODUCTION

The development of organic synthetic tools continues to flourish and expand in a relentless manner.[1] This growth is a response to voids in efficient methodology needed to build increasingly complex synthetic targets of biological importance. In particular, the field of stereoselective synthesis of natural products containing polyol units has captured a lot of interest in recent years.[2-4] Some of the recent advances in the developement of stereocontrolled reactions has been reviewed by Hanessian.[5]

Due to their high reactivity and the predictability of both the regio- and stereochemical outcome of ring opening reaction, epoxides are often key intermediates in the course of total synthesis. However it was not until the very recent discovery of the stereoselective epoxidation of allylic alcohols[6] that optically active epoxides became readily available synthons. The diverse application of these hydroxy epoxides accessible by the Sharpless asymmetric epoxidation is reflected in their use in the syntheses of biologically active compounds such as the 1,3-polyol antibiotics; ionomycin[7,8], oligomycin[9], rutamycin[9], cytovaricin[9,10], amphotericin B[11,12], mycoticin A & B[13]; immunosuppressants: (-)-FK-506[14]; hypocholesterolemic compounds such as (+)-compactin[15], (+)-mevinolin[15] and (+)-breynolide[16]; and in the synthesis of amino acids.[17] In spite of the wide application of these epoxides, the prefixed carbon skeleton of the allylic alcohols creates some limitations in their use. All syntheses of optically active epoxides whether by epoxidation of an alkene (equation 1[6], 2[18], 3A[19] and 3B[20]) or ring closure reactions (equation 4[21], 5[22] and 6[23]) suffer from the same restriction i.e. the carbon content of the molecule is not altered during the epoxide forming sequence.



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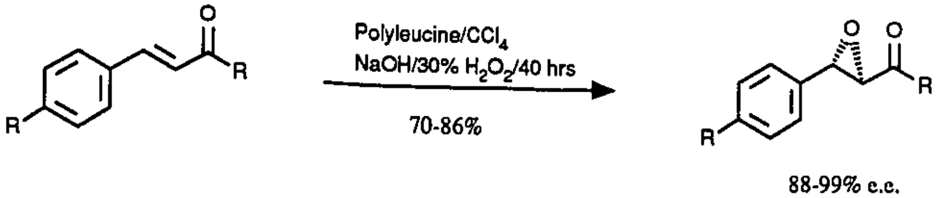

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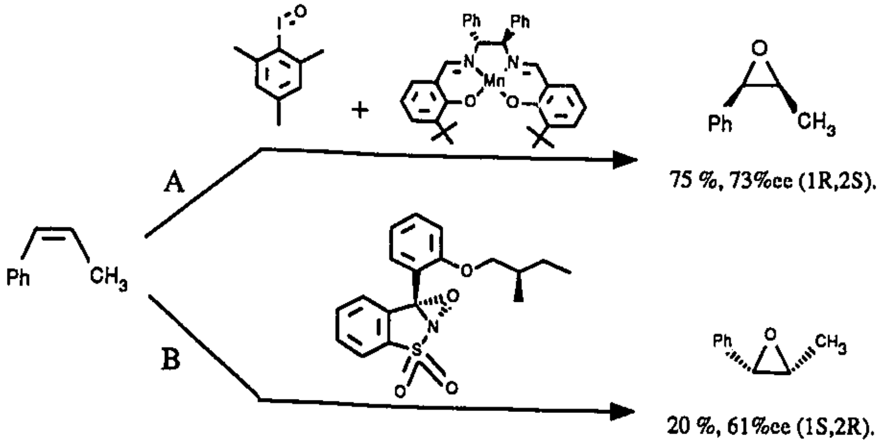

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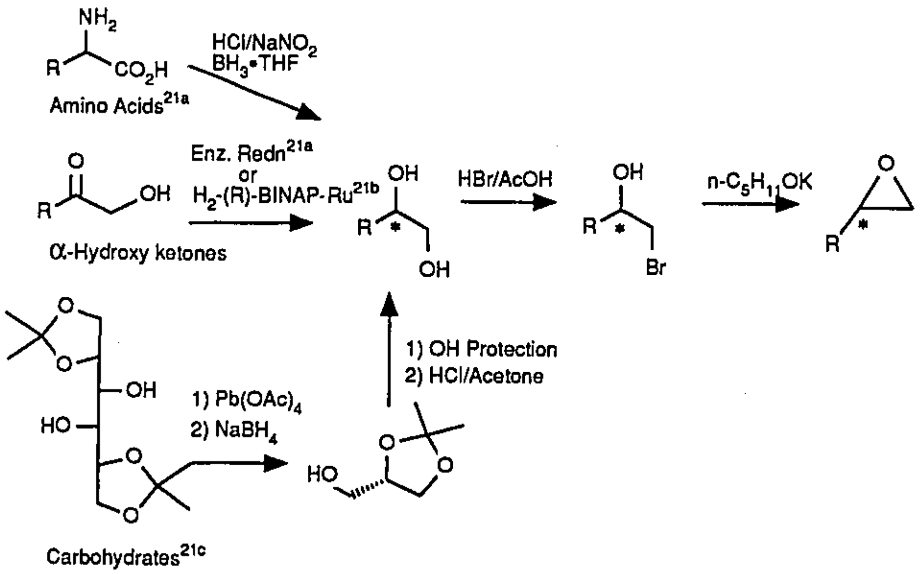

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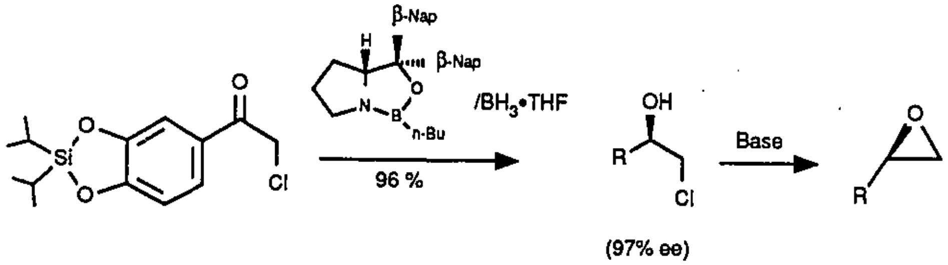

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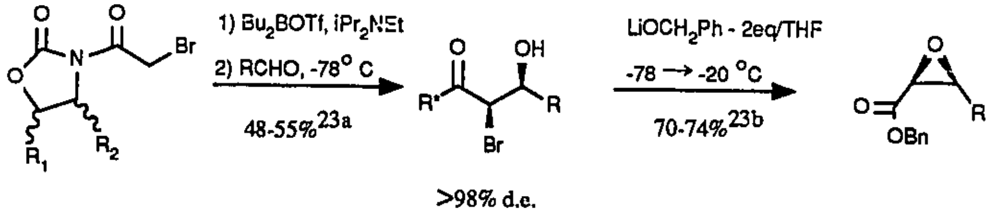
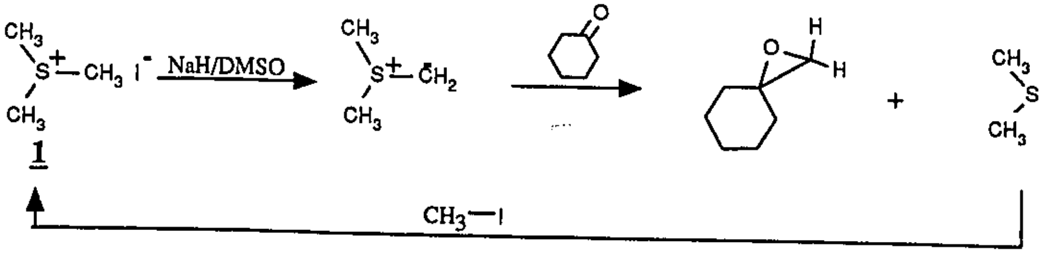


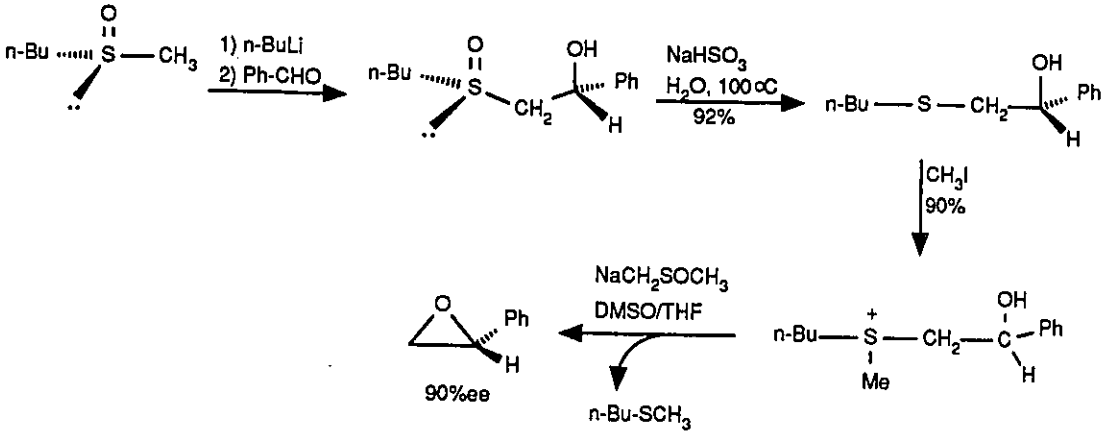
(6)

A complementary asymmetric synthesis of epoxides in which a C-C bond and a C-O bond is formed is lacking. Such a method would allow the preparation of oxiranes from smaller prochiral units. Ideally, like the Sharpless epoxidation methodology, this strategy would be catalytic in nature. The general methodology for such a process was first demonstrated in 1962 by Corey and Chaykovsky[24] using dimethylsulfonium methylide derived from trimethylsulfonium iodide, 1 (Scheme 1).



Scheme 1.

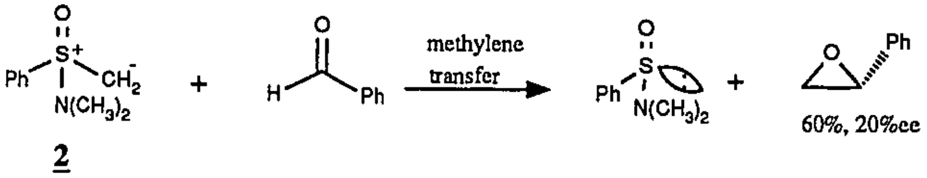
The closest known analogies to this concept which yield optically active epoxides from smaller units involve the condensation of α-lithiosulfoxides derived from optically active sulfoxides with carbonyl compounds followed by a 3-step sequence (Scheme 2).[25]



Scheme 2.

This sequence is impractical except in special circumstances due to its length and the fact the stereogenic center in the starting sulfoxide must be sacrificed.

The preparation of oxiranes in only moderate optical purity has been reported in the reaction of aldehydes such as benzaldehyde and the optically active sulfoximine 2 (equation 7).[26]



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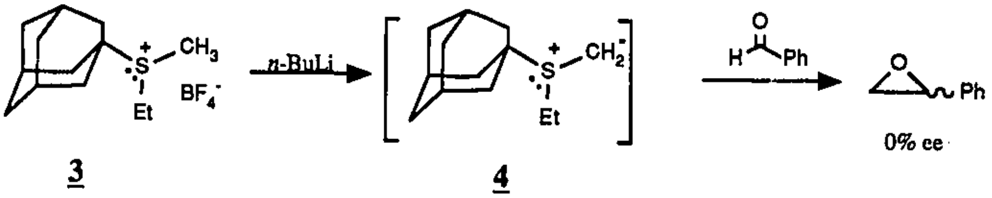
Initial attempts to generate optically active epoxides from sulfur ylide and carbonyl compound reaction were reported by Trost and Hammen[27]. These authors showed that the sulfur ylide derived from sulfonium salt 3 transferred its methylene group to benzaldehyde with essentially no enantiofacial selectivity (equation 8). The lack of chiral induction was not due to racemization of sulfur chirality during generation of ylide 4 since deuteration of the ylide regenerated optically pure monodeuterated 3. The Trost results probably disuaded further research in this area for a number of years.



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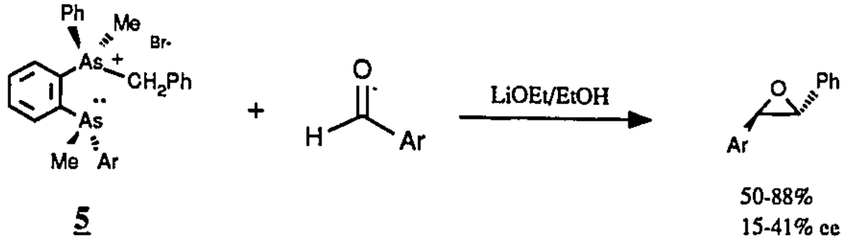
A claim of the enantioselective synthesis of 2-phenyloxirane from benzaldehyde *via* Me_2S^{+}-$^{-}CH_2$ generated by the presence of catalytic amounts of an optically active β-oxido-quaternary ammonium zwitterion, under phase-transfer conditions[28] was later shown to be in error.[29]

In 1983, new hopes in this field were rekindled with the extension of these studies to include the chiral arsonium salts 5. Benzylidene transfer from the ylide derived from 5 to benzaldehydes gave *trans*-2,3-diaryloxiranes with substantial asymmetric induction (equation 9).[30]



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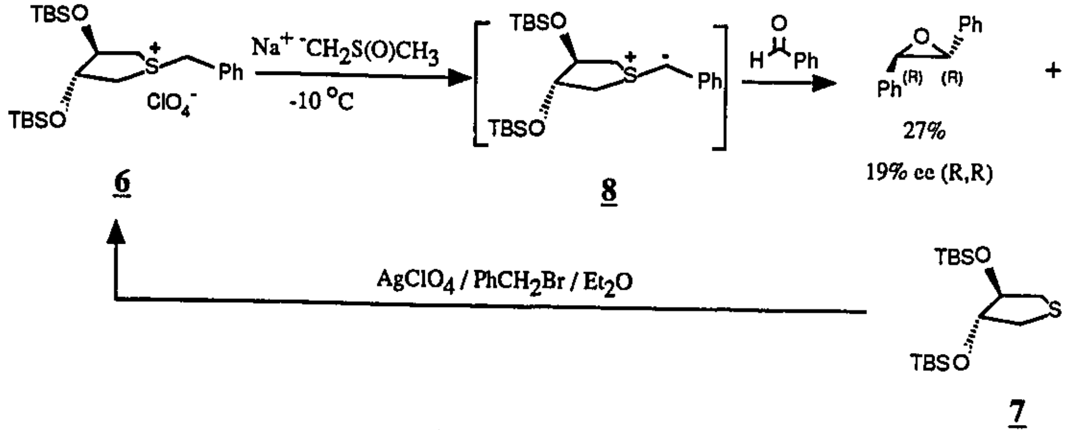
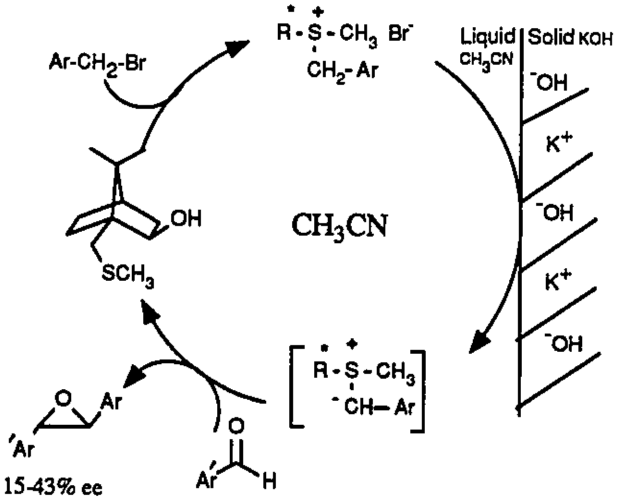
For the past few years, our laboratory has embarked on a program to design and prepare chiral non-racemic sulfur ylides capable of transferring asymmetry in reactions with a carbonyl compound. The first representative of this new class of reagents was uncovered with the preparation of a C_2 symmetric thiolanium salt 6. The salt was obtained from S-benzylation of the sulfide 7, available from L-tartrate in 6 steps. The S-benzylylide 8 sucessfully transferred its benzylidene group to produce *trans*-stilbene oxide with modest enantiomeric excess (Scheme 3).[31a] Important new development in



Scheme 3.

this field have recently been disclosed by Furukawa and Sugihara.[31b] They demonstrated that several optically active sulfides derived from 10-camphorsulfonic acid could function as both mediators and chiral auxiliaries for the formation of optically active oxiranes. Thus, a one-pot reaction system composed of the enantiomeric sulfide, alkyl halides and aldehydes in the presence of solid potassium hydroxide under liquid-solid two-phase conditions afforded optically active 1,2-diaryloxiranes with moderate enantiomeric excess. Under these conditions the sulfides are alkylated to sulfonium salts and converted to the corresponding ylides *in situ* (Scheme 4). A large solvent effect was observed for the chemical yield of the oxiranes. The best chemical yields (≈40% based on the aldehyde) were found with acetonitrile as solvent. Although the turnover cycle for the reaction was not thoroughly examined, the highest observed ratio of product to catalyst (i.e. the sulfide) was a modest 2.



Scheme 4.

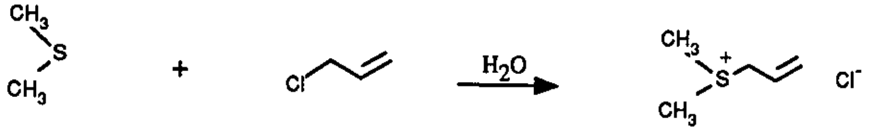
This thesis is largely concerned with the exploration of the use of more efficient sulfide auxiliaries for the synthesis of enantiomerically pure epoxides. These auxiliaries will be divided into two chapters. First, the preparation of thiolanium salts from C-2 symmetric thiolanes and the degree of asymmetric delivery of the benzylidene group by the corresponding S-benzylylides onto aromatic aldehydes is discussed. In the second part, the design and synthesis of thiane derived from camphoric acid is described. A proposal which accounts for the origin of the excellent chiral induction in the transfer of alkylidene group to both aldehydes and ketones is presented. The scope and limitations of these camphoric acid derived thianium salts as well as the design of potentially more efficient sulfur ylide reagents is also discussed.

1. THE CHEMISTRY OF THE SULFONIUM GROUP.

In order to design sulfur ylides suitable for the above stated purpose the fundamental physical and chemical properties of the sulfonium salt and ylides need to be understood. Coverage will not be thorough because of the availability of other reviews on this subject.[32,33-36] Instead, only information judged pertinent to the judicious choice of a sulfur containing chiral auxiliary has been selected.

1.1 Synthesis of Sulfonium Salts.

Dialkyl sulfides have sufficient nucleophilicity to react with primary alkyl halides. The reaction may be accelerated by use of polar solvents such as methanol, acetone, acetonitrile or nitromethane as the transition state and products are more polar than the reactants.



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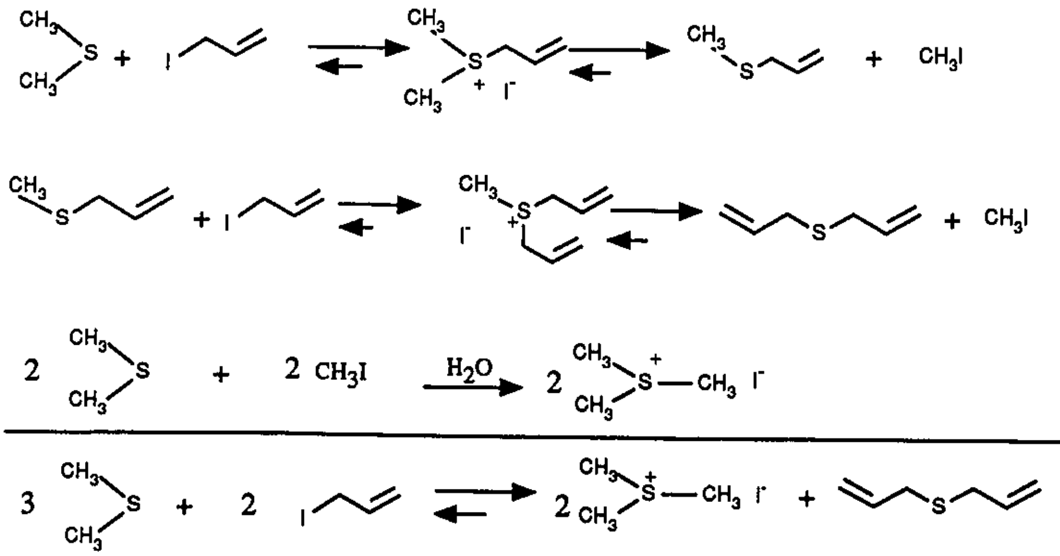
Alkyl iodides are the most reactive of the simple alkyl halides but, in general, the reaction rate decreases with chain elongation or chain branching. The alkylation of a sulfide is reversible with the ease of reversal being dependent on the nucleophilicity of the counter ion (I⁻>Br⁻>Cl⁻). There is also a tendency for the formation of the salt containing the alkyl groups to have the lowest molecular weight.[37] For instance, the reaction of allyl iodide with dimethyl sulfide in methanolic solution yielded trimethylsulfonium iodide *via* the following series of reactions (equations 11-13).[38]



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(12)

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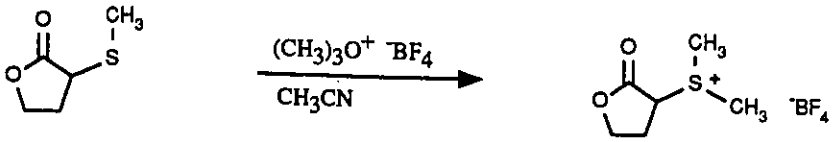
(14)

The reversible alkylation of a nucleophile can be supressed by the formation of salts composed of non-nucleophilic anions like sulfate, sulfonates, trifluoromethanesulfonates, tetrafluoroborates and perchlorates. The treatment of secondary and tertiary alcohols with a mixture of acetic and sulfuric acid in the presence of dialkylsulfides leads to the formation of sulfonium bisulfate salts, presumably *via* the intermediate carbocations.[39] Primary alcohols will react with dialkyl sulfides in the presence of 70% perchloric acid to give the trialkylsulfonium perchlorate salt, provided that water is removed during the reaction by azeotropic distillation (equation 15).[40]

$$R_2S \quad + \quad R'OH \xrightarrow[-H_2O]{70\%\ HClO_4} R_2\overset{+}{S}-R'\ ClO_4^- \qquad (15)$$

R=R'=Et
R=R'=*n*-Pr
R=R'=*n*-Bu
R=R'=Bn
R=*n*-Bu, R'=Bn

For acid-sensitive sulfides, as well as heat sensitive sulfonium salts, milder conditions are required. To this end, a variety of alkylating agents including dialkyl sulfates,[41] alkyl sulfonates[42] and alkyl trifluoromethanesulfonates (alkyl triflates)[43,44] have been used in combination with reactive sulfides. Unreactive sulfides can be methylated or ethylated in good yield by treatment with trimethyl- and triethyloxonium tetrafluoroborates in dichloromethane.[45,46] Other alkyl groups can also be introduced onto sulfur *via* activation of the corresponding alkyl halide. For example, a wide variety of sulfides react, with a series of unreactive secondary alkyl halides (usually bromides or iodides) in the presence of silver tetrafluoroborate (or perchlorate). Best yields were obtained (40-90%) in acetone, acetonitrile, nitromethane or dichloromethane (equation 17, 18).[27,47-49] Although very general, this method has been claimed to lead to mixtures of



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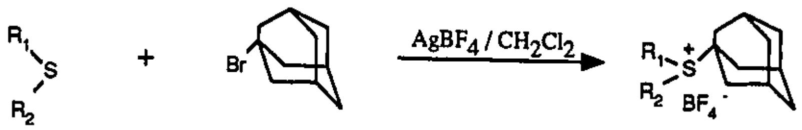
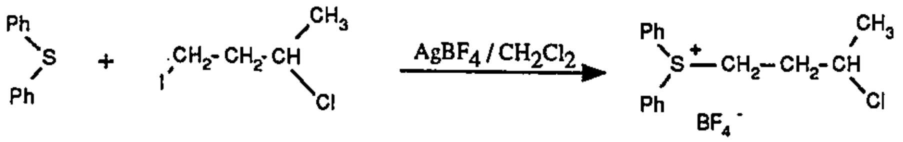


(17)[27]

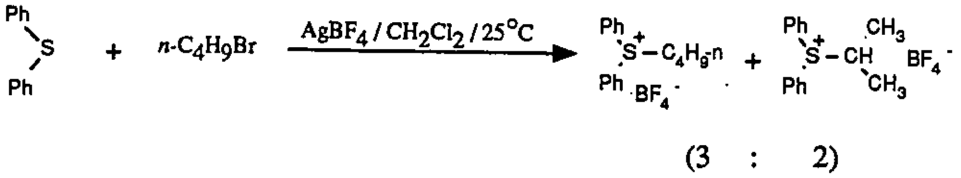
40 - 90%

R_1=CH_3, R_2=Et
R_1=Et, R_2=allyl
R_1=Bn, R_2=allyl



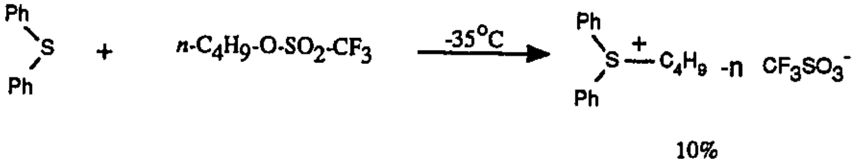
(18)[49]

primary and secondary alkylsulfonium salts when primary *n*-alkyl halides are used (equation 19).[50] In these cases, the triflate esters of saturated alcohols could be used to



(19)

alkylate sulfides, giving the intact *n*-alkyl sulfonium triflates, albeit in poor yields.[50]



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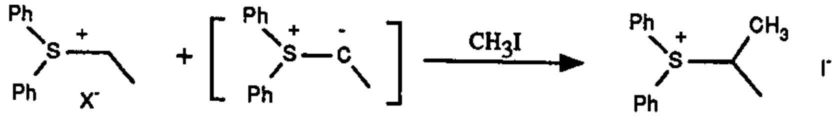
Sulfonium salts can be prepared by both inter-(equation 21) and intramolecular alkylation (equation 22) of the ylides precursors.[49,51]



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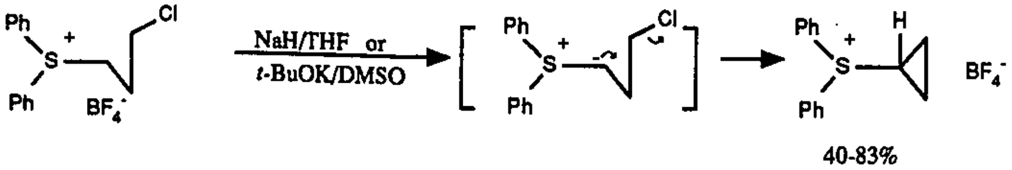
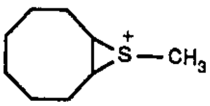


(22)

1.2 Stability of Sulfonium Salts

Although stable S-alkyl thiiranium, thiirenium and thietanium salts such, as **9**, **10** and **11** exist, the preparation of stable 3- and 4-membered ring sulfonium salts in general



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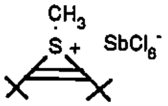

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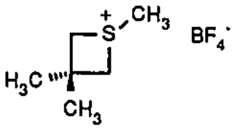


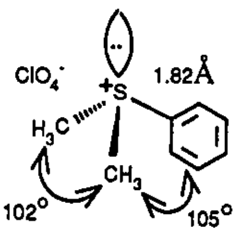
11

requires low temperatures and the absence of nucleophilic reagents or solvents which could cause ring opening. Due to this lack of stability the chosen chiral sulfide must not contain a thiiran nor thietane ring.

Other sulfonium salts having a non-nucleophilic counter ions including non-cyclic *n*-, *iso*- and *tert*-alkyl groups as well as cyclic salts constituted of five-, six-, seven- and higher-membered ring, are all generally chemically stable.[52]

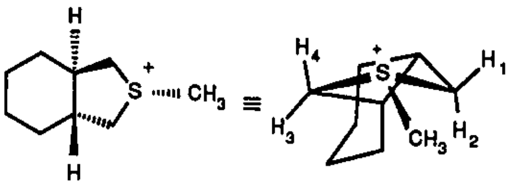
1.3 Structure of Sulfonium Salts

Based on various X-ray diffraction studies of cyclic and non-cyclic-S-methyl sulfonium salts,[53] the sulfonium cations are shown to exhibit pyramidal geometry with the sulfur atom lying approximately 0.8Å above the base of the pyramid defined by the three bonded carbon atoms. The mean value for a C-S$^+$ bond length is 1.81Å; the mean value for a C-S$^+$-C bond angle is 102.5°. These experimental values agree well with the



electronic state of the sulfur bonds. In its sp^3 hybridized state the electronic structure of sulfur atom is $1s^2 2s^2 2p^6 (3sp^3)^2 (3sp^3)^2 (3sp^3)^1 (3sp^3)^1$. Two of the σ bonds formed by the overlap of two singly occupied $(3sp^3)^1$ hybridized orbitals on sulfur with singly occupied $(2sp^3)^1$ orbitals of 2 different carbon atoms. The formation of a 3rd σ bond between sulfur and carbon may be viewed as involving one $(3sp^3)^2$ filled orbital on sulfur and an empty $(2sp^2)^0$ orbital on the carbon (i.e. as in a carbocation).[54] Thus, according to VSEPR theory the three σ bonds and the remaining unshared pair of electrons [in an $(3sp^3)^2$ orbital] in a trialkylsulfonium cation are expected to be distributed tetrahedrally, i.e. the lone pair of electrons forces the atoms to adopt a pyramidal geometry with the sulfur atom at the apex.

Stereochemical analyses of thiolanium ions have also been carried out by using n.m.r. spectroscopy.[55,56] Two limiting conformations exist for the thiolane ring: one is the half-chairs, **<u>13A</u>** and **<u>13B</u>**, and the other is the envelope form, **<u>13B'</u>**. In the half-chair conformation, carbon C-4 is above and carbon C-3 is below the plane containing the C_2-S-C_5 atoms. This spacial arrangement has a maximum degree of staggering at the C_3-C_4 carbons. For cation **<u>12</u>**, the five-membered ring is rigidly held in the half-chair form because of the *trans* ring fusion. This form enforces a high degree of puckering at the C_3 and C_4 carbons.



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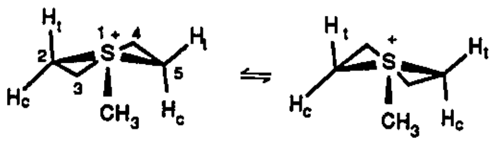
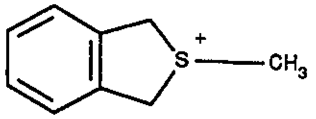


<u>13A</u> **<u>13B</u>**

half-chair conformations

In the envelope form **<u>14A</u>**, one atom is out of the plane formed by the remaining four atoms. The structure has a maximum staggering at the C_2-S-C_5 bonds. An example of this envelope fixed form is seen in salt **<u>14</u>**. The flat aromatic ring in cation **<u>14</u>** ensures that the fused thiolan ring adopts an envelope conformation.



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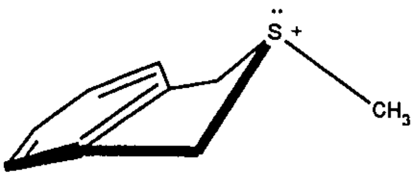
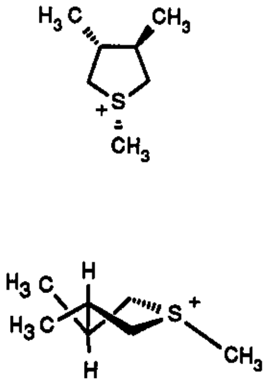


envelope form **14A**

Qualitative information on the preferred conformation of various methyl substituted S-methylthiolanium cations **15**, **16** and **17** was deduced by the comparison of their ^1H and ^{13}C n.m.r. signals with those observed for the conformationally rigid model cation **12**. The signals for the salts were also compared with the 1,3,3-trimethylthiolanium cation **18**[57] which, exists in a half-chair ring conformation. The thiolanium cations **15**-**18** are adequately described in terms of a half-chair conformation with the exception of the 1,2-dimethyl and 1,2,3-trimethylthiolanium cation. In the case of methyl groups in the 1,2- or 1,2,3-positions the half-chair is appreciably deformed to a quasi-envelope with C_3 out of the plane (see **17**).[58]



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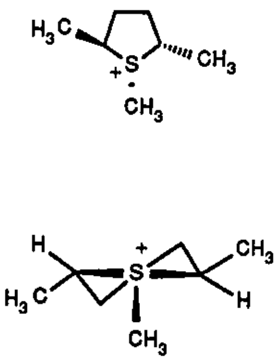

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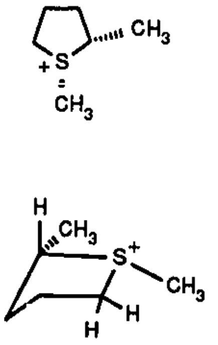

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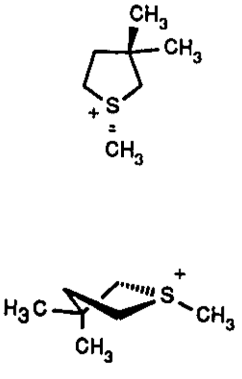

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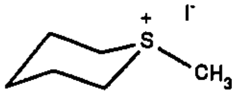
In the cation **15** and **16**, the substituents as well as the S-methyl group occupy a quasi-equatorial position, whereas in **18**, the *cis*-methyl at C-3 prefers a quasi-axial orientation. Unfortunately, there is no X-ray data available to support the conformational preferences of these S-methyl-methyl substituted thiolanium cations.

The stereochemistry of thianium salts, on the other hand, are better known and some X-ray data for S-methylthianium salts have been reported (see **19**, **20** and **21**). In these salts, there is a preference for the six-membered ring to adopt a chair form in a conformation which would allow the sulfur substituent to be in an equatorial position such as in **19** and **20**.[53] In the salts **19** and **20**, conformational analysis revealed that the bond angles around the sulfur atom are such that the exocyclic $^{+}S-CH_3$ group is arranged almost *anti* to the $C_{(\alpha)}-C_{(\beta)}$ bonds. Studies of the thianium cation in solution also support the preferred equatorial orientation but not to a great extend. In fact, a low temperature (-90°C) ^{13}C n.m.r. conformational equilibrium study of substituted thianium cations showed both conformers to be present with only marginal excess of one over the other (equation 23, 24 and 25).[59] The sulfur substituent was placed into either the equatorial or



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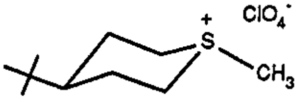

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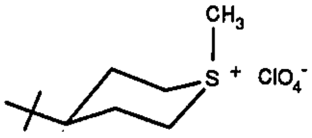

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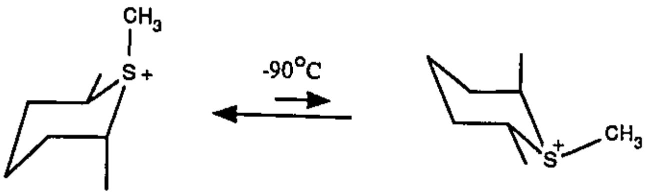
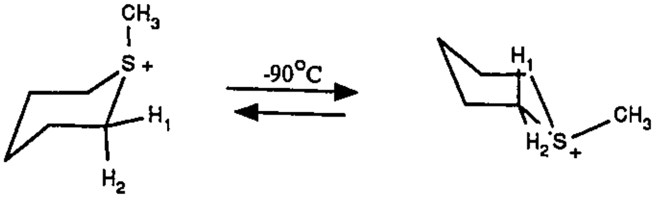
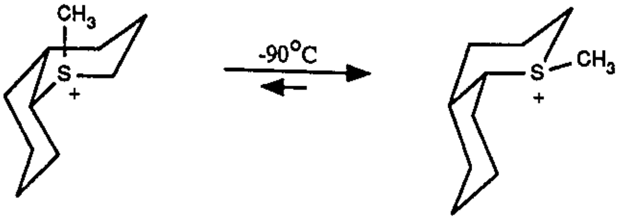


K=0.6 (23)

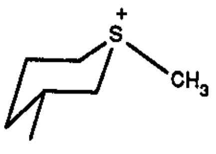


K=1.0 (24)



K=1.8 (25)

the axial position provided that a bulky substituent, which would compete for the equatorial position is simultaneously present in the six membered ring cation. For example, in *trans*-4-*t*-butyl-S-methylthianium cation **20** in solution both the S-Me and the *t*-butyl group are equatorial. The *cis*-4-*t*-butyl-S-methyl thianium cation exists only in the conformation depicted in **21**, having an axial S-Me since this allows the more bulky *t*-butyl group to be placed equatorially. Similarly, *cis* isomer **22** exists exclusively in the diequatorial conformation whereas in the *trans* isomer **23** the conformation having equatorial C-3 methyl and axial S-Me groups is the more stable.



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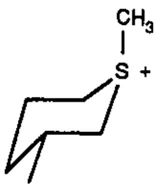

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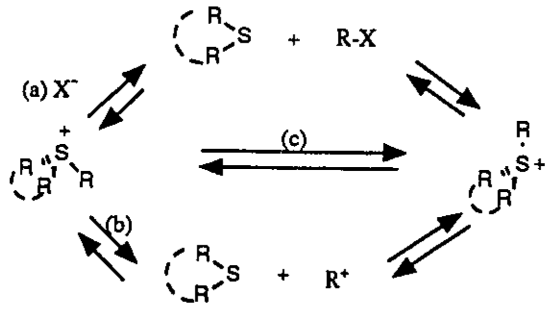
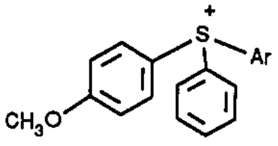
1.4 Stereomutation of Sulfonium Salts

Sulfonium salts can undergo configurational change at sulfur by: (a) S_N2 attack at the α-carbon followed by reformation of the salt, (b) reversible dissociation into a carbocation ion and neutral sulfide molecule *via* an S_N1 mechanism; or (c) pyramidal inversion at sulfur (Scheme 5). Thus sulfonium salts are subject to epimerization or racemization *via* route (a) if the counter anion is a good nucleophile such as halide ion or by process (b) if carbon sulfur bond cleavage leads to a relatively stable carbocation (for example a R=CH_2-*p*-methoxyphenyl group). Epimerization at sulfur *via* pyramidal inversion will dominate over an S_N1 process if at least one substituent attached to sulfur is bulky for example adamantyl, *t*-butyl and phenyl groups.[59] Path (a) could be eliminated if the sulfonium salt has a non nucleophilic counter anion such as tetrafluoroborate or perchlorate. Thus enantiomers of triarylsulfonium ion <u>24</u> have not been isolated due to their rapid pyramidal inversion at room temperature.[60] Optically active alkyldiaryl-sulfonium salts <u>25</u> have been resolved and were also found to racemize slowly at 25°C in methanol. Similarly, dialkylarylsulfonium salts <u>26</u> recemized even more



Scheme 5. Processes involved in the epimerization of a sulfonium salt.



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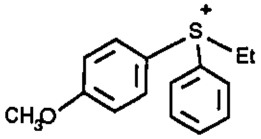

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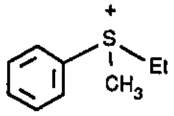

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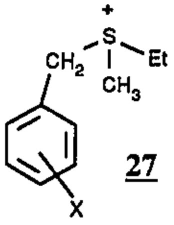

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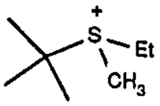

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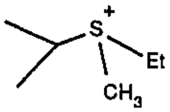

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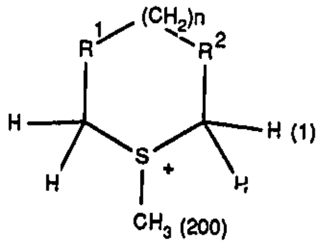
slowly (~10 times less) than the alkyl diarylsulfonium salts 25. In these cases racemization rates were measured in methanol at 50°C.

Trialkylsulfonium salts containing a tertiary alkyl group such as in 28 or a benzyl group like in 27 undergo racemization at 50°C in ethanol surprisingly, mainly by pyramidal inversion (Scheme 5, path (c)) rather than by a heterolytic dissociation to generate *t*-butyl cation (Scheme 5, path (b)). However, there is evidence to suggest that the *p*-methoxybenzylethylmethylsulfonium salt (27; X=4-OCH_3) racemizes principally by C-S bond heterolysis.[61] Interestingly, the isopropyl substituent in 29 had approximatively the same effect on racemization as the phenyl group in 26. The relative rates of isomerization of 29 to 26 were 1.5:1 at 50°C in methanol. Trialkylsulfonium salts lacking serious steric congestion as in cyclic salts including 15, 16, 17, 19, 20 and 21 racemized most slowly; complete racemization occurred upon heating at 100°C for a 50 hour period in water.[58] High ring strain during pyramidal inversion[62] is believed to account for the slow rates of racemization of the cyclic sulfonium salts.

Thus the chosen chiral auxiliary must not only preserve its conformational integrity but should be designed so that the stereochemical information at the sulfur atom is not lost by facile pyramidal inversion.

1.5 Deprotonation of Sulfonium Salts

The *alpha* protons of the sulfonium ion are fairly acidic with the pKa of Me_3S^+ having been calculated to be ≅18.9.[63] A kinetic acidity study performed on a series of $(RCH_2)_2S^+\text{-}CH_3$ has demonstrated that the S^+-methyl group exchanged its protons about 200 times more rapidly than the S-methylene or S-methine protons.[64] This can be interpreted in terms of the electron-releasing effect of the alkyl groups which would destabilize the transition state for proton removal. R^1 and R^2 had little effect on the $S^+\text{-}CH_3$ exchange rate constants regardless of whether R^1 and R^2 were simple alkyl groups part of a 5-, 6- or 7-membered ring system, **30**, (R^1=R^2= $-CH_2-$; n=0,1,2). On the other hand geometry has a significant effect on the relative acidities of the α-methylene protons. *Ab initio* calculations on $H_2S^+\text{-}CH_2^-$ show a minimum energy structure for this ylide when the lone pairs on the carbon and the sulfur are orthogonal (⊥). Maxima in energy were found when the carbon lone pair-sulfur lone pair dihedral angles were at 0 and 180° (11.0 and 7.6 Kcal mole^{-1} respectively) (Figure 1). Thus the arrangement depicted in **31** is more stable than that depicted in **32** and **33**. Since hydrogen-deuterium exchange in the thiolanium ion is believed to have a transition state which resembles a carbanion (ylide)[64], it seems reasonable that protons having a gauche (or at best an orthogonal) relationship to the sulfur lone pair in a given sulfonium cation should exchange most rapidly. It is



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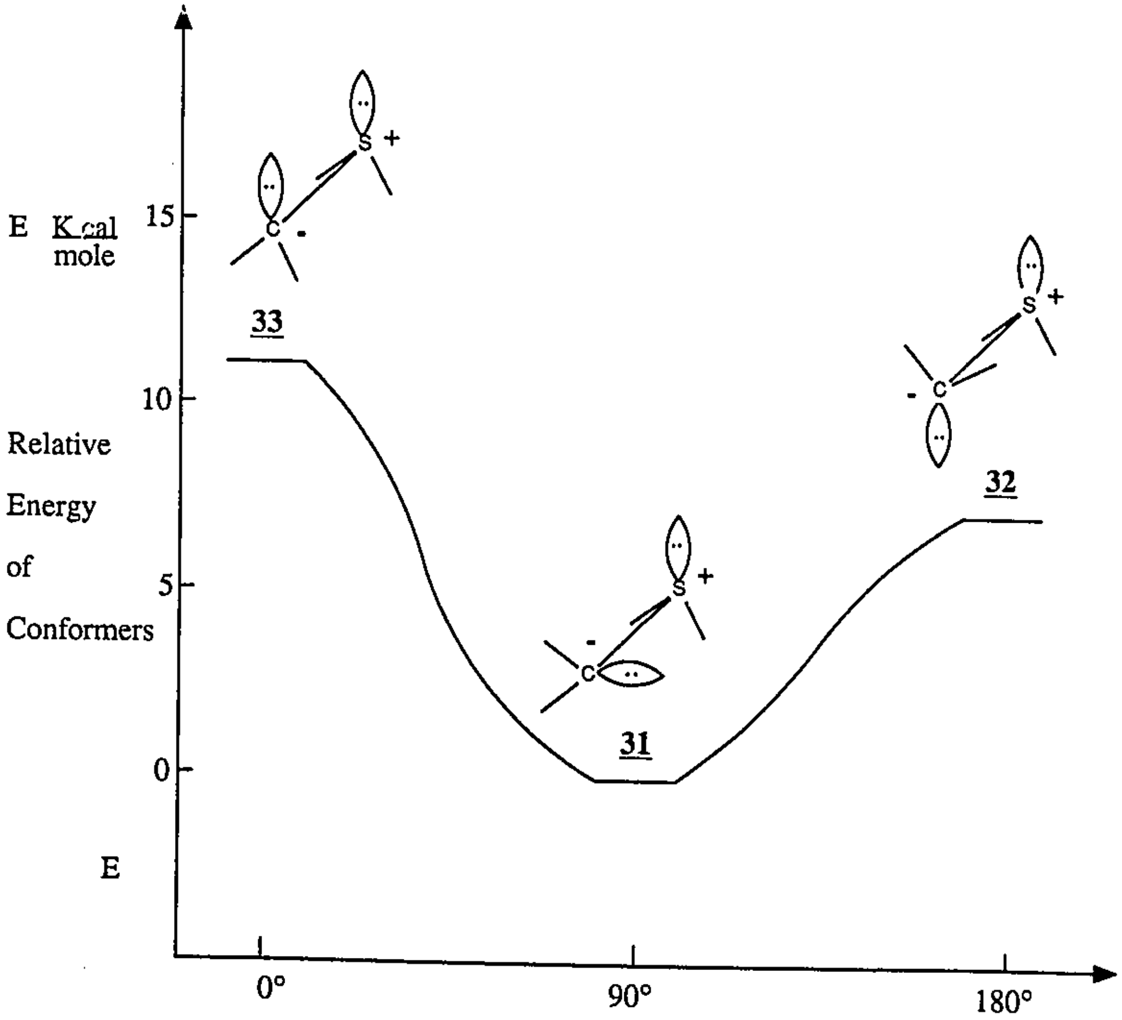
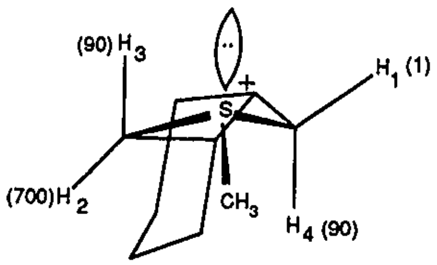


Figure 1. Lone pair(S)-lone pair(C) torsional angle, degrees.

noteworthy that such stereoselective H-D exchanges can only be observed for a conformationally static proton. In conformationally mobile sulfonium salts, the rate of H-D exchange for a given α-methylene proton corresponds to an average of the different rates of exchange for that proton in each of the conformers multiplied by their distribution at equilibrium (under NaOD, in D_2O exchange conditions). For example, the conformationally rigid thiolanium cation <u>34</u> displays considerable stereoselectivity with its $H_{(2)}$ being exchanged most rapidly. The relative rate of deprotonation of the four ring protons in <u>34</u> are shown in parenthesis.[57] Examination of a scale model of <u>34</u> reveals that the methylene proton-lone pair(s) dihedral angle is close to ortogonality for H_2 (100°) and measures for other protons as follow: H_4(125°); H_3(30°) and H_1(5°). The latter, the least acidic, has a dihedral angle close to 0°.[65] Similarly, for the conformationally constrained



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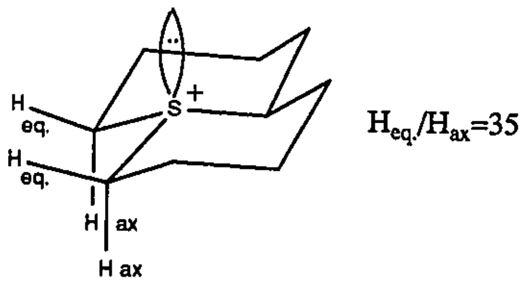


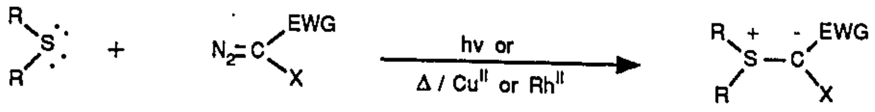
35

compound **35**, it was reported that the equatorial protons exchanged 35 times faster than the axial ones.[66] In more flexible thiolanium salts like **13** and **18**, which exist as an equilibrium between two half-chair forms **13A** and **13B** (page 13), the proton H_c (*cis* to the S-methyl group) is closer to orthogonality with the S-lone pair than is the proton H_t (*trans* to S-Me). Correspondingly, a reactivity ratio for H_c:H_t was found to be ≈12:1.[64,67] Hydrogen-deuterium exchange occurs without stereoselectivity in homologous 6- and 7-membered rings. In these compounds, the α-methylene protons H_1 and H_2 adopt similar equatorial positions thus having similar dihedral angles formed from the C-H_1 and C-H_2 bonds with the lone pair of the sulfur due to conformational equilibrium (equation 24).[65]

Thus the chosen chiral sulfide auxiliary should produce sulfonium salts having a greater acidity for the α-hydrogens of the groups to be transferred, for example benzyl, allyl or methyl,than in other α positions. Serious competitive deprotonation is expected to occur between the α-hydrogens of the chiral auxiliary and the group to be transferred if the latter contains: methylene protons (ex Me_2S^+-ethyl, -*n*-propyl,...-*n*-octyl...etc), or worse a methine proton (ex Me_2S^+-*i*-propyl).

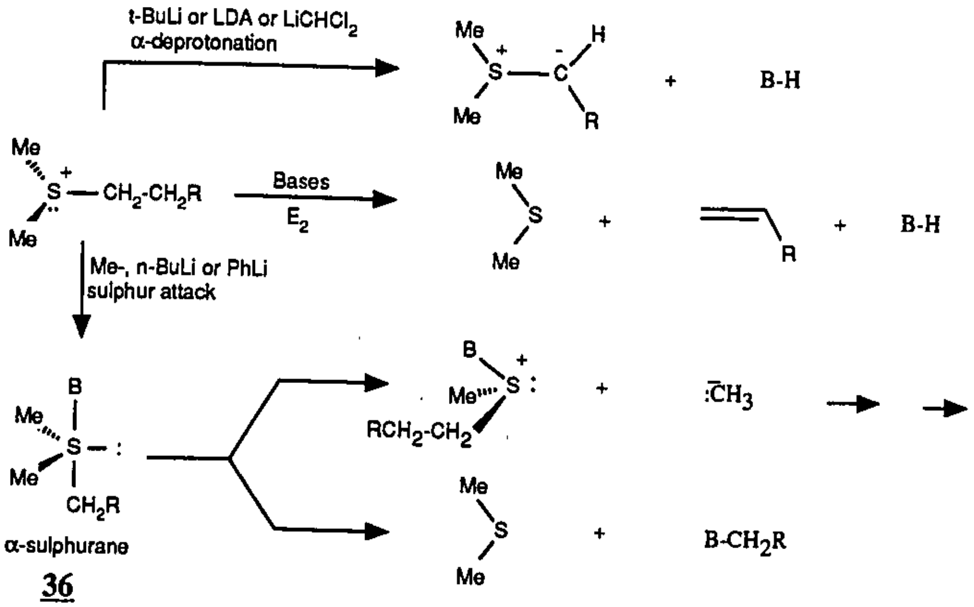
1.6 Synthesis of Sulfur Ylides

Sulfur ylides can be prepared directly from the sulfide and a diazo compound *via* a photolytic or thermal process in the presence of a catalytic amount of Cu^{II} or Rh^{II} (equation 26). Yields are generally good if the diazo compound bears at least one strongly electron-accepting conjugative group. The method thus gives a good direct route to stabilized sulfur ylides.[68-70] Non-stabilized ylides, on the other hand, are prepared by exploiting the high acidity of sulfonium salts. Thus α-deprotonation of the preformed alkylsulfonium salt can be achieved by treatment with a strong, non-nucleophilic base (e.g. *t*-butyl-lithium, lithium dialkylamides, lithium dichloromethide, dimsylsodium or potassium *t*-butoxide) at -70°C (Scheme 6)[71]. This process of ylide generation is



(26)

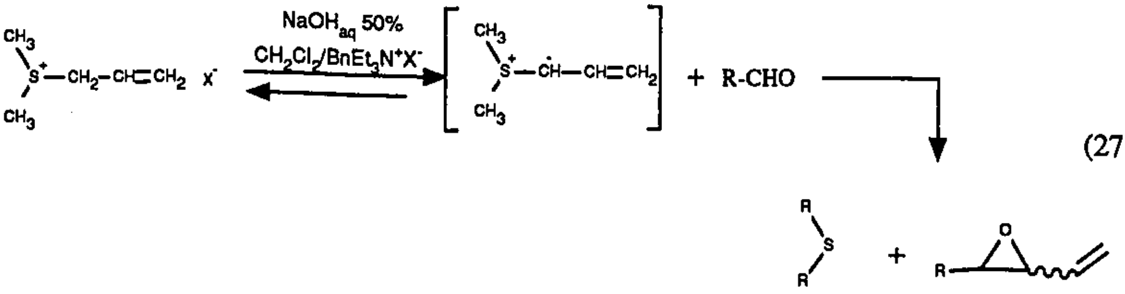
R=methyl, aryl; X=EWG=COMe, CO_2Me, CO_2Et; EWG=COt-Bu, X=H



Scheme 6.

considered to be irreversible.[32] The choice of the correct base to α-deprotonate a sulfonium salt selectively varies with the nature of each individual salt. In fact, two other reactions (i.e. α-sulfurane formation and E_2 elimination) (Scheme 6) compete with the formation of the ylide. The use of a more nucleophilic base (*n*-BuLi, MeLi and PhLi) tends to yield many by-products, often mainly the result of the decomposition of a α-sulfurane 36 formed by the attack of the base on the positive sulfur atom.[72]

Sulfur ylide formation and subsequent transfers of a methylene, allylidene or benzylidene group to aldehydes and ketones can be carried out under typical phase transfer conditions i.e. 50% aqueous sodium hydride-methylene chloride system in the presence of tetraalkylammonium salts (equation 27).[73,74]



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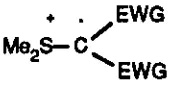
1.7 Stability of Sulfur Ylides

The stability of an ylide depends on the nature and number of anion-stabilizing groups present on the ylidic carbon. Thus, the ylides of type 37, possessing two electron-withdrawing groups (for example: carboxyl, cyano, nitro or sulfonyl) seem to be indefinitely stable at room temperature. Sulfur ylides of the form 38 which are stabilized



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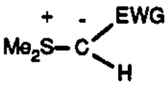

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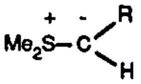

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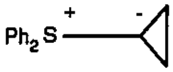
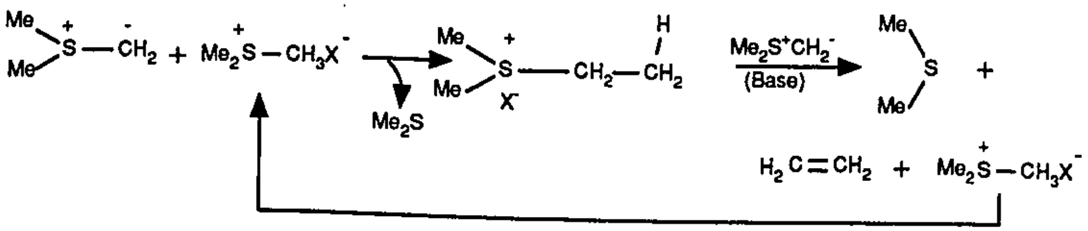
EWG=COR, CO_2R, CN, NO_2, SO_2R; R=H, alkyl, vinyl or aryl by the conjugative influence of only one EWG group, are stable enough to be isolated. Slow decomposition at room temperature necessitates cold storage. Unstabilized ylides like <u>39</u> (i.e. those which bear only alkyl, aryl or vinyl substituents) do not enjoy such a long lifespan and are usually generated and manipulated *in situ* at -70°C. The half-lives of some ylides are known and are listed in Table 1.[32,75] In a synthetic reaction these ylides usually function as nucleophiles; but in an absence of an electrophile they decompose in different ways depending on the alkyl substituent of the ylide. Trimethylsulfonium ylides decompose to give ethylene, probably *via* alkylation of the ylide with a catalytic amount of the trimethylsulfonium halide (equation 28).[76] In this case the formation of ethylene

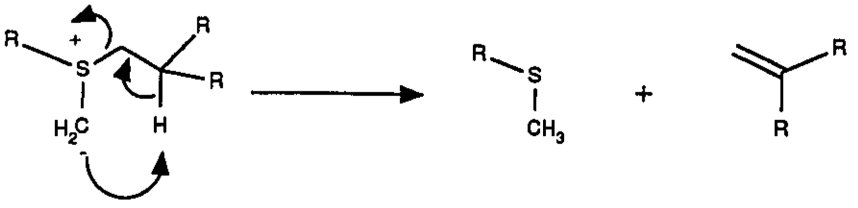
TABLE 1. Approximate half-lives of some unstabilized sulfur ylides.[32,75]

Structure	$t_{\frac{1}{2}}$ (min.)	Temperature (°C)
$Me_2\overset{+}{S}-\overset{-}{C}H_2$	few minutes	10
	2.5	25
$Ph_2\overset{+}{S}-\overset{-}{C}H-CH_3$	5	20
$Ph_2\overset{+}{S}-\overset{-}{C}H-CH=CH_2$	30	-15



(28)

requires the presence of a β-hydrogen in the presursor ethyldimethylsulfonium cation (generated *in situ*). In general, the presence of β-hydrogens in the trialkylsulfonium ylide will lead mainly to the formation of alkenes by an α′,β-elimination (equation 29).[77]



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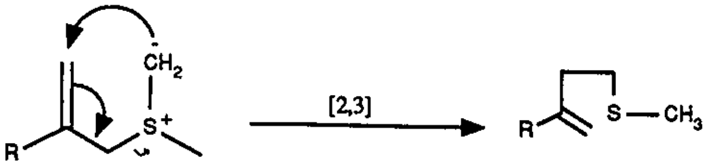
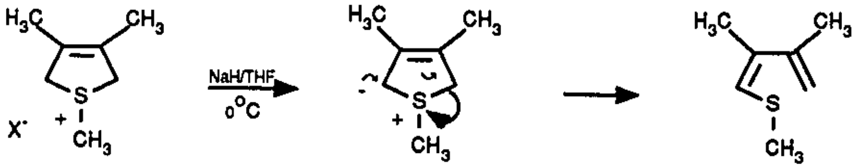
Allylic sulfonium ylides undergoe a facile [2,3]-sigmatropic rearrangement to give homoallylic sulfides by complete allylic inversion (equation 30).[32,75,77] The sigmatropic



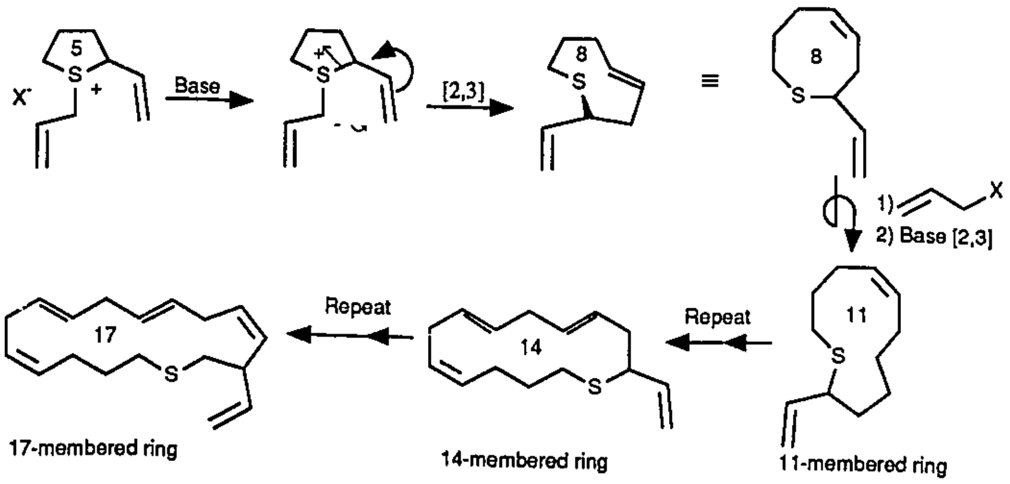
(30)

rearrangement proceeds at 0°C to room temperature in the case of the substituted 2,5-dihydrothiophenium cation (equation 31)[78] and at temperatures as low as -40°C and



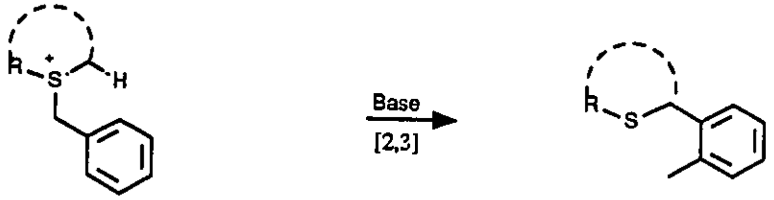
(31)

lower in the case of 2-vinylthiacycloalkanes (Scheme 7).[79] The latter case has proven to be of synthetic value as an easy iterative three-carbon ring expansion process (Scheme 7).[32,77] When the allylic portion is part of an aromatic ring, the alkyl sulfonium ylide

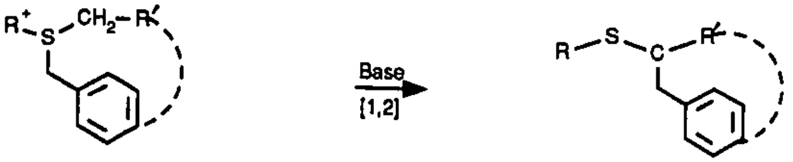


Scheme 7. Iterative α-vinylsulfonium allylide "ring expansion reaction".

decompose by a [2,3]-sigmatropic (Sommelet-Hauser) rearrangement, or *via* a [1,2]-sigmatropic (Stevens) rearrangement.[32] The former reaction (equation 32) is favored in protic solvents and results in *ortho* functionalization of the aromatic compound while the latter reaction (equation 33) is favored in aprotic solvents.



(32)

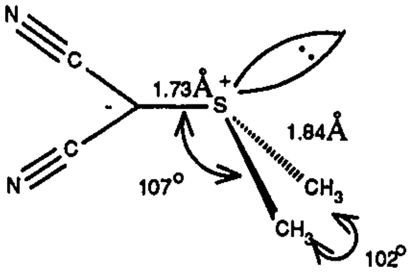


(33)

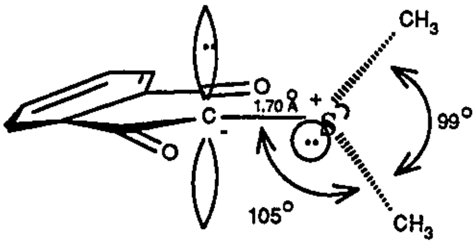
As a consequence of the α′-β elimination, and [2,3] and [1,2]-sigmatropic rearrangements in the sulfur ylides, the chiral sulfide auxiliary should have as few β-hydrogens as possible and should not contain any α-vinyl or α-phenyl groups.

1.8 Structure of Sulfur Ylides[32]

The X-ray structural analyses of stable sulfonium ylides, for example **40** and **41**, show that the geometry about the sulfur atom closely resembles that of normal sulfonium salts. The arrangement is clearly pyramidal with the sulfur atom lying approximately ≈0.73Å above the plane defined by its three bonded atoms. The pyramidal structure is slightly lower, (by 0.07Å) than in the sulfonium salt, and is probably a consequence of a somewhat shorter (1.71Å) S^+-C^- ylide bond as compared with the other two S^+-C bonds (1.80Å) in the ylide. The arrangement of the three atoms around the ylide carbon atom is very close to planar and the S^+-methyl groups are roughly equally distributed on either side of the plane containing the four atoms ($\overset{+}{S}-\overset{-}{C}\genfrac{}{}{0pt}{}{C}{C}$) of the ylide group.

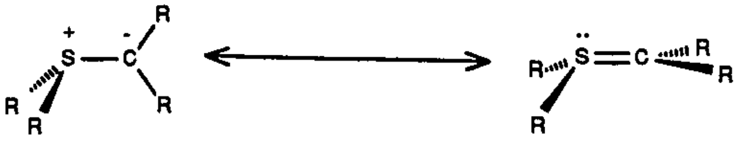


40



41

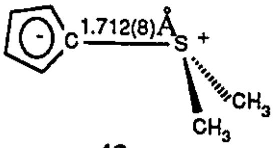
The importance of the resonance form which includes a sulfur-carbon double bond **42B** is still being questioned.[34,80-82] As mentioned earlier, the carbon-sulfur bond length



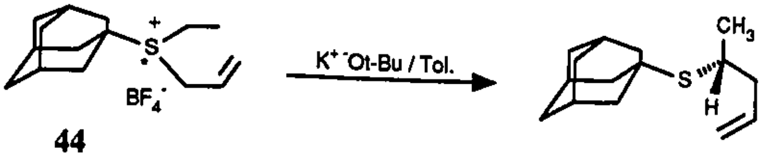
42A **42B**

(≈1.71Å) for the stabilized ylides **40** and **41**, lies between that of a C-S single bond

(≈1.8Å) and C-S double bond (1.56Å) of carbon disulfide.[83] While taking into account the electrostatic charge attraction which also contributes to a shorter S^+-C^- ylide bond, Adrianov and Struchkov[82,84] have argued that the S^+-C^- bond length of 1.712(8) in ylide **43** was indicative of a resonance distribution with an 80% contribution from canonical form **42A** and only a 20% contribution from the double-bonded structure **42B**. The existence of pyramidal geometry at a stabilized ylide C^- is likely to be difficult to detect, since the negative charge on the carbon in these compounds is delocalized into the carbon skeleton. Further, the ylidic carbon in compounds such as **40**, **41** and **43** will adopt planar geometry irrespective of the C-S bond character. The dipole moment studies on **40** (μ=8.08D) and **43** (μ=5.7D) suggest that there is a large amount of charge separation.[85,86] Nonetheless, in all three of these molecules there appears to be a slight, but significant displacement of the ylide carbon atom from the plane defined by its three substituents. The displacements from this plane are 0.020Å, 0.041Å and 0.015Å, which correspond respectively to the ylides **40**, **41** and **43**. While all of these distances are small, they do suggest a slight non-planarity of the ylide carbon atom.[53] Unfortunately, due to their instability, no X-ray studies on unstabilized ylides are available to confirm their spatial arrangement. Evidence gathered from chemical behavior studies performed with non-stabilized ylides support the pyramidal geometry for the sulfur. The fact that optically active **44** rearranges to R-adamantylthio-1-pentene (equation 34) possessing 94%



43

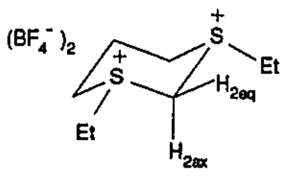


44

48%, 94ee

(34)

optical purity indicates a high degree of transfer of asymmetry from the sulfur to the carbon[27] in the intermediate ylide. Also, the deprotonation of the optically active sulfonium salt 3 followed by reprotonation with deuteriofluoroboric acid led to the recovery of deuterated 3 with no loss of optical purity. These observations suggest that there is nonplanarity at both the sulfur and carbon atoms. The 1,3-bissulfonium ylides present a favorable environment for the detection of pyramidal geometry at the negatively charged carbon. An nmr study involving H-D exchange on the cyclic 1,3-bissulfonium salt 45 showed that the exchange of the equatorial proton at C-2 was stereoselective thus requiring a pyramidal configuration at the carbon.[87] Four years later after, it was shown by nmr that the ylide 46 retained its asymmetry. Following elaborate nmr and other studies performed on other 1,3-bissulfonium ylides (i.e. $R_2S^{+}\text{-}^{-}CH\text{-}^{+}SRR'\ BF_4^{-}$), Wolfe et al., concluded that:



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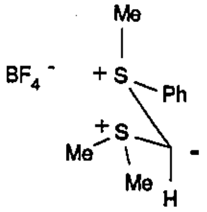


46

> "the static, dynamic and chemical properties of 1,3-sulfonium ylides are consistent with a charge-localized structure in which both sulfur atoms and the ylide carbon have pyramidal configurations".[88]

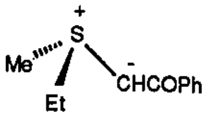
In summary, the structural studies of stabilized ylides combined with the chemical behavior of unstabilized ylides fail to support the existence of appreciable double-bond character between the ylide carbon and the sulfur atom. However, some stabilization over and above electrostatic interaction seems necessary to account for the acidity of the sulfonium salts. Streitwieser and Ewing[89,90] suggested that the main mechanism by which sulfur stabilizes adjacent carbanionic centers is due to a polarization of the sulfur atom.

However, the greater polarizability of sulfur as compared with oxygen is attributed, at least in part, to the presence of low lying *d* orbitals on the sulfur.

In this work, the ylides will be considered to be pyramidal at sulfur in all cases with the ylidic carbon C^- having either mostly a planar geometry in resonance-stabilized ylides or being mainly pyramidal in the case of non-stabilized ylides.

1.9 Stereomutation of Sulfur Ylides

Ylides racemize by pyramidal inversion more easily than their parent sulfonium cations. Darwish and Tomilson[91] found that the stabilized sulfonium ylide, 47, racemized 200 times faster than the corresponding sulfonium cation in methanol at 50°C. The activation energy for the barrier to pyramidal inversion was found to be 23.3[91], 23.6 and 23.9[92] Kcal/mol respectively for the stabilized ylides 47, 48 and 49. Further, the study of 1,3-bis-sulfonium salts and their ylides by Wolfe *et al.*[88] confirmed that pyramidal inversion is faster in unstabilized ylides. These authors concluded that ylide formation reduced the barriers to pyramidal inversion at sulfur by about 5 Kcal/mol. Pseudorotation at sulfur requires a transition state in which the sulfur would tend to become planar.[93] An attractive explanation for a lowering of the activation energy for inversion at sulfur during ylide formation could be the result of a more efficient $C_{p\pi}$-$S_{d\pi}$ overlap in the planar transition state. Heathcock *et al.*[65] concluded, from an elegant study of 1-thioniabicyclo-[4.4.0]decane salts, 35, 50, and their respective kinetic ylides, 51 and 52, that these



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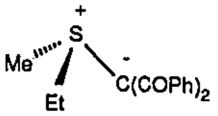

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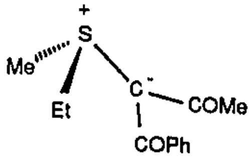

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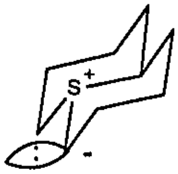

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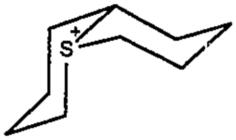

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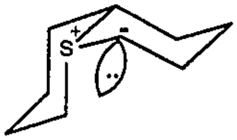
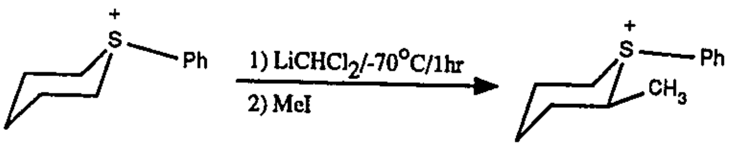
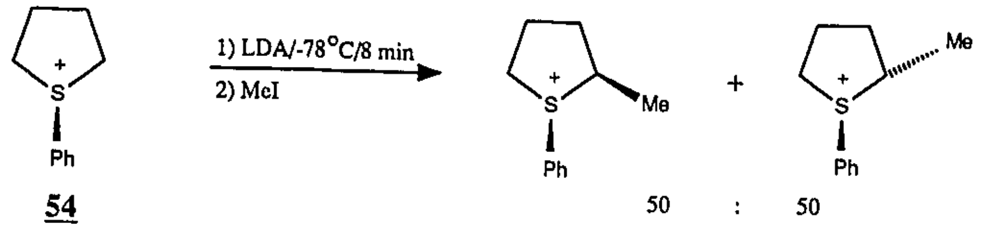


52

unstabilized ylides do not undergo stereomutation, either at the sulfur or at the carbon at -72°C but upon warming to -23°C for 2 h the ylides equilibrate by pyramidal inversion at both the sulfur and the carbon. If this observation is general for all ylides, it may well explain the maintenance of configuration at the sulfur in the unstabilized 1-adamantylethylsulfonium methylide, 4, reported by Trost and Hammen.[27] Although no experimental conditions for the deprotonation of the corresponding salt are provided, the low stability of such an unstabilized ylide demands generation at low temperature (≈-70°C), thereby ensuring that pyramidal inversion is negligible. In the same report, Templeton, Heathcock *et al.* investigated the alkylation of ylides 51 and 52 and hypothesized that ΔG^{*} for pyramidal inversion of the carbanion exceeds ΔG^{*} for methylation (or alkylation with carbonyl compound). Additional experimental evidence on the stereochemical outcome of the methylation of cyclic sulfonium ylides was reported by Garbesi[94]. As seen in equation (35) the six membered ring sulfonium salt 53 afforded mainly the equatorially methylated products, but showed no selective H/D exchange (page 19). On the other hand, the thiolanium salts 54 and 55, which display high H/D exchange selectivity (page 19), exhibit no selectivity in lithiation-methylation experiments (equation 36 and 37). One of the explanations put forward by the author was that the intermediate

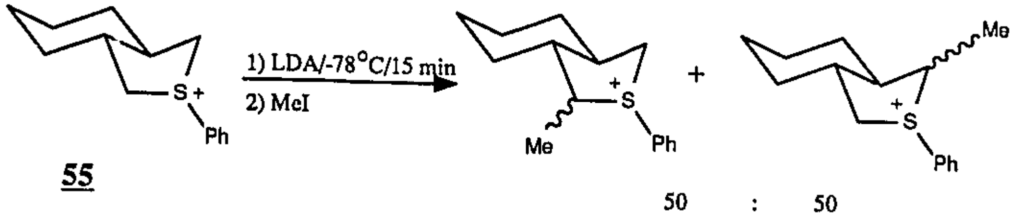


53 95% (35)



54

(36)



55

(37)

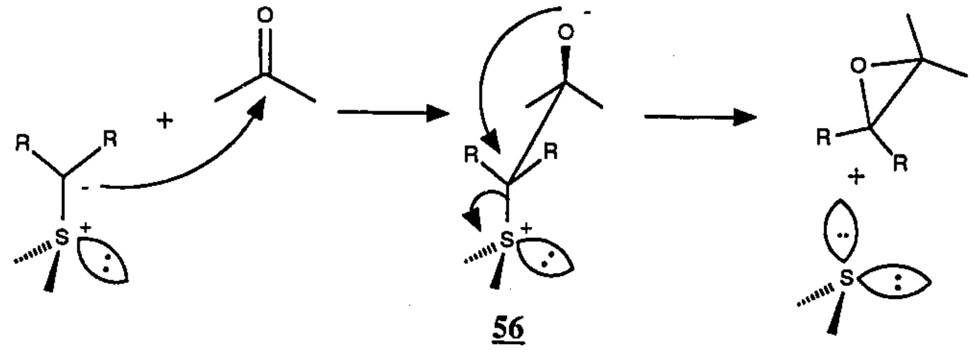
All four monomethylated product are formed in comparable amounts.

ylide is pyramidal at the carbon, and that the initially formed kinetic ylide may inverts its configuration during the alkylation step. This explanation demands that pyramidal inversion at the carbanionic carbon occurs rapidly at -70°C. This finding is in contrast with the results of Templeton and Heathcock on the 1-thioniabicyclo[4.4.0]decane salts 50 described above. The corresponding ylides, structures 51 and 52, which only undergo stereomutation at carbon at -23°C, but had prolonged stablility at -72°C is thus a consequence of the bicyclo[4.4.0]decane structure.

Enantioselective epoxidation *via* a sulfur ylide involves hydroxyalkylation of the ylidic carbon by a carbonyl compound. Therefore, the sulfides to be considered as potential chiral auxiliaries are ones which can give the assurance that stereomutation at the sulfur in such an alkylation of derived ylides, would be either unlikely, or have no stereochemical consequence.

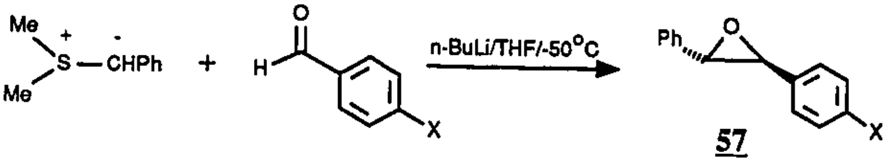
1.10 Mechanistic Aspect of the Corey-Chaykovsky Epoxidation Reaction

The mechanism for the reaction of sulfonium ylides and a carbonyl group was first proposed by Johnson and co-workers.[95] It involves nucleophilic addition of the sulfonium ylide to a carbonyl group thereby generating the *trans*-betaine intermediate 56 (Scheme 8). This intermediate is converted into an oxirane by means of an intramolecular S_N2



Scheme 8.

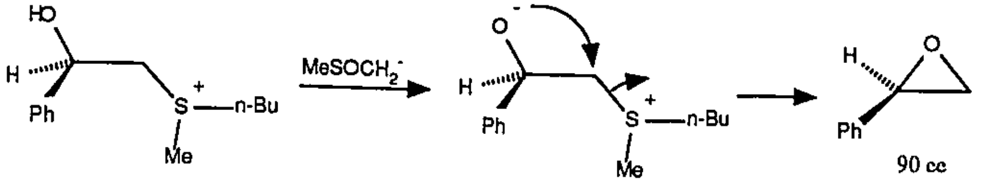
reaction at the carbon; the oxygen acting as the nucleophile and the sulfide as the leaving group. The stereochemistry of the epoxides of type 57 is consistent with a nucleophilic addition-1,3-elimination mechanism (equation 38).[96] This mechanism requires an



X=H, 58%
X=Cl, 63%
X=NO_2, 72%

(38)

inversion at the original ylide stereocenter during the subsequent intramolecular nucleophilic displacement of the sulfide by the neighboring alkoxide anion.[49] It is further substantiated by an independent synthesis of the conjugated acid of a betaine, which yields an oxirane after deprotonation (equation 39, 40, 41, 42). The stereochemical integrety observed in the cyclization step establishes that the formation of betaines from non-stabilized ylides must be essentially irreversible.[97-99] Conversely, the corresponding



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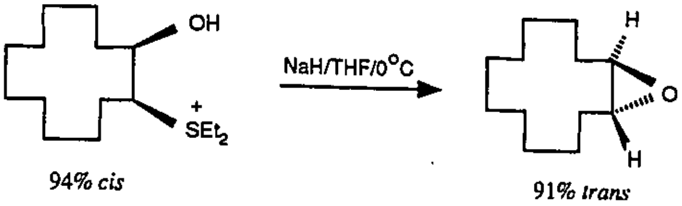

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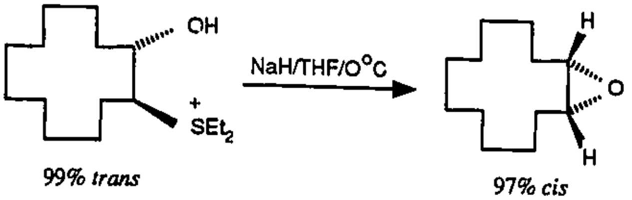

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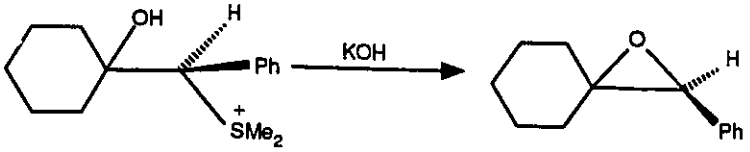
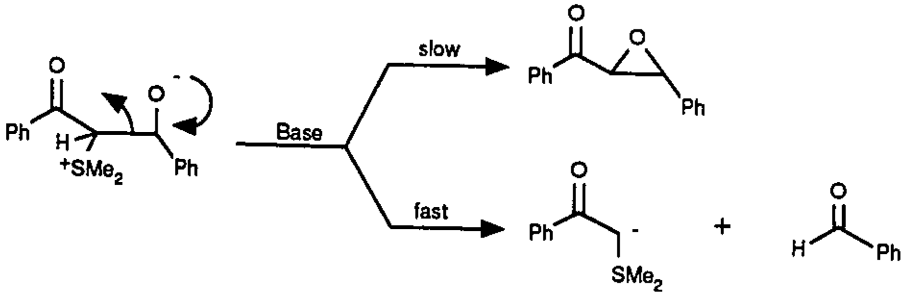


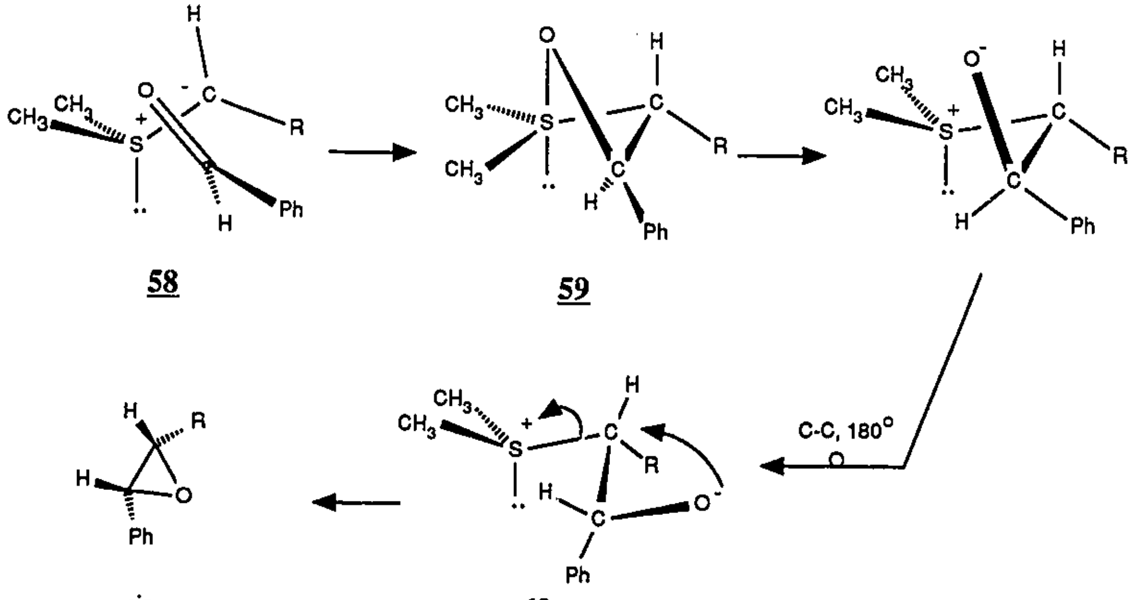
(42)

betaines produced from stabilized ylides revert to ylide and the aldehyde faster than 1,3-elimination (Scheme 9).[100]



Scheme 9.

It has also been proposed that the sulfonium methylide reacts *via* a symmetry allowed $2_{\pi a}$-$2_{\pi s}$ four-center transition state as shown in 58. The intermediate 59



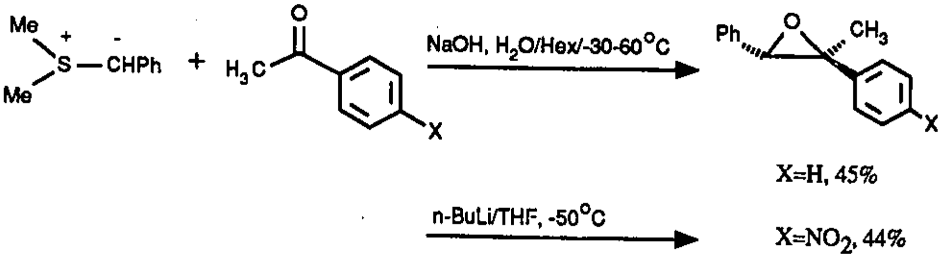
58

59

cis

60

obtained from this head to head addition would then open to the betaine 60 which, by rotation of 180° around the C-C bond, undergoes an 1,3-elimination of the sulfide to give a *cis* epoxide. This mechanism is not compatible with the observation of the various ratios of *trans* to *cis* epoxide in the reaction involving substituted ylides and aldehydes. In cases involving reaction of a benzylsulfonium ylide with aromatic aldehydes and unsymmetrically substituted aromatic ketones, only *trans*-oxiranes have been reported (equation 38 and 43).[101] It has been shown that these results are partly incorrect and typically up to 10% of *cis*-stilbene oxides are also obtained.[102] Nevertheless the above conclusion concerning the $2_{\pi s}$+$2_{\pi a}$ mechanism still holds.



(43)

Theoretical studies of the H_3S^+-CH_2^- + H_2C=O system have shown that the sulfurane intermediate **62**, having apical oxygen atom could possibly form upon a 2+2 cycloaddition, although no oxathietanes are known experimentally.[103] The activation energy for ring opening of the cyclic intermediate was calculated to be quite high (i.e. ≈38.3 Kcal/mole) and consequently it would be easier for these intermediates to revert to the reactants, ylide and aldehyde, rather than form epoxides (Figure 2). On the other hand, for head to tail addition, as depicted in Scheme 8, the reaction part consisted of only one transition structure **61**, and further no *trans*-betaine intermediate **56** was found to be stable. The activation energy for the *trans*- addition was calculated to be 10.6 Kcal/mole. The transition structure was postulated to be: "typical of a nucleophile adding to a carbonyl group with the C-C-O angle ≈106.6°, the C-C bond hardly formed, and the C=O bond weakly elongated.[104] The structure is slightly skewed (dihedral angle S-C-C-O =2.3°)."[103] This initial nucleophilic addition of an ylide to a carbonyl function will be considered as the relevant path for the design of sulfide auxiliaries. It is also consistant with the proposal of Johnson (Scheme 8) and with experimental evidence available (equation 38-42). The subsequent question of the structure **56** being a transition state **61** rather than an intermediate **56** is not crucial to this study since, as mentioned earlier, this intermediate **56**, if it exists, was shown not to revert to starting material.

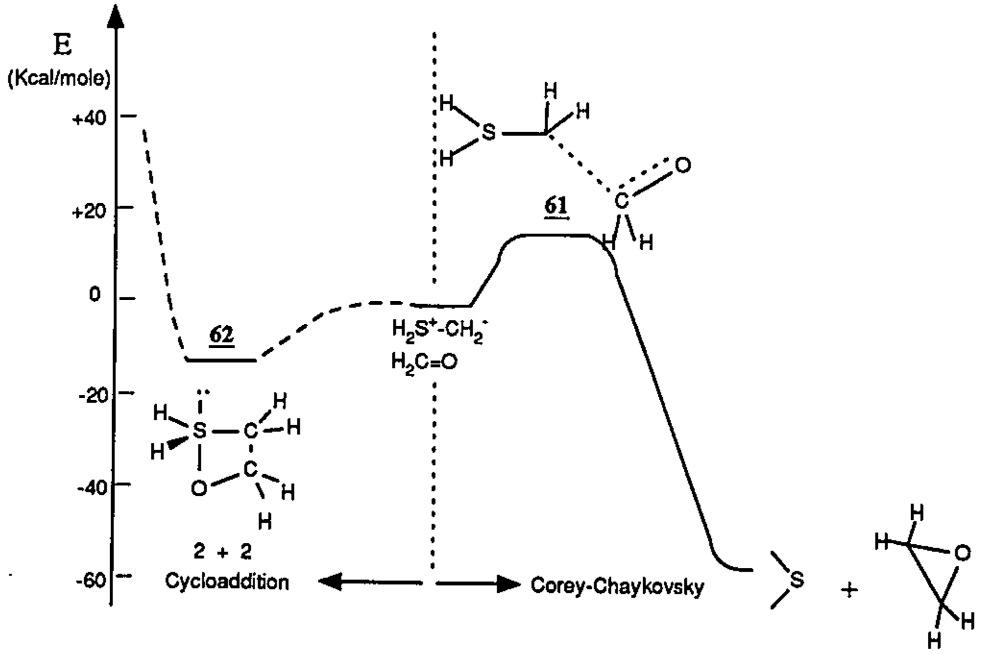


Figure 2. Energy profile of the 2 + 2 cycloaddition (left-hand side) and Corey-Chaykovsky reactions (right-hand side) for sulfonium ylide.

1.11 Design of a Chiral Sulfide

The design of the sulfide should be tailored to give a practical and enantioselective synthesis for oxiranes. To accommodate the first goal, that is, practicality, a suitable sulfide reagent would have to meet the following fundamental criteria:

1) The sulfide should be obtained from an inexpensive, readily available, starting material and likewise reagents. It is preferable for the starting material to already be chiral. Failing this, asymmetry should be easily introduced by efficient, known reactions, thus avoiding the need for resolution.

2) The chiral sulfide should be easily prepared from the starting material in a minimum of synthetic steps. The synthesis should be adaptable to large scale preparations.

3) The chiral sulfide should be available in both its enantiomeric forms.

4) The sulfide should be of low volatility, thereby facilitating efficient recovery.

5) The sulfide should catalyze the formation of optically active epoxides over a reasonable time period and with good turn over ratios. In such a reaction, the sulfide is alkylated *in situ* and subsequently deprotonated to the corresponding ylide which in turns react with a carbonyl compound, present in the reaction medium, to give the epoxide and regeneration of the sulfide catalyst.

The sulfide molecule must also fulfill the following criteria in order to succeed in the second goal, that is of <u>inducing high enantioselectivity</u> in the <u>alkylidene transfer</u>. The following criteria are a response to the constraints of the chemistry of the sulfonium group:

6) The sulfide sulfur should be part of a cyclic structure so as to minimize conformational partitioning (Section 1.3). A rigid system should be advantageous.

7) The sulfide should have a structure such that the stereochemical integrity at the sulfur is preserved not only in the alkylation step of the sulfur moiety but as well in the sulfonium salt and most importantly, in the sulfur ylide state (Section 1.4, 1.9).

8) The sulfide auxiliary should have its stereogenic center(s) dedicated to the transposition of asymmetry located as close as possible to the reaction center.

9) The sulfide should have sufficient nucleophilicity to undergo sulfur alkylation with simple alkyl halides without the need of metal cation (Ag^+, Hg^+, Section 1.1). This constitutes a prerequisite for epoxidation under catalytic conditions.

10) The sulfide structure should not contain other heteroatoms (O, N, S) nor an α-vinyl nor an α-phenyl substituent to the sulfur atom. The presence of these structural elements would result in competing reaction pathes during the sulfur alkylation step in the former case and during the ylide formation step in the latter case. These side reactions lead to elimination and rearrangement products, respectively (Section 1.7).

Several years ago our laboratory began a survey of sulfide reagents composed of a five membered ring (thiolanes) possessing C_2 symmetry. The choice of such a reagent is quite appealing in that other C_2-symmetric reagents performed quite well in providing high asymmetric induction in various catalytic reaction systems.[105] Some of the most spectacular applications are the use of:

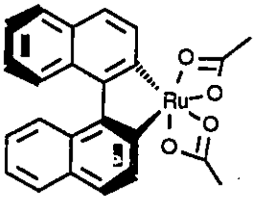
a) all carbon based auxiliaries such as binaptyl ruthenium, 63, as hydrogenation catalyst for ketones, β-keto ester, allylic and homoallylic alcohols:[106];

b) phosphorus base auxiliaries such as Binap, 64, diop, 65; chiraphos, 66, have been used as ligands in transition metals complex catalysts used in a variety of homogeneous reductions of alkenes;

c) oxygen-base auxiliaries such as ethyl tartrate in the Sharpless epoxidation of allylic alcohols, binaphtyl-derived boron 67 and titanium derived auxiliary 68 as Lewis acid in the catalysis of D.A. and ene reaction; and

d) nitrogen-base auxiliaries such as 69 and 70 in osmium tetroxide dihydroxylation of olefins.

Other C_2 symmetric auxiliaries have been used in stoichiometric amounts. Notable examples include *trans*-2,5-dimethylborolane 71 in the hydroboration of alkenes and the tricyclic amine 72 in the alkylation of a vinylogous urethane. There is, however, a lack of sulfur-based auxiliaries such as 73, analogous to 72. The thiolanes auxiliaries 73, 74 and 7 fulfill some of the chemical criteria described earlier (pages 34-36).



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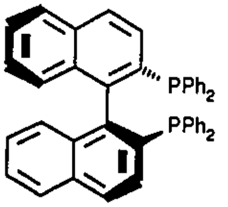

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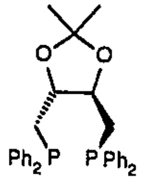

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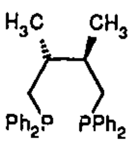

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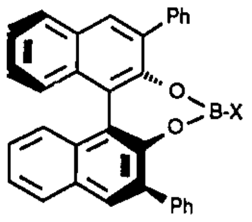

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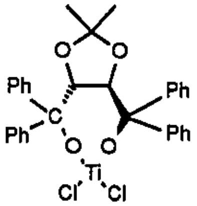

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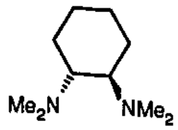

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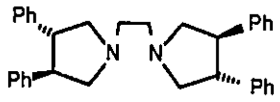

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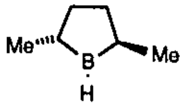

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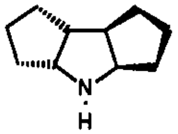

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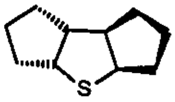

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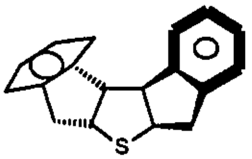

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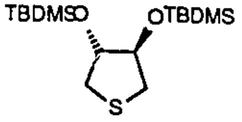

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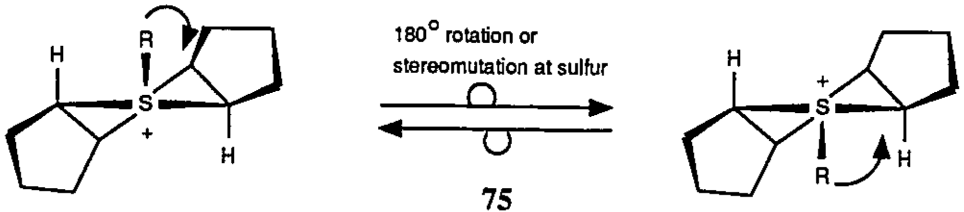
The advantage of the cyclic sulfides, especially 73, is that they minimize conformational partioning to a twisted-chair form having both fused rings in a quasi-equatorial position such as depicted in 75 and the conformational integrety of the molecule is preserved throughout the reaction (sulfide, sulfonium salt & ylide). The stereochemical integrity at sulfur is assured at all times since alkylation of the α or β-face of the sulfide followed by potential stereomutation at the sulfur atom would always deliver the same salt and hence to a conformationally homogenous ylide. The fused cyclopentane



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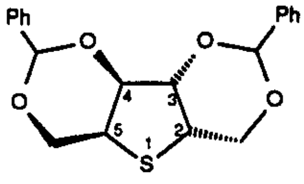
rings would not only provide an all carbon frame auxiliary, but would also provide, substituents close to the reaction center (α to the sulfur atom). Unfortunately, the possible practical application of dicyclopentanothiolane 73 and related thiolane 74 have been seriously hampered by the difficulty in preparing these C_2 symmetric sulfides.[107] It was decided to probe the feasibility of this process with the 3,4-substituted thiolane 7, which can be prepared from the readily available (+)-dimethyltartrate. The observation of low but significant asymmetric induction using the thiolane 7 (Scheme 3) confirmed that epoxides can be obtained via the sulfur ylide route and suggested the possibility of obtaining optically active epoxides with much greater optical purity. C_2 symmetric thiolanes which should be more suitable for this purpose probably require substituents at C-2 and C-5. The synthesis of several examples of such reagents necessitated some compromise in the criteria outlined on page 34. The use of mannitol as a starting material has many advantages and resulted in reasonably efficient synthesis of the chiral thiolane 76 and 77, but the inclusion of oxygen in the auxiliary had adverse effects. The simple *trans*-2,5-disubstituted thiolane 78 was chosen as the third auxiliary in this series. It was anticipated that this would be obtained *via* classical resolution of the corresponding diacid.



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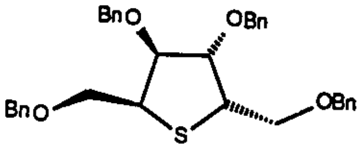

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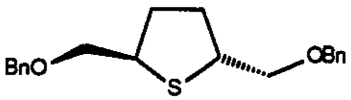

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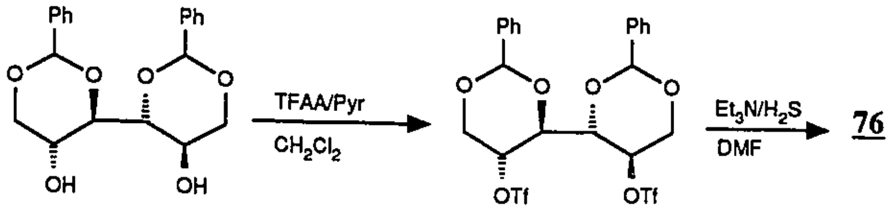
II CHAPTER 1

2. SYNTHESIS OF C_2 SYMMETRIC THIOLANES

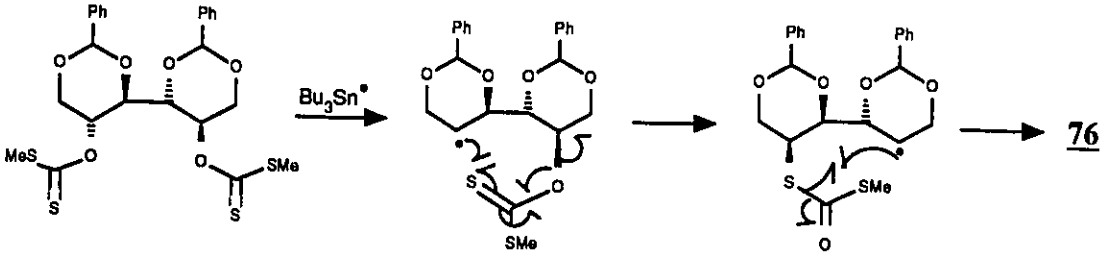
2.1 (2S,3S,4S,5S)-(-)-Di-O-benzylidene-3,4-bis-hydroxy-2,5-bis-hydroxymethylthiolane, 76.

The sulfide 76 was first prepared in our laboratory in 35% overall yield starting from commercially available mannitol[107] as shown in equation 44. It was independently



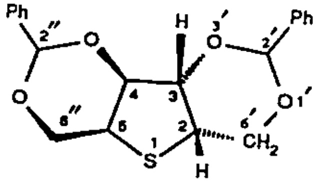
(44)

reported[108] in 1988 that the tetrahydrothiophene 76 could be prepared in 80% yield *via* a Barton-McCombie[109] radical deoxygenation of bis(dithiocarbonate) 79 with tri-*n*-butyltin hydride in toluene. The novel incorporation of a sulfur atom during a deoxygenation process was explained by the sequence 79 → 80 → 81 → 76 and necessitates migration of a dithiocarbonate group by intramolecular attack of a carbon-centered radical at the thiocarbonyl sulfur in 80. The product 76 obtained *via* these two different synthetic



79 80 81

pathways was identical. The compound displayed proton nmr resonances at δ3.94, δ4.27, δ4.55 and δ5.49 besides the aromatic signals found at δ7.34-7.51 (Figure 3). The signal at



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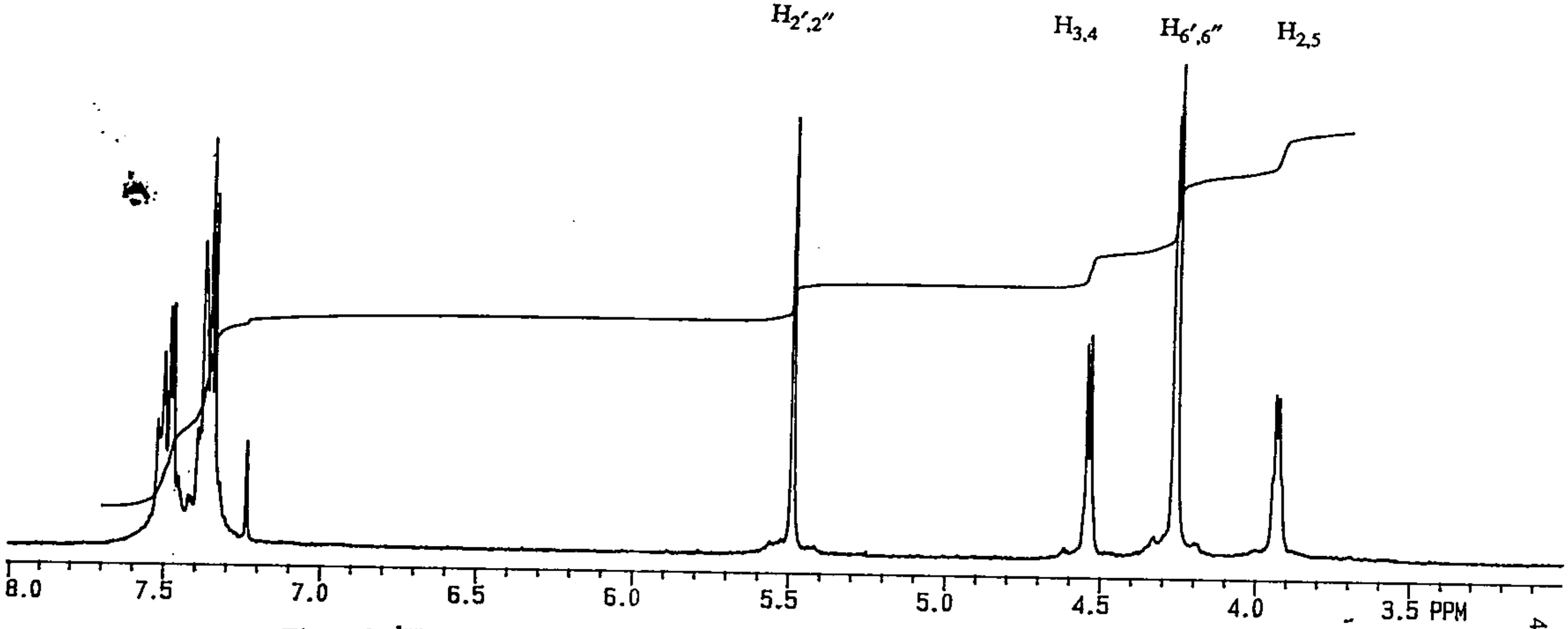
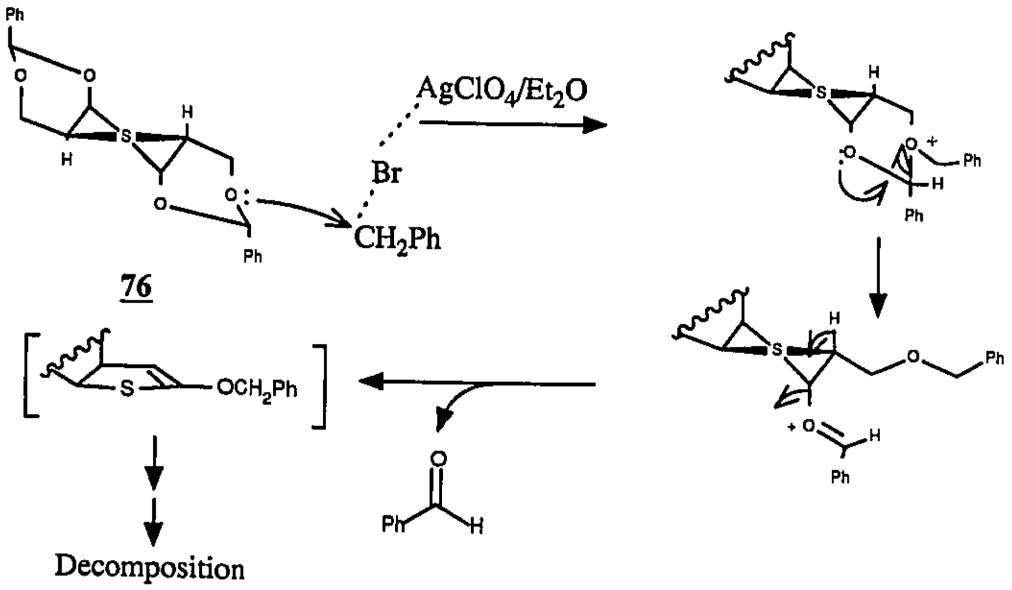


Figure 3. ^{1}H nmr spectrum of (2S,3S,4S,5S)-di-O-benzylidene-3,4-hydroxy-2,5-bis-hydroxymethylthiolane **76**.

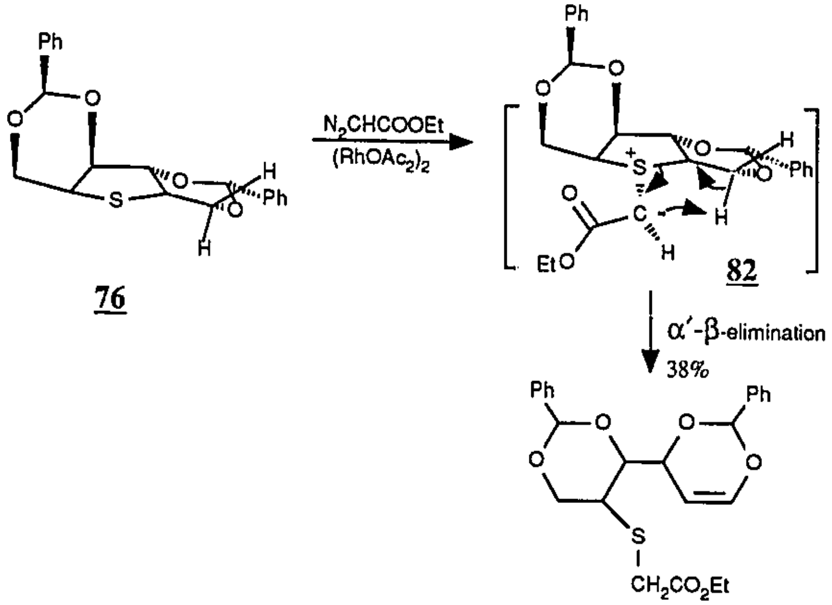
δ3.94 (m) and δ4.55 (d, J=2.4 Hz) were assigned to the methine protons at C-2 & 5 and C-3 & 4 respectively. The coupling constant of 2.4 Hz suggests a *cis* relationship between H-2 and H-3. The signal at δ4.27 has the appearance of a multiplet which was assigned to the hydroxy methylenes while the signal at δ5.49 was, as expected, a singlet and attributed to the proton attached to the acetal carbon. The mass spectrum showed a molecular ion peak at m/z=356 (27%) which is consistent with the proposed empirical formula $C_{20}H_{20}O_4S$. The fact that only ^{1}H and ^{13}C resonances for half of the molecule are observed is indicative that the C_2 symmetry of the starting material has been preserved.

Unfortunately, the attempted synthesis of the corresponding S-benzylthiolanium cation using benzyl bromide and silver perchlorate resulted in the complete decomposition of the starting material. Analysis (TLC and ^{1}H NMR) revealed the presence of benzaldehyde whose formation probably results from the fragmentation of the benzylidene acetal protecting group initiated by alkylation at oxygen (Scheme 10). An attempt to prepare stabilized ylide <u>82</u> from thiolane <u>76</u> and ethyldiazoacetate in the presence of a



Scheme 10.

catalytic amount of rhodium acetate failed and gave instead a mixture of diethyl fumarate and maleate, some unreacted starting thiolane and the product <u>**83**</u>. The diethyl fumarate and maleate are the result of a formal "dimerization" of the rhodium stabilized carbenoid. Purification of the crude reaction mixture *via* chromatotron (CCl_4-Et_2O/ 9:1) afforded <u>**83**</u> in 38% yield. The proton resonances at δ6.80 and δ5.24, which appear as doublets of doublets, are consistent with a vinyl ether moiety with proton nearest to the ether functionality assigned to the signal at δ6.80; while the proton attached to the other olefinic carbon resonates at δ5.24. Two distinctive singlets at δ5.96 and 5.64 are attributed to the proton attached to the acetal carbons. The signals at δ4.17(q, 2H), δ3.38(AB, 2H), δ3.10(br.d. 1H) and δ1.31(t, 3H) were consistent with the partial structure R_2CH-S-CH_2-COOEt where the AB signal at δ3.38 corresponds to the protons adjacent to the sulfur and carbonyl functions. The ^{13}C nmr spectrum showed 12 non-aromatic resonances with that at δ170.24 being attributed to the carbon of ester carbonyl group. The signal at δ145.38 was assigned to the vinylogous carbon attached to the oxygen. On the basis of this information the structure assigned to this unexpected substance was the elimination product <u>**83**</u>. It is quite likely, that upon treatment of thiolane <u>**76**</u> with carboethoxycarbene generated *in situ*, the desired ylide <u>**82**</u> was formed but this decomposed subsequently *via* an α'-β (or E_{1CB}) elimination to give <u>**83**</u> (Scheme 11).



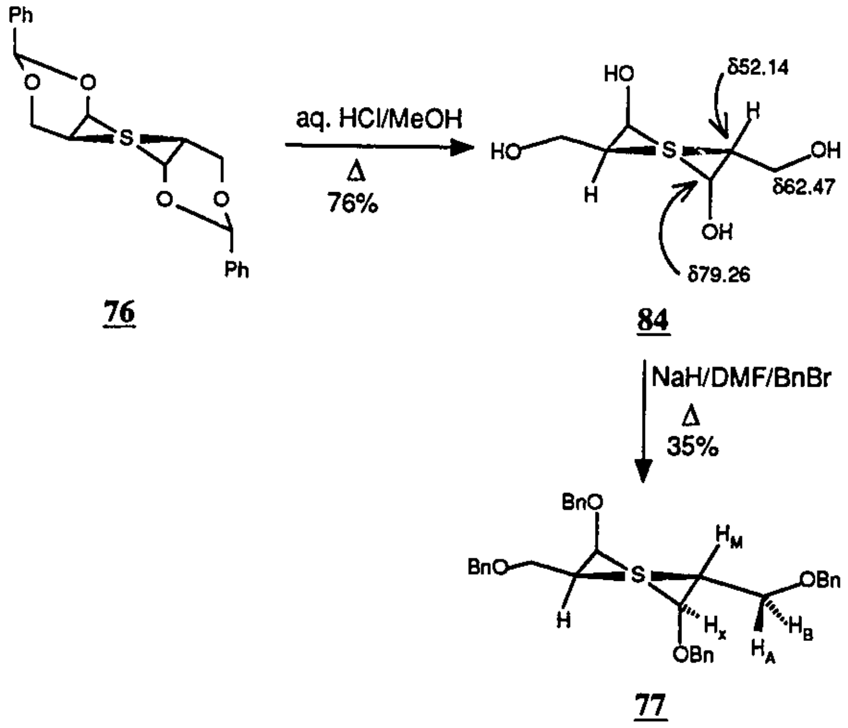
83

Scheme 11.

Although the decomposition of thiolane 76 happens *via* two completely different mechanism, the relief of strain associated with these processes is common. A molecular model of 76 showed that the thiolane ring most probably adopts a half chair conformation in which both the C-2 and C-5 substituents are in a quasi equatorial position. Also, both benzylidene acetal moieties are in a chair conformation. This model indicates that there is some rigidity and strain in the 5-membered ring caused by the two trans fused 6,5 ring junction. Thus the beautifully C_2 symmetric thiolane 76 was not suitable for the intended purpose. This work showed that an acetal function in the auxiliary was not stable to very reactive alkylation agents required to generate a sulfonium salt from 76. The conversion of the oxygen in 76 from acetals to benzyl ethers should alleviate this problem and at the same time also eliminate any strain in the thiolane ring due to the additional fused six-membered rings. The target auxiliary thus became 77.

2.2 (2S,3S,4S,5S)-(-)-Tetra-O-benzyl-3,4-bis-hydroxy-2,5-bis-hydroxymethylthiolane 77.

The hydrolysis of thiolane 76 to the tetraol 84 was accomplished in 76% yield using a 15% aq. HCl methanolic solution (Scheme 12). The product displayed a complex proton spectra, however, the ^{13}C nmr spectrum was most informative showing only three resonances at δ52.14 (methines at C-2 and C-5), δ62.47 (methylenes) and δ79.26 (methines at C-3 and 4). The tetraol was then perbenzylated by conventional means (NaH, DMF, BnBr) to yield the tetrabenzyl derivative, 77, in 35% yield. The proton nmr spectra of this material was much more informative than its precursor and showed in addition to the aromatic and benzylic protons four multiplets in the δ3.5-4.5 region (Figure 4). The signals at δ3.56 appear as the A part of the ABM system, while those at δ3.78 and δ3.86 can be assigned to the B and M part of the ABMX pattern. The X part of this



Scheme 12.

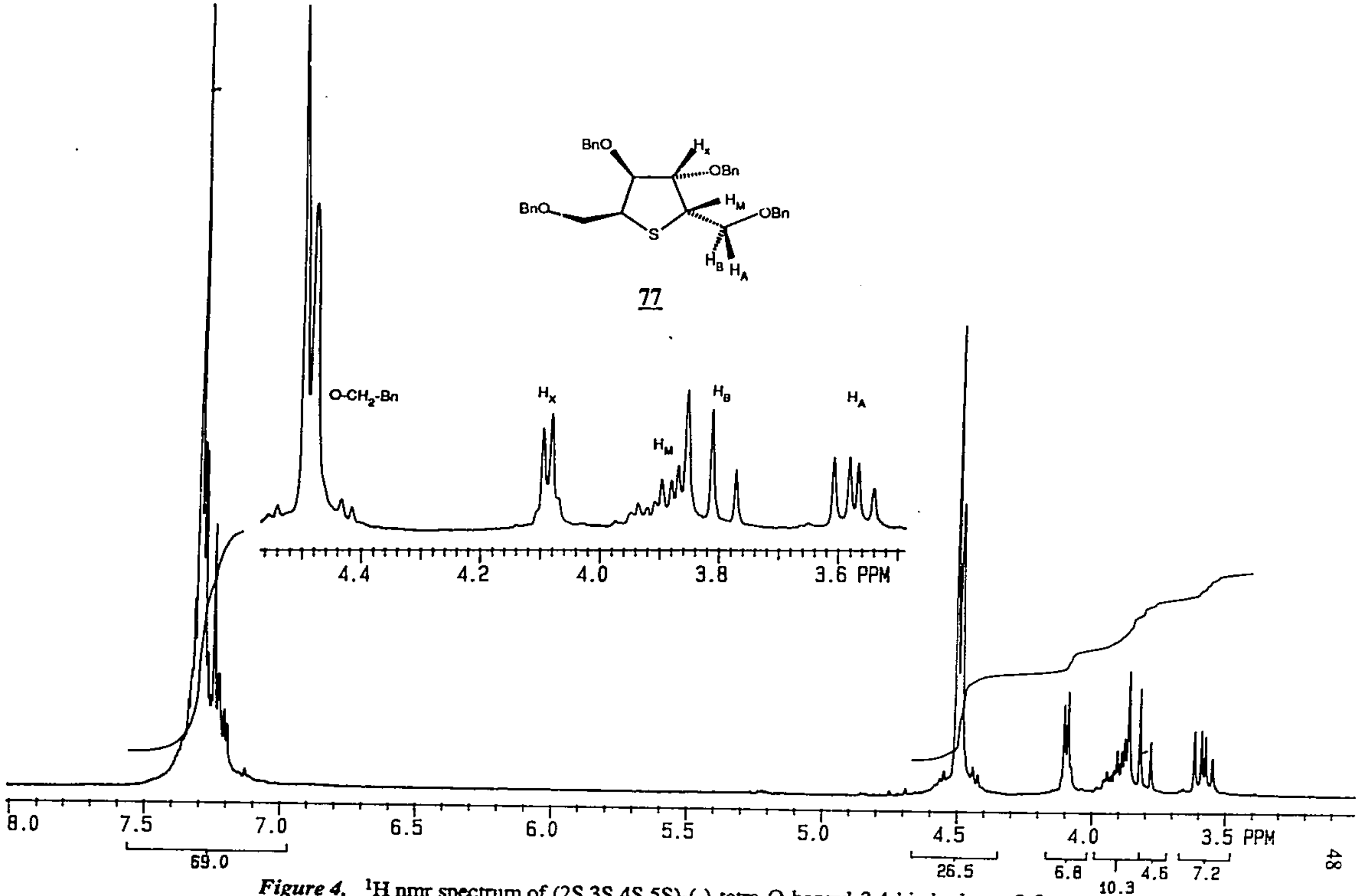
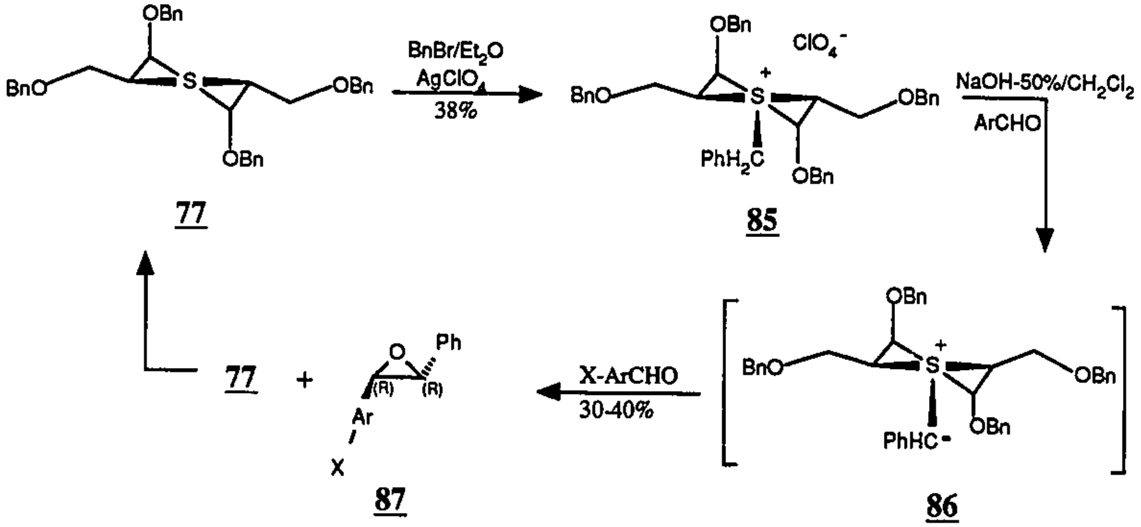


Figure 4. ^1H nmr spectrum of (2S,3S,4S,5S)-(-)-tetra-O-benzyl-3,4-bis-hydroxy-2,5-bis-hydroxymethylthiolane 77.

system resonates as a doublet at δ4.08. The HOMCOR (Homonuclear Correlation Spectroscopy) spectrum of 77 is shown in Figure 5. The ^{13}C nmr also supports the presence of C_2 symmetry in this molecule since only three aliphatic δ48.11 methines at C_2 and C_5, δ69.09 (CH_2OBn methylene) and δ82.43 methines at C_3 and C_4, two benzylic (δ72.45 and δ73.18) and six aromatic resonances were observed. Mass spectroscopy did not show a parent molecular ion peak, although a peak at m/z=433 (7%) occurred which corresponds to the mass of a fragment having lost one benzyloxy group (i.e.: M^+ $-OCH_2Ph$).

The alkylation of thiolane 77 with benzyl bromide in the presence of silver perchlorate was successful giving the corresponding S-benzylthiolanium perchlorate 85 as a white foam in 38% yield was characterized by a complex proton nmr spectrum (Figure 6) which demonstrated the absence of C_2 symmetry. This material displayed moderate stability (e.g. the salt slowly turned into a thick brown gum) and was used without further purification (Scheme 13). Reversible ylide generation was achieved under phase transfer



Scheme 13.

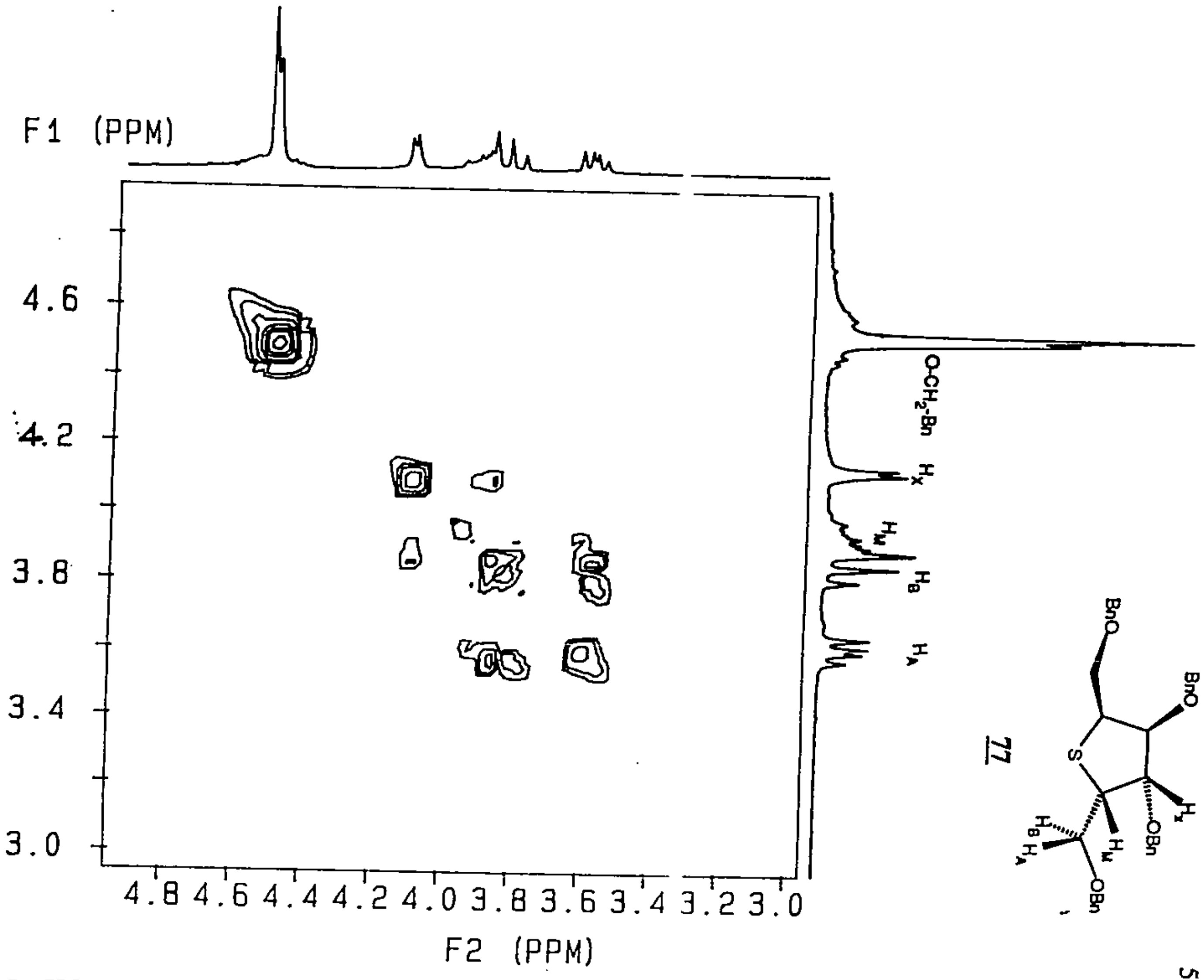


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Figure 5. HOMCOR spectrum of (2S,3S,4S,5S)-(-)-tetra-O-benzyl-3,4-bis-hydroxy-2,5-bis-hydroxymethylthiolane 77.

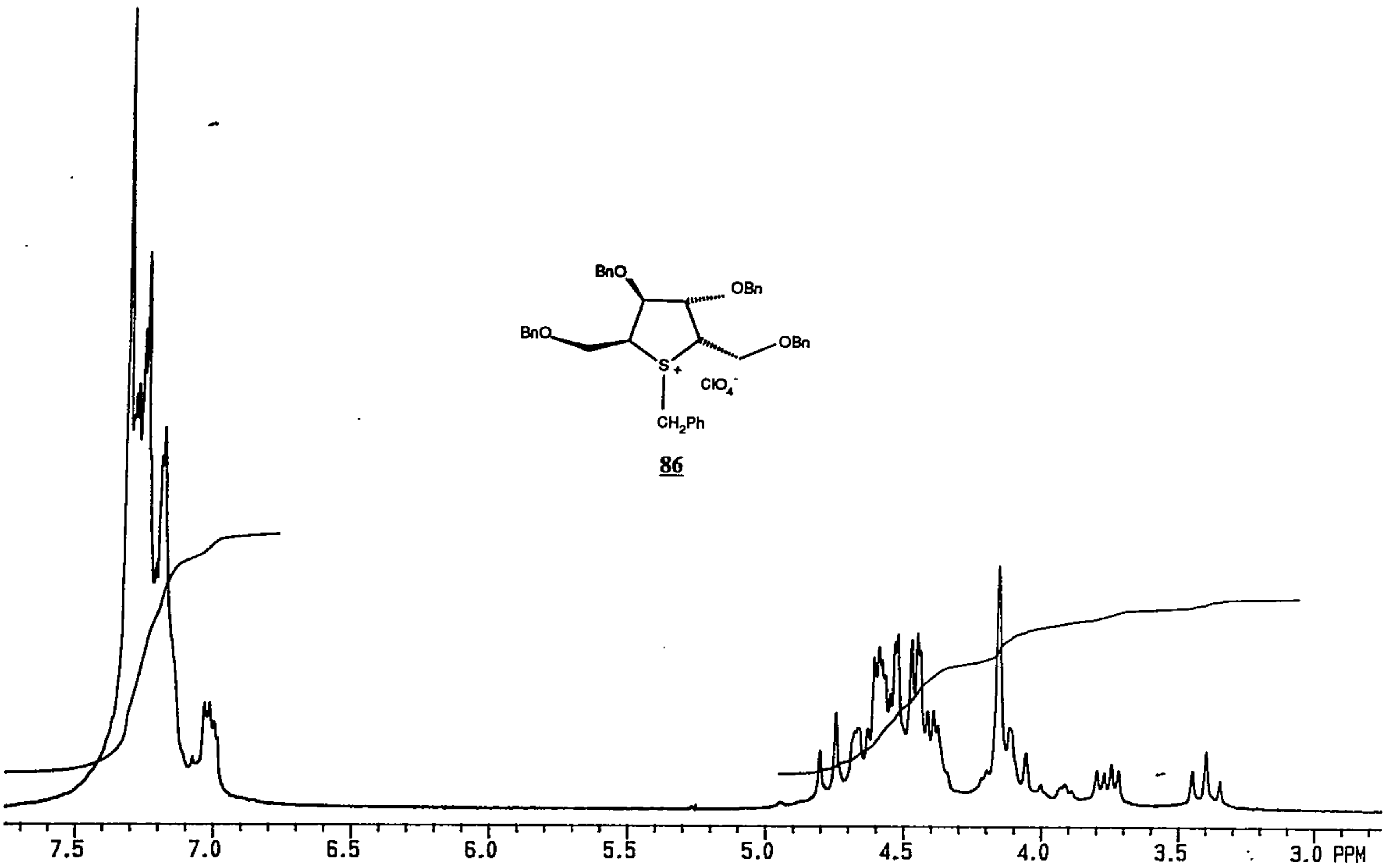


Figure 6. ^{1}H nmr spectrum of <u>86</u>

conditions (NaOH-50%/CH_2Cl_2-PTC/O°C) (Section 1.6), in the presence of reactive aldehydes such as benzaldehyde and *p*-nitrobenzaldehyde. Under these conditions, these electrophiles are compatible with the base used and their coexistence allows for reaction with the ylide as soon as is it generated *in situ*. This method of ylide generation proved to be successful in avoiding α′,β-elimination such as was encountered in 82. The results are shown in Table 2. The enantiomeric excess was based on optical rotation values reported for optically pure compounds.[30] Other optical rotation figures reported by Ziffer and Imuta[110] are too high and do not correlate well with $Eu(hfc)_3$ shift nmr experiments. For details see page 132.

TABLE 2. Preparation of stilbene oxide 87 *via* the sulfur ylide 86.

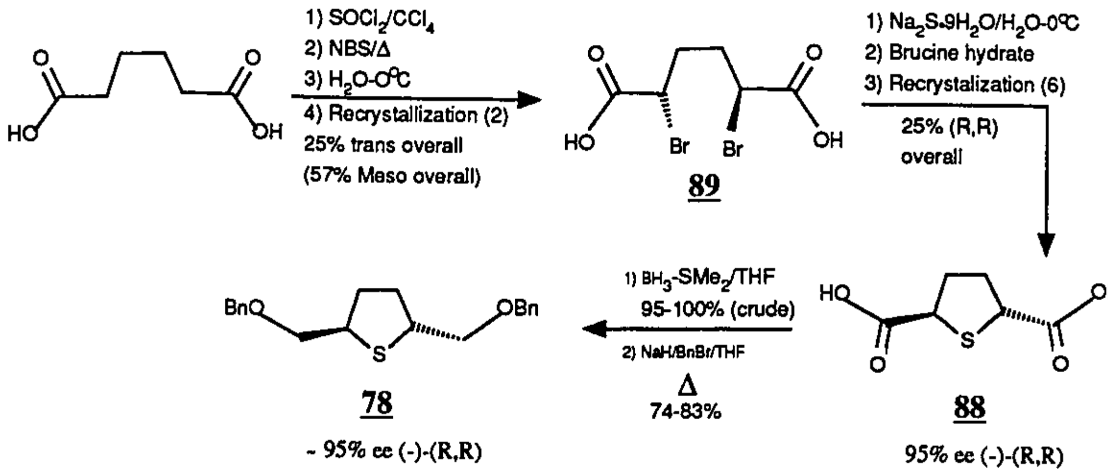
Aldehyde	*trans* Epoxide 87 yield (%)	Absolute configuration[a]	Enantiomeric excess[b] (%)	Recovery of thiolane 77 (%)
PhCHO	X=H; (27%)	(+)-R,R	79	44
4-$NO_2C_6H_4$CHO	X=4-NO_2; (41%)	(+)-R,R	83	56

a) Base on sign of $[\alpha]_D$ measurement.[110]
b) Base on specific rotations figures reported for optically pure compounds.[30]

From the results in Table 2, it can be seen that although the chemical yields are still low, the enantiomeric purity of the epoxides produced improved by a factor of 4 in comparison with the epoxides obtained *via* ylides 8 (Scheme 3). The rotation +230 (c=1.25, acetone) for *trans*-stilbene oxide indicate that it had a 2R,3R configuration.[30] In addition, 44% of the theoretical amount of thiolane 77 (calculated from thiolane 77) could be recovered with essentially no loss of optical purity. A discussion of an apparent dichotomy is given in Section 4.2 (page 150).

2.3 (2R,5R)-(-)-Di-O-benzyl-2,5-bis-hydroxymethylthiolane 78

The precursor (-)-(2R,5R)-thiolane dicarboxylic acid 88 was prepared according to Scheme 14, starting from adipic acid.[111] Thus, adipic acid was converted to adipoyl chloride and brominated *in situ*.[112] Hydrolysis gave a mixture of *cis* and *trans*-α,α-dibromo adipic acid which were separated by repetitive crystallization. The *trans* (d,l) diacid, 89, was cyclized by treatment with sodium sulfide to give the racemic acid, 88, which was resolved with brucine. The optically active (-)-(R,R')-thiolane-2,5-dicarboxylic acid 88 (95% optical purity) was reduced with borane in THF and subsequently benzylated using standard conditions (NaH, BnBr, THF) to give the corresponding optically active thiolane, 78. Assuming no loss of optical activity during the last two synthetic sequences, the thiolane 78 should have 95% enantiomeric purity. The proton nmr spectrum of 78 is shown in Figure 7. This thiolane displayed resonances at δ1.84-2.12, δ3.43, δ3.48, δ3.61, δ4.51 and δ4.58 in addition to the aromatic signals found at δ7.26-7.37. The signals at δ1.84-2.12 (m, 4H) were assigned to the protons at C-3 and C-4. The signals at δ3.43 and δ3.48 form the A and B part of an ABX pattern and were attributed to the protons of the hydroxymethylene groups at C-2 and C-5. The X part



Scheme 14. Synthesis of thiolane 78.

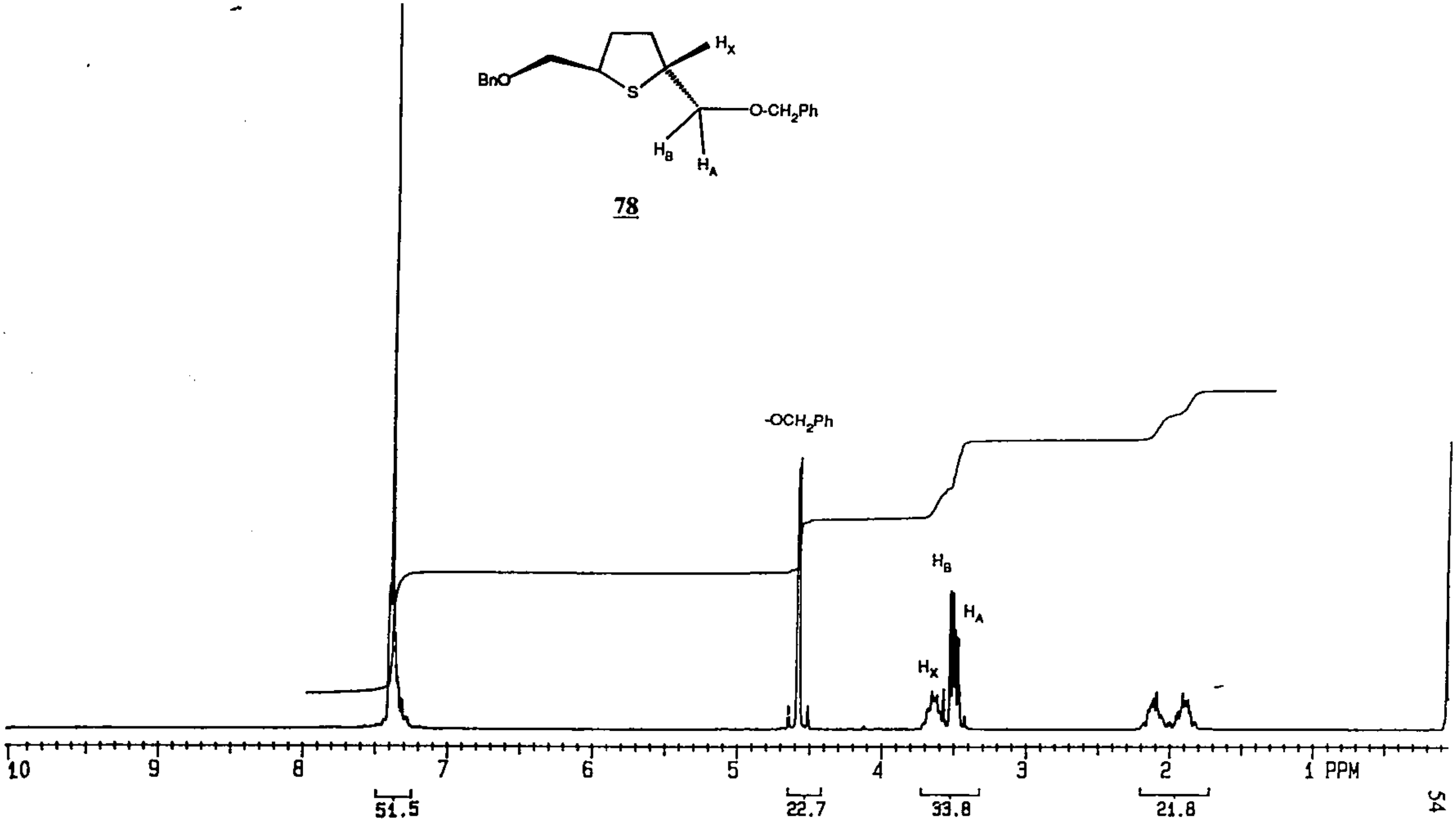
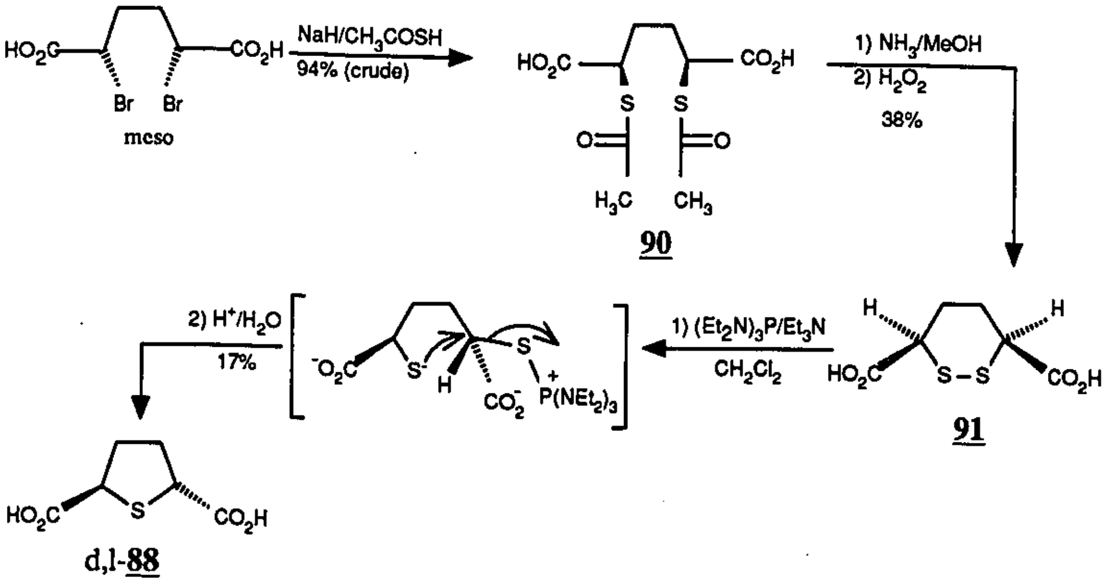


Figure 7. ^{1}H nmr spectrum of (2R,5R)-(-)-di-O-benzyl-2,5-bis-hydroxymethyl-tetrahydrothiophene 78.

of the ABX system resonated as a multiplet at δ3.61 and were assigned to the protons at C-2 and C-5. The signals at δ4.51 and δ4.58, also an AB system pattern was due to the benzylic protons. The ^{13}C spectrum of 78 showed three methylene at δ37.08, δ73.01 and δ74.11, a methine carbon at δ47.34 and three aromatic resonances. The fact that only ^{1}H and ^{13}C resonances for half of the molecule are observed, confirmed that the thiolane 78 is C_2 symmetric. Furthermore, the mass spectrum, which showed a molecular ion peak at m/z=328(M^+, 1%), and the elemental analysis were consistent with an empirical formula: $C_{20}H_{24}O_2S$.

Unfortunately, the overall yield for the preparation of thiolane 78 starting from adipic acid was only ≈4.5%. The major loss of material occurred during the bromination of adipic acid since more than two thirds of the product produced was meso-α,α-dibromoadipic acid. An effort was made to convert this product into the racemic *trans*-thiophene-2,5-dicarboxylic acid, 88, by the sequence depicted in Scheme 15. The meso-α,α-dibromoadipic acid was treated with sodium thioacetate to afford the corresponding dithio ester, 90. Hydrolysis with ammonia dissolved in methanol followed



Scheme 15.

by oxidation with hydrogen peroxide gave the *meso*-1,2-dithian-3,6-dicarboxylic acid **91**, albeit, in modest yield.[113] The desulfurization sequence employing hexaethylphosphorous triamide did produce *trans*-thiolane-2,5-dicarboxylic acid d,l-**88** but in very low yield. The poor overall yield of this process does not justify the effort needed to convert meso-α,α-dibromoadipic acid into d,l-**88** and the process was therefore abandoned.

Nonetheless, a sufficient amount of thiolane **78** was prepared for an academic study of its chemical behavior. Benzylsulfonium salt **92** was obtained in 58% yield upon treatment of the precursor thiolane, **78**, with benzyl bromide in ether followed by addition of $AgClO_4$. Isolation of the salt was achieved by decantation of the ether, addition of CH_2Cl_2 and filtration to remove the insoluble silver bromide that formed. The snow white amorphous, hygroscopic solid, **92**, thus obtained was characterized by a complex proton (Figure 8) and carbon-13 nmr spectrum which demonstrated the absence of C_2 symmetry. The signal for the S^+-C$\underline{H}_2$-Ph appeared as an AB pattern at δ4.63 and δ4.51. The observation of only one AB pattern demonstrated that only one sulfonium salt had formed as predicted from the C_2 symmetry of thiolane **78**. This conclusion is further supported by the ^{13}C spectrum of **92** which contained 9 aliphatic carbon resonances (eight for the thiolanium auxiliary and one for the S^+-$\underline{C}H_2$-Ph).

The sulfur ylide **93** was generated from the salt **92** with NaOH under phase transfer conditions (Scheme 16) in the presence of aromatic aldehydes. These conditions were identical to those used for the preparation of the ylide **86**. The results are shown in Table 3.

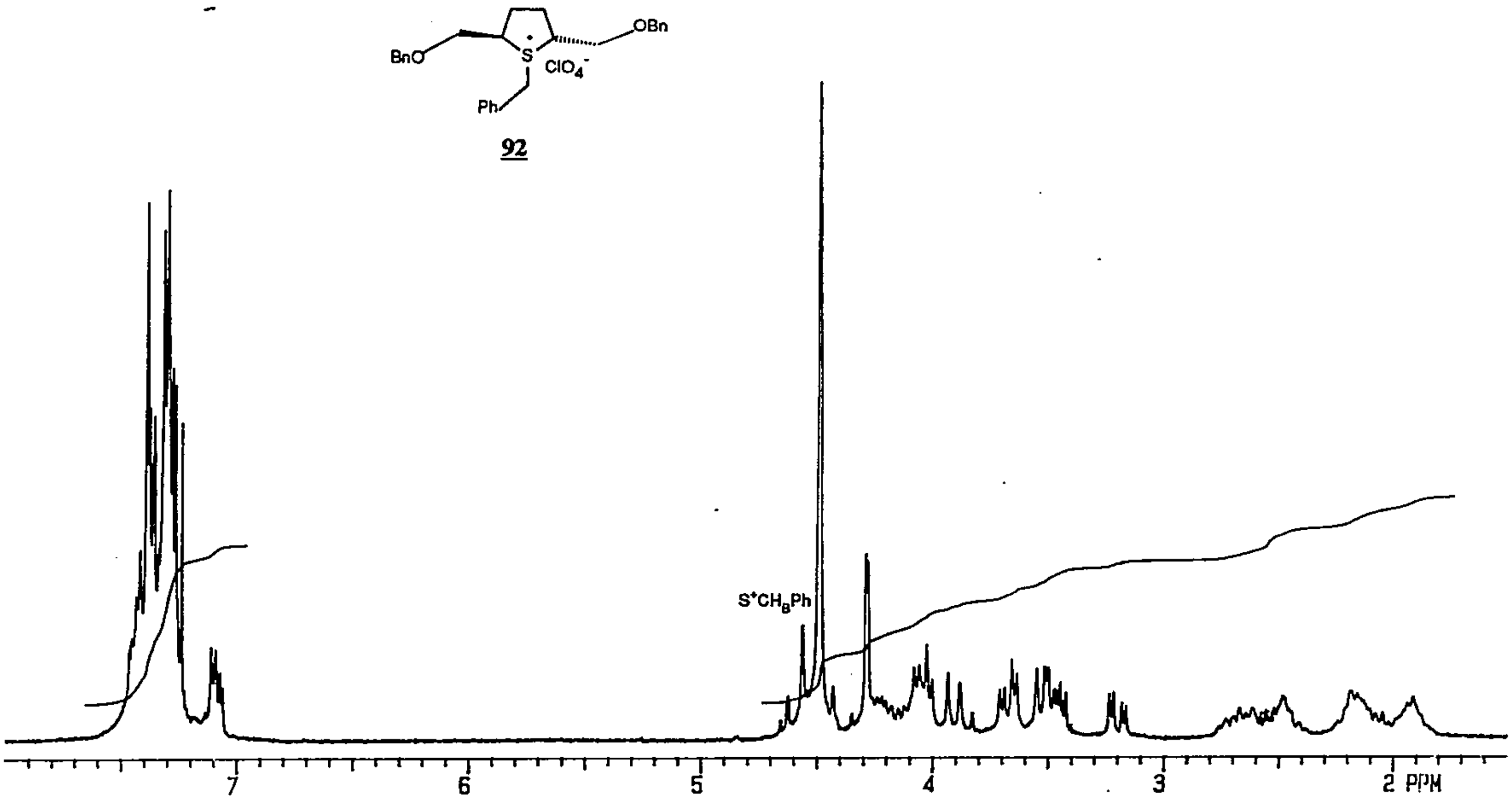
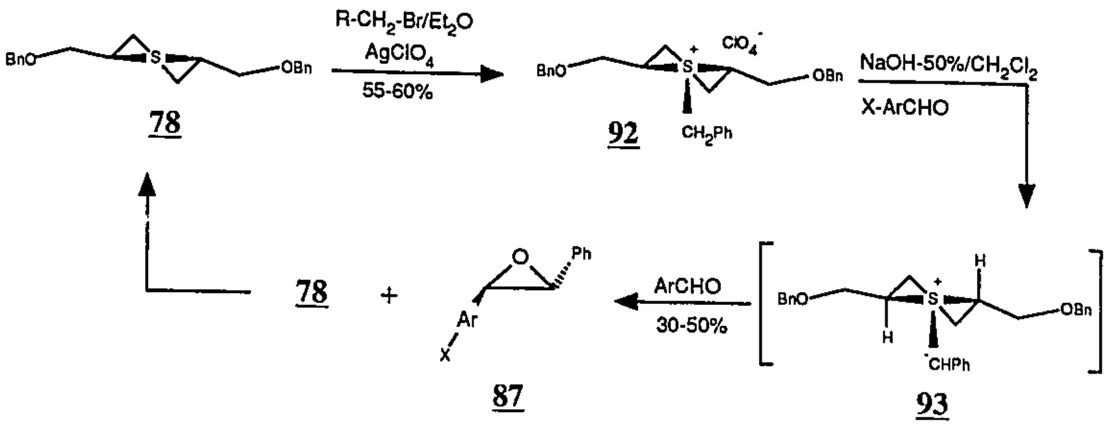


Figure 8. ^{1}H nmr spectrum of sulfonium salt <u>92</u>.



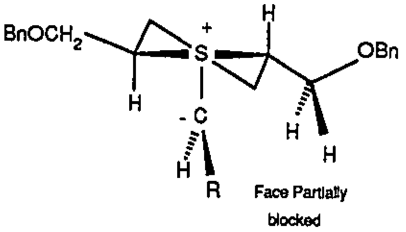
Scheme 16.

Table 3. Preparation of stilbene oxides 87 *via* the sulfur ylide 93.

Aldehyde	*trans* Epoxide 87[a]	Absolute configuration[b]	Enantiomeric excess[c] (%)	Recovery of thiolane 78 (%)
PhCHO	X=H; 53%	(+)-R,R	74 (77)[d]	80
4-ClC$_6$H$_4$-CHO	X=Cl; 31%	(+)-R,R	67 (73)[e]	88

a) *cis* Epoxide were also present in 7-15% yield.
b) Base on sign of $[\alpha]_D$ measurement[110]
c) Base on specific rotations figures reported for optically pure compounds.[30]
d) Base on the 95% optical purity of 78.
e) Base on the 92% optical purity of 78.

This Table shows that the resultant epoxides have the same absolute configuration and similar optical purities as those isolated from tetra-substituted ylide 86. The lack of complete asymmetric induction must therefore be due to insufficient shielding of one of the ylidic carbon faces. The five-membered ring of 93 probably adopts a half-chair conformation, in which the steric bulk of the C-2 substituent is relatively far from the ylidic carbon face.



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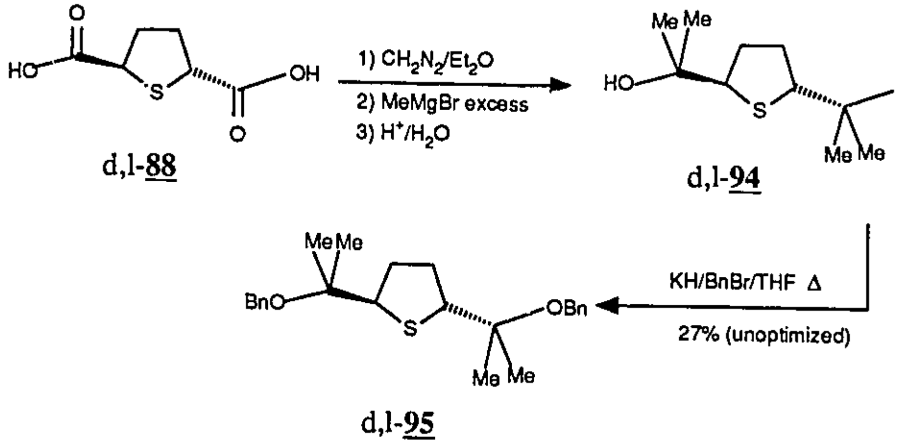
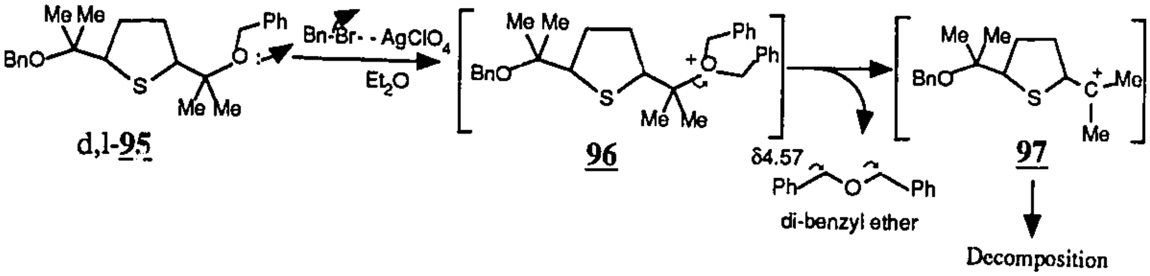
One potential way to remedy to this situation is to increase the steric demand of the C-2 and C-5 groups. However an increase in the steric congestion at these positions may decrease the ability of the sulfur to approach an electrophile thus contributing to a reduction in its nucleophilicity. Indeed, while thiolane itself can be alkylated efficiently with benzyl bromide in boiling water or acetone, the addition of a substituent at C-2 and C-5, as in thiolane 78, required the use of silver salts in the alkylation reaction. The possibility of alkylating the sulfur of highly hindered thiolane was tested with racemic 95. Thus, the addition of methyl magnesium iodide to the methyl ester of *trans*-2,5-thiolane dicarboxylate 88 gave thiolane 94 which was subsequently benzylated using KH/BnBr in THF to afford the bisbenzylether derivative 95 (Scheme 17). This thiolane displayed an intense ^{1}H resonance at δ1.35 equivalent to twelve protons attributed to the four methyl groups. The signals observed at δ1.92(m), δ3.79(m), are typical of hydrogens bonded to the C-3 and C-4, and C-2 and C-5 carbons respectively. Other resonances at δ4.49 (AB, 4H) and δ7.28 (m, 10H) were assigned to benzylic and aromatic protons. The number of signals observed was consistent with C_2 symmetric geometry.



Scheme 17.

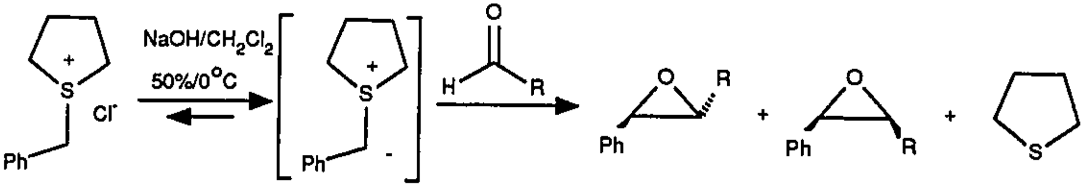
Alkylation of thiolane 95 under standard conditions ($BnBr/Et_2O/AgClO_4$) led to its complete destruction. The proton nmr showed a very complex pattern with numerous signals between δ0.60 and δ1.80 replacing the previous single resonance at δ1.35 for the four methyl groups. Interestingly, one singlet at δ4.57 was intense and was attributed to the presence of dibenzyl ether. This assignment was supported by an observed increase in the amplitude of the resonance at δ4.57 when spiked with authentic dibenzyl ether. The decomposition of thiolane 95 and the formation of $(PhCH_2)_2O$ could be considered to be initiated by an alkylation at oxygen (i.e. 95 → 96 → 97, Scheme 18).



Scheme 18.

2.4 Thiolane as C_2 Symmetric Mediator.

To have some potential for organic synthesis, the desired epoxides must be synthesized with high e.e. and in high *trans/cis* or *cis/trans* ratios. To fill a void in the literature on this matter, a study of the variations in the *trans/cis* ratio for a series of epoxides obtained *via* the reaction between S-benzylthiolanium ylide 99 and a variety of carbonyl compounds was carried out in our laboratory[102] (Scheme 19). The reactions were carried out under conditions similar to those used for optically active sulfonium salts (i.e. NaOH 50%/ CH_2Cl_2/ PTC/ 0°C/ 1-3 hours) and the results are summarized in Table 4. When very bulky aldehydes were used as the carbonyl component the epoxides produced were composed mainly of *trans*-stilbene oxides (entry 1-4). In contrast, when much smaller aldehydes were involved, a notable increase in the amount of the corresponding *cis*-epoxide was obtained with an augmentation in the steric demand of the aldehydes (entry 5-7). A rationale for this apparent contradiction can be found in Section 4.2.1.



Scheme 19.

TABLE 4. Ratio of epoxide produced *via* S-benzyl thiolanium ylide 99.[102]

Entry No.	Aldehyde RCHO	% of Epoxide composition[a]				*trans*/*cis* Ratio	Isolated chemical yield (%)
			trans	:	*cis*		
			 **100 A-G**		 **101A-G**		
1	R=*t*-Bu	**A**	100	:	0	∞	42
2	R=4-MeC_6H_4-	**B**	93	:	7	13.3	46
3	R=Ph	**C**	88	:	12	7.3	54
4	R=4-$NO_2C_6H_4$-	**D**	83	:	17	4.9	79
5	R=Me-	**E**	69	:	31	2.2	30
6	R=Et-	**F**	61	:	39	1.6	35
7	R=*i*-Pr	**G**	44	:	56	0.79	31

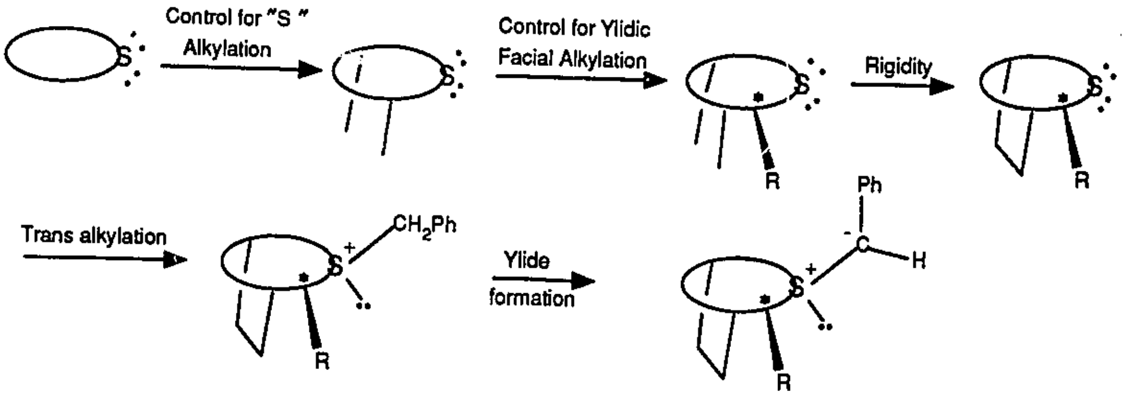
a) Base on integration of proton signals obtained from crude reaction mixtures.

III CHAPTER 2

3. CAMPHORIC ACID DERIVED AUXILIARIES.

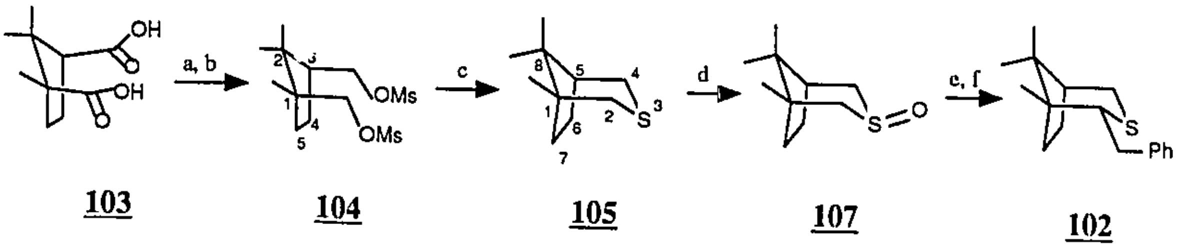
Preliminary results obtained in the preparation of optically active epoxides by the reaction of sulfur ylides (derived from C_2 symmetric thiolanes) with aromatic aldehydes shed some light on the structural features required for an ideal auxiliary. In summary, it was found that C_2 symmetric thiolanes are not rigid enough and adopt a quasi-chair form which results in only partial shielding of one of the ylide faces. The problem associated with the presence of an oxygen atom was evident on several occasions. An attempt to increase the steric bulk of the C-2 and C-5 substituents and thus increase the optical purity of the product epoxides was counter productive since it decreased substantially the nucleophilicity of the sulfur and prevented sulfonium salt formation.

Therefore, it was decided to explore the possibility of synthesizing non-C_2-symmetric sulfide auxiliaries which, like the C_2-symmetric thiolanes, would give only one sulfonium salt and thus have potential for use in the preparation of optically active epoxides. The redesign of such a chiral sulfide begins with a cyclic ring containing a sulfur atom. Structural elements necessary to accomplish the goal of generating a single sulfur ylide in which one face is strongly shielded were introduced as depicted formally in Scheme 20. Examination of molecular models indicated that thiane **<u>102</u>** looked very



Scheme 20.

promising since it should yield a single sulfonium salt and then a single ylide resulting from initial exo S-alkylation. Based on literature precedent[114,115], this tailored chiral auxiliary 102 should be readily available from (1R,3S)-(+)-camphoric acid 103 *via* Scheme 21. The precursor 103 is commercially available in both enantiomerically pure forms.[116]



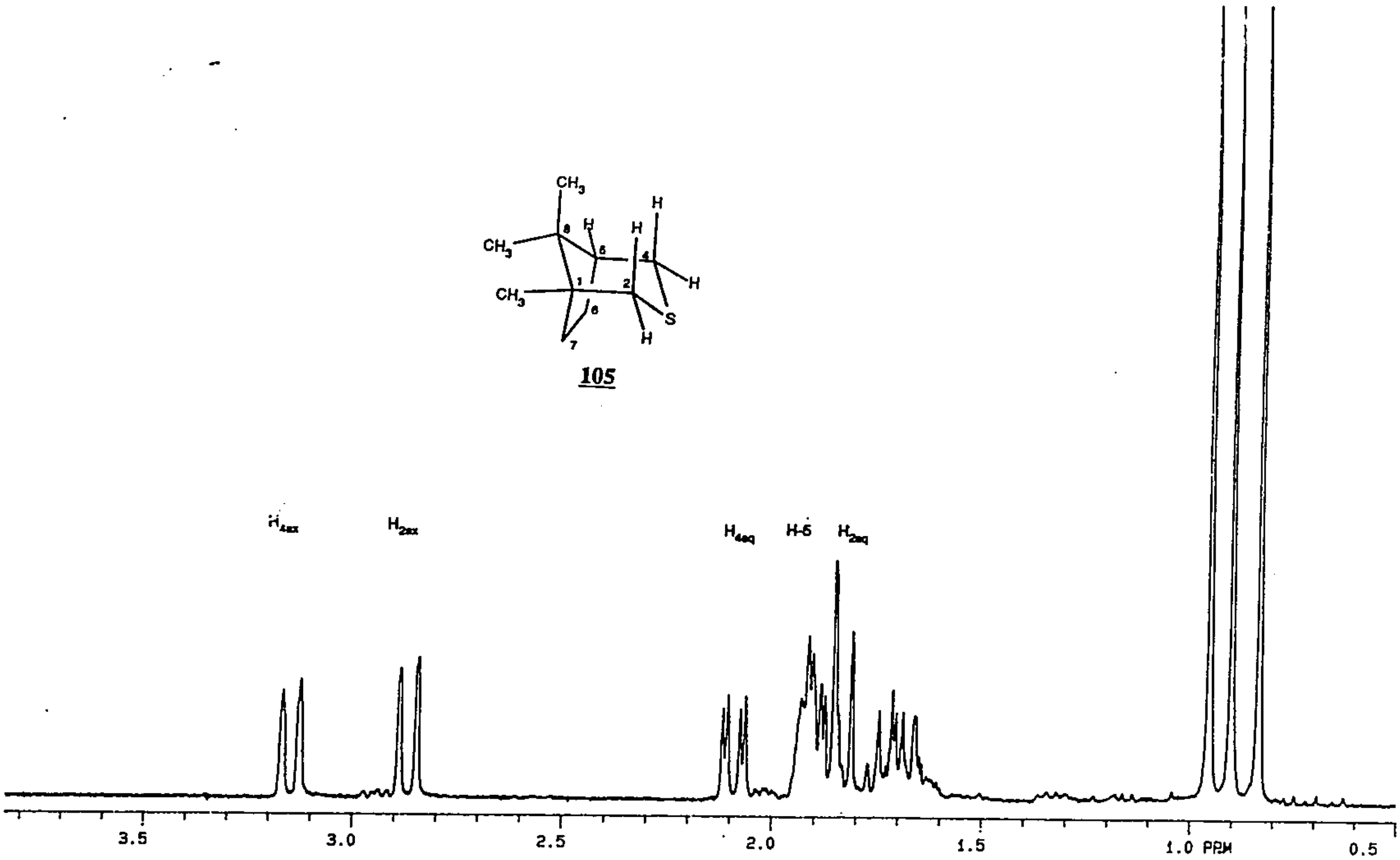
a) $BH_3 \cdot SMe_2$, THF; b) MsCl, Et_3N, CH_2Cl_2; c) $Na_2S \cdot 9H_2O$, DMF; d) MMPP, EtOH-H_2O
e) MeLi, THF, BnBr; f) $SnCl_2 \cdot 2H_2O$, AcCl, CH_3CN-DMF.

Scheme 21.

3.1 Synthesis of (1R,5S)-(+)-1,8,8-Trimethyl-3-thiabicyclo[3.2.1]octane 105

(1R,3S)-(+)-Camphoric acid 103 was reduced with the borane dimethylsulfide complex in THF and gave cleanly (1R,3S)-(+)-1,2,2-trimethyl-1,3-bis(hydroxymethyl)-cyclopentane.[117] Mesylation of this diol was carried out using standard conditions (mesyl chloride and triethylamine in CH_2Cl_2) to give dimesylate 104 in 90% overall yield. The ^1H nmr spectrum showed two methyl singlets at $\delta 2.96$ and $\delta 2.97$ and thus confirmed that this compound had the expected two distinct mesylate functions. The remaining spectroscopic properties were also in agreement with structure 104 and are recorded in the Experimental Section.

The cyclization using $Na_2S \cdot 9H_2O$ in DMF at 70°C was carried out on the crude dimesylate 104 and gave the desired thiolane 105 in 52% yield. This compound had a noticeable pine-like scent. The proton nmr spectrum of this thiane is shown in Figure 9.



105

Figure 9. ^{1}H nmr spectrum of (1R,5S)-(+)-1,8,8-trimethyl-3-thiabicyclo[3.2.1]octane **105**.

The three high singlets at δ0.82, δ0.87 and δ0.94 were attributed to the methyl groups. The middle portion of the spectrum consisted of a multiplet from δ1.60 to δ1.95, which was assigned to the protons on C-2, C-5, C-6 and C-7 while the three lower field signals at δ2.08, δ2.85 and δ3.14 were due to the protons α to the sulfur. The proton homonuclear correlation spectrum (HOMCOR) is shown in Figure 10. This spectrum indicated that the signal at δ2.85 was coupled with the signal at δ1.82. Both resonances were due to an AB system and were assigned to the protons at C-2. The HOMCOR spectrum also showed that the signal at δ2.08 was coupled with the signals at δ3.14 and the multiplet at δ1.9. The two signals at δ3.14 and δ2.08 which appeared as the AB part of an ABX pattern were assigned respectively to the protons at C-4. The X part of the ABX system, due to the proton at C-5, resonated as a multiplet at δ1.9. The nOe experiment proved to be useful in the assignment of the stereochemistry of the protons α to the sulfur. The nOe difference spectra obtained by the selective irradiation of each of the methyl groups at C-8 and C-1 in thiane **105**, are shown in Figure 11 and summarized in Figure 12. The irradiation of the

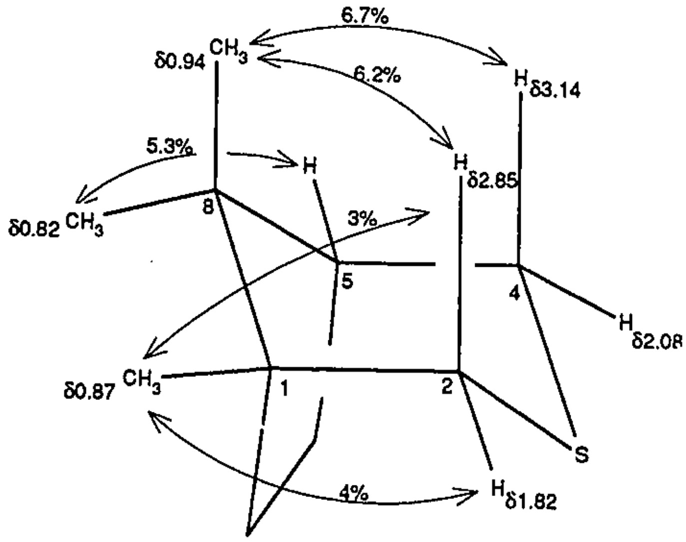


Figure 12. Summary of the nOe differences observed in **105** from the irradiation of the methyl groups at C-8 and C-1.

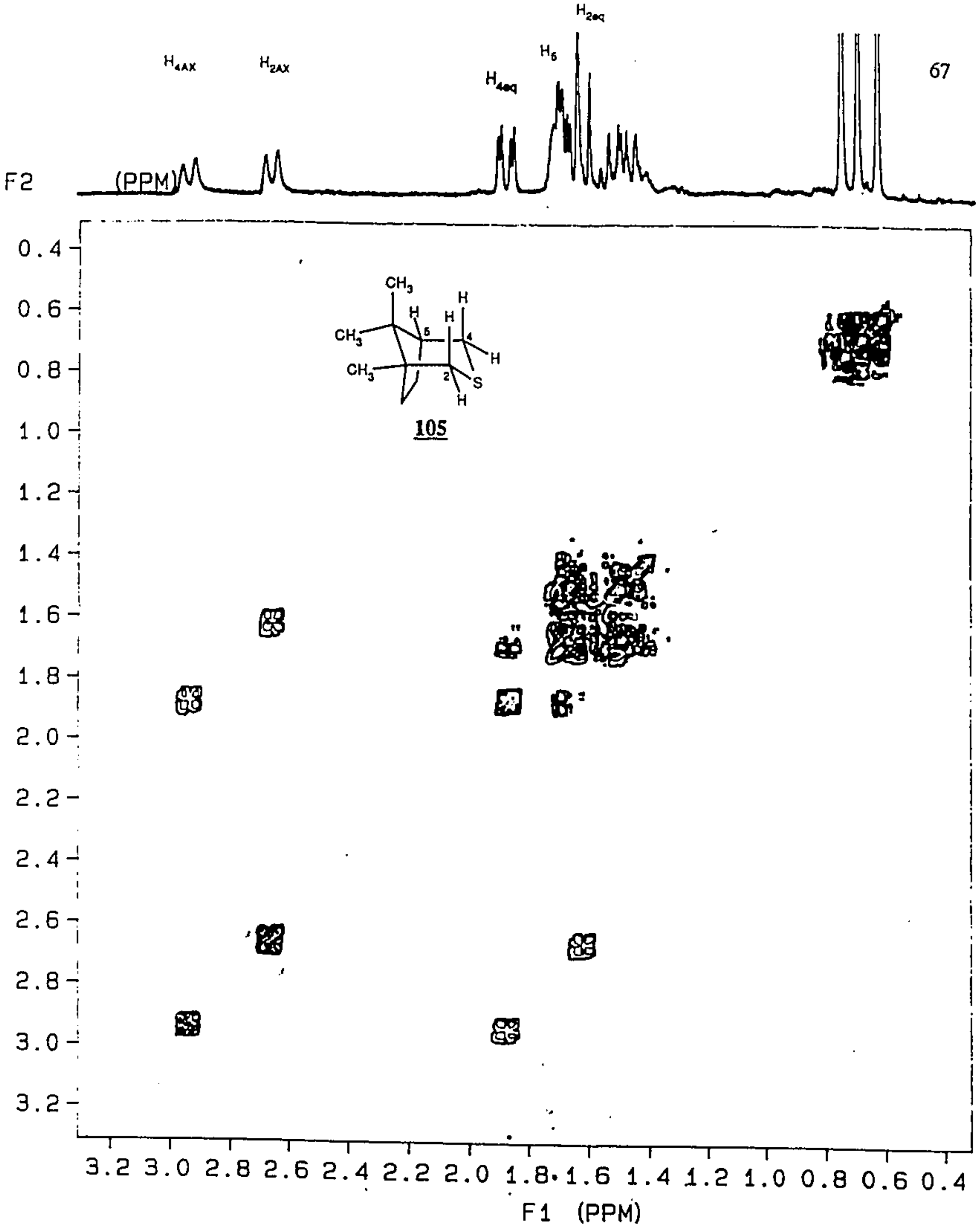


Figure 10. HOMCOR spectrum of (1R,5S)-(+)-1,8,8-timethyl-3-thiabicyclo[3.2.1]-octane **105**.

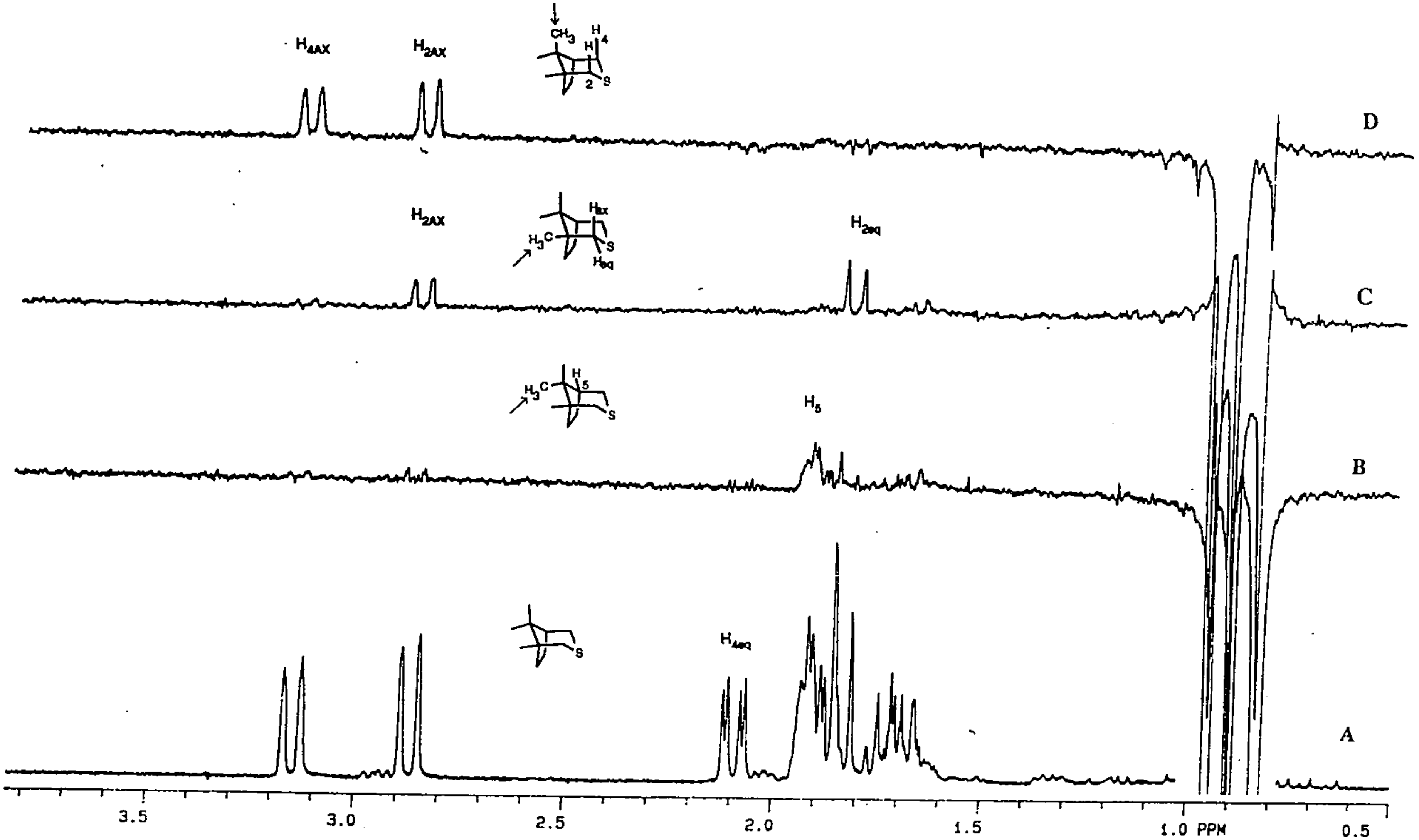


Figure 11. A) ^{1}H nmr spectrum of <u>105</u>.
B-D) nOe difference spectra obtained upon irradiation of the methyl signals at:
B) $\delta 0.82(Me_{C\text{-}8eq})$; C) $\delta 0.87(Me_{C\text{-}1})$ and D) $\delta 0.94(Me_{C\text{-}8ax})$.

axial methyl group at C-8 (Figure 11-D) resulted in a positive nOe for the two proton signals at δ3.14 and δ2.85. These were therefore assigned to the axial protons at C-4 and C-2, respectively. The signal at δ3.14 for proton H_{4ax} appeared as a doublet because of the absence of vicinal coupling with the proton at C-5. Indeed, inspection of the molecular model of this compound revealed that the dihedral angle between these two protons is close to 90°C. Irradiation of the C-1 methyl (Figure 11-C), resulted in a selective nOe with the proton signals at δ2.85 and δ1.82. Since the former signal was assigned to H_{2ax}, the latter signal must be attributed to the equatorial proton at C-2 (H_{2eq}). Irradiation of the equatorial methyl group at C-8 (Figure 11-B), showed an nOe with the multiplet at δ1.90 due to its proximity to the proton at C-5. The careful assignment of each key proton and the various correlation and nOe experiments may appear overzealous to the reader. These data proved crucial to the confirmation of the unusual stereochemistry of the sulfoxide alkylation products (see below).

Addition of $AgClO_4$ to a solution of thiane **105** and benzyl bromide in anhydrous ether gave 88% of S-benzylsulfonium salt **106** as a white solid. This material was relatively stable at room temperature. The ^{1}H nmr spectrum of this salt is shown in Figure 13. As expected, this spectrum showed definite downfield chemical shifts for the resonances attributed to the protons α to the sulfur atom in comparison with those observed for thiolane **105**. The benzylic protons were observed at δ4.76 and appeared as a singlet. The three singlet signals at δ0.59, δ0.81 and δ0.98 were attributed to the methyl groups at C-8 and C-1. The absence of other major singlets in this region confirmed that a single sulfonium salt had been formed. The expected equatorial stereochemistry of the S-benzylation in **106** was based on nOe experiments which are shown in Figure 14 and summarized in Figure 15. The crux of the assignment was the irradiation of the benzylic protons (Figure 14-E) which resulted in a positive nOe with all the protons α to the sulfur. No nOe could be detected for the proton at C-6 and C-7 (i.e., from δ1.6 to δ2.15). Equatorial alkylation is not surprising since an S-axial benzyl group would suffer from

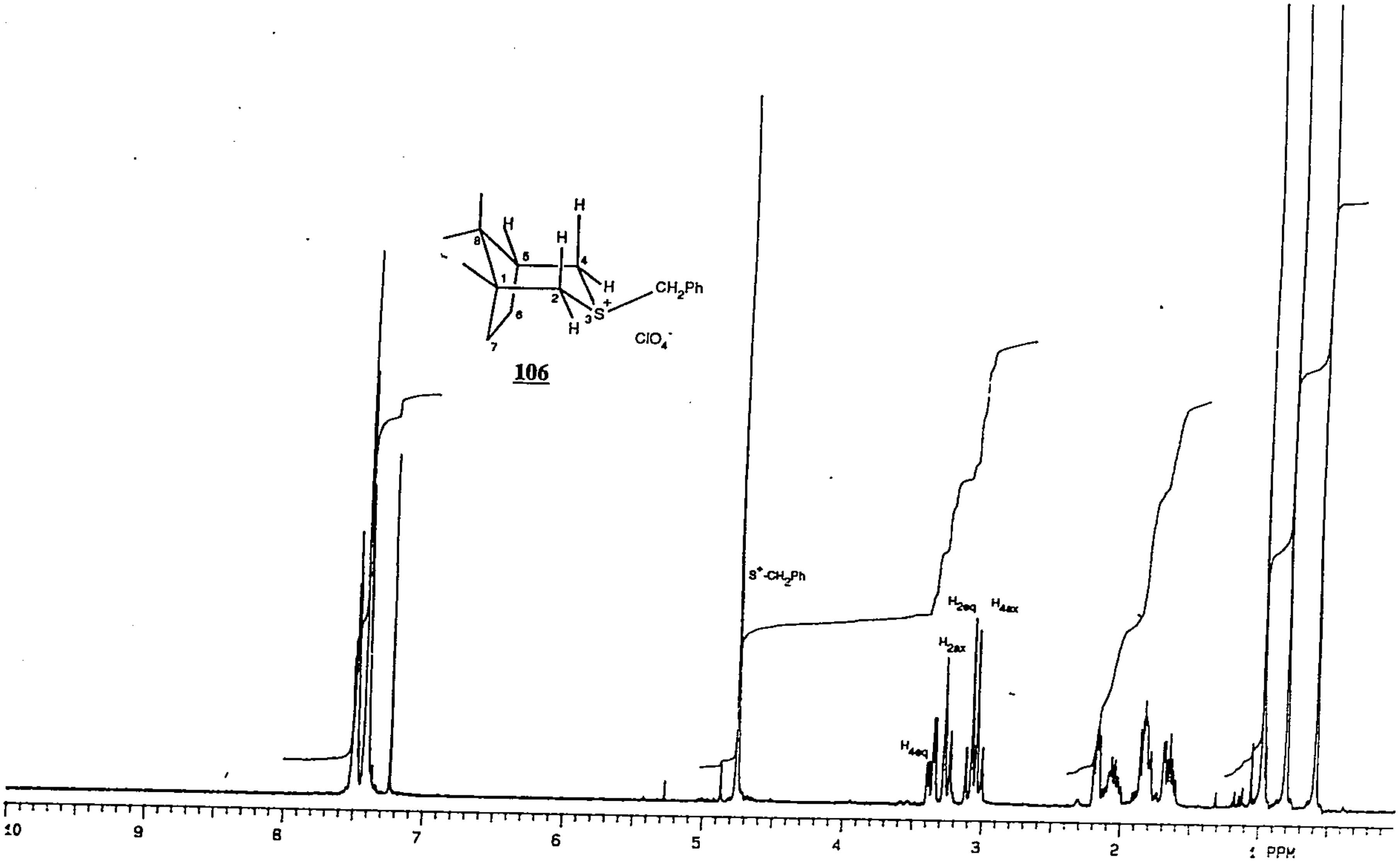


Figure 13. ^{1}H nmr spectrum of (1R,3R,5S)-(-)-3-benzyl-1,8,8-trimethyl-3-thianiumbicyclo-[3.2.1] octane perchlorate **106**.

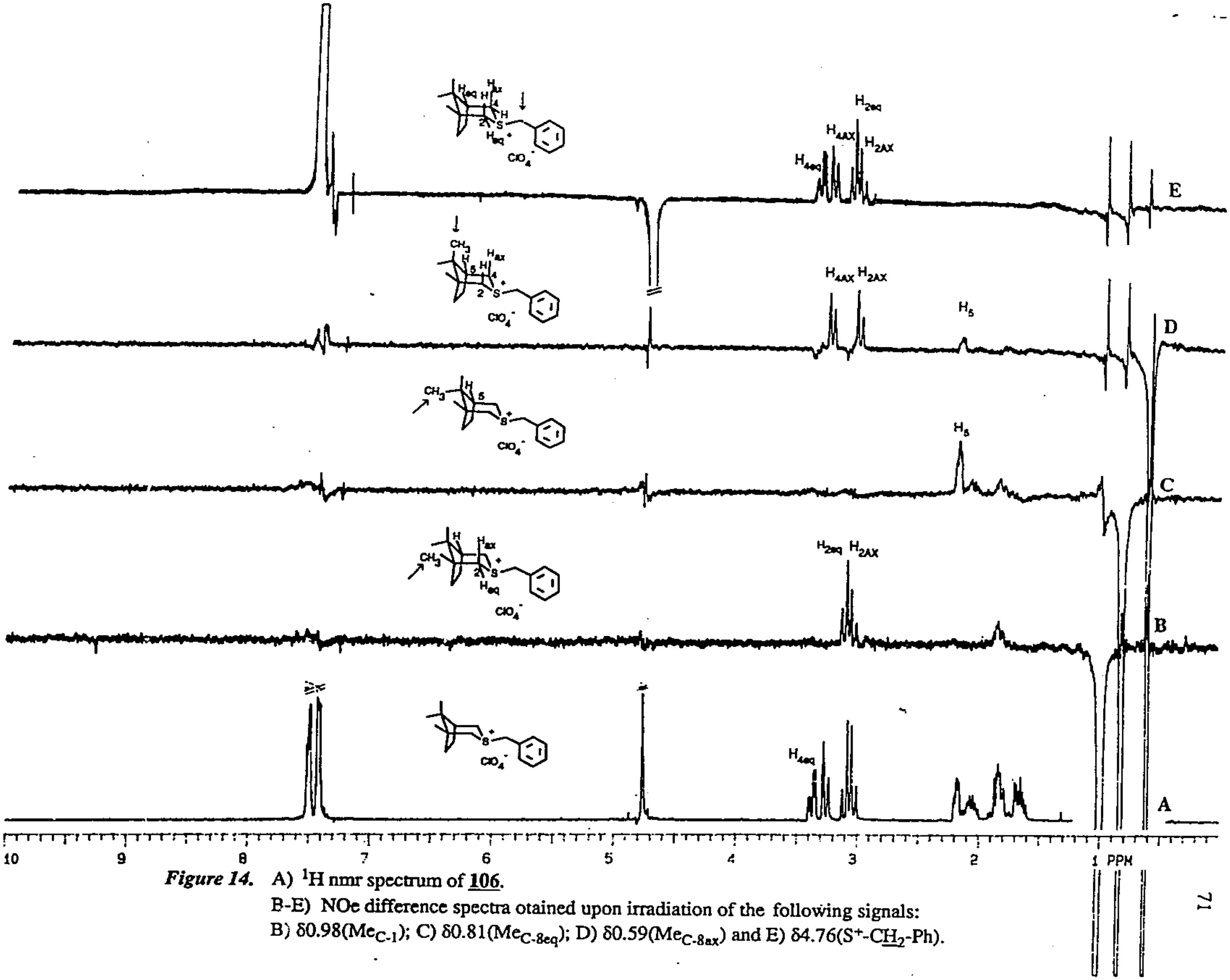


Figure 14. A) ^1H nmr spectrum of **106**.
B-E) NOe difference spectra otained upon irradiation of the following signals:
B) δ0.98($Me_{C\text{-}1}$); C) δ0.81($Me_{C\text{-}8eq}$); D) δ0.59($Me_{C\text{-}8ax}$) and E) δ4.76(S^+-$C\underline{H}_2$-Ph).

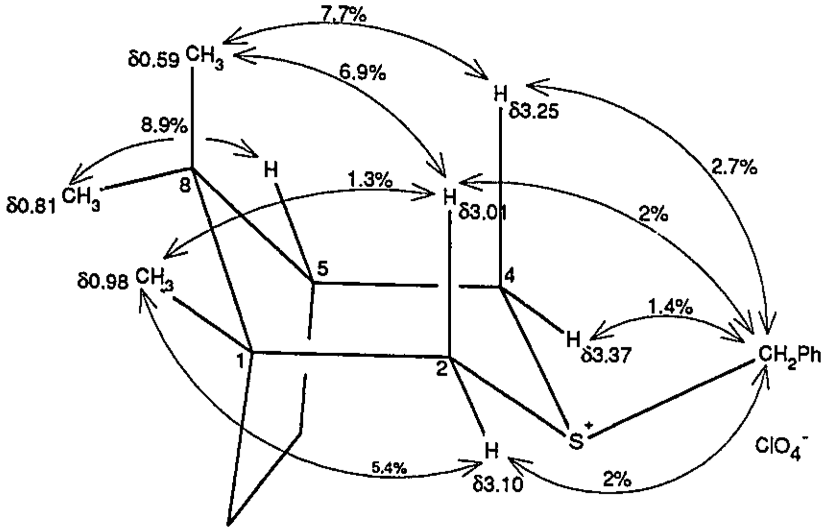


Figure 15. NOe difference observed in **106** from the irradiation of the S^+-CH_2Ph and the C-1 and C-8 methyl signals.

two 1,3-syn diaxial interactions with the protons at C-6 and C-7.

An epoxidation reaction using sulfonium salt **106**, benzaldehyde and NaOH under phase transfer catalysis gave a mixture of *cis*- and *trans*-stilbene oxides in 16% and 39% yield, respectively. The *trans*-isomer was optically active with an $[\alpha]_D$=+45° (c=1, acetone). The absolute configuration is (R,R) and the enantiomeric excess is 15% based on comparison with the literature value of +291° (c=0.05, acetone).[30]

The catalytic properties of sulfide **105** were investigated under conditions similar to those reported by Furukawa *et al.*[31b] The reaction system was composed of acetonitrile (as solvent), sulfide **105**, benzyl bromide and benzaldehyde in the presence of powdered KOH under biphasic conditions. After two days the chemical yields, calculated on the basis of the aldehyde being the limiting reagent, were 5% and 30% for the *cis*- and *trans*-stilbene oxides, respectively. The *trans*-isomer was optically active with an $[\alpha]_D$=+28.4 (c=2, acetone). This corresponds to ≈10% enantiomeric excess again in favor of the (R,R) isomer. The turnover number for the reaction was ≈0.65 and was based on the sulfide.

3.2 Synthesis of 2 and 4 Substituted-1,8,8-Trimethyl-3-thiabicyclo[3.2.1]octanes Auxiliaries.

The asymmetric induction in the synthesis of stilbene oxides *via* **105** was surprisingly high. Based on previous studies with *trans*-2,5-disubstituted thiolanes and molecular model examination it was expected that thiane auxiliaries bearing a substituent α to the sulfur would give substantially higher asymmetric induction in epoxide preparation. The preparation of **102** which was designed for this purpose is shown in Scheme 21.

The oxidation of sulfide **105** with magnesium monoperoxy phthalate (MMPP)[118] was carried out overnight at room temperature in an ethanol-water (1:1 ratio) mixture. As anticipated, the oxidation was stereoselective and provided a single sulfoxide isomer in 89% yield. The crude material was easily purified by sublimation (i.e. 110-115°C/0.25 torr) and give a white crystalline solid, m.p. 240-241°C. This compound displayed a strong absorption at 1028 cm^{-1} in the ir spectrum which is characteristic for a sulfoxide functionality. The ^1H nmr spectrum, shown in Figure 16, is quite similar to the one obtained for S^+-benzylthianium cation **106** with the exception that the signals attributed to the benzyl group are missing. The protons α to the sulfoxide functionality were the most deshielded and resonated at δ3.36, δ3.08, δ2.87 and δ2.76. The HOMCOR spectrum is shown in Figure 17. The results of a series of nOe difference experiments performed on **107** are shown in Figure 18 and summarized in Figure 19. The key nOe spectrum obtained from the selective irradiation of the axial methyl at C-8 (Figure 18-D) resulted in an nOe with the two signals at δ2.87 and δ2.76 which were therefore assigned unambigously to the axial protons at C-4 and C-2, respectively. By the same rationale as the one put forward for the benzylation of sulfur in **105**, equatorial S-oxidation was assumed. This deduction was later confirmed by an X-ray structure analysis of a 2-substituted derivative of **107**.

The metallation of cyclic sulfoxides and the stereochemistry of their alkylation has

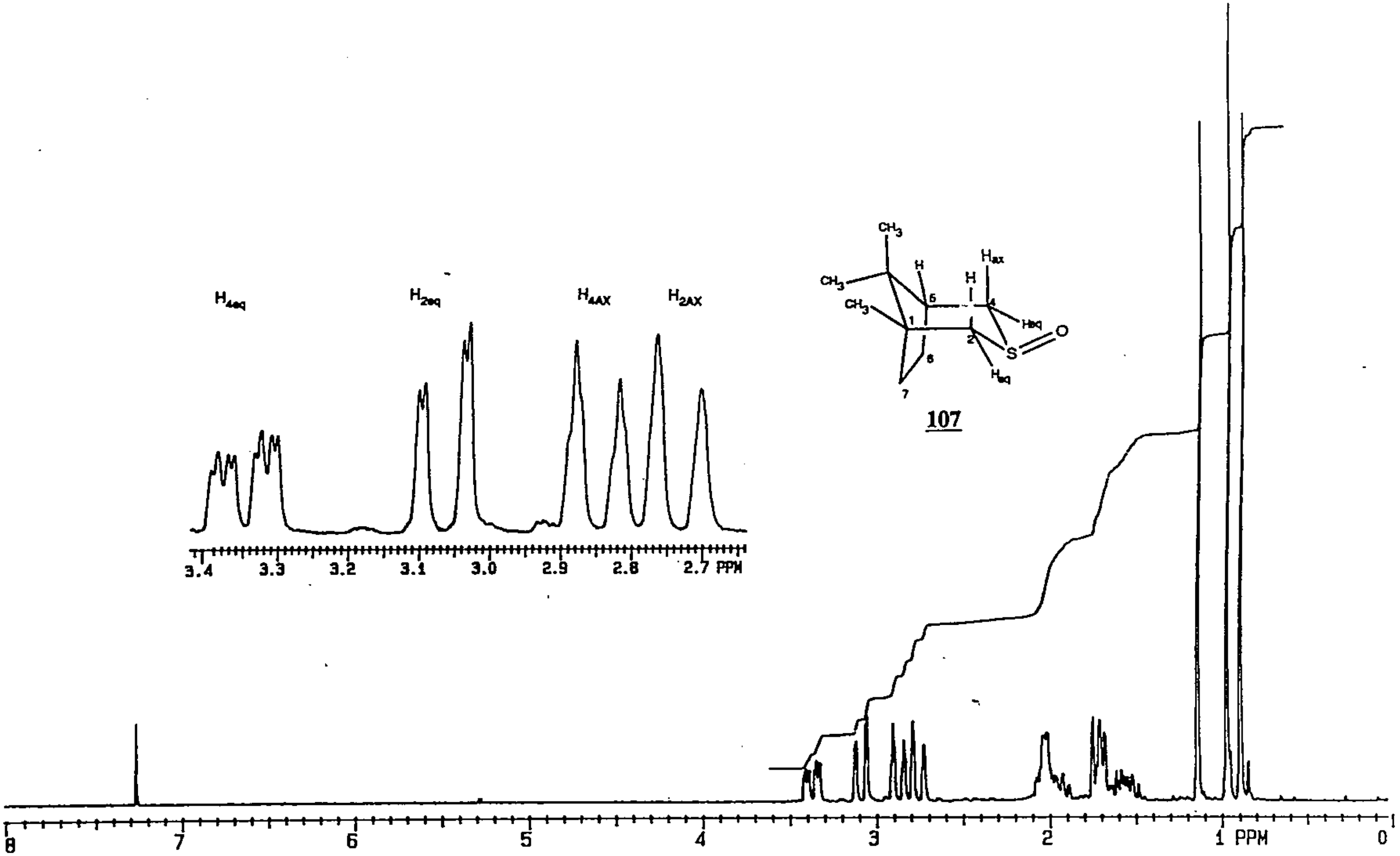


Figure 16. ^{1}H nmr spectrum of (1R,3R,5S)-(+)-1,8,8-trimethyl-3-thiabicyclo[3.2.1]octane-3-oxide **107**.

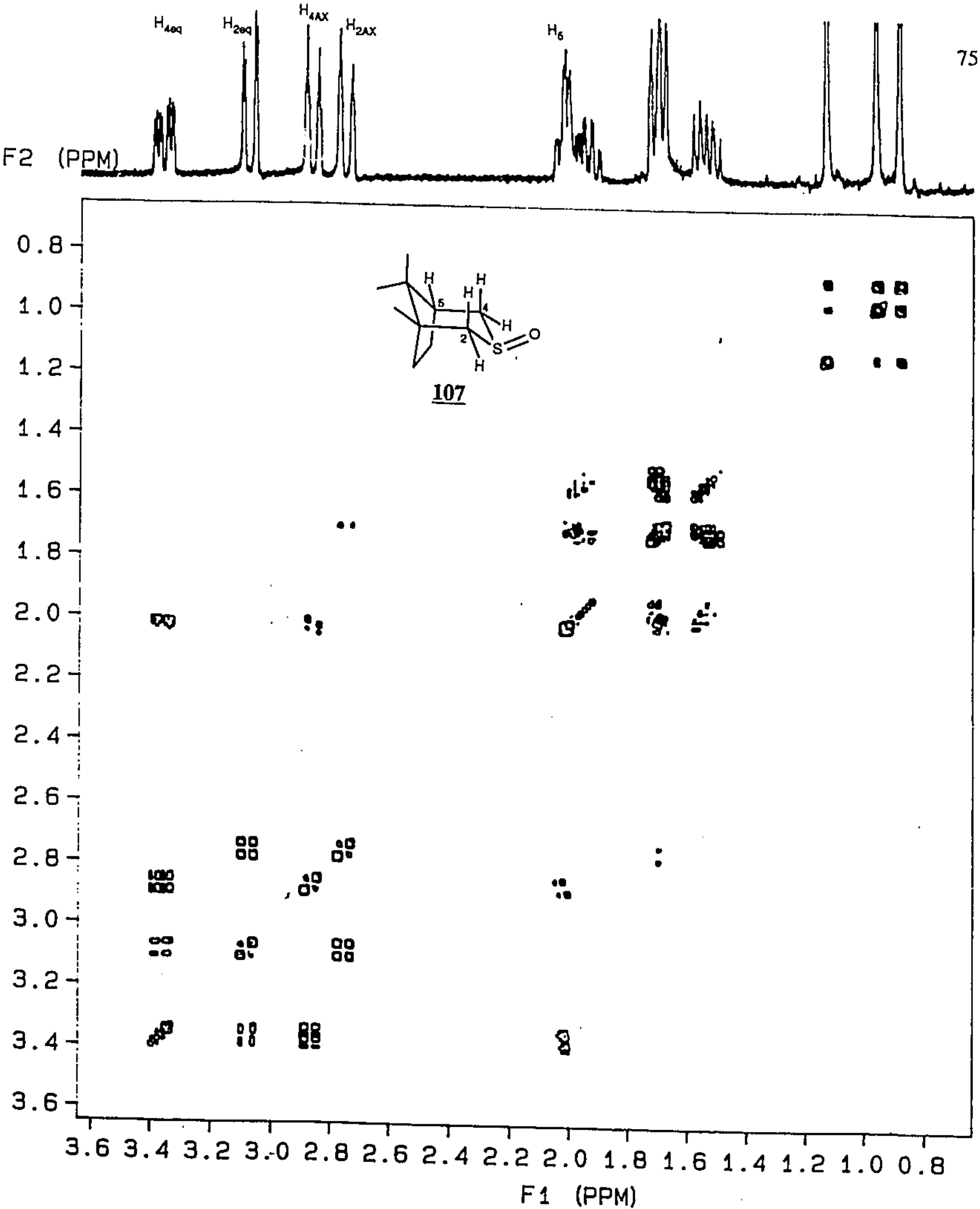


Figure 17. HOMCOR spectrum of (1R,3R,5S)-(+)-1,8,8-trimethyl-3-thiabicyclo[3.2.1] octane-3-oxide **107**.

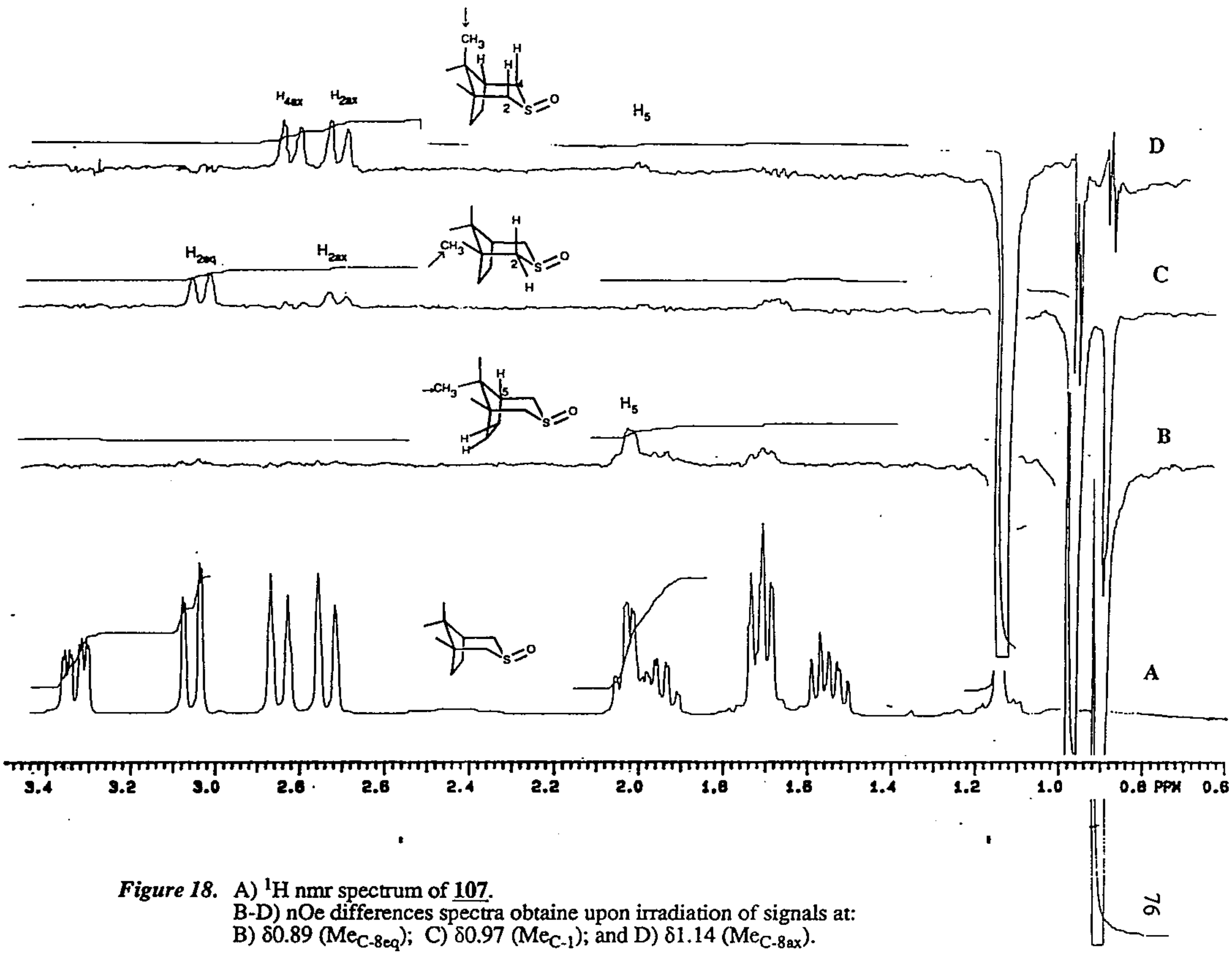


Figure 18. A) ^{1}H nmr spectrum of <u>107</u>.
B-D) nOe differences spectra obtaine upon irradiation of signals at:
B) δ0.89 ($Me_{C\text{-}8eq}$); C) δ0.97 ($Me_{C\text{-}1}$); and D) δ1.14 ($Me_{C\text{-}8ax}$).

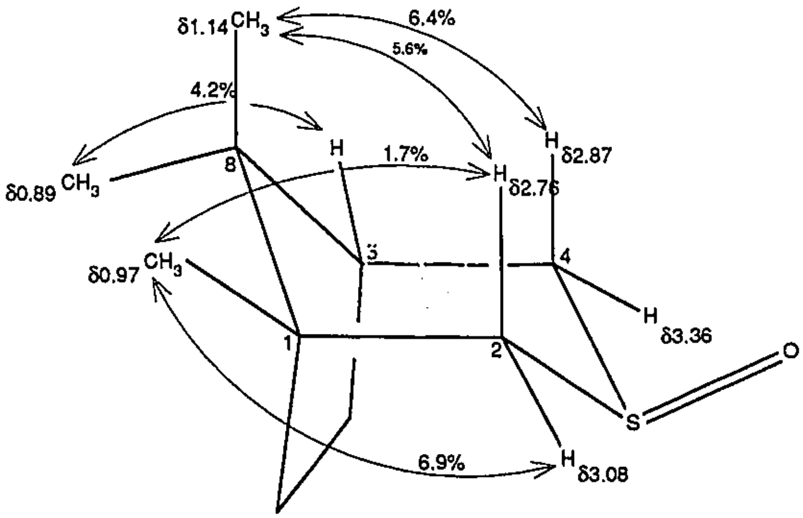
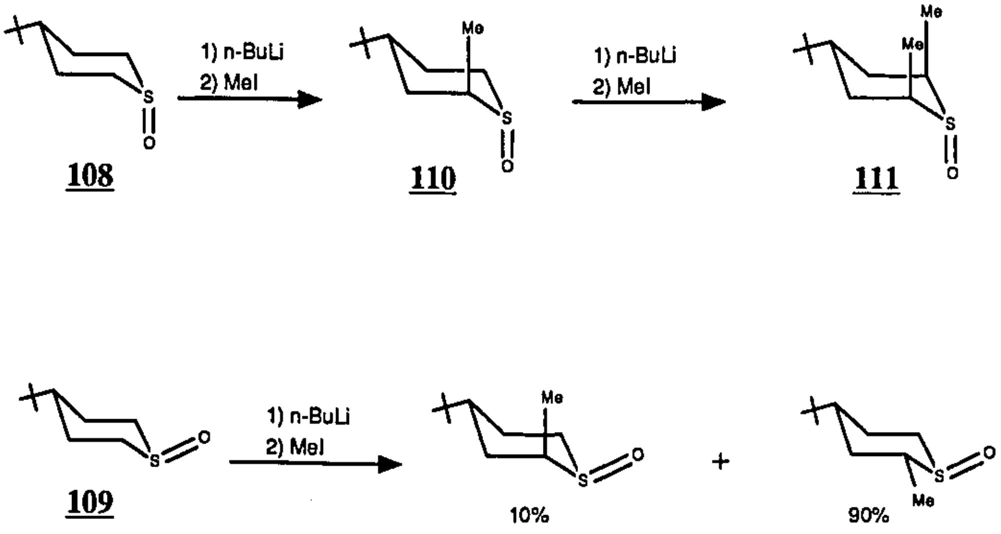


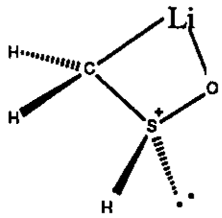
Figure 19. Summary of nOe's observed in <u>107</u> upon irradiation of the methyl substituents at C-8 and C-1.

previously been reported.[36b,114] For instance, the lithiation and subsequent methylation of 4-*t*-butylthian-1-oxides <u>108</u> and <u>109</u> resulted, in both cases, in the introduction of a methyl group *trans* to the S=O function (Scheme 22)[115]. The high "*trans*" stereoselectivity of



Scheme 22.

these methylation was shown to occur even upon further methylation of sulfoxide **110** which yielded exclusively the thermodynamically disfavored 2,6-diaxially substituted thian-1-oxide **111**. It has been suggested that deprotonation occurs *cis* to the oxygen. This would place the lithium *cis* to oxygen in the α-sulfinylcarbanion. *Ab initio* molecular orbital calculations on the α-sulfinylcarbanion $[H\text{-}\overset{\overset{O}{\|}}{S}\text{-}CH_2^{-}\,Li^{+}]$ revealed a greater stability for the chelated structure **112** relative to other non-chelated structures such as **113** and **114**. In the latter two structures, the lithium atom is anti-periplanar to the S=O bond in **113** and gauche to it in **114**. In view of these calculations, it was proposed that:



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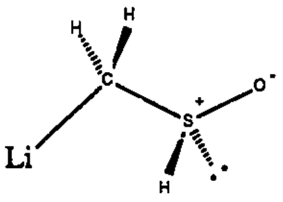
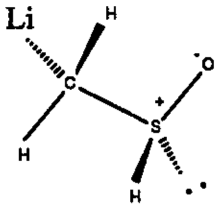


113



114

Calculated Relative Energy	0 Kcal/mol	38.7 Kcal/mol	40.7 Kcal/mol

> "the stereochemical behavior of an *alpha*-lithiosulfoxide is completely dominated by the strong intramolecular Li-O bond. It is, therefore, clear that protonation with retention will occur *cis* to oxygen, but alkylation with inversion will place the new C-C bond *trans* to oxygen."[36b]

Based on the result obtained by Marquet and coworkers for **109** it was confidently expected that compounds **115** or the analog bearing an equatorial benzyl group at C-4 could be prepared from **107**.

The deprotonation of 107 was best accomplished with methyllithium in THF at 0°C. When benzyl bromide was used as the electrophile two compounds were produced in a 2:1 ratio which could be separated by chromatography. The major isomer was however best isolated by fractional crystallization induced by storing the reaction mixture overnight in a refrigerator. This predominant isomer, m.p. 109-110 °C, was obtained in 43% yield and was found to be the more polar. The i.r. spectrum showed strong absorptions at 1036 and 1038 cm^{-1} (i.e., for the S=O bond vibration) for the lesser and more polar fractions respectively. The EIMS spectrum (m/e 276 M^{+}, 15%) and the elemental analysis for both fractions were in agreement with an empirical formula of $C_{17}H_{24}OS$. This is consistant with monobenzylated sulfoxide derivatives of 107. Figure 20 shows the proton spectra from δ0.5 to δ4.5 for the starting material 107 (Figure 20-**B**), the less polar (Figure 20-**A**) and the more polar α-benzyl substituted sulfoxides (Figure 20-**C**). A comparison of the starting sulfoxide and the less polar fraction (Figure 20-**B** and **A**) showed that the signals for H_{2eq}(δ3.06) and H_{2ax}(δ2.74) remain almost unaffected by the reaction. These observations clearly indicate that the benzyl substituent in this less polar fraction occupies the C-4 position. Analogously, for the more polar fraction (Figure 20-**C**), showed that the H_{4eq} and H_{4ax} signals at δ3.23 and δ2.77 respectively remained relatively unaffected thus indicating that alkylation had occurred at the C-2 position.

A preliminary analysis of the nmr of these compounds suggested that they were the expected equatorial benzylation products. Since an unequivocal assignment was important, from the point of view of understanding the asymmetric induction process, it was decided that it would be worthwhile to confirm the structure by carrying out a single crystal X-ray structure determination. Fortunately, a suitable crystal could be obtained by recrystallization from ether. The structure obtained from the X-ray analysis of 116 is shown in stereoview (using an ORTEP drawing): from the top through C-8 (Figure 21A)

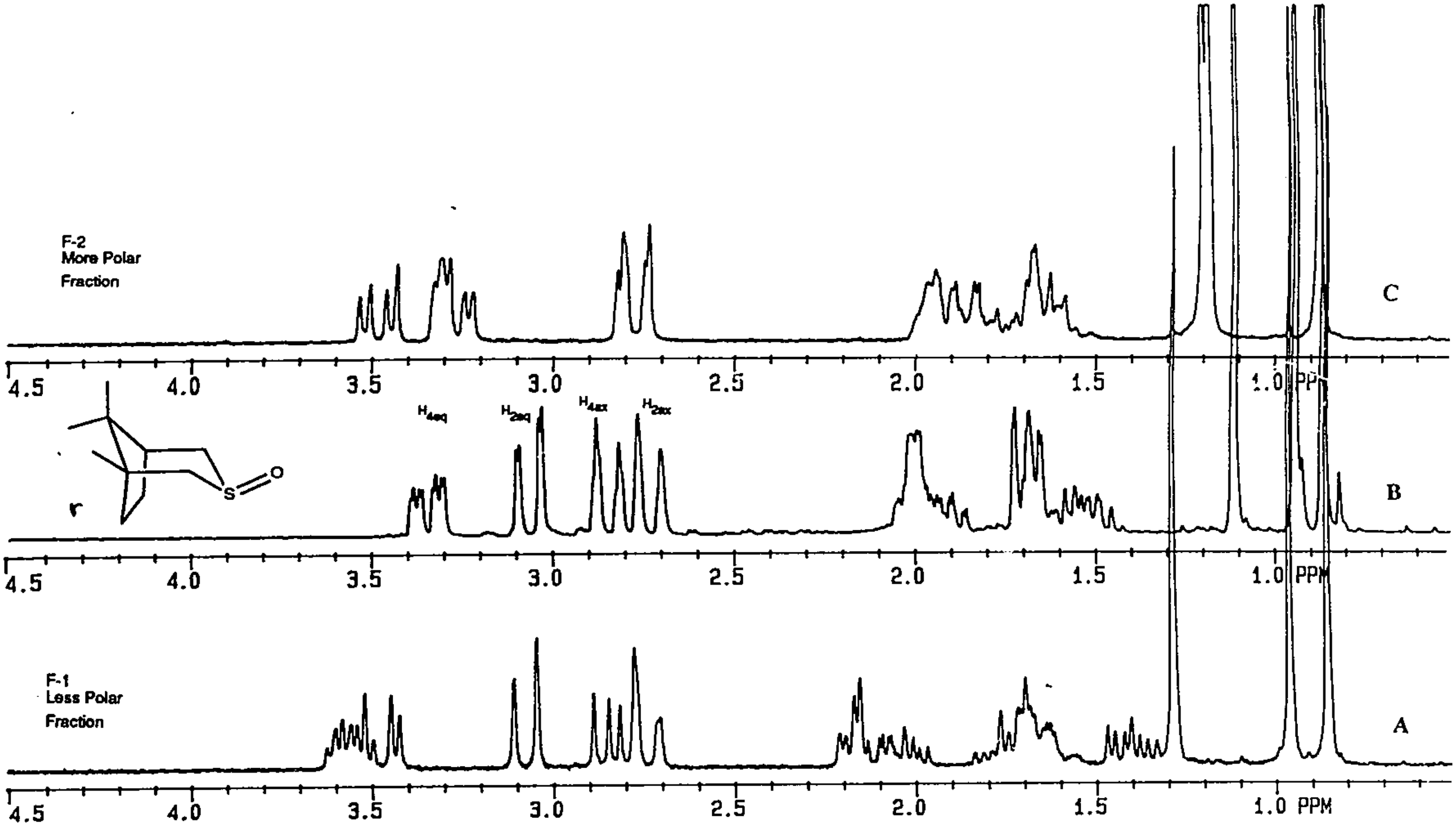


Figure 20. ^{1}H nmr spectra (200 MHz) from δ0.5 to δ4.5 of:
A) The less polar monobenzyl sulfoxide
B) Starting sulfoxide **107**.
C) The more polar monobenzyl sulfoxide.

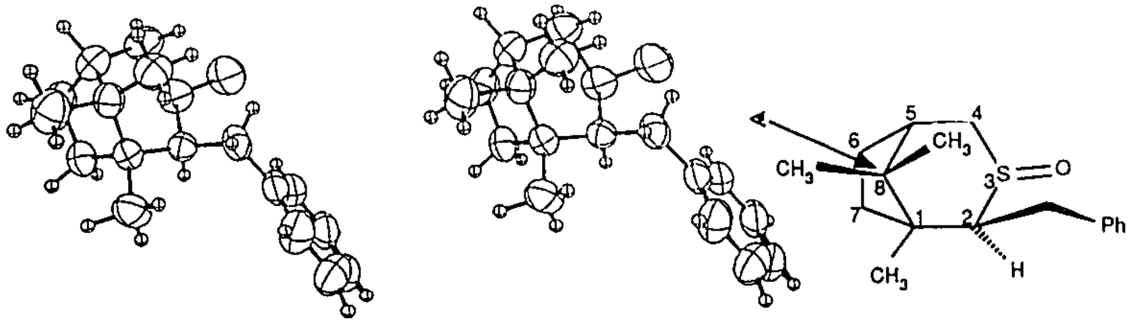


Figure 21A. ORTEP (top) stereoview of structure <u>116</u> as determined by X-ray analysis.

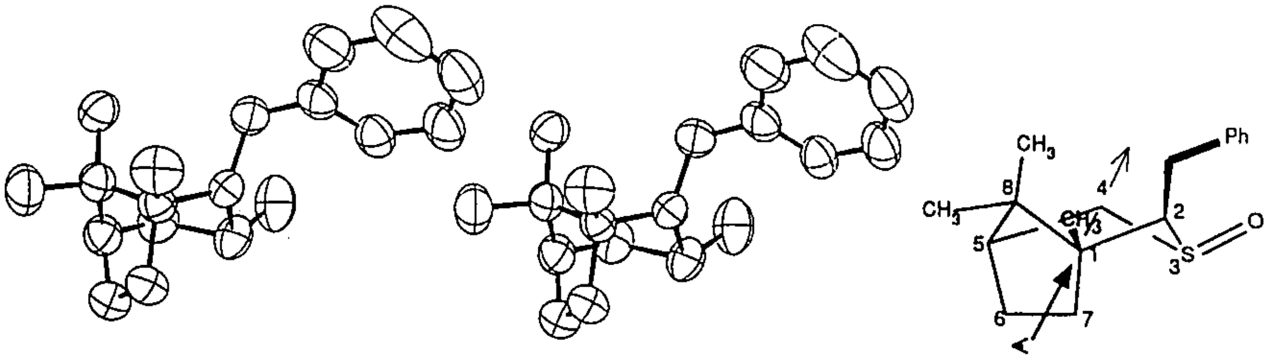


Figure 21B. ORTEP (side stereoview along the C-1, C-4 axis) of the X-ray crystal structure of <u>116</u>. Hydrogen atoms were omitted for clarity.

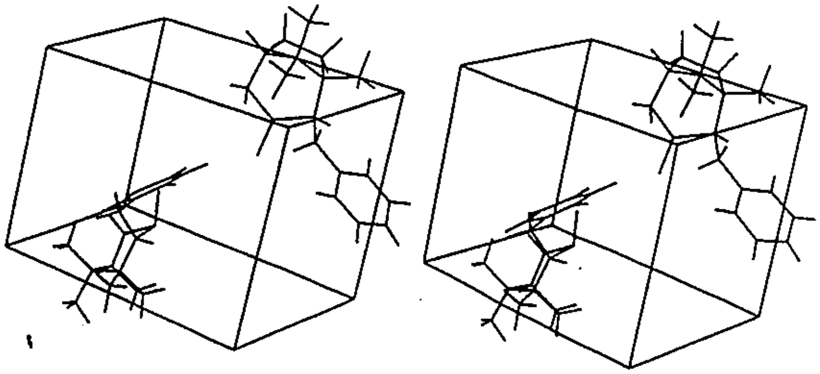


Figure 21C. Crystal structure of compound <u>116</u>. Bond stick stereoview of crystal packing.

and through the CH_3-C_1-C_4 axis (Figure 21B); Figure 21C shows a bond stick version seen through the plane containing C-1, C-2, C-4 and C-5 (bottom left of crystal), while the fourth diagram (Figure 21C) shows the bottom face seen through C-8 (top right of crystal). As expected the benzyl group was located at C-2; *however, surprisingly, this substituent was axial!* This more polar fraction was thus unequivocally assigned to (1R,2S,3R,5S)-(+)-2-benzyl-1,8,8-trimethyl-3-thiabicyclo[3.2.1]octane-3-oxide **116**. Interestingly, the dihedral angle between H_5 and H_{4eq} is 48.7(±37) while the one between H_5 and H_{4ax} is 87.2(±30). The torsion angles for H-C_2-CPh-H_A and H-C_2-CPh-H_x were found to be 123.9°(±26) and 123.5°(±30), respectively. Thus the phenyl group is eclipsed with respect to the proton at C-2 and lies between the C-1 methyl group and the S=O functionality. Astonishingly the chair form of the thiane-3-oxide moiety in **116** is preserved (Figure 21C bottom left of crystal) despite the presence of an enhanced 1,3-syn-diaxial interaction between the axial methyl at C-8 and the axial benzylic methylene group.

The unexpected results necessitated the development of a reliable deductive method to establish the stereochemistry of the other α-sulfinyl carbanion reaction products since X-ray analysis was not possible for all products. Since the structure of **116** is known, it was judged a valuable exercise to verify that the various nmr spectroscopic techniques would give results consistent with the X-ray data. The use of ^1H nmr, HOMCOR and nOe data allowed for an unambiguous assignment of all protons α to the sulfur. These are shown in Figure 22, 22A, 22B, 23, 24 and 25. The 500 MHz nmr spectrum of **116** is shown in Figure 22. Figure 22A, shows the expanded portion of the spectrum containing the protons α to sulfur as well as the benzyl protons, while Figure 22B shows the signals attributed to the back bone of the molecule. The HOMCOR plot is shown in Figure 23. The nOe difference experiments performed on **116** are shown in Figure 24 and summarized in Figure 25. Unfortunately the resonances for the axial groups at C_8 and C-1 resonated too closely to each other (Figure 22, $\Delta\delta \leq 0.015$) to allow selective irradiation of one of them. Nontheless, simultaneous irradiation of these groups (Figure

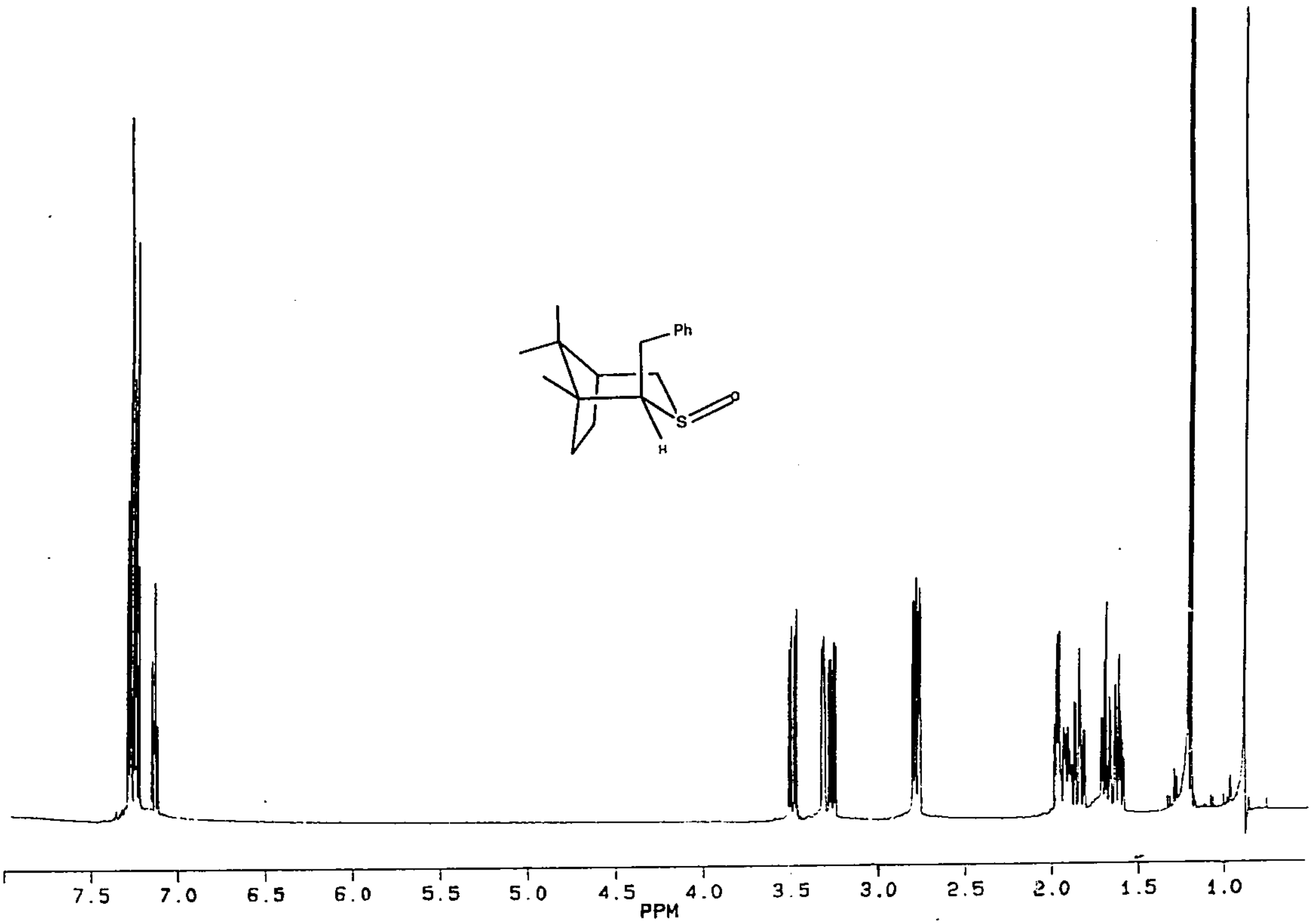


Figure 22. 500 MHz ^{1}H nmr spectrum of (1R,2S,3R,5S)-(-)-2-benzyl-1,8,8-trimethyl-3-thiabicyclo[3.2.1]octane-3-oxide **116**.

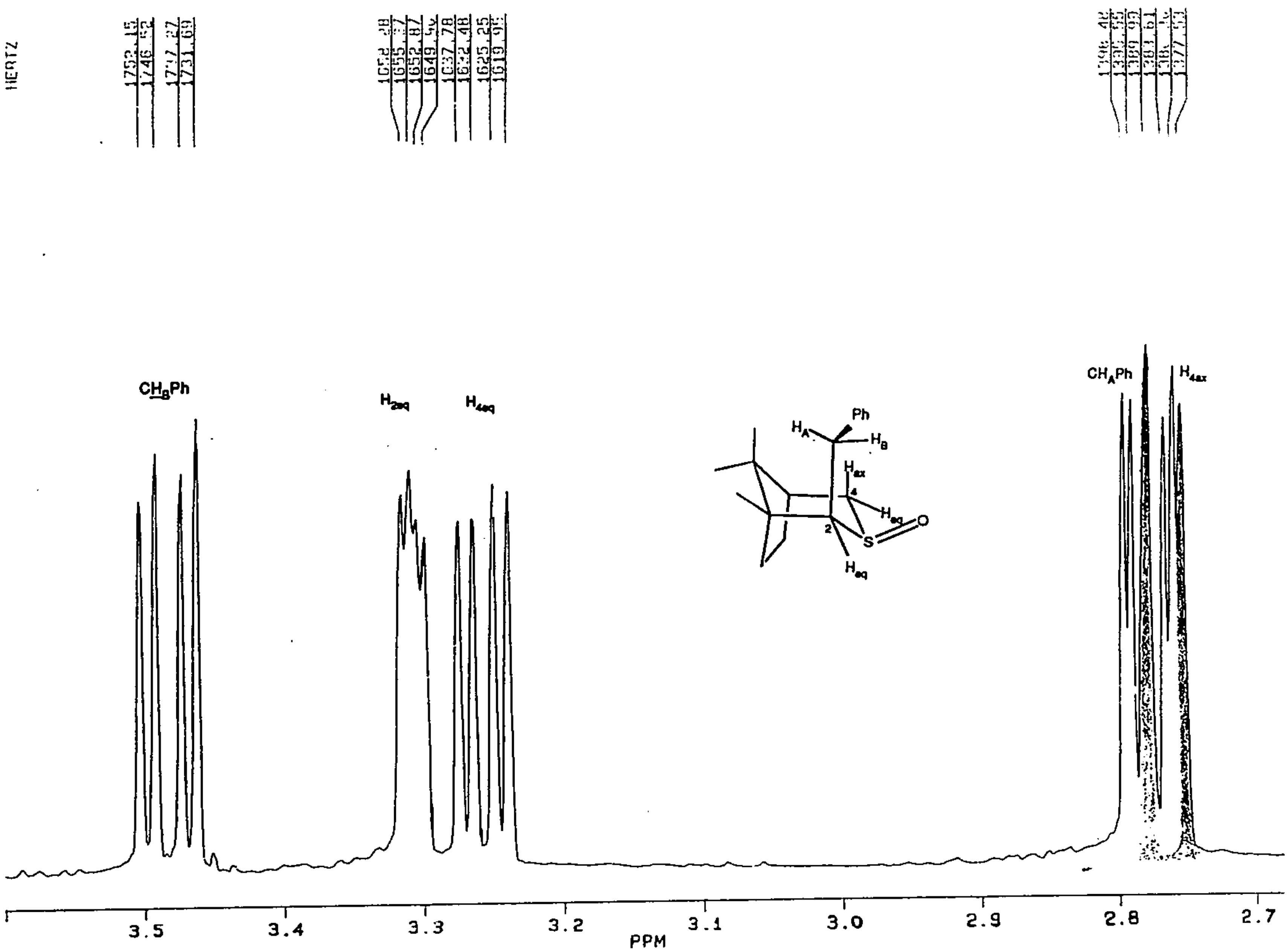


Figure 22A. Expansion of the δ2.7 to 3.5 region of the nmr spectrum of <u>**116**</u> seen in Figure 21 .

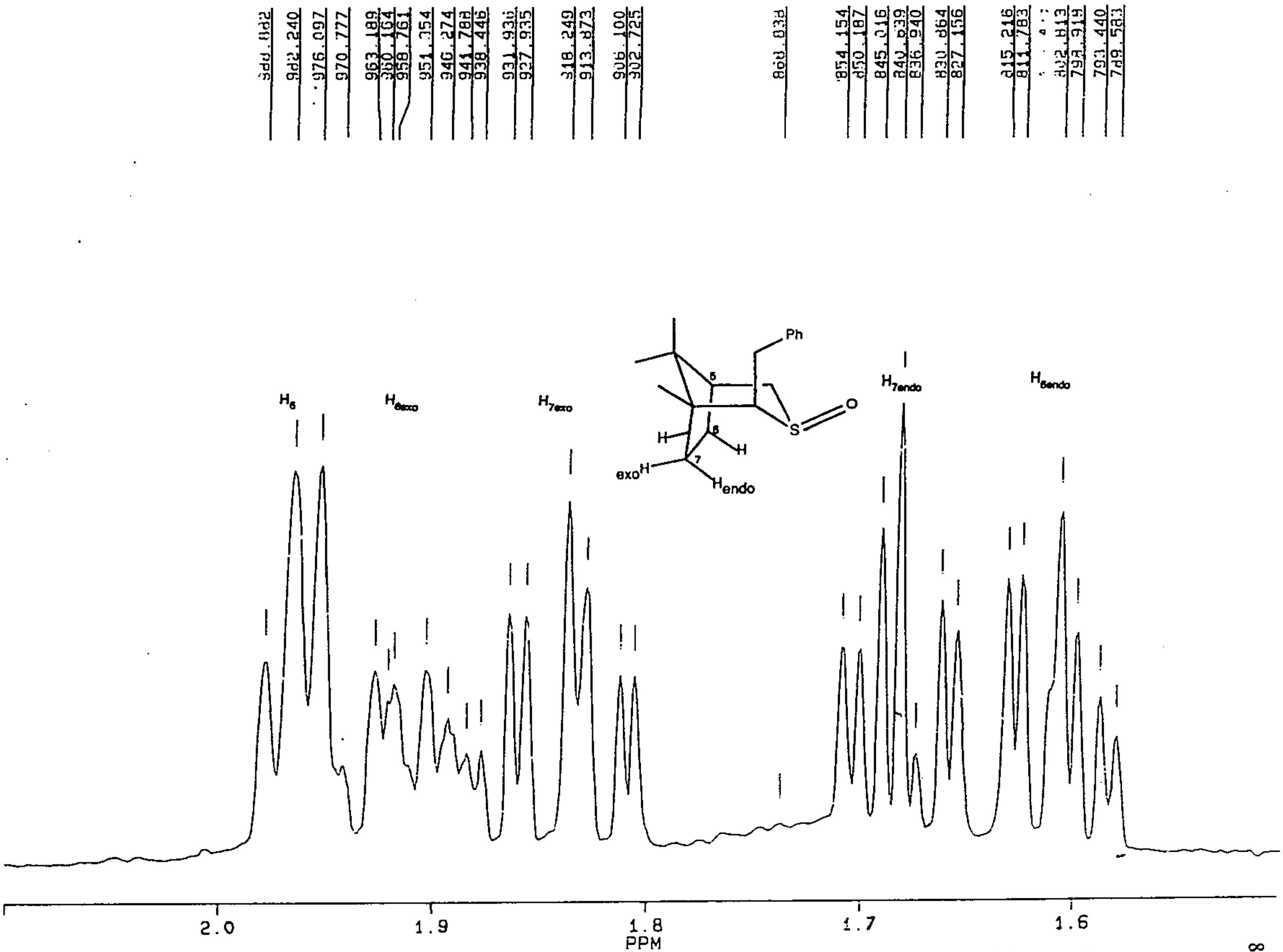


Figure 22B. Expansion of region between δ1.4 and 2.1 of the pmr spectrum of **<u>116</u>** shown in Figure 21.

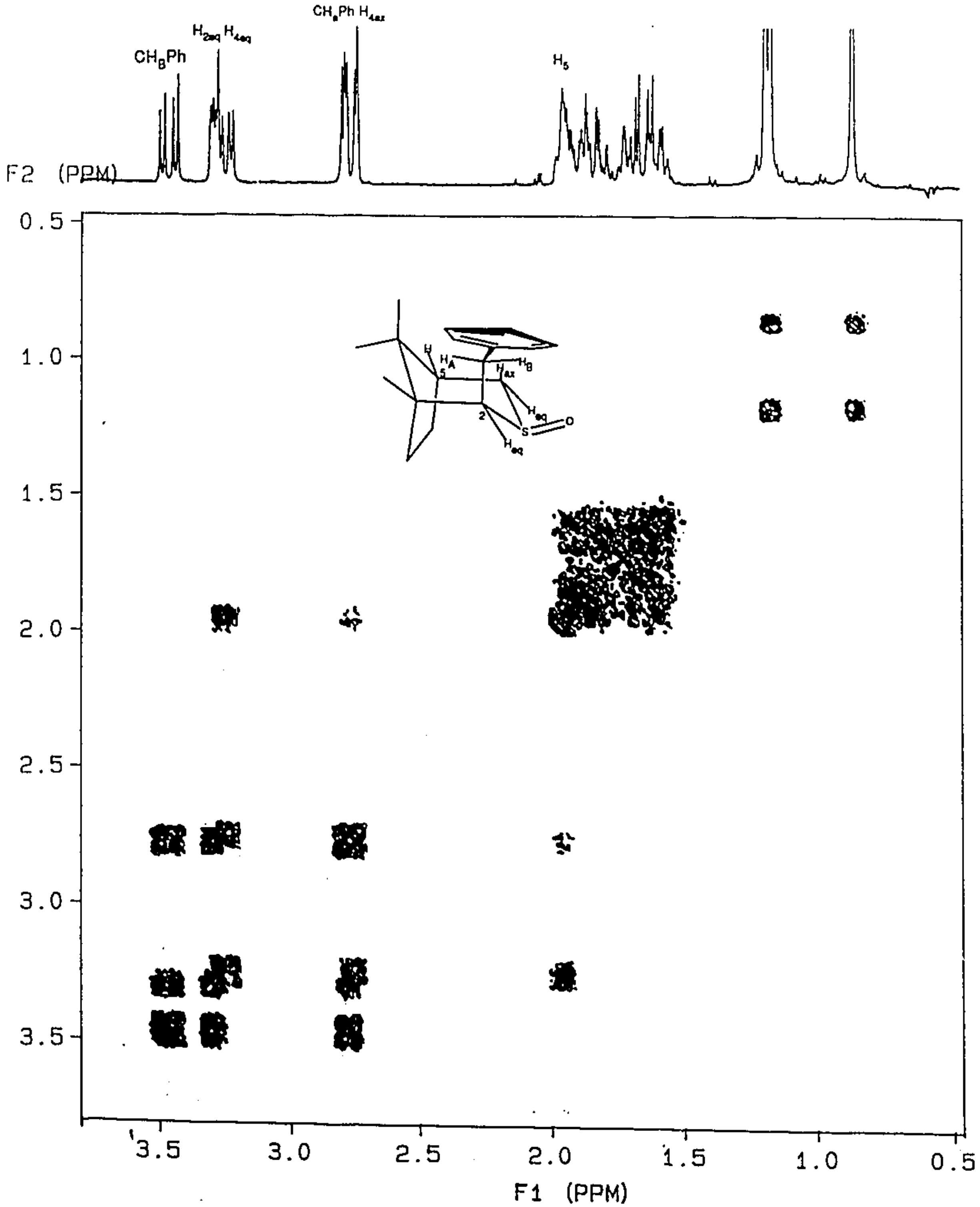


Figure 23. HOMCOR spectrum of (1R,2S,3R,5S)-(-)-2-benzyl-1,8,8-trimethyl-3-thiabicyclo-[3.2.1]octane-3-oxide **<u>116</u>**.

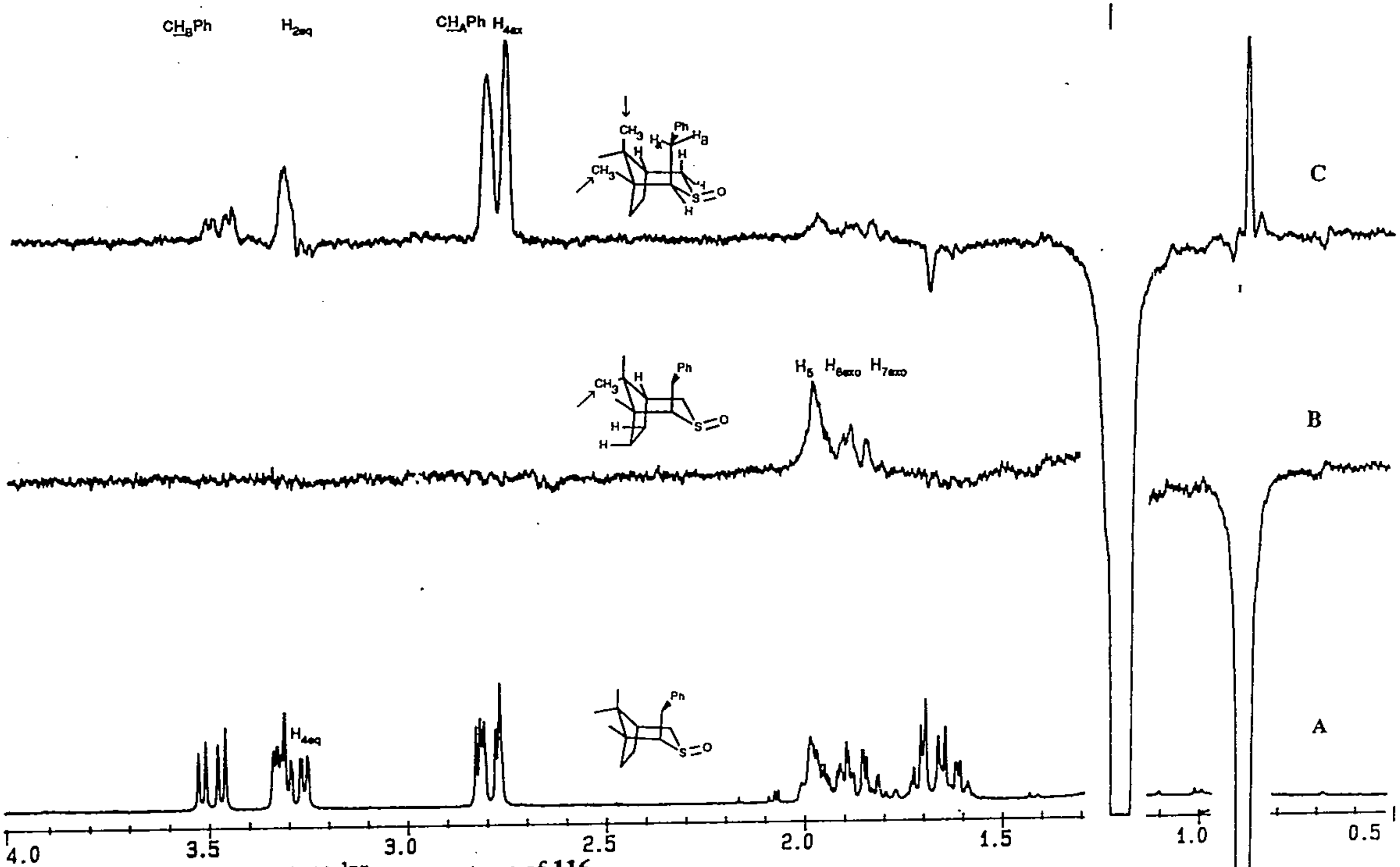


Figure 24. A) ^{1}H nmr spectrum of <u>116</u>.
B-C) NOe difference spectra obtained upon irradiation of the following signals:
B) $\delta 0.88$ ($Me_{C\text{-}8eq}$) and C) $\delta 1.19$ ($Me_{C\text{-}1} + Me_{C\text{-}8ax}$).

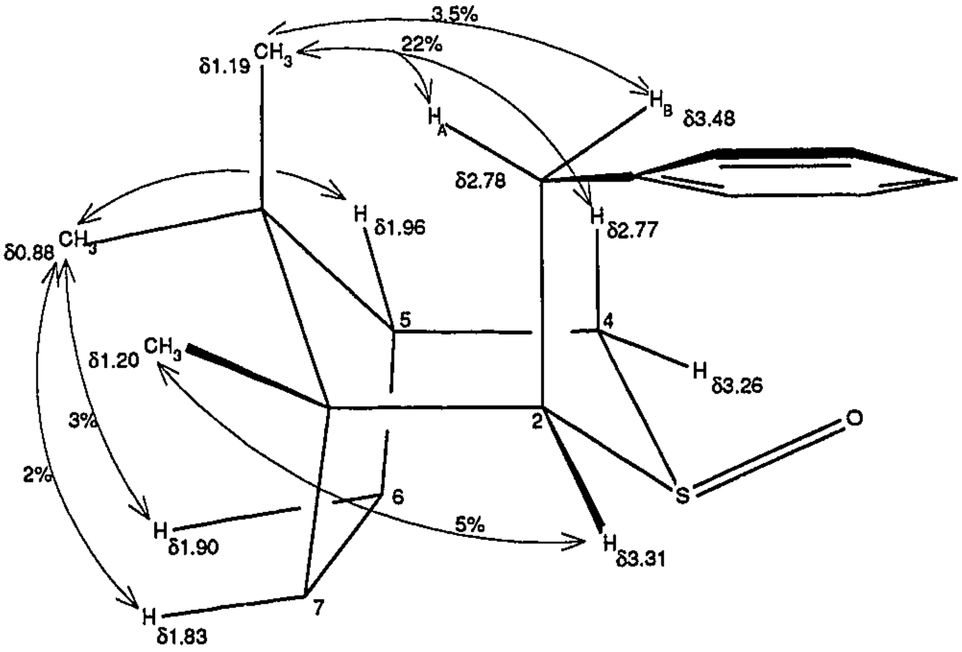


Figure 25. Summary of nOe differences observed in 116 upon irradiation of the methyl groups at C-8 and C-1.

21-C) produced a noticeable nOe (22%) for the signals at δ2.77-2.78 as well as a smaller one for the signals at δ3.31 and δ3.48. The complex signal at δ2.775 was assigned to -C$\underline{H}_A$Ph and H_{4ax} while the benzylic doublet of doublets at δ3.48 was assigned to C$\underline{H}_B$Ph which was more distant from both methyl groups (i.e., C-1 and C-8 axial). The key outcome of the nOe experiments was that the resonance at δ3.26 did not show an nOe with any of the methyl groups and thus it was assigned to the equatorial proton at C-4 (H_{4eq}). The nOe's observed for the benzylic protons were due to a syn-diaxial relationship with the axial methyl at C-8.

The ^1H nmr spectrum also provided some indication of the stereochemistry of 116 in solution. In the case of 116, the nmr resonance for H_{4eq} showed a vicinal coupling with H_5 of 5.3 Hz while the signal for H_{4ax} did not show any such coupling. These numbers correspond to dihedral angles of 36° between H_5 and H_{4eq} and of 84° between H_5 and

H_{4ax}. The coupling constant found between H_{2eq} and -C$\underline{H}_A$Ph was 3Hz while that between H_{2eq} and -C$\underline{H}_B$Ph was ≅5.5Hz. The dihedral angle between H_{2eq} and -C$\underline{H}_A$Ph (*J*=3Hz) and between H_{2eq} and -C$\underline{H}_B$Ph (*J*=5.5Hz) were thus estimated to be 115° and 130° respectively. The above angles were based on the Karplus correlation curve.[119] These data confirmed that the phenyl group is essentially eclipsed with the proton at C-2 in solution. These were quite close to the values obtained from the X-ray analysis.

The excellent correlation between the nmr and X-ray results for **116** gives one confidence that nmr studies could be used to determine the stereochemistry of both the 2- and 4-substituted-3-thiabicyclo[3.2.1]octane-3-oxides obtained from **107**.

This methodology was applied to the other α-benzylation product (i.e. the less polar fraction) and again the data clearly confirmed that the structure of this isomer was axial. The 500 MHz proton nmr of **107** is shown in Figure 26. Figure 26A shows an expanded portion of the spectrum due to both the α sulfur and benzylic protons, while Figure 26B shows the signals attributed to the backbone of the molecule. The HOMCOR plot is shown in Figure 27 while the nOe difference experiments performed on **117** are shown in Figure 28 and summarized in Figure 29. Irradiation of the axial methyl group at C-8 (Figure 28-D) resulted in nOe's with three resonances at δ2.83, δ2.74 (H_{2ax}) and δ2.18 (H_5). The signal at δ2.83 showed the largest nOe with the C-8 axial methyl and was assigned to C$\underline{H}_A$Ph which is closest in space to that group. The methine proton at C-4 (δ3.58) did not show an nOe with either the C-8 or C-1 methyls, therefore it is equatorial (H_{4eq}). On the basis of this data, the benzyl substituent of **117** must occupy the axial position at C-4. The vicinal coupling constant between H_{4eq} and C$\underline{H}_A$Ph was 8.4 Hz and the one between H_{4eq} and C$\underline{H}_B$Ph was 4.9 Hz correspond to dihedral angles of 150° for the former case and of ≅40° for the latter. Hence the spatial arrangement of the phenyl group in **117** is partially skewed with respect of the other C-4 substituent. Conformer **117**, as depicted in Figure 29, best represents this compound in solution.

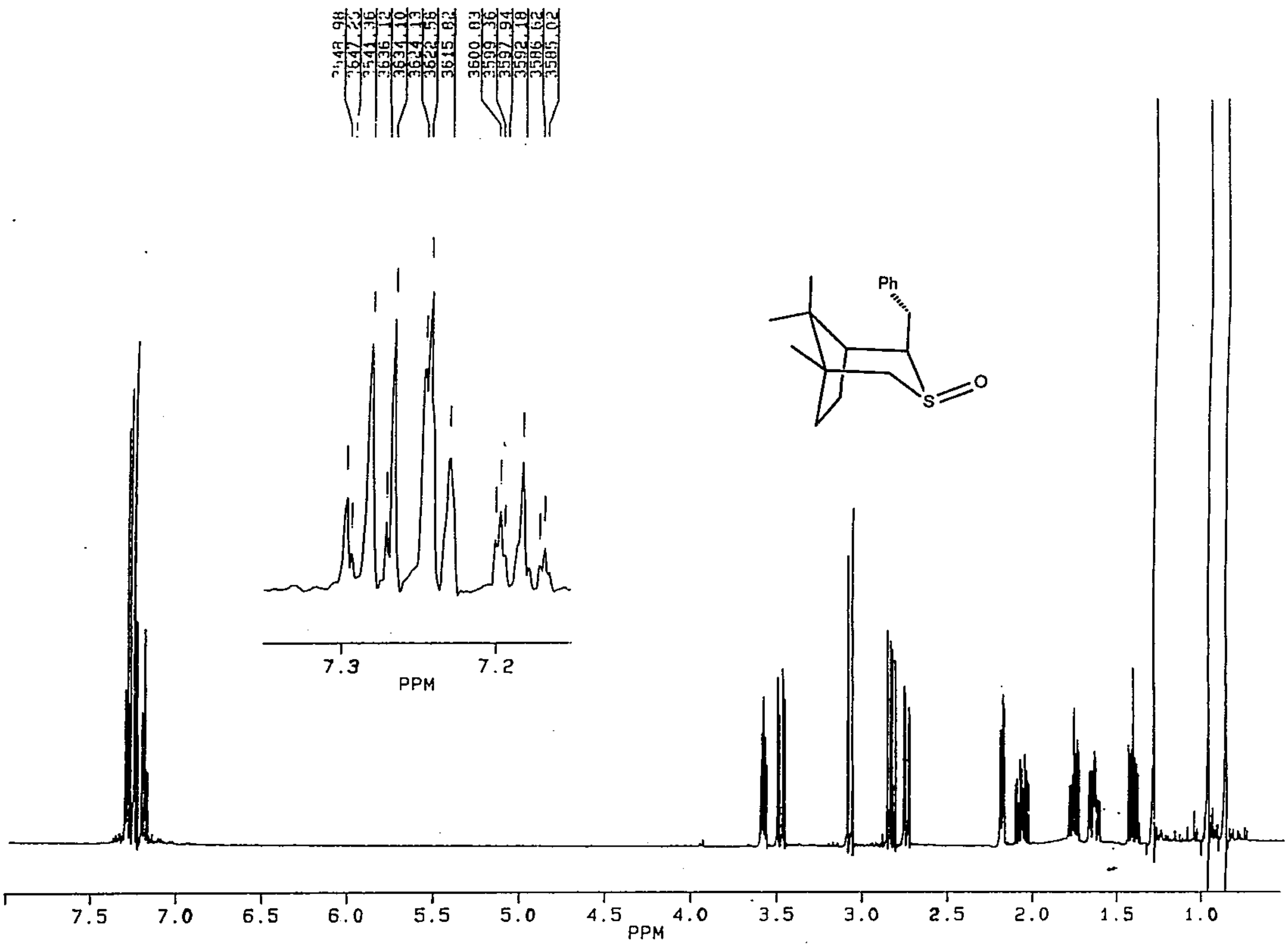
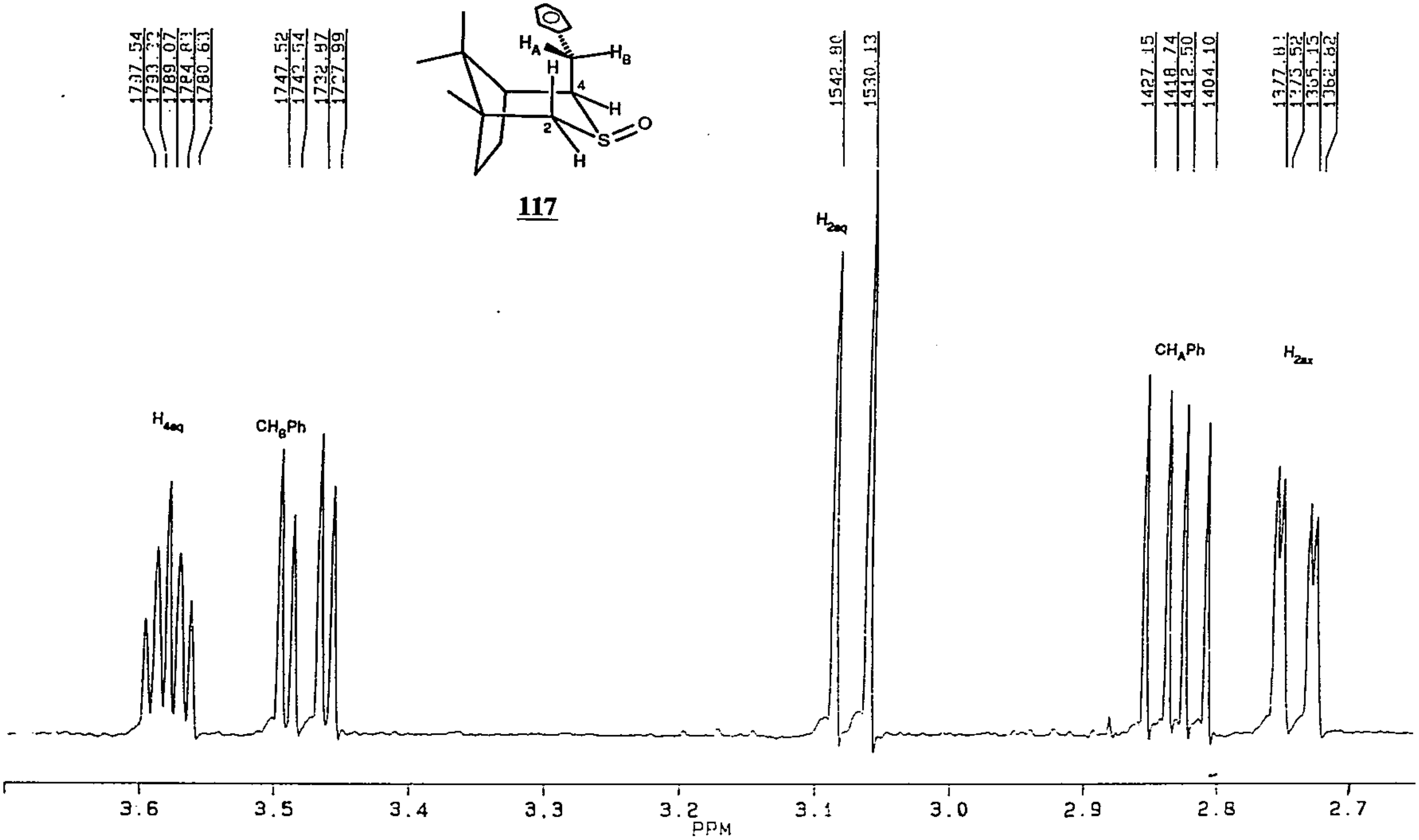


Figure 26. 500 MHz ^{1}H nmr of (1R,3S,4R,5S)-(+)-4-benzyl-1,8,8-trimethyl-3-thiabicyclo[3.2.1]-octane-3-oxide <u>117</u>.



117

Figure 26A. Expansion of the δ2.7 to 3.7 region of the spectrum shown in Figure 26.

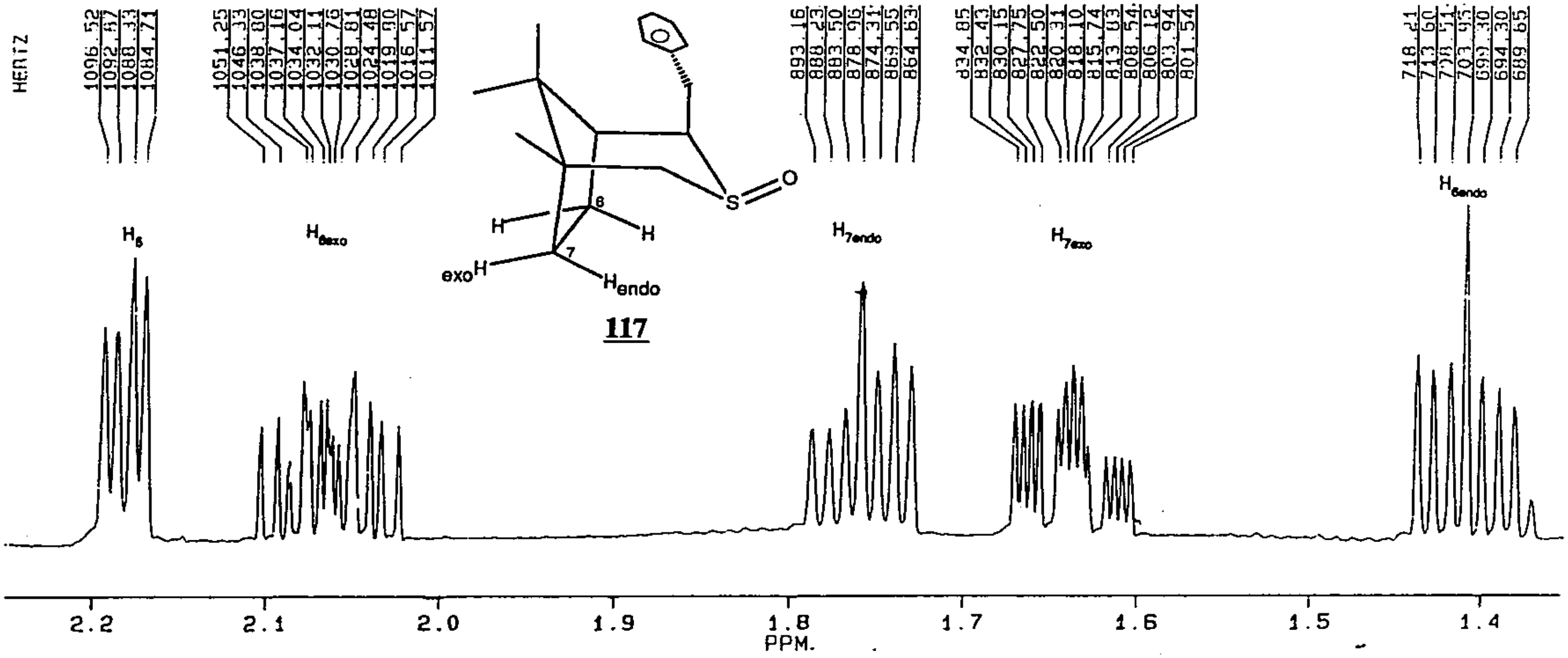


Figure 26B. Expansion between δ1.3 and 2.2 of the spectrum shown in Figure 26.

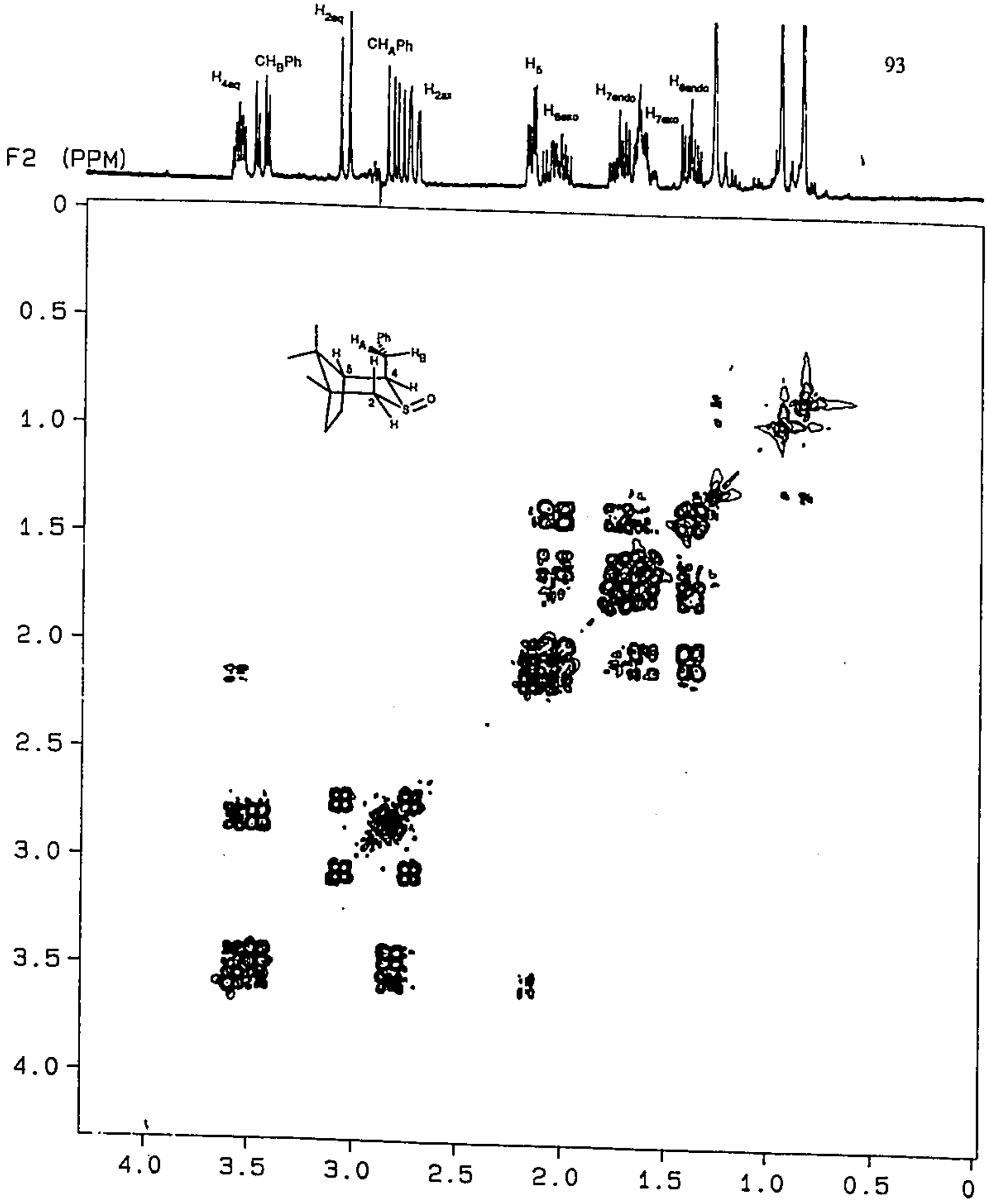


Figure 27. HOMCOR spectrum of (1R,3S,4R,5S)-(+)-4-benzyl-1,8,8-trimethyl-3-thiabicyclo-[3.2.1]-octane-3-oxide <u>117</u>.

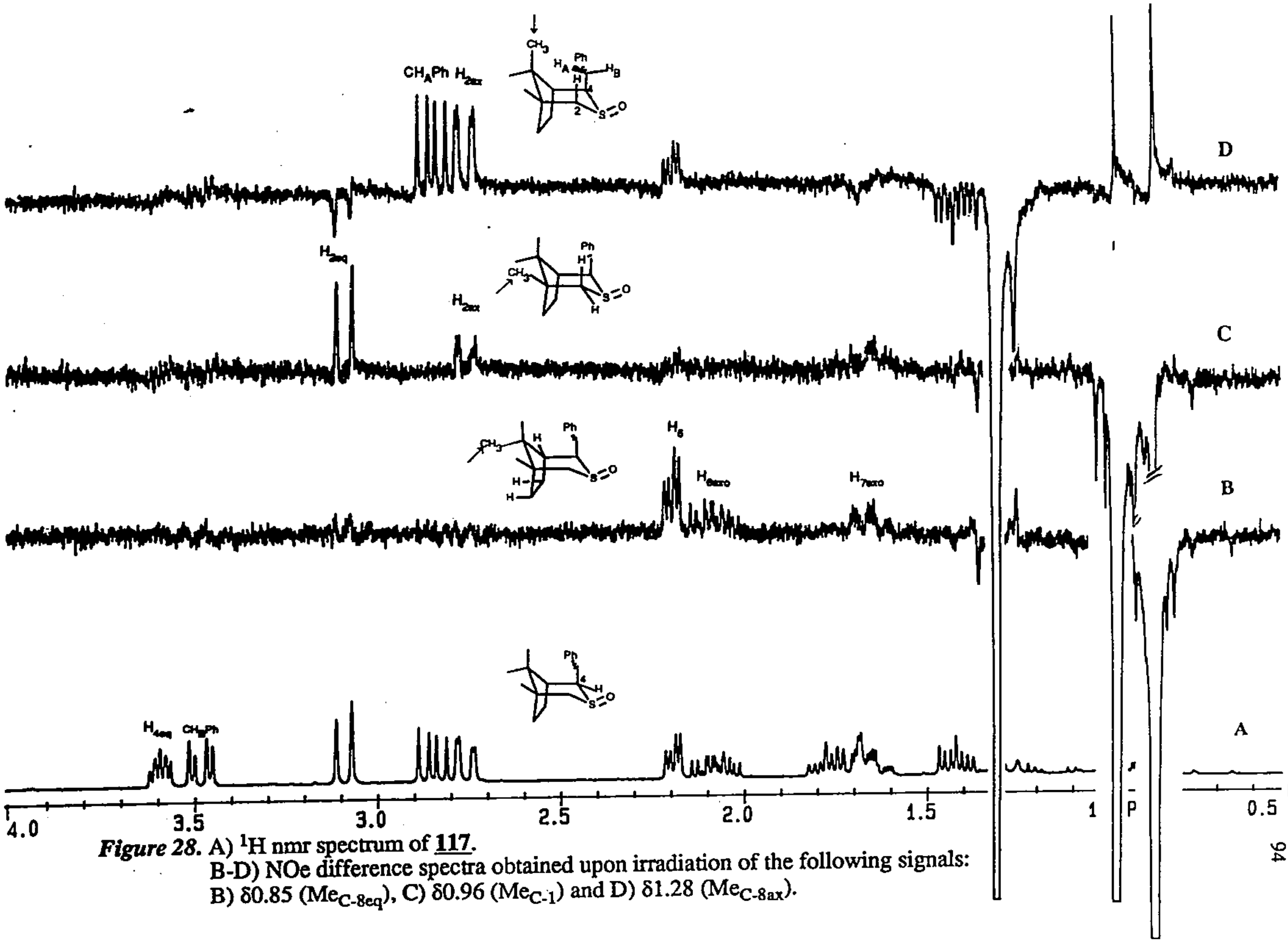


Figure 28. A) ^{1}H nmr spectrum of <u>117</u>.
B-D) NOe difference spectra obtained upon irradiation of the following signals:
B) δ0.85 ($Me_{C\text{-}8eq}$), C) δ0.96 ($Me_{C\text{-}1}$) and D) δ1.28 ($Me_{C\text{-}8ax}$).

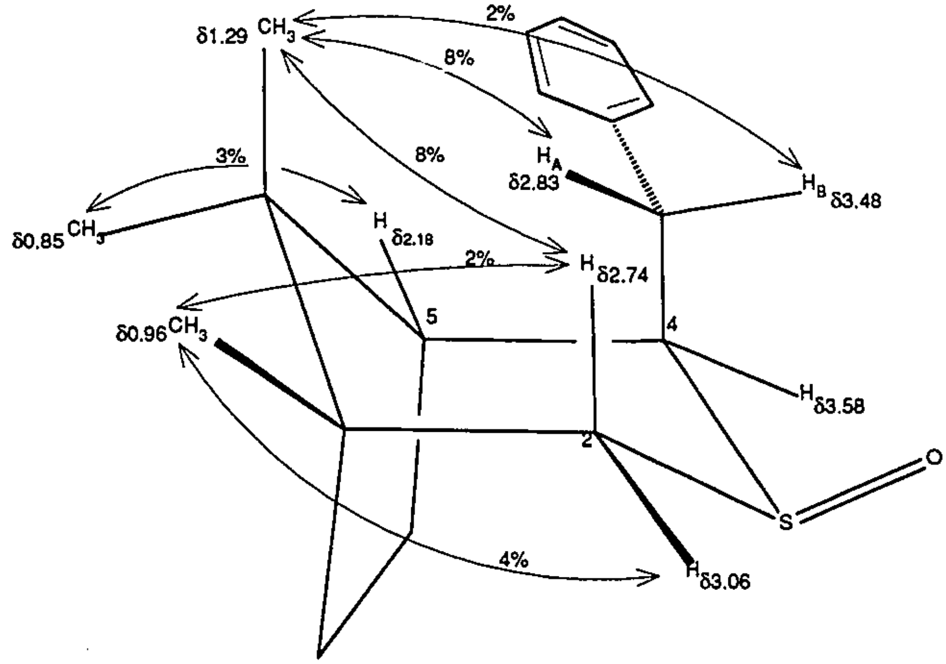


Figure 29. Summary of nOe's observed in 117 upon irradiation of the methyl groups at C-8 and C-1.

In conclusion the above products were found to result from axial benzylation contrary to expectations based on the earlier work on *t*-butylthiane-1-oxide **108** and **109**[114,115] (page 77). If the deprotonation had occur *cis* to the sulfoxide in thiabicyclo[3.2.1]octane-3-oxide **107**, which should be favored by the formation of a chelate structure similar to **112**; then it would be expected to give **116** and **117** as long as alkylation of the carbanion occurs with retention of configuration. It is not clear why the two systems would behave differently (if they did). Indeed, a plausible alternate explanation exists. There is a small possibility that the stereochemistry of the sulfoxide functionality in either 4-*t*-butylthian-1-oxide **108** or the alkylated products **110** and **111** may have been misassigned. These compounds have been characterized solely on the basis of proton nmr and none of them have been rigorously studied by X-ray analysis. It may be necessary to verify the earlier studies and also carry out an investigation of the behaviour of the carbanions derived from the axial sulfoxide analog of <u>**107**</u> in order to gain a better understanding of this problem. Nontheless, the results obtained from benzylation of the α-sulfinyl carbanion derived from <u>**107**</u> again demonstrate the importance of a stereoelectronic effect in the reactions of α-sulfinyl carbanions which were first studied in detail by various workers in the 1970's.[114,115] The introduction of axial substituents to structure <u>**107**</u> should be considerably more difficult than in the monocyclic thiacyclohexanes since the bicyclic system is considerably more rigid and the 8-axial methyl group is forced towards the C-2 and C-4 axial substituents by the two carbon bridge. Axial benzylation in the reaction of the anions of <u>**107**</u> is not unique since the introduction of an α-isopropyl group also occurs preferentially with axial stereochemistry (see below).

The alkylation of <u>**107**</u> with 2-iodopropane was carried out in the same manner as the reaction with benzyl bromide described earlier. Again, the reaction gave two alkylation products in 40% yield, along with some recovered starting material (24%). The two isopropyl derivatives of <u>**107**</u> were produced in a 4:1 ratio in favor of the less polar isomer.

The ir spectrum for the major isomer showed a strong absorption at 1025 cm^{-1}, due to the S=O band vibration. The ^{13}C nmr spectrum showed the expected 13 resonances. The ^{1}H nmr spectrum of this material is shown in Figure 30. The resonances for the isopropyl substituent are clearly visible as two methyl doublets at δ1.07 and δ1.14 and a methine multiplet at δ2.42. The remainder of the spectrum consisted of resonances for the 1,8,8-trimethyl-3-thiabicyclo[3.2.1]octane-3-oxide system. The HOMCOR spectrum of <u>**118**</u>, is shown in Figure 31. NOe's obtained from the selective irradiation of each of the three methyl groups at C-8 and C-1 in <u>**118**</u>, are shown in Figure 32 and summarized in Figure 33. Key features of these experiments include the irradiation of the C-8 axial methyl (Figure 32-D) which resulted in nOe's with the signals at δ2.31 (H_5), δ2.42

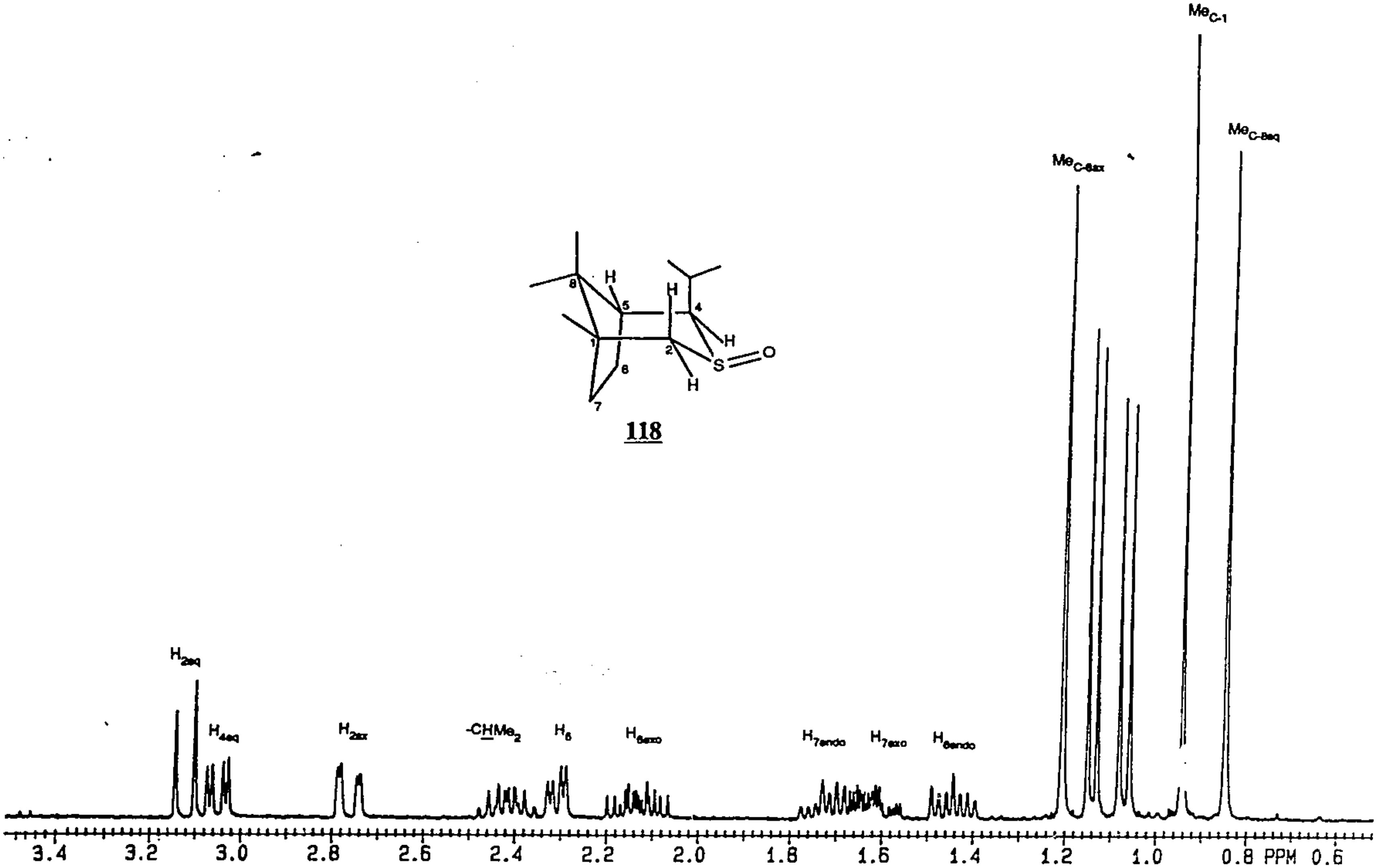


Figure 30. ^{1}H nmr spectrum of (1R,3S,4R,5S)-(+)-4-isopropyl-1,8,8-trimethyl-3-thiabicyclo-[3.2.1]octane-3-oxide **118**.

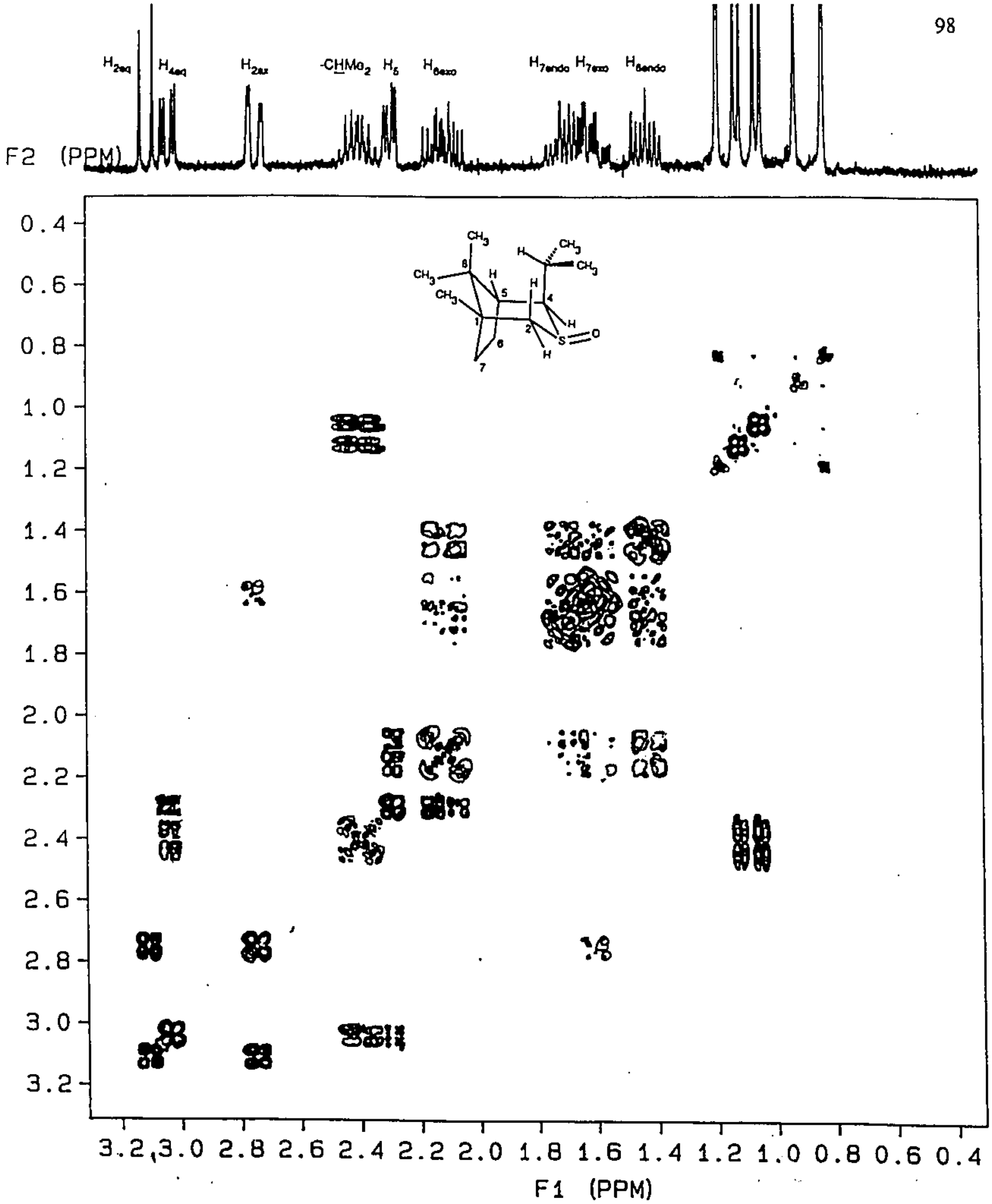


Figure 31. HOMCOR spectrum of (1R,3S,4R,5S)-(+)-4-isopropyl-1,8,8-trimethyl-3-thiabicyclo-[3.2.1]octane-3-oxide <u>118</u>.

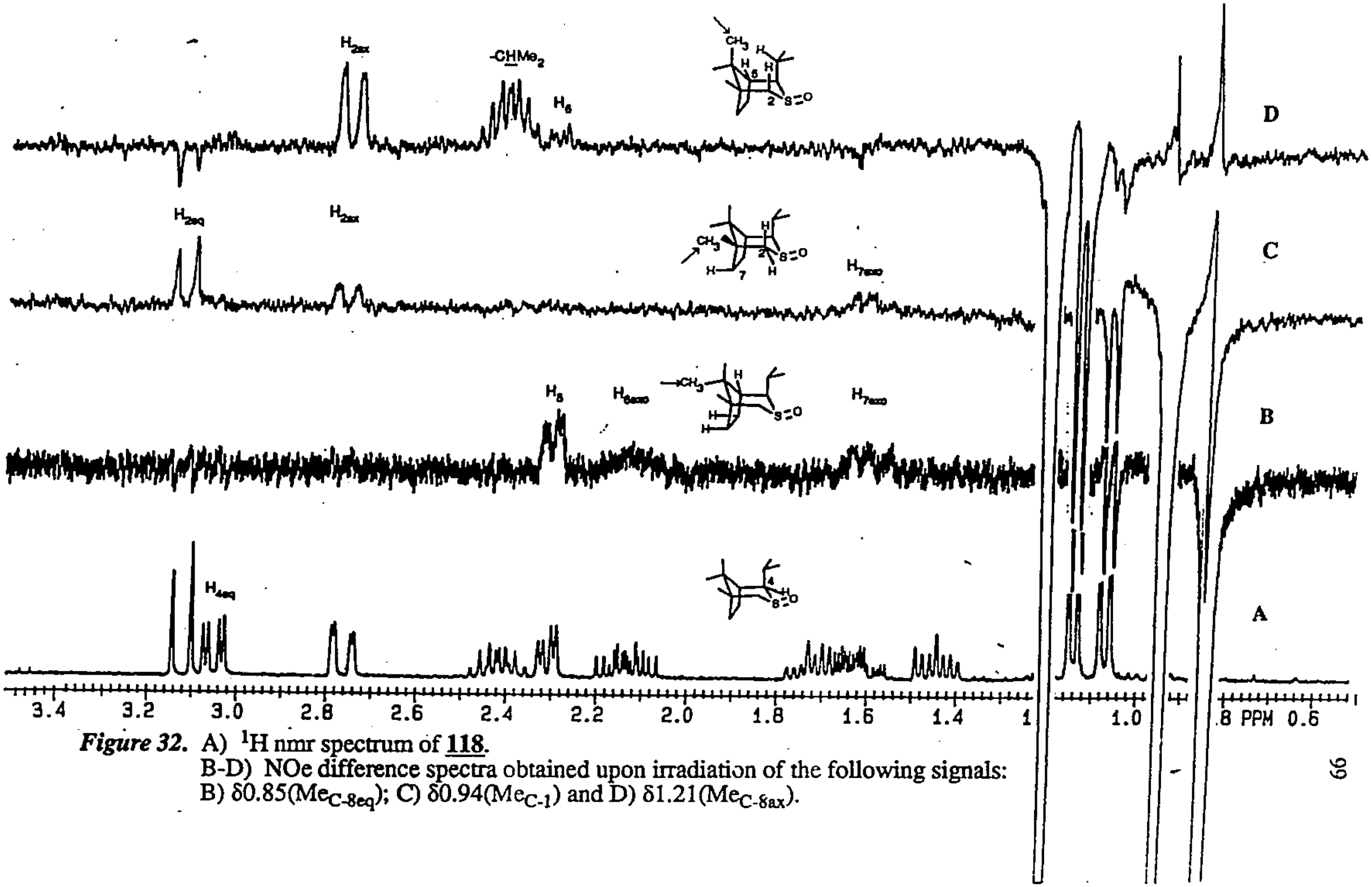


Figure 32. A) ^{1}H nmr spectrum of <u>118</u>.
B-D) NOe difference spectra obtained upon irradiation of the following signals:
B) δ0.85($Me_{C\text{-}8eq}$); C) δ0.94($Me_{C\text{-}1}$) and D) δ1.21($Me_{C\text{-}8ax}$).

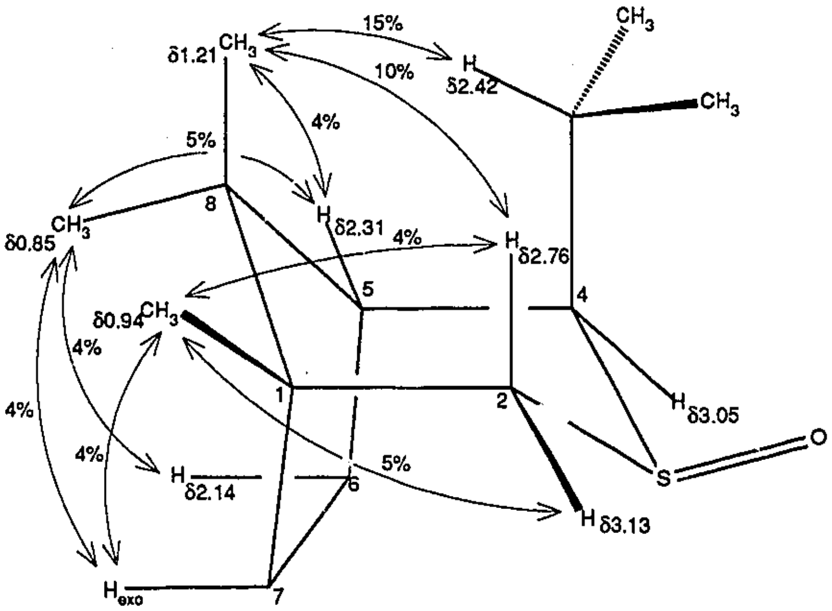


Figure 33. Summary of the nOe's observed in <u>118</u> upon irradiation of the methyl groups at C-8 and C-1.

(-CHMe$_2$) and δ2.76 (H$_{2ax}$). Importantly, the percentage of nOe with the isopropyl methine proton was quite high (15%) implying that these substituents are close in space. The signal at δ3.05, for the methine proton at C-4, did not show an nOe with any of the irradiated methyl groups at C-8 and C-1 and was therefore assigned to the equatorial proton at C-4. These data clearly established that the isopropyl moiety occupies the axial position at C-4. Furthermore, the vicinal coupling constant between H$_{4eq}$ and -C$\underline{H}$Me$_2$ was determined to be J=10.6 Hz from the proton spectrum (Figure 30). Such a large vicinal coupling constant corresponds to a dihedral angle of 180°[119] indicating that these protons are close to antiperiplanarity. The conformer depicted in Figure 33 best represents <u>118</u> in solution.

The minor and more polar isomer displayed a strong ir absorption at 1030 cm^{-1} (S=O bond vibration). The ^{13}C nmr spectrum contained a total of 13 resonances and the

^1H nmr spectrum of this compound is shown in Figure 34. The resonances for the isopropyl substituent appeared as two methyl doublets at δ1.02 and δ1.18, as well as a methine octet at δ2.24. The HOMCOR spectrum of **119**, is shown in Figure 35 and the nOe experiments carried out by selectively irradiating each of the three methyl groups in **119**, are shown in Figure 36 and summarized in Figure 37. The irradiation of the axial

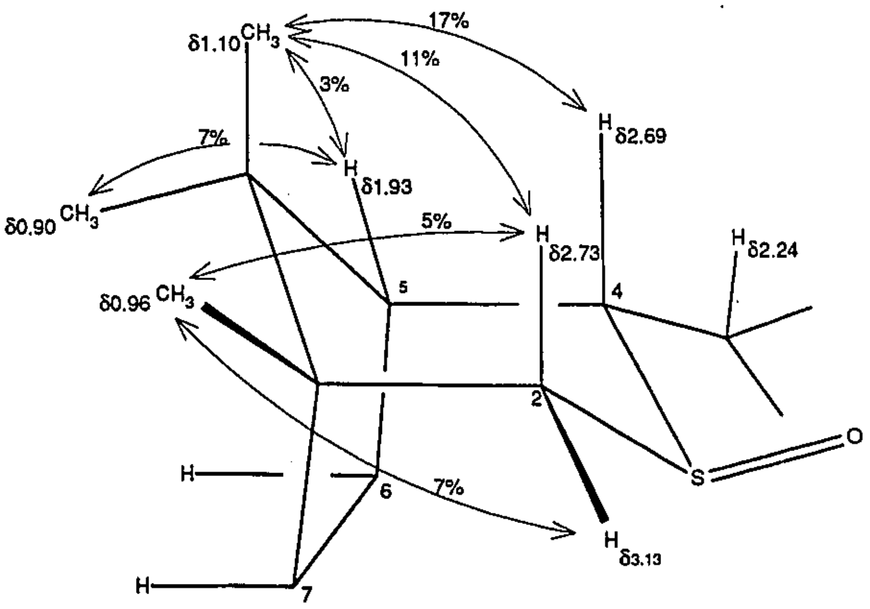


Figure 37. Summary of the nOe's observed in **119** upon irradiation of the methyl groups at C-8 and C-1.

methyl group at C-8 (Figure 36-D) resulted in nOe's with the following three signals: δ2.73 (H_{2ax}), δ2.69 and δ1.93 (H_5). The resonance at δ2.69, which was coupled with the isopropyl methine proton and H_5, was assigned to the axial proton at C-4 (H_{4ax}). On the basis of the above data the isopropyl moiety is equatorial at C-4. This compound represents the first, and only, equatorially substituted product obtained in the alkylation of

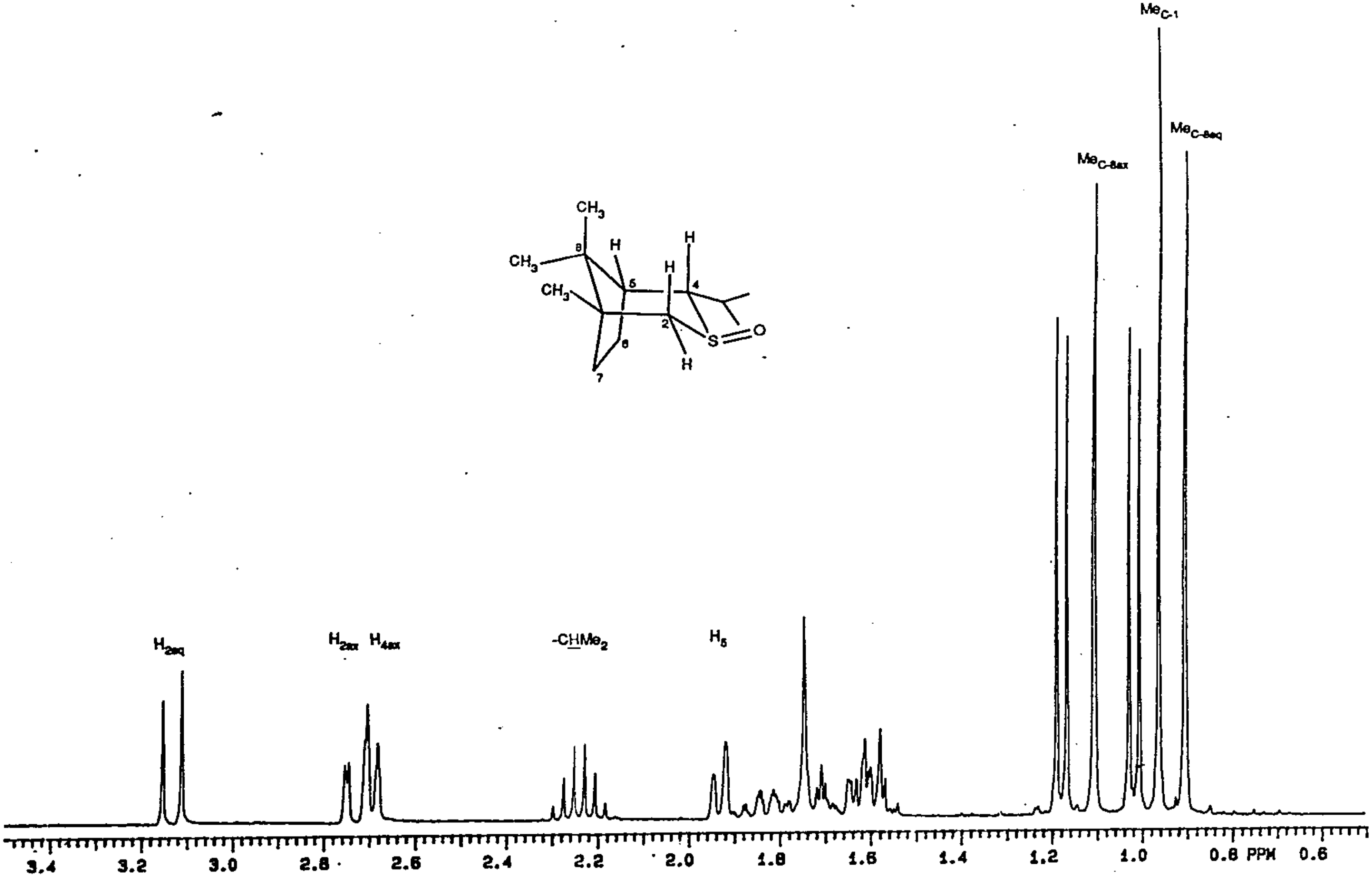


Figure 34. ^{1}H nmr spectrum of (1R,3S,4S,5S)-(+)-2-isopropyl-1,8,8-trimethyl-3-thiabicyclo-[3.2.1]octane-3-oxide <u>119</u>.

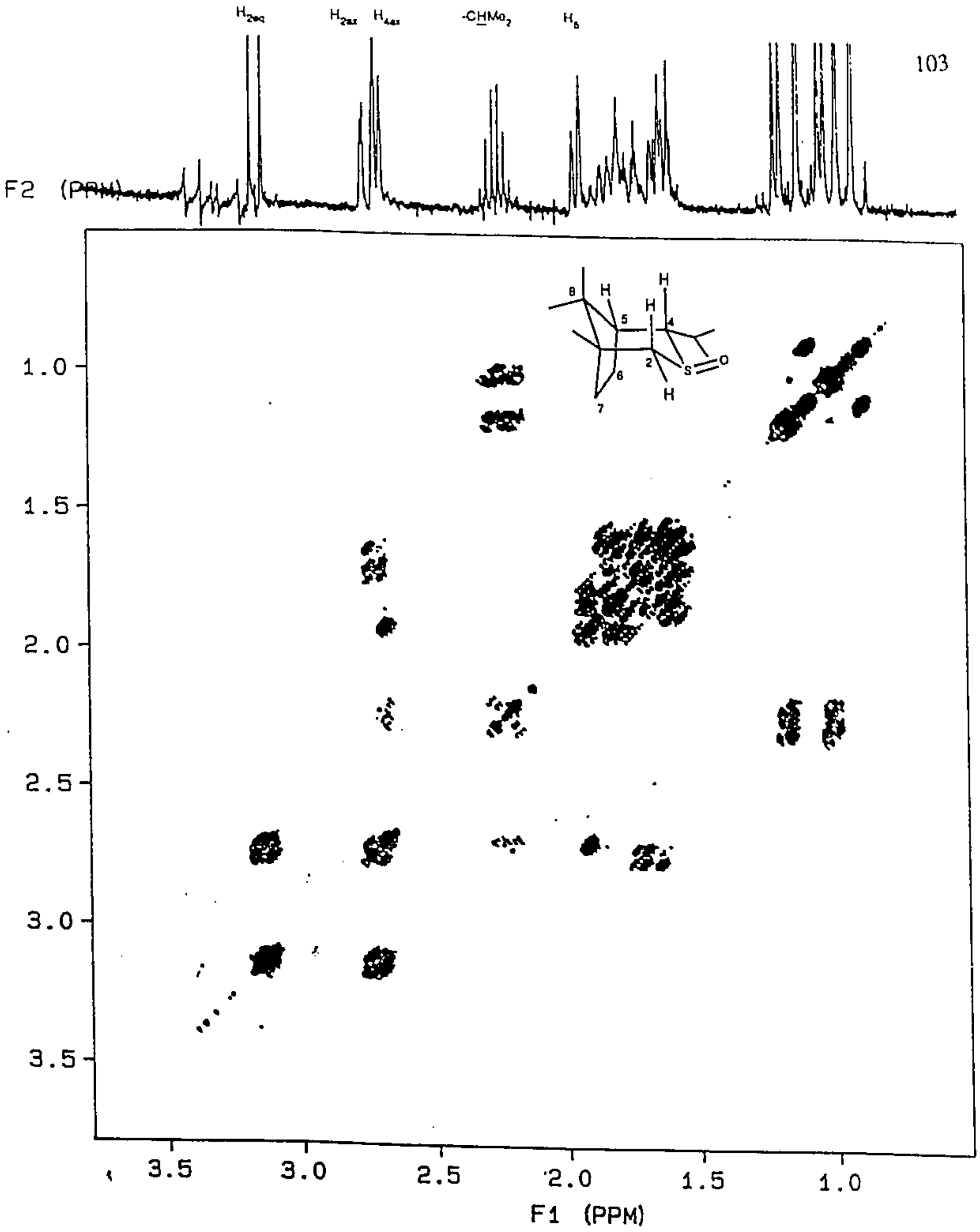


Figure 35. HOMCOR spectrum of (1R,3S,4S,5S)-(+)-2-isopropyl-1,8,8-trimethyl-3-thiabicyclo-[3.2.1]octane-3-oxide <u>**119**</u>.

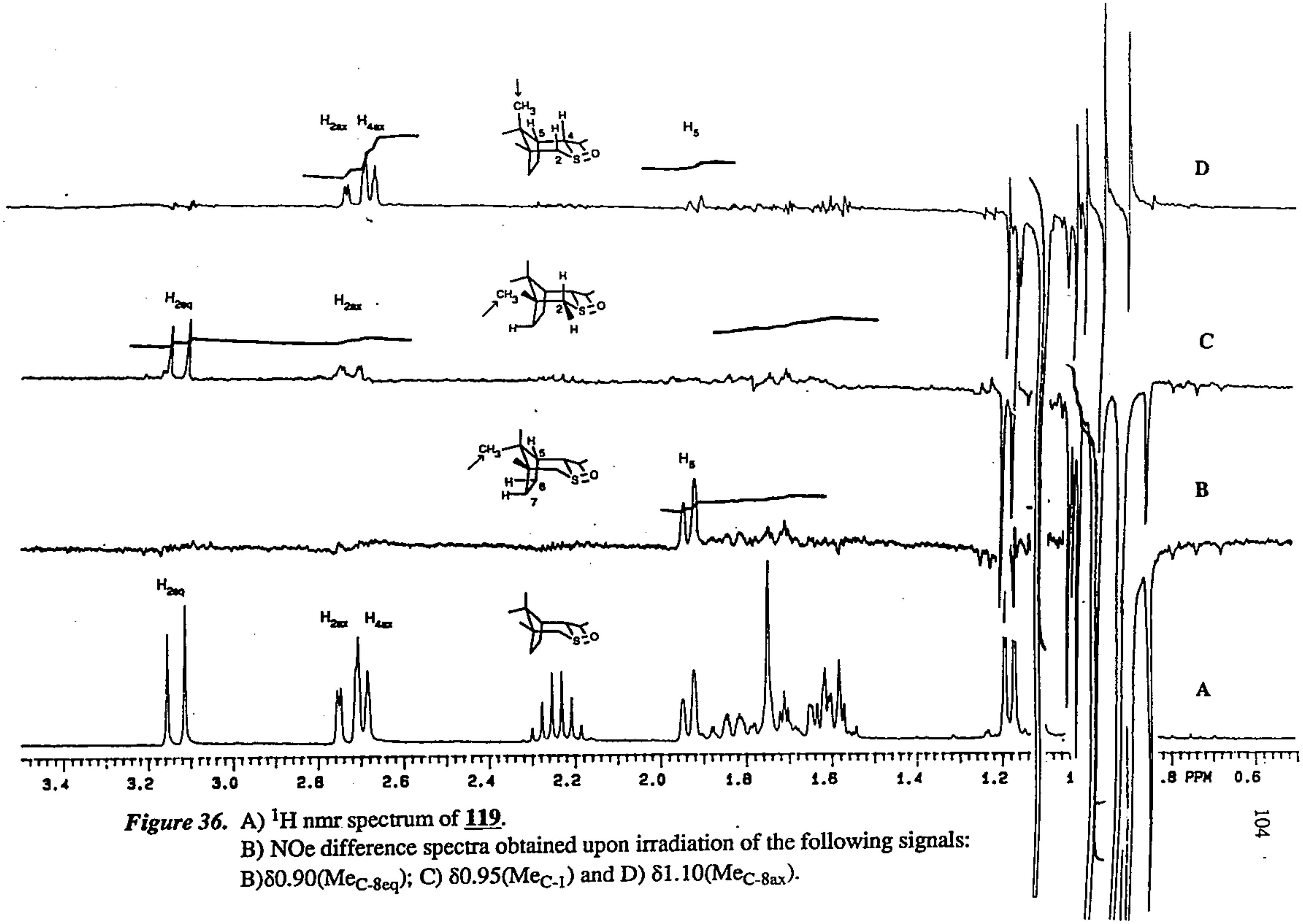
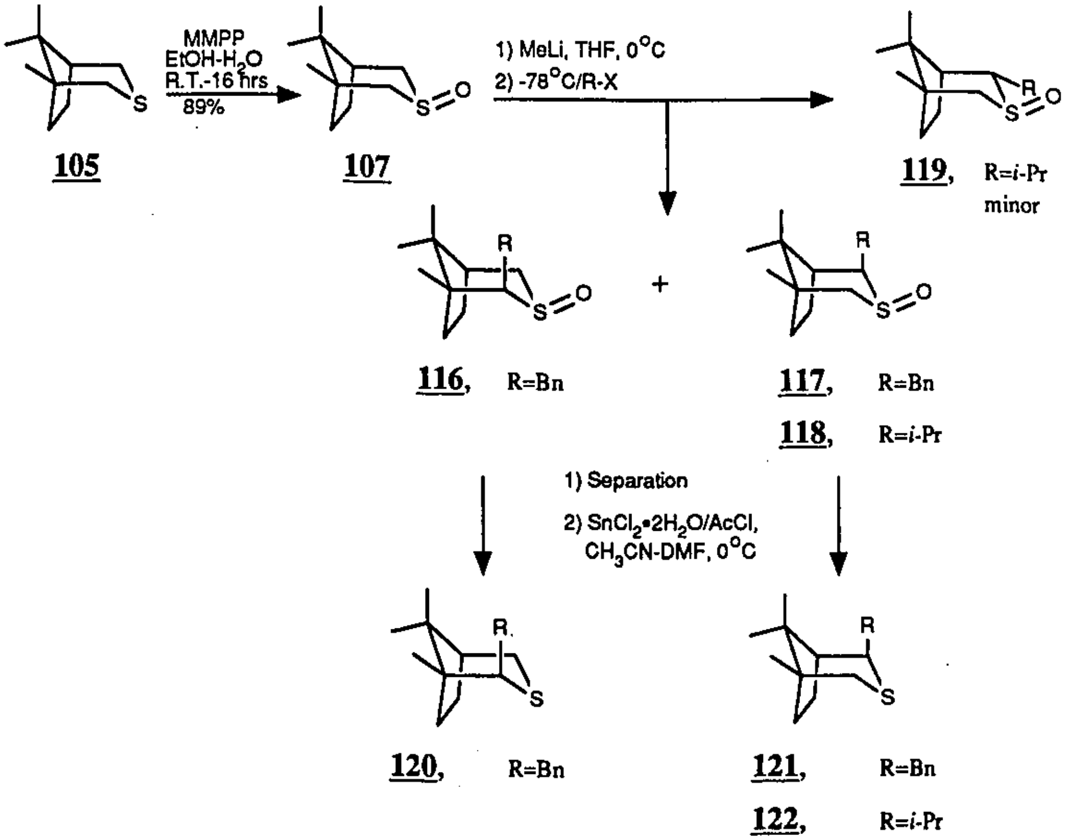


Figure 36. A) ^{1}H nmr spectrum of **<u>119</u>**.
B) NOe difference spectra obtained upon irradiation of the following signals:
B)δ0.90($Me_{C\text{-}8eq}$); C) δ0.95($Me_{C\text{-}1}$) and D) δ1.10($Me_{C\text{-}8ax}$).

an α-sulfinyl carbanion of 107.

Alkylation of 107 did not provide the expected precursors required to prepare sulfur auxiliaries such as 102. Nevertheless these compounds were thought to be valuable as models for further study of the asymmetric epoxidation reaction. The originaly proposed Scheme 21 was revised to Scheme 23 to provide the sulfides 120 - 122. Unfortunately the yield of the unique equatorially substituted sulfoxide 119 was insufficient to pursue its study as a sulfide auxiliary.



Scheme 23. Synthesis of 2- and 4-substituted-1,8,8-trimethyl-3-thiabicyclo[3.2.1] octanes 120 - 122.

The reduction of the sulfoxide functionality in compounds **116**, **117** and **118** was accomplished by addition of a mixture of acetyl chloride and stannous chloride to a solution of the sulfoxide in acetonitrile and DMF (Scheme 23)[120]. The reaction provided the desired sulfides **120**, **121** and **122** as colorless oils in 90-92% isolated yields. These sulfides were also carefully analyzed by ^1H nmr but only the key evidence is presented to support the assignment of the protons at C-4 and C-5. The coupling constant between these protons was used as a tool to evaluate the change in thiane geometry (see Section 2.3). The structure depicted for these sulfides are in agreement with the conclusion arrived at in the following Section.

The proton nmr spectrum of 2-benzyl sulfide **120** (Figure 38) demonstrated that the proton α to the sulfur and the benzylic protons resonated from δ2.2 to δ3.3. The HOMCOR spectrum of the region from δ0 to δ4 is shown in Figure 39. The nOe's obtained from the irradiation of each of the three methyl groups in **120** are shown in Figure 40 and summarized in Figure 41. Irradiation of the equatorial methyl group at C-8 (Figure 40-B) gave an nOe with the multiplet at δ1.96 (H_5). Irradiation of the C-1 methyl (Figure 40-C) could not be performed selectively because of the close proximity of the C-8 axial methyl signal. For the combined irradiation the most significant nOe's were observed for the following signals: δ2.51 (H_{2eq}), δ2.94 ($C\underline{H}_APh$) and δ3.25 ($C\underline{H}_BPh$). When the irradiation was focused mainly on the C-8 axial methyl group, (Figure 40-D), the strongest nOe's were observed with the signals at δ3.25 ($C\underline{H}_BPh$) and δ3.30. The latter was therefore assigned to H_{4ax}. The resonance at δ2.20 did not display an nOe in any of the above experiments and was therefore assigned to H_{4eq}.

The proton nmr spectrum of the benzylsulfide **121** is shown in Figure 42. The protons α to sulfur and the phenyl group resonated between δ2.01 to δ2.96. The HOMCOR spectrum of this region, which is shown in Figure 43, demonstrated that the resonance at δ3.10 was coupled with the one at δ2.88. Integration of the proton spectrum indicated that the former resonance represented two protons; only vicinal coupling was

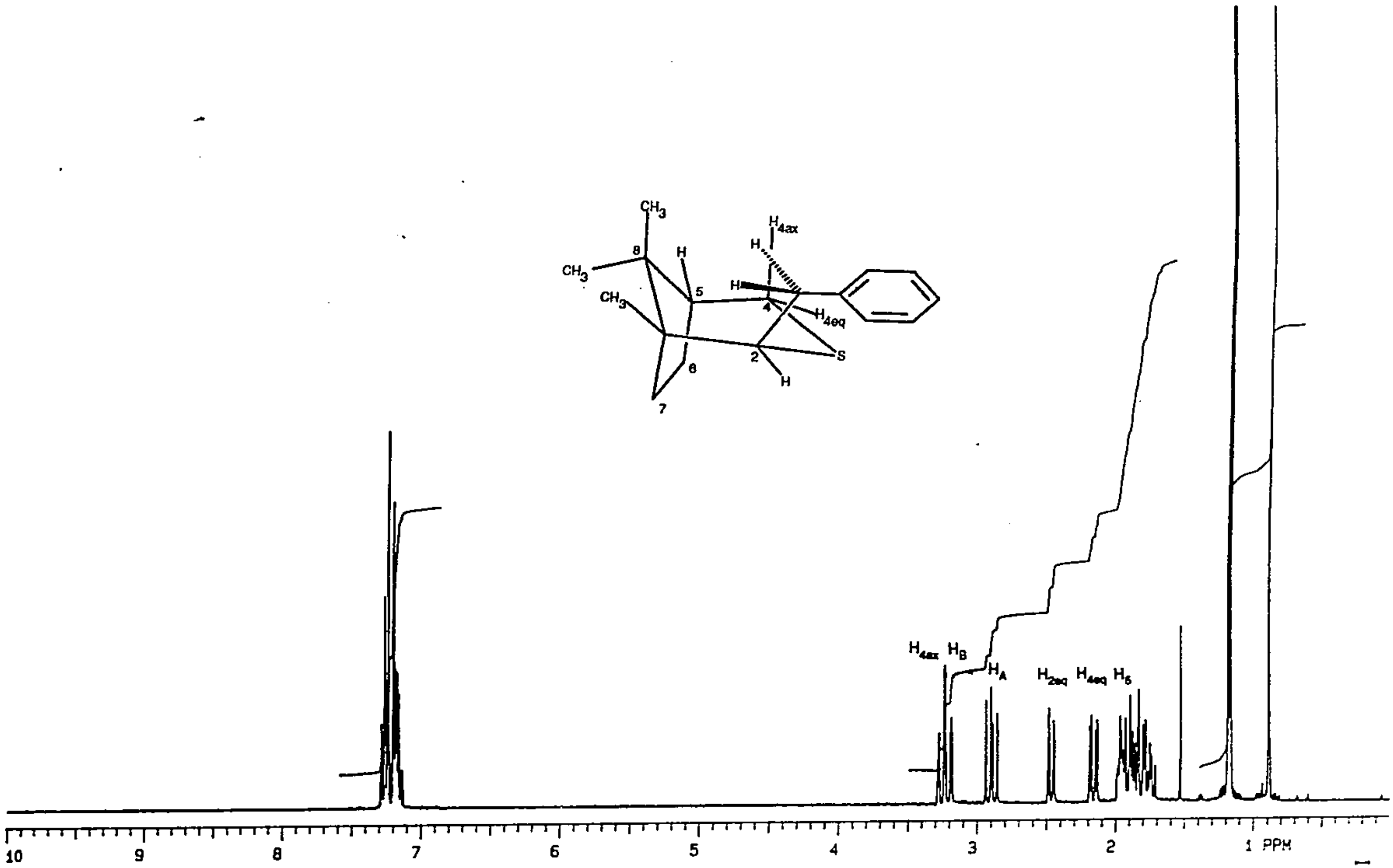


Figure 38. ^{1}H nmr spectrum of (1R,2S,5S)-(-)-2-benzyl-1,8,8-trimethyl-3-thiabicyclo[3.2.1]-octane **120.**

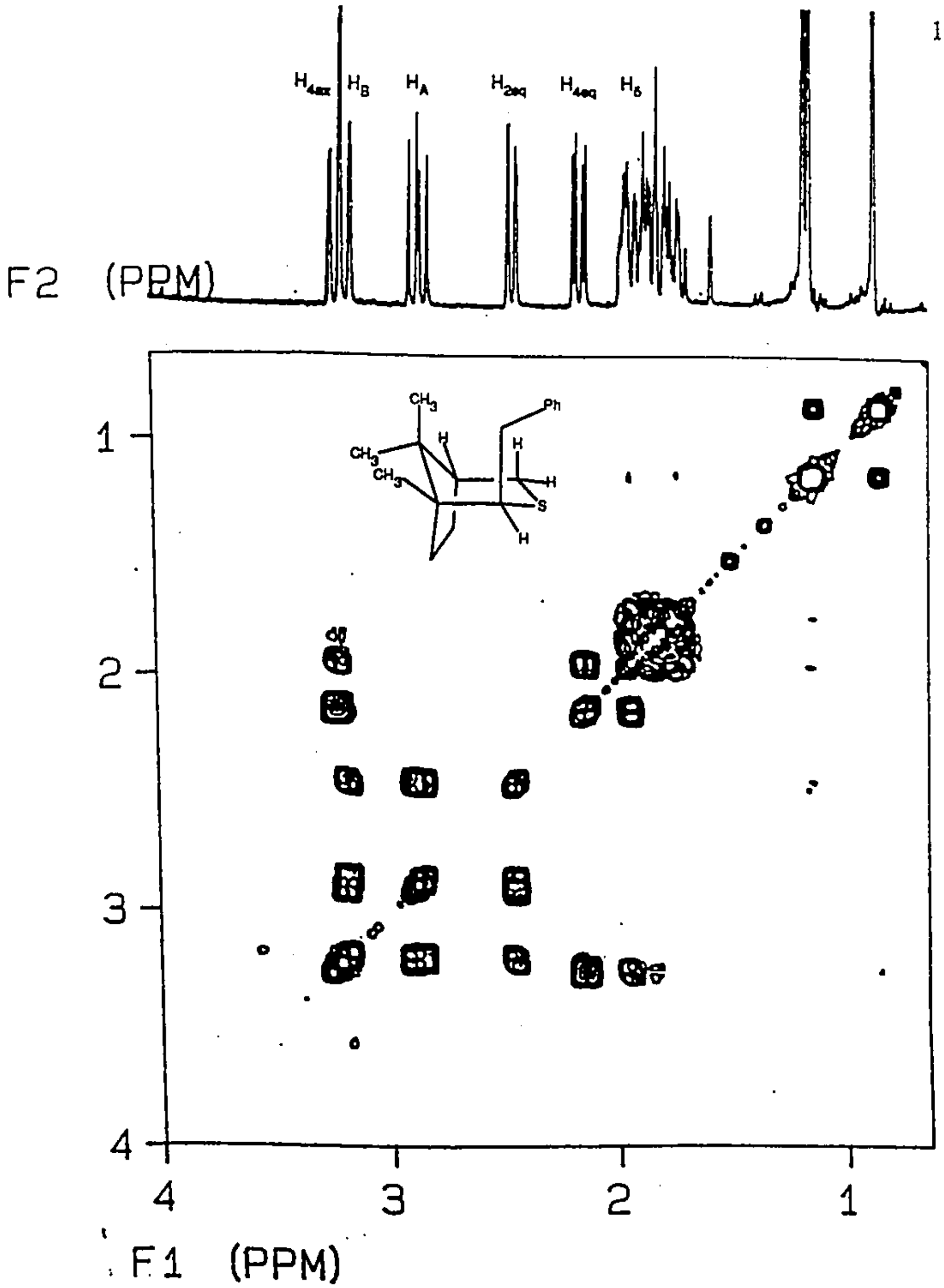


Figure 39. HOMCOR spectrum of (1R,2S,5S)-(-)-2-benzyl-1,8,8-trimethyl-3-thiabicyclo-[3.2.1]octane <u>**120**</u>.

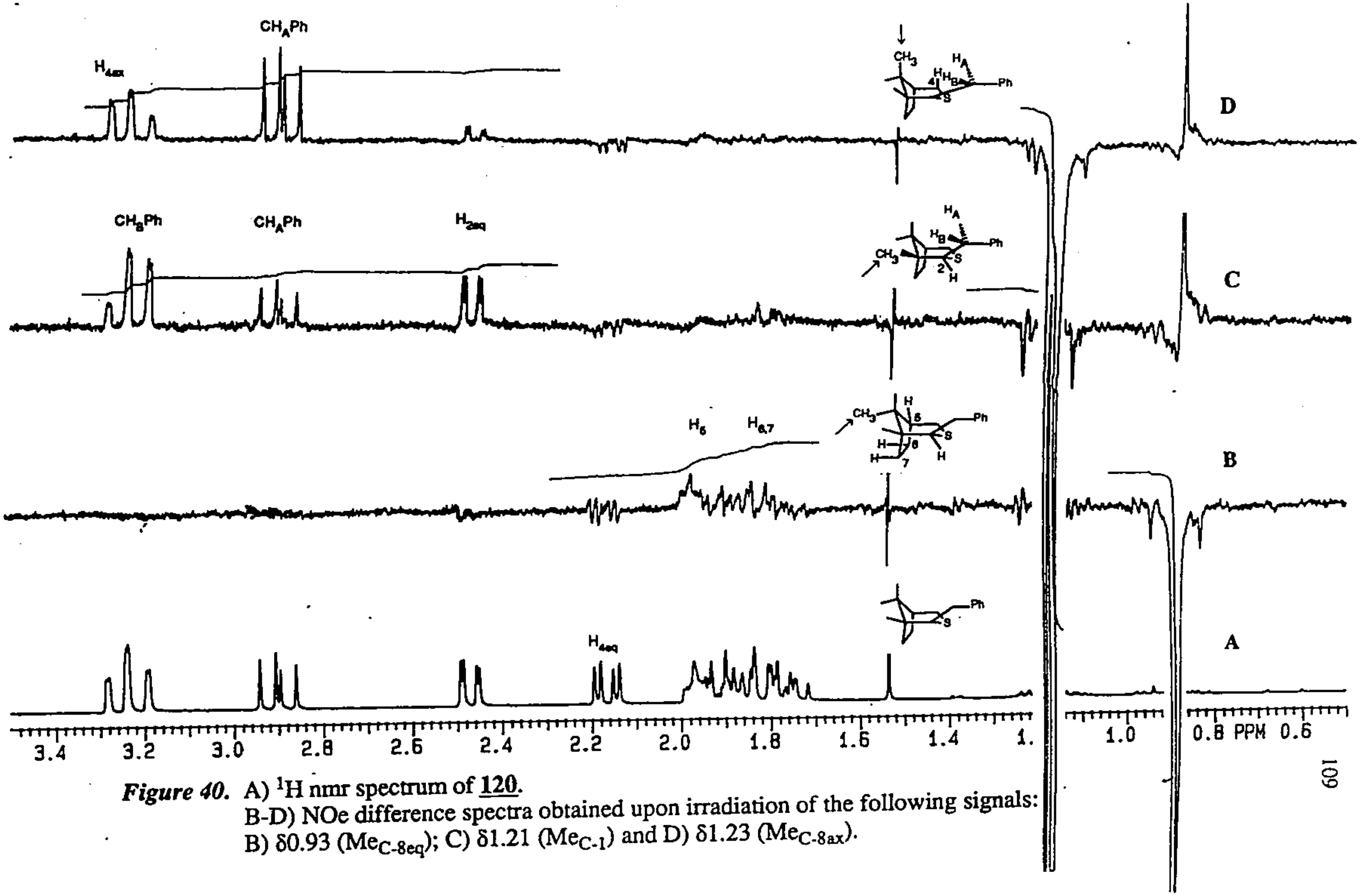


Figure 40. A) ^{1}H nmr spectrum of 120.
B-D) NOe difference spectra obtained upon irradiation of the following signals:
B) δ0.93 (Me_{C-8eq}); C) δ1.21 (Me_{C-1}) and D) δ1.23 (Me_{C-8ax}).

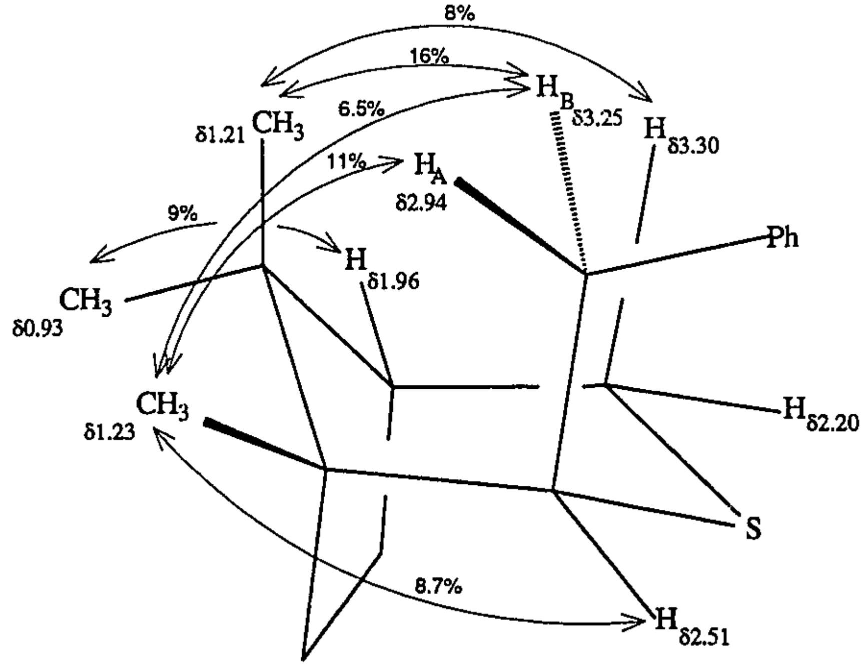


Figure 41. Summary of the nOe's in <u>**120**</u> obtained from the irradiation of the methyl groups at C-8 and C-1.

detected. The resonance at δ3.10 was attributed to the two benzylic protons. Because of the coincidence of their chemical shifts, no geminal coupling for these protons was seen. Thus this signal constitutes the X_2 part of AX_2 system. The signal at δ2.88 forms the A part of this system and was assigned to the equatorial proton at C-4 (H_{4eq}). The nOe experiments achieved by the selective irradiation of each of the methyl groups in <u>**121**</u> is shown in Figure 44 and summarized in Figure 45. The irradiation of the equatorial methyl at C-8 (Figure 44-B) resulted in an nOe with the multiplet at δ1.90 due to the proton at C-5. Saturation of the C-1 methyl proton (Figure 44-C) resulted in nOe's with two peaks at δ2.01 and δ2.96 which were correlated with themselves in the HOMCOR spectrum. These protons resulted in an AB system and were assigned to H_{2eq} and H_{2ax}, respectively. Irradiation of the axial C-8 methyl (Figure 44-D) resulted in enhancements with the two proton signals at δ3.09 (for the two -C<u>H</u>$_2$Ph protons) and δ2.96 for H_{2ax}.

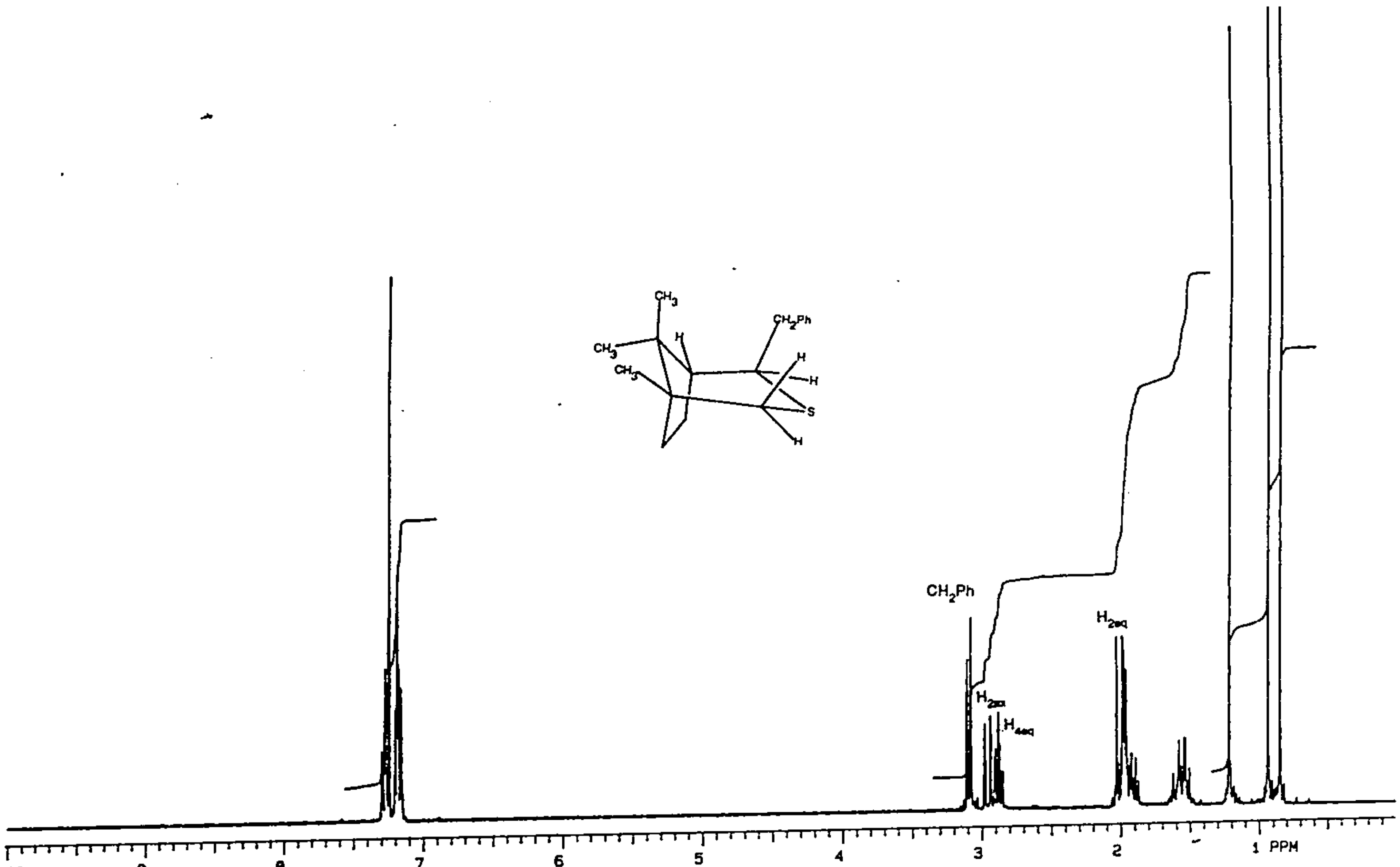


Figure 42. ^{1}H nmr spectrum of (1R,4R,5S)-(+)-4-benzyl-1,8,8-trimethyl-3-thiabicyclo[3.2.1]-octane **121.**

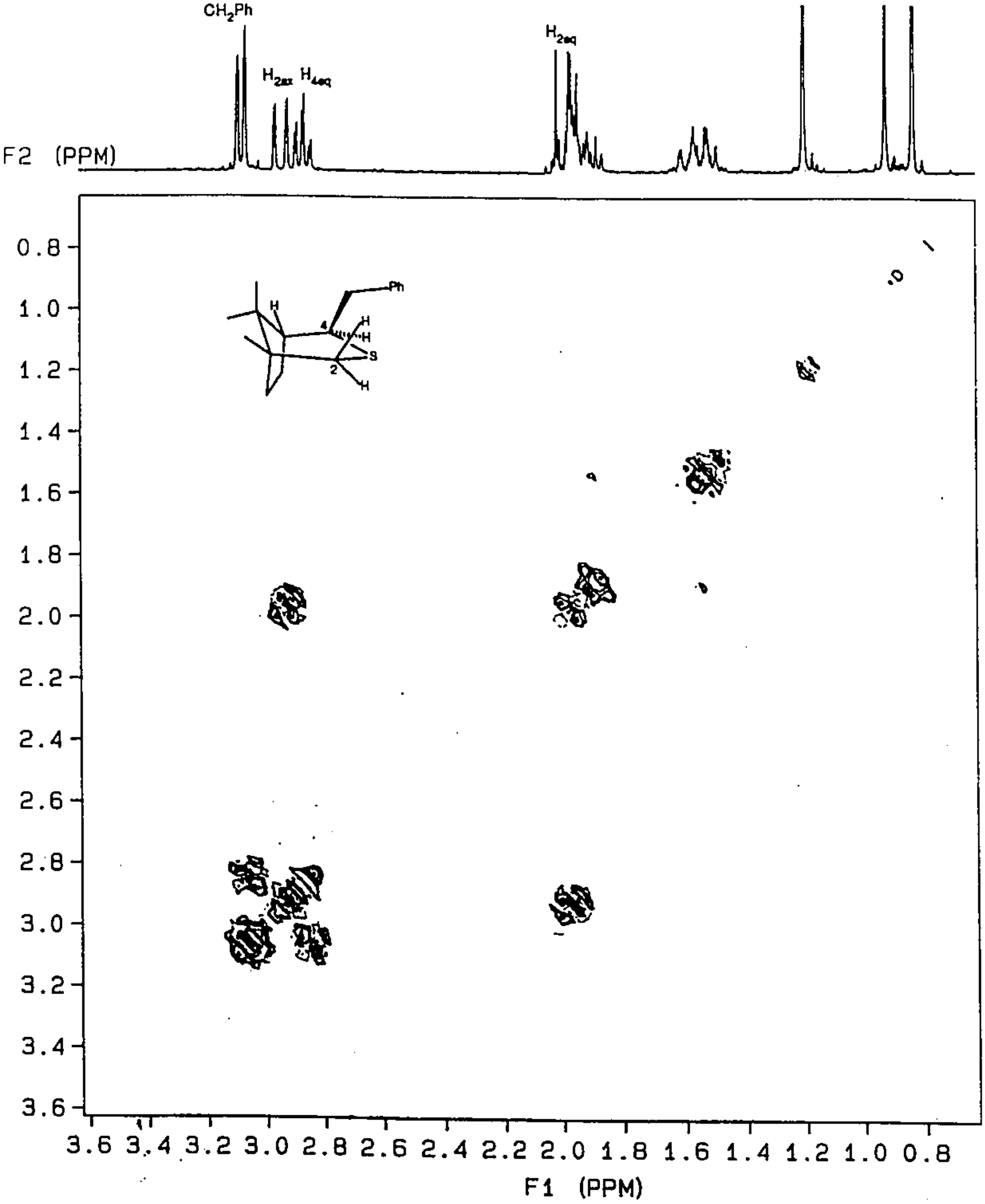


Figure 43. HOMCOR spectrum of (1R,4R,5S)-(+)-4-benzyl-1,8,8-trimethyl-3-thiabicyclo-[3.2.1]octane **<u>121</u>**.

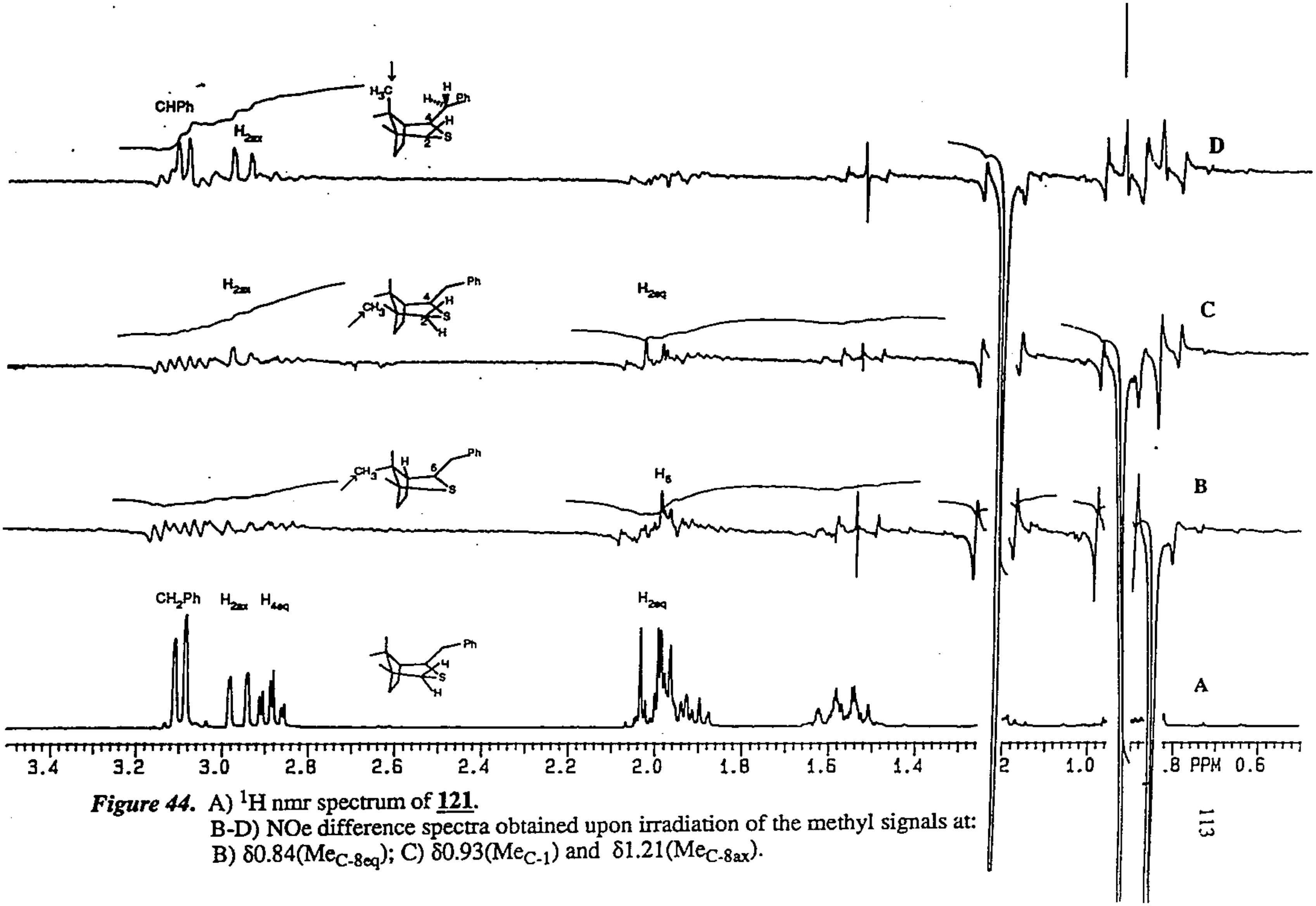


Figure 44. A) ^{1}H nmr spectrum of **121**.
B-D) NOe difference spectra obtained upon irradiation of the methyl signals at:
B) $\delta 0.84(Me_{C\text{-}8eq})$; C) $\delta 0.93(Me_{C\text{-}1})$ and $\delta 1.21(Me_{C\text{-}8ax})$.

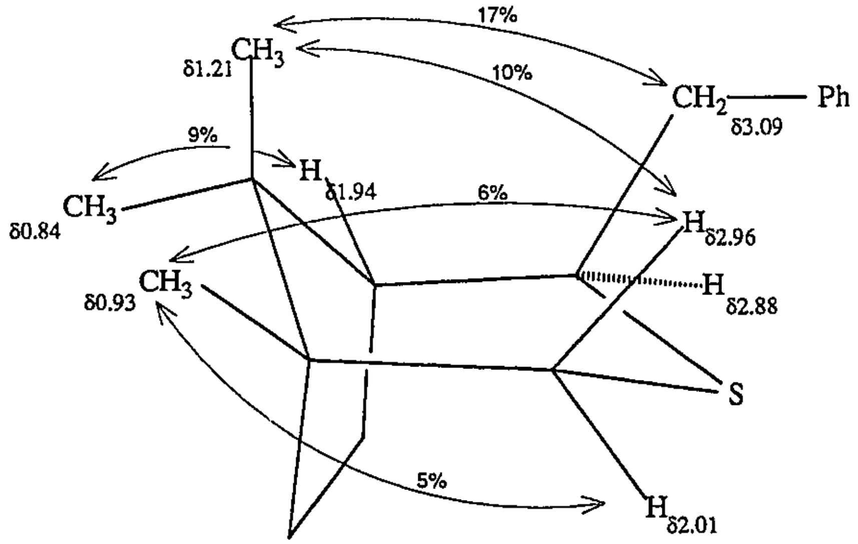


Figure 45. Summary of nOe's arising from irradiation of the substituents at C-8 and C-1 in **121**.

The proton nmr spectrum of the axial isopropylsulfide **122** displayed a complex spectum (Figure 46). Fortunately two key protons were clearly visible: a doublet at δ1.96 and a multiplet at δ2.07 attributed to a proton α to the sulfur and the second to the isopropyl methine proton, respectively. The other two α protons resonated at δ2.23 and δ2.85. The HOMCOR spectrum (Figure 47) indicated that the signal at δ2.23 was coupled with the isopropyl methine signal at δ2.07 and thus corresponds to the methine proton at C-4. A series of nOe experiments carried out by the selective irradiation of each of the methyls in **122** is shown in Figure 48 and summarized in Figure 49. Irradiation of the C-1 methyl protons (Figure 48-C), showed nOe's with two coupled proton signals at δ2.85 (H_{2ax}) and δ1.92 (H_{2eq}). Irradiation of the axial methyl at C-8 (Figure 48-D), produced two distinctive nOe's: a powerful enhancement (19%) with the multiplet at δ2.07 (-C<u>H</u>Me$_2$), which stresses their closeness in space, and a more modest interaction (10%) with H_{2ax} at δ2.85. The signal at δ2.23, which did not show an nOe upon irradiation of the methyl substituents, was assigned to H_{4eq}.

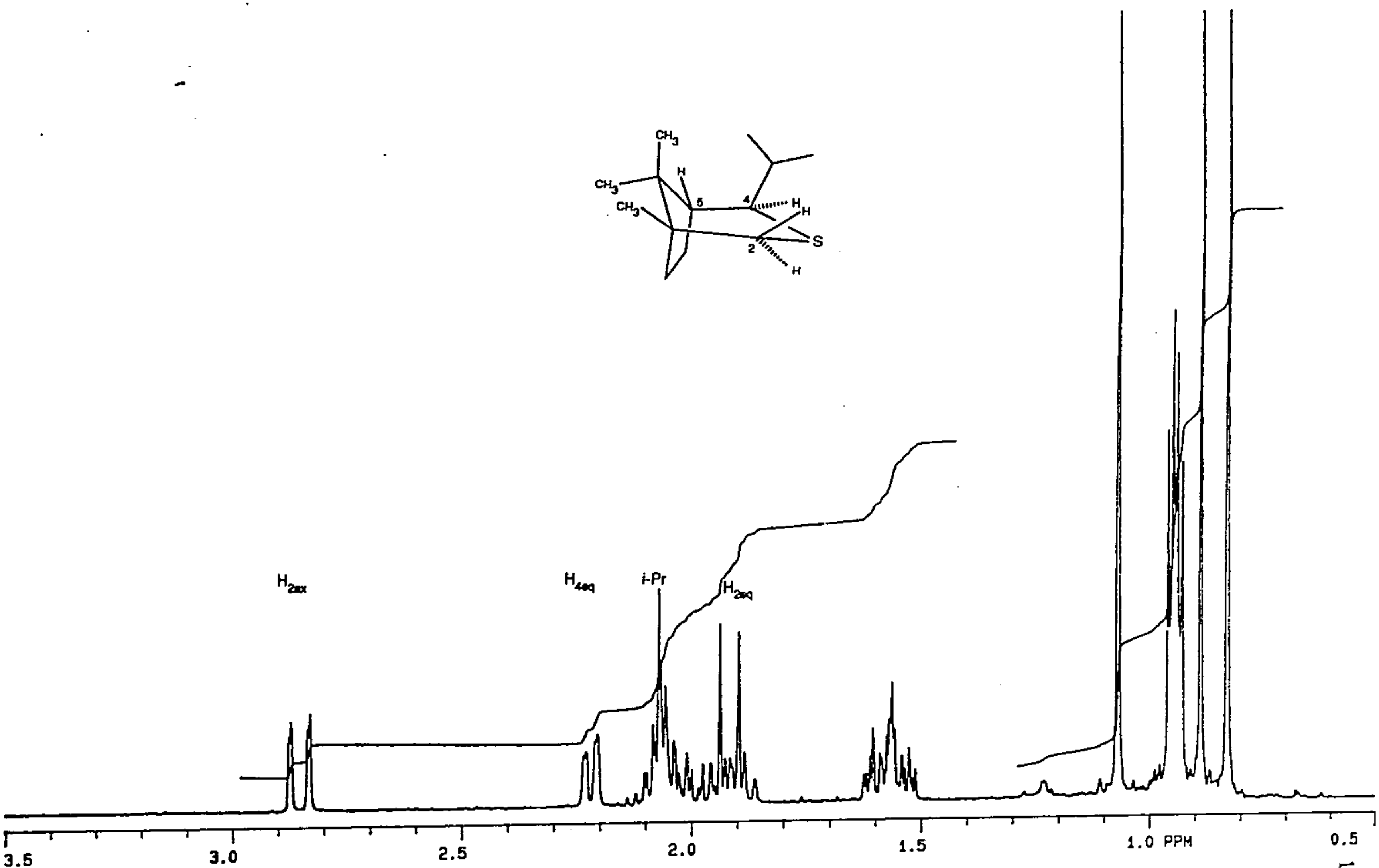


Figure 46. ^{1}H nmr spectrum of (1R,4R,5S)-(+)-4-isopropyl-1,8,8-trimethyl-3-thiabicyclo-[3.2.1]octane **122**.

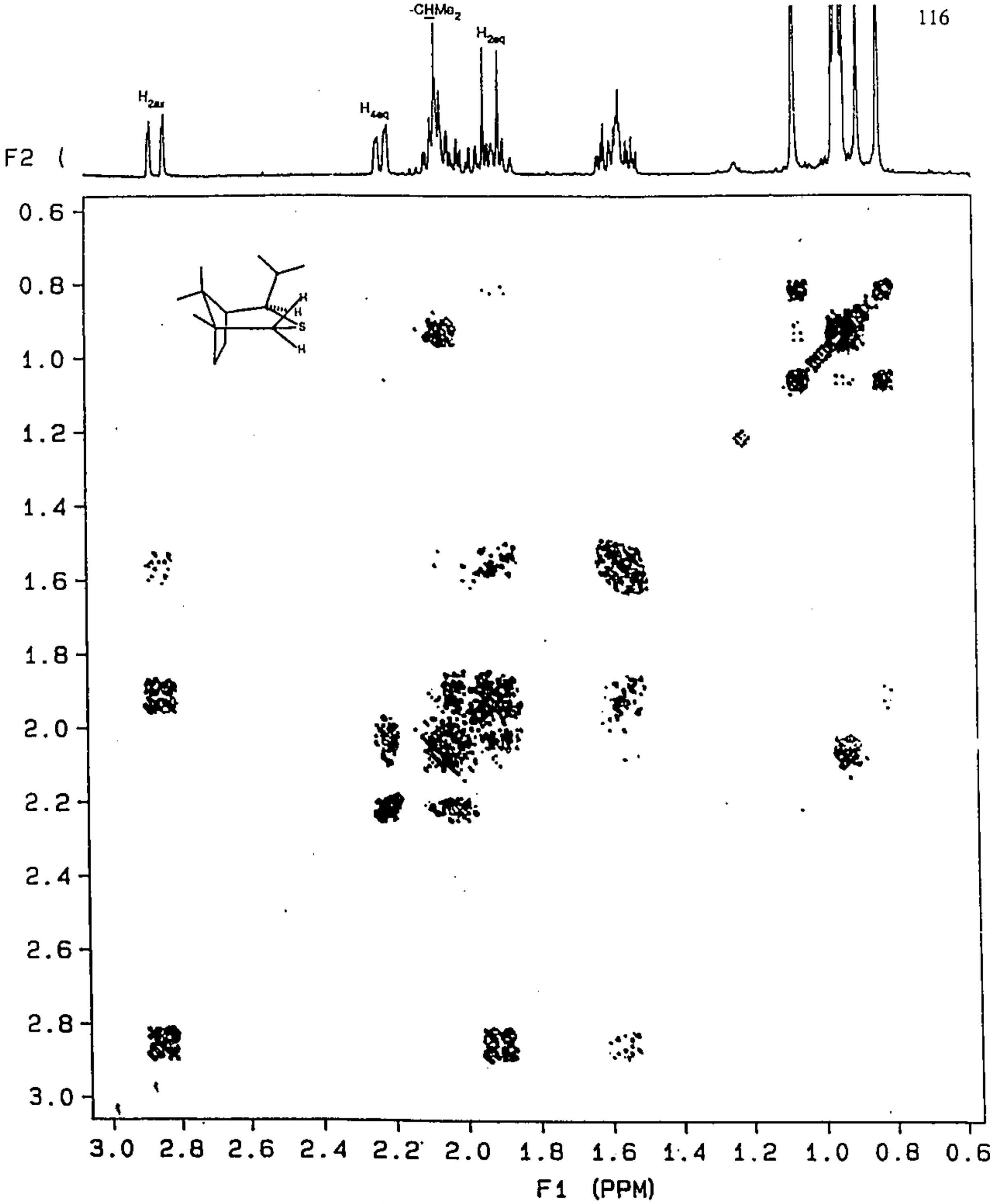


Figure 47. **HOMCOR spectrum of (1R,4R,5S)-(+)-4-isopropyl-1,8,8-trimethyl-3-thiabicyclo-[3.2.1]octane 122.**

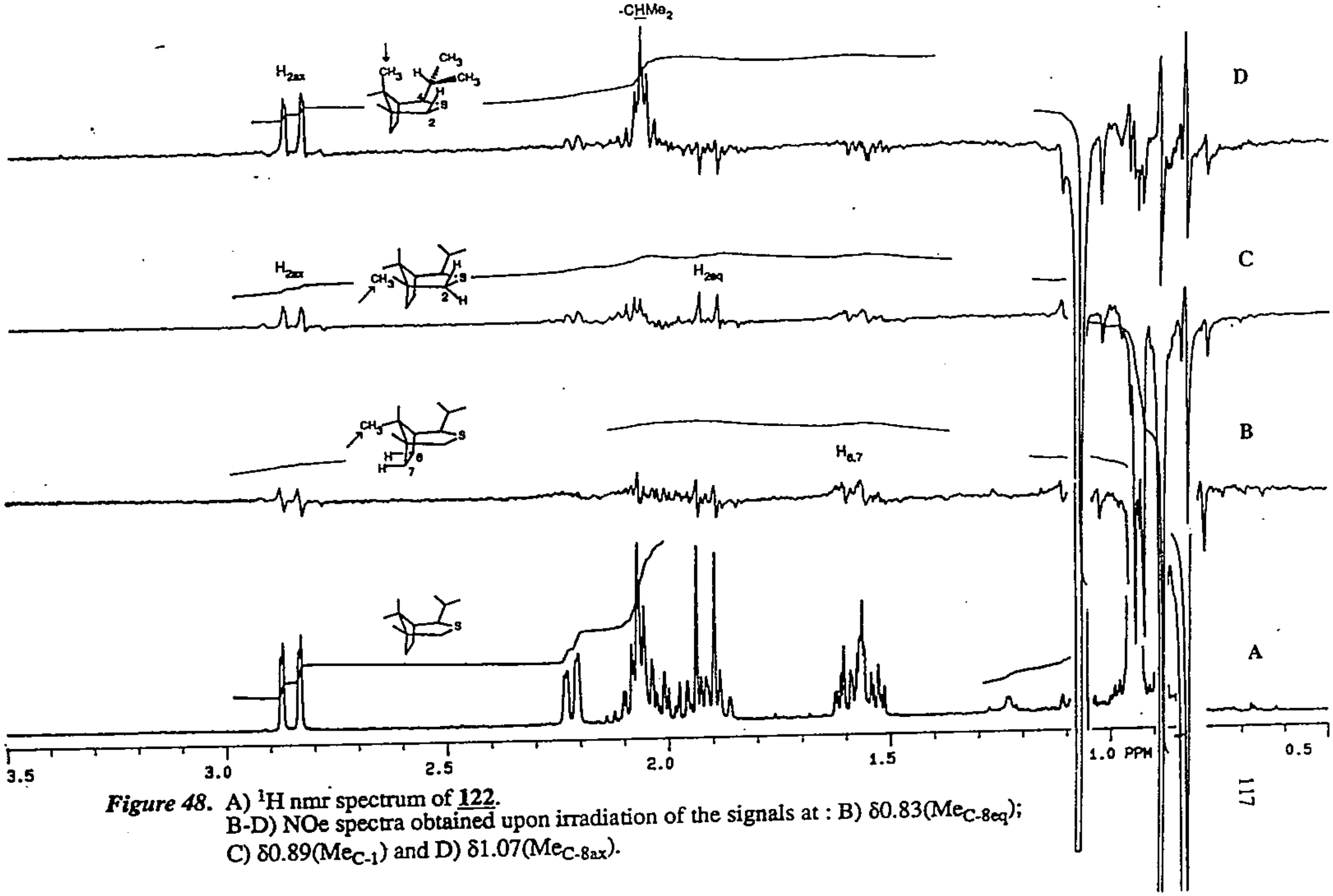


Figure 48. A) ^{1}H nmr spectrum of <u>122</u>.
B-D) NOe spectra obtained upon irradiation of the signals at : B) δ0.83($Me_{C\text{-}8eq}$);
C) δ0.89($Me_{C\text{-}1}$) and D) δ1.07($Me_{C\text{-}8ax}$).

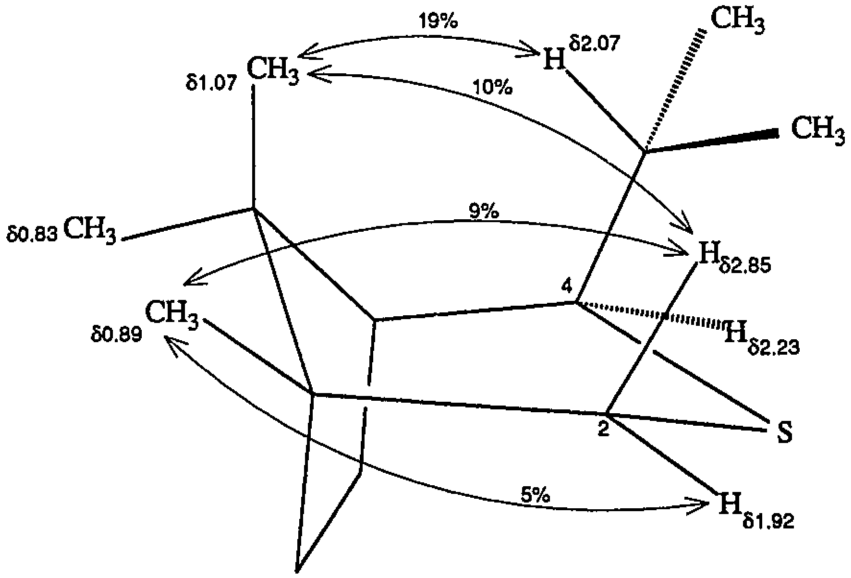


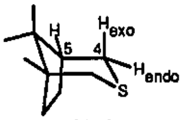
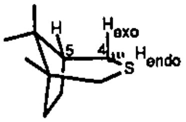
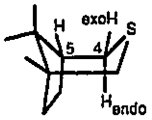
Figure 49. Summary of the nOe's observed in 122 upon irradiation of the methyls at C-8 and C-1.

3.3 Conformation Analysis of the 3-Thiabicyclo[3.2.1]octane Ring

In the thiabicyclo[3.2.1]octane system, atoms C-1, C-5 and C-8 have a fixed conformation. Atoms C-2, S and C-4 can adopt either a boat, chair or a half chair conformation. In the half chair conformation C-1, C-2, S, C-4 and C-5 are all in the same plane. Table 5 summarizes the torsional angles between H_5 and the protons at C-4 which were estimated from inspection of a Dreiding molecular model of 105. Variations in the conformation for the thiane ring in the α-substituted thiabicyclo[3.2.1]octane were determined utilizing the changes in vicinal coupling constants between H_5-H_{4exo} and H_5-H_{4endo} (Karplus Equation) as monitored by ^1H nmr. The vicinal coupling constant, as well as the corresponding torsonial angles between H_5 and the protons at C-4, for compounds 105 to 122 are recorded in Table 6.

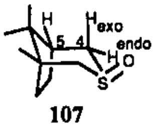
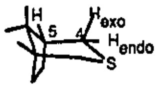
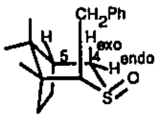
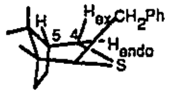
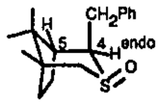
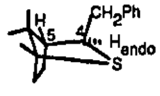
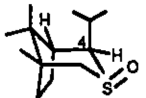
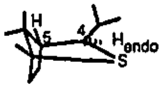
Sulfoxides 107 and 116 displayed similar torsional angles which were consistent

TABLE 5. Estimation of the torsional angles in <u>105</u> from inspection of Dreiding molecular models.

Conformation of <u>105</u>	Torsional angles	
	H_5 - H_{4exo}	H_5 - H_{4endo}
 Chair	80°	40°
 Half-Chair	40	80
 Boat	10	110

with the chair conformation of the thiane ring. Both of the 4-substituted sulfoxides <u>117</u> and <u>118</u> show the torsional angle between H_5 and H_{4endo} to be ten degrees larger than for the parent sulfoxide <u>107</u>. This indicates a small degree of flattening of the C-2, S and C-4 portion of the thiane ring. A similar distortion of the thiane ring did not occur in <u>116</u> since this would place the C-2 benzyl substituent syn-periplanar to the C-1 methyl group. Table 6 shows clearly that reduction of the sulfoxide functionality to the sulfide was accompanied by significant flattening of the thiane ring. Thianes <u>121</u> and <u>122</u> were the most affected and displayed torsional angles (between H_5 and H_{4endo}) twenty degrees larger than for the starting sulfoxide <u>107</u>. According to Table 5 these angles suggested a thiane ring in which the C-2, S and C-4 portions of the ring are in a conformation between

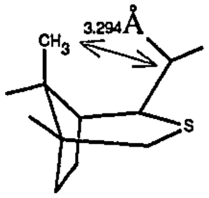
TABLE 6. Estimation of torsional angles in analogues of 3-thiabicyclo[3.2.1]octane from ^{1}H nmr spectroscopy.

Compound (No.)	*J* Vicinal (Hz) (Torsion angle)[a]		Compound (No.)	*J* Vicinal (Hz) (Torsion angle)	
	$H_5 - H_{4exo}$	$H_5 - H_{4endo}$		$H_5 - H_{4exo}$	$H_5 - H_{4endo}$
 **107**	0 - 1 Hz (84 - 68°)	5.1 Hz (38°)	 **105**	0 - 0.5 Hz (84 - 70°) 2,8 60°	3.3 Hz (50°) 3,8 54°
 **116**	0 Hz (84°) (87.2° ± 30)[b]	5.3 Hz (36°) (48.7° ± 37)[b]	 **120**	2.0 Hz (60°)	4.3 Hz (44°)
 **117**	—	3.6 Hz (48° or 117°)	 **121**	—	2.3 Hz (56° or 110°)
 **118**	—	3.3 Hz (50° or 115°)	 **122**	—	1.7 Hz (62° or 106°)

a) Deduction of dihedral angles from measured coupling constant s was based on the Karplus correlation curve.[119]

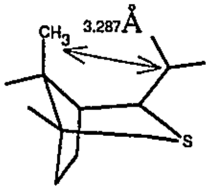
b) Obtained from the X-ray single crystal diffraction of **116**.

a chair and a half-chair. Flattening of the thiane ring in these systems becomes energetically favourable since it results in considerable reduction of the steric interactions between the newly introduced substituents and the syn C-8 methyl group compared to the chair conformation. This last statement is also supported by theoretical calculations carried out on 4-isopropyl sulfide **122** which showed that the global minimum is half chair structure **122A**.[121] This was calculated to be 4.7 Kcal/mole more stable than a quasi-chair structure, **122B**, 9.5 Kcal/mole more stable than the boat structure, **122C**, and 45.0 Kcal/mole more stable than the chair structure, **122D**.



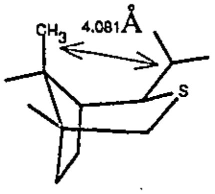
122A

$\Delta H_f = -45.7$



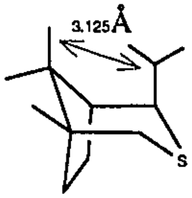
122B

$\Delta H_f = -41.0$



122C

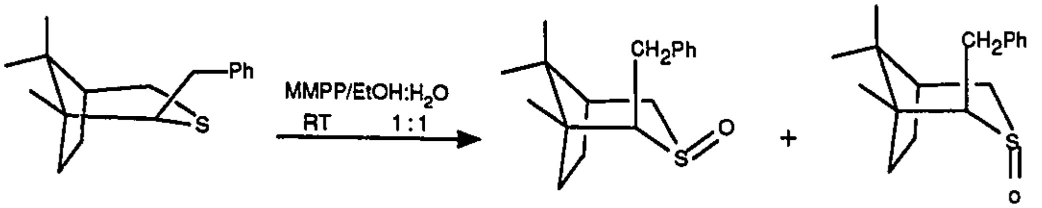
$\Delta H_f = -31.5$



122D

$\Delta H_f = +4.0$

It was impossible to predict with any certainty the stereochemistry of S-alkylation for **120** - **122**. To investigate the selectivity further it was decided to reoxidize 2-benzyl sulfide **120**, (equation 45). Careful oxidation of thiane **120** gave an inseparable mixture of



120 **116eq** 47 : 53 **116ax** (45)

sulfoxides. The i.r. spectrum of the crude mixture showed a strong absorption at 1035 cm^{-1}, characteristic for a sulfoxide functionality. It should be noted that no strong absorption near 1300 cm^{-1} and 1150 cm^{-1} was found thus indicating the absence of a sulfone. The ^{1}H nmr spectrum of the crude product (Figure 50), displayed six methyl singlets in the region from δ0.86 to δ1.22. This demonstrated the presence of two compounds, and by comparison with the ^{1}H nmr spectrum of sulfoxide **116** (Figure 20-C, page 80), the signals attributed to this equatorial sulfoxide were labelled "**116eq**" in Figure 50. The remaining signals were thus due to the axial sulfoxide isomer **116ax**; these were

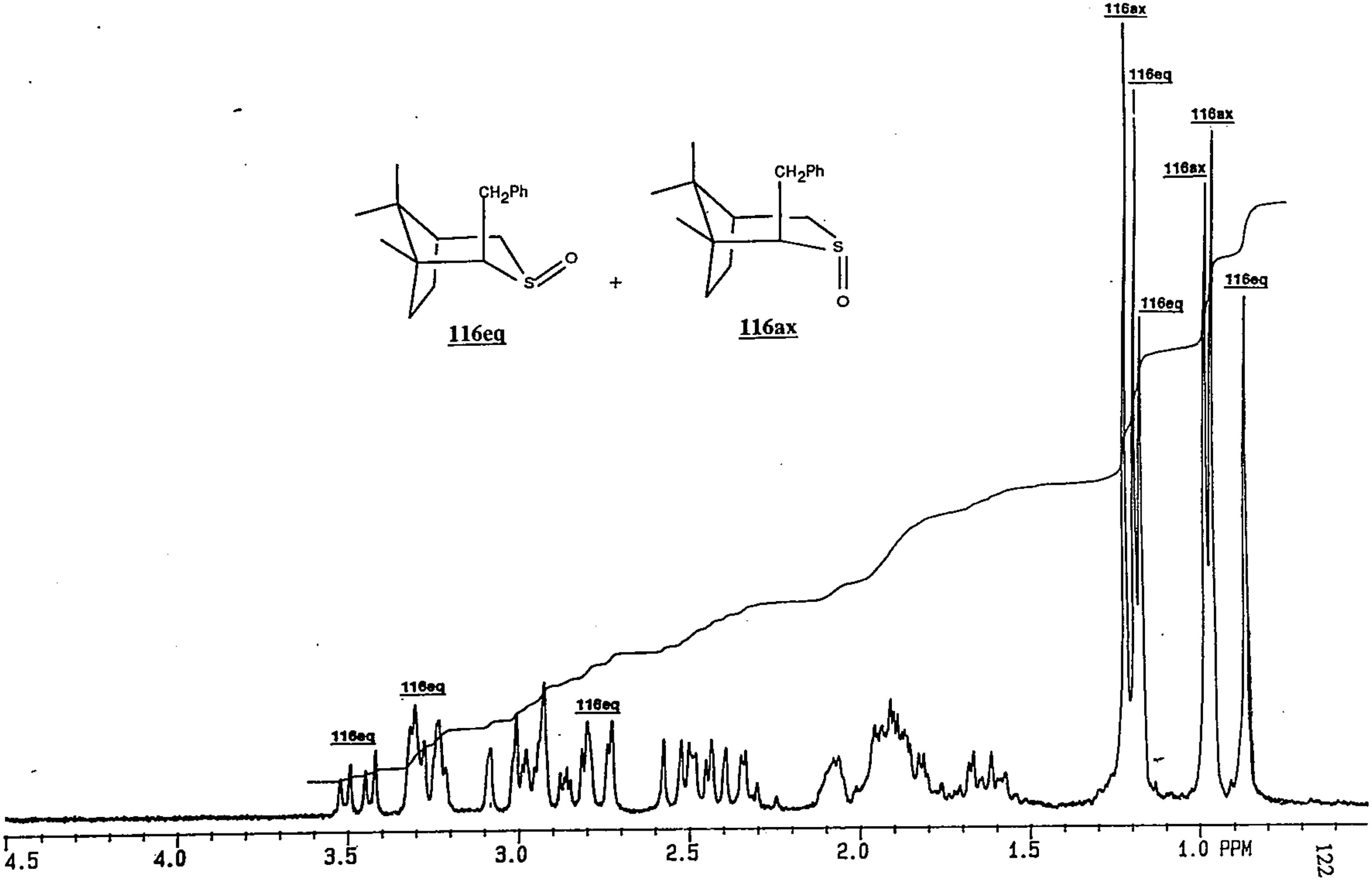


Figure 50. ^{1}H nmr of the crude mixture obtained from the oxidation of thiane **120**.

labelled "**116ax**". Integration of the methyl signals for **116eq** *versus* **116ax** gave essentially a 1:1 ratio. This leads one to conclude that for a 3-thiabicyclo[3.2.1]octane in a conformation similar to **122B**, the sulfide faces are equally hindered by the methylene at C-6 and C-7 as by an *exo*-benzyl substituent at C-2.

3.4 Synthesis and Conformation Analysis of the 3-Thianiumbicyclo[3.2.1]octane Salts.

Addition of $AgClO_4$ to a solution of thiane **120** and benzyl bromide in anhydrous ether gave the S-alkylated product **123** (62% yield) as a white foam. This material could be stored for several months at room temperature without deterioration. The nmr spectrum of this compound is shown in Figures 51 and 51A. The two S-benzylic protons appeared as an AB quartet at δ4.17 and δ4.53. Surprisingly, one diastereomer predominated. Integration of the methyl signals revealed that the minor isomer, methyl singlets at δ0.94, δ1.29 and δ1.43, corresponded to only 10% of the S-alkylated products. An attempt to purify this material by recrystallization (CH_2Cl_2+Et_2O) gave a white solid which had a ^1H nmr identical to the starting material. This result may be interpreted as being due to either an unsuccessful fractional recrystallization or a relatively rapid isomerization of the sulfonium salt to a 9:1 thermodynamic equilibrium. The ^1H nmr spectrum showed significant downfield chemical shifts for the resonances attributed to the ring hydrogens α to the sulfur atom in comparison with those observed for thiane **120**. Unfortunately this caused a partial overlap with the resonances due to the C-2 benzylic protons. The HOMCOR spectrum of salt **123** (Figure 52) showed that the multiplet at δ2.33 (H_5) was correlated with the signals at δ3.72. The latter signals were further characterized by a series of nOe experiments which are shown in Figure 53 and summarized in Figure 54. Sequential irradiation of the methyl at C-1 and axial methyl at

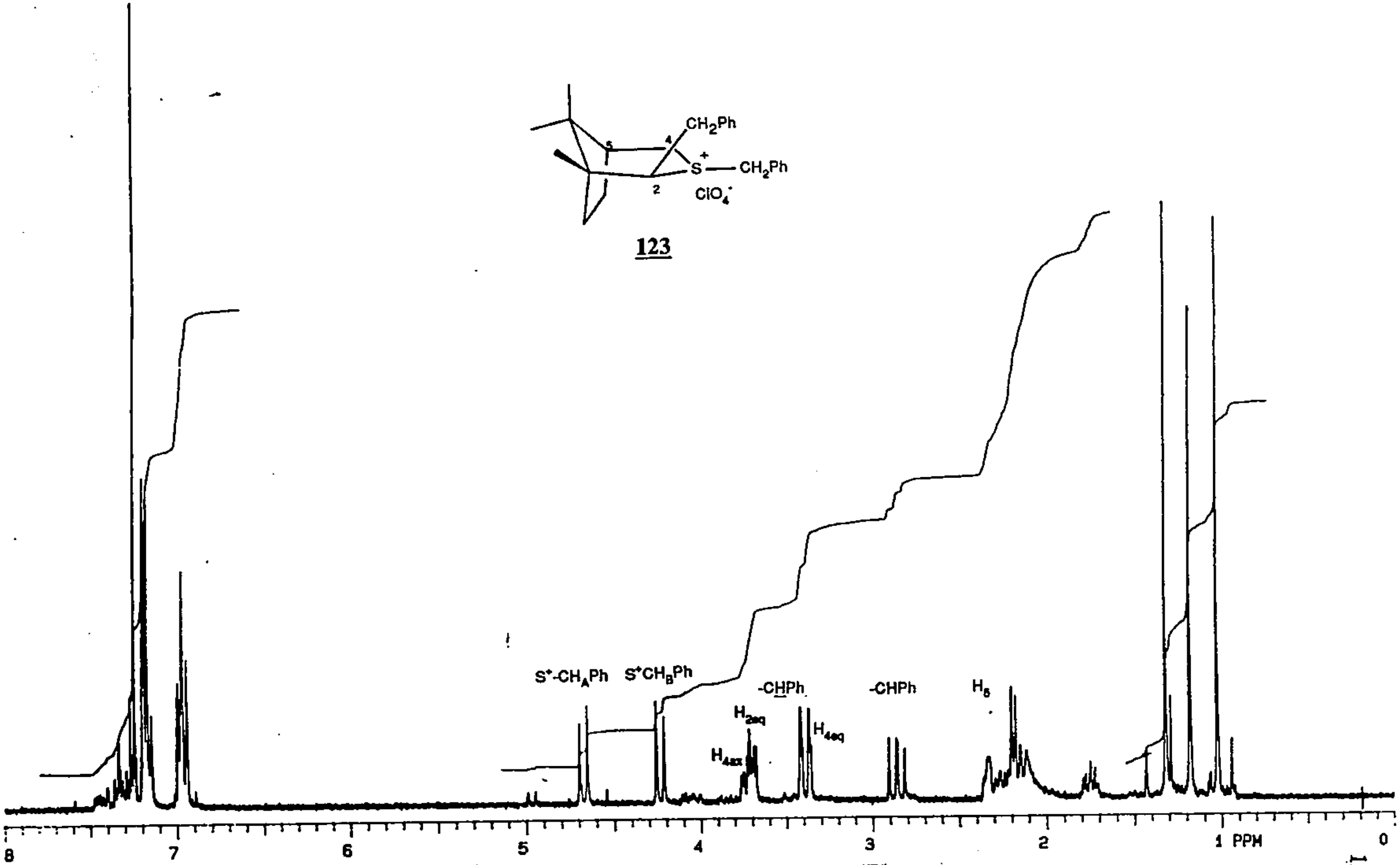


Figure 51. 300 MHz ^{1}H nmr spectrum of (1R,2S,3R,5S)-(-)-2,3-dibenzyl-1,8,8-trimethyl-3-thianiumbicyclo[3.2.1]octane perchlorate **123**.

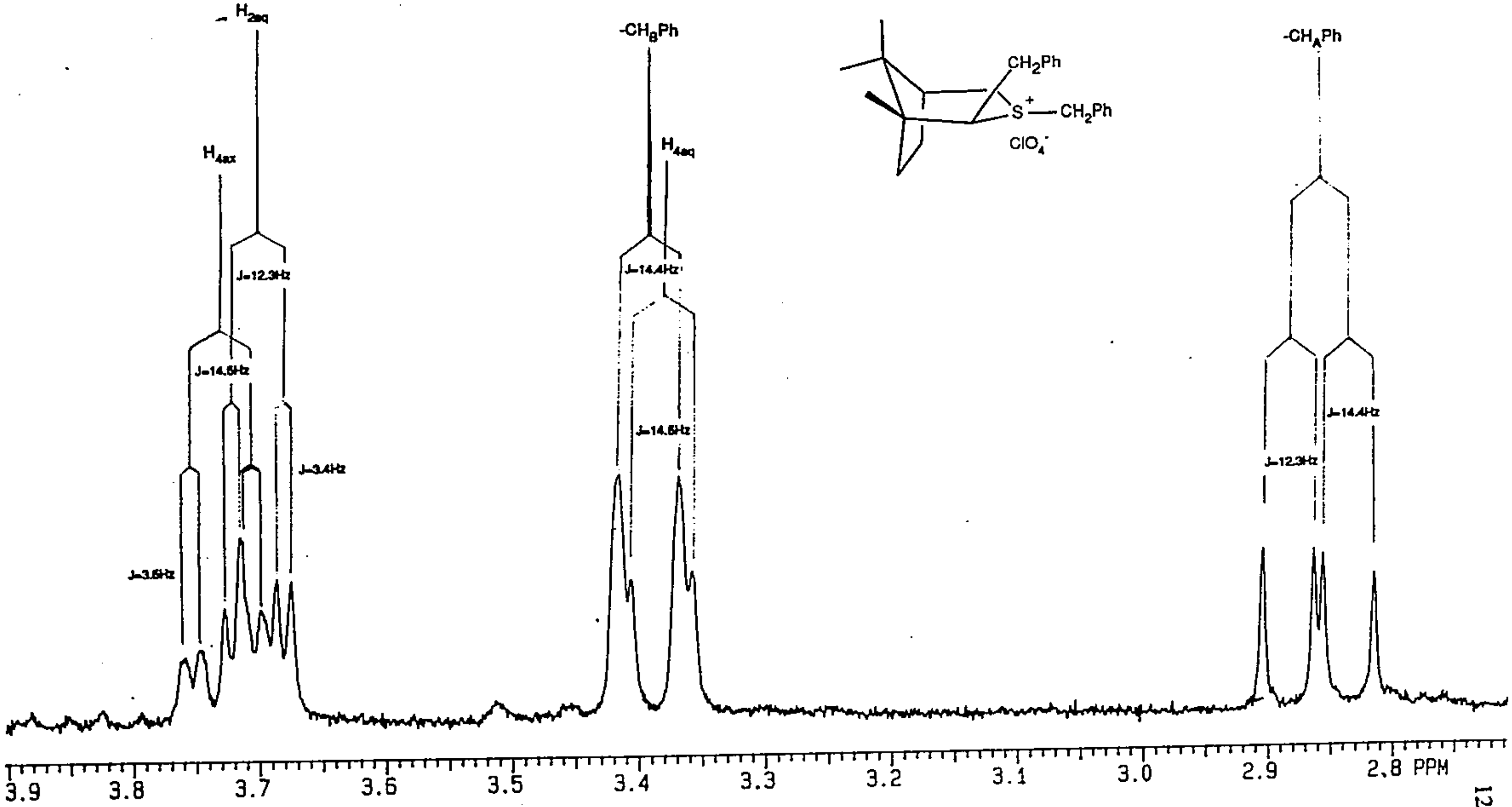


Figure 51A. Expansion of the δ2.7 to δ4.0 region of the ^{1}H nmr spectrum of <u>123</u> seen in Figure 51.

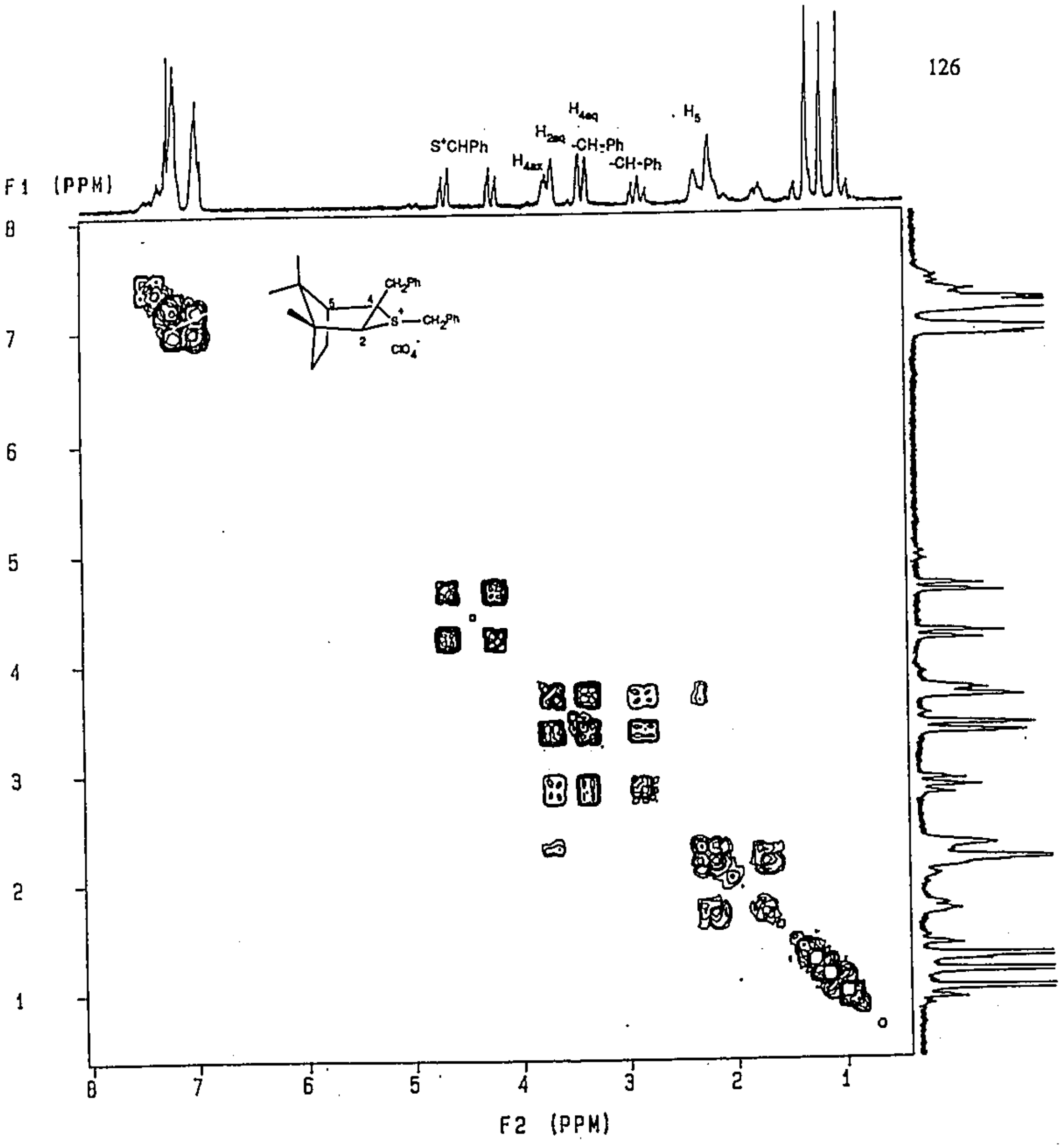


Figure 52. HOMCOR plot of (1R,2S,3R,5S)-(-)-2,3-dibenzyl-1,8,8-trimethyl-3-thianiumbicyclo-[3.2.1]octane perchlorate **<u>123</u>**.

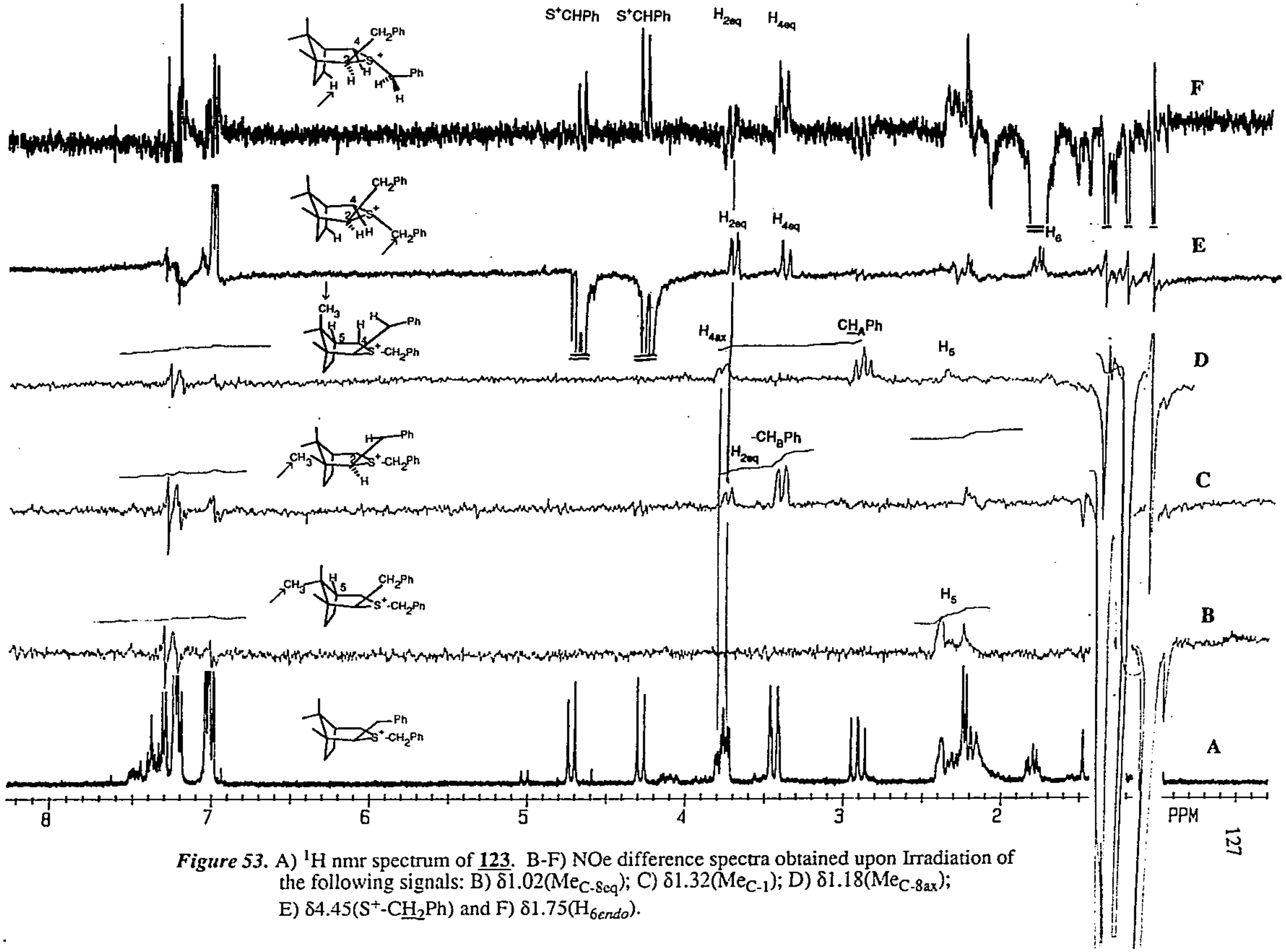


Figure 53. A) ^{1}H nmr spectrum of <u>123</u>. B-F) NOe difference spectra obtained upon Irradiation of the following signals: B) δ1.02(Me$_{C\text{-}8eq}$); C) δ1.32(Me$_{C\text{-}1}$); D) δ1.18(Me$_{C\text{-}8ax}$); E) δ4.45(S$^+$-C$\underline{H}_2$Ph) and F) δ1.75(H$_{6endo}$).

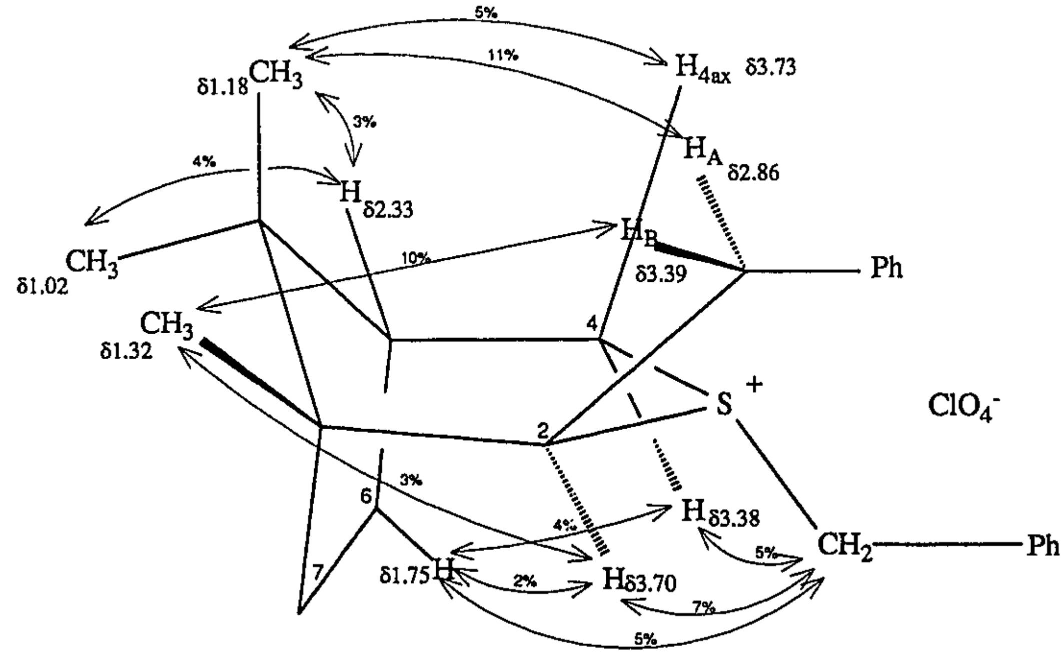


Figure 54. NOe's observed in <u>123</u> from irradiation of the S^+-$C\underline{H}_2Ph$, H_{6endo} and C-1 and C-8 methyl signals.

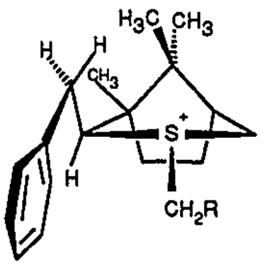
C-8 (Figure 54-C and 54-D respectively), clearly demonstrated that the upfield portion of these signals (δ3.70) arose from H_{2eq} while the downfield part (δ3.73) was due to H_{4ax}. The nOe experiments were also useful in the determination of the stereochemistry of the S-benzyl group in <u>123</u>. For instance, irradiation of the S-benzylic protons (Figure 53-E) produced nOe's with the following signals: δ3.70 (H_{2eq}), δ3.38 (H_{4eq}), δ2.15 and δ1.75. The latter two resonances corresponded to the *endo*-protons at C-7 and C-6. Fortunately, the multiplet at δ1.75 was isolated from the other resonances and its selective irradiation (Figure 53-F) resulted in a positive nOe with the signals at δ4.67 and δ4.23 for the S-benzylic protons. An nOe was also detected for H_{2eq} (δ3.70) and a stronger nOe for H_{4eq} (δ3.38). Thus S-alkylation had occurred preferentially *trans* to the C-2 benzyl group. This is in contrast with salt <u>106</u>, in which equatorial S-alkylation had occur preferentially.

The alkylation of thiane 120 with p-$ClC_6H_4CH_2I$ in dry ether in the presence of $AgClO_4$ afforded 124. The nmr spectrum of 124 was quite similar to that observed for 123 except for an aromatic *para* pattern.

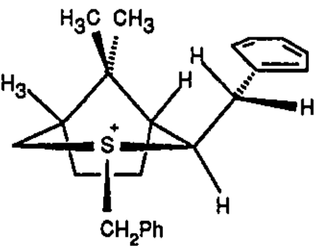
The alkylation of thiane 120 with $Me_3O^{+-}BF_4$ in CH_2Cl_2 afforded the S-methyl sulfonium salt 125. The ^1H nmr spectrum of crude 125 was similar to that observed for 123 except for the S-benzyl protons which were replaced by an S-methyl singlet at δ2.62. There was also an additional singlet at δ2.68 which accounted for 22% of the S-alkylated products.

S-Alkylation of thianes 121 and 122 were carried out under standard conditions ($PhCH_2Br/AgClO_4/Et_2O$) and gave the corresponding thianium salts 126 and 127, respectively.

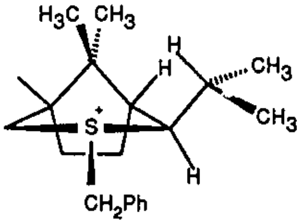
Table 7 summarizes some of the key torsional angles needed for conformational assessment of the 3-thianiumbicyclo[3.2.1]octane cation such as 123 and all the other sulfonium salts described in this chapter. Comparison of the dihedral angles for H_5-H_{4exo} or -H_{4endo} with those in Table 5 indicated that the thaiane ring exists in a chair form in the salt 106 or in a half chair form in the salts 123, 124 - 127. The torsional angles between the proton of the substituent and the adjacent proton at C-2 or C-4 confirm the conformations as depicted in 123A, 126A and 127A. Salts like 123A have the phenyl substituent parallel to the S^+-CH_2Ph bond while in cation 126A the phenyl substituent of the C-4 benzyl group lies above H_5. In 127A one of the methyl groups is parallel to the S^+-CH_2Ph bond while the other is pointing toward H_5.



123-A

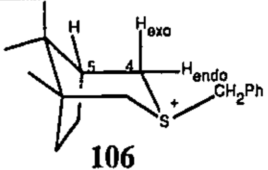
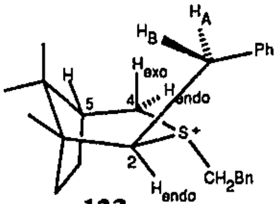
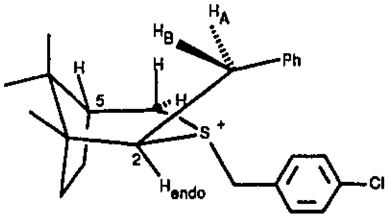
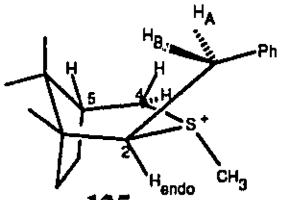
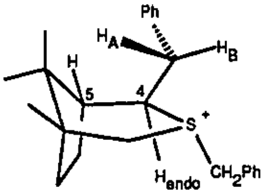
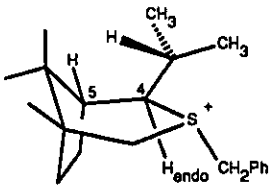


126-A



127-A

TABLE 7. Estimation of torsional angles in compounds consisting of the 3-thianiumbicyclo-[3.2.1]octane cation from ^1H nmr spectroscopy.

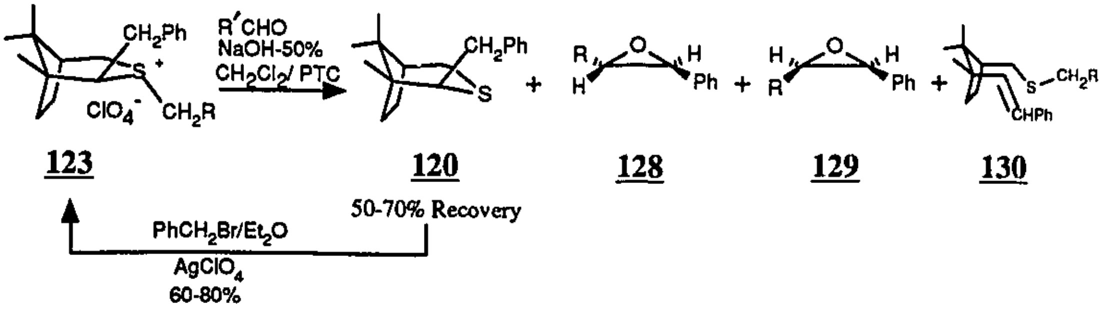
Compound	Vicinal coupling constant (Torsional angles)[a]			
	H_5-H_{4exo}	H_5-H_{4endo}	Other	
 **106**	0 Hz (84°)	3.9 Hz (46°)	——	——
 **123**	3.5 Hz	0 Hz	H_{2endo}-CH_APh 12.3 Hz (180°)	H_{2endo}-CH_BPh 3.4 Hz (50°)
 **124**	3.6 Hz (48°)	0 Hz (84°)	H_{2endo}-CH_APh 12.5 Hz (180°)	H_{2endo}-CH_BPh 2.5 Hz (55°)
 **125**	4.7 Hz (42°)	0 Hz (84°)	H_{2endo}-CH_APh 13.0 Hz (180°)	H_{2endo}-CH_BPh 3.5 Hz (50°)
 **126**	——	0 Hz (84°)	H_{4endo}-CH_APh 9.4 Hz (162°)	H_{4endo}-CH_BPh 7.1 Hz (20°)
 **127**	——	0 Hz (84°)	H_{4endo}-$C\underline{H}Me$ 11.4 Hz (180°)	

a) Deduction of dihedral angles from measured coupling constants was based on the Karplus correlation curve.[119]

3.5 Epoxidation Using Thiane <u>120</u> as Auxiliary.

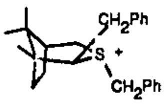
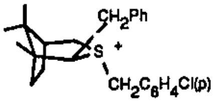
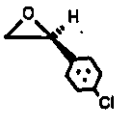
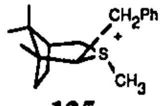
Despite the discouraging results obtained from the oxidation of thiane <u>120</u>, its catalytic properties were investigated under conditions identical to those for thiane <u>105</u> (page 72). Unfortunately, after three days at room temperature, the heterogeneous mixture of thiane <u>120</u>, KOH and benzyl bromide had not yielded any stilbene oxide. The presence of an additional *exo*-benzyl substituent had reduced considerably the nucleophilicity of the sulfur atom as compared with thiane <u>105</u>.

The unexpectedly high selectivity of the S-benzylation of <u>120</u> led to an exploration of the optically active epoxides syntheses by a reaction of the sulfur ylide derived from <u>123</u> with a variety of carbonyl compounds. These reactions were carried out initially under PTC (CH_2Cl_2/50%; NaOH/BTEAC) at 0°C for 3 hours then at room temperature for the same period of time (Scheme 24). The results are summarized in Table 8. The transfer of the benzylidene group from <u>123</u> to benzaldehyde gave a mixture of *trans* and *cis*-stilbene oxides <u>128a</u> and <u>129a</u> in a 4.8:1 ratio (46%), as well as <u>120</u> (57%) and 22% of a new material. The ^{1}H nmr of the latter compound showed the following resonances: three methyl singlets (δ0.66, δ0.85 and δ1.03); several multiplets from δ1.35-2.6; a methylene singlet (δ3.73, S-C$\underline{H}_2$Ph); two olefinic methine doublets (δ6.33 and δ6.42; d,



Scheme 24.

TABLE 8. Asymmetric epoxidation using thiane 120 as auxiliary.[a]

Sulfonium perchlorate	Aldehyde or ketone	Epoxides 128 (*trans*)			Epoxides 129 (*cis*)			Recovered thiane yield (%)	β-elimination (e.g. 130) yield (%)
			Yield (%)	% ee[b] (confign)[c]		Yield (%)	% ee[b] (confign)[c]		
 123	PhCHO	128a	38	>96 (S,S)	129a	8	meso	57	22
	4-MeC$_6$H$_4$CHO	128b	32	>96 (S,S)				70	15
	C$_6$H$_{11}$CHO	128c	9	84 (-)	129c	14	86 (+)	56	32
	Cyclohexanone	 131	<5	>96 (S)[98]				46	35
 124	CH$_2$O	 132	49	24 (S)[124]				84	10
 125	4-ClC$_6$H$_4$CHO	132	46	<4 (S)[124]				70	5

a Typically the reactions were carried out in CH$_2$Cl$_2$/NaOH 50%/ cat. BnEt$_3$NCl / CH$_2$Cl$_2$ - 0°C on 1-mmole scale.

b From integration of Eu(hfc)$_3$-shifted, proton NMR spectra at 300 MHz of chiral epoxides.

c Based on $[\alpha]_D$ measurements.[30,110]

J=16.5 Hz) and aromatic resonances (δ7.18-δ7.39). This material was identified as β-elimination product 130.

The *trans*-stilbene oxide 128a was separated from the *cis*-isomer and gave a rotation of -285° which clearly indicated a 2S,3S configuration.[30] The reported rotation values for the enantiomerically pure 2R,3R-*trans*-stilbene oxide are: $[\alpha]_D$=+384°

(c=0.502, EtOAc)[122], +342° (c=1.11, EtOH)[110] and +291° (c=0.056, acetone)[122]. Based on these standards, the optical purity of the 2S,3S-*trans*-stilbene oxide obtained from **123** should be as low as 74% or as high as 98% ee.

The enantiomeric excess for these reactions was more conveniently measured in the presence of small amounts of the chiral shift reagent tris[3-(heptafluoropropyl-hydroxymethylene)-(+)-camphorato] europium (III) [Eu(hfc)$_3$]. In the case of the *trans*-styrene oxide the ^{1}H nmr resonance due to the two epoxide protons was found to separate easily into two singlets. The ratio of the intensities of these peaks was taken as the ratio of the enantiomeric epoxides. The data obtained in this manner is shown in Figure 55. It can be seen from Figure 55-C that the 2R,3R enantiomer could not be detected by this analytical method. It was therefore concluded that the 2S,3S-*trans*-stilbene produced from **123** was at least 96% ee. Thus the correct rotation for the R,R isomer is close to $[\alpha]_D$=+291° (c=0.056, acetone)[122].

The reaction of **123** with *p*-methylbenzaldehyde gave only the *trans*-epoxide (**128b**, Table 8). It was not possible to detect any enantiomeric impurity in this product using the chiral shift reagent [Eu(hfc)$_3$] (Figure 56-C). A rotation of -289° indicated that this enantiomer had a 2S,3S configuration.[30,110]

Benzylidene transfer from **123** to cyclohexanecarboxaldehyde under the usual conditions afforded a mixture of *trans* and *cis*-epoxides **128c** and **129c** in low yield. The ^{1}H nmr spectra, in the presence of [Eu(hfc)$_3$], for the *trans*- and *cis*-epoxides respectively are shown in Figures 57 and 58. The optical purity of the epoxide was measured to be about 85% ee in both cases .

When cyclohexanone was used as the carbonyl component, a poor yield of spiro-2-cyclohexyl-3-phenyl oxirane **131** was obtained. This compound had a rotation of -37° (c= 0.16, CH_2Cl_2) which confirmed the 3S configuration.[98] The optical purity was determined to be ≥96% with [Eu(hfc)$_3$] (Figure 59).

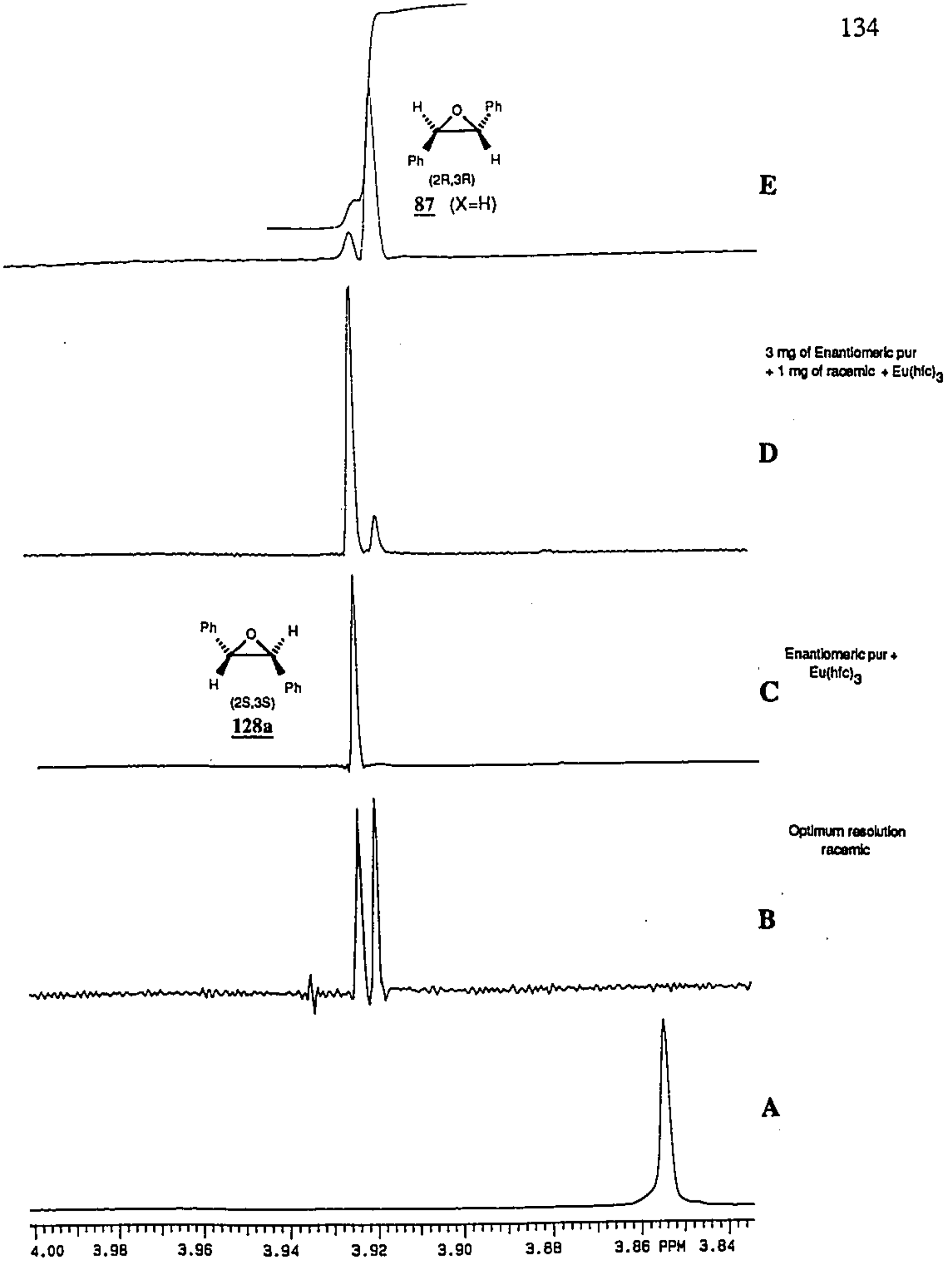


Figure 55. A) Expansion from δ3.84 to δ4.0 of the 300 MHz ^{1}H nmr spectrum of *trans*-stilbene oxide. B-E) Eu(hfc)$_3$-20Hz shifted, proton nmr spectra of racemic *trans*-stilbene oxide; C) *trans*-stilbene oxide produced by <u>123</u>; D) a mixture of 3 mg of C and 1 mg of B; E) Optically active *trans*-stilbene oxide produced by <u>127</u>.

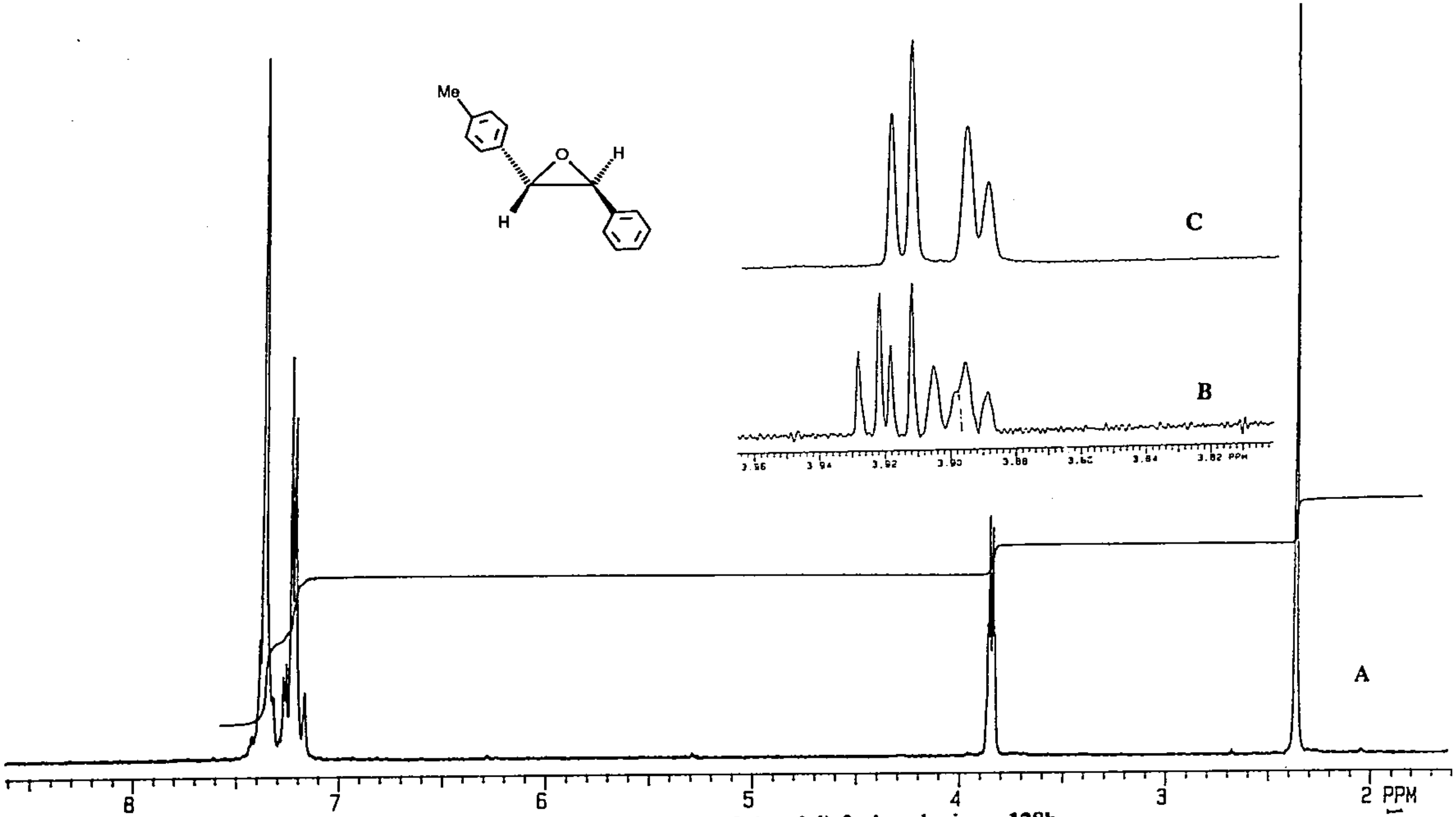


Figure 56. A) 200 MHz ^{1}H nmr spectrum of *trans*-2-(*p*-tolyl)-3-phenyloxirane **128b**.
B-C) Expansion between δ3.8 and δ3.96 of the Eu(hfc)$_3$-24 Hz shifted 300 MHz nmr spectra of: B) racemic **128b** and C) Optically active **128b** produced from **123**.

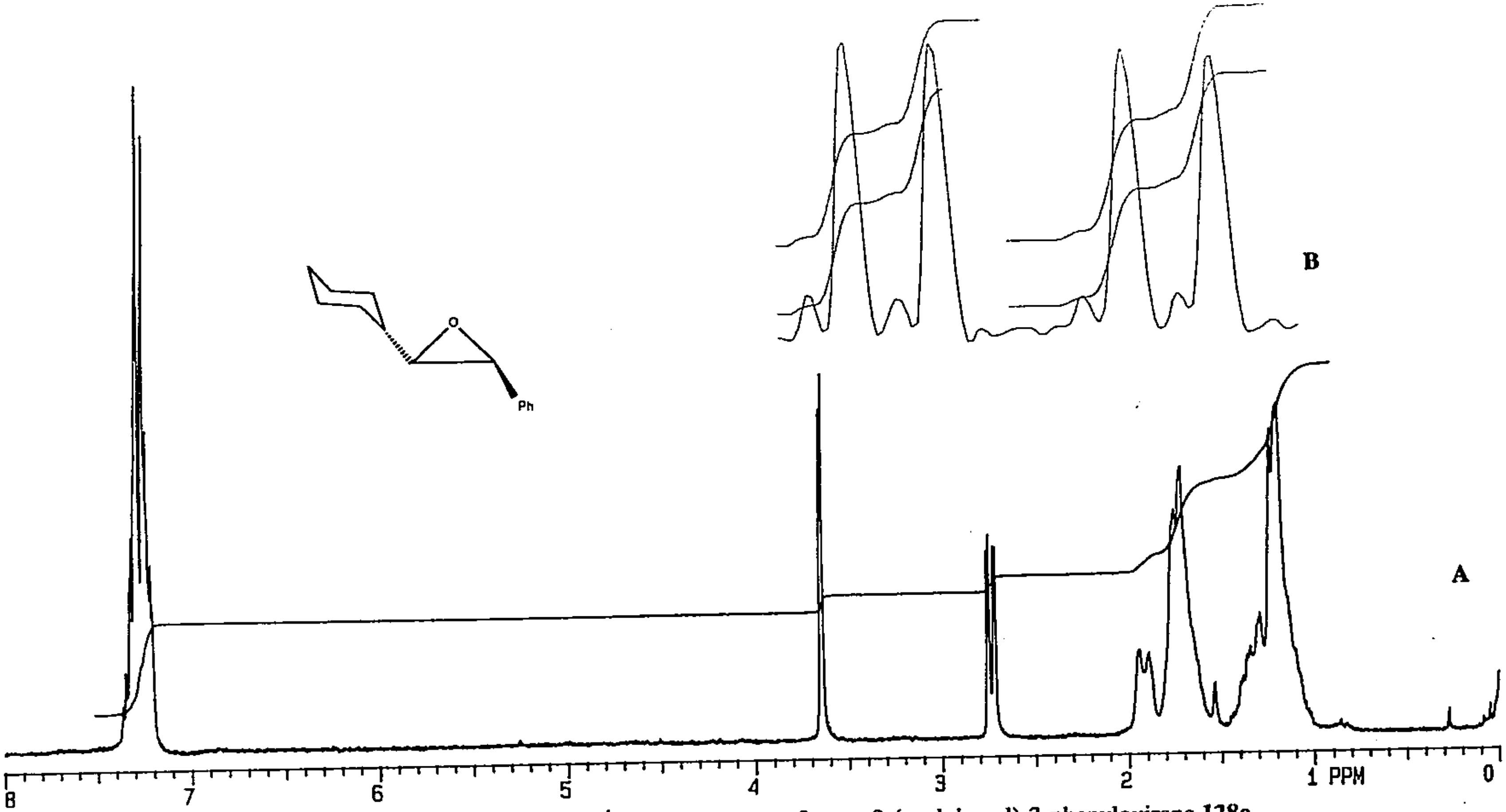


Figure 57. A) 200 MHz ^{1}H nmr spectrum of *trans*-2-(cyclohexyl)-3-phenyloxirane **128c**.
B) Expansion of the δ4.16 to δ4.3 region of the Eu(hfc)$_3$-55 Hz shifted 300 MHz nmr spectrum of optically active **128c** produced from **123**.

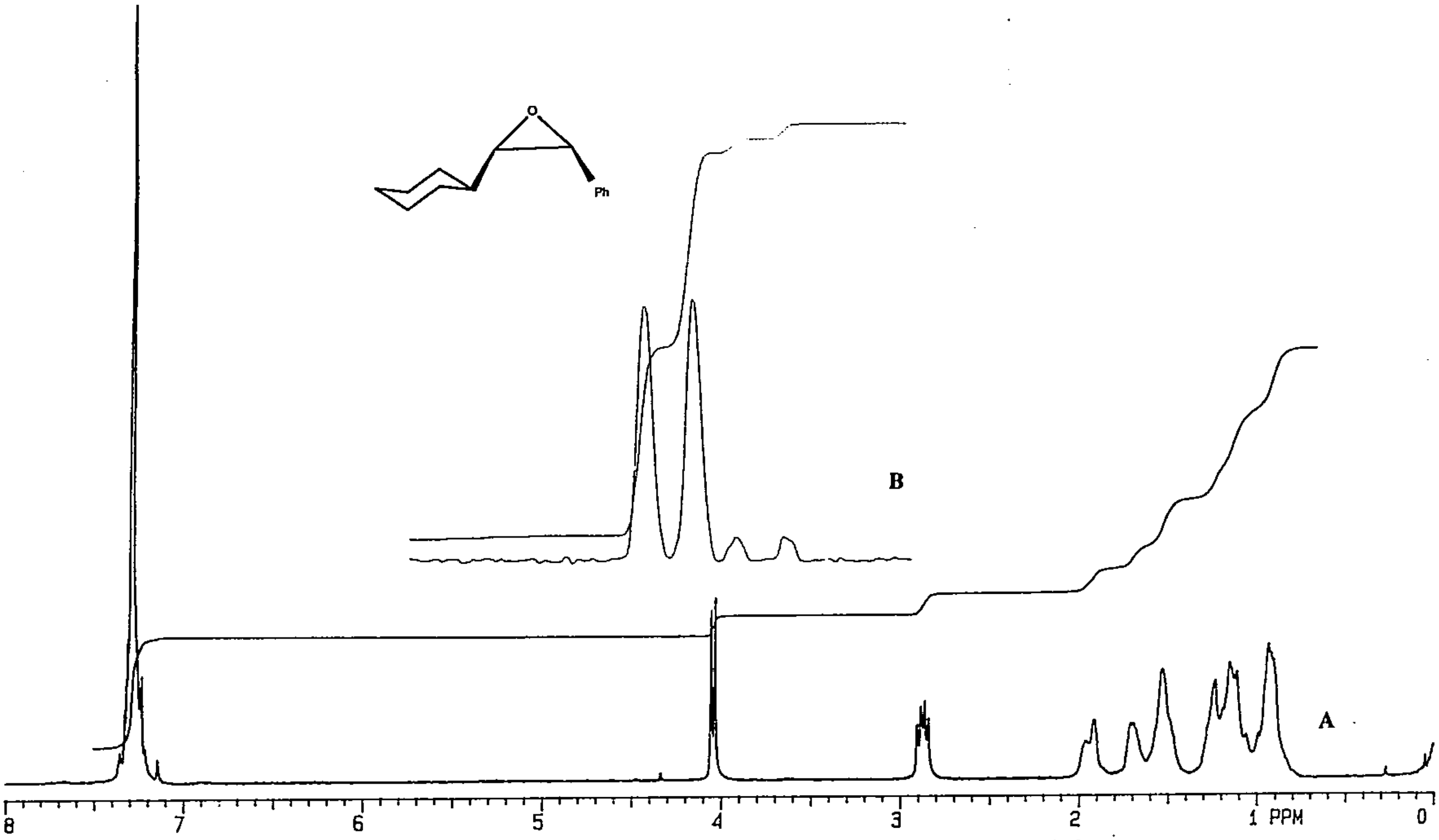


Figure 58. A) 200 MHz ^{1}H nmr spectrum of *cis*-2-(cyclohexyl)-3-phenyloxirane <u>**129c**</u>.
B) Expansion of the δ2.80 to δ2.83 area of the Eu(hfc)$_3$-60 Hz shifted 300 MHz nmr spectrum of optically active <u>**129c**</u> produced from <u>**123**</u>.

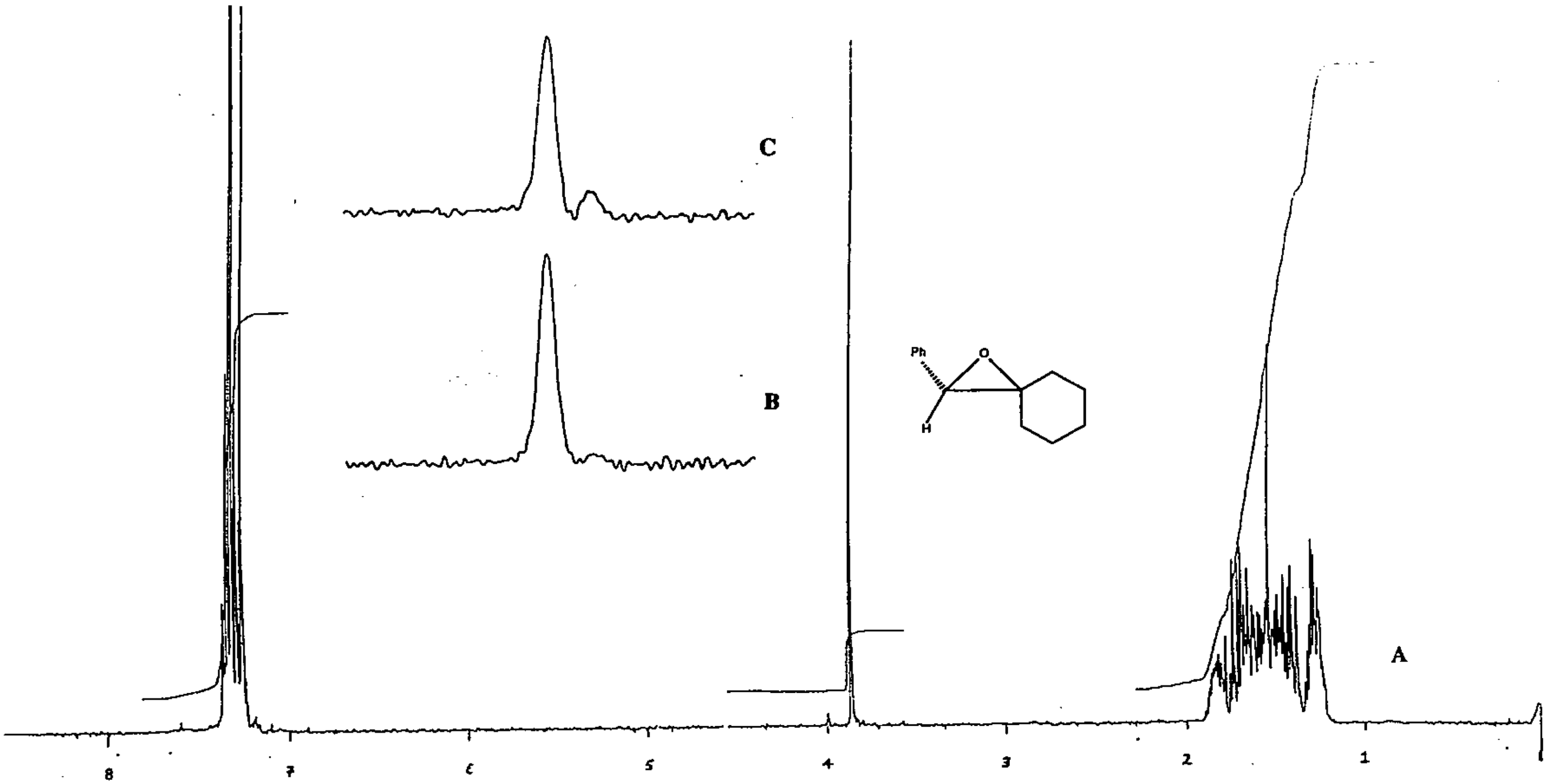


Figure 59. A) 300 MHz ^1H nmr spectrum of 2-phenyl-1-oxaspiro[2.5]octane <u>131</u>. B-C) Expansion from δ2.80 to δ2.83 of the Eu(hfc)$_3$-25 Hz shifted 300 MHz nmr spectra of: B) Optically active <u>131</u> produced from <u>123</u>; and C) a mixture of 2 mg of B) and 1 mg of racemic <u>131</u>.

Reaction of **123** with formaldehyde produced styrene oxide, but it was lost during manipulation due to its high volatility. The transfer of the *p*-chlorobenzylidene group from **124** to formaldehyde gave the *p*-chlorostyrene oxide **132** in 49% yield. The Eu(hfc)$_3$ shifted ^{1}H nmr spectrum of **132**, (Figure 60), indicated that the optical purity of this material was 24%. Groves and Meyers[123], reported a greater Eu(hfc)$_3$ induced shift for the benzylic hydrogen of (+)-4-chlorostyrene oxide than for the corresponding hydrogen in the (-)-isomer (see Figure 60-C). The former isomer was later reported to have an (R) absolute configuration.[124] Based on these data the S-enantiomer of **132** was produced in excess (Figures 60-**B** and 60-**C**).

Transfer of the methylene group from the ylide derived from **125** to *p*-chlorobenzaldehyde afforded racemic **132**. This result is consistent with the lack of chiral induction reported by Trost during the transfer of a methylene group to benzaldehyde from optically active sulfonium salts of type **3** (equation 8).

3.6 Epoxidation Using Thianes 121 and 122 as Auxiliaries.

Having on hand an enantioselective synthesis of the *trans*-2S,3S-stilbene oxides *via* thiane **120**, the use of thianes such as **121** and **122** which have a substituent at C-4, offers the possibility of generating the *trans*-2R,3R-stilbene oxides. The transfer of the benzylidene group from **126** to benzaldehyde gave the (2R,3R)-enantiomer of *trans*-stilbene oxide but with only 34% optical purity (see Table 9). No other experiment was carried out using this auxiliary.

Benzylidene transfer from **127** to benzaldehyde gave the *trans*-epoxide **128a**, which had a (2R,3R)-configuration. The optical purity was determined to be 74% ee (Figure 55-E). When *p*-chlorobenzaldehyde was used as the carbonyl component, a mixture of *trans* and *cis*-epoxides **128d** and **129d** in a 2.4:1 ratio were obtained in 55% yield. Both epoxides were shown to be formed with about 65% e.e. (Table 9). The

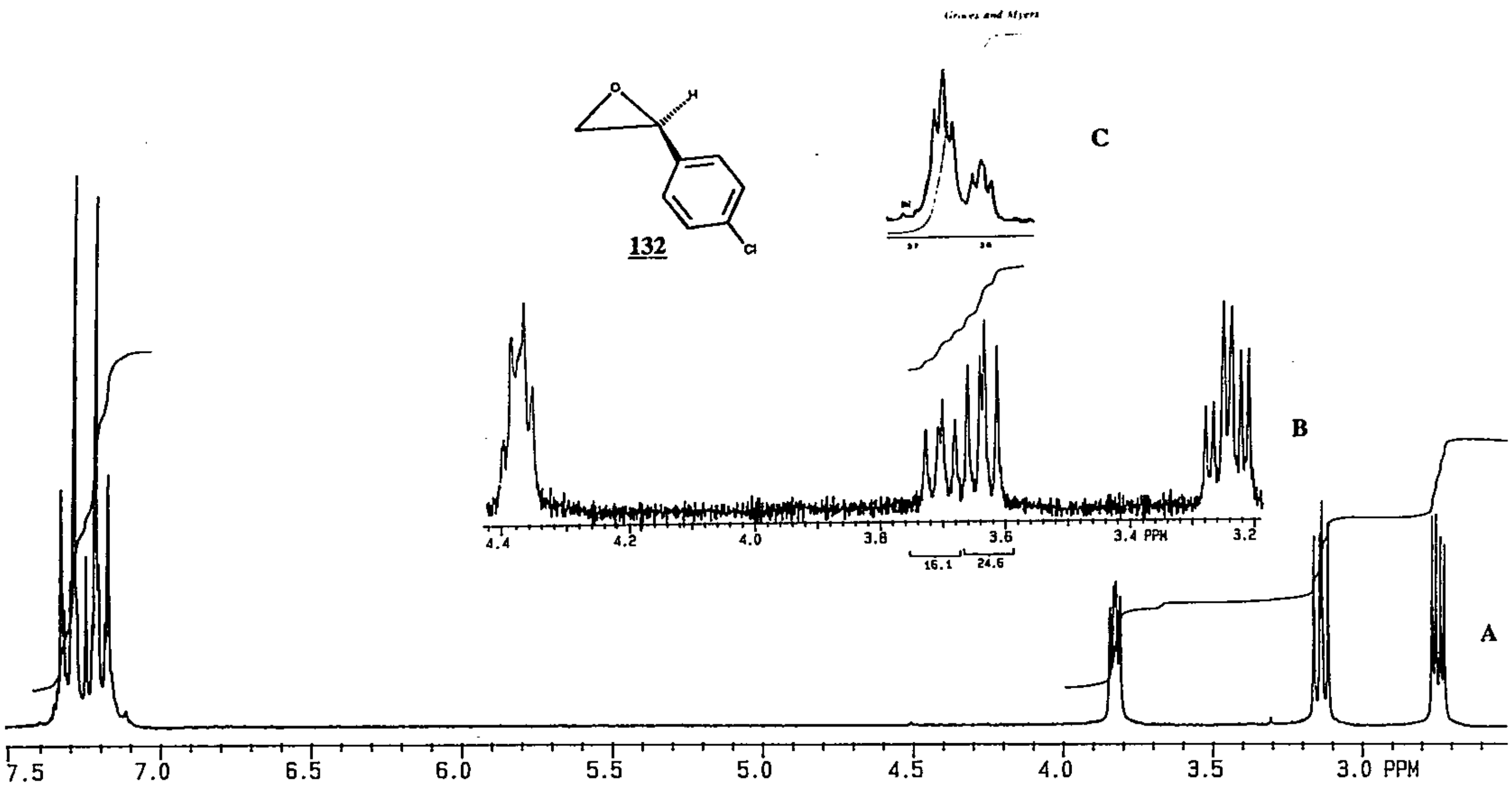
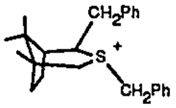
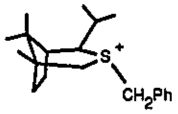


Figure 60. A) 200 MHz ^{1}H nmr of 4-chlorostyrene oxide 132. B) Expansion of the δ3.2 to δ4.4 region of the Eu(hfc)$_3$-100 Hz shifted 200 MHz nmr spectrum of optically active 132 produced from 123. C) Reproduction of the Eu(hfc)$_3$-shifted, proton nmr spectrum at 350 MHz of optically active (R)-(+)-*p*-chlorostyrene oxide as reported by Groves and Meyers.[123,124]

TABLE 9. Asymmetric epoxidation using thiane 121 and 122 as auxiliaries.[a]

Sulfonium perchlorate	Aldehyde or ketone	Epoxides 128 (*trans*) Yield (%)	Epoxides 128 (*trans*) % ee[b] (confign)[c]	Epoxides 129 (*cis*) Yield (%)	Epoxides 129 (*cis*) % ee[b] (confign)[c]	Recovered thiane Yield (%)	β-elimination (e.g. 130) Yield (%)
 126	C_6H_5CHO	87 (X=H) 45	34 (R,R)	129a 12	*meso*	66	-
 127	C_6H_5CHO	87 (X=H) 42	73 (R,R)	129c 20	*meso*	58	-
	4-ClC_6H_4CHO	87 (X=Cl) 52	63 (R,R)	129d 25	66 (-)	68	-

a Typically the reactions were carried out in CH_2Cl_2/NaOH 50%/ cat. $BnEt_3NCl$ / CH_2Cl_2 - 0°C on a 1-mmol scale.

b From the integration of $Eu(hfc)_3$-shifted, proton NMR spectra of the chiral epoxides at 300 MHz.

c Based on $[\alpha]_D$ measurements.[30,110]

enantiomeric purity of the *cis* isomer was determined by shift nmr (Figure 61) and that of the *trans*-isomer, analogous to 128a, by optical rotation[122]. No β-elimination products were detected in the reaction involving these auxiliaries.

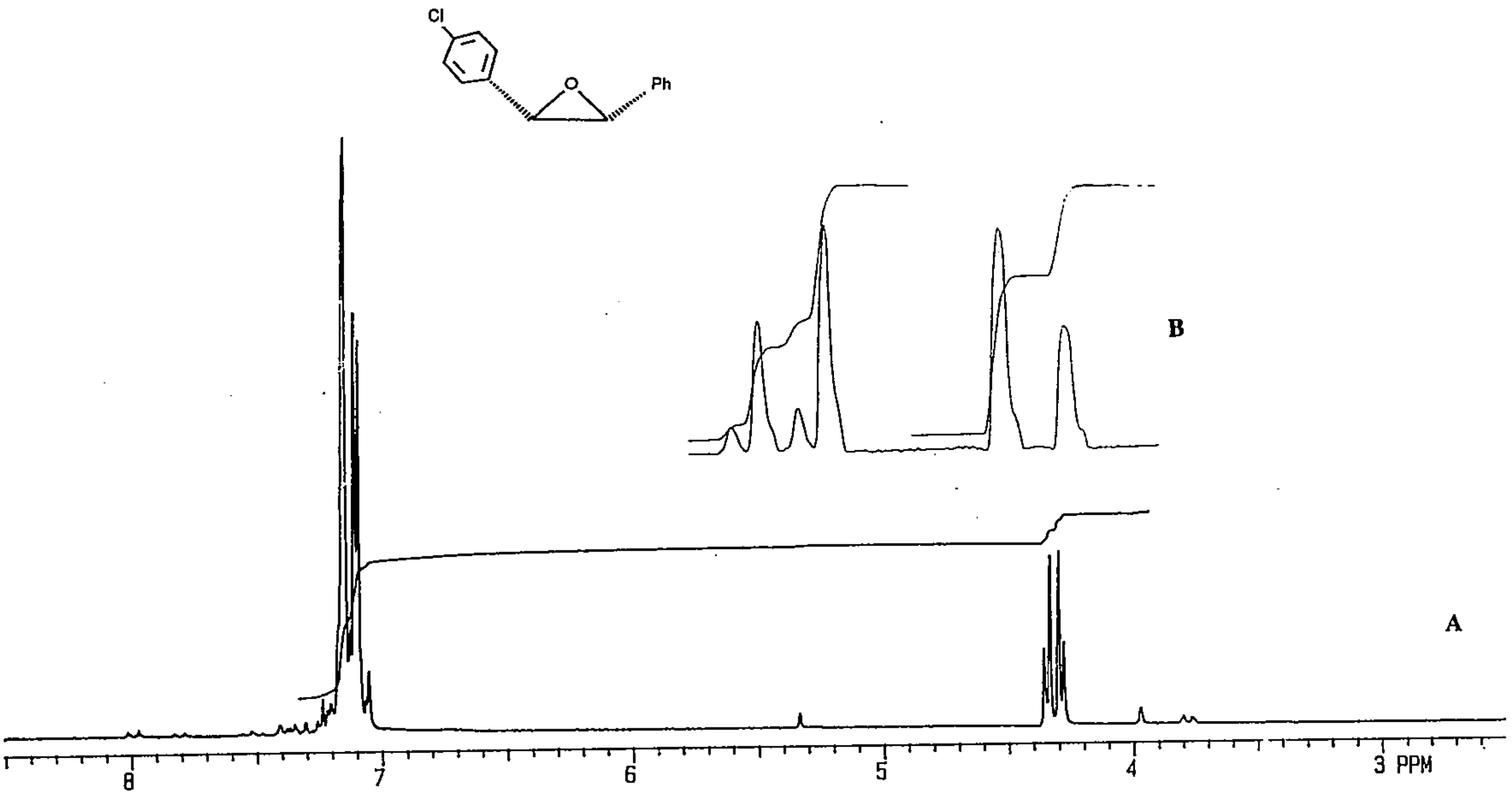


Figure 61. A) 200 MHz ^{1}H nmr of *cis*(-)-2-(*p*-chlorophenyl)-3-phenyl oxirane **129d**.
B) Expansion from δ4.35 to δ4.46 of the Eu(hfc)$_3$-23 Hz shifted 300 MHz nmr spectrum of optically active **129d** generated *via* **127**.

IV CHAPTER 3:

4. DISCUSSION

4.1 Camphoric Acid Derived Auxiliaries, General Comments.

The results obtained from salt **123** bearing an α-benzyl substituent produced *trans*-(2S,3S)-stilbene oxides with an enantiomeric purity eight times greater than the one produced *via* salt **106** whose asymmetry results from the methyl group at the β carbon (C-1). The stilbene oxides generated from salt **123** have the opposite absolute configuration (i.e. 2R,3R) as that from salt **106**, yet both auxiliaries have substituents on the same side of the thianiumbicyclo[3.2.1]octane ring.

4.1.1 Proposed Mechanism for Asymmetric Induction *via* Camphoric Acid Derived Sulfur Ylides.

A serious difficulty arises with the rationalization of the asymmetry observed in the epoxidation reaction. The structure of unstabilized sulfur ylides and the detailed transition states for epoxide formation are not precisely known. Nonetheless, on the basis of the chemistry described in Section 1 a model may be put forward. All models presented in this section are in agreement with the following criteria;

1) The preferred conformation of the auxiliary in the sulfonium salt is assumed to be retained in the ylide. The evidence discussed in Sections 1.3 and 1.8 support the hypothesis that there is negligible change in sulfur bonding and geometry for the auxiliary in going from the sulfonium salt to the ylide.

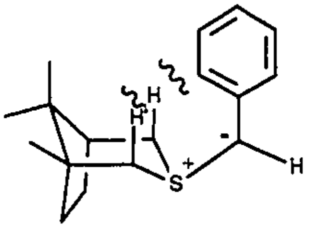
2) The geometry of the ylidic carbanion is assumed to be a quasi-planar in the case of S-benzyl ylides. This allows for delocalization of the negative charge on the ylidic carbon throughout the aromatic system (Section 1.8). Pyramidal geometry is assigned to the sulfur atom in both the sulfonium salt and the ylide (page 27).

3) The configuration around the sulfur and the ylide carbanion σ bond is

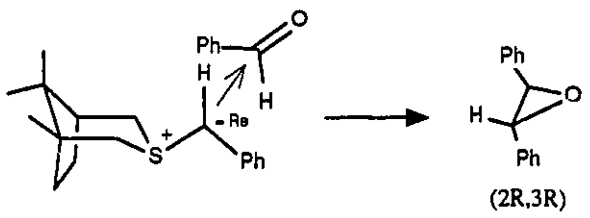
fixed in such a way as to allow orthogonality between the lone pair on both the sulfur and carbon atoms (Section 1.5, Figure 1, **31**).

4) The mechanism of the addition of the ylide to the carbonyl group is considered to involve a head-to-tail approach in which the oxygen and sulfur atoms orient themselves close to anti-periplanarity. This step is assumed to be non-reversible for allyl, benzyl and non-stabilized sulfur ylides (Section 1.10).

It is possible that deprotonation of benzylthiolanium salt **106** would generate two distinct ylide conformations around the S^+-C^- bond: **133A** and **133B**. These conformers do not directly equilibrate by rotation around the ylide σ bond. The barrier to rotation in the simple ylide H_2S^{+}-$^{-}CH_2$ was calculated to be between 10 and 20 Kcal/mole.[103] Conformational change under reversible ylide generation conditions is therefore more likely *via* a protonation and deprotonation sequence. Conformers **133B** should predominate over **133A** since the phenyl ring on the ylide interacts sterically with the axial hydrogens at C-2 and C-4. In conformation **133B** the methyl at C-1 partially obstructs the *Si*-face of the ylide resulting in a small preference for electrophilic attack on the *Re*-face. Such a mode of addition would produce the (2R,3R)-product in low ee.

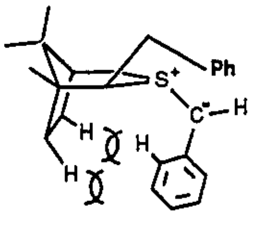


133A

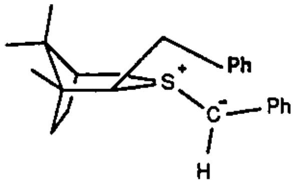


133B

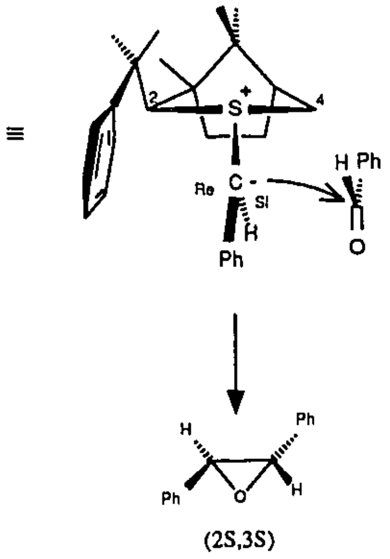
In the case of salt **123**, the nOe clearly confirmed that S-benzylation had occurred *trans* to the 2-benzyl group. The torsional angles for this compound as determined by proton nmr indicated a half-chair conformation such as 123A. Assuming that the conformational preference for the 2-benzyl-3-thianiumbicyclo[3.2.1]octane part of 123A is preserved, two conformations 134A and 134B are possible for the ylide. The latter



134A

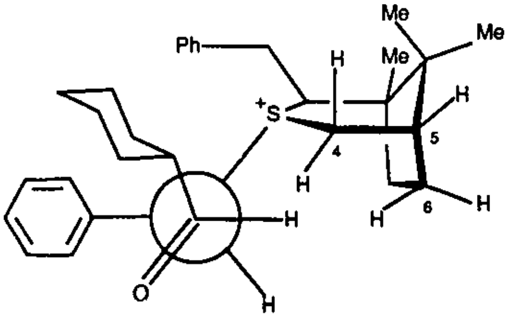


134B



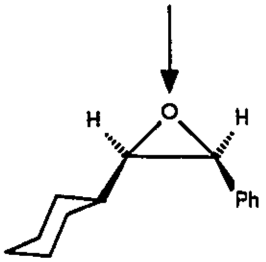
conformation should be strongly favored since the aryl group which is in the same plane as the thiane ring has severe steric interactions with the *endo* hydrogens on the two-carbon bridge. Electrophilic attack on ylide 134B by the carbonyl group is expected to occur preferentially from the *Si*-face of the ylide (i.e., adjacent to C-4). This mode of addition generates an S configuration for the "carbanion fragment" of the epoxides. The stereochemistry of the second center is dependent on the face presented by the carbonyl group to the ylide carbon and is reflected in the ratio of *trans* to *cis* epoxides. The hypothesis that facial selectivity with respect to the ylide carbon controls the stereochemical outcome infers that all transfer from 134B will result in epoxides having an excess of (S) chirality at the benzylic carbon. If isomeric chiral epoxides are produced for a given carbonyl reagent, the optical purity of these epoxides should be comparable.

The results shown in Table 8 are in agreement with these predictions. This is best illustrated in the reaction of cyclohexanecarboxaldehyde with ylide **134B** (Table 8) which verified that the *trans*- and *cis*-epoxides **128c** and **129c** had the same optical purity. Interestingly, the 40:60 *trans*/*cis* product mixture for **128c** and **129c** is consistent with that obtained from the reaction between 2-methylpropanal and ylide **99** (Table 4, entry 7, page 62). The steric interaction between the phenyl and cyclohexyl substituents in **135A** seems to be comparable to those between the cyclohexyl and the C-4, C-5 and C-6 hydrogens (**135B**).

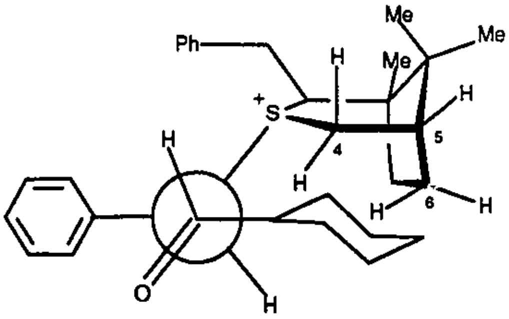


135A

(addition to the *Si*-face)
of the aldehyde

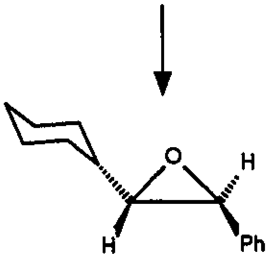


cis-(2R,3R)-**129c**



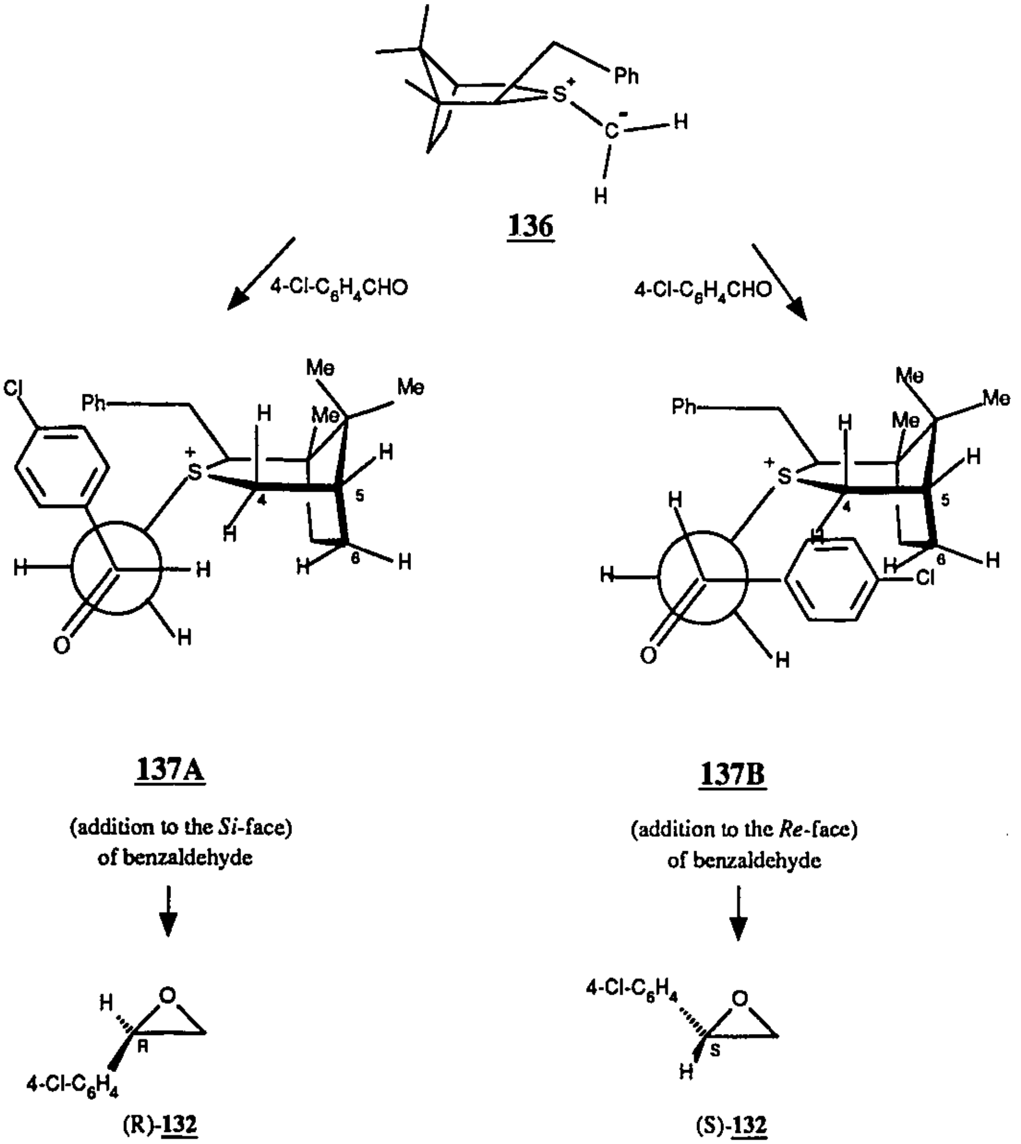
135B

(addition to the *Re*-face)
of the aldehyde



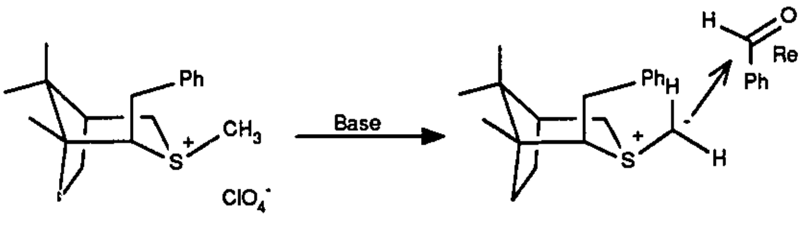
trans-(2S,3S)-**128c**

When smaller carbonyl compounds such as cyclohexancarboxaldehyde and formaldehyde instead of aromatic aldehydes are reacted with ylide **134B**, a net decrease in the enantiomeric purity of the final product was observed. One must concluded that the C-2 benzyl substituent did not provide sufficient steric bulk to preclude completely reaction on the *Re*-face of ylide. The transfer of methylene from ylide **136** to *p*-chlorobenzaldehyde, giving *p*-chlorostyrene oxide **132**, without significant optical induction was somewhat surprising. Inspection of molecular models of **137A** and **137B** showed that ylide **136** should add preferentially *via* **137A** rather than **137B** since the aryl ring on the aldehyde should have somesteric interactions with the hydrogens on C-4, C-5 and C-6 of the ylide **136**. This mode of addition, to the *Si*-face of the aldehyde should



give R-styrene oxide in excess.

The disappointing result may be explained in the following manner. The methylation of **120**, unlike its benzylation produced a side product (≅22%) which could be attributed to the axial S-Me isomer **138**. The corresponding methylene ylide **139** would

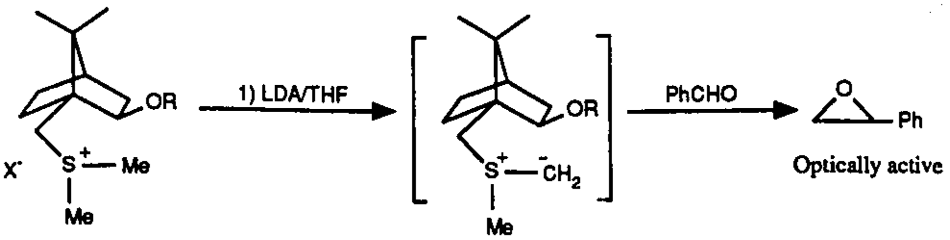


138 **139**

preferentially add to the *Re*-face of the aldehyde. This mode of addition is in opposition to the one in **137A**. There is also the possibility that these ylides undergo stereomutation at sulfur under the reaction conditions (Section 1.9). In such a case, a random mixture of ylides **136** and **139** would be generated at any given time. Other optically active methylene ylides such as sulfoximine **2** (equation 7) and the ylide derived from

2 (7)

dimethylsulfonium salt **140** (equation 46) have been reported to be successful in this

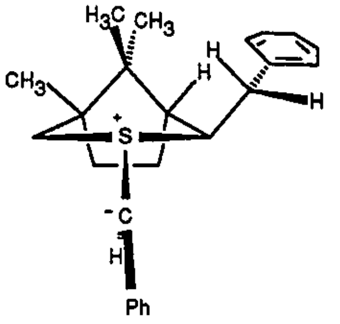


(46)

140 **A** R=H, X=BF_4^-
B R=Me, X=I^-

reaction. Unfortunately, the optical purity of the styrene oxide produced in equation 46 had not been mentioned. Paradoxically, the Trost result (equation 8) disagrees with those above.

The excess of *trans*-(2R,3R)-stilbene oxide obtained from the ylide derived from sulfonium salt **126** and **127** is due to the shielding of the *Si*-face of the ylide carbon by either the benzyl of isopropyl group. The low asymmetric induction observed for transfer of the benzyl group is due to inadequate blocking of the *Si*-face of the ylide by the C-4 benzyl group. The conformational preference of the C-4 benzyl group in ylide **141** is probably similar to that in salt **126A**. The greater mobility of the C-4 benzyl group in **141** as compared to **134B** is due to the absence of a methyl group at C-5 in the former.



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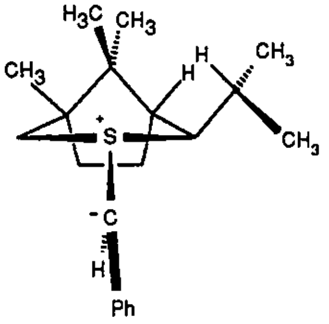


142

Ylide structure **142**, which has one of the methyl groups of the C-4 isopropyl substituent blocking the *Si*-face of the ylide carbon, should be generated from the deprotonation of salt **127A**. Consequently the enantiomeric purity of the *trans*-(2R,3R)-stilbene oxide obtained for ylide **142** was essentially two fold of that produced *via* ylide **141**.

4.2 C_2-Symmetric Thiolane Auxiliaries, General Comments.

The results obtained with ylide **86**, which produced trans-(2R,3R)-stilbene oxides with enantiomeric purity four times that obtained *via* ylide **8** clearly emphasized the importance of having the substituents responsible for the asymmetric induction on the carbon α to the sulfur atom. Surprisingly, the stilbene oxides obtained from ylide **86** have the same absolute configuration (R,R) as those from the ylide **8** (Scheme 3). It was expected that the epoxides from these two ylides would have opposite absolute configuration due to the change in the local sense of chirality between the substituents at C_2-(S) and C_5-(S) in ylide **86** and those at C-3 (R) and C-4 (R) in ylide **8**. It can therefore be concluded that in ylide **86**, the asymmetric induction caused by substituent at C-3 (S) and C-4 (S) is opposite to that exerted by those at C-2 (S) and C-5 (S).

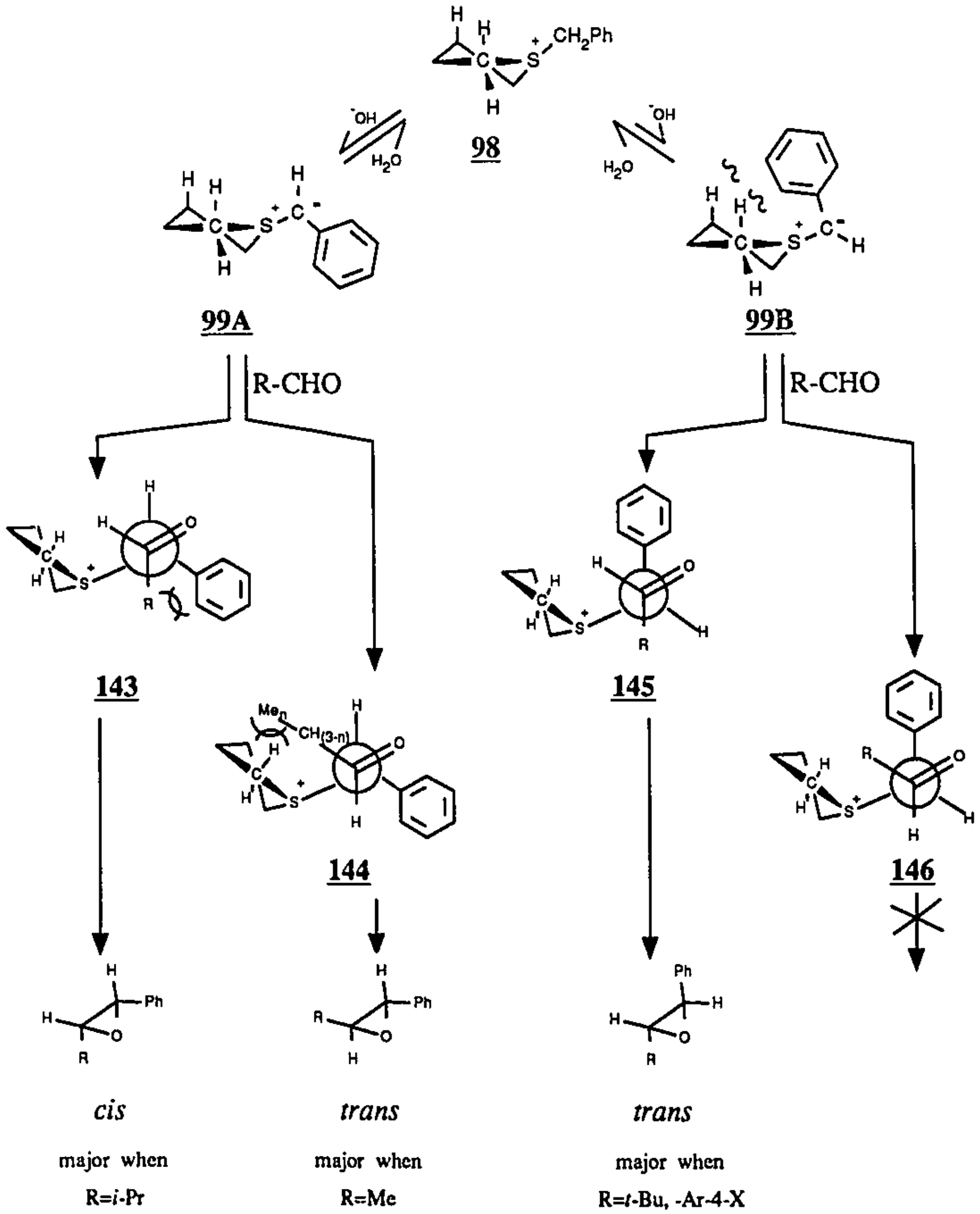
The potential adverse effect of the substituents at C-3 and C-4 on the degree of asymmetric induction obtained with the ylide **86** could be eliminated either by inversion of configuration at these position to produce an all *anti*-substituted C_2 symmetric thiolane, or by removal of the substituents at C_3 and C_4. The first option offers the advantage of a readily available starting material (iditol). However as experienced in preparation of sulfonium salt **85**, the presence of oxygen containing substituents lowers the nucleophilicity of the thiolane sulfur and decreases the yield of sulfonium salt. The alternative option avoids the extra oxygen functionality but suffers from the fact that there is no known readily available optically pure starting material. Nonetheless C-2 and C-5 disubstituted C_2-symmetric thiolane **78** was prepared. Table 3 shows clearly that the ylide, **93**, derived from **78**, gave epoxides having the same absolute configuration and similar optical purities as those isolated from the tetra-substituted ylide **86**. Thus, while the removal of the C-3 and C-4 oxygen containing substituents on ylide **86** improved the alkylation and recovery of thiolane **78** (Scheme 16), presumably due to the elimination of side reactions, it did not affect the amount of enantiomeric excess obtained in the stilbene oxides, **87**. The hypothesis that substituents at C-3 and C-4 had an adverse effect on the degree of asymmetric induction in the reactions of the ylide **86** was not supported by this data. The role played by the substituents at C-3 and C-4 relative to those at C-2 and C-5 in ylide **78** is therefore judged to be small.

The *trans/cis* ratio of epoxides obtained from S-benzylthiolanium ylide **99** and aliphatic aldehydes (Table 4, page 62) showed an apparently contradictory trend. For the series $R_1RCHCHO$ the amount of *cis*-epoxide increased from 31% for R_1=R_2=H to 39% *cis* for R_1=CH_3, R=H to 56% for R_1=R_2=CH_3 suggesting that increased size of the alkyl group favoured the formation of *cis*-epoxides. However pivaldehyde gave only *trans*-epoxide. Aromatic aldehydes also gave greater than 90% *trans*-stilbene oxides.

From these results one may ask why is there such an inconsistency in the behavior of ylide **99**? Also, how could two ylides, **8** and **93**, with substituents at positions 2 and 5 and 3,4 respectively, having opposite local senses of chirality provide epoxides with the same absolute configuration?

4.2.1 Proposed Mechanism for Asymmetric Induction *via* C_2 Symmetric Thiolanium Ylides.

These results can be rationalized in the following manner. Deprotonation of 3-benzyl-3-thianiumbicyclo[3.2.1]octane perchlorate salt **98** should generate two ylide structures in two distinct conformations around the ylidic S^+-C^- bond: **99A** and **99B**. Conformer **99A**, which has the phenyl group located syn periplanar to the sulfur lone pair, has no steric interactions with the thiolane ring and should predominate over conformer **99B**. In the latter conformation the phenyl ring is antiperiplanar with the sulfur lone pair and is positioned over the thiolane ring. In such an orientation, non-bonded interactions take place between the aromatic moiety and the quasi-axial hydrogens at C-2 and C-4 of the thiolane ring. The two possible approaches by the aldehydes for each of these ylide conformers are depicted in the Newman projections **143**, **144**, **145** and **146** (Scheme 25). Addition mode **143** has one gauche interaction between the phenyl group of the ylide and

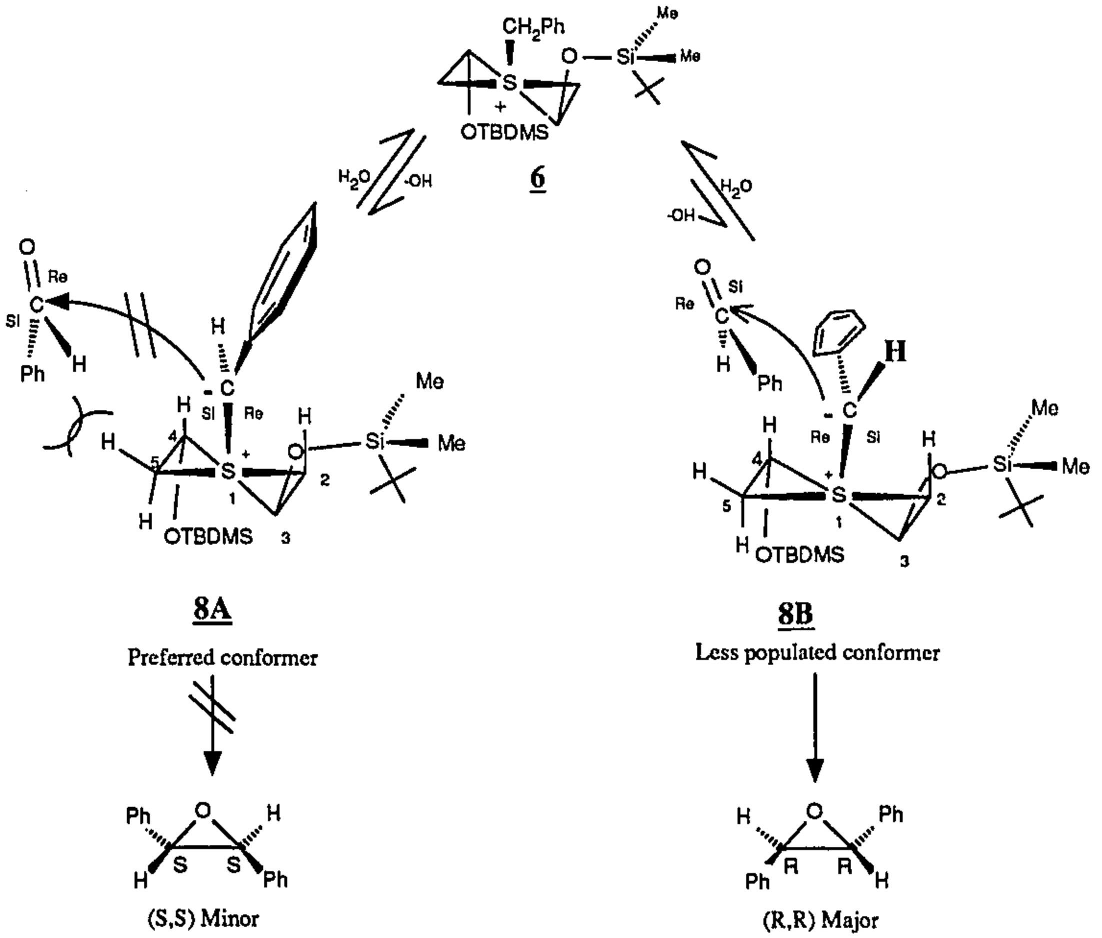

98
99A
99B
R-CHO
R-CHO
143
144
145
146
cis
major when
R=*i*-Pr
trans
major when
R=Me
trans
major when
R=*t*-Bu, -Ar-4-X

Scheme 25.

the substituent of the aldehyde, while addition 144 has a gauche interaction between the aldehyde substituents and the side of the thiolanium cation (CH_2). It would seem that the latter interaction increases in importance over 143 as the steric demand of the aldehyde substituent increases and as a result, the *cis*-epoxide is eventually produced in major amounts (Table 4, entry 5 to 7). This effect could be viewed as the result of orthogonality between the ylide carbon fragment and the thiolanium cation coupled with restricted rotation around the connective σ-bond of these two moieties. The overall net effect in 144 is that each side of the thiolanium cation is on a collision course with the substituent of the aldehyde, provided that there is a β-substituent. Thus with acetaldehyde, the only significant interaction in 144 is the gauche interaction of the α-methyl with the sulfur atom. In the case of propanal and 2-methylpropanal, in addition to the above gauche interaction, there is a secondary interaction between the methylene side of the thiolanium ring and one or two β-methyl substituent according to the aldehyde used. The interaction between the phenyl ring and the aldehyde substituent in 143 is not believed to increase to the same extend as for 144 with the increase in the steric bulk of the substituent. The phenyl group adopts a favorable coplanarity with the ylidic fragment which would allow delocalization of the charge on the carbanion. When the aldehyde substituent is quite large, (i.e., R=*t*-butyl and phenyl) addition modes 143 and 144 are no longer the favored routes as steric congestion becomes excessively large. Ylide 99A then reprotonates and the reaction path changes to allow the much less abundant conformer, 99B, to approach the bulky aldehyde with the least possible interaction (i.e. 145), giving mainly a *trans*-epoxide again. Reaction *via* 146, which suffers from adverse steric interaction since all the three large substituents are gauche to each other, was rejected as a realistic mode of addition.

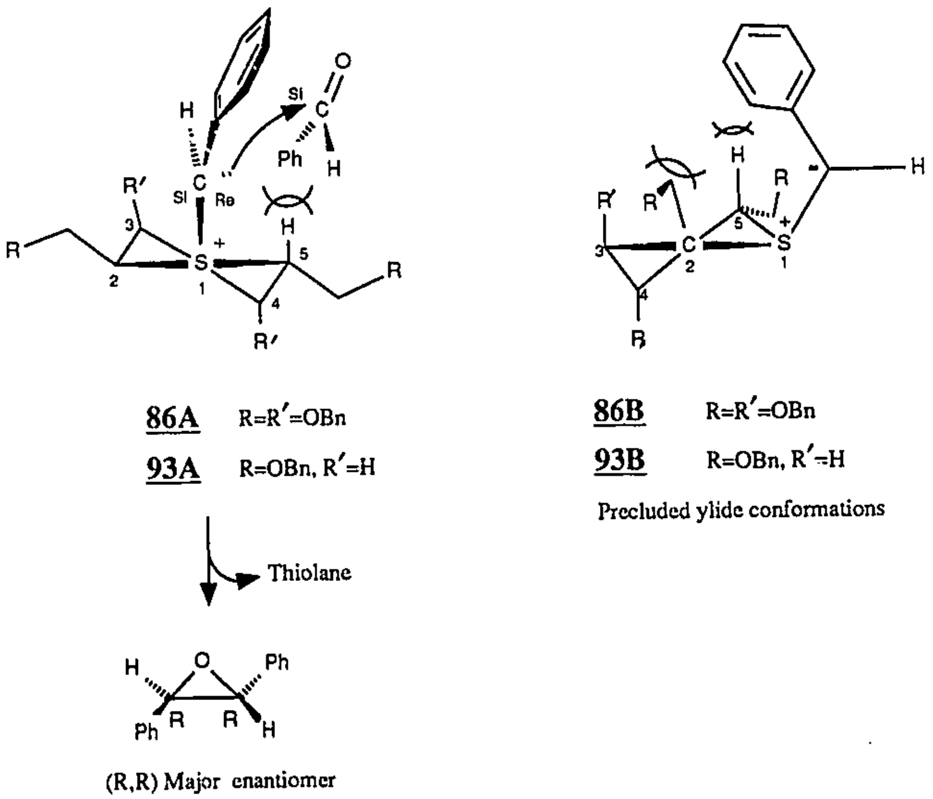
This proposed mechanism (Scheme 25) is consistent with the formation of (R,R)-*trans*-stilbene oxide with ylide 8. Thus, assuming that the conformational preference for equatorial disposition of the substituents in the thiolanium salt is preserved in the thiolanium ylides, deprotonation of salt 6 would generate two distinct ylide conformers: 8A and 8B (Scheme 26). The major conformer, 8A, has the phenyl group located *anti*-periplanar to the thiolanium ring while in the less abundant conformer 8B the phenyl substituent is in a more crowded position over the thiolane ring. In conformation 8A the *Re*-face of the carbanion is partially blocked by the TBDMSO- group at C-3, while in conformation 8B it is the *Si*-face of the ylide which is shielded by the same group. The approach of benzaldehyde by its *Re*-face towards the *Si*-face of ylide 8A to give a *trans*-product with (S,S) stereochemistry is inhibited by non-bonded interactions between the phenyl ring of benzaldehyde and the quasi-equatorial proton at C-5 (α to sulfur). The presentation of the *Si*-face of the aldehyde (not shown in Scheme 26) would lead to the formation of a *cis*-stilbene oxide. This *cis*-epoxide is only observed in minor quantities since its formation is hampered by the interaction of the two incoming phenyl substituents. Therefore, it would appear that even if ylide 8 exists mostly in conformation 8A its subsequent reactions with benzaldehyde are strongly inhibited. Instead it is believed to reprotonate thereby regenerating sulfonium salt 6. On the other hand, in the case of ylide structure 8B, the *Si*-face of the aldehyde can approach the more accessible *Re*-face of ylide 8B without serious non-bonded interactions. This is the most favorable benzylidene transfer to benzaldehyde and affords the observed *trans*-stilbene oxide with (R,R) as the major isomer.

Rationalization of the asymmetry observed for the epoxidation reaction involving ylides 86 and 93 is consistent with the ylide conformation depicted in 86A and 93A (Scheme 27). The conformations 86B and 93B are ruled out due to severe steric congestion occurring between the phenyl group and the substituent at C-2 of the thiolanium cation. An examination of models of 86A and 93A suggests that the attack of the open *Re*-face of the ylide on the *Si*-face of the aldehyde is favored giving the expected (R,R) *trans*-stilbene oxide as the major isomer. This mode of addition does involve a steric interaction between the incoming phenyl group and the proton at C-5 of the



Scheme 26.

thiolanium ring. However, the only alternative mode of addition of the aldehyde (i.e. on the *Re*-face) would lead to the formation of the minor cis-product observed (not shown in Scheme 27). The production of *cis*-stilbene oxide is hampered by the presence of a more serious steric interaction between the two phenyl substituents.



86A R=R′=OBn

93A R=OBn, R′=H

86B R=R′=OBn

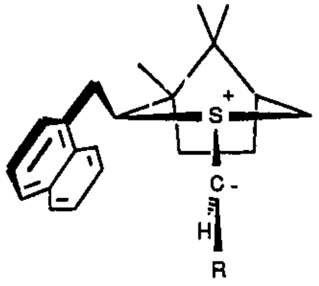
93B R=OBn, R′=H

Precluded ylide conformations

Scheme 27.

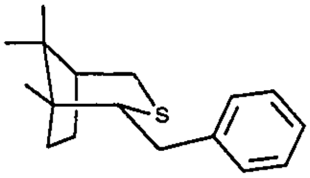
4.3 Design of Potentially Better Sulfur Auxiliaries.

The low e.e. obtained from the transfer of a benzylidene group by **134B** to aliphatic aldehydes could probably be enhanced by substitution of the phenyl substituent with an α-naphthyl group (i.e., ylide **147**).



147

The poor nucleophilicity of the sulfur atom in sulfur auxiliaries **120**, **121** and **122**, were a problem. It was shown that the *exo*-benzyl group in **120** controls S-alkylation. However, this effect was in opposition to that exerted by the C-6 and C-7 ethyl bridge. Therefore, both top and bottom faces of the thiane were hindered. The originally planned thiane, **102**, having an *endo*-2-benzyl or α-naphthyl substituent, **148**, should show an enhancement in sulfur nucleophilicity. Both the benzyl group and the C-6 and C-7 ethyl bridge would favor axial S-alkylation even for a small electrophile such as a methyl cation.



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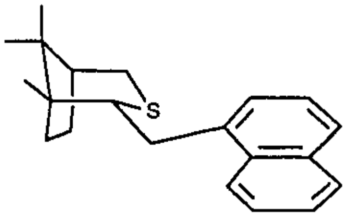
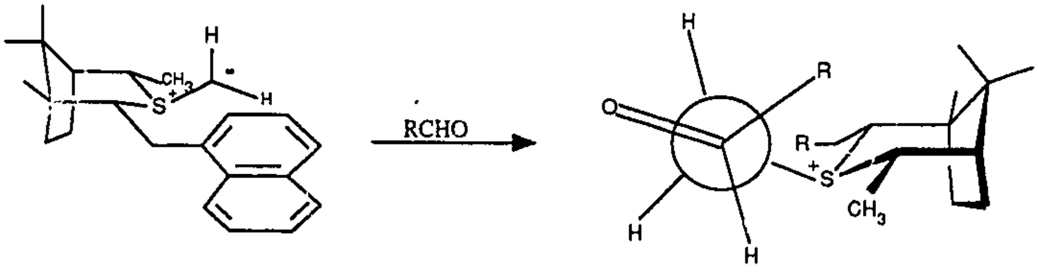


148

Thianes having an *endo*-α-naphthyl substituent at C-2 and a smaller methyl group at C-4, **149**, may provide ylides capable of better interactions with the aldehyde substituent (equation 47). These should give higher *cis:trans* product ratio as well as better asymmetric induction in the transfer of a methylene group to a carbonyl compound. All these auxiliaries could be made according to Scheme 28.



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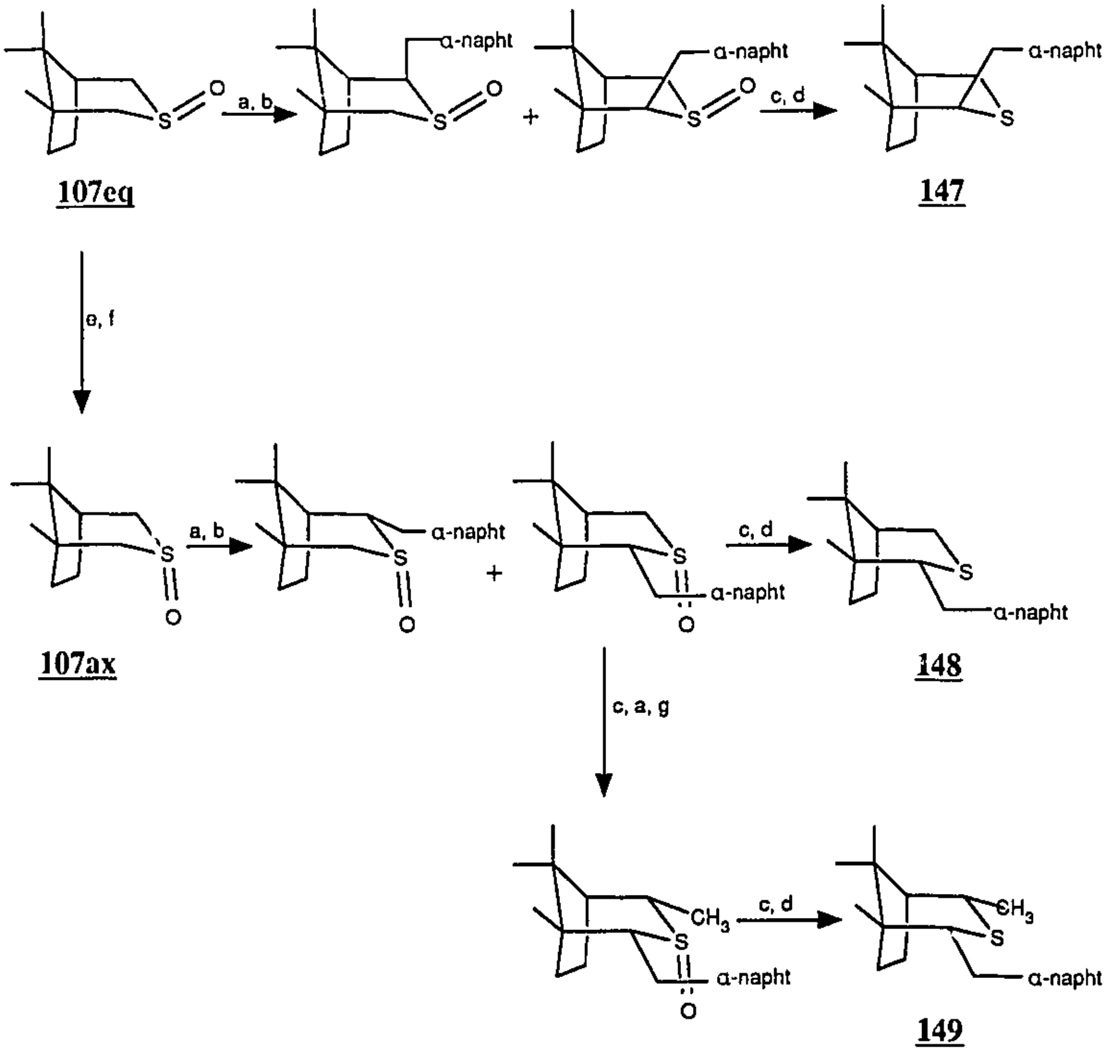


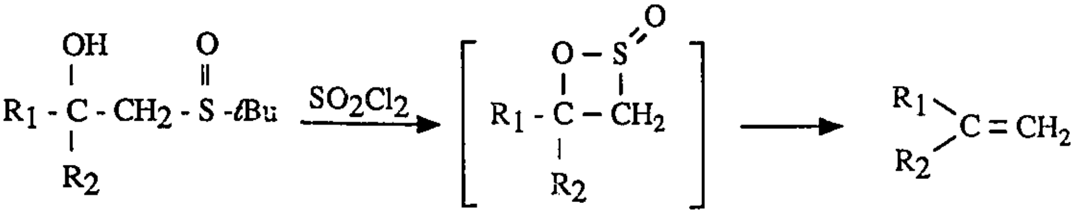
a) MeLi/THF/-10°C; b) Br-CH$_2$-αnapht; c) SiO$_2$ Separation; d) AcCl, SnCl$_2$, DMF/CH$_3$CN; e) Me$_3$O$^+$BF$_4^-$/CH$_2$Cl$_2$; f) NaOH$_{aq}$; g) CH$_3$I.

Scheme 28.

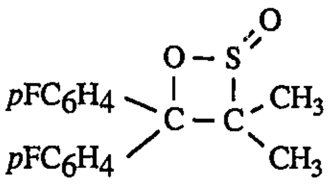
PART B: SYNTHESIS AND CHARACTERIZATION OF 3,4-(DIPHENYLMETHYL)-1,5-DIOXA-2-THIANE-2-OXIDES.

V INTRODUCTION

A number of years ago it was reported that β-hydroxy-*t*-butyl sulfoxides, **150**, reacted with SO_2Cl_2 or N-chlorosuccinimide (NCS) giving alkenes.[125] β-Sultines, **151**, were shown to be intermediates in this process. These compounds were generally found to be unstable but several tetrasubstituted derivatives were isolated and characterized.[126] An X-ray analysis was carried out on compound **152**.[127] As part of a search for other examples of relatively stable β-sultines, the isolation of *cis*-3,4-diphenyl-1,2-oxathietane-2-oxide, **153**, was attempted. The *cis*-compound was expected to show a significantly puckered four membered ring in order to relieve some of the interaction between the *cis*-phenyl substituents[126,127] and thus a considerable increase in stability was expected for this compound as compared to its *trans*-isomer. A relatively slow loss of SO_2 from **153** to form *cis*-stilbene was anticipated.



150 **151**



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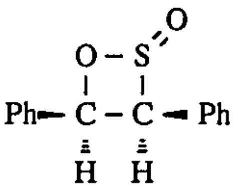
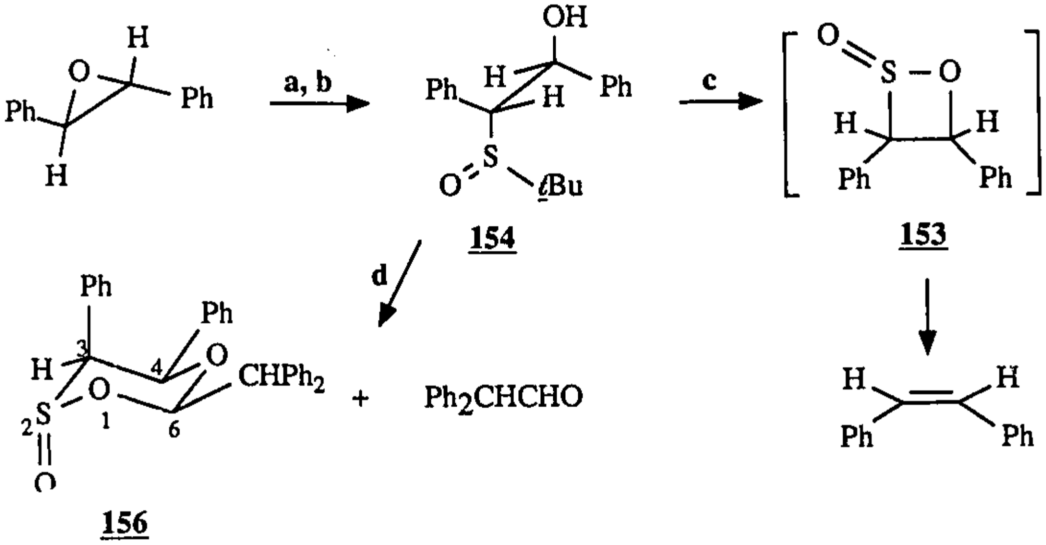


153

5. RESULTS AND DISCUSSION

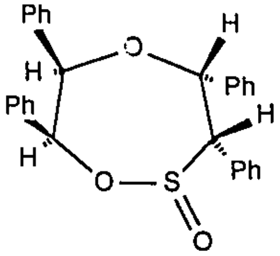
The expected precursor for **153**, *erythro*-β-hydroxysulfoxide **154**, was prepared unambiguously from *trans*-stilbene oxide *via* the series of reactions shown in Scheme 29. The reaction of **154** with NCS in refluxing benzene gave the expected *cis*-stilbene, presumably *via* **153**, in 50% isolated yield; no trace of *trans*-stilbene was observed. When the reaction of **154** with SO_2Cl_2 at -78°C in CH_2Cl_2, in an effort to isolate **153**, a crystalline product m.p. 161-162°C was isolated. This product was obtained in up to 60% yield and was accompanied by diphenylacetaldehyde (35%).



(a) *t*-BuSH/KOH; (b) MCPBA; (c) NCS/benzene/Δ; (d) SO_2Cl_2/CH_2Cl_2/-78°C.

Scheme 29.

The elemental analysis of this material indicated a molecular formula of $C_{28}H_{24}O_3S$. The proton nmr showed 4 unique resonances, each as a doublet with J=3.0 Hz, at δ3.49, δ4.53, δ6.17 and δ6.67 in addition to 20 aromatic hydrogens. The infrared spectrum had a strong band at 1125 cm^{-1} which is indicative of a sultine.[128] These data did not correspond to β-sultine **153** and the 7-membered sultine **155** was originally proposed for the structure of this material.[129] Attempts to confirm the assignment of **155** for this new material were made by carrying out a series of chemical transformations. The results of these experiments were contradictory and ambiguous.[129,130] This stucture and its peculiar chemical behavior of this new substance were considered sufficiently unusual to warrant further inverstigation. In the end the structure was shown by single crystal X-Ray structure determination to be the unusual δ-sultine **156** (Figure 62). As far as can be determined this compound, which may be considered as an acetal derived from diphenylacetaldehyde and a β-hydroxysulfinic acid, represents a new heterocyclic system, namely a 1,5-dioxa-2-thiane-2-oxide.



155

The X-ray structure of **156** (Figure 62) shows a 6-membered heterocyclic ring containing two oxygen and one sulfur atom. The sulfur and one oxygen are adjacent to one another with the sulfur carrying an additional oxygen thus forming a sulfinate ester groups. The six membered ring exists in a chair conformation with the S=O bond axial. Such an arrangement is typically preferred in cyclic δ-sulfinates.[123,131] The two phenyl substituents are *cis* to each other occupying axial positions at C_3 and equatorial position C_4. This arrangement is confirmed by ^{1}H nmr of **156** which shows a 3Hz coupling constant between the remaining hydrogens at C-3 and C-4. The benzydryl group at C-6 is equatorial.

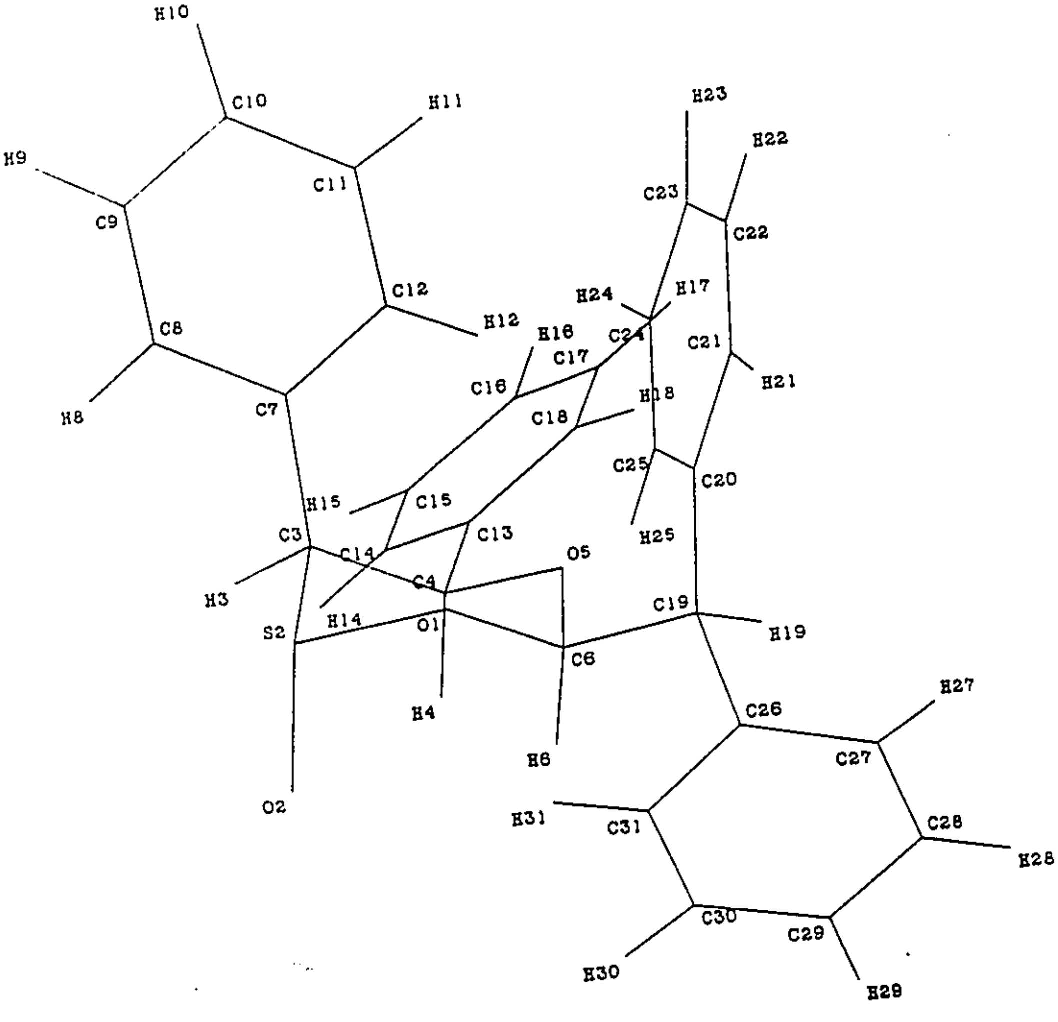
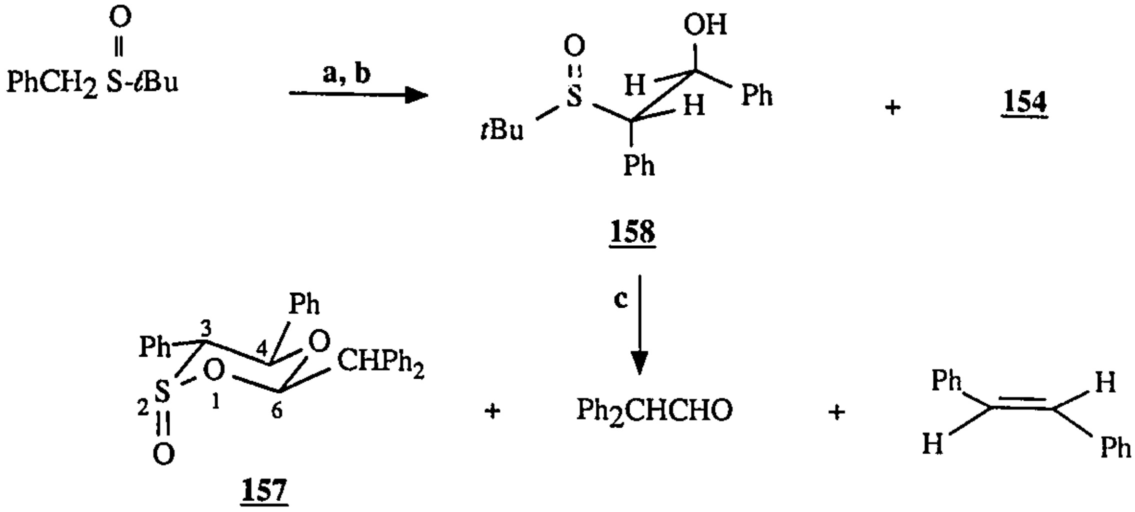


Figure 62. The molecular structure of (2R*, 3S*, 4R*, 6R*)-3,4-diphenyl-6-(diphenylmethyl)-1,5-dioxa-2-thiane-2-oxide 156 showing atomic numbering. Hydrogen atoms have been omitted.

Photolysis of **156** in quartz apparatus with a medium pressure mercury lamp gave an isomeric sultine **157** in quantitative yield. This compound was also obtained by a reaction involving *threo*-β-hydroxysulfoxide **158**, shown in Scheme 30. In the latter reaction diphenylacetaldehyde was again a by-product; *trans*-stilbene was also formed.



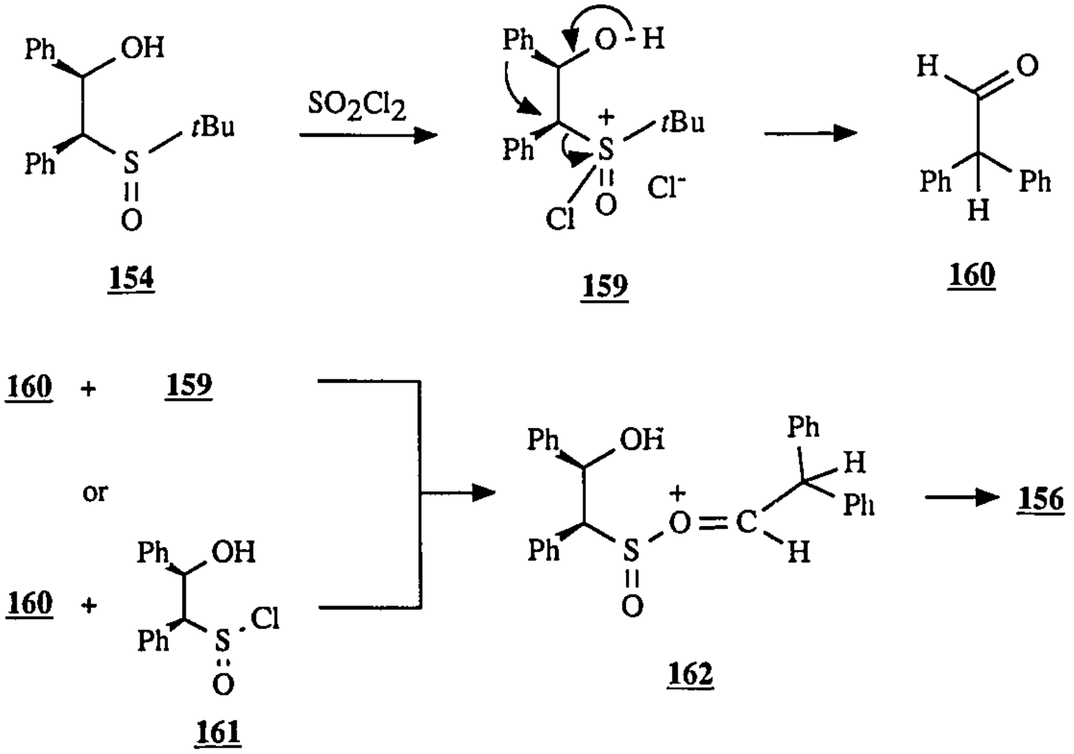
(a) LDA/THF/-78°C; (b) PhCHO; (c) SO_2Cl_2/CH_2Cl_2/-78°C.

Scheme 30.

The proton NMR spectrum of sultine **157** (i.r.; 1120 cm^{-1}) indicated a diaxial relationship between the C-3 and C-4 hydrogens (δ4.02 and δ5.86, J= 11 Hz); the remaining non-aromatic hydrogens appear as doublets at δ4.43 and δ6.67 (J= 4 Hz). The data obtained from the two modes of preparation comfirm the structure as **157**.

Examples of the photolability of benzylic carbon sulfur bonds in sulfoxides are known.[132] Cleavage of this bond in **156** should lead to a diradical which, after bond rotation, may recombine to give **157**. Complete isomerization of **156** to **157** is reasonable since this places all carbon substituents of the ring in a favorable equatorial position. The S=O bond remains axial.

The mechanism for the formation of these unusual heterocycles has not been investigated. A possible route to 156 is shown below in Scheme 31.



Scheme 31. Proposed mechanisms for the formation of 156.

Reaction of hydroxysulfoxide 154 with SO_2Cl_2 should give the chlorooxosulfonium species 159.[131c] This species can react further in several possible ways: (i) cyclization to β-sultine 153, (ii) fragmentation to diphenylacetaldehyde and *t*-BuS(O)Cl or (iii) loss of *t*-BuCl, or 2-methylpropene and HCl to give β-hydroxysulfinyl chloride 161. Interaction of diphenylacetaldehyde or its enol with either 159 or 161 could lead to oxonium ion 162, or the related enol ether, either of which should cyclize to 156. A similar pathway seems plausible for the conversion of 158 to 157.

EXPERIMENTAL

6.0 GENERAL REMARKS

Melting points were determined on a Hoover Uni-melt apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 783 Ratio Recording Infrared spectrophotometer neat, with KBr or thin film. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on Varian XL-300 or Gemini-200 spectrometer using $CDCL_3$ as a solvent unless otherwise specified. Chemical shifts are reported in ppm downfield from $(CH_3)_4Si$ as an internal standard. Multiplicities are reported as s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet; b, broad. Low- and high-resolution mass spectra were recorded on a VG mass spectrometer with a DANI 7070 gas chromatograph. The mass specrral data (MS, HRMS) are reported as *m/z* with the intensity indicated in parentheses as a percent of the base peak. Microanalyses were performed by M-H-W Laboratories, Phoenix AZ, U.S.A.

In addition to column chromatography, separations were carried out on a centrifugally accelerated, radial, thin-layer chromatograph (Chromatotron Model 7924 TM) using silica gel PF-254 with $CaS0_4 \cdot 1/2\ H_20$ type 60 (Merck 7749) as adsorbent. For column chromatography, silica gel (normal type) from Terochem Laboratories was used.

Tetrahydrofuran (THF) was dried as follows: THF (500 mL), sodium metal (5g) and benzophenone (10g) were refluxed under nitrogen until a deep blue color formed and persisted. After an additional 2 hours of gentle reflux, THF was distilled into an oven dried, nitrogen-flushed flask.

All solvents were distilled prior to utilization. Di*iso*propylamine, triethylamine, dimethyl sulfoxide (DMSO), hexamethylphosphoramide (HMPA) and dimethylformamide (DMF) were distilled over calcium hydride under a nitrogen atmosphere prior to use. Methylene chloride was dried by distillation from phosphorus pentoxide. The light petroleum ether used had a boiling range of 30-60°C; ether refers to diethyl ether. All reactions were carried out under nitrogen unless otherwise noted; hypodermic syringes were used to transfer solutions.

Work up.

The usual work up involved extraction with the specified solvent, washing the organic extracts with saturated sodium chloride solution, drying the organic phase with magnesium sulfate and evaporating the solvents under reduced pressure (i.e. a rotary evaporator followed by high vaccum).

6.1 PART A

General Procedure A: Preparation of Thiolanium and Thianium Perchlorates.

To a stirred solution of the substituted thiolane or thiane (1 mmol) and benzyl bromide (171 mg, 1 mmol) in dry ether (5.0 mL) was added a solution of anhydrous silver perchlorate[135] (228 mg, 1.1 mmol) dissolved in dry ether (10 mL). A yellow precipitate of silver bromide was immediately formed. The resultant mixture was stirred at room temperature for 2 hours. The ether was decanted and the residue was washed with small portions of anhydrous ether (2 X 5 mL). Extraction of the residue with CH_2Cl_2 (3 X 20 mL) followed by filtration and concentration gave the thiolanium or thianium perchlorate salt as a white foam.

General Procedure B: Synthesis of Optically Active Oxiranes From Sulfonium Salts.

Thiolanium or thianium perchlorate (1 eq), carbonyl compound (1 to 2eq) and $BnEt_3N^+Cl^-$ (50 mg) were dissolved in 10 mL of CH_2Cl_2. The resulting solution was cooled at 0°C and 3 mL of NaOH (50%) was added dropwise. The reaction mixture was stirred vigorously at 0°C for 3 h and at room temperature for an additional 3 h period. The mixture was extracted with CH_2Cl_2 (3 X 20 mL) and the organic layer was evaporated to dryness. The crude oil was analyzed by ^1H nmr and chromatographed on silica gel (hexanes:EtOAc, 20:1) as eluent to give the corresponding thiolane or thiane, *trans*-substituted oxirane and *cis*-substituted oxirane. The % ee was determined by $[\alpha]_D$ or whenever feasible by using ^{1}H NMR spectroscopy with tris[3-[(heptafluoropropyl)-hydroxymethylene]-(+)-camphorato]europium (III) as a chiral shift reagent[30]. Chemical yields are based on the thiolanium or thianium perchlorate used.

General Procedure C: Synthesis of Optically Active Oxiranes From Thiolanes or Thianes.

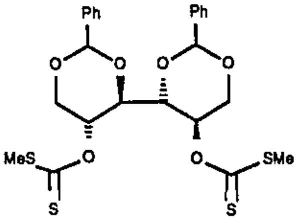
The thiolane or thiane (1 eq) and benzyl bromide (1 eq) in dry ether (5.0 mL) was added to a solution of anhydrous silver perchlorate[135](1.1 eq) dissolved in dry ether (10 mL). The resulting mixture was stirred at room temperature for a 2 hours. The silver bromide that precipitated was extracted with ether (2 X 5 mL) and CH_2Cl_2 (3 X 20 mL). The combined extracts were evaporated to dryness on a rotary evaporator. The semi-solid residue obtained was used as one equivalent of thiolanium or thianium perchlorate in the general procedure B.

In these reactions, the *in situ* formed sulfonium salts were assumed to be quantitative and final yields of products are based on the starting thiolane.

General Procedure D: Reduction of Sulfoxides to Sulfides.[120]

The sulfoxide (1 mmol) was dissolved in CH_3CN (5 mL) and DMF (2 mL) and stirred at 0°C. Stannous chloride dihydrate (1.5 mmol) and AcCl (5 mmol) were added. This reaction mixture was stirred at 0°C for 1 hr and then at room temperature for an additional hour. The CH_3CN was removed on a rotary evaporator. The residue was diluted with H_2O (10 mL) and extracted into hexanes (5 x 10 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure to give crude sulfide. The sulfide thus obtained was purified by chromatography on a pad of SiO_2 (4 g) using hexanes/EtOAc (20:1) as eluent..

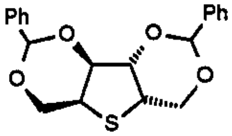
1,3;4,6-di-O-Benzylidene-2,5-bis(S-methyl-dithiocarbonate)-D-mannitol 79.[108]



To a solution of 1,3;4,6-di-O-benzylidene-D-mannitol (10 g, 3.4 mmol)[136] and imidazole (50 mg) in THF (200 mL) was slowly added a suspension of NaH (2 g, 83 mmol) in THF (50 mL). Vigorous gas evolution was observed. After the reaction mixture had stirred for 40 min, carbon disulfide (12.7 g, 167 mmol) was added at once. Stirring was continued for 30 min and iodomethane (10 g, 70 mmol) was added in a single portion. The reaction mixture was stirred another 15 min and glacial acetic acid (5 mL) was added dropwise to destroy any excess of sodium hydride. The THF was removed on a rotatory evaporator to give a semi-solid residue. Work up using CH_2Cl_2 (3 X 100 mL) as a solvent gave 14.4 g of a crude solid. Recrystallization from Et_2O gave 13.7 g (91%) of 79 as a pale yellow solid.

M.P. 213-214°C, (lit.[108] m.p. 210°C).

(2S,3S,4S,5S)-(-)-di-O-Benzylidene-3,4-bis-hydroxy-2,5-bis-(hydroxymethyl)thiolane. 76.

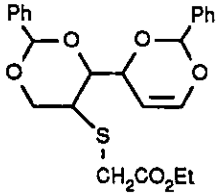


A solution of dixanthate 79 (1 g, 1.85 mmol), tri-*n*-butyltin hydride (1.61 g, 5.5 mmol) and AIBN (25 mg) in toluene (60 mL) was refluxed for 3 h. TLC (CH_2Cl_2) indicated that the reaction was completed. Removal of toluene under reduced pressure gave a white residue which was pre-purified by column chromatography (Hexane:CH_2Cl_2, 95:5 and then CH_2Cl_2:EtOAc, 95:5) to give 727 mg of a white solid. TLC (CCl_4:Et_2O, 9:1) showed that some impurities were present in this material. Chromatotron chromatography (CCl_4:Et_2O, 9:1) gave 465 mg of <u>76</u> as a white solid.

M.P. 211-212°C, (lit.[108] m.p. 210°C);

$[\alpha]_D$= -102° (c=1.25, $CHCl_3$), (lit.[108], $[\alpha]_D$= -103°, $CHCl_3$).

Preparation of Compound 83.

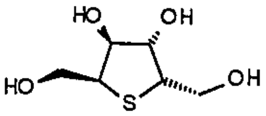


Thiolane <u>76</u> (100 mg, 0.28 mmol), ethyl diazoacetate (172 mg, 1.5 mmol) and rhodium (II) acetate (100 mg) in 10 mL CH_2Cl_2 were stirred at room temperature for 2 days. The yellow oil remaining after solvent removal was chromatographed on the chromatotron (CCl_4:Et_2O, 9:1) giving sequentially 46 mg of diethyl fumarate, 51 mg of starting sulfide <u>76</u>, 34 mg of diethyl maleate (eluted third) and 47 mg (38%) of compound <u>83</u> as a pale yellow oil.

^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3H, J= 7.1 Hz, CH_3), 3.10 (d, 1H, J= 1.9 Hz), 3.38 (AB, 2H, J= 15.3 Hz), 4.17 - 4.45 (m, 5H), 5.02 (dd, 1H, J= 8.2 Hz, J= 1.5 Hz), 5.24 (dd, 1H, J= 6.5 Hz, J= 1.5 Hz), 5.64 (s, 1H), 5.96 (s, 1H), 6.80 (dd, 1H, J= 6.5 Hz, J= 1.3 Hz), 7.27 - 7.40 (m, 6H), 7.50 - 7.56 (m, 4H).

^{13}C NMR (Acetone-d_6) δ: 13.32 (CH_3), 31.67 (CH_2), 41.05 (CH), 60.86 (CH_2), 69.98 (CH_2), 74.72 (CH), 81.84 (CH), 97.46 (CH), 100.02 (CH), 101.20 (CH), 125.59 (4CH), 127.55 (4CH), 128.30 (CH), 128.45 (CH), 136.48 (CR_4), 137.35 (CR_4), 145.38 (CR_4) and 170.24 (CR_4, $\underline{C}O_2Et$).

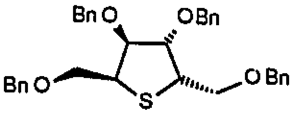
(2S,3S,4S,5S)-3,4-Bis-hydroxy-2,5-bis(hydroxymethyl)thiolane 84.



Di-O-benzylidene acetal 76 (356 mg, 1 mmol) was dissolved in 10 mL of methanol and 2 mL of 15% HCl solution was added. The solution was refluxed for 30 min TLC (CH_2Cl_2:MeOH, 9:1) indicated that no starting material remained. The solvents were removed on a rotary eveporator and the residual oil was separated by column chromatography (CH_2Cl_2:MeOH, 9:1, then 85:15) giving 138 mg (76%) of compound 84 as a colorless thick oil.

^{1}H NMR (Acetone-d_6) δ 3.60-3.75 (m, 4H, CH_2OH), 3.85-3.95 (m, 2H), 4.31 (m, 2H);
^{13}C NMR (Acetone-d_6) δ: 52.14 (2CH), 62.47 (2CH_2, $\underline{C}H_2$-OH), 79.26 (2CH).

(2S,3S,4S,5S)-(-)-Tetra-O-benzyl-3,4-bis-hydroxy-2,5-bis(hydroxymethyl)thiolane 77.



To a suspension of NaH (216 mg, 9 mmol) in 10 mL of DMF was added $Bn(Et)_3N^+I^-$ (20 mg) and tetraol 84 (300 mg, 1.66 mmol). The reaction mixture was stirred vigorously for 1 hr and a solution of benzyl bromide (1.42 g, 8.3 mmol) in 10 mL of DMF was slowly added. After complete addition the mixture was allowed to stir at room temperature overnight. The solution was hydrolyzed with 10 mL of H_2O then acidified with a 10% HCl solution (pH=1). Work up using Et_2O (3 X 20 mL) gave 550 mg of a crude oil. Separation (Chromatotron, CH_2Cl_2:Hexane, 70:30) gave 312 mg (35%) of 77 as a colorless thick oil;

$[\alpha]_D$= -32.7° (c=1.25, CH_2Cl_2);

IR (thin film) ν_{max}**:** 3080, 3040, 2850, 1500, 1460, 1365, 1210, 1140-1050, 740 and 705 cm^{-1};

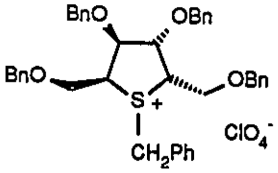
^{1}H NMR (CDCl$_3$) δ 3.56 (dd, 1H, *J*= 8.05 Hz, *J*= 5.1 Hz), 3.78 (d, 2H, *J*= 8.05 Hz), 3.86 (dd, 1H, *J*= 5.3 Hz, *J*= 3.2 Hz), 4.08 (d, 2H, *J*= 2.9 Hz), 4.47 (s, 4H), 4.48 (s, 4H) and 7.15 - 7.32 (m, 20 H);

^{13}C NMR (CDCl$_3$) δ: 48.11 (2 CH), 69.09 (2 CH_2), 72.45 (2 CH_2), 73.18 (2 CH_2), 82.43 (2 CH), 127.67, 127.76, 127.83, 128.44, 138.10 and 138.29;

CIMS m/z (%) 433 (M^+-OBn, 6.6), 150 (27), 149 (100) and 133 (11.5);

Anal. Calcd. for $C_{34}H_{36}O_4S$: C, 75.52; H, 6.71; S, 5.93. Found: C, 75.62; H, 6.77; S, 6.12.

(2S,3S,4S,5S)-(-)-1-Benzyl-tetra-O-benzyl-3,4-bis-hydroxy-2,5-bis(hydroxymethyl)-thiolanium perchlorate 86.



The thiolanium salt 86 was prepared from thiolane 77 with a 38% yield following the general procedure A.

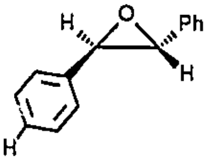
$[\alpha]_D$= -106.7° (c=4, CH_2Cl_2);

^{1}H NMR (CDCl$_3$) δ 3.40 (t, 1H, *J*= 10 Hz), 3.75 (dd, 1H, *J*= 10 Hz, *J*= 5 Hz), 3.9 - 4.2 (m, 4H), 4.35 - 4.70 (m, 12 H) and 7.0-7.4 (m, 25 H);

^{13}C NMR (CDCl$_3$) δ: 45.59, 61.21, 62.81, 65.09, 66.26, 73.23, 73.31, 73.52, 73.83, 80.61, 82.20, 127.37, 128.03, 128.25, 128.36, 128.43, 128.58, 128.64, 128.83, 128.90, 129.36, 130.00, 130.40, 136.11, 136.34, 136.50 and 136.64.

PREPARATION OF OXIRANES *VIA* THE SULFUR YLIDE 86 (Table 2).

(R,R)-(+)-*trans*-Stilbene Oxide 87 (X=H).



The *trans*-stilbene oxide 87 (X=H) was prepared from thiolane 77 (266 mg, 0.50 mmol), benzyl bromide (84 mg, 0.48 mmol) and benzaldehyde (106 mg, 1 mmol) according to the general procedure C. The following products were obtained in order of elution, 26 mg (27%) of (R,R)-(+)-*trans*-stilbene oxide 87 (X=H):

M.P. 55 - 56°C, (lit.[110] m.p. 69°C)

$[\alpha]_D$= +230° (c=1.25, acetone), {lit.[122], $[\alpha]_D$= +292°, (c=0.056, acetone)};

e.e.= 79%;

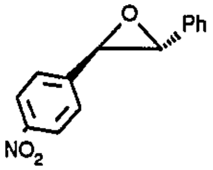
^{1}H NMR ($CDCl_3$) δ 3.89 (s, 2H), 7.36-7.40 (m, 10 H);

EIMS m/z (%) 196 (M^+, 50), 195 (M^+, 44), 178 (23), 167 (100), 90 (87) and 89 (83);

and 117 mg (44%) of recovered thiolane 77:

$[\alpha]_D$= -31.9° (c=1.64, CH_2Cl_2).

(R,R)-(+)-*trans*-2-(*p*-Nitrophenyl)-3-phenyloxirane 87 (X=NO_2).



The stilbene oxide 87 (X=NO_2) was prepared from thiolane 77 (143 mg, 0.26 mmol), benzyl bromide (50 mg, 0.29 mmol) and *p*-nitrobenzaldehyde (150 mg, 1 mmol) according to the general procedure C. The following products were isolated in order of elution: 26 mg of 87 (X=NO_2) and 80 mg of recovered thiolane 77.

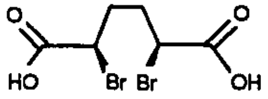
M.P. 120 - 121°C, (lit.[110] m.p. 127°C);

$[\alpha]_D$= +230° (c=1.25, EtOH), {lit.[110], $[\alpha]_D$= +278° (c=1.01, EtOH)};

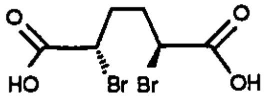
e.e.= 83%;

^{1}H NMR ($CDCl_3$) δ 3.83 (d, 1H, *J*= 1.80 Hz), 3.95 (d, 1H, *J*= 1.80 Hz), 7.30-7.41 (m, 5H, phenyl), 7.49 (dd, 2H, *J*= 7.0 Hz, *J*= 2.0 Hz) and 8.22 (dd, 2H, *J*= 7.0 Hz, *J*= 2.0 Hz).

Preparation of *cis*- and *trans*-2,5-Dibromo adipic acid 89.[112,137]



Meso



89

Adipic acid (29.2 g, 0.20 mol) and thionyl chloride (115 mL) in 40 mL of CCl_4 were stirred and heated to 65°C for 1 h. *n*-Bromosuccinimide (100 g, 0.56 mol) in 200 mL of CCl_4 followed by addition of HBr (48%, 7 drops) to the reaction mixture. This solution was heated at 70°C for 15 minutes, then at 85°C for a 2 hours. The reaction mixture was diluted with 200 mL of CCl_4 and cooled to 0°C (kept overnight). The succinimide that precipitated was filtered and washed with CCl_4 (2 x 20 mL). The filtrate was evaporated under reduced pressure to give a pale green oil which was hydrolyzed by pouring it on 600 g of crushed ice and then stirring for 8 h (or best overnight). The *cis*-2,5-dibromo adipic acid that precipitate was filtered and dried under vaccum to give 23.97 g, (39% yield);

M.P. 195 - 197°C, (lit.[137] m.p. 191 - 193°C).

The filtrate was extracted with diethyl ether (10 x 100 mL) and the combined extracts were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave a crude amorphous pale yellow solid. The residue was finely powdered and stirred with 100 mL of H_2O for 4 hours. The undissolved portion of the residue was filtered to give an additional amount of 1.5 g (2.5%) of *cis*-1,5-dibromoadipic acid.

M.P. 191-193°C.

The aqueous filtrate was allowed to dry slowly in a well ventillated area to give 32.29 g of *trans*-dibromo acid. The crude *trans*-dibromo acid was recrystallized from 32 mL of formic acid. It was sometimes necesssary to freeze the solution to -10°C and then let it thaw slowly from 0°C up to 5°C to initiate the crystallization. The crystals were filtered to give a total amount of 17.84 g of material (29%).

M.P. 125 - 130°C.

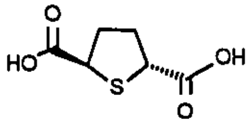
Evaporation of the formic acid filtrate to half of its initial volume gave a 2nd crop 5.3 g (8.7%);

M.P. 133 - 136°C.

Recristallization of a sample gave a white solid which corresponds to the *trans*-2,5-dibromoadipic acid <u>89</u>.

M.P. 136 - 138°C, (lit.[137] m.p. 138 - 139°C).

trans-Thiolane-2,5-dicarboxylic Acid *d,l*-88.



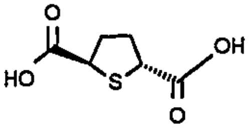
A warm solution of $Na_2S{\bullet}9H_2O$ (25 g, 85 mmol) and NaOH (20.5 g, 0.51 mmol) dissolved in 40 mL of H_2O was added dropwise to an ice-cold solution of d,l-2,5-dibromoadipic acid <u>89</u> (20.5 g, 67 mmol) in 80 mL of H_2O. The temperature of the reaction mixture was kept below 5°C during the addition of the basic sodium sulfide solution. After the addition was completed the reaction mixture was kept at 5°C overnight. Acidification with ice-cold 20% H_2SO_4 solution (pH≤1) followed by work up using Et_2O (5 X 100 mL) as solvent gave 11.1 g of *d,l*-<u>88</u> (m.p. 155-158°C). Recrystallization was carried out by dissolving the crude material into a minimum amount of boiling EtOAc (32 mL) and then triturating with 32 mL of hexanes to afford (after standing overnight at 5°C) a total amount of 9.48 g (80%) of compound *d,l*-88 as white crystals;

M.P. 158 - 160°C, (lit.[111], m.p. 165 - 166°C);

^{1}H NMR (Acetone-d_6) δ 2.03-2.09 (br.s, 2H, H_2O), 2.15-2.36 (m, 4H) and 4.04-4.09 (m, 2H);

^{13}C NMR (Acetone-d_6) δ: 33.44 ($\underline{C}H_2$), 48.90 ($\underline{C}H$) and 174.48 ($\underline{C}O_2H$).

(2R,5R)-(-)-Thiolane-2,5-dicarboxylic Acid 88.



(-) 2R, 5R

To a boiling solution of brucine hydrate (21.3 g, 49.5 mmol) in 100 mL of H_2O was added (*d,l*)-*trans*-tetrahydrothiophene-2,5-dicarboxylic acid ***d,l*-88** (8.10 g, 46 mmol). The resulting yellow solution was boiled for 2 minutes then cooled to 5°C and left overnight. The precipitate that formed was filtered and dried under vaccum. Recrystallization from H_2O (8 times in weight) was repeated 4 times to give 4.34 g of the brucine salt.

$[\alpha]_D$= -86.7°, (lit.[111] $[\alpha]_D$ -91.4°).

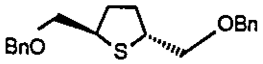
The brucine salt was acidified with 20% H_2SO_4 solution at pH<1. Work up using diethyl ether (1 x 20 mL and 5 x 10 mL) as solvent gave 1.25 g (31%) of compound 88 as a white solid;

M.P. 180.5 - 181°C, (lit.[111] m.p. 179 - 180°C);

$[\alpha]_D$= -213.2°, (lit.[111] $[\alpha]_D$= -225.3°);

e.e.= 94.6%.

Preparation of (2R,5R)-(-)-Di-O-benzyl-2,5-bis(hydroxymethyl)thiolane 78.



(-) 2R, 5R

$BH_3{\bullet}SMe_2$ (10M, 1.5 mL) was added to a cold solution (-30°C) of (2R,5R)-(-)-tetrahydrothiophene-2,5-dicarboxylic acid 88 (625 mg) dissolved in 30 mL of anhydrous THF. The reaction mixture was stirred vigorously overnight, during which time the bath temperature rose to 25°C. The excess of $BH_3{\bullet}SMe_2$ was destroyed by dropwise addition of an acetic acid solution (5 mL, AcOH:H_2O, 1:1). The solution was stirred until the evolution of H_2 had ceased (~15 minutes). Acidification (pH 1) followed by work up (EtOAc, 5 x 15 mL) gave 544 mg (100% yield) of crude (2R,5R)-2,5-bishydroxymethyl-thiolane as a colorless oil. This material was used without further purification.

To a solution of NaH (125 mg, 5.2 mmol) in dry THF (30 mL) was added (2R,5R)-2,5-(dihydroxymethyl)-tetrahydrothiophene (300 mg, 2.03 mmol) dissolved in 10 mL of THF. The reaction mixture was refluxed and stirred vigorously for 2 hours, then cooled to room temperature. The yellowish suspension was treated with benzyl bromide (850 mg, 5.0 mmol) and stirring was continued overnight at room temperature. Hydrolysis of the crude mixture with H_2O (30 mL) followed by work up (CH_2Cl_2, 3 x 30 mL) gave 1.35 g of crude material. Separation of this material (Chromatotron, hexane:ethyl acetate 10:1) gave 553 mg (83% yield) of compound 78 as a pale yellow oil.

$[\alpha]_D=$ -75.2° (c=0.625, CH_2Cl_2);

IR (thin film) ν_{max} 3035, 2940, 2880, 1365, 1120-1070, 740 and 700 cm^{-1};

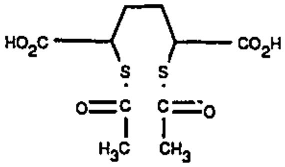
^{1}H NMR ($CDCL_3$) δ ppm 1.84-1.88 (m, 2H), 2.05 - 2.12 (m, 2H), 3.43 (ABX dd, 2H, J_{AB}= 12.8 Hz, J_{AX}= 6.96 Hz), 3.48 (ABX dd, 2H, J_{BX}= 12.8 Hz, J_{AB}= 6.96 Hz), 3.55 - 3.66 (m, 2H), 4.51(d, 2H, J_{AB}= 12.1 Hz), 4.58 (d, 2H, J_{BA}= 12 Hz), 7.26 - 7.37 (m, 10H);

^{13}C NMR ($CDCl_3$) δ: 32.08 (C̲-3, C̲-4), 47.34 (C̲-2, C̲-5), 73.01, 74.11, 127.68, 128.45 and 138.35;

EIMS m/z (%) 328 (M^+, 1.2), 221 (77), 220 (77), 207 (22), 131 (69), 99 (98) and 92 (100);

Anal. Calcd. for $C_{20}H_{24}O_2S$: C, 73.13; H, 7.36; S, 9.76. Found: C, 72.94; H, 7.36; S, 9.89.

meso-Di-S-acetyl-2,5-dithioladipic Acid 90.



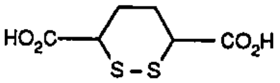
Thiolacetic acid (22 g, 0.13 mol) was added dropwise to an ice-cold suspension of NaH (16 g, 0.67 mol) in 100 mL of THF. After the addition completed the reaction mixture was stirred at 0°C until the evolution of H_2 had ceased (~10 min). *cis*-2,5-Dibromoadipic acid ***meso*-88** (40 g, 0.13 mol) dissolved into 400 mL of THF was slowly added. The reaction mixture was allowed to warm to room temperature overnight. Hydrolysis was carried out with 20 mL of glacial acetic acid followed by addition of 150 mL of H_2O and a 20% H_2SO_4 solution (pH=1). Work up (ether, 4 X 100 mL) gave 36.5 g of compound **90** as a yellow solid. This crude material was used without further purification.

A small sample was treated with an excess etheral solution of diazomethane to give the corresponding dimethyl ester of **90** as a pale yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$) δ 1.71 - 1.77 (m, 2H), 1.93 - 2.01 (m, 2H), 2.30 (s, 6H, 2 X -CO-CH_3), 3.67 (s, 6H, 2 X -CO_2-CH_3) and 4.11 - 4.16 (m, 2H);

^{13}C NMR (200 MHz, $CDCl_3$) ppm 28.86 (C̲H_2), 30.05 (-SCH_3), 44.89 (C̲H), 52.61 (-O-C̲H_3), 171.54 (-C̲O_2R) and 193.53 (-S-C̲OR).

meso-1,2-Dithiane-3,6-dicarboxylic Acid 91.[113]

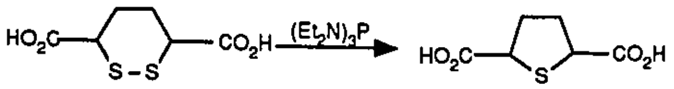


Gaseous ammonia was passed through a solution of 90 (35 g, 0.12 mol) in 300 mL of methanol at 0°C until saturated. The solution was kept at room temperature for 4 hours then the solvent was removed under reduced pressure. The residue was acidified with a 10% H_2SO_4 solution at pH=1. Work up using Et_2O (4 X 100 mL) and EtOAc (2 X 100 mL) as solvents gave a total amount of 23.8 g of *meso*-2,5-dithioladipic acid as a brownish solid. This crude material was oxidized immediately without further purification.

meso-2,5-Dithioladipic acid (23.8 g) dissolved into 100 mL of a 5% $NaHCO_3$ solution was added $NaHCO_{3(s)}$ until a pH=8-9 was reached. The solution was cooled to 0°C and upon addition of $FeCl_3$ (100 mg), a dark purple colour developed. The reaction mixture was slowly titrated with 30% H_2O_2 until the colour dissapeared (7-8 mL) and then acidified with a 20% H_2SO_4 solution (pH≤1, ~50 mL). Work up using Et_2O (4 X 100 mL) and EtOAc (2 X 100 mL) gave 11.2 g of a semi-solid. Recrystallization from H_2O (20 mL) gave 8.65 g of compound 91 as cream crystals. Evaporation of the mother liquor to 6 mL gave a 2nd crop of compound 91 (0.77g).

M.P. 200 - 202°C (lit.[113] m.p. 199°C).

Selective Desulfurization of 91; Preparation of *d,l*-88.

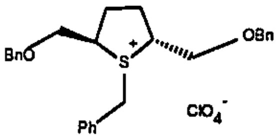


A solution of disulfide 91 (208 mg, 1 mmol), triethylamine (208 mg, 2 mmol) and hexaethylphosphorous triamide (365 mg, 1.4 mmol) in 10 mL of CH_2Cl_2 was stirred overnight at room temperature. Sulfur (100 mg, 3.1 mmol) was added to quench excess of phosphine and the resulting mixture was acidified with a 5% H_2SO_4 solution at pH=1. The solution was filtered and the filtrate was extracted with CH_2Cl_2 (2 X 10 mL). ^{1}H

NMR and TLC analysis of the CH_2Cl_2 extracts showed only the presence of $(Et_2N)_3P=S$, which was discarded. Extraction of the aqueous phase with Et_2O (3 X 15 mL) gave (after removal of solvent) 25 mg (17%) of pure compound <u>*d,l*-88</u>;

M.P. 159 - 160°C.

<u>(2R,5R)-(-)-1-Benzyl-di-O-benzyl-2,5-bis(hydroxymethyl)thiolane 92</u>.



The thiolanium salt <u>92</u> was prepared from thiolane <u>78</u> in 58% yield following the general procudure A. This material is hygroscopic and slowly melted to a colorless gum. No melting point was attempted.

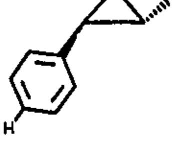
$[\alpha]_D$= -58.3 (c=3.2, CH_2Cl_2).

^{1}H NMR was very complex (see Figure 8);

^{13}C NMR and DEPT (200 MHz, $CDCl_3$) ppm 30.83 ($\underline{C}H_2$), 31.20 ($\underline{C}H_2$), 40.97 ($\underline{C}H_2$), 62.07 ($\underline{C}H$), 63.63 ($\underline{C}H$), 65.75 ($\underline{C}H_2$), 67.90 ($\underline{C}H_2$), 73.26 ($-CH_2$), 73.46($-CH_2$), 127.4 (CR_4), 136.58 (CR_4), 137.7 ($\underline{C}R_4$), 127.85 (CH), 128.05 (CH), 128.17 (CH), 128.37 (CH), 128.51 (CH), 128.72 (CH), 129.61 (CH), 129.86 (CH) and 130.54 (CH).

<u>PREPARATION OF OXIRANES *VIA* THE SULFUR YLIDE 93 (Table 3).</u>

<u>(2R,3R)-(+)-*trans*-Stilbene Oxide 87 (X=H)</u>.



The *trans*-stilbene oxide <u>87</u> (X=H) was prepared from thiolanium salt <u>92</u> (206 mg, 0.40 mmol) and benzaldehyde (106 mg, 1 mmol) according to the general procedure B.

The following products were obtained: 41 mg (53%) of (2R,3R-(+)-<u>87</u> (X=H);

$[\alpha]_D$= +214.2° (c=1.08, acetone), {lit.[122] $[\alpha]_D$= +291° (c=0.056, acetone)};

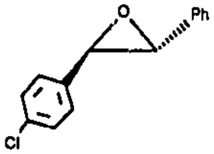
e.e. 74%;

and 104 mg (80%) of recovered thiolane <u>78</u>;

$[\alpha]_D$= -76.3° (c=1.25, CH_2Cl_2).

(2R,3R)-(+)-*trans*- and *cis*-2-(*p*-Chlorophenyl)-3-phenyloxirane 87 (X=Cl) and 129d.

The optically active oxirane <u>87</u> (X=Cl) was prepared from thiolanium salt <u>92</u> {305 mg, 0.59 mmol; prepared from thiolane <u>78</u> $[\alpha]_D$=-69.4 (c=2.5, CH_2Cl_2)}, benzyl bromide (171 mg, 1 mmol) and *p*-chlorobenzaldehyde (140 mg, 1 mmol) according to the general procedure C. The following products were obtained: 42 mg (31%) of *trans*-oxirane <u>87</u> (X=Cl) as a white solid;



M.P. 97 - 98°C, (lit.[110] m.p. 100°C);

$[\alpha]_D$= +233° (c=1, EtOH), {lit.[122] for 2R,3R-enantiomer $[\alpha]_D$=+350° (c=1.36, EtOH)};

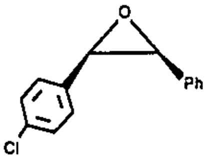
e.e. 72%.;

IR (KBr) ν_{max} 3060, 3000, 1600, 1500, 1100, 1020, 850, 830, 760, 700 and 850 cm^{-1};

^{1}H NMR (200 MHz, $CDCl_3$) δ 3.80 (d, 1H, *J*= 1.83 Hz), 3.82 (d, 1H, *J*= 1.83 Hz), 7.25 (d, 2H, *J*= 7.98 Hz), 7.34 (d, 2H, *J*= 7.98 Hz) and 7.33 - 7.35 (m, 5H);

EIMS m/z (%) 230 (M^+, 28), 232 (M^++2, 10), 201 (M^+-CHO, 18), 203 (28), 195 (M^+-Cl, 38), 165 (56), 139 (43), 141 (14), 105 (53) and 89 (100);

7.5 mg (5.6%) of optically active (+)-*cis*-2-(*p*-chlorophenyl)-3-phenyloxirane **<u>129d</u>** as a colorless oil (eluted second);



[α]$_D$= +6.46° (c=0.65, EtOH);

IR (thin film) ν_{max} 3080, 3040, 2990, 1605, 1180, 1100, 1020, 905, 875, 810, 750 and 700 cm^{-1};

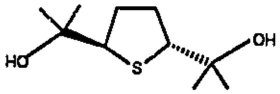
^{1}H NMR (CDCl$_3$) δ 4.29 (d, 1H, *J*= 4.31 Hz), 4.34 (d, 1H, *J*= 4.22 Hz) and 7.06 - 7.23 (m, 9H);

EIMS m/z (%) 230 (M$^+$, 19), 232 (M$^+$+2, 6), 201 (59, M$^+$-CHO), 203 (20), 195 (M$^+$-Cl, 31%), 165 (44), 139 (33), 141 (11), 105 (51) and 89 (100);

and 169 mg (88%) of recovered thiolane 78 (eluted last);

[α]$_D$= -68.3° (c=2.0, CH$_2$Cl$_2$).

trans-2,5-bis-(2-Hydroxypropyl)-thiolane 94.



A solution of MeMgI was prepared from Mg° (2.00 g, 83 mmol) and CH$_3$I (10 g, 70 mmol) in 60 mL of Et$_2$O. After the dissolution of most of the magnesium metal, the reaction was cooled to -30°C and a solution of methyl *trans*-thiophene-2,5-dicarboxylate (1.80 g, 8.8 mmol) in 40 mL of Et$_2$O was added. The reaction mixture was allowed to warm to room temperature over 2 hours and then heated to reflux for an additional 2 hours. The reaction was cooled to -20°C and hydrolyzed with 5 mL of a saturated solution of NH$_4$Cl followed by 10% HCl until a pH=3 was reached. Work up using EtOAc (5 X 20 mL) gave 2.29 g of crude material. Separation (Chromatotron, CH$_2$Cl$_2$:EtOAc, 9:1) gave 1.34 g (74%) of compound 94 as a colorless oil which crystallized on standing as white needles;

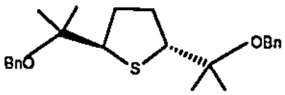
M.P. 55 - 56°C;

IR (thin film) ν_{max} 3430(OH), 2980 and 1140 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 1.13, 1.14 and 1.16 (s, 12 H, 4 X -CH_3), 1.66 - 1.83 (m, 2H), 1.92 - 2.05 (m, 2H), 2.68 (br.s, 2H, 2 X OH) and 3.31 - 3.47 (m, 2H);

EIMS m/z (%) 204 (M^+, 1), 189 (M^+-CH_3, 5), 171 (21), 128 (19), 117 (34) and 59 (100).

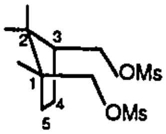
trans-Di-O-benzyl-2,5-bis-(2-hydroxypropyl)-thiolane 95.



To a solution of *trans*-2,5-bis-(2-hydroxypropyl)-thiolane 94 (600 mg, 2.9 mmol) dissolved in 30 mL of THF was added 30 mg of Bn(Et)$_3N^+I^-$. Potassium hydride (300 mg, 7.5 mmol) was added and the mixture was vigorously stirred and heated to reflux for 1 hour. Benzyl bromide (1.11 g, 6.5 mmol) was added and the reflux was continued overnight. Unfortunately, due to a condenser failure, the reaction mixture evaporated and overheated for 1 hour. Nonetheless, hydrolysis of the brown residue with 20 mL of H_2O followed by the usual work up (CH_2Cl_2, 3 X 20 mL) gave 530 mg of a crude residue. Separation (Chromatotron, Hex:EtOAc, 15:1) gave 310 mg of compound 95 as a pale yellow oil;

^{1}H NMR ($CDCl_3$) δ 1.35 (s, 12H), 1.60 - 2.25 (m, 4H), 3.77 - 3.80 (m, 2H), 4.45 (d, 2H, J= 12 Hz), 4.53 (d, 2H, J_{AB}= 12 Hz) and 7.15 - 7.40 (m, 10H).

(1R,3S)-Di-O-methanesulfonyl-1,2,2-trimethyl-1,3-bis(hydroxymethyl)cyclopentane 104.



To a -30°C solution of (1R,3S)-(+)-1,2,2-trimethyl-1,3-bis(hydroxymethyl)-cyclopentane[117] (17.0 g, 0.10 mol) dissolved in 600 mL of dry CH_2Cl_2 was added triethylamine (30.6 mL, 0.22 mol) and dropwise, a solution of methanesulfonyl chloride (17.0 mL, 0.22 mol) in 100 mL of CH_2Cl_2. The mixture was stirred at -30°C for 5 min., then at 0°C for one hour. The reaction mixture was washed with a 5% HCl solution and the organic phase was dried over $MgSO_4$. Removal of the solvent yielded compound <u>**104**</u> (32.6 g, 99%) as a pale yellow oil, which later solidified. This crude material was used without further purification;

MP 69 - 70 °C;

IR (KBr) ν_{max} 3026, 2963, 1351, 1175, 975, 940, 860, 839 and 526 cm^{-1};

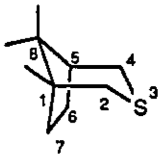
^{1}H NMR (200 MHz, $CDCl_3$) δ 0.82 (s, 3 H), 1.00 (s, 3 H), 1.03 (s, 3 H), 1.29 - 1.48 (m, 2 H), 1.56 - 1.72 (m, 1H), 1.86 - 2.04 (m, 1H), 2.20 - 2.37 (m, 1H), 2.97 (s, 3H), 2.96 (s, 3H), 3.98(d, 1H, *J*= 9.5 Hz), 4.06 (dd, 1H, *J*= 9.6 Hz, *J*= 8.0 Hz), 4.10 (d, 1H, *J*= 9.5 Hz) and 4.22 (dd, 1H, *J*= 9.6 Hz, *J*= 6.0 Hz);

^{13}C NMR (200 MHz, $CDCL_3$) 18.20, 20.42, 23.46, 24.67, 33.10, 36.78, 36.99, 44.38, 46,71, 47.19, 71.27 and 75.14 ppm;

EIMS *m/e* (%) 232 ($M^{+\cdot}$-HO_3SCH_3, 0.4), 136 ($M^{+\cdot}$-2 x HO_3SCH_3, 34), and 121 (100);

Anal. Calcd for $C_{12}H_{24}O_6S_2$: C, 43.88; H, 7.36; S, 19.52. Found: C, 44.00; H,7.30; S,19.74.

<u>**(1R,5S)-(+)-1,8,8-Trimethyl-3-thiabicyclo[3.2.1]octane (105).**</u>



To a warm (70-100°C) suspension of freshly powdered $Na_2S{\cdot}9H_2O$ (30.0 g, 0.125 mol) in 300 mL of DMF was added dropwise (over 30 min.) a solution of the above dimesylate (32.6 g, 0.22 mol) in 100 mL of DMF. The reaction mixture was put under reflux for a 3 h period. The heterogenous solution was cooled, diluted with 300 mL of water and then extracted with hexanes (3 X 200 mL). The combined organic extracts were dried over $MgSO_4$ and the hexanes were removed to yield 11.3 g of a white semi-solid. Column chromatography using hexanes as eluent gave 8.65 g (52%) of compound 105 as a white crystalline compound having a camphoraceous odour;

M.P. 200 - 201 °C;

$[\alpha]^{23}{}_D$ +22.2° (c = 2.1, CH_2Cl_2);

IR (KBr) ν max 2920, 1451, 1385, 1366, 1243, 1087cm^{-1};

^{1}H NMR (200 MHz, $CDCl_3$) δ 0.82 (s, 3 H), 0.89 (s, 3 H), 0.94 (s, 3 H), 1.60 - 1.95 (m, 5 H), 1.82 (d, 1H, *J*= 12.6 Hz), 2.08 (dd, 1H, *J*= 12.3, 3.4 Hz), 2.85 (dd, 1H, *J*= 12.6, *J*= 0.8 Hz) and 3.14 (d, 1H, *J*= 12.3 Hz);

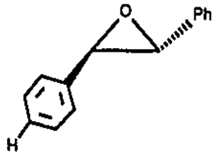
^{13}C NMR and DEPT (200 MHz, $CDCL_3$) 18.34 (CH_3), 21.38 (CH_3), 25.60 (CH_3), 26.60 (CH_2), 30.93 (CH_2), 35.64 (CH_2), 37.04 (CH_2), 41.98 (CR_4), 43,47 (CR_4), 46.33 (CH) ppm;

EIMS *m/e* (relative intensity) 171 ($M^{+\cdot}$+ 1, 7), 170 ($M^{+\cdot}$, 25), 169 ($M^{+\cdot}$- 1, 100), 136 (14), 121 (26), 107 (20), 93 (27), 81 (30), 55 (34);

Anal. Calcd for $C_{10}H_{18}S$: C, 70.52; H, 10.65; S, 18.82. Found: C, 70.30; H,10.42; S,18.60.

Thiane 105 as Chiral Auxiliary and a Mediator for the synthesis of stilbene oxides 87 (X=H).

Thiane 105 (170 mg, 1 mmol) and powdered KOH (200 mg, 3.6 mmol) were dissolved in 10 mL of CH_3CN. To this solution was added a mixture of benzyl bromide (376 mg, 2.2 mmol) and benzaldehyde (213 mg, 2.0 mmol) and vigorous stirring was carried out. After 2 days at room temperature the solution was evaporated under reduced pressure and the product separated by chromatotron chromatography (Hexane:EtOAc, 20:1) gave 134 mg (79% recovery) of thiane 105. Further elution gave 118 mg (30%) of (2R,3R)-(+)-stilbene oxide 87 (X=H);

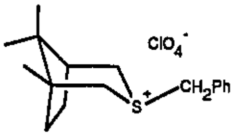


$[\alpha]_D$= +28.4° (c=2, acetone), {lit.[122] $[\alpha]_D$= +291° (c=0.056, acetone)};

e.e.= 10%;

Eluted last was 19 mg (5%) of *cis*-stilbene oxide **101C**.

(1R,3R,5S)-(-)-3-Benzyl-1,8,8-trimethyl-3-thianiumbicyclo[3.2.1]octane perchlorate 106.



The thianium salt **106** was prepared from thiane **105** in 88% yield following the general procedure A. This material is stable at room temperature and can be stored for several months without noticeable decomposition.

MP 182 - 183°C;

$[\alpha]_D$ -7.44° (c = 4.3, $CHCl_3$);

IR (KBr) ν_{max} 3064, 2962, 2883, 1457, 1088, 708 and 622 cm^{-1};

^1H NMR (200 MHz, $CDCl_3$) δ 0.59 (s, 3H, $-CH_3$), 0.81 (s, 3H, $-CH_3$), 0.98 (s, 3H, $-CH_3$), 1.61 - 1.71 (m, 1H), 1.78 - 1.87 (m, 2H), 1.98 - 2.20 (m, 2H), 3.01 (d, 1H, J_{AB}= 12.38 Hz), 3.10 (d, 1H, J_{AB}= 12.41 Hz), 3.25 (d, 1H, J_{AB}= 12.08 Hz), 3.37 (dd, 1H, J_{AB}= 12.08 Hz, J_{BX}= 3.89 Hz), 4.76 (s, 2H) and 7.37 - 7.52 (m, 5H);

^{13}C NMR and DEPT (200 MHz, $CDCL_3$) 17.40 (CH_3), 20.56 (CH_3), 23.88 (CH_3), 25.72 ($-CH_2$), 34.46 ($-CH_2$), 37.37 ($-CH_2$), 41.68 ($-CH_2$), 42.11 (CR_4), 43.97 ($\underline{C}H_2$), 44.03 (CH), 44.20 (CR_4), 126.25 (CR_4), 129.66 (2CH), 130.36 (CH) and 131.49 (2CH) ppm;

Anal. Calcd. for $C_{17}H_{25}ClO_4S$: C, 56.56; H, 6.98; S, 8.88. Found: C, 56.34; H, 6.85; S, 8.69.

Preparation of Stilbene Oxides 87 (X=H) *via* the thiolanium salt 106.

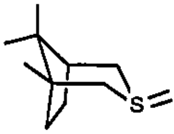
Following the general procedure B, thiolanium salt **106** (635 mg, 1.8 mmol) and benzaldehyde (250 mg, 2.4 mmol) reacted to produce 247 mg (82%) of recovered thiolane **105**; 135 mg (39%) of compound (2R,3R)-(+)-87 (X=H);

$[\alpha]_D$= +45° (c=1.0, acetone), {lit.[122] $[\alpha]_D$= +291° (c=0.056, acetone)};

e.e.= 15%;

and 56.1 mg (16%) of *cis*-stilbene oxide **101C**.

(1R,3R,5S)-(+)-1,8,8-Trimethyl-3-thiabicyclo[3.2.1]octane-3-oxide 107.



A solution of magnesium monoperphthalate hexahydrate (MMPP, 13.84 g, 28 mmol) in H_2O (170 mL) was added dropwise to a solution of **105** (8.65 g, 51 mmol) in ethanol (340 mL) and the mixture was kept at room temperature overnight. The ethanol was removed under reduced presure and the aqueous phase was concentrated to 50 mL, diluted with saturated aqueous $NaHCO_3$ solution (100 mL) and extracted with CH_2Cl_2 (3 X 200 mL). The combined organic extracts were dried over $MgSO_4$ and the solvents evaporated. The white residue was sublimed (110-115°C/0.2 mm) to afford the sulfoxide **107** (8.44 g, 89%) as a white crystalline solid;

MP 240-241 °C;

$[\alpha]^{23}_D$ +27.8° (c=2.8, $CHCl_3$);

IR (KBr) ν_{max} 2930, 1459, 1390, 1028 (S=O)cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (s, 3 H), 0.96 (s, 3 H), 1.14 (s, 3 H), 1.52 - 1.58 (m, 1 H), 1.69 - 1.73 (m, 2 H), 1.86 - 2.05 (m, 2 H), 2.76 (br.d, 1H, *J*= 12.5 Hz), 2.87 (br.d, 1H, *J*= 12.4 Hz), 3.08 (dd, 1H, *J*= 12.5, *J*= 1.8 Hz) and 3.36 (ddd, 1H, *J*= 12.4, *J*= 5.1, *J*=1.9 Hz);

^{13}C NMR and DEPT (200 MHz, $CDCl_3$) ppm 18.60 (CH_3), 21.31 (CH_3), 23.18 (CH_3), 26.14 (CH_2), 35.26 (CH_2), 42.54 (CR_4), 44.29 (CR_4), 45.16 (CH), 53.24 (CH_2) and 59.23 (CH_2);

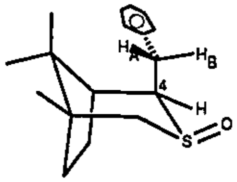
EIMS m/e (relative intensity) 186 ($M^{+\cdot}$, 26), 169 (72), 137 (29), 121 (30), 107 (59), 95 (58), 81 (68), 41 (100);

Anal. Calcd. for $C_{10}H_{18}OS$: C, 64.46; H, 9.73: S, 17.21. Found: C, 64.26; H, 9.63; S, 17.20.

<u>(1R,3S,4R,5S)-(+)-4-Benzyl-1,8,8-trimethyl-3-thiabicyclo[3.2.1]octane-3-oxide 117 and (1R,2S,3R,5S)-(-)-2-benzyl-1,8,8-trimethyl-3-thiabicyclo[3.2.1]octane-3-oxide 116.</u>

To a -30°C solution of (1R,3R,5S)-(+)-1,8,8-trimethyl-3-thiabicyclo[3.2.1]-octane-3-oxide <u>107</u> (2.0 g, 10.7 mmol) in 50 mL of THF containing a trace amount of *o*-phenanthroline, was added methyllithium (1.4 M, 1.2 eq) in THF. A deep red coloration appeared and a methane evolution was immediately observed. The temperature was raised to ≈ -10°C (salt/ice bath) for 30 min. and then cooled to -78°C. After 15 min., benzyl bromide (5 eq) was added. The reaction mixture was stirred at -78°C for 3 hrs and then the temperature was allow to rise slowly to room temperature overnight. To the resulting orange yellow solution was added 30 mL of water and 50 mL of ether. The organic phase was separated and the aqueous layer was extracted with dichloromethane (2 X 40 mL). The organic layers were combined, dried ($MgSO_4$) and evaporated to dryness (excess benzyl bromide was evaporated at 70°C/0.2 mm). The crude yellow oil was purified on silica gel using hexanes:*t*-butanol (85:15) as eluent to give first (1R,3S,4R,5S)-(+)-4-benzyl-1,8,8-trimethyl-3-thiabicyclo[3.2.1]octane-3-oxide

117 (713 mg, 24%) as a clear oil. Recrystallization from ether gave a white solid;



MP 64 - 65°C;

$[\alpha]^{23}_D$ +171.6° (c=4.0, $CHCl_3$);

IR (KBr) ν_{max} 2921, 1455, 1036 (S=O), 745, 724, 704 cm^{-1};

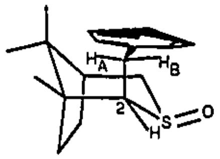
^1H NMR (500 MHz, $CDCl_3$) δ 0.85 (s, 3 H), 0.96 (s, 3 H), 1.28 (s, 3 H), 1.41 (ddd, 1H, *J*= 14.3, *J*= 9.6, *J*= 4.8 Hz), 1.64 (dddd, 1H, *J*= 14.1, *J*= 12.4, *J*= 4.6 , *J*= 2.36 Hz), 1.76 (ddd, 1H, *J*= 14.1, *J*= 9.6, *J*= 4.8 Hz), 2.06 (dddd, 1H, *J*= 14.3, *J*= 12.4, *J*= 8.1, *J*= 4.8 Hz), 2.18 (dd, 1H, *J*= 8.1, *J*= 3.6 Hz), 2.74 (dd, 1H, *J*= 12.7, *J*= 2.3 Hz), 2.83 (dd, 1H, J= 14.6, *J*= 8.4 Hz), 3.06 (d, 1H, *J*= 12.7 Hz), 3.47 (dd, 1H, *J*= 14.6, *J*= 4.9 Hz), 3.52 (ddd, 1H, *J*= 8.4, *J*= 4.9, *J*= 3.6 Hz) and 7.17 - 7.30 (m,5 H);

^{13}C NMR and DEPT (200 MHz, $CDCl_3$) ppm 21.23 (CH_3), 21.31 (CH_3), 24.99 (CH_3), 28.52 (CH_2), 31.02 (CH_2), 34.31 (CH_2), 43.16 (CR_4), 44.77 (CR_4), 48.28 (CH), 58.21 (CH_2), 64.89 (CH), 126.15 (CH), 128.61 (2CH), 129.08 (2CH), 141.04 (CR_4);

EIMS *m/e* (relative intensity) 276 ($M^{+\cdot}$, 15), 259 (71), 213 (18), 169 (34), 109 (87), 91 (100);

Anal. Calcd. for $C_{17}H_{24}OS$: C, 73.86; H, 8.75; S, 11.59. Found: C, 74.01; H, 8.64; S, 11.38.

A second compound was eluted and identified as (1R,2S,3R,5S)-(-)-2-benzyl-1,8,8-trimethyl-3-thiabicyclo[3.2.1]octane-3-oxide 116 (1.28 g, 43%), a colorless oil which solidified on standing. Recrystalization from ether gave white needles:



MP 109 - 110°C;

$[\alpha]^{23}_{D}$= -213.6° (c=2.0, CH_2Cl_2);

IR (KBr) ν_{max} 2929, 1493, 1457, 1038 (S=O), 759, 738, 707 cm^{-1};

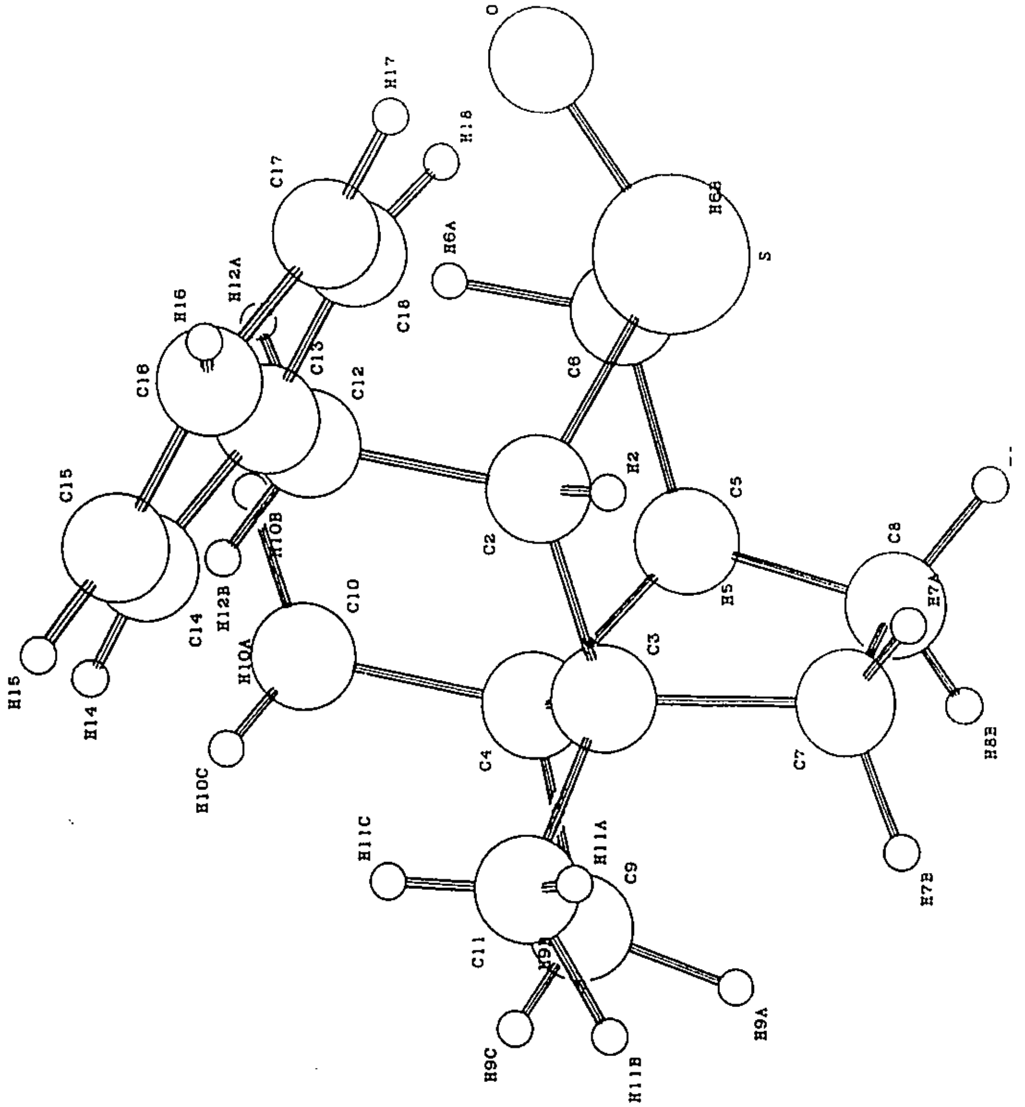
^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (s, 3 H), 1.19 (s, 3 H), 1.20 (s, 3 H), 1.60 (ddd, 1H, *J*= 12.8, *J*= 9.4, *J*= 3.8 Hz), 1.68 (ddd, 1H, *J*= 13.8, *J*= 9.4, *J*= 3.5 Hz), 1.83 (ddd, 1H, *J* = 13.8, *J*= 11.6, *J*= 3.8 Hz), 1.90 (m, 1 H), 1.96 (dd, 1H, *J*= 12.8, *J*= 5.3 Hz), 2.77 (d, 1H, *J*= 12.5 Hz), 2.79 (dd, 1H, *J*= 15.0, *J*= 2.9 Hz), 3.26 (dd, 1H, *J*= 12.5, *J*= 5.3 Hz), 3.31 (dd, 1H, *J*= 5.5, *J*= 2.9 Hz), 3.48 (dd, 1H, *J*= 15.0, *J*= 5.5 Hz) and 7.09-7.35 (m, 5 H);

^{13}C NMR and DEPT (200 MHz, $CDCl_3$) ppm 21.30 (CH_3), 22.27 (CH_3), 25.26 (CH_3), 25.95 (CH_2), 29.45 (CH_2), 38.30 (CH_2), 42.99 (CR_4), 45.90 (CH), 47.45 (CR_4), 51.33 (CH_2), 71.29 (CH), 125.80 (CH), 128.47 (2CH), 129.19 (2CH), 143.36 (CR_4);

EIMS *m/e* (relative intensity) 276 ($M^{+\cdot}$, 15), 259 (M^+-17, 47), 169 (41), 157 (52), 129 (56), 91 (100);

Anal. Calcd. for $C_{17}H_{24}OS$: C, 73.86; H, 8.75; S, 11.59. Found: C, 74.00; H, 8.92; S, 11.41.

<u>X-ray Crystal Structure Data for 116.</u>


O
H17
H18
C17
H6B
S
H6A
C18
H12A
H16
C13
C12
C16
C6
H2
C15
C5
C2
H10B
C8
C10
H12B
H5
H7A
C14
C3
H10A
H15
H14
C4
C7
H8B
H10C
H11C
H11A
C9
H7B
C11
H9B
H9A
H9C
H11B

```
   Space Group and Cell Dimensions    Monoclinic,    P 21
a   7.1706(4)    b  12.9961(19)    c   8.4847(9)
beta 104.750(6)
        Volume   764.64(14)A**3

Empirical formula : C17 H24 S O


Cell dimensions were obtained from  24 reflections with 2Theta angle
in the range 100.00 - 120.00 degrees.

Crystal dimensions :  0.20  X  0.30  X  0.20  mm

FW =     276.43      Z =     2      F(000) =      297.97

Dcalc  1.201Mg.m-3, mu   1.74mm-1, lambda 1.54056A, 2Theta(max) 119.8

The intensity data were collected on a Picker diffractometer,
using the theta/2theta scan mode.
The h,k,l ranges are :--      -8   7,     0  14,     0   9
No. of reflections measured                         1446
No. of unique reflections                           1419
No. of reflections with Inet > 2.5sigma(Inet)  1375
No correction was made for absorption


The last least squares cycle was calculated with
 43 atoms, 268 parameters and 1375 out of 1419 reflections.
Weights based on counting-statistics were used.

The residuals are as follows :--
For significant reflections,  RF 0.036, Rw 0.037 GoF  7.76
For all reflections,          RF 0.037, Rw 0.040.
where RF = Sum(Fo-Fc)/Sum(Fo),
      Rw = Sqrt[Sum(w(Fo-Fc)**2)/Sum(wFo**2)] and
     GoF = Sqrt[Sum(w(Fo-Fc)**2)/(No. of reflns - No. of params.)]
The maximum shift/sigma ratio was  0.724.

In the last D-map, the deepest hole was  - 0.130e/A**3,
and the highest peak   0.130e/A**3.

Secondary ext. coeff. =    6.243510      sigma =    0.235724
```

Table of Atomic Bonds Distances in Angstroms

S-O	1.491(3)
S-C(2)	1.843(3)
S-C(6)	1.819(5)
C(2)-C(3)	1.550(4)
C(2)-C(12)	1.530(5)
C(2)-H(2)	0.90(4)
C(3)-C(4)	1.553(5)
C(3)-C(7)	1.555(5)
C(3)-C(11)	1.537(5)
C(4)-C(5)	1.542(5)
C(4)-C(9)	1.545(6)
C(4)-C(10)	1.527(6)
C(5)-C(6)	1.521(6)
C(5)-C(8)	1.523(6)
C(5)-H(5)	1.15(5)
C(6)-H(6A)	1.12(5)
C(6)-H(6B)	0.75(5)
C(7)-C(8)	1.540(6)
C(7)-H(7A)	0.98(4)
C(7)-H(7B)	1.01(5)
C(8)-H(8A)	0.98(5)
C(8)-H(8B)	0.93(5)
C(9)-H(9A)	1.05(5)
C(9)-H(9B)	1.01(6)
C(9)-H(9C)	0.88(5)
C(10)-H(10A)	0.96(5)
C(10)-H(10B)	1.10(4)
C(10)-H(10C)	0.89(5)
C(11)-H(11A)	0.88(7)
C(11)-H(11B)	1.09(5)
C(11)-H(11C)	0.89(6)
C(12)-C(13)	1.495(6)
C(12)-H(12A)	0.92(4)
C(12)-H(12B)	0.98(4)
C(13)-C(14)	1.387(6)
C(13)-C(18)	1.390(5)
C(14)-C(15)	1.377(8)
C(14)-H(14)	0.92(5)
C(15)-C(16)	1.388(10)
C(15)-H(15)	0.99(7)
C(16)-C(17)	1.367(8)
C(16)-H(16)	0.92(6)
C(17)-C(18)	1.374(6)
C(17)-H(17)	1.03(5)
C(18)-H(18)	0.94(4)
H(7A)-H(7B)	1.54(5)
H(8A)-H(8B)	1.53(6)
H(9A)-H(9C)	1.46(6)
H(10A)-H(10C)	1.54(7)
H(11A)-H(11B)	1.50(7)
H(11A)-H(11C)	1.47(9)
H(12A)-H(12B)	1.49(5)

Table of Atomic Angles in Degrees

O-S-C(2)	107.99(16)
O-S-C(6)	105.76(22)
C(2)-S-C(6)	98.02(20)
S-C(2)-C(3)	110.71(23)
S-C(2)-C(12)	113.0(3)
S-C(2)-H(2)	97.3(18)
C(3)-C(2)-C(12)	120.2(3)
C(3)-C(2)-H(2)	105.9(18)
C(12)-C(2)-H(2)	106.9(19)
C(2)-C(3)-C(4)	114.2(3)
C(2)-C(3)-C(7)	108.5(3)
C(2)-C(3)-C(11)	107.1(3)
C(4)-C(3)-C(7)	101.6(3)
C(4)-C(3)-C(11)	114.6(3)
C(7)-C(3)-C(11)	110.7(3)
C(3)-C(4)-C(5)	100.7(3)
C(3)-C(4)-C(9)	111.4(4)
C(3)-C(4)-C(10)	117.2(3)
C(5)-C(4)-C(9)	107.6(3)
C(5)-C(4)-C(10)	113.9(4)
C(9)-C(4)-C(10)	105.8(4)
C(4)-C(5)-C(6)	110.6(4)
C(4)-C(5)-C(8)	103.3(4)
C(4)-C(5)-H(5)	111.7(21)
C(6)-C(5)-C(8)	112.1(4)
C(6)-C(5)-H(5)	112.2(19)
C(8)-C(5)-H(5)	106.4(21)
S-C(6)-C(5)	112.4(3)
S-C(6)-H(6A)	96.9(23)
S-C(6)-H(6B)	103(3)
C(5)-C(6)-H(6A)	114.7(22)
C(5)-C(6)-H(6B)	110(3)
H(6A)-C(6)-H(6B)	117(4)
C(3)-C(7)-C(8)	106.5(3)
C(3)-C(7)-H(7A)	110.7(20)
C(3)-C(7)-H(7B)	111.6(23)
C(8)-C(7)-H(7A)	113.3(20)
C(8)-C(7)-H(7B)	113.1(24)
H(7A)-C(7)-H(7B)	101(3)
C(5)-C(8)-C(7)	105.2(3)
C(5)-C(8)-H(8A)	113(3)
C(5)-C(8)-H(8B)	111(3)
C(7)-C(8)-H(8A)	110(3)
C(7)-C(8)-H(8B)	110.7(25)
H(8A)-C(8)-H(8B)	106(3)
C(4)-C(9)-H(9A)	116.5(21)
C(4)-C(9)-H(9B)	109(3)
C(4)-C(9)-H(9C)	109(3)
H(9A)-C(9)-H(9B)	101(3)
H(9A)-C(9)-H(9C)	97(4)
H(9B)-C(9)-H(9C)	122(4)
C(4)-C(10)-H(10A)	111.0(24)
C(4)-C(10)-H(10B)	114.7(21)
C(4)-C(10)-H(10C)	107(3)
H(10A)-C(10)-H(10B)	102(3)
H(10A)-C(10)-H(10C)	112(4)
H(10B)-C(10)-H(10C)	108(3)
C(3)-C(11)-H(11A)	112(4)
C(3)-C(11)-H(11B)	109.5(24)
C(3)-C(11)-H(11C)	104(3)
H(11A)-C(11)-H(11B)	97(4)
H(11A)-C(11)-H(11C)	112(5)
H(11B)-C(11)-H(11C)	120(4)
C(2)-C(12)-C(13)	113.2(3)
C(2)-C(12)-H(12A)	111.1(22)
C(2)-C(12)-H(12B)	108.9(18)
C(13)-C(12)-H(12A)	109.4(24)
C(13)-C(12)-H(12B)	110.8(19)
H(12A)-C(12)-H(12B)	102(3)
C(12)-C(13)-C(14)	121.5(4)
C(12)-C(13)-C(18)	121.4(4)
C(14)-C(13)-C(18)	117.1(4)
C(13)-C(14)-C(15)	120.9(5)
C(13)-C(14)-H(14)	116(3)
C(15)-C(14)-H(14)	122(3)
C(14)-C(15)-C(16)	120.7(5)
C(14)-C(15)-H(15)	123(3)
C(16)-C(15)-H(15)	115(3)
C(15)-C(16)-C(17)	119.1(5)
C(15)-C(16)-H(16)	132(3)
C(17)-C(16)-H(16)	108(3)
C(16)-C(17)-C(18)	119.9(5)
C(16)-C(17)-H(17)	115.1(25)
C(18)-C(17)-H(17)	125.0(25)
C(13)-C(18)-C(17)	122.3(4)
C(13)-C(18)-H(18)	115.4(22)
C(17)-C(18)-H(18)	122.1(23)

1 Torsion angles

O	S	C2	C3	156.1(3)	O	S	C2	C12	[illegible] 1(2)
O	S	C2	H2	-93.8(19)	C6	S	C2	C3	[illegible].6(2)
C6	S	C2	C12	-91.4(3)	C6	S	C2	H2	156.7(19)
O	S	C6	C5	-162.3(4)	O	S	C6	H6A	-42.0(22)
O	S	C6	H6B	78.5(32)	C2	S	C6	C5	-51.0(2)
C2	S	C6	H6A	69.3(22)	C2	S	C6	H6B	-170.1(32)
S	C2	C3	C4	-64.6(2)	S	C2	C3	C7	47.8(2)
S	C2	C3	C11	167.3(4)	C12	C2	C3	C4	69.9(3)
C12	C2	C3	C7	-177.6(4)	C12	C2	C3	C11	-58.1(3)
H2	C2	C3	C4	-169.0(19)	H2	C2	C3	C7	-56.6(19)
H2	C2	C3	C11	62.9(19)	S	C2	C12	C13	-105.9(3)
S	C2	C12	H12A	17.7(23)	S	C2	C12	H12B	130.3(18)
C3	C2	C12	C13	120.4(4)	C3	C2	C12	H12A	-115.9(23)
C3	C2	C12	H12B	-3.3(18)	H2	C2	C12	C13	-0.1(19)
H2	C2	C12	H12A	123.5(30)	H2	C2	C12	H12B	-123.9(26)
C2	C3	C4	C5	72.5(3)	C2	C3	C4	C9	-173.6(4)
C2	C3	C4	C10	-51.6(3)	C7	C3	C4	C5	-44.0(2)
C7	C3	C4	C9	69.9(3)	C7	C3	C4	C10	-168.1(4)
C11	C3	C4	C5	-163.3(4)	C11	C3	C4	C9	-49.5(3)
C11	C3	C4	C10	72.6(3)	C2	C3	C7	C8	-94.3(3)
C2	C3	C7	H7A	29.3(19)	C2	C3	C7	H7B	141.8(23)
C4	C3	C7	C8	26.3(2)	C4	C3	C7	H7A	149.9(20)
C4	C3	C7	H7B	-97.6(23)	C11	C3	C7	C8	148.4(4)
C11	C3	C7	H7A	-87.9(19)	C11	C3	C7	H7B	24.5(23)
C2	C3	C11	H11A	-54.9(37)	C2	C3	C11	H11B	-162.4(22)
C2	C3	C11	H11C	67.0(32)	C4	C3	C11	H11A	177.3(38)
C4	C3	C11	H11B	69.8(22)	C4	C3	C11	H11C	-60.8(32)
C7	C3	C11	H11A	63.2(37)	C7	C3	C11	H11B	-44.3(22)
C7	C3	C11	H11C	-174.9(33)	C3	C4	C5	C6	-74.0(3)
C3	C4	C5	C8	46.2(2)	C3	C4	C5	H5	160.2(20)
C9	C4	C5	C6	169.3(5)	C9	C4	C5	C8	-70.5(3)
C9	C4	C5	H5	43.5(20)	C10	C4	C5	C6	52.4(3)
C10	C4	C5	C8	172.6(5)	C10	C4	C5	H5	-73.4(20)
C3	C4	C9	H9A	-51.1(21)	C3	C4	C9	H9B	-165.7(28)
C3	C4	C9	H9C	58.2(29)	C5	C4	C9	H9A	58.4(21)
C5	C4	C9	H9B	-56.3(27)	C5	C4	C9	H9C	167.6(29)
C10	C4	C9	H9A	-179.5(22)	C10	C4	C9	H9B	65.8(27)
C10	C4	C9	H9C	-70.3(29)	C3	C4	C10	H10A	179.0(25)
C3	C4	C10	H10B	64.0(20)	C3	C4	C10	H10C	-56.9(25)
C5	C4	C10	H10A	61.9(25)	C5	C4	C10	H10B	-53.2(20)
C5	C4	C10	H10C	-174.1(26)	C9	C4	C10	H10A	-56.1(25)
C9	C4	C10	H10B	-171.2(21)	C9	C4	C10	H10C	67.9(25)
C4	C5	C6	S	71.1(3)	C4	C5	C6	H6A	-38.3(22)
C4	C5	C6	H6B	-174.2(32)	C8	C5	C6	S	-43.7(2)
C8	C5	C6	H6A	-153.1(23)	C8	C5	C6	H6B	71.1(32)
H5	C5	C6	S	-163.4(20)	H5	C5	C6	H6A	87.2(30)
H5	C5	C6	H6B	-48.7(37)	C4	C5	C8	C7	-29.8(2)
C4	C5	C8	H8A	-150.0(26)	C4	C5	C8	H8B	90.2(24)
C6	C5	C8	C7	89.4(4)	C6	C5	C8	H8A	-30.8(25)
C6	C5	C8	H8B	-150.6(24)	H5	C5	C8	C7	-147.5(20)
H5	C5	C8	H8A	92.2(32)	H5	C5	C8	H8B	-27.6(31)
C3	C7	C8	C5	1.9(2)	C3	C7	C8	H8A	124.1(26)
C3	C7	C8	H8B	-118.5(24)	H7A	C7	C8	C5	-120.1(20)
H7A	C7	C8	H8A	2.1(32)	H7A	C7	C8	H8B	119.6(31)
H7B	C7	C8	C5	124.9(23)	H7B	C7	C8	H8A	-112.9(34)

H7B	C7	C8	H8B	4.5(33)
C8	C7	H7A	H7B	-121.7(26)
C3	C7	H7B	H7A	-118.0(28)
H7A	C7	H7B	H7A	0.0(24)
C7	C8	H8A	H8B	120.1(31)
C5	C8	H8B	H8A	123.7(30)
H8A	C8	H8B	H8A	0.0(31)
H9B	C9	H9A	H9C	-125.1(46)
C4	C9	H9C	H9A	-121.6(33)
H9B	C9	H9C	H9A	108.9(46)
H10B	C10	H10A	H10C	-116.2(40)
C4	C10	H10C	H10A	-123.0(30)
H10B	C10	H10C	H10A	112.3(39)
C3	C11	H11A	H11C	117.7(42)
H11B	C11	H11A	H11C	-127.5(56)
H11C	C11	H11A	H11C	0.0(40)
H11A	C11	H11B	H11A	0.0(45)
C3	C11	H11C	H11A	-122.0(40)
H11B	C11	H11C	H11A	114.2(50)
C2	C12	C13	C18	63.6(3)
H12A	C12	C13	C18	-60.9(23)
H12B	C12	C13	C18	-173.7(19)
C13	C12	H12A	H12B	-117.9(27)
C2	C12	H12B	H12A	-118.0(24)
H12A	C12	H12B	H12A	0.0(27)
C12	C13	C14	H14	-1.5(27)
C18	C13	C14	H14	-179.3(28)
C12	C13	C18	H18	-1.9(21)
C14	C13	C18	H18	175.9(22)
C13	C14	C15	H15	-175.5(32)
H14	C14	C15	H15	3.4(41)
C14	C15	C16	H16	178.4(30)
H15	C15	C16	H16	-6.8(43)
C15	C16	C17	H17	180.0(24)
H16	C16	C17	H17	2.9(37)
C16	C17	C18	H18	-174.6(22)
H17	C17	C18	H18	3.7(31)
C8	H8A	H8B	C8	0.0(4)
C10	H10A	H10C	C10	0.0(5)
H11C	H11A	H11B	C11	28.0(27)
H11B	H11A	H11C	C11	-37.4(35)

C3	C7	H7A	H7B	118.6(26)
H7B	C7	H7A	H7B	0.0(28)
C8	C7	H7B	H7A	121.9(29)
C5	C8	H8A	H8B	-122.5(32)
H8B	C8	H8A	H8B	0.0(29)
C7	C8	H8B	H8A	-119.7(29)
C4	C9	H9A	H9C	115.9(30)
H9C	C9	H9A	H9C	0.0(35)
H9A	C9	H9C	H9A	0.0(27)
C4	C10	H10A	H10C	121.1(31)
H10C	C10	H10A	H10C	0.0(31)
H10A	C10	H10C	H10A	0.0(30)
C3	C11	H11A	H11B	-114.9(40)
H11B	C11	H11A	H11B	0.0(28)
H11C	C11	H11A	H11B	127.5(64)
C3	C11	H11B	H11A	117.0(35)
H11C	C11	H11B	H11A	-121.5(54)
H11A	C11	H11C	H11A	0.0(45)
C2	C12	C13	C14	-114.1(4)
H12A	C12	C13	C14	121.3(23)
H12B	C12	C13	C14	8.6(18)
C2	C12	H12A	H12B	116.3(26)
H12B	C12	H12A	H12B	0.0(23)
C13	C12	H12B	H12A	116.9(24)
C12	C13	C14	C15	177.5(5)
C18	C13	C14	C15	-0.3(3)
C12	C13	C18	C17	-176.8(5)
C14	C13	C18	C17	1.0(3)
C13	C14	C15	C16	-1.3(3)
H14	C14	C15	C16	177.7(28)
C14	C15	C16	C17	2.2(3)
H15	C15	C16	C17	176.9(32)
C15	C16	C17	C18	-1.5(3)
H16	C16	C17	C18	-178.6(30)
C16	C17	C18	C13	-0.1(3)
H17	C17	C18	C13	178.3(23)
C7	H7A	H7B	C7	0.0(3)
C9	H9A	H9C	C9	0.0(8)
C11	H11A	H11B	C11	0.0(10)
C11	H11A	H11C	C11	0.0(5)
C12	H12A	H12B	C12	0.0(4)

```
BIVOET -- Best Measurable Bijvoet Differences

This routine selects reflections for which the Bijvoet difference is
  MOST significant, i.e. (Fc+ - Fc-)/Sigma(Fo) is largest.
If Fo- is available (Fc+ - Fc-) is compared to (Fo+ - Fo-).
Before running the routine Structure Factors must be calculated with :--
 (1) A refined structure
 (2) The dispersion flag "Yes" for all atoms
 (3) An ETA parameter of 1.0.
If this has not been done, abort the run by requesting 0 reflections.

        h    k    l    Fc+           Fc-    Del/Sig   Fo+            Fo-    Sense
   1   -2    2    2    6.864 <        8.397 -87.263    8.143 <        10.007   +
   2    1    6    1    9.781   >      8.509  57.429    9.950   >       9.360   +
   3   -2    4    2    9.526   >      8.434  53.901    9.578   >       8.593   +
   4    0    5    3    9.128 <       10.219 -47.539   10.545 <        12.310   +
   5   -3    5    2    9.672   >      8.545  45.624    9.926   >       8.949   +
   6    2    3    2    7.032 <        7.952 -43.234    8.000 <         9.212   +
   7    1    4    2    2.980 <        3.913 -43.023    3.420 <         4.704   +
   8   -1    4    4    2.691 <        3.752 -41.184    3.492 <         4.698   +
   9   -2    3    3    9.613 <       10.448 -40.289   11.055 <        12.193   +
  10   -2    4    1   11.160 <       12.172 -37.235   12.662 <        14.374   +
  11    1    3    4    7.562   >      6.658  36.155    8.062   >       7.420   +
  12   -1    3    2   15.169   >     14.151  35.081   15.888   >      15.165   +
  13   -4    3    2   11.808   >     10.928  34.413   12.459   >      11.751   +
  14    2    5    2    5.530   >      4.686  34.304    5.557   >       5.015   +
  15   -1    6    3    6.228   >      5.386  34.110    6.814   >       6.216   +
  16    3    4    1    4.773   >      3.913  34.051    5.080   >       4.305   +
  17    3    3    1    7.345   >      6.564  33.595    7.279   >       6.566   +
  18   -3    3    3    3.456 <        4.260 -32.764    3.955 <         5.182   +
  19    1    5    3   12.201   >     11.457  30.678   12.762   >      12.759   +
  20   -2    3    4    5.012 <        5.733 -30.076    5.407 <         6.269   +
  21   -4    5    2    8.916   >      8.065  30.010    8.921   >       8.310   +
  22   -2    2    1   18.877 <       20.328 -29.741   20.611 <        22.467   +
  23    0    4    4    7.327   >      6.607  29.402    7.750   >       7.375   +
  24    1    2    1   21.374 <       22.921 -29.217   21.807 <        23.961   +
  25    3    3    3    5.906   >      5.069  29.212    5.772   >       4.985   +
  26    3    6    1    9.761   >      8.970  28.482    9.792   >       9.556   +
  27   -2    4    3    8.546   >      7.916  28.240    8.808   >       8.284   +
  28    1    2    3    8.196 <        8.718 -25.612    9.027 <         9.773   +
  29   -1    6    4    8.626   >      7.942  24.957    8.986   >       8.764   +
  30   -2    5    1    4.006 <        4.561 -24.697    4.736 <         5.660   +
  31   -2    6    3    9.708   >      9.095  23.684   10.229   >      10.117   +
  32    0    3    3   23.781   >     22.455  22.552   24.456   >      23.870   +
  33   -4    2    4   11.385 <       11.998 -22.040   12.506 <        13.183   +
  34    0    6    4    3.867 <        4.442 -19.666    4.218 <         5.278   +
  35    0    4    0   19.498   >     18.182  19.576   19.419   >      18.684   +
  36   -1    4    2    7.561 <        7.918 -19.124    8.461 <         9.115   +
  37    0    5    4   15.688   >     15.125  17.660   16.419 <        16.680     -
  38    1    5    4    9.707   >      9.233  17.285   10.295 <        10.391     -
  39   -4    2    2    5.273 <        5.702 -17.007    5.581 <         6.189   +
  40    5    3    1    3.548 <        4.120 -16.558    3.578 <         4.335   +
  41   -1    3    1   28.619 <       29.814 -15.312   30.026 <        31.760   +
  42    0    6    0   12.513   >     11.780  14.520   13.198   >      13.105   +
  43    3    5    2   10.813   >     10.516  10.801   11.134 <        11.364     -
  44    3    2    1   21.309 <       22.017 -10.768   23.161 <        24.417   +
  45   -4    2    3   10.849 <       11.106 -10.045   12.092 <        12.633   +
```

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  46    -4    5    1   8.834   >    8.582   8.987   9.571 <     9.786    -
  47    -5    2    2   4.834 <      5.080  -8.258   5.529 <     6.043   +
  48     1    7    0  12.110 <     12.277  -7.006  13.098 <    14.272   +
  49     2    2    3  11.348 <     11.427  -3.385  11.972 <    12.452   +

Out of  49 TOTAL measurements, (Fo+ - Fo-) has the SAME sign as (Fc+ - Fc-)
in  45 cases and the OPPOSITE sign in   4 cases.

                    Cumulative Binomial Distribution

The Absolute Structure of the Model is CONFIRMED
Based on  49 Measurements,  45 of which Support the Model
The Probability that the Above Statement is WRONG is 0.1206E-15
```

Table of Atomic Parameters x,y,z and Biso.
E.S.Ds. refer to the last digit printed.

	x	y	z	Biso
S	0.66733(13)	0.81076	0.90017(12)	6.00(5)
O	0.6762 (4)	0.7873 (3)	0.7302 (3)	8.49(19)
C2	0.4203 (5)	0.8533 (3)	0.8934 (4)	4.24(15)
C3	0.3740 (4)	0.8352 (3)	1.0600 (4)	4.26(15)
C4	0.3715 (5)	0.7202 (3)	1.1090 (4)	4.81(17)
C5	0.5889 (6)	0.6952 (4)	1.1515 (5)	5.62(19)
C6	0.6595 (8)	0.6867 (4)	0.9975 (7)	6.36(24)
C7	0.5444 (6)	0.8774 (4)	1.1968 (5)	5.41(19)
C8	0.6798 (6)	0.7858 (4)	1.2573 (6)	6.26(22)
C9	0.3023 (9)	0.7071 (5)	1.2660 (6)	6.8 (3)
C10	0.2479 (7)	0.6471 (4)	0.9842 (6)	5.73(21)
C11	0.1874 (7)	0.8943 (5)	1.0566 (6)	6.00(22)
C12	0.2738 (6)	0.8230 (4)	0.7352 (4)	5.18(18)
C13	0.2099 (5)	0.9117 (3)	0.6222 (4)	4.96(17)
C14	0.0212 (7)	0.9470 (5)	0.5851 (5)	7.0 (3)
C15	-0.0338 (9)	1.0312 (5)	0.4857 (6)	8.3 (3)
C16	0.0991 (9)	1.0841 (5)	0.4228 (5)	7.2 (3)
C17	0.2851 (7)	1.0493 (4)	0.4562 (4)	6.11(24)
C18	0.3388 (6)	0.9646 (3)	0.5541 (4)	5.29(20)
H2	0.441 (4)	0.921 (3)	0.888 (3)	3.5 (7)
H5	0.625 (6)	0.623 (3)	1.232 (5)	7.7 (11)
H6A	0.556 (7)	0.649 (4)	0.892 (5)	7.9 (11)
H6B	0.763 (6)	0.669 (4)	1.018 (5)	6.5 (12)
H7A	0.608 (5)	0.935 (3)	1.156 (4)	4.5 (8)
H7B	0.497 (6)	0.912 (4)	1.286 (5)	7.7 (10)
H8A	0.810 (6)	0.802 (4)	1.249 (5)	8.8 (11)
H8B	0.690 (5)	0.773 (3)	1.367 (6)	7.6 (11)
H9A	0.371 (5)	0.752 (3)	1.366 (5)	6.6 (10)
H9B	0.334 (7)	0.636 (4)	1.311 (6)	8.5 (13)
H9C	0.186 (7)	0.734 (4)	1.251 (5)	7.6 (13)
H10A	0.258 (6)	0.578 (4)	1.025 (5)	7.4 (11)
H10B	0.294 (6)	0.639 (3)	0.871 (5)	7.1 (10)
H10C	0.128 (6)	0.671 (3)	0.959 (5)	6.0 (10)
H11A	0.196 (9)	0.960 (5)	1.033 (7)	12.0 (21)
H11B	0.173 (6)	0.904 (4)	1.181 (5)	8.0 (11)
H11C	0.096 (8)	0.862 (4)	0.982 (6)	9.5 (16)
H12A	0.322 (5)	0.772 (4)	0.681 (5)	6.1 (10)
H12B	0.164 (5)	0.790 (3)	0.762 (4)	4.9 (8)
H14	-0.063 (7)	0.912 (4)	0.632 (5)	8.0 (13)
H15	-0.165 (9)	1.062 (5)	0.462 (6)	11.4 (17)
H16	0.088 (7)	1.140 (4)	0.354 (6)	8.4 (12)
H17	0.376 (6)	1.092 (4)	0.406 (5)	7.5 (11)
H18	0.467 (5)	0.942 (3)	0.587 (4)	5.8 (9)

Biso is the Mean of the Principal Axes of the Thermal Ellipsoid

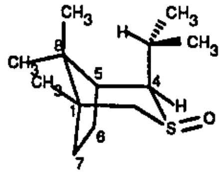
Table of u(i,j) or U values *100.
E.S.Ds. refer to the last digit printed

	u11(U)	u22	u33	u12	u13	u23
S	6.42(5)	8.20(7)	9.17(7)	0.06(6)	3.76(5)	0.66(6)
O	12.03(22)	12.1 (3)	10.56(20)	1.75(21)	7.29(18)	1.08(21)
C2	5.43(19)	5.04(22)	5.75(18)	-0.13(15)	1.63(15)	-0.05(16)
C3	5.35(17)	5.81(24)	5.05(16)	-0.23(16)	1.36(14)	-0.49(16)
C4	5.84(21)	7.00(25)	5.63(20)	-0.18(18)	1.80(16)	0.22(18)
C5	6.73(24)	7.2 (3)	7.22(24)	0.49(20)	1.47(19)	1.00(22)
C6	6.1 (3)	8.2 (3)	10.3 (4)	1.63(25)	2.9 (3)	1.3 (3)
C7	7.09(24)	7.5 (3)	5.63(22)	-0.64(22)	0.96(19)	-0.76(21)
C8	7.0 (3)	9.2 (4)	6.7 (3)	-0.71(24)	0.27(20)	0.55(25)
C9	8.7 (3)	10.3 (4)	7.4 (3)	-0.3 (3)	3.27(25)	1.7 (3)
C10	7.5 (3)	6.0 (3)	8.2 (3)	-1.06(23)	1.86(23)	0.08(23)
C11	6.8 (3)	7.9 (3)	8.4 (3)	0.98(24)	2.35(23)	-1.3 (3)
C12	7.65(23)	6.4 (3)	5.50(19)	-1.22(23)	1.36(18)	-1.01(20)
C13	7.44(24)	6.94(23)	4.11(16)	-0.45(20)	0.84(16)	-0.91(17)
C14	7.4 (3)	11.7 (4)	6.9 (3)	0.1 (3)	0.96(22)	0.6 (3)
C15	9.1 (4)	14.0 (6)	7.5 (3)	3.6 (4)	0.1 (3)	1.0 (3)
C16	12.5 (5)	8.6 (3)	5.31(23)	1.3 (3)	0.3 (3)	0.65(25)
C17	10.2 (3)	8.2 (3)	4.61(20)	-0.2 (3)	1.56(21)	0.07(20)
C18	8.0 (3)	7.05(25)	5.07(19)	0.19(22)	1.64(19)	-0.05(19)

Anisotropic Temperature Factors are of the form
Temp=-2*Pi*Pi*(h*h*u11*astar*astar+---+2*h*k*u12*astar*bstar+---)

(1R,3S,4R,5S)-(+)-4-(1-Methylethyl)-1,8,8-trimethyl-3-thiabicyclo[3.2.1]octane-3-oxide 118 and (1R,3S,4S,5S)-(+)-4-(1-Methylethyl)-1,8,8-trimethyl-3-thiabicyclo-[3.2.1]octane-3-oxide 119.

Using the above procedure for 116 and 117, the sulfoxide 107 (1 g, 5.4 mmol) was deprotonated with 1.4 M MeLi solution in Et_2O (4.6 mL, 6.4 mmol) and then alkylated with 2-iodopropane (3.4 g, 20 mmol) to give 1.17 g of an orange crude oil. Chromatography on the chromatotron using Hexane:EtOAc (100 mL portions of 3:1, 2:1→1:1→1:2 and 1:3) as eluent gave 500 mg (39%) of a mixture of 118 and 119 followed by 238 mg (24%) of recovered sulfoxide 107. The mixture of diastereomers 118 and 119 was separated using CH_2Cl_2:EtOAc (70:30) as eluent to give 392 mg (32%) of 118 as an amorphous solid. Recrystallization from Et_2O gave white needles.



118

MP 70 - 71°C;

$[\alpha]^{23}_D$ +137° (c=2.1, CH_2Cl_2);

IR (KBr) ν_{max} 2970, 1480, 1370, 1230 and 1025 (S=O) cm^{-1};

^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85 (s, 3H, $-CH_3$), 0.94 (s, 3H, $-CH_3$), 1.07 (d, 3H, J= 6.8 Hz), 1.14 (d, 3H, J= 6.0 Hz), 1.21 (s, 3H, $-CH_3$), 1.34 - 1.50 (m, 1H), 1.55 - 1.68 (m, 1H) 1.68 - 1.78 (m, 1H), 2.06 - 2.21 (m, 1H), 2.31 (dd, 1H, J= 8.7, J= 3.3 Hz), 2.35 - 2.48 (m, 1H), 2.76 (br.d, 1H, J= 13, J= 1.0 Hz), 3.05 (dd, 1H, J= 10.6, J= 3.3 Hz) and 3.13 (d, 1H, J= 13 Hz);

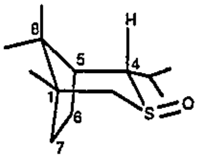
^{13}C NMR and DEPT (200 MHz, $CDCl_3$) ppm 19.23 ($-CH_3$), 20.69 ($-CH_3$), 21.90 ($-CH_3$), 24.41 ($-CH_3$), 25.70 ($-CH_3$), 26.93 (CH), 28.41 (CH_2), 33.98 ($-CH_2$), 42.15 ($-CR_4$), 44.80 ($-CR_4$), 46.85 (CH), 59.32 ($-CH_2$) and 69.39

(-CH);

EIMS ***m/e*** (relative intensity) 228 ($M^{+\cdot}$, 6), 211 (M^+-17, 83), 165 (18), 123 (24), 109 (100), 95 (37), 83 (41), 81 (25), 69 (38), 67 (27), 55 (69) and 41 (67);

Anal. Calcd. for $C_{17}H_{24}OS$: C, 68.36; H, 10.59; S, 14.03. Found: C, 68.61; H, 10.55; S, 13.77.

Further elution gave 88 mg (7%) of compound 119 as a pale yellow oil.



119

$[\alpha]_D$ +133° (c=4.6, CH_2Cl_2);

IR (KBr) ν_{max} 2932, 1463, 1390, 1374, 1031 (S=O, strong) cm^{-1};

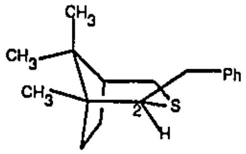
^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (s, 3H, CH_3), 0.96 (s, 3H, $-CH_3$), 1.02 (d, 3H, *J*= 6.9 Hz), 1.10 (s, 3H, $-CH_3$), 1.18 (d, 3H, *J*= 6.8 Hz), 1.47 - 1.84 (m, 4H, *J*= 6.7 Hz), 1.93 (br.d, 1H), 2.16 - 2.32 (m, 1H, *J*= 6.8 Hz), 2.69 (br.d, 1H, *J*= 6.8 Hz), 2.73 (dd, 1H, *J*= 12.5, *J*= 2.2 Hz) and 3.13 (d, 1H, *J*= 12.5 Hz);

^{13}C NMR and DEPT (200 MHz, $CDCl_3$) ppm 19.02 ($-CH_3$), 20.27 ($-CH_3$), 20.61 ($-CH_3$), 21.59 ($-CH_3$), 23.31 ($-CH_2$), 23.74 ($-CH_3$), 28.48 ($-CHMe_2$), 36.19 ($-CH_2$), 44.11 ($-CR_4$), 44.98 ($-CR_4$), 46.99 (CH), 61.08 ($-CH_2$) and 67.79 (-CH);

EIMS ***m/e*** (relative intensity) 229 ($M^{+\cdot}$+1, 1.3), 228 (M^+, 5), 212 (M^+-OH, 16), 211 (100), 165 (11), 123 (20), 109 (100), 95 (36), 69 (36), 55 (44) and 41 (50);

Anal. Calcd. for $C_{13}H_{24}OS$: C, 68.36; H, 10.59; S, 14.03. Found: C, 67.97; H, 10.84; S, 13.81.

(1R,2S,5S)-(-)-2-Benzyl-1,8,8-trimethyl-3-thiabicyclo[3.2.1]octane 120.



Following the general procedure D, the reduction of (1R,2S,3R,5S)-(-)-2-benzyl-1,8,8-trimethyl-3-thiabicyclo[3.2.1]octane-3-oxide **116** (1 g, 3.62 mmol) provided 0.85 g (90%) of compound **120** as a colorless oil;

$[\alpha]^{23}D$ -181.5° (c=2.0, CH_2Cl_2);

IR (neat) ν_{max} 2950, 1500, 1470, 1455, 1395, 760, 705 cm^{-1};

^1H NMR (200 MHz, $CDCl_3$) δ 0.93 (s, 3 H), 1.21 (s, 3 H), 1.23 (s, 3 H), 1.78 - 2.00 (m, 5 H), 2.20 (dd, 1H, *J*= 12.4, *J*= 3.9 Hz), 2.51 (dd, 1H, *J*= 10.6, *J*= 1.5 Hz), 2.94 (dd, 1H, *J*= 13.6, *J*= 10.6 Hz), 3.25 (dd, 1H, *J*= 13.6, *J*= 1.5 Hz), 3.30 (d, 1H, *J*= 12.4 Hz) and 7.20 - 7.35 (m, 5 H);

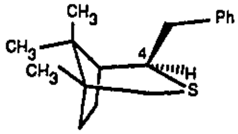
^{13}C NMR and DEPT (200 MHz, $CDCL_3$) ppm 20.89 (CH_3), 21.81 (CH_3), 26.40 (CH_2), 27.27 (CH_3), 30.11 (-CH_2), 41.15 (-CH_2), 42.53 (-CH_2), 42.90 (CR_4), 46.56 (CH), 47.26 (CR_4), 57.09 (CH), 126.01 (CH), 128.31 (-2CH), 129.16 (-2CH) and 142.64 (-CR_4);

EIMS ***m/e*** (relative intensity) 260 ($M^{+\cdot}$, 1.3), 169 (M^+-CH_2Ph, 100), 135 (18), 107 (10), 91 (26);

HRMS calcd for $C_{17}H_{24}S$: 260.1600. Found: 260.1616;

Anal. Calcd for $C_{17}H_{24}S$: C, 78.40; H, 9.28; S, 12.31. Found: C, 78.66; H, 9.19; S, 12.19.

(1R,4R,5S)-(+)-4-Benzyl-1,8,8-trimethyl-3-thiabicyclo[3.2.1]octane 121.



Following the general procedure D, reduction of the sulfoxide **117** (380 mg, 1.4

mmol) gave 330 mg (92%) of compound 121 as a colorless oil.

$[\alpha]^{23}$D +161° (c=2, CH_2Cl_2);

IR (neat) ν_{max} 2960, 1500, 1458, 1392, 760, 722 and 705 cm^{-1};

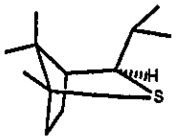
^{1}H NMR (200 MHz, $CDCl_3$) δ 0.845 (s, 3H, -CH_3), 0.93 (s, 3H, -CH_3), 1.21 (s, 3H, -CH_3), 1.50 - 1.62 (m, 2H), 1.87 - 2.02 (m, 2H), 1.97 (m, 1H), 2.01 (d, 1H, *J*= 12.2 Hz), 2.88 (dd, 1H, *J*= 7.6 Hz, *J*= 2.3 Hz), 2.96 (d, 1H, *J*= 12.2 Hz), 3.09 (d, 1H, *J*= 7.5 Hz) and 7.16 - 7.31 (m, 5H);

^{13}C NMR and DEPT (200 MHz, $CDCL_3$) ppm 21.00 (CH_3), 21.41 (CH_3), 26.75 (CH_3), 30.66 (CH_2), 34.38 (-CH_2), 37.41 (-CH_2), 42.50 (-CH_2-Ph), 43.06 (CR_4), 45.93 (CR_4), 50.22 (CH), 51.36 (CH), 126.17 (CH,), 128.41 (-CH, 2C), 129.14 (-CH, 2C) and 141.22 (-CR_4);

EIMS ***m/e*** (relative intensity) 260 ($M^{+\cdot}$, 2.6), 169 (M^+-CH_2Ph, 100), 135 (27) and 91 (Ph-CH_2^+, 26);

Anal. Calcd for $C_{17}H_{24}S$: C, 78.40; H, 9.28; S, 12.31. Found: C, 78.55; H, 9.33; S, 12.09.

(1R,4R,5S)-(+)-4-(1-methylethyl)-1,8,8-trimethyl-3-thiabicyclo[3.2.1] octane 122.



Following the general procedure D, reduction of the sulfoxide 118 (425 mg, 1.86 mmol) afforded 357 mg (90%) of compound 122 as a colorless oil;

$[\alpha]^{23}$D= +168° (c=2, CH_2Cl_2);

IR (neat) ν_{max} 2965, 2880, 1465 and 1394 cm^{-1};

^{1}H NMR (200 MHz, $CDCl_3$) δ 0.83 (s, 3H), 0.89 (s, 3H), 1.07 (d, 3H, *J*= 6.0 Hz), 0.93 (d, 3H, *J*= 6.0 Hz), 0.95 (s, 3H), 1.51 - 1.63 (m, 2H), 1.85 - 2.12 (m, 3H), 1.92 (d, 1H, *J*= 12.3 Hz), 2.07 (m, 1H) 2.33 (dd, 1H, *J*= 7.3 Hz, *J*= 1.7

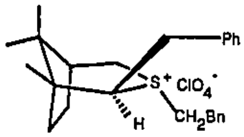
Hz), 2.85 (br.d, 1H, *J*= 12.3 Hz);

^{13}C NMR and DEPT (200 MHz, CDCL$_3$) ppm 19.56 (CH$_3$), 21.09 (CH$_3$), 21.13 (CH$_3$), 23.49 (CH$_3$), 26.60 (-CH$_3$), 30.72 (CH$_2$), 34.44 (CH$_2$), 34.94 (-CH), 37.04 (CH$_2$), 42.33 (CR$_4$), 43.03 (CR$_4$), 46.94 (CH) and 58.18 (CH);

EIMS *m/e* (relative intensity) 212 (M$^{+\cdot}$, 13), 169 (M$^+$-CHMe$_2$, 100), 135 (29) and 95 (24);

Anal. Calcd for C$_{13}$H$_{24}$S: C, 73.51; H, 11.39; S, 15.09. Found: C, 73.43; H, 11.14; S, 14.86.

(1R,2S,3R,5S)-(-)-2,3-Dibenzyl-1,8,8-trimethyl-3-thianiumbicyclo[3.2.1]octane perchlorate 123.



Following the procedure A, compound 123 (338 mg, 75%) was obtained as a white foam and used without further purification;

M.P. 78 - 80 °C;

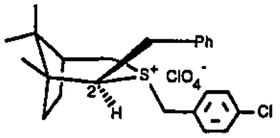
[α]$^{23}_{D}$ -78.2° (c=4, CH$_2$Cl$_2$);

IR (KBr) ν$_{max}$ 2949, 1495, 1455, 1090, 754, 701, 622 cm^{-1};

^{1}H NMR (300 MHz, CDCl$_3$) δ 1.02 (s, 3H), 1.18 (s, 3H), 1.32 (s, 3H), 1.75 (m, 1H), 2.09 - 2.33 (m, 4H), 2.86 (dd, 1H, *J*= 14.4 Hz, *J*= 12.3 Hz), 3.38 (d, 1H, *J*= 14.6 Hz), 3.39 (dd, 1H, *J*= 14.4 Hz, *J*= 3.4 Hz), 3.70 (dd, 1H, *J*= 12.3 Hz, *J*= 3.4 Hz), 3.73 (dd, 1H, *J*= 14.6 Hz, *J*= 3.5 Hz), 4.23 (d, 1H, *J*= 13.0 Hz), 4.67 (d, 1H, *J*= 13.0 Hz) and 6.94-7.33 (m, 10 H);

^{13}C NMR and DEPT (200 MHz, CDCL$_3$) ppm 20.85 (CH$_3$), 21.03 (CH$_3$), 24.86 (CH$_3$), 25.99 (CH$_2$), 38.40 (CH$_2$), 39.23 (CH$_2$), 39.31 (CH$_2$), 42.26 (CR$_4$), 43.55 (CH), 47.16 (CR$_4$), 49.99 (CH$_2$), 66.83 (CH), 127.04 (CR$_4$), 127.68 (CH), 129.28 (2CH), 129.69 (2CH), 129.75 (2CH), 130.07 (CH), 130.33 (2CH) and 135.56 (CR_4).

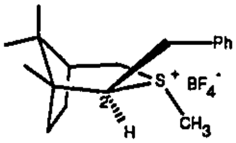
(1R,2S,3R,5S)-2-Benzyl-3-(*p*-chlorophenylmethyl)-1,8,8-trimethyl-3-thianium-bicyclo[3.2.1]octane perchlorate 124.



Similar to the general procedure A, thiane 120 (260 mg, 1 mmol) was alkylated with α-iodo-4-chlorotoluene (252 mg, 1 mmol) to give 358 mg (72%) of the corresponding thianium salt 124 as a white foam. This material was use immediately without further purification.

^{1}H NMR (200 MHz, $CDCl_3$) δ 1.01 (s, 3H, $-CH_3$), 1.14 (s, 3H, $-CH_3$), 1.30 (s, 3H, $-CH_3$), 1.70 - 1.90 (m, 1H), 2.00 - 2.38 (m, 4H), 2.78 (dd, 1H, *J*= 14.5 Hz, *J*= 12.45 Hz, -CHPh), 3.29 (dd, 1H, *J*= 14.5 Hz, *J*= 2.5 Hz, -CH-Ph), 3.40 (dd, 1H, *J*= 12.45 Hz, *J*= 2.5 Hz, C_2-H_{eq}), 3.51 (d, 1H, *J*= 14.3 Hz, C_4-H_{4eq}), 3.83 (dd, 1H, *J*= 14.3 Hz, *J*= 3.6 Hz, C_4-H_{4ax}), 4.31 (d, 1H, *J*= 12.9 Hz, S^+_3-CH-PhCl), 4.78 (d, 1H, *J*= 12.9 Hz, S^+-CH-PhCl) and 6.78 - 7.30 (m, 9H, Ar-H);

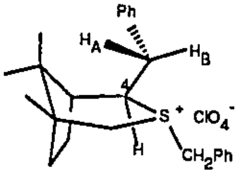
(1R,2S,3S,5S)-2-Benzyl-3-methyl-1,8,8-trimethyl-3-thianium[3.2.1]octane tetrafluoroborate 125.



To an ice-cold solution of thiane 120 (261 mg, 1 mmol) in 15 mL of CH_2Cl_2 was added $Me_3O^+BF_4^-$ (150 mg, 1 mmol). The reaction mixture was vigorously stirred at 0°C for 1 hour, then at room temperature for an additional 1 hour. This solution containing compound 125 was used without further purification. A sample was evaporated to dryness to give crude <u>125</u> as a white foam. ^{1}H nmr spectrum showed the presence of two S^+-CH_3 signals at δ2.62 (88%) and δ2.68 (22%). The major isomer has the following resonances;

^{1}H NMR (200 MHz, $CDCl_3$) δ 0.986 (s, 3H, -CH_3), 1.14 (s, 3H, -CH_3), 1.165 (s, 3H, -CH_3), 1.69 - 2.30 (m, 5H, $H_{5,6,7}$), 2.62 (s, 3H, -S^+-CH_3), 2.68 (s, 3H, S^+-$C\underline{H}_3$), 2.88 (dd, 1H, J_{gem}= 14 Hz, J_{vic}= 13 Hz, -$C\underline{H}_A$-Ph), 3.24 (d, 1H, J_{gem}= 14.3 Hz, H_{4eq}), 3.44 (dd, 1H, J_{gem}= 14.6 Hz, J_{vic}= 3.5 Hz, -$C\underline{H}_B$PH), 3.70 (dd, 1H, J_{gem}= 13.0 Hz, J_{vic}= 3.5 Hz, H_{2eq}), 3.76 (dd, 1H, J_{gem}= 14.4 Hz, J_{vic}= 4.7 Hz, H_{4eq}) and 7.19 - 7.36 (m, 5H, Ar-H).

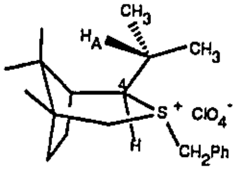
<u>(1R,3S,4R,5S)-3,4-Dibenzyl-1,8,8-trimethyl-3-thianiumbicyclo[3.2.1]octane perchlorate 126.</u>



Following the general procedure A, the S-benzylation of thiane <u>121</u> (260 mg, 1 mmol) gave 319 mg (71%) of the corresponding thianium salt <u>126</u> as a white foam.

^{1}H NMR (200 MHz, $CDCl_3$) δ 0.95 (s, 3H, -CH_3), 1.07 (s, 3H, -CH_3), 1.135 (s, 3H, -CH_3), 1.60 - 1.67 (m, 1H), 1.84 - 1.93 (m, 2H), 2.07 - 2.22 (m, 2H), 2.90 (dd, 1H, J_{gem}= 14.2 Hz, J_{vic}= 9.4 Hz, H_A at C-4-$C\underline{H}_2$-Ph), 3.09 (dd, 1H, J_{gem}= 14.2 *Hz*, J_{vic}= 7.1 Hz, H_B at C-4-$C\underline{H}_2$Ph), 3.28 (d, 1H, J_{gem}= 14.5 Hz, H_{2ax}), 3.46 (d, 1H, J_{gem}= 14.5 Hz, H_{2eq}), 3.61 (dd, 1H, J_{vic}= 9.4 Hz, J_{vic}= 7.1 Hz, H_{4eq}), 4.32 (d, 1H, J_{gem}= 12.7 Hz, S^+-$C\underline{H}_2$-Ph), 4.76 (d, J_{gem}= 12.7 Hz, S^+-$C\underline{H}_2$-Ph) and 6.84 - 7.42 (m, 20H, Ar-H).

(1R,3S,4R,5S)-3-Benzyl-4-(1-methylethyl)-1,8,8-trimethyl-3-thianiumbicyclo[3.2.1]-octane perchlorate 127.



Following the general procedure A, the S-benzylation of thiane 122 (212 mg, 1 mmol) gave 258 mg (64%) of the corresponding thianium perchlorate 127.

^{1}H NMR (200 MHz, CDCl$_3$) δ 0.30 (d, 3H, J= 6.4 Hz, *i*pr-CH$_3$), 0.90 (d, 3H, J= 6.6 Hz, *i*pr-CH$_3$), 0.94 (s, 3H, -CH$_3$), 0.95 (s, 3H, -CH$_3$), 1.05 (s, 3H, -CH$_3$), 1.65 - 2.42 (br.m, 6H, H$_{5,6,7}$ and *i*pr-C$\underline{H}$Me$_2$), 2.93 (d, 1H, J_{vic}= 11.4 Hz, H$_{4eq}$), 3.29 (d, 1H, J_{gem}= 14.3 Hz, H$_{2eq}$), 3.48 (d, 1H, J_{gem}= 14.3 Hz, H$_{2ax}$), 4.54 (d, 1H, J_{gem}= 12.3 Hz, S$^+$-CHPh), 5.07 (d, 1H, J_{gem}= 12.3 Hz, S$^+$-C$\underline{H}$-Ph) 7.36 - 7.39 (m, 3H, *m,p*-Ar-H), and 7.48 - 7.53 (m, 2H, *o*-Ar-H).

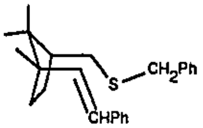
PREPARATION OF OXIRANES USING THIANE 120 AS AUXILIARY (Table 8).

(S,S)-(-)-Stilbene oxide 128a and *meso*-Stilbene oxide 129a and 130a (R=Ph).

The epoxidation reaction using the thianium perchlorate 123 (338 mg, 0.75 mmol) and benzaldehyde (106 mg, 1.0 mmol) was carried out using the general procedure B. Separation (Chromatotron, Hexane:Et$_2$O, 98:2) of the crude reaction mixture thus obtained gave thiane 120 (111 mg, 57% recovery);

$[\alpha]_D$= -181.2° (c=2.0, CH$_2$Cl$_2$);

followed by a β-elimination product identified as [(1S,3S)-(+)-1,2,2-trimethyl-1-(*trans*-phenylvinyl)-3-(benzylthiomethyl)]-cyclopentane 130a (R=Ph, 58 mg, 22%), a colorless oil;



$[\alpha]^{23}$D= +86.5° (c = 1.5, CH_2Cl_2);

IR (thin film) ν_{max} 3026, 2957, 2871, 1600 (C=C), 1493, 1491, 747, 696 cm^{-1};

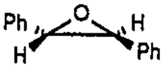
^{1}H NMR (200 MHz, Me_2CO-d_6) δ 0.66 (s, 3H), 0.85 (s, 3H), 1.03 (s, 3H), 1.35-1.53 (m, 2H), 1.95-2.13 (m, 3H), 2.26 (dd, 1H, *J*= 11.5, *J*= 10.5 Hz), 2.55 (dd, 1H, *J*= 11.5, *J*= 3.0 Hz), 3.73 (s, 2H), 6.33 (d, 1H, *J*= 16.5 Hz), 6.42 (d, 1H, *J*= 16.5 Hz) and 7.18 - 7.39 (m, 10H);

^{13}C NMR and DEPT (200 MHz, $CDCl_3$) ppm 19.21 (CH_3), 21.49 (CH_3), 22.56 (CH_3), 27.84 (CH_2), 33.86 (CH_2), 34.71 (CH_2), 36.76 (CH_2), 46.30 (CR_4), 46.39 (CH), 50.23 (CR_4), 126.01 (2CH), 126.83 (CH), 126.93 (CH), 127.32 (CH), 128.37 (2CH), 128.50 (2CH), 128.90 (2CH), 137.44 (CH), 138.17 (CR_4), 138.75 (CR_4);

HRMS calcd for $C_{24}H_{30}S$: 350.2070. Found: 350.2049;

Anal. Calcd for $C_{24}H_{30}S$: C, 82.22; H, 8.62; S, 9.14. Found: C, 82.34; H, 8.76; S, 9.26.

Further elution gave (S,S)-(-)-stilbene oxide <u>128a</u> (57 mg, 39%) as white needles;



M.P. 68°C, (lit.[110] 69°C);

$[\alpha]_D$ -285° (c=1, acetone), {lit.[122] for (R,R)-enantiomer $[\alpha]_D$= +291° (c=0.056, acetone)};

e.e.= 96$^+$%; The % ee was determined by Eu(hfc)$_3$ shifted ^{1}H NMR spectrum (see Figure 55C).

^{1}H NMR (200 MHz, $CDCl_3$) δ 3.84 (d, 2H, *J*= 2.0 Hz), 7.36 - 7.40 (m, 10H);

EIMS ***m/e*** (relative intensity) 196 ($M^{+\cdot}$, 50), 195 ($M^{+\cdot}$-1, 45), 178 (23), 167 (100), 152 (18), 105 (18), 90 (87), 89 (83).

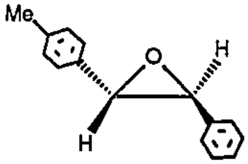
The last compound eluted was identified as meso-stilbene oxide <u>129a</u> (12 mg, 8%), an amorphous solid;

mp 37-38°C;

^{1}H NMR (200 MHz, CDCl$_3$) δ 4.35 (s, 2H), 7.10-7.18 (m, 10H);

EIMS *m/e* (relative intensity) 196 (M$^{+\cdot}$, 45), 195 (M$^{+\cdot}$-1, 34), 167 (100), 105 (55).

(S,S)-(-)-2-(*p*-tolyl)-3-phenyloxirane 128b.



Following the general procedure C, the epoxidation reaction using thiane **120** (260 mg, 1 mmol), benzyl bromide (171 mg, 1 mmol) and *p*-tolualdehyde (120 mg, 1 mmol) gave 181 mg (70%) of recovered thiane **120**; 53 mg (15%) of β-elimination product **130a** (R=Ph) and 67 mg (32%) of **128b** as white needles.

m.p. 61-62°C, (lit.[110] m.p. 62°C);

$[\alpha]_D$= -289.2° (c=2, EtOH), {lit.[139] for (S,S)-enantiomer, $[\alpha]_D$= -300° (c=1.14, EtOH)};

e.e.= 96%. The %e.e. was determined by Eu(hfc)$_3$ shifted ^{1}H nmr spectrum (see Figure 56C).

^{1}H NMR (200 MHz, CDCl$_3$) δ 2.34 (s, 3H, CH$_3$), 3.81 (d, 1H, *J*= 2.0 Hz), 3.83 (d, *J*= 2.0 Hz), 7.16 (d, 2H, *J*= 8.5 Hz), 7.22 (d, 2H, *J*= 8.5 Hz) and 7.25 - 7.36 (br.s, 5H);

EIMS: m/z (%) 210 (M$^+$, 32), 209 (M$^+$-H, 15), 195 (M$^+$-CH$_3$, 42), 181 (M$^+$-CHO, 100), 167 (33), 66 (43), 165 (37), 105 (35), 104 (27) and 103 (30).

(-)-*trans*- and (+)-*cis*-2-Cyclohexyl-3-phenyloxiranes 128c and 129c.

Following the general procedure C, the epoxidation reaction using thiane **120** (260 mg, 1 mmol), benzyl iodide (218 mg, 1 mmol) and cyclohexanecarboxaldehyde

(112 mg, 1 mmol) gave, after work up and chromatography (Chromatotron, Hexane:Et_2O, 98:2) 146 mg (56%) of recovered thiane **120**, 112 mg (32%) of the β-elimination product **130a** (R=Ph) and 19 mg (9%) of (-)-*trans*-2-cyclohexyl-3-phenyloxirane **128c**, a colorless oil:

$[\alpha]_D$= -25.2° (c=1.3, $CHCl_3$);

e.e.= 84%. The %e.e. was determined by Eu(hfc)$_3$ shifted ^1H nmr spectrum (see Figure 57B);

IR (thin film) ν_{max} 2935, 2860, 1600, 1455, 880, 757 and 702 cm^{-1};

^1H NMR (200 MHz, $CDCl_3$) δ 1.07 - 1.40 (m, 6H), 1.62 - 1.89 (m, 4H), 1.92 - 1.94 (m, 1H), 2.74 (dd, 1H, *J*= 6.7 Hz, *J*= 2.0 Hz), 3.64 (dd, 1H, *J*= 2.0 Hz) and 7.20 -s 7.35 (m, 5H);

^{13}C NMR and DEPT (200 MHz, $CDCl_3$) ppm 25.32 (CH_2), 25.47 (CH_2), 26.06 (CH_2), 28.80 (CH_2), 29.38 (CH_2), 40.31 (CH), 57.28 (CH), 67.24 (CH), 125.49 (2CH), 127.88 (CH), 128.40 (2CH) and 138.21 (CR_4);

EIMS: ***m/z* (%)** 202 M^+, 11), 173 (M^+-CHO, 7), 120 (M^+-cyclohexyl, 20), 107 (34), 96 (58), 91 (46) and 81 (100);

HRMS calcd for $C_{14}H_{18}O$: 202.1358. Found: 202.1364;

Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.96; O, 7.92. Found: C, 82.96; H, 9.12.

Further elution gave 29 mg (14%) of (+)-*cis*-2-cyclohexyl-3-phenyloxirane **129c** as a colorless oil;

$[\alpha]_D$= +44.5° (c=1.8, $CHCl_3$);

e.e.= 86%. The %e.e. was determined by Eu(hfc)$_3$ shifted ^1H nmr spectrum (see Figure 58B);

IR (thin film) ν_{max} 2926, 2851, 1600, 1450, 877, 745 and 700 cm^{-1};

^{1}H NMR (200 MHz, $CDCl_3$) δ 0.86 - 1.26 (m, 7H), 1.46 - 1.71 (m, 3H), 1.91 - 1.97 (m, 1H), 2.87 (dd, 1H, *J*= 8.6 Hz, *J*= 4.2 Hz), 4.04 (d, 1H, *J*= 4.2 Hz) and 7.23 - 7.32 (m, 5H);

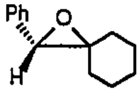
^{13}C NMR and DEPT (200 MHz, $CDCl_3$) ppm 24.95 (CH_2), 25.03 (CH_2), 25.96 (CH_2), 27.87 (CH_2), 30.10 (CH_2), 34.70 (CH), 57.25 (CH), 63.75 (CH), 126.31 (2CH), 127.33 (CH), 127.96 (2CH) and 135.96 (CR_4);

EIMS m/e (relative intensity %) 202 (M^+, 10), 173 (M^+-CHO, 6), 120 (M^+-cyclohexyl, 16), 107 (36), 96 (57), 91 (40) and 81 (100);

HRMS calcd for $C_{14}H_{18}O$: 202.1358. Found: 202.1353;

Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.96; O, 7.92. Found: C, 82.89; H, 8.93.;

(2S)-(-)-2-Phenyl-1-oxaspiro[2.5]octane 131.



Following the general procedure C, the epoxidation reaction using thiane 120 (296 mg, 1.14 mmol), benzyliodide (248 mg, 1.14 mmol), $AgClO_4$ (1.14 mmol) and cyclohexanone (233 mg, 2.60 mmol) gave after repetitive chromatography (Chromatotron, Hexane:EtOAc, 20:1; CCl_4, 100 and CCl_4:Et_2O, 98:2) 137 mg (46%) of recovered thiane 120, 139 mg (35%) of the β-elimination product 130a (R=Ph) and 5 mg (2.3%) of compound 131 as a colorless oil;

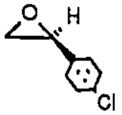
$[\alpha]_D$= -37° (c=0.16, CH_2Cl_2), {lit.[98] for S-enantiomer $[\alpha]_D$= -26.5° (c= 2.5, pentane);

e.e.= 96%. The %e.e. was determined by $Eu(hfc)_3$ shifted ^{1}H nmr spectrum (see Figure 59B);

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 - 1.81 (m, 10H), 3.85 (s, 1H) and 7.24 - 7.35 (m, 5H).

(S)-4-Chlorostyrene oxide 132.

Following the general procedure C, the epoxidation reaction using thiane **120** (260 mg, 1 mmol), α-iodo-4-chlorotoluene (252 mg, 1 mmol), $AgClO_4$ (220 mg, 1.06 mmol) and 30% formaldehyde aqueous solution (2 mL, excess) gave 218 mg (84%) of recovered thiane **120**, 38 mg of β-elimination product identified as [(1S,3S)-1,2,2-trimethyl-1-(*trans*-phenylvinyl)-3-(α-thiomethyl-4-chlorotolyl)]cyclopentane **130b** (R=4-Cl-C_6H_4); further elution gave 76.4 mg (49%) of **132**.



e.e.= 24%. The %e.e. was determined by $Eu(hfc)_3$ shifted ^1H nmr spectrum (see Figure 60B);

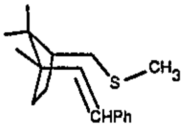
IR (thin film) ν_{max} 3500, 3060, 3000, 2920, 1600, 1500, 1420, 1390, 1200, 1100, 1020, 990, 885 and 840 cm^{-1};

^1H NMR (200 MHz, $CDCl_3$) δ 2.72 (dd, 1H, J= 5.5 Hz, J= 2.5 Hz), 3.12 (dd, 1H, J= 5.5 Hz, J= 4.0 Hz), 3.81 (dd, 1H, J= 4.0 Hz, J= 2.5 Hz), 7.18 (d, 2H, J= 8.5 Hz) and 7.29 (d, 2H, J= 8.5 Hz);

EIMS m/e (relative intensity %) 154 (M^+, 37), 156 (M^++2, 12), 153 (M^+-1, 17), 155 (M^++1, 8), 125 (M^+-CHO··, 100), 127 (40), 124 (M^+-CH_2O, 34), 126 (22), 119 (M^+-Cl, 82) and 89 (100).

4-Chlorostyrene oxide 132 and 130c (R=H).

Following the general procedure B, the epoxidation reaction using the thianium tetrafluoroborate **125** (1 mmol) and *p*-chlorobenzaldehyde (150 mg, 1.07 mmol) gave 183 mg (70%) of thiane **120**, 14 mg (5%) of β-eliminattion product identified as [(1S,3S)-1,2,2-trimethyl-1-(*trans*-phenylvinyl)-3-(methylthiomethyl)]cyclopentane **130c** (R=H);



$[\alpha]_D$= +62° (c=1.0, $CHCl_3$);

IR (thin film) ν_{max} 3040, 2990, 2940, 1600, 1500, 970, 750 and 700 cm^{-1};

^1H NMR (200 MHz, $CDCl_3$) δ 0.698 (s, 3H, $-CH_3$), 0.897 (s, 3H, $-CH_3$), 1.038 (s, 3H, CH_3), 1.23 - 1.55 (m, 5H), 2.11 (s, 3H), 2.31 (dd, 1H, J_{gem}=J_{vic}= 11.5 Hz), 2.60 (dd, 1H, J= 11.3 Hz, J= 3.0 Hz), 6.29 (s, 2H) and 7.15 - 7.38 (m, 5H);

^{13}C NMR (200 MHz, $CDCl_3$) ppm 16.21, 19.43, 21.61, 22.74, 28.00, 34.88, 37.07, 46.36, 46.77, 50.28, 125.91, 126.72, 127.24, 128.42, 128.76 and 137.36;

EIMS m/e (relative intensity %) 274 (M^+, 27), 259 (M^+-15, 17), 226 (13), 183 (19), 169 (23), 157 (18), 144 (53), 129 (100), 91 (49) and 69 (79);

HRMS calcd for $C_{18}H_{26}S$: 274.1757. Found: 274.1740.

Further elution gave 71 mg (46%) of compound 132;

$[\alpha]_D$= -0.13 (c=2, CH_2Cl_2);

e.e.= 0-4%. The %e.e. was determined by $Eu(hfc)_3$ shifted ^1H nmr spectrum.

PREPARATION OF (R,R)-(+)-*trans*-STILBENE OXIDE 87 (X=H) USING THIANE 121 AS AUXILIARY (Table 9).

Following the general procedure B, the epoxidation using the thianium perchlorate 126 (300 mg, 0.66 mmol) and benzaldehyde (140 mg, 1.32 mmol) gave 113 mg (66%) of thiane 121: {$[\alpha]_D$= +163.3° (c=2.0, CH_2Cl_2)}, 58 mg (45%) of (R,R)-(+)-87 (X=H);

$[\alpha]_D$= +106.88° (c=1.25, acetone), {lit.[122] for the R,R-enantiomer, $[\alpha]_D$= +291° (c=0.056, acetone)};

e.e.= 34%. The %e.e. was determined by Eu(hfc)$_3$ shifted ^{1}H nmr spectrum;

Further elution gave 15 mg (12%) of *meso*-stilbene oxide <u>**129a**</u>.

PREPARATION OF OXIRANES USING THIANE 122 AS AUXILIARY (Table 9).

(R,R)-(+)-*trans*-Stilbene Oxide 87 (X=H).

Following the general procedure B, the epoxidation reaction using the thianium salt <u>**127**</u> (390 mg, 0.97 mmol) and benzaldehyde (160 mg, 1.51 mmol) gave 119 mg (58%) of thiane <u>**122**</u> {$[\alpha]_D$= +167.3 (c=2, CH_2Cl_2)}, 79 mg (42%) of (R,R)-(+)-<u>**87**</u> (X=H);

$[\alpha]_D$= +198.4° (c=2, acetone), {lit.^{122} for the R,R-enantiomer $[\alpha]_D$= +291° (c=0.056, acetone)};

e.e.= 73%. The %e.e. was determined by Eu(hfc)$_3$ shifted ^{1}H nmr spectrum (see Figure 55E).;

Further elution gave 39 mg of *meso*-stilbene oxide <u>**129a**</u>.

(R,R)-(+)-*trans*- and (-)-*cis*-2-(*p*-chlorophenyl)-3-phenyloxirane 87 (X=Cl) and 129d.

Following the general procedure B, the epoxidation reaction using the thianium salt <u>**127**</u> (202 mg, 0.43 mmol) and *p*-chlorobenzaldehyde (100 mg, 0.71 mmol) gave 72 mg (68%) of thiane <u>**122**</u>, 60 mg (52%) of (R,R)-(+)-*trans*-<u>**87**</u> (X=Cl);

$[\alpha]_D$= +221° (c=1, EtOH), {lit.^{122} for (2R,3R)-enantiomer $[\alpha]_D$= +350° (c=1.36, EtOH)};

e.e.= 63%. The %e.e. was determined from the optical rotation figures. The Eu(hfc)$_3$ shift ^{1}H nmr method was unsatisfactory due to insufficient resolution of methine protons.

Further elution gave 29 mg (25%) of (-)-*cis*-<u>129d</u>;

[α]$_D$= -2.02° (c=1.18, EtOH);

e.e.= 66%. The %e.e. was determined Eu(hfc)$_3$ shifted ^{1}H nmr spectrum (see Figure 61B).

6.2 PART B

<u>Benzyl *t*-butyl sulfide.</u>

Benzyl chloride (70.0 g, 0.55 mole) was added dropwise at room temperature to a stirred methanolic solution (MeOH:H_2O 1:1, 250 mL) of *t*-butyl mercaptan (50.0 g, 0.55 mole) and potassium hydroxide (34 g, 0.60 mole). The mixture was heated under reflux for 16 h, then cooled. The resulting biphasic mixture was extracted into 300 mL of CH_2Cl_2, washed twice with 100 mL of 5% NaOH solution and twice with 100 mL of H_2O. The organic extract was dried over anhydrous calcium chloride, and removal of solvent gave the crude sulfide, which was further purified by distillation under reduced pressure, yielding benzyl *t*-butyl sulfide (83.3 g, 84%), b.p. 80 °C at 0.15 mmHg;

IR ν_{max} (NaCl) 2800, 1600, 1495, 1450, 1362, 1168, 715 and 697 cm^{-1};

^{1}H NMR 1.35 (s, 9H), 3.75 (s, 2H), 7.1 - 7.4 (m, 5H).

<u>Benzyl *t*-butyl sulfoxide</u>.

The purified sulfide was dissolved in 150 mL of ethyl acetate, and stirred at -60°C while a solution of *m*-chloroperoxybenzoic acid 80% (28 g, 0.11 mole) in 100 mL of ethyl acetate was added dropwise. After the addition completed, the solution was stirred at -30°C for 30 min and then at room temperature for 1 hr. The reaction was washed with 10% sodium bisulfite solution (3 X 100 mL) followed by 5% sodium hydroxide solution

(3 X 100 mL). The ethyl acetate layer was dried over $CaCl_2$ and evaporated under reduced pressure. The residual solid was separated by flash chromatography (as increasing polarity of the solvents: CH_2Cl_2 /Hexane 75:25 to CH_2Cl_2 / EtOAc 50:50 and finally with EtOAc) to yield the sulfoxide (15.7 g, 72%) as a white solid. The product was further purified by vacuum sublimation at 79°C (0.05 mmHg);

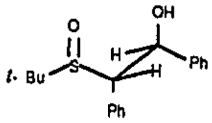
M.P. 74 - 75 °C;

IR ν_{max} **($CHCl_3$)** 1050 cm^{-1};

^{1}H NMR 1.45 (s, 9H), 3.55 (d, 1H, *J*= 12 Hz), 3.84 (d, 1H, *J*= 12 Hz), 7.28 (br.s, 5H).

threo- and *erythro*-1,2-Diphenyl-2-t-butylsulfinylethanol 158 and 154.

Scheme 30: From benzyl *t*-butyl sulfoxide. Benzyl *t*-butyl sulfoxide (10.0 g, 51 mmol) was dissolved in 50 mL of THF and cooled to -78°C under N_2. This solution was stirred vigorously while a solution of lithium diisopropylamide (prepared from 2.5N n-butyl lithium in hexanes (21 mL, 52 mmol) and diisopropylamine (7.2 mL, 51 mmol) in THF (150 mL) cooled to -70°C), was added by cannula. Stirring was maintained for a further 30 min, and then a solution of benzaldehyde (5.42 g, 51 mmol) in 50 mL of THF was added dropwise. The reaction mixture was then stirred for an additional 30 min at room temperature, quenched with 100 mL of water and the THF removed under reduced pressure. The aqueous phase was extracted with CH_2Cl_2 (3 X 100 mL). The combined organic extracts were dried ($CaCl_2$) and the solvent was evaporated. The crude product was purified by column chromatography (CH_2Cl_2 / hexanes / EtOAc 35:35:30) to provide two products. *threo*-1,2-Diphenyl-2-*t*-butyl-sulfinylethanol <u>158</u> was obtained as a white solid (7.3 g, 47%);



M.P. 167.5 - 168 °C (dec.);

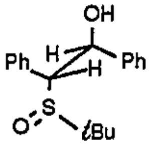
IR ν_{max} ($CHCl_3$) 3500 - 3180, 1050, 1030, 1005, and 1000 cm^{-1};

^1H NMR ($CDCl_3$) 1.20 (s, 9H), 4.00 (d, 1H, *J*= 8 Hz), 5.27 (dd, 1H, *J*= 8 Hz, *J*= 2 Hz), 6.08 (d, 1H, *J*= 2 Hz, *J*= 1 Hz, OH), 6.95 (br.s, 10 H);

CIMS m/z (%) 303 (M^++1, 67%), 229 (96), 197 (91), 181 (96), 180 (100), 107 (62), 105 (60);

Anal. Calcd. for $C_{18}H_{22}O_2S$: C, 71.50; H, 7.33; S, 10.68. Found: C, 71.27; H, 7.36; S, 10.47.

The second compound to elute (with gradient elution CH_2Cl_2/EtOAc; 1:1 to 0:1) was the *erythro*-1,2-diphenyl-2-*t*-butylsulfinylethanol <u>154</u> as a white solid (3.8 g, 25%);



M.P. 165.5 - 166 °C (dec.);

IR ν_{max} ($CHCl_3$) 3340, 1058, 1030, 702 cm^{-1};

^1H NMR ($CDCl_3$) 1.15 (s, 9H), 4.01 (d, 1H, *J*= 3 Hz), 4.65 (d, 1H, *J*= 6 Hz -OH), 5.72 (dd, 1H, *J*= 6, *J*= 2 Hz), 6.8 - 7.3 (br.s, 10H);

CIMS m/z (%) 303 (M^++1, 55%), 229 (77), 197 (100), 181 (58), 180 (71), 107 (47), 105 (41);

Anal. Calcd. for $C_{18}H_{22}O_2S$: C, 71.50; H, 7.33; S, 10.68. Found: C, 71.27; H, 7.03; S, 10.24.

This isomer was identical with the compound obtained as in Scheme 29.

From *erythro*-1,2-diphenyl-2-*t*-butylthioethanol. (Scheme 29) *trans*-Stilbene oxide (1.96 g, 1 mmol), *t*-butyl mercaptan (0.99 g, 1.1 mmol) and KOH (0.6 g 1.1 mmol) were heated under reflux in 20 mL of 1-propanol for 8 hours. The reaction mixture was cooled, poured into water and extracted with dichloromethane (3 x 50 mL.) The organic extract was dried and evaporated. The crude product was distilled at 150 - 160°C (0.05 mmHg) to give 2.2 g (75%) of a pale yellow oil which solidified on standing to a pale yellow solid;

m.p. 59 - 61°C;

IR ν_{max} (CHCl$_3$) 3350 cm^{-1};

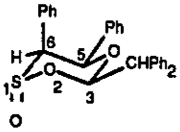
^{1}**H NMR** 1.20 (s, 9H), 2.5 (br.s, 1H), 4.2 (d, 1H, *J*= 6 Hz), 5.0 (d, 1H, *J*= 2 Hz), 7.2 (m, 10H).

The purified erythro-1,2-diphenyl-2-*t*-butlythioethanol (5.6 g, 20 mmol) was oxidized with *m*-chloroperoxybenzoic acid (4.4 g, 25.5 mmol) in 200 mL of CH$_2$CH$_2$ to give 4.5 g (75%) of *erythro*-1,2-diphenyl-2-*t*-butylsulfinylethanol 154.

cis-Stilbene.

Hydroxy-sulfoxide 154 (604 mg, 2 mmol) and N-chlorosuccinimide (280 mg, 2.1 mmol) in 100 mL of benzene were put under reflux for 1 hr. The reaction mixture was cooled and the solvent removed on a rotary evaporator. The crude residue was separated by column chromatography (CH$_2$CH$_2$ / hexane; 1:1) to afford *cis*-stilbene (185 mg, 51%); ^{1}**H NMR (CDCl$_3$)** δ 6.55 (s, 2H), 7.2 (s, 10H).

(2R*,3S*,4R*,6R*)-3,4-Diphenyl-6-(diphenylmethyl)-1,5-dioxa-2-thiane-2-oxide 156.



The erythro-1,2-diphenyl-2-*t*-butylsulfinylethanol 154 (0.50 g, 1.6 mmol) in 10 mL of CH$_2$Cl$_2$ was cooled to -78°C under an inert atmosphere. The solution was stirred vigorously while a 1.0M solution of sulfuryl chloride in CH$_2$Cl$_2$ (1.85 mL, 1.85 mmol) was added dropwise by syringe. Stirring was maintained for a further 20 min at -78 °C and the reaction mixture was quenched by addition of 100 mL of 10% NaHSO$_3$ solution. Separation of the organic layer, extraction of the aqueous layer with CH$_2$Cl$_2$ (2 x 25 mL) drying (CaCl$_2$), and removal of solvent from the combined organic layers gave a pale yellow oil. The oily residue was purified on the Chromatotron (gradient elution; Hex/CH$_2$Cl$_2$; 1:0 to 0:1) to provide diphenylacetaldehyde (85 mg, 26%) as a pale yellow oil and then δ-sultine <u>156</u> (199 mg, 55%) as a viscous colorless oil which crystallized on standing;

M.P. 160 - 162 °C;

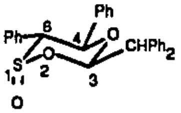
IR ν_{max} **(CHCl$_3$)** 1125 cm^{-1};

^{1}H NMR (CDCl$_3$) δ 3.47 (d, 1H, *J*= 3 Hz), 4.52 (d, 1H, *J*= 3 Hz), 6.15 (d, 1H, *J*= 3 Hz), 6.64 (d, 1H, *J*= 3 Hz), 6.72 - 7.44 (br.m, 20H);

^{13}C NMR 55.3, 66.3, 73.9, 94.3 132-139 (Ar-C);

Anal. Calcd. for $C_{28}H_{24}O_3S$: C, 76.35; H, 5.45; S, 7.20. Found: C, 76.72; H, 5.66; S, 7.15.

<u>(2R*,3R*,4R*,6R*)-3,4-Diphenyl-6-(diphenylmethyl)-1,5-dioxa-2-thiane-2-oxide</u> <u>157</u>.



Using the procedure described above, a solution of *threo*-1,2-diphenyl-2-*t*-butylsulfinylethanol <u>158</u> (1.0 g, 33 mmol) was treated with SO_2Cl_2 (3.3 mL, 3.3 mmol) to yield *trans*-stilbene (410 mg, 69%), diphenylacetaldehyde (100 mg, 15%) and the δ-sultine <u>157</u> (49 mg, 7%), as a white solid;

m.p. 162 - 163 °C;

IR ν_{max} **(CHCl$_3$)** 1120 cm^{-1};

^{1}H NMR 4.03 (d, 1H, *J*= 11 Hz), 4.42 (d, 1H, *J*= 4Hz), 5.85 (d, 1H, *J*= 11 Hz), 6.68 (d, 1H, *J*= 4Hz), 7.05 - 7.37 (br.m, 20H);

Anal. Calcd. for $C_{28}H_{24}O_3S$: C, 76.35; H, 5.45; S, 7.20. Found: C, 76.57; H, 5.45; S, 7.15.

Photoisomerisation of δ-sultine <u>156</u> to δ-sultine <u>157</u>. A solution containing sultine <u>156</u> (300 mg) in benzene : acetone (40 mL + 10 mL) was irradiated for thirty minutes using a 500 watt Hanovia lamp and a Corex filter. The solvent was removed in vacuo and the residual material was crystallized from methylene chloride-pentane to yield 295 mg of a fluffy white compound. All the physical data (mp, ir and nmr) were identical to that of **157**, above.

X-ray Crystal Structure Data for (2R*,3S*,4R*,6R*)-3,4-Diphenyl-6-(1,1-diphenylmethyl)-1,5-dioxa-2-thiane-2-oxide **156**.

Crystal Data: $C_{28}H_{24}O_3S$ fw = 440.55

Triclinic, $P\bar{1}$, a= 9.1150(15), b= 10.126(2), c= 13.316(2)Å, α= 108.57(2), β= 95.70(2), χ=99.91(2)°, V=1132.0(4)Å^3, p_c= 1.293 g. cm^{-3}, μ= 1.44 mm^{-1}, (24°C, CuK$_{\alpha 1}$, λ=1.540562Å), z=2, F(100)=464.

Suitable crystals of **156** were obtained by slow diffusion of a diethyl ether top solvent layer into a concentrated solution containing **156** in dichloromethane. A crystal measuring approximately 0.15 x 0.25 x 0.35 mm was selected and mounted on a glass fibre. Intensity data was collected using a Picker diffractometer using the $\Theta/2\Theta$ scan mode. Unit cell dimensions were obtained from 26 reflections with 2Θ between 100 and 117°. The calculated density assumes two molecules per unit cell. The data was collected to a maximum Bragg angle of 120°. Out of 5021 reflections measured 3372 were unique of which 2500 were considered observed with $I_{net} > 2.5\sigma (I_{net})$. No absorption correction was made. The structural solution was made by direct methods followed by least squares refinement using the NRCVAX series of programmes (133, 134). Fourier difference map. gave all non hydrogen atoms. Hydrogen atoms were placed at calculated positions and refined. The final least squares cycle was calculated with 56 atoms, 386 parameters using 2500 significant reflections. Weights based on counting statistics were used. The residuals on significant reflections were RF= 0.049, Rw= 0.055 and GoF(S)= 2.01. For all reflections RF= 0.070, Rw= 0.058, where $R_F=\Sigma|F_o-F_c|/\Sigma(F_o)$, $R_w=[\Sigma(w(F_o-F_c)^2/\Sigma(wF_o^2)]^{\frac{1}{2}}$, and GoF(S)= [Σ(w(Fo-Fc)^2/((number of reflections)-(number of parameters))]$^{\frac{1}{2}}$. The maximum shift to sigma ratio was 0.002. In the last D-map the deepest hole was -0.300eÅ^{-3} and the highest peak 0.430eÅ^{-3} indicating an absence of solvent molecules.

TABLE OF BOND DISTANCES AND ANGLES.

The following Atoms are from the CD File
* Indicates that there are Symmetry Equivalents of an atom.

Name	x	y	z
S(2)	0.97062	0.79940	0.93849
O(1)	0.90326	0.62581	0.89521
O(2)	0.86750	0.87015	1.00526
O(5)	0.73009	0.60687	0.74696
C(3)	0.92756	0.82663	0.80837
C(4)	0.76093	0.75641	0.76235
C(6)	0.74663	0.57766	0.84269
C(7)	1.04770	0.78572	0.74246
C(8)	1.17226	0.88893	0.74996
C(9)	1.28966	0.85524	0.69572
C(10)	1.28392	0.71651	0.63234
C(11)	1.16176	0.61375	0.62468
C(12)	1.04398	0.64548	0.67864
C(13)	0.71122	0.77417	0.65675
C(14)	0.70114	0.90647	0.65284
C(15)	0.65226	0.92416	0.55778
C(16)	0.61175	0.80913	0.46363
C(17)	0.62206	0.67763	0.46598
C(18)	0.67113	0.65868	0.56109
C(19)	0.70199	0.41636	0.81458
C(20)	0.81952	0.34050	0.76082
C(21)	0.81479	0.30456	0.64966
C(22)	0.92351	0.23923	0.60185
C(23)	1.03417	0.20634	0.66026
C(24)	1.03908	0.24173	0.77031
C(25)	0.93163	0.30774	0.81818
C(26)	0.65768	0.36869	0.90642
C(27)	0.55829	0.24197	0.88583
C(28)	0.51938	0.19050	0.96488
C(29)	0.58343	0.26631	1.07032
C(30)	0.68058	0.39413	1.09419
C(31)	0.71812	0.44593	1.01366
H(3)	0.93373	0.93324	0.82982
H(4)	0.69270	0.80428	0.81286
H(6)	0.68428	0.62772	0.88854
H(8)	1.16859	0.98591	0.78593
H(9)	1.37123	0.93297	0.69382
H(10)	1.37581	0.69700	0.60259
H(11)	1.16038	0.51886	0.59210
H(12)	0.96367	0.57035	0.67271
H(14)	0.72506	0.97990	0.71028
H(15)	0.64715	1.01477	0.56050
H(16)	0.58012	0.81813	0.39071
H(17)	0.59741	0.59804	0.40232
H(18)	0.67604	0.56913	0.56451
H(19)	0.60613	0.39676	0.76615
H(21)	0.73713	0.33466	0.61223
H(22)	0.91291	0.22644	0.53106
H(23)	1.11183	0.15386	0.62866
H(24)	1.11805	0.21993	0.81046
H(25)	0.93152	0.33153	0.88854
H(27)	0.50735	0.20147	0.81972

H(28)	0.45791	0.10487	0.95277
H(29)	0.56561	0.22766	1.12825
H(30)	0.74175	0.43912	1.17376
H(31)	0.78537	0.53611	1.02916

TABLE OF BOND DISTANCES AND ANGLES.

S(2)-O(1)	1.6468(24)
S(2)-O(2)	1.4763(25)
S(2)-C(3)	1.854(4)
O(1)-C(6)	1.453(4)
O(5)-C(4)	1.435(4)
O(5)-C(6)	1.397(4)
C(3)-C(4)	1.534(5)
C(3)-C(7)	1.502(4)
C(3)-H(3)	1.01(3)
C(4)-C(13)	1.509(5)
C(4)-H(4)	1.03(3)
C(6)-C(19)	1.525(5)
C(6)-H(6)	0.96(3)
C(7)-C(8)	1.376(5)
C(7)-C(12)	1.396(5)
C(8)-C(9)	1.380(6)
C(8)-H(8)	0.95(3)
C(9)-C(10)	1.378(6)
C(9)-H(9)	0.99(4)
C(10)-C(11)	1.358(6)
C(10)-H(10)	0.99(3)
C(11)-C(12)	1.377(5)
C(11)-H(11)	0.92(3)
C(12)-H(12)	0.94(4)
C(13)-C(14)	1.375(6)
C(13)-C(18)	1.391(5)
C(14)-C(15)	1.376(7)
C(14)-H(14)	0.86(4)
C(15)-C(16)	1.376(7)
C(15)-H(15)	0.92(4)

C(16)-C(17)	1.361(7)
C(16)-H(16)	1.02(5)
C(17)-C(18)	1.383(6)
C(17)-H(17)	0.94(4)
C(18)-H(18)	0.93(3)
C(19)-C(20)	1.528(5)
C(19)-C(26)	1.516(5)
C(19)-H(19)	0.98(3)
C(20)-C(21)	1.401(5)
C(20)-C(25)	1.364(6)
C(21)-C(22)	1.381(6)
C(21)-H(21)	0.97(4)
C(22)-C(23)	1.363(8)
C(22)-H(22)	0.90(4)
C(23)-C(24)	1.387(7)
C(23)-H(23)	1.00(4)
C(24)-C(25)	1.375(6)
C(24)-H(24)	0.95(5)
C(25)-H(25)	0.89(4)
C(26)-C(27)	1.367(6)
C(26)-C(31)	1.392(5)
C(27)-C(28)	1.366(7)
C(27)-H(27)	0.88(5)
C(28)-C(29)	1.378(8)
C(28)-H(28)	0.90(5)
C(29)-C(30)	1.359(8)
C(29)-H(29)	0.98(5)
C(30)-C(31)	1.383(7)
C(30)-H(30)	1.06(5)
C(31)-H(31)	0.96(4)

O(1)-S(2)-O(2)	108.56(14)
O(1)-S(2)-C(3)	97.19(13)
O(2)-S(2)-C(3)	104.62(16)
S(2)-O(1)-C(6)	115.98(22)
C(4)-O(5)-C(6)	113.63(23)
S(2)-C(3)-C(4)	107.64(23)
S(2)-C(3)-C(7)	108.84(24)
S(2)-C(3)-H(3)	103.6(16)
C(4)-C(3)-C(7)	119.94(25)
C(4)-C(3)-H(3)	105.5(16)
C(7)-C(3)-H(3)	110.0(16)
O(5)-C(4)-C(3)	111.6(3)
O(5)-C(4)-C(13)	108.34(24)
O(5)-C(4)-H(4)	108.8(17)
C(3)-C(4)-C(13)	112.6(3)
C(3)-C(4)-H(4)	110.4(15)
C(13)-C(4)-H(4)	104.9(17)
O(1)-C(6)-O(5)	110.2(3)
O(1)-C(6)-C(19)	108.4(3)
O(1)-C(6)-H(6)	109.6(16)
O(5)-C(6)-C(19)	107.80(25)
O(5)-C(6)-H(6)	108.0(18)

C(15)-C(16)-H(16)	123.2(24)
C(17)-C(16)-H(16)	117.8(24)
C(16)-C(17)-C(18)	121.0(4)
C(16)-C(17)-H(17)	120(3)
C(18)-C(17)-H(17)	118(3)
C(13)-C(18)-C(17)	120.5(4)
C(13)-C(18)-H(18)	117.3(19)
C(17)-C(18)-H(18)	122.1(19)
C(6)-C(19)-C(20)	112.2(3)
C(6)-C(19)-C(26)	114.6(3)
C(6)-C(19)-H(19)	99.4(17)
C(20)-C(19)-C(26)	112.1(3)
C(20)-C(19)-H(19)	113.4(16)
C(26)-C(19)-H(19)	104.3(17)
C(19)-C(20)-C(21)	119.8(3)
C(19)-C(20)-C(25)	121.9(3)
C(21)-C(20)-C(25)	118.3(4)
C(20)-C(21)-C(22)	119.6(4)
C(20)-C(21)-H(21)	115.9(18)
C(22)-C(21)-H(21)	124.4(18)
C(21)-C(22)-C(23)	121.4(4)
C(21)-C(22)-H(22)	111.8(24)

C(19)-C(6)-H(6)	112.8(17)	C(23)-C(22)-H(22)	126.8(24)
C(3)-C(7)-C(8)	118.9(3)	C(22)-C(23)-C(24)	119.2(4)
C(3)-C(7)-C(12)	123.0(3)	C(22)-C(23)-H(23)	124.3(23)
C(8)-C(7)-C(12)	117.9(3)	C(24)-C(23)-H(23)	116.5(23)
C(7)-C(8)-C(9)	121.1(3)	C(23)-C(24)-C(25)	119.5(5)
C(7)-C(8)-H(8)	117.5(21)	C(23)-C(24)-H(24)	118(3)
C(9)-C(8)-H(8)	120.8(21)	C(25)-C(24)-H(24)	122(3)
C(8)-C(9)-C(10)	120.3(4)	C(20)-C(25)-C(24)	122.0(4)
C(8)-C(9)-H(9)	119.6(22)	C(20)-C(25)-H(25)	116(3)
C(10)-C(9)-H(9)	119.5(22)	C(24)-C(25)-H(25)	121(3)
C(9)-C(10)-C(11)	119.0(4)	C(19)-C(26)-C(27)	120.2(3)
C(9)-C(10)-H(10)	116.5(19)	C(19)-C(26)-C(31)	123.1(3)
C(11)-C(10)-H(10)	124.0(19)	C(27)-C(26)-C(31)	116.7(4)
C(10)-C(11)-C(12)	121.4(4)	C(26)-C(27)-C(28)	122.8(4)
C(10)-C(11)-H(11)	121.4(22)	C(26)-C(27)-H(27)	116(3)
C(12)-C(11)-H(11)	116.6(22)	C(28)-C(27)-H(27)	120(3)
C(7)-C(12)-C(11)	120.2(4)	C(27)-C(28)-C(29)	119.8(5)
C(7)-C(12)-H(12)	121.6(22)	C(27)-C(28)-H(28)	124(4)
C(11)-C(12)-H(12)	118.2(22)	C(29)-C(28)-H(28)	115(4)
C(4)-C(13)-C(14)	120.4(3)	C(28)-C(29)-C(30)	119.1(5)
C(4)-C(13)-C(18)	121.8(3)	C(28)-C(29)-H(29)	121.7(24)
C(14)-C(13)-C(18)	117.7(4)	C(30)-C(29)-H(29)	119.1(24)
C(13)-C(14)-C(15)	121.2(4)	C(29)-C(30)-C(31)	120.6(4)
C(13)-C(14)-H(14)	120(3)	C(29)-C(30)-H(30)	115(3)
C(15)-C(14)-H(14)	118(3)	C(31)-C(30)-H(30)	122(3)
C(14)-C(15)-C(16)	120.6(4)	C(26)-C(31)-C(30)	120.9(4)
C(14)-C(15)-H(15)	117.1(23)	C(26)-C(31)-H(31)	117.4(22)
C(16)-C(15)-H(15)	122.2(23)	C(30)-C(31)-H(31)	121.7(22)
C(15)-C(16)-C(17)	118.9(4)		

COMPOUND 6. PARAMETER TABLES.

14-Jun-1990

Table . Atomic Parameters x,y,z and Biso.
E.S.Ds. refer to the last digit printed.

	x	y	z	Biso
S 2	0.97062(10)	0.79940(9)	0.93849(6)	3.68(4)
O 1	0.9033 (3)	0.62581(23)	0.89521(16)	3.79(11)
O 2	0.8675 (3)	0.8702 (3)	1.00526(17)	4.96(13)
O 5	0.7301 (3)	0.60687(23)	0.74696(16)	3.55(11)
C 3	0.9276 (4)	0.8266 (3)	0.80837(24)	3.29(15)
C 4	0.7609 (4)	0.7564 (3)	0.7623 (3)	3.39(15)
C 6	0.7466 (4)	0.5777 (4)	0.8427 (3)	3.54(16)
C 7	1.0477 (4)	0.7857 (3)	0.74246(23)	3.18(15)
C 8	1.1723 (4)	0.8889 (4)	0.7500 (3)	4.37(18)
C 9	1.2897 (5)	0.8552 (5)	0.6957 (3)	5.47(22)
C10	1.2839 (5)	0.7165 (5)	0.6323 (3)	4.77(21)
C11	1.1618 (5)	0.6137 (5)	0.6247 (3)	4.81(20)
C12	1.0440 (4)	0.6455 (4)	0.6786 (3)	4.26(18)
C13	0.7112 (4)	0.7742 (4)	0.6567 (3)	3.56(16)
C14	0.7011 (5)	0.9065 (4)	0.6528 (4)	5.02(21)
C15	0.6523 (5)	0.9242 (5)	0.5578 (4)	6.0 (3)
C16	0.6117 (5)	0.8091 (5)	0.4636 (4)	5.27(23)
C17	0.6221 (5)	0.6776 (5)	0.4660 (3)	5.11(23)
C18	0.6711 (4)	0.6587 (4)	0.5611 (3)	4.09(19)
C19	0.7020 (4)	0.4164 (4)	0.8146 (3)	3.62(16)
C20	0.8195 (4)	0.3405 (3)	0.7608 (3)	3.75(16)
C21	0.8148 (5)	0.3046 (4)	0.6497 (3)	4.32(19)
C22	0.9235 (6)	0.2392 (5)	0.6019 ([illegible])	5.43(24)
C23	1.0342 (6)	0.2063 (5)	0.6603 (4)	5.65(24)
C24	1.0391 (6)	0.2417 (5)	0.7703 (4)	5.6 (3)
C25	0.9316 (5)	0.3077 (4)	0.8182 (3)	4.69(22)
C26	0.6577 (4)	0.3687 (4)	0.9064 (3)	4.05(18)
C27	0.5583 (6)	0.2420 (5)	0.8858 (4)	6.2 (3)
C28	0.5194 (7)	0.1905 (6)	0.9649 (5)	7.8 (3)
C29	0.5834 (6)	0.2663 (7)	1.0703 (4)	6.7 (3)
C30	0.6806 (6)	0.3941 (6)	1.0942 (4)	6.7 (3)
C31	0.7181 (5)	0.4459 (5)	1.0137 (3)	5.99(24)
H 3	0.934 (3)	0.933 (3)	0.8298 (21)	2.9 (6)
H 4	0.693 (3)	0.804 (3)	0.8129 (22)	3.0 (6)
H 6	0.684 (3)	0.628 (3)	0.8885 (22)	2.7 (6)
H 8	1.169 (4)	0.986 (4)	0.786 (3)	5.0 (9)
H 9	1.371 (5)	0.933 (4)	0.694 (3)	6.8 (11)
H10	1.376 (4)	0.697 (3)	0.603 (3)	4.4 (8)
H11	1.160 (4)	0.519 (4)	0.592 (3)	4.6 (9)
H12	0.964 (4)	0.570 (4)	0.673 (3)	5.7 (10)
H14	0.725 (5)	0.980 (4)	0.710 (3)	7.3 (12)
H15	0.647 (4)	1.015 (4)	0.560 (3)	5.2 (10)
H16	0.580 (5)	0.818 (5)	0.391 (4)	7.9 (12)
H17	0.597 (5)	0.598 (5)	0.402 (3)	8.2 (13)
H18	0.676 (4)	0.569 (3)	0.5645 (24)	3.6 (8)
H19	0.606 (3)	0.397 (3)	0.7561 (22)	2.8 (6)
H21	0.737 (4)	0.335 (3)	0.6122 (25)	3.5 (8)
H22	0.913 (4)	0.226 (4)	0.531 (3)	5.2 (9)
H23	1.112 (4)	0.154 (4)	0.629 (3)	6.2 (10)
H24	1.118 (5)	0.220 (5)	0.810 (4)	8.1 (14)
H25	0.932 (5)	0.332 (4)	0.889 (3)	7.3 (12)

H27	0.507	(5)	0.201	(5)	0.820	(4)	9.4 (16)
H28	0.458	(7)	0.105	(6)	0.953	(4)	11.5 (19)
H29	0.566	(5)	0.228	(4)	1.128	(3)	7.2 (12)
H30	0.742	(6)	0.439	(5)	1.174	(4)	10.8 (15)
H31	0.785	(4)	0.536	(4)	1.029	(3)	5.8 (10)

Biso is the Mean of the Principal Axes of the Thermal Ellipsoid

Table of u(i,j) or U values *100.
E.S.Ds. refer to the last digit printed

	u11(U)	u22	u33	u12	u13	u23
S 2	5.17(6)	4.53(5)	3.00(4)	-0.11(4)	0.62(4)	0.16(4)
O 1	5.30(15)	4.58(14)	3.66(12)	0.12(11)	0.26(11)	0.86(10)
O 2	7.52(18)	5.67(16)	4.18(13)	0.33(14)	2.22(13)	-0.12(11)
O 5	5.44(15)	4.18(13)	3.36(12)	0.19(11)	0.59(10)	1.05(10)
C 3	4.47(20)	3.53(19)	3.91(17)	0.49(15)	0.90(15)	0.61(14)
C 4	4.59(20)	3.75(19)	4.31(18)	1.05(16)	1.43(16)	0.77(15)
C 6	4.42(20)	4.83(21)	3.74(18)	0.59(17)	0.75(15)	1.02(15)
C 7	4.11(19)	4.35(19)	3.08(16)	0.50(15)	0.59(14)	0.72(14)
C 8	5.30(23)	4.82(22)	5.30(22)	0.08(19)	1.09(18)	0.59(18)
C 9	5.2 (3)	7.2 (3)	7.0 (3)	-0.69(22)	2.19(21)	1.21(23)
C10	4.77(23)	8.3 (3)	4.64(21)	1.69(22)	1.66(18)	1.25(20)
C11	6.3 (3)	6.3 (3)	4.91(22)	1.84(22)	2.05(19)	0.22(20)
C12	5.44(23)	4.50(21)	5.38(21)	0.58(19)	1.98(18)	0.43(18)
C13	3.79(19)	4.45(20)	5.12(20)	0.75(16)	1.05(15)	1.41(16)
C14	5.9 (3)	4.51(25)	7.4 (3)	0.20(20)	-0.80(22)	1.36(22)
C15	6.6 (3)	5.3 (3)	11.2 (4)	0.53(23)	-0.5 (3)	4.3 (3)
C16	6.0 (3)	7.6 (3)	6.8 (3)	0.79(23)	0.66(22)	3.47(25)
C17	7.4 (3)	7.2 (3)	4.86(23)	2.03(24)	1.24(21)	1.79(21)
C18	6.5 (3)	4.88(23)	4.69(21)	2.18(20)	1.45(18)	1.78(17)
C19	4.68(21)	4.69(21)	3.77(18)	0.06(17)	-0.11(16)	1.34(15)
C20	5.33(22)	3.77(19)	4.27(19)	-0.19(17)	0.34(17)	0.93(15)
C21	6.4 (3)	5.00(23)	4.35(20)	0.47(20)	0.61(19)	1.14(17)
C22	9.3 (4)	6.2 (3)	4.49(23)	0.73(24)	2.11(24)	1.00(20)
C23	7.5 (3)	5.8 (3)	8.0 (3)	1.47(24)	2.7 (3)	1.57(23)
C24	7.0 (3)	7.4 (3)	6.9 (3)	1.9 (3)	0.93(24)	2.09(24)
C25	6.0 (3)	6.2 (3)	4.99(23)	1.24(21)	0.65(20)	1.33(20)
C26	5.00(22)	6.06(24)	4.46(19)	0.82(19)	0.60(16)	2.21(17)
C27	9.6 (4)	7.2 (3)	5.9 (3)	-1.3 (3)	0.8 (3)	3.00(24)
C28	11.1 (5)	9.3 (4)	9.3 (4)	-1.2 (4)	2.3 (3)	5.1 (3)
C29	7.5 (3)	12.8 (5)	8.4 (4)	3.0 (3)	3.5 (3)	7.0 (3)
C30	8.1 (3)	12.3 (5)	5.4 (3)	0.5 (3)	1.30(24)	4.6 (3)
C31	8.0 (3)	8.9 (3)	4.96(23)	-1.1 (3)	0.93(22)	2.63(23)
H 3	3.6(8)					
H 4	3.8(8)					
H 6	3.4(8)					
H 8	6.3(11)					
H 9	8.6(14)					
H10	5.6(10)					
H11	5.9(11)					
H12	7.2(13)					
H14	9.2(15)					
H15	6.6(12)					
H16	10.0(16)					
H17	10.4(16)					
H18	4.5(10)					
H19	3.5(8)					
H21	4.5(10)					
H22	6.5(12)					
H23	7.9(13)					
H24	10.2(18)					
H25	9.2(16)					

H27	12.0(20)
H28	14.6(24)
H29	9.1(15)
H30	13.7(20)
H31	7.4(13)

Anisotropic Temperature Factors are of the form
Temp=-2*Pi*Pi*(h*h*u11*astar*astar+---+2*h*k*u12*astar*bstar+---)

CLAIMS TO ORIGINAL RESEARCH

1. Two optically active thiolanes, **77** derived from mannitol and **78** derived from α,α-dibromoadipic acid, were prepared and converted into S-benzylsulfonium salts **85** and **92**, respectively. The reaction of these salts with benzaldehyde under phase transfer conditions gave *trans*-(2R,3R)-stilbene oxide in about 40% chemical yield and up to 80% enantiomeric excess.

2. 1,8,8-Trimethyl-3-thiabicyclo[3.2.1]octane **105** was prepared from camphoric acid. This thiane served as a catalyst for a one pot bi-phasic reaction between benzaldehyde and benzyl bromide which gave *trans*-(2R,3R)-stilbene oxide in 30% chemical yield and 10% enantiomeric excess.

3. Several 2- and 4-substituted-1,8,8-trimethyl-3-thiabicyclo[3.2.1]octane-3-oxides (**116**, **117**, **118** and **119**) were prepared by the alkylation of the α-lithio derivative of sulfoxide **107**. The X-ray crystal structure of **116** was obtained. The preferred mode of alkylation was found to be *syn* to the sulfoxide function resulting in axial alkylation. This finding was highly surprising since the earlier literature led one to expect equatorial alkylation products.

4. Thiane **120** was converted into S-methyl (**125**) and S-benzylsulfonium salts (**123** and **124**). All these salts were transformed into their corresponding sulfur ylides, which in turn were reacted with carbonyl compounds under phase transfer conditions to produce optically active epoxides. Benzylidene transfer from ylide **134B** to substituted benzaldehydes gave *trans*-(2S,3S)-stilbene oxides with ee's approaching enantiomeric purity. Using the ylides **141** and **142**, the *trans*-(2R,3R)-stilbene oxides were produced in 34% e.e. and ≅70% e.e.,

respectively. In contrast, transfer of the methylene group of sulfonium ylide **134B** to 4-chlorobenzaldehyde gave 4-chlorostyrene oxide in 48% chemical yield but without significant asymmetric induction.

5. The reaction of the β-hydroxysulfoxides **154** and **158** with SO_2Cl_2 has been re-investigated. The originally assigned structure of the products was shown to be in error. The correct structure, based on single crystal X-ray structure determination was shown to be $(2R^*,3S^*,4R^*,6R^*)$-3,4-diphenyl-6-(diphenylmethyl)-1,5-dioxa-2-thiane-2-oxide **156**. This represents a new novel heterocyclic ring system.

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