National Library of Canada
Acquisitions and Bibliographic Services Branch
395 Wellington Street
Ottawa, Ontario
K1A 0N4

Bibliothèque nationale du Canada
Direction des acquisitions et des services bibliographiques
395, rue Wellington
Ottawa (Ontario)
K1A 0N4

Your file Votre référence

Our file Notre référence

NOTICE

The quality of this microform is heavily dependent upon the quality of the original thesis submitted for microfilming. Every effort has been made to ensure the highest quality of reproduction possible.

If pages are missing, contact the university which granted the degree.

Some pages may have indistinct print especially if the original pages were typed with a poor typewriter ribbon or if the university sent us an inferior photocopy.

AVIS

La qualité de cette microforme dépend grandement de la qualité de la thèse soumise au microfilmage. Nous avons tout fait pour assurer une qualité supérieure de reproduction.

S'il manque des pages, veuillez communiquer avec l'université qui a conféré le grade.

La qualité d'impression de certaines pages peut laisser à désirer, surtout si les pages originales ont été dactylographiées à l'aide d'un ruban usé ou si l'université nous a fait parvenir une photocopie de qualité inférieure.

Canada

ISBN 0-612-00577-1

UNIVERSITÉ D'OTTAWA
UNIVERSITY OF OTTAWA

To my loving wife

Lorraine

and

Family

"Chance favors the trained mind."

Louis Pasteur

"To stand on the summit of reflection

is difficult,

and in the course of things

who cannot step forward

steps back."

Gaias Velleius Paterculus

"When you have eliminated the impossible,

whatever remaining, however improbable

must be the truth."

Sir Arthur Connan Doyle

ACKNOWLEDGEMENTS

The financial support of the Natural Sciences and Engineering Research Council of Canada and the University of Ottawa is gratefully acknowledged.

I acknowledge and thank my thesis supervisor Professor Tony Durst, whose knowledge and enthusiasm of organic chemistry have been an inspiration to me. Although very busy, he always found time to provide insightful advice and gentle guidance throughout my graduate career.

A special thanks goes to C. Bensimon for X-ray services, R. Capoor and G. Facey for NMR services and C. Kazakoff for mass spectral services.

I thank my wife Lorraine who has never once stopped believing in me and subsequently provided endless support throughout my graduate career.

A heart-felt thanks goes to my colleague Terry Connolly for his patient and diligent proof-reading of this thesis and three years of friendship - may we enjoy many more.

Lastly, I wish to thank doctors S. Shakya, K. Koh and M. Jung who have all helped to further develop my knowledge of organic chemistry.

TABLE OF CONTENTS

LIST OF FIGURES

PART A: LITHIATED BICYCLIC SULFOXIDES.

PART B: THE SYNTHESIS OF OPTICALLY ACTIVE α-AMINO ESTERS VIA KINETIC DYNAMIC RESOLUTION

LIST OF TABLES

LIST OF ABBREVIATIONS AND SYMBOLS

Ac	acetyl
AIBN	azabis(isobutyronitrile)
Ar	aryl
Bu	butyl
°C	degrees Celsius
CI	chemical ionization
cm	centimeters
d	doublet
dd	doublet of doublets
dt	doublet of triplets
DTBP	di-t-butylphenol
EG	ethylene glycol
EI	electron impact
eq.	equivalents
GC	gas chromatograph
h	hours
Hz	Hertz
HRMS	high resolution mass spectrum
int	integration
IR	infrared
J	coupling constant
m	multiplet
M	molar
M^+	parent molecular ion
m/e	mass/elementary charge
min	minutes
mmol	millimoles

mp	melting point
Pr	propyl
MS	mass spectroscopy
μs	microseconds
nm	nanometers
NMR	nuclear magnetic resonance
ns	nanoseconds
p	page
q	quartet
rx	reaction
s	seconds or singlet
t	triplet
t-Bu	tertiary butyl
tfc	tris[3-(trifluoromethylhydroxymethylene)-camphorato]
THF	tetrahydrofuran

ABSTRACT

PART A: LITHIATED BICYCLIC SULFOXIDES

The stereochemistry of the reaction of the lithio derivatives of two sets of isomeric 3-thia[3.2.1]octane-3-oxides with electophiles such as benzyl bromide, acetone and D_2O has been studied. Introduction of the deuterium always occurred *cis* to the S=O bond as expected on the basis of earlier results described by Marquet for the related thiane-S-oxides. In contrast, benzyl groups were introduced either *cis* or *trans* to the existing S=O bond. The results are most readily rationalized in terms of a planar configuration at the α-carbanion center. The unexpected *cis* benzylations are due to steric hindrance of the preferred approach *anti* to the S=O bond by either the ethano bridge or the 8-*endo* methyl group.

PART B: THE SYNTHESIS OF OPTICALLY ACTIVE α-AMINO ESTERS VIA KINETIC DYNAMIC RESOLUTION

The synthesis of N-protected optically active α-amino esters from racemic α-halo esters via kinetic dynamic resolution will be described. This methodology is general in nature and provides the desired optically active N-protected amino esters in 70-95% yield with diastereomeric excesses in the range of 85 to >98%. Applications and mechanistic aspects of the reaction will be discussed.

Part A: Lithiated Bicyclic Sulfoxides.

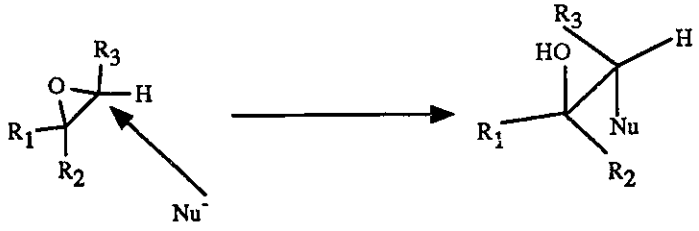
Chapter 1. Introduction:

1.1 Epoxides in organic synthesis.

The epoxide is an important functional group in synthetic organic chemistry. Epoxides owe this importance to the fact that the highly strained three-membered ring opens easily under both nucleophilic and electrophilic reactions conditions. This high reactivity is due to ring strain since the bond angles, which average 60°, are considerably less than the normal tetrahedral angle of 109.5° or the divalent oxygen angle of 110° for open chain ethers.[1]

Epoxides can be opened in a stereospecific and highly regioselective manner, under basic conditions as shown in Scheme 1.[2] The ring opening reaction is very general and since a great deal of structural diversity in the nucleophile is tolerated, it has found many applications in the synthesis of a variety of compounds.[3,4]

Scheme 1

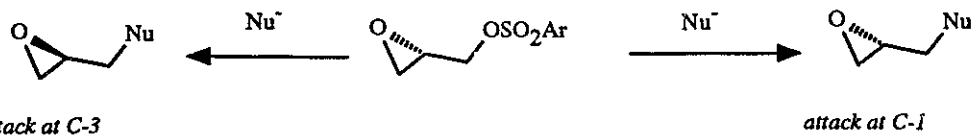


R_1,R_2,R_3 = alkyl or aryl

If the epoxide is enantiomerically pure, nucleophilic ring opening leads to enantiomerically pure products. Recent applications of this regiospecific ring opening of enantiomerically pure epoxides have been demonstrated in the synthesis of both homochiral β-adrenergic blocking agents[5] and precursors to β-hydroxybutyric acids[6a] (see Scheme 3). The key epoxide intermediates in both cases are glycidyl arenesulfonates as shown in

Scheme 2.

Scheme 2

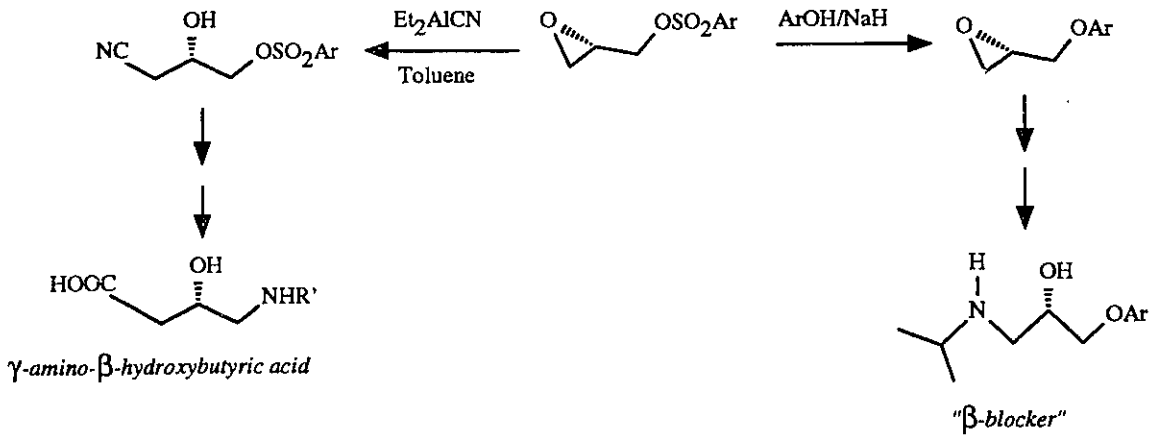


attack at C-3 *attack at C-1*

Glycidyl arenesulfonates present a challenging problem to the synthetic chemist since they possess two different sites of reactivity. Reaction at C-1 to directly displace the sulfonate, competes with reaction at C-3 to open the epoxide. Unfortunately, once the epoxide is opened at C-3, the intermediate alkoxide ion then displaces the sulfonate to regenerate an epoxide of opposite configuration. Thus, poor regioselectivity in the reaction of these epoxides with various nucleophiles results in a decrease in enantiomeric excess in the products synthesized.

Sharpless et al.[6b] have demonstrated that the regiochemistry in the reaction of these epoxides with various nucleophiles is easily controlled by careful choice of reaction conditions, as shown in Scheme 3.

Scheme 3

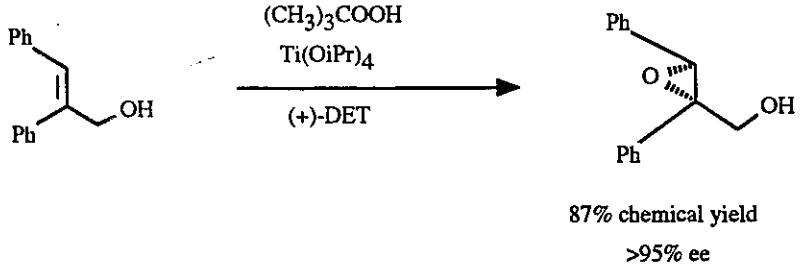


1.2 Asymmetric synthesis of epoxides.

There are several excellent methods which allow the synthetic chemist to carry out asymmetric epoxidations of alkenes.

The most recognized method is that of the Sharpless Asymmetric Epoxidation.[7] This metal catalyzed process utilizes (+) or (-)-diethyl tartrate, titanium tetraisopropoxide and *tert*-butyl hydroperoxide. Usually the process is stiochiometric, but depending on the reactivity of the allylic alcohol that is being epoxidized, catalytic amounts of both titanium tetraisopropoxide and diethyl tartrate may be used. A typical example of this process is shown in Scheme 4.

Scheme 4



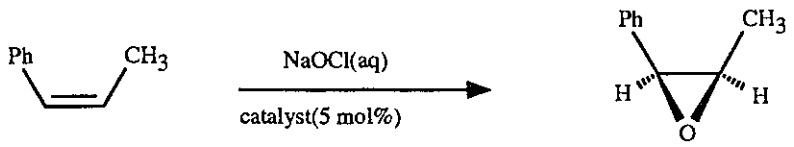
87% chemical yield

>95% ee

The product epoxy alcohols are typically obtained in 80-95% yield with ee's ranging from 90 to >99%.

More recently, an asymmetric epoxidation procedure for unfunctionalized olefins has appeared.[8] Jacobsen et al. have developed a metal catalyzed, catalytic epoxidation system utilizing chiral Mn (III) Salen complexes[9] and sodium hypochlorite. The procedure works best on bulky *cis*-substituted olefins with chemical yields typically in 75-85% and ee's as high as >90%. A typical example is illustrated in Scheme 5.

Scheme 5



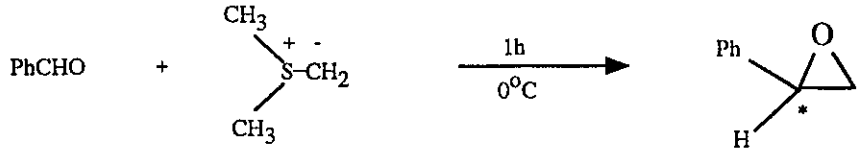
81% chemical yield

92% ee

1.3 Preparation of epoxides from carbonyl compounds and sulfur ylides.

In the early 1960's Corey and coworkers[10] demonstrated that epoxides could be formed by the reaction of sulfur ylides with carbonyl compounds as shown in Scheme 6.

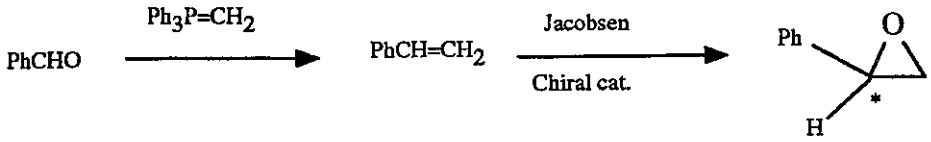
Scheme 6



A major advantage of the sulfur ylide route to epoxides is that it utilizes carbonyl compounds rather than alkenes as starting materials. In contrast to the oxidation of alkenes which generates two C-O bonds, reacting a sulfur ylide with a carbonyl compound results in the formation of both a C-C and a C-O bond. Thus, using a carbonyl compound and

sulfur ylide accomplishes in one operation, the same result as a Wittig reaction followed by an epoxidation (Scheme 7).

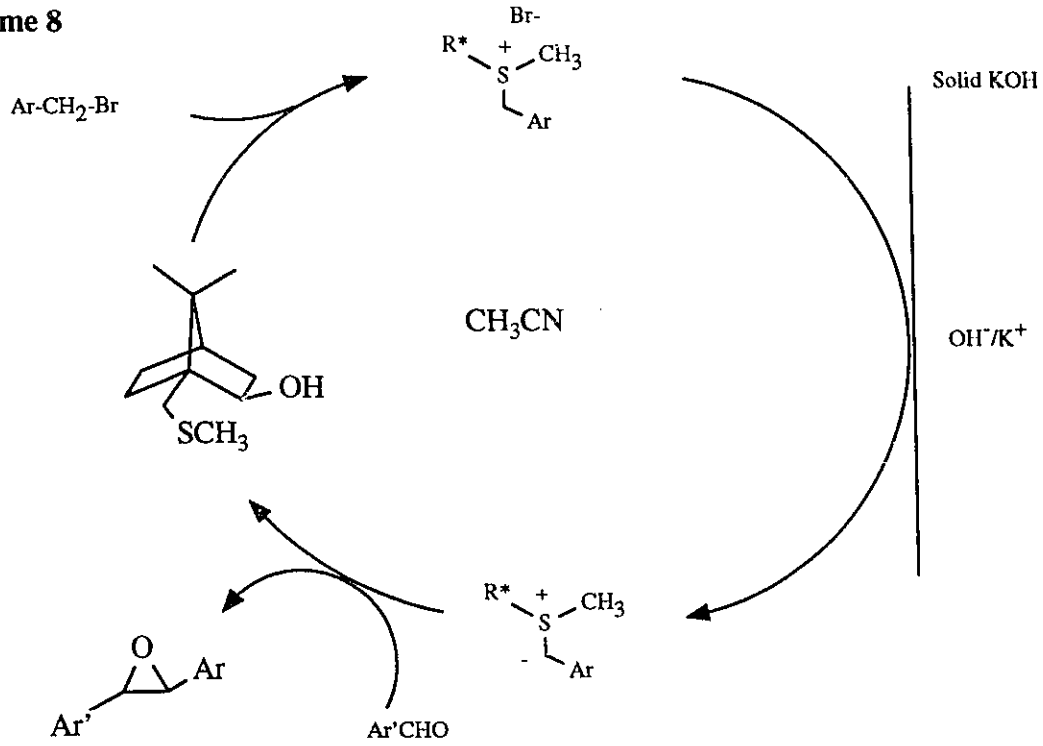
Scheme 7



One should note that if the carbonyl compound is prochiral a new chiral center is formed by the attack of the ylide on the carbonyl compound and that use of a chiral sulfur ylide might result in enantiomerically enriched epoxides.

In 1989 Furukawa and Sugihara[11] reported that optically active sulfides derived from 10-camphorsulfonic acid could be alkylated in the presence of base and reacted with carbonyl compounds to yield 1,2-diaryloxiranes in 20% chemical yield with enantiomeric excesses of up to 43-47% (Scheme 8).

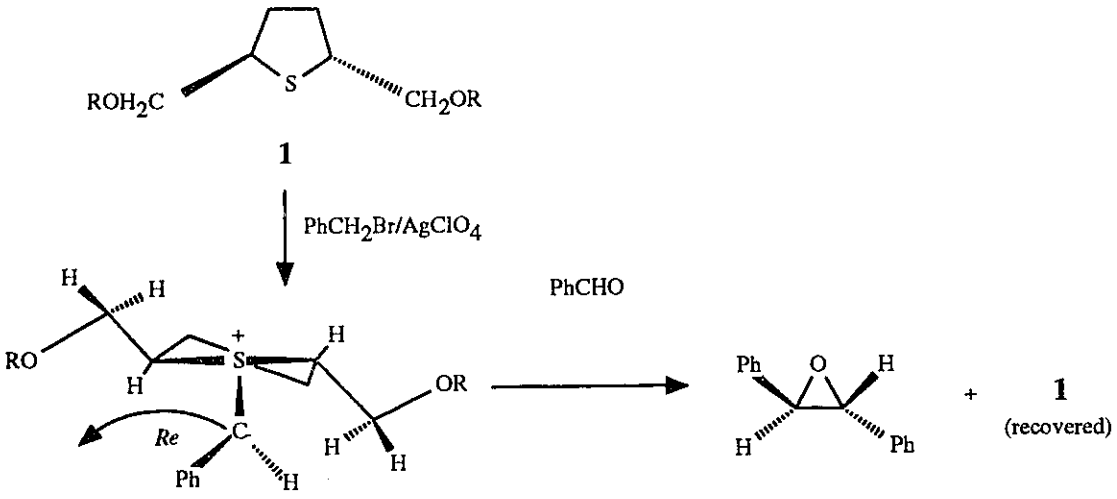
Scheme 8



An attractive feature of this reaction is that ylide formation and reaction with the aldehyde is carried out as a one-pot procedure under liquid-solid phase conditions. The above process is catalytic with respect to the sulfide but the turnover is very low (less than 2).

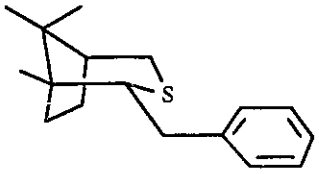
Independently Breau, Ogilvie and Durst[12] were also designing chiral auxiliaries capable of transferring asymmetry in the reaction of a sulfur ylide with a carbonyl compound. Breau chose to use the C_2-symmetrical auxiliary **1**, shown in Scheme 9 which was derived from adipic acid. Auxiliary **1** was then alkylated to give the benzylated sulfonium salt, which when reacted with base and a carbonyl compound produced *trans*-stilbene oxides in 27-41% chemical yield with enantiomeric excesses as high as 64-83%. The sulfide auxiliary was typically recovered in 80% yield.

Scheme 9

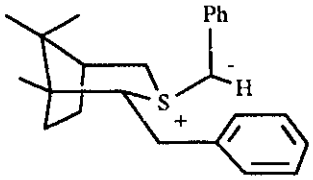


In order to ensure transfer of asymmetry in ylide-carbonyl reactions only one ylide should be formed and this ylide should show considerable facial selectivity due to a built-in steric bias. The possibility of obtaining only one ylide structure is enhanced if only one sulfonium salt precursor is obtained. The latter condition was met in the case of the C_2-symmetric sulfide **1**; alkylation of which can yield only one salt. Examination of molecular models was not convincing that only one ylide structure would result from the deprotonation of sulfonium salt **1** however, preferential formation of ylide **1a** was suggested to account for the moderate asymmetric induction in the formation of the stilbene oxides.

Breau, using simple molecular models then designed the sulfide **2** as a potential chiral auxiliary. He rationalized that benzylation of **2** should occur solely in the equatorial position and that the ylide derived from such a sulfonium salt should have structure **3**, in which the small hydrogen rather than the large phenyl group is opposite the equatorial 2-benzyl group.



2

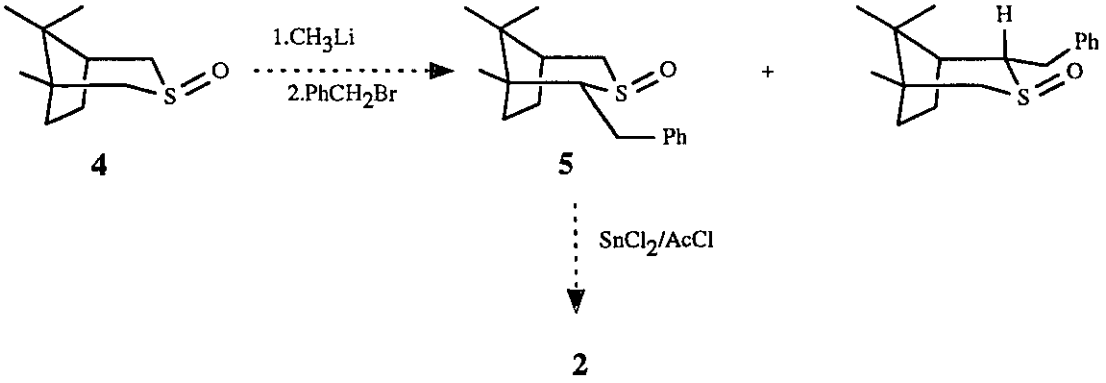


3

The prediction was that benzaldehyde would attack **3** from behind the plane and result in the preferential formation of S,S-*trans*-stilbene oxide.

Breau expected **2** to be accessible via benzylation of the sulfoxide **4** followed by reduction with $SnCl_2$/AcCl,[13] as shown in Scheme 10.

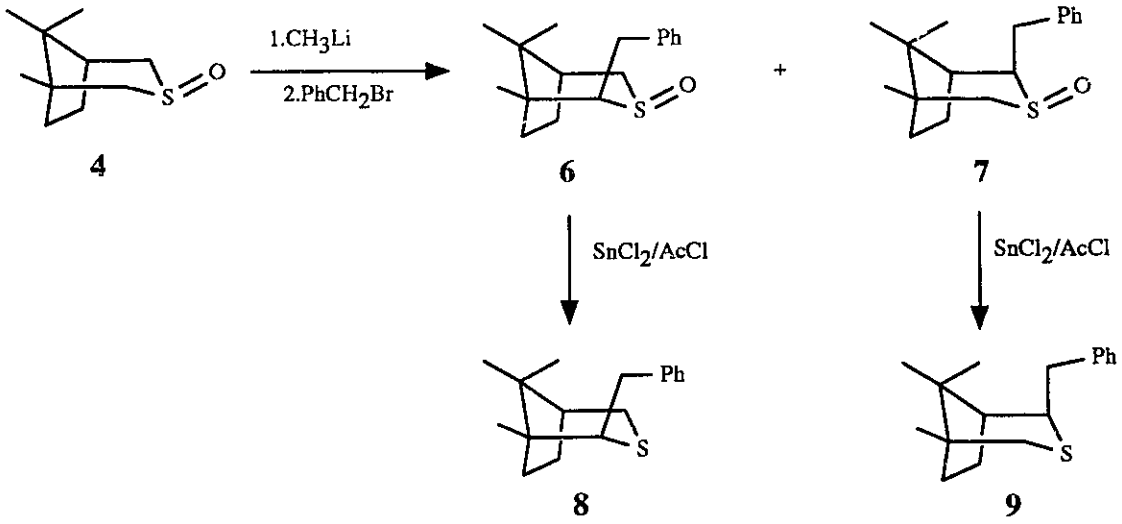
Scheme 10



4 **5** **2**

In the event, this sequence did not lead to **4** or its regioisomer but instead led to the axial substituted sulfoxides **6** and **7** shown in Scheme 11. The structure of **6** was confirmed by an X-ray structure determination while the structure of **7** was determined by NMR.

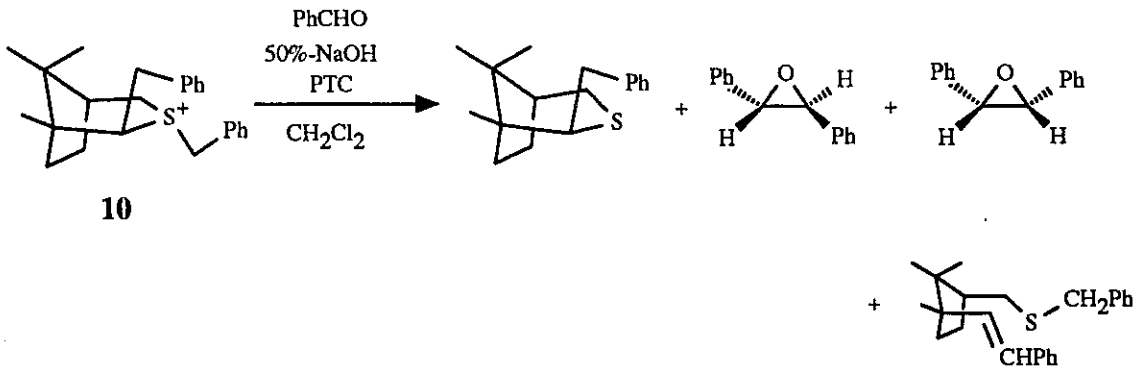
Scheme 11



4 **6** **7** **8** **9**

Sulfides **8** and **9** were in themselves interesting chiral auxiliaries. Asymmetric catalytic epoxidation experiments were attempted using thiane **8**, benzyl bromide and KOH. After 3 days only starting materials were present. However, alkylation using benzyl bromide and $AgClO_4$ in ether furnished a single sulfonium salt, **10**. Epoxidation reactions were carried out under phase transfer conditions in CH_2Cl_2 with 50% NaOH and benzyltriethylammonium chloride for 3 hours at O °C and the products obtained are shown in Scheme 12.[14]

Scheme 12

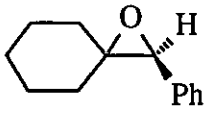


10 **11**

The *trans*- and *cis*-stilbene oxides where obtained in 48% chemical yield with a 4.8:1 ratio

along with 57% recovered thiolane which was still optically pure. Compound **11** was obtained in 22% yield and resulted from a β-elimination. The epoxides were carefully separated and the optical purity of the *trans*-stilbene oxide was determined to be >96% by NMR using the chiral shift reagent $Eu(hfc)_3$. The overall chemical yield for the *trans* epoxide was 38% and the *meso* compound was obtained in 8% yield. The reaction of other aldehydes and ketones with sulfonium salt **10** are presented in Table 1.

Table 1. Asymmetric epoxidation using sulfonium salt **10**.[a]

	Epoxides			
Aldehyde	*Trans*		*Cis*	
or ketone	yield (%)	% ee[b] (confign)[c]	yield (%)	% ee[b] (confign)[c]
PhCHO	38	>96 (S,S)	8	meso
4-MeC_6H_4CHO	32	>96 (S,S)	-	-
$C_6H_{11}CHO$	9	84 (-)	14	86 (+)
Cyclohexanone			<5	>96 (S)[14]

a Reactions were carried out in CH_2Cl_2/NaOH 50%/cat. $BnEt_3NCl$/0°C on 1 mmole scale.

b From integration of $Eu(hfc)_3$ shifted proton NMR spectra at 300 Mhz.

c Based on $[\alpha]_D$ measurements.[15,16]

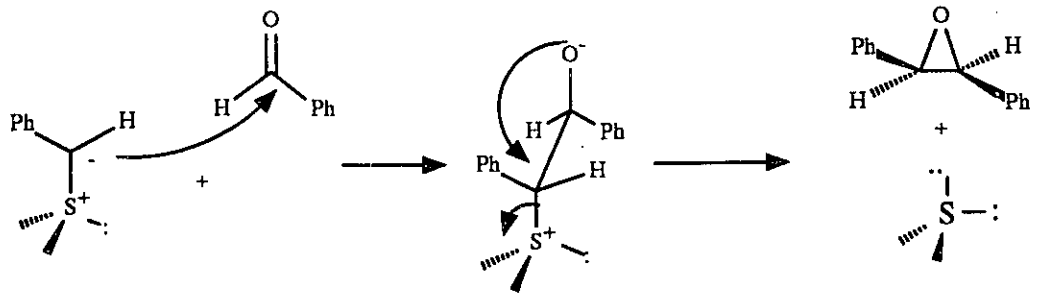
When thiane **9** was alkylated with benzyl bromide and subjected to the above reaction conditions, using benzaldehyde as the electrophile, the (R,R)-*trans*-stilbene oxide was obtained in 45% chemical yield and only 34% ee.

In order to fully appreciate the effectiveness of auxiliary **8** it is necessary to spend a few paragraphs examining the mechanism of its reaction with electrophiles.

Scheme 13 depicts the nucleophilic attack of a sulfur ylide on a molecule of

benzaldehyde.

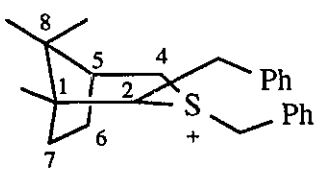
Scheme 13



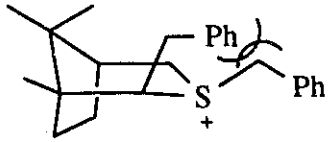
A 1,3-elimination then follows resulting in the regeneration of the sulfide auxiliary (which may be realkylated) and the epoxide. The stereochemistry of the oxiranes obtained supports the formation of a *trans*-betaine[17a] intermediate shown in Scheme 13. While the above mechanism is the most accepted one an alternate mechanism involving a 2+2 cycloaddition resulting in the formation of an oxathietaine-type intermediate (a four membered ring as in a Wittig reaction[17b]) has also been proposed to explain this reaction.[17c]

Careful NMR analysis of **8** revealed that the thiane exists in a "twist boat" conformation.[18] Alkylation of **8** with benzyl bromide has the potential to produce two diastereomers, **A** and **B** shown in Figure 1. For steric reasons alkylation *trans* to the C-2 benzyl group is favored resulting in **A**. In theory it is possible for the ylide of **A** to adopt more than one conformation however, **12A** is preferred while **12B** is not because of steric interactions between the phenyl substituent and the *exo* hydrogens on the C_2 bridge.

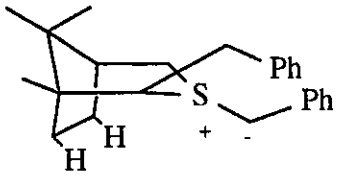
Figure 1. Possible Configurations and Conformations of Sulfonium Salt **10** and the ylide **12**.



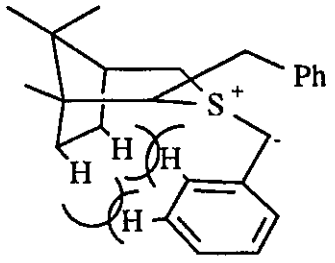
A



B



12A

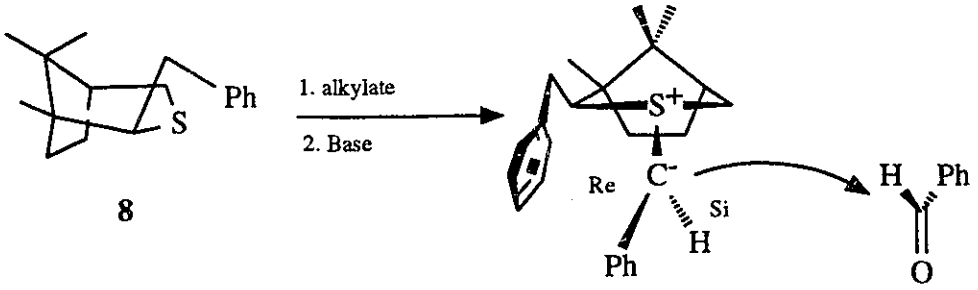


12B

The C-1 methyl group is essential because it forces the C-2 benzyl substituent forward and prevents it from "swinging" out to the side of the molecule. This is the basis for the facial selectivity observed in the reactions of the ylide **12** with aldehydes and ketones.

Since ylide **12** is "locked" in the conformation depicted in Scheme 14, the benzyl substituent in the C-2 axial position effectively blocks one face of the ylide from attack. The net result is approach of the carbonyl compound from the *Si*-face leading to formation of the (S)-oxirane.

Scheme 14

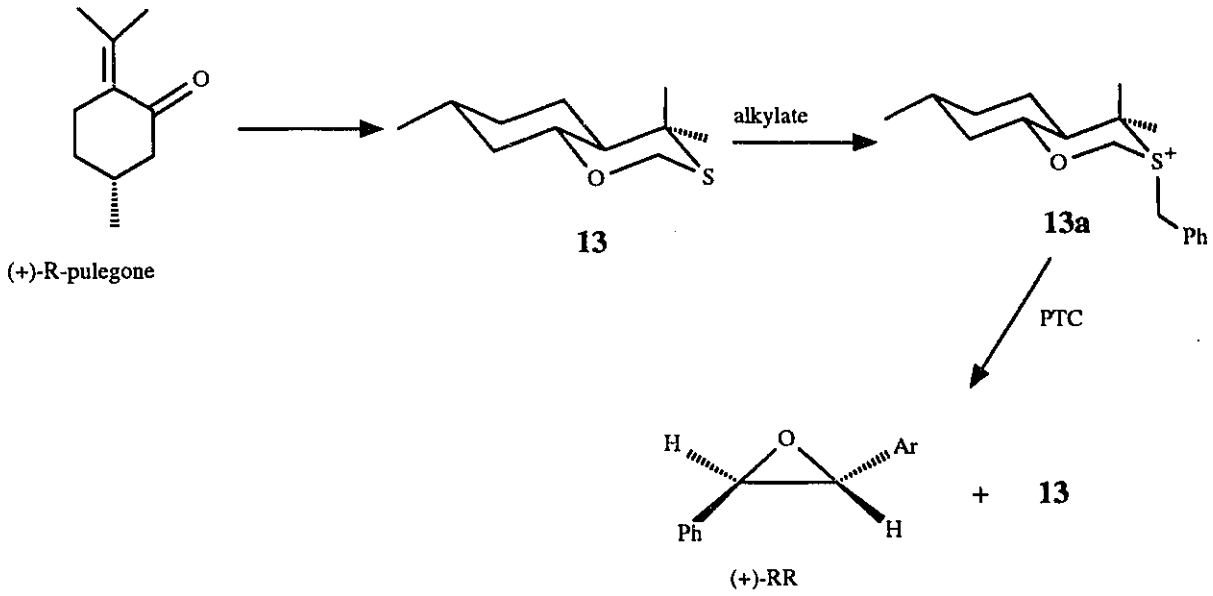


8 **12**

The stereochemistry of the second center in the oxirane is dependent upon the face of the carbonyl group presented to the ylide carbon and is reflected in the *trans:cis* ratio of epoxides.

In 1992, A. Solladie-Cavallo et al.[19] reported a second example of high asymmetric induction in the reaction of a sulfur ylide with aromatic aldehydes. Starting from the natural product (+)-R-pulegone and using standard methodology[20] Eliel's oxathiane **13**, was obtained in good yield. The oxathiane was alkylated with benzyl bromide in the presence of $AgClO_4$ to afford only one diastereomer of the sulfonium salt in 70% yield. Reaction of this salt with benzaldehyde under phase transfer conditions afforded only the (R,R)-*trans*-epoxides in 70-80% chemical yield with enantiomeric purities of 70-100% (Scheme 15). The oxathiane was recovered in 78-85% yield.

Scheme 15

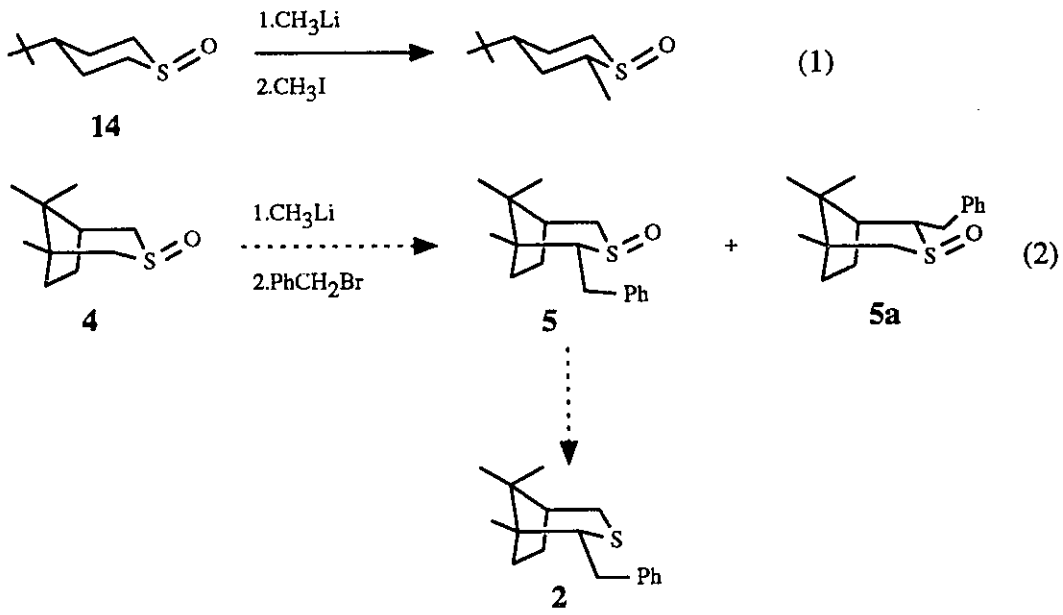


A unique feature of oxathaine **1** is that the oxygen atom in the ring controls alkylation of the sulfur atom through a 1,3-anomeric-type interaction. This is highly effective in ensuring the formation of only one sulfonium salt, i.e. **13a**. Attack of an aldehyde on the ylide derived from **13a** occurs preferentially from the front and yields (R,R)-*trans*-stilbene oxides).

1.4 The Objective.

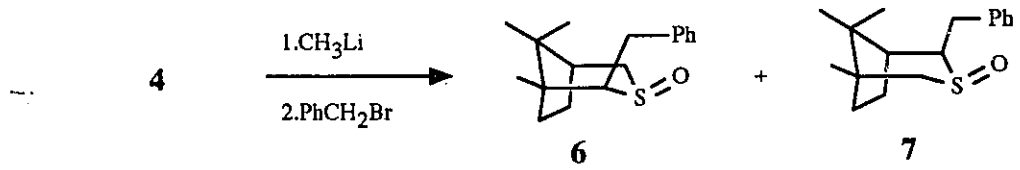
Based on work by Marquet et al.[21,22] in the 1970's concerning the stereochemistry of the reactions of lithio sulfoxides derived from *trans*-4-*t*-butylthiane-S-oxide **14** (shown in Scheme 16, equation 1), Breau originally expected that benzylation of sulfoxide **4** via initial treatment with methyllithium followed by benzyl bromide should yield a mixture of equatorially benzylated sulfoxides **5** and **5a** (Scheme 16, equation 2). Reduction of the former sulfoxide would lead to the desired thiane **2**.

Scheme 16



As previously discussed, the stereochemical result of the alkylation was opposite of what was expected (see Scheme 17).

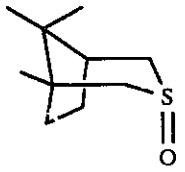
Scheme 17



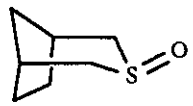
Breau's benzylation of the anion of **4** was surprising in two aspects. It contradicted the observation of the Marquet group that in thianes, alkylation occurred preferentially *trans* to the S=O bond. Furthermore, molecular models indicated that the observed axial benzylation products **6** and **7** were considerably more hindered than the desired equatorial alkylations product **5** and **5a**.

In order to gain insight into this unexpected result it was decided to investigate the reaction of the anion of **4** with CH_3OD, CH_3COOD and acetone as representative examples of the reaction of sulfoxide anions with other electrophiles. It was known from the work of

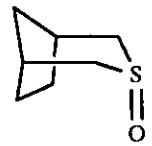
Marquet[21,22] that deuteration of lithio sulfoxide carbanions occurred with opposite stereochemistry than alkylation and thus, a comparison of the stereochemistry of the reaction of different electrophiles was considered worthwhile. It was also hoped that a study of the reactions of the anion of the isomeric sulfoxide **15** and the simpler bicyclic sulfoxides **16** and **17** with both benzyl bromide and CH_3OD/CH_3COOD might shed light on the problem. These studies constitute the first part of this thesis.



15



16



17

Chapter 2. Stereochemical Results in the Trapping of Lithio Derivatives of Bicyclic Sulfoxides.

2.1 General Comments.

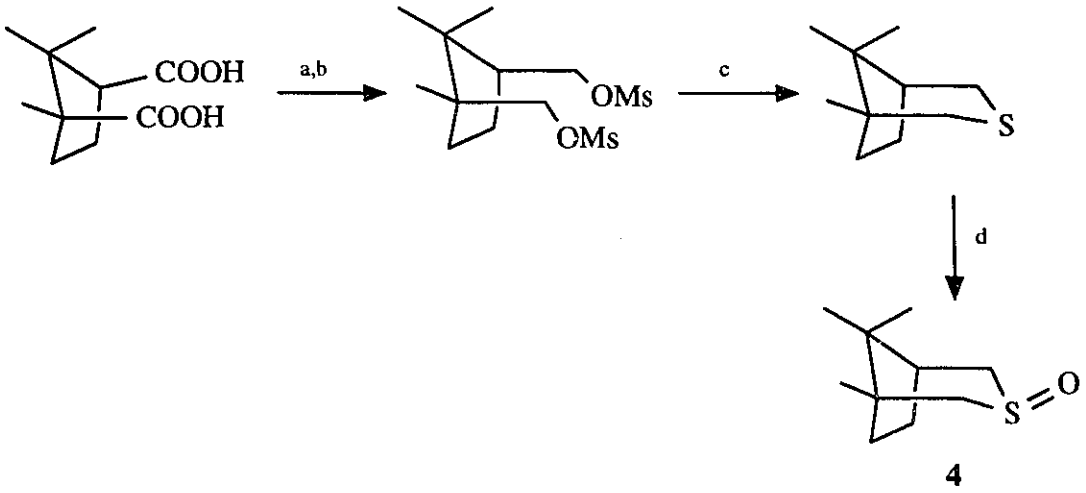
As mentioned in section 1.4, Marquet and coworkers studied extensively the stereochemical results of deuteration and alkylation of the α-sulfinyl carbanions in cyclic sulfoxides.[21,22] In all cases reported, deuteration gave opposite stereochemical results when compared with alkylation. For example, deuteration occurred *cis* to the existing S=O bond while alkylation occurred *trans* to the S=O bond (the reasons for this will be discussed in chapter 3). In the results obtained by Breau, alkylation of **4** not only occurred *cis* rather than *trans* to the S=O bond but the benzyl group entered into what appeared to be the more hindered axial position.

In an effort to gain insight into the reason for this unusual result the lithio derivative of sulfoxide **4** was deuterated and also reacted with acetone and the stereochemistry of these reactions were determined. Subsequently, sulfoxide **15** (an epimer of **4**) and the related bicyclic sulfoxides **16** and **17**, lacking the three methyl groups present in **4** and **15** were prepared and the stereochemistry of the deuteration and benzylation of their respective α-anions were determined in order to gain understanding of the unusual result obtained with **4**.

2.2 Synthesis of bicyclic sulfoxides 4, 15, 16 and 17.

Bicyclic sulfoxide **4** was synthesized from (1R,3S)-(+)-camphoric acid using a procedure developed by Breau in Scheme 18.[18,23]

Scheme 18



4

a)$LiAlH_4$,THF; b)MsCl,Et_3N,CH_2Cl_2; c)$Na_2S.9H_20$,DMF; d)MMPP,EtOH-H_2O

Camphoric acid was reduced using lithium aluminum hydride in THF and then converted to the dimesylate by treatment with MsCl and triethylamine. The cyclization was carried out using $Na_2S.9H_20$ in DMF to afford the thiolane which was oxidized using MMPP[24] to furnish sulfoxide **4**. Compound **4** was purified by sublimation at 110-115°C/0.25 Torr to give a white crystalline solid with a mp 241 °C in 39% overall chemical yield. This solid displayed a strong IR absorption at 1028 cm^{-1}, very characteristic of a sulfoxide functionality. Breau obtained **4** in 35% overall chemical yield and reported a mp 241-242 °C.

The following paragraphs will describe and analyze the NMR spectra of **4**. The analyses are identical to those originally described by Breau in his Ph.D. thesis and are only reviewed in this thesis because several more detailed spectra have since been obtained.

The ^1H NMR spectrum of **4** shown in Figure 2A and 2B shows three different methyl groups (Figure 2A was taken from Breau's Ph.D. thesis). The protons α to the sulfoxide

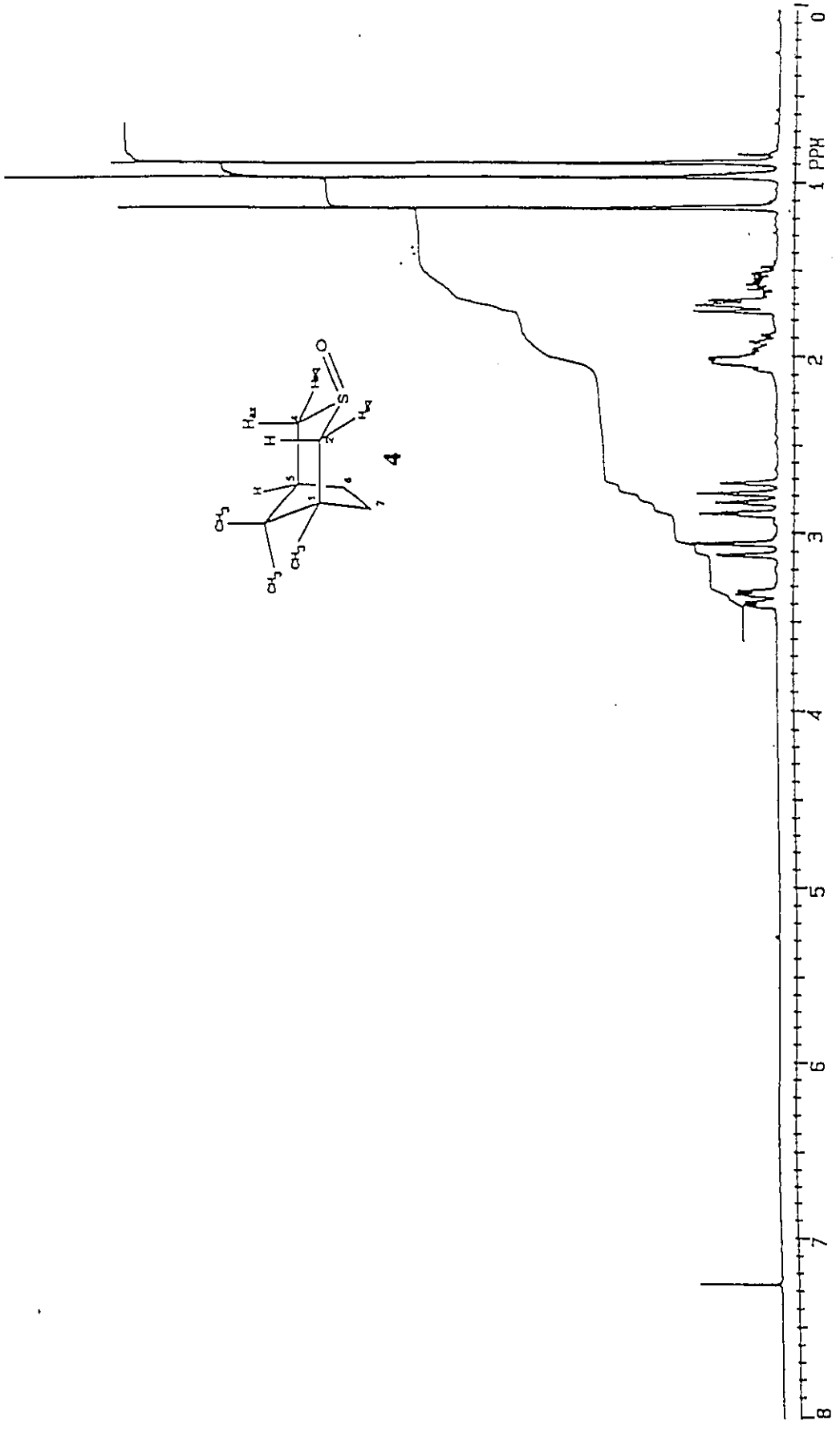


Figure 2A. 200 MHz ^{1}H NMR of **4** in $CDCl_3$.

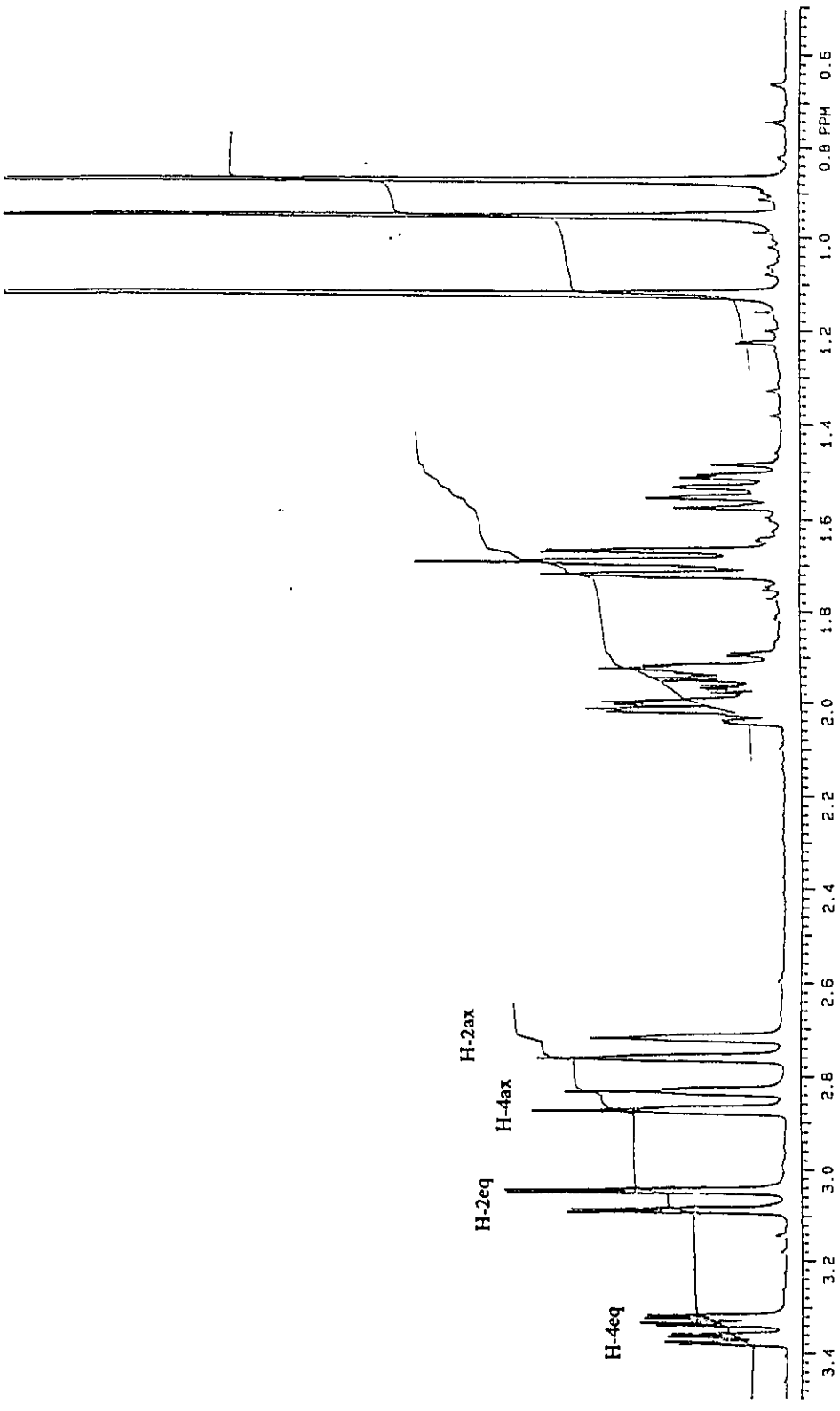


Figure 2B. 300 MHz ^{1}H NMR spectrum of **4** in $CDCl_3$.

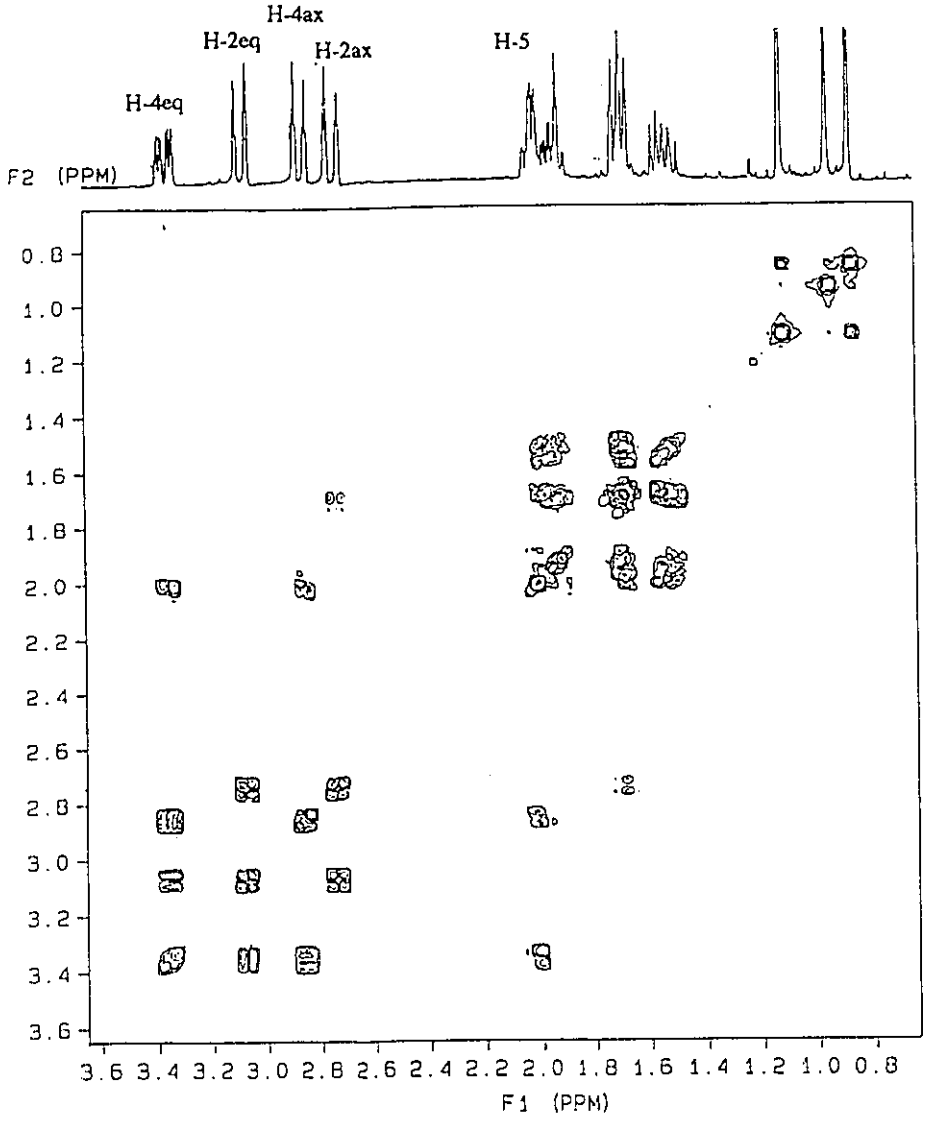
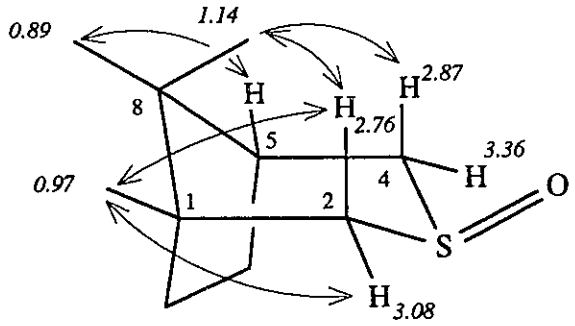


Figure 2C. 300 MHz HOMCOR spectrum of **4** in $CDCl_3$.

function are deshielded and appear at δ2.70-3.40 ppm. Irradiation of the methyl signal at 1.14 ppm (see Figure 3) showed enhancements with the resonances at 2.87 and 2.76 ppm only which suggested that the methyl signal at 1.14 ppm corresponded to the C-8 *endo* methyl and the resonances at 2.87 and 2.76 ppm belonged to the C-4 and C-2 axial protons. Examination of a 300 MHz HOMCOR or COSY spectrum (Figure 2C) indicated the resonance at 2.76 ppm displayed a strong geminal coupling of approximately 12.5 Hz to the resonance at 3.08 suggesting that these hydrogens resided on the same carbon. By analogy, a similar geminal coupling of 12.4 Hz between the other axial hydrogen at 2.87 ppm and the resonance at 3.36 ppm indicated that these hydrogens also were on the same carbon. A 1.8 Hz "W"-type coupling between the resonance at 3.36 ppm and the resonance at 3.08 ppm (each on different carbons α- to the sulfur) indicated that these signals corresponded to the C-4 and C-2 equatorial protons but it was still not obvious which hydrogen belonged on which carbon. Irradiation of the methyl group at 0.97 ppm showed enhancements on only the axial hydrogen at 2.76 ppm and the equatorial hydrogen at 3.08 ppm indicating that the resonance at 0.97 ppm corresponded to the C-1 methyl group and subsequently the signals at 2.76 and 3.08 belonged to the C-2 axial and equatorial hydrogens respectively. As a consequence of this assignment the resonances at 2.87 and 3.36 ppm were assigned to the C-4 axial and equatorial protons respectively. The fact that H-4eq displayed a vicinal coupling of 1.9 Hz to H-5 at approximately 2.05 ppm (which was identified by irradiation of the remaining methyl group at 0.89 ppm) verified that the assignments were correct. This vicinal coupling along with the 1.8 Hz W-type coupling indicated that the six membered ring exists in a chair conformation.

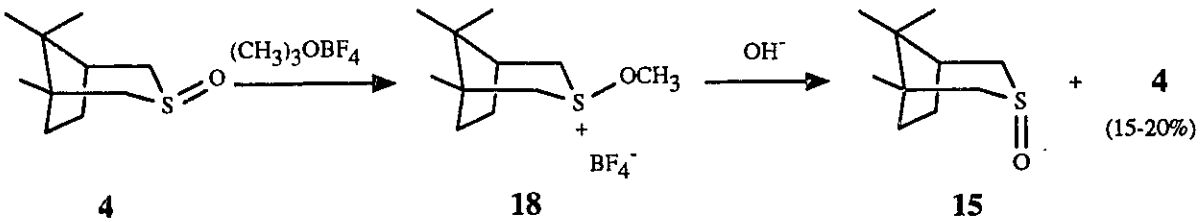
Figure 3. Summary of nOe's observed in **4** upon irradiation of methyl substituents at C-1 and C-8.



*numbers in italics indicate chemical shift values

Sulfoxide **15** was prepared from sulfoxide **4** as illustrated in Scheme 19. Sulfoxide **4** was dissolved in freshly distilled CH_2Cl_2 and cooled to 0°C. Trimethyloxonium tetrafluoroborate[25] was then added and the mixture stirred for 3 h. Addition of diethyl ether produced a precipitate which was filtered off. This precipitate, compound **18**, was obtained in 70% chemical yield and identified by ^1H NMR on the basis that four different methyl groups at 0.95, 1.10, 1.18 and 4.20 ppm were visible. The C-4 and C-2 equatorial and axial hydrogens were deshielded and appeared at 4.35, 4.10, 3.40 and 3.25 ppm respectively.

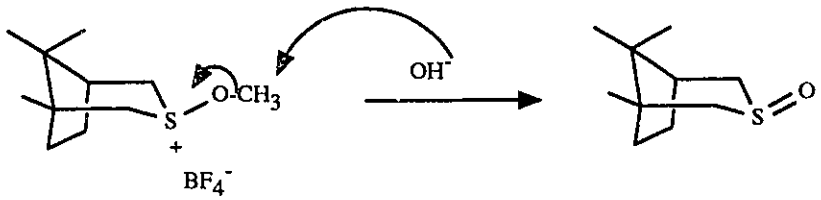
Scheme 19



Compound **18** was then subjected to reaction with 0.2 N NaOH and after work-up an 80:20 mixture (determined by capilliary column GC analysis) of isomeric sulfoxides **15** and **4**

were produced. This was unusual since alkoxysulfonium salts usually hydrolyze cleanly by attack of hydroxide at sulfur yielding sulfoxides with inversion of configuration. It was theorized that perhaps attack at sulfur is hindered by the ethano bridge thus allowing attack at the methoxy group to compete as shown in Scheme 20. This might have been avoided by using triethyloxonium tetrafluoroborate but since separation of the products was possible this approach was considered unnecessary.

Scheme 20



18 **4**

Separation of the isomeric sulfoxides by column chromatography using toluene:acetone (2:1) produced **15** in 75% yield as a white solid, mp 171°. The IR spectrum showed a strong absorption at 1030 cm^{-1}, indicative of a sulfoxide and HRMS confirmed a molecular formula of $C_{10}H_{18}OS$. Figures 4 to 6 show some of the spectral data which was examined.

An obvious difference between sulfoxides **15** and **4**, is that the C-4 and C-2 axial protons of **15** are more deshielded than the C-4 and C-2 equatorial protons and appear at approx. 3.15 and 3.00 ppm respectively. The opposite convention was observed in sulfoxide **4** where the C-4 and C-2 equatorial hydrogens were more deshielded than the

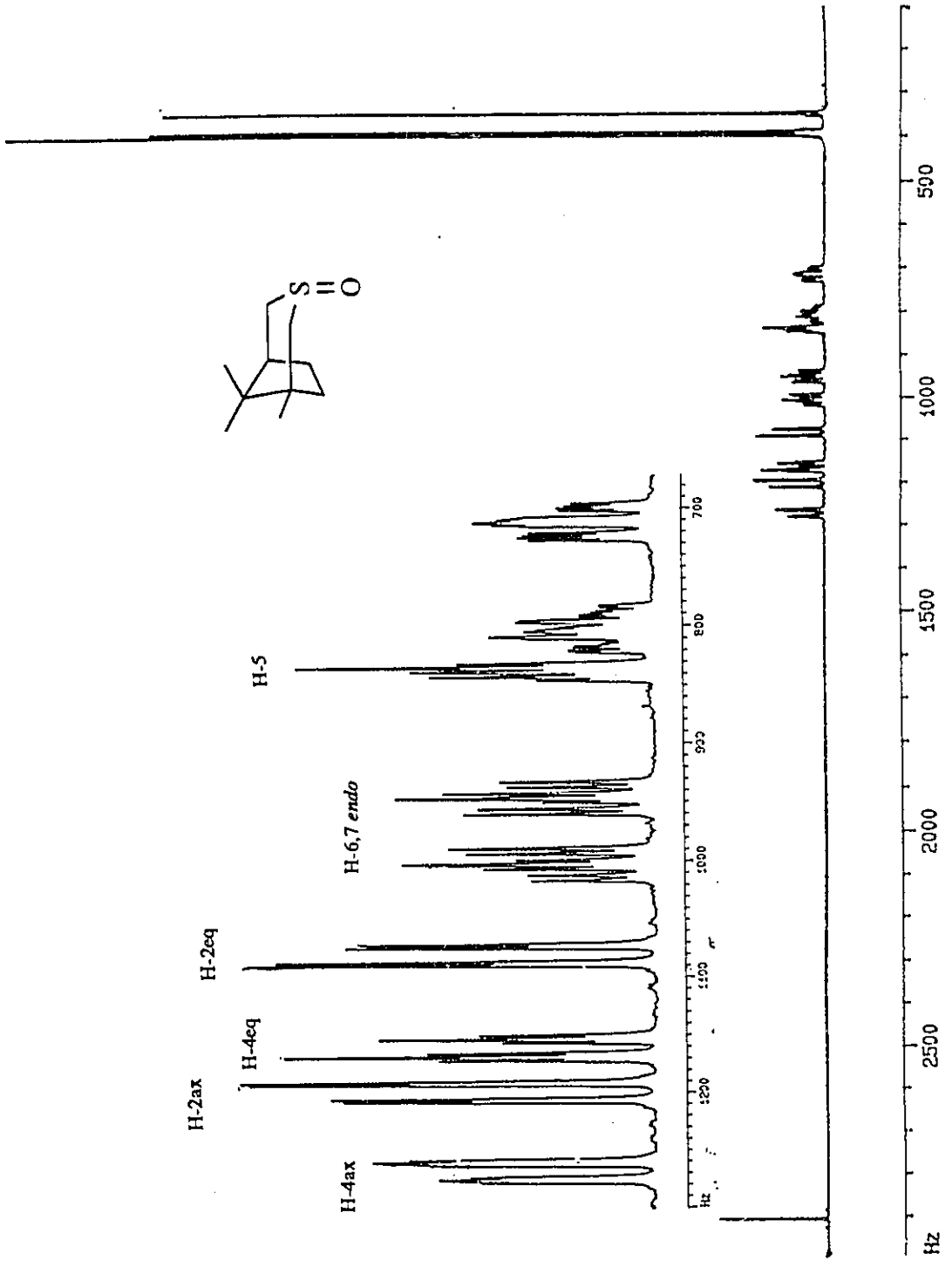


Figure 4. 400 MHz. ^{1}H NMR spectrum of **15** in $CDCl_3$.

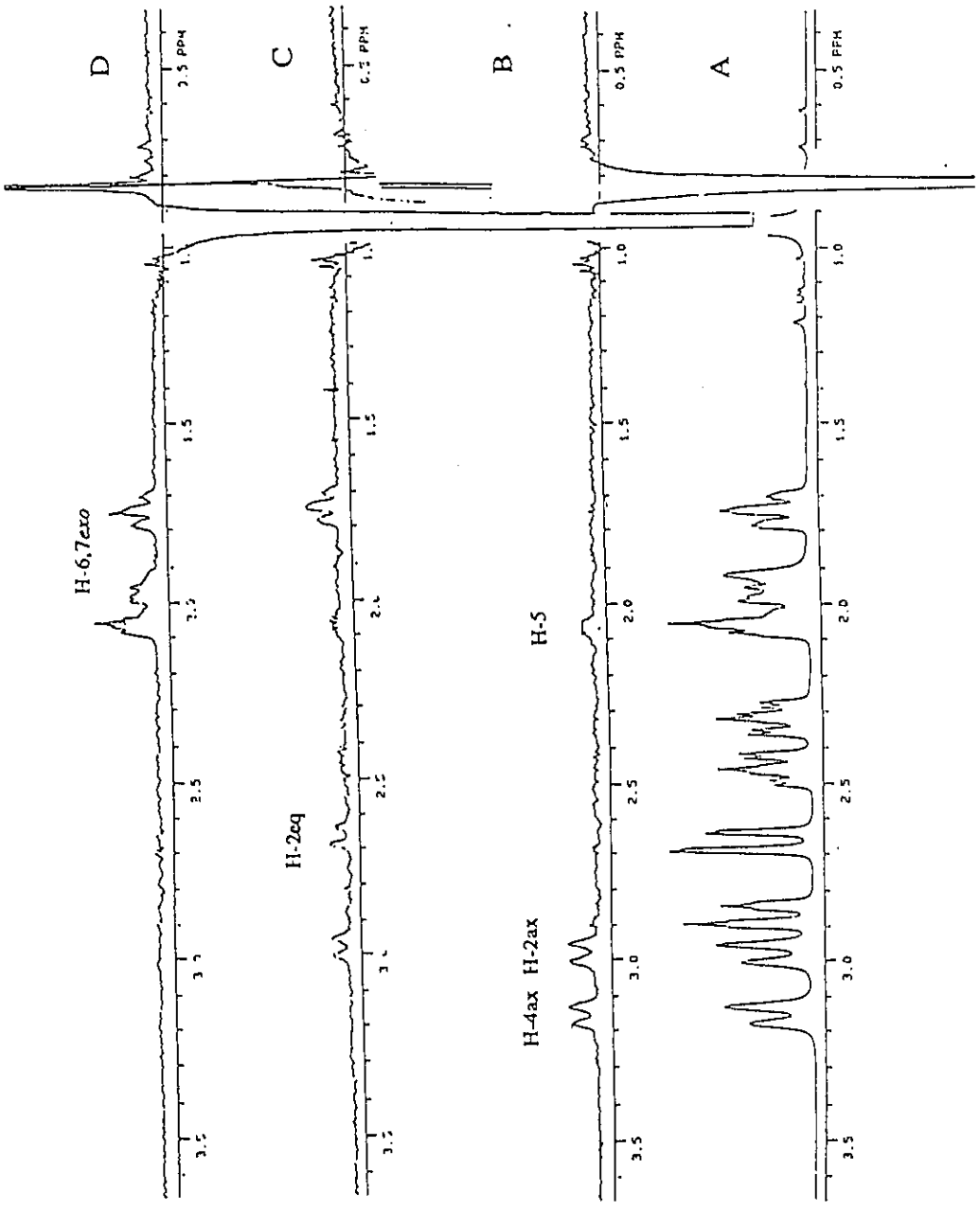


Figure 5. A) 300 MHz ^{1}H NMR spectrum of **15** in $CDCl_3$.
B-D) nOe difference spectrum obtained by irradiation of:
B) C-8*endo* methyl (0.82 ppm), C) C-1 methyl (0.93 ppm)
D) C-8*exo* methyl (0.96 ppm).

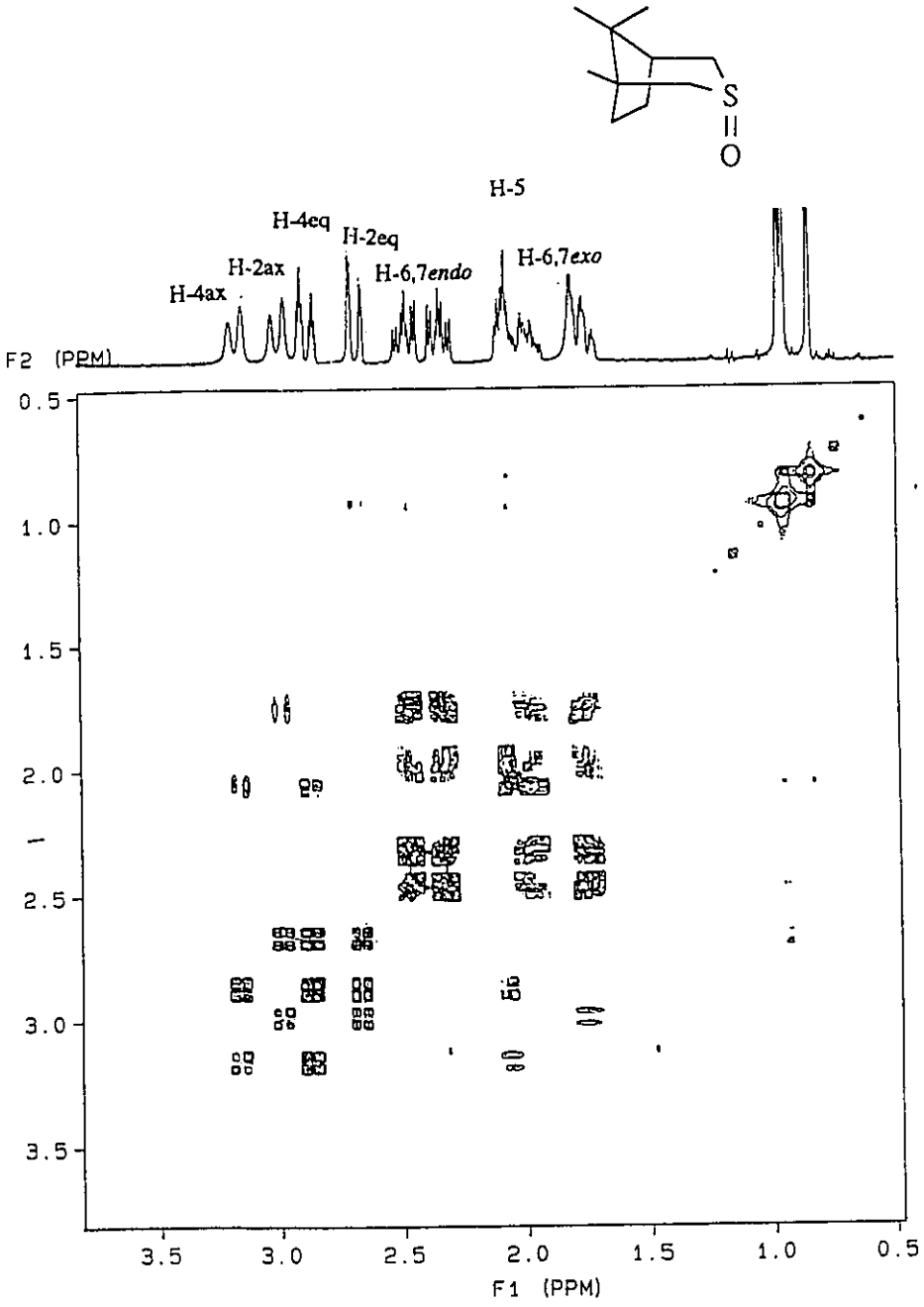


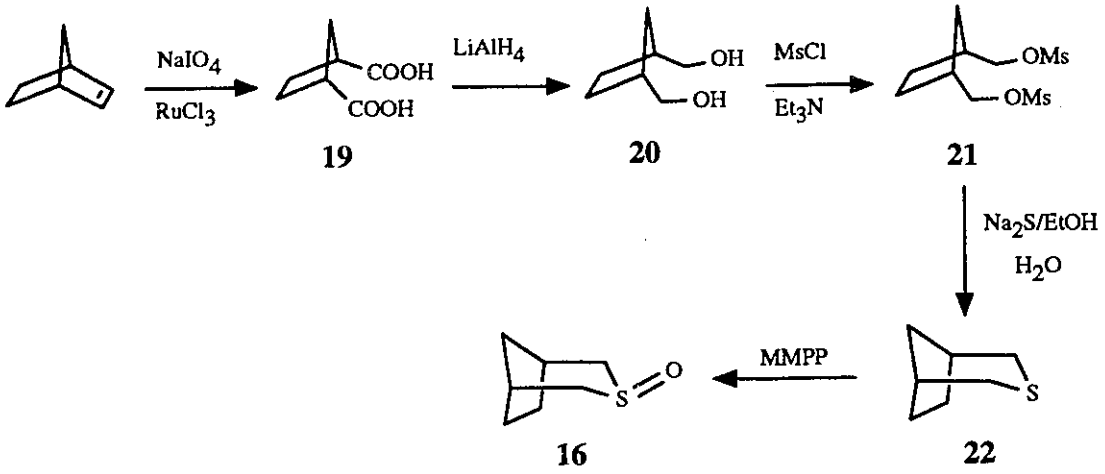
Figure 6. 300 MHz HOMCOR of **15** in $CDCl_3$.

axial ones. Also, the *endo*- and *exo*-protons on C-6 and C-7 are well separated because the *endo* hydrogens are much closer to the sulfoxide oxygen atom and as a result, are deshielded[26] and appear at 2.30-2.55 ppm. The assignments for the C-2 and C-4 axial and equatorial protons are described below.

Irradiation of the methyl group at 0.82 ppm produced nOe's on the resonances at 3.15, 3.00 and 2.07 ppm (see Figure 5). Since the H-5 proton in sulfoxide **4** displayed a chemical shift value of δ 2.05 and there existed no reason why this proton resonance should shift in **15**, the resonance at 2.07 ppm was assigned as H-5. Subsequently, since the resonances at 3.15 and 3.00 ppm were too far down field to correspond to the C-6 and C-7 *exo* hydrogens (which would be affected if the C-8 *exo* proton had been irradiated) the resonance at 0.82 ppm was assigned as the C-8 *endo* methyl group and the resonances at 3.15 and 3.00 ppm were assigned as the C-4 and C-2 axial hydrogens. Using the same reasoning from the assignments of sulfoxide **4**, the geminal coupling between the axial proton at 3.15 ppm and the resonance at 2.85 ppm (see Figure 6) indicated that these protons were on the same carbon. A similar argument lead to the conclusion that the axial proton at 3.00 ppm and the proton at 2.70 ppm also were on the same carbon. The fact that both protons at 3.15 and 2.85 ppm (on the same carbon) displayed a vicinal coupling to the H-5 proton indicated that both of these protons were on C-4 and subsequently the protons at 3.00 and 2.70 ppm were determined to be on C-2. This last assignment was also confirmed by irradiation of the methyl group at C-1 which displayed nOe's enhancements to both of these hydrogens. The observation of a 1.4 Hz W-type coupling between the resonances at 2.85 and 2.70 ppm further confirmed these protons as H-4eq and H-2eq.

Bicyclic sulfoxide **16**, lacking the three methyl groups was prepared as outlined in Scheme 21. Commercially available norborene was oxidized to the corresponding diacid by treatment with $RuCl_3$ and $NaIO_4$[27] in 70% yield.

Scheme 21



Compound **19** was then subjected to reduction with $LiAlH_4$ in THF to yield **20** as a colourless liquid in 93% yield. This diol was then treated with methanesulfonyl chloride and triethylamine in CH_2Cl_2 to give compound **21** in 76% yield after purificaton. Using a previously described procedure[28] the mesylates were displaced and the thiane was formed in 82% chemical yield and was used without further purification. Oxidation of thiane **22** to the corresponding equatorial sulfoxide **16** was accomplished with magnesium monoperoxyphthalate (MMPP)[24] in 75% chemical yield after sublimation at 90-110°C/1 Torr.

Sulfoxide **16** was a white crystalline solid with a mp 196°C. The IR spectrum showed a strong absorption at 1032 cm^{-1} indicating the presence of a sulfoxide moiety. EIMS and HRMS were both consistent with a compound having a molecular formula of $C_7H_{12}OS$.

The proton NMR spectrum of **16** obtained using $CDCl_3$ as a solvent was quite disappointing since many of the resonances overlapped. When the same sample was run in benzene-d_6 all of the resonances separated as shown in Figure 7. Such a dramatic effect occurs because repulsive interactions between the benzene ring and the oxygen of the S=O bond produce an anisotropic effect which results in a shielding of the hydrogens furthest removed from the oxygen atom.[29]

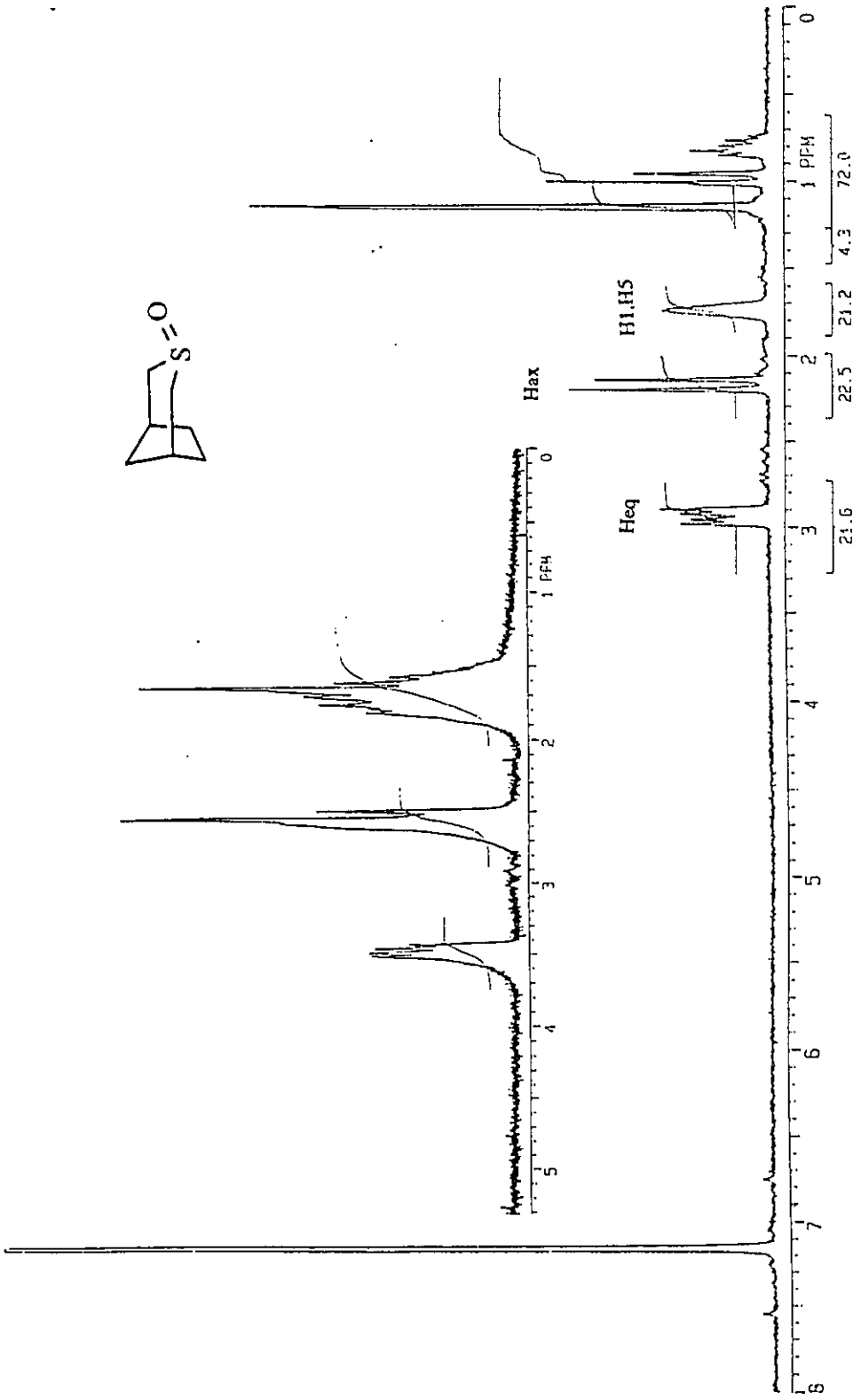


Figure 7. 200 MHz ^{1}H NMR of **16** in Benzene-d_6 with inset in $CDCl_3$.

Initially, based only on the trend observed in the analysis of equatorial sulfoxide **4** where the equatorial hydrogens were more deshielded than the axial ones, the resonance at 2.95 ppm in sulfoxide **16** was assigned as the C-4 and C-2 equatorial hydrogens. Subsequently, the resonance at 2.18 ppm was assigned to the C-4 and C-2 axial protons. The C-1 and C-5 protons were assigned to the resonance at 1.75 ppm based on the fact that the many different vicinal couplings to these hydrogens would be expected to make the resonance quite broad in its line shape. Unfortunately, nOe experiments were not effective with this sulfoxide because the distances between most atoms (i.e. H-8_{endo} and H-2ax or H-4ax) was greater than three angstroms. However, as shown in Figure 8 the COSY of **16** depicted a vicinal coupling between the C-1/C-5 hydrogens and the C-4/C-2 equatorial hydrogens but showed no evidence of vicinal coupling between the C-1/C-5 and the C-4/C-2 axial hydrogens. Based upon the fact that in simple molecular models the dihedral angle between H-5 and H-4ax is 90° and as a consequence no coupling is expected, it was concluded that the C-4 equatorial hydrogens were correctly assigned at 2.95 ppm. The fact that the C-4 and C-2 equatorial hydrogens displayed a strong geminal coupling to the resonance at 2.18 ppm confirmed that this resonance which was previously assigned as the C-4 and C-2 axial hydrogens, was assigned correctly.

The isomeric bicyclic sulfoxide **17** was obtained via conversion of **16** into intermediate **23** (in 80% yield) as described previously, followed by treatment with aqueous base.

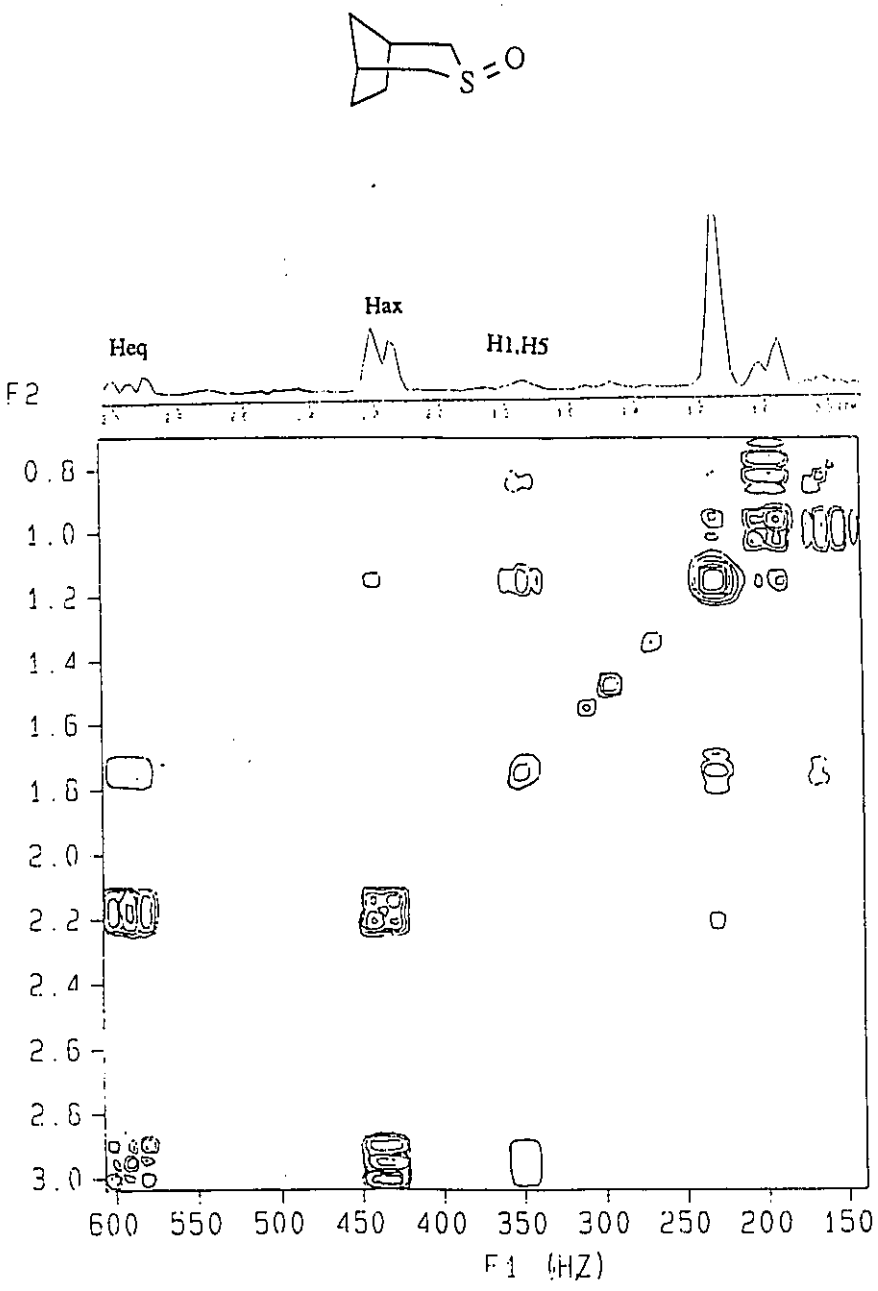
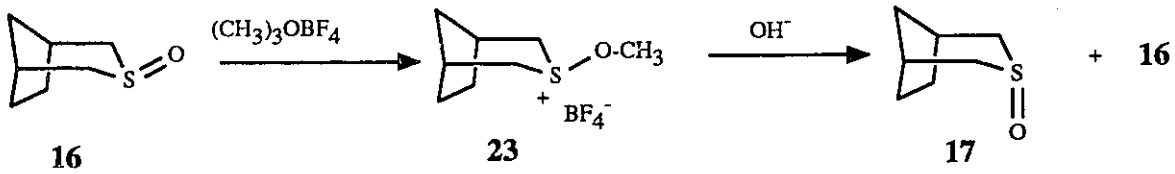


Figure 8. 200 MHz HOMCOR spectrum of **16** in Benzene-d_6

Scheme 22.



16 **23** **17**

GC analysis of the mixture showed an 80:20 mixture of **17** to **16**, a similar ratio to that obtained on the hydrolysis of **18**. The isomeric sulfoxides were separated by column chromatography using a 10:1 mixture of dioxane:toluene. Compound **17** was obtained in 70% yield as a white crystalline solid (mp 210°C) was purified by sublimation at 90-110°C/1 Torr. The IR spectrum showed a strong S=O stretching absorption at 1028 cm^{-1} and HRMS confirmed a molecular formula of $C_{14}H_{12}OS$.

The proton NMR of **17** is shown in Figure 9. In order to obtain maximum separation between the various resonances, all NMR work was carried out in benzene-d_6.

By applying the same logic used in the assignment of the H-1 and H-5 protons in sulfoxide **16**, the C-1/C-5 protons in **17** were assigned to the resonance at 1.93 ppm. Examination of the COSY spectrum of **17** (Figure 10) revealed that the C-1/C-5 protons coupled only to the resonance at 2.60 ppm which was expected to be either the axial or equatorial protons on C-4/C-2. The resonance at 2.60 ppm displayed a strong geminal coupling to the resonance at 2.04 ppm suggesting that the protons at this resonance were also on the C-4/C-2 carbons. Analysis of **17** using simple molecular models showed that if the six membered ring adopted a half-chair conformation to minimize steric interactions between the sulfoxide oxygen and the ethano-bridge, the dihedral angle between the C-2 and C-4 equatorial hydrogens and the C-1/C-5 hydrogens would be 85-90° while the dihedral angle with the same axial hydrogens would be 26°. A dihedral angle of 85-90° using the Karplus correlation curve corresponds to a coupling constant of 0 Hz while a dihedral angle of 26° corresponds to 8 Hz. On this basis, the resonance at 2.04 ppm was

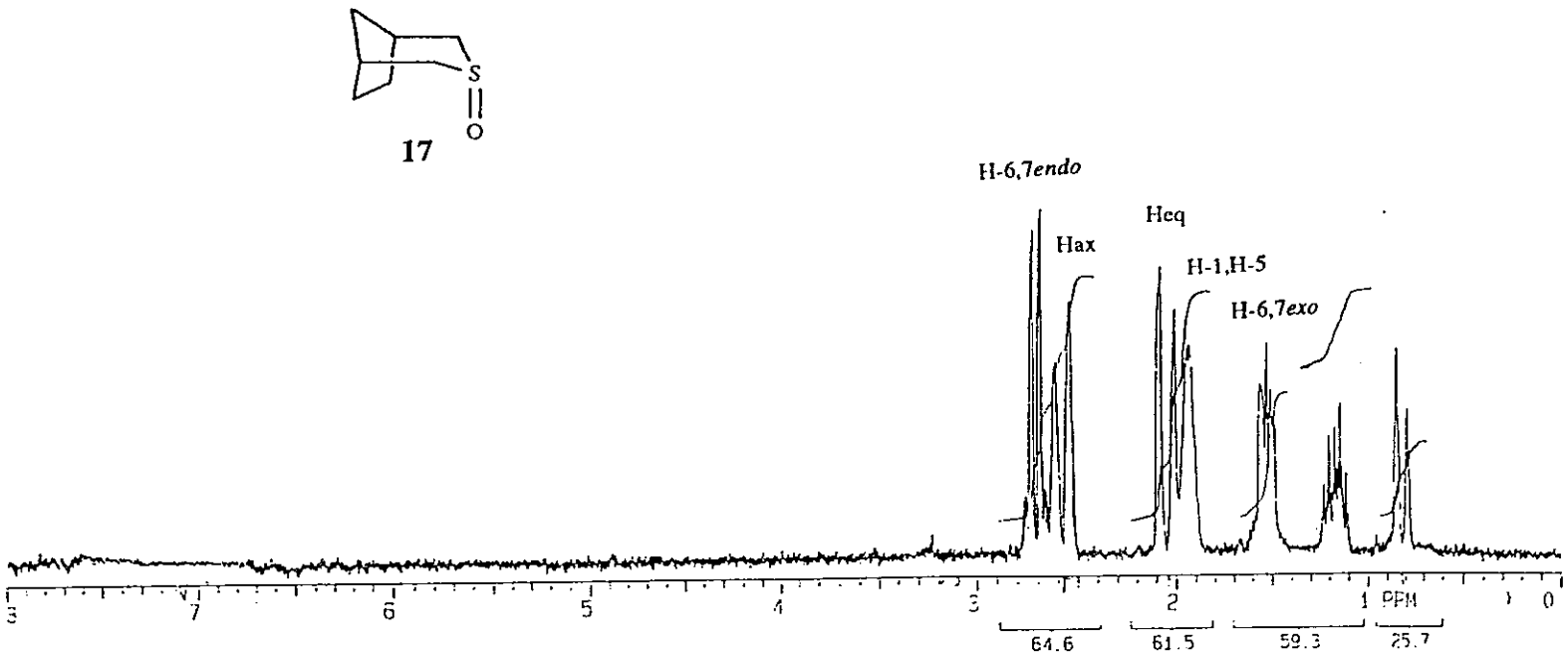


Figure 9. 200 MHz ^{1}H NMR spectrum of **17** in Benzene-d_6.

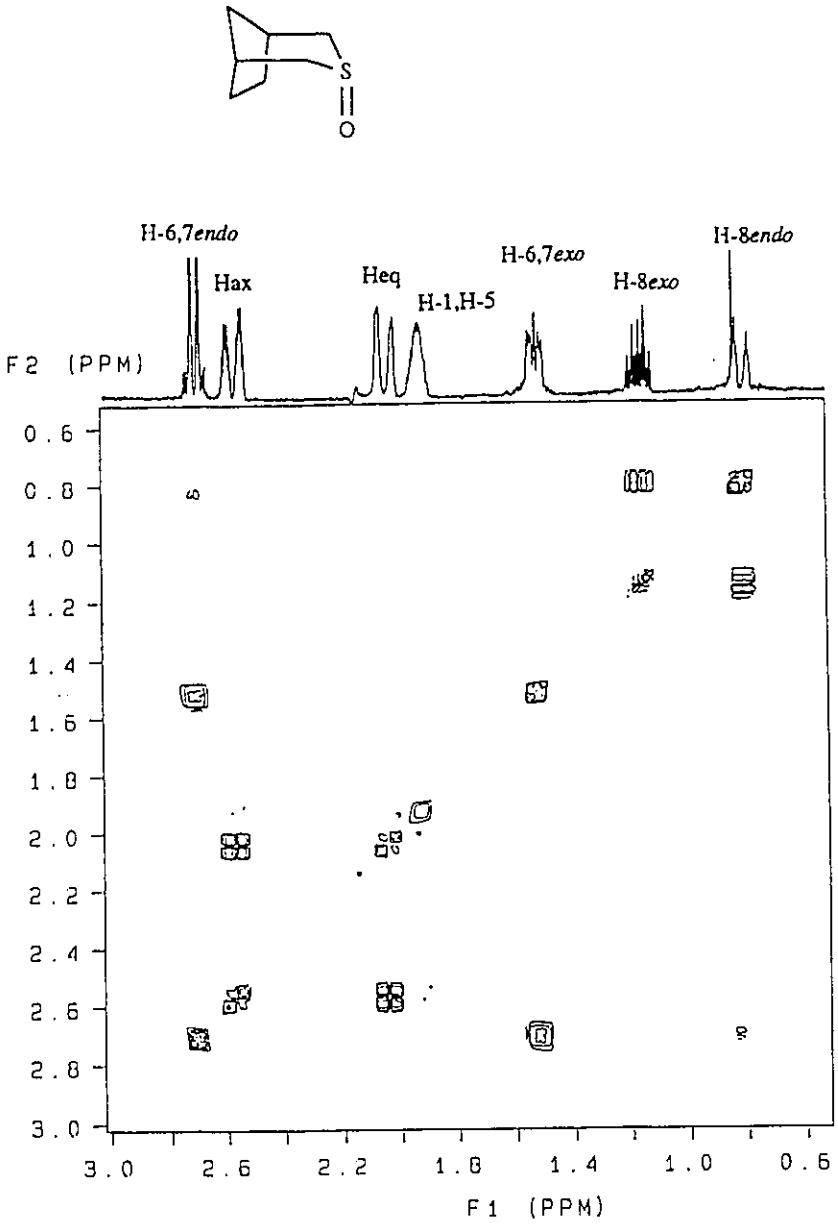


Figure 10. 300 MHz HOMCOR spectrum of **17** in Benzene-d_6.

assigned as the C-2 and C-4 equatorial hydrogens and the resonance at 2.60 ppm to the axial hydrogens. Subsequently, the most deshielded resonance at 2.70 ppm was assigned to the C-6 and C-7 *endo* hydrogens which were dramatically deshielded due to their close proximity to the oxygen of the sulfoxide bond. A COSY connectivity between the C-6 and C-7 *endo* hydrogens and the resonance at 1.5 ppm (integrating to two protons) identified this resonance as the C-6 and C-7 *exo* hydrogens. A W-type coupling between the C-6/C-7 *endo* hydrogens at 2.70 ppm to the resonance at 0.82 ppm identified the C-8 *endo* hydrogen and a geminal coupling between this hydrogen and the signal at 1.20 ppm identified the C-8 *exo* hydrogen at 1.20 ppm.

2.3 Reactions and product stereochemistries of the lithio derivatives of sulfoxides 4, 15, 16 and 17.

A) General comments:

Generation of the lithio derivatives of the sulfoxides and their subsequent quenching was carried out in oven dried glassware using the procedure outlined below. The sulfoxide was dissolved in carefully dried THF under a dry nitrogen atmosphere. This solution was then cooled to -78 °C followed by the addition of 1.2 eq of methyllithium. The yellow coloured solution was allowed to stir at -78 °C for a period of 30 to 60 min to ensure complete anion formation. The electrophile was then added neat via syringe. Depending on the electrophile employed, varying amounts were used. In the case of benzyl bromide, 5 eq were used while only 1.2 eq of reagent grade acetone was employed. Large excesses of CH_3OD and CH_3COOD were added to the reaction mixtures when deuteration experiments were carried out. After addition of the electrophile, the mixtures were slowly warmed to room temperature over a period of 3 to 5 h. Usual workup followed by column

chromatography produced the desired compounds in pure form unless indicated otherwise. Yields refer to those of purified products.

B) Structure elucidation of 2-benzylated-1,8,8-trimethyl-3-thiabicyclo[3.2.1]octane -3-oxide (6) : a "model".

As mentioned in the preceding chapter, the X-ray structure of **6** obtained by Breau (Figure 11) demonstrated that the benzyl group had entered the more hindered axial position at C-2 in sulfoxide **4**.

Through careful NMR analysis it is possible to verify the correct stereochemistry of **6** and show that the solution conformation is virtually identical to that of the crystalline form. Subsequently, using the NMR studies of **6** as a model the same NMR approach can by employed to determine the stereochemistry of the other products in this study with considerable confidence.

In this section the stereochemistry of **6**, determined by X-ray analysis, will be verified by NMR studies and based on this model the products obtained from the other lithio sulfoxides will be discussed in sequence. In the subsequent chapter, the stereochemical results will be rationalized in terms of the structure of the α-sulfinyl carbanion. The spectra (Figures 12 and 13), analyses and arguments described below verifying the stereochemistry of **6** were all taken from Breau's Ph.D. thesis.[18]

Breau isolated compound **6** in 43% yield. The compound had a mp 109-110 °C and strong IR absorptions at 1038 cm^{-1}, characteristic of S=O bond stretching. The minor, less polar fraction (compound **7**) was isolated in 24% yield, had a mp 64-65 °C and showed a similar IR absorption at 1036 cm^{-1}. Breau compared the ^1H NMRs of the starting sulfoxide **4** and the less polar fraction (Figure 12A) and observed that the signals for H-2eq (δ3.06)

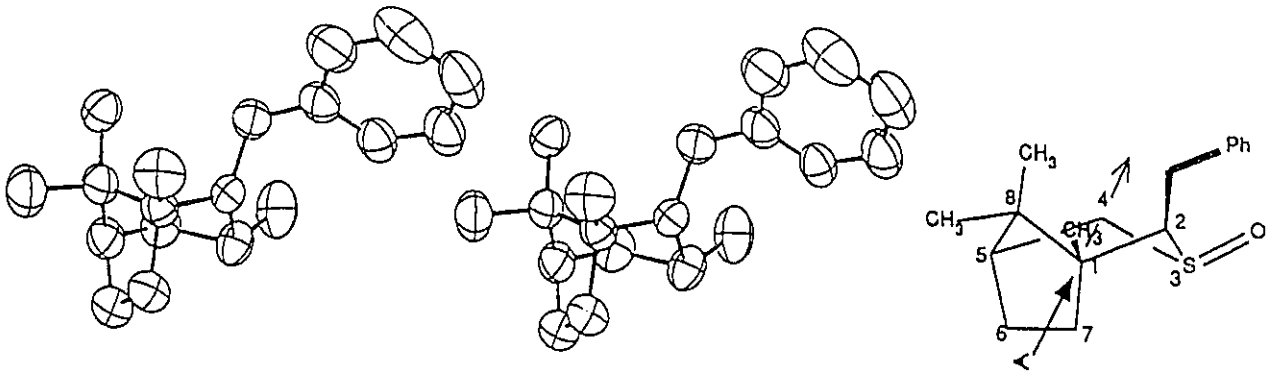


Figure 11. ORTEP of the X-ray crystal of **6.**

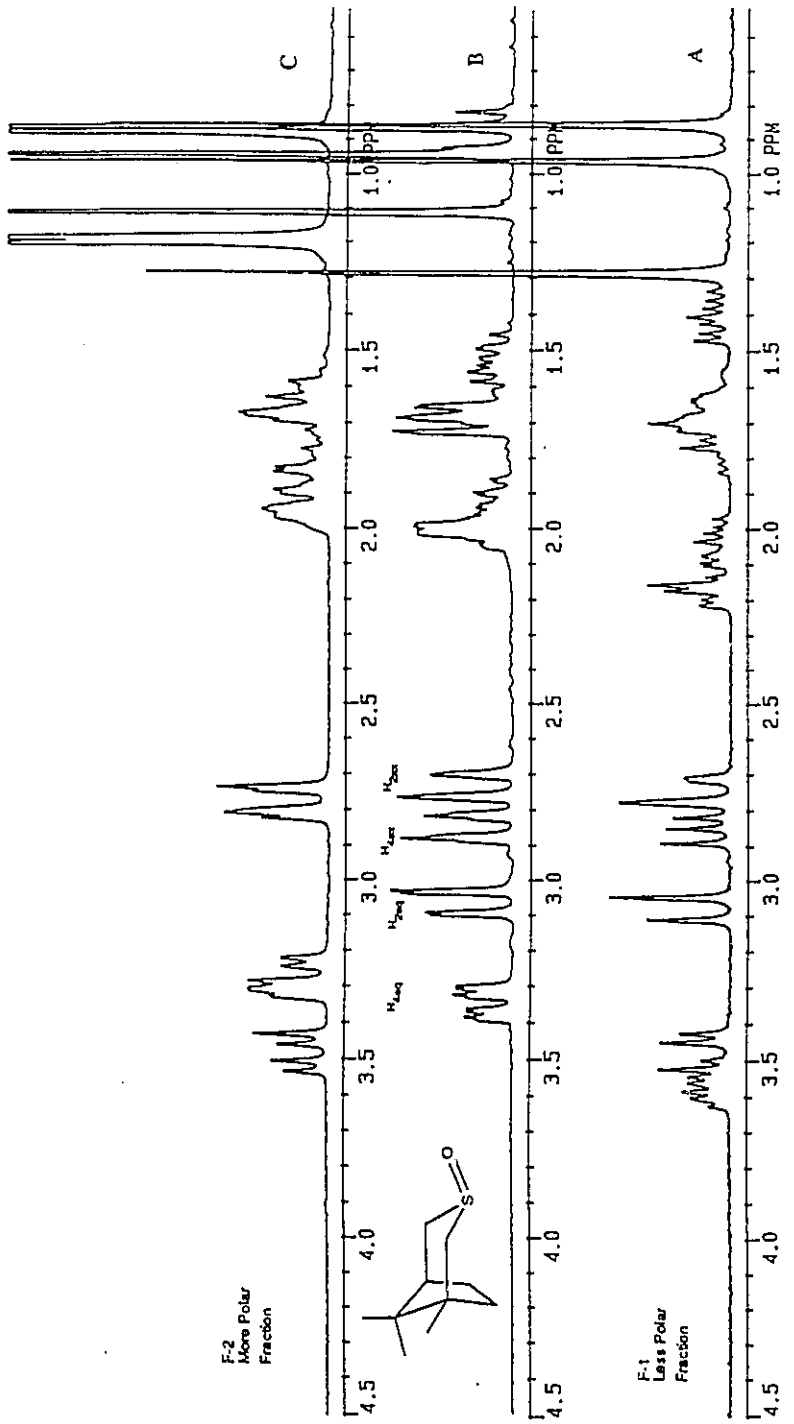


Figure 12. A) 200 MHz ^{1}H NMR spectrum of monobenzylated **4** in $CDCl_3$.
B) 200 MHz ^{1}H NMR spectrum of **4** in $CDCl_3$.
C) 200 MHz ^{1}H NMR spectrum of more polar monobenzylated **4**.

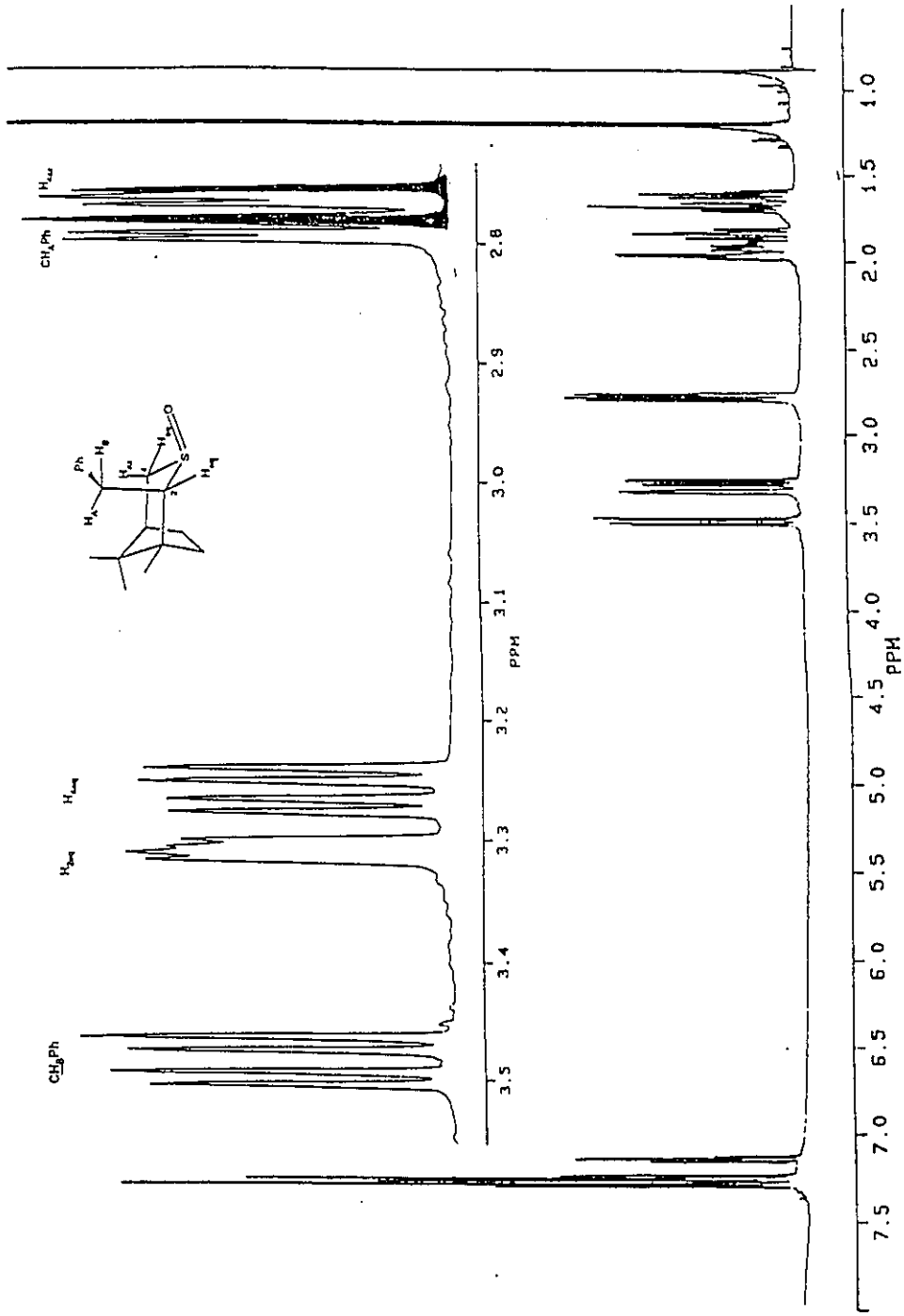


Figure 13A. 300 MHz ^{1}H NMR spectrum of **6** in $CDCl_3$.

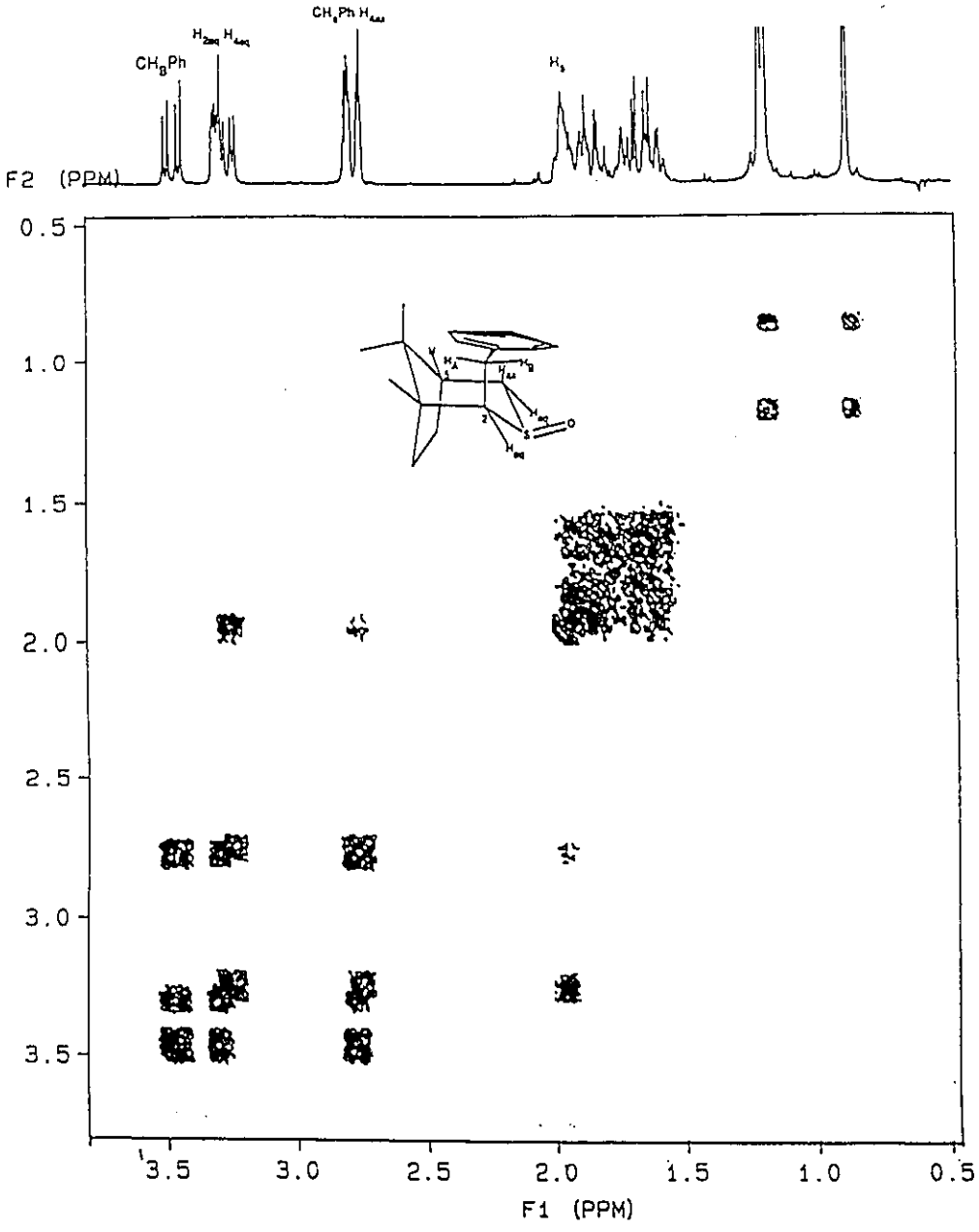


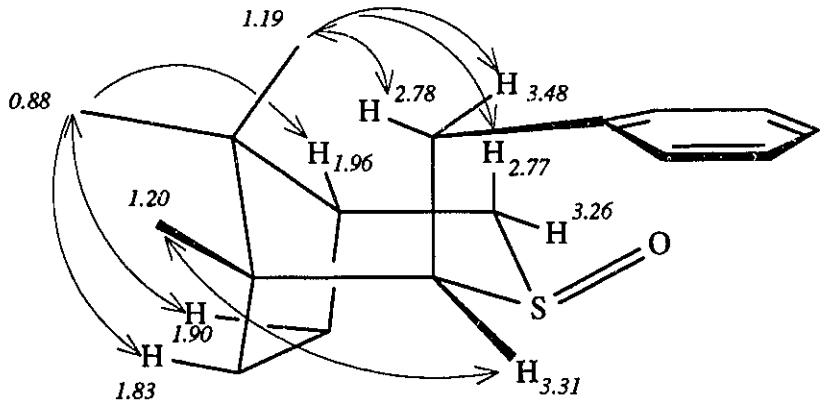
Figure 13B. 300 MHz HOMCOR spectrum of **6** in $CDCl_3$.

and H-2ax (δ2.74) remained at almost the same chemical shift value suggesting that in the less polar fraction the benzyl substituent occupies the C-4 position. Analogously, for the more polar fraction (Figure 12C) the H-4eq and H-4ax signals at 3.23 and 2.77 ppm respectively, remained unaffected suggesting that the benzyl substituent was in the C-2 position. The structure of compound **7**, having the benzyl group in the C-4 position has been discussed by Breau[18] and will not be dealt with.

Figure 14 summarizes the nOe difference experiments performed on **6** by Breau. After examination of the proton NMR of **6** shown in Figure 13A, Breau determined that the resonance at 3.48 ppm was likely one of the benzylic hydrogens because it was one of the most deshielded hydrogens and displayed an ABX type coupling pattern. A COSY correlation (Figure 13B) displayed a geminal coupling between the resonance at 3.48 ppm and the signal at 2.78 ppm which suggested that the resonance at 2.78 corresponded to the other benzylic hydrogen. Each of these benzylic hydrogens displayed a vicinal coupling to the resonance at 3.31 ppm suggesting that this proton resided either on C-4 or C-2. The fact that this resonance showed no evidence of other vicinal couplings suggested to Breau that the proton was on C-2 and not C-4. Interestingly, analysis of the coupling constants between H-2 - H_A (3.0 Hz) and H-2 - H_B (5.5 Hz) suggested that the phenyl ring essentially eclipses H-2 thus, H_B is considerably closer to the sulfoxide oxygen atom. This trend is reflected in the fact that the resonance for the H_B is considerably more deshielded than that of H_A. Irradiation of the methyl group at 1.20 ppm produced an nOe enhancement only on the resonance at 3.31 and consequently was assigned as the C-1 methyl group. This verified that the proton at 3.31 was on C-2 and also suggested that the benzyl group was in an axial position at C-2. Irradiation of the methyl group at 1.19 ppm showed an enhancement on the signal at 2.77 ppm and to different degrees on the benzylic signals H_A at 2.78 and H_B at 3.48 ppm and was subsequently assigned as the C-8 *endo* methyl group. The fact that enhancements were observed on the benzylic hydrogens upon irradiation of the C-8 *endo*

methyl group further verified that the benzyl substituent was in an axial position at C-2. The proton at 2.77 ppm was then assigned as the C-4 axial proton and a geminal coupling between this resonance at the one at 3.26 ppm identified the C-4 equatorial proton as the resonance at 3.26 ppm. The assignments of the C-4 protons were further verified by the fact that the C-4 equatorial proton displayed a vicinal coupling of 5.3 Hz to the proton at C-5 which was identified by irradiation of the remaining methyl group at 0.88 ppm. The C-4 axial proton displayed no evidence of vicinal coupling to H-5. Using the Karplus correlation curve[30] Breau calculated dihedral angles of 36° and 84° respectively. This proved that the thiane ring existed in a chair conformation.

Figure 14. Summary of nOe differences in **6** observed upon irradiation of C-8 and C-1 methyl groups.



* numbers in italics represent chemical shift values.

The fact that the Breau's stereochemical result from the NMR study of **6** was in agreement with the structure determined by X-ray, showed that it was possible to determine the stereochemistry of **6** by using NMR. As a result, we felt confident that use of this model would enable us to determine the regio- and stereochemistry of the benzylated and

deuterated products of the other lithio sulfoxides prepared in this study.

C) Other reactions of the lithio derivative of 4.

i) Deuteration: By comparison of the NMR of the deuterated product (Figure 15) with that of the parent sulfoxide **4** (Figure 2), it was possible to determine not only the regio- and stereochemistry of deuterium incorporation but also the amount of deuterium incorporated. As can be seen from Figure 2, the integrations corresponding to the axial protons are drastically diminished while those for the equatorial protons are unchanged and remain at one proton each when compared to the integrations for the methyl signals. Closer examination of the integrations revealed approximately 30% (+/- 3-5%) incorporation of deuterium in the H-4ax position and 70% incorporation in the H-2ax position. The crude yield of both deuterated products was 92%.

Deuteration experiments were also carried out using CH_3COOD. While the stereochemistry of the deuterated product was unchanged, the regioselectivity differed in that incorporation in H-4ax was 45% (+/- 3-5%) and H-2ax was 55%. The crude overall chemical yield was comparable to the first experiment.

ii) Reaction with acetone: The lithio derivative of sulfoxide **4** was reacted with reagent grade acetone to produce only (1R,3S,4R,5S)-4-(1-methyl-ethan-1-ol)-1,8,8-trimethyl-3-thiabi cyclo[3.2.1]thiane-3-oxide (**24**) in 50% yield based on 38% recovered starting material. Substance **24** showed a strong IR absorption at 1010 cm^{-1}, indicative of a sulfoxide.

Figure 16 shows the proton NMR spectrum of the **24**, Figure 17A displays selected nOe experiments and 17B shows the COSY spectrum. Unfortunately since the proton NMR of **24** was dramatically different from that of the starting material it was not immediately obvious if the substituent was on the C-2 or C-4 carbon. Examination of the COSY spectrum suggested that the resonances at 3.04 and 3.15 ppm were either the C-2 or C-4

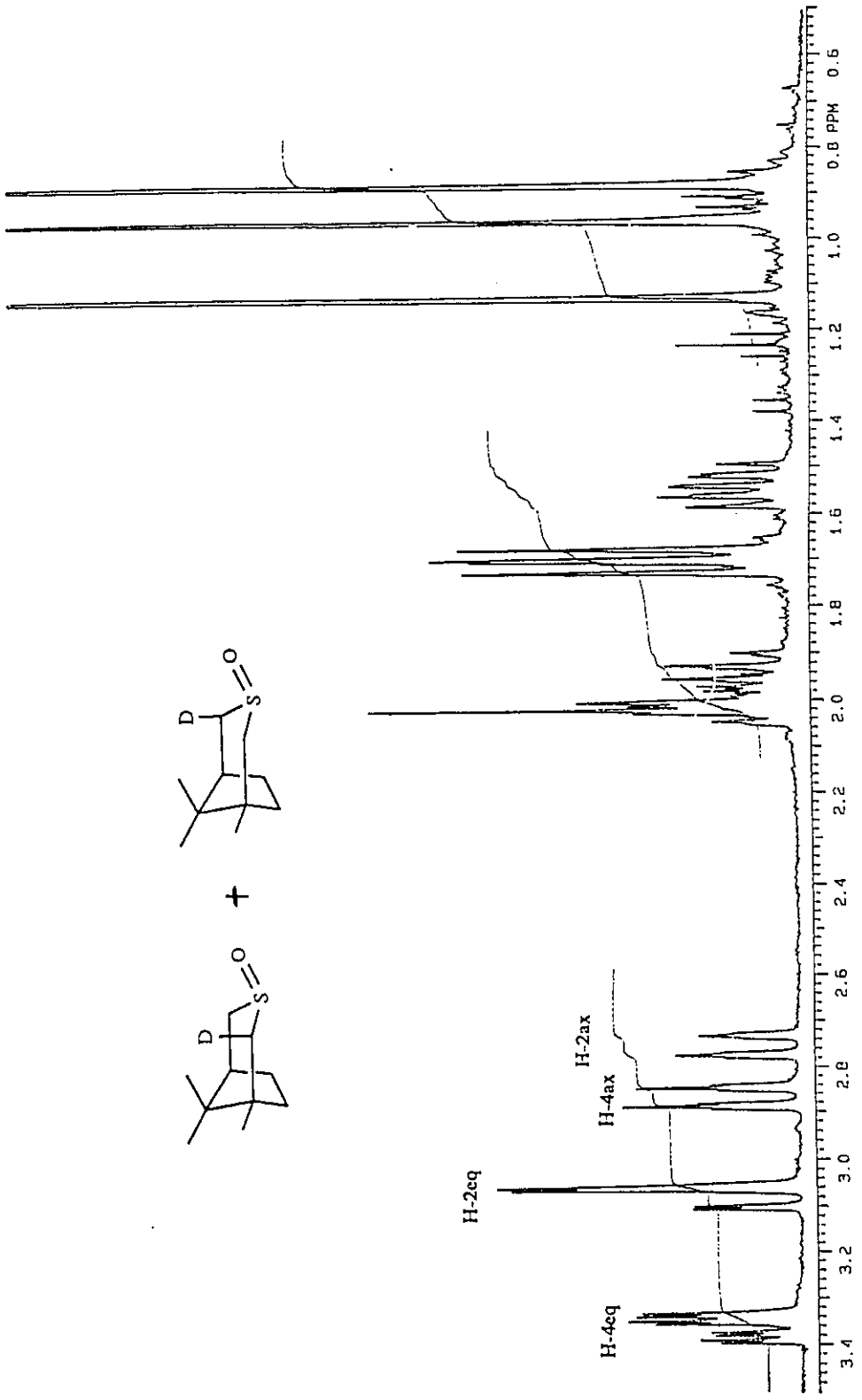


Figure 15. 300 MHz ^{1}H NMR of **4** after incorporation of deuterium.

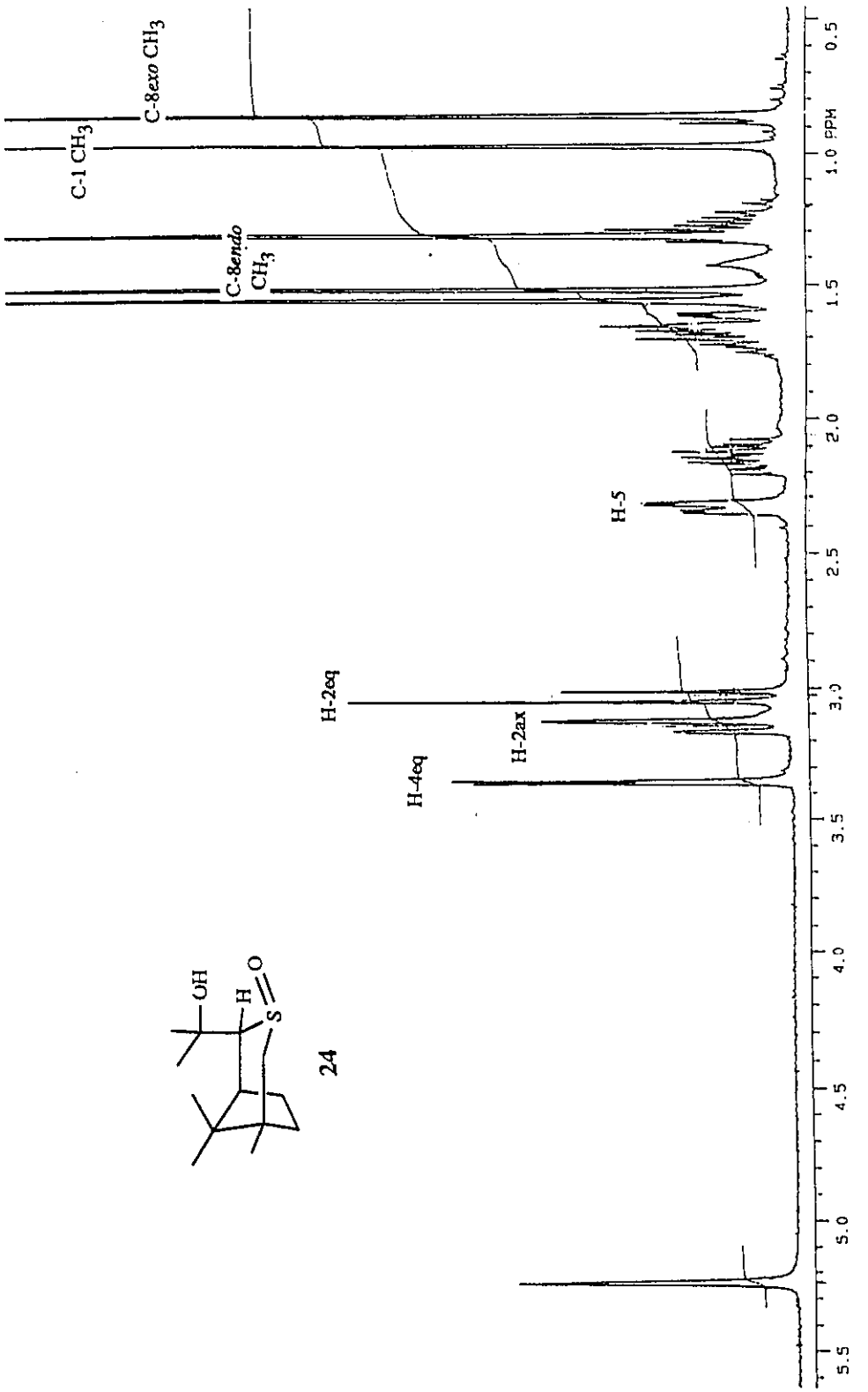


Figure 16. 200 MHz ^{1}H NMR spectrum of **24** in $CDCl_3$.

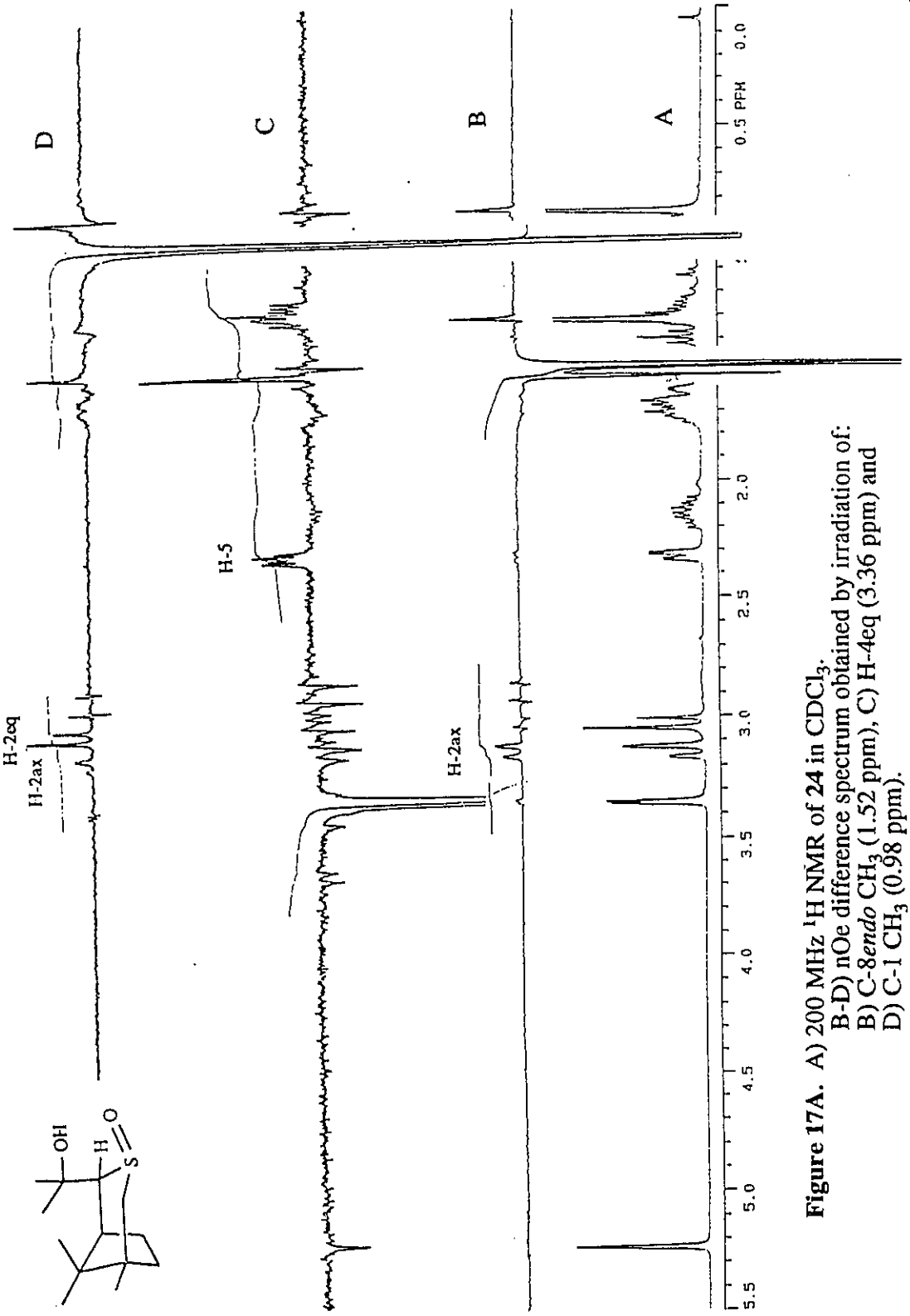


Figure 17A. A) 200 MHz ^{1}H NMR of **24** in $CDCl_3$.
B-D) nOe difference spectrum obtained by irradiation of:
B) C-8*endo* CH_3 (1.52 ppm), C) H-4eq (3.36 ppm) and
D) C-1 CH_3 (0.98 ppm).

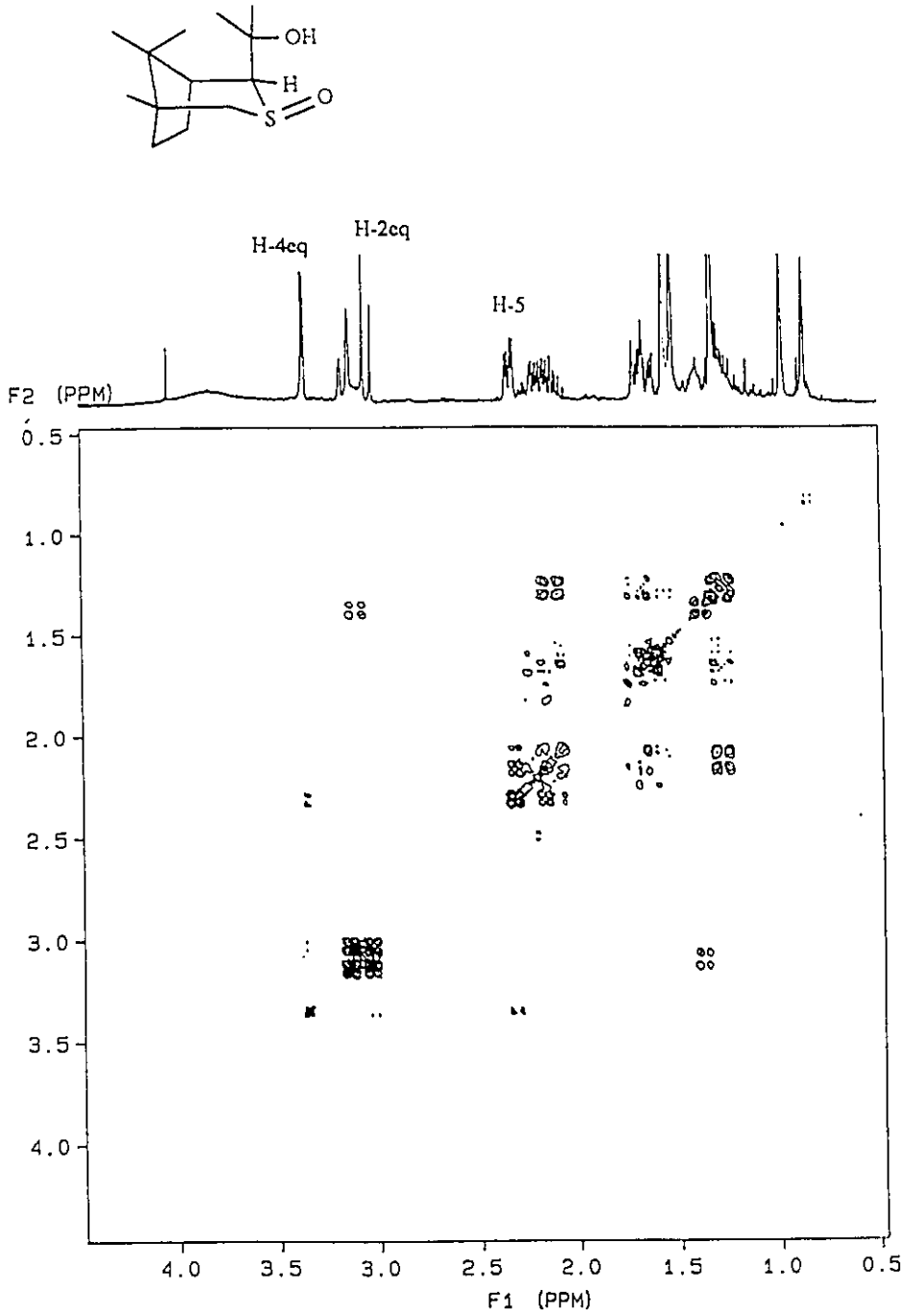
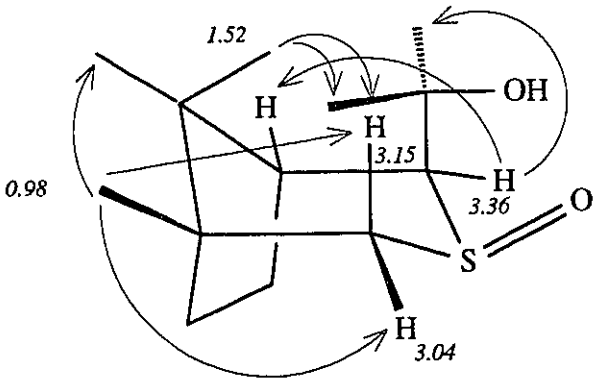


Figure 17B. 300 MHz HOMCOR spectrum of **24** in $CDCl_3$.

axial and equatorial protons since they were an AB-type system and coupled strongly to each other. Only the one hydrogen at 3.15 ppm showed an nOe with the methyl group at 1.52 ppm and consequently the proton at 3.15 ppm was determined to be axial and the methyl group at 1.52 ppm was assigned as the C-8 *endo* methyl group. Because the resonance at 3.04 ppm showed a correlation to the axial proton but no nOe to the C-8 *endo* methyl, it was assigned as an equatorial hydrogen and since both the axial and equatorial hydrogens displayed an nOe with the methyl group at 0.98 ppm, both hydrogens were determined to be on C-2 and the methyl group at 0.98 ppm was on C-1. The C-2 equatorial hydrogen showed a weak W-type coupling to the resonance at 3.36 ppm which was subsequently assigned as the C-4 equatorial hydrogen thus indicating that the substituent was in the C-4 axial position. This conclusion was further verified by the fact that irradiation of the C-4 equatorial hydrogen resulted only in an nOe with H-5 and one of the methyl groups on the substituent at C-4 but not the C-8 *endo* methyl at 1.52 ppm. A coupling between H-4eq and H-5 of 3.0 Hz indicates that the thiane ring exists in a chair conformation. Figure 18 shows a summary of some of the more crucial nOe interactions.

Figure 18. Summary of crucial nOe's in **24**

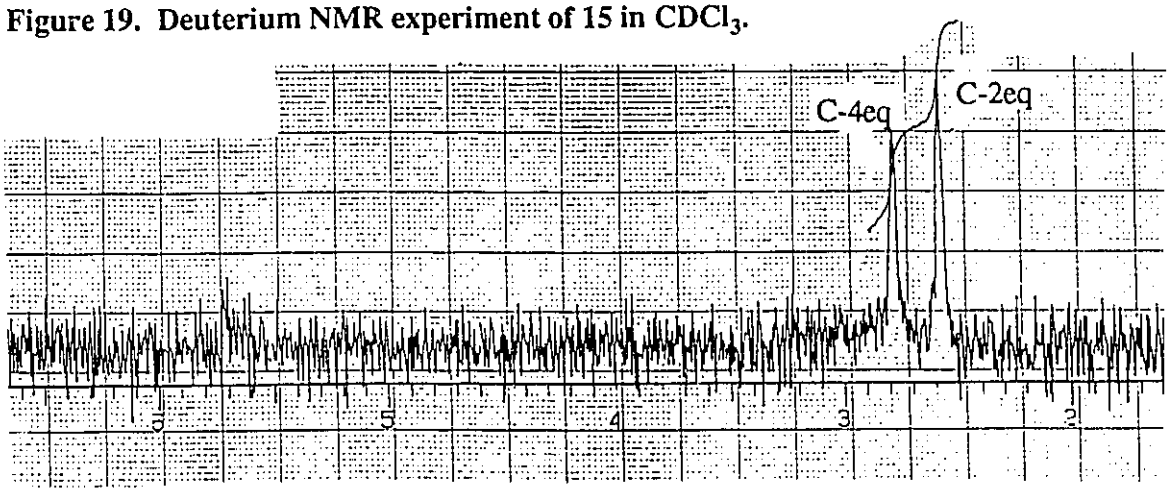


*numbers in italics indicate chemical shift values (ppm)

D) Reactions of the lithio derivative of sulfoxide 15.

i) Deuteration: Reaction of sulfoxide **15** with CH_3COOD was stereoselective for the equatorial position at C-2 and C-4 giving 45% and 55% (+\- 3-5%) incorporation respectively. A deuterium NMR experiment shown in Figure 19 displayed only two separate resonances as expected corresponding to C-2 eq and C-4 eq products.

Figure 19. Deuterium NMR experiment of 15 in $CDCl_3$.



ii) Benzylation: Sulfoxide **15** was benzylated to produce 4-benzyl-(1R,3R,5S)-1,8,8-trimethyl-3-thiabicyclo[3.2.1]octane -3- oxide (**25**) as a white crystalline solid with mp 122°C, in 60% yield based on 30% recovered starting material. The IR spectrum of **25** displayed a strong sulfoxide absorption (1032 cm^{-1}) and CIMS supported a molecular formula of $C_{17}H_{24}OS$. The ^1H NMR of **25** is shown in Figure 20 and selected nOe experiments are presented in Figure 21.

Examination of the proton NMR suggested that the resonance at 3.30 ppm was likely one of the benzylic hydrogens (H_A) since it displayed an ABX-type splitting pattern. Irradiation of this signal produced an nOe only at 3.06 ppm indicating that one of the two protons at that position was the other benzylic hydrogen (H_B). The fact that no enhancements were observed on any of the methyl groups suggested that the substituent was in an equatorial position. Irradiation of the benzylic proton H_B (not shown in Figure 21)

produced an nOe with the other benzylic proton H_A as expected and the C-5 hydrogen at 1.90-2.06 ppm indicating that the benzyl group was located on C-4. Analysis of the COSY spectrum (not shown) of **25** showed a weak correlation between the C-5 hydrogen and the resonance at 2.86 ppm which was subsequently assigned as a C-4 hydrogen. Since early nOe experiments indicated that the benzyl substituent was in an equatorial position, the fact that this correlation was present suggested that the six membered ring was adopting a half chair conformation to relieve steric interactions between the sulfoxide oxygen and the ethano bridge as in the parent sulfoxide **15**. Irradiation of the methyl group at 0.87 ppm produced nOe's on the C-4 hydrogen at 2.86 ppm and on one of the protons at 3.06 ppm. The fact that the benzylic proton H_B at 3.06 ppm displayed no enhancements on any of the methyl groups in an earlier experiment meant that the nOe was from the C-2 axial proton. Thus the resonance at 2.86 ppm and the other proton at 3.06 ppm were identified as the C-4 and C-2 axial hydrogens and the methyl group at 0.87 ppm was identified as the C-8 *endo*-methyl. This verified that the benzyl substituent was in an equatorial position at C-4. When the methyl group at 1.09 ppm was irradiated an nOe for the C-2 axial hydrogen and a weak nOe on the resonance at 2.94 ppm was observed. This indicated that the methyl group was at the C-1 position and the resonance at 2.94 ppm corresponded to the C-2 equatorial proton. The observation that the nOe for the C-2 equatorial hydrogen was weaker than that of the C-2 axial hydrogen was consistent with a half chair conformation for the six membered ring.

A summary of the nOe's observed and the stereochemistry of **25** is presented in Figure 22. The fact that no C-2 equatorially substituted product was isolated suggests that the steric demands at this position are severe.

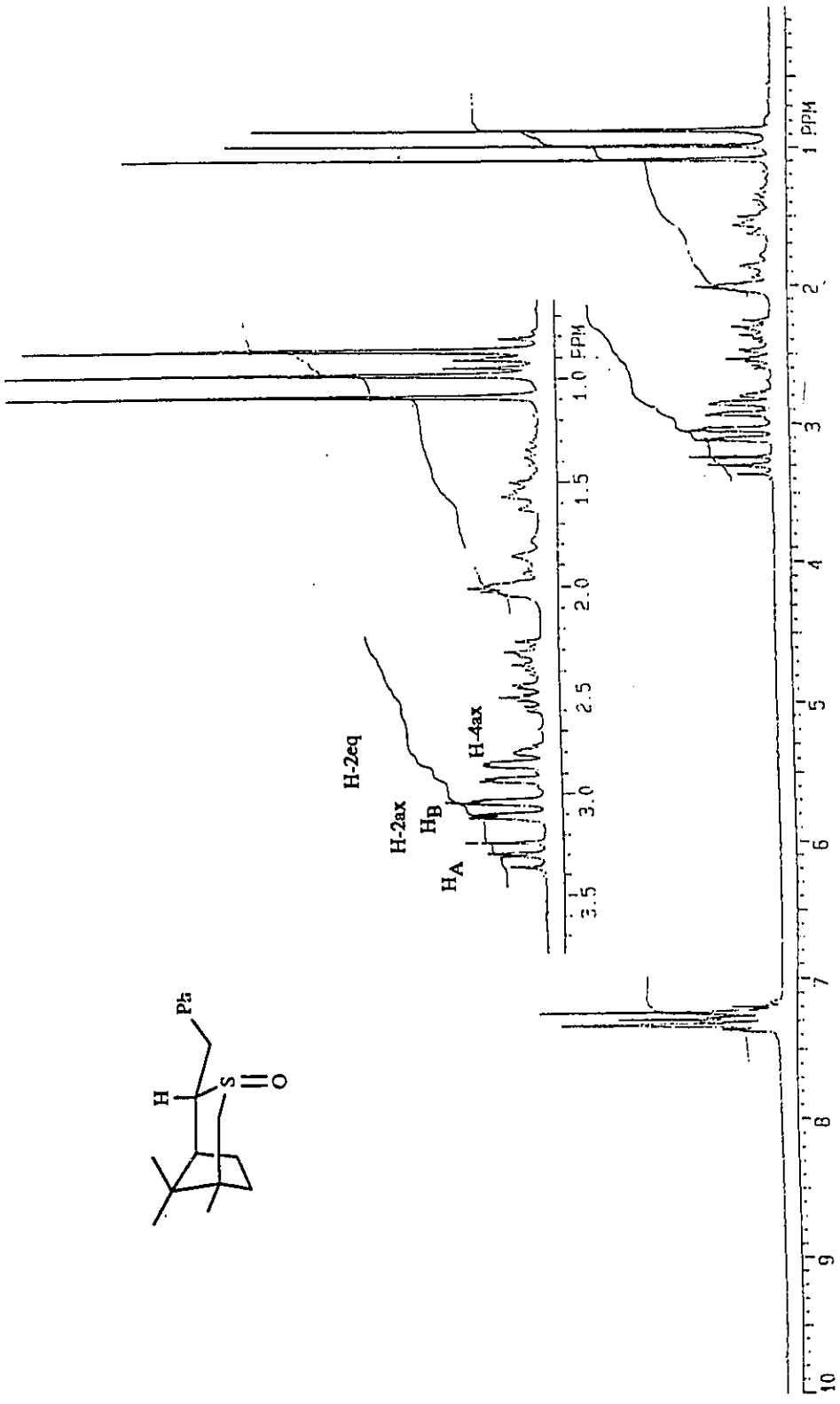


Figure 20. 200 MHz ^{1}H NMR spectrum of **25** in $CDCl_3$.

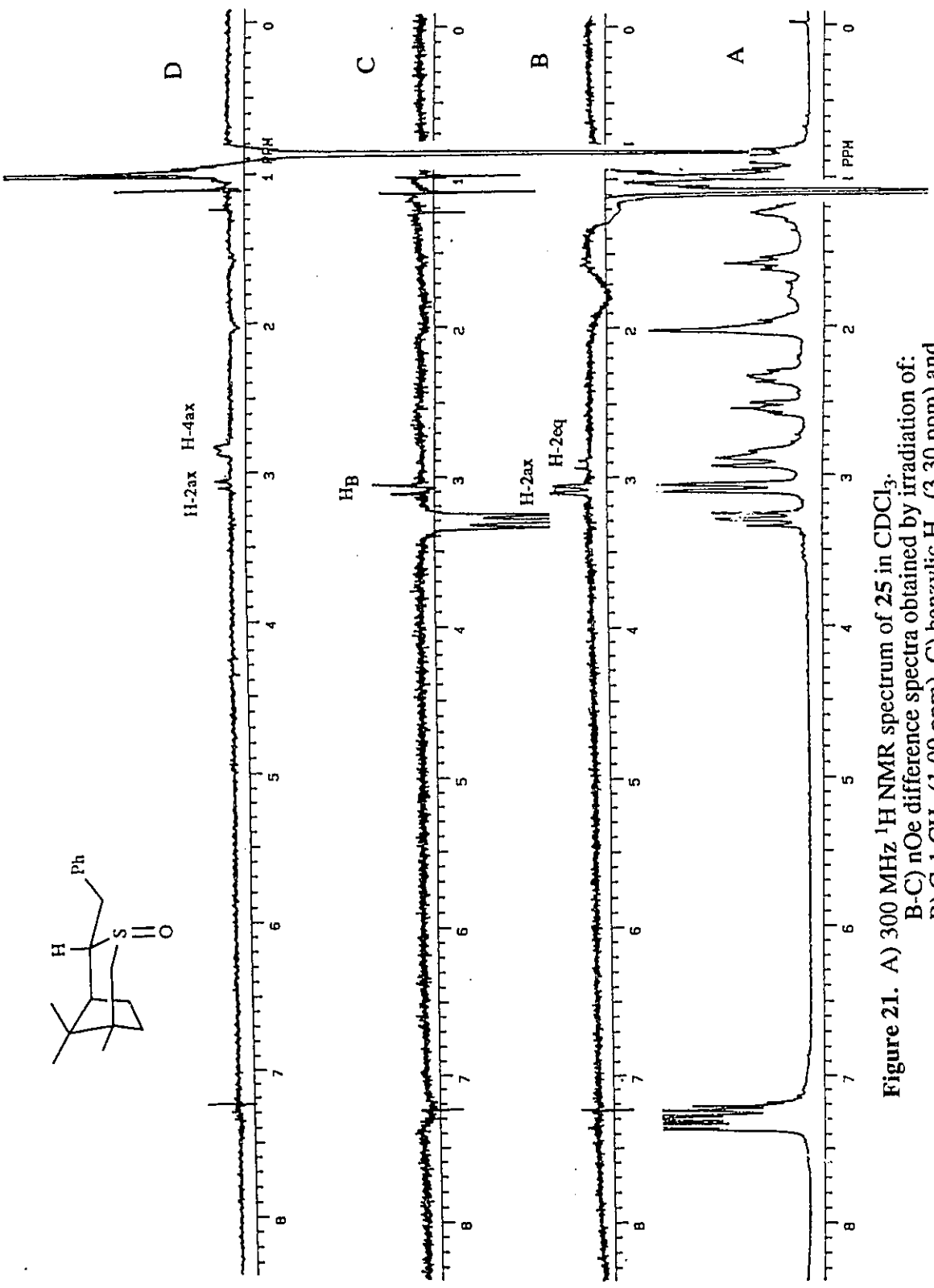
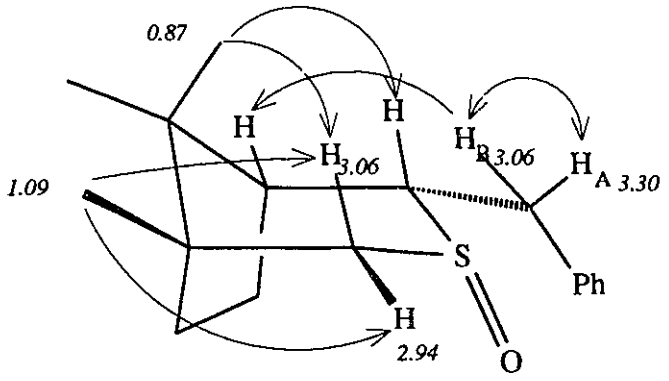


Figure 21. A) 300 MHz ^{1}H NMR spectrum of **25** in $CDCl_3$.
B-C) nOe difference spectra obtained by irradiation of:
B) C-1 CH_3 (1.09 ppm), C) benzylic H_A (3.30 ppm) and
D) C-8*endo* CH_3 (0.87 ppm).

Figure 22. Summary of nOe's for compound **25.**



*numbers in italics indicate chemical shift values (ppm)

iii) Reaction with acetone: The lithio derivative of sulfoxide **15** was reacted with acetone to give (1R,3R,4S,5S)-4-(1-methyl-ethan-1-ol)-1,8,8-trimethyl-3-thiabicyclo-[3.2.1]-octane-3-oxide (**26**) as a colourless oil in 54% chemical yield, based on 23% recovered starting material. A strong stretching absorption at 1137 cm^{-1} was displayed in the IR spectrum. EIMS and HRMS both confirmed that the compound had a molecular formula of $C_{13}H_{24}O_2S$.

The proton NMR spectrum for **26** is shown in Figure 23 and a HETCOR and COSY are shown in Figures 24 and 25. The resonances at 2.26-2.38 ppm and 2.92-3.01 ppm corresponded to two protons each and analysis of the individual signals in these areas was difficult due to overlap. A heteronuclear correlation or HETCOR (Figure 24) identified one of the protons at 2.26-2.38 ppm and the proton at 2.44 ppm as methine protons. Since one of these signals corresponded to the C-5 hydrogen and since the COSY spectrum displayed a correlation between these two resonances, the other methine hydrogen was assigned as H-4 which subsequently indicated that the substituent was located on C-4. The resonance at 2.74 ppm which was part of an AB spin system, showed a coupling of 15.3 Hz to one

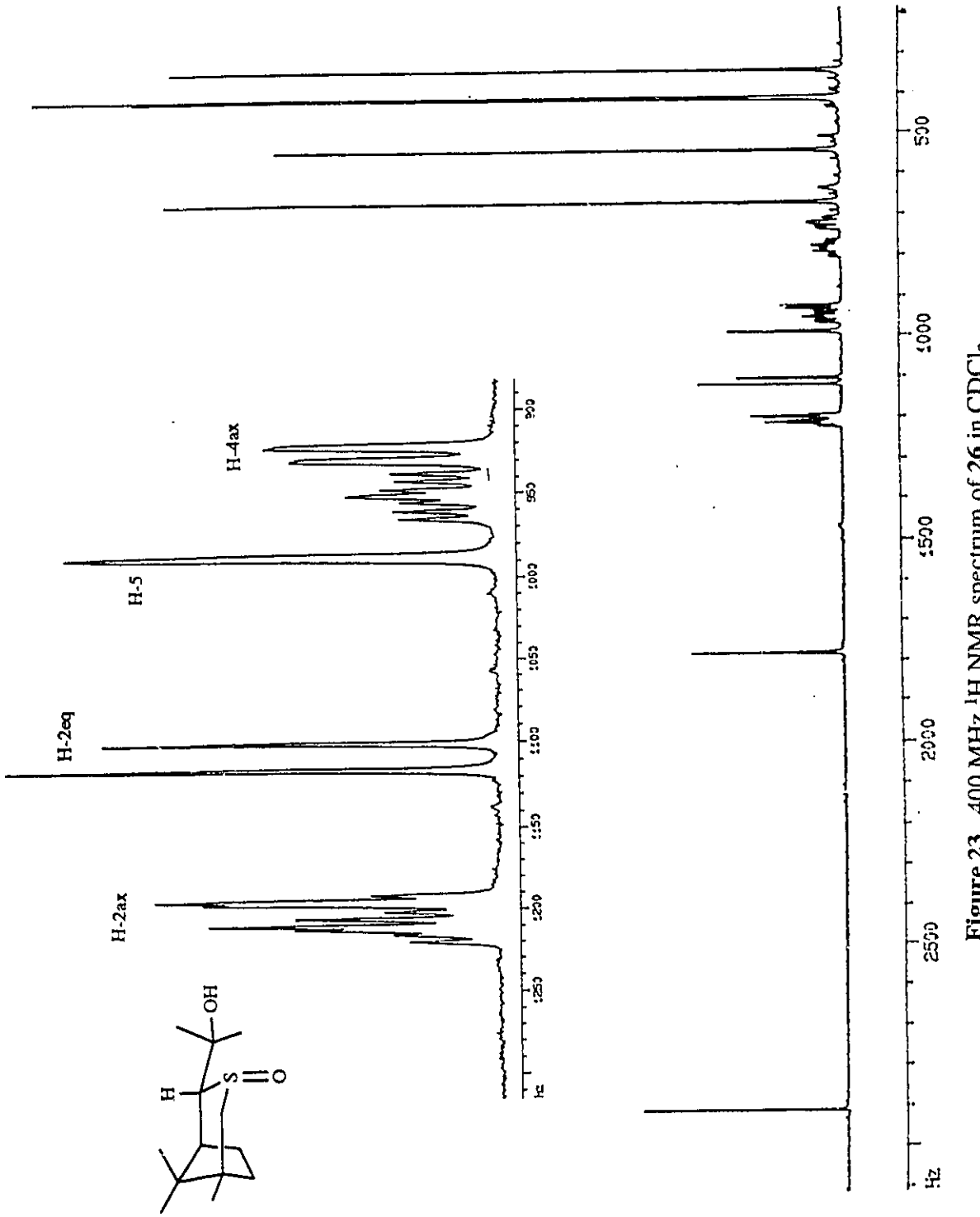


Figure 23. 400 MHz ^{1}H NMR spectrum of **26** in $CDCl_3$.

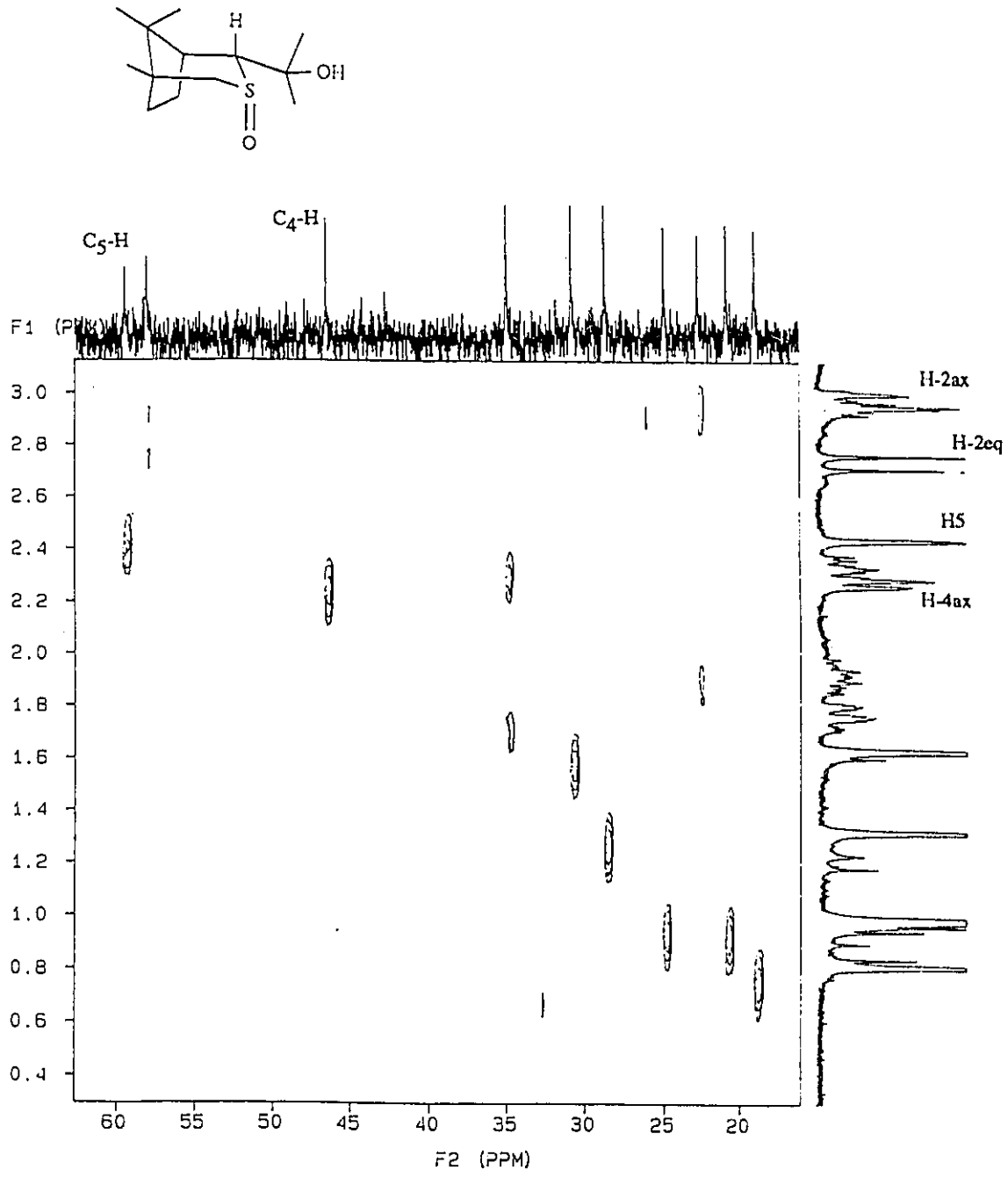


Figure 24. 300 MHz HETCOR spectrum of **26** in $CDCl_3$.

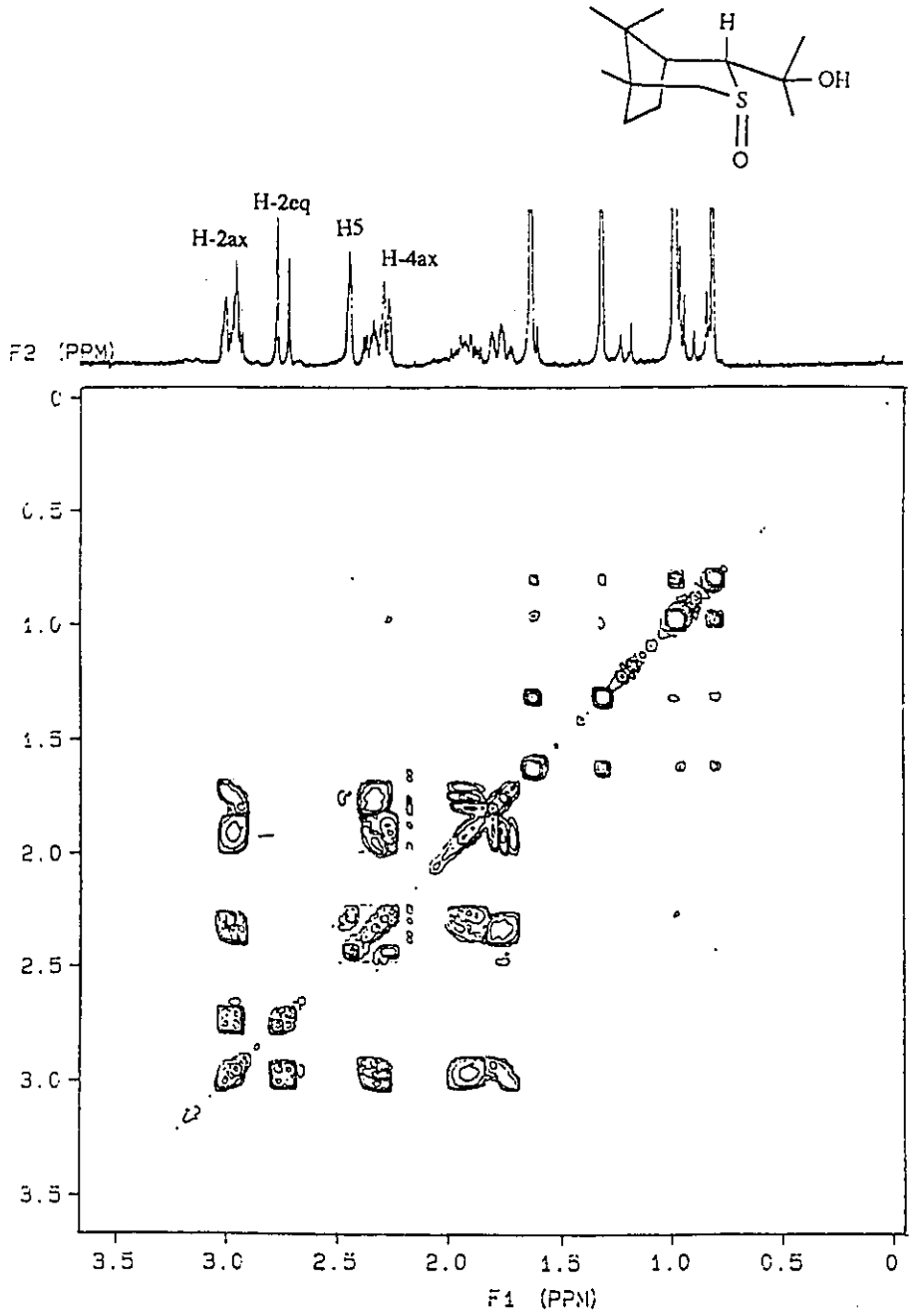
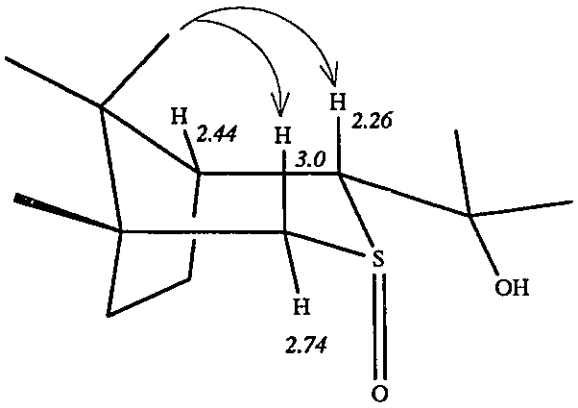


Figure 25. 300 MHz HOMCOR spectrum of **26** in $CDCl_3$.

of the protons at 2.92-3.01 ppm suggesting that the these protons resided on C-2. Irradiation of the methyl signal at 0.81 ppm produced nOe enhancements with the C-2 proton at 2.92-3.03 ppm and the C-4 hydrogen at 2.26-2.38 ppm which proved that these protons were in an axial position and that the substituent was in an equatorial position at C-4. The fact that no W-type coupling was observed between the C-2 equatorial proton at 2.74 ppm and the C-4 proton at 2.26-2.38 ppm further verified that the substituent occupied an equatorial position. The nOe's for compound **26** are summarized in Figure 26.

Figure 26. Summary of nOe's for compound **26.**



*numbers in italics indicate chemical shift values (ppm)

E) Reactions of the lithio derivative of 16.

i) Deuteration: A comparison between the proton NMR of the deuterated product with the proton NMR of the starting sulfoxide **16** showed 32% incorporation of deuterium into only the axial positions (see Figure 27). The mixture of deuterated and non-deuterated products was obtained in 90% chemical yield based on recovered starting material.

ii) Benzylation: Reaction of the α-sulfinyl carbanion of **16** with benzyl bromide

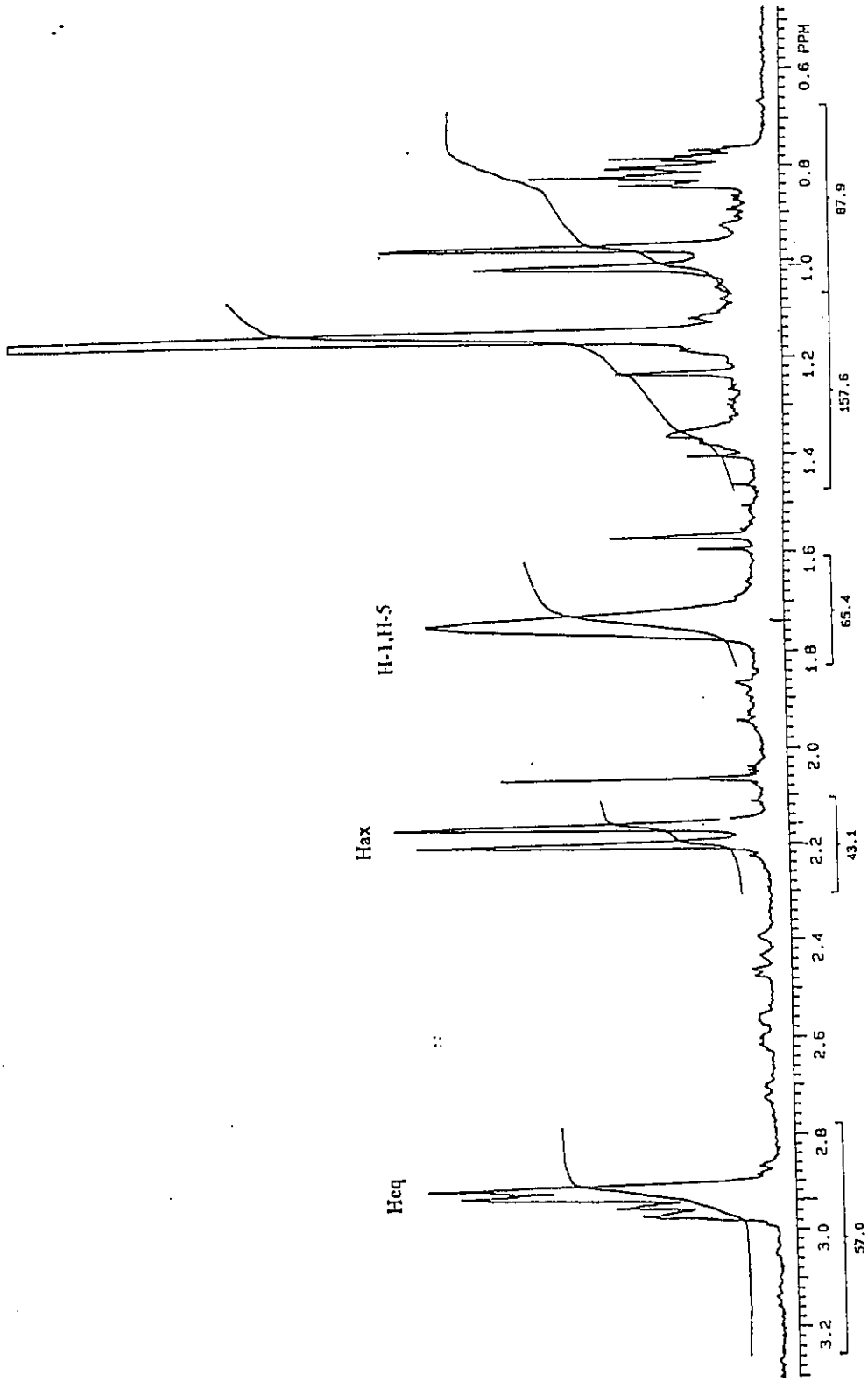


Figure 27. 200 MHz ^{1}H NMR of **16** after incorporation of deuterium.

produced (1R,2R,3S,5S)-2-benzyl-3-thiabicyclo[3.2.1]octane-3-oxide (**27**) in 60% chemical yield after purification based on 49% recovered starting material. Compound **27** existed as a pale yellow solid, mp 146°C and displayed a strong S=O stretching absorption at 1032 cm^{-1}. Both EIMS and HRMS confirmed that the compound isolated had a molecular formula of $C_{14}H_{18}OS$.

Figure 28 depicts the proton NMR's of **27** in both $CDCl_3$ and benzene-d_6 and once again the solvent effects were dramatic. Analysis of a NOESY NMR experiment (Figure 29) allowed the benzylic hydrogens H_A and H_B (J_{AB}=14 Hz) to be assigned to the resonances at 3.70 and 2.40 ppm respectively. The COSY spectrum of **27** (Figure 30) showed that both benzylic hydrogens coupled strongly to the resonance at 3.05 ppm (J=1.4 and 6.6 Hz) which was subsequently assigned as the C-2 hydrogen. The C-2 hydrogen coupled to the resonance at 1.94 ppm which was assigned as H-1. By examination of simple molecular models H-1 was expected to couple only to the C-7 *exo*- and C-8 *exo*-hydrogens based on the fact that the dihedral angles between H-1 and the C-7 and C-8 *endo*-hydrogens were 90°. As expected, H-1 showed a correlation to the multiplet at 1.20 ppm (which integrated for four hydrogens and represented the protons on the ethano bridge) and also to the resonance at 0.60 ppm which was assigned as the C-8 *exo*-hydrogen. Since the NOSEY experiment showed a strong correlation between the C-8 *exo*-hydrogen and to the resonance at 1.45 ppm, the C-8 *endo*-hydrogen was assigned at 1.45 ppm. The fact that this hydrogen displayed an NOSEY correlation to the benzylic hydrogen (H_B) at 2.40 ppm suggested that the benzyl substituent was in an axial position at C-2 and that the resonance at 3.05 ppm was the C-2 equatorial hydrogen.[31] The C-4 hydrogens were assigned to 2.75 and 2.25 ppm based on data from the NOSEY and COSY experiments and the C-4 axial hydrogen was assigned to 2.25 ppm since it displayed a correlation to the C-6 *exo*-hydrogen at 1.20 ppm via a W-type coupling. The remaining C-4 equatorial hydrogen showed a

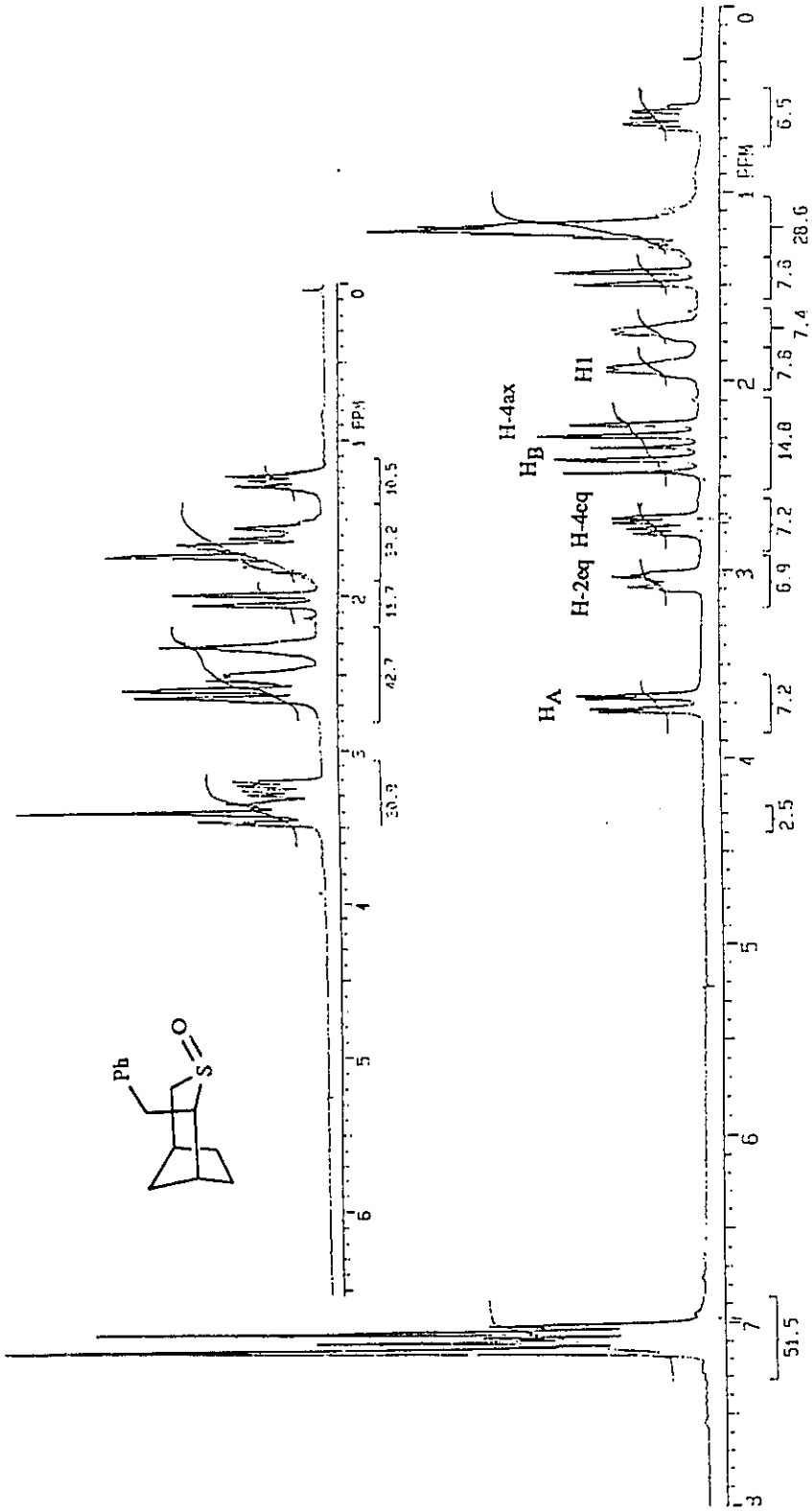


Figure 28. 200 MHz ^{1}H NMR of **27** in Benzene-d_6 with inset in $CDCl_3$.

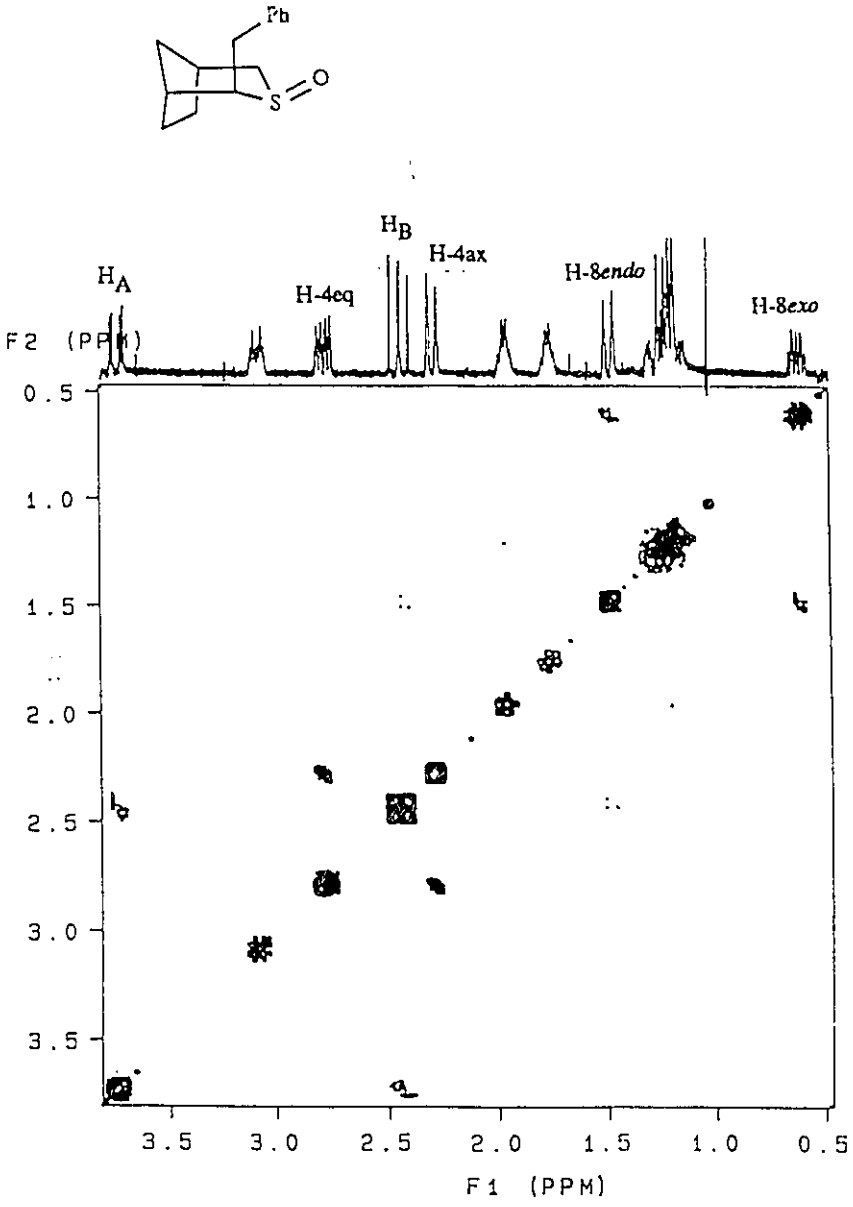


Figure 29. 200 MHz NOESY spectrum of **27** in Benzene-d_6.

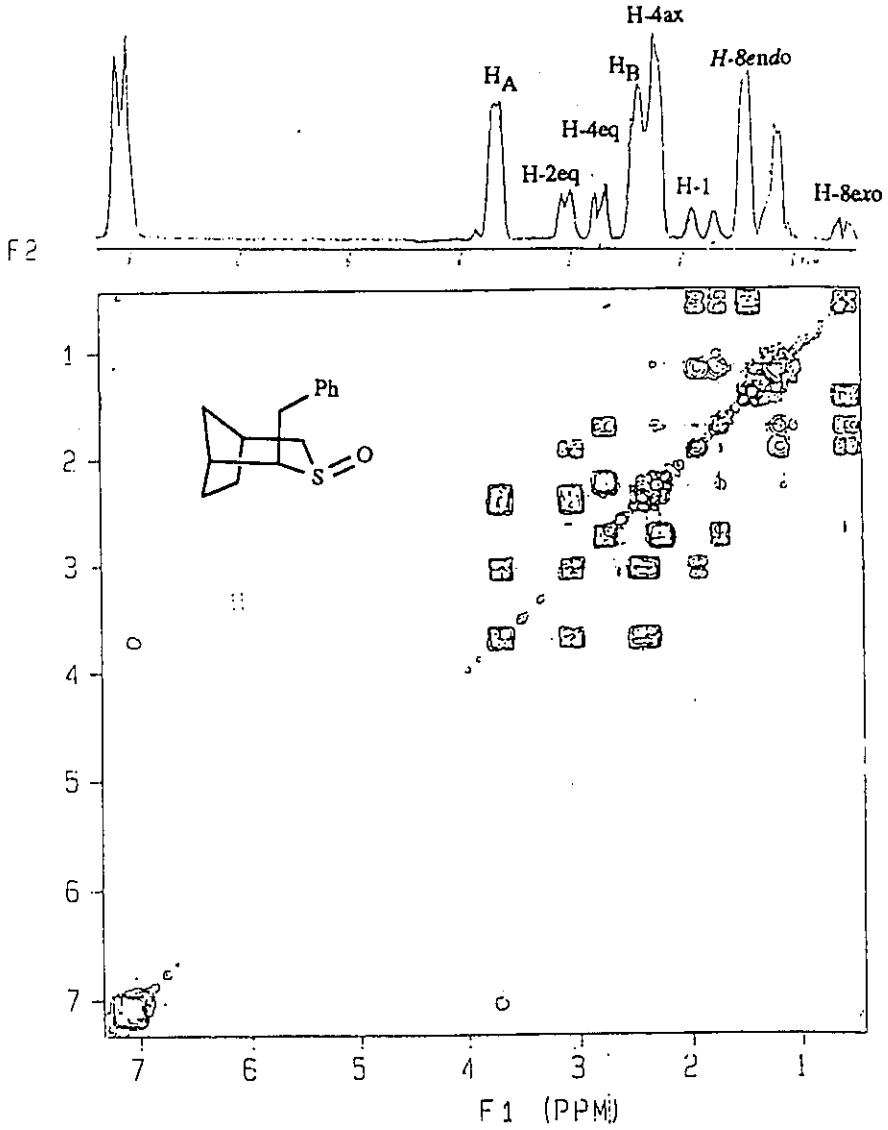
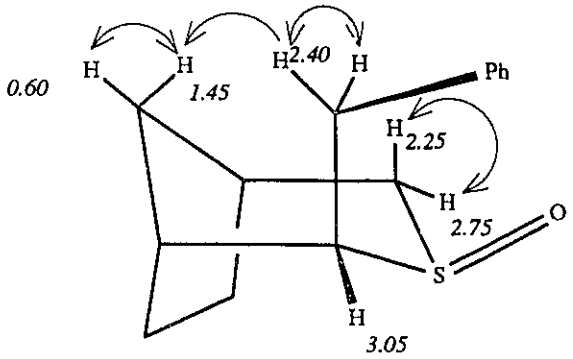


Figure 30. 200 MHz HOMCOR spectrum of **27** in Benzene-d_6.

W-type coupling to H-2eq at 3.05 ppm providing further verification that the benzyl substituent occupied an axial position at C-2.

Figure 31. A summary of the NOSEY and COSY data for **27**.



*numbers in italics indicate chemical shift values (ppm)

F) Reactions of the lithio derivative of sulfoxide 17.

i) Deuteration: The lithio derivative of sulfoxide **17** was reacted with CH_3COOD as described earlier. The ^1H NMR of the product was compared to that of the starting material and it was subsequently deterimined that the deuterium had entered in the equatorial position. The mixture of deuterated and non-deuterated product was obtained in 90% yield.

ii) Benzylation: After usual work-up and purification by column chromatography, (1S,2R,3R,5S)-2-benzyl-3-thiabicyclo[3.2.1]octane-3-oxide (**28**) was obtained in 62% yield based on 38% recovered starting material. The IR displayed a strong sulfoxide absorption at 1027 cm^{-1} and both EIMS and HRMS confirmed a molecular formula of $C_{14}H_{18}OS$.

Determination of the stereochemistry of compound **28** proved to be quite challenging. As shown in Figure 32, the different deuterated solvents had a slight effect on the chemical shifts of the various resonances, but a great deal of overlap occurred in all solvents. The region at 2.55-2.75 ppm integrated to a total of four hydrogens and analysis of individual resonances in this region was quite difficult. Examination of the proton spectrum in

benzene-d_6 suggested that the resonance at 2.22 ppm integrating to one proton was part of an ABX spin system. The fact that the splitting of this resonance was consistent with that already observed for benzylic hydrogens in compounds **6**, **25** and **27** suggested that the proton at 2.22 ppm was benzylic in nature. A NOSEY experiment shown in Figure 33 displayed a correlation between the benzylic proton at 2.22 ppm and one of the other four protons at 2.55-2.75 ppm suggesting that one of the four hydrogens in this region was the other benzylic hydrogen. In the 300 MHz COSY of **28** (Figure 34) the benzylic hydrogen at 2.22 ppm displayed a coupling of approximately 8.0 Hz to the resonance at 3.08 ppm which was subsequently assigned as the C-2 hydrogen. Based on trends observed with other products in this study (i.e. chemical shift and line shape) the C-1 and C-5 hydrogens were assigned as the resonance at 2.03 ppm and the fact that the C-2 hydrogen at 3.08 ppm displayed no correlation to this resonance was initially a point of concern. Examination of the structure of **28** using molecular models indicated that if the six membered ring adopted a half hair conformation the dihedral angle between the C-1 or C-5 hydrogens and the C-2 or C-4 equatorial hydrogens would be approximately 90°, which would correspond to a coupling constant of J=0 Hz. The fact that no coupling was observed between the C-2 hydrogen and H-1 suggested that the C-2 hydrogen was in a equatorial position and the benzyl substituent was in an axial position. The H-1 and H-5 resonance at 2.03 ppm displayed a strong correlation to the proton at 1.0 ppm which was assigned as the C-8 *exo*-hydrogen on the basis that the C-8 *endo*-hydrogen should not show coupling to H-1 or H-5 because the dihedral angle is 90°. The C-8 *exo*-hydrogen displayed a coupling to the resonance at 1.30 ppm which was subsequently assigned as the C-8 *endo*-hydrogen. The C-8 *endo*-hydrogen showed a correlation via a W-type coupling to the hydrogens at 2.55-2.75 ppm which indicated that two of the remaining three hydrogens in this region must belong to the C-6 and C-7 *endo*-hydrogens. The C-5 hydrogen at 2.03 ppm also showed a correlation to the resonance at 2.34 ppm and as a result was assigned as the C-4

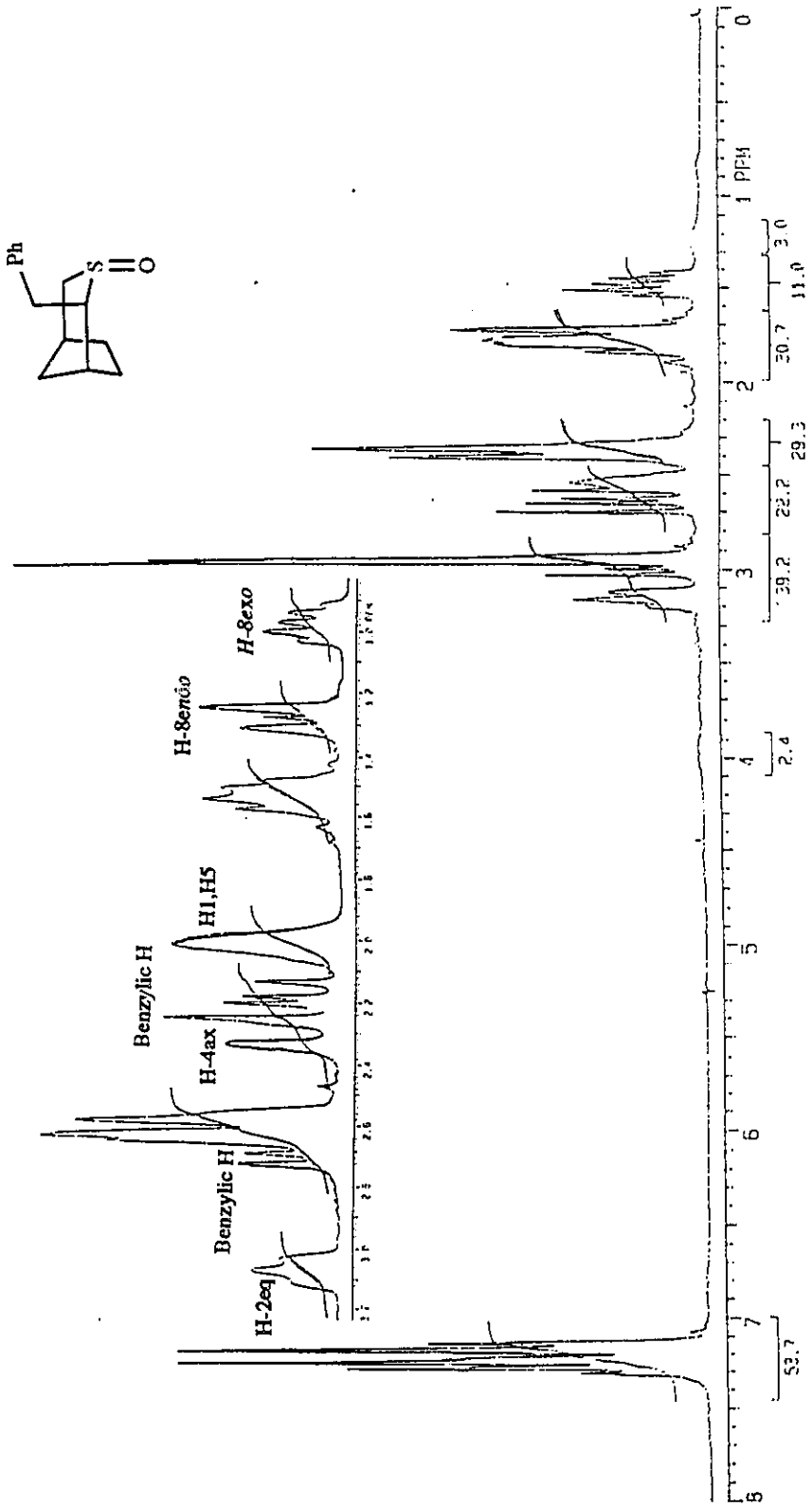


Figure 32. 200 MHz ^{1}H NMR of **28** in $CDCl_3$ with inset in Benzene-d_6.

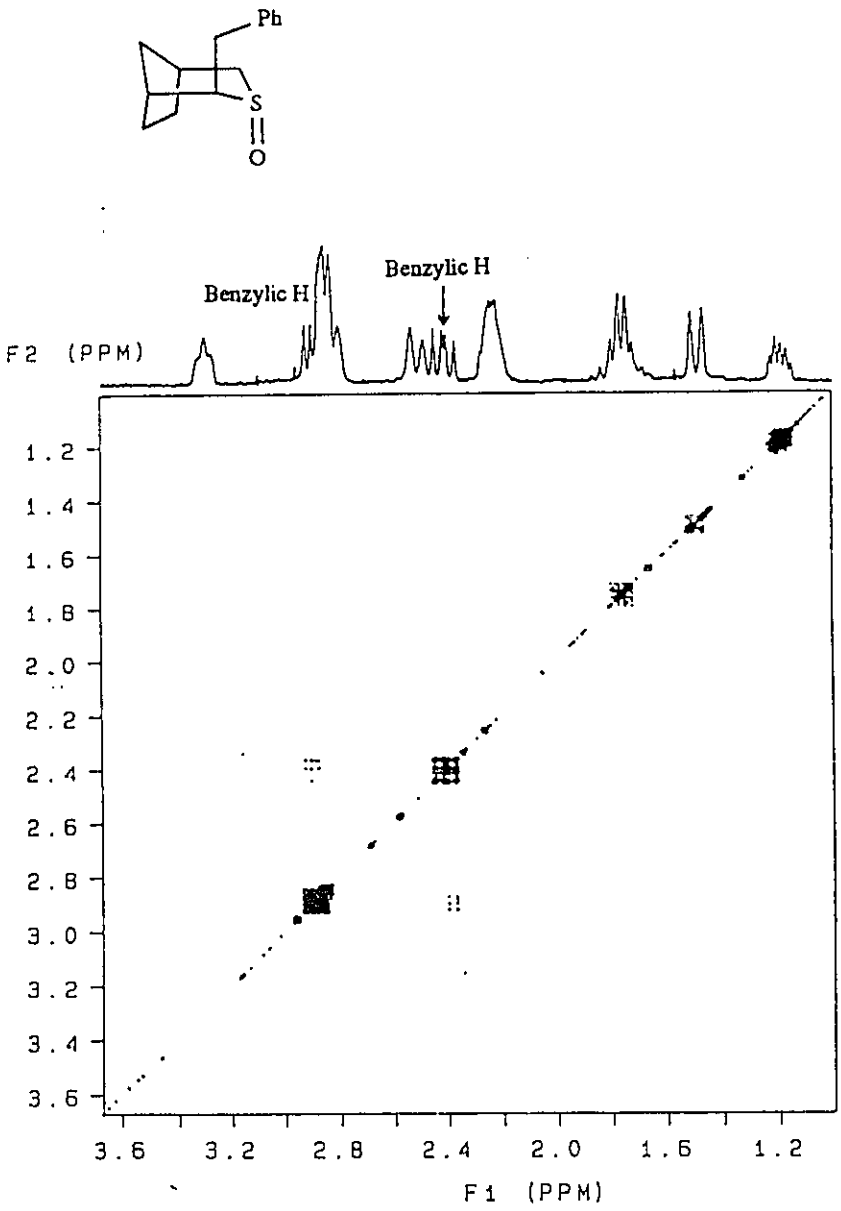


Figure 33. 300 MHz NOESY spectrum of **28** in Benzene-d_6.

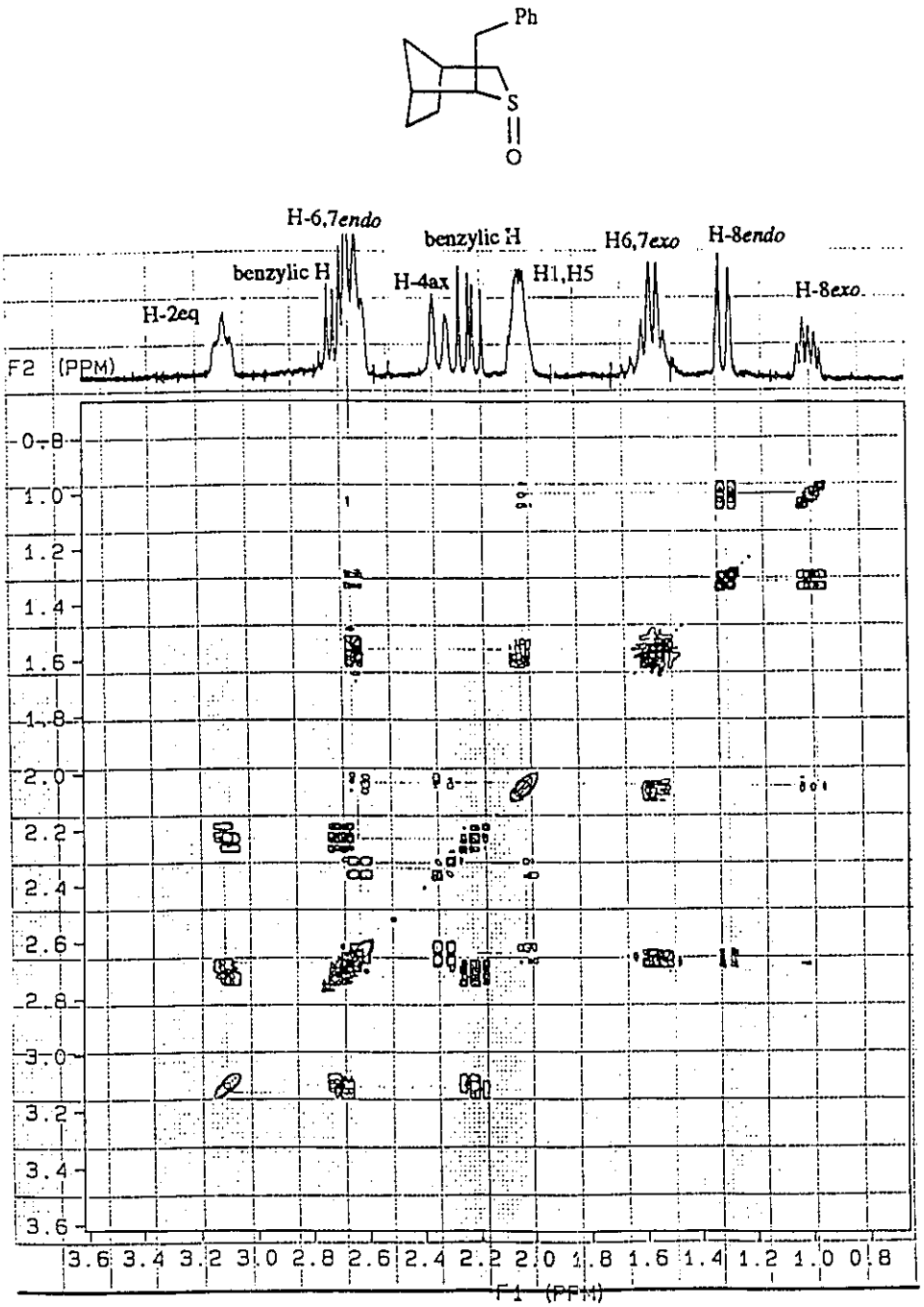


Figure 34. 300 MHz HOMCOR spectrum of **28** in benzene-d_6.

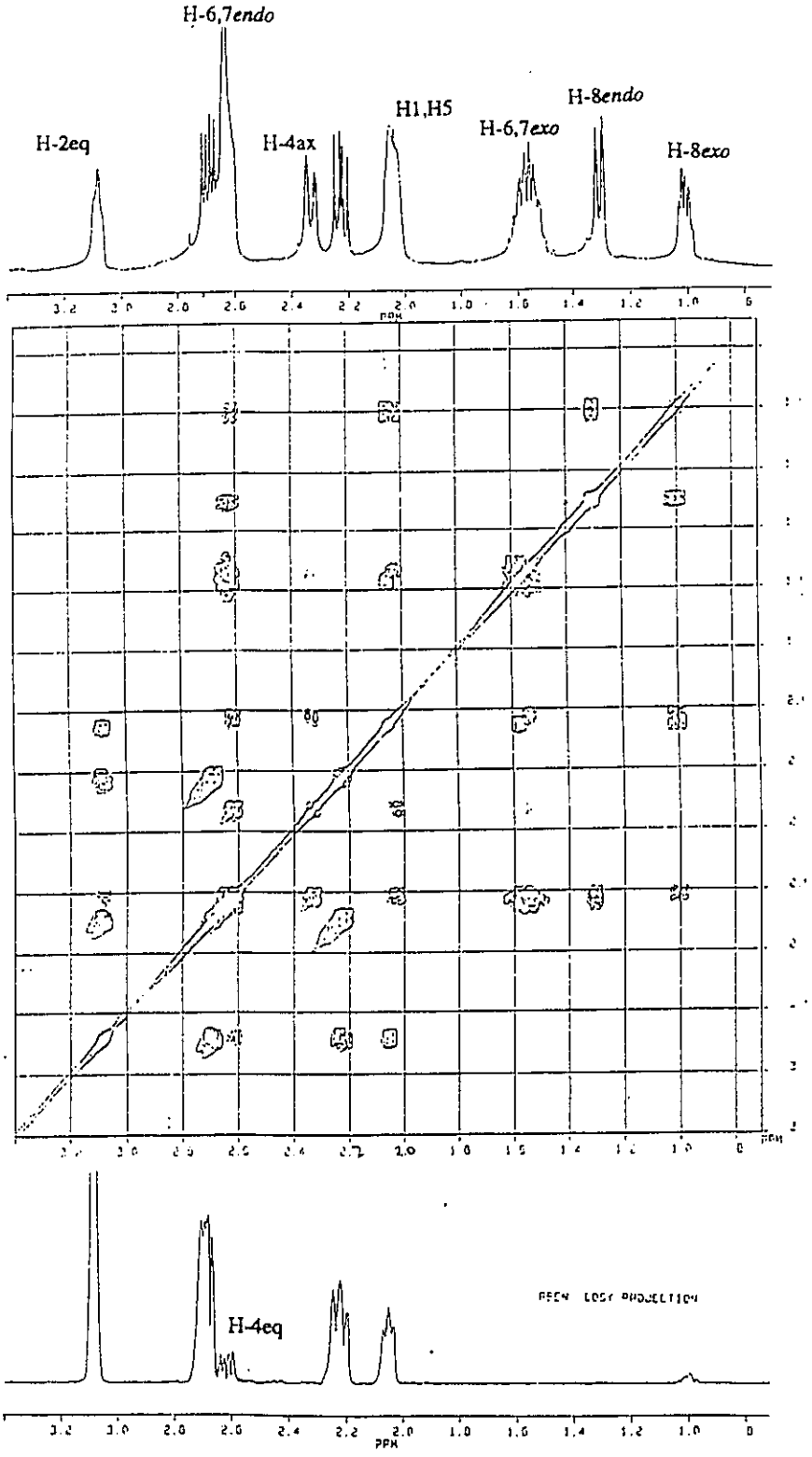
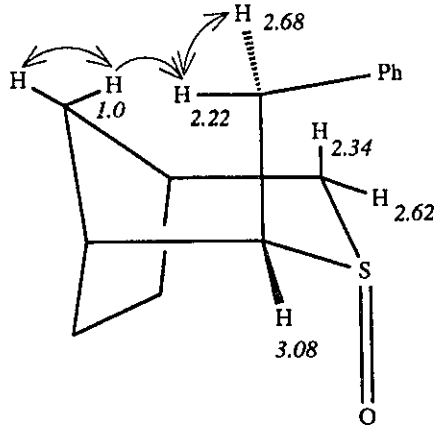


Figure 35. 500 MHz HOMCOR spectrum of **28** in Benzene-d_6 with inset of "cross-section".

axial proton since it was expected to couple to H-5 but the H-4eq was not. Having identified three of the four hydrogens in the area of 2.55-2.75 ppm and all other crucial hydrogens on **28**, it was deduced that the remaining "hidden" proton at 2.55-2.75 ppm must be the H-4eq. This deduction was supported by the fact that H-4ax displayed a distinct coupling to the 2.55-2.75 ppm region and since H-4ax is not expected to couple to the C-6 *endo* or the benzylic hydrogen present in this region the observed coupling must have been due to H-4eq. A 500 MHz COSY "cross section" shown in Figure 35 revealed the C-4 equatorial hydrogen exactly as predicted. This high field spectrum also displayed a W-type coupling between H-2eq at 3.08 ppm and H-4eq which provided further verification that the benzyl group occupied an axial position at C-2.

Figure 36. Crucial nOe's and stereochemistry of compound **28**.



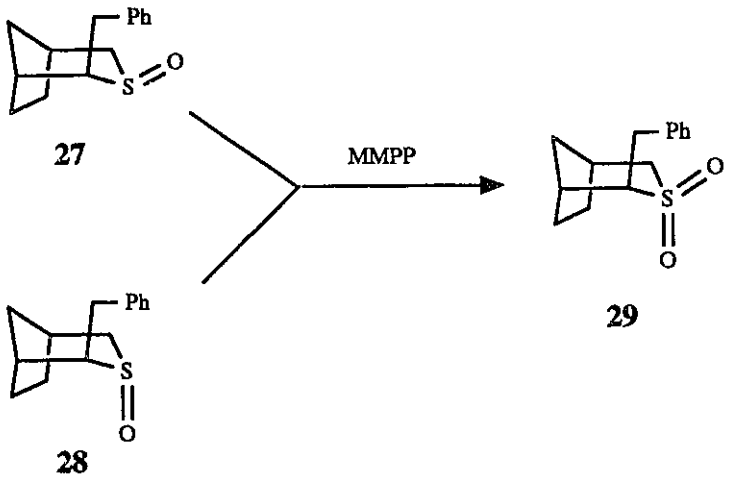
*numbers in italics indicate chemical shift values (ppm)

2.4 Verification of the assigned stereochemistry of 27 and 28 by oxidation to the corresponding sulfone.

We were very confident that the assigned stereochemistry for **27** was correct. However, due to the complicated nature of the NMR spectra of **28** we desired additional

confirmation of its assigned stereochemistry. Consequently it was decided to oxidize **27** and **28** to their sulfones as shown in Scheme 23. The reasoning was that if the stereochemistry of both **27** and **28** were assigned correctly, identical compounds should be obtained after oxidation. Furthermore, the NMR of the sulfone could provide alternate proof that the original assignments made earlier were correct.

Scheme 23



Each of the benzylated sulfoxides were oxidized using MMPP[24] in H_2O and EtOH for 2 days. Usual work-up of both reactions afforded only compound **29** in 90-95% yield as a white solid. This material, which had a mp 132 °C showed strong IR absorptions at 1084 and 1115 cm^{-1} was assigned structure **29** on the basis of the NMR spectra shown in Figures 37, 38 and 39.

Figure 37A shows the proton NMR spectra of **29** in $CDCl_3$ and Figure 37B shows the same compound in benzene-d_6. By examination of the proton NMR of **29** in $CDCl_3$ it seemed plausible that the resonances at 3.50 and 2.79 ppm corresponded to benzylic hydrogens since they were part of an ABX spin system. An unsymmetrized ROESY experiment shown in Figure 38 depicted nOe enhancements between the resonances at 3.50 and 2.79 ppm indicating that these protons were close together. As a consequence,

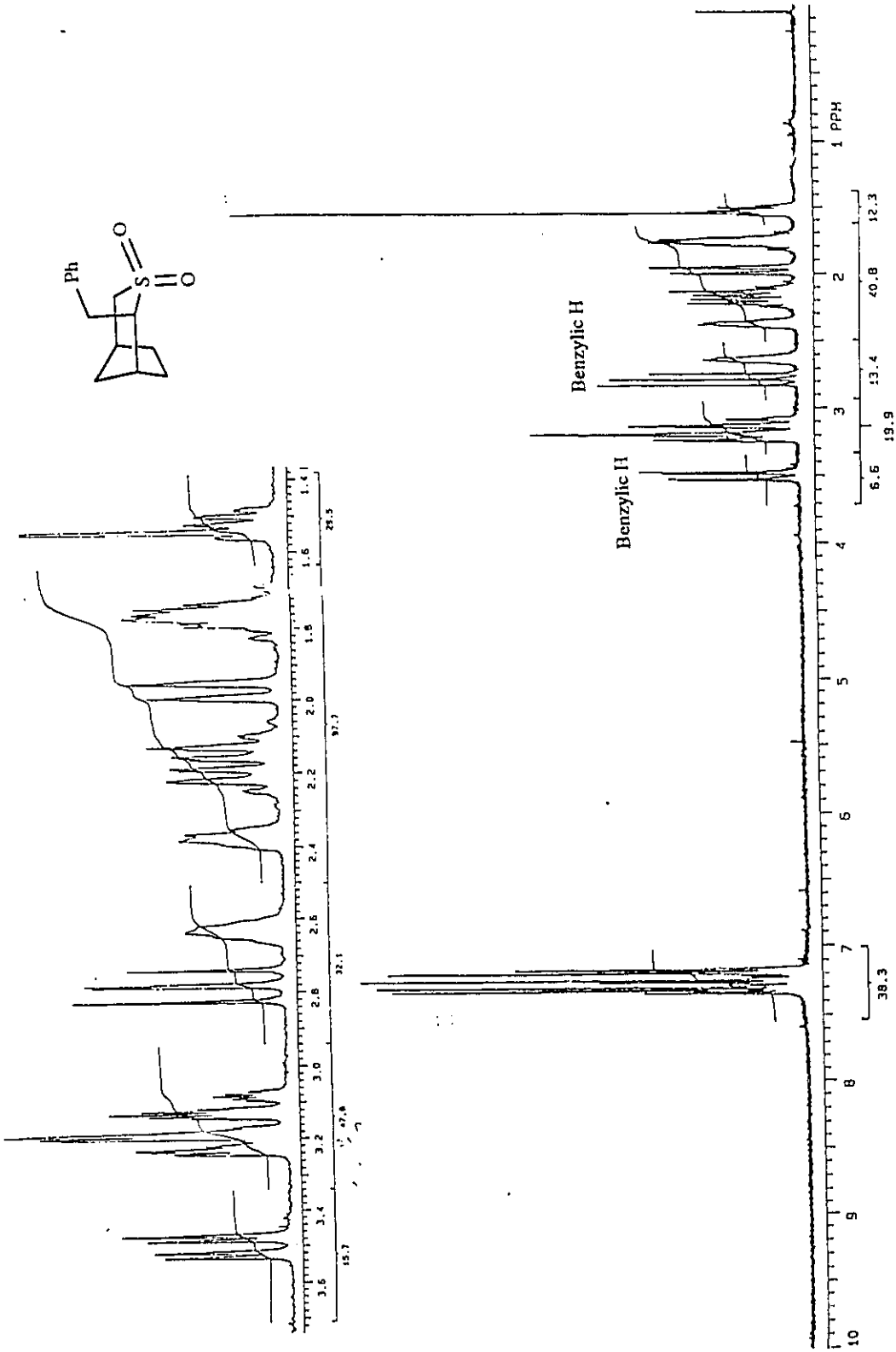


Figure 37A. 200 MHz ^{1}H NMR of **29** in $CDCl_3$.

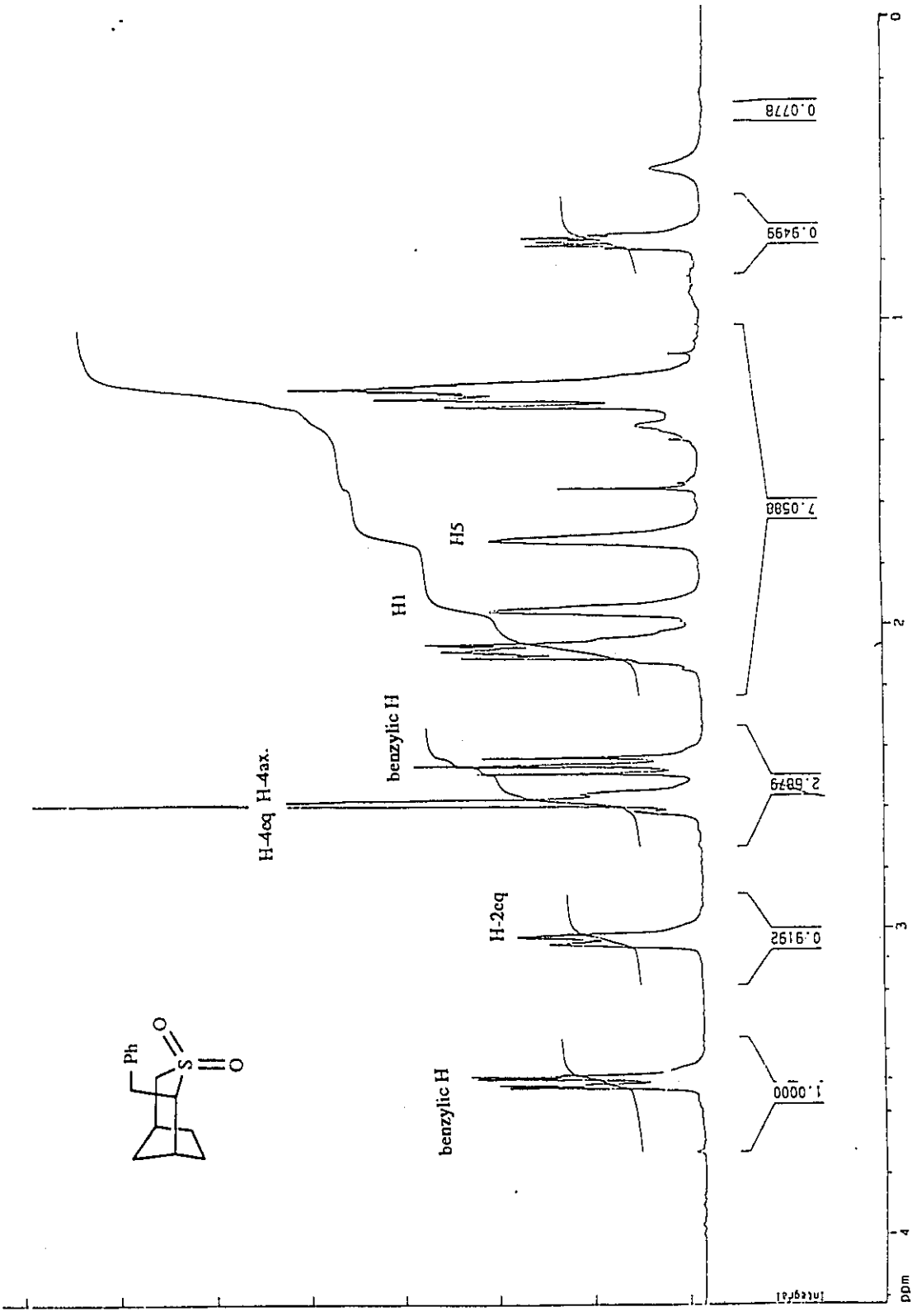


Figure 37B. 500 MHz ^{1}H NMR spectrum of **29** in benzene-d_6.

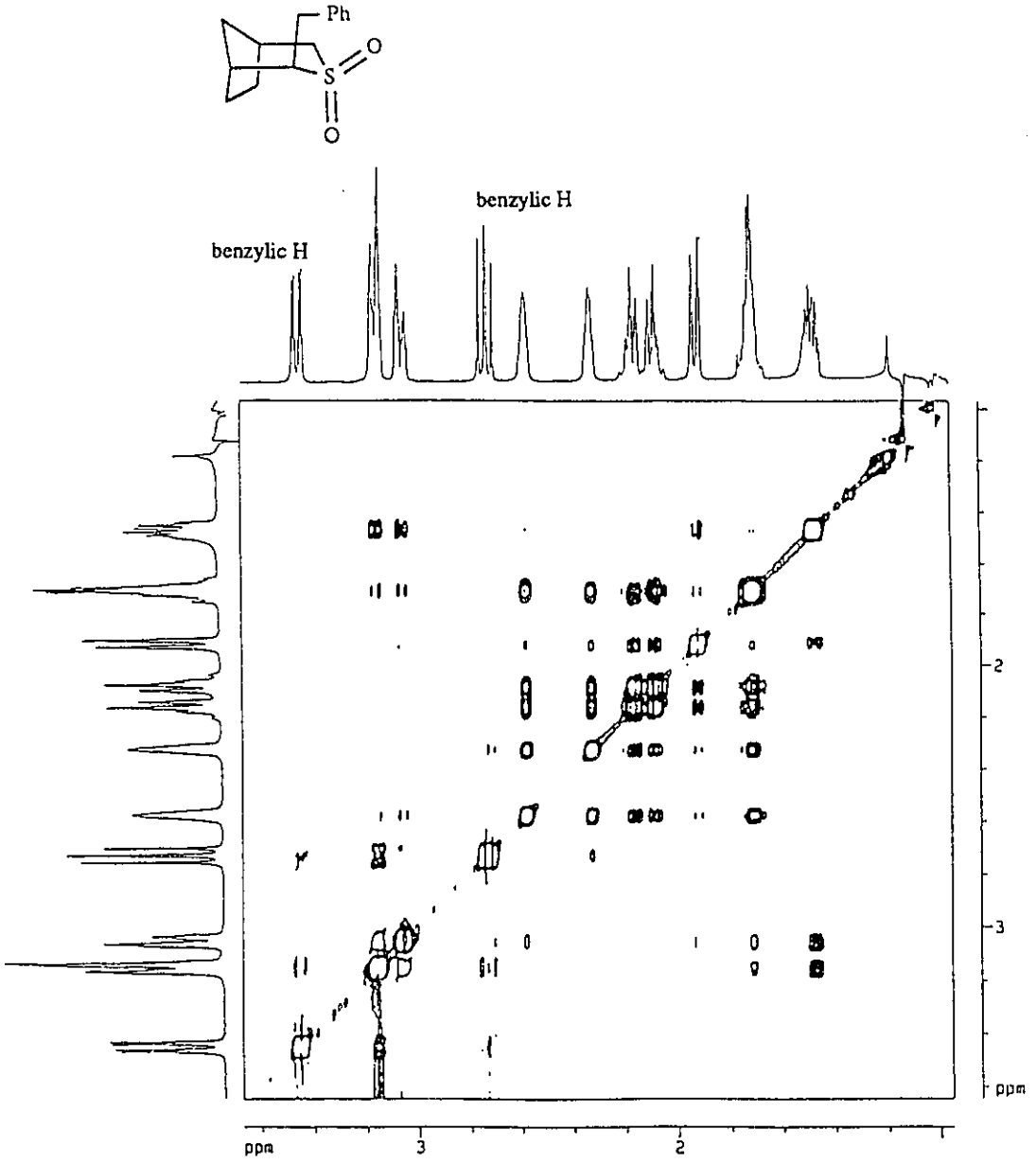


Figure 38. 500 MHz unsymmetrized ROESY spectrum of **29** in $CDCl_3$.

these resonances were assigned as benzylic hydrogens. Comparison of the proton NMR's of **29** in $CDCl_3$ and benzene d_6 revealed that the chemical shifts of the protons assigned as benzylic in the $CDCl_3$ spectrum were only minutely affected when the spectrum was taken in benzene d_6. Thus, the resonances at 3.50 and 2.46 ppm in Figure 37B and 39 were assigned as benzylic hydrogens also. The 500 MHz COSY spectrum shown in Figure 39 displayed a correlation between the resonances at 3.50 and 2.46 ppm which was also consistent with the assignment that these signals corresponded to the benzylic hydrogens. In addition to coupling to one another, each of the benzylic protons displayed a correlation to the resonance at 3.04 ppm which was subsequently assigned as the C-2 hydrogen. The C-2 hydrogen resonance at 3.04 ppm showed a coupling to the proton at 1.96 ppm which corresponded to the C-1 hydrogen. This assignment was made on the basis that the proton at 1.96 ppm as well as the one at 1.73 ppm displayed a characteristic line shape which, based on the analysis of earlier spectra in this study made these protons easily identifiable. The C-1 hydrogen displayed a W-type coupling to the C-5 hydrogen at 1.73 ppm and this hydrogen showed a correlation to the multiplet at 2.60 ppm (representing two protons) which suggested that this resonance corresponded to H-4ax and H-4eq. The C-2 hydrogen at 3.04 ppm also coupled to the multiplet at 2.60 ppm. Such a coupling could only arise if the C-2 hydrogen were participating in a W-type coupling with the C-4 equatorial hydrogen. Subsequently, the C-2 hydrogen was determined to be in the equatorial position, the C-4 axial and equatorial protons were assigned to the signal at 2.60 ppm and the benzyl substituent was verified to be at C-2 in an axial position.

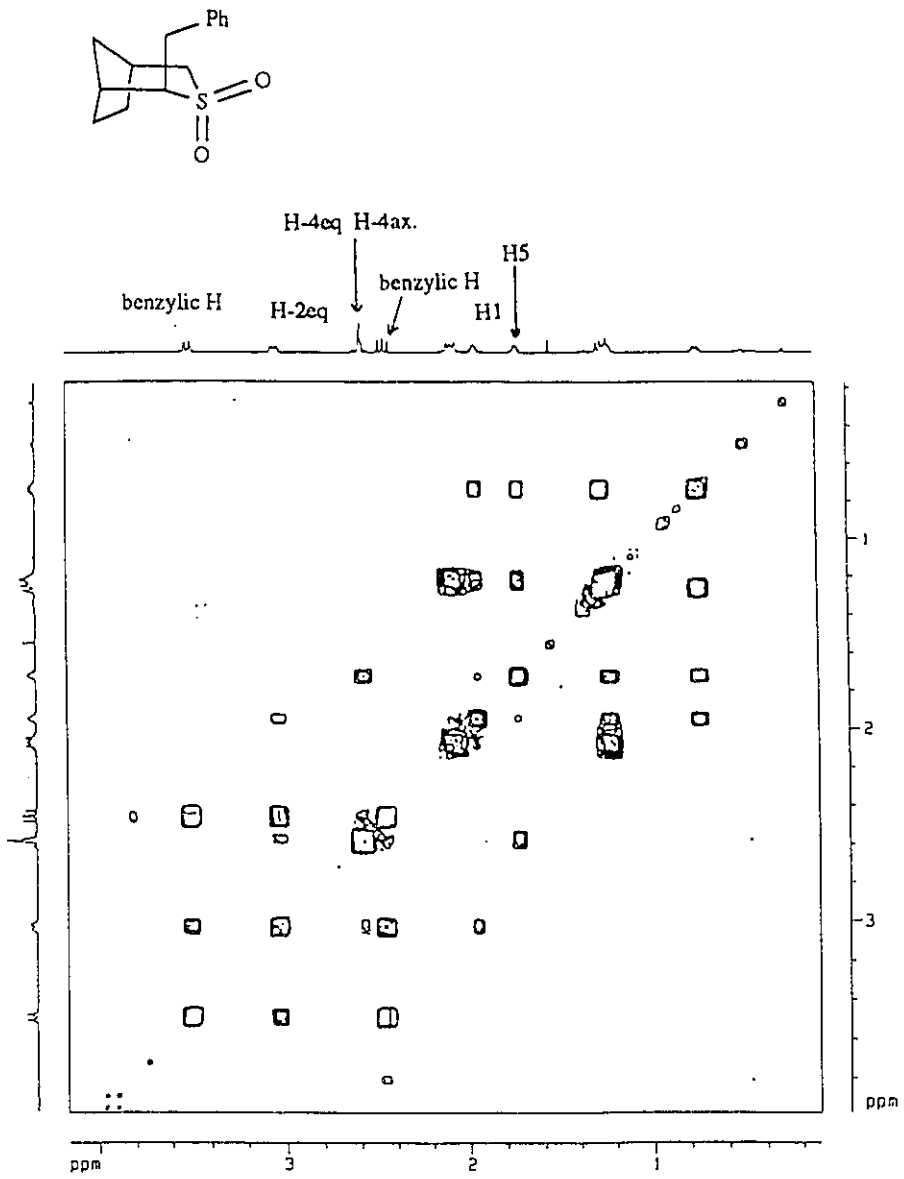


Figure 39. 500 MHz HOMCOR spectrum of **29** in benzene-d_6.

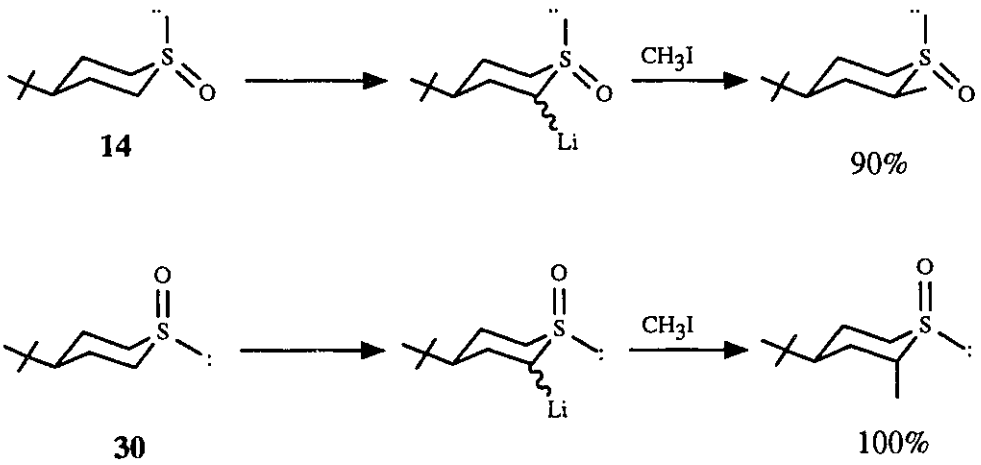
Chapter 3. Discussion.

3.1 Introduction and general discussion of results.

As pointed out in the introduction, examination of the stereochemistry of the reactions of α-sulfinyl carbanions from both a theoretical and experimental point of view was of considerable interest in the 1970's, especially to the Marquet group.[21,22] While the Marquet group did an impressive amount of work in this area, many other groups have conducted similar studies into the stereochemical reactions of other lithio sulfoxides.[32]

Marquet and coworkers concentrated their studies on the lithio derivatives of conformationally fixed 4-*t*-butylthiane-S-oxides such as **14** and its isomer **30**, shown in Scheme 24.

Scheme 24.



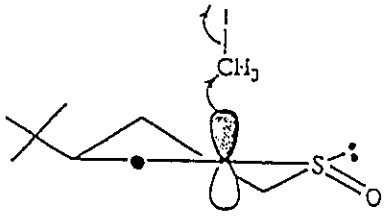
These alkylations proceeded with very high selectivity. In all examples studied, Marquet et al. found that the methylation products as well as deuteration products were highly dependent upon the S=O geometry. Reaction of the lithio sulfoxide species with methyl iodide resulted in highly preferential introduction of the methyl group *trans*, while deuterium entered *cis* to the existing S=O bond.

In order to rationalize these results, Marquet looked closely at the conformation of the lithio sulfoxide in THF at various temperatures.

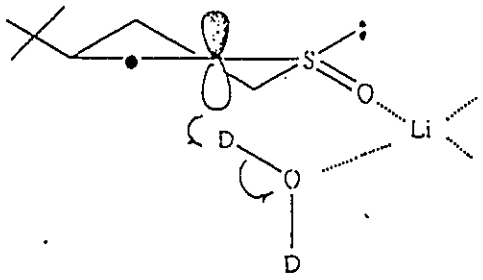
At that time, as today, there was considerable controversy over whether α-sulfinyl anions existed in a planar or pyramidal conformation. Early theoretical calculations done by Wolfe et al.[33] indicated that a pyramidal carbanion as opposed to a planar one would be highly favorable. The configuration of such a carbanion would have the electron pair *gauche* to both the S=O bond and the lone pair of the sulfur. Unfortunately, the Marquet results cannot be rationalized using this approach. It should also be pointed out that other experimental data pertaining to other lithio derivatives of sulfoxides could also not be rationalized by the "gauche effect". Obviously, a new model needed to be developed.

Since the lithio derivatives of **14** and **30** were quite stable at room temperature for several hours, NMR experiments were carried out and an analysis of H-H and ^{13}C-H coupling constants was possible. Using this approach Marquet et al. ruled out the possibility of a pyramidal α-sulfinyl anion existing in THF[34a] and proposed the following conformation for lithio-4-*t*-butylthiane-S-oxides.

^{1}H NMR studies of lithiated **14** indicated that the thiane ring existed in a half chair conformation as shown by **31** and **32**. In this conformation the methine hydrogen of the carbanion bisects the dihedral angle of the two hydrogens in the α-position.



31



32

^{13}C NMR experiments consistently showed a large increase with respect to the initial sulfoxide in the J^{1}-^{13}C-H coupling constant of the anionic carbon (ΔJ=+18-19 Hz).

Marquet theorized that since an increase of negative charge on a carbon results in a decrease of the ^1J coupling constant for a given hybridization state, the increased values of ^1J which were observed must therefore reflect a rehybridization[34a] of the anionic carbon. Since the experimentally observed increase in the ^1J coupling constant was slightly greater than that observed in diphenylmethyllithium for which all data was consistent with a nearly sp^2 hybridized benzylic carbon,[34b,c] Marquet proposed that the anionic carbon of the lithio sulfoxide of 4-*t*-butylthiane was planar in nature and not pyramidal. This conclusion was found to be consistent with the experimental data obtained from other lithio dialkyl or benzylalkylsulfoxides.[35]

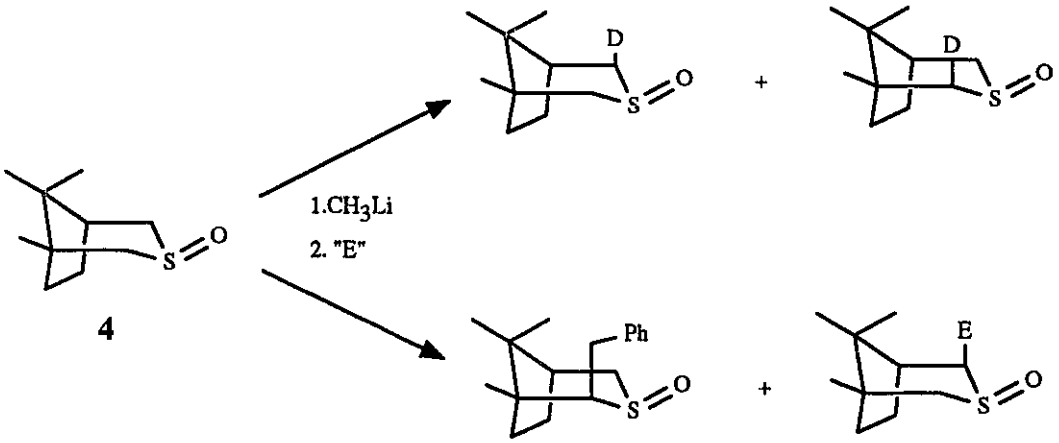
Having determined the conformation of the sulfoxide ring and proposing that the α-sulfinyl carbanion was planar rather than pyramidal in nature, Marquet developed the following explanation to rationalize the stereochemical results observed when lithio 4-*t*-butylthiane-S-oxides were reacted with various electrophiles.

The alkylation with methyl iodide *trans* to the S=O bond was ascribed to a combination of steric and electronic effects. As the electrophilic carbon of methyl iodide approaches the p-orbital of the carbanion, a bond begins to form in a typical S_2N fashion. As this bond forming reaction proceeds the carbon-iodine bond begins to break and as a result a negative charge begins to accumulate on the iodine atom. If the methyl iodide is approaching the p-orbital of the anionic carbon *syn* to the S=O bond, a repulsive effect between the developing negative charge on the iodide and the oxygen of the S=O bond occurs; consequently the *syn* approach is disfavored. However, approach of the methyl iodide *anti* to the S=O bond as shown in **31** is preferred over the *syn* approach since the repulsive effect between the developing negative charge on the iodide leaving group and the S=O dipole is less severe. When an electrophile capable of hydrogen bonding such as D_2O is used internal chelation as shown in **32** favors introduction of the electrophile *cis* to the S=O bond.[21a,36] To verify this hypothesis Marquet reacted the lithio 4-*t*-butylthiane-S-oxide

with trimethylphosphate, a methylating agent with the ability to form hydrogen bonds and as expected the methyl substituent was introduced *cis* to the S=O bond. This resulted from *syn* attack of the trimethylphosphate on the p-orbital of the carbanion which was made possible by its ability to hydrogen bond to the oxygen of the S=O bond. Simpkins et al[37] have recently reported similar stereoselectivity in the alkylation of *trans*-4-*t*-butyl(diphenyl)siloxythiane oxide with various electrophiles. In all cases the electrophiles employed were not capable of hydrogen bonding to the oxygen of the sulfoxide bond and subsequently entered in a position *trans* to the S=O bond.

Now let us review the stereochemical results obtained upon alkylation and deuteration of bicyclic sulfoxide **4**, summarized in Scheme 25.

Scheme 25

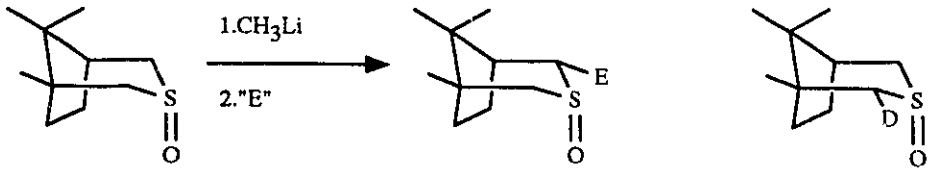


4 **6** **7** E=CH_2Ph **24** E=$C(CH_3)_2OH$

The results obtained in the trapping of the lithio derivatives of **4** differ with those obtained from **14** in two ways. Firstly, alkylation occurred *cis* rather than *trans* to the S=O bond and secondly, deuteration occurred with the same stereochemical sense as alkylation. In the lithio thiane-S-oxides derived from **14** opposite stereochemical results were observed with these two different electrophiles.[21,22]

The same trend was observed in the reaction of the lithio derivatives of sulfoxide **15**.

Scheme 26



15 E=D

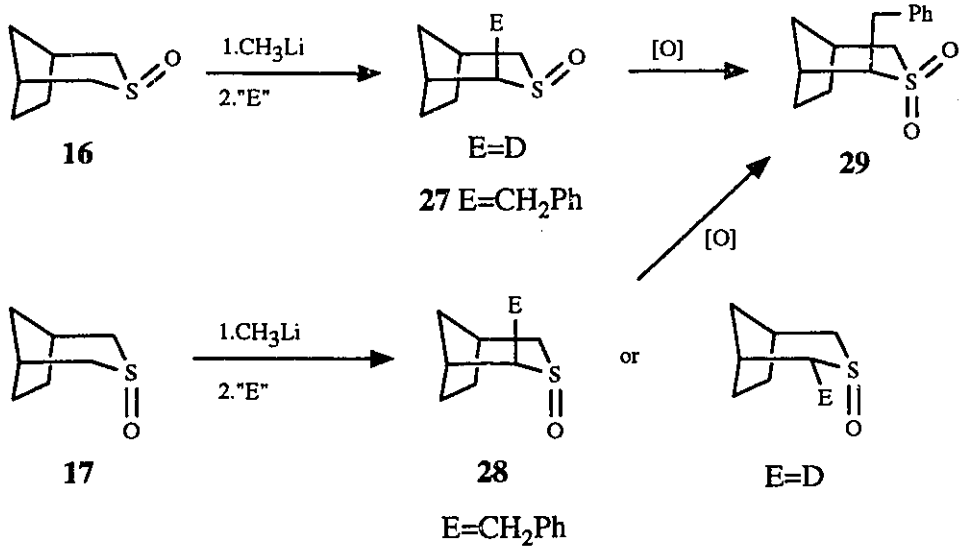
25 E=CH_2Ph

26 E=$C(CH_3)_2OH$

Reaction with CH_3COOD was expected to produce a product which had a *cis* relationship between the deuterium and the S=O bond, while the alkylated products were expected to have a *trans* relationship between the substituent and the S=O bond. In all cases, careful analysis by NMR had shown that the electrophile had entered into an equatorial position such that the new substituent was *cis* to the S=O bond.

The fact that the lithio derivatives of both **4** and **15** reacted with CH_3COOD and different alkylating agents in the same stereochemical sense was intriguing. The results of reacting the lithio derivatives of the norbornene based bicyclic sulfoxides **16** and **17** have already been discussed in detail and are summarized in Scheme 27.

Scheme 27



The stereochemical outcome when lithiated bicyclic sulfoxide **16** was reacted with various electrophiles was identical to the results described for the lithio derivatives of **4** and **15**. In other words, reaction with either CH_3COOD or benzyl bromide produced products which had incorporated the electrophile *cis* to the S=O bond. In contrast, lithiated sulfoxide **17** gave different results. Alkylation and deuteration occurred with opposite stereochemistry. Deuterium was incorporated *cis* to the S=O bond while alkylation occurred *trans*. These last results are in agreement with predictions using Marquet's model. Deuterium favors introduction *cis* to the S=O bond because of hydrogen bonding to the oxygen of the S=O bond, while benzyl bromide favors *trans* incorporation because there are less repulsive interactions in the transition state between the developing negative charge on the bromide leaving group and the S=O dipole. Our model and subsequent rationalization put forward to explain these very surprising and unusual results is described in the following section.

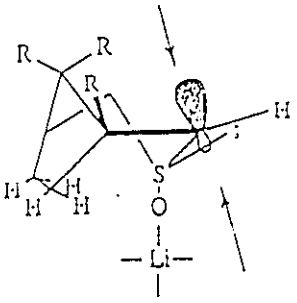
3.2 Explanation of results.

The most recent molecular calculations by Wolfe[38] and a crystal structure determination of the lithio derivative of $PhCH(CH_3)S(O)Ph$ by Boche[39] favor a pyramidalized α-carbanion. Given that the α-carbanion is pyramidal in nature, the energetically favorable conformation has been shown to have the lone pair orbital nearly antiperiplanar to the S=O bond as shown in Figure 40. The resultant angle between the lone pair orbital and the sulfur lone pair is approximately 85°. Although not conclusive, the available data indicates that there may not be much energy difference between the pyramidalized and the planar conformations.[39a]

Figure 40.

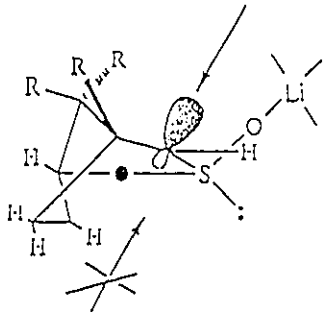
The preferred pyramidal carbanion conformation shown in Figure 40 is extremely difficult to attain in our bicyclic system without significant angle distortions and steric interactions. For example, in the axial sulfoxides **15** and **17**, the carbanion lone pair is at best *anti*- to the S=O bond and the angle with the lone pair on sulfur is only 60° rather than 85° (see Figure 41). With the equatorial sulfoxides **4** and **16**, a similar conformation may be obtained if the bicyclic system adopts a "twist boat" conformation as illustrated in Figure 42. While such a conformation is theoretically possible, it should be extremely unfavorable due to the close proximity of the C-8 *endo*-methyl group and the oxygen atom of the sulfoxide.

Figure 41.



15, R=CH_3; **17**, R=H

Figure 42.

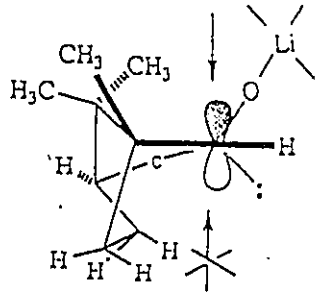


4, R=CH_3; **16**, R=H

Attempts to rationalize the unusual stereochemical results which we obtained using a pyramidalized α-carbanion led to many inconsistencies. It seemed reasonable that the lithio derivative of **17** (Figure 41, R=H) should give preferentially axial benzylation *trans* to the S=O bond. However such an approach in **15** (Figure 41, R=CH_3) is blocked by the C-8 *endo* methyl group and as a result of this hindrance benzylation occurred in an equatorial fashion. Benzylation of **4** and **16** using the same rationale, should afford only the *trans*-1,2-diequatorially substituted products in both cases, but only the more hindered axial products were obtained presumably because the anticipated approach was hindered by the ethano bridge.

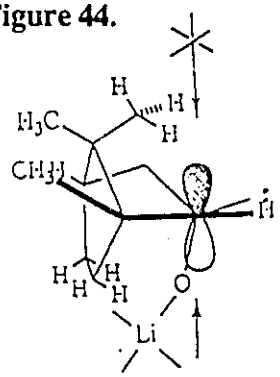
A self-consistent picture for all lithiated sulfoxides in this study is obtained if a planar configuration at the α-carbanion, arranged such that the p orbital is nearly eclipsed with the S=O bond[21b,38,39] is assumed. Attack by benzyl bromide *trans* to the S=O bond in the lithio derivative of **4** is severely hindered by the *endo* hydrogens on the ethano bridge (see Figure 43). It is important to note that in this model, the C-8 *endo* methyl group points behind the plane and does not impede approach of the electrophile. Consequently, benzyl bromide must add *cis* to the sulfoxide oxygen which results in the formation of the axially substituted product.

Figure 43.



Lithio derivative of **4.**

Figure 44.



Lithio derivative of **15.**

No change in the stereochemical outcome should be expected upon removal of the three methyl groups and none was observed. Thus, the lithio derivative of **16** like that of **4** reacted with electrophiles to produce products with deuterium and benzyl groups in the axial position.

In the case of the axial sulfoxides **15** and **17**, alkylation *trans* to the sulfoxide oxygen is hindered by the C-8 *endo* methyl group in **15** (see Figure 44) but not when this methyl group was removed as in **17**. Thus for **15**, benzylation and deuteration both occurred *syn* to the S=O bond resulting in equatorially substituted products, while for **17** deuteration occurred *cis* to the S=O bond and alkylation occurred *trans* since there was no C-8 *endo* methyl group present to impede the approach of benzyl bromide.

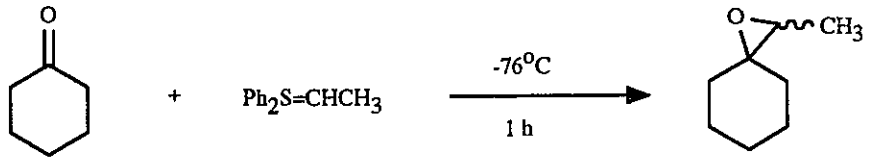
Chapter 4. The Design of Alternate Auxiliaries.

4.1 Introduction.

As mentioned in chapter one, the synthetic usefulness of epoxide forming reactions using sulfur ylides and carbonyl compounds has been well demonstrated in the last 15-20 years. While examples discussed in chapter one dealt only with the formation of stilbene oxide type systems via the transfer of aryl groups, the importance of alkyl group transfer should not be overlooked.

Work by Corey et al.[40] in the late 1960's demonstrated that sulfonium alkylides while less stable, can be synthesized and reacted with carbonyl compounds to form epoxides via the transfer of an alkyl group as shown in Scheme 28. This reaction worked equally well when transferring an isopropyl group to form epoxides containing a gem dimethyl group.

Scheme 28.

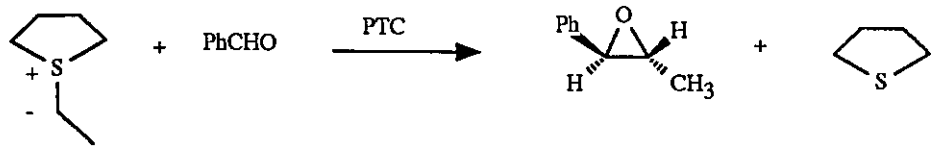


Independently, Trost et al.[41] showed that it was possible to transfer a cyclopropyl group from a sulfur ylide to a carbonyl compound and subsequently form spiroepoxides. Compounds such as these are important synthetic intermediates because upon heating they undergo a ring enlargement to form substituted cyclobutanones.

Other more recent examples of the transfer of alkyl groups in the reactions of sulfur ylides and carbonyl compounds can be found in the literature throughout the last seven years.[42,43,44]

Unpublished work by McKee, Breau and Durst[45] in the late 1980's demonstrated that the ylide **33a** transferred an ethyl group to benzaldehyde in an epoxide forming reaction in 75% yield (Scheme 29) with a high *trans/cis* ratio of epoxides. This was quite remarkable since there was three S^+-CH_2R groups in the sulfonium salt but only the ethylidene group (R=CH_3) was transferred.

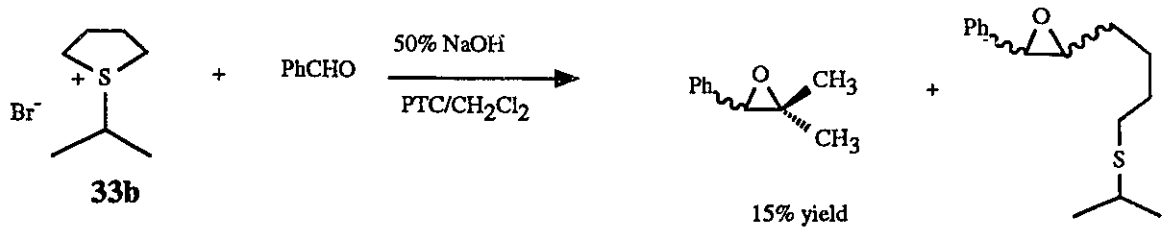
Scheme 29.



33a

Even more surprising was that the isopropylidene group could be transferred from ylide **33b** albeit, as the minor product. The importance of transferring an isopropylidene group has been illustrated by Van Tamelen et al.[46] who used diphenylsulfonium isopropylide to synthesize [3-^{3}H]-4-norsqualene-2,3-oxide and [5-^{3}H]-homosqualene-2,3-oxide in an attempt to learn more about the critical polycyclization of squalene-2,3-oxide and related terpenoid epoxides.

Scheme 30.



33b

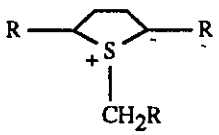
15% yield

85% yield

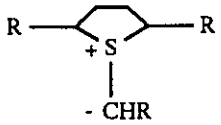
The crude product ratio in Scheme 30 was 85:15 in favor of the rearranged compound. Since the rearranged product was produced as a result of ylide formation on the tetrahydrothiophene ring and because this was the major product of the reaction, it was

concluded that formation of the ylide in this position rather than on the isopropyl group was highly favored.

The first section of this chapter deals with the attempted syntheses of two different 2,5-disubstituted tetrahydrothiophene derivatives. It was expected that alkyl substituents at the 2,5 positions in the thiolane ring would decrease the ratio of **34**:**35** and as a consequence, species **35** should be the predominate ylide. Subsequent reaction of **35** with a carbonyl compound would then result in the transfer of the $-CH_2R$ group as desired. In addition it was hoped that such an auxiliary might also allow for the efficient transfer of an isopropyl group.

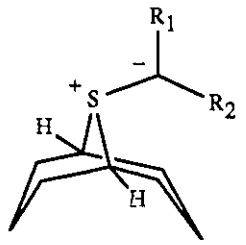


34



35

In the final section of this chapter the synthesis of a 9-thiabicyclo[3.2.1]nonane auxiliary and its ability to transfer an alkyl group will be described. It was expected that this auxiliary would be superior to the 2,5-disubstituted tetrahydrothiophenes because it was extremely easy to synthesize and the acidity of the α-hydrogens at the bridge of the two rings would be drastically reduced thus favoring the formation of species **36** and **36'** shown below.

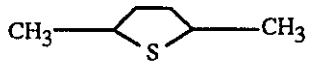


36 R_1=H R_2=alkyl

36' R_1=R_2=CH_3

4.2 2,5-Disubstituted Tetrahydrothiophene Derivatives.

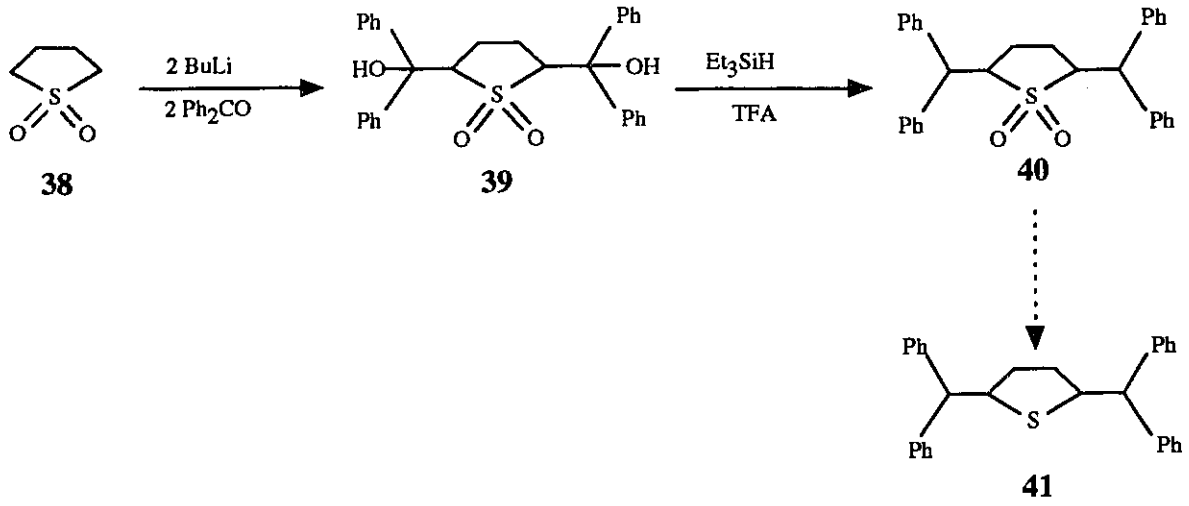
Compound **37** was considered as a possible auxiliary however, due to the fact that it was extremely volatile and had a very offensive odor, it was not pursued.



37

Since larger substituents were required on the thiolane ring, compound **41** shown in Scheme 31 was investigated.

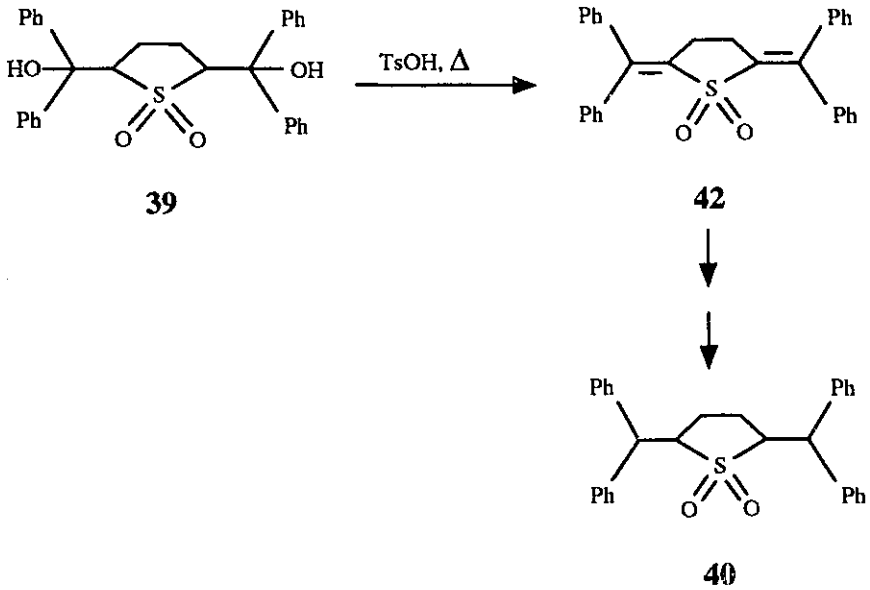
Scheme 31



Following a literature procedure[47] sulfolane **38** was dissolved in THF and cooled to 0°C under a nitrogen atmosphere. Then, 2.2 eq of butyllithium were added and the mixture stirred for 2 min after which time a solution of benzophenone (2.1 eq) in THF was added and the reaction mixture allowed to warm to room temperature. Work up afforded compound **39** in only 25% yield as a white solid with a mp 312 °C (lit. mp 312-313°C)[47]. The ^{1}H NMR and CIMS both supported a structure consistent with that of **39**.

Initial attempts to remove the hydroxyl groups met with little success. TFA and $NaBH_4$[48] gave only starting material after 2 days and attempted hydrogenolysis using both H_2, Pd/C[49] or cyclohexene, Pd/C[50] proved futile. In an attempt to circumvent this problem it was decided to synthesize **42** (Scheme 32) which was expected to readily undergo reduction and furnish compound **40**.

Scheme 32



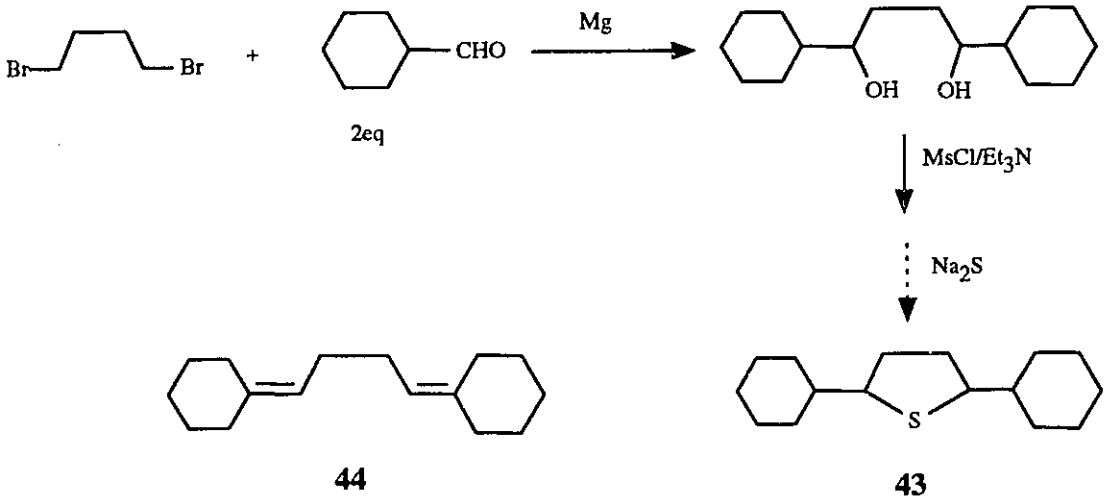
39 **42** **40**

Reaction of compound **39** with one equivalent of TsOH in refluxing toluene provided **42** as a white solid with mp 231°C. ^{1}H NMR and EIMS were consistent with the structure of **42** and HRMS indicated a molecular formula of $C_{30}H_{24}O_2S$. The IR spectra displayed two bands at 1005 and 1025 cm^{-1} indicating that a sulfone moiety was present. Attempts to reduce alkene **42** using transfer hydrogenation[50], standard hydrogenation[49] or $NaBH_4$ in EtOH[51] were all unsuccessful and resulted only in starting material. Consequently, this approach was abandoned.

A final attempt to reduce diol **39** proved successful when Et_3SiH and TFA were used.[52] After 5 h at room temperature the reaction mixture was neutralized with $NaHCO_3$ and extracted with hexanes to afford **40** as a white crystalline solid (mp 224°C) in 65% yield. ^{1}H NMR and CIMS both supported the structure of compound **40**. The IR spectrum displayed prominent stretching absorptions at 1115 and 1034 cm^{-1}. Attempts to reduce sulfone **40** to the corresponding 2,5-disubstituted tetrahydrothiophene derivative using $LiAlH_4$[53], Dibal-H[54] and SmI_2-HMPA[55] all proved unsuccessful. As a result, attempts to synthesize this particular auxiliary were abandoned.

Compound **43** was also expected to possess great potential as an auxiliary. As shown in Scheme 33, the diol was prepared in 55% chemical yield by a di-Grignard reaction[56] with 1,4-dibromobutane and two equivalents of cyclohexanecarboxaldehyde in THF.

Scheme 33



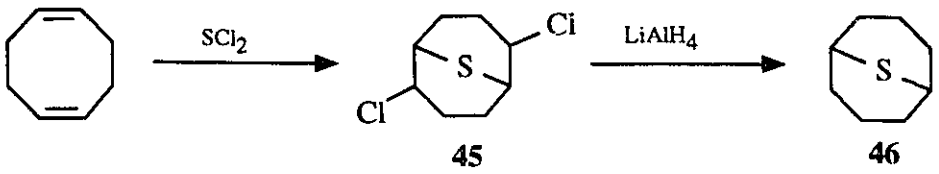
44 **43**

The resulting diol was then treated with $MsCl/Et_3N$ in CH_2Cl_2 to give the corresponding dimesylate. Unfortunately all attempts to cyclize this compound resulted in elimination of the mesylates to give **44**, as evidenced by the appearance of olefinic signals in the ^1H NMR of the crude mixture. No further attempts to cyclize the dimesylate were made.

4.3 9-Thiabicyclo[3.3.1]nonane auxiliary.

For the reasons outlined in the introduction of this chapter, auxiliary **46** looked very promising. 9-Thiabicyclo[3.3.1]nonane **46**, was synthesized using a procedure published by Weil et al.[57] as outlined in Scheme 34.

Scheme 34



45 **46**

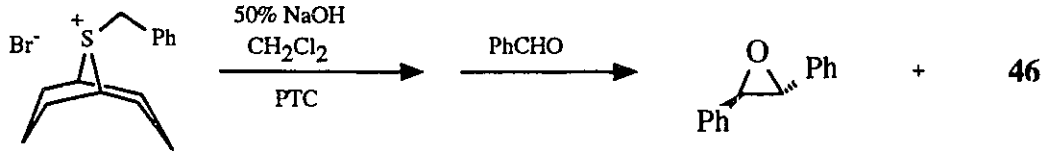
1,5-Cyclo-octadiene was reacted with SCl_2[58] to furnish 2,6-dichloro-9-thiabicyclo[3.3.1]nonane **45**, in 80% yield. This compound was then treated with $LiAlH_4$ in THF to give 9-thiabicyclo[3.3.1]nonane **46**, in 84% yield.

Initial epoxide forming reactions using auxiliary **46** and benzaldehyde were done with its benzyl sulfonium salt.

Alkylation of **46** by reaction with benzyl bromide in CH_3CN for 24 h at room temperature produced the benzylated sulfonium salt **47**, in 97% yield which was fully characterized.

Compound **47** was subjected to the earlier described phase transfer reaction conditions and reacted with benzaldehyde as shown in Scheme 35.

Scheme 35



47 **48**

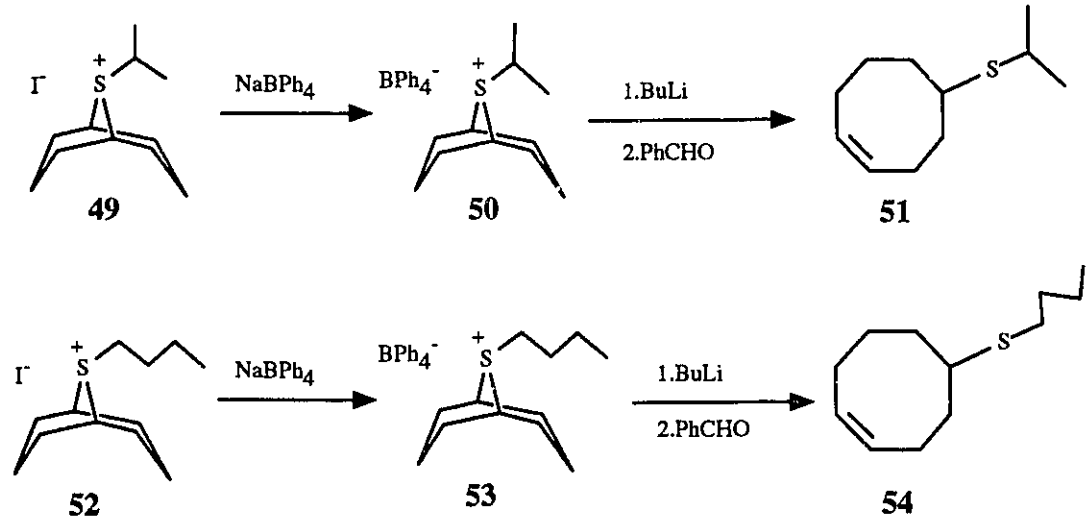
After 10 h a crude ^1H NMR revealed that all of the starting material had been consumed. Usual workup followed by analysis of all products revealed that only the *trans* epoxide **48** had been formed in 76% yield; 70% of sulfide **46** was recovered. Particularly encouraging was the fact that the crude NMR showed no evidence of rearrangement products (i.e. Sommelett[59] reaction resulting from ylide formation on the sulfonium ring). The use of

benzylated tetrahydrothiophene sulfonium salts in the past[45], had always resulted in 5-15% of rearranged product due to the Sommelett reaction.

Also encouraging was the fact that **48** was obtained in high yield. In past experiments the *trans*-epoxides were obtained in only 38% yield using the camphor derived auxiliary and 54% using the unsubstituted tetrahydrothiophene auxiliary.

Since the above results were very promising, sulfonium salts **49** and **52** (Scheme 36) were synthesized by heating **46** in CH_3CN with an excess of the appropriate alkyl iodide.

Scheme 36

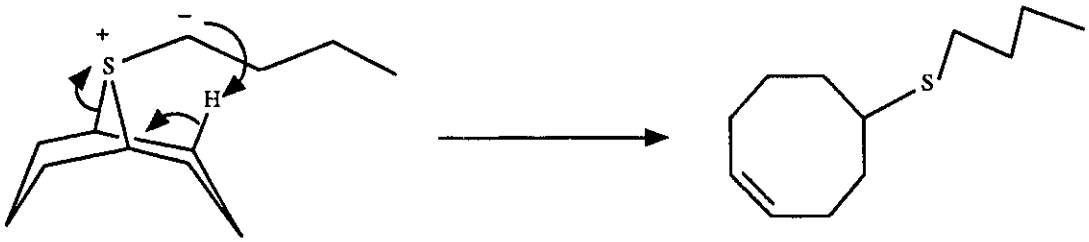


The salts **49** and **52** were obtained in 30-50% yield and their initial reactions with benzaldehyde under phase transfer conditions using 50% NaOH were unsuccessful, furnishing only starting materials. The observation that only starting materials were recovered suggested that ylide formation was not occurring and subsequently it was decided to use butyllithium as a base to ensure ylide formation.

The fact that these reactions now had to be carried out in THF presented a problem since salts **49** and **52** were only sparingly soluble. This necessitated formation of the boron tetraphenyl sulfonium salts[60] **50** and **53** which were very soluble in THF. As a standard

procedure, a solution of each salt was dissolved in dry THF, reacted with butyllithium for five min at -78°C to affect ylide formation and then subsequently allowed to react with 1.1 equivalents of benzaldehyde for 5 h. Usual workup of each reaction followed by a ^{1}H NMR of the crude mixture revealed that all of the starting material had been consumed and that the only products formed were **51** and **54**, which resulted from an intramolecular β-elimination as hypothesized in Scheme 37.

Scheme 37



This result was disappointing since sulfonium salt **33** and its derivatives with other alkyl substituents had shown no evidence of rearrangement products resulting from a β-elmination.

Compounds **51** and **54** were not fully characterized as their formation was clearly evidenced by ^{1}H NMR of the crude reaction mixtures.

At this point, another interesting project dealing with the asymmetric synthesis of α-amino esters presented itself and all work relating to sulfonium salts and asymmetric epoxidations was discontinued.

Experimental Section:

General Remarks:

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infra red spectra were recorded using a Bomem IR Spectrometer. In most cases solution IR were taken using reagent grade methylene chloride as solvent. Optical rotations were performed on a Perkin-Elmer 241 polarimeter in the solvents and concentrations specified. Proton and carbon nuclear magnetic resonance spectra were recorded on either a 500 MHz, Brucker 400 MHz, Varian XL-300 or Gemini 200 MHz spectrometer, using $CDCl_3$ or benzene d_6 as solvent. Chemical shifts are reported in ppm downfield from TMS as an internal standard. Multiplicities are reported as s, singlet; bs, broad singlet; d, doublet; bd, broad doublet; dd, doublet of doublets; dm, doublet of multiplets; t, triplet; q, quartet; m, multiplet. Low and high resolution mass spectra were recorded on a VG Mass Spectrometer with a DANI 7070 gas chromatograph. MS peak intensities are given as a percent of the base peak and are shown in parentheses. GC analysis was done on a Varian 3400 GC using a four meter column with OV-101 as packing. Microanalyses were performed using a Perkin Elmer Series II 2400 analyzer at the University of Ottawa or by M-H-W Laboratories, Phoenix AZ, U.S.A..

Chromatographic separations were performed using 230-400 Mesh SiO_2 from Terochem Laboratories in the solvent systems specified.

All solvents were dried and distilled prior to utilization; THF was distilled over sodium-benzophenone and methylene chloride was distilled over P_2O_5.

PART A: Lithiated Bicyclic Sulfoxides.

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

A solution of magnesuim monoperphthalate hexahydrate MMPP, (13.84 g, 28 mmol) in H_2O was added dropwise to a solution of the sulfide 8.65 g, 51 mmol in ethanol (340 mL) and the mixture was stirred at room temperature overnight. The ethanol was removed under reduced pressure and the aqueous phase was concentrated to 50 mL, diluted with sat. Na_2CO_3 solution (100 mL) and extracted with dichloromethane (3 X 200 mL). The combined organic extracts were dried ($MgSO_4$) and the solvents were evaporated. The white residue was sublimed (120°C/1 Torr) to afford sulfoxide **4** as a white crystalline solid (8.4g, 89% yield): m.p. 240-241 °C; $[\alpha]^{23}_D$ +27.8° (c=2.8, $CHCl_3$); IR (CH_2Cl_2): 2930, 1459, 1390, 1028 (S=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.88 (s, 3H), 0.96 (s, 3H), 1.12 (s, 3H), 1.52-1.58 (m, 1H), 1.69-1.73 (m, 2H), 1.86-2.05 (m, 2H), 2.76 (br. d, 1H, J=12.5 Hz), 2.87 (bd, 1H, J=12.4 Hz), 3.08 (dd, 1H, J=12.5, J=1.8 Hz), 3.36 (ddd, 1H, J=12.4, J=5.1, J=1.9 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 18.6, 21.3, 23.2, 26.1, 35.3, 42.5, 44.3, 45.2, 53.2, 59.2; EIMS m/e (relative intensity): 186 (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,64.24; H, 9.63; S, 17.20.

(1R,3R,5S)-1,8,8-trimethyl-3-thiabicyclo[3.2.1]octane-3-oxide (15).

To 795 mg (1.0 eq) of $(CH_3)_3OBF_4$ under nitrogen, was added to a solution of 1.0 g of sulfoxide **4** (5.38 mmol) in 20 mL of freshly distilled CH_2Cl_2. The solution was cooled to 0°C and stirred for 3 h. The solution was then filtered to remove any unreacted $(CH_3)_3OBF_4$ and 30 mL of diethyl ether was added which produced a precipitate. The precipitate was filtered off and dried under high vaccuum to give 1.02g (70% yield) of the alkoxy sulfonium salt **18** as white crystals: ^1H NMR δ: 0.95 (s, 3H), 1.10 (s, 3H), 1.91 (s,

3H), 1.75-2.10 (m, 4H), 2.30 (m, 1H), 3.22 (dm, 1H, J=12 Hz), 3.40 (dt, 1H, J=12 Hz), 4.09 (dd, 1H, J=12, 3.2 Hz), 4.20 (s, 3H), 4.33 (ddd, 1H, J=12.0, 4.0, 3.3 Hz). This material was utilized without further purification as described below.

Compound **18** (1.98g 6.8 mmol) was dissolved in 100 mL of 0.2 N NaOH and stirred for two days. Extraction with 3 X 100 mL of ethyl acetate, drying with $MgSO_4$ and evaporation of solvent gave 1.23g (95% yield) of white crystals. Analysis by gas chromatograph showed a 80:20 mixture of **15** to **4**. These were separated on silica gel using toluene:acetone (2:1) as a solvent system. The axial sulfoxide was then sublimed at 110°C/1 Torr to remove water: mp 171°C; $[\alpha]^{24}_D$ +19.4° (c=0.5, $CHCl_3$); IR (CH_2Cl_2): 2954, 1488, 383, 1030 (S=O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.82 (s, 3H), 0.93 (s, 3H), 0.96 (s, 3H), 1.68-1.82 (m, 2H), 1.90-2.10 (m, 2H), 2.26-2.51 (m, 2H), 2.62-2.70 (dd, 1H, J=7.6, 1.4 Hz), 2.82-2.90 (dt, 1H, J=7.6, 1.2 Hz), 3.10-3.20 (bd, 1H, J=7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.7, 21.6, 24.5, 25.7, 34.4, 41.2, 42.7, 44.8, 51.5, 57.9; EIMS m/e (relative intensity): 186 (32.8), 169 (100), 107 (70), 95 (68.8), 81 (81.3), 55 (59.4), 41 (98). HRMS calcd for $C_{10}H_{18}OS$ (M+) 186.1078, found 186.1075.

(1R,3S)-1,3-cyclopentanedicarboxylic acid (19).[27]

Norbornene (9.4 g, 0.1 mole) and 0.2 g (1 mmol) of rhuthenium chloride in 100 mL of chloroform were placed in a 2 l round bottom flask (RBF) and stirred at room temperature. A solution of $NaIO_4$ (8.56g, 4 eq) dissolved in 800 mL of H_2O was then added and the mixture was allowed to stir for 2 days with occasional shaking. The organic and aqueous phases were separated and filtered to remove any rhuthenium oxide. The aqueous phase was saturated with NaCl and extracted with ethylacetate (3 X 400 mL). The organic layer was dried ($MgSO_4$) and rotovaped to dryness to yield 11.0g (70% yield) of **19** as a white crystalline solid, which was used without further purification: mp 114°C (lit.[27] mp 114 °C); ^1H NMR (200 MHz, $CDCl_3$) δ: 1.80-2.10 (m, 6H), 1.20-1.36 (m, 2H), 2.80-3.05 (m, 2H);

CIMS (ether) m/e (relative intensity): 233 (23), 215 (32), 158 (100), 149 (100), 141 (62), 125 (26).

(1R,3S)-1,3-Bis(hydroxymethyl)-cyclopentane (20).

A solution of 6.0 g (0.038 mmol) of 1,3-cyclopentanedicarboxylic acid[4] in 100 mL of dry THF was added dropwise over 40 min to 3.16 g (2.2 eq) of $LiAlH_4$ in 100 mL of dry THF under nitrogen. The reaction mixture was then refluxed for 3 h, cooled to room temperature and treated sucessively with 3.16 mL of H_2O ; 3.16 mL of 15% NaOH and 9.6 mL of H_2O. The precipitate was filtered and the solvent was evaporated to give 4.63 g (93% yield) of **20** as a clear colourless liquid which was used without further purification: IR (CH_2Cl_2): 3614, 3435, 2903, 1029 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.09 (m, 2H), 1.32-1.40 (m, 2H), 1.70-2.0 (m, 4H), 2.05-2.20 (m, 2H), 3.05 (d, 4H, J= 13.3 Hz); CIMS (ether) m/e (relative intensity): 205 (4.3), 131 (1.2), 94 (11.6), 81 (77), 79 (38), 67 (100), 41 (56).

(1R,5S)-3-Thiabicyclo[3.2.1]octane (22).

Compound **20** (3.48 g, 0.27 mole) was placed in 200 mL of CH_2Cl_2 and cooled to 0°C. 8.21 mL (2.2 eq) of distilled triethylamine was added to the emulsion and the reaction mixture became homogeneous. A solution of 4.55 mL of methanesulfonyl chloride (2.2 eq) in 50 mL of CH_2Cl_2 was added and the solution stirred for 3 h at 0°C. The reaction mixture was then washed with 2 X 60 mL of 10% HCl. Further workup afforded 6.68 g (76%) of (1R,3S)-Di-O-Methanesulfonyl-1,3- bis(hydroxymethyl)cyclopentane (**21**) as an oil which solidified on standing overnight to a pale white solid: IR (CH_2Cl_2): 2921, 1350, 1176, 955, 836 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.04 (m, 1H), 1.40 (m, 2H), 1.80 (m, 2H), 2.05 (m, 1H), 1.35 (m, 2H), 2.97 (s, 6H), 4.10 (q, 4H); EIMS m/e (relative intensity): 284 (3.3), 111 (31), 94 (70), 81 (95), 79 (100), 67 (37), 41 (29). The compound was used in the next

step without further purification.

To a refluxing solution of 120 mL of 3:1 ethanol-H_2O containing 3.31 g (1.0 eq) of $Na_2S.9H_2O$ was added 3.31 g (1.0 eq) of $Na_2S.9H_2O$ dissolved in 30 mL of water and 3.71 g (0.013 mole) of **21** dissolved in 150 mL of hot ethanol. The addition was performd dropwise over 2 h and reflux was continued for another 30 min. After addition of 130 mL of H_2O a steam distillation was performed. H_2O (300 mL) was added to the distillate and the white precipate which was produced was extracted with hexanes (3 X 200 mL), dried with $MgSO_4$ and evaporated to dryness to give 1.35g (82% yield) of sulfide **22** as a white solid: mp 174 °C (lit.[28] mp 174°C); ^1H NMR (200 MHz, $CDCl_3$) δ: 1.60 (bd, 1H, J=20 Hz), 1.50-1.64 (m, 1H), 1,68-1.90 (m, 4H), 2.18 (dm, 2H, J=14.0 Hz), 2.40 (bs, 2H), 2.90 (bd, 2H, J=14.0 Hz); ^{13}C NMR (200 MHz, $CDCl_3$) δ: 29.3, 35.1, 35.5, 38.5; EIMS m/e (relative intensity): 128 (92), 113 (31), 80 (100), 79 (63), 67 (100), 66 (51), 41 (51).

Exo-(1R,5S)-3-thiabicyclo[3.2.1]octane-3-oxide (16).

A solution of 1.1 g (8.6 mole) of sulfide **22** in 20 mL of 95% ethanol was placed in a 50 mL round bottom flask which was then cooled to -15°C. A solution of MMPP (2.34 g, 0.55 eq) in 20 mL of H_2O was added slowly via a dropping funnel. The solution was allowed to warm up to room temperature over 24 hours. The ethanol was evaporated and 5 mL of $NaHCO_3$ and 5 mL of brine were then added and the aqueous layer extracted with ethylacetate (4 X 20 mL). The organic layer was dried ($MgSO_4$) and evaporated to dryness. The product **16**, sublimed at 90-110°C/1 Torr to give 900 mg (75% yield) of white crystals: mp 196 °C; IR (CH_2Cl_2): 2946, 1436, 1032 (S=O) cm^{-1}; ^1H NMR (300 MHz, benzene d_6) δ: 0.73-0.87 (m, 1H), 1.0 (bd, 1H, J=12 Hz), 1.16 (bs, 4H), 1.74 (bs, 2H), 2.18 (d, 2H, J=12 Hz), 2.94 (dm, 2H, J=12 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 28.9, 34.9, 38.7, 58.5; EIMS m/e (relative intensity): 144 (34), 127 (41), 93 (19), 81 (100), 79 (45), 67 (34). HRMS caldc. for $C_7H_{12}OS$ (M+) 144.0609, found 144.0620.

Endo-(1S,5R)-3-thiabicyclo[3.2.1]octane-3-oxide (17).

Solid $(CH_3)_3OBF_4$ (399 mg, 2.7 mmol) and a solution of 2.7 mmol of **16** in 15 mL of CH_2Cl_2 were allowed to react until all of the $(CH_3)_3OBF_4$ had dissappeared. The solution was filtered and 20 mL of ether was added, which produced a white precipate. The precipitate compound **23**, was filtered off and isolated as a white solid in 80% yield: ^1H NMR (200 MHz, $CDCl_3$) δ: 1.70 (m, 3H), 2.00 (m, 3H), 2.87 (m, 2H), 3.45 (d, 2H, J=13.3 Hz), 4.03 (s, 3H), 4.18 (dd, 2H, J=13.0, 6.6 Hz).

Compound **23** (590 mg, 2.4 mmol) was dissolved in 5 mL of 15% NaOH solution and allowed to stir at room temperature for 3 h. Usual workup and extraction (4 X 15 mL) with EtOAc afforded 280 mg (82% yield) of white crystals. GC analysis showed that the product was a 80:20 mixture of **17** to **16**. Separation on silica gel with dioxane:toluene (10:1), gave the axial sulfoxide **17** as a white crystalline solid (mp 210°C) which sublimed at 90-110°C/1 Torr: IR (CH_2Cl_2): 1028 (S=O) cm^{-1}; ^1H NMR (200 MHz, benzene d_6) δ: 0.82 (bd, 1H, J=13.3 Hz), 1.20 (m, 2H), 1.52 (m, 2H), 1.93 (bs, 2H), 2.04 (bd, 2H, J=16.0 Hz), 2.60 (bd,2H, J=16 Hz), 2.70 (qq, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 28.3, 33.4, 37.2, 54.4; EIMS m/e (relative intensity): 144 (30), 127 (45), 81 (100), 79 (55.3), 67 (33.6), 41 (39.3), 39 (35.7). HRMS calcd for $C_7H_{12}OS$ (M+) 144.0609, found 144.0620.

Deuterations:

The deuterations of all four parent sulfoxides **4**, **15**, **16** and **17** were carried out as follows; 0.5 mmole of the desired sulfoxide was placed in a flame dried flask under nitrogen atmosphere and dissolved in 5 mL of dry THF. This solution was then cooled to -30°C and 1.2 eq of methyllithium was added and the solution stirred for 10 min. CH_3COOD (1.5 mL) was then added and the reaction mixture allowed to slowly warm to room temperature. Water (5 mL) was added, the aqueous phase separated and extracted

with ethyl acetate (3 X 10 mL). The combined organic phases were dried ($MgSO_4$) and evaporated to dryness to give the appropriate deuterated sulfoxide (yields varied from 25-92%). [N.B.- if too large a volume of water is used, the yield of deuterated sulfoxide is substantially decreased because of the high solubility of the sulfoxide in aqueous media.]

^1H NMR's were all taken on a 300 MHz Varian XL spectrometer using $CDCl_3$ or benzene d_6 (for sulfoxides **16** and **17**). The regio and stereochemistry of deuterium incorporation was determined by comparison with the ^1H NMR of the parent sulfoxide.

(1R,3S,4R,5S)-(+)-4-(1-methyl-ethan-1-ol)-1,8,8-trimethyl-3-thiabicyclo-[3.2.1]-octane -3-oxide (24).

Sulfoxide **4** (93 mg, 0.5 mmol) was dissolved in THF (5 mL) and placed in a flame dried 25 mL round bottom flask under nitrogen. This was cooled to -10°C and 1.2 eq of methyllithium was added and the solution stirred for 45 min. Reagent grade acetone (1.2 eq) was then added via syringe and the solution stirred for 2 min after which time the reaction mixture was slowly warmed up to room temperature. Following treatment with sat. NH_4Cl, extraction with ethylacetate (3 X 15 mL) and drying with $MgSO_4$, the solution was evaporated under reduced pressure to give a yellow oil. The crude product was purified on silica using hexane:ethylacetate (1:1) to give 36 mg of a yellow oil (50% yield based on 38% recovered starting material): IR (CH_2Cl_2): 2930, 1140, 1010 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.85 (s, 3H), 0.98 (s, 3H), 1.21-1.35 (m, 1H), 1.30 (s, 3H), 1.52 (s, 3H), 1.58 (s, 3H), 1.60-1.78 (m, 2H), 2.08-2.21 (m, 2H), 2.30-2.38 (dd, 1H, J=6.0, 3.0 Hz), 3.04 (d, 1H, J=8.0 Hz), 3.15 (d, 1H, J=8.0 Hz), 3.36 (d, 1H, J=3.0 Hz), 5.23 (br. s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 20.7, 21.1, 25.3, 28.6, 29.8, 33.8, 35.4, 41.9, 45.3, 48.5, 58.6, 67.5, 74.1.

(1R,3R,4S,5S)-4-benzyl-1,8,8-trimethyl-3-thiabicyclo[3.2.1]octane-3-oxide (25).

A solution of 120 mg (0.65 mmol) of **15** in dry THF was cooled under nitrogen to -20°C using a NaCl/ice bath and reacted with 1.2 eq of methyllithium for 30 min, after which time the reaction was cooled to -78°C. After 15 min, 0.39 mL (5 eq) of benzyl bromide was added by syringe and stirring continued for 3 h at -78°C. The solution was then allowed to warm to room temperature overnight and 10 mL of H_2O and 20 mL of ether were added: The organic layer was separated and the aqueous layer was further extracted with dichloromethane (2 X 30 mL). Purification of the product on silica gel with hexanes:*t*-butanol (85:15) gave 59 mg of **25** (60% yield, based on 30% recovered starting material) as a colourless crystalline solid, mp 122 °C; IR (CH_2Cl_2): 2920, 1472, 1032 cm^{-1}; ^1H NMR (75 MHz, $CDCl_3$) δ: 0.99 (s, 3H), 1.09 (s, 3H), 1.50-1.68 (m, 1H), 1.90-2.06 (m, 2H), 2.26-2.60 (m, 2H), 2.78-2.94 (m, 2H), 3.06 (dd, 2H, J=13.9, 2.6 Hz), 3.30 (dd, 1H, J=14.1, 11.1), 7.14-7.36 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 18.8, 19.0, 25.3, 26.3, 29.9, 30.7, 43.8, 44.2, 46.7, 50.2, 64.1, 126.5, 128.4, 129.7, 138.6; CIMS (ether) m/e (relative intensity): 277 (77), 261 (17), 149 (100), 75 (100), 59 (100), 29 (62).

(1R,3R,4S,5S)-4-(1-methyl-ethan-1-ol)-1,8,8-trimethyl-3-thiabicyclo-[3.2.1]octane-3-oxide (26).

A solution of 120 mg (0.65 mmol) of **15** was dissolved in 5 mL of dry THF at -10°C and allowed to react with 1.2 eq of methyllithium for 45 min, after which time 0.60 mL (1.2 eq) of distilled reagent grade acetone was added. After stirring the solution for 2 min the mixture was slowly warmed up to room temperature. Work up consisted of adding 10 mL of EtOAc and washing with sat. NH_4Cl (2 X 30 mL), drying with $MgSO_4$ and evaporating the solvent under reduced pressure. Usual workup afforded a yellow oil, which was purified by column chromatography with hexanes:acetone (2:1), to give 66 mg of **15** as a colourless oil (54% yield, based on 23% recovered starting material): IR (CH_2Cl_2): 2929,

1381, 1137, 996 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.81 (s, 3H), 0.97 (s, 3H), 0.99 (s, 3H), 1.32 (s, 3H), 1.63 (s, 3H), 1.72-1.94 (m, 2H), 2.26-2.38 (m, 2H), 2.44 (bs, 1H), 2.74 (d, 1H, J=15.3 Hz), 2.92-3.01 (m, 2H), 3.80 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.0, 20.7, 22.7, 25.0, 28.7, 30.8, 25.0, 42.7, 44.2, 46.5, 58.1, 59.5, 74.6; EIMS m/e (relative intensity): 244 (1.8), 227 (11.1), 209 (30.1), 169 (61), 209 (61), 59 (72), 43 (100), 41 (82). HRMS calcd for $C_{13}H_{24}O_2S$ (M+) 244.1498, found 244.1490.

(1R,2R,3S,5S)-2-benzyl-3-thiabicyclo[3.2.1]octane-3-oxide (27).

Compound **16** (150 mg, 1.04 mmol) in 5 mL of THF and cooled to -78°C. 1.2 eq of methyllithium was added and the solution was stirred for 1 h, after which time 0.62 mL (5 eq) of benzyl bromide was added. The solution was stirred at -78°C for another 3 h, then allowed to warm up to toom temperature slowly. The resulting yellow solution was evaporated to dryness and the crude product was purified on silica gel with acetone:toluene (1:1) to give 75 mg (60% yield based on 49% recovered starting material) of **27** as a yellow crystalline solid: mp 146°C; IR (CH_2Cl_2): 2929, 2873, 1494, 1458, 1032 (S=O) cm^{-1}; ^1H NMR (300 MHz, benzene d_6) δ: 0.60 (m, 1H), 1.20 (m, 4H), 1.45 (d, 1H, J=18.0 Hz), 1.75 (m, 1H), 1.94 (m, 1H), 2.25 (d, 1H, J=13.3 Hz), 2.40 (dd, 1H, J=14.0, 5.0 Hz), 2.70 (dd, 1H, J=13.3, 6.6 Hz), 3.05 (m, 1H), 3.70 (dd, 1H, J=14.0, 3.3 Hz), 7.00-7.20 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 27.7, 28.3, 28.5, 31.3, 34.3, 36.8, 53.5, 61.8, 126.3, 128.6, 128.8, 138.8; EIMS m/e (relative intenstiy): 234 (5), 217 (29), 171 (27), 129 (14), 91(100), 87 (0.8). HRMS calcd for $C_{14}H_{18}OS$ (M+) 234.1079, found 234.1089.

(1S,2R,3R,5S)-2-benzyl-3-thiabicyclo[3.2.1]octane-3-oxide (28).

110 mg (0.76 mmol) of **17** in 5 mL of dry THF at -78 °C was reacted with 1.2 eq of methyllithium. The reaction mixture was stirred for 1 hour, after which time, 0.45 mL (5 eq) of benzyl bromide was added. The mixture was stirred for an additional 3 h at -78°C

and then allowed to slowly warm up to room temperature. Usual workup followed by purification on silica gel with acetone:toluene (1:1) gave 72 mg of **28**, as a yellow oil (62% yield based on 38% recovered starting material): IR (CH_2Cl_2): 1027 (S=O) cm^{-1}; ^1H NMR (500 MHz, benzene d_6) δ: 1.00 (m, 1H), 1.30 (bd, 1H, J=10.8 Hz), 1.57 (m, 2H), 2.03 (m, 2H), 2.22 (dd, 1H, J=13.5, 6.48 Hz), 2.34 (br. d, 1H, J=13.3 Hz), 2.62 (m, 3H), 2.68 (dd, 1H, J=13.5, 6.48 Hz), 3.05 (m, 1H), 6.90-7.20 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 27.1, 28.8, 31.0, 32.2, 36.1, 37.0, 52.0, 66.7, 126.3, 128.8, 129.0, 138.0; EIMS m/e (relative intensity): 234 (1.2), 217 (15.2), 171 (13), 91 (100), 77 (9), 28 (41). HRMS calcd for $C_{14}H_{18}OS$ (M+) 234.1079, found 234.1069.

(1S,2R,5S)-2-benzyl-3-thiabicyclo[3.2.1]octane-3,3-dioxide (29).

A solution of 39 mg (0.17 mmol) of sulfoxide **27** or **28** was dissolved in 4 mL of ethanol and 49 mg (0.6 eq) of MMPP in 4 mL of H_2O was added and the solution was stirred for two days at room temperature. Addition of 8 mL of sat. $NaHCO_3$ and 2 mL of hexanes followed by the usual workup afforded 4.4 mg (95% yield) of **29** as a white solid: mp 132 °C; IR (CH_2Cl_2): 2942, 1301, 1178, 1115, 1084 cm^{-1}; ^1H NMR (500 MHz, benzene d_6) δ: 0.72 (m, 1H), 1.20 (m, 3H), 1.73 (bs, 1H), 1.96 (bs, 1H), 2.08 (m, 2H), 2.46 (t, 1H, J=10 Hz), 2.60 (m, 2H), 3.04 (d, 1H, J=12.5 Hz), 3.50 (dd, 1H, J=12.5, 4.2 Hz), 7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 137.2, 129.1, 128.9, 126.9, 71.2, 59.9, 37.0, 35.4, 34.8, 31.1, 28.6, 26.8; EIMS m/e (relative intenisty): 250 (6.9), 184 (29.6), 169 (6.2), 143 (13.4), 129 (19.0), 117 (41.2), 104 (23.2), 91 (100), 81 (35.3), 67 (16), 41 (16). HRMS calcd for $C_{14}H_{18}O_2S$ (M+)250.1028, found 250.1014

Bis-1,1-diphenyl(1,1-dioxy-2,5-thiolanyl)carbinol (39).

Sulfolane (3.0 g, 2.38 ml, 0.025 mole) was placed in a 250 mL flame dried round bottom flask (RBF) and 50 mL of dry THF were added and the solution cooled to -78 °C

under a nitrogen atmosphere. Butyllithium was added (28.0 mL, 2.0 eq) and the reaction mixture was allowed to stir at low temperature for 2 min after which time benzophenone (9.1 g, 2.0 eq) dissolved in dry THF was added and the reaction mixture allowed to warm to room temperature. Acidification with 10% HCl produced a precipitate which was removed by filtration and recrystallized from $CHCl_3$ to produce 3.0 g (25% yield) of adduct **39** as a white solid: mp 312 °C (lit.[36] mp 312-313 °C); IR (CH_2Cl_2): 3410, 1120, 1036 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.71 (m, 2H), 2.30 (m, 2H), 4.26 (m, 2H), 4.45 (s, 2H), 7.10-7.60 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.3, 70.2, 124.7, 124.8 (2), 125.6, 125.7, 127.0, 127.6, 127.7, 128.1, 128.3, 128.4 (2), 129.9 (2), 143.9, 144.0; CIMS (ether) m/e (relative intensity): 467 (M^+-H_2O, 17), 449 (59), 403 (21), 385 (10), 285 (90), 181 (31), 149 (100).

Bis-1,1-diphenyl-2,5-thiolanyl-carbinol (40).

Compound **39** (1.0 g, 0.0021 mole) was added to 40 mL of TFA. After stirring at room temperature for 2 min, triethylsilane (0.84 mL, 2.5 eq) was added and the reaction mixture stirred for 4 h after which time the solution was neutralized with a saturated solution of $NaHCO_3$. The aqueous phase was extracted with 3 X 60 mL of CH_2Cl_2 and dried with $MgSO_4$. Evaporation of the solvent produced 616 mg (65% yield) of compound **40** as a white solid: mp 224 °C; IR (CH_2Cl_2): 1115, 1034 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.50 (m, 4H), 4.00 (m, 2H), 4.25 (d, 2H), 7.10-7.40 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 28.0, 52.0, 66.5, 127.0, 127.7, 127.8, 128.2, 128.3, 128.4, 128.5, 128.5, 140.3, 141.7; CIMS (ether) m/e (relative intensity) 453 (98), 193 (13), 167 (34), 149 (100); Anal. Calcd for $C_{30}H_{28}O_2S$: C, 79.61; H, 6.23. Found: C, 79.56; H, 6.41.

Bis-(1,1-diphenyl-dehydro)-2,5-thiolanyl-carbinol (42).

Compound **39** (250 mg, 0.51 mmole) and 120 mg of TsOH were dissolved in 25 ml of

toluene and refluxed for 5 h. The solution was cooled in an ice bath, washed with 2 X 15 mL of saturated $NaHCO_3$. The organic solvent was evaporated to furnish 168 mg (74% yield) of **42** as a white solid: mp 231 °C; IR (CH_2Cl_2): 1005, 1025 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 2.92 (s, 4H), 7.10-7.45 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.9, 127.8, 128.2, 128.3, 128.5, 128.6, 129.5, 137.3, 138.3, 140.3, 146.1; EIMS m/e (relative intensity):448 (55), 400 (32), 192 (100). HRMS calcd for $C_{30}H_{24}O_2S$ (M^+) 448.1491, found 448.1470.

2,6-Dichloro-9-thiabicyclo[3.3.1]nonane (45).

1,5-Cyclooctadiene (23.7 mL, 0.194 mole) was added via syringe to a 250 ml RBF containing 100 mL of dry CH_2Cl_2 which had been previously cooled to -70 °C under a nitrogen atmosphere. A solution of SCl_2[58] in 60 mL of CH_2Cl_2 was then added dropwise to the above solution via a dropping funnel over a period of 1 h. The reaction mixture was then warmed to room temperature. Evaporation of the solvent produced a pale yellow solid which was recrystallized from CH_2Cl_2 to produce 33 g (80% yield) of compound **45** as a white solid: mp 101-102 °C (lit.[57] mp 101-102 °C); ^1H NMR (200 MHz, $CDCl_3$) δ: 2.10-2.41 (m, 6H), 2.63 (m, 2H), 2.84 (m, 2H), 4.70 (m, 2H); EIMS m/e (relative intensity): 210 (23), 175 (100), 139 (24), 105 (30). HRMS calcd for $C_8H_{12}SCl_2$ (M^+) 210.0035, found 210.0062.

9-Thiabicyclo[3.3.1]nonane (46).

$LiAlH_4$ (0.91 g, 0.024 mole) was added to 20 mL of dry THF in a 250 mL flame dried RBF under nitrogen. This was followed by the dropwise addition of a solution of 5 g (1.0 eq) of **45** in 60 mL of THF over the period of 1 h. When the addition was complete the reaction mixture was refluxed for 1.5 h and then cooled to room temperature. Excess $LiAlH_4$ was destroyed by the successive addition of 0.9 mL of H_2O, 0.9 mL 15% NaOH

and 2.7 mL of H_2O. The heterogeneous solution was filtered and the solvent was evaporated to produce a white solid which was purified by recrystallization from MeOH to produce 2.85 g (84% yield) of **46** as a white solid: mp 170 °C (lit.[57] mp 170-171 °C); ^1H NMR (200 MHz, $CDCl_3$) δ: 1.51-2.30 (m, 12H), 2.80 (bs, 2H); EIMS m/e (relative intensity): 142 (69), 113 (33), 101 (68), 87 (100), 67 (61). HRMS calcd for $C_8H_{14}S$ (M^+) 142.0813, found 142.0824.

9-Benzyl-9-thianiumbicyclo[3.3.1]nonane bromide (47).

In a 25 mL RBF was placed 200 mg (1.4 mmole) of sulfide **46** and 0.84 mL (5.0 eq) of benzyl bromide. 5 mL of CH_3CN was added and the solution was refluxed for 16 h after which time copious amounts of a white precipitate was visible. The reaction mixture was cooled to room temperature and 15 mL of ether was added and the precipitate was removed by filtration. The precipitate which was subsequently identified as compound **47** was obtaine in 97% yield as a white crystalline solid and was used without further purification: mp 188 °C ; IR (CH_2Cl_2): 2980, 1670, 1002 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.72-3.60 (m, 14H), 4.00 (bs, 2H), 7.30-7.70 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.0, 20.3, 22.5, 30.0, 39.3, 40.3, 127.4, 129.6, 129.8, 130.3; FAB-MS (glycerol) m/e (relative intensity): 544 ($C_2^+Br^-$, 4), 233 (C^+, 89), 185 (63), 141 (29).

***Trans*-(+/-)-stilbene oxide (48).**

Compound **47** (200 mg, 0.64 mmole) was dissolved in 5 mL of CH_2Cl_2 and placed in a 25 mL RBF. 50% NaOH (2 mL), 30 mg of N-benzyltriethylammonium chloride and 0.07 mL (1.1 eq) of freshly distilled benzaldehyde were subsequently added to the solution and the reaction mixture was stirred at room temperature for 24 h at which time TLC revealed that all of the benzaldehyde had been consumed. The organic layer was seperated and the aqueous layer was extracted with 3 X 10 mL of ether. All organic layers were combined

and the solvent evaported. Epoxide **48** was isolated in 76% yield via column chromatography using Hexanes:EtOAc (25:1) as a pale yellow solid: mp 68 °C (lit.[61] mp 69 °C); ^{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 (50), 195 (45), 178 (23), 167 (100), 152 (18), 105 (18), 90 (87), 89 (83): $[\alpha]_D^{23}$ 0.0 ° (c 1.08, CH_2Cl_2); HRMS calcd for $C_{14}H_{12}O$ (M^+) 196.0888, found 196.0870.

9-Isopropyl-9-thianiumbicyclo[3.3.1]nonane iodide (49).

Sulfide **46** (600 mg, 4.2 mmole), isopropyl iodide (4.2 mL, 10.0 eq) and 10 mL of CH_3CN were combined in a 50 mL RBF and refluxed for 2 days. After cooling the reaction mixture to room temperature, 40 mL of ether were added and the resulting precipitate was removed by filtration. The precipitate was recrystallized from ether/CH_2Cl_2 to produce 458 mg (35% yield) of **49** as a white crystalline solid: mp 201-202 °C; IR (CH_2Cl_2): 2939, 1486, 918 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.55 (d, 6H), 1.90-2.51 (m, 12H), 3.90 (bs, 2H), 4.45 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.1, 18.1, 19.9, 20.1, 23.8, 34.8, 39.7, 40.1; FAB-MS (glycerol) m/e (relative intensity): 682 ($C_3^+I^-$, 3.4), 497 ($C_2^+I^-$, 57), 185 (C^+, 100), 143 (52).

9-Isopropyl-9-thianiumbicyclo[3.3.1]nonane tetraphenylborate (50).

In a 250 mL round bottom flask (RBF), 1 g (3.2 mmole) of compound **49** was dissolved in 40 mL of H_2O and 1.09 g (1.0 eq) of sodium tetraphenylborate was added and the mixture was stirred for 30 min at room temperature. The precipitate which formed was filtered off and recrystallized from acetone/ether to produce 1.08 g (67% yield) of compound **50** as a white crystalline solid: mp 300 °C; IR (CH_2Cl_2): 2254, 912, 650 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.10-2.60 (m, 12H), 2.80 (d, 6H, J= 6.0 Hz), 4.03 (bs, 2H), 4.28 (m, 1H); ^{13}C NMR (75 Hz, $CDCl_3$) δ: 17.2, 18.3, 19.7, 21.0, 24.6, 34.6, 39.4, 40.2,

126.2, 126.4, 128.0, 128.3, 128.5, 131.7, 134.6, 136.5, 140.6; FAB-MS (glycerol) m/e (relative intensity): 185 (C^+, 100), 137 (31).

9-(*n*-Butyl)-9-thianiumbicyclo[3.3.1]nonane iodide (52).

Sulfide **46** (500 mg, 3.5 mmole), 4.0 mL (10 eq) of iodobutane and 10 mL of CH_3CN were combined in a 25 mL round bottom flask (RBF) and refluxed for 24 h. After cooling the reaction mixture to room temperature, 20 mL of ether were added and the resulting precipitate was removed by filtration. The precipitate was recrystallized from CH_2Cl_2/ether to produce 570 mg (50% yield) of compound **52** as a white crystalline solid: mp 214 °C; IR (CH_2Cl_2): 2840, 850, 660 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.01 (t, 3H, J=6.3 Hz), 1.80-2.43 (m, 16H), 3.72 (t, 2H, J=6.5 Hz), 4.01 (bs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.6, 17.7, 20.0, 21.9, 22.2, 25.9, 29.8, 34.2, 40.5; FAB-MS (glycerol) m/e (relative intensity): 525 ($C_2{}^+I^-$, 40), 199 (C^+, 100).

9-(*n*-Butyl)-9-thianiumbicyclo[3.3.1]nonane tetraphenylborate (53).

In a 50 mL round bottom flask (RBF), 100 mg (0.31 mmole) of compound **52** was dissolved in 5 mL of H_2O and 106 mg (1.0 eq) of sodium tetraphenylborate was added and the reaction mixture stirred at room temperature for 15 min. The precipitate which formed almost immediately was filtered off and recrystallized from acetone/ether to produce 108 mg (68% yield) of **53** as a white crystalline solid: mp 237 °C; IR (CH_2Cl_2): 1502, 1006, 690 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.97 (t, 3H, J=6.2 Hz), 1.52-2.60 (m, 16H), 3.57 (t, 2H, J=6.2 Hz), 3.90 (bs, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 14.0, 17.8, 20.2, 22.4, 25.8, 30.1, 31.8, 37.2, 40.2, 126.1, 126.8, 128.0, 128.3, 128.5, 131.5, 134.3, 136.2, 140.1; FAB-MS (glycerol) m/e (relative intensity): 716 ($C_2{}^+BPh_4$, 2.3), 199 (C^+, 100).

REFERENCES

Part A: Lithiated Bicyclic Sulfoxides.

1. Morrison, R.; Boyd R. Organic Chemistry 5th edition; Allyn and Bacon Inc., London: **1987**, p 715.
2. Carey, F.; Sundberg, R. Advanced Organic Chemistry 3rd edition Part B; Plenum Press, New York, **1990**, p 633.
3. a) Oishi, T.; Nakata, T. *Synthesis*, **1990**, *8*, 635-45.
   b) Mori, Y.; Suzuki, M. *Tetrahedron Lett.*, **1989**, *30*, 4383-86.
4. Mori, Y.; Suzuki, M. *Tetrahedron Lett.*, **1989**, *30*, 4387-88.
5. Klunder, J.M.; Ko, S.Y.; Sharpless, B.K. *J. Org. Chem.*, **1986**, *51*, 3710.
6. a) Klunder, J.M.; Onami, T.; Sharpless, B.K. *J. Org. Chem.*, **1989**, *54*, 1295.
   b) *ibid. J. Org. Chem.*, **1984**, *54*,1295.
7. Katsuki, T.; Sharpless, B.K. *J. Am. Chem. Soc.*, **1980**, *102*, 5974.
8. Wu, Y.D.; Houk, K.N. *Chemtracts: Org. Chem.*, **1990**, *3*(5), 350.
9. Zhang, W.; Jacobsen, E.N. *J. Org. Chem.*, **1991**, *56*, 2296.
10. a) Corey, E.J.; Chaykovsky, M. *J. Am. Chem. Soc.*, **1962**, *84*, 3782.
    b) *ibid., J. Am. Chem. Soc.*, **1965**, *87*, 1353.
    c) *ibid., Tetrahedron Lett.*, **1963**, 169.
11. Furukawa, N.; Sugihara, V.; Fujihara, H. *J. Org. Chem.*, **1989**, *54*, 4222-24.
12. Breau, L.; Ogilvie, W.W.; Durst, T. *Tetrahedron Lett.*, **1990**, *31*, 35.
13. Kaiser, G.V.; Cooper, R.D.G.; Roehler, R.E.; Murphy, C.F.; Weber J.A.; Wright, I.G.; Van Heyningen, E.M. *J. Org. Chem.* **1970**, *35*, 2340-33.
14. Breau, L.; Durst, T. *Tetrahedron: Asymmetry*, **1993**, *2*, 367-70.
15. Allen, D.G.; Wild, S.B. *Organometallics*, **1983**, *2*, 394-99.
16. Ziffer, D.H.; Imuto, M. *J. Org. Chem.*, **1979**, *44*, 2505-09.

17. a) Johnson, A.W.; Hruby, V.J.; Willaims, J.L. *J. Am. Chem. Soc.*, **1964**, *86*, 918.

b) Vedejs, E.; Marth, C.F. *J. Am. Chem. Soc.*, **1988**, *110*, 3948 and references therein.

c) Durst, T.; Breau, L.; Ben, R.N. *Phosphorus, Sulfur and Silicon*, **1993**, *74*, 215-32.

18. Breau, L., Ph.D. Thesis, University of Ottawa, **1991**.

19. a) Solladie-Cavallo, A.; Abid, A. *Tetrahedron*, **1992**, *48*, 2453-64.

b) Solladie-Cavallo, A.; Abid, A.; Schmidt, M.; Fischer, J.; DeCian, A. *Tetrahedron: Asymmetry*, **1992**, *3*, 1597-1602.

20. Eliel, E.L.; Lynch, J.E.; Fumitaka, K.; Frye, S.U. *Org. Synth.*, **1987**, *65*, 215.

21. a) Chassaing, G.; Lett, R.; Marquet, A. *Tetrahedron Lett.*, **1978**, 471.

b) Chassaing, G.; Marquet, A. *Tetrahedron*, **1978**, *34*, 1399.

22. a) Bory, S.; Lett, R.; Moreau, B.; Marquet, A. *Tetrahedron Lett.*, **1972**, *48*, 4921.

b) Bory, S.; Marquet, A. *Tetrahedron Lett.*, **1973**, *42*, 4155.

23. a) Lavielle, S.; Bory, S.; Moreau, B.; Luche, M.J.; Marquet, A. *J. Am. Chem. Soc.*, **1978**, *100*, 1558-63.

b) Lett, R.; Bory, S.; Moreau, B.; Marquet, A. *Bull. Soc. Chim. Fr.*, **1973**, 2851.

24. Brougham, P.; Cooper, M.S.; Cummerson, D.A.; Heaney, H.; Thompson, N. *Synthesis*, **1987**, 1015-16.

25. Anderson, K.; Caret, R.; Karup-Nielsen, I. *J. Am. Chem. Soc.*, **1974**, *96*, 8026.

26. Durst, T., Comprehensive Organic Chemistry Vol. 3.; Pergamon Press, Oxford: **1979**, p 123.

27. Clark, R. *Org. Prep. Proced. Int.*, **1974**, *6*, 49-51.

28. Birch, S.F.; Dean, R.A. *Ann.*, **1954**, *585*, 234-40.

29. Fraser, R.R.; Durst, T.; McClory, M.R.; Viau, R.; Wigfield, Y.Y. *Internat. J. Sulfur Chem. (A)*, **1971**, *1*, 133.

30. Jackman, J.L.; Sternhell, S. Applications of NMR Spectroscopy in Organic Chem.,

2nd Ed.; Pergamon, New York: **1969**.

31. The structure of **27** was misassigned in an earlier conference proceeding; see reference # 17c.

32. See reference #26, p 121.

33. a) Rauk, A.; Wolfe, S.; Csizmadia, I.G. *Can. J. Chem.*, **1969**, *47*, 113.

b) Wolfe, S.; Rouk, A.; Csizmadia, I.G. *J. Am. Chem. Soc.*, **1969**, *91*, 1567.

34. a) Lett. R.; Chassaing, G. *Tetrahedron*, **1978**, *34*, 2705.

b) Waack, R.; Doran, M.A.; Baker, E.B.; Olah, G.A. *J. Am. Chem. Soc.*, **1966**, *88*, 1272.

c) Brooks, J.J.; Rhine, W.; Stucky, G.D. *ibid.*, **1972**, *94*, 7339.

35. Lett. R.; Chassaing, G.; Marquet, A. *J. Organometallic Chem.*, **1976**, *111*, C17.

36. Beillmann, J.F.; Vicens, J.J. *Tetrahedron Lett.*, **1974**, *34*, 2915.

37. Simpkins, N.S.; Cox, P.J.; Persad, A. *Synlett*, **1992**, *197*.

38. Wolfe, S.; Stolow, A.; LaJohn, L.A. *Tetrahedron Lett.* **1983**, *24*, 4071.

39. a) Boche, G. *Agnew. Chem. Int. Ed. Engl.*, **1989**, *28*, 277.

b) Marsch, M.; Massa, W.; Harms, K.; Baum, G.; Boche, G. *ibid.*, **1986**, *25*, 1011.

40. a) Corey, E.J.; Jautelat, M.; Oppolzer, W. *Tetrahedron Lett.*, **1967**, **24**, 2325-28.

b) Corey, E.J.; Oppolzer, W. *J. Am. Chem. Soc.*, **1964**, *86*, 1899.

c) Corey, E.J.; Jautelat, M. *J. Am. Chem. Soc.*, **1967**, *89*, 3912.

41. a) Trost, B.M.; Bogdanowicz, M.J. *J. Am. Chem. Soc.*, **1973**, *95*, 5321.

b) *ibid.*, 5298.

42. Meyers, A.I.; Romo, D. *Tetrahedron Lett.*, **1989**, *30*, 1745.

43. Kreif, A.; Lecomte, P., Demoute, J.P.; Dumont, W. *Synthesis*, **1990**, 275.

44. Kreif, A.; Dumont, W. *Tetrahedron Lett.*, **1988**, *29*, 1083-84.

45. McKee, S.; Breau, L.; Durst, T. unpublished results.

46. Van Tamelen, E.E.; Pedlar, A.D.; Li, E.; James, D.R. *J. Am. Chem. Soc.*, **1977**, *99*,

6778.

47. Truce, W.E.; Klingler, T.C. *J. Org. Chem.*, **1970**, *35*, 1834-38.

48. Gribble, G.W.; Leese, R.M. *Synthesis*, **1976**, 172-6.

49. Rylander, Catalytic Hydrogenation over Platinum Metals; Academic Press, New York: **1967**, 449-68.

50. Brieger and Nestrick *Chem. Rev.*, **1974**, *74*, 567-80.

51. Meyer *J. Chem. Educ.*, **1981**, *58*, 628.

52. Doyle; DeBruyn; Koorstra *J. Am. Chem. Soc.*, **1972**, *94*, 3659.

53. a) Witney, J.A.; Cram, D.J. *J. Org. Chem.*, **1970**, *35*, 3964.

b) Weber, W.; Stromquist, P.; Ito T.I. *Tetrahedron Lett.* **1974**, *30*, 2595.

54. Gardner, J.N.; Kaiser, S.; Krubiner, A.; Lucas, H. *Can. J. Chem.*, **1973**, *51*, 1419.

55. Handa, Y.; Inanaga, J.; Yamaguchi, M. *J. Chem. Soc. Chem. Commun.*, **1989**, 298.

56. a) Cannone, P.; Foscolos, G.; LeMay, G. *J. Chem. Soc. Chem. Commun.*, **1979**, 691.

b) Holtkamp, H.C.; Blomverg, C.; Bickelhaupt, F. *J. Organometallic Chem.*, **1969**, *19*, 279.

57. Weil, E.D.; Smith, K.J.; Gruber, R.J. *J. Org. Chem.*, **1966**, *31*, 1669.

58. SCl_2 was prepared according to the following procedure: Feher, F. Handbook of Prep. Inorganic Chem. Vol 1., 2nd ed., edited by Brauer, G.; Academic Press, New York: **1963**, p 370.

59. Lepley; Giumanin *Mech. Mol. Migr.*, **1971**, *3*, 297-440.

60. A typical procedure to exchange the I^- counterion with the BPh_4^- is as follows: The sulfonium salt **49** (1.0 g, 3.2 mmole) was placed in a 100 mL RBF and 40 mL of H_2O were then added. $NaBPh_4$ (1.09 g, 1.05 eq) was then added and the solution was stirred at room temperature for 30 min after which time the precipitate which formed was filtered off and dried. The crude product was recrystallized from acetone/ether to produce 1.08 g (67% yield) of sulfonium salt **50**.

Part B: The Synthesis of Optically Active α-Amino Esters via Kinetic Dynamic Resolution.

Chapter 1. Introduction:

1.1 The importance of amino acids.

Amino acids are important molecules which constitute the basic structural units of all proteins and enzymes and subsequently are found incorporated into many natural products. Since many of these natural products possess unusual pharmacological activity the chemistry involving amino acids has been studied for decades.

Today, amino acid chemistry is at the forefront of modern chemical science and finds applications in all disciplines such as biology, medicine, biochemistry and chemistry. Recent understandings of enzyme mechanisms, protein conformations and other properties related to molecular recognition have lead researchers to a greater understanding of many biological pathways and disease processes. This understanding combined with recent advances in molecular biology have necessitated the development of efficient asymmetric syntheses for both natural and unnatural α-amino acids which are utilized in the synthesis of new pharmaceuticals and other valuable materials.

The following sections will review only the most recent and interesting advances pertaining to the asymmetric synthesis of α-amino acids. Since there is a great deal of material on this subject in the literature, it is possible to describe only the more general approaches in the briefest of detail. There are however many excellent books and reviews which have been written on this subject.[1-3]

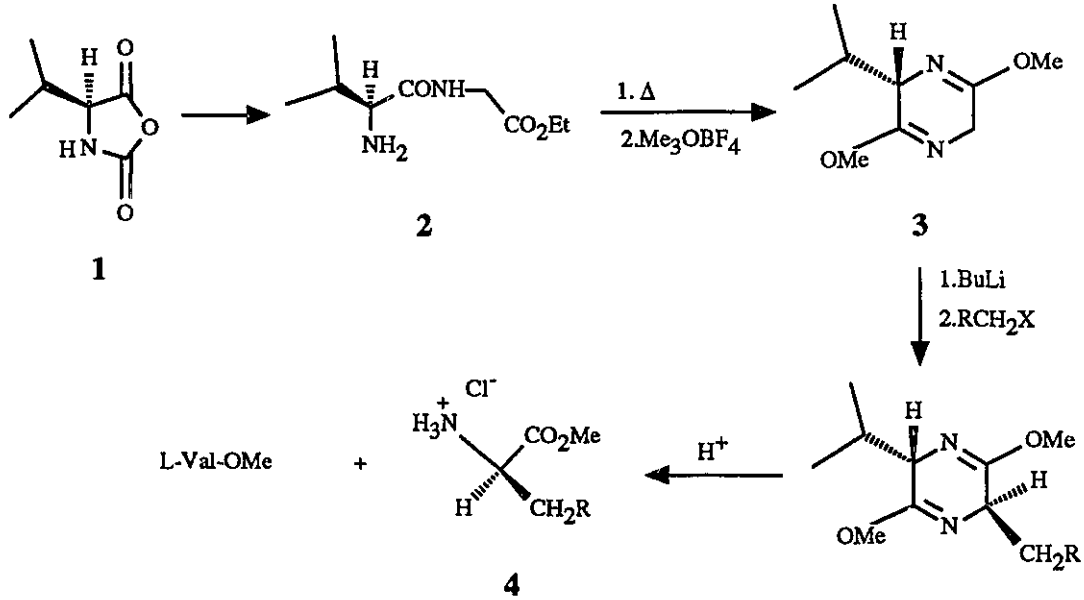
In order to facilitate review of the asymmetric synthesis of α-amino acids several different methodologies have been identified as outlined in the following section.

1.2 Asymmetric syntheses of α-amino acids.

A) Asymmetric derivatization of glycine.

This approach is based upon the fact that glycine, the simplest amino acid offers the greatest versatility for asymmetric derivatization. One of the more general protocols involves metallation of a bis-lactim ether followed by electrophilic quench to furnish the homologated bis-lactim ether which is then hydrolyzed under acidic conditions to yield the new amino ester.[4] Scheme 1 illustrates this process with the most frequently used bis-lactim ether derived from L-valine and glycine.[5] L-Valine was converted to the N-carboxyanhydride **1**, by treatment with $COCl_2$ and was then reacted with one equivalent of glycine to furnish **2**. Compound **2** was heated and then subjected to reaction with trimethyloxonium tetrafluoroborate to give the bis-lactim ether **3**. This ether was metallated with BuLi and the anion quenched with an appropriate electrophile to furnish the alkylated bis-lactim ether which was subsequently hydrolyzed with 0.25 N HCl resulting in the new amino ester **4** and L-valine methyl ester which could be recovered.

Scheme 1.

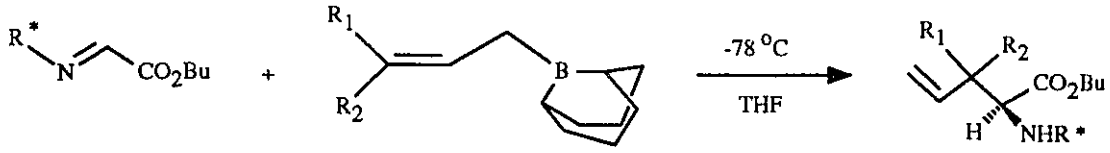


A wide variety of structural diversity is tolerated with respect to the nature of the

electrophile in these reactions and the desired amino esters are typically obtained in 55-90% yield with ee's of 65 to >95%. There are many variations of this reaction that utilize glycine enolates in conjunction with other directing groups such as imidazolidinones,[6] oxazolidinones,[7] oxazolines,[8] oxazinones[9] and transition metal complexes[10] but these will not be discussed since they are only variations of the same theme and all produce amino acids or esters in comparable yields and ee's.

It is also possible to synthesize optically pure amino acids using "glycine cation equivalents" and a chiral directing group. An excellent example of this was reported by Yamamoto et al.[11] who studied the additions of various allylic organometallic reagents to several chiral amines (Scheme 2). The N-protected amino esters were obtained in 75-94% yield and depending on the nature of the chiral directing group (R*) enantiomeric excesses of 80-96% were obtained.

Scheme 2.



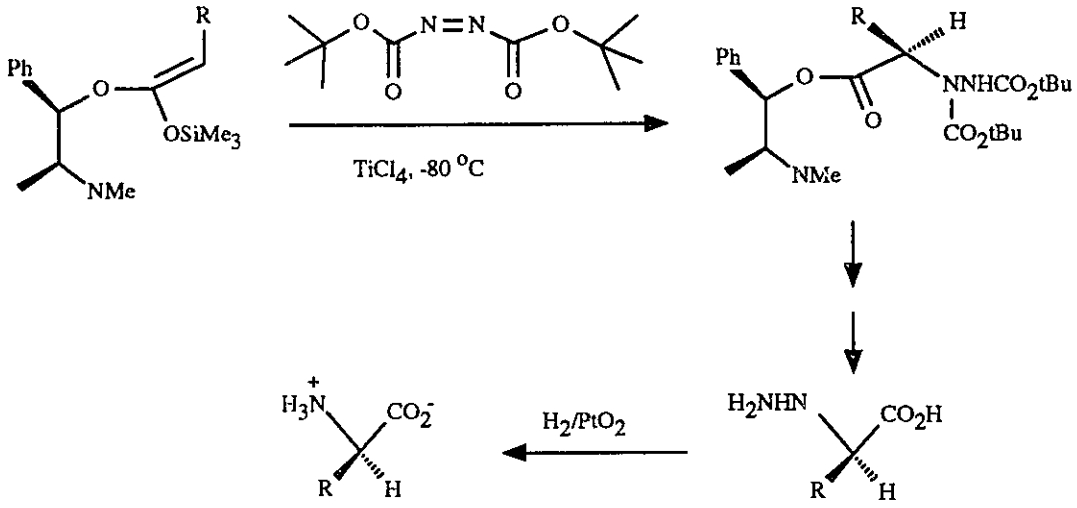
B) Electrophilic and nucleophilic amination of chiral enolates and α-substituted acids.

Electrophilic amination of chiral enolates is a very recent concept in the synthesis of α-amino acids. This is quite surprising since electrophilic amination of diethyl malonate with azodicarboxylates has been known since 1924.[12]

In 1986 Gennari and coworkers[13] condensed ketenesilyl acetals with di-*tert*-butylazodicarboxylate at -80 °C in the presence of $TiCl_4$ to afford the α-hydrazido adducts. Subsequent removal of the Boc groups via treatment with TFA followed by hydrolysis of the chiral auxiliary with LiOH and purification by ion-exchange column and

recrystallization furnished the α-hydrazino amino acids **5** in 78-85% yield with ee's >98%. The N-N bond was later cleaved with H_2 on a platinum catalyst to afford the α-amino acids.

Scheme 3.



5

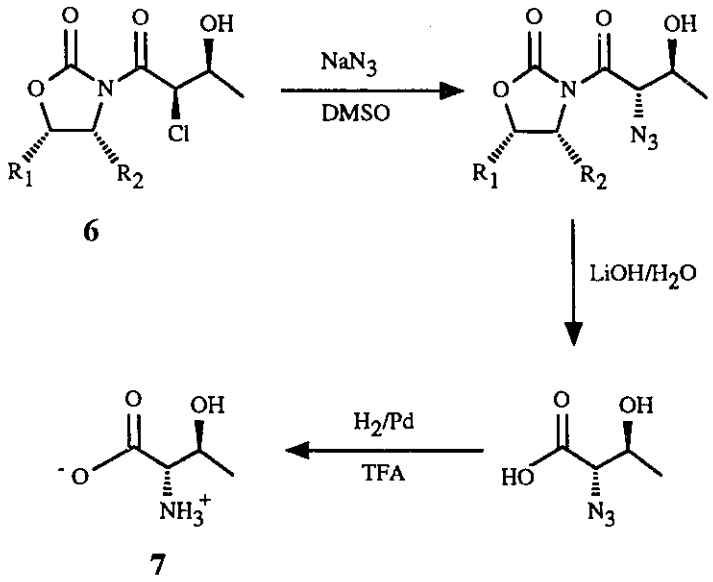
To date, many different chiral auxiliaries have been utilized with similar enolates including several of the Evans chiral carboximides[14] and the Oppolzer sulfamides.[15]

The chiral enolates have also been reacted with other sources of electrophilic nitrogen including benzenediazonium tetrafluoroborate[16] and 2,4,6-triisopropylbenzenesulfonyl azide[17]. In all cases comparable yields and ee's were obtained.

Nucleophilic amination of α-substituted acids involves the displacement of a leaving group α- to a carboxylic acid function resulting in optically active α-amino acids and α-amino acid derivatives. The best example to illustrate this methodology is an elegant synthesis of β-hydroxy-α-amino acids by Evans et al.[18] shown in Scheme 4. The α-halo amide **6**, obtained from a highly diastereoselective aldol condensation using di-n-butylboron triflate at low temperatures was isolated in 75-80% yield. Compound **6** was reacted with NaN_3 in DMSO to furnish the azide via a clean S_N2 displacement of the chloride ion. The chiral auxiliary was removed by reaction with $LiOH/H_2O$ in dioxane and subsequent

reduction of the azide using H_2/Pd in TFA furnished L-*allo*-threonine **7**, in 82% overall yield.

Scheme 4.

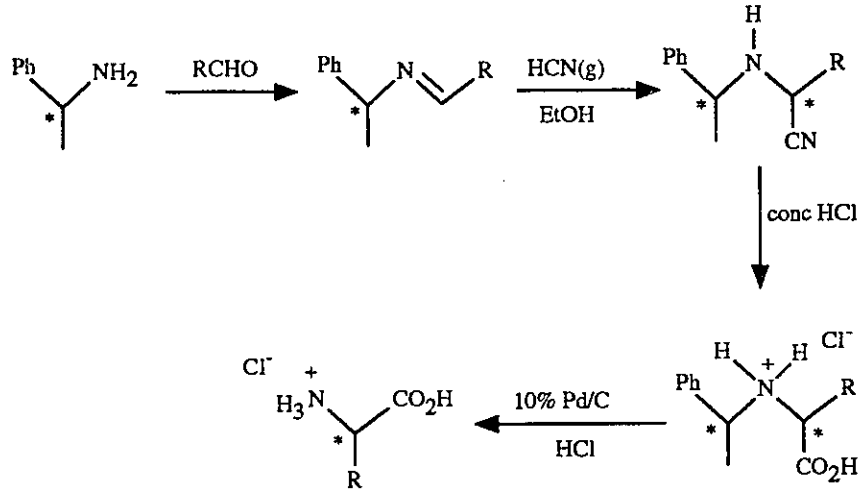


C) Asymmetric Strecker Synthesis.

Despite the fact that the Strecker Synthesis of α-amino acids has been known since 1850[19] and is recognized as one of the most convenient methods for the synthesis of amino acids on a preparative scale, there have been very few examples in the literature dealing with asymmetric versions of this reaction.

The general protocol[20] involves the condensation of an optically active amine with an aldehyde and subsequent addition of HCN or NaCN to the imine. The cyano group is then hydrolyzed under acid conditions yielding a carboxylic acid and the chiral auxiliary is removed as shown in Scheme 5. The ee's of this reaction are highly dependent upon the nature of the chiral auxiliary and range from 55-95%. Overall chemical yields vary from 20-70%.

Scheme 5.



D) Asymmetric hydrogenation of dehydroamino acids.

The asymmetric hydrogenation of dehydroamino acids is an extremely useful preparative approach to the synthesis of a variety of optically active α-amino acids. There exist two basic methodologies: heterogeneous hydrogenation of dehydroamino acids that contain an appended chiral auxiliary[21] and homogeneous hydrogenation of achiral dehydroamino acids using optically active, soluble hydrogenation catalysts.

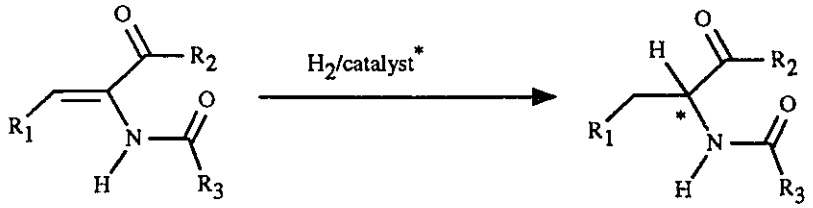
While both of these methodologies have found extensive use in the area of asymmetric synthesis, the latter has been studied and reviewed extensively. Consequently only the asymmetric hydrogenation of dehydroamino acids using optically active, soluble hydrogenation catalysts will be discussed here.

Modification of Wilkinson's hydrogenation catalyst with optically active phosphine ligands such as (S)-BINAP and (S,S)-CHIRAPHOS has lead to the development of new catalysts which undergo many different asymmetric reactions with very high selectivity.[22]

Work in this area done by Knowles et al.[23] at Monsanto lead to the development of a practical industrial synthesis for (S)-DOPA. As shown in Scheme 6, the reaction generally

involves the asymmetric reduction of Z-N-acylated dehydroamino acids to the corresponding amino acids with a cationic rhodium catalyst complexed to a chiral bisphosphine ligand. The ee's of the reduced products are dependent upon the nature of the chiral bisphosphine ligands and range from 87-95% however, the high ee's are generally restricted to the only the Z-isomers of the olefins. The reactions tend to be relatively insensitive to the nature of the R groups.

Scheme 6.



R_1=aryl

R_2,R_3=alkyl

E) Resolution of α-amino acid derivatives.

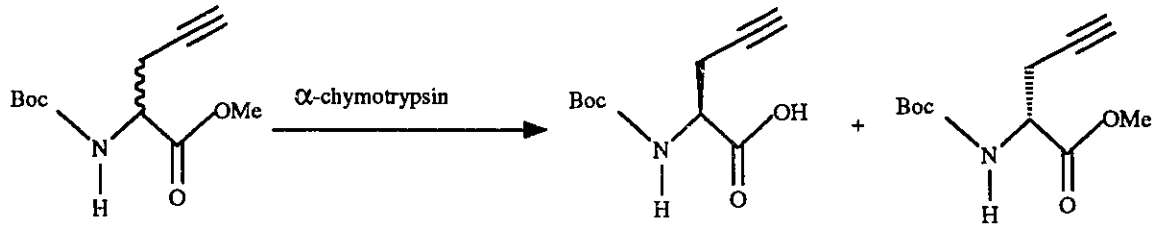
Racemic α-amino acid derivatives may be resolved under enzymatic or non-enzymatic conditions. This process is based upon the principle that one of the two enantiomers being resolved will react faster or slower than the other. In a kinetic or non-enzymatic resolution[24a] one enantiomer is often discarded and since many organic syntheses can be quite costly, kinetic resolutions are often avoided unless there exists no alternative asymmetric method which can be employed.

In contrast, the synthesis of α-amino acids using purified, immobilized, cell-free or whole cell systems has become an important commercial method to prepare amino acids on both large and intermediate scales.[24b] These reactions are very versatile in nature due to the fact that a great number of enzymes exist in biological systems. For example, there are

amidases, hydantoinases, acylases, esterases and nitrilases and each is capable of hydrolyzing or cleaving a very specific organic functional group. A typical example of this methodology is illustrated in Scheme 7.

Abood et al.[25] synthesized the racemic N-Boc protected α-amino ester **8** which was subjected to reaction with α-chymotrypsin (an esterase) in a phosphate buffer at pH 8 to afford N-Boc-L-propargylglycine (**9**) in 96% yield based on 50% conversion in 88% ee. After one recrystallization **9** was obtained in 67% yield and was enriched to 99% ee.

Scheme 7.



8 **9**

An attractive feature of these reactions is that the unreacted enantiomer of **8** could be recovered and epimerized to yield a racemate. This racemate could be reacted with the enzyme again and thus allow for yields greater than the 50% theoretical yield of the desired enantiomer.

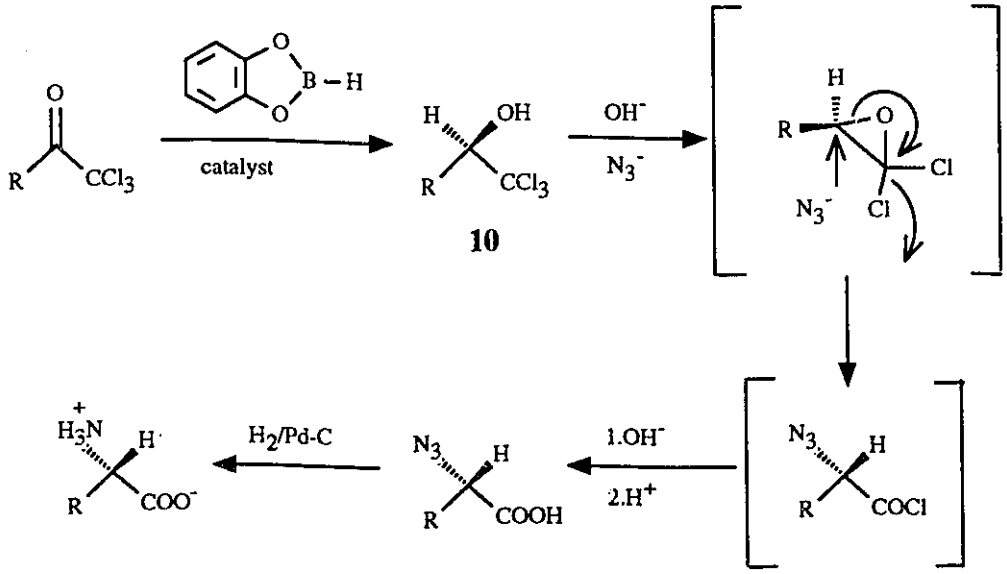
In contrast to the hydrolytic reactions described above there exist several important commercial syntheses of amino acids which require co-factors and involve asymmetric bond forming reactions on prochiral substrates.[26] These reactions will not be discussed here and are only mentioned for completeness.

F) Miscellaneous Methods.

Throughout the scientific literature there are a variety of α-amino acid syntheses that are not related to any of the general procedures discussed previously. Most of these

syntheses involve a molecular rearrangement such as a Claisen[27] or Schmidt[28] rearrangement while others involve the use of chiral phase transfer catalysts in enantiospecific alkylations.[29] However, in 1992 Corey and Link[30] published a communication outlining a general, catalytic and enantioselective synthesis of α-amino acids which utilized neither of these approaches as shown in Scheme 8. Trichloromethyl ketones which were obtained via standard literature procedures[31] were reduced with catecholborane in the presence of (S)-oxazaborolidine with greater than 93% ee to yield (trichloromethyl)carbinols **10**. Treatment of the (R)-(trichloromethyl)carbinols with NaOH and NaN_3 in aqueous 1,2-dimethoxyethane at room temperature afforded the (S)-α-azido acids with clean inversion of configuration in 82-91% yield. To account for this Corey et al. theorized that the reaction proceeded via the *gem*-dichlorooxirane intermediate shown in Scheme 8. Subsequent reduction of the azido acids using H_2/Pd-C produced the (S)-α-amino acids in 88-94% yield.

Scheme 8.



The reaction tolerates a wide range of "R" groups, both alkyl and aryl in nature and is so general that recently it has also been applied to the enantioselective synthesis of α-aryloxy-

and α-hydroxy acids.[32]

In summary, the chemistry of amino acids and their asymmetric synthesis are two very important and well developed fields of research. While the syntheses described in this chapter represent the most recent and significant contributions in this area new and improved variations of these methods are always appearing in the literature. Each methodology has its own advantages and disadvantages over other approaches and subsequently a thorough examination of each method is necessary before it is employed.

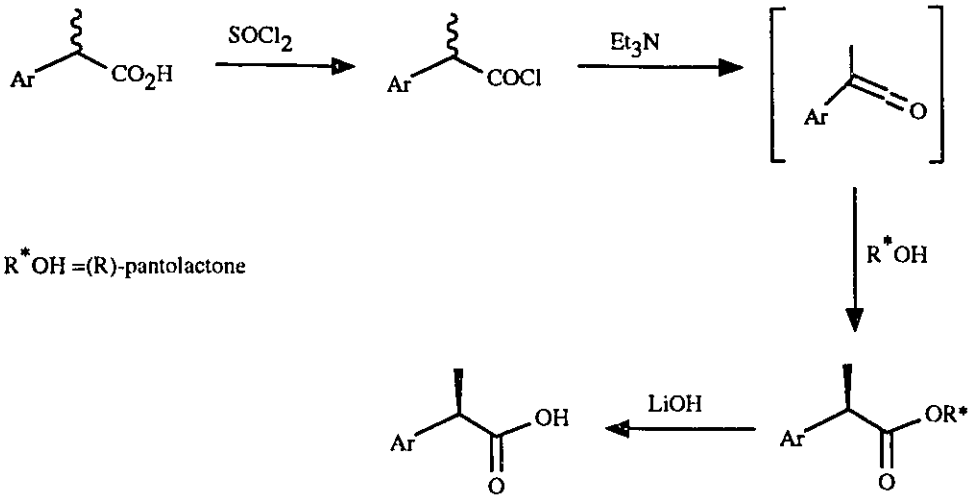
The remaining portion of this thesis will describe a unique reaction which demonstrates great potential for use in the asymmetric synthesis of α-amino acids. In early 1992 while working on a relatively new project in our lab K. Koh a postdoctoral fellow, observed an odd and unexpected experimental result which he, Durst and myself have subsequently developed into an unusual asymmetric synthesis of N-protected α-amino esters. This synthesis involves both a nucleophilic amination of a chiral α-substituted ester and a dynamic kinetic resolution. The mechanism and applications of this reaction are described in the following chapter.

Chapter 2. A Novel Synthesis of Optically Active N-benzylated α-Amino Esters.

2.1 Introduction.

In 1989 Larsen et al.[33] reported a synthesis of 2-arylpropionic acids with diastereomeric excesses between 94-99.5% via the reaction of in-situ generated arlymethylketenes with a variety of optically active α-hydroxy esters such as lactates, mandelates, tartrates and (R)-pantolactone. The best results, having chemical yields greater than 90% and diastereomeric excesses of >99.5% were obtained when the arylmethylketenes were trapped with (R)-pantolactone yielding (R)-arylmethyl esters. These esters were later hydrolyzed to the corresponding arylpropionic acids as shown in Scheme 9.

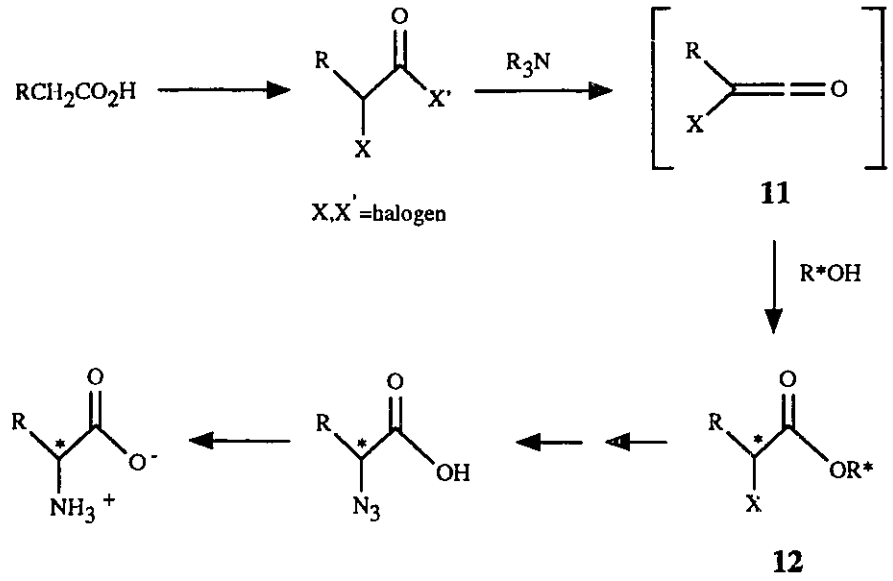
Scheme 9.



Durst and Koh[34a] rationalized that the reaction of α-halogenated ketenes (**11**) with similar chiral alcohols should generate optically active α-halo esters **12**, with high diastereomeric excesses. As shown is Scheme 10 reaction of the corresponding α-halo esters with NaN_3 was expected to proceeded with clean inversion of configuration and

subsequent hydrolysis of the ester would furnish azido acids. Reduction of the azido group would result in optically active[34b] α-amino acids[18,35] or other α-heteroatom substituted acids.[36]

Scheme 10.



Koh generated the α-halo ketenes by reacting the corresponding α-halo acid halides with a tertiary amine in THF at -78 °C and then trapped these intermediates with various chiral α-hydroxy esters. From these experiments Koh reached the following conclusions. (R)-Pantolactone was a superior chiral auxiliary which provided the highest diastereomeric ratios. The ratios obtained when using this auxiliary were two to eight times higher than those observed when (S)-methyl lactate and (S)-methyl mandelate were employed. This observation was consistent with that reported by Larsen et al.. Koh also observed that the nature of the substituent on the α-halo acid halide had a pronounced effect on the diastereoselectivities obtained when the ketene was trapped with pantolactone. Generally, the highest diastereomeric excesses where obtained when large R groups on the α-halo acid halides were employed. Typically, the α-halo esters were obtained in 55-84% yield with

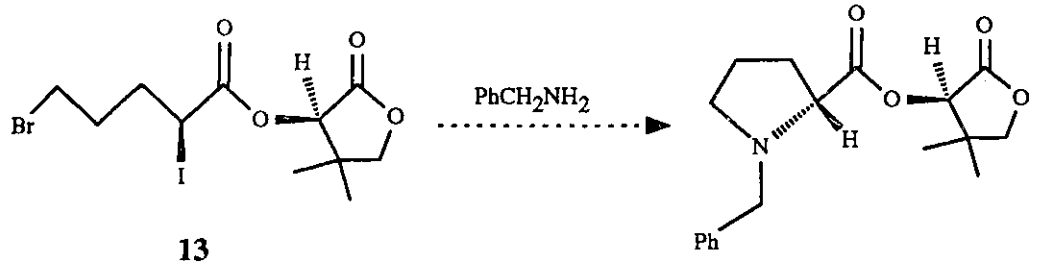
diastereomeric excesses (de's) of 75 to >95%.

Hydrolysis of the chiral auxiliary on several of the α-halo esters (**12**) using LiOH resulted in previously characterized α-halo acids whose absolute configurations were known. A comparison between the optical rotations measured by Koh with those previously reported in the literature showed that in most cases the α-halo acids had the (S) configuration,[37] which was consistent with those reported by Larsen et al. for non-halogenated ketenes. In general all α-halo acids were obtained in 65-75% yield with de's 65-89%.

Koh then demonstrated that reaction of the α-halo esters with NaN_3 in DMF gave the expected azido esters with inversion of configuration and only slight epimerization. Saponification of one of the azido esters produced the corresponding azido acid but the final step, reduction of the azido group was not thought to be necessary since this procedure had been previously reported and well documented.[30] The α-azido acid was obtained in 70% yield and 72% ee after saponification.

Since the reaction of α-halogenated ketenes with pantolactone proceeded with good to excellent diastereoselectivities and was applicable to widely different structures it was rationalized that this methodology could be used to synthesize N-benzyl-(R)-proline derivatives. Durst and Koh surmised that reaction of α-halo ester **13** with benzylamine would lead to the (R)-pantolactone ester of N-benzyl-(R)-proline via two S_N2 displacements as shown in Scheme 11. The following section will describe the unexpected result which was obtained.

Scheme 11.



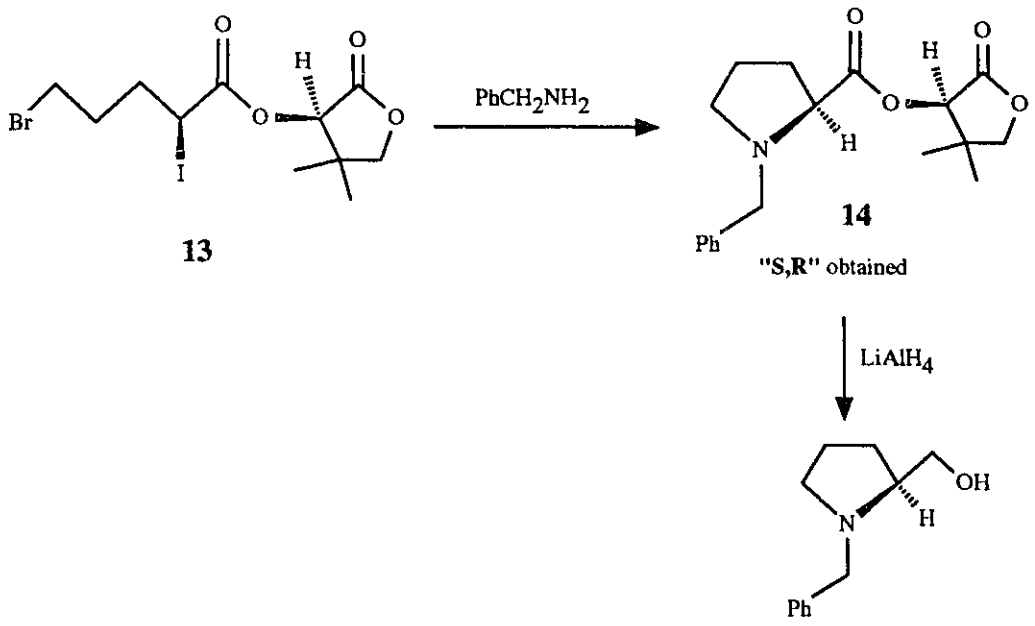
13

"R,R" Expected

2.2 A serendipitous synthesis of N-benzylated-(S)-α-amino esters.

Koh obtained **13** as a 6:1 ratio of (S,R):(R,R) diastereomers via the previously described ketene trapping reaction. Only the (S,R) diastereomer is shown in Scheme 11 and the stereochemistry at the α-carbon was previously verified. Reaction of this mixture of diastereomers with benzylamine in THF with Et_3N for two days at room temperature furnished the (R)-pantolactone ester of N-benzyl-proline as a 5:1 ratio of diastereomers in approximately 70% yield.[38a] Reduction of ester **14** by reaction with $LiAlH_4$ at room temperature for 12 h gave the known N-benzyl-pyrrolidine-2-methanol, which was shown to be the (S) enantiomer and not the expected (R) enantiomer. This meant that ester **14** had the (S,R) configuration rather than the expected (R,R) configuration. An X-ray structure analysis of the product verified this.

Scheme 12.



This experimental result was intriguing for two reasons. Firstly, it was highly unusual that an S_N2 displacement of the halogen α- to the ester carbonyl should proceed with retention of configuration. It has been well established that S_N2 reactions always furnish products with inversion of configuration at the reacting center,[39] unless neighbouring group participation is involved. Such a mechanism is unlikely in the conversion of **13** to **14**. Secondly and perhaps more intriguing was the observation that the optically pure (S,R) product formed via retention of configuration was isolated in greater than 50% chemical yield. Based on the above result and the experimental data from other reactions which will be discussed in the following paragraphs, the following explanation was proposed.

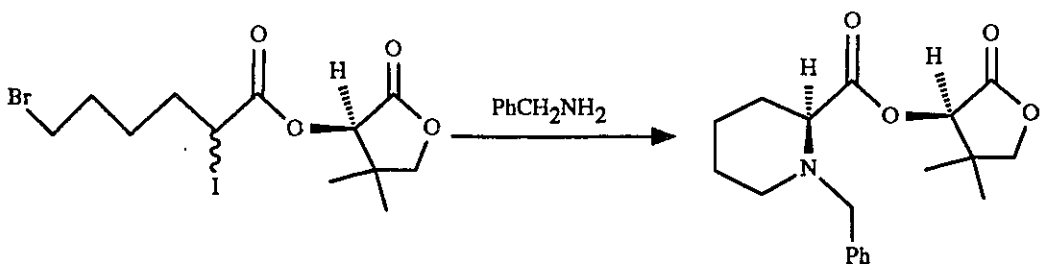
One of the diastereomers reacted at a much faster rate with benzylamine than the other and since its product was always obtained in greater than 50% yield (regardless of the ratio of the starting materials) it was concluded that there must be an epimerization during the course of reaction. Since the products were shown to be configurationally stable under the reaction conditions, this epimerization must occur before displacement of the halogen by

benzylamine. Since Br^- is a good leaving group but can also function as a nucleophile, it followed that the interconversion or epimerization of each diastereomer must be catalyzed by the Br^- ion which is released as amino ester formation progresses.

As stated earlier, reaction of a 6:1 (SR/RR) diastereomeric mixture of **13** produced **14** as a 5:1 (SR/RR) mixture of diastereomers. When Koh started with a 1:1 mixture of diastereomers of **13** he obtained predominantly the (S,R) diastereomer of **14** in 75% yield as a 7:1 diastereomeric mixture. This ring closure reaction was not limited to just benzylamine. Starting from a 1:1 mixture of **13** (S,R as the predominant diastereomer), the same ring closure could be affected using 1-aminohexane, resulting in the formation of the N-hexylproline analogue of **14** which was obtained in 53% yield as a 7:1 mixture of diastereomers. Again the (S,R) diastereomer was the predominant product; it was shown to be configurationally stable under the reaction conditions.

The ring closure reaction was also applicable to the formation of six membered rings as shown in Scheme 13. Starting with a 1:1 mixture of the 2-iodo-6-bromo derivative the (R)-pantolactone ester of (S)-pipecolinic acid was obtained as a 10:1 mixture of diastereomers. The minor diastereomer was removed by column chromatography yielding the pure (S,R) diastereomer in 62% yield.

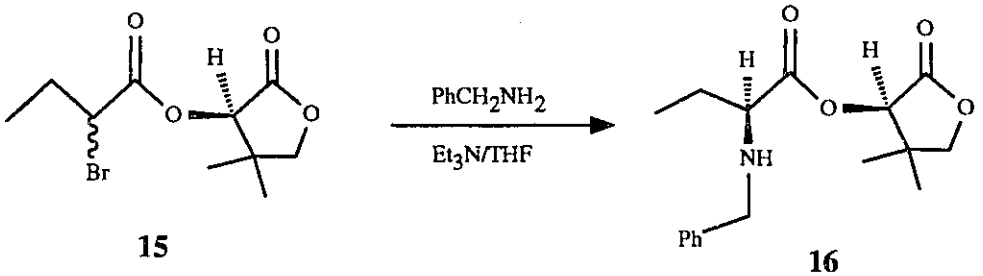
Scheme 13.



In addition to the formation of cyclic amino esters, Koh applied the above reaction to the formation of non-cyclic α-amino esters. For example, reaction of a 4:5 ratio of

diastereomers **15** (in Scheme 14) with benzylamine and triethylamine in THF for 2 days produced a 7:1 mixture of the (S)- and (R)-2-N-benzylaminobutanoic esters **16**.

Scheme 14.

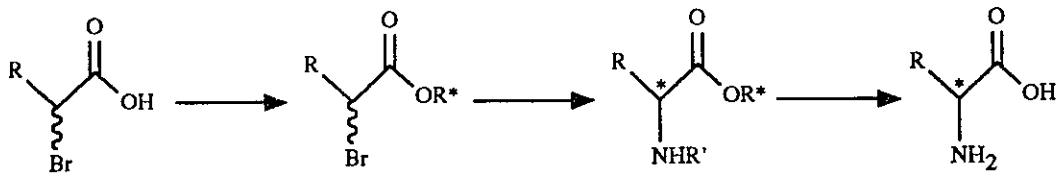


15 **16**

However, when an 11:1 (SR/RR) mixture of α-halo ester **15** was reacted under identical conditions a 1:2 (SR/RR) ratio of **16** was obtained. This observation was consistent with the result obtained when different diastereomeric ratios of **13** were reacted with benzylamine. The fact that the diastereomeric ratios of the products in these reactions were highly dependent upon the diastereomeric ratios of the starting materials was consistent with the hypothesis that one diastereomer reacted much faster with benzylamine and that the less reactive isomer was epimerized by Br^- ion to the faster reacting one. In addition, the fact that an 11:1 (SR/RR) mixture of **15** gave a 1:2 (SR/RR) of **16** while a 4:5 (SR/RR) mixture produced a 7:1 (SR/RR) suggested that the rate of epimerization by Br^- was comparable to the rate of amino ester formation. It was later discovered that the epimerization of the α-halo esters could be facilitated by the addition of a catalytic amount (0.2 molar equivalents) of I^- in the form of tetra-*n*-hexylammonium iodide which served to convert the slower reacting 2-(S)-isomer into the faster reacting 2-(R)-isomer.

The above results indicated that considerable potential existed to develop an efficient synthesis of both common and unusual optically active α-amino acids which utilized racemic α-halo acids as starting materials as shown in Scheme 15.

Scheme 15.



R=alkyl one diastereomer one enantiomer

The following chapter will describe in more detail the mechanistic aspects of this reaction including its advantages and limitations as a novel and efficient synthesis for both common and unusual optically active α-amino acids. Since it was not immediately evident why this reaction gave such unusually high diastereomeric ratios in the amino esters, various strategies aimed at improving these ratios were employed with the hope that we might also gain valuable mechanistic insight into this unusual reaction. Thus, while it may seem somewhat unorthodox to present the detailed mechanism of this reaction first, followed by the experimental results upon which we founded the mechanism, this is the approach which was ultimately decided upon.

Chapter 3. Discussion.

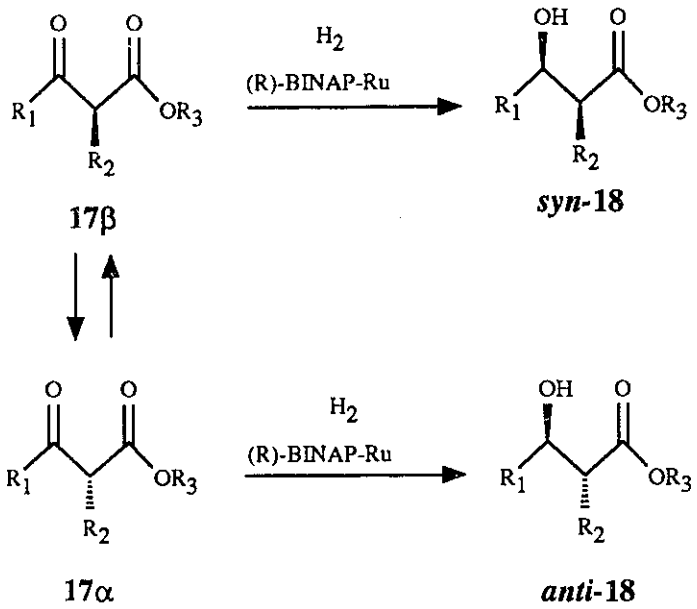
3.1 Mechanistic aspects of this Kinetic Dynamic Resolution.

As outlined in the introduction there exist a variety of excellent methods to synthesize α-amino acids and esters. Our method described in the previous chapter takes advantage of significant differences in the rate of displacement of bromine or iodine from diastereomeric α-halo esters and consequently is conceptually different than other approaches discussed earlier. While all kinetic resolutions have this in common, the major advantage this method has over others is that the slower reacting diastereomer is converted to the faster reacting isomer in-situ. As a result the maximum yield of the optically pure α-amino ester is 100% rather than only 50%.

Reactions of this type are rare in the literature and are referred to as "Kinetic Dynamic Resolutions". In 1985 Meijer et al.[40] reported an unusual dynamic enzymatic resolution which utilized a hydantoinase from *Bacillus brevis*. This enzyme selectively hydrolyzed one isomer of *p*-hydroxyphenyl hydantoin to (R)-N-carbamoyl-*p*-hydroxylphenylglycine. The unreacted L-isomer spontaneously racemized under the reaction conditions and was subsequently converted to the desired product. Thus 100% of a racemic substrate was converted to only one asymmetric product.

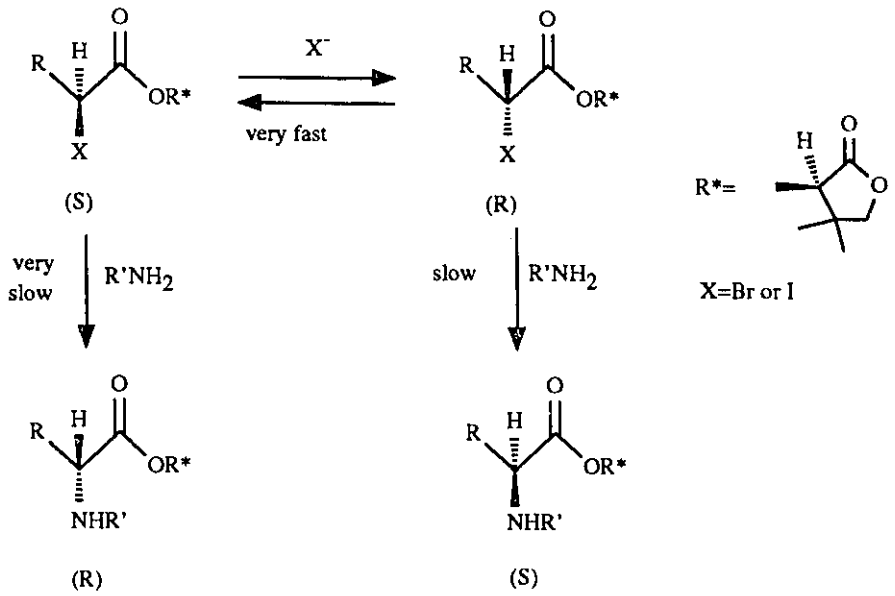
Another example which did not involve biological enzymes and consequently is regarded as a classical kinetic dynamic resolution was reported by Noyori et al.[41] in 1989. As shown in Scheme 16 these researchers took advantage of the fact that the stereoselective hydrogenation of **17β** was a much slower process than the dynamic stereomutation between **17α** and **17β**. As a consequence it was possible to convert a racemic starting material in 100% yield into a single chiral product. For example, starting with a racemic mixture of **17**, *syn* and ***anti-18*** were formed in ratios as high as 99:1.

Scheme 16.



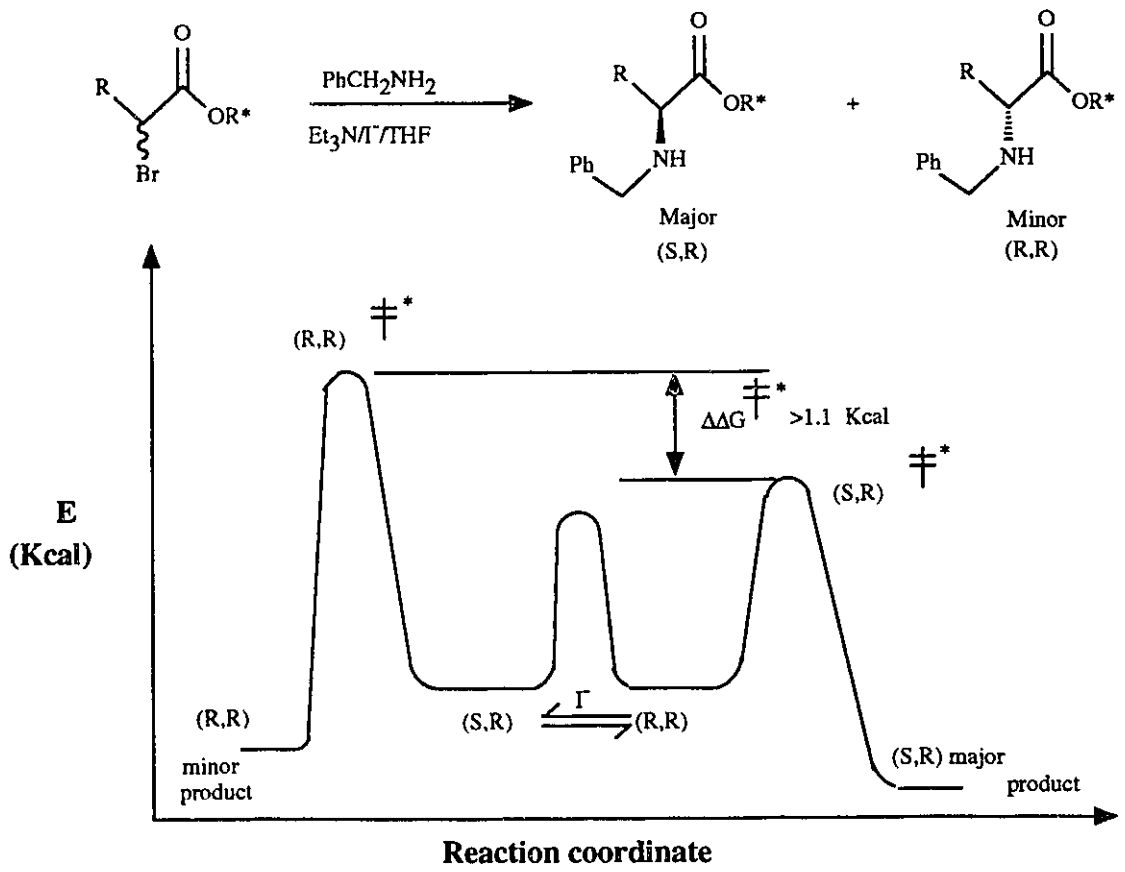
Much like the above reaction, our methodology takes advantage of the rate differences between displacement of the bromide from the (S,R) and the (R,R) diastereomer with benzylamine. As shown in Scheme 17 the epimerization between the (S,R) and (R,R)-α-halo esters with Br^- or I^- is fast while reaction of the amine nucleophile with each isomer is slow in comparison. However, reaction of the (R,R) diastereomer with benzylamine is much faster than reaction with the (S,R) isomer. Consequently as the reaction precedes the supply of faster reacting diastereomer is constantly being replenished by epimerization of the slower reacting (S,R) diastereomer.

Scheme 17.



This principle may also be illustrated in terms of a qualitative free energy diagram as shown in Figure 1. This qualitative energy diagram helps to emphasize that the energy barrier to epimerization by Br^- or I^- is less than the energy of activiation (E_{act}) of displacement by benzylamine and thus interconversion between the two diastereomers occurs readily. It should be noted that the two diastereomers of the α-halo ester are approximately equal in energy. This was verified by the fact that a 10:1 mixture of isomers (SR/RR) left to epimerize for 8 h at room temperature with a catalytic amount of I^- ion always resulted in a 1.1:1.0 mixture of SR:RR diastereomers. Another important point which is well illustrated by this diagram is that the E_{act} for the conversion of the (S,R)-α-halo ester to the (R,R)-amino ester is greater than the corresponding (R,R)-α-halo ester to (S,R)-amino ester conversion. By analyzing the product ratios obtained from several reactions it is possible to determine the approximate energy difference between the two transition states.[42] Since reaction of several racemic mixtures of α-halo esters with benzylamine at room temperature produced a 7:1 to 10:1 ratio (SR/RR) of products, we may conclude that the energy difference for the (S,R) transition state is approximately 0.8-1.3 Kcal/mole less in energy than the (R,R) transition state.

Figure 1. A qualitative free energy diagram for:



As mentioned in section 2.2 other amine nucleophiles may be used in this reaction. In fact, one of the advantages of this methodology is that it is quite easy to synthesize unusual N-substituted α-amino esters whose synthesis by conventional methods would be quite challenging. However, since the crucial step of this reaction involves the epimerization of the slower reacting (S,R)-diastereomer to the faster reacting (R,R)-isomer, many other heteroatom nucleophiles may be tolerated in this reaction provided that their relative rate of reactivity is less than that of Br^- or I^- ion.

Table 1 shows the relative rates of reactivity for various nucleophiles with iodomethane in methanol.[43] While these relative rates can be useful for our reaction, the actual numbers

should be interpreted with caution since the reactions in Table 1 were performed in a polar protic solvent which disfavors S_N2 reactions. For example, in MeOH the relative rates of reaction for halide ions are $Cl^- << Br^- << I^-$. In a nonpolar aprotic solvent such as THF the overall trend in reactivity remains unaffected (i.e. $Cl^- < Br^- < I^-$) however the relative rate of reaction for Cl^- will increase dramatically while the relative rate of I^- will increase only slightly. As a result of this it would be incorrect to expect that under our reaction conditions the relative rate of reaction for Br^- would be approximately twice that of NH_3 (a representative amine) as shown in Table 1. The only conclusion that may be drawn is that NH_3 will react at a slower rate than the Br^- and consequently amine nucleophiles work well in our reaction.

Table 1. Relative Rates of Reaction of Various Nucleophiles With Iodomethane in Methanol.[a]

Nucleophile	Rel. Rate	Nucleophile	Rel. Rate
CH_3OH	1	N_3^-	603 000
NO_3^-	32	Br^-	617 000
F^-	500	CH_3O^-	1 950 000
$CH_3CO_2^-$	20 000	Me_2Se	2 090 000
Cl^-	23 500	CN^-	5 010 000
Et_2S	219 000	Et_3As	7 940 000
NH_3	316 000	I^-	26 300 000
Me_2S	347 000	HS^-	100 000 000

a) MeOH was arbitrarily set at a relative rate of 1.

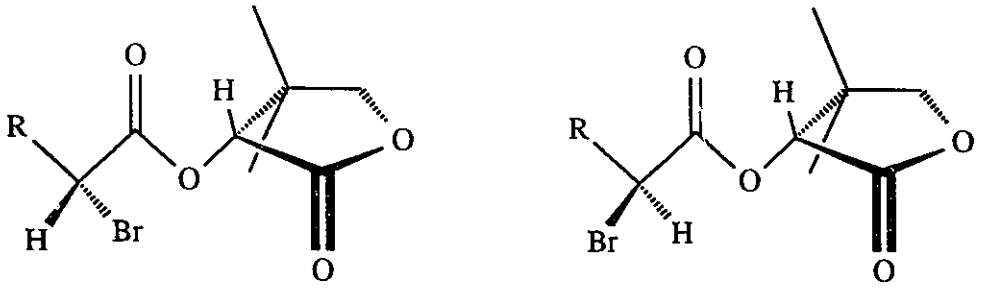
Based on this it was expected that various sulfides and carboxylate anions may also serve as efficient nucleophiles in our reaction. The experimental results obtained from using different amines and other heteroatom nucleophiles will be discussed in detail in one of the

following sub-sections.

As explained earlier one of the unique features of our dynamic kinetic resolution is that it is possible to obtain predominately one diastereomer by reacting a non-chiral amine with a racemic α-halo ester of (R)-pantolactone. In order for this methodology to be useful on either a semi-preparatory or industrial scale the diastereomeric excesses (de's) of the products had to be improved. In the reaction of benzylamine with α-halo ester **13**, Koh obtained a 7:1 (SR/RR) mixture which corresponded to a de of 75%. While this was quite good our reaction would only be genuinely useful if de's of 95-99% were obtained. Consequently, various strategies aimed at improving the de's were employed. These included utilizing other chiral auxiliaries, varying the size and nucleophilicity of nucleophiles, altering the reaction medium in various ways and increasing the size of the α-substituent on the α-halo-pantolactone ester. It was hoped that in addition to discovering the optimal conditions which would yield the highest de's for this reaction, we might also gain valuable insight into the mechanism of this reaction and consequently understand why one diastereomer reacted at a much slower rate than the other.

The following paragraphs will describe the reactive conformation that we propose for the faster reacting (R,R) diastereomer (Figure 2). This conformation was proposed on the basis of experimental results using other chiral auxiliaries, conformational analysis of the α-halo pantolactone esters and examination of the X-ray structures from several of the reaction products. The conformation of the slower reacting (S,R) diastereomer of α-halo-(R)-pantolactone ester is also shown in Figure 2.

Figure 2. Proposed Conformation of the α-Bromo-(R)-Pantolactone Esters



Faster reacting "R,R" diastereomer

Slower reacting (S,R) diastereomer

There are three key aspects to the conformations shown in Figure 2. Firstly, the ester function exists in the "cisoid" conformation as opposed to the "transoid" and does not interconvert between the two. This is known experimentally and is based on calculations by Houk et al.[44,45] who determined that the cisoid conformation of an ester function is approximately 7 Kcal/mole more stable than the transoid conformation.

Secondly, the ester and lactone carbonyl groups should be perpendicular to each other. This criteria is based on both molecular modeling and X-ray structure analysis. In all structures modeled the dihedral angle between the pantolactone hydrogen in the 1-position of the ring and the ester carbonyl was between 1 to 15°. When the dihedral angle is of this magnitude, the ester carbonyl and the pantolactone hydrogen are almost eclipsed and as a result the ester and lactone carbonyls are perpendicular to each other. This same trend was also observed in the X-ray structure analyses of the products as shown in Figure 3. While there is no certainty that the solid state structure of the products should have the same conformational properties of the α-halo esters, it seems reasonable to expect that the carbonyl groups in the α-halo esters will be perpendicular to each other based on both stereoelectronic interactions and steric effects. For instance, if the carbonyl groups were at 180° to each other simple molecular models predict severe steric interactions between the ester carbonyl and the *gem*-dimethyl group.

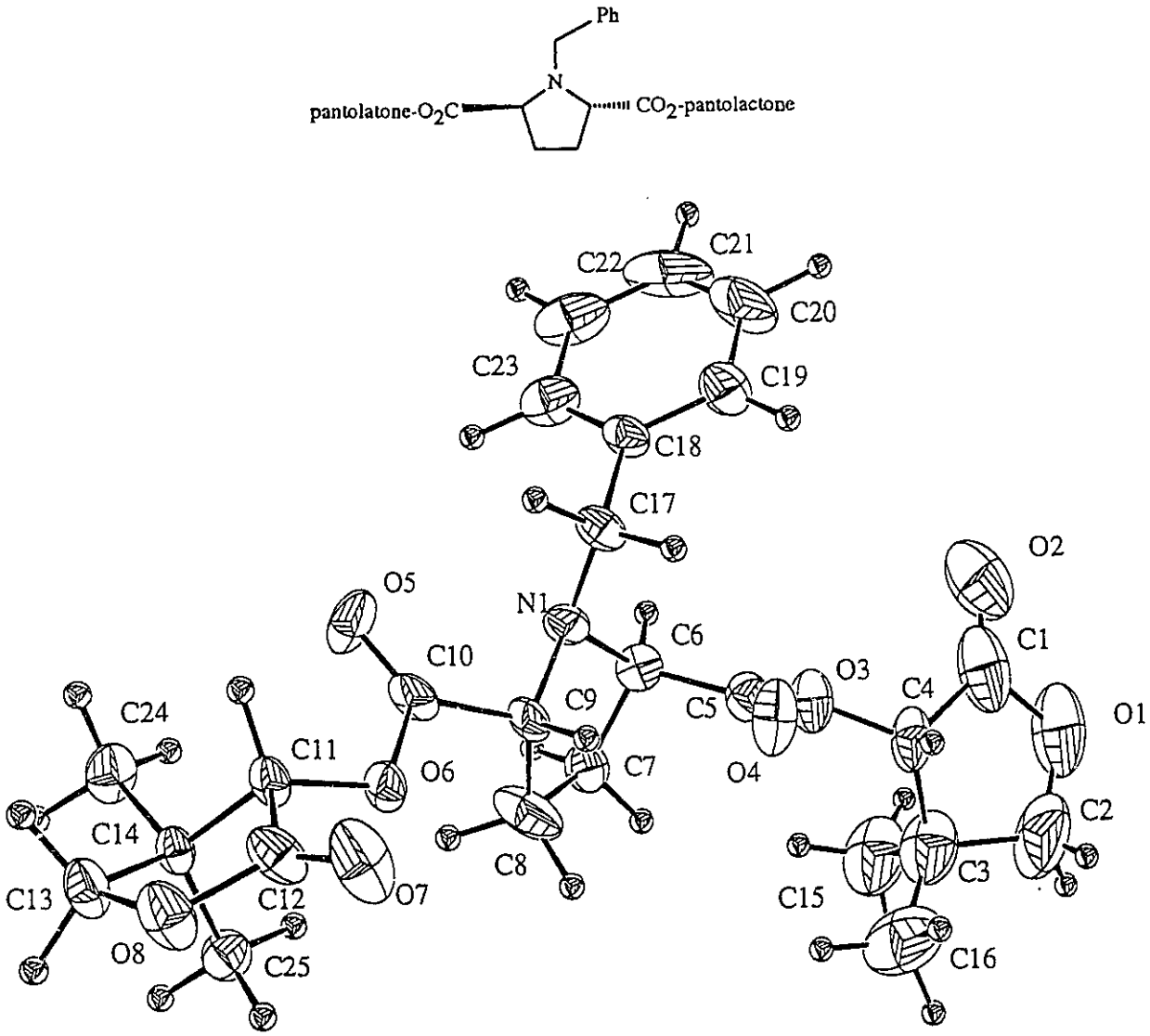
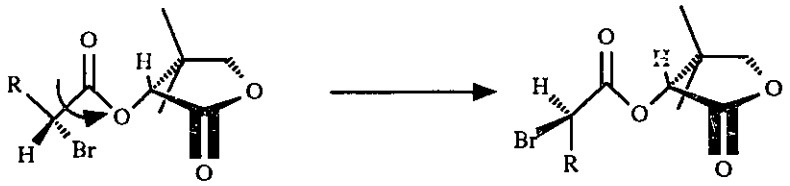


Figure 3. ORTEP of C_2 symmetric product which displays perpendicular arrangement of carbonyl groups.

Thirdly, the bromine atom is most likely perpendicular to the ester carbonyl since it has been shown experimentally that in this conformation a halogen α- to an sp^2 hybridized center is typically displaced more rapidly by a nucleophile.[46] The reason for this is that in this conformation the incoming nucleophile can participate in a non-bonding interaction with the p-orbital of the carbonyl carbon. This effect is commonly referred to as a "neighboring orbital overlap" and greatly enhances the rate of displacement.

In addition to the structures shown in Figure 2 each of the diastereomers can exist in one of several possible rotamer conformations obtained via rotation of the C_1-C_2 bond. While there are many rotamers possible we are only interested in those which have the bromine atom perpendicular to the ester carbonyl group for the reasons explained in the preceding paragraph. Given this criteria all but one out of the many possible rotamers for each diastereomer may be disregarded. Figure 4 shows the Newman projections for the four rotamers of our α-bromo pantolactone esters.

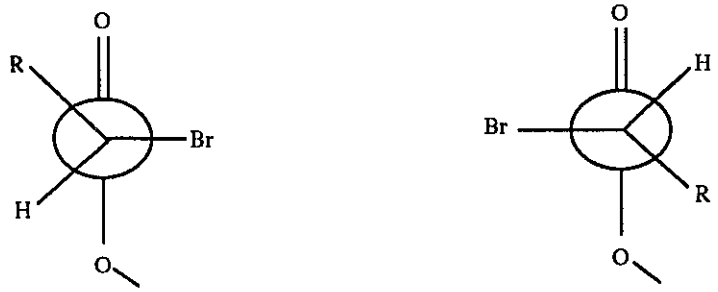
Figure 4. Rotamers of the faster reacting (R,R) and slower reacting (S,R) diastereomer.



Faster reacting (R,R) diastereomer

I **II**

Slower reacting (S,R) diastereomer

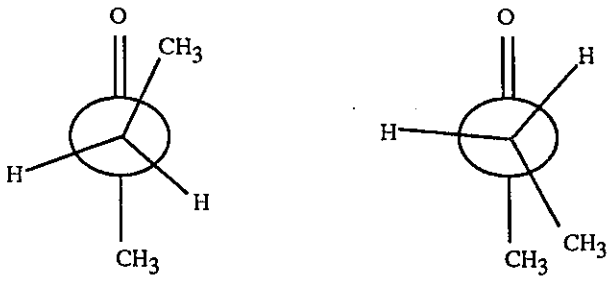


III **IV**

We have rationalized that while it is possible for all four conformations to undergo reaction with an amine nucleophile, only conformations **I** and **III** actually react to form the desired N-protected α-amino esters. Conformations **II** and **IV** do not react because they pass through transition states which are much higher in energy than the transition states from conformers **I** and **III**. The transition states derived from **II** and **IV** are disfavored because each has an eclipsing interaction between the large R group and ether oxygen of the

ester function. In contrast, **I** and **III** are favored since the eclipsing interaction between the R group and the carbonyl group represent an energy minimum. These conclusions are based on the conformational analysis of 2-butanone[47] as shown in Figure 5A.

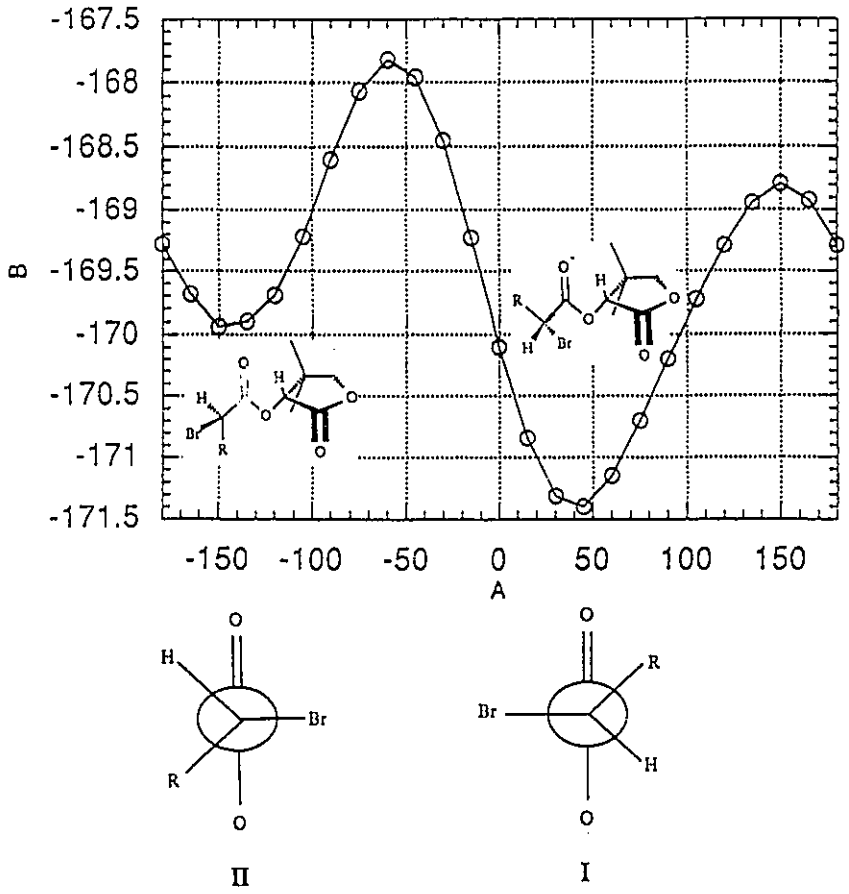
Figure 5A. Conformations of 2-butanone.



Ab initio calculations show that arrangement of the methyl group so that it partially eclipses the carbon-oxygen double bond is favored over the conformation that has the methyl group partially eclipsing the ether oxygen by 2.8 Kcal/mole. Semi-empiracle calculations using AM1 on the faster reacting (R,R or S,S) diastereomer where R=CH_3 were in agreement with this precednent. Figure 5B depicts an energy profile as the dihedral angle between the methyl group and carbonyl group of the ester function is rotated through 360°. As shown in Figure 5B conformation **I** is at an energy minimum while **II** is about 1.5 Kcal/mole higher in energy. Part of the energy difference between minima **I** and **II** may be due to more favorable electrostatic interactions between the lactone carbonyl group and the bromine atom. Nevertheless, the trend that R partially eclipsing the carbonyl oxygen is more stable then R partially eclipsing the ether oxygen holds.

In summary, it was concluded that the α-bromo esters are quite rigid and are "locked" in the conformations depicted by Figure 2. We propose that delivery of the nucleophile is facilitated through hydrogen bonding and a favorable electrostatic with the lactone carbonyl group. For instance, benzylamine can hydrogen bond to the lactone carbonyl of

Figure 5B. Energy minima for the faster reacting diastereomer.



both the (R,R)- and (S,R)-α-halo esters but can only displace the bromine atom from conformer **I** of the (R,S) diastereomer. This leads to formation of the (S,R)-amino ester as the major product. Reaction via conformer **III** leads to the minor product. In this case benzylamine approaches *anti-* to the lactone carbonyl resulting in formation of the (R,R)-amino ester. Molecular models indicate that the *gem*-dimethyl group on the pantolactone ring would hinder but not completely prevent approach of the benzylamine. Additionally approach from this direction is not facilitated by hydrogen bonding thus, the rate of reaction via **III** is much slower than via **I**.

As mentioned earlier the evidence on which the above mechanistic rationale is based was obtained from direct experimentation, conformational analysis, literature precedents and the X-ray analysis of several reaction products. The next sections will discuss experiments that were performed and how these support our proposed mechanism.

3.2 Optimization and applications of this Kinetic Dynamic Resolution.

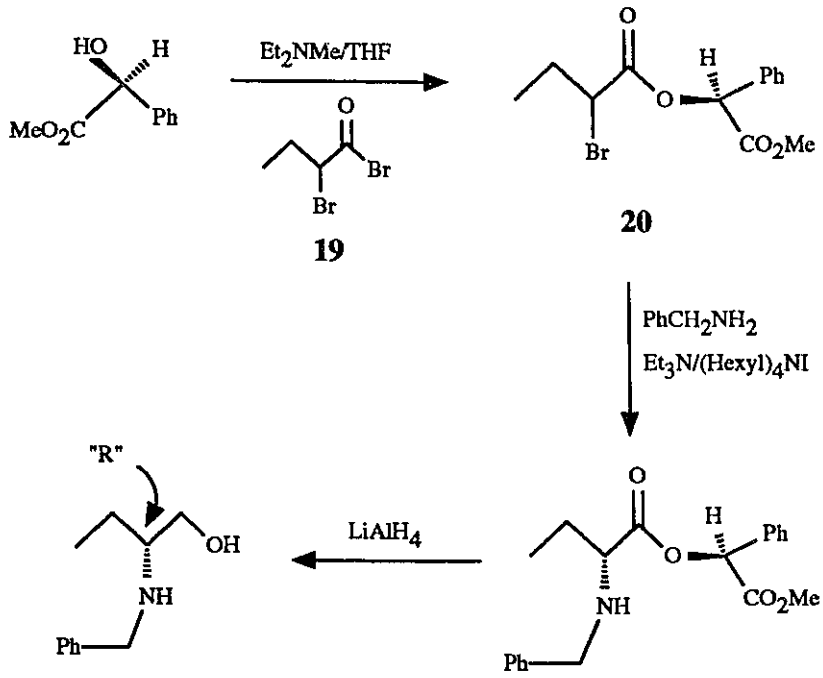
A) Other Auxiliaries:

To date, the best diastereomeric ratios of N-protected (S)-α-amino esters are obtained when (R)-pantolactone is employed as the chiral auxiliary. While it may seem ironic that the first auxiliary used in these reactions would be the best one, in retrospect it is not surprising. (R)-Pantolactone has been shown to be a unique chiral auxiliary and in addition to the highly seiective trapping of arylmethylketenes reported by Larsen et al.[33] it has been utilized in many different asymmetric reactions such as rhodium(II) catalyzed cyclpropanations[48] and metal coordinated-Lewis acid catalyzed Diels-Alder reactions.[49] In all examples very high levels of diastereoselectivity or diastereofacial selectivity were observed. Despite the success with using (R)-pantolactone as a chiral auxiliary many other auxiliaries have and are continually being tested since one of the most obvious ways to improve this reaction would be to employ a better auxiliary.

The first alternate auxiliary to be tested was (S)-methyl mandelate. The synthesis of its α-halo ester and subsequent reaction with benzylamine will be described below. This was a general procedure and unless stated otherwise was used in the synthesis of all other α-halo esters. All yields refer to purified products.

2-Bromobutyryl bromide **19**, and all other α-halo acids required, were either obtained commercially and used without further purification or synthesized via a standard literature procedure.[50] The ester was synthesized by a dropwise addition of a THF solution of α-halo acid bromide **19** to a solution of (R)-pantolactone (2.0 eq) and triethylamine (2.0 eq) also in dry THF at 0 °C over the period of 5 minutes. The reaction mixture was then quenched with water and subjected to extractive work up. Purification by column chromatography yielded racemic α-halo ester **20** in 91% chemical yield as shown in Scheme 18. It is important to note that the ketene reaction was done at 0 °C in order to ensure that the α-halo ester was obtained as an approximate 1:1 mixture (SR/RR) of diastereomers.[34a]

Scheme 18.



Compound **20** was then reacted with tetra-*n*-hexylammoniun iodide, benzylamine (1.2 eq) and Et_3N (2.0 eq) in THF at room temperature. A TLC of the reaction mixture 3 days later showed that all of the starting material had been consumed. The solvent was then evaporated under reduced pressure and the crude reaction mixture was dried under high vacuum for 2 hours. In the proton NMR of the crude mixture the resonance at 5.59 ppm which corresponded to the methine hydrogen in the position α- to the methyl ester consisted of two closely spaced singlets, one for each diastereomer (i.e. the SR and RR products). An expansion and integration of this region indicated a 2:1 mixture of diastereomers and upon purification of the crude reaction mixture by column chromatography **21** was obtained as a 2:1 mixture of diastereomers in 60% yield (Figure 6). The predominate stereochemistry and verification of the diastereomeric ratio were determined by reduction of **21** with $LiAlH_4$ in THF to give the known N-benzyl-2-amino-butanol. An $[\alpha]^{23}_D$ -14.72° (c 0.55, CH_2Cl_2)

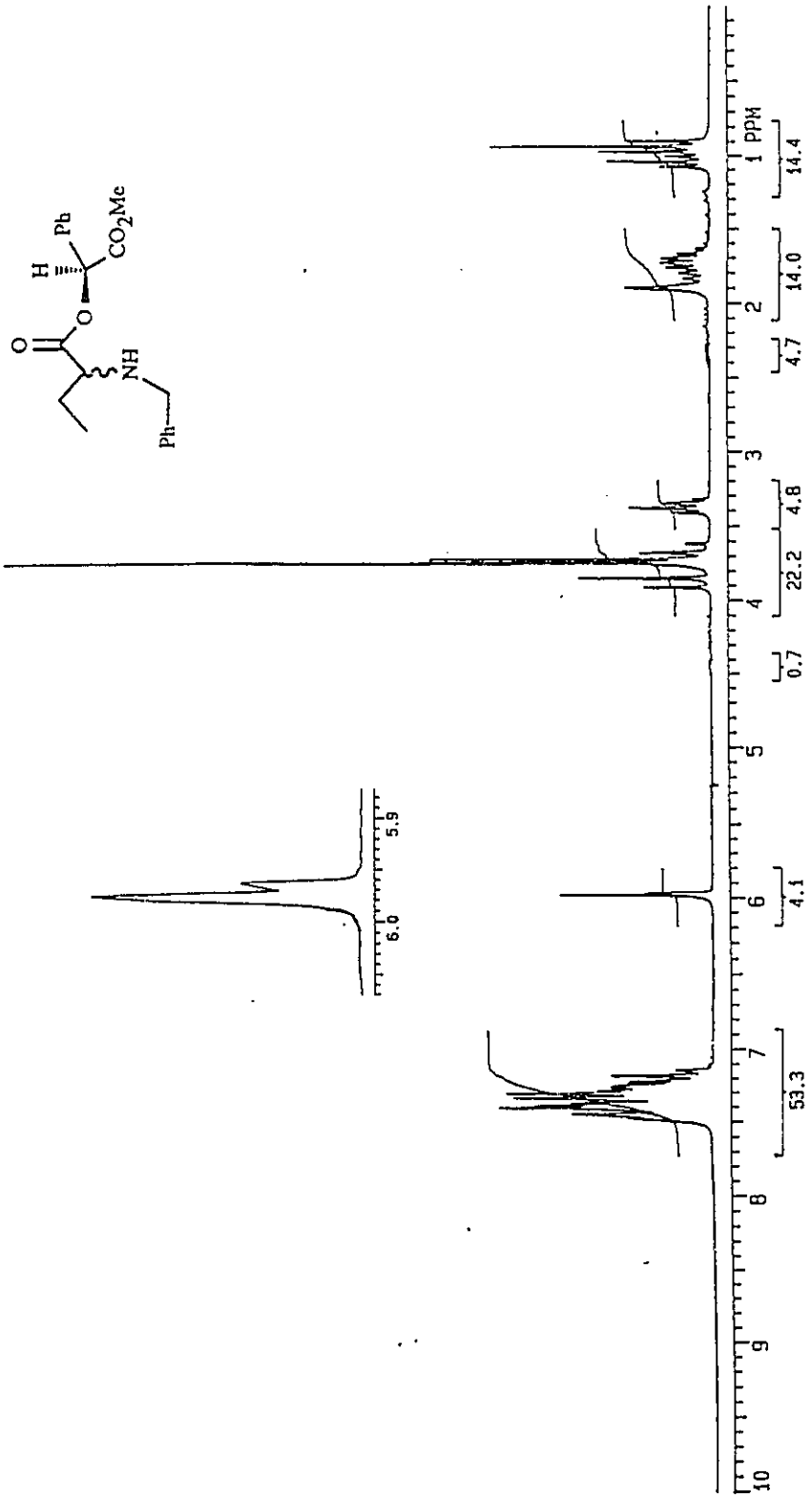


Figure 6. 200 MHz ^{1}H NMR spectrum of **21** in $CDCl_3$. Inset shows crude diastereomeric ratio.

confirmed a 2:1 mixture of R:S N-benzyl-2-amino-butanol.[51a] In should be emphasized that the chiral auxiliary (S)-methylmandelate produced a product that possessed predominately the "R" stereochemistry at the reacting center while (R)-pantolactone yielded the opposite stereochemistry. The ratio of 2:1 obtained using (S)-methylmandelate was identical to that obtained by Koh when he used (S)-methyl lactate as a chiral auxiliary.[51b] These results suggested that the best auxiliaries would likely possess a rigid five or six membered ring as part of their structure. The above reaction was repeated using the α-halo ester of *trans*-2-phenyl-cyclohexanol **22** which was prepared as described previously and obtained in 60% yield. Elemental analysis confirmed an empirical formula of $C_{16}H_{21}O_2Br$. The proton NMR of **22** was quite complicated but it was evident upon examination of the resonances at 0.60 ppm and 3.85 ppm (both triplets) that **22** was obtained as a 2:1 mixture of diastereomers, not a 1:1. The α-halo ester was subsequently epimerized by reaction with tetra-*n*-hexylammonium iodide in THF for 18 h and then subjected to reaction with benzylamine for two days. A proton NMR of the crude reaction mixture was quite complicated because of the presence of large amounts of ammonium salts. The salts were removed by triturating the crude reaction mixture with Et_2O and filtering off the insoluble precipitate. This simplified the proton NMR and revealed that the methyl group for each of the N-benzylated amino ester products (structure **23** shown in Figure 7) had separate resonances at 0.50 and 0.70 ppm. An expansion and integration of the region between 0-1.0 ppm confirmed a diastereomeric ratio of 2:1. Both isomers of **23** were isolated together in 92% yield. The predominate stereochemistry at the carbon α- to the carbonyl group was not determined. This result confirms the importance of having a carbonyl group present in the ring of the auxiliary.

(R)-Diacetone-glucose which possesses a five membered furan ring was also examined as a possible chiral auxiliary as shown in Scheme 19. The α-halo ester **24** was obtained in 63% yield and was subjected to the predescribed reaction conditions with benzylamine over

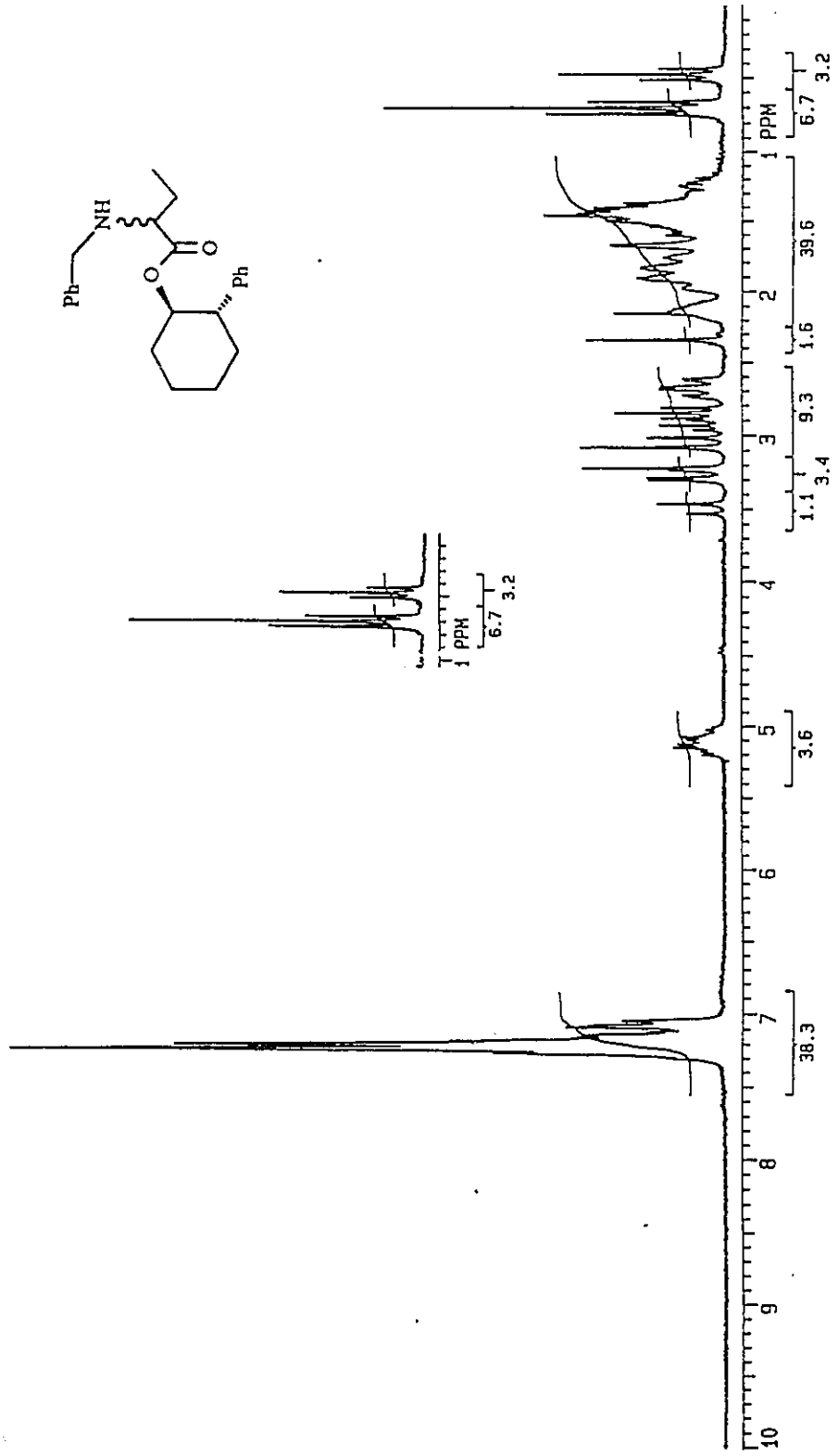
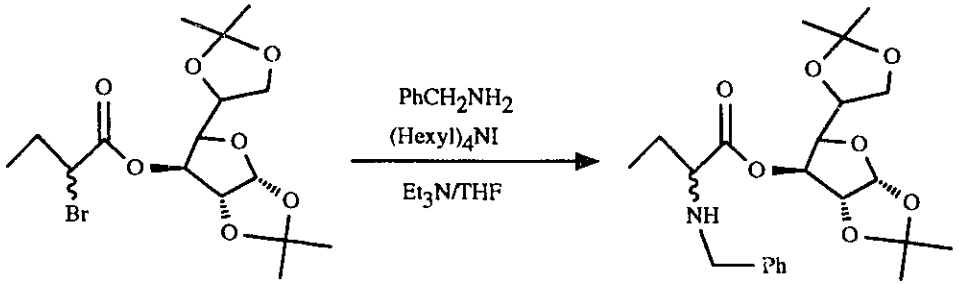


Figure 7. 200 MHz ^{1}H NMR spectrum of **23** in $CDCl_3$. Inset shows crude diastereomeric ratio.

a period of two days after which time TLC revealed that all of **24** had been consumed. Usual work up followed by a proton NMR of the crude reaction mixture indicated a diastereomeric ratio of 2:1. Again the predominate diastereomer was not determined.

Scheme 19.

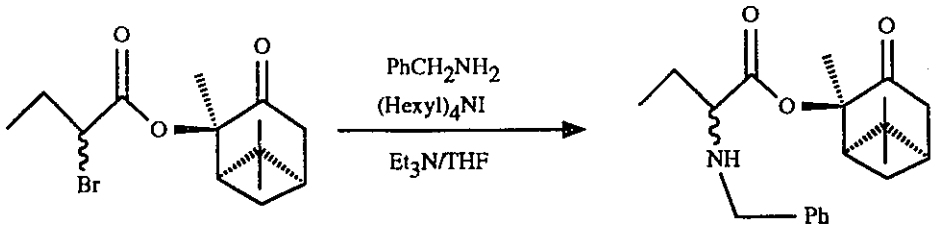


24 **25**

The results obtained from using (1R,2S)-2-phenyl-cyclohexanol and (R)-diacetone glucose as chiral auxiliaries suggested that while a rigid ring structure was necessary in the auxiliary, the best chiral auxiliaries would also possess α-hydroxy esters or lactones. As a consequence of this it was not surprising that the (R)-pantolactone auxiliary produced products with the best diastereomeric ratios.

Earlier experiments by Koh had shown that in addition to the above criteria the alcohol of the auxiliary should be secondary and not tertiary. When Koh synthesized α-halo ester **26** and subjected this compound to the previously described reaction conditions he obtained a 2:1 diastereomeric mixture of the N-benzylated-α-amino esters shown in Scheme 20.[51c]

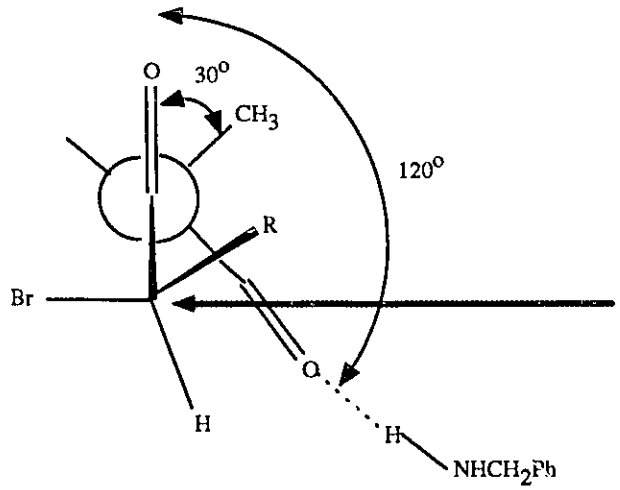
Scheme 20.



26

This experiment indicates that the magnitude of the dihedral angle between the ester carbonyl and the α-hydrogen on the pantolactone ring was very important. Molecular model studies using PC Model revealed that in substrate **26** the corresponding angle was approximately 30° as opposed to 1-15° which was observed in the (R)-pantolactone ester. With a dihedral angle of this magnitude the ester and pinenone carbonyls are no longer perdendicular to each other but rather are at approximately 120°. In such a conformation displacement of the α-halogen via the amine aided by hydrogen bonding to the pinenone carbonyl is geometrically difficult assuming that the halogen possesses a dihedral angle of 90° to the ester carbonyl and the nucleophile must approach *anti-* to the halogen at 180°. Figure 8 illustrates a probable conformation for ester **26**. Most of the pinene ring has been omitted in order to make the figure more clear. The shaded arrow indicates the optimal angle and trajectory which the amine nucleophile should have in order to successfully displace the bromine atom.

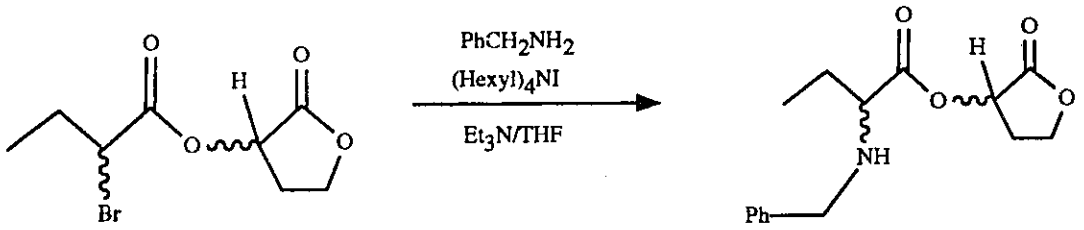
Figure 8.



Molecular models indicate that the approach of benzylamine *anti-* to the pinenone carbonyl in the slower reacting (S,R) diastereomer would be sterically hindered. Thus, based upon the fact that only a 2:1 mixture of diastereomers was obtained by Koh it was concluded that a dihedral angle of no more than 15° was tolerated between the ester carbonyl and the α-hydrogen of the pantolactone ring. If the dihedral angle was larger than 15° one could expect a decrease in the diastereomeric ratios obtained.

At this point the last and perhaps most obvious aspect of the (R)-pantolactone auxiliary left to investigate was the *gem*-dimethyl group. The speculation that the *gem*-dimethyl group partially occluded one face of the α-halo ester and subsequently blocked reaction of the benzylamine from that side was supported by the following experiment outlined in Scheme 21.[51c]

Scheme 21.

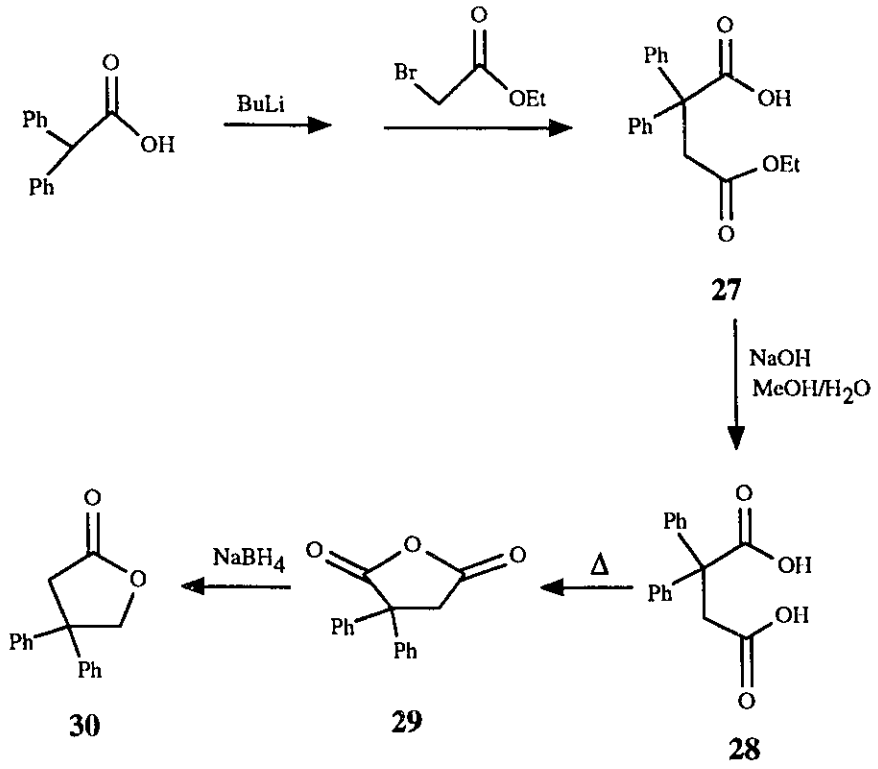


1:1.5 mixture of diastereomers

This experiment performed by K. Koh produced a 1:1.5 mixture of the diastereomeric α-halo esters and as a result clearly demonstrates that the *gem*-dimethyl group plays a significant role in this asymmetric process. Since such a dramatic effect was observed upon the removal of the *gem*-dimethyl moiety it was rationalized that incorporation of larger substituents would augment the facial selectivity and should provide higher diastereomeric ratios. With this in mind the pantolactone derivative having a *gem*-diphenyl substituent instead of the *gem*-dimethyl group was synthesized as outlined in Scheme 22. Based on a literature procedure by Morand and Kayser[52] diphenylacetic acid was reacted with 2.0 eq of butyllithium in THF followed by 1.1 eq of ethyl bromoacetate to furnish compound **27**, mp 127-128 °C in 90% yield. Compound **27** was hydrolyzed to give the diacid **28**, (93%) which displayed IR absorptions at 3312, 1715 and 1065 cm^{-1} and had a mp of 174 °C (lit.[52] mp 175 °C). The diacid was then heated to 185-200 °C in a sand bath until all of the solid had melted. The liquid was then removed from the sand bath and allowed to cool to room temperature to yield anhydride **29**. Compound **29**, mp 90 °C (lit.[52] mp 89-91 °C) was obtained in 76% yield and displayed prominent IR absorptions at 1865 and 1788 cm^{-1}. The proton NMR spectra of **29** was consistent with that reported in the literature. The anhydride was subsequently reduced by $NaBH_4$ in THF at room temperature for 24 h to produce lactone **30**, mp 109 °C (lit.[52] mp 109-110°C) in 70% yield. The IR spectra of **30** showed strong absorptions at 1784 (lit. 1780 cm^{-1}) and 1031 cm^{-1} characteristic of a lactone and the

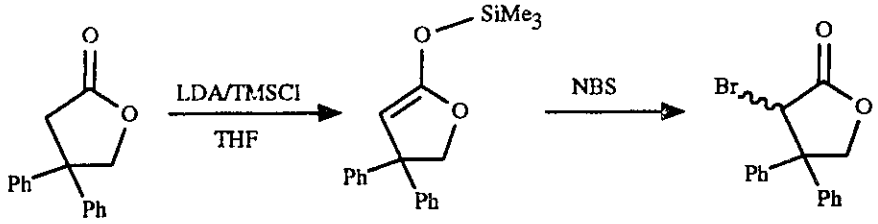
proton NMR was identical to that reported previously in the literature by Morand et al..

Scheme 22.



Much to our surprise, hydroxylation of **30** proved quite difficult. Initially, since an optically active hydroxylated product was not essential and an expedient synthesis was desired it was decided to brominate **30** in the α-position and then subsequently displace the halogen with hydroxide ion. The first attempts to brominate **30** using NBS and AIBN or benzoyl peroxide in CCl_4 produced only starting material as evidenced by NMR. Subsequent attempts using LDA and NBS also failed producing a mixture of starting materials and unidentified products. However, addition of **30** to a solution of TMSCl and LDA followed by treatment with solid NBS[53] produced the brominated diphenyl lactone **31** (mp 142 °C) in 45% yield via the enolsilyl ether intermediate shown in Scheme 23.

Scheme 23.

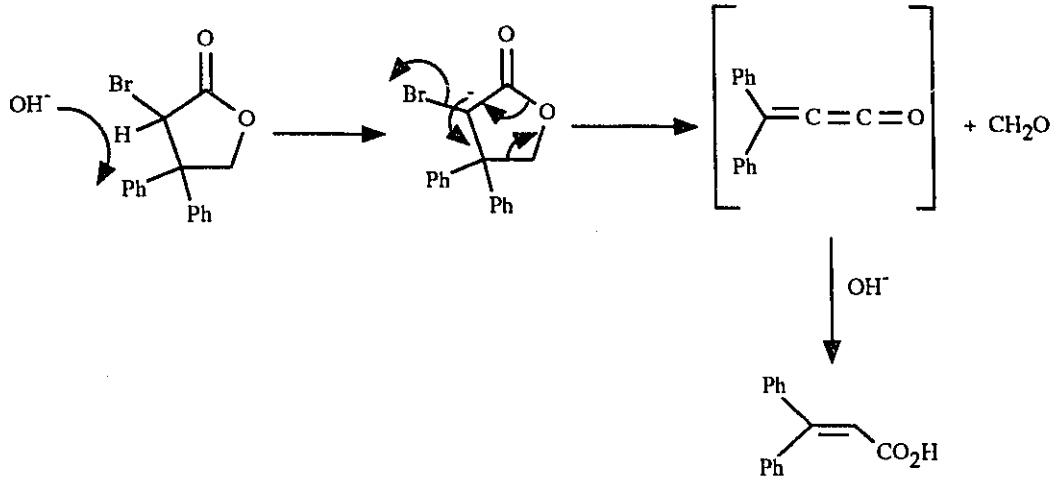


31

In the proton NMR of **31** the two doublets at 5.20 and 4.80 ppm respresented an AB type spin system (J_{AB}=10 Hz) which corresponded to the methylene group on the lactone ring. The resonance respresenting the proton α- to the carbonyl group appeared as a singlet and overlapped with the part of the AB spin system at 5.20 ppm. As a consequence of this the more downfield portion of the AB system is not symmetrical. The proton integration also confirmed that the doublet at 5.20 ppm was respresentative of two hydrogens.

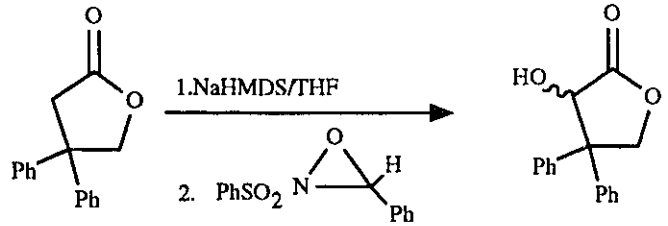
Attempts to displace the bromine under mild conditions using 5% $NaHCO_3$ in acetone failed and produced only starting material. Similarly reaction of **31** with a 40% solution of NaOH in MeOH at room temperature failed to produce the desired α-hydroxy lactone. However when the above reaction mixture was refluxed for 1 day, TLC showed that all of the starting material had been consumed. Work up of the reaction mixture produced a white solid which had a mp 156-158 °C and was identified as β-phenylcinnamic acid (lit. mp 158-160 °C[54]). Mass spectral analysis also confirmed this conclusion. A plausible mechanism by which this product was formed is shown in Scheme 24.

Scheme 24.



At this point no further attempts to displace the halogen were made. Instead direct hydroxylation of lactone **30** with (+/-) *trans*-2(phenylsulfonyl)-3-phenyl oxaziridine was attempted. This reagent was synthesized by epoxidation of N-benzylidenebenzene sulfonamide with *m*-CPBA.[55] Reaction of lactone **30** with NaHMDS in THF followed by addition of a THF solution containing the oxaziridine reagent at -78 °C and usual work up produced the desired α-hydroxy lactone in 60% yield as shown in Scheme 25.[56]

Scheme 25.

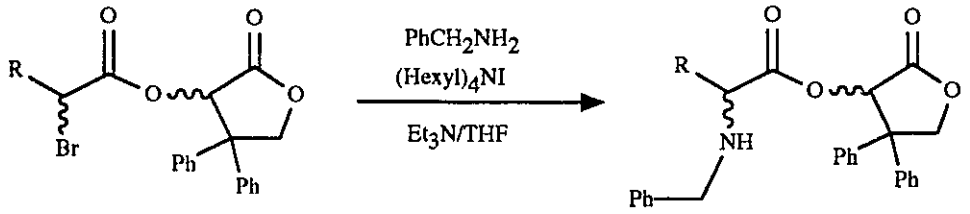


30 **32**

Compound **32** was fully characterized and the proton NMR was very similar to that of **31**. Two doublets at 4.45 and 5.18 ppm (J=9.6 Hz) represented the methylene hydrogens while the proton α- to the carbonyl appeared as a singlet at 5.10 ppm. The corresponding α-halo ester **33** was prepared via a DCC coupling[57] of **32** with α-bromobutyric acid in 52% yield as

a colourless oil and was fully characterized. Epimerization of **33** by treatment with tetra-*n*-hexylammonium iodide and subsequent reaction with benzylamine as described previously furnished the N-benzylated α-amino ester **34** in 93% yield as a colourless oil in a 3:1 mixture of diastereomers (see Scheme 26). It was not possible to separate the diastereomers by column chromatography. Figure 9 shows the proton NMR of the purified product while the inset shows a 500 MHz proton NMR of the crude diastereomeric ratio. The resonance at 6.50 ppm represents the α-proton on the lactone ring and each singlet corresponds to one of the two diastereomers.

Scheme 26.



33 R=CH_3CH_2-
35 R=Ph-

34 R=CH_3CH_2-
36 R=Ph-

Since this was an unexpected result α-halo ester **35**, a derivative of **33** was synthesized and fully characterized. Reaction of **35** under identical conditions with benzylamine produced a 3.5:1 diastereomeric mixture of **36** as white crystals (mp 101 °C) in 97% yield. The major diastereomer (which was still a mixture of enantiomers) was separable by recrystalization and was fully characterized. A proton NMR of the purified product is shown in Figure 10 and a 200 MHz expansion of the region at 6.40 ppm shows the crude diastereomeric ratio. An X-ray structure analysis of **36** (Figure 11) confirmed that the recrystallized product had the RS/SR configurations at the two chiral centers. Thus, the relative configuration of the major product produced was consistent with that obtained when (R)-pantolactone was used. While an obvious explanation for why the

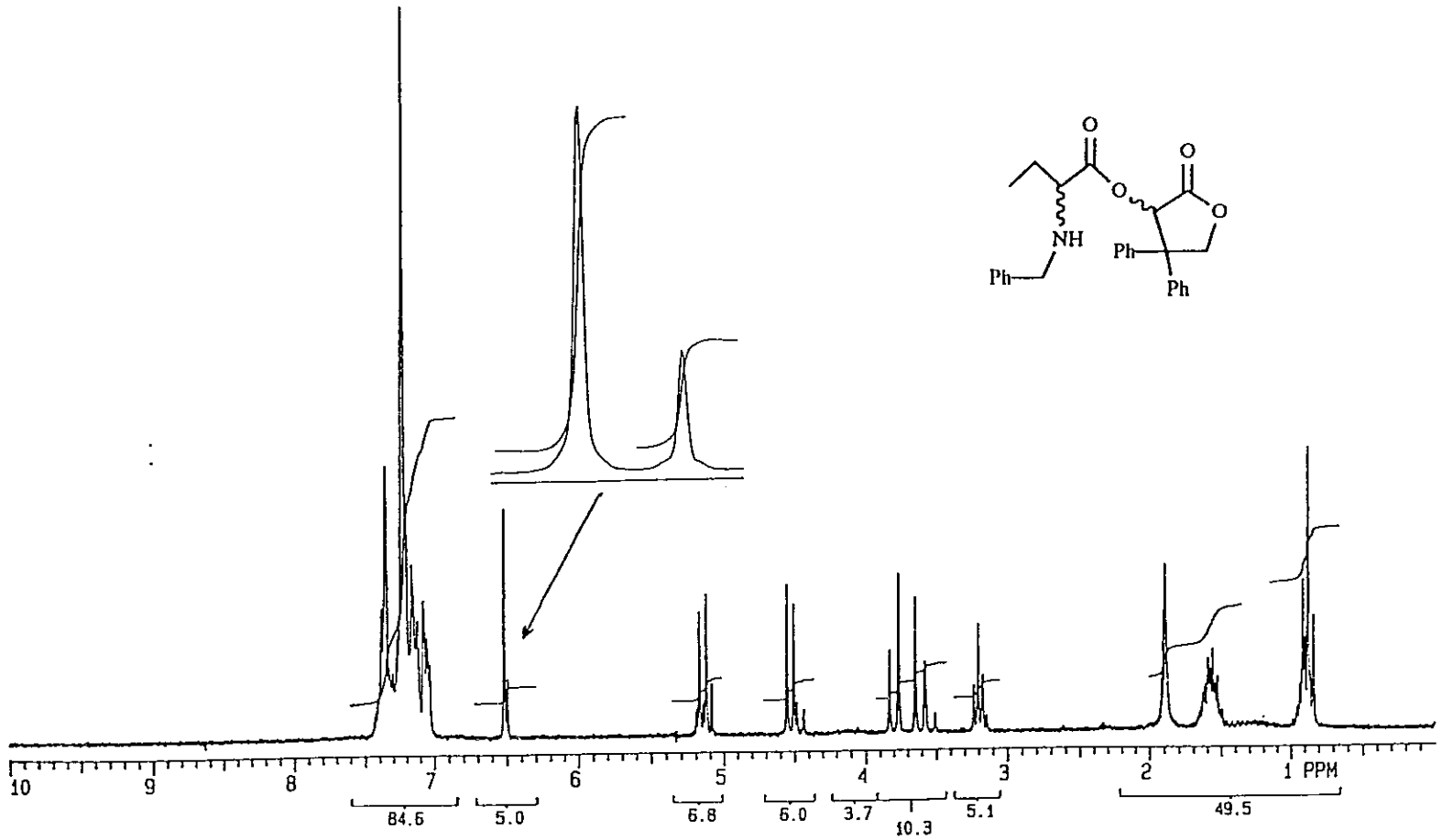


Figure 9. 200 MHz ^{1}H NMR spectrum of **34** in $CDCl_3$. Inset shows 500 MHz expansion with crude diastereomeric ratio.

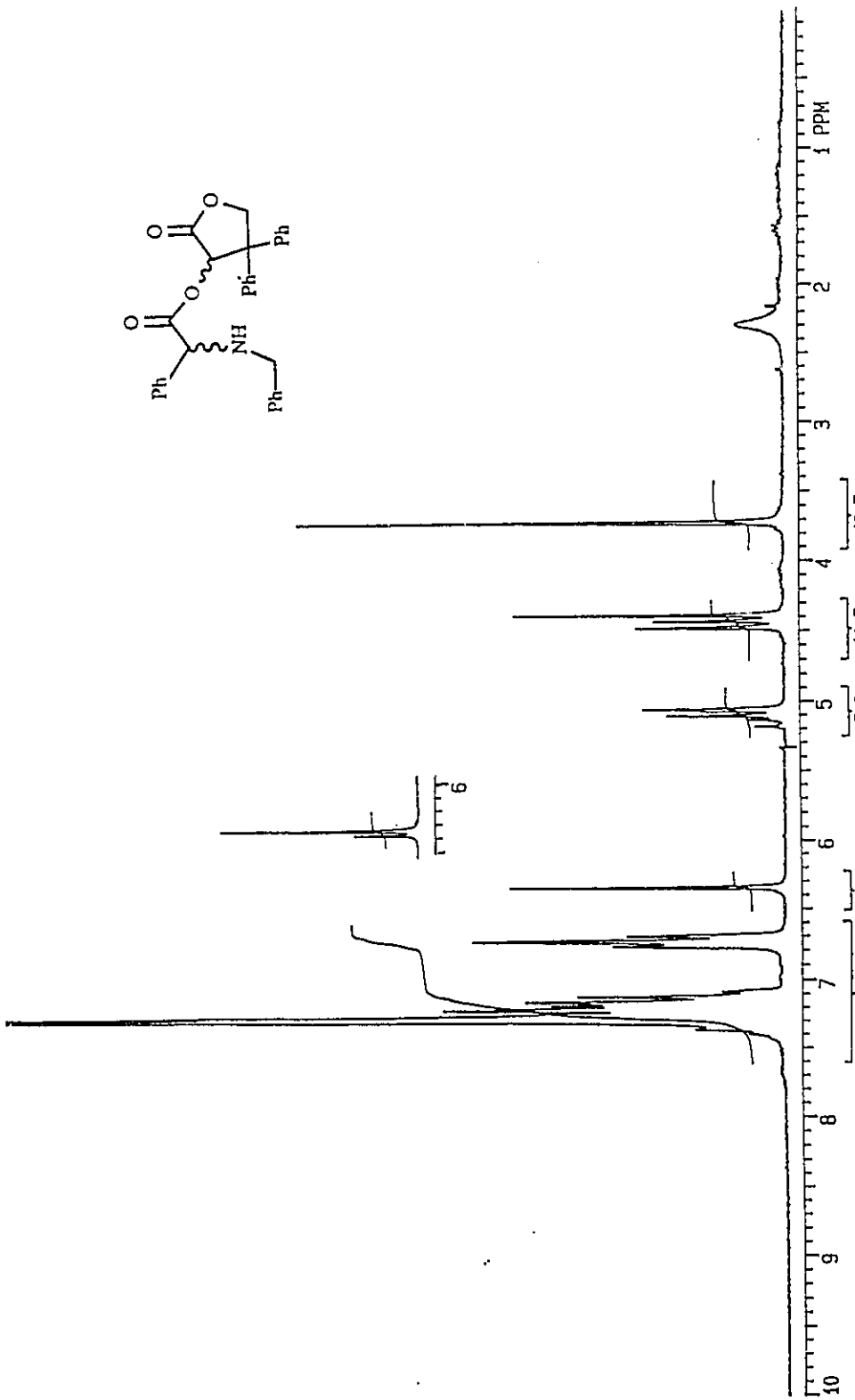


Figure 10. 200 MHz ^{1}H NMR spectrum of **36** in $CDCl_3$. Inset shows crude diastereomeric ratio.

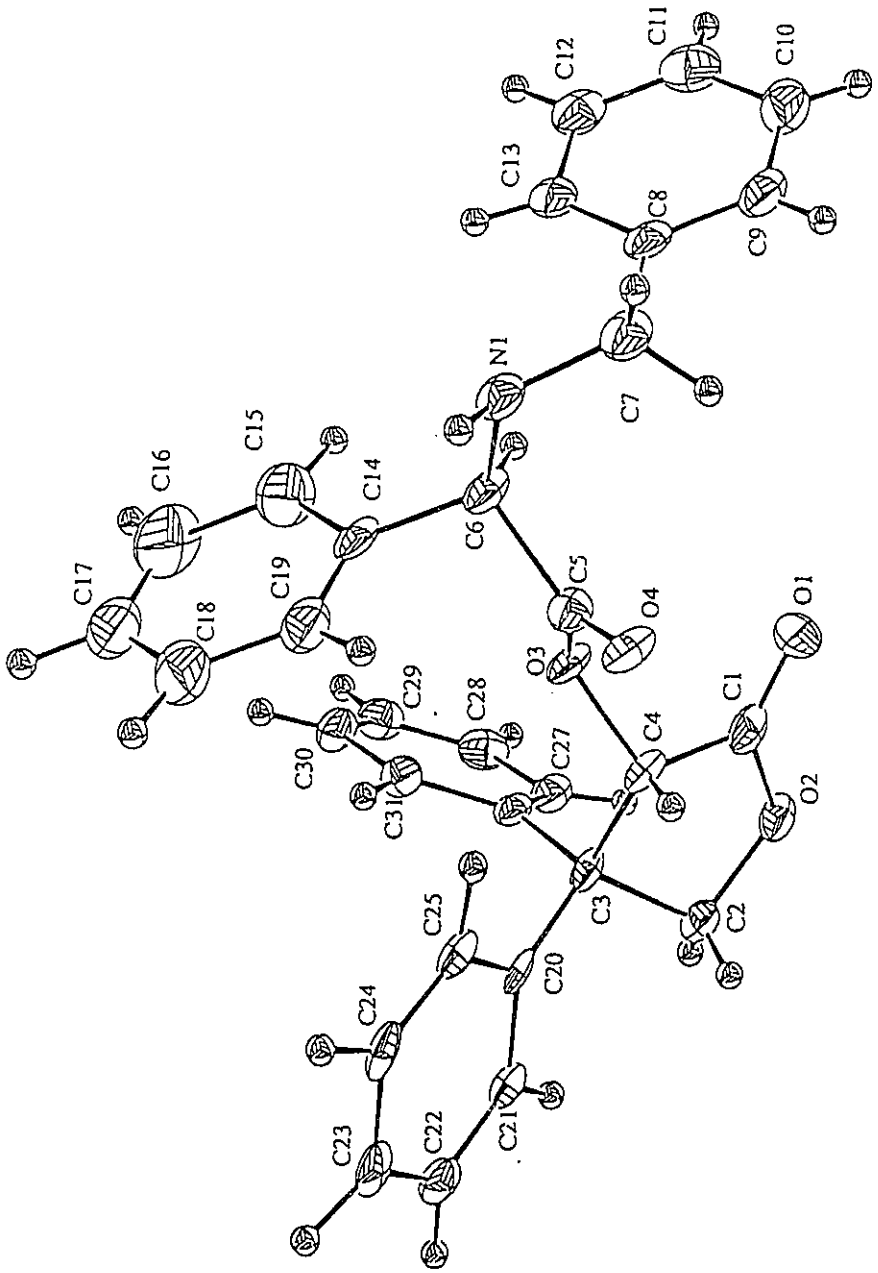
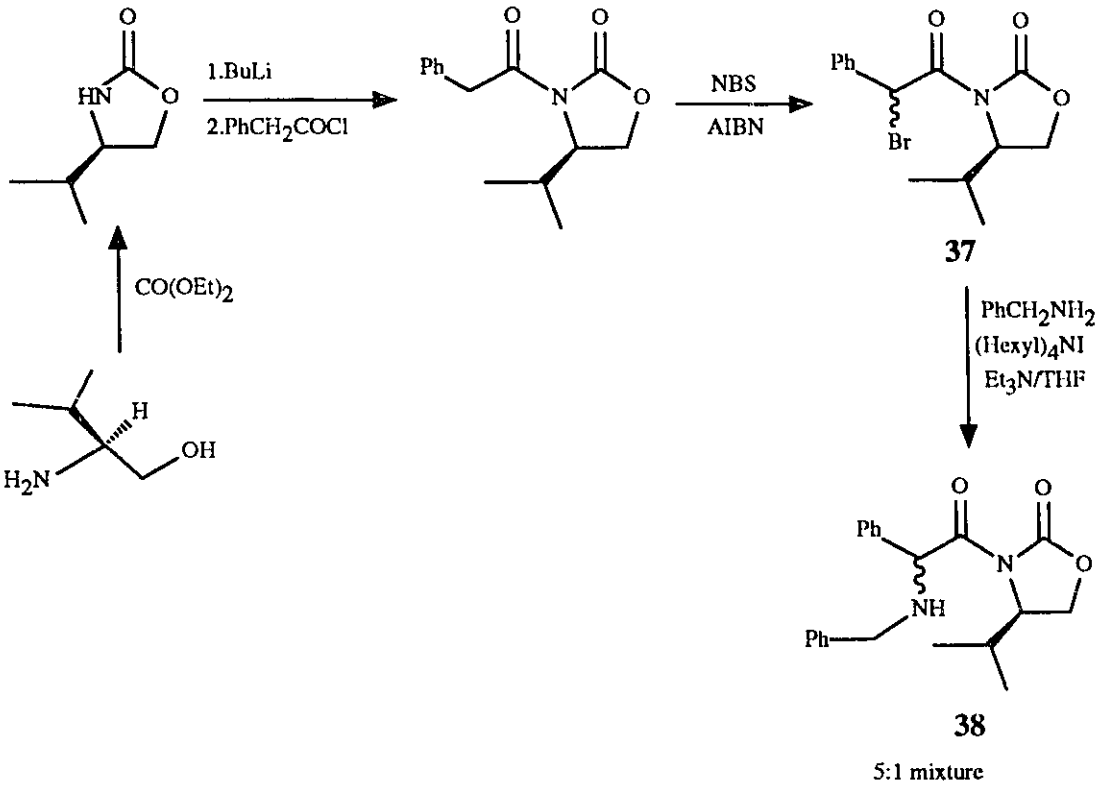


Figure 11. X-ray crystal structure of **36** (major product).

gem-diphenyl-α-hydroxy lactone is a poorer auxiliary than (R)-pantolactone has eluded us, it is important to note that increasing the size of the R group on **33** and **35** appeared to have a positive effect on the diastereomeric ratios. This aspect will be discussed in the next section.

Another auxiliary which showed great potential was an Evans's oxazolidinone. Using a standard literature procedure[58] the corresponding 3-isopropyl-oxazolidinone (prepared from (S)-valinol and diethycarbonate) was reacted with butyllithium and phenylacetyl chloride as shown in Scheme 27. The adduct which was obtained in 50% yield was then subjected to bromination using NBS and AIBN to produce α-halo amide **37** in 76% yield which was fully characterized. Reaction of **37** with benzylamine as described earlier produced the desired product **38** in 85% yield and a proton NMR of the crude product indicated that both diastereomers were present in a 5:1 ratio based on the integration of the remaining benzylic hydrogen at 6.82 and 6.90 ppm.

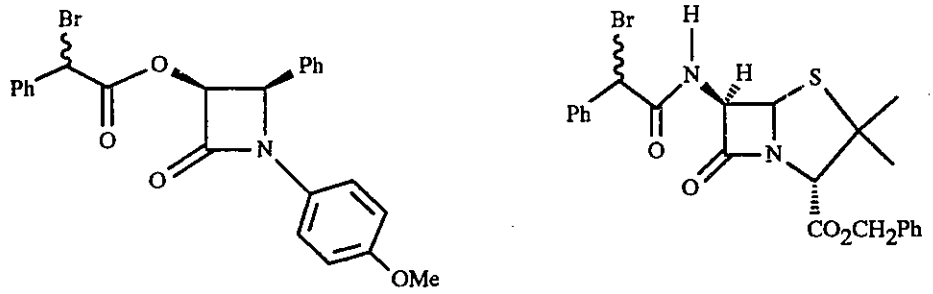
Scheme 27.



While a ratio of 5:1 is not an improvement over (R)-pantolactone the oxazolidinone auxiliary appears to be the second best auxiliary for these reactions. Investigations using other oxazolidinone auxiliaries are currently being conducted in our laboratory.

Two different β-lactam auxiliaries shown in Figure 12 have also been tested. However reaction of the corresponding α-halo compounds with benzylamine produced mixtures of multiple products, none of which were identified.

Figure 12.



It was hypothesized that initial displacement of the α-halogen took place and this was followed by an intramolecular nucleophilic attack of the amine on the lactam carbonyl which resulted in an opening of the β-lactam ring. This hypothesis was supported by the observations that IR spectra of the crude product mixtures showed no characteristic β-lactam absorptions.

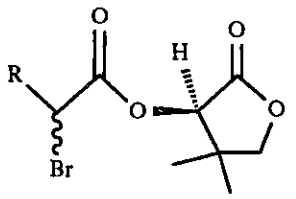
In summary the use of (R)-pantolactone as a chiral auxiliary in these reactions produces products that have the highest de's. Obviously pantolactone is a very special auxiliary, nevertheless efforts are still underway in our laboratory to find other auxiliaries which will provide higher diastereomeric ratios of the desired products.

B) Effect of larger R groups on the α-halo substrate.

In order to properly investigate the effect that larger R groups on the α-bromo-pantolactone ester had on the diastereomeric ratios of the products, one had to choose the nature of the R group carefully. For example, Figure 13 depicts two possible α-halo-pantolactone esters which possess large R groups but neither one would be acceptable for this investigation. For instance, based upon results obtained by Koh[51c] it was known that compound **39** reacted extremely slowly with N_3^- presumably because an S_N2 reaction adjacent to a neopentylic center is difficult. Since the rate of reaction of N_3^- is generally much faster than benzylamine, the reaction of benzylamine with compound **39** would take considerably longer than the 3 days required under our typical reaction

conditions and consequently would not be practical. Concerning compound **40**, Koh observed that its reaction with benzylamine generated significant amounts of elimination product while the desired N-substituted α-amino ester was formed in only trace amounts.[51c]

Figure 13.



39 R=*t*-butyl

40 R=CH_2Ph

Based upon these unpublished observations it was decided to synthesize an α-bromo-pantolactone ester in which R=Ph. There were two reasons for this choice. Firstly, the phenyl substituent is large and secondly elimination to form an olefin is impossible. Another attractive feature to utilizing an α-halo ester of this type is that displacement of the halogen will be much faster since the halogen is benzylic in nature. As a consequence of this it was anticipated that the time required for the reaction to reach completion using this α-bromo ester would be considerably shorter.

Compound **41** was synthesized via a DCC coupling of racemic α-bromophenylacetic acid with (R)-pantolactone and was obtained in 80% yield after column chromatography as a 1:1 mixture of diastereomers. The NMR of compound **41** (Figure 14) displayed four well separated methyl resonances (two for each diastereomer) and two separate resonances at 5.51 and 5.48 ppm which corresponded to the methine hydrogen on the pantolactone ring. Also each diastereomer displayed a unique resonance at 5.36 and 5.34 ppm which corresponded to the benzylic methine proton. Integration and comparison of the resonances for each diastereomer confirmed a 1:1 diastereomeric mixture. Compound **41** was then

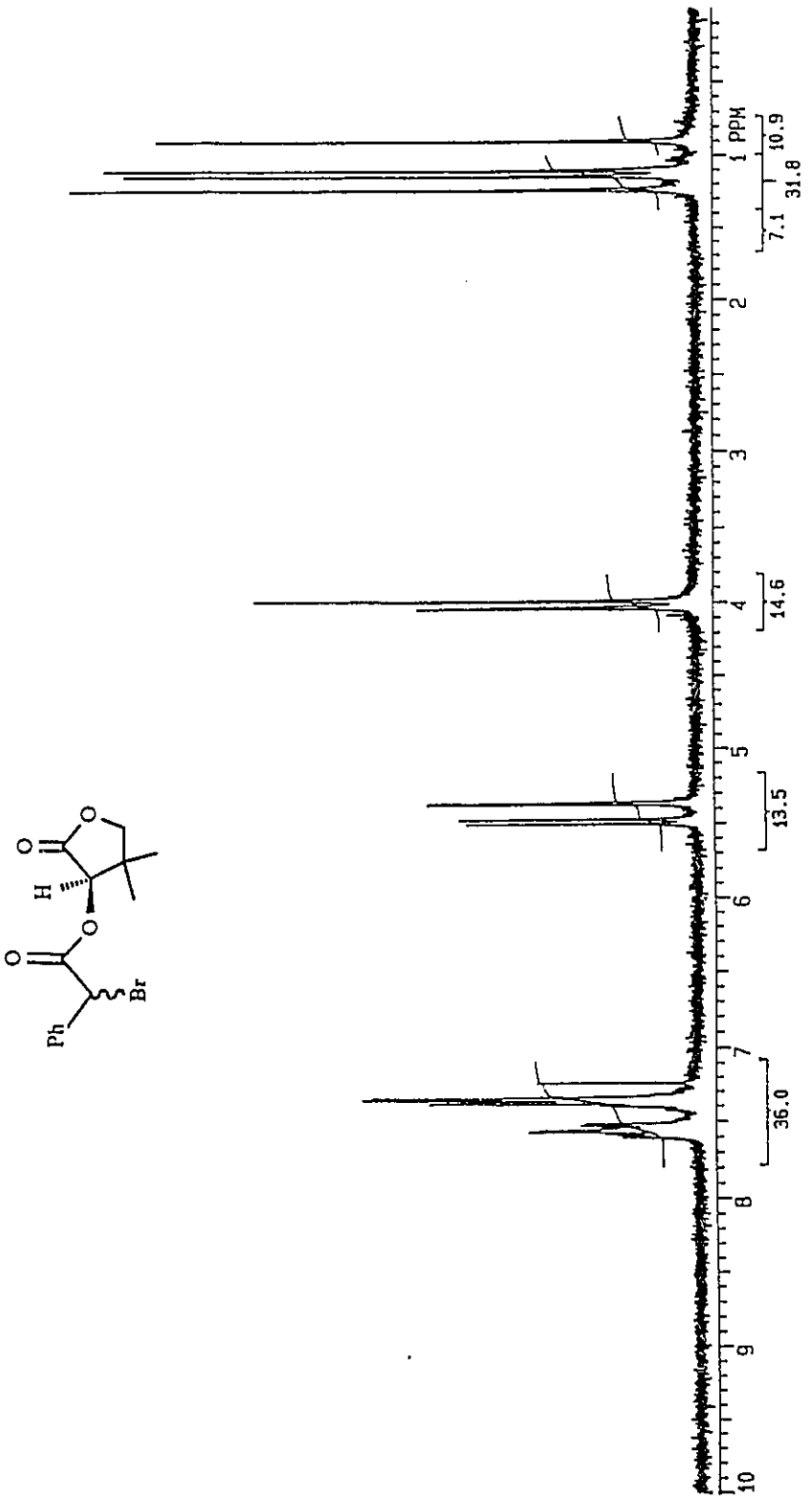
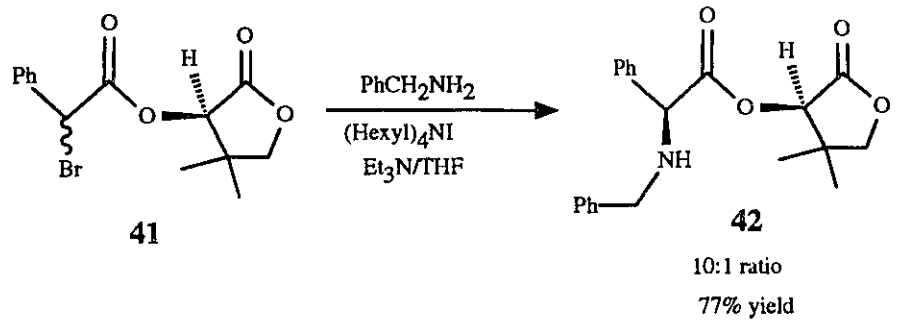


Figure 14. 200 MHz ^{1}H NMR spectrum of **41** in $CDCl_3$.

subjected to reaction with benzylamine under the typical conditions as shown in Scheme 28. A TLC after 12 h indicated that all of the starting material had been consumed and a proton NMR of the crude reaction mixture revealed that the desired products had been formed in 10:1 diastereomeric ratio. Compound **42** was purified and obtained in 77% yield as a 10:1 mixture of diastereomers[38a] as shown in Figure 15. The predominant (S) stereochemistry was verified by reduction to the known (S)-N-benzylglycinol.[38b]

Scheme 28.



This result confirmed that the size of the R group on the α-halo ester had a direct effect upon the diastereomeric ratios obtained in the final products. This conclusion was also supported by the unpublished results of A. Reid an NSERC summer student. Reid synthesized the α-bromo ester shown in Scheme 29 using 1-napthylacetic acid and performed a typical displacement reaction. While yields of the desired displacement product were always low (due to formation of the amide product) the diastereomeric ratios were consistently better than 10:1.[59] An explanation for these observations which is consistent with our mechanistic rationale is outlined below.

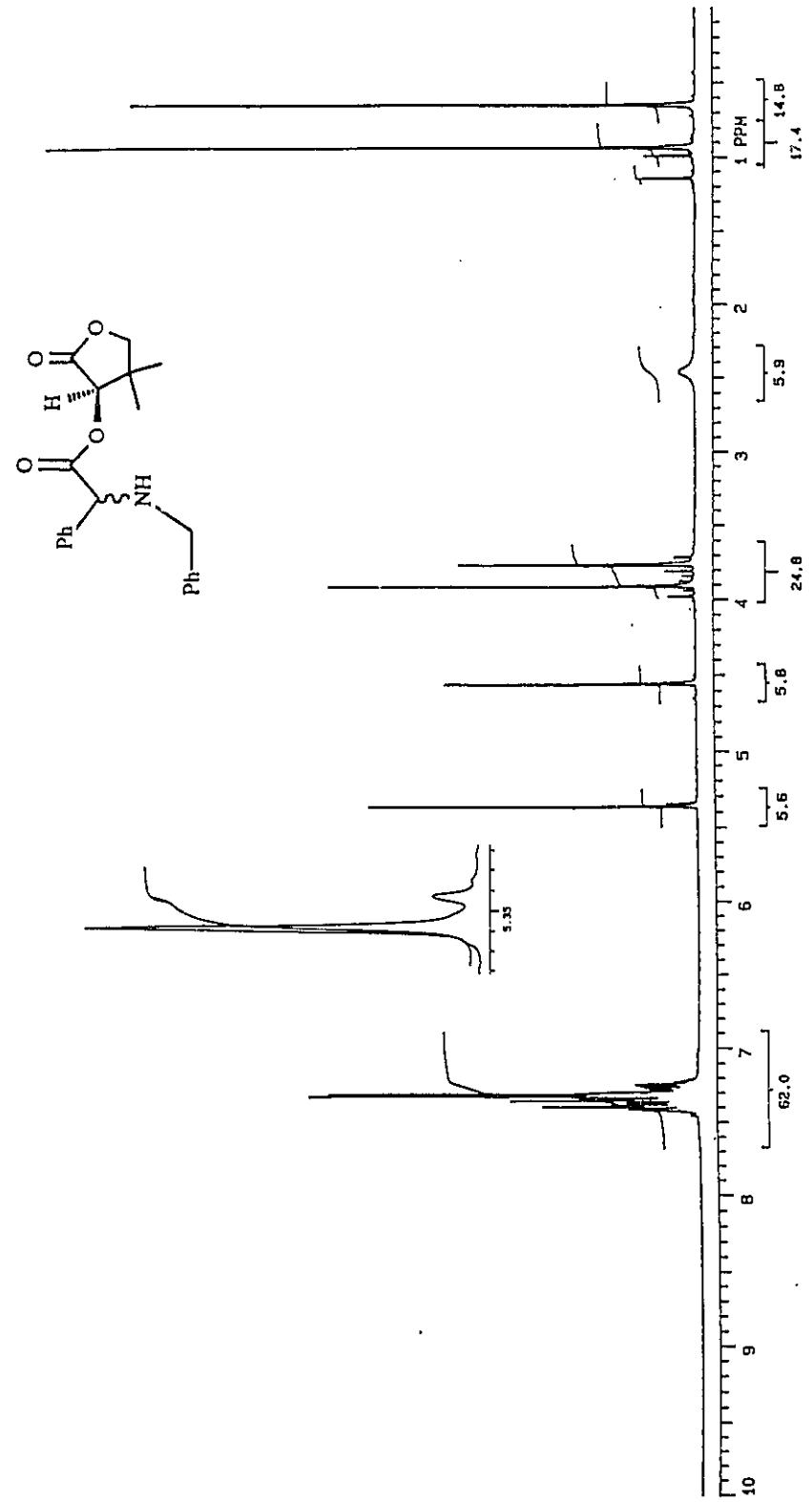
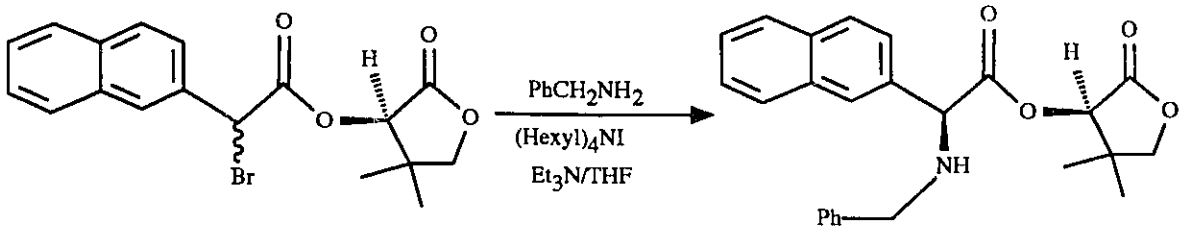


Figure 15. 300 MHz ^{1}H NMR spectrum of **42** in $CDCl_3$. Inset shows crude diastereomeric ratio.

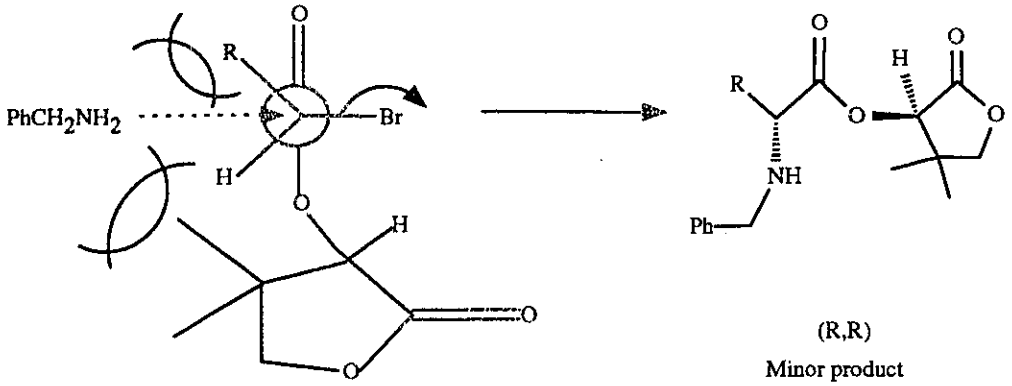
Scheme 29.



>10:1 ratio
55% yield

As mentioned in section 3.1 the slower reacting (S,R)-diastereomer (conformer **III**) could undergo a direct S_N2 displacement reaction with benzylamine if the amine approached *anti-* to the lactone carbonyl. This approach, while probably not favored is possible since the *gem*-dimethyl group of the pantolactone does not completely block this side of the molecule. However, as the size of the R group increases it would become increasingly difficult for the benzylamine to successfully displace the bromine as illustrated in Figure 16 due to steric interactions not only with the *gem*-diphenyl but also with the R group. Since both of the interactions are additive, the net result would be a decrease in the rate of formation of the (R,R)-N-benzyl-α-amino ester and an increase in the optical purity of the desired (S,R) product.

Figure 16. Reaction of slower reacting (S,R)-isomer with benzyl amine *anti-* to the lactone carbonyl.



(S,R)
Slower reacting

(R,R)
Minor product

N.B. as the size of R increases the steric interactions between it and the amine nucleophile increase and disfavor reaction reaction in this manner.

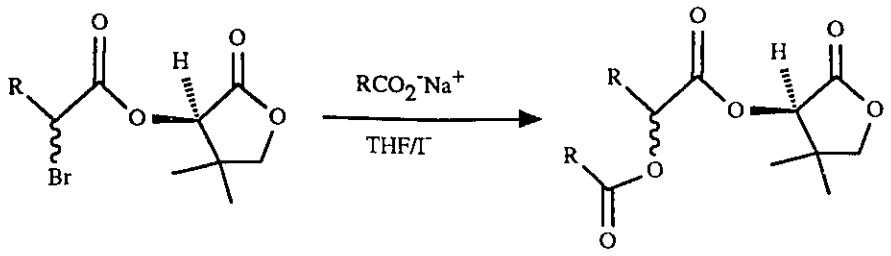
C) The effect of different nucleophiles and their relative rates of reactivity.

i) Other heteroatom nucleophiles. As eluded to in section 3.1 dealing with the general mechanistic aspects of this unusual reaction the possibility of utilizing nucleophiles other than nitrogen was possible. The crucial factor to be considered was the relative rate of reactivity of the nucleophile in question compared to that of bromide ion. In other words, if the nucleophile reacted at a much faster rate than the bromide ion which was responsible for converting the slower reacting (S,R) diastereomer into the faster reacting (S,R) isomer, the diastereomeric ratios in the products would be quite low.

We have had moderate success using other heteroatoms as nucleophiles under our reaction conditions. One strategy involved using oxygen nucleophiles to synthesize optically active α-hydroxy esters and acids. Compounds such as these are important and versatile building blocks in organic synthesis.[60]

Initial experiments by Koh using the sodium and triethylammonium salts of acetic, pivalic and benzoic acids gave the expected substitution products as shown in Scheme 30 but with no diastereoselectivity.

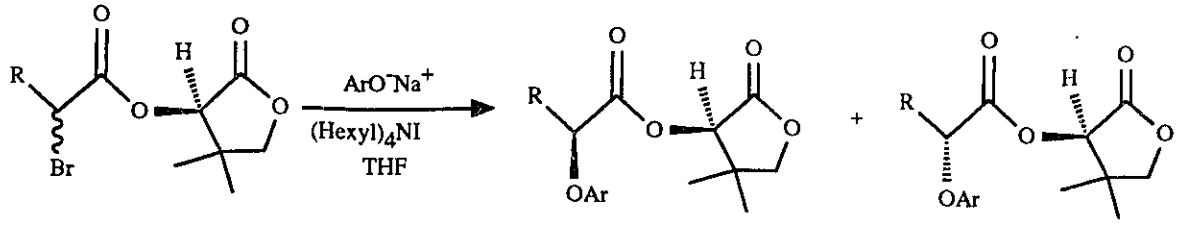
Scheme 30.



50-78% yield
1:1 mixture

However Koh discovered that when a variety of sodium aryloxides were used as oxygen nucleophiles, the desired α-aryloxy esters were obtained in 55-76% isolated yield with diastereoselectivities ranging from 88:12 to 95:5 as shown in Scheme 31.[61]

Scheme 31.



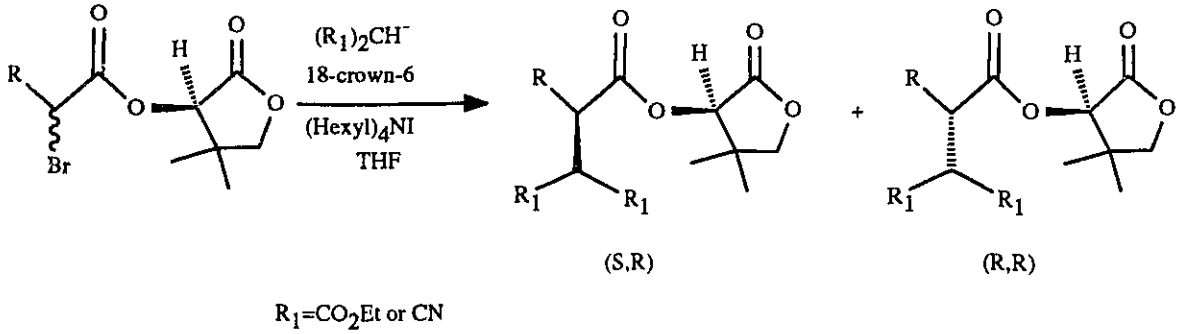
(S,R) (R,R)
55-76% yield
de's 76-90%

The (R)-pantolactone group was removed in several representative cases to furnish the desired α-aryloxy acids in 75-80% yield with the expected (S)-stereochemistry.

Some work has also been done using different carbon nucleophiles but the diastereoselectivities obtained were not as high as those obtained with the oxygen or

nitrogen nucleophiles. The best results were obtained when a highly stabilized anion such as a diethyl malonate anion was used in the presence of catalytic amounts of 18-crown-6 ethers. In general, products were obtained in 50-60% isolated yields with de's 80-85%.[62]

Scheme 32.

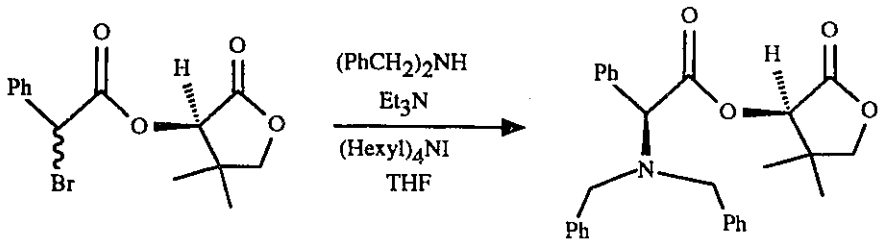


To date no other heteroatom nucleophiles (for example phosphorus) have been examined however a great deal of work has been done with respect to different nitrogen nucleophiles and these interesting results are presented in the next section.

ii) The effects of different nitrogen nucleophiles. As discussed earlier, the difference in reactivity of a nitrogen nucleophile as compared to the bromide ion is approximately two fold. This large rate difference makes nitrogen nucleophiles the ideal choice for our reaction. Based on the fact that increasing the size of the R substituent on the α-halo ester produced an increase in diastereoselectivity it seemed reasonable that an increase in the size of the amine nucleophile may also have a similar effect. In order to test this hypothesis α-halo ester **41** was reacted with dibenzylamine under our typical reaction conditions. After 30 h TLC revealed that all of the starting material had been consumed. Usual work up followed by a 200 MHz proton NMR of the crude reaction mixture suggested that only one diastereomer had been produced (this conclusion was also supported by a 500 MHz NMR). Purification by column chromatography furnished **43** as a pale yellow solid (mp 83

°C) in 70% yield as one diastereomer (Figure 17).

Scheme 33.



43

(S,R) only

70% yield

To verify that the above reaction was highly stereoselective it was repeated in refluxing toluene without any iodide ion present. It was theorized that increasing the reaction temperature would decrease the diastereoselectivity of the reaction and by utilizing toluene as a solvent the Br^- ion generated during the reaction would be precipitated from the solution as Et_3NH^+/Br^- and consequently would not cause epimerization of the starting material. After 3 hours a TLC revealed that the all of the starting material had been consumed and a 500 MHz proton NMR of the crude reaction mixture displayed both the (S,R) and (R,R) diastereomers of the N,N-dibenzyl-α-amino-pantolactone ester in approximately a 2:1 ratio as shown in Figure 18. Based on this evidence, it was concluded that reaction of **41** with benzylamine under typical reaction conditions produced **43** in 70% yield and >98% de. No attempt to define a lower limit on the diastereoselectivity of this reaction using NMR or HPLC was made.

For the purpose of comparison, α-halo ester **15** was reacted with dibenzylamine under typical reaction conditions as shown in Scheme 34. After reaction at room temperature for a period of one week, a TLC of the reaction mixture indicated the presence of starting material and several other spots. Careful separation via column chromatography furnished

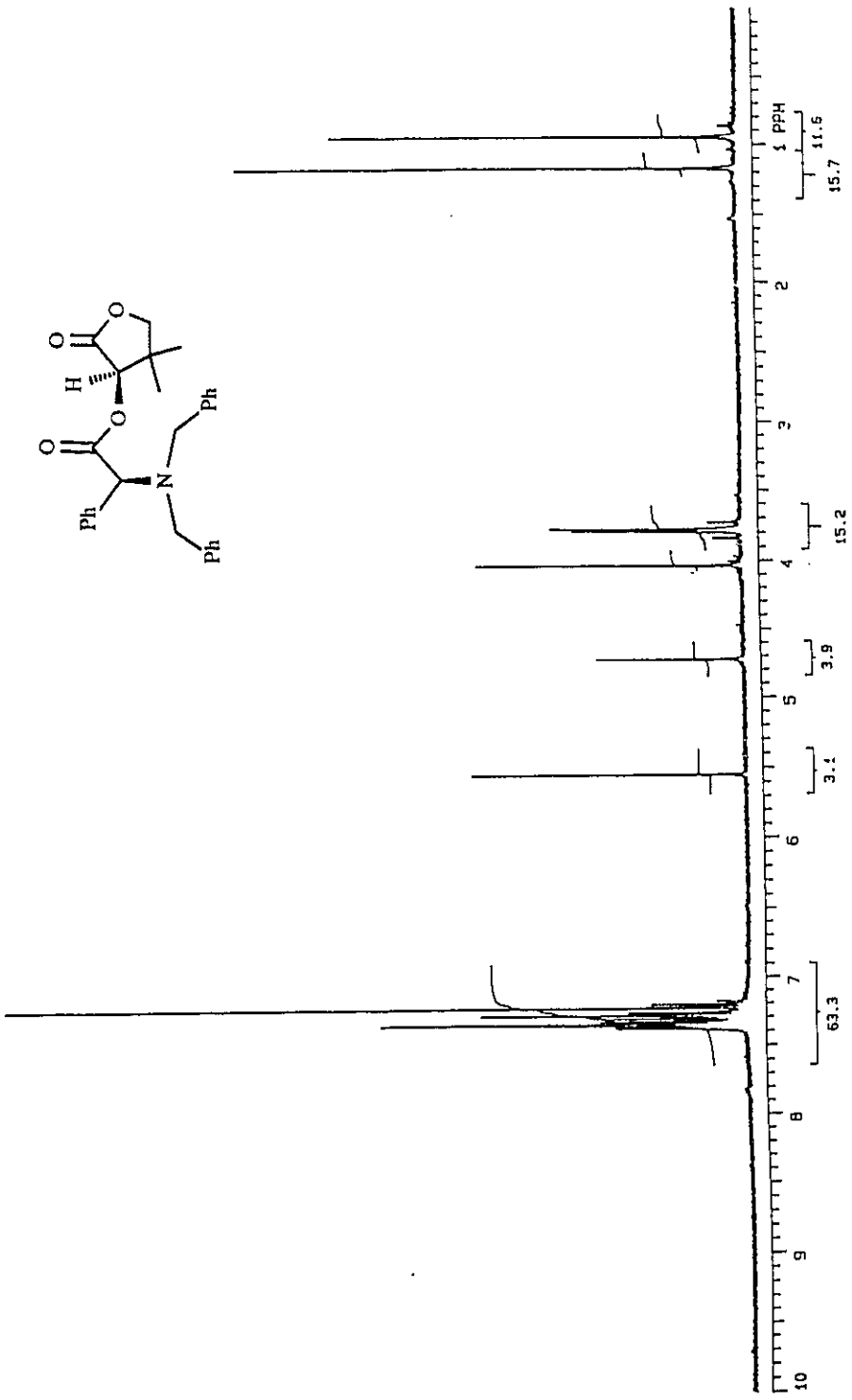


Figure 17. 300 MHz ^{1}H NMR spectrum of **43** in $CDCl_3$.

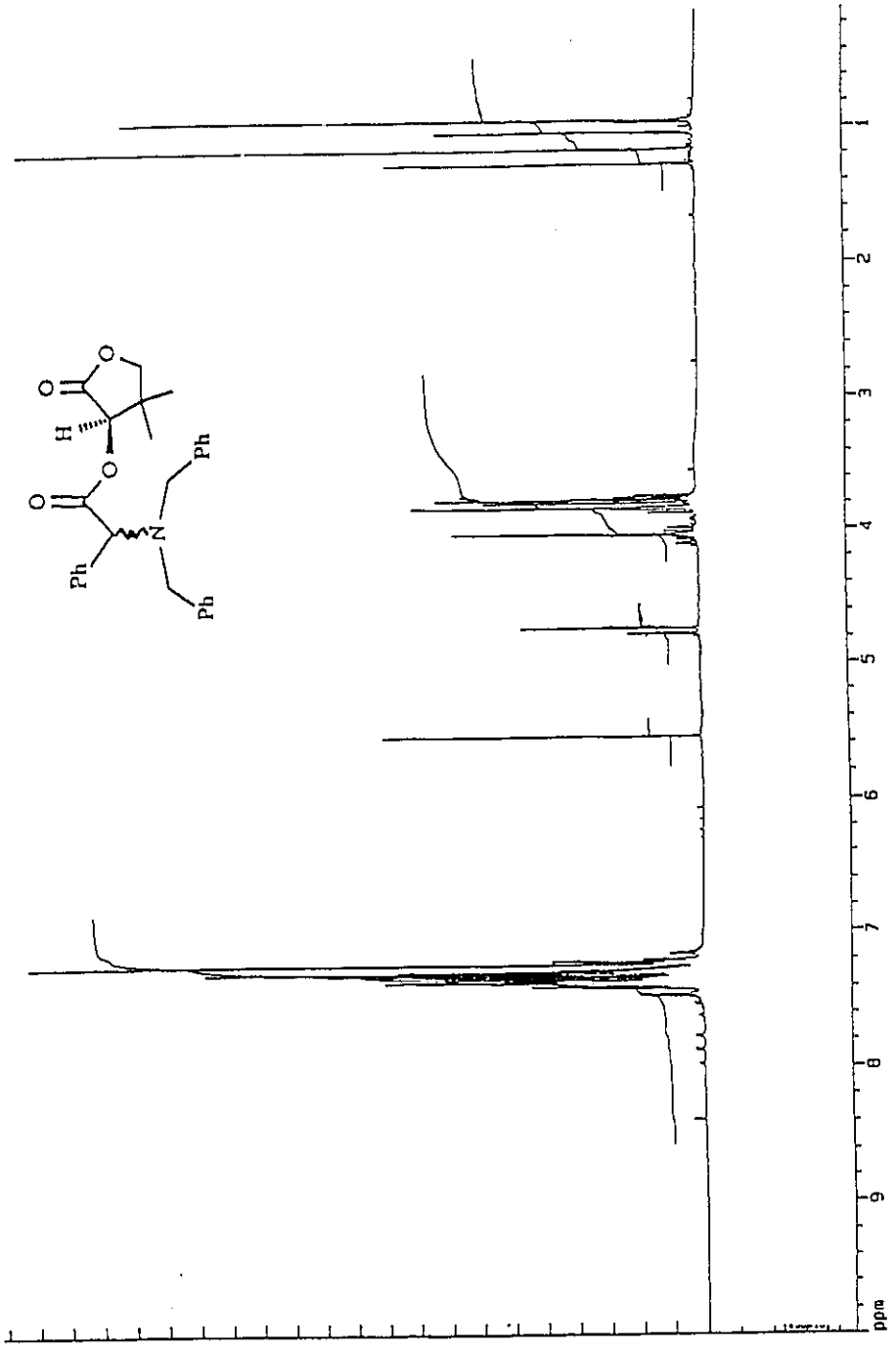
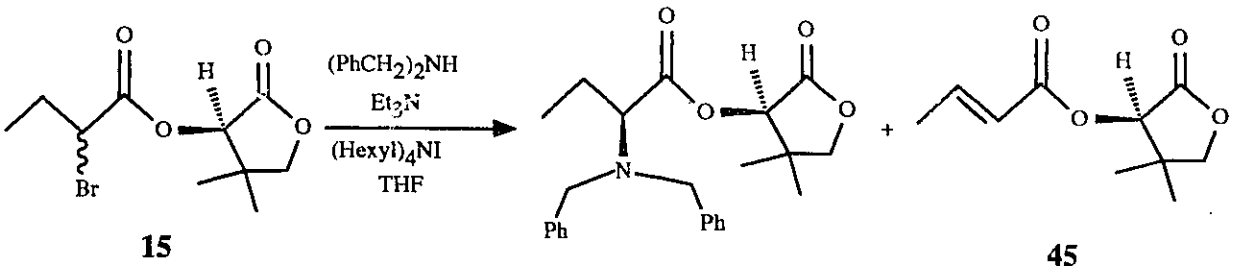


Figure 18. 500 MHz ^{1}H NMR spectrum of **43** after reaction in Toluene.

compound **44** in only 30% yield as a 12:1 mixture of diastereomers.

Scheme 34.



15 **44** **45**

12:1 ratio (SR/RR)

30% yield

20% yield

By comparing the proton NMR of purified **44** (Figure 19) with that of the crude reaction mixture it was concluded that the crude diastereomeric ratio was 12:1. The starting material was recovered in 40% yield and the elimination product **45** was obtained in 20% yield. Several other minor products were not identified. The above experiment served to emphasize the dramatic effect a large nucleophile can have on diastereoselectivity, but it also re-emphasized the importance of a large R group on the α-halo ester. While increasing the size of the nucleophile can have a dramatic effect on the diastereomeric ratios of the products, if the amine is too large its rate of reaction with the α-halo ester decreases and the elimination reaction which produces compound **45** will compete with formation of the desired product.

Compounds **43** and **44** are potential precursors to N,N-dibenzylamino aldehydes and ketones which have been shown to undergo highly diastereoselective additions with RMgX, RLi, R_2CuLi and lithium enolates to form β-amino alcohols.[63] Recent work in our lab has dealt with the synthesis of other N,N-dibenzyl-α-amino esters which have been obtained in 70-85% yield with de's >98%. These esters can be transformed into the desired N,N-dibenzylamino aldehydes or ketones.

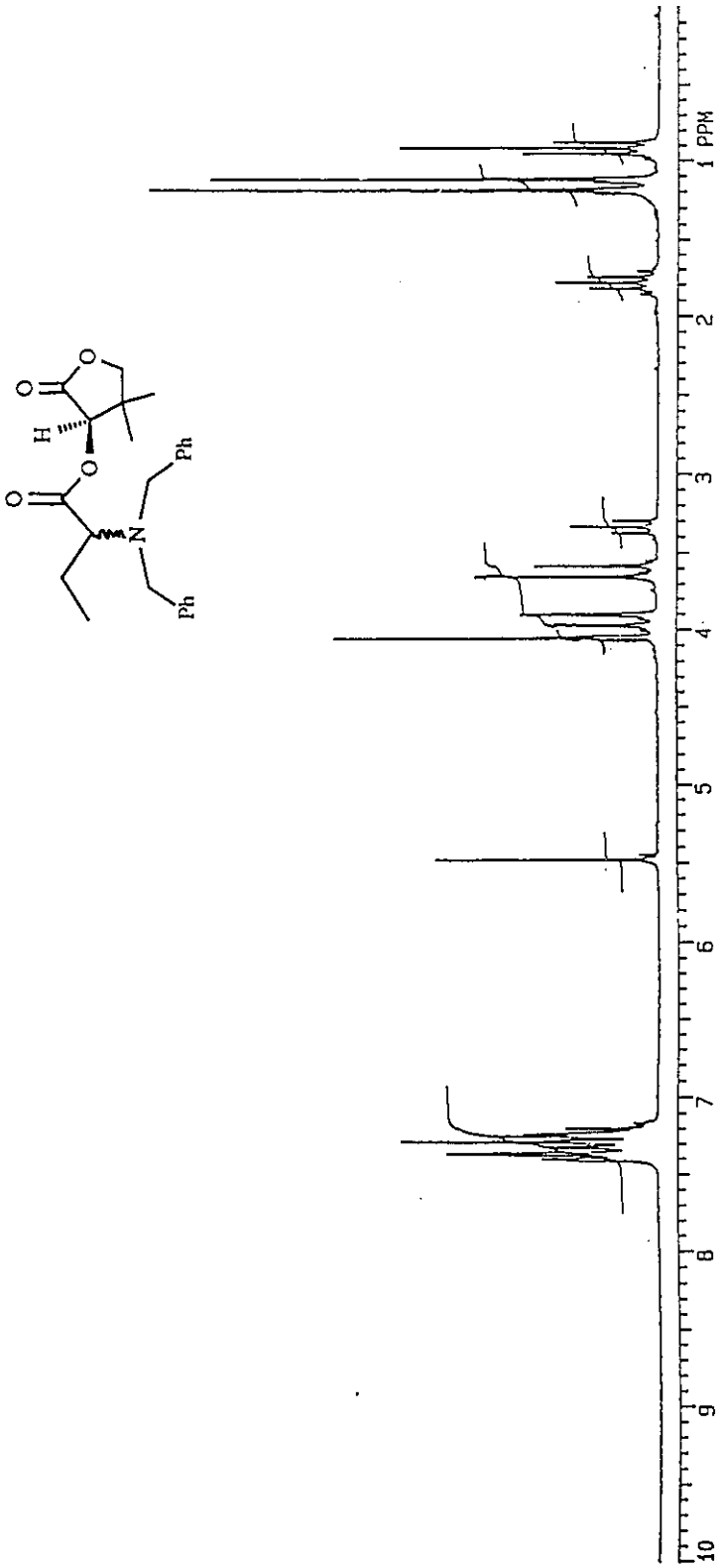
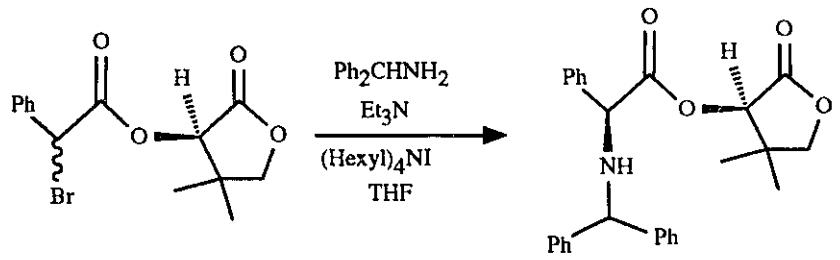


Figure 19. 200 MHz ^{1}H NMR spectrum of **44** in $CDCl_3$.

Several other sterically demanding benzylamine derivatives have been reacted with ester **41**. Aminodiphenylmethane or benzyhydrylamine produced only one diastereomer when used a nucleophile as shown in Scheme 35. Compound **46** was isolated in 78% yield as a colourless oil. The NMR of the purified product is shown in Figure 20.

Scheme 35.

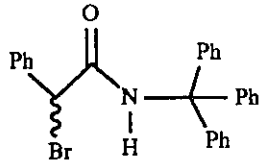


46

one diastereomer

78% yield

The production of only one diastereomer was again confirmed by repeating the reaction using refluxing toluene as a solvent, which decreased the diastereoselectivity and produced both isomers. The use of an extremely bulky amine such as tritylamine (Ph_3CNH_2) failed to produce any of the desired displacement product. Instead, the pantolactone group was displaced and an amide bond formed, producing compound **47** and (R)-pantolactone. Compound **47** was not fully characterized and it was concluded that if the amine was too large it could not successfully displace the halogen and subsequently reacted at the ester carbonyl.



47

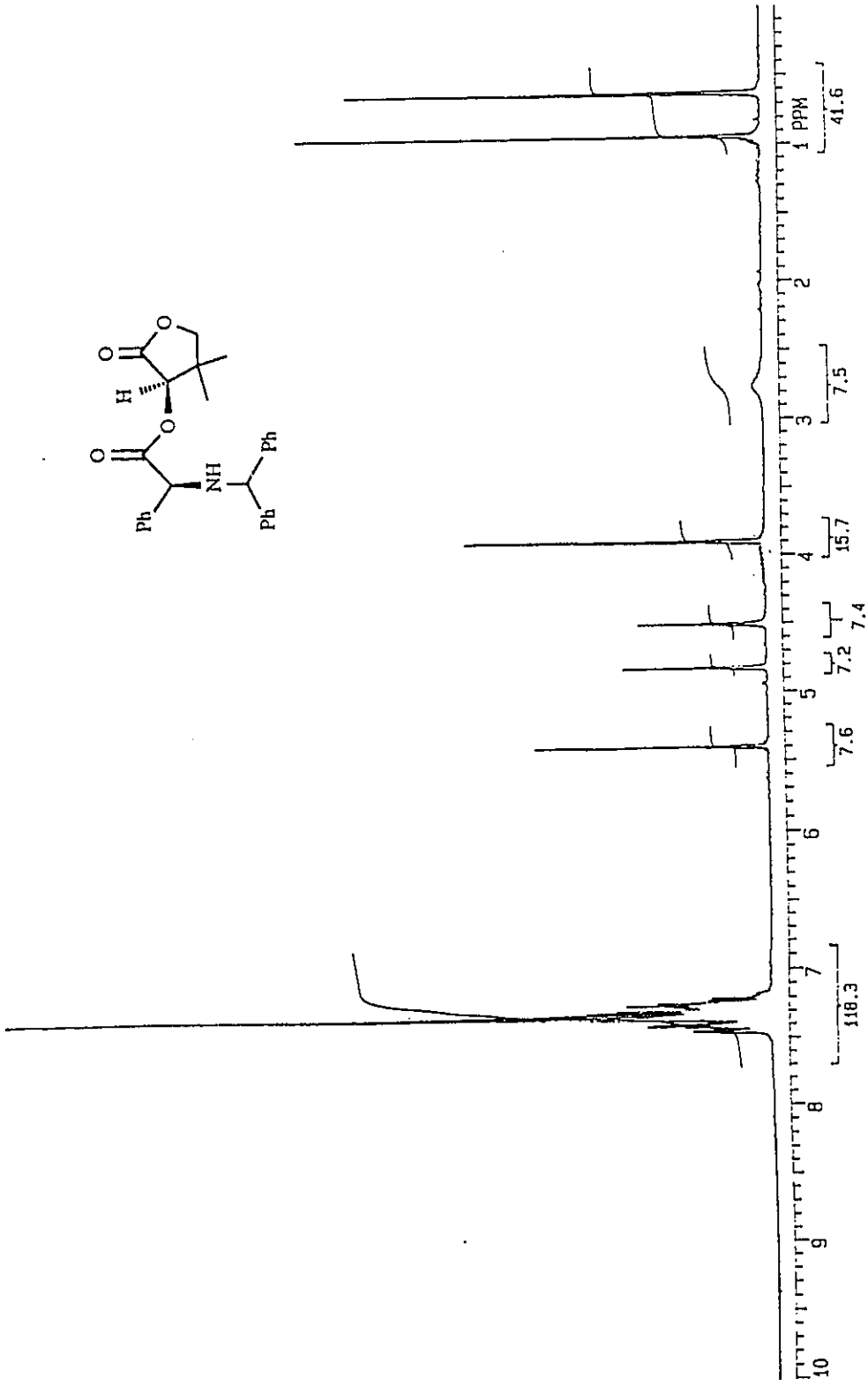
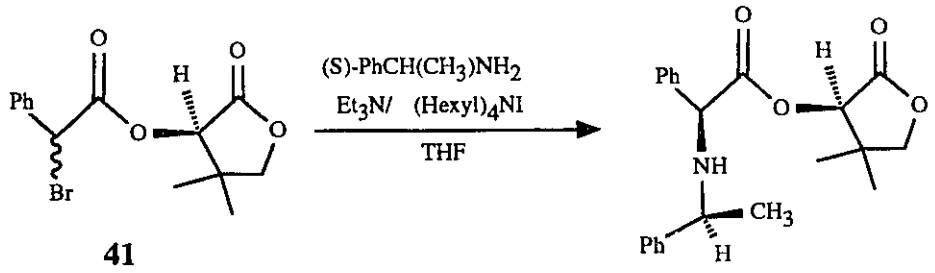


Figure 20. 200 MHz ^{1}H NMR spectrum of **46** in $CDCl_3$.

The reaction of α-halo ester **41** with chiral derivatives of benzylamine was also investiga. ' Reaction of **41** with 1.1 eq of (S)-methylbenzylamine over a 14 h period produced compound **48** as a colourless oil in 84% yield. Examination by NMR as well as a $Eu(DPM)_3$ shift experiment verified that only one isomer was produced. The proton NMR of the purified product is shown in Figure 21.

Scheme 36.



41

48

one diastereomer

84% yield

Reaction of ester **41** with (R)-methylbenzylamine proceeded equally well and furnished **48a** in 83% isolated yield and again only one isomer as verified by an $Eu(DPM)_3$ NMR shift experiment (see Figure 21). The stereochemistry at the α-carbon was not determined in either case but is assumed to be "S".

Since the one of the strengths of our synthetic method is its ability to produce unusual N-substituted optically active α-amino esters several aryl amines were examined as nucleophiles. The first amine of this type to be utilized in our reaction was *para*-methoxyaniline or anisidine. As illustrated in Scheme 37, reaction of α-halo ester **41** with anisidine at room temperature for 10 h produced a single diastereomer of compound **49** as needle like crystals (mp 118-120 °C) in 75% yield (see Figure 22).[38a] A 500 MHz proton NMR of the crude reaction mixture revealed no evidence of the other diastereomer.

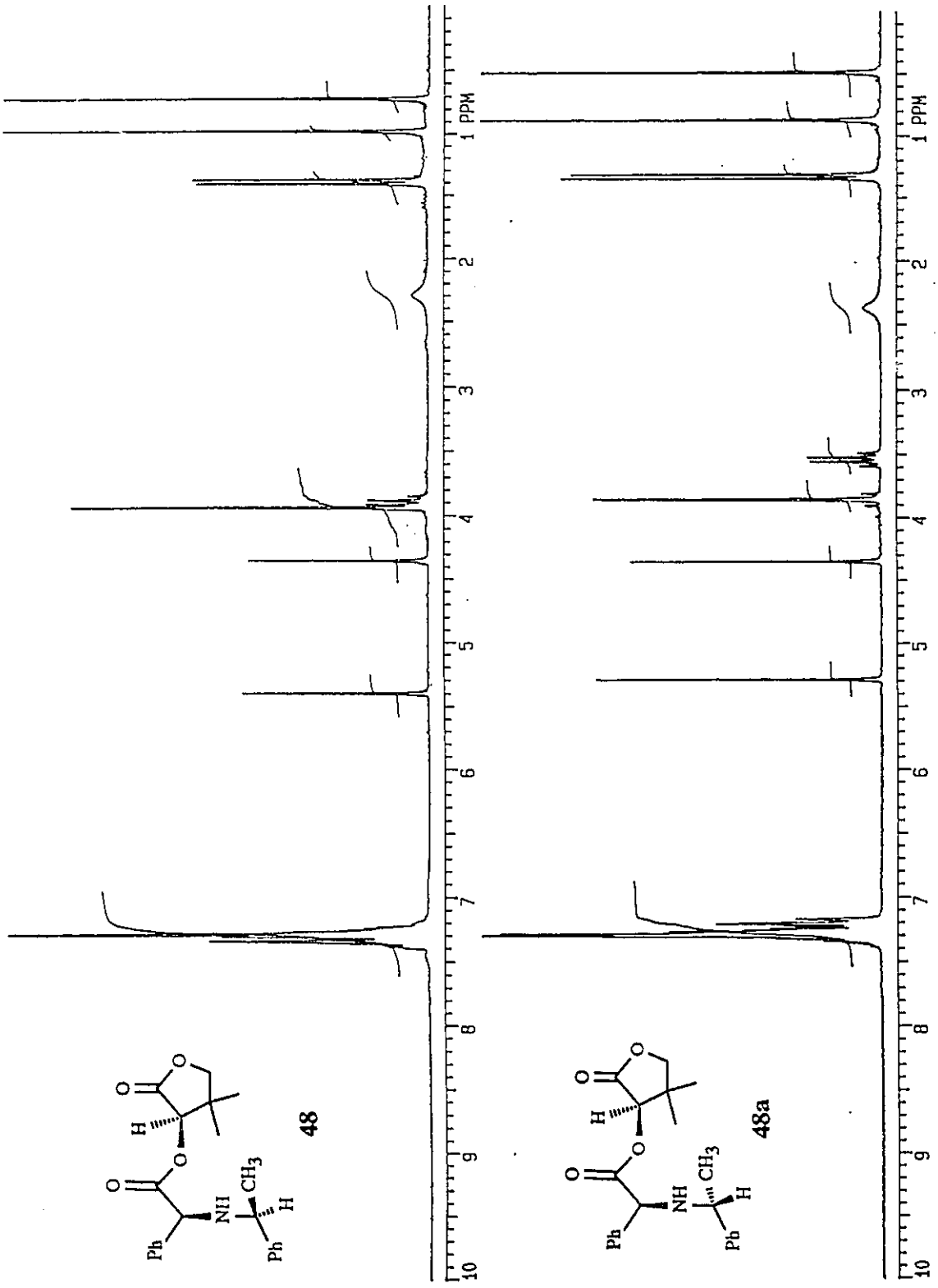


Figure 21. 200 MHz ^{1}H MMR spectra of **48** and **48a** in $CDCl_3$.

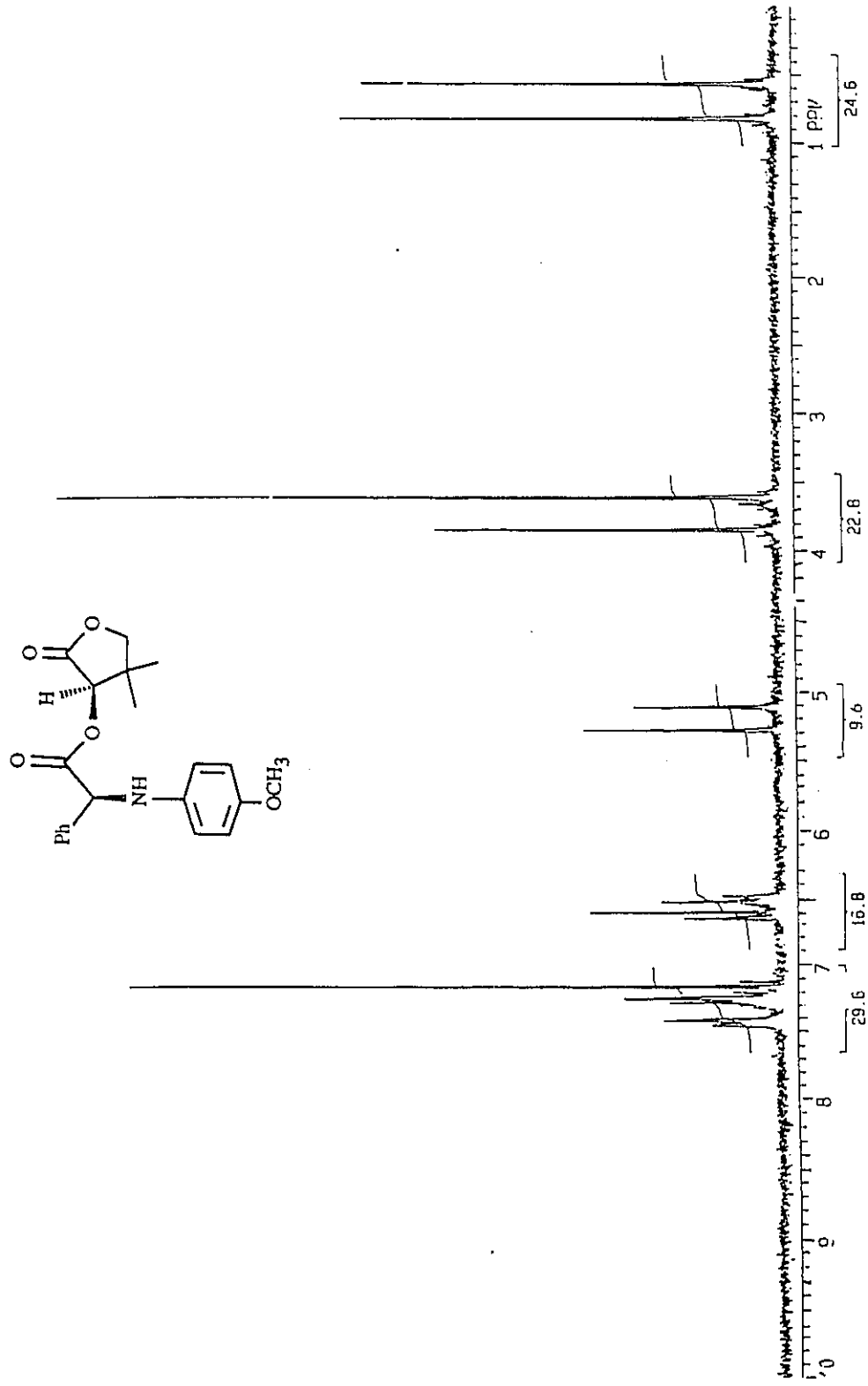
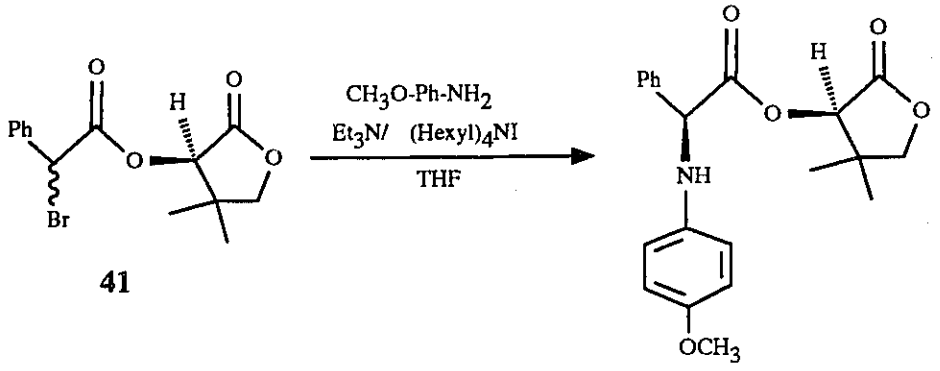


Figure 22. 200 MHz ^{1}H NMR spectrum of **49** in $CDCl_3$.

Scheme 37.



41

49

one diastereomer

75% yield

To verify that the reaction was highly stereoselective it was repeated in refluxing toluene. A proton NMR of this crude reaction mixture illustrated in Figure 23 clearly depicts both diastereomers and verifies that if the reaction is done using THF as solvent only one diastereomer is produced.

Many experiments have demonstrated that not only the size of the amine is important but also its relative nucleophilicity. As shown in Scheme 38 reaction of α-halo ester **41** with *para*-amino phenol produced **50** as a 12:1 ratio of diastereomers. Compound **50** was isolated in 75% yield as a colourless oil.

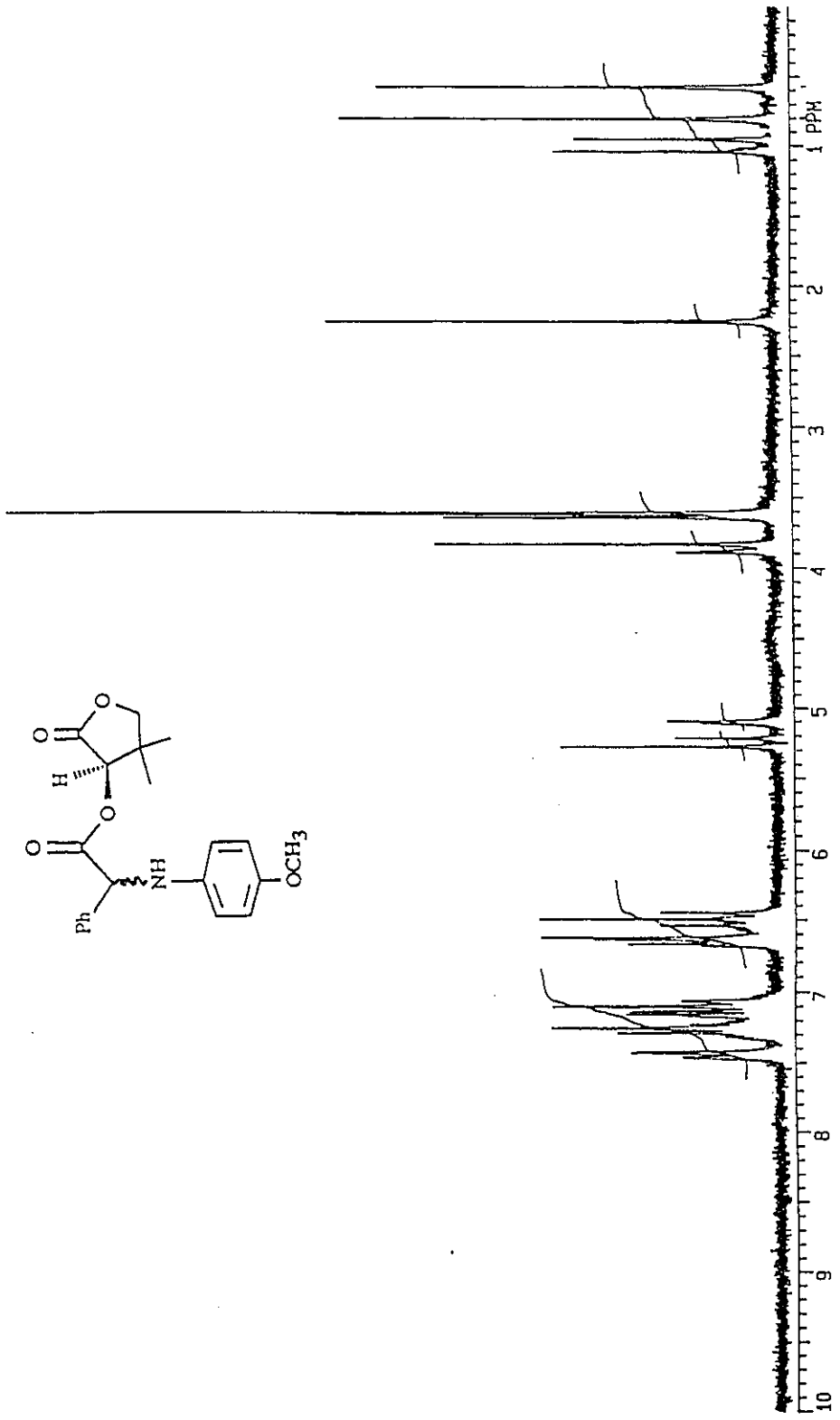
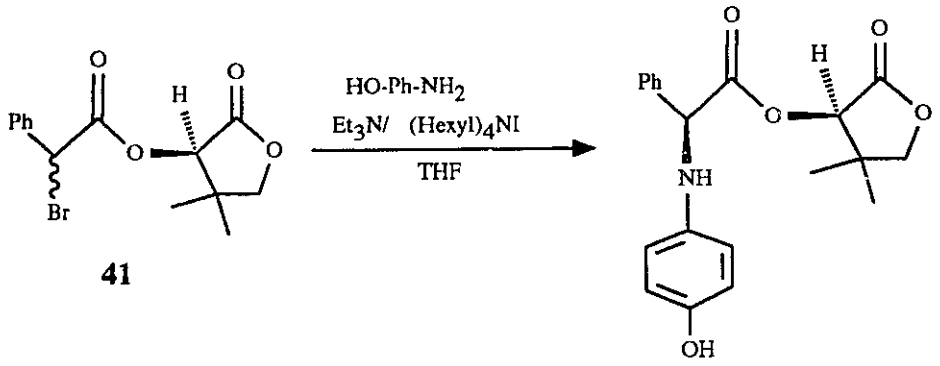


Figure 23. 200 MHz ^{1}H NMR spectrum of **49** after reaction in Toluene.

Scheme 38.



41

50

12:1 mixture (SR/RR)

75% yield

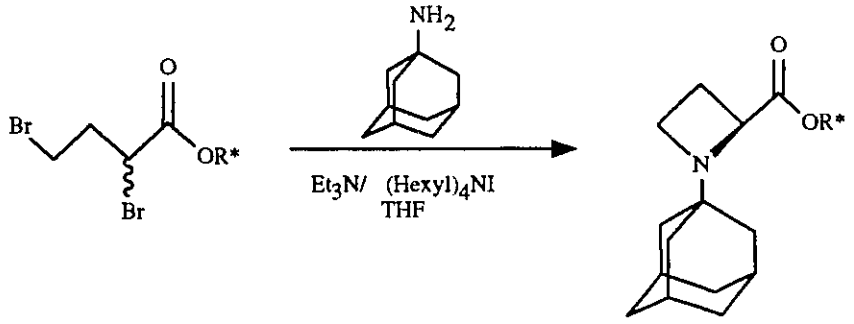
This result was not surprising based on the fact that a predominant amount of the *p*-amino phenol exists as the phenolate under our reaction conditions. The phenolate of *p*-amino phenol is more nucleophilic than anisidine and reacts with the α-halo ester at a much faster rate. Due to this increased rate of reaction there is less time for I^- or Br^- to effect epimerization of the slower reacting (S,R) diastereomer into the faster reacting (R,R) isomer and consequently a decrease in diastereoselectivity is observed.

The above result was very valuable in that it demonstrated that seemingly small differences in the nucleophilicity of various nitrogen nucleophiles can have dramatic effects upon the diastereoselectivity of our reaction.

One of the more unconventional nucleophiles to be employed in our reaction was 1-aminoadamantane. Initial diastereomeric ratios obtained from its reaction with α-halo ester **41** ranged from 15:1 to 20:1. Of particular interest to us was the possible synthesis of compound **52**. Compounds of this nature containing an azetidine ring to which was attached an adamantyl group have been patented by Scherring Corporation as possible anit-parkinson agents.[64] As illustrated in Scheme 39 formation of **52** was envisioned by reaction of 1-aminoadamantane with (R)-pantolacto-2,5-dibromobutanoate under our

typical reaction conditions. Unfortunately, a proton NMR of the crude reaction mixture revealed that only trace amounts of **52** were formed. The major product in the reaction resulted from elimination of the halogen which was evidenced by the presence of deshielded olefinic protons. No attempts were made to optimize the reaction conditions. 1-Amino adamantane was used successfully in the reaction with α-phenyl ester **41**. The yield and diastereomeric ratio were 75% and 15:1.[59]

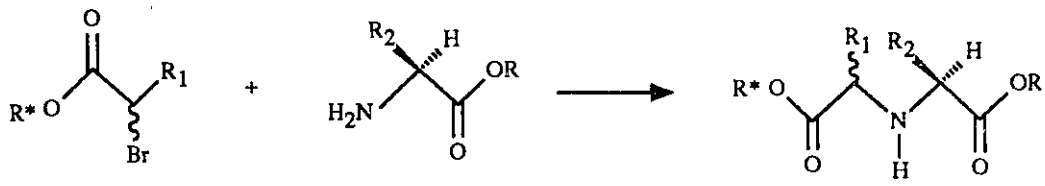
Scheme 39.



52

Based on the experimental observations that the best diastereomeric ratios in the products are obtained when a large and relatively non-basic amine is utilized, optically active α-amino esters seemed like potentially good nucleophiles. Reaction of nucleophiles of this nature with an α-halo ester would lead to unusual compounds which possessed an aminodicarboxy unit as shown in Scheme 40.

Scheme 40.



R*=(R)-pantolactone

53

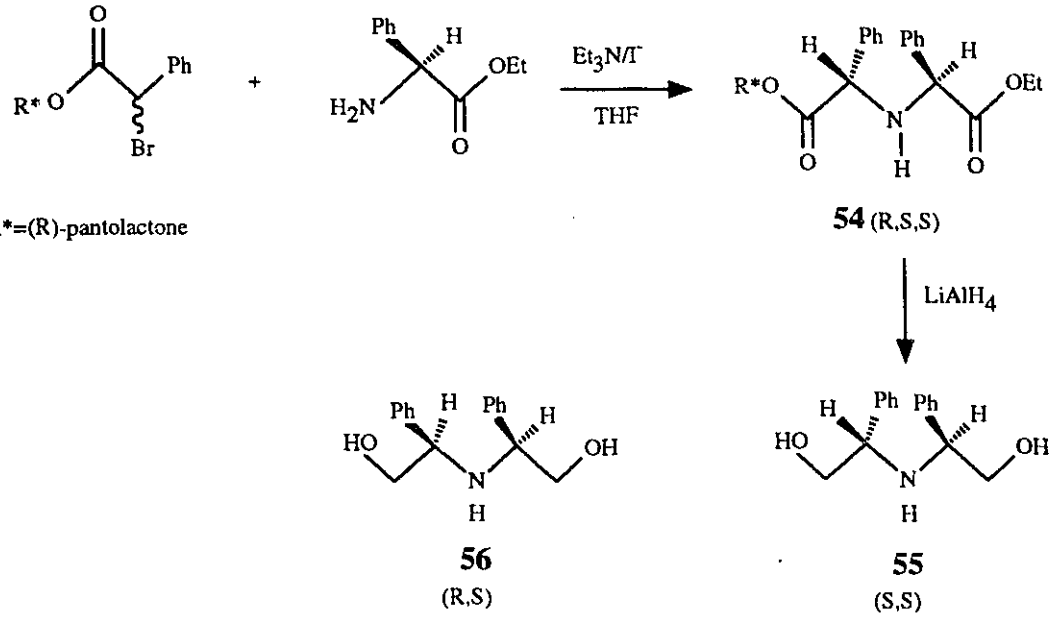
Subsequent hydrolysis of the ester groups in **53** would produce a secondary amine

containing two acidic groups. Compounds of this nature are related to a class of natural products known as nopalines and octapines and have become increasingly important.[65] In addition to having interesting properties, derivatives of these compounds have been implicated as tumor promoters in eucaryotic cells.[66,67]

Of particular interest to us as synthetic chemists was the potential to use our newly founded methodology to synthesize C_2 symmetric β,β'-dihydroxyamines via the procedure outlined in Scheme 40. Subsequent purification and reduction of **53** where R_1=R_2 would produce the desired dihydroxyamines. Compounds of this nature have been employed as tridentate chiral modifiers in the asymmetric reduction of prochiral ketones[68] and utilized as key building blocks in the construction of diaza-18-crown-6 ether derivatives.[69] The C_2 symmetric backbone has also been recently identified as an essential structural feature for the binding of HIV-1 protease inhibitors.[70]

Reaction of α-bromophenylacetic-(R)-pantolactone ester with (S)-phenylglycine ethyl ester[71] as shown in Scheme 41 produced **54** (RSS/RRS ratio=18:1) in 80% isolated yield. The diastereomeric ratio was comparable to the results obtained when other nucleophiles were employed in the reaction. Reduction with $LiAlH_4$ produced the desired (S,S)-amino diol **55** $[\alpha]_D^{23}$ +133.5° (c 1.4, CH_2Cl_2) in 73% yield.[72] Similar treatment α-bromophenylacetic-(R)-pantolactone ester with (R)-phenylglycine ethyl ester resulted in a 70% yield of the (RSR) isomer of **54**; reduction gave the *meso* diol **56**, $[\alpha]_D^{23}$ 0° (c 0.85, CH_2Cl_2).

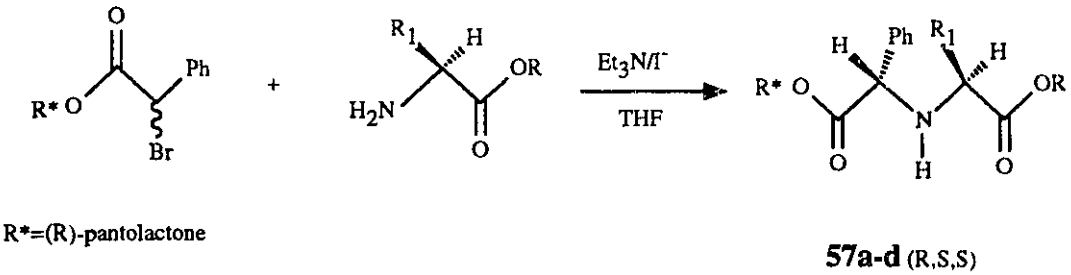
Scheme 41.



Although not pertinent to this subsection, but related to the synthesis of C_2 symmetrical compounds, Koh utilized this reaction to synthesize optically active C_2-symmetric 2,5-disubstituted pyrrolidines[72] which served to further demonstrate the versatility of our reaction.

Use of optically active α-amino esters as nucleophiles was not only limited to the synthesis of C_2-symmetric diols as shown in Scheme 41. Reaction of α-bromophenylacetic-(R)-pantolactone ester with other optically active α-amino esters gave a series of amino diesters as shown in Scheme 42.

Scheme 42.



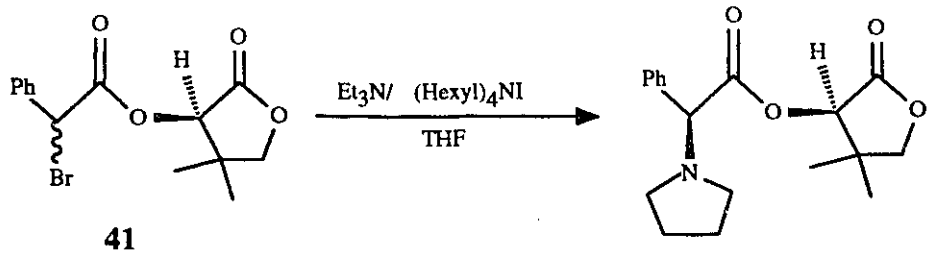
The reduction products derived from **57** no longer possess C_2 symmetry, nevertheless they show that a variety of optically active β,β'-dihydroxyamines can be prepared by this methodology. The hydrolysis of products **57** would lead to optically active compounds related to the octopines and nopalines which share one common nitrogen atom. Compounds with similar structures have been identified as inhibitors of angiotensin-converting enzyme as well as thermolysin.[67a] Some derivatives are also components of peptide antibiotics.[67b] The results using different optically active α-amino esters are summarized in Table 2.

Table 2. Summary of reactions with other α-amino esters.

Product	Amino ester	Isolated yield (%)	Diastereomer Ratio (RSS/RRS)
57a	Glycine ethyl ester	70	12:1
57b	(S)-phenylalanine methyl	60	9:1
57c	(S)- " t-butyl	77	27:1
57d	(S)-proline methyl	74	10:1
57e	(S)- " t-butyl	90	8:1

Of particular significance is the ratio obtained when (S)-proline ethyl and *t*-butyl esters are utilized. Whether the *t*-butyl or methyl ester was used the diastereomeric ratios obtained were approximately equal. Due to the fact that the (S)-proline ester is a secondary amine it is more basic than the other α-amino esters in Table 2. As explained earlier, this increased relative basicity results in a decrease in diastereoselectivity. This explanation is supported by the observation that reaction of α-bromophenylacetic- (R)-pantolactone ester with pyrrolidine under typical reaction conditions results in only a 4:1 diastereomeric ratio of products as shown in Scheme 43.

Scheme 43.



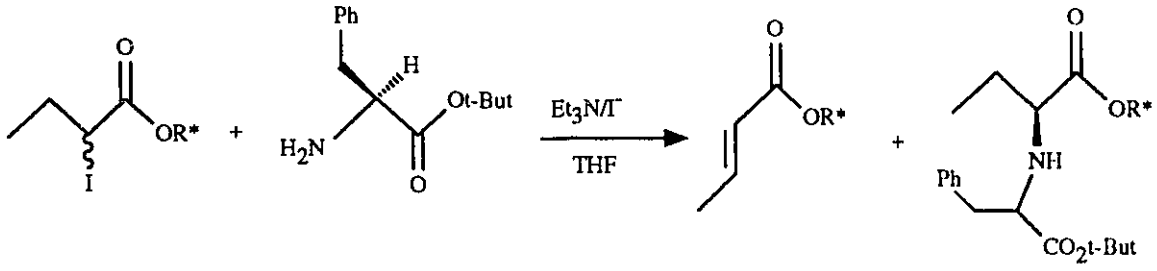
41 **58**

4:1 mixture (SR/RR)

87% yield

The reaction of optically α-amino esters with non-aromatic analogs of racemic α-halo esters was accompanied by significant amounts of elimination product which was clearly evident by a proton NMR of the crude reaction mixtures. However, close inspection of these NMR's indicated that in the trace amount of product that was formed the diastereomeric enrichment was still in the >15:1 range as shown in Scheme 44.

Scheme 44.



R*=(R)-pantolactone

>15:1

trace amount

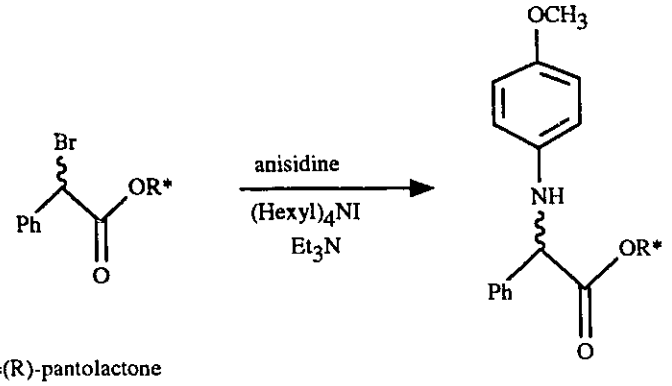
In summary it has been demonstrated that the proper choice of nitrogen nucleophile in our reaction is essential. In general, increasing the bulk of the amine nucleophile increases diastereoselectivity. However, if the nucleophile becomes too large reaction at the ester carbonyl leading to the formation of amides is preferred.

D) Hydrogen bonding.

The previous sections have successfully demonstrated that through careful choice of the chiral auxiliary, nucleophile and R group on the α-halo ester, very high diastereoselectivities may be obtained using our dynamic kinetic resolution. As the diastereoselectivity of the reaction was improved it became more difficult to identify the minor diastereomer with absolute certainty. For instance when a diastereomeric ratio of less than 10:1 (82% de) was obtained, the minor diastereomer was relatively easy to identify, however as de's increased it was difficult to discern the resonances of the minor diastereomer from those of other small impurities in the reaction. In order to overcome this problem it became necessary to synthesize the minor diastereomer. As proven earlier the simplest way to accomplish this was to change the solvent that the reaction was performed in. It was also rationalized that utilizing a solvent which did not favor S_N2 type reactions and hydrogen bonding should decrease the diastereoselectivity of the reaction and subsequently produce the minor diastereomer in a higher chemical yield.

The reaction of α-bromophenylacetic-(R)-pantolactone ester **41** and anisidine, was chosen as a representative reaction to study since it produced only the (S,R) diastereomer. The effects that different solvents had on the diastereoselectivity of this reaction are summarized in Table 3. This strategy proved to be very effective for synthesizing the minor (R,R) diastereomer.

Table 3. Solvent effect on the formation of (R)-pantolacto-N-(ρ-methoxyphenyl)-2-amino-2-phenylethanoate.



R*=(R)-pantolactone

Solvent	Poduct Ratio (SR/RR)
Et_2O	14:1
DMF	3:1
Toluene/Δ	2:1

The low ratio obtained when DMF was used as solvent compared to ether and THF provided some experimental evidence that the high diastereoselectivities of our reaction were also dependent upon hydrogen bonding interactions. Since DMF has a high dielectric constant and an excellent ability to accept hydrogen bonds, it impedes the ability of the amine nucleophile to hydrogen bond to the lactone carbonyl (see section 3.2).

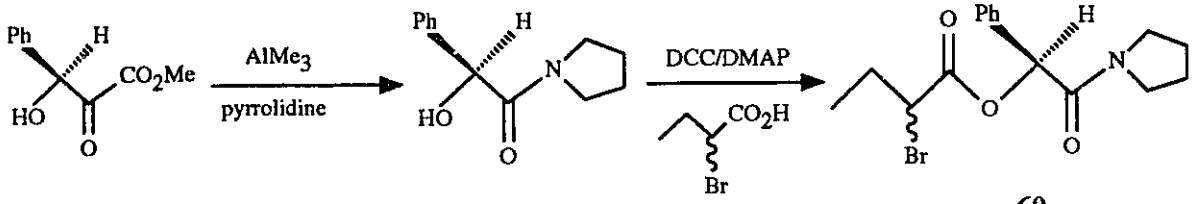
It was theorized that if hydrogen bonding was important in the mechanism of this reaction it should be possible to improve the reaction if the ester oxygen of the auxiliary was replaced by a nitrogen atom. The carbonyl group of the resulting amide is more basic than that of the ester and would hydrogen bond more readily with the amine nucleophile. This should increase the rate of displacement of bromide in the faster reacting isomer only which would be reflected in higher diastereomeric ratios of the products.

The ideal chiral auxiliary to use for this purpose was the lactam corresponding to (R)-pantolactone. Initial efforts by M. Jung to prepare this were not successful[73] and subsequently it was decided to first synthesize the amide derivative of (S)-methyl

mandelate. Since this auxiliary gave only modest product diastereomeric ratios it would be easier to determine the effect of the ester to amide change.

As shown in Scheme 45 reaction of (S)-methyl mandelate with 2 equivalents of trimethylaluminum and pyrrolidine[74] resulted in the formation of auxiliary **59** as a white solid (mp 91-92 °C) in 50% yield. A DCC coupling of auxiliary **59** with racemic 2-bromo-butanoic acid produced compound **60** as a white solid (mp 76 °C) in 70% yield.

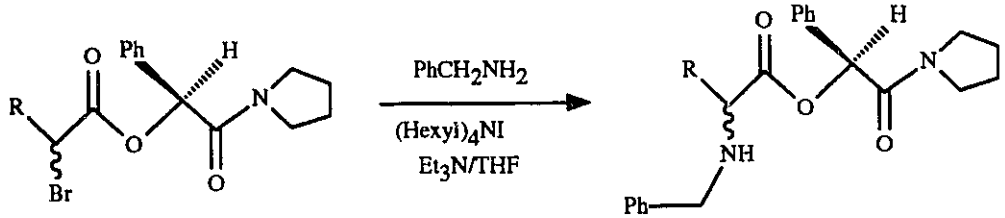
Scheme 45.



59 **60**

Reaction of compound **60** with benzylamine under typical reaction conditions gave **62** in 82% yield as a 4:1 ratio of diastereomers. The proton NMR of the purified product is shown in Figure 24. Previously, reaction of the (S)-methyl mandelate ester of 2-bromobutanoic acid produced only a 2:1 (SR/RR) diastereomeric ratio of the desired N-benzyl-2-amino-(R)- pantolactone ester.

Scheme 46.



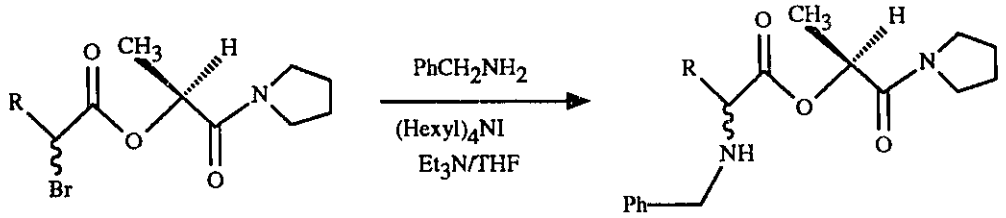
60 R=ethyl
63 R=Ph

62 R=Ethyl, 4:1 (SR/RR)
64 R=Ph, 10:1 (SR/RR)

The α-bromophenyl derivative, **63** was synthesized in 40% yield using the same procedure

and subjected to identical reaction conditions. The product, compound **64** was obtained in 82% yield as a 10:1 diastereomeric ratio of (SR/RR). Experimental data obtained by M. Jung with the amide derivative of (S)-methyl lactate displayed the same trends and are presented in Scheme 47. In both cases the results obtained using the amide auxiliary are superior to those obtained when the (S)-methyl lactate auxiliary is employed.

Scheme 47.



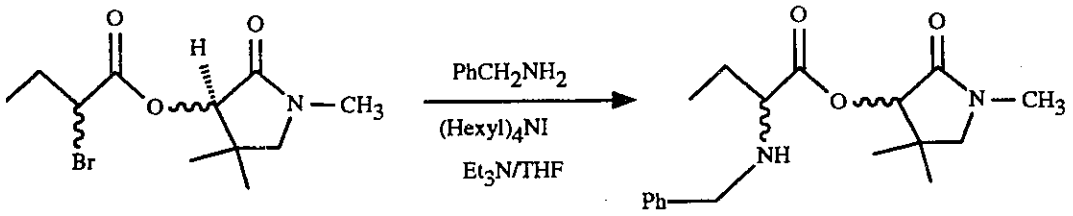
65 R=ethyl
67 R=Ph

66 R=Ethyl, 4:1 (SR/RR)
68 R=Ph, 8:1 (SR/RR)

All of the above results clearly indicate that hydrogen bonding of the amine nucleophile to the lactone carbonyl of the (R)-pantolactone auxiliary is an important aspect of the reaction and increases the diastereomeric ratios.

Much later, the lactam derivative of (R)-pantolactone shown in Scheme 48 was successfully synthesized by M. Jung and tested in our reaction. The coupling of this auxiliary to 2-bromo-butanoic acid was accomplished using DCC/DMAP and reaction of this compound with benzylamine under typical reaction conditions produced **69** as a 9:1 mixture of diastereomers in 64% isolated yield.

Scheme 48.



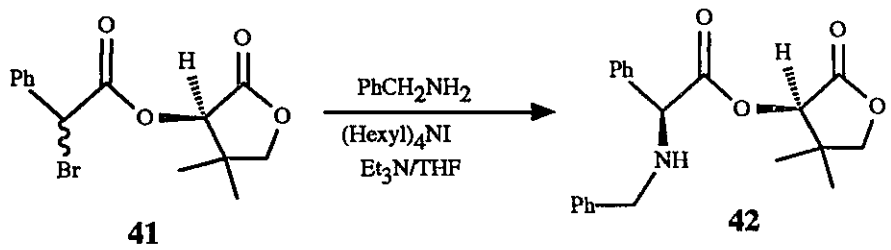
69

E) Miscellaneous aspects of this reaction.

Several other obvious aspects of this reaction were examined in an attempt to improve diastereoselectivity and gain more insight into the nature of the mechanism. However not all of the investigations discussed below proved useful.

i) The effect of temperature: Generally if one lowers the reaction temperature of a diastereoselective reaction, higher diastereoselectivities are obtained. Koh and Durst observed this effect in the trapping of α-halo ketenes with chiral alcohols[34a] and the same trend is applicable in the reaction of the pantolactone ester of α-bromophenylacetic acid. As shown in Scheme 49 reaction of this ester with benzylamine at -15 °C for 24 hours under typical reaction conditions resulted in the formation of **42** in 84% isolated yield as a 20:1 (SR/RR) mixture of diastereomers. Reaction at room temperature produced **42** in a 10:1 ratio (SR/RR) diastereomers.

Scheme 49.



41 **42**

20:1 ratio

84% yield

In a similar reaction, ester **41** was treated with pyrrolidine at -15 °C to furnish compound **58** (from Scheme 43) in 87% yield as a 8:1 ratio (SR/RR) of diastereomers, a marked improvement over the 4:1 ratio observed at room temperature. Reaction of alkyl derivatives of ester **41** at lower temperatures were not investigated since reaction times would be in excess of one week and this would be impractical.

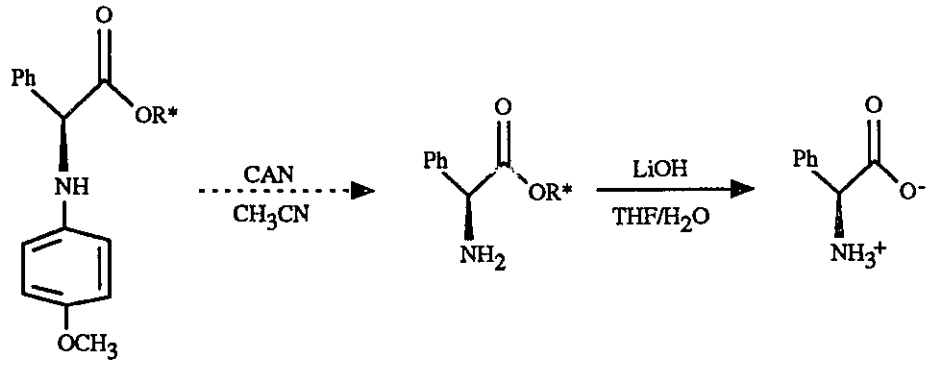
ii) Increasing the amount of iodide in the reaction mixture: Under typical reaction conditions only a catalytic amount of *n*-hexylammonium iodide (0.2 equivalents) is utilized. It was rationalized that increasing the amount of iodide ion present in the reaction mixture might make the epimerization reaction much more efficient and subsequently result in the formation of products with higher diastereomeric ratios. In the event, utilization of up to one molar equivalent of *n*-hexylammonium iodide had no effect on diastereoselectivity, suggesting that epimerization using on 0.2 eq is rapid enough. Using alternate sources of iodide ion such as lithium iodide also had no measurable effect on the diastereoselectivities of this reaction.

3.3 Deprotection of N-protected α-amino esters.

The N-protected α-amino esters synthesized in this thesis were not deprotected to form free amino esters but we anticipate no problem in doing this. Koh successfully demonstrated that the (R)-pantolactone auxiliary can be removed without racemization

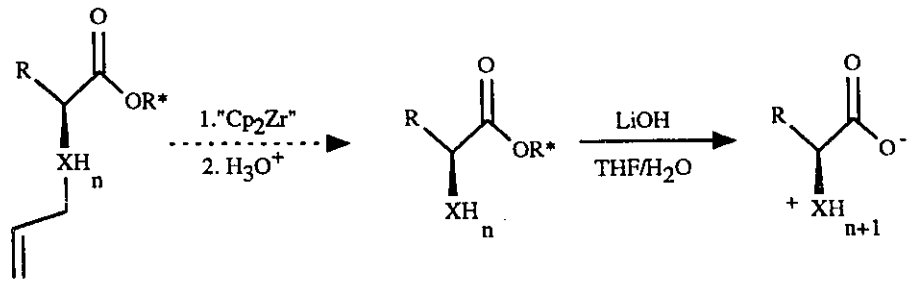
using LiOH in THF/H_2O[34a] and we have also demonstrated that an N-benzyl group can be removed under standard conditions (H_2/Pd/C, MeOH/AcOH) to yield a free amino ester.[38a] It should be noted that when deprotecting phenyl glycine amino esters added care should be taken since compounds of this nature are prone to racemization. Cleavage of many other N-protecting groups discussed in this thesis are theoretically feasible and would furnish optically active free amines and amino acids. For instance the benzyl groups on dibenzylamine are easily removable via standard hydrogenolysis[75]and as shown in Scheme 50 the *p*-methoxyphenyl group might be removed using ceric ammonium nitrate.[76]

Scheme 50.



A *p*-hydroxyphenyl group might also be removed under similar oxidative conditions using DDQ.[77] While the use of allyl-type nucleophiles was not discussed in this thesis it is possible that such groups are could be removed as shown in Scheme 51.[78]

Scheme 51.



X=O,N

n=0 or 2

Experimental Section

PART B: The Synthesis of Optically Active α-Amino Esters via Kinetic Dynamic Resolution

For General remarks please refer to Part A of the experimental section.

General procedures for the preparation of α-bromo esters:

1) Procedure A.[34a]

A representative procedure for the preparation of the many α-bromo esters synthesized during the course of this research is as follows: A solution of the appropriate α-bromo acid halide (obtained commercially or prepared via literature procedure[50]) in dry THF was added dropwise to a solution of triethylamine and the desired alcohol (2.0 eq each) in THF at 0 °C over a 1h period. The reaction mixture was then quenched with H_2O and subjected to extractive work up. The combined organic layers were dried using $MgSO_4$ and evaporated under reduced pressure. Crude products were then purified by column chromatography using the appropriate solvent system and fully characterized.

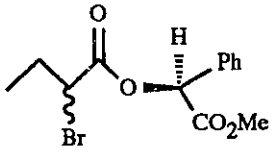
2) Procedure B.

In an alternate procedure, the appropriate α-bromo acid was subjected to a DCC coupling.[57] A typical procedure is as follows: The appropriate alcohol, α-bromo acid (1.0 eq), DCC (1.0 eq), and DMAP (0.1 eq) were dissolved in dry CH_2Cl_2 and stirred at room temperature under a nitrogen atmosphere until TLC verified that the alcohol had been consumed. The precipitate was filtered off and the organic phase washed with 3 X 20 mL of H_2O and 1 X 20 mL of 10% HCl. The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure to furnish the crude product which was purified via column chromatography.

Typical procedure for the Kinetic Dynamic Resolution:

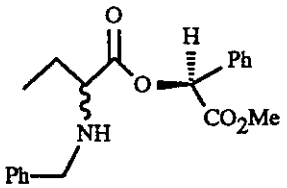
The appropriate α-halo ester was dissolved in 5-10 mL of dry THF. Triethylamine (2.0 eq), tetra-*n*-hexylammonium iodide (0.2 eq) and the desired amine (1.05 eq) were added. The reaction mixture was stirred under a nitrogen atmosphere until TLC verified that all of the starting material had been consumed. The precipitate was filtered off and the filtrate evaporated under reduced pressure to furnish the crude product. At this point, a proton NMR was taken of the crude mixture in order to determine the diastereomeric ratio and the crude product was then purified via column chromatography. It should be pointed out that if the presence of ammonium salts in the crude reaction mixture made determination of the diasteromeric ratio difficult, these salts were removed from the crude mixture through the addition of 20-30 mL of ether and filtration. The filtrate was then evaporated and a proton NMR was taken.

(S)-Methyl-mandelic ester of 2-bromobutanoic acid (20).



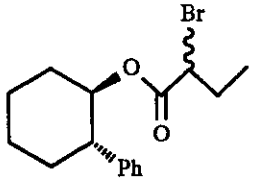
Compound **20** was prepared using procedure A. The crude product was purified via column chromatography using Hexanes:EtOAc (10:1) as elutant to furnish **20** in 91% yield as a colourless oil: IR (CH_2Cl_2): 2948, 1750, 1748, 1497, 1145, 1033 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.05 (m, 3H), 2.10 (m, 2H), 3.70 (s, 3H), 4.30 (m, 1H), 5.94 (s, 1H), 7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.6, 28.4, 52.3, 75.2, 75.4, 127.5, 128.8, 129.4, 133.0, 133.1, 168.5, 168.8; CIMS (ether) m/e (relative intensity): 389 (0.6), 317 (17), 315, (17), 297 (100), 282 (23), 257 (26), 237 (43), 149 (100), 105 (67).

((S)-Methyl-mandelic)-N-benzyl-2-amino-butanoic ester (21).



Ester **21** was prepared under the typical reaction conditions utilizing α-bromo ester **20** and benzylamine as a nucleophile. The crude product was obtained as a 2:1 mixture (RS/SS) of diastereomers and was isolated via column chromatography using toluene:acetone 17:1 as elutant. The mixture of diastereomers was obtained in 60% yield as a colourless oil: IR (CH_2Cl_2): 3527, 2945, 1739, 1680, 1495, 1092, 1067 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.95, 1.05 (both t, total 3H, J=7.8 Hz), 1.60-1.92 (m, 2H), 3.40 (m, 1H), 3.60-3.92 (m, 5H), 6.00, 6.01 (both s, total 1H), 7.10-7.50 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 9.7, 9.8, 26.1, 26.2, 51.5, 51.6, 52.3, 52.4, 61.4, 74.2, 74.3, 126.8, 127.4, 128.1, 128.2, 128.5, 128.6, 128.7, 129.0, 133.4, 139.2, 168.9, 174.4; CIMS (isobutylene) m/e (relative intensity): 342 (100), 194 (11), 148 (100), 106 (12). Anal. Calcd for $C_{20}H_{23}O_4N$: C, 70.36; H, 6.79. Found C, 70.52; H, 6.83.

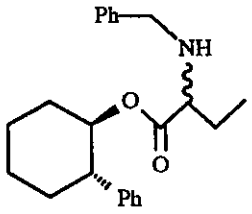
α-Bromo ester 22.



The α-bromo ester derived from *trans*-2-(S)-phenylcyclohexanol was prepared via procedure A. The crude product was obtained as a colourless oil in 60% yield after column chromatography using Hexanes:EtOAc (5:1) as solvent: IR (CH_2Cl_2): 2980, 1720, 1328,

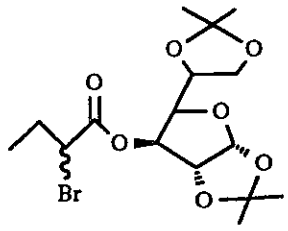
1032, 852 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.60 (m, 3H), 1.30-2.20 (m, 10H), 3.85 (m, 1H), 4.80 (m, 1H), 5.00 (m, 1H), 7.20 (m, 5H); CIMS (ether) m/e (relative intensity): 327 (4), 325 (4), 249 (11), 171 (14.2), 158 (100), 143(17), 130 (33). Anal. Calcd for $C_{16}H_{21}O_2Br$: C, 59.26; H, 6.52. Found C, 59.14; H, 6.54.

N-Benzyl-α-amino ester 23.



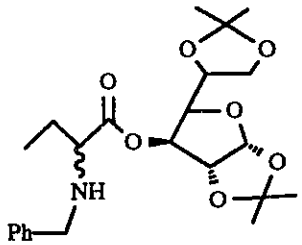
Reaction of ester **22** with benzylamine under typical reaction conditions produced compound **23** in a diastereomeric ratio of 2:1. Both isomers were isolated together in 92% yield as a pale yellow oil: IR (CH_2Cl_2): 2936, 1725, 1494, 1188, 1013 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.50, 0.70 (both t, total 3H, J=8.1 Hz), 1.10-2.40 (m, 11H), 2.60-3.52 (m, 4H), 5.10 (m, 1H), 7.20 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 9.4, 10.0, 24.7, 25.8, 26.2, 26.6, 32.4, 32.6, 34.1, 34.3, 49.8, 49.9, 51.4, 51.2, 61.8, 62.1, 75.9, 76.2, 126.5, 126.7, 127.4, 127.6, 128.2 (2), 128.3, 139.8, 143.1, 174.7, 174.8; CIMS (isobutylene) m/e (relative intensity): 352 (100), 194 (18), 159 (40), 148 (94), 106 (14). Anal. Calcd for $C_{23}H_{29}NO_2$: C, 78.59; H, 8.32. Found C, 78.25; H, 8.09.

(R)-Diacetone glucose ester of 2-bromobutanoic acid (24).



α-Bromo ester **24** was prepared via procedure A and the crude product was purified on silica using Hexanes:EtOAc (5:1). **24** was isolated in 63% yield as a yellow oil: IR (CH_2Cl_2): 3479, 2913, 1743, 1206, 1156, 1080, 1026 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.00 (t, 3H, J=8.2 Hz), 1.27 (s, 3H), 1.28 (s, 3H), 1.35 (s, 3H), 1.50 (s, 3H), 2.0 (m, 2H), 3.90-4.20 (m, 5H), 4.45 (t, 1H, J=4.2 Hz), 5.31 (bs, 1H), 5.87, 5.89 (both s, total 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 11.6, 11.7, 25.1, 26.1, 26.5, 26.6, 28.1, 49.5, 47.0, 60.1, 67.3, 67.4, 71.9, 72.1, 76.5, 79.8, 79.9, 82.7, 82.8, 167.8, 168.1; CIMS (ether) m/e (relative intensity): 411 (38), 409 (39), 393 (12), 351 (100), 293 (20), 273 (56), 215 (14), 185 (22), 149 (57), 127 (36), 101 (82).

(R)-Diacetone glucose ester of N-benzyl-2-amino-butanoic acid (25).



Compound **25** was prepared using the typical reaction conditions. The crude product was obtained as a 2:1 mixture of diastereomers and was isolated as such in 83% yield as a yellow oil: IR (CH_2Cl_2): 2917, 1740, 1378, 1164, 1076, 1024, 848 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.90 (t, 3H, J=7.8 Hz), 1.23 (s, 3H), 1.24 (s, 3H), 1.40 (s, 3H), 1.50 (s, 3H),

1.75 (m, 1H), 3.20 (m, 1H), 3.60 (d, 1H, J=12.3 Hz), 3.80 (d, 1H, J=12.3 Hz), 3.95 (m, 6H), 4.35, 4.36 (both d, total 1H, J=3.5 Hz), 5.29, 5.35 (both d, total 1H, J=3 Hz), 5.80, 5.82 (both d, total 1H, J=4 Hz), 7.25 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 10.2, 25.0, 25.1, 25.2, 26.1, 26.4, 26.6, 26.7, 26.8, 51.2, 52.0, 61.8, 67.4, 67.7, 72.1. 72.3, 75.9, 80.0, 81.2, 83.2, 83.4, 85.0, 105.0, 105.2, 127.1, 128.2, 128.3, 139.5, 173.9. Anal. Calcd for $C_{23}H_{32}NO_7$: C, 63.57; H, 7.42. Found C, 63.72; H, 7.60.

Preparation of 2,2-diphenylsuccinic acid (28).

Diphenylacetic acid (5 g, 0.024 mole) was dissolved in 150 mL of dry THF and placed in a 250 mL flame dried RBF under nitrogen atmosphere. The solution was then cooled to 0 °C and butyllithium (21.1 mL, 2.2 eq) was added slowly via syringe. When the addition was complete, the dark orange solution was allowed to stir at 0 °C for 2 min after which time ethyl bromoacetate (2.9 mL, 1.1 eq) was added via syringe and the reaction mixture was warmed to room temperture. The reaction mixture was quenched with 30 mL of saturated NH_4Cl and the organic layer was separated and evaporated under reduced pressure to produce a pale yellow solid. This crude product was re-dissolved in CH_2Cl_2 and extracted with 3 X 30 mL of saturated $NaHCO_3$. The aqueous layer was then separated, acidified with conc. HCl and the resulting precipitate was removed by filtration to furnish 6.3 g of **27** as a white solid: mp 127-128 °C; IR (CH_2Cl_2): 3481, 2908, 1741, 1702, 1496, 1197, 1020 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.10 (t, 3H, J=8.0 Hz), 3.50 (s, 2H), 3.95 (q, 2H, J=8.0 Hz), 7.25 (m ,10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.7, 43.8, 57.5, 60.8, 127.2, 127.9, 128.6, 141.8, 170.8, 178.1; CIMS (isobutylene) m/e (relative intensity): 299 (1), 253 (15), 225 (100), 180 (34), 167 (19), 103 (19).

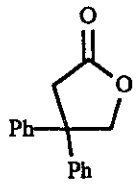
Compound **27** (6.0 g, 0.02 mole) was dissolved in 80 mL of MeOH and 20 mL of 40% NaOH solution (w/w) was then added and the reaction mixture refluxed for 3 h. The mixture was then cooled to room temperature and the MeOH was evaporated under reduced

pressure. After the addition of 30 mL of H_2O, the aqueous phase was acidified to pH 1.0 using conc. HCl and extracted with 4 X 40 mL of EtOAc. The organic phase was dried with $MgSO_4$ and evaporated to dryness to yield 930 mg (93% yield) of **28** as a white solid: mp 174 °C (lit.[52] mp 175 °C); IR (CH_2Cl_2): 3312, 1715, 1065 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 3.62 (s, 2H), 7.40 (m, 10H), 9.80 (bs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 51.5, 60.5, 126.8, 127.0, 127.2, 127.3, 127.5, 127.7, 128.1, 128.3, 137.6, 141.3, 170.8, 178.3.

2,2-Diphenylsuccinic anhydride (29).

Compound **28** (480 mg, 1.79 mmole) was heated in a sand bath to 185 °C and held at this temperature until all of the compound had melted. The liquid was allowed to cool to room temperature and after standing overnight, 340 mg (76% yield) of anhydride **29** was obtained as a white crystalline solid which was used without further purification: mp 90 °C (lit.[52] 89-91 °C); IR (CH_2Cl_2): 1865, 1788, 1496, 1071, 1029 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 3.76 (s, 2H), 7.30 (m, 10H); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 43.5, 76.3, 126.7, 127.0, 127.8, 128.1, 128.6, 128.9, 139.2, 141.5, 168.0, 171.9.

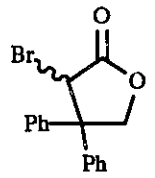
3,3-Diphenylbutyro-lactone (30).



Compound **29** (288 mg, 1.15 mmole) was dissolved in dry THF under a nitrogen atmosphere and cooled to 0 °C. 48 mg (1.1 molar eq) of $NaBH_4$ was added and the reaction mixture stirred for 36 h after which time no more bubbling was observed. The THF was removed under reduced pressure and 20 mL of $CHCl_3$ was added to the reaction mixture. The solution was cooled in an ice bath while 20 mL of 10% HCl was added over 2 h. The

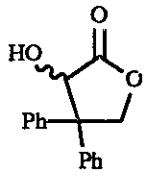
organic layer was separated and the aqueous layer extracted with 3 X 15 mL of $CHCl_3$. All organic layers were combined and dried with $MgSO_4$, the solvent evaporated under reduced pressure to yield 185 mg (68% yield) of **30** as a white solid: mp 109 °C (lit.[52] mp 109-110 °C); IR (CH_2Cl_2): 1784, 1325, 1031 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 3.18 (s, 2H), 4.80 (s, 2H), 7.25 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 41.6, 76.7, 126.1, 127.1, 128.7, 143.5, 175.3.

2-Bromo-3,3-diphenylbutyro-lactone (31).



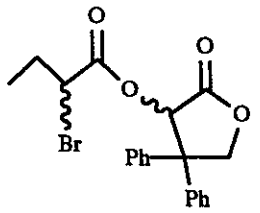
Compound **30** (525 mg, 2.21 mmole) dissolved in 10 mL of dry THF was added to a solution of LDA (1.2 eq) and TMSCl (0.49 mL, 1.75 eq) in THF at -78 °C under nitrogen atmosphere. The resulting yellow coloured solution was allowed to stir at -78 °C for 1.5 h, after which time solid NBS (413 mg, 1.05 eq) was added in one portion to the reaction mixture. Stirring was continued for another 15 min at -78 °C and then the solution was warmed to 0 °C over the period of 3 h. The reaction mixture was quenched with 10 mL of saturated NH_4Cl, the organic layer was then separated and dried with $MgSO_4$. The solvent was removed under reduced pressure and the crude product purified on silica using Hexanes:EtOAc (5:1) as solvent to produce 314 mg (45% yield) of **31** as a white solid: mp 142 °C; IR (CH_2Cl_2): 2980, 1797, 1490, 1016, 850 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 4.80 (d, 1H, J=10.1 Hz), 5.20 (d, 2H, J=10.1 Hz), 7.10-7.40 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.4, 72.4, 72.6, 126.3, 127.4, 127.8, 128.1, 128.4, 128.5, 137.3, 141.7, 171.5; EIMS m/e (relative intensity): 318 (5), 316 (5), 236 (42), 207 (23), 179 (100), 165 (40), 105 (28), 43 (62). HRMS calcd for $C_{16}H_{13}O_2Br$ (M^+) 316.0098, found 316.0076.

(+/-)-2-Hydroxy-3,3-diphenylbutyro-lactone (32).



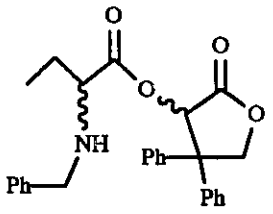
A solution of NaHMDS (0.6 mL, 1.2 eq) in dry THF was cooled to -78 °C under nitrogen atmosphere and a solution of **30** (118 mg, 0.5 mmole in 5 mL of THF) was added via cannula and the solution stirred at -78 °C for 30 min. This was followed by the addition of (+/-)-*trans*-2-(phenyisulfonyl) -3-phenyloxaziridine (196 mg, 1.5 eq in 5 mL of THF) via cannula to the reaction mixture. The solution was allowed to stir at -78 °C for another 20 min at which time 10 mL of saturated NH_4Cl was added. The organic layer was separated, dried with $MgSO_4$ and evaporated under reduced pressure. The crude product was purified via column chromatography using Hexanes:EtOAc (4:1) as solvent to produce 76 mg (60% yield) of **32** as a white solid: mp 168-170 °C; IR (CH_2Cl_2): 3551, 1791, 1496, 1133, 1012, 852 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 2.20 (bs, 1H), 4.45 (d, 1H, J=9.6 Hz), 5.10 (s, 1H), 5.18 (d, 1H, J=9.6 Hz), 7.30 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ :55.7, 73.2, 73.4, 126.4, 127.4, 127.5, 128.1, 128.4, 128.7, 137.1, 141.7, 175.2; EIMS m/e (relative intensity): 254 (7), 197 (9), 180 (100), 165 (35), 105 (17), 91 (13), 77 (13). HRMS calcd for $C_6H_{10}O_3$ (M^+) 254.0943, found 254.0941.

((+/-)-2-Hydroxy-3,3-diphenylbutyro)lactone ester of 2-bromo-butanoic acid (33).



Compound **33** was prepared using procedure B and was purified on silica using Hexanes:EtOAc (3:1) as solvent. The desired product was obtained in 52% yield as a colourless oil: IR (CH_2Cl_2): 2930, 1802, 1752, 1498, 1074, 1016 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.90 (m, 3H), 1.50-2.20 (m, 2H), 4.10 (m, 1H), 4.50, 4.60 (both d, total 1H, J=9.6 Hz), 5.15 (d, 1H, J=9.6 Hz), 6.39, 6.41 (both s, total 1H), 7.25 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.2, 11.3, 27.4, 27.8, 54.9 (2), 55.4, 55.5, 72.5, 73.7, 126.1, 127.4, 127.6, 128.1 (2), 128.9, 137.8, 140.6, 167.5, 168.2, 170.0, 170.1; EIMS m/e (relative intensity): 404 (4), 402 (4), 291 (3), 236 (4), 211 (39), 180 (100), 165 (18), 41 (38). HRMS calcd for $C_{20}H_{19}O_4Br$ (M^+) 402.0466, found 402.0461.

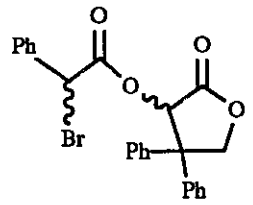
((+/-)-2-Hydroxy-3,3-diphenylbutyro)lactone ester of N-benzyl-2-amino-butanoic acid (34).



Compound **34** was synthesized using typical reaction conditions. The crude product showed a 3:1 mixture of diasteromers which were isolated together via column chromatography using Hexanes:EtOAc (3:1) in 93% yield: IR (CH_2Cl_2): 2912, 1799, 1746, 1376, 1073, 1015, 870 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.90 (m, 3H), 1.60 (m, 2H), 1.90 (bs, 1H), 3.20 (m, 1H), 3.50, 3.60 (both d, total 1H, J=10.2 Hz), 3.80 (d, 1H, J=10.2

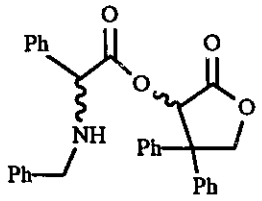
Hz), 4.46, 4.52, (both d, total 1H, J=9.6 Hz), 5.15 (d, 1H, J=9.6 Hz), 6.48, 6.52 (both s, total 1H), 7.25 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 9.9, 10.0, 25.9, 26.3, 51.6, 55.2, 61.6, 62.0, 71.7, 71.9, 74.3, 74.5, 126.5, 126.8, 127.1, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.7, 129.3, 138.8, 141.1, 170.9, 173.7; CIMS (isobutylene) m/e (relative intensity): 430 (100), 237 (42), 194 (81), 148 (100). Anal. Calcd for $C_{27}H_{27}NO_4$: C, 75.50; H, 6.33. Found C, 75.61; H, 6.35.

((+/-)-2-Hydroxy-3,3-diphenylbutyro)lactone ester of 2-bromo-2-phenylethanoic acid (35).



Compound **35** was prepared using procedure B and was obtained in 56% isolated yield after purification by column chromatography using Hexanes:EtOAc (3:1) as solvent: IR (CH_2Cl_2) 2930, 1802, 1752, 1498, 1136, 1073 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 4.50, 4.54 (both d, total 1H, J=9.6 Hz), 5.10, 5.40 (both d, total 1H, J=9.6 Hz), 5.30, 5.35 (both s, total 1H), 6.35, 6.40 (both s, 1H), 6.80-7.50 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 44.5, 46.5, 73.3, 73.8, 126.0, 126.2, 127.4, 127.5, 128.0, 128.1, 128.3, 128.5, 128.6, 128.9, 129.0, 129.1, 166.3, 169.8, 169.9; EIMS m/e (relative intensity): 452 (2), 450 (2), 371 (25), 325 (21), 237 (78), 181 (99), 165 (98), 118 (98), 90 (100). HRMS calcd for $C_{24}H_{19}O_4Br$ (M^+) 450.0466, found 450.0452.

((+/-)-2-Hydroxy-3,3-diphenylbutyro)lactone ester of N-benzyl-2-amino-2-phenyl-ethanoate (36).



Compound **36** was obtained using the typical procedure described earlier. A proton NMR of the reaction mixture revealed that the crude product was a mixture of diastereomers in a 3.5:1 ratio and was purified as such on silica using Hexanes:EtOAc (2:1) as elutant. The diastereomic mixture was obtained in 97% yield as a white solid and was recrystallized from ether/hexanes to furnish a single X-ray quality crystal of the major diastereomer: mp 101 °C; IR (CH_2Cl_2): 3450, 2840, 1800, 1751, 1496, 1132, 1074, 869 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.40 (bs, 1H), 3.70 (s, 2H), 4.36 (s, 1H), 4.45 (d, 1H, J=9.6 Hz), 5.08 (d, 1H, J=9.6 Hz), 6.32 (s, 1H), 6.70 (m, 4H), 7.20 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 50.8, 54.5, 63.8, 72.3, 73.2, 73.3, 125.8, 126.5, 126.7, 127.1, 127.4, 127.6, 127.9, 128.1, 128.2, 128.4, 128.5, 128.7, 136.9, 137.7, 138.8, 140.5, 170.3, 171.4; CIMS (isobutylene) m/e (relative intensity): 478 (100), 237 (5), 196 (50), 106 (21).

X-ray crystal structure data for 36.

1. Data Collection.

A crystal of $C_{31}H_{27}NO_4$ having approximate dimensions of 0.20 X 0.30 X 0.20 mm was mounted on a glass capillary. All of the measurements were made on a Rigaku diffractonmeter with Mo Kα radiation.

Cell constants and an orientation matrix for data collection were obtained from least-squares refinement using the setting angles of 25 reflections in the range 40<2theta<45 corresponding to a triclinic cell with dimensions: a=11.470,.003, b=11.6150,.0022,

c=9.715,.003, α=94.107,.024, β=100.016,.023 and γ=102.642,.017. For Z=2 and FW=477.55, the calculated density is 1.284 g/cm^3. Based on the systematic absences, the space group was determined to be P -1.

The data was collected at a temperature of -160 °C using the omega2theta scan technique to maximum value of 44.9°.

2. Data Reduction.

A total of 3426 reflection were collected. The unique set contains only 3234 reflections. The standards were measured after every 150 reflections and no crystal decay was noticed. The data was corrected for Lorentz and polarization effects,[79] but no absorption correction was made.

3. Solution and Refinement.

The structure was solved by direct methods and all atoms were refined anistotropically except the hydrogen. The hydrogen atoms were found by differences Fourier map. The final cycle of full matrix least-squares refinement was based on 2790 observed reflections (I>2.5 sigma(I)) and 434 variable parameters. Weights based on counting statistics were used. The maximum and minimum peaks on the final differences Fourier map corresponded to 0.310 and -0.280 e/A3, respectively.

All calculations were performed using the NRC/VAX crystallographic software package.[80]

Table of Atomic Bond Distances in Angstroms

O1-C1	1.189(5)	C14-C15	1.385(6)
O2-C1	1.362(5)	C14-C19	1.379(6)
O2-C2	1.465(5)	C15-C16	1.398(6)
O3-C4	1.440(4)	C15-H15	1.13(4)
O3-C5	1.349(4)	C16-C17	1.362(7)
O4-C5	1.202(4)	C16-H16	0.90(4)
N1-C6	1.458(5)	C17-C18	1.383(6)
N1-C7	1.473(5)	C17-H17	1.04(4)
N1-H1	0.91(3)	C18-C19	1.391(6)
C1-C4	1.503(5)	C18-H18	1.00(3)
C2-C3	1.544(5)	C19-H19	1.03(3)
C2-H2A	0.91(3)	C20-C21	1.412(5)
C2-H2B	1.05(3)	C20-C25	1.375(5)
C3-C4	1.557(5)	C21-C22	1.384(5)
C3-C20	1.511(5)	C21-H21	1.03(3)
C3-C26	1.549(5)	C22-C23	1.376(6)
C4-H4	0.93(3)	C22-H22	0.95(3)
C5-C6	1.536(5)	C23-C24	1.402(6)
C6-C14	1.511(5)	C23-H23	1.13(3)
C6-H6	1.09(3)	C24-C25	1.385(5)
C7-C8	1.508(6)	C24-H24	1.05(3)
C7-H7A	1.02(3)	C25-H25	1.01(3)
C7-H7B	0.91(3)	C26-C27	1.377(5)
C8-C9	1.369(6)	C26-C31	1.398(5)
C8-C13	1.401(5)	C27-C28	1.411(5)
C9-C10	1.370(6)	C27-H27	0.94(3)
C9-H9	0.85(3)	C28-C29	1.369(6)
C10-C11	1.412(6)	C28-H28	1.01(3)
C10-H10	0.92(3)	C29-C30	1.366(6)
C11-C12	1.376(6)	C29-H29	0.96(3)
C11-H11	0.95(3)	C30-C31	1.404(5)
C12-C13	1.389(6)	C30-H30	0.95(3)
C12-H12	1.02(3)	C31-H31	1.02(3)
C13-H13	0.93(3)		

Table of Atomic Bond Angles in Degrees

C1-O2-C2	108.8(3)	C12-C13-H13	123.2(18)
C4-O3-C5	117.2(3)	C6-C14-C15	119.9(4)
C6-N1-C7	114.6(3)	C6-C14-C19	121.4(3)
C6-N1-H1	106.1(22)	C15-C14-C19	118.8(4)
C7-N1-H1	124.1(21)	C14-C15-C16	119.5(4)
O1-C1-O2	122.7(3)	C14-C15-H15	114.9(18)
O1-C1-C4	128.6(4)	C16-C15-H15	124.8(19)
O2-C1-C4	108.7(3)	C15-C16-C17	121.8(4)
O2-C2-C3	106.8(3)	C15-C16-H16	117.1(24)
O2-C2-H2A	108.2(17)	C17-C16-H16	120.6(24)
O2-C2-H2B	104.6(16)	C16-C17-C18	118.7(4)
C3-C2-H2A	105.7(18)	C16-C17-H17	131.7(21)
C3-C2-H2B	114.1(16)	C18-C17-H17	109.0(21)
H2A-C2-H2B	116(3)	C17-C18-C19	120.2(4)
C2-C3-C4	96.7(3)	C17-C18-H18	116.0(20)
C2-C3-C20	111.2(3)	C19-C18-H18	123.1(20)
C2-C3-C26	111.9(3)	C14-C19-C18	121.0(4)
C4-C3-C20	113.6(3)	C14-C19-H19	116.2(17)
C4-C3-C26	112.0(3)	C18-C19-H19	122.7(17)
C20-C3-C26	110.7(3)	C3-C20-C21	118.6(3)
O3-C4-C1	108.6(3)	C3-C20-C25	123.4(3)
O3-C4-C3	113.7(3)	C21-C20-C25	117.9(3)
O3-C4-H4	110.4(17)	C20-C21-C22	119.5(4)
C1-C4-C3	104.8(3)	C20-C21-H21	118.1(15)
C1-C4-H4	108.9(16)	C22-C21-H21	122.4(15)
C3-C4-H4	110.2(17)	C21-C22-C23	122.3(4)
O3-C5-O4	124.7(3)	C21-C22-H22	116.9(20)
O3-C5-C6	108.9(3)	C23-C22-H22	120.8(20)
O4-C5-C6	126.4(3)	C22-C23-C24	118.3(4)
N1-C6-C5	114.5(3)	C22-C23-H23	128.8(14)
N1-C6-C14	111.0(3)	C24-C23-H23	112.8(14)
N1-C6-H6	107.9(17)	C23-C24-C25	119.4(4)
C5-C6-C14	107.2(3)	C23-C24-H24	109.9(15)
C5-C6-H6	104.1(16)	C25-C24-H24	130.4(15)
C14-C6-H6	111.9(16)	C20-C25-C24	122.6(4)
N1-C7-C8	114.5(3)	C20-C25-H25	115.3(16)
N1-C7-H7A	122.1(19)	C24-C25-H25	122.0(16)
N1-C7-H7B	106.7(19)	C3-C26-C27	122.6(3)
C8-C7-H7A	99.5(19)	C3-C26-C31	118.5(3)
C8-C7-H7B	108.0(20)	C27-C26-C31	118.9(3)
H7A-C7-H7B	105(3)	C26-C27-C28	120.5(3)
C7-C8-C9	119.0(3)	C26-C27-H27	122.6(17)
C7-C8-C13	122.6(3)	C28-C27-H27	116.4(17)
C9-C8-C13	118.3(4)	C27-C28-C29	119.7(4)
C8-C9-C10	123.0(4)	C27-C28-H28	121.3(16)
C8-C9-H9	117.9(20)	C29-C28-H28	118.9(16)
C10-C9-H9	119.1(20)	C28-C29-C30	120.9(3)
C9-C10-C11	118.7(4)	C28-C29-H29	116.1(18)
C9-C10-H10	126.2(19)	C30-C29-H29	122.9(18)
C11-C10-H10	114.2(19)	C29-C30-C31	119.8(4)
C10-C11-C12	119.2(4)	C29-C30-H30	124.2(18)

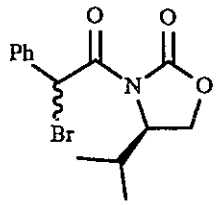
C10-C11-H11 120.4(19)
C12-C11-H11 119.6(19)
C11-C12-C13 121.0(4)
C11-C12-H12 119.1(18)
C13-C12-H12 119.8(18)
C8-C13-C12 119.8(4)
C8-C13-H13 116.6(18)
C31-C30-H30 115.9(18)
C26-C31-C30 120.2(4)
C26-C31-H31 120.5(16)
C30-C31-H31 118.7(16)

Torsion angles

C2	O2	C1	O1	-178.8(4)	C2	O2	C1	C4	0.4(2)
C1	O2	C2	C3	23.5(2)	C1	O2	C2	H2A	-89.8(15)
C1	O2	C2	H2B	144.9(15)	C5	O3	C4	C1	-102.4(3)
C5	O3	C4	C3	141.3(3)	C5	O3	C4	H4	16.9(14)
C4	O3	C5	O4	-4.0(2)	C4	O3	C5	C6	177.4(3)
C7	N1	C6	C5	63.3(2)	C7	N1	C6	C14	-175.1(4)
C7	N1	C6	H6	-52.1(14)	H1	N1	C6	C5	-77.5(18)
H1	N1	C6	C14	44.2(18)	H1	N1	C6	H6	167.1(23)
C6	N1	C7	C8	74.0(3)	C6	N1	C7	H7A	-45.9(16)
C6	N1	C7	H7B	-166.6(17)	H1	N1	C7	C8	-153.3(18)
H1	N1	C7	H7A	86.8(24)	H1	N1	C7	H7B	-33.9(24)
O1	C1	C4	O3	33.6(2)	O1	C1	C4	C3	155.4(4)
O1	C1	C4	H4	-86.7(14)	O2	C1	C4	O3	-145.6(4)
O2	C1	C4	C3	-23.7(2)	O2	C1	C4	H4	94.2(14)
O2	C2	C3	C4	-35.1(2)	O2	C2	C3	C20	-153.7(4)
O2	C2	C3	C26	81.9(3)	H2A	C2	C3	C4	79.9(15)
H2A	C2	C3	C20	-38.6(15)	H2A	C2	C3	C26	-163.0(15)
H2B	C2	C3	C4	-150.2(15)	H2B	C2	C3	C20	91.2(14)
H2B	C2	C3	C26	-33.2(14)	C2	C3	C4	O3	153.0(3)
C2	C3	C4	C1	34.5(2)	C2	C3	C4	H4	-82.5(14)
C20	C3	C4	O3	-90.4(3)	C20	C3	C4	C1	151.1(4)
C20	C3	C4	H4	34.1(14)	C26	C3	C4	O3	36.1(2)
C26	C3	C4	C1	-82.4(3)	C26	C3	C4	H4	160.6(14)
C2	C3	C20	C21	-45.1(2)	C2	C3	C20	C25	139.1(4)
C4	C3	C20	C21	-152.9(4)	C4	C3	C20	C25	31.2(2)
C26	C3	C20	C21	79.9(3)	C26	C3	C20	C25	-95.9(3)
C2	C3	C26	C27	-8.3(2)	C2	C3	C26	C31	170.5(4)
C4	C3	C26	C27	99.0(3)	C4	C3	C26	C31	-82.1(3)
C20	C3	C26	C27	-133.0(4)	C20	C3	C26	C31	45.9(2)
O3	C5	C6	N1	-164.9(4)	O3	C5	C6	C14	71.4(3)
O3	C5	C6	H6	-47.3(14)	O4	C5	C6	N1	16.5(2)
O4	C5	C6	C14	-107.2(3)	O4	C5	C6	H6	134.1(14)
N1	C6	C14	C15	106.5(3)	N1	C6	C14	C19	-73.1(3)
C5	C6	C14	C15	-127.7(4)	C5	C6	C14	C19	52.7(2)
H6	C6	C14	C15	-14.1(14)	H6	C6	C14	C19	166.2(14)
N1	C7	C8	C9	-172.0(4)	N1	C7	C8	C13	11.0(2)
H7A	C7	C8	C9	-40.1(16)	H7A	C7	C8	C13	142.9(16)
H7B	C7	C8	C9	69.3(17)	H7B	C7	C8	C13	-107.6(17)
N1	C7	H7A	H7B	-121.4(21)	C8	C7	H7A	H7B	111.7(20)
H7B	C7	H7A	H7B	0.0(21)	N1	C7	H7B	H7A	131.0(21)
C8	C7	H7B	H7A	-105.5(19)	H7A	C7	H7B	H7A	0.0(20)
C7	C8	C9	C10	-176.2(4)	C7	C8	C9	H9	3.2(16)
C13	C8	C9	C10	0.9(2)	C13	C8	C9	H9	-179.7(17)
C7	C8	C13	C12	177.4(4)	C7	C8	C13	H13	4.6(15)
C9	C8	C13	C12	0.4(2)	C9	C8	C13	H13	-172.4(16)
C8	C9	C10	C11	-1.4(2)	C8	C9	C10	H10	-170.0(17)
H9	C9	C10	C11	179.2(17)	H9	C9	C10	H10	10.6(23)
C9	C10	C11	C12	0.6(2)	C9	C10	C11	H11	-169.0(17)
H10	C10	C11	C12	170.6(17)	H10	C10	C11	H11	0.9(23)

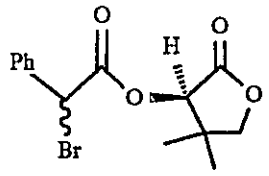
C10	C11	C12	C13	0.6(2)	C10	C11	C12	H12	-176.7(15)
H11	C11	C12	C13	170.3(17)	H11	C11	C12	H12	-7.0(22)
C11	C12	C13	C8	-1.1(2)	C11	C12	C13	H13	171.1(16)
H12	C12	C13	C8	176.1(15)	H12	C12	C13	H13	-11.6(21)
C6	C14	C15	C16	178.2(5)	C6	C14	C15	H15	7.9(16)
C19	C14	C15	C16	-2.2(2)	C19	C14	C15	H15	-172.4(17)
C6	C14	C19	C18	-177.6(4)	C6	C14	C19	H19	5.7(14)
C15	C14	C19	C18	2.7(2)	C15	C14	C19	H19	-174.0(15)
C14	C15	C16	C17	0.5(2)	C14	C15	C16	H16	-171.6(22)
H15	C15	C16	C17	169.7(17)	H15	C15	C16	H16	-2.4(26)
C15	C16	C17	C18	0.7(2)	C15	C16	C17	H17	170.6(19)
H16	C16	C17	C18	172.5(22)	H16	C16	C17	H17	-17.6(27)
C16	C17	C18	C19	-0.2(2)	C16	C17	C18	H18	170.5(18)
H17	C17	C18	C19	-172.2(19)	H17	C17	C18	H18	-1.5(25)
C17	C18	C19	C14	-1.5(2)	C17	C18	C19	H19	174.9(15)
H18	C18	C19	C14	-171.6(18)	H18	C18	C19	H19	4.9(22)
C3	C20	C21	C22	-177.2(4)	C3	C20	C21	H21	3.8(12)
C25	C20	C21	C22	-1.2(2)	C25	C20	C21	H21	179.8(13)
C3	C20	C25	C24	175.8(4)	C3	C20	C25	H25	-9.1(14)
C21	C20	C25	C24	-0.1(2)	C21	C20	C25	H25	175.1(14)
C20	C21	C22	C23	2.7(2)	C20	C21	C22	H22	178.9(17)
H21	C21	C22	C23	-178.3(13)	H21	C21	C22	H22	-2.2(21)
C21	C22	C23	C24	-2.9(2)	C21	C22	C23	H23	174.9(12)
H22	C22	C23	C24	-178.9(17)	H22	C22	C23	H23	-1.1(20)
C22	C23	C24	C25	1.5(2)	C22	C23	C24	H24	176.5(13)
H23	C23	C24	C25	-176.6(12)	H23	C23	C24	H24	-1.6(16)
C23	C24	C25	C20	-0.1(2)	C23	C24	C25	H25	-174.9(15)
H24	C24	C25	C20	-173.9(13)	H24	C24	C25	H25	11.3(18)
C3	C26	C27	C28	177.0(4)	C3	C26	C27	H27	-11.4(14)
C31	C26	C27	C28	-1.9(2)	C31	C26	C27	H27	169.7(15)
C3	C26	C31	C30	-177.6(4)	C3	C26	C31	H31	-6.7(14)
C27	C26	C31	C30	1.4(2)	C27	C26	C31	H31	172.3(14)
C26	C27	C28	C29	1.3(2)	C26	C27	C28	H28	176.5(15)
H27	C27	C28	C29	-170.8(15)	H27	C27	C28	H28	4.4(20)
C27	C28	C29	C30	-0.2(2)	C27	C28	C29	H29	177.8(16)
H28	C28	C29	C30	-175.5(15)	H28	C28	C29	H29	2.4(21)
C28	C29	C30	C31	-0.3(2)	C28	C29	C30	H30	-177.0(16)
H29	C29	C30	C31	-178.1(16)	H29	C29	C30	H30	5.2(21)
C29	C30	C31	C26	-0.3(2)	C29	C30	C31	H31	-171.3(14)
H30	C30	C31	C26	176.7(16)	H30	C30	C31	H31	5.6(20)
C7	H7A	H7B	C7	0.0(4)					

(α-Bromo-phenylacetic)-2-isopropyl-oxazolidinone (37).



Compound **37** was obtained in 75% yield after purification by column chromatography using Hexanes:EtOAc (5:1) as a yellow oil: IR (CH_2Cl_2): 2946, 1780, 1706, 1379, 1197, 1101, 972 cm^{-1}; ^{1} H NMR (200 MHz, $CDCl_3$) δ: 0.50-1.40 (m, 6H), 2.10-2.60 (m, 1H), 4.00-4.50 (m, 3H), 6.82, 6.90 (both s, total 1H), 7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.2, 14.4, 17.5, 44.1, 45.8, 58.5, 63.1, 63.2, 128.3, 128.5, 128.9, 129.0, 129.2, 129.3, 134.7, 135.2, 152.9, 166.8, 167.2; EIMS m/e (relative intensity): 327 (75), 325 (75), 246 (100), 196 (100), 198 (100), 170 (100), 91 (100), 89 (100), 83 (19), 41 (94), 27 (96). HRMS calcd for $C_{14}H_{16}NO_3Br$ (M^+) 325.0310, found 325.0333.

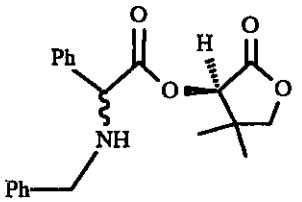
(R)-Pantolacto-2-bromo-2-phenylethanoate (41).



Compound **41** was prepared using procedure B and was purified on silica using Hexanes:EtOAc (3:1). The desired product was obtained 72% yield as a colourless oil which solidified on standing in the freezer: mp 143-144 °C; IR (CH_2Cl_2): 3014, 1800, 1762, 1076, 1136 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.88, 1.10, 1.15, 1.23 (all s, total 6H), 3.98, 4.05 (both s, total 2H), 5.34, 5.36 (both s, total 1H), 5.48, 5.51 (both s, total 1H), 7.25-7.60 (m, 5H); ^{13}C NMR (375MHz, $CDCl_3$) δ: 20.1, 20.3, 23.2, 23.4, 40.2 (2), 45.6 (2), 47.3 (2), 77.8 (2), 78.4 (2), 128.5, 128.7, 129.1, 129.6, 130.1, 135.3, 136.1, 167.8, 168.3,

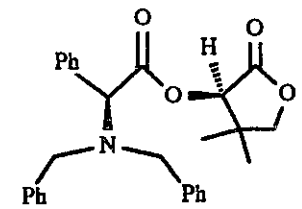
172.1; CIMS (ether) m/e (relative intensity): 329 (34), 327 (34), 283 (9), 247 (100), 219 (9), 196 (12), 169 (17). Anal. Calcd for $C_{14}H_{15}O_4Br$: C, 51.40; H, 4.62. Found C, 51.61; H, 4.70.

(R)-Pantolacto-N-benzyl-2-amino-2-phenylethanoate (42).



A proton NMR of the crude reaction mixture revealed that **42** was formed as a 10:1 mixture of diastereomers. After purification by column chromatography using Hexanes:EtOAc (3:1) the mixture of diastereomers was obtained in 84% yield as a colourless oil: IR (CH_2Cl_2): 2949, 1784, 1780, 1109, 1007 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.40, 0.92, 1.00, 1.18 (all s, total 6H), 2.40 (bs, 1H), 3.75, 3.90, 3.92, 4.00 (all s, total 4H), 4.55, 4.56 (both s, total 1H), 5.46, 5.47 (both s, total 1H), 7.20-7.50 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 18.9, 22.4, 40.1, 50.9, 63.7, 74.9, 75.8, 126.9, 127.4, 128.1, 128.2, 128.4, 128.5, 137.5, 138.9, 171.8, 171.9; CIMS (isobutylene) m/e (relative intensity): 260 (70), 247 (90), 226 (10), 131 (100), 118 (55), 105 (82). Anal. Calcd for $C_{21}H_{23}O_4N$: C, 71.36; H, 6.55. Found C, 71.21 ; H, 6.45.

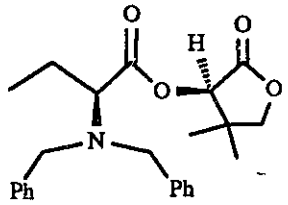
(R)-Pantolacto-(N,N-dibenzyl)-2-amino-2-phenylethanoate (43).



Compound **43** which was obtained as a single diastereomer was purified on silica using

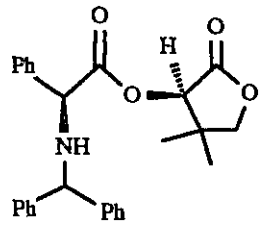
Hexanes:EtOAc (3:1) and was obtained in 70% yield as a pale orange solid: mp 83 °C; IR (CH_2Cl_2): 2931, 1794, 1748, 1127, 1077 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.95 (s, 3H), 1.27 (s, 3H), 3.78 (ABq, 4H, J=9.6 Hz), 4.05 (s, 2H), 4.70 (s, 1H), 5.60 (s, 1H), 7.20-7.40 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.6, 22.7, 39.8, 53.7, 65.2, 74.7, 75.9, 127.7, 128.0, 128.1, 128.3, 128.4, 128.7, 135.9, 138.9, 170.5, 171.7; CIMS (isobutylene) m/e (relative intensity): 444 (1), 443 (1), 288 (2), 286 (55), 91 (100). Anal. Calcd for $C_{28}H_{29}O_4N$: C, 75.82; H, 6.59. Found C, 75.42; H, 6.58.

(R)-Pantolacto-(N,N-dibenzyl)-2-amino-butanoate (44).



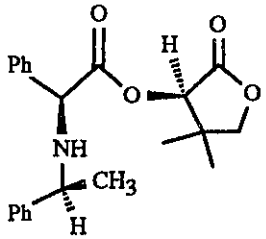
Compound **44** which was obtained as a 12:1 mixture of diastereomers was purified as such by column chromatography using Hexanes:EtOAc (3:1) and isolated in 30% yield as a colourless oil: IR (CH_2Cl_2): 2810, 1782, 1740, 1325, 1072, 1010, 850 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.90 (t, 3H, J=8.0 Hz), 1.10, 1.11, 1.20, 1.22 (all s, total 6H), 1.80 (m, 2H), 3.35 (t, 1H, J=8.2 Hz), 3.60, 3.62 (both d, 2H, J=12 Hz), 3.95, 3.98 (both d, total 2H, J=12 Hz), 4.05 (s, 2H), 5.45, 5.50 (both s, total 1H), 7.30 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ:10.8, 20.2, 22.8, 22.9, 40.1, 54.2, 62.1, 74.8, 76.2, 126.9, 128.2, 128.9, 139.5, 171.6, 172.1; CIMS (isobutylene) m/e (relative intensity): 396 (100), 304 (2), 238 (84), 237 (8), 131 (33), 115 (33). Anal. Calcd for $C_{24}H_{29}O_4N$: C, 72.88; H, 7.39. Found C, 72.92; H, 7.32.

(R)-Pantolacto-(N-diphenylmethyl)-2-amino-2-phenylethanoate (46).



Compound **46** was obtained as a single diastereomer and was isolated by column chromatography using Hexanes:EtOAc (3:1) in 78% yield as a colourless oil: IR (CH_2Cl_2): 2915, 1793, 1749, 1352, 1075, 1019, 850 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.60 (s, 3H), 0.95 (s, 3H), 2.70 (bs, 1H), 3.90 (s, 2H), 4.50 (s, 1H), 5.40 (s, 1H), 7.30 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.9, 22.5, 40.1, 62.2, 64.2, 75.3, 75.8, 127.2, 127.4, 127.6, 128.3, 128.4, 128.5, 128.7, 128.9, 129.0, 132.1, 140.1, 141.2, 171.2, 172.0, 172.3; EIMS m/e (relative intensity): 429 (3), 352 (14), 316 (9), 272 (99), 182 (100), 167 (97), 152 (86), 84 (48). HRMS calcd for $C_{27}H_{27}O_4N$ (M^+) 429.1941, found 429.1932.

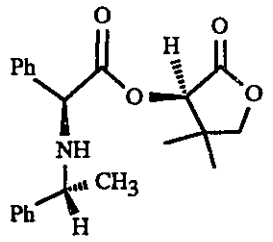
(R)-Pantolacto-(N-(S)-methylbenzyl)-2-amino-2-phenylethanoate (48).



Compound **48** which was obtained as a single diastereomer was isolated by column chromatography using Hexanes:EtOAc (3:1) in 84% yield as a colourless oil: IR (CH_2Cl_2): 2914, 1793, 1748, 1371, 1144, 1077, 1012 cm^{-1}; ^1H NMR (200 MHZ, $CDCl_3$) δ: 0.70 (s, 3H), 0.95 (s, 3H), 1.40 (d, 3H, J=8.1 Hz), 2.30 (bs, 1H), 3.90 (q, 1H, J=8.1 Hz), 3.95 (s, 2H), 4.35 (s, 1H), 5.40 (s, 1H), 7.30 (m, 10H); ^{13}C NMR (74 MHz, $CDCl_3$) δ: 19.3, 22.7,

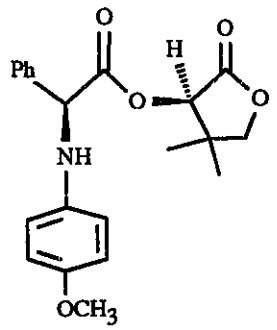
24.5, 40.2, 56.4, 62.8, 75.2, 76.0, 127.0, 127.1, 128.1, 128.2, 128.4, 128.7, 138.1, 144.4, 171.8, 173.0; CIMS (isobutylene) m/e (relative intensity): 368 (100), 320 (16), 264 (80), 249 (10), 210 (67), 162 (11), 105 (91). Anal. Calcd for $C_{22}H_{25}O_4N$: C, 71.91; H, 6.83. Found C, 71.52 ; H, 6.80.

(R)-Pantolacto-(N-(R)-methylbenzyl)-2-amino-2-phenylethanoate (48a).



This compound was obtained in 83% yield after purification on silica using Hexanes:EtOAc (3:1) as a colourless oil. Refer to Figure 21 for the corresponding proton NMR spectra.

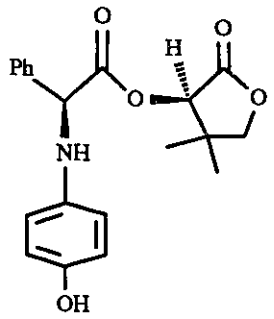
(R)-Pantolacto-(N-(*p*-methoxyphenyl))-2-amino-2-phenylethanoate (49).



Compound **49** which was obtained as a single diastereomer was purified by column chromatography using Hexanes:EtOAc (3:1) and isolated in 75% yield as needle-like crystals: mp 118-120 °C; IR (CH_2Cl_2): 2929, 1795, 1753, 1514, 1161, 1075 cm^{-1}; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.1, 22.6, 40.4, 55.6, 62.0, 75.7, 76.0, 115.0, 121.1, 127.4,

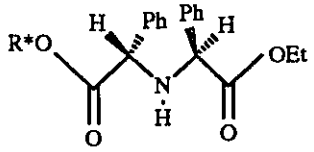
127.6, 128.1, 128.5, 128.8, 128.9, 129.0, 129.1, 130.4, 131.8; EIMS m/e (relative intensity): 369 (10), 212 (100), 210 (13), 196 (4), 77 (9). HRMS calcd for $C_{21}H_{23}O_5N$ (M^+) 369.1570, found 369.1595.

(R)-Pantolacto-(N-(*p*-hydroxyphenyl))-2-amino-2-phenylethanoate (50).



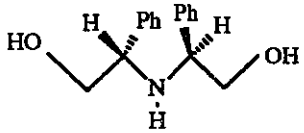
Compound **50** was obtained as a 12:1 mixture of diastereomers and isolated as such by column chromatography using Hexanes:EtOAc (1:1) in 75% yield as a colourless oil: IR (CH_2Cl_2): 3586, 2900, 1794, 1749, 1515, 1376, 1165, 1075, 1007, 822 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.70, 0.80, 0.90, 1.10 (all s, total 6H), 3.95, 4.00 (both s, total 2H), 4.55, 4.60 (both d, total 1H, J=6.3 Hz), 5.20, 5.25 (both d, total 1H, J=6.3 Hz), 5.40, 5.45 (both s, total 1H), 6.50 (d, 2H, J=7.0 Hz), 6.80 (d, 2H, J=7.0 Hz), 7.30-7.60 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.3, 18.8, 19.4, 22.2, 22.5, 30.5, 40.1, 61.3, 61.5, 75.3, 75.4, 75.7, 75.9, 114.0, 115.0, 115.8, 126.7, 127.1, 128.1, 128.3, 128.5, 128.6, 137.2, 139.5, 147.9, 171.1; EIMS m/e (relative intensity): 355 (7), 198 (100), 196 (12), 105 (32), 77 (15). HRMS calcd for $C_{20}H_{21}O_5N$ (M^+) 355.1420, found 355.1430.

(R)-Pantolacto-2-((S)-phenylglycine ethyl ester)-2-phenylethanoate (54).



Compound **54** which was obtained as an 18:1 mixture of isomers was purified by column chromatography using Hexanes:EtOAc (3:1) and isolated in 80% yield as a colourless oil: IR (CH_2Cl_2): 2992, 1794, 1749, 1735, 1376, 1165, 1075, 1007 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.50, 0.60, 0.80, 1.00 (all s, total 6H), 1.22 (t, 3H, J=7.5 Hz), 3.95 (s, 2H), 4.20 (m, 3H), 4.30 (s, 1H), 4.50 (s, 1H), 5.40 (s, 1H), 7.40 (m, 10); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 12.0, 19.4, 22.2, 40.5, 60.8, 62.2, 62.3, 75.8, 76.0, 127.1, 128.8, 128.0, 128.3, 128.5, 128.9, 130.1, 137.3, 171.0, 172.2; CIMS (isobutylene) m/e (relative intensity): 426 (100), 412 (12), 352 (55), 247 (30), 131 (22), 105 (24).

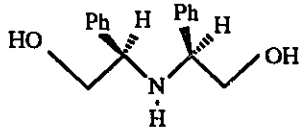
(S,S)-Bis-ethanol amine (55).



Compound **54** (92 mg, 0.216 mmole) was dissolved in 5 mL of THF and placed in a 25 mL RBF under nitrogen atmosphere. $LiAlH_4$ (20 mg, 2.5 molar eq) was added and the reaction mixture stirred at room temperature for 24 h after which time the excess $LiAlH_4$ was destroyed by the successive addition of 0.02 mL of H_2O, 0.02 mL of 15% NaOH and 0.60 mL of H_2O. The heterogeneous solution was filtered and the solid was washed several times with 10 mL portions of THF. The filtrate was evaporated and the crude product was purified by column chromatography using Hexanes:EtOAc:MeOH (4:4:1) to produce the

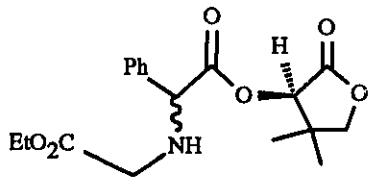
desired aminodiol in 73% yield as a colourless oil: IR (CH_2Cl_2): 3215, 2910, 1324, 1072 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 3.10 (bs, 3H), 3.85 (m, 6H), 7.40 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 60.7, 66.6, 127.1, 127.5, 128.4, 139.1; CIMS (isobutylene) m/e (relative intensity): 341 (20), 258 (100), 240 (12), 226 (30), 138 (14), 121 (20), 102 (25); $[\alpha]_D^{23}$ +133.5 (c 1.4, CH_2Cl_2). Anal. Calcd for $C_{16}H_{19}O_2N$: C, 74.68; H, 7.44. Found C, 74.62; H, 7.45.

(R,S)-*Meso*-Bis-ethanol amine (56).



Compound **56** was isolated in 70% yield via column chromatography using Hexanes:EtOAc:MeOH (4:4:1) and was obtained as a colourless oil: IR (CH_2Cl_2): 3215, 2910, 1326, 1070 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 2.40 (bs, 3H), 3.70 (m, 6H), 7.35 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 63.4, 64.4, 127.8, 128.4, 128.6, 128.7, 128.8, 129.2, 136.5, 136.6; CIMS (isobutylene) m/e (relative intensity): 341 (20), 258 (100), 240 (12), 138 (14), 121 (20), 102 (25); $[\alpha]_D^{23}$ 0.0°.

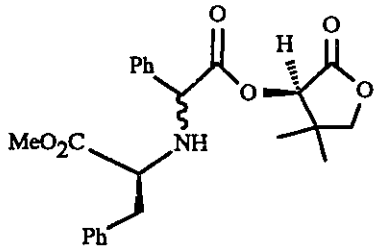
(R)-Pantolacto-2-(N-(2'-aminoethyl-ethanoate))-2-phenylethoate (57a).



Compound **57a** which was obtained as a 12:1 mixture of diastereomers was purified as such via column chromatography using Hexanes:EtOAc (3:1) to furnish a pale yellow oil in 70% yield: IR (CH_2Cl_2): 2920, 1784, 1774, 1378, 1198, 1109, 1015 cm^{-1}; ^1H NMR (200

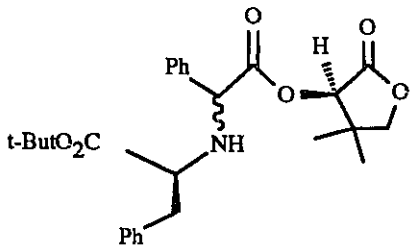
MHz, $CDCl_3$) δ: 0.52, 0.90, 1.00, 1.05 (all s, total 6H), 1.20 (t, 3H, J=8.0 Hz); 3.30 (bs, 3H), 3,90 (ABq, 2H, J=11.2 Hz), 4.10 (q, 2H, J=8.0 Hz), 4.60 (s, 1H), 5.25, 5.30 (both s, total 1H), 7.30 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.6, 13.7, 18.5, 18.8, 19.4, 19.8, 22.9, 22.1, 22.3, 22.5, 42.0, 45.2, 62.7, 63.8, 75.0, 75.3, 76.1, 127.2, 127.3, 128.1, 128.2, 128.4, 128.5, 128.7, 128.8, 128.9, 129.0, 129.3, 129.4, 129.8, 133.6, 167.2, 171.2; EIMS m/e (relative intensity): 349 (5), 276 (100), 236 (66), 219 (13), 192 (100), 135 (44), 118 (100), 91 (100), 40 (8). HRMS calcd for $C_{18}H_{23}NO_6$ (M^+) 349.1525, found 349.1542.

(R)-Pantolacto-(2-((S)-phenylalanine methyl ester))-2-phenyl ethanoate (57b).



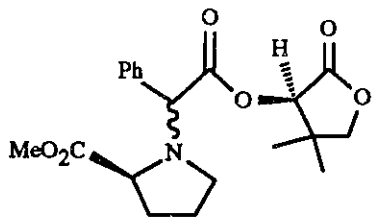
Compound **57b** which was obtained as a 9:1 mixture of diastereomers was purified as such using column chromatography with Hexanes:EtOAc (3:1) to furnish a colourless oil in 60% yield: IR (CH_2Cl_2): 2910, 1792, 1746, 1283, 1160 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.50, 0.85, 0.95, 1.11 (all s, total 6H), 1.60 (bs, 1H), 2.95 (m, 2H), 3.35 (t, 1H, J=8.3 Hz), 3.60, 3.65 (both s, 3H), 3.90 (s, 2H), 4.50, 4.52 (s, 1H), 5.30 (s, 1H), 7.20 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.5, 18.6, 22.3, 22.5, 39.3, 40.0, 51.6, 59.0, 62.7, 74.9, 75.3, 75.7, 75.8, 126.4, 127.7, 128.0, 128.2, 128.3, 129.0, 136.7, 136.8, 170.9, 173.8; CIMS (isobutylene) m/e (relative intensity): 426 (100), 334 (2), 268 (9), 115 (12). Anal. Calcd for $C_{24}H_{27}NO_6$: C, 67.76; H, 6.37. Found C, 67.82; H, 6.41.

(R)-Pantolacto-2-((S)-phenylalanine *t*-butyl ester)-2-phenyl ethanoate (57c).



Compound **57c** was obtained as a 27:1 mixture of diastereomers which was purified as such using column chromatography with Hexanes:EtOAc (3:1) to furnish a brown oil in 77% yield: IR (CH_2Cl_2): 2926, 1791, 1775, 1495, 1371, 1153, 1110 cm^{-1}: ^1H NMR (200 MHz, $CDCl_3$) δ: 0.56 (s, 3H), 0.90 (s, 3H), 1.35 (s, 9H), 3.00 (m, 3H), 3.52 (t, 1H, J=8.0 Hz), 3.89, 3.91 (both s, total 2H), 4.48, 4.52 (both s, total 1H), 5.32, 5.34 (both s, total 1H), 7.25 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.5, 18.8, 22.3, 22.5, 27.4, 27.5, 39.4, 40.0, 60.7, 63.6, 64.7, 74.8, 75.3, 75.7, 76.0, 81.2, 126.3, 127.5, 127.9, 128.5, 129.0, 129.2, 129.8, 136.8, 137.5, 171.2, 171.7; CIMS (isobutylene) m/e (relative intensity): 468 (75), 452 (14), 412 (100), 367 (7), 300 (83), 247 (43), 208 (43), 131 (99), 105 (62). Anal. Calcd for $C_{27}H_{33}NO_6$: C, 69.35; H, 7.11. Found C, 69.52; H, 7.14.

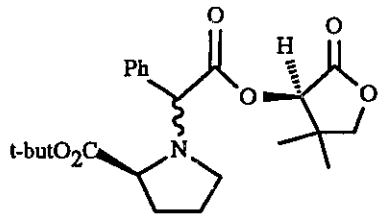
(R)-Pantolacto-2-((S)-proline methyl ester)-2-phenylethanoate (57d).



Compound **57d** was obtained as a 10:1 mixture of diastereomers and was purified as

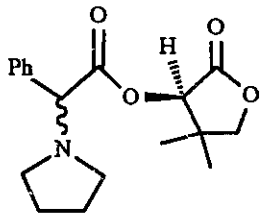
such using column chromatography with Hexanes:EtOAc (3:1) to furnish a colourless oil in 74% yield: IR (CH_2Cl_2): 2980, 1792, 1749, 1720, 1453, 1146, 1076, 1011 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.65, 0.90, 1.00, 1.12 (all s, total 6H), 1.70-2.20 (m, 4H), 2.70-3.00 (m, 2H), 3.60 (s, 3H), 3.75 (m, 1H), 3.88, 3.90 (s, total 2H), 4.60, 4.80 (s, total 1H), 5.30, 5.35 (s, total 1H), 7.30 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.5, 19.0, 22.4, 22.5, 23.0, 29.3, 40.0, 49.8, 51.3, 62.3, 68.3, 74.6, 75.7, 128.2, 128.5, 136.3, 170.2, 171.7, 174.0; CIMS (isobutylene) m/e (relative intensity): 316 (M^+-$C_2H_3O_2$, 42), 218 (46), 85 (39), 43 (100). Anal. Calcd for $C_{20}H_{25}NO_6$: C, 63.98; H, 6.71. Found C, 62.13; H 6.54.

(R)-Pantolacto-2-((S)-proline *t*-butyl ester)-2-phenylethanoate (57e).



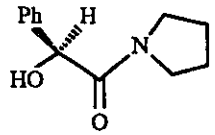
Compound **57e** was obtained as a 8:1 mixture of diastereomers and was purified as such using column chromatography with Hexanes:EtOAc (3:1) to furnish a colourless oil in 90% yield: IR (CH_2Cl_2): 2918, 1792, 1750, 1742, 1471, 1145, 1076, 1012, 844 cm^{-1}: ^1H NMR (200 MHz, $CDCl_3$) δ: 0.70, 1.00, 1.05, 1.10 (all s, total 6H), 1.45 (s, 9H), 1.70-2.20 (m, 4H), 2.80 (m, 2H), 3.70 (m, 1H), 3.90 (s, 2H), 4.78, 4.84 (both s, total 1H), 5.30, 5.35 (both s, total 1H), 7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.0, 22.4, 22.9, 22.7, 29.5, 40.0, 49.2, 62.7, 67.2, 74.6, 75.7, 80.5, 127.9, 128.0, 128.2, 128.5, 128.8, 129.7, 132.9, 136.7, 170.4, 171.6, 173.0; CIMS (isobutylene) m/e (relative intensity): 316 (M^+-$C_5H_9O_2$, 100), 204 (20). Anal. Calcd for $C_{22}H_{31}NO_6$: C, 65.16; H, 7.71. Found C, 64.93; H, 7.32.

(R)-Pantolacto-2-pyrrolidino-2-phenylethanoate (58).



Compound **58** which was obtained as a 4:1 mixture of diastereomers was purified as such using column chromatography with Hexanes:EtOAc (3:1) to furnish a colourless oil in 87% yield: IR (CH_2Cl_2): 2907, 1787, 1756, 1471, 1131, 1010, 856 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.60, 0.90, 1.00, 1.10 (all s, total 6H), 2.80 (bs, 4H), 2.30-2.70 (m, 4H), 3.80-4.10 (m, 3H), 5.25, 5.35 (both s, total 1H), 7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.7, 19.7, 22.3, 22.7, 22.9, 23.0, 29.8, 40.1, 51.2, 52.1, 72.5, 73.1, 74.4, 74.8, 75.6, 75.7, 128.0, 128.1, 128.3, 136.2, 170.4, 171.3; CIMS (isobutylene) m/e (relative intensity): 318 (100), 316 (9), 160 (92), 131 (25), 115 (13). Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.11; H, 7.30. Found C, 68.32; H, 7.41.

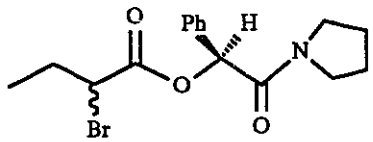
(S)-Pyrrolidino-mandelic amide (59).



A solution of (S)-methyl mandelate (1.32g, 8 mmole in 30 mL of dry CH_2Cl_2) was added dropwise to a premixed solution of Me_3Al (8 mL, 2.0 eq) and pyrrolidine (1.34 mL, 2.0 eq) in 40 mL THF. The reaction mixture was allowed to stir for 2 days at room temperature under nitrogen after which time the solution was poured in 50 mL of 10% HCl. After the vigorous bubbling subsided, the organic layer was separated and the aqueous layer was washed with 3 X 30 mL EtOAc. The organic layers were combined, dried with $MgSO_4$

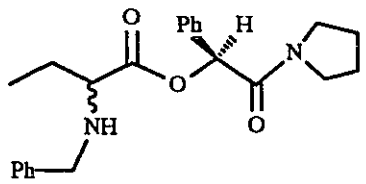
and evaporated to dryness to furnish 820 mg (50% yield) of a white solid which was identified as **59** and used without further purification: mp 91-92 °C; IR (CH_2Cl_2): 3055, 2883, 1641, 1380, 1067, 778 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.89 (bs, 1H), 1.70 (m, 4H), 3.75 (m, 1H), 3.20-3.60 (m, 3H), 5.90 (s, 1H), 7.25 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.6, 25.7, 45.7, 46.4, 72.3, 127.6, 128.4, 128.8, 138.8, 170.6; EIMS m/e (relative intensity): 205 (1), 177 (2), 149 (3), 129 (2), 107 (29), 98 (100), 55 (89). HRMS calcd for $C_{12}H_{15}NO_2$ (M^+) 205.1103, found 205.1090.

α-Bromo ester 60.



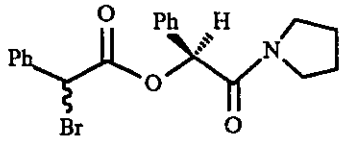
Compound **60** which was synthesized using procedure B was purified by column chromatography using Hexanes:EtOAc (1:1) to furnish the desired compound in 70% yield as a white solid: mp 76 °C; IR (CH_2Cl_2): 2865, 1743, 1712, 1363, 1221, 1099, 844 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.90 (q, 3H, J=7.2 Hz), 1.60-2.20 (m, 6H), 3.00 (m, 1H), 3.30 (m, 1H), 3.50 (m, 2H), 4.20 (q, 1H, J=7.2 Hz), 5.92, 5.95 (both s, total 1H), 7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.7, 23.7, 25.9, 28.4, 28.5, 45.8, 45.9, 46.2, 47.5, 47.6, 128.5, 128.6, 128.7 (2), 128.8, 128.9, 129.3, 129.4, 133.0, 133.2, 165.5, 165.6, 169.1, 169.6; EIMS m/e (relative intensity): 355 (1), 353 (1), 317 (2), 274 (2), 187 (6), 160 (12), 119 (1), 98 (100), 69 (55), 55 (34). HRMS calcd for $C_{16}H_{20}NO_3Br$ (M^+) 353.0627, found 353.0599.

N-Benzylated-α-amino ester 62.



Compound **62** was obtained as a 4:1 mixture of diastereomers and was purified as such via column chromatography using Hexanes:EtOAc (1:1) to furnish the desired product as a pale yellow oil in 82% yield: IR (CH_2Cl_2): 2908, 1747, 1656, 1492, 1170, 1031 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.80, 0.90 (both t, total 3H, J=8.0 Hz), 1.50-2.00 (m, 8H), 3.00 (m, 1H), 3.20-3.80 (m, 5H), 5.92, 5.98 (both s, total 1H), 7.10-7.40 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 10.0, 10.2, 23.7, 26.0, 26.3, 45.8, 46.2, 51.8, 51.9, 61.7, 61.8, 74.3, 74.4, 126.7, 126.8, 128.2, 128.3 (2), 128.4, 128.6, 128.9, 129.2, 133.8, 139.9, 166.0, 175.1; CIMS (isobutylene) m/e (relative intensity): 381 (100), 275 (13), 190 (50), 189 (11), 148 (46).

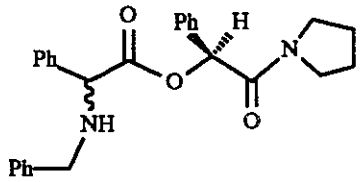
α-Bromo ester 63.



Compound **63** which was synthesized using procedure B was purified by column chromatography using Hexanes:EtOAc (1:1) to furnish the desired compound in 40% yield as a colourless oil: IR (CH_2Cl_2): 2896, 1748, 1711, 1356, 1137, 1024, 849 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.70 (m, 4H), 3.05 (m, 1H), 3.20-3.60 (m, 3H), 5.40 (s, 1H), 5.95, 6.00 (both s, total 1H), 7.40 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.7, 24.9, 26.0, 33.8, 45.9, 46.3, 75.8, 75.9, 128.4, 128.5, 128.7 (2), 128.8, 128.9, 129.0, 129.2, 129.4, 129.5, 131.1, 135.3, 135.6, 165.5, 167.9, 168.2; CIMS (isobutylene) m/e (relative intensity): 404

(20), 402 (20), 352 (11), 324 (79), 322 (17), 225 (77), 206 (48), 188 (100), 160 (76), 137 (17), 107 (20).

N-Benzylated-α-amino ester 64.



Compound **64** which was obtained as a 10:1 diastereomeric mixture was purified as such by column chromatography using Hexanes:EtOAc (1:1) to furnish the desired product as a colourless oil in 82% yield: IR (CH_2Cl_2): 2901, 1747, 1656, 1497, 1176, 1032 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.70 (m, 4H), 2.15 (bs, 1H), 3.05 (m, 1H), 3.30 (m, 1H), 3.50 (m, 2H), 3.70, 3.76 (both s, total 1H), 4.45, 4.50 (both s, total 1H), 5.92, 5.98 (both s, total 1H), 7.25 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.5, 25.7, 45.6, 46.0, 51.1, 63.8, 74.6, 126.7, 127.3, 127.7, 128.0, 128.3, 128.4, 128.9, 133.2, 137.3, 139.2, 165.8, 172.6; CIMS (isobutylene) m/e (relative intensity): 429 (44), 323 (9), 242 (18), 196 (72), 188 (21), 160 (31), 106 (34). Anal. Calcd for $C_{27}H_{28}N_2O_3$: C, 75.67; H, 6.58. Found C, 75.82; H, 6.62.

REFERENCES

Part B: The Synthesis of Optically Active α-Amino Esters via Kinetic Dynamic Resolution.

1. Williams, R.M. Synthesis of Optically Active α-Amino Acids; Pergamon Press, New York: **1989**, p.1-304.
2. Kochetkov, K.A.; Beliko, V.M. Modern Asymmetric Synthesis of α-Amino Acids; *Russian Chemical Reviews*, **1987**, *56*, 1045.
3. O'Donnell, M.J. α-Amino Acid Synthesis; *Tetrahedron*, **1988**, *44*, 5253-5614.
4. Schoilkoph, U. *Tetrahedron*, **1983**, *39*, 2085.
5. Schollkoph, U.; Groth, U.; Deng, C. *Angew. Chem. Int. Ed. Engl.*, **1981**, *20*, 798.
6. a) Naef, R.; Seebach, D. *Helv. Chim. Acta*, **1985**, *68*, 135.
   b) Calderari, G.; Seebach, D. *ibid.*, **1985**, *68*, 1592.
7. Fadel, A.; Salaun, J. *Tetrahedron Lett.*, **1987**, *28*, 2243.
8. a) Schmidt, U.; Siegel, W. *Tetrahedron Lett.*, **1987**, *28*, 2849.
   b) Seebach, D.; Aebi, J.D. *ibid.*, **1983**, *24*, 3311.
9. Dellaria, J.F.; Santarsiero, B.D. *Tetrahedron Lett.*, **1988**, *29*, 6079.
10. a) Ito, Y.; Sawamura, M.; Haysshi, J.; Matsuoka, M.; Matsumoto, Y. *Tetrahedron Lett.*, **1987**, *28*, 4849.
    b) Belokon, Y.N.; Sagyan, A,S.; Djamgaryan, S.M.; Bakhumtov, V.I.; Belikov, V.M. *Tetrahedron*, **1988**, *44*, 5507.
11. Yamamoto, Y.; Ito, W.; Maruyama, K. *J. Chem. Soc., Chem. Commun.*, **1985**, 1131.
12. Diels, O.; Behncke, H. *Chem. Ber.*, **1924**, *57*, 653.
13. Gennari, C.; Colombo, L.; Bertolini, G. *J. Am. Chem. Soc.*, **1986**, *108*, 6394.
14. Evans, D.A.; Britton, T.C.; Dorow, R.L.; Dellaria, J.F. *J. Am. Chem. Soc.*, **1986**, *108*, 6395.

15. Oppolzer, W.; Moretti, R. *Tetrahedron*, **1988**, *44*, 5541.

16. Guanti, G.; Banfi L.; Narisano, E. *Tetrahedron*, **1988**, *44*, 5553.

17. Evans, D.; Britton, T.C. *J. Am. Chem. Soc.*, **1987**, *109*, 6881.

18. Evans, D.A.; Sjogren, E.B.; Weber, A.E.; Conn, R.E. *Tetrahedron Lett.*, **1987**, *28*, 32.

19. Strecker, A. *Liebigs Ann. Chem.*, **1850**, *75*, 27.

20. Harada, K.; Okawara *J. Org. Chem.*, **1987**, *38*, 707.

21. For references pertaining to this methodology see:

a) Takasaki, M., Harada, K. *J. Chem. Soc. Chem., Commun.*, **1987**, 571.

b) Kanmera, T.; Lee, S.; Aoyagi, H.; Izumiya, N. *Tetrahedron Lett.*, **1979**, 4483.

22. Halpern, J. Asymmetric Synthesis, Vol. 5 (Chiral Catalysis); Academic Press, Orlando: **1985**, chapter 2.

23. a) Vineyard, B.D.; Knowles, W.S.; Sabacky, M.J. *J. Mol. Catal.*, **1983**, *19*, 159.

b) Vineyard, B.D.; Knowles, W.S.; Sabacky, M.J.; Bachman, G.L.; Weinkauff, D.J. *J. Am. Chem. Soc.*, **1977**, *99*, 5946.

24. a) Kayan, H.B.; Fiand, J.C. *Topics in Stereochemistry* edited by Eliel, E.L. and Wilen, S.H., **1988**, *18*, 249 and also Chen, C.S; Sih, C.J. *Angew. Chem. Int. Ed. Engl.*, **1989**, *28*, 695.

b) Izumi, Y.; Chibata, I.; Itoh, T. *Angew. Chem. Int. Ed. Engl.*, **1978**, *17*, 176.

25. Abood, N.A.; Nosal, R. *Tetrahedron Lett.*, **1994**, *35*, 3669.

26. For examples of this strategy refer to:

a) Nakamichi, K.; Nabe, K.; Yamada, S.; Tosa, T.; Chibata, I. *Appl. Microbiol. Biotechnol.*, **1984**, *19*, 100.

b) Hummel, W.; Weiss, N.; Kula, M.R. *Arch. Microbiol.*, **1984**, *137*, 47.

27. Castelhano, A.L.; Pliura, D.H.; Taylor, G.J.; Hsiech, K.C.; Krantz, A. *J. Am. Chem. Soc.*, **1984**, *106*, 2734.

28. Georg, G.; Guan, X.; Kant, J. *Tetrahedron Lett.*, **1988**, *29*, 403.

29. O'Donnell, M.J.; Bennett, W.D.; Wu, S. *J. Am. Chem. Soc.*, **1989**, *111*, 2353.

30. Corey, E.J.; Link, J.O. *J. Am. Chem. Soc.*, **1992**, *114*, 1906-08.

31. Gallina, C.; Giordano, C. *Synthesis*, **1989**, 466-68.

32. Corey, E.J.; Link, J.O. *Tetrahedron Lett.*, **1992**, *33*, 3431.

33. Larsen, R.D.; Corley, E.G.; Davis, P.; Reider, P.J.; Grabowski, E.J. *J. Am. Chem. Soc.*, **1989**, *111*, 7650-51.

34. a) Durst, T.; Koh, K. *Tetrahedron Lett.*, **1992**, *33*, 6799.

b) In this thesis the phrase "optically active" is synonymous with non-racemic or other nonmenclature of this nature.

35. Evans, D.A.; Ellman, J.A.; Dorrow, R.L. *Tetrahedron Lett.*, **1987**, *28*, 1123.

36. Strijtveen, B.; Kellog, R.M. *J. Org. Chem.*, **1986**, 51, 3664.

37. In the case of the *t*-butylbromo ketene, the absolute configuration was determined to be (R) as opposed to (S).

38. a) Koh, K.; Ben, R.N.; Durst, T. *Tetrahedron Lett.*, **1993**, *34*, 4473.

b) Kaseda, T.; Kikuchi, T.; Kibayashi, C. *Tetrahedron Lett.*, **1989**, *30*, 4539.

39. Morrison R.; Boyd, R. Organic Chemistry, 5th ed.; Allyn and Bacon Inc., London: **1987**, p. 184.

40. Meijer, E.M.; Boestan, W.H.J.; Schoemaker, H.E.; Van Balken , J.A.M. Biocatalysts in Organic Synthesis; Edited by Tramper, J.; Van der Plas, H.C.; Linko, P., Elsevier Publishing, Amsterdam: **1985**, p. 135.

41. Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.*, **1989**, *111*, 9134.

42. Vollhardt, K.P.; Schore, N.E. Organic Chemistry; W.H. Freeman, New York: **1994**, p. 63.

43. Table 1. was taken from Volhardt, K.P.C.; Schore, N.E. Organic Chemistry, 2nd ed.;

W.H. Freeman and Company, New York: **1994**, p. 197.

44. Loncharich, R.T.; Schwartz, T.R.; Houk, K.N. *J. Am. Chem. Soc.*, **1987**, *109*, 14.

45. Wiberg, K.B.; Laidig, K.E. *J. Am. Chem. Soc.*, **1987**, *109*, 5935.

46. Streitwieser, A. Solvolytic Displacement Reactions; McGraw-Hill Book Company Inc., New York: **1962**, p. 26.

47. Allinger, K.B.; Kuchsiang, C.; Rahman, M.; Pathiaseril, A. *J. Am. Chem. Soc.*, **1991**, *113*, 4505.

48. Davis, H.M.L.; Cantrell, W.R. *Tetrahedron Lett.*, **1991**, *32*, 6509-12.

49. Poll, T.; Sobczak, A.; Hartmann, H.; Helmchen, G. *Tetrahedron Lett.*, **1985**, *26*, 3095-98.

50. Harpp, D.W.; Black, C.J.; Gleason, J.G.; Smith, R.A. *J. Org. Chem.*, **1975**, *40*, 3420.

51. a) The $[\alpha]_D^{23}$ of optically pure N-benzyl-2-amino butanol was determined by K. Koh.

b) This result was reported incorrectly as a 4:1 ratio in an earlier publication. See reference 38a.

c) Koh, K. unpublished results.

52. Morand, P,; Kayser, M. *Can. J. Chem.*, **1978**, *56*, 1524.

53. Opplozer, W. et al. *Tetrahedron Lett.*, **1986**, *27*, 831.

54. Britelli, D.R. *J. Org. Chem.*, **1981**, *46*, 2514-20.

55. Vishwakarma, L.C.; Stringer, O.D.; Davis, F.A. *Org. Syn.*, *66*, 203.

56. Davis, F.A.; Vishwakarma, L.C.; Billmers, J.M.; Finn, J. *J. Org. Chem.*, **1984**, *49*, 3241.

57. Hassner, A.; Alxanian, V. *Tetrahedron Lett.*, **1978**, *46*, 4475.

58. Evans, D.A.; Gage, J.R. *Org. Syn.*, **1989**, *68*, 77.

59. A. Reid unpublished results.

60. Hanessian, S. Total Synthesis of Natural Products: The Chiral Approach; Pergamon

Press, New York: **1983**, chapter 2.

61. Koh, K.; Durst, T. *J. Org. Chem.*, **1994**, *59*, 4683.

62. Koh, K.; Ben, R.N. unpublished results.

63. a) Reetz, M.; Rolfing, K.; Griebenow, G. *Tetrahedron Lett.*, **1994**, *35*, 1969.

b) Goh, J.B.; Lagu, B.R.; Wurster, J.; Liotta, D.C. *Tetrahedron Lett.*, **1994**, *35*, 6029.

64. Davies, J.S. Amino Acids and Peptides; Chapman and Hall, New York: **1985**.

65. Salvadori, S.; Tomatis, R.; Balboni, G.; Marchetti, P.; D'Angeli, G; Lazarus, L.H. *Peptides*, **1992**, 185.

66. Drummond, M. *Nature*, **1979**, *281*, 343.

67. a) Miyazawa, T.; Hiramatsu, S.; Yasuhiro, T.; Yamado, T.; Kuwata, S. *Bull. Chem. Soc. Jpn.*, **1985**, *58*, 1976.

b) Miyazawa, T. *Bull. Chem. Soc. Jpn.*, **1980**, *53*, 2555.

68. a)De Vries, E.F.J.; Brussee, J.; Kruse, C.G.; Van der Gen, A. *Tetrahedron Asymmetry*, **1994**, *5*, 377.

b) Evans, D.A.; Nelson, S.G.; Gagne M.R.; Muci, A.R. *J. Am. Chem. Soc.*, **1993**, *115*, 9800.

69. De Vries, E.F.J.; Steenwinkel, P.; Brussee, J.; Kruse, C.G.; Van der Gen, A. *J. Org. Chem.*, **1993**, *58*, 4315.

70. Madhusoodan, V.H.; Bhat, T.N.; Kempf, D.J.L Baldwin, E.T.; Liu, B.; Gulnik, S.; Wideburg, N.E.; Norbeck, D.W.; Appelt, K.; Erikson, J.W. *J. Am. Chem. Soc.*, **1994**, *116*, 847.

71. Prepared by a standard literature procedure: McKenzie, A.; Wills, G.O. *J. Chem. Soc.*, **1925**, *127*, 283.

72. Koh, K.; Ben, R.N.; Durst, T. *Tetrahedron Lett.*, **1994**, *35*, 375.

73. Jung, M. unpublished results.

74. Basha, A.; Lipton, M.; Weinreb, S.M. *Tetrahedron Lett.*, **1977**, 4171-74.

75. Lagu, B.; Liotta, D.C. *Tetrahedron Lett.*, **1994**, *35*, 547.

76. Kronenthal, D.R.; Han, C.Y.; Martha, K.T. *J. Org. Chem.*, **1982**, *47*, 2765-68.

77. Murakami, M.; Hajime, I,; Yoshihiko, I. *J. Org. Chem.*, **1993**, *58*, 6766.

78. Taguchi, T.; Hisanaka, I.; Hanzawa, Y. *J. Org. Chem.*, **1993**, *58*, 774-5.

79. Gabe, E.J.; LePage, Y.; Charland, J.P.; Lee, F.L.; White, P.S. *J. Appl. Cryst.*, **1989**, *22*, 384-87.

80. Scattering factors from Int. Tab. Vol. 4: *International Tables for X-ray Crystallography*, **1974**, *4*.

CLAIMS TO ORIGINAL RESEARCH

PART A: Lithiated Bicyclic Sulfoxides.

1) The reaction of the lithio derivatives of several isomeric bicyclic sulfoxides with various electrophiles (such as benzyl bromide, acetone and D_2O) was investigated.
2) The stereochemistry of these products was determined using advanced two dimensional NMR techniques.
3) A rational based on a planar or sp^2 hybridized α-carbanion was proposed to account for the unusual stereochemical results observed in the products.

PART B: The Synthesis of Optically Active α-Amino Esters via Kinetic Dynamic Resolution.

1) (R)-Pantolactone was shown to be the best auxiliary in our kinetic dynamic resolution amongst ten auxiliaries tested.
2) An explanation for the difference in reactivity between the (R,R) and (S,R) diastereomers of the α-bromo-(R)-pantolactone esters was proposed. The effect of changing the size of the nucleophile; R group on the ester and solvent was investigated and shown to be consistent.
3) A number of N-substituted optically active α-amino esters were prepared in good yields with high diastereomeric excesses using this methodology.