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Asymmetric synthesis of chiral amines and benzazepine alkaloids from chiral sulfoxides

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ASYMMETRIC SYNTHESIS OF CHIRAL AMINES AND BENZAZEPINE ALKALOIDS FROM CHIRAL SULFOXIDES

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ABDOL REZA HAJIPOUR

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DECLARATION

This is to certify that the work described in this thesis has not been submitted for a higher degree at any other university or Institution.

Abdol Reza Hajipour

ACKNOWLEDGEMENTS

I would like to thank the following people for their help during my research and production of this thesis:

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Abbreviations.

The following abbreviations are used throughout this thesis:

HOAc	acetic acid
Ac_2O	acetic anhydride
Bu	butyl
CH_2Cl_2	dichloromethane
CI	chemical ionization
conc.	concentrated
3-CPBA	3-chloroperoxybenzoic acid
DCM	dichloromethane
DIBAL	diisobutylaluminium hydride
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
d.r.	diastereomeric ratio
e.e.	enantiomeric excess
EI	electron impact
eq.	equation
ES	electrospray
Et_3N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
equiv.	(molar) equivalents
Et_2O	diethyl ether

FAB	fast atom bombardment
i-	iso
h	hour
IR	infrared
LDA	lithium diisopropylamide
lit.	literature
m.p.	melting point
MeOH	methanol
Me	methyl
min.	minutes
MS	mass spectrum
n-	normal
NMR	nuclear magnetic resonance
Oct	octyl
Ph	phenyl
PhH	benzene
ppm	part per million
Pr	propyl
$PhCH_3$	toluene
Py	pyridine
R.T.	room temperature
s-	secondary
t-	tertiary

THF	tetrahydrofuran
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
p-Tol	*p*-Tolyl
TMS	trimethylsilyl
TsOH	*p* -Toluenesulfonic acid
TLC	thin layer chromatography

ABSTRACT

This thesis investigates the application of chiral sulfoxides to the asymmetric synthesis of chiral amines and benzazepine alkaloids, the results are presented in four chapters.

In Chapter 1, the addition of the anions of methyl phenyl sulfoxide and the novel methyl 2-methoxy-1-naphthyl sulfoxide to nitrones was shown to be a diastereoselective process under kinetically controlled conditions. The stereochemistry of these adducts was determine by chemical correlation with known β-amino sulfoxides.

Chapter 2 is an extension of this method and describes the addition of lithiated methyl phenyl sulfoxide to oxaziridines. The relative stereochemistry of the major and minor adducts from these reactions was determined by ^{1}H NMR spectroscopic analysis. A new method for the synthesis of oxaziridines by the oxidation of imines with Oxone® is also reported.

In Chapter 3, an attempt was made to extend this methodology to the synthesis of β-amino sulfoxide (7), from the addition of methyl phenyl sulfoxide to nitrile oxides, benzohydroximinoyl chlorides and nitriles, and then reduction of the products by either sodium triacetoxyborohydride or sodium cyanoborohydride. However the diastereoselection of these reductions was poor.

Chapter 4 deals with an attempt to solve the problems encountered with the synthesis of β-amino sulfoxide (2) in Chapters 1, 2, and 3. β-Keto 2-methoxy-1-naphthyl sulfoxides (1) were prepared and converted to β-amino sulfoxide (2) via a number of methods. These methods included reductive alkylation of (1) and the conversion of (1) to its β-sulfinyl enamine followed

by diastereoselective reduction. Attempts to use the β-amino sulfoxide (2) for the synthesis of benzazepine alkaloids via a Pummerer type cyclization failed to give the expected product, however a novel rearrangement product was isolated and characterized.

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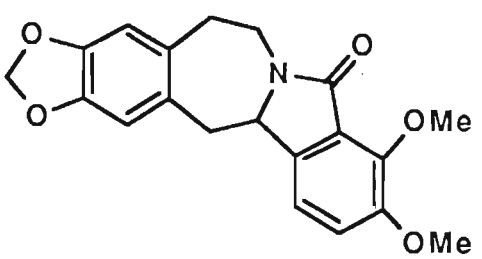
INTRODUCTION

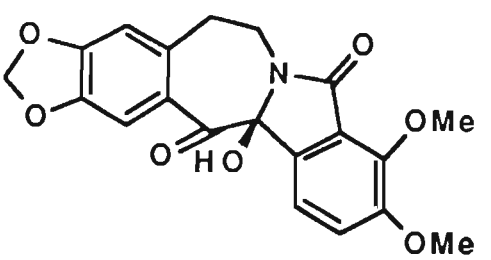
INTRODUCTION

Benzazepine Alkaloids

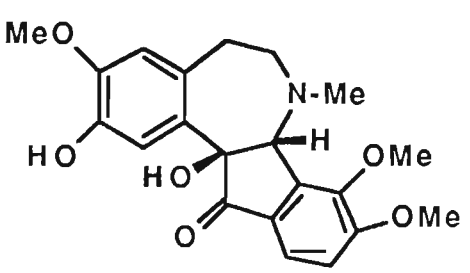
The benzazepine ring system occurs in the biologically active rhoeadine alkaloids[1](e.g. alpinene) and isoindolbenzazepine alkaloids (e.g. lennoxamine and chilenine) and related natural products (e.g. fumarofine, puntranine and turkiyenine) .



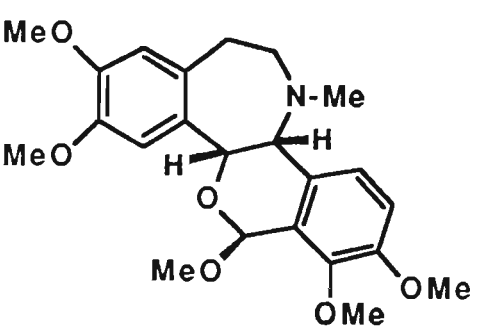
Lennoxamine



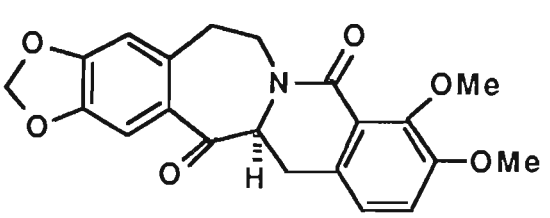
Chilenine



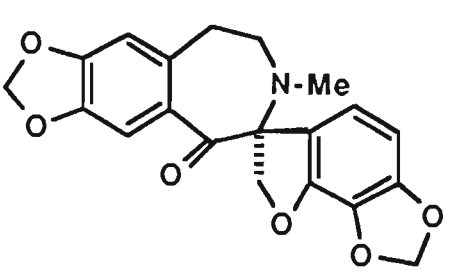
Fumarofine



Alpinene



Puntranine

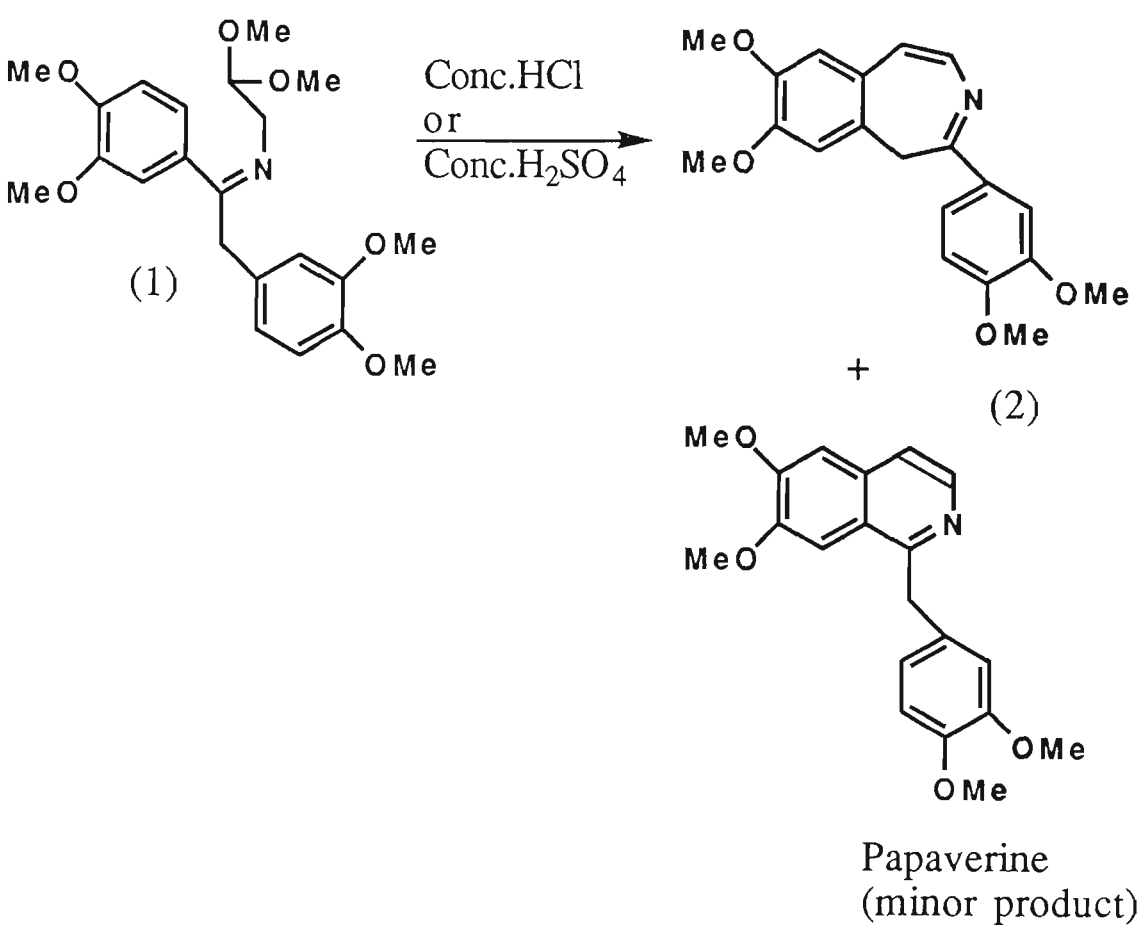


Turkiyenine

Other simpler substituted benzazepine are being intensively developed as central nervous system (C.N.S.)[1] and cardiovascular pharmaceutical agents.[2]

The rhoeadines are present within plants of the genus *Papaver*, family *Papaveraceae*.[3] There are approximately thirty of these kinds of compounds, of which about ten have not been isolated from plants, but were obtained through acid-catalysed isomerization of the natural products. Several approaches to the synthesis of the benzazepine ring system have been described. Attempted Pomeranz-Fritsch cyclization of the imine acetal (1) in an effort to obtain papaverine afforded mainly the benzazepine (2), cyclization having occurred in the direction of the more highly activated ring as shown in Scheme 1.[4,5]

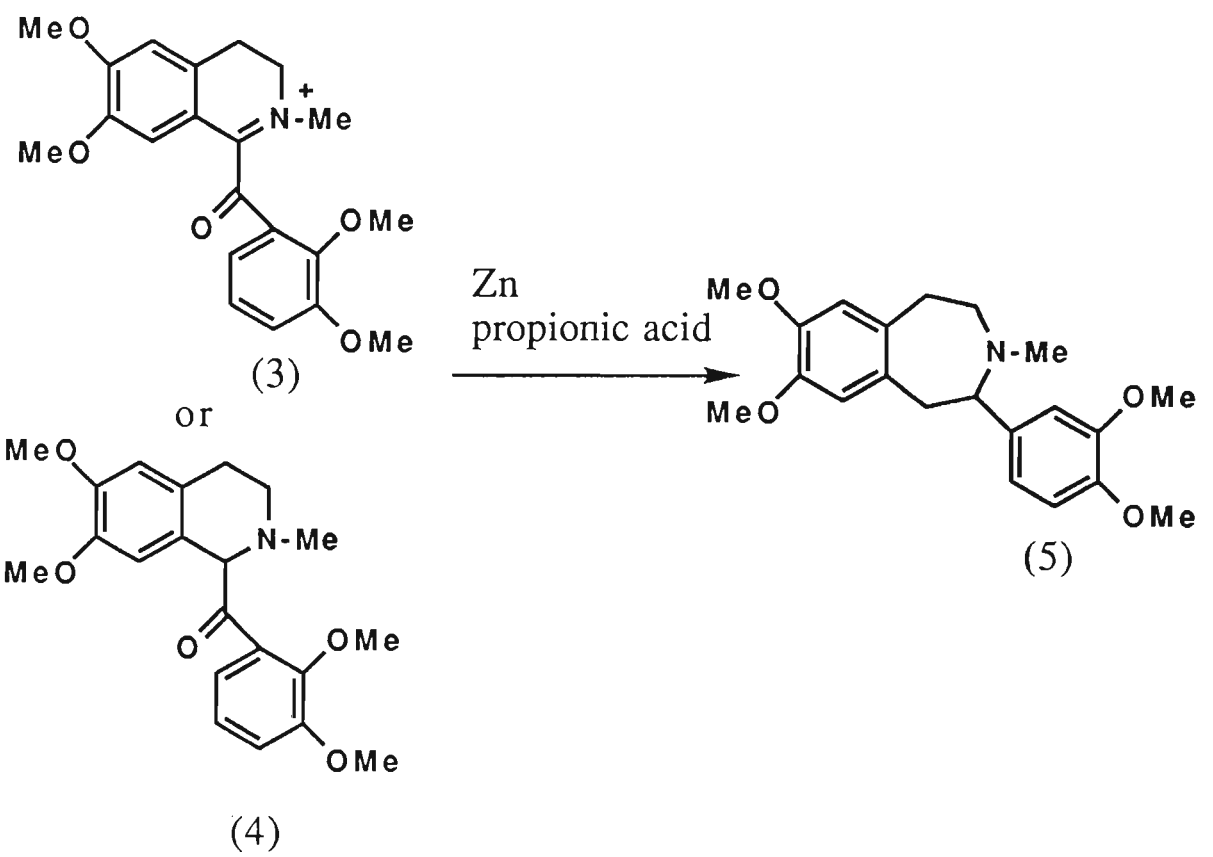
Scheme 1. Cyclization of imine acetal (1).



Papaverine
(minor product)

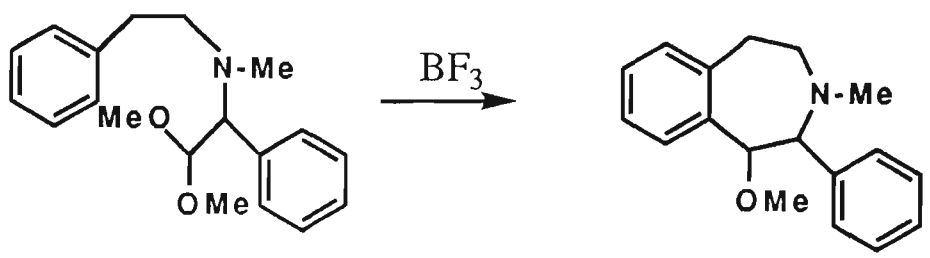
In 1969, Reby and co-workers reported the synthesis of benzazepine (5) by reduction of either ketonic immonium salt (3) or α-amino ketone (4) with zinc in propionic acid (Scheme 2).[6]

Scheme 2. Synthesis of benzazepine (5) by reduction of either ketonic immonium salt (3) or α-amino ketone (4) with zinc in propionic acid.



Cyclization of the amino acetal (6) through Lewis acid catalysis has been reported to yield the benzazepine (7) as shown in Scheme 3.[7]

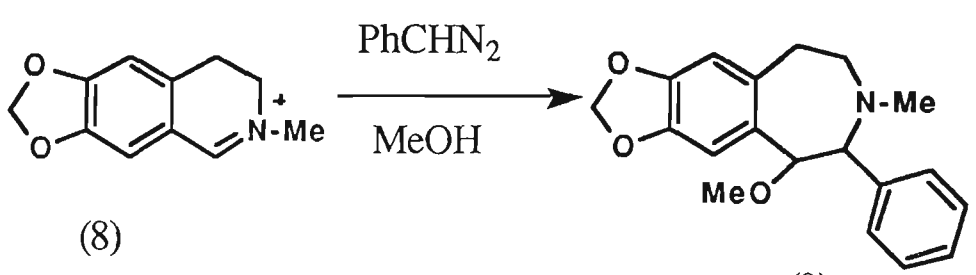
Scheme 3. Cyclization of the amino acetal (6) via Lewis acid catalysis to benzazepine (7).



(6) (7)

Treatment of the immonium salt (8) with phenyl diazomethane in methanol furnished the benzazepine (9) as shown in Scheme 4.[8]

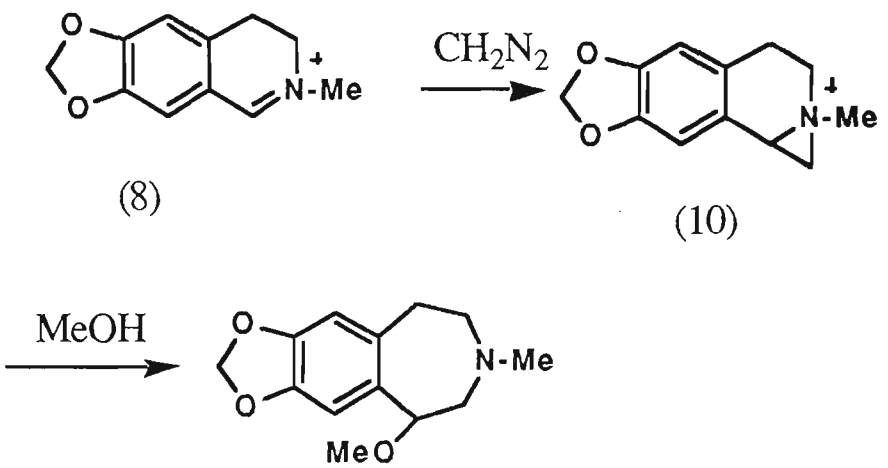
Scheme 4. Synthesis of benzazepine (9) from immonium salt (8).



(8) (9)

In a related study it was found that treatment of the immonium salt (8) with diazomethane led to the aziridinium salt (10). Solvolytic ring expansion of (10) generated benzazepine (11) [9] (Scheme 5).

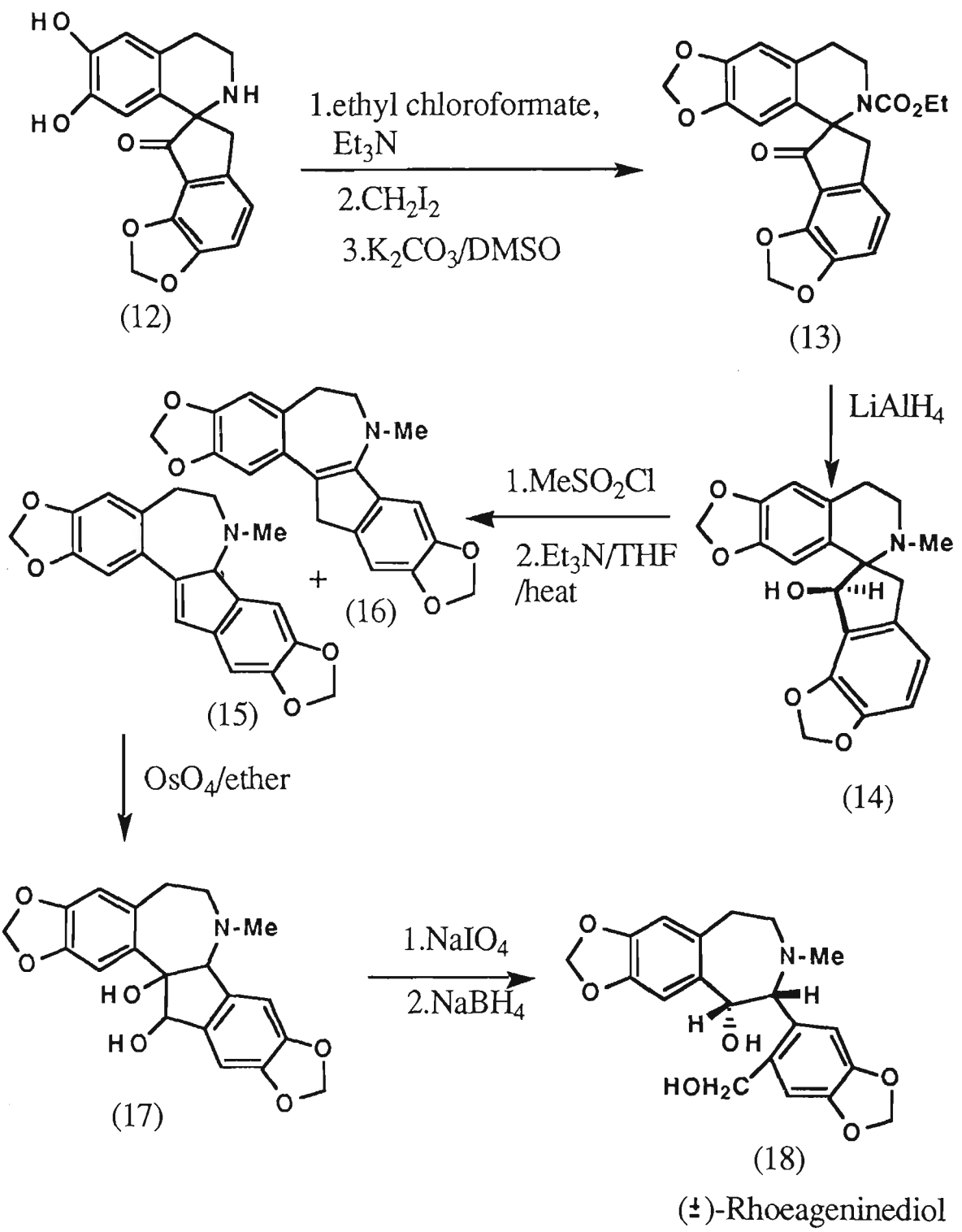
Scheme 5. Synthesis of benzazepine (11) from immonium salt (8).



(8) (10) (11)

A preparation of racemic rhoeageninediol has been achieved by Irie and co-workers starting with the synthetic diphenolic ketone (12) by the steps shown in Scheme 6.[10] Lithium aluminium hydride reduction of ketone (13) occurred from the less hindered side of the carbonyl group and produced the alcohol (14). Upon heating with methanesulfonyl chloride in triethylamine and THF, a skeletal rearrangement occurred and compounds (15) and (16) were obtained in a (1:1) ratio. Compound (15) reacted with osmium tetraoxide and the glycol (17) that was obtained was readily converted to the target alkaloid (18).

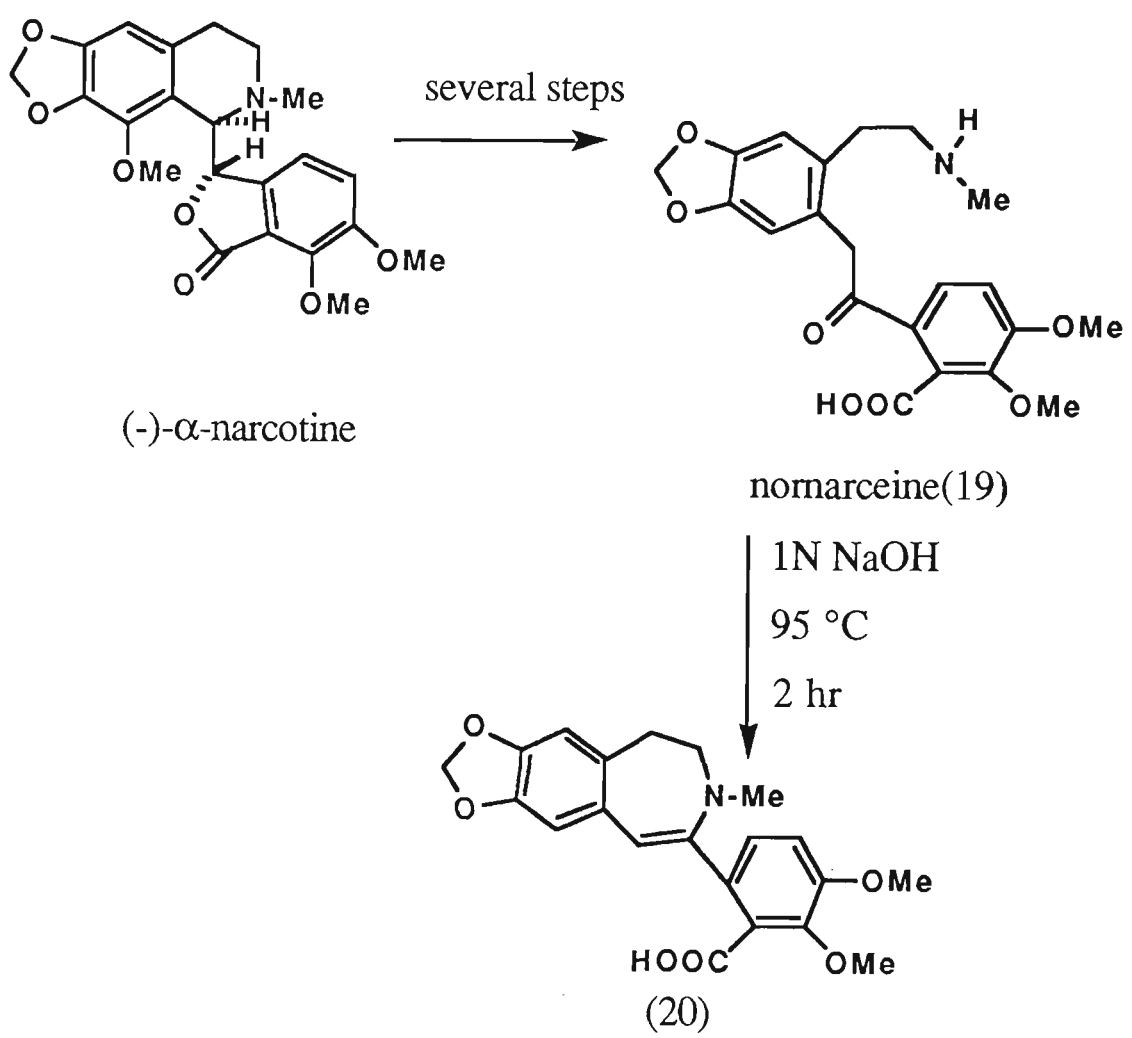
Scheme 6. Synthesis of racemic rhoeageninediol (18) from diphenolic ketone (12).

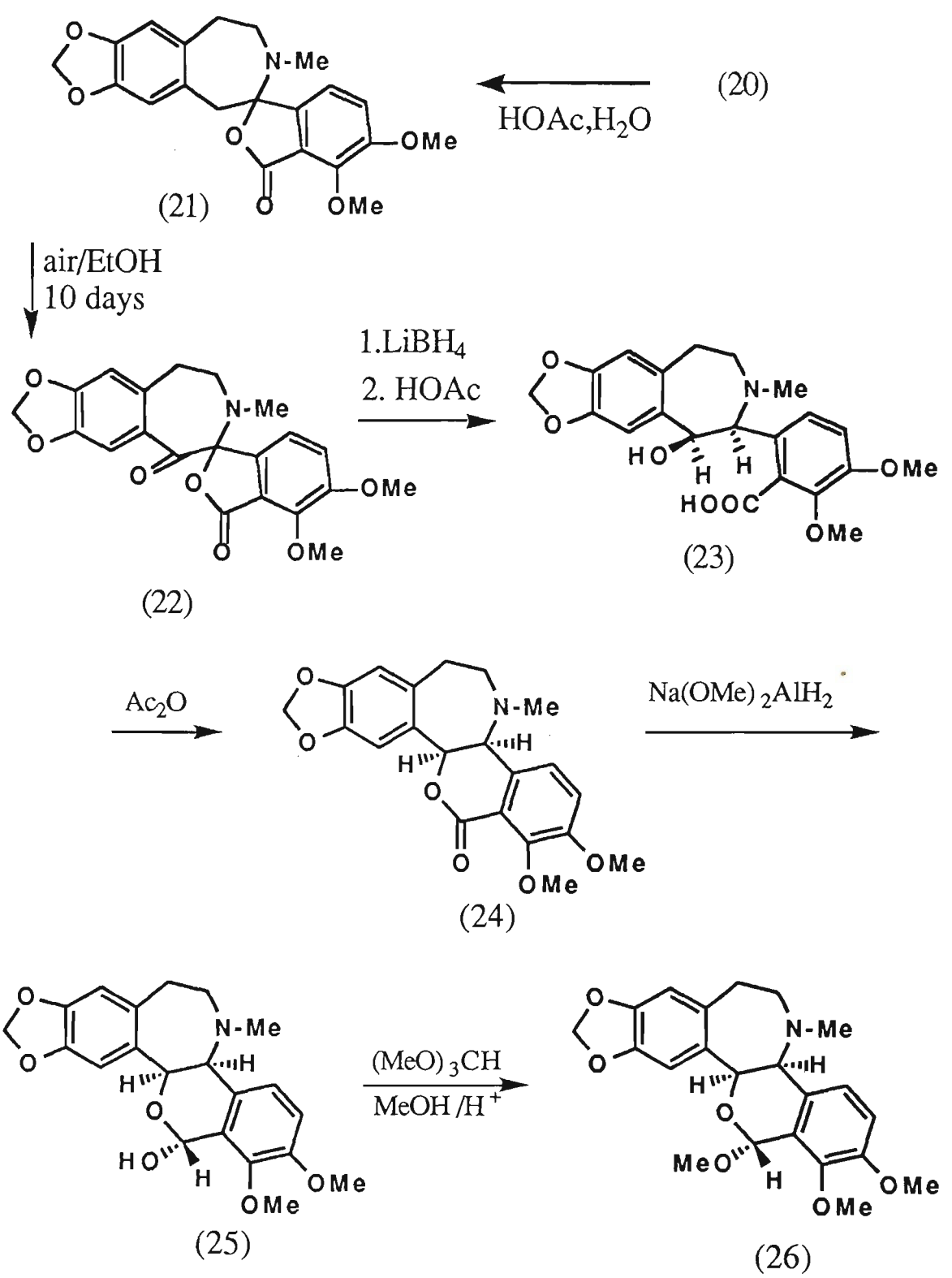


Klotzer and co-workers have reported a very interesting conversion of nornarceine (19) into the rhoeadine analogues (25) and (26). Nornarcine (19) that was derived from (-)-narcotine was first heated with 1 N sodium hydroxide to produce enamine (20), this compound readily cyclized in aqueous acetic acid to the γ-lactone (21). Upon standing in air (21) oxidised to the ketone (22). Lithium

borohydride reduction and neutralisation by acetic acid converted (22) to (23). Cyclization of (23) under different conditions led to the thermodynamically more stable *cis* δ-lactone (24) which was reduced to the hemiacetal (25). The stereochemistry of the methyl iodide salt of (25) was confirmed by X-ray analysis, compound (26) could also be prepared from (25) as shown in Scheme 7.[11]

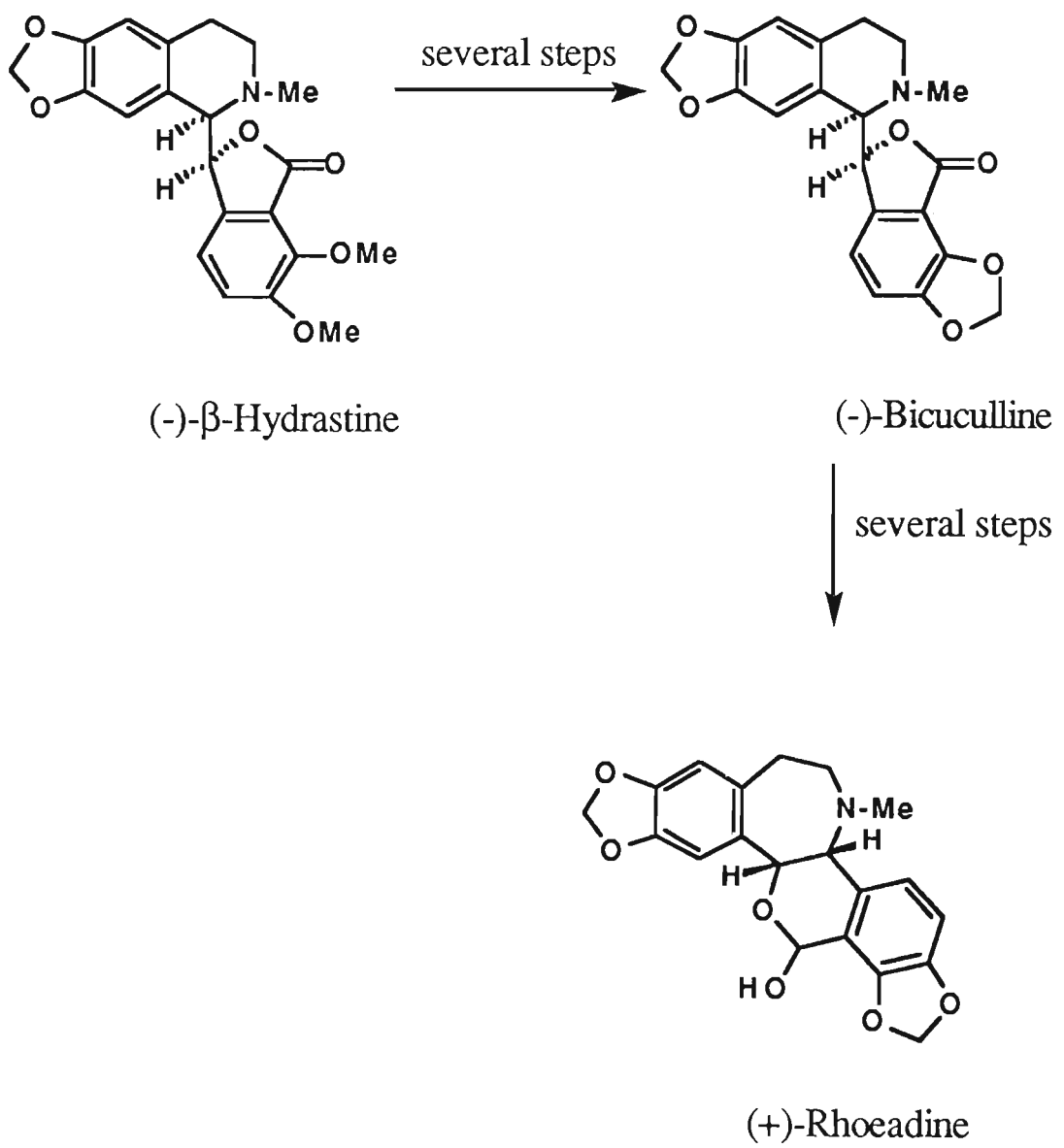
Scheme 7. Synthesis of rhoeadine analogues (25) and (26) from nornacine (19).





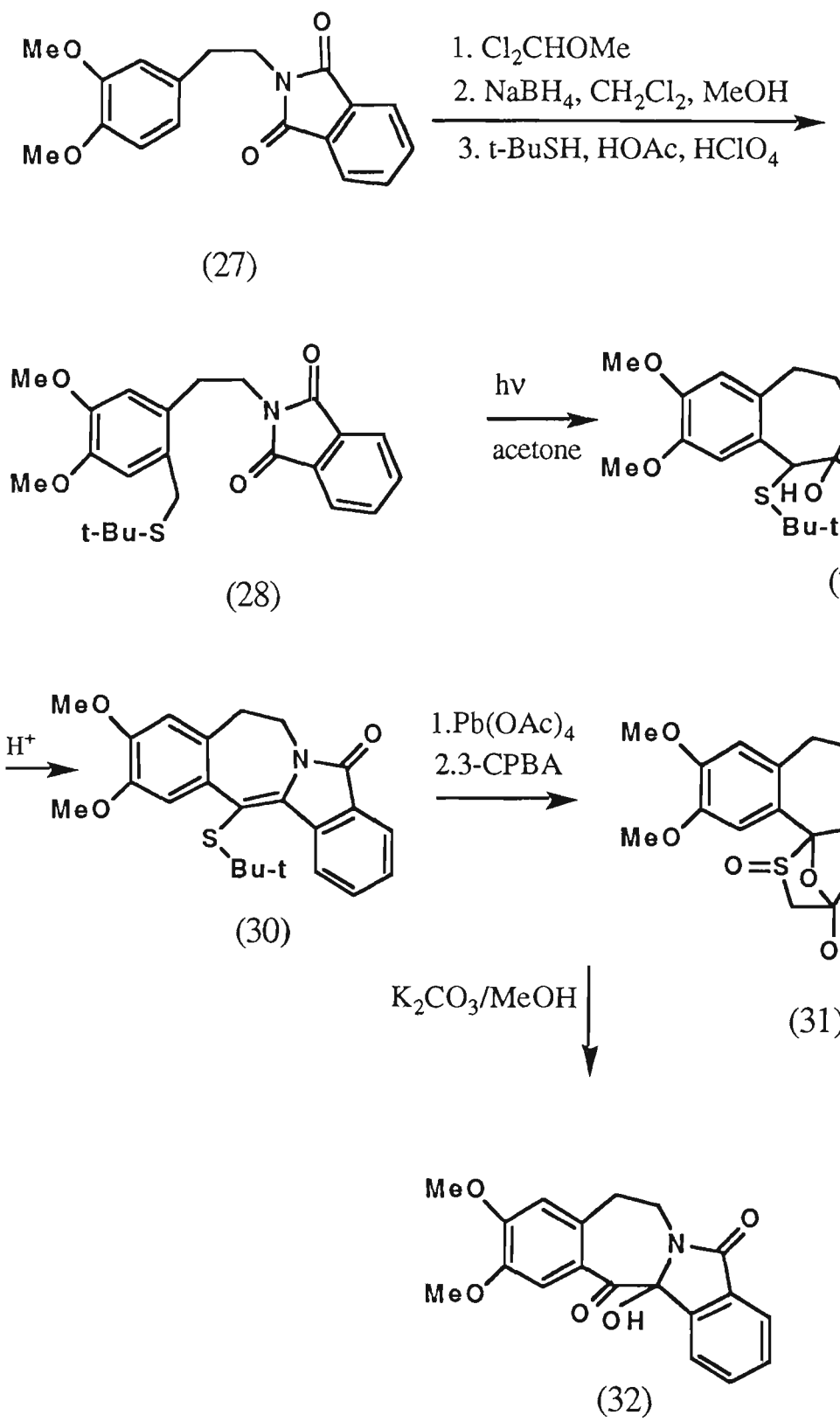
As an extension of the above synthesis, the phthalideisoquinoline alkaloid (-)-bicuculline was converted into the naturally occurring (+)-rhoeadine. Since (-)-bicuculline was derived from (-)-β-hydrastine whose synthesis had been reported in 1950, this conversion has been described as the first total synthesis of natural (+)-rhoeadine (Scheme 8).[12]

Scheme 8. Synthesis of (+)-rhoeadine from (-)-β-hydrastine.



Mazzochi and co-workers reported the synthesis of the fully functionalised ring system of the berberine alkaloid chileine (32) in an eight step synthesis.[13] Compound (30) was readily prepared from the easily available (27) by a five step synthesis in 68 % overall yield. Compound (30) was treated with lead tetraacetate and then 3-chloroperoxybenzoic acid (3-CPBA) to give (31), hydrolysis of this compound with potassium carbonate in methanol gave the target molecule (32), as shown in Scheme 9.

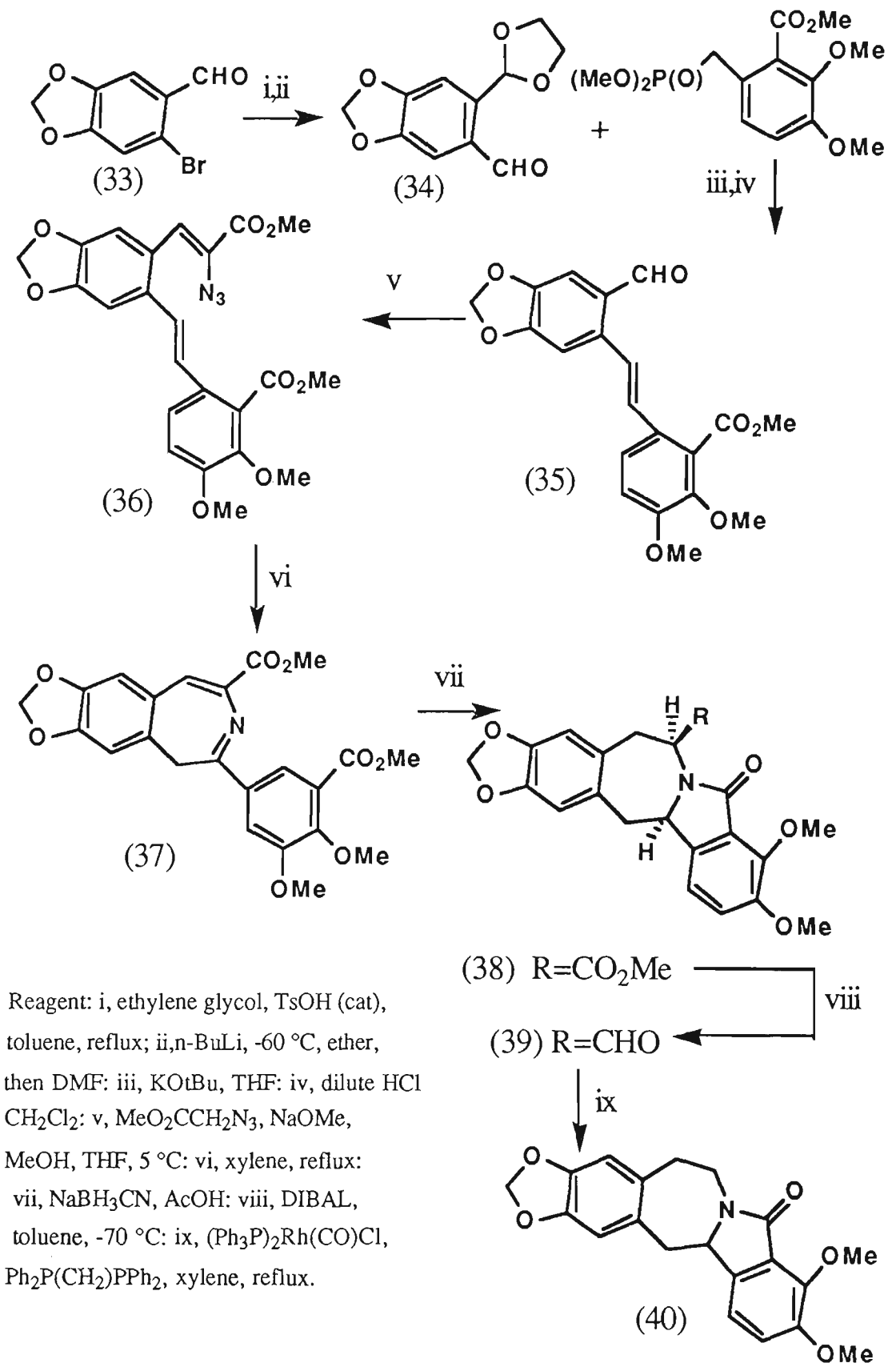
Scheme 9. Synthesis of berberine alkaloid chileine (32) from compound (27).



The benzazepine alkaloid lennoxamine (40),[14] has been prepared from 6-bromopiperonal (33) in nine steps by a route

which involves formation of the 2-arylbenzazepine (37) from the azide (36) as shown in Scheme 10.

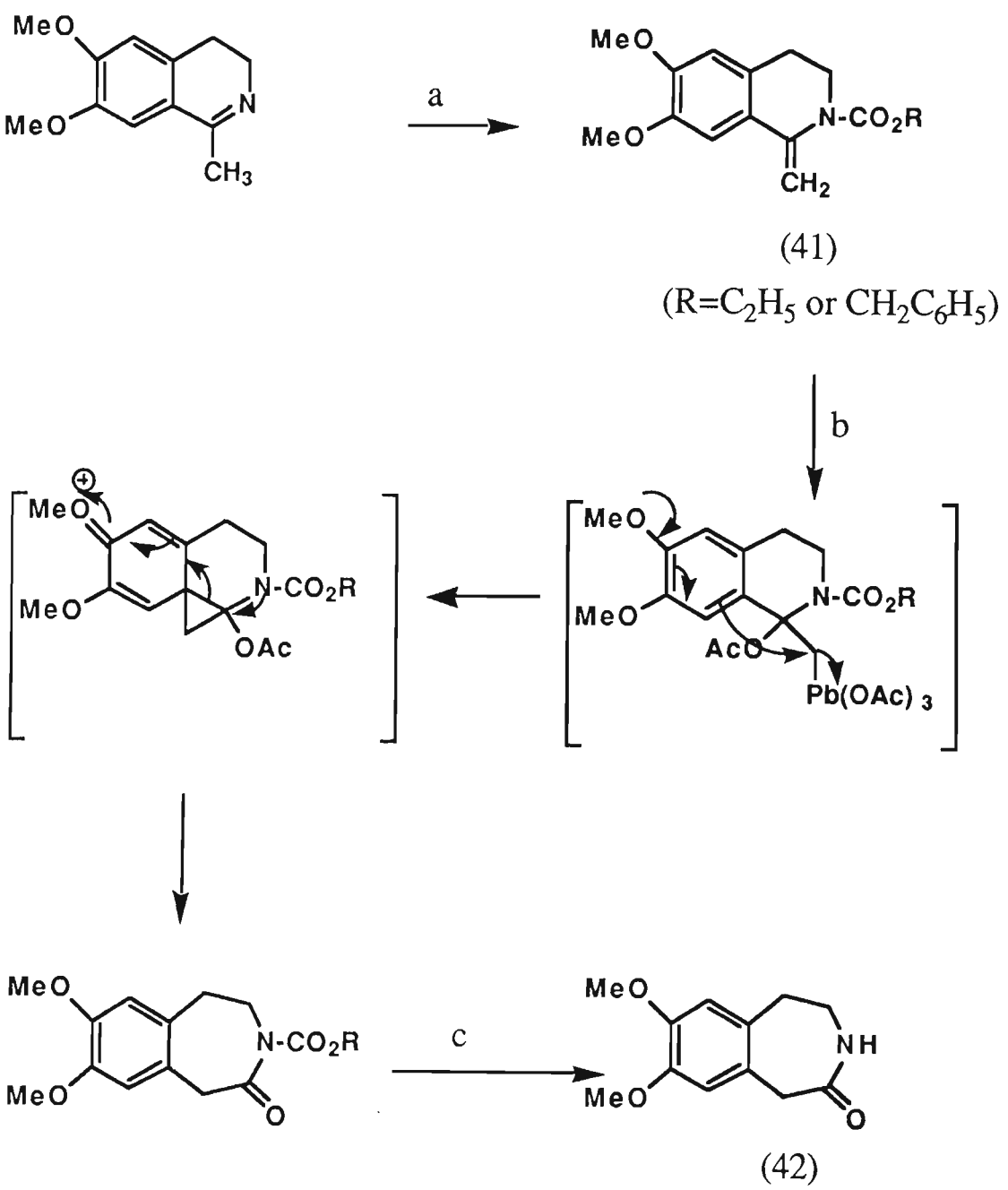
Scheme 10. Synthesis of lennoxamine (40) from 6-bromopiperonal (33).



Reagent: i, ethylene glycol, TsOH (cat), toluene, reflux; ii,n-BuLi, -60 °C, ether, then DMF: iii, KOtBu, THF: iv, dilute HCl CH_2Cl_2: v, $MeO_2CCH_2N_3$, NaOMe, MeOH, THF, 5 °C: vi, xylene, reflux: vii, $NaBH_3CN$, AcOH: viii, DIBAL, toluene, -70 °C: ix, $(Ph_3P)_2Rh(CO)Cl$, $Ph_2P(CH_2)PPh_2$, xylene, reflux.

Lenz reported a facile formation of 3-benzazepines (42) by oxidative ring expansion of isoquinoline enamides (41). This method is useful for the synthesis of alkyl substituted or unsubstituted benzazepines (42), as shown in Scheme 11.[15]

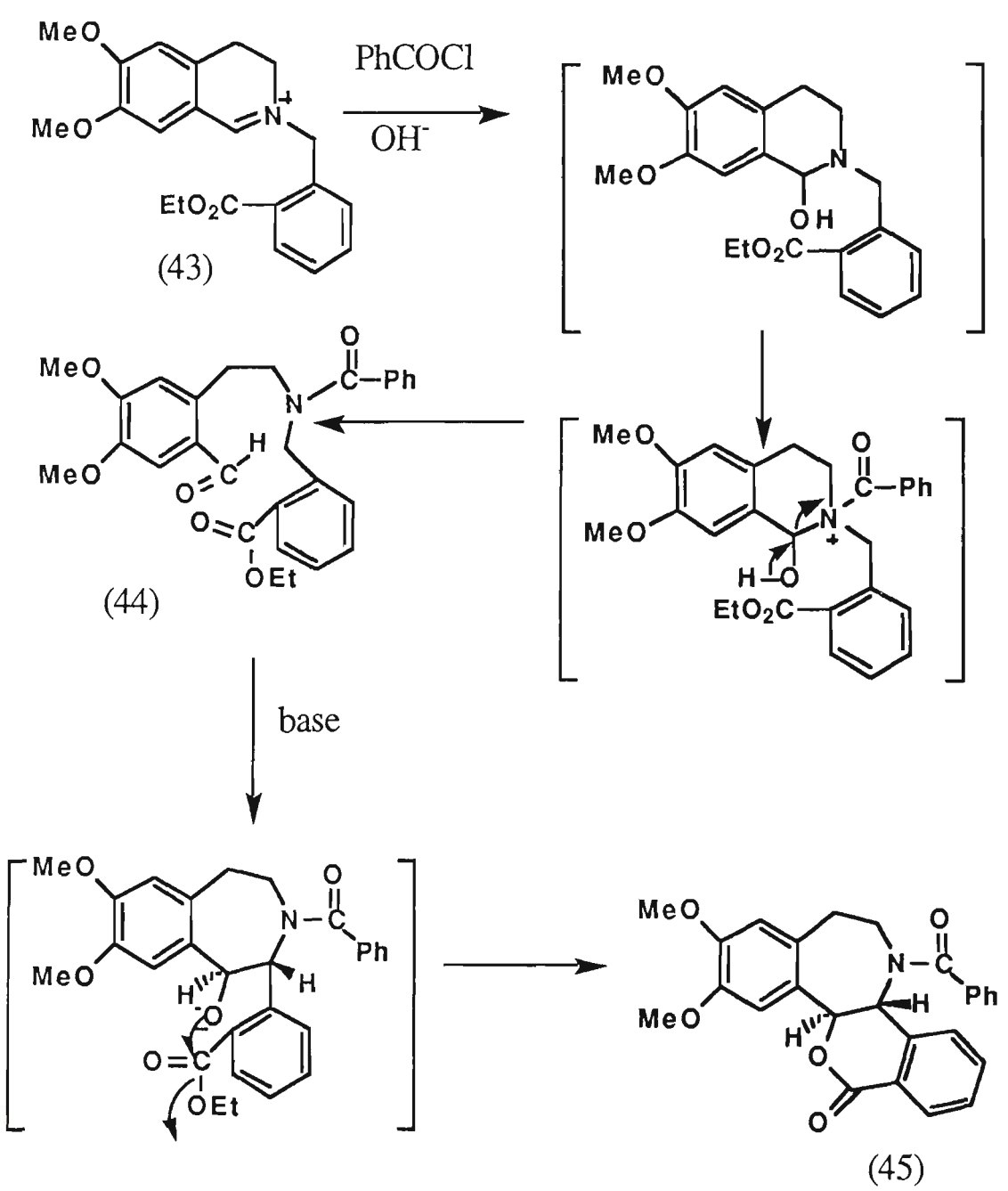
Scheme 11. Synthesis of 3-benzazepines (42) from isoquinoline enamides (41).



Reagent: (a) diethyl pyrocarbonate; (b) lead tetraacetate/acetic acid; (c) Pd/H_2.

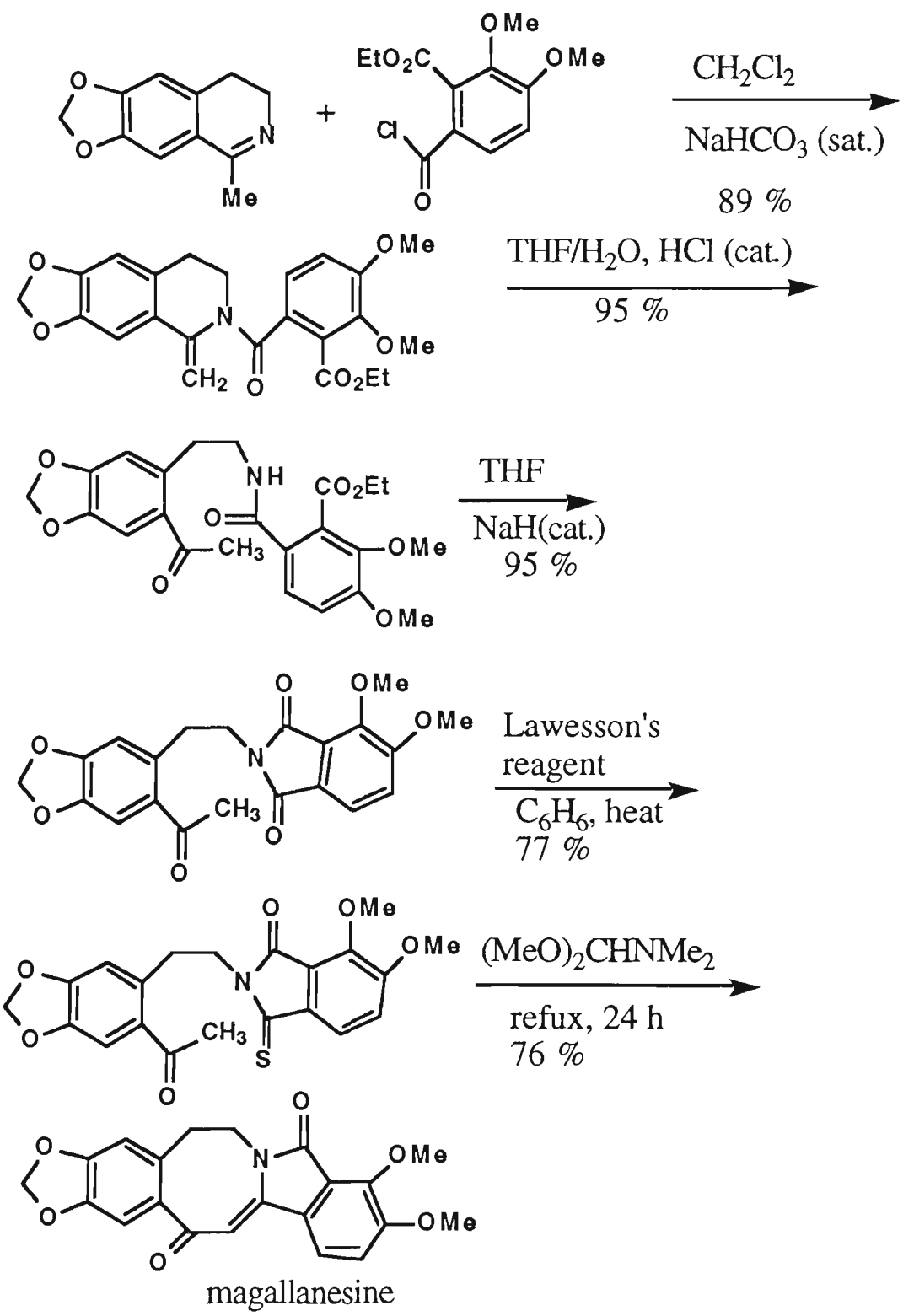
In 1975, Shamma and co-worker reported the synthesis of *trans*-rhoeadine analogue (45). They treated immonium salt (43) under Schotten-Baumann conditions and obtained the aldehydoamide (44). Cyclization of (44) under basic conditions gave the benzazepine (45) as outlined in Scheme 12.[16]

Scheme 12. Synthesis of *trans*-rhoeadine analogue (45) from immonium salt (43) under Schotten-Baumann conditions.



Recently Danishefsky and co-workers reported the total synthesis of the isoindolbenzazepine alkaloid magallanesine via amide acetal-mediated intramolecular condensation of a methyl ketone with an activated unsymmetrical phthalimide as shown in Scheme 13.[17]

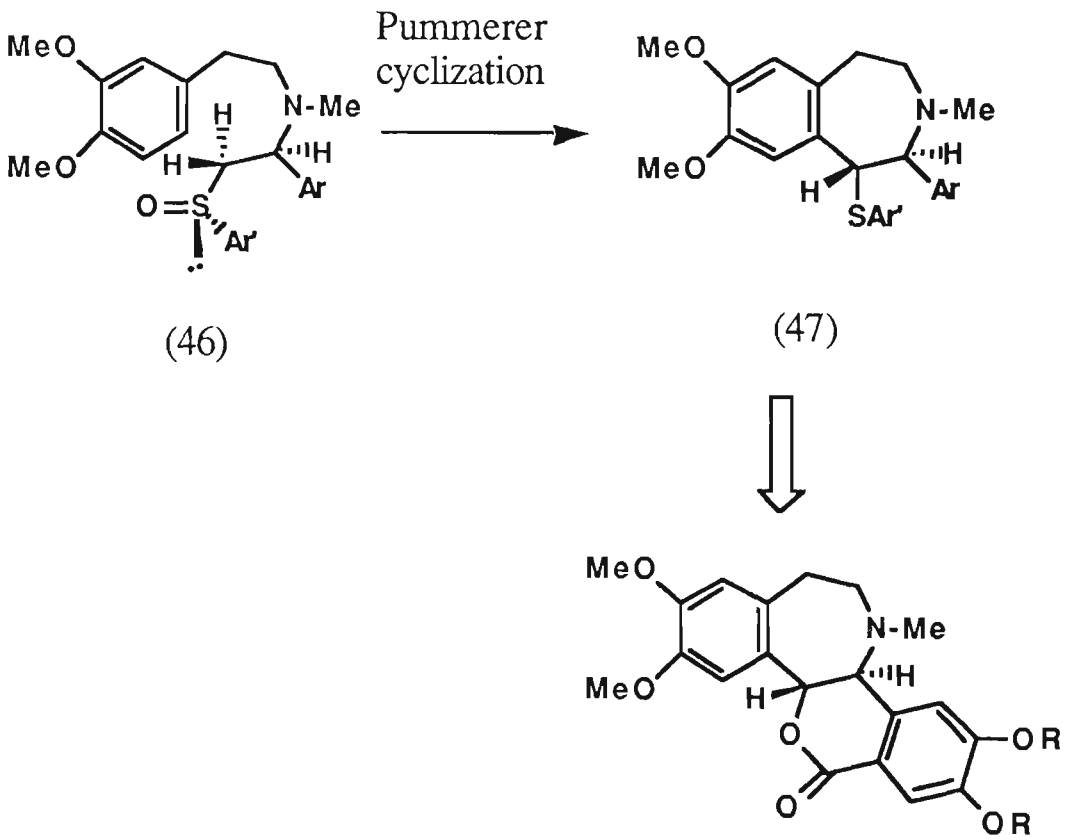
Scheme 13. Synthesis of isoindolobenzazepine alkaloid magallanesine.



magallanesine

While the synthesis of a few benzazepine alkaloids and their analogues have been reported, no general method for the asymmetric synthesis of these compounds has been developed. The aim of this project is to develop a general method for the asymmetric synthesis of these compounds and their analogues for pharmaceutical evaluation as potential new drugs. The method that we planned to use is outlined in Scheme 14. We expected that cyclization of the enantiomerically pure β-amino sulfoxide (46) under Pummerer reaction conditions would give the benzazepine compound (47). Compound (47) could then be converted to rhoedine and related benzazepine compounds (Scheme 14).

Scheme 14. Synthesis of benzazepine compound (47) from β-amino sulfoxide (46).

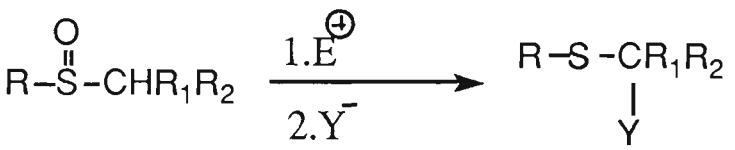


(46) (47)

The Pummerer reaction, involves the formation of an α-functionalised sulfide from a sulfoxide bearing at least one α–hydrogen atom. The reaction can also be described as an internal redox process

where the S=O group is reduced and the α-carbon is oxidised (Scheme 15).

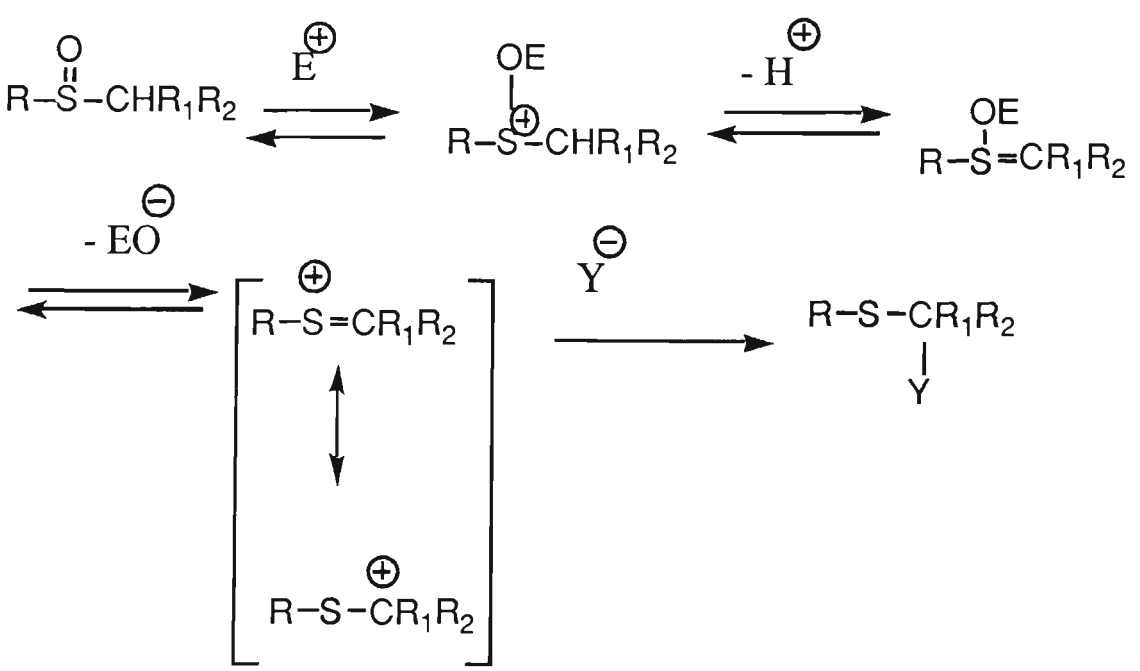
Scheme 15. Pummerer type reaction.



Y=OH ,OOCR , Halogen , OR , SR , NR_2 .

A generalised mechanism for the Pummerer reaction has been reported as shown in Scheme 16.[18]

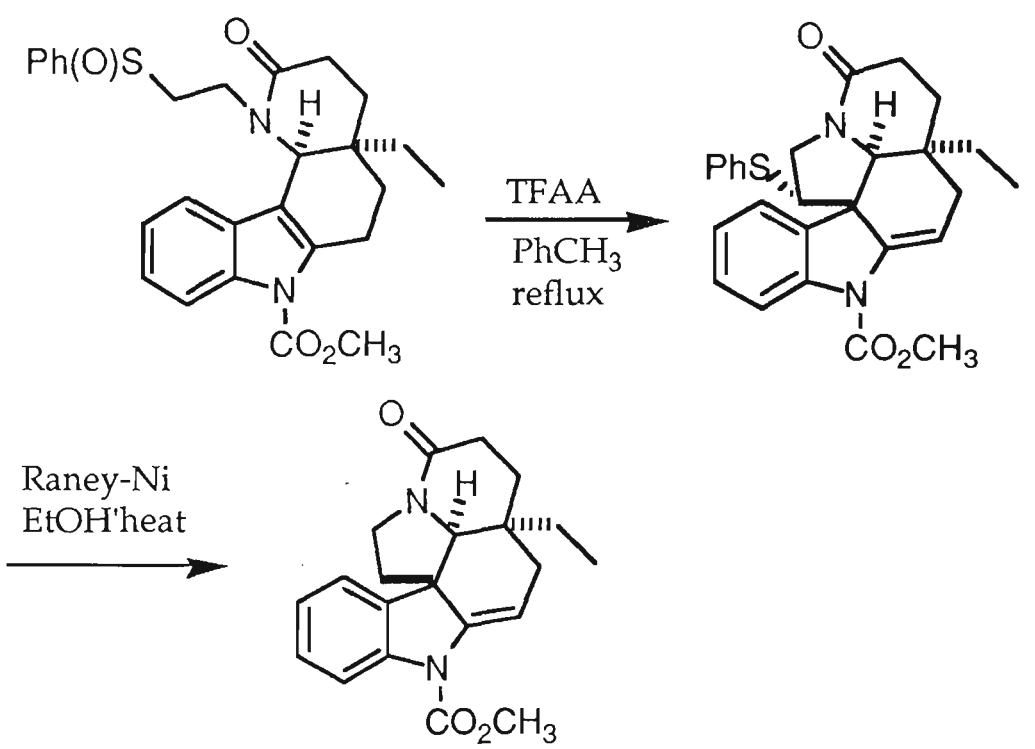
Scheme 16. General mechanism for the Pummerer reaction.



The Pummerer reaction is particularly useful in natural product chemistry, because of its mild conditions and its compatibility with other

functional groups in the molecule. Representative is the synthesis of the indole alkaloid vindoline as shown in Scheme 17.[19]

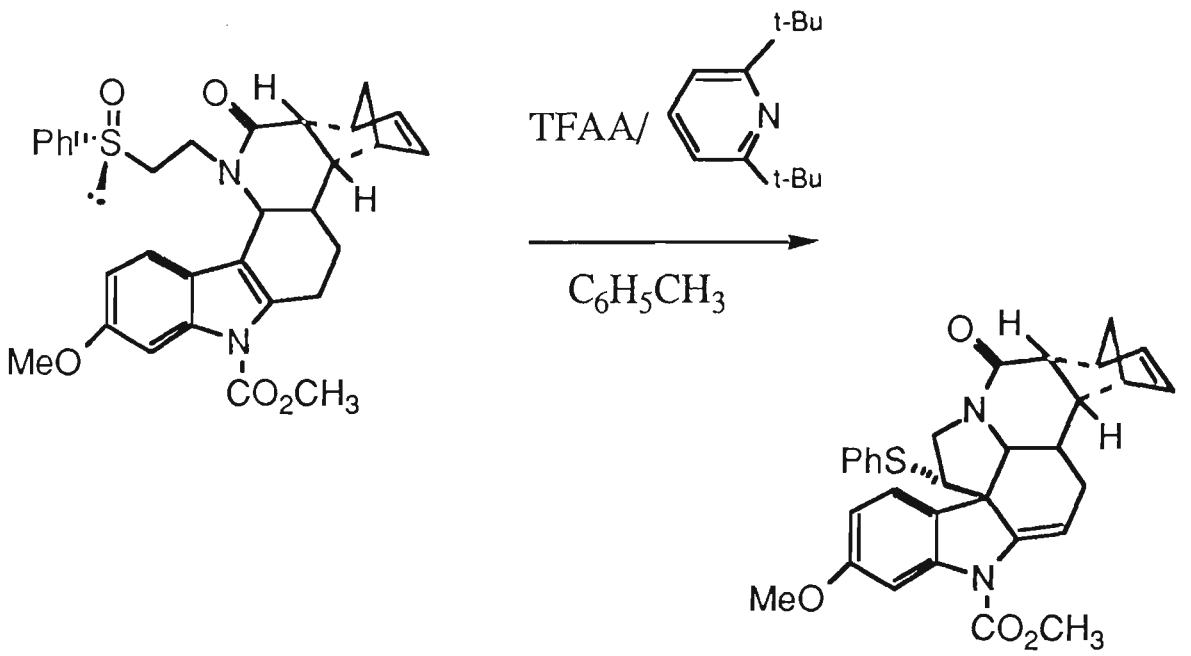
Scheme 17. Synthesis of vindoline via the Pummerer reaction.



Vindoline

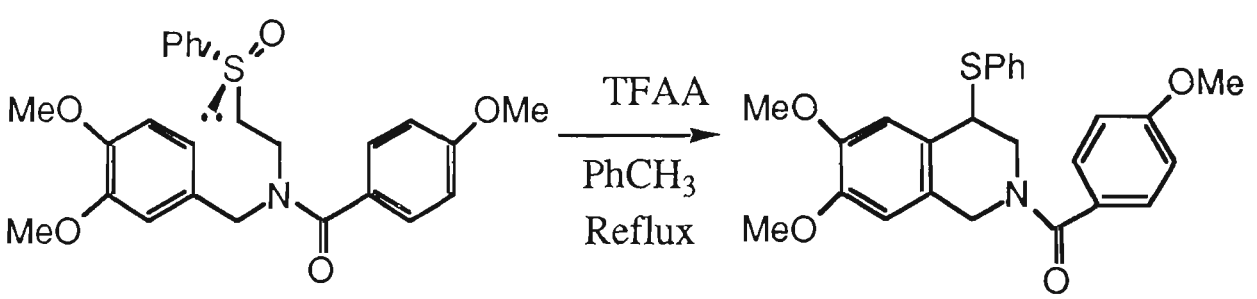
Magnus and co-workers reported, the synthesis of a number of indole alkaloids by employing this useful method as shown in Scheme 18.[20]

Scheme 18. Synthesis of indole alkaloids via the Pummerer reaction.



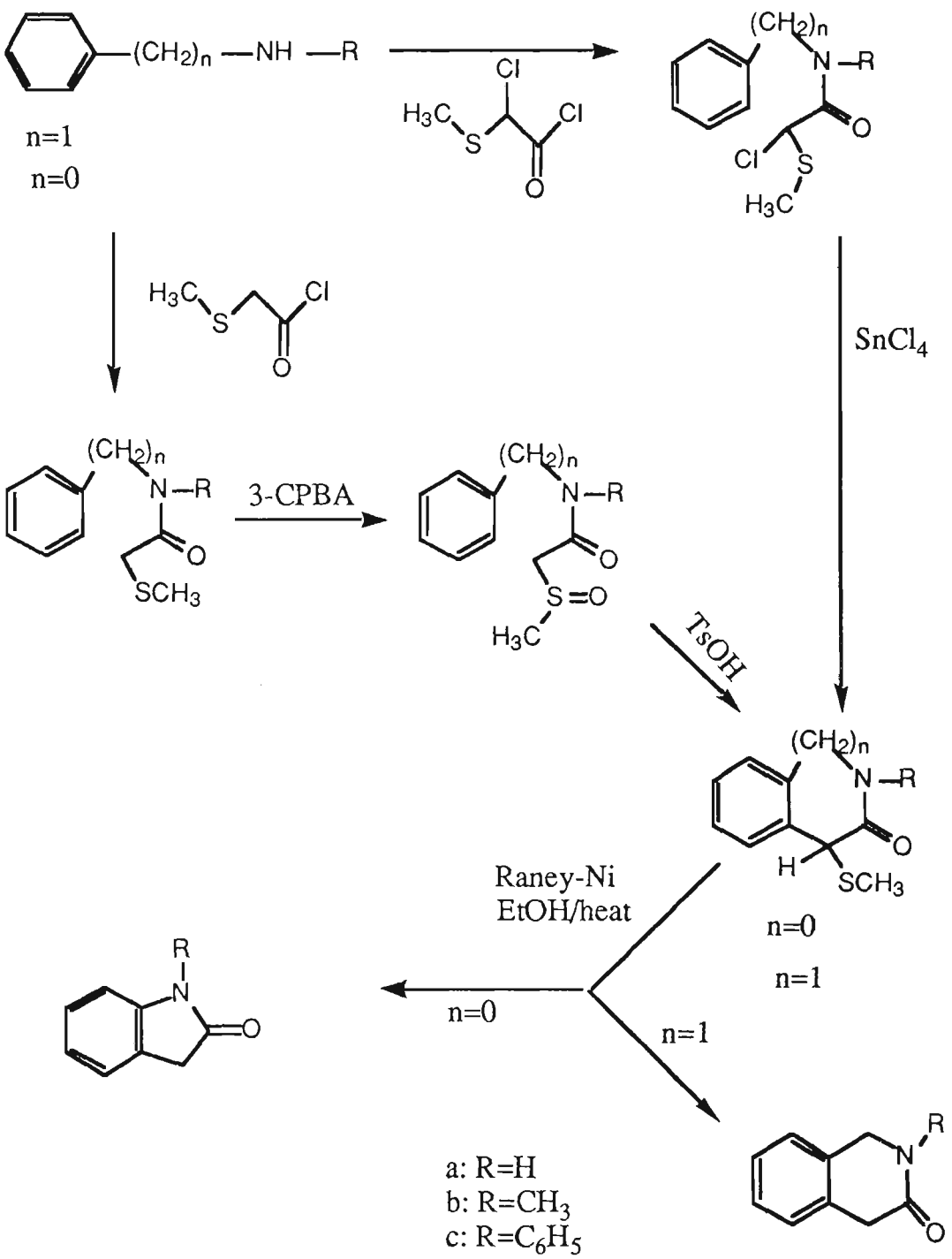
Takano and co-workers have recently developed the synthesis of the 1,2,3,4-tetrahydroisoquinoline framework by employing the sulfoxide mediated cyclization reaction as outlined in Scheme 19.[21]

Scheme 19. Synthesis of the 1,2,3,4-tetrahydroisoquinoline framework via the Pummerer reaction.



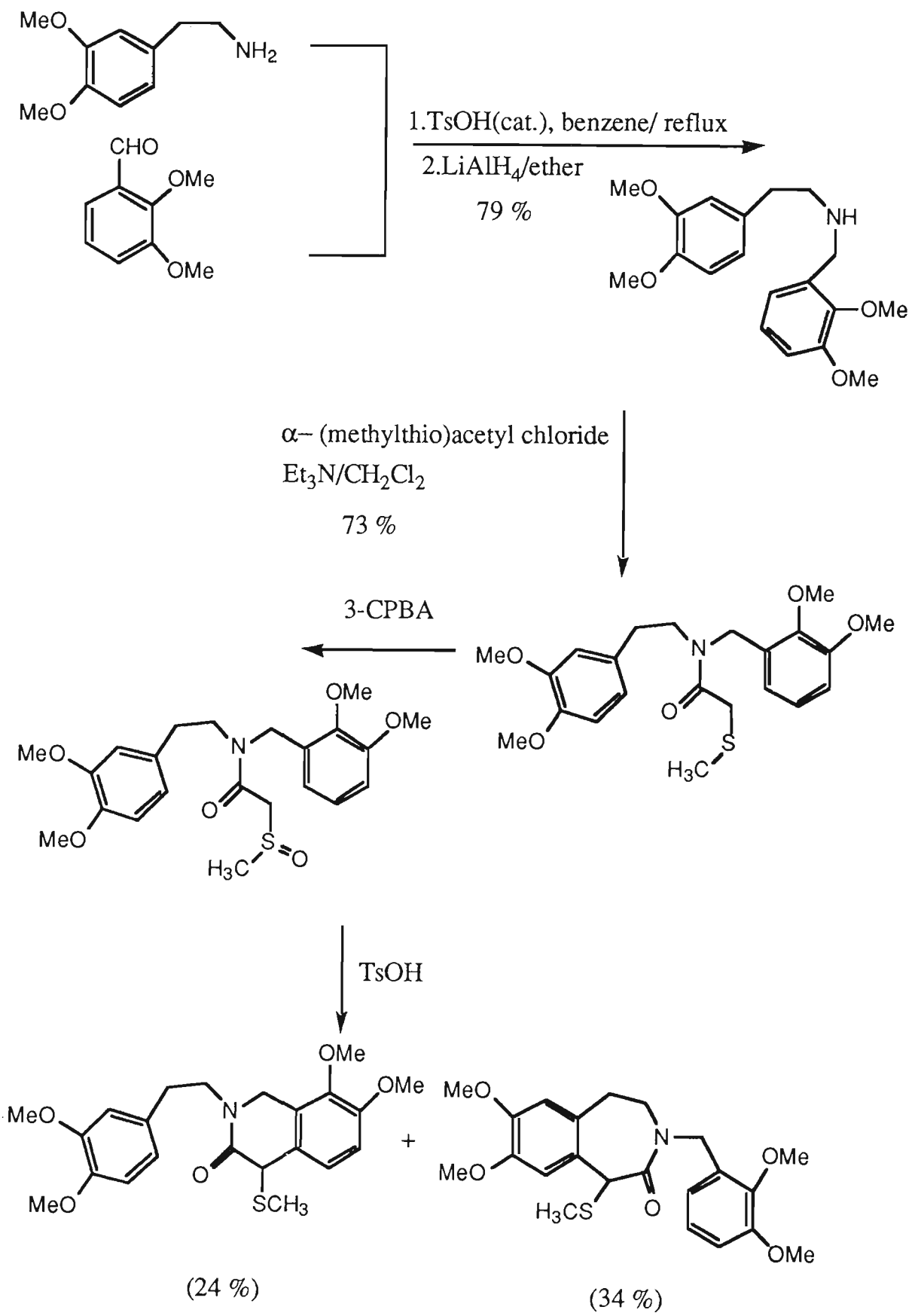
Tamura and co-workers recently reported the synthesis of oxindoles and 3-oxo-1,2,3,4-tetrahydroisoquinolines via the Pummerer reaction, the method they used is outlined in Scheme 20.[22]

Scheme 20. Synthesis of oxindoles and 3-oxo-1,2,3,4-tetrahydroisoquinolines via the Pummerer reaction.



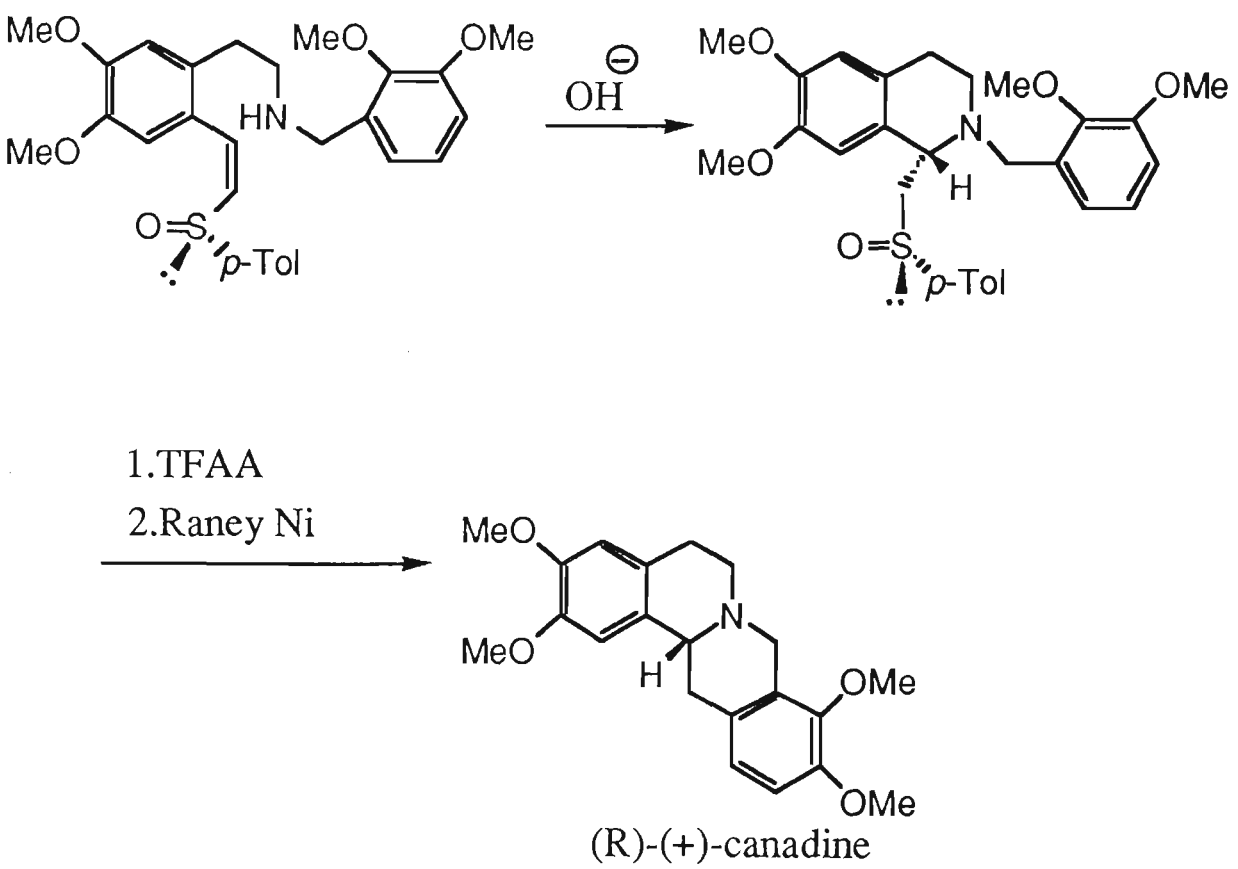
Hanaoka and co-workers reported the Pummerer cyclization reaction as shown in Scheme 21.[23] Noteworthy, as far as this thesis is concerned, was the formation of the seven membered benzazepine ring systems via the Pummerer cyclization reaction.

Scheme 21. Synthesis of the benzazepine ring system via the Pummerer reaction.



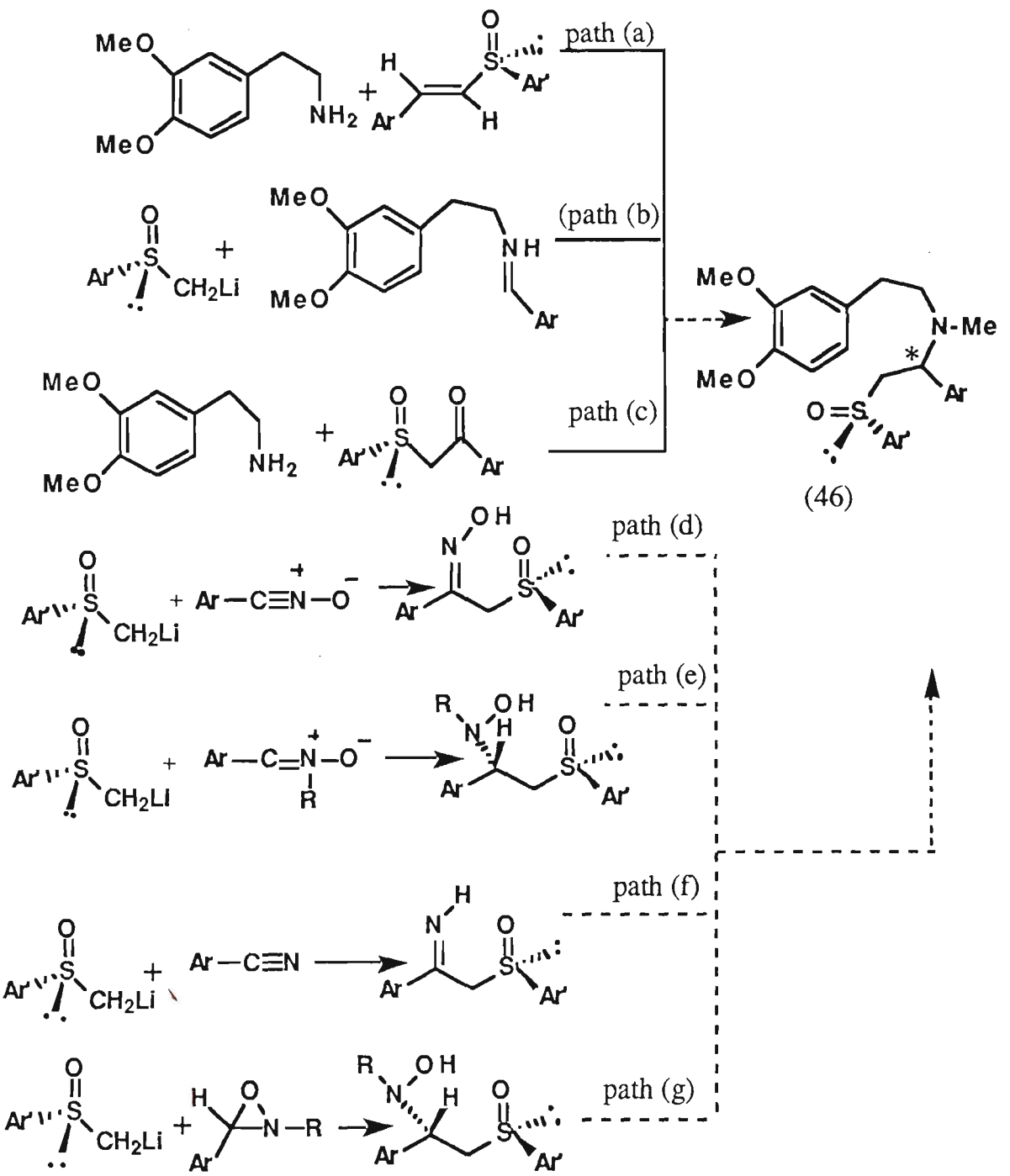
Similarly, intramolecular Michael additions to chiral vinyl sulfoxides, followed by an intramolecular Pummerer reaction has yielded the tetrahydroprotoberberine alkaloid *(R)*-(+)-canadine as shown in Scheme 22.[24]

Scheme 22. Synthesis of (*R*)-(+)-canadine via the Pummerer reaction.



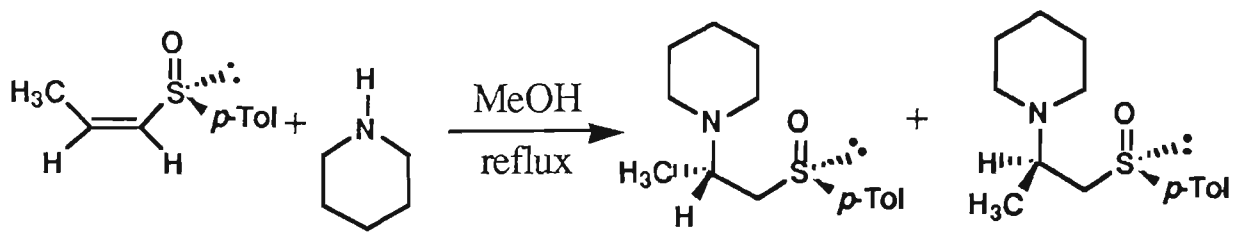
In principle several methods can be used for the synthesis of the β-amino sulfoxide (46), as shown in paths (a), (b), (c), (d), (e), (f) and (g) in Scheme 23. These methods will now be discussed individually.

Scheme 23. Methods for the synthesis of the β-amino sulfoxide (46).



In 1971, Stirling reported that the conjugate addition of piperidine to *(R)-(Z)*-propenyl *p*-tolyl sulfoxide in methanol solution at reflux for 24 h gave a mixture of two diastereomeric adducts in a ratio of 87:13 as outlined in Scheme 24.[25]

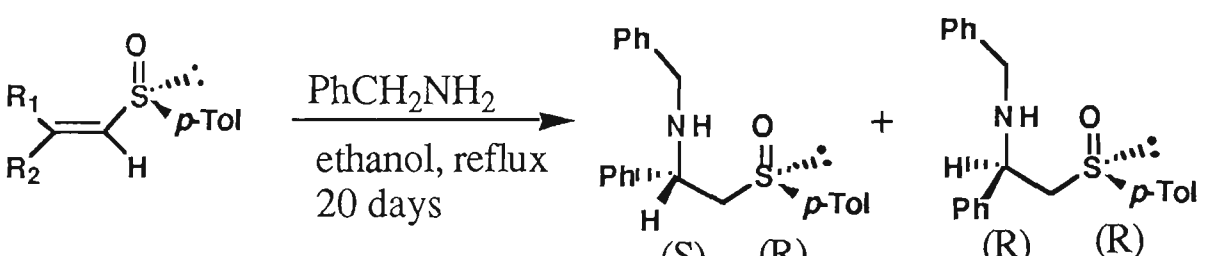
Scheme 24. Conjugate addition of piperidine to *(R)*-*(Z)*-propenyl *p*-tolyl sulfoxide



87 : 13

Pyne has investigated the addition of benzylamine to isomeric *(E)* - and *(Z)*- *(R)*- vinyl sulfoxides and found that these reactions were diastereoconvergent. The same major diastereomeric adduct was obtained from either isomeric vinyl sulfoxide and under apparently kinetically controlled conditions (Scheme 25 and Table 1).[26] In principle this reaction could be used for preparation of the target β-amino sulfoxide (46), as shown in path (a) of Scheme 23.

Scheme 25. Addition of benzylamine to isomeric *(E)* - and *(Z)*- *(R)*- vinyl sulfoxides



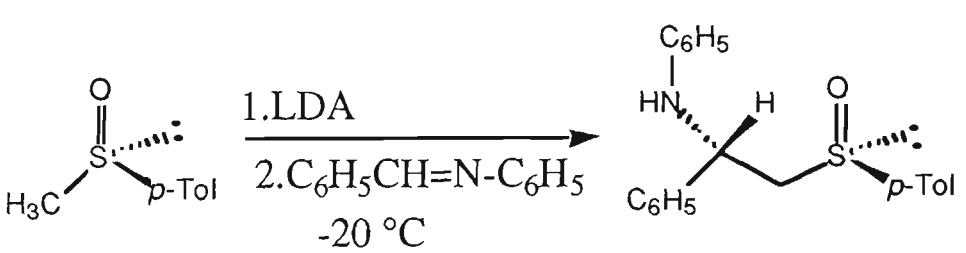
(Z)-isomer, R_1=Ph, R_2=H
(E)-isomer, R_1=H, R_2=Ph

Table 1. Addition of benzylamine to isomeric *(E)* - and *(Z)*-*(R)*- vinyl sulfoxides.

vinyl sulfoxide	time (days)	solvent	diastereoselection (R,S):(R,R)	yield (%)
(Z)	20	ethanol	87:13	53
(Z)	7	PhH	75:25	6
(E)	7	ethanol	86:14	64
(E)	20	ethanol	85:15	72
(E)	6	PhH	84:16	50

In 1973, Tsuchihashi, reported that the addition of lithiated *(R)*-(+) methyl *p*-tolyl sulfoxide (48b) to *N*-benzylideneaniline gave a single diastereomeric product that had the *(1S, Rs)* absolute stereochemistry (Scheme 26).[27]

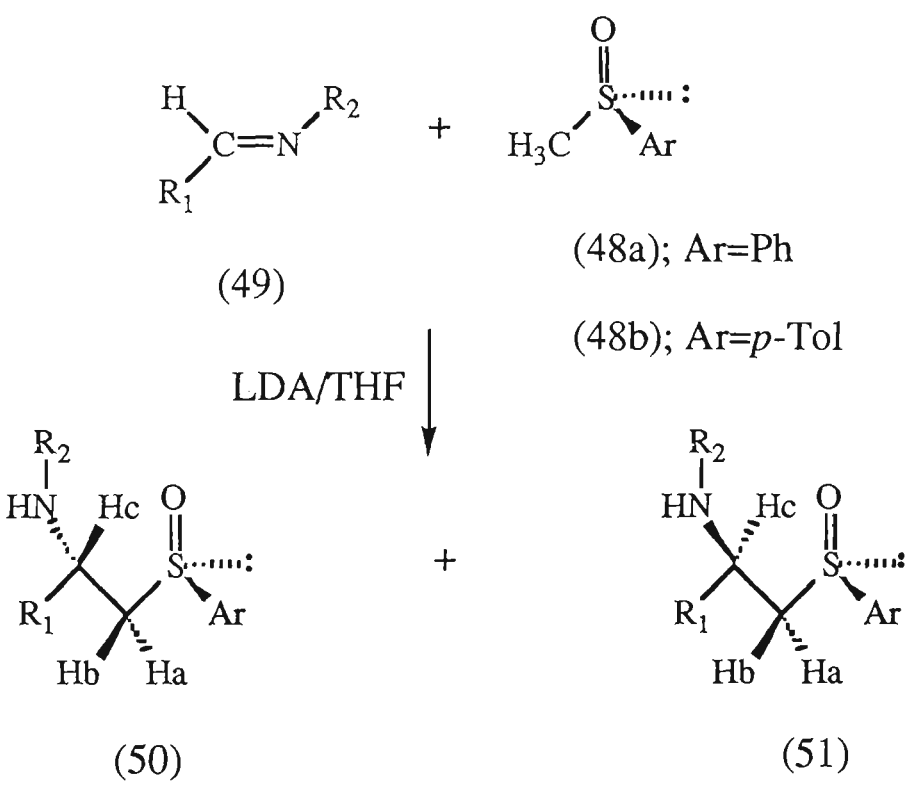
Scheme 26. Addition of lithiated (*R*)-(+) methyl *p*-tolyl sulfoxide (48b) to *N*-benzylideneaniline.



(R)-(+)-(48b)

However, the generality of this process was not demonstrated. Recently Pyne[28] and Kagan[29] have independently repeated this reaction and have obtained a 82:18 (Scheme 27 and Table 2) and 92:8 (Scheme 28, and Table 3) mixture of the diastereoisomers of (50a) and (51a) respectively.

Scheme 27. The addition of sulfoxide (48) to imines (49) in THF.[28]



a: R_1=Ph R_2=Ph

b: R_1=furanyl R_2=Ph

c: R_1=Ph R_2=CH_3

d: R_1=CH_3CH_2 R_2=Ph

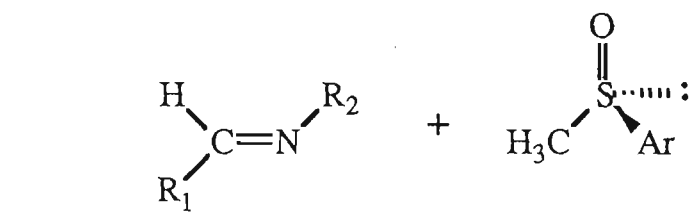
e: R_1=$(CH_3)_2CH$ R_2=Ph

f: R_1=$(CH_3)_2CHCH_2$ R_2=Ph

Table 2. The addition of sulfoxide (48) to imine (49) in THF.[28]

entry	imine (49)	sulfoxide (48)	temp. (°C), time (h)	yield (%)	diastereo selection (50):(51)
1	(49a)	(48a)	-78, 5	96	82:18
2	(49a)	(48b)	0, 5 min.	95	86:14
3	(49b)	(48a)	-45, 2	86	88:12
4	(49b)	(48b)	0, 10 min.	96	91:9
5	(49c)	(48a)	0, 2	86	88:12
6	(49c)	(48b)	0, 10 min.	89	91:9
7	(49d)	(48a)	-45, 2	85	79:21
8	(49d)	(48b)	-45, 2	90	80:20
9	(49e)	(48a)	-45, 2	72	81:19
10	(49f)	(48b)	-45, 2	78	81:19

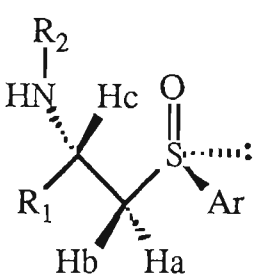
Scheme 28. Addition of (+)-*(R)* methyl *p*-tolyl sulfoxide (48b) to imines (49).[29]



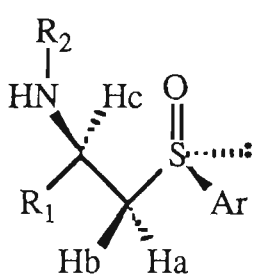
(49)

(48b); Ar=*p*-Tol

LDA/THF



(50)



(51)

a: R_1=Ph R_2=Ph

g: R_1=Ph R_2=*p*-$MeOC_6H_4$

h: R_1=*p*-$MeOC_6H_4$ R_2=Ph

i: R_1=*p*-$MeOC_6H_4$ R_2=*p*-$MeOC_6H_4$

j: R_1=*p*-$NO_2C_6H_4$ R_2=*p*-$MeOC_6H_4$

k: R_1=Ph R_2=Me

l: R_1=Ph R_2=*n*-Pr

m: R_1=Ph R_2=*i*-Pr

n: R_1=Ph R_2=cyclopropyl

Table 3. Condensation of (*R*)-(+) methyl *p*-tolyl sulfoxide (48b) with $R_1CH=NR_2$.[29]

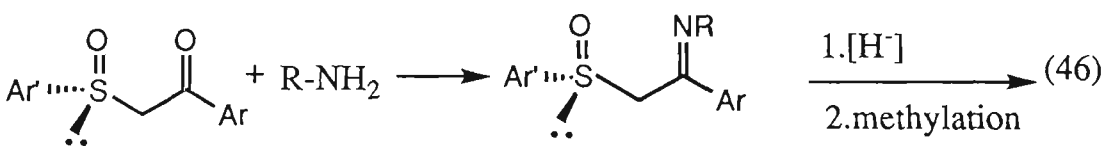
entry	R_1	R_2	diastereoselection (50):(51)	yield (%)
1	Ph	Ph	92:8	99
2	Ph	*p*-$MeOC_6H_4$	86:14	32
3	*p*-$MeOC_6H_4$	Ph	86:14	30
4	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	95:5	74
5	*p*-$NO_2C_6H_4$	*p*-$MeOC_6H_4$	76:24	95
6	Ph	CH_3	82:18	84
7	Ph	*n*-Pr	90:10	76
8	Ph	*i*-Pr	88:12	27
9	Ph	cyclopropyl	84:16	21

In principle these methods can be used to synthesise the starting material (46) as shown in path (b) of Scheme 23, however *N*-alkyl imines are reported to be less reactive than *N*-aryl imines.[28]

When we started this project the chemistry outlined in path (c) of Scheme 23 had no literature precedent. During the course of this project both Hua[30a] and Carreno[30b] reported the diastereoselective reductions of cyclic β-sulfinyl enamines. After these publications the reduction of

acyclic β-sulfinyl enamines with L-Selectride and DIBAL was also reported.[31a,b] It is proposed that readily available β-keto sulfoxide (52)[32] can be converted to its corresponding imine, which upon diastereoseletive reduction should afford the desired chiral β-amino sulfoxide (46), as shown in Scheme 29.

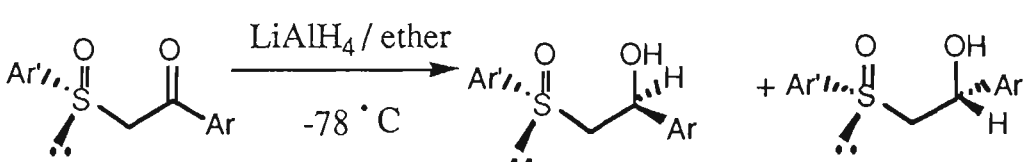
Scheme 29. Synthesis of the β-amino sulfoxide (46) from β-keto sulfoxide (52).



(52) Ar'=*p*-Tol or Ph Ar=aryl R=alkyl

The reduction of β-keto sulfoxides to give β-hydroxy sulfoxides with high diastereoselectivity has been reported by Solladie[33] as shown in Scheme 30.

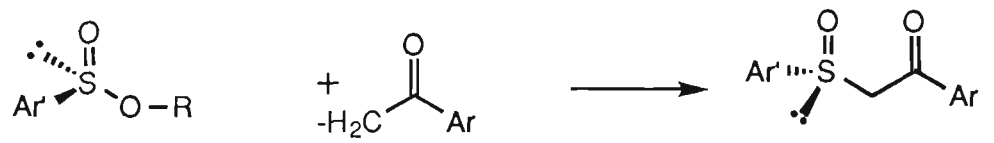
Scheme 30. Reduction of β-keto sulfoxide (52) to give β-hydroxy sulfoxides



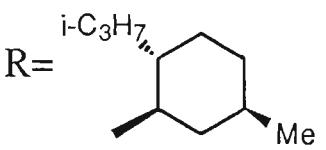
(+)-(*R*)-(52) 9 : 1

In principle several methods can be employed to synthesis the β-keto sulfoxide (52). Andersen synthesis can be performed between a ketone enolate and a menthyl sulfinate (53) as shown in Scheme 31.[34]

Scheme 31. Synthesis of β-keto sulfoxide (52) from menthyl sulfinate (53).

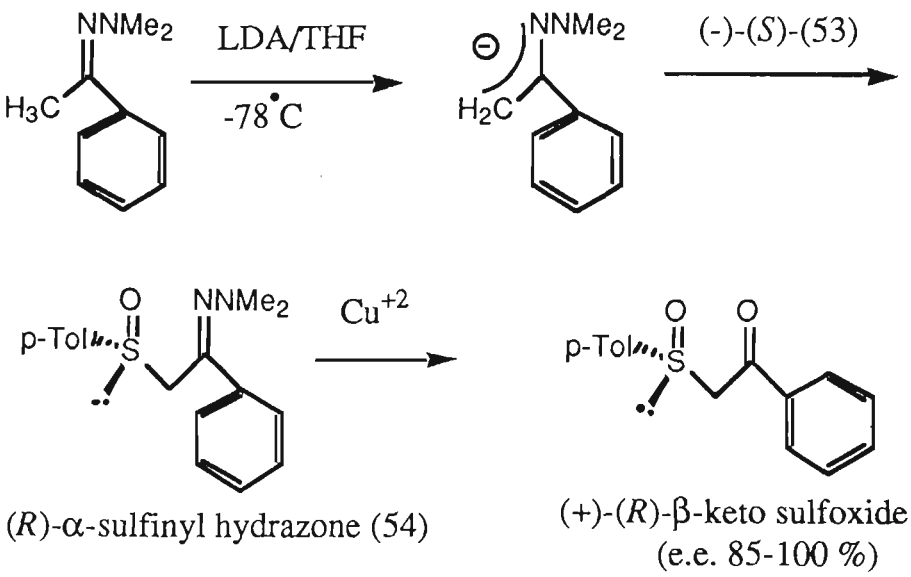


(-)-(*S*)-(53) (52)



α-Sulfinyl hydrazone *(R)*-(54) has been prepared from the reaction of (-)-*(S)*-(53) and α-metallated acetophenone *N*,*N*-dimethylhydrazone. Cupric ion catalyzed hydrolysis of *(R)*-(54) gave the (+)-*(R)*-β-keto sulfoxide (52) in high enantiomeric purity (e.e. 85-100 %) as shown in Scheme 32.[35]

Scheme 32. Synthesis of (+)-(*R*)-β-keto sulfoxide (52) from the addition of α-metallated acetophenone *N*,*N*-dimethylhydrazone to (-)-(*S*)-(53).

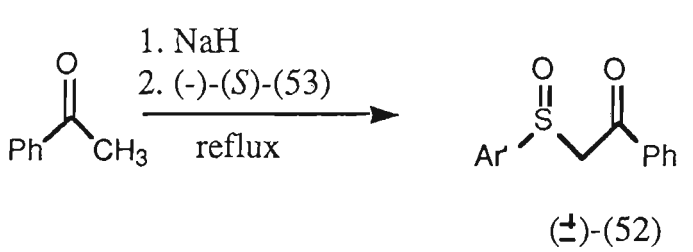


(*R*)-α-sulfinyl hydrazone (54)

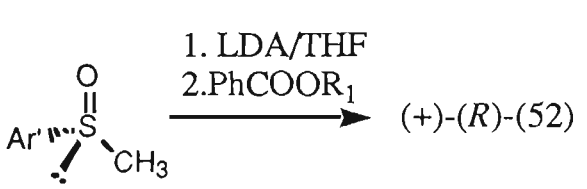
(+)-(*R*)-β-keto sulfoxide (52)
(e.e. 85-100 %)

It must be noted that β-keto sulfoxide (52) which was obtained in racemic[34,36] form, from the reaction of the sodium enolate of acetophenone and (-)-(*S*)-(53) can be synthesised in high enantiomeric purity by the addition of α-metallated (+)-(*R*)- (48b) to a carboxylic acid ester as outlined in Scheme 33.[34,36]

Scheme 33. Synthesis of the β-keto sulfoxide (52).



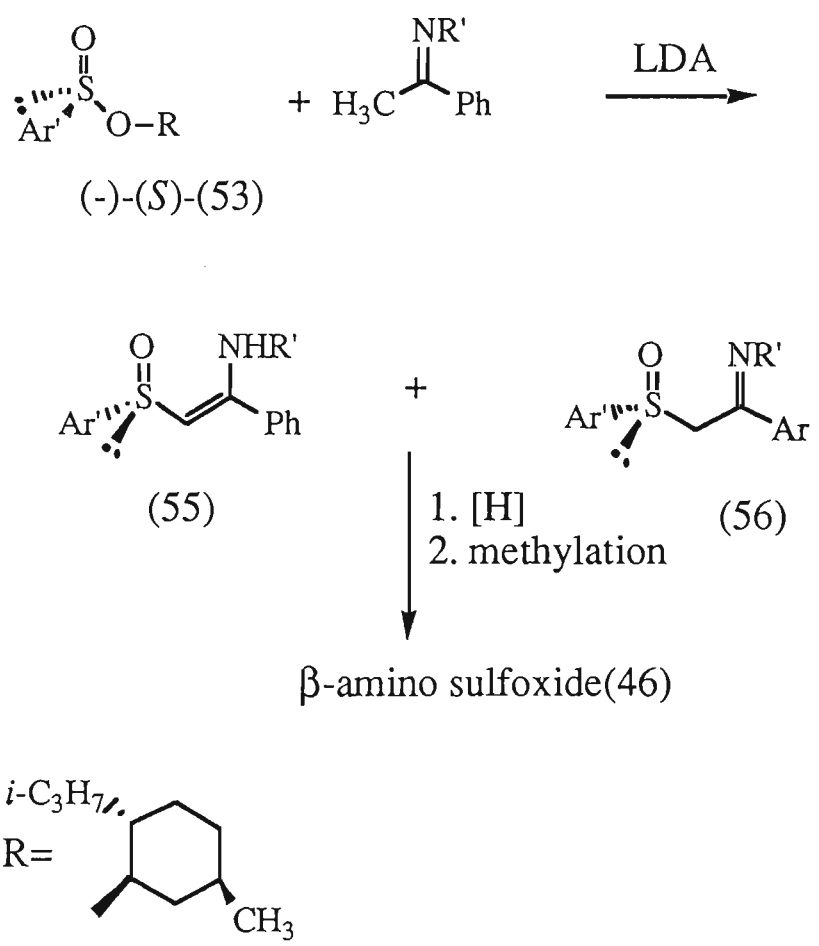
(±)-(52)



(+)-(*R*)-(48b)

β-Amino sulfoxide (46) can in principle also be synthesised by condensation of an α-lithiated imine with the optically pure (-)-(*S*)-sulfinate-(53) to produced the optically active β-enamine-(55) or β-imino sulfoxide (56).[37] These compounds could in principle be converted to the β-amino sulfoxide (46) as outlined in Scheme 34.

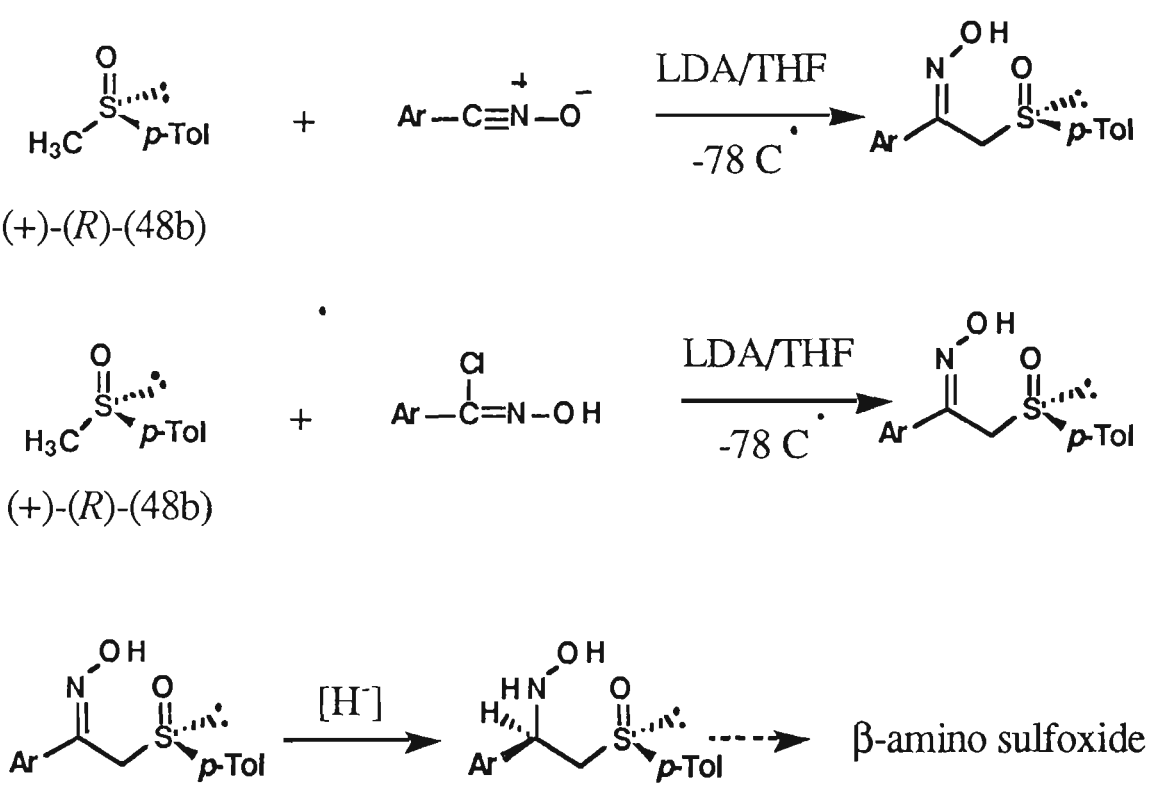
Scheme 34. Synthesis of the β-amino sulfoxide (46) from (-)-*(S)*-(53).



In 1983 Annunziata and Cinquini reported the addition of the carbanion of methyl *p*-tolyl sulfoxide (+)-*(R)*-(48b) to nitrile oxides and readily available benzohydroximidyl chlorides gave α-sulfinyl oximes as outlined in Scheme 35.[38]

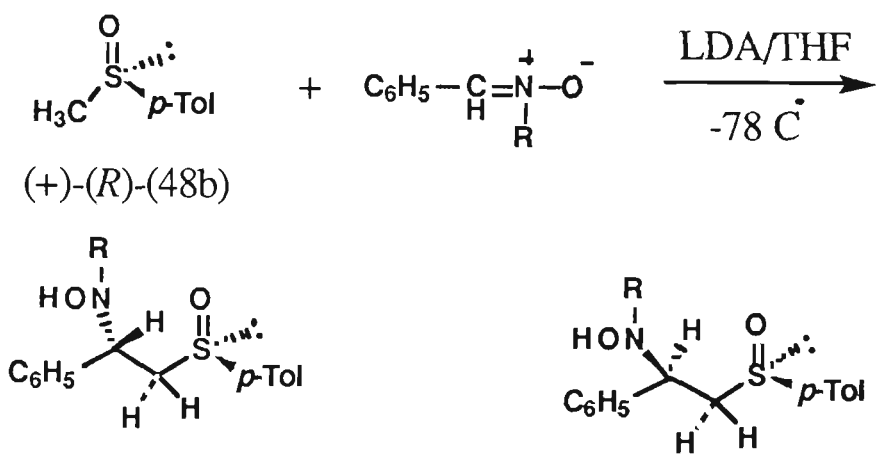
These products could in principle be converted to the desired β-amino sulfoxide (46) by a diastereoselective reduction of the oxime group followed by manipulation of the resulting chiral β-hydroxylamine sulfoxide (Scheme 35).

Scheme 35. Synthesis of β-amino sulfoxide (46).



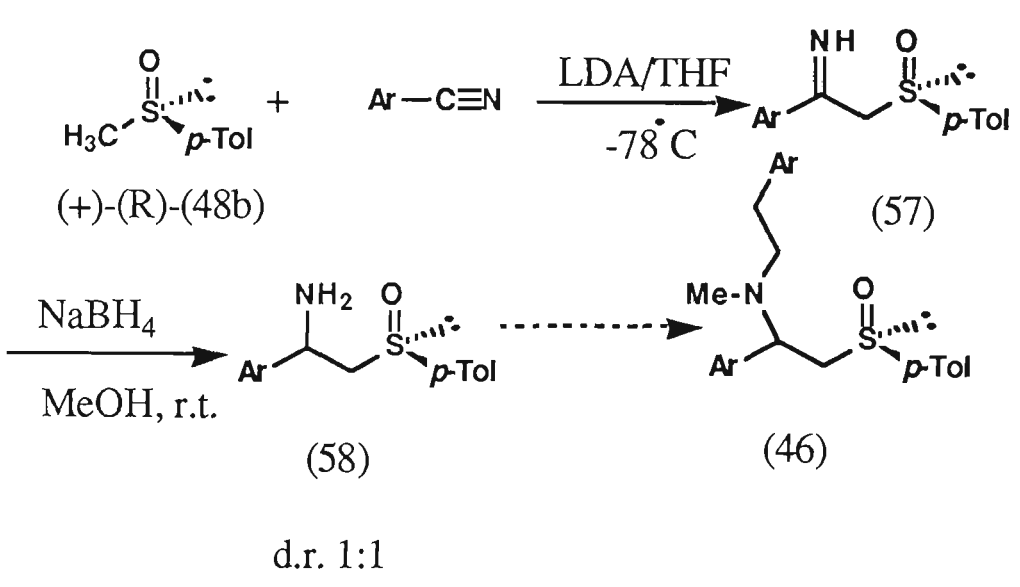
The same workers also reported that the addition of the carbanion of (+)-*(R)*-(48b) to nitrones gave chiral β–hydroxylamino sulfoxides (Scheme 36). As mentioned above these compounds should be readily converted to β-amino sulfoxide (46).[38]

Scheme 36. Synthesis of β-hydroxyamino sulfoxides from the addition of (+)-*(R)*-(48b) to nitrones.



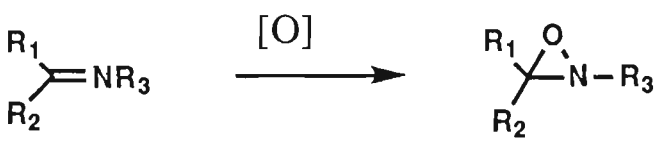
In 1973, G-I.Tsuchihashi and co-workers reported that the addition of the anion of (+)-*(R)*-(48b) to benzonitrile gave imine (57) which upon reduction with sodium borohydride gave the β-aminosulfoxide (58).[27] The diastereoselectivity of this latter reaction, however, was poor (d.r.=1:1). This method may be used for the synthesis of β-amino sulfoxide (46) as outlined in Scheme 37 if a method for improving the diastereoselectivity of the reduction step could be developed.

Scheme 37. Synthesis of β-amino sulfoxide (46) from the addition of (+)-*(R)*-(48b) to benzonitrile.



Oxaziridines may properly be regarded as the isomers of nitrones and can be readily converted to their analogue nitrones.[39] In some cases the preparation of the nitrone is not possible, but its isomer (oxaziridine) can be readily synthesised by oxidation of the corresponding imine as outlined in Scheme 38.

Scheme 38. Synthesis of oxaziridines from oxidation of imines.

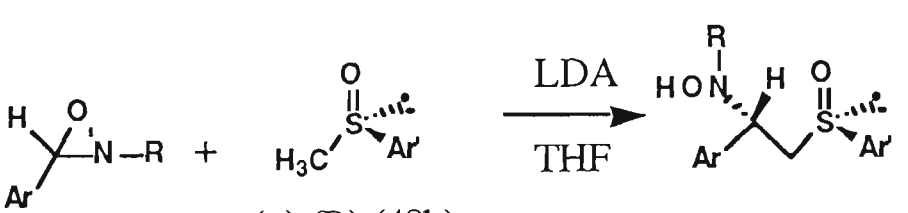


oxaziridine

R_1, R_2, R_3=H, alkyl or aryl

In principle the oxaziridine may be used as a starting material for synthesis of β-amino sulfoxide (46) as shown in Scheme 39.

Scheme 39. Synthesis of β-amino sulfoxide (46) from addition of the (+)-*(R)*-(48b) to oxaziridine.



(+)-(R)-(48b)

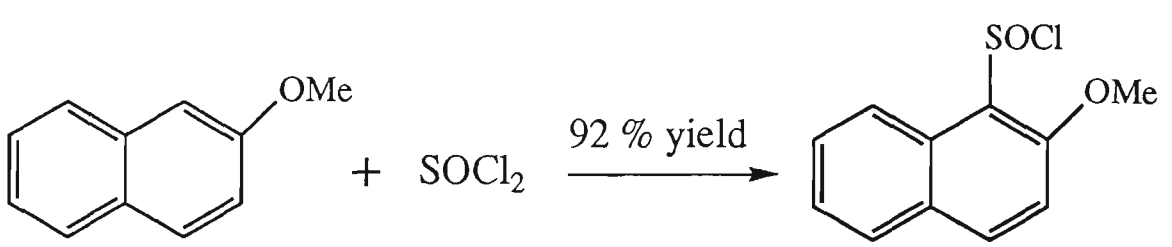
⋯⋯→ β-amino sulfoxide (46)

Asymmetric synthesis of sulfoxides

In order to improve the diastereoselectivity of some of the reactions proposed in paths (a)-(g) in Scheme 23 the sterically hindered 2-methoxy-1-naphthyl sulfoxides will be prepared in this project and their diastereoselective reactions will be examined. *t*-Butyl sulfoxides generally show a much greater degree of diastereoselectivity in their reactions when compared with the traditional *p*-tolyl sulfoxides.[40] The steric demand of the 2-methoxy-1-naphthyl group should be similar to that of a *t*-butyl group, but preparation of the latter sulfoxides in high enantiomeric purity is not easy.[41]

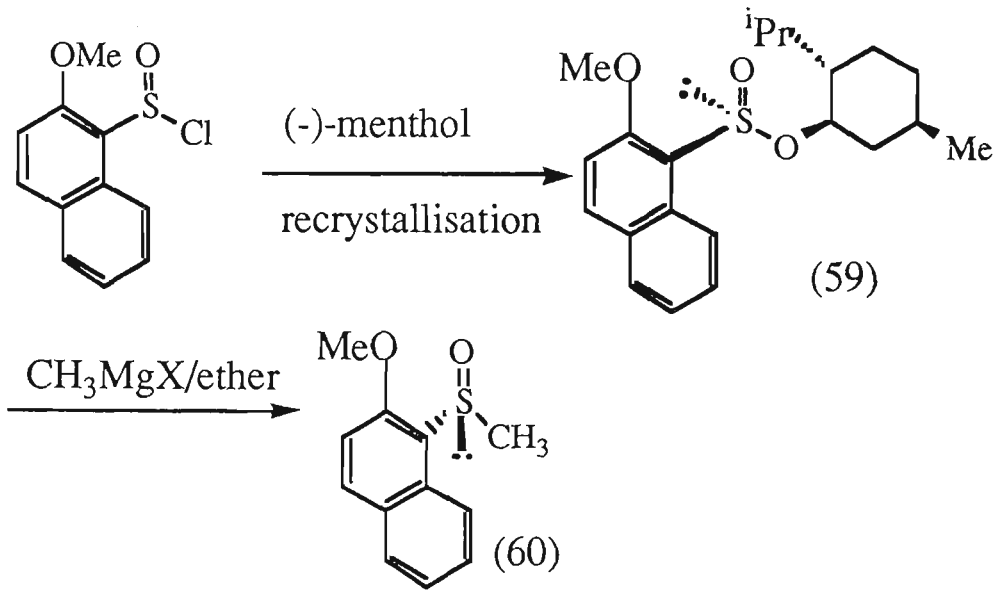
In 1985 Bell reported the preparation of arylsulfinyl chlorides in high yield by direct chlorosulfination of some aromatic ethers (e.g. 2-methoxynaphthalene) as outlined in Scheme 40.[42]

Scheme 40. Synthesis 2-methoxy-1-naphthylsulfinyl chloride from chlorosulfination of 2-methoxynaphthalene.



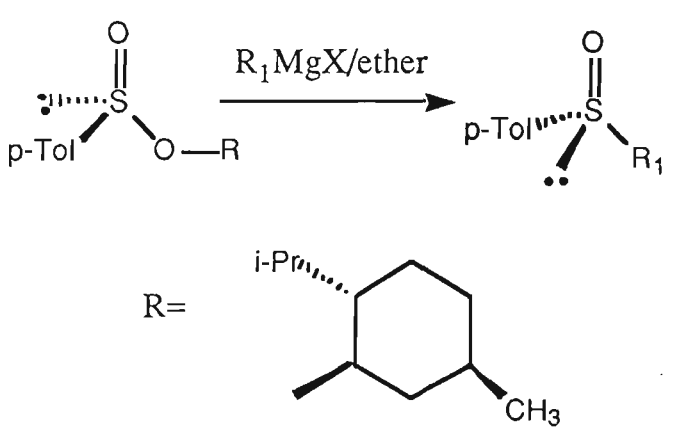
This sulfinyl chloride is very useful, because in principle it can be used to prepare the hindered methyl 2-methoxy-1-naphthyl sulfoxide (60) in high enantiomeric purity as shown in Scheme 41.

Scheme 41. Synthesis of menthyl 2-methoxy-1-naphthyl sulfoxide (60).



One of the most reliable methods reported for the synthesis of optically active sulfoxides is the reaction of optically active sulfinate esters with Grignard reagents. This extremely useful method was first reported by Gilman,[43] and applied to an optically active series of sulfoxides by Andersen (Scheme 42).[44,45]

Scheme 42. Synthesis of optically active sulfoxides from optically active sulfinate esters.



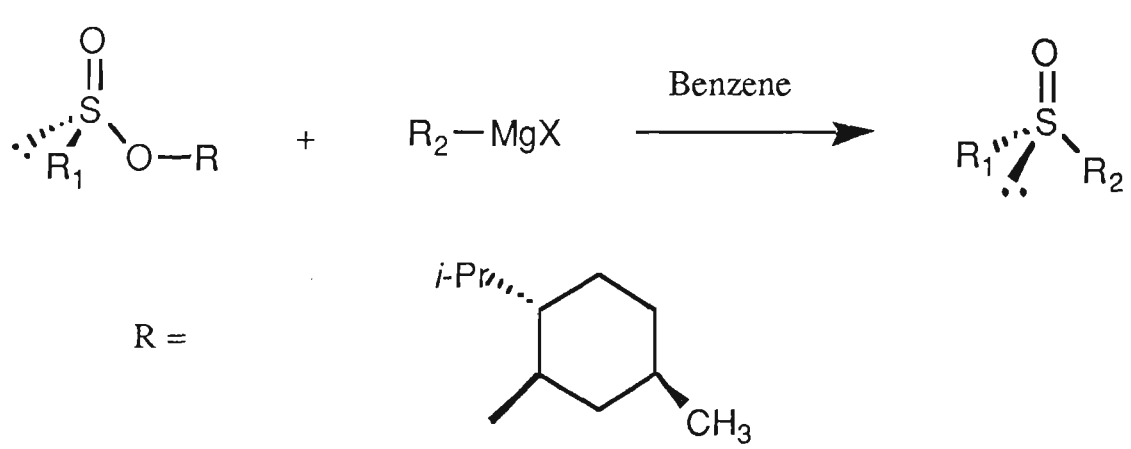
However, in many cases this method affords chiral sulfoxides in moderate or low yields depending on the structure of both starting materials, i.e., sulfinate ester and Grignard reagent. For example, Anderson,[44] obtained optically active ethyl *p*-tolyl sulfoxide in 62 %

yield. Moreover, he also reported,[45,46] that the reaction between *O*-menthyl methanesulfinate and phenylmagnesium bromide results in the formation of the crude methyl phenyl sulfoxide in 50 % yield only.

As a result of the extensive studies on the synthesis of chiral sulfoxides by the method discussed above, Harpp and co-workers[47] came to the conclusion that the conditions must be carefully selected, otherwise considerable quantities of sulfides and other impurities which are difficult to separate are produced. They recommended the use of organolithium cuprates instead of Grignard reagents for conversion of sulfinates to sulfoxides. However, in this case also the yields of the sulfoxides were in the range between 16 % and 59 %.

Recently Drabowicz and co-workers[48a] have mentioned a striking effect of benzene as solvent on the yield and stereospecificity of the reaction of (-)-O-menthyl *p*-toluenesulfinate and Grignard reagents (Scheme 43), they have improved the yield and e.e. by this method as shown in Table 4.

Scheme 43. Synthesis of sulfoxides in benzene.



(-)-Menthyl *p*-toluenesulfinate was obtained from treatment of (-)-menthol with *p*-toluenesulfinyl chloride followed by a fractional crystallisation of the mixture of the two diastereoisomers.[48b]

Table 4. Synthesis of optically active sulfoxides $R_1R_2S(O)$ by reaction of optically pure (-)-O-menthyl sulfinates with Grignard reagents in benzene or ether.

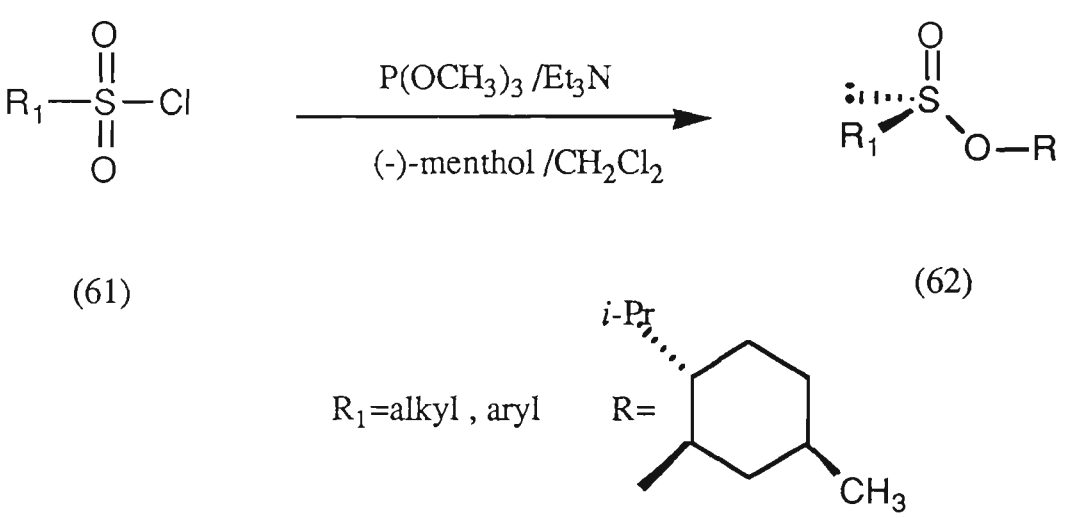
Sulfinate ester			Sulfoxide				sulfide
R_1	$[\alpha]_D$* deg	solvent	R_2	yield (%)	$[\alpha]_D$* deg	optical purity (%)	yield (%)
Tol	-195.0	benzene	Me	82	+150.1	89.5	0
Tol	-195.0	ether	Me	61	+143.0	85.0	4.5
Tol	-210.0	ether	Me	55	+143.2	55.1	
Tol	-195.0	benzene	Et	95	+198.0	97.5	1.7
Tol	-195.0	ether	Et	62	+184.5	90.8	5.7
Tol	-201.0	ether	*i*-Pr	40	+173.2	98.2	
Tol	-195.0	benzene	*i*-Pr	79	+172.5	97.7	trace
Tol	-195.0	ether	*i*-Pr	22	+176.5	100.0	3.6
Tol	-198.0	ether	*n*-Bu		+186.0	99.5	
Tol	-195.0	benzene	*n*-Bu	73	+187.0	100.0	0
Tol	-195.0	ether	Ph	88	+20.0	91.0	
Tol	-205.0	benzene	Ph	52	+20.7	94.0	
Tol	-210.0	ether	Ph	59	+21.8	99.1	
Me	-60.2	benzene	*n*-Pr	72	-48.1	34.6	trace
Me	-60.2	ether	*n*-Pr	58	-47.4	34	3.7
n-Bu	-49.3	benzene	Me	68	+40.0	35.7	
n-Bu	-49.3	ether	Me	56	+41.2	36.8	

* solvent $CHCl_3$

This useful method was later used for the preparation of diaryl and alkyl aryl sulfoxides.[49,50] The evidence that inversion takes place at sulfur was determined by chemical correlation and O.R.D. studies.[51-56] The absolute configuration of (-)-methyl *p*-tolylsulfinate was previously established by correlation with (-)-methyl *p*-iodobenzenesulfinate, studied by X-ray diffraction analysis.[57]

An extremely convenient one step synthesis of menthyl sulfinate esters (62) has been recently reported.[58] This involved the <u>in situ</u> reduction of the corresponding sulfonyl chloride (61) in the presence of (-)-menthol as shown in Scheme 44. For comparison, menthyl benzenesulfinate was obtained in 92% yield via this new method, that was only available in 62 % yield using previous methods.[59]

Scheme 44. Synthesis of menthyl sulfinate esters (62) from sulfonyl chloride (61).

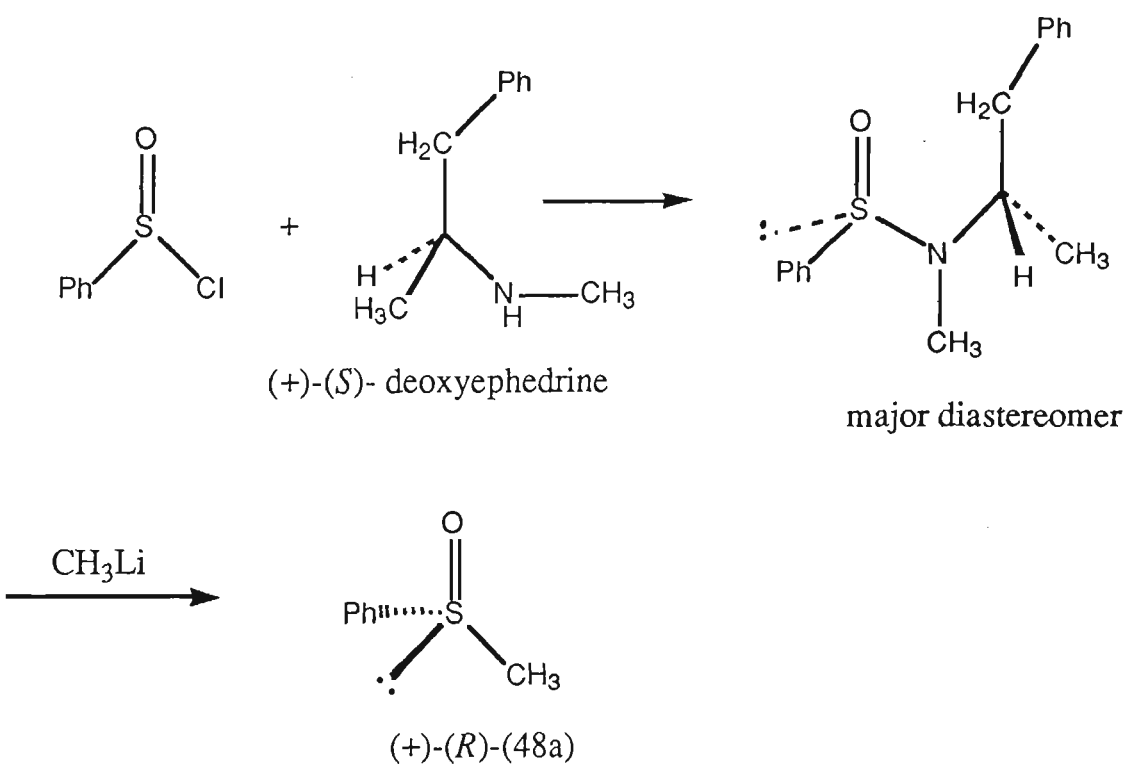


(61) (62)

Other related methods for the synthesis of sulfoxides have also been developed.[60] The use of the chiral sulfinamide, prepared from benzenesulfinyl chloride and (+)-*(S)*- deoxyephedrine, has been reported (Scheme 45).[60a] In comparison to the asymmetric synthesis of sulfinate

esters, this method is much more stereospecific and at low temperature (-70°C) the diastereoisomer ratio is about (3:1), and fractional crystallisation is easier. After crystallisation, the major diastereoisomer of the sulfinamide was treated with methyllithium and (+)-(*R*)-phenyl methyl sulfoxide (48a) was obtained in a reasonable yield. However the enantiomeric purity of the sulfoxides can be lowered by racemization involving methyl group exchange between methyllithium and the methyl sulfoxides.

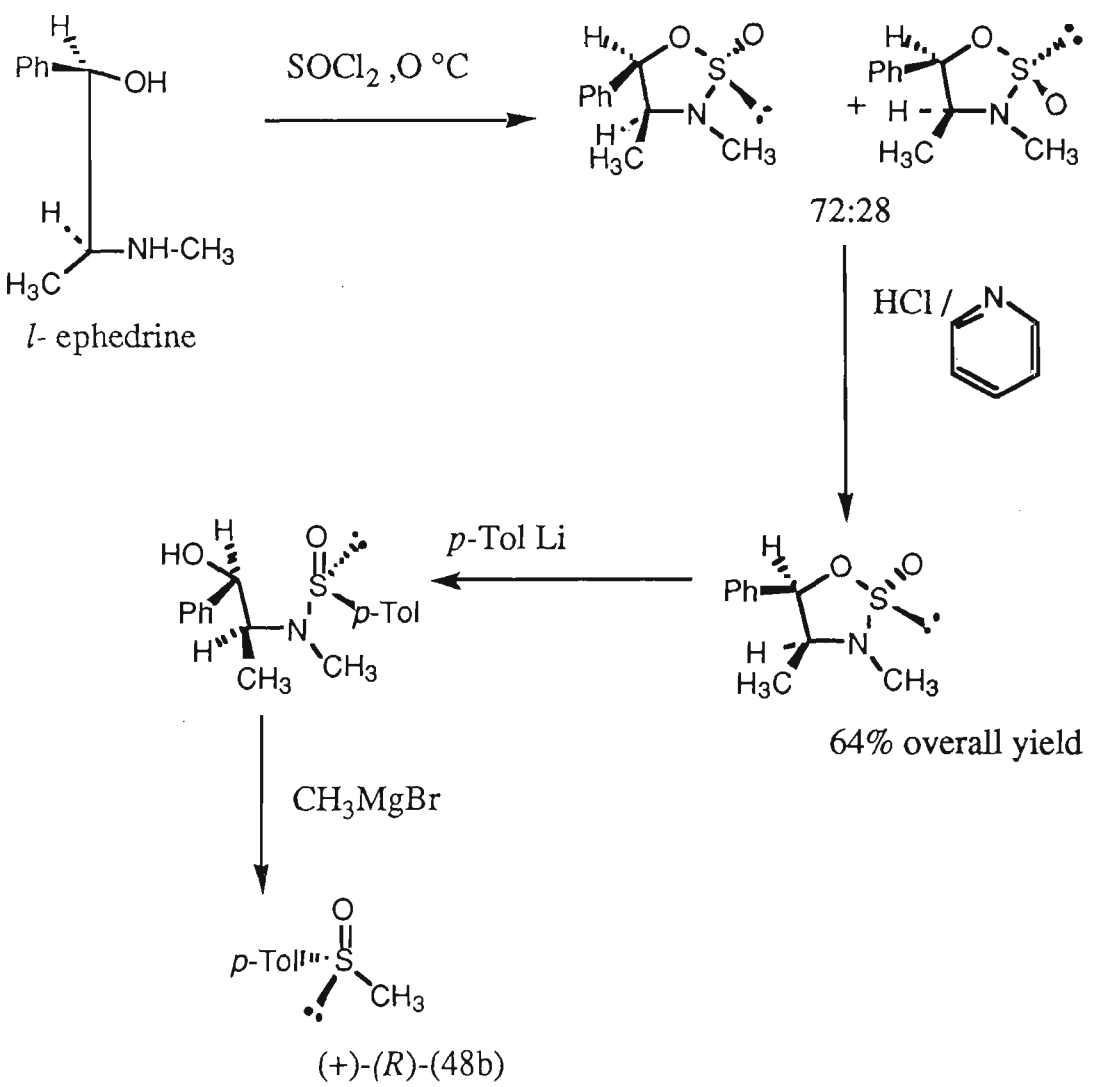
Scheme 45. Synthesis of (+)-(*R*)-(48a) from (+)-(*S*)-deoxyephedrine.



An excellent related approach was proposed, [60b] which consists of using *l*- ephedrine to obtain diastereoisomeric 1,2,3-oxathiazolidine-2-oxides, which were epimerized at the sulfur centre in acidic medium, the equilibrium being displaced towards the less soluble isomer which then precipitated in an overall yield of 64%. Treatment of the major

diastereoisomer with *p*-tolyllithium gave the corresponding sulfinamide in high yield, which after reaction with methylmagnesium bromide gave optically pure sulfoxide in 25% yield. Use of methyllithium gave 85 % enantiomerically pure (+)-*(R)*-*p*-tolyl methyl sulfoxide (48b) in 70 % yield (Scheme 46).

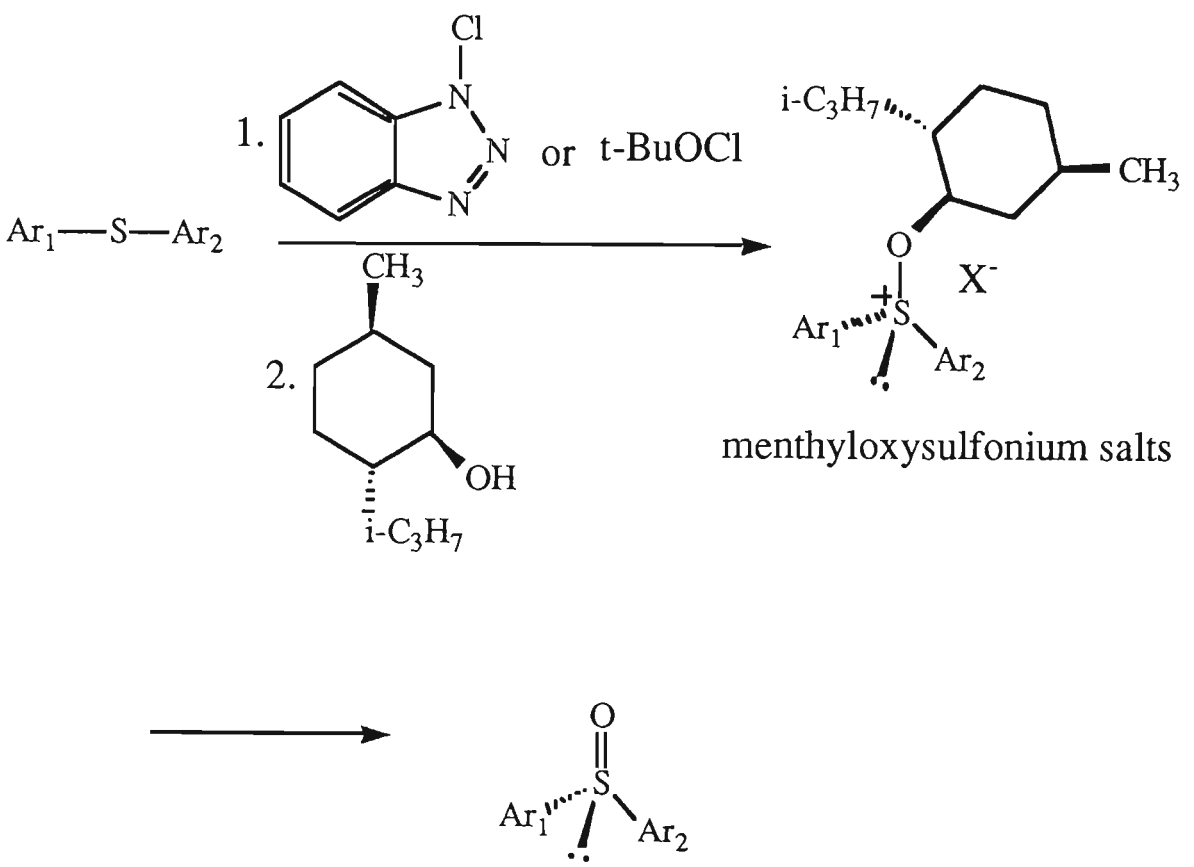
Scheme 46. Synthesis of (+)-*(R)*-*p*-tolyl methyl sulfoxide (48b) from *l*- ephedrine.



Optically active diaryl sulfoxides have been prepared by oxidation of diaryl sulfides to the diastereomeric menthyloxysulfonium salts which were separated by fractional crystallisation and then hydrolysed with

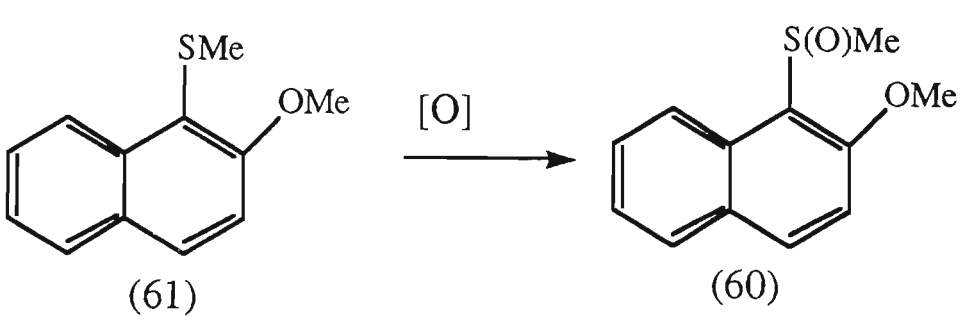
aqueous sodium hydroxide to give the optically active sulfoxides (Scheme 47).[61]

Scheme 47. Synthesis of optically active diaryl sulfoxides.



Other methods that could be used to prepare (60) include the oxidation of the sulfide (61) using an optically active oxidising agent (Scheme 48)

Scheme 48. Oxidation of sulfide (60) to sulfoxide (59) by employing a chiral oxidising reagent.



A convenient and efficient method for synthesis of chiral sulfoxides is oxidation of a prochiral sulfide with an optically active oxidising agent. As shown in Table 5, by using optically active titanium tartrate reagents it is possible to oxidise prochiral sulfides to chiral sulfoxides.[62]

Table 5. Asymmetric oxidation of R_1-S-R_2 to optically active sulfoxides $R_1R_2S(O)$.

R_1	R_2	Oxidant	Yield (%)	$[\alpha]_D^*$	e.e. (%)
Me	*p*-Tol	A	90	+132.0	91.0 *(R)*
Me	*p*-Tol	B	60	+128.5	88.3 *(R)*
Me	*p*-Tol	C	46	+93.5	64.5 *(R)*
Me	Ph	A	80	+130.0	89.0 *(R)*
Me	*p*-ClC_6H_4	A	95	+97.0	78.0 *(R)*
Me	*p*-BrC_6H_4	A	70	+77.0	80.0 *(R)*
Et	*p*-Tol	A	71	+139	74.0 *(R)*

A: Ti(OPr-i)4+(*R*,*R*)-diethyl tartrate+H_2O+t-BuOOH (1:2:1:1.1) in CH_2Cl_2

B: Ti(OPr-i)4+(*R*,*R*)-diethyl tartrate+t-BuOOH (1:4:2) in CH_2Cl_2

C: Ti(OPr-i)4+(*R*,*R*)-diethyl tartrate+t-BuOOH (1:4:2) in toluene

* solvent CH_2Cl_2

Kinetic resolution of racemic sulfoxides is also an important technique in the preparation of optically active sulfoxides. Many successful and less successful attempts to obtain optically active sulfoxides via kinetic resolution have been described. [63,64]

Recently, β-cyclodextrin has been used to resolve racemic sulfoxides via the formation of an inclusion complex. However the optical purity of the sulfoxides that have been resolved were very poor, and enantiomeric excesses (e.e.) were less than 15% in most cases.[65,66]

The formation and separation of the optically active diastereomeric transition metal complexes, [67] chromatography over optically active stationary phases,[68,69] and kinetic resolution by partial oxidation of sulfides or reduction of sulfones with chiral reagents,[70,71] constitute other methods which generally exhibit poor to moderate enantiomeric excesses.

Several micro-organisms are able to oxidise sulfides into optically active sulfoxides.[72,73] Among them Aspergillus niger was one such microbe capable of this oxidation, but was found to be extremely substrate specific. Henbest [72], discovered that in this case enantiomeric excesses varied extremely from methyl *p*-tolyl sulfoxide (e.e. 32%) to t-butyl *p*-tolyl sulfoxide (e.e. 99%). Recently Ohta,[74] mentioned that Cornybacterium equi IFO 3730 was able to oxidise many alkyl aryl sulfides to alkyl aryl sulfoxides in high enantiomeric purity (e.e. 82-100%).

For convenience we have decided to use the Andersen method for the synthesis of sulfoxide (60).

CHAPTER 1

Chapter 1

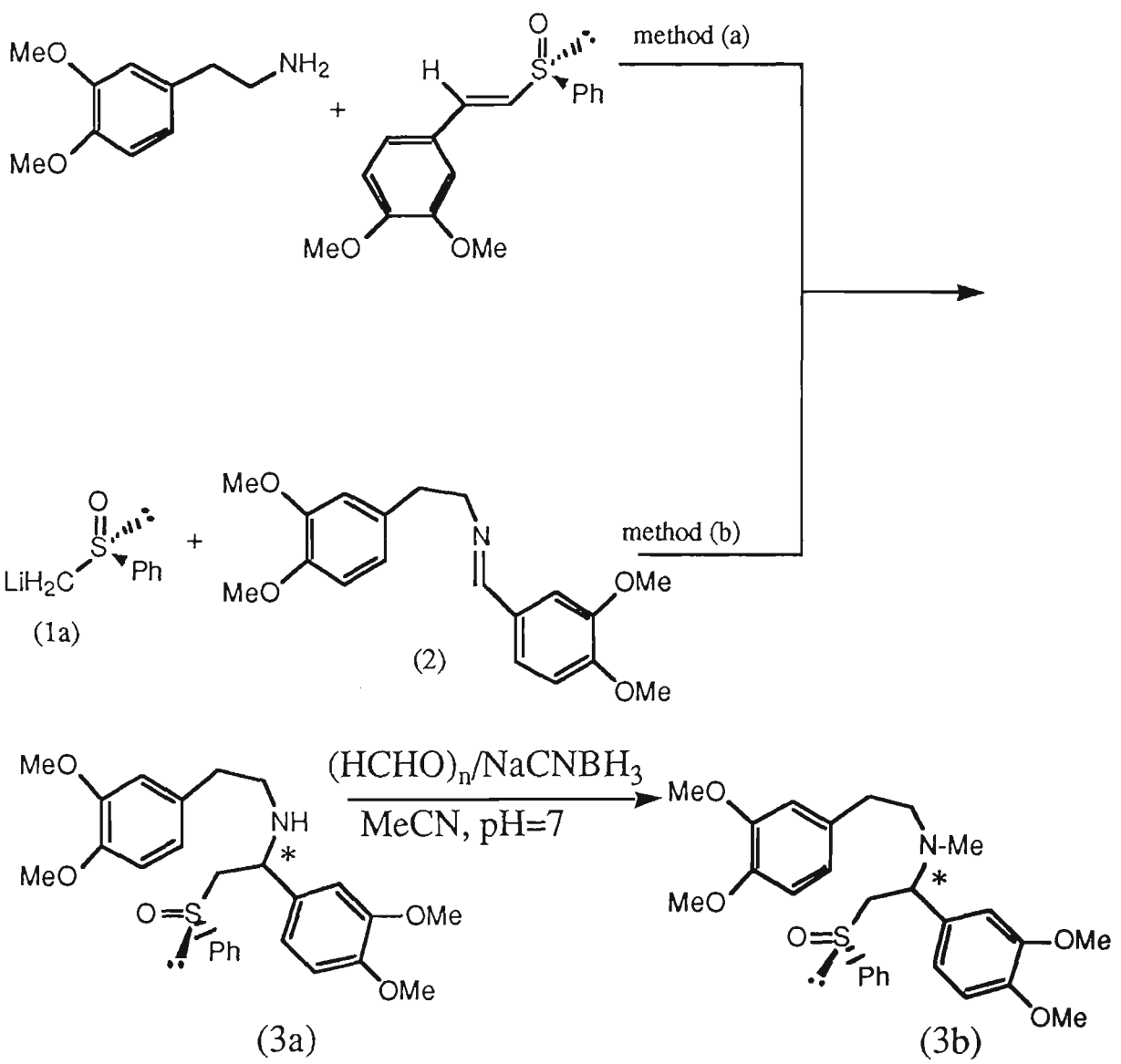
Diastereoselective Addition of Lithiated Methyl Phenyl and 2-Methoxy-1-naphthyl Sulfoxide to Nitrones

The aim of this study was to evaluate the potential of the chemistry outlined in paths (a), (b) and (e) as methods for preparing chiral β-aminosulfoxide (46) as was outlined in the Introduction in Scheme 23.

We first attempted to prepare β-aminosulfoxide (3a) from either addition of 2-(3',4'-dimethoxyphenyl)ethylamine to phenyl 3,4-dimethoxy-β-styryl sulfoxide (Scheme 1.1, method (a)) or the addition of lithiated methyl phenyl sulfoxide (1a) to imine (2) as outlined in Scheme 1.1, method (b). In both of these reactions the yields of the adduct were poor (10-25 %) and the diastereoselectivity was only modest (d.r. = 2:1).

To prepare β-amino sulfoxide (3a) in good yield and high diastereoselectivity it was decided to examine the addition reaction of lithiated sulfoxide (1a) to nitrones (4). Since nitrones are more reactive than imines towards addition of organometallic reagents,[38] a better chemical yield was expected in the addition step.

Scheme 1.1 Preparation of β-aminosulfoxide (3)



method (a)	yield=25 %	d.r=2:1
method (b)	yield=10 %	d.r=2:1

As was described in the introduction, in 1983 Annunziata and Cinquini [38] reported that the addition of lithiated (+)-*(R)*-methyl *p*-tolyl sulfoxide (1b) to three nitrones (Scheme 1.2) at -78 °C in THF. The diastereoselectivity of these reactions was found to increase as the steric demand of the R2 group of the nitrone increased (Table 1.1). That is, the order of diastereoselectivity was *t*-Bu > Ph > Me. No spectral data were reported for the diastereomeric adducts and the stereochemical

outcomes of these reactions were not determined. Furthermore the generality of this reaction was not investigated.

Scheme 1.2 The addition of *(R)*-(1b) to nitrone $R_1CH=N(O)R_2$ (4).[38]

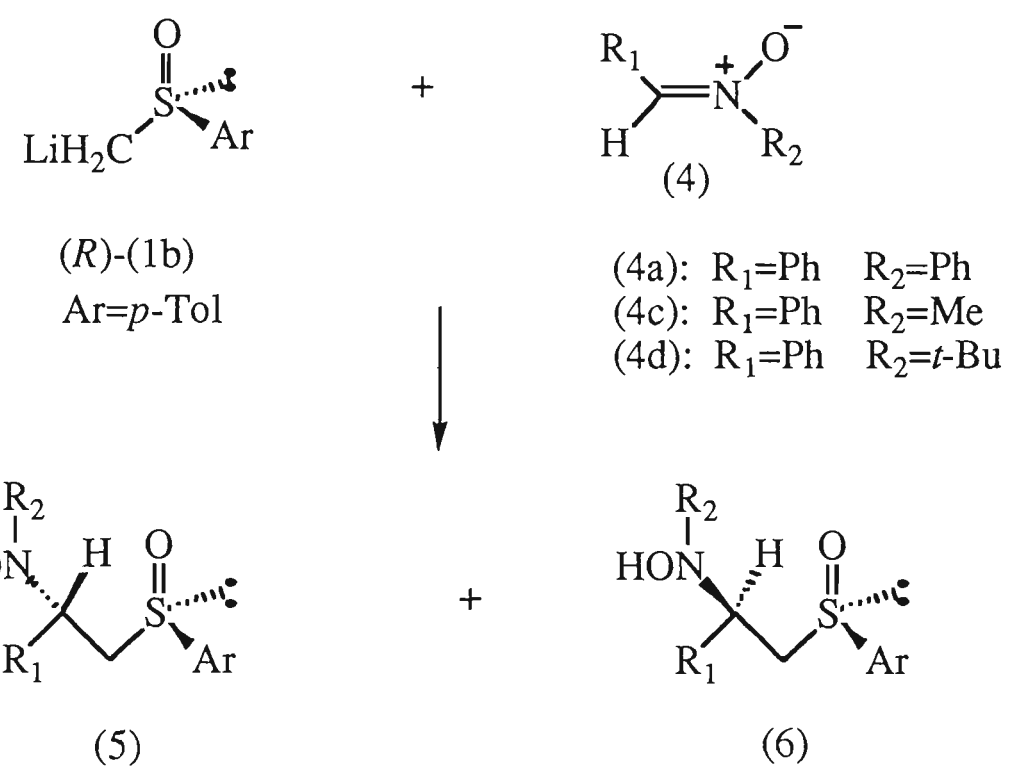


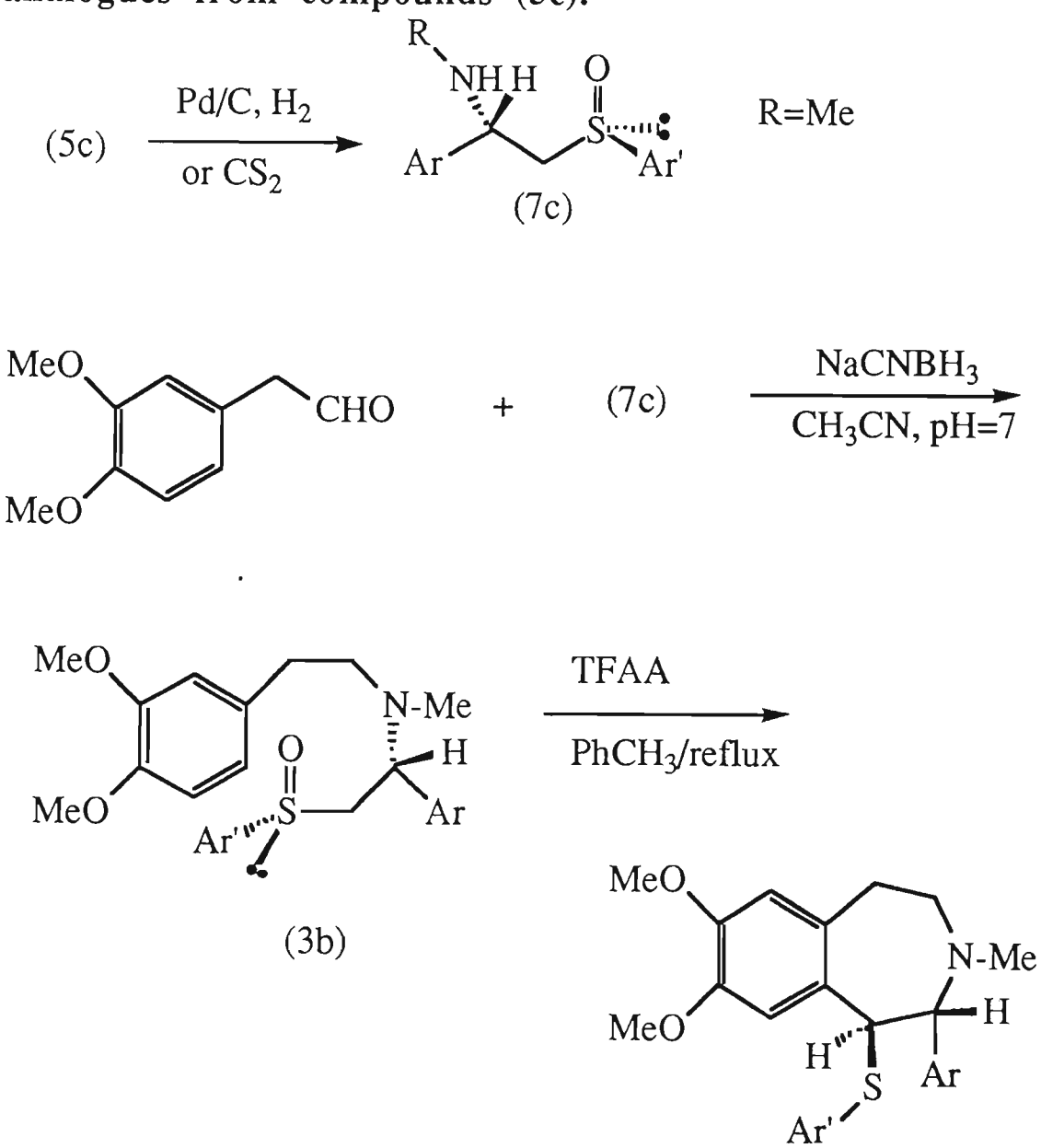
Table 1.1 The addition of *(R)*-(1b) to nitrone $R_1CH=N(O)R_2$ (4), at -78° C, in THF.[38]

nitrone (4)	yield (%) (5)+(6)	diastereomeric ratio (5):(6)*	$[\alpha]_D$ (c 1, $CHCl_3$)	m.p. (°C)
(4a)	85	75:25	+64.3	97-100
(4c)	77	82:18	+236	178
(4d)	84	100:0	+138	152

*stereochemistry of the major and minor diastereoisomers were not determined.

The initial aim of this research was to investigate the generality of this reaction and also to use the compound (5) and or (6) as a starting material for the asymmetric synthesis of benzazepine alkaloids and analogues as outlined in Scheme 1.3. The second purpose of this study was to compare the diastereoselectivity of this method with that of the other methods described in the Introduction (Scheme 23) and determine the stereochemical outcome of these addition reactions.

Scheme 1.3. Proposed synthesis of benzazepines and their analogues from compounds (5c).

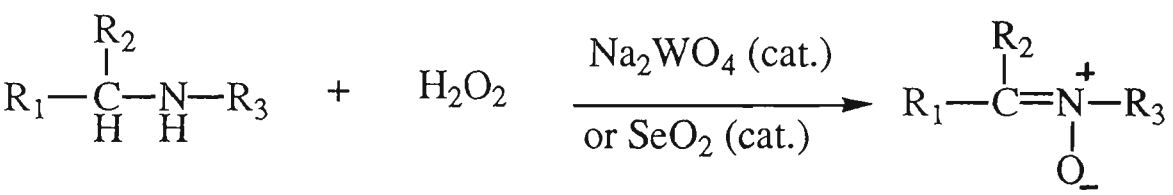


PREPARATION OF NITRONES

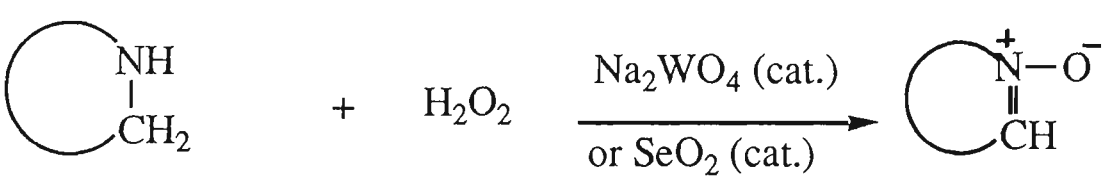
Nitrones are highly valuable synthetic intermediates and excellent trapping reagents.[75] Generally nitrones have been prepared mainly by using the following five methods as shown in Schemes 1.4-1.9.

Oxidation of secondary amines with hydrogen peroxide in the presence of sodium tungstate or selenium dioxide gives the corresponding nitrones. This is a general method for synthesis of acyclic and cyclic nitrones from their corresponding secondary amines in a single step, in good to excellent yields, as shown in Scheme 1.4.[76]

Scheme 1.4. Synthesis of nitrones via oxidation of secondary amines.



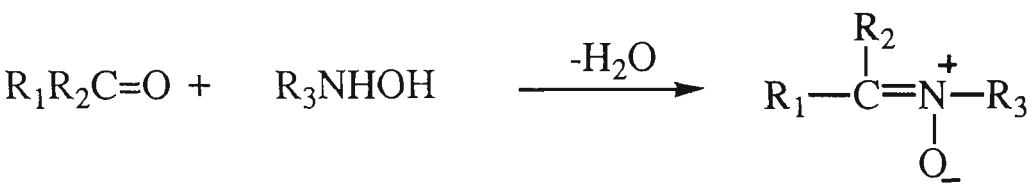
or R_1=alkyl,aryl or H
R_2=alkyl, aryl or H
R_3=alkyl or aryl



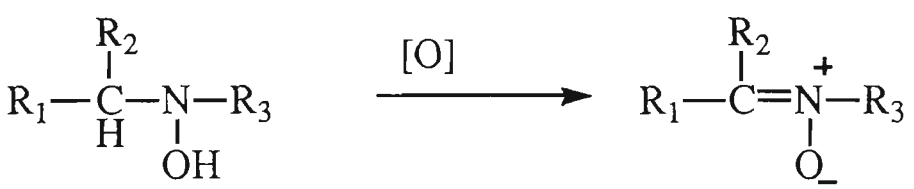
Condensation of carbonyl compounds with *N*-monosubstituted hydroxylamines (Scheme 1.5) [77] and oxidation of *N,N*-disubstituted hydroxylamines (Scheme 1.6),[78] are other typical methods. However preparation of the starting hydroxylamines is generally very tedious. Cyclic hydroxylamines can be prepared by thermal decomposition of the corresponding tertiary amine *N*-oxides.[79] The method shown in

Scheme 1.5 proceeds best when R2=alkyl or aryl and R1 is a non sterically demanding group. If R1 is a sterically demanding then the resulting steric effects result in low yields of the nitrone. This method is of general application and is useful to prepare a wide variety of nitrones. In most cases the reaction proceeds more readily with aldehydes rather than ketones.

Scheme 1.5. Synthesis of nitrones via condensation of carbonyl compounds with *N*-monosubstituted hydroxylamines.

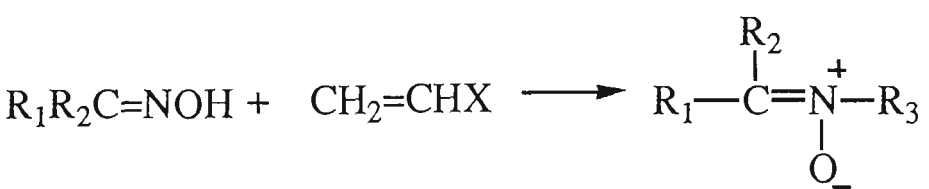


Scheme 1.6. Synthesis of nitrones via oxidation of *N,N*-disubstituted hydroxylamine.



Oximes undergo Michael addition to electron deficient alkenes to generate nitrones as shown in Scheme 1.7.[80]

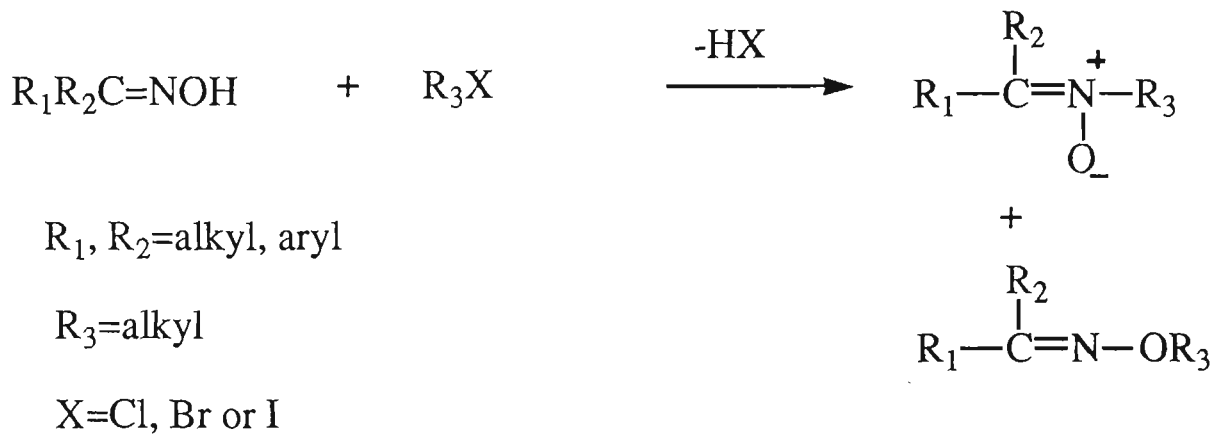
Scheme 1.7. Synthesis of nitrones via Michael addition to electron deficient alkenes.



R_1 and R_2= alkyl, aryl or H, X=electron withdrawing group

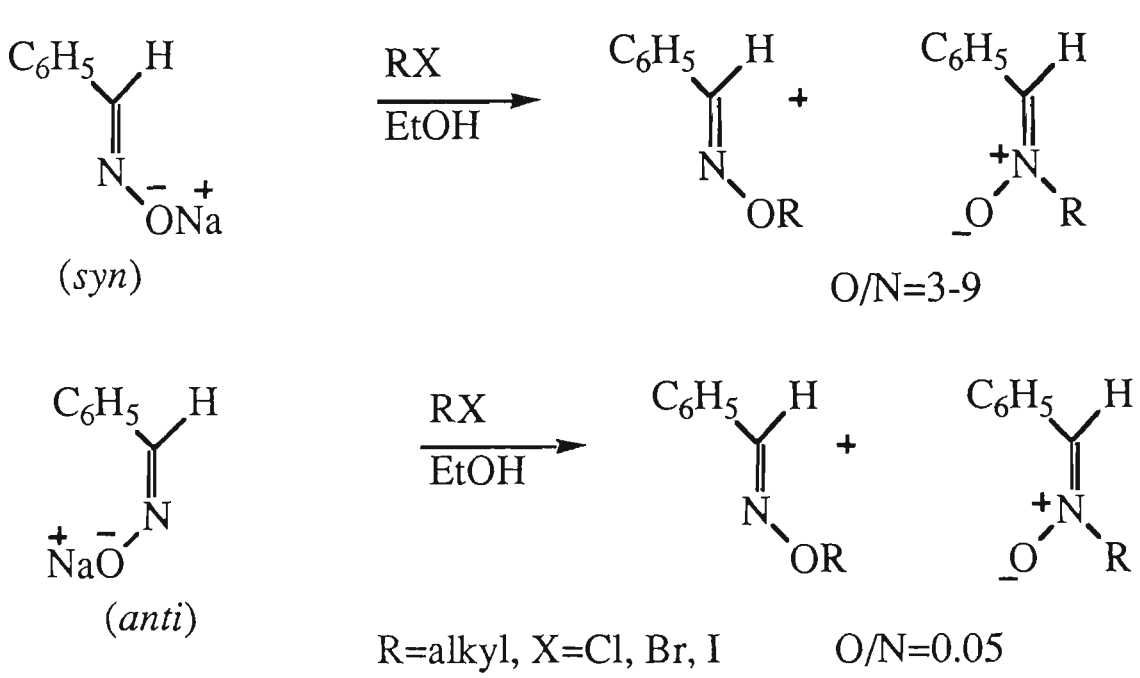
Alkylation of oximes gives rise to a mixture of oxime ethers and nitrones as shown in Scheme 1.8.[81]

Scheme 1.8. Synthesis of nitrones via alkylation of oximes.



The percentage of the respective oxime ether and nitrone depends on the nature of the starting oxime, the alkyl halide, and the experimental conditions. For example, *anti*-benzaloxime is readily *N*-alkylated by various alkyl halides whereas *syn*-benzaloxime is largely *O*-alkylated.[81] These results offer a convenient route to α-phenyl-*N*-substituted nitrones and α-phenyl-*o*-substituted ethers as outlined in Scheme 1.9.

Scheme 1.9. Alkylation of *anti*-benzaloxime and *syn*-benzaloxime.



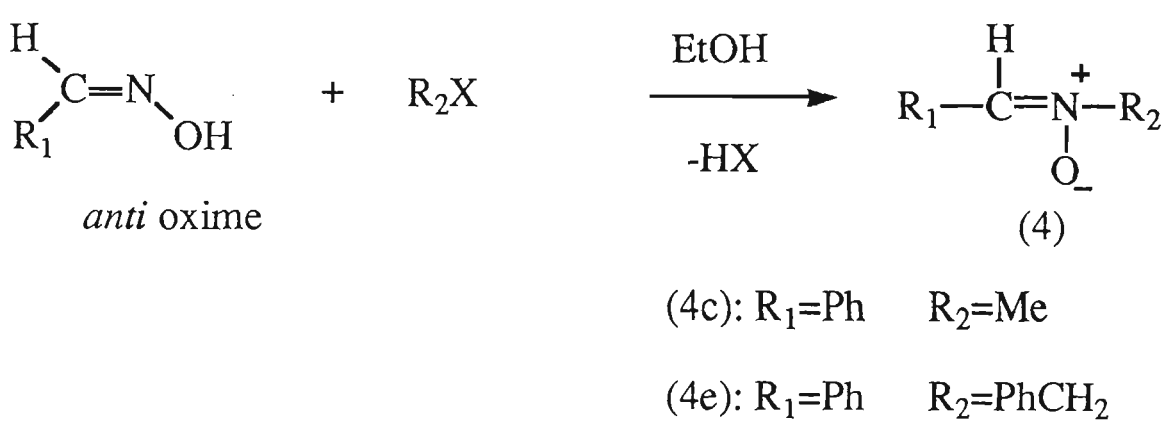
In this work the starting nitrones were prepared by three different methods.

Method A.

Alkylation of *anti* benzaldehyde oxime

The nitrones (4c) and (4e) were prepared by alkylation of *anti* benzaldehyde oxime. [81] In this project the alkylation of this oxime gave nitrones (4c) and (4e) in 75 % yield after recrystallization of the crude reaction mixture as outlined in Scheme 1.10.

Scheme 1.10. Synthesis of nitrones (4c) and (4e) by alkylation of *anti* benzaldehyde oxime.

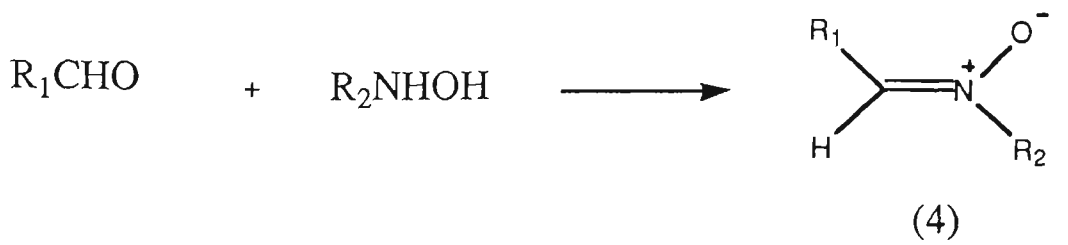


Method B.

Condensation of *N*-substituted hydroxylamines with aldehydes.

Nitrones (4a), (4b), (4d), and (4f) were prepared by condensation of a *N*-substituted hydroxylamine with an aldehyde as shown in Scheme 1.11.[77] In general the yields were good to excellent (80-95 %).

Scheme 1.11. Synthesis of nitrones (4a), (4b), (4d) and (4f).



(4)

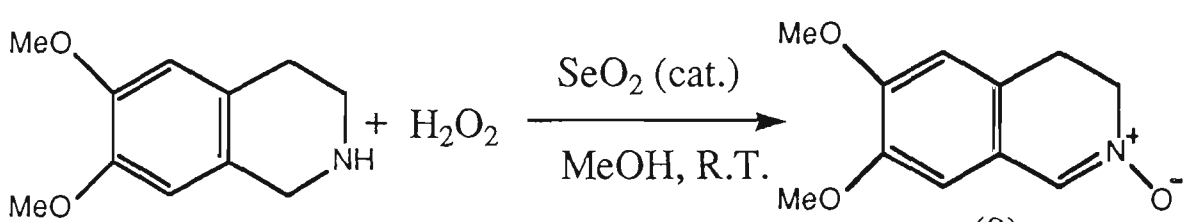
(4a):	R_1=Ph	R_2=Ph	95 % yield
(4b):	R_1=2-furanyl	R_2=Ph	85 % yield
(4d):	R_1=Ph	R_2=*t*-Bu	85% yield
(4f):	R_1=Me	R_2=*t*-Bu	80 % yield

Method C.

Catalysed oxidation of secondary amines with hydrogen peroxide.

Nitrone (9) was prepared in 91% yield by oxidation of 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline with selenium dioxide as shown in Scheme 1.12. [76]

Scheme 1.12. Synthesis of nitrone (9).

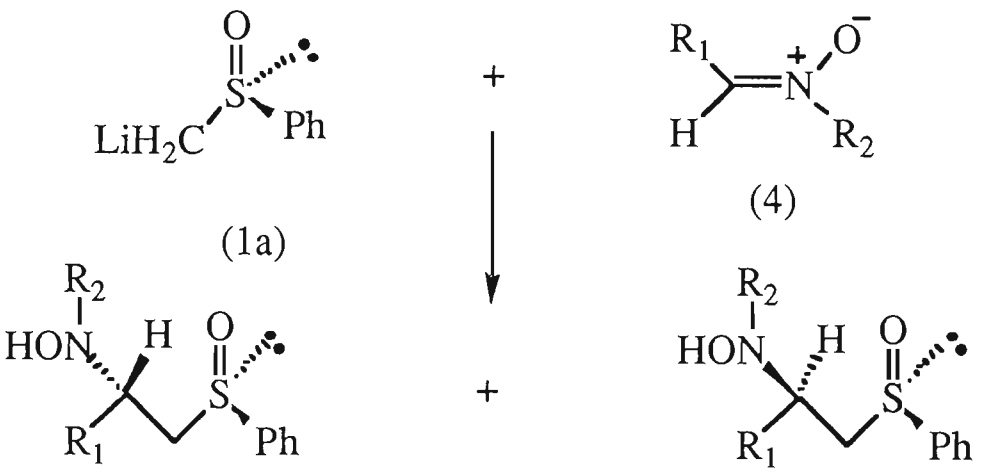


(9)
yield 91%

Addition of lithiated methyl phenyl sulfoxide (1a) to nitrones (4a)-(4f) and (9).[82]

Addition of a solution of the nitrone (4) or (9) in dry THF to a solution of racemic lithiated methyl phenyl sulfoxide (1a) (prepared from 1.2 equiv. of LDA and 1 equiv. of methyl phenyl sulfoxide at -78° C in THF) for 1 h afforded a mixture of the racemic diastereomeric β-hydroxylamine sulfoxides (5) and (6), and (10) and (11) respectively in good to excellent yield, after purification by simple column chromatography (Table 1.2). The product diastereoselectivities, as determined by ^{1}H NMR (400 MHz) spectroscopic analysis of the crude reaction products, ranged from 50:50 to 86:14. Although (5) and (6), and (10) and (11) are racemic only one enantiomer is shown to help simplify the discussion as outlined in Scheme 1.13 and 1.14.

Scheme 1.13. Addition of lithiated methyl phenyl sulfoxide (1a) to nitrones (4a)-(4f).



(1a) (4)

(5) (6)

(a); R_1=Ph R_2=Ph

(b); R_1=2-furanyl R_2=Ph

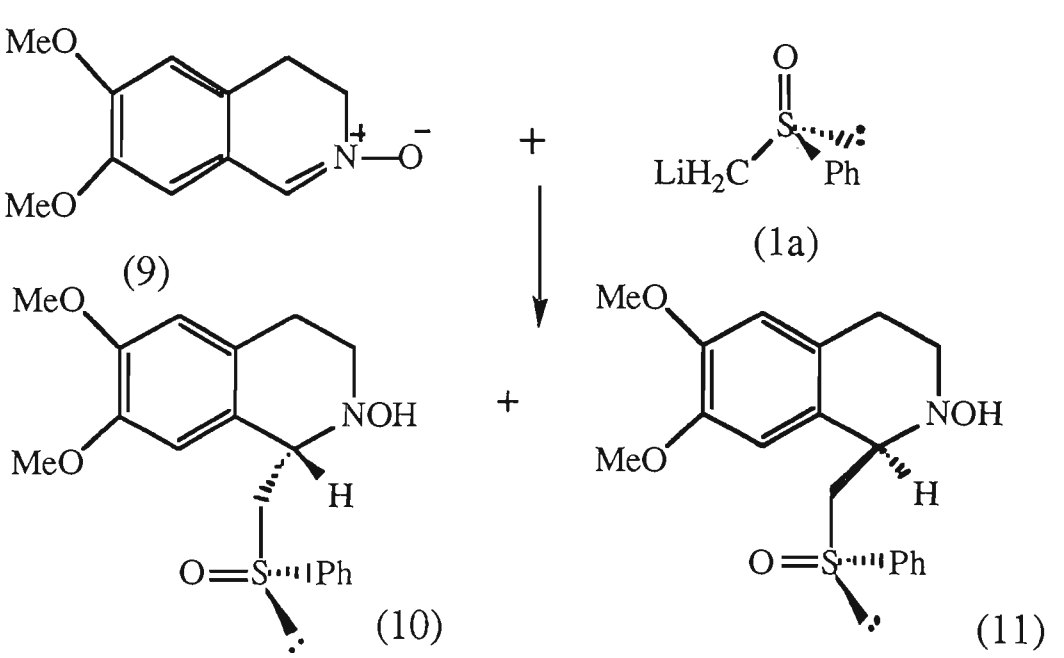
(c); R_1=Ph R_2=Me

(d); R_1=Ph R_2=*t*-Bu

(e); R_1=Ph R_2=Ph-CH_2

(f); R_1=Me R_2=*t*-Bu

Scheme 1.14. Addition of lithiated methyl phenyl sulfoxide (1a) to nitrone (9).



(9) (1a)

(10) (11)

Table 1.2. Addition of lithiated methyl phenyl sulfoxide (1a) to nitrones (4a)-(4f) and (9).[82]

entry	nitrone	yield (%)	diastereoselection (5):(6) and (10):(11)
1	(4a)	73	83:17
2	(4b)	79	79:21
3	(4c)	74	67:33
4	(4d)	86	85:15
5	(4e)	83	67:33
6	(4f)	85	50:50
7	(9)	92	86:14*

82. S.G. Pyne, and A.R. Hajipour, *Tetrahedron*, 48, 9385 (1992).

* Ratio of (10):(11).

As found previously for nitrones [38b] of the type $R_1CH=N(O)R_2$, the product diastereoselection increases, although not as dramatically as that reported before, as the steric demand of the *N*-substitutent of the nitrone increases (Table 1.2, entries 1-5). The highest product diastereoselection was obtained with the isoquinoline nitrone (9) as shown in Table 1.2 (entry 7).[82]

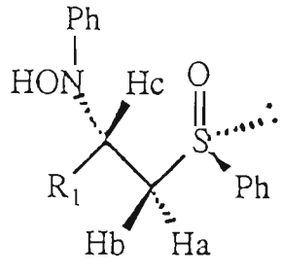
Figure 1.1 shows a copy of the ^1H NMR spectrum of the crude reaction mixture from the reaction of lithiated methyl phenyl sulfoxide (1a) and nitrone (4b) at -78° C in THF. The protons Hc of the diastereoisomers (5b) and (6b) are clearly evident as a doublet of doublets at δ 5.14 (dd, J=4.8, 10.0 Hz, 1H) and δ 5.22 (dd, J=6.7, 10.5 Hz, 1H) respectively. Integration of these signals indicated that the diastereomer ratio was 79:21.

Figure 1.2 shows a copy of the ^1H NMR spectrum of the crude reaction mixture from the reaction of lithiated methyl phenyl sulfoxide (1a) and nitrone (4e) at -78° C in THF. The protons Hc of the diastereoisomers (5e) and (6e) are clearly evident as a doublet of doublets at δ 4.36 (5.2, 8.4 Hz, 1H) and δ 4.26 (6.4, 10.4 Hz, 1H) respectively. Integration of these signals indicated that the ratio of the major and minor diastereoisomers (5e), and (6e), was 67:33.

Figure 1.3 shows a copy of the ^1H NMR spectrum of the crude reaction mixture from the reaction of lithiated methyl phenyl sulfoxide (1a) and isoquinoline nitrone (9) at -78° C in THF. The two methoxy groups of the diastereoisomers (10) and (11) are clearly evident as singlets at δ 3.86, 3.79 and δ 3.84, 3.78 for the major and minor diastereoisomers respectively. Integration of these signals indicated that the ratio of the major and minor diastereoisomers (10), and (11), was 86:14.

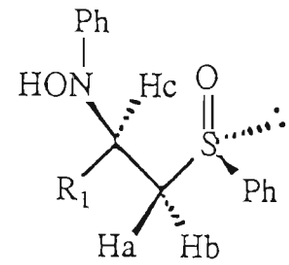
These diastereoselectivities were in general the same as those reported from the reaction of lithiated methyl phenyl sulfoxide (1a) and analogous imines as described in the Introduction in Table 2 and Scheme 27.[28]

Figure 1.1. ^1H NMR spectrum ($CDCl_3$) of the crude reaction mixture from the reaction of lithiated methyl phenyl sulfoxide (1a) and nitrone (4b).



(5b)

R_1=2-furanyl



(6b)

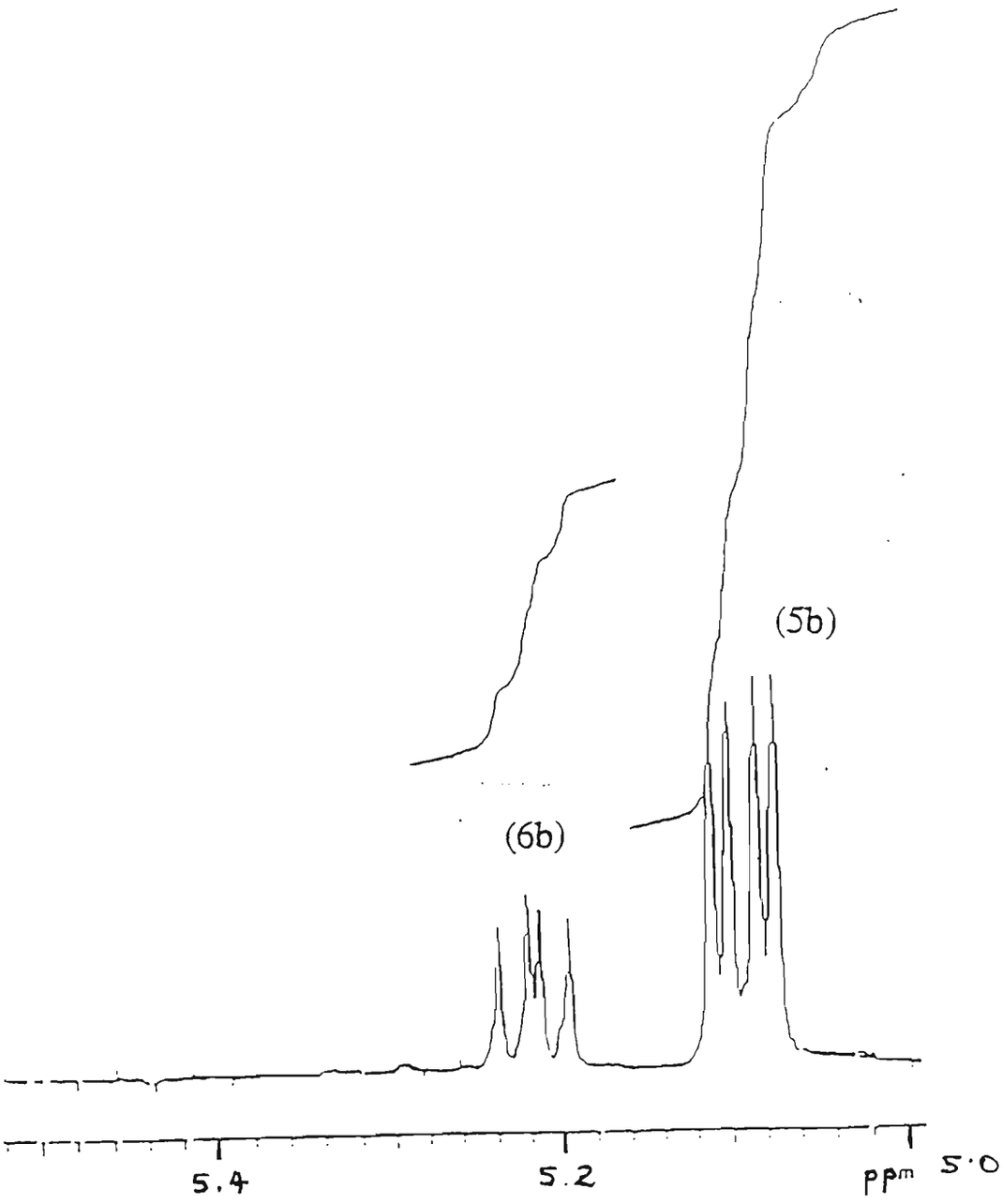
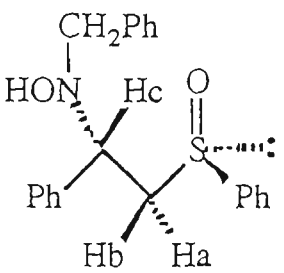
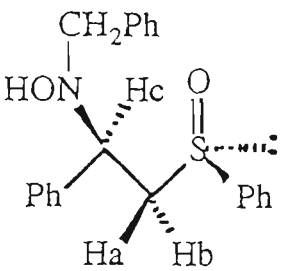


Figure 1.2. ^{1}H NMR spectrum ($CDCl_3$) of the crude reaction mixture from the reaction of lithiated methyl phenyl sulfoxide (1a) and nitrone (4e).



(5e)



(6e)

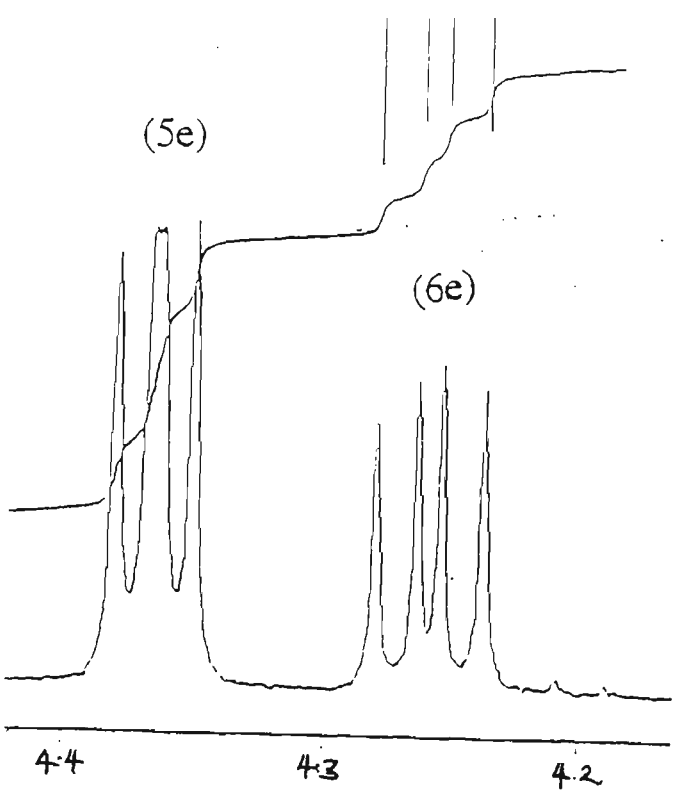
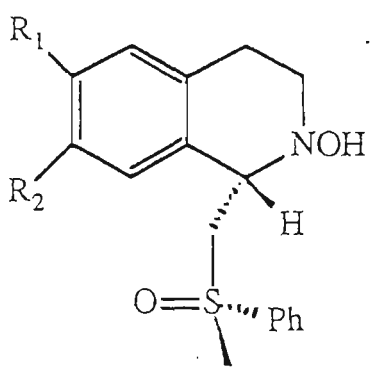
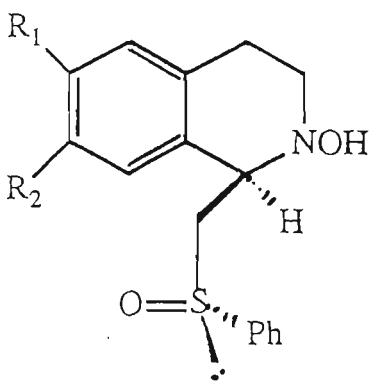


Figure 1.3. ^1H NMR spectrum ($CDCl_3$) of the crude reaction mixture from the reaction of lithiated methyl phenyl sulfoxide (1a) and nitrone (9).



(10)



(11)

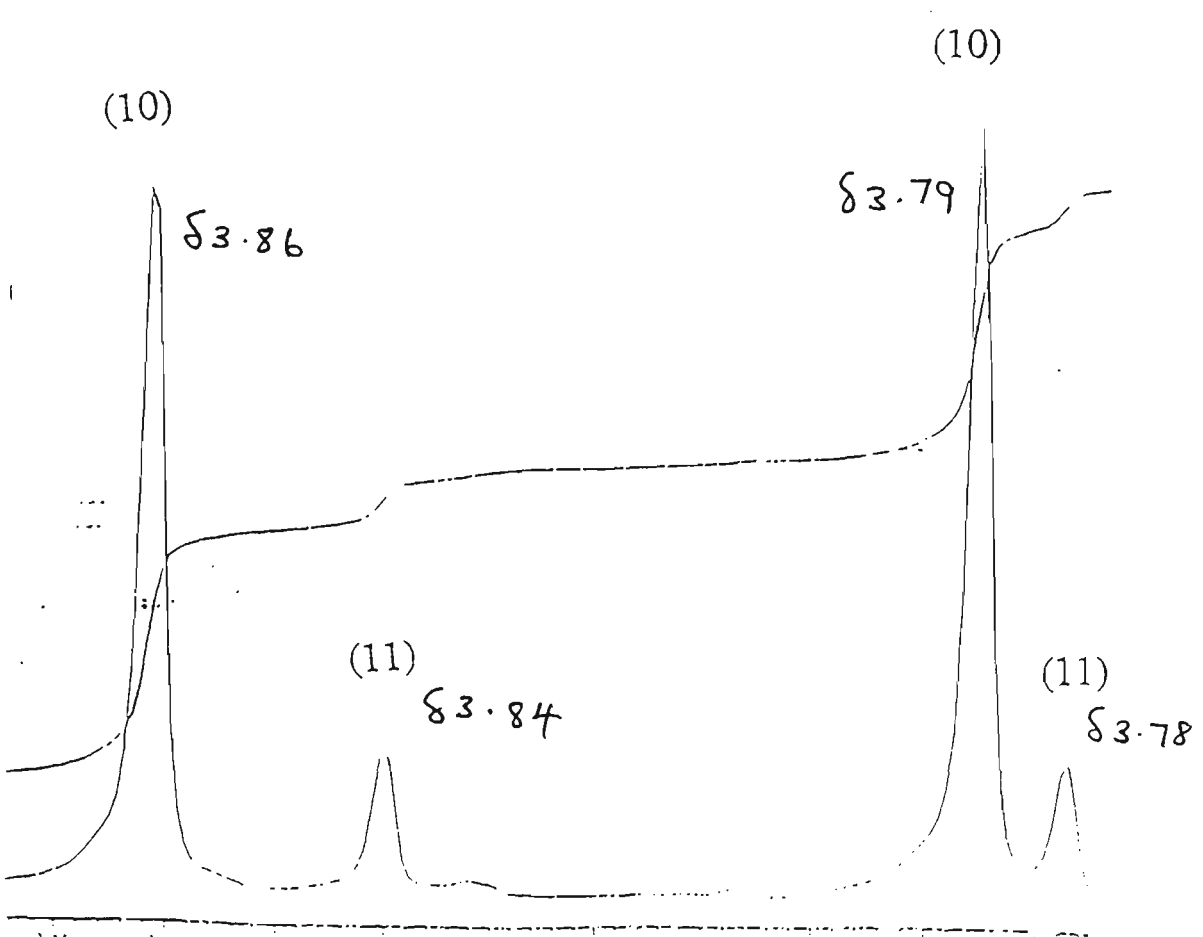
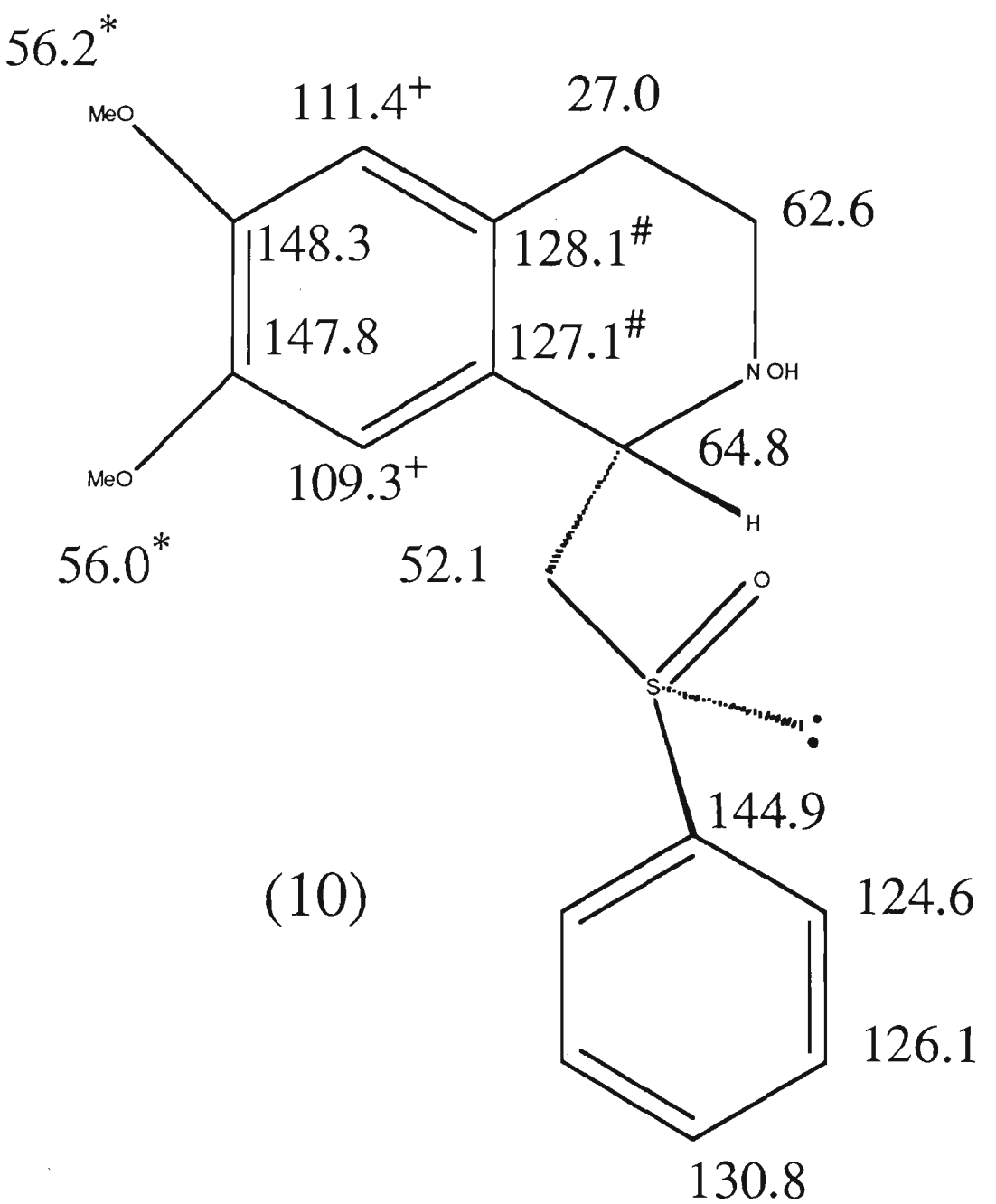


Figure 1.4 shows the ^{13}C NMR assignments for the isoquinoline (10). These assignments were made by analogy with the analogous compound described in reference 28 and from a DEPT NMR spectrum.

Figure 1.4. ^{13}C NMR ($CDCl_3$) spectral assignments for the adduct (10).



(10)

*, +, # these assignments may be interchanged

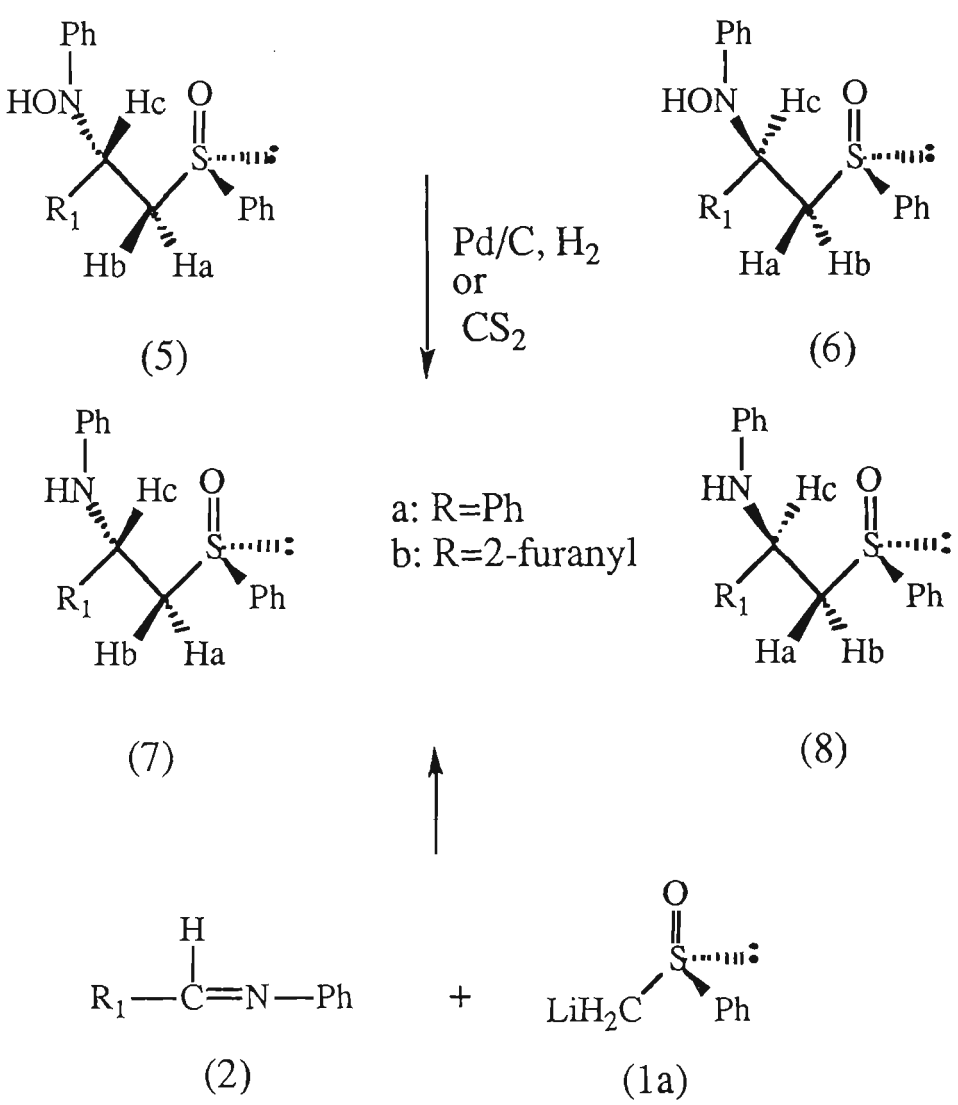
Proof of stereochemistry.

The relative *(1S*,Rs*)* stereochemistry of the major diastereomeric products (5a) and (5b) from the reaction of (1a) to the nitrones (4a) and (4b) was established by ^{1}H NMR spectroscopic analysis using *(1S*,Rs*)* (7a) and *(1S*,Rs*)* (7b) of known absolute stereochemistry as reference compounds.[28] The compounds (7a) and (7b) are the major diasteromeric products from the reaction of lithiated methyl phenyl sulfoxide (1a) and the imines (2) (a: R=Ph, b: R=2-furanyl) as shown in Scheme 1.15.[28] Hydrogenolysis of a mixture of (5a) and (6a) (d.r.=83:17) and a mixture of (5b) and (6b) (d.r.=79:21) over palladium on carbon in acetic acid at one atmosphere pressure of hydrogen or treatment of these compounds with carbon disulfide[83] gave a mixture of (7a) and (8a) (d.r.=83:17) and a mixture of (7b) and (8b) (d.r.=79:21) respectively in good yield (Scheme 1.15). The ^{1}H NMR spectra of the major diastereoisomer in these mixtures was identical to that reported for *(1S*,Rs*)* (7a) and *(1S*,Rs*)* (7b),[28] while the ^{1}H spectra of the minor diastereoisomer in these mixtures was identical to that reported for (1*R*,Rs**) (8a) and (1*R*,Rs**) (8b).[28] The relative stereochemistry of (5c,d and e) was assumed to be *(1S*,Rs*)* based on the similarity of their ^{1}H NMR spectra to that of (5a). In all cases, except (5b) and (6b), H_c for the major diastereoisomer (5) was observed slightly downfield from H_c in the minor diastereoisomer (6) as shown in Table 1.3. Compounds (5b) and (6b) may adopt different conformations to those of (5a, b-e) and (6a, b-e) due to the H-bonding between the furan oxygen and the *N*-hydroxylamine group.

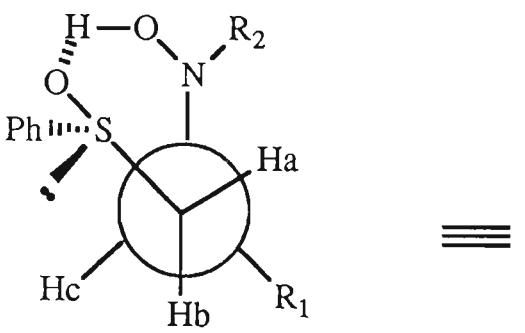
In general, in each diastereomeric pair of compounds ((5) and (6)) the more highly deshielded diastereotopic methylene proton (Ha) has a large coupling constant to Hc. The other diastereotopic methylene proton Hb is generally observed at higher field and has a smaller coupling

constant to Hc (Table 1.3). Based on this spectroscopic information we tentatively assign the H-bonded structures (A) and (B) to (5) and (6) respectively, as shown in the Newman projections in Scheme 1.16. In these H-bonded conformations R_1 and the sulfoxide group would be expected to be *anti* to minimize steric interactions. Based on these conformations we can then tentatively assign the diastereotopic methylene protons Ha and Hb as shown in Scheme 1.16. In both conformations (A) and (B), Ha is gauche to the hydroxyamino group which may contribute to the observed deshielding of this proton relative to Hb in the ^1H NMR spectrum.

Scheme 1.15. Preparation of amines (7a), (7b), (8a) and (8b).

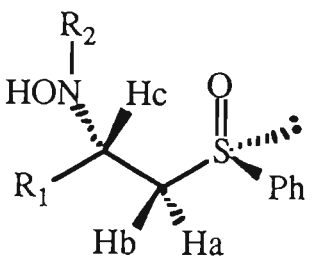


Scheme 1.16. Possible H-bonded structures for compounds (5) and (6).

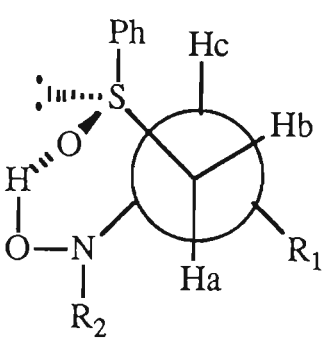


(A)
J_{bc}=small coupling
J_{ac}=large coupling

≡

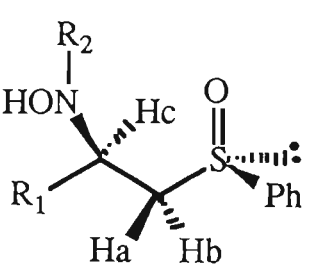


(5) major diastereomer



(B)
J_{bc}=small coupling
J_{ac}=large coupling

≡



(6) minor diastereomer

(a): R_1=Ph R_2=Ph

(b): R_1=2-furanyl R_2=Ph

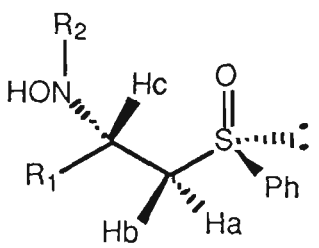
(c): R_1=Ph R_2=Me

(d): R_1=Ph R_2=*t*-Bu

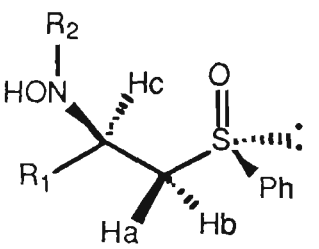
(e): R_1=Ph R_2=$PhCH_2$

(f): R_1=Me R_2=*t*-Bu

Table 1.3. ^1H NMR ($CDCl_3$) chemical shifts and coupling constants (Hz) for compounds (5) and (6).



(5)



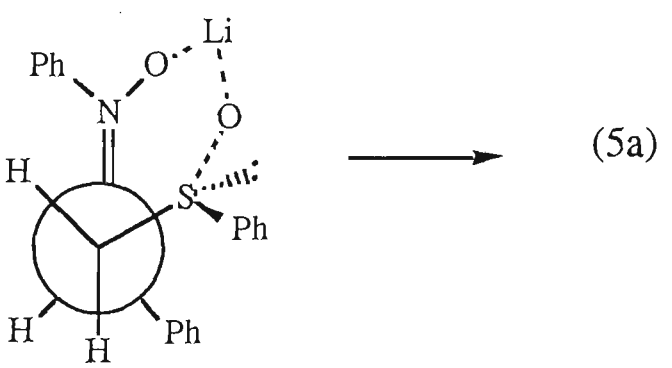
(6)

Compound	chemical shifts (ppm)			coupling constants (Hz)		
	Ha	Hb	Hc	Jac	Jbc	Jab
(5a)	3.82	3.20	5.18	10.8	6.0	14.0
(6a)	*a*	*a*	5.01	12.0	8.4	-
(5b)	3.76	3.25	5.14	10.0	4.8	13.2
(6b)	*a*	*a*	5.22	10.5	6.7	-
(5c)	3.72	3.05	4.11	9.6	6.8	13.6
(6c)	3.45	3.25	3.92	6.0	4.0	13.0
(5d)	3.58	2.94	4.55	11.0	4.0	13.2
(6d)	3.64	3.01	*a*	10.8	6.4	13.6
(5e)	3.39	3.32	4.36	8.4	5.2	13.6
(6e)	*a*	3.06	4.26	10.4	6.4	13.6

[a] obscured by other peaks in the ^1H NMR spectrum.

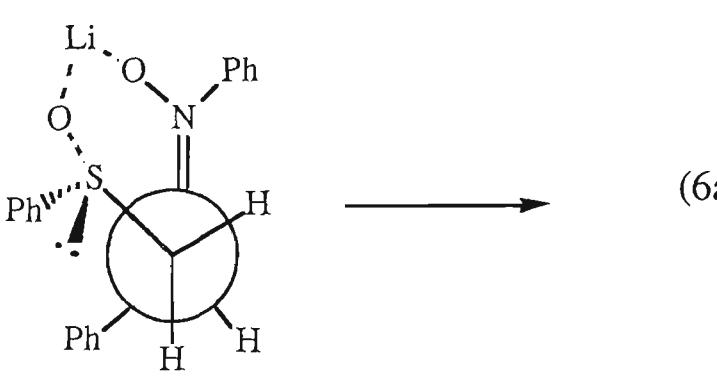
The two possible chelated, seven member ring transition states (C) and (D) for the reaction of lithiated sulfoxide (1a) and nitrone (4a) are shown in (Scheme 1.18). One would expect little difference in free energy between transition states (C) and (D) since the C-Ph group of the nitrone experiences a gauche steric interaction with the sulfoxide group in both (C) and (D). Consequently the product diastereoselectivities are only modest to good. Clearly this gauche steric interaction is less severe in transition state (C) since the S-Ph group is projected away from the C-Ph group of the nitrone.

Scheme 1.18. Possible transition states for the addition of lithiated sulfoxide (1a) to nitrone (4a).



(5a)

(C)

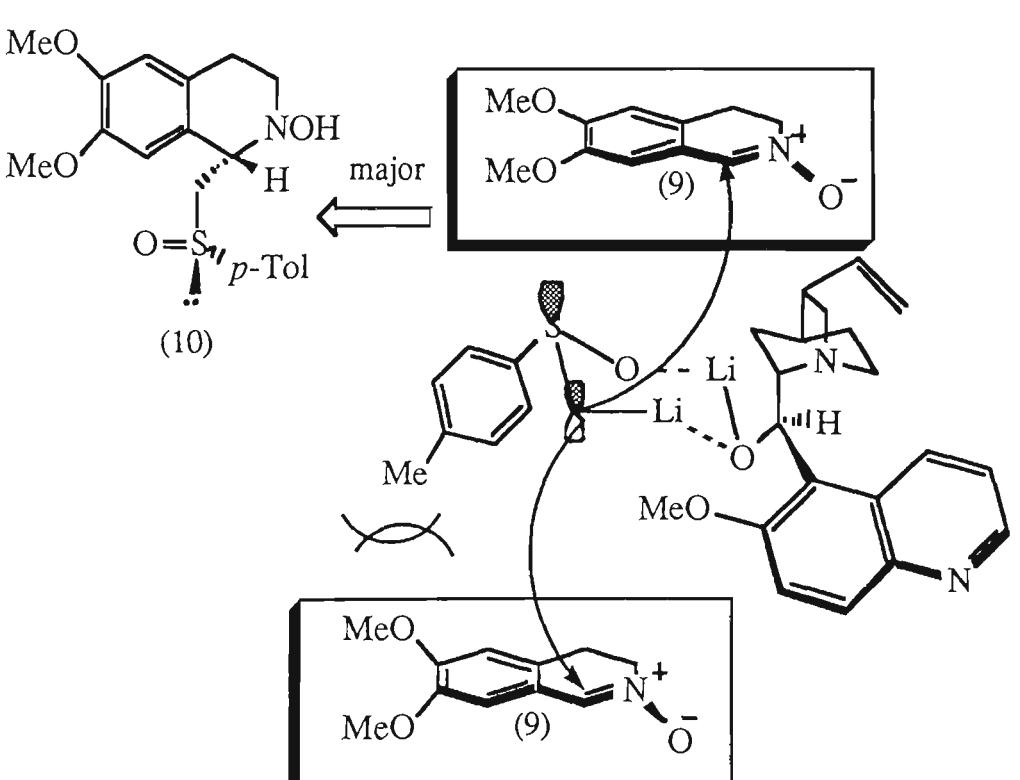


(6a)

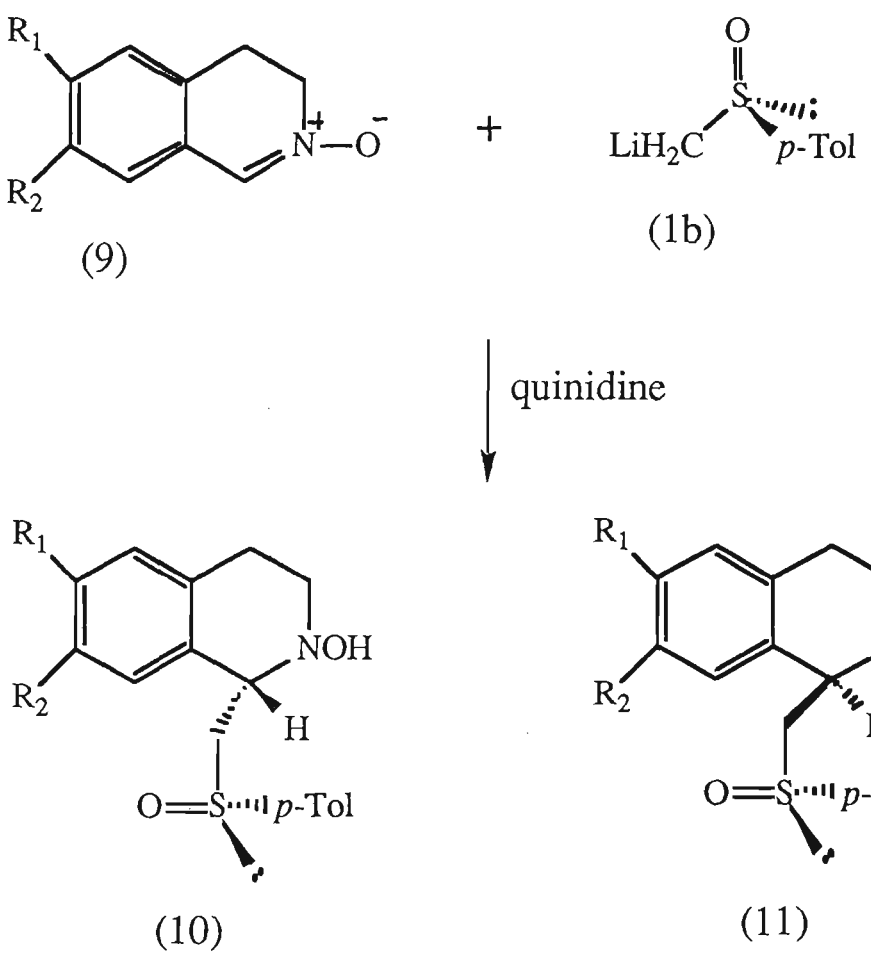
(D)

After publication of our work,[82] S-I. Murahashi and co-workers reported[84] the addition of lithiated *(R)*-(1b) to isoquinoline nitrone (9). In this report the addition of optically active lithiated (*R*)-(1b) to the nitrone (9) has been studied extensively. However, in this study the diastereoselection of the addition has been improved by using quinidine as a chiral additive as outlined in Schemes 1.19, 1.20 and Table 1.3. A mechanism for this reaction was proposed that involved chelation of the lithiated sulfoxide and the quinidine. In this reaction, addition from the bottom face of the nitrone is favoured, since the addition from the top face side is disfavoured by steric hindrance of the methyl and methoxy groups as shown in Scheme 1.19. Interestingly, the diastereoselectivity for this reaction in the absence of quinidine was 64:36 which is less than that observed by us in this study (d.r.=86:14). The ^{1}H NMR spectrum of the major diastereoisomer (10) from our work[82] is identical to that reported by Murahashi.[84]

Scheme 1.19. The mechanism of the addition of lithiated sulfoxide (1b) to isoquinoline nitrone (9) in the presence of quinidine.



Scheme 1.20. Reaction of *(R)*-(1b) with isoquinoline (9) by using quinidine as an auxiliary in THF at -78° C.



a: R_1=R_2=MeO

b: R_1=R_2=H

c: R_1=$PhCH_2O$ R_2=MeO

d: R_1=MeO R_2=$PhCH_2O$

e: R_1R_2=-OCH_2O-

Table 1.3. Reaction of *(R)*-(1b) with isoquinoline (9) in THF at -78° C in the presence of quinidine.

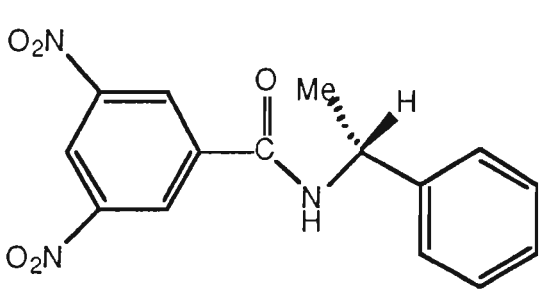
nitrone	yield (%)	diastereoisomer ratio of (10):(11)	m.p. of pure enantiomer (10), °C	$[\alpha]_D^*$ of (10)
(9a)	68	92:8	154.0-155.0	+106.6
(9b)	78	89:11	147.0-148.0	+89.5
(9c)	58	92:8	153.5-154.5	+68.7
(9d)	60	94:6	131.0-131.5	+94.9
(9e)	81	88:12	83.0-83.5	+90.5

* solvent $CHCl_3$

Pyne and others have shown that a much improved diastereoselection can be achieved when sterically hindered versions of *p*-tolyl sulfoxides are employed.[40] Unfortunately these sulfoxides are not readily prepared in high enantiomeric purity and therefore their use in asymmetric synthesis has been limited.[41] We have developed a convenient method for the synthesis of (+)-*(R)* methyl 2-methoxy-1-naphthyl sulfoxide in high enantiomeric purity and examined its addition reaction to a C-aryl *N*-methyl nitrone.

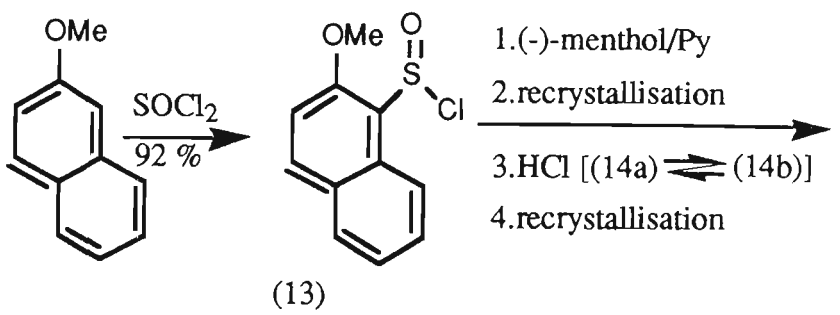
In 1985, Bell[42] reported a convenient synthesis of 2-methoxy-1-naphthalenesulfinyl chloride (13) from the chlorosulfination of 2-methoxynaphthalene with thionyl chloride. We have found that (13) can be converted to a mixture (*ca* 1:1)) of (-)-*(S)*-(14a) and (+)-*(R)*-(14b)

menthyl 2-methoxy-1-naphthalenesulfinates. The less soluble diastereoisomer, (-)-*(S)*-(14a) was obtained diastereomerically pure by selective crystallisation from acetone. Diastereomerically pure (-)-*(S)*-(14a) was obtained in 73% overall yield by successive treatment of the mother liquors with a few drops of concentrated hydrochloric acid (to effect epimerization at sulfur of (14b)) and further recrystallization from acetone according to the method developed by Solladie (Scheme 1.21).[85] The relative and absolute stereochemistry of (14a) was determined by a single crystal X-ray structural determination.[86b] The absolute stereochemistry of (14a) was evident from the sign of its optical rotation ($[\alpha]_D^{26}$ -183 (c 1.2, $CHCl_3$)) when compared that of (-)-*(S)*- methyl *p*-tolyl sulfinate. Treatment of (14a) with methylmagnesium iodide in ether/benzene at room temperature gave (+)-*(R)* methyl 2-methoxy-1-naphthyl sulfoxide (15) in 76 % yield.[86a] The enantiomeric purity of (15) was determined to be 98% from ^1H NMR chiral shift studies using (-)-*(R)*-*N*-(3,5-dinitrobenzoyl)-α-phenylethylamine (12) as a chiral shift reagent.[87] To determine the enantiomeric purity of (15) we mixed it with one equivalent of chiral reagent (12) in a NMR tube. In the ^1H NMR spectrum the methoxy groups for both enantiomers of the sulfoxide were evident at δ 3.983 and δ 3.974 for the major and minor enantiomers respectively (Fig 1.5).

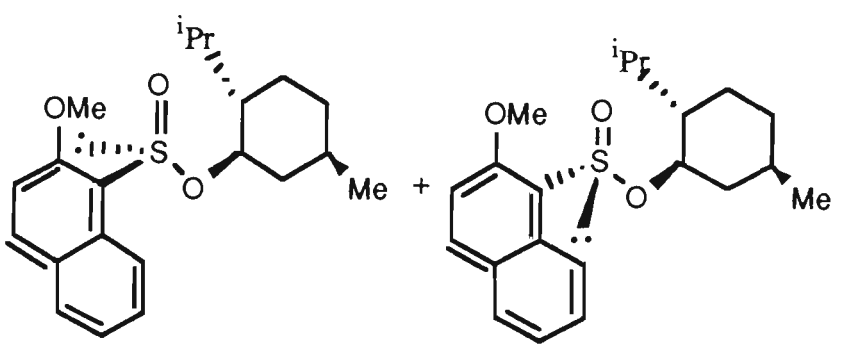


(12)

Scheme 1.21.

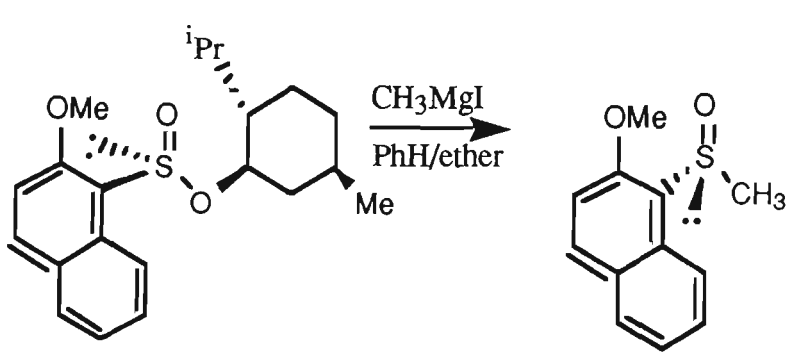


(13)



(-)-(S)-(14a) (+)-(R)-(14b)

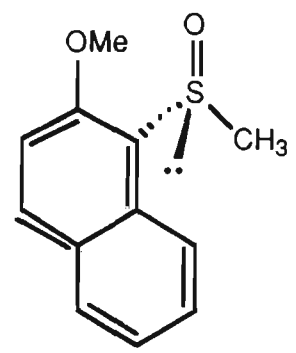
yield:73 %
m.p. 103° C
$[\alpha]_D^{26}$ -183 (c 1.2, $CHCl_3$)



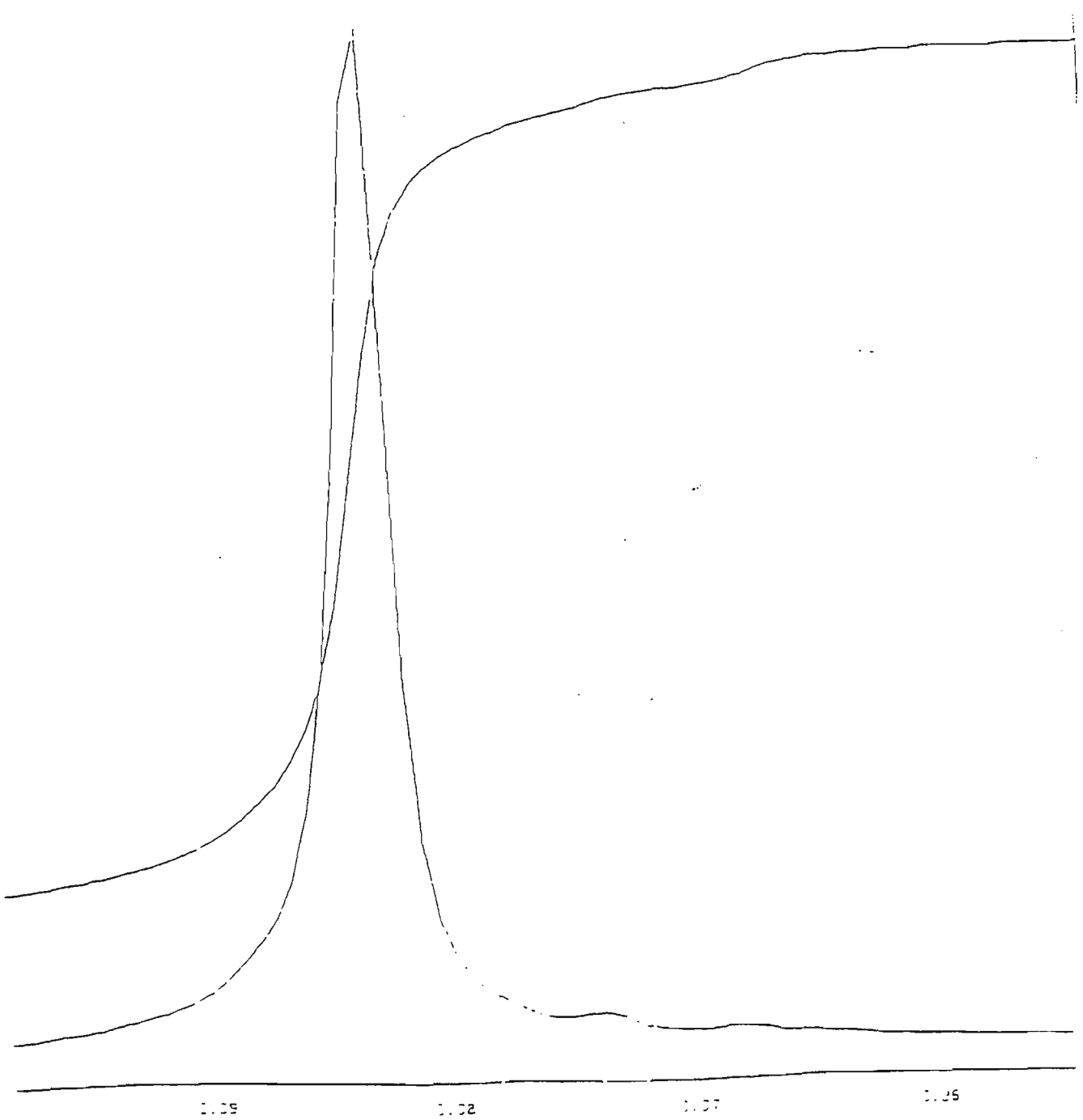
(-)-(S)-(14a) (+)-(R)-(15)

yield: 76 %
m.p. 102-3 °C
$[\alpha]_D^{22}$ +107 (c, 0.1, $CHCl_3$)
e.e. 98 %

Figure1.5. ^1H NMR spectrum ($CDCl_3$) of methyl 2-methoxy-1-naphthyl sulfoxide (15) with the chiral shift reagent (12).

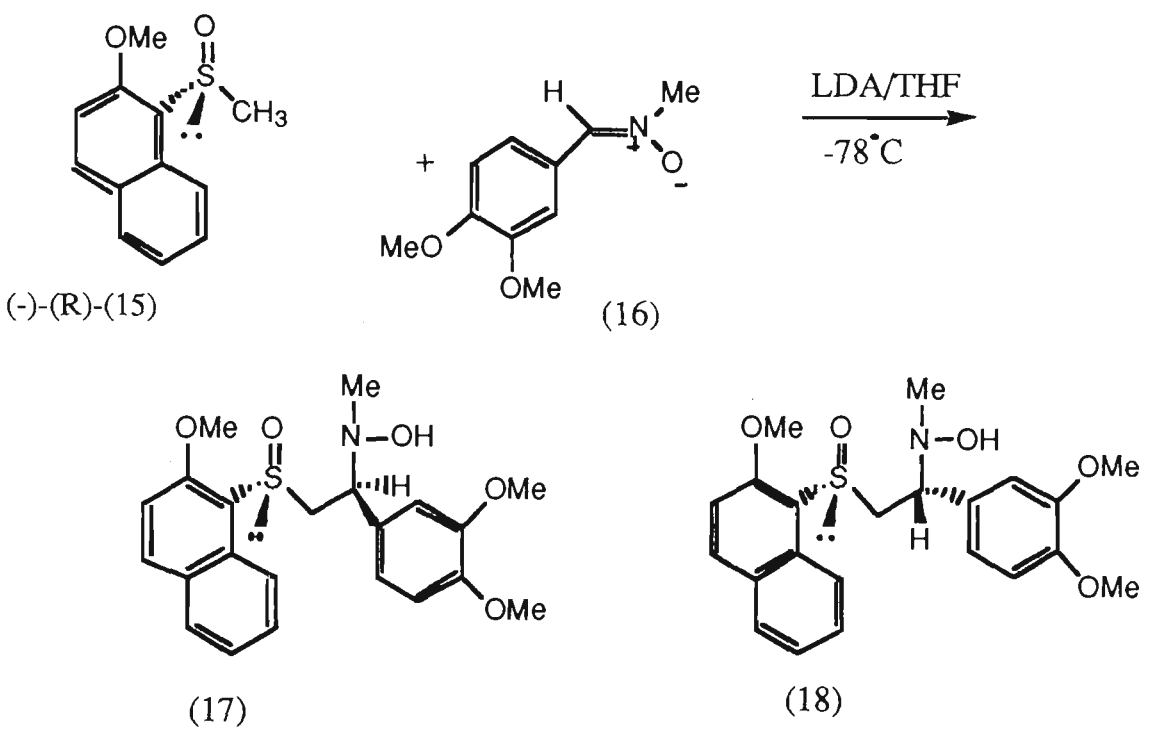


(+)-(R)-(15)



The addition of the lithium derivative of sulfoxide (+)-*(R)*-(15) to the nitrone (16) at -78° C gave a mixture of the hydroxylamines (17) and (18) in 63 % yield with a diastereoselectivity of (75:25) after purification by column chromatography (Scheme 1.22). While the diastereoselectivity was slightly better than that for the addition of lithiated methyl phenyl sulfoxide (1a) to PhCH=N(O)Me, it was still only modest and alternative methods were sought for the synthesis of β-amino sulfoxides.

Scheme 1.22.



d.r.=75:25

yield=63 %

In conclusion, nitrones offer enhanced reactivity over imines towards 1,2-addition of lithiated sulfoxides and even the dialkyl substituted nitrone (4f) gave products in good yield. By introducing a bulky group such as the 2-methoxy-1-naphthyl into the sulfoxide the diastereoselectivity was increased, but only marginally.

Experimental

General Procedures

(a) Melting Points (m.p.)

Melting points were determined on a Reichert hot stage apparatus and are uncorrected.

(b) Infrared (IR) Spectra

Infrared Spectra were recorded on a Bio Rad Fourier Transform Infrared Spectrophotometer model FTS-7 as mulls in nujol unless otherwise stated.

(c) ^{1}H Nuclear Magnetic Resonance (NMR) Spectra

^{1}H NMR spectra were recorded on a JEOL FX 90Q Fourier Transform NMR Spectrometer operating at 90 MHz, or a Varian Unity 400 Fourier Transform NMR Spectrometer operating at 400 MHz. The spectra were measured in $CDCl_3$ unless otherwise stated, relative to tetramethylsilane (0.00 ppm). Each signal is described in terms of chemical shifts in ppm from tetramethylsilane, multiplicity, coupling constant (Hz), intensity and assignments in that order with the use of the following abbreviations: s, singlet: d doublet: t, triplet: q, quartet: and m, multiplet.

(d) ^{13}C Nuclear Magnetic Resonance (NMR) Spectra

^{13}C NMR spectra were recorded on a JEOL FX 90Q Fourier Transform NMR Spectrometer (22.5 MHz) or a Varian Unity 400 Fourier Transform NMR Spectrometer (100 MHz). The spectra were measured in $CDCl_3$ unless otherwise stated, relative to $CDCl_3$ (77.0 ppm).

(e) Mass Spectra (MS)

Low Resolution Mass were recorded on a Vacuum Generator VG 12-12 mass spectrometer

(f) Microanalyses were performed by the Australian National University Analytical Services Unit, Canberra or the Queensland University, Chemistry School, Queensland.

(g) Column Chromatography

The chromatography adsorbent used was silica gel (0.063-0.2 mm, Merck) unless otherwise indicated.

(h) Optical rotations were recorded with a JASCO, DIP-370, Digital Polarimeter.

(i) Tetrahyrofuran and ether were dried over sodium metal and distilled from a purple suspension of disodium benzophenone anion and stored under nitrogen. CH_2Cl_2, $CHCl_3$, and DMF were distilled from calcium hydride.

(j) Reactions involving n-BuLi, LDA, or sodium hydride were performed in glassware that had been oven-dried and cooled in a desiccator prior to use and under an atmosphere of dry nitrogen.

General procedure for the preparation of nitrones (4c) and (4e).

A solution was prepared from 1.15 g (0.05 mol) of sodium and 6.05 g (0.06 mol) of *anti*-benzaldoxime[81a] in 100 mL of absolute ethanol. To the magnetically stirred solution was added 0.053 mol of the appropriate alkyl halide in one portion and the reaction mixture was stirred at room temperature until the pH was below 7 as shown by a wet pH paper. The solvent was then evaporated and the residue was treated twice with 50 mL of chloroform. The inorganic material was removed by filtration and the combined filtrate was evaporated. The crude product was purified by crystallisation or column chromatography.

***C*-Phenyl *N*-methyl nitrone (4c).**

The crude product was purified by column chromatography (silica gel, MeOH/EtOAc 2:8) and then crystallised from DCM/hexane to give white crystals m.p. 84-86 °C (lit.[81b] 85-86 °C) in 75 % yield.

***C*-Phenyl *N*-benzyl nitrone (4e)**

The crude product was purified by crystallisation from ethanol, to give white crystals in 75 % yield, m.p. 102-103 °C, (lit.[81c] 102-103 °C).

General procedure for the preparation of nitrones, (4a), (4b), (4d) and (4f) and (16).[77a]

Equimolar amounts of the appropriate hydroxylamine and aldehyde were dissolved in the minimum amount of ethanol. The mixture was allowed to stand at room temperature overnight, filtered, and then

recrystallised from a suitable solvent or purified by column chromatography to afford the nitrone in 80-95 % yield.

C-Phenyl *N*-phenyl nitrone (4a)

Crystallisation from ethanol, gave nitrone (4a) as white crystals m.p. 114 °C (lit.[77a,b] 114-115° C) in 95 % yield.

C-2-Furanyl *N*-phenyl nitrone (4b)

Crystallisation from benzene/hexane, gave nitrone (4b) in 85 % yield, m.p. 81-82 °C as red crystals. ^{1}H NMR δ 8.23 (s, 1 H), 6.1-7.8 (m, 8 H). MS m/z 188.2 (100 %, M^+). Anal calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.50 %. Found: C, 70.62; H, 4.81; N 7.72 %.

C-Phenyl *N*-*t*-Bu nitrone (4d)

The residue was purified by column chromatography on silica gel with EtOAc/MeOH (10:1) as eluent. The product was obtained as fluffy crystals, m.p. 72 °C (lit.[77b] 72-74 °C), in 85 % yield.

C-Methyl *N*-*t*-Bu nitrone (4f).

Distillation of the residue at 56 °C/3mmHg (lit.[77c] 46 °C/1.4 mmHg) afforded a yellow liquid in 80 % yield.

_C_-3,4-Dimethoxyphenyl _N_-methyl nitrone (16).

Crystallisation from ethanol, gave nitrone (16) as white crystals m.p. 119-121 °C in 85 % yield. ^{1}H NMR δ 8.28 (s, 1 H), 6.6-7.8 (m, 3 H), 3.85(2xs, 6 H), 2.63 (s, 3H). MS m/z 195.2 (100 %, M^+). Anal calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.17 %. Found: C, 61.49; H, 6.75; N, 7.15 %.

.

6,7-Dimethoxy-3,4-dihydroisoquinoline _N_-oxide (9)

To a solution of SeO_2 (0.14 g, 1.3 mmol) and tetrahydroisoquinoline (5 g, 23.0 mmol) in methanol (50 mL) was added dropwise an aqueous 30 % hydrogen peroxide solution (8.6 g, 75.6 mmol) at 0° C under nitrogen. After addition was completed, stirring was continued at room temperature for 3 h. Excess hydrogen peroxide was then destroyed with sodium hydrogen sulfite (4 mL, 45 % w/v) and the methanol was evaporated under reduced pressure. The remaining aqueous solution was extracted with dichloromethane (4x100 mL). Column chromatography on alumina (eluent, $CHCl_3$/MeOH 9:1) gave nitrone (9) as a yellow crystalline solid in 91 % yield, m.p. 96.5 °C (lit.[76] 96.5 °C).

Reaction of (1a) with Nitrones (4):

A General Procedure:

Methyl phenyl sulfoxide (0.28 g, 2.0 mmol) in anhydrous tetrahydrofuran (5 mL) was added dropwise to a cooled (-78°C), stirred solution of LDA, prepared from diisopropylamine (0.58 mL, 4 mmol) and n-butyllithium (2.45 mL, 4 mmol of 1.6 M solution in hexane) in

THF (5 mL). The mixture was allowed to reach -20°C, and was then cooled again to -78°C, and treated with a solution of the nitrone (4) (2 mmol) in THF (15 mL). The mixture was stirred for 30 min. at -78°C and then quenched with saturated aqueous NH_4Cl. The mixture was warmed to room temperature and then extracted with DCM (2 x 20 mL). The combined extracts were washed with water, dried ($MgSO_4$) and then evaporated to dryness. The crude product was then purified by column chromatography on silica gel using ethyl acetate/hexane (1:1) as the eluent. The diastereoselection of these reactions was determined from ^1H NMR (400 MHz) spectroscopic analysis of the crude reaction product.

(*R$_S$,1*S**)-*N*-Phenyl-*N*-(1-phenyl-2-phenylsulfinyl)ethylhydroxylamine (5a).**

M.p. 162-163 °C. IR (nujol) 3502, 3320, 1030 cm^{-1}. ^1H NMR δ 7.68-7.05 (m, 12H), 6.7-6.5 (m, 3H), 5.18 (dd, J = 6.0, 10.8 Hz, 1H), 3.82 (dd, J = 10.8, 14 Hz, 1H), 3.20 (dd, J = 6, 14 Hz, 1H). ^{13}C NMR δ 153.3, 146.2, 143.8, 141.1, 130.2, 128.1, 126.3, 121.3, 118.6, 114.1, 110.4, 105.3, 60.2, 56.4. MS m/z 337 (100, M^+), 321, 229, 213, 195, 185, 135, 125. Anal calcd for $C_{20}H_{19}NO_2S$: C, 71.2; H, 6.32; N, 4.4%. Found: C, 71.4; H, 6.3; N, 4.4%.

(*R$_S$,1*R**)-*N*-Phenyl-*N*-(1-phenyl-2-phenylsulfinyl)ethylhydroxylamine (6a).**

^1H NMR (in part) δ 5.01 (dd, J=8.4, 12 Hz, 1H).

(*R$_S$,1*S**)-*N*-Phenyl-*N*-(1-(2'-furanyl)-2-phenylsulfinyl)ethylhydroxylamine (5b).**

M.p. 152-4 °C. IR (nujol) 3501, 3166, 1600, 1460, 1030 cm-1. ^1H NMR δ 7.8-7.15 (m, 8H), 6.82-6.23 (m, 5H), 6.2 (m, 1H), 5.14 (dd, J =

4.8, 10.0 Hz, 1H), 3.76 (dd, J = 10.0, 13.2 Hz, 1H). 3.25 (dd, J = 4.8, 13.2 Hz, 1H). ^{13}C NMR δ 149.6, 142.2, 141.3, 130.2, 128.5, 127.8, 123.5, 121.8, 116.4, 109.5, 108.5, 58.1, 56.4. MS(CI) m/z 312 ($M+H^+$) , 218, 185 (100), 125. Anal calcd for $C_{18}H_{17}NO_3S$: C, 66.0; H, 5.2; N, 4.3%. Found: C, 65.8; H, 5.4; N, 4.2%.

(R_S^*,1R^*)-*N*-Phenyl-*N*-(1-(2'-furanyl)-2-phenylsulfinyl)ethylhydroxylamine (6b).

^1H NMR (in part) δ 5.22 (dd, J = 6.7, 10.5 Hz,1H).

(R_S^*,1*S)-*N*-Methyl-*N*-(1-phenyl-2-phenylsulfinyl)ethylhydroxylamine (5c).**

Oil. IR (film) 3600-3200(br), 3300 (sharp), 1035 cm^{-1}. ^1H NMR δ 7.52 (d, J = 8.2 Hz, 2H), 7.27 (dd, J = 4, 6.4 Hz, 1H), 4.11 (dd, J = 6.8, 9.6 Hz, 1H), 3.72 (dd, J = 9.6, 13.6 Hz, 1H), 3.05 (dd, J = 6.8, 13.6 Hz, 1H), 2.55(s, 3H). ^{13}C NMR δ 141.2, 140.9, 140.6, 129.6, 128.3, 127.2, 126.6, 123.6, 65.0, 59.1, 33.8, 20.9. MS(CI) m/z 276 (100, $M+H^+$), 229 (32, $M+H^+$- NMeOH), 136 (75), 125 (100).

(R_S^*,1R^*)-*N*-Methyl-*N*-(1-phenyl-2-phenylsulfinyl)ethylhydroxylamine (6c).

^1H NMR (in part) δ 3.92 (dd J = 4, 6 Hz, 1H): 3.45 (dd, J = 4, 13 Hz, 1H), 3.25 (dd, J = 6, 13 Hz, 1H): 2.51(s, 3H).

(R_S^*,1S^*)-*N*-*tert*-Butyl-*N*-(1-phenyl-2-phenylsulfinyl)ethylhydroxylamine (5d).

M.p. 144-146 °C: IR (nujol) 3520, 3330, 1030 cm^{-1}. ^1H NMR δ 8.2 (m, 1H), 7.2-7.8 (m, 9H), 4.55 (dd, J = 4.0, 11 Hz, 1H), 3.58 (dd, J = 11, 13.2 Hz, 1H), 2.94 (dd, J = 4.0, 13.2 Hz, 1H), 0.981 (s, 9H). ^{13}C NMR δ 144.6, 130.5, 129.5, 128.5, 127.3, 126.9, 126, 125, 69.3, 63.7, 28.8, 26.8. MS(CI) m/z 318 (75, M+H^+), 302 (19), 262 (25). Anal calcd for $C_{18}H_{23}NO_2S$: C, 68.1; H, 7.3; N, 4.4%. Found: C, 68.2; H, 7.4; N, 4.4%.

(R_S^*,1R^*)-*N*-*tert*-Butyl-*N*-(1-phenyl-2-phenylsulfinyl)ethylhydroxylamine (6d).

^1H NMR (in part) δ 3.64 (dd, J = 10.8, 13.6 Hz, 1H), 3.01 (dd, J = 6.4, 13.6 Hz, 1H), 1.021 (s, 9H).

(R_S^*,1*S)-*N*-Benzyl-*N*(1-phenyl-2-phenylsulfinyl)ethylhydroxylamine (5e).**

M.p. 159-160 °C. IR (nujol), 3509, 3330, 2950, 1030cm^{-1}. ^1H NMR δ 7.2-7.8 (m, 15H) 4.36 (dd, J = 5.2, 8.4 Hz, 1H), 3.84 (d, J = 13.6 Hz, 1H), 3.68 (d, J = 13.6 Hz, 1H), 3.39 (dd, J = 5.2, 13.6 Hz, 1H), 3.32 (dd, J = 8.4, 13.6 Hz, 1H). MS(CI) m/z 352 (M+H^+, 20), 337 (75), 230 (50), 211 (100), 197 (60), 142 (100), 127 (100), 106 (80). Anal calcd for $C_{21}H_{21}NO_2S$: C, 71.8; H, 6.0; N, 4.0%. Found: C, 72.0; H, 6.3; N, 4.0%.

(R_S^*,1R^*)-*N*-Benzyl-*N*-(1-phenyl-2-phenylsulfinyl)ethylhydroxylamine (6e).

^{1}H NMR (in part) δ 4.26 (dd, J = 6.4, 10.4 Hz, 1H), 3.06 (dd, J = 6.4, 13.6 Hz, 1H).

(R_S^*,1S^*)-*N*-*tert*-butyl-*N*-(1-phenylsulfinyl)-2-propylhydroxylamine (5f) and (R_S^*,1R^*)(6f).

Oil. IR (nujol) 3700-3000 (br), 1630, 1050 cm^{-1}. ^{1}H NMR (on 1:1 mixture) δ 7.7 (m, 2H), 7.5 (m, 3H), 3.82-3.66 (m, 1H), 3.13 (dd, J = 10.0, 13.6 Hz, 0.5H), 3.06 (dd, J = 10.4, 14 Hz, 0.5H), 2.83 (dd, J = 6.4, 14 Hz, 0.5H), 2.73 (dd, J = 4, 13.6 Hz, 0.5H), 1.21 (s, 4.5H), 1.19 (s, 4.5H), 1.18 (d, J = 6.4 Hz, 1.5H). ^{13}C NMR (on a 60 : 40 mixture, the minor isomer is shown in brackets) δ 144.6 (144.7), 130.5 (130.3), 129.0 (128.9), 124.0 (123.9), 66.4 (64.4), 58.7 (59.3), 52.2 (50.0) 27.1 (26.8), 15.0(15.2). MS(CI) m/z 251 (50, M+H$^+$), 234 (100), 169 (80), 142 (100), 127 (60), 111 (90).

(R_S^*,1S^*)-1,2,3,4-Tetrahydro-2-hydroxy-6,7-dimethoxy-1-(phenylsulfinyl)isoquinoline (10).

M.p. 155-156 °C. IR (nujol) 3630-3150, 3400 (sharp), 1115, 1032 cm^{-1}. ^{1}H NMR (in part) δ 7.78 (dd, J = 2, 7.6 Hz, 1H), 7.45 - 7.65 (m, 4H), 6.63 (s, 1H), 6.47 (s, 1H), 4.45 (dd, J = 4.8, 6.0 Hz, 1H) 3.86 (s,3H), 3.79 (s, 3H), 3.53 (dd, J = 4.8, 14 Hz, 2H), 3.30 (dd, J = 6.0, 14 Hz, 1H), 3.2 (t, 2H), 3.12 (dd, J = 5.2, 8.8, 1H). ^{13}C NMR δ 148.3, 147.8, 144.9, 130.8, 128.1, 127.1, 126.1, 124.6, 111.4, 109.3, 64.8, 62.6, 56.2, 56.0, 52.1, 27.0. MS(CI) m/z 347 (25, M+H$^+$), 205 (30), 192

(29), 154 (100), 136 (100). Anal calcd for $C_{18}H_{21}NO_4S$: C, 62.2; H, 6.1; N, 4.0%. Found: C, 62.0; H, 6.2; N, 4.0%.

(R_S^*,1R^*)-1,2,3,4-Tetrahydro-2-hydroxy-6,7-dimethoxy-1-(phenylsulfinyl)isoquinoline (11).

^{1}H NMR (in part) δ 6.61 (s, 1H), 6.44 (s,1H), 4.41 (br, 1H), 3.84 (s, 3H), 3.78 (s, 3H).

Hydrogenolysis of (5a+6a) and (5b+6b) to (7a+8a) and (7b+8b) respectively.

A mixture of the hydroxylamines (5a) and (6a) (d.r.=87:13) or (5b) and (6b) (d.r.=79:21) (1.0 mmol), and 10% palladium on charcoal (237 mg, 2.0 mmol) in acetic acid (5 mL) was stirred vigorously under an atmosphere of hydrogen at room temperature for 60 h. The catalyst was then separated by filtration through celite and the filtrate was then evaporated under reduced pressure. The residue was dissolved in 1M HCl (10 mL) and the solution was washed with ether (5 mL). The aqueous layer was made basic with 8M NaOH and the solution was extracted with dichloromethane (3x5 mL). The combined organic extracts were dried (Na_2SO_4), filtered and then evaporated to dryness to give a mixture (7a) and (8a) (d.r.=83:17) or (7b) and (8b) (d.r.=79:21) in 65 and 70% yield respectively. The ^{1}H NMR spectra of the major diastereomeric products (7a) and (7b) were identical to the ^{1}H NMR spectra of the major diastereoisomeric products prepared from the reaction of lithiated sulfoxide (1a) and the imines (2a) and (2b) (Scheme 1.15).[28]

2-Methoxy-1-naphthylsulfinyl chloride[42]

Powdered 2-methoxynaphthalene (7.9 g, .05mol) was stirred at room temperature under a $CaCl_2$ guard tube during the addition of thionyl chloride (11.9 g, 0.1 mol) in one lot. After a few minutes the bright yellow solution began to evolve HCl and within 1 h had solidified to a yellow mass. Dry benzene (10 mL) was added and the mixture was heated to effect solution. Cooling to 5° C gave bright yellow crystals. The crystals were collected, washed with dry benzene (10 mL) and then pentane (10 mL), and dried under high vacuum (0.01 mm Hg). Yield 11.0 g (91.5 %), m.p. 118-120 °C (lit.[42] 118-120 °C).

(-)-*(S)*-*(l)*-Menthyl 2-methoxy-1-naphthalenesulfinate (14a).

To a stirred solution of (-)-menthol (0.17 mol, 26.4 g) in dry DCM (350 mL) at 0 °C was added a solution of 2-methoxynaphthylsulfinyl chloride (0.17 mol, 40.56 g) in DCM (100 mL) dropwise over 10 min. Pyridine (13.4g, 0.17 mol) was then added and the mixture was stirred at 0 °C for 2 h and then at room temperature overnight. The reaction mixture was then filtered and the clear solution was washed with 10% aqueous HCl (100 mL), dried ($MgSO_4$) and then the solvent was removed under reduced pressure. The residue was dissolved in acetone (10 mL) and allowed to crystallise at 5°C. The crystals were collected by vacuum filtration. To the mother liquor was added two drops of concentrated HCl and a second crop of crystals were collected after crystallisation at 5 °C. This process was repeated a further two times and gave (14a) in a combined yield of 73%, m.p. 103 °C. ^{1}H NMR δ 9.12 (dd, 1H, J_{ortho} 9.2, J_{meta} 1.6 Hz) 7.2-7.9 (m, 5 H), 4.01 (s, 3 H, OCH_3), 4.14 (m, 1 H), 0.68-1.00 (m, 9 H, $(\underline{CH_3})_2CH$, and $\underline{CH_3}$), 1.00-2.40 (m, 8 H). MS m/z, 359.50 (100 %, M^+). $[\alpha]_D^{26}$ -183 (c 1.2, $CHCl_3$). Anal. Calcd for

$C_{21}H_{28}O_3S$: C, 69.96; H, 7.83; S, 8.89 %. Found: C, 69.68; H, 7.82; S, 8.49 %.

(+)-*(R)* -Methyl 2-methoxy-1-naphthyl sulfoxide (15).

To a solution of (-)-*(S)*-menthyl 2-methoxy-1-naphthalenesulfinate (10.8 g, 30 mmol,) in dry benzene (120 mL) at room temperature under nitrogen was added dropwise, via syringe over 30 min. a solution of methylmagnesium iodide [prepared from magnesium (2 g) and methyl iodide (6.2 mL) in diethyl ether (70 mL)]. After the addition was complete, the reaction mixture was stirred at room temperature for 2 h and then quenched by the addition of saturated ammonium chloride solution (30 mL). The organic solvents were evaporated and the aqueous layer was extracted with hexane (50 mL) to remove menthol and then four times with chloroform (50 mL). The combined chloroform extract was dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, ethyl acetate). The second fraction was collected and evaporated to give 3.35 g (76 % yield) of compound (15) as white needles, m.p 102-103° C, $[\alpha]_D^{26}$ +106.58 (c 1.2, $CHCl_3$). MS m/z 221 (100 %, M+). ^1H NMR δ 9.12 (dd, 1H, J_{ortho} 9.2, J_{meta} 1.6 Hz), 7.2-7.9 (m, 5 H) 4.01 (s, 3 H, OCH_3), 2.5 (s, 3 H, CH_3). Anal calcd. for $C_{12}H_{12}SO_2$: C, 65.43; H, 5.49; S, 14.55 %. Found: C, 65.44; H, 5.47; S, 14.56 %.

(*R*)-*N*-Methyl-*N*-[1-(3,4-dimethoxyphenyl)-2-(2'-methoxy-1'-naphthylsulfinyl)]ethylhydroxylamine (17) and (18)

Methyl 2-methoxy-1-naphthyl sulfoxide (2.0 mmol, 0.44 g) in anhydrous tetrahyrofuran (5 mL) was added dropwise to a cooled

(-78° C), stirred solution of LDA. (prepared from diisopropyamine (4 mmol, 0.58 mL) and n-butyllithium (4 mmol, 2.45 mL of 1.6 M solution in hexane in THF (5 mL)). The mixture was allowed to reach -20°C, and was then cooled again to -78°C, and treated with a solution of the nitrone (16) (2 mmol) in THF (15 mL). The mixture was stirred for 30 min. at -78°C and then quenched with saturated aqueous NH_4Cl. The mixture was warmed to room temperature and then extracted with DCM (2 x 20 mL). The combined extracts were washed with water, dried ($MgSO_4$) and then evaporated to dryness to give a thick oil in 78 % yield. The diastereomeric ratio of the crude product was determined by 400 MHz ^1H NMR spectroscopic analysis. The crude product was then purified by column chromatography on silica gel using ethyl acetate/hexane (1:1) as the eluent to give white crystals (63 %).

(*Rs,1S*) -*N*-Methyl-*N*-[1(3,4-dimethoxyphenyl)-2-(2'-methoxy-1'-naphthylsulfinyl)]ethylhydroxylamine (17)

M.p. 132-133 °C. IR (nujol) 3502, 3320, 1030 cm^{-1}. ^1H NMR δ 8.99-6.5 (m, 9H), 4.88 (dd, J = 4.8, 10.8 Hz, 1H), 3.88(3xs, 9 H), 3.22 (dd, J = 10.8, 14 Hz, 1H), 3.18 (dd, J = 4.8, 14 Hz, 1H), 2.65 (s, 3H). ^{13}C NMR δ 183.3, 178.23, 170.54, 168.65, 160.24, 155.4, 148.3, 144.8, 141.6, 132.2, 126.8, 126.3, 124.5, 119.7, 117.3, 112.6, 60.2, 58.4, 57,8. 56.2, 55.6, 46.4, 34.7. MS m/z 367 (100 %, M^+), 321, 229, 213, 195, 185, 135, 125. Anal calcd for $C_{22}H_{25}NO_5$: C, 68.93; H, 6.57; N, 3,65 %. Found: C, 68.86; H, 6.51; N, 3.69 %.

(*Rs,1R*) -*N*-Methyl-*N*-[1(3,4-dimethoxyphenyl)-2-(2'-methoxy-1'-naphthylsulfinyl)]ethylhydroxylamine (18)

^1H NMR (in part) δ 4.68 (dd, J=6, 10.8 Hz, 1H).

(-)-*(R)*-*N*-(3,5-Dinitrobenzoyl)-α-phenylethylamine (12)

To a solution of (+)-1-phenylethylamine (0.05 mol, 5.9 g) in $CHCl_3$ (100 mL) was added 3,5-dinitrobenzoyl chloride (0.05 mol, 11.4g) in $CHCl_3$(100 mL) dropwise over 20 min. at room temperature. Pyridine (0.05 mol, 3.94 g) was then added in one portion. After stirring at room temperature for 1 h the solvent was evaporated at reduced pressure and the residue was crystallised with ethanol/hexane to give (12) in 90 % yield as a white crystals, $[\alpha]_D^{26}$ -17.5, (c 1.1, acetone), m.p.159 °C (lit.[87] 159-160 °C).

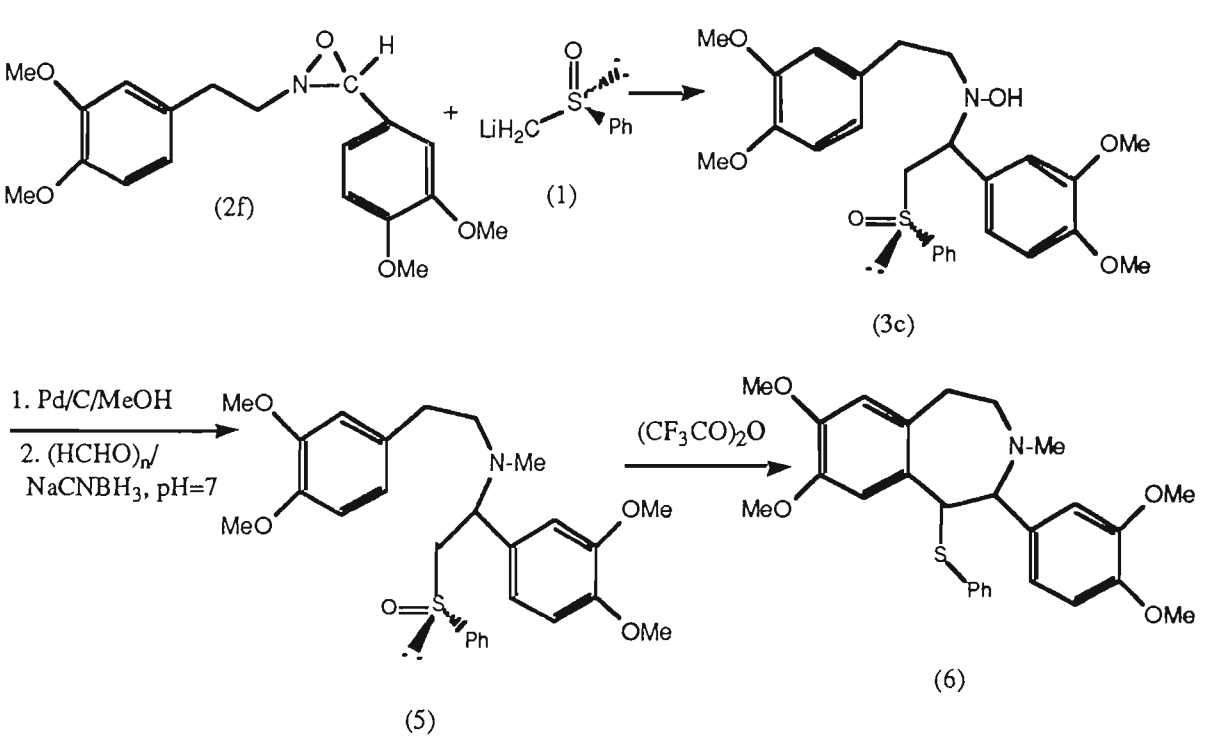
CHAPTER 2

Chapter 2

Diastereoselective Addition of Lithiated Methyl Phenyl Sulfoxide to Oxaziridines

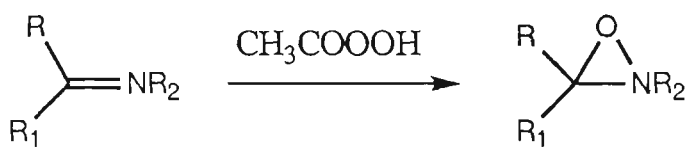
As was described in the Introduction, oxaziridines can in principle be used for the synthesis of β-hydroxylamino sulfoxides (3c), which would be very valuable starting materials for the synthesis of the benzazepine ring system (6), via Pummerer cyclization as outline in Scheme 2.1. Like lithiated sulfoxide (1), oxaziridine (2f) is also chiral and under normal conditions the reaction of lithiated sulfoxide (1) with (2f) would be expected to give a 1:1 mixture of the diastereoisomers of (3c). However under conditions that may allow for kinetic resolution (i.e. in which the stoichiometric ratio of (2f):(1) is >2:1), then these reactions may be diastereoselective.

Scheme 2.1. Addition of lithiated sulfoxide (1) to oxaziridine (2f).



To prepare the β-amino sulfoxide (5) we required an efficient method for the synthesis of a number of oxaziridines.[88] These compounds have been previously prepared from the oxidation of imines with peroxyacetic acid as shown in Table 2.1.[39]

Table 2.1 Oxidation of imines with peroxyacetic acid.



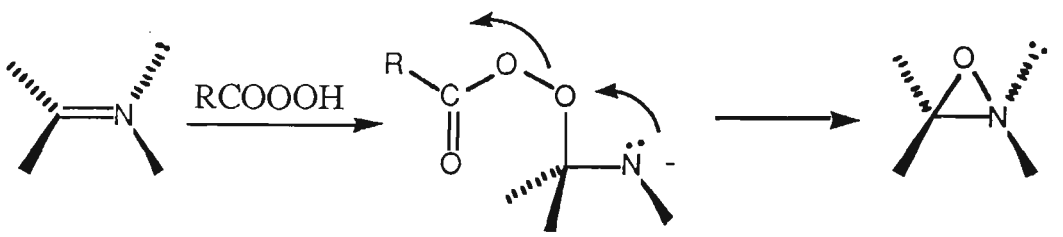
R	R1	R2	yield %
H	H	*t*-Bu	46
H	H	*t*-Oct	60
Ph	H	*t*-Bu	71
p-O2NC6H4	H	*i*-Pr	60

To date there have been in excess of two hundred examples of reactions showing exclusive oxaziridine formation. During these studies over the past twenty years[89] into the oxidation reaction of imines, oxaziridine have been identified as the normal products from peroxy acid oxidation of imines. However, in a minority of cases, nitrones (imine *N*-oxides) were found to be major products.

The accepted mechanism for the synthesis of oxaziridines from the reaction of peroxy acid and imines proceeds by a two-step

process (Scheme 2.2).[89] The initial step involves nucleophilic attack of the peroxy acid at the imino group followed by an intramolecular nucleophilic ring closure step. Nucleophilic attack of the peroxy acid to yield oxaziridines is particularly favoured with *C*-alkyl substituted imines.

Scheme 2.2. Mechanism for the formation of oxaziridines from imines.



When nucleophilic attack is hindered by non bonding interactions at the imino carbon then electrophilic attack at the more accessible imino nitrogen atom will occur to yield nitrones.[89]

Oxaziridines have been previously prepared from the oxidation of imines with peroxyacetic acid which was prepared from 90 % hydrogen peroxide[39] or 3-chloroperoxybenzoic acid (3-CPBA).[90,91] The latter reagent is expensive and in our hands gave mixtures of the corresponding oxaziridine and the nitrone.

More recently buffered Oxone® (potassium peroxymonosulfate)[92] in a two phase system of toluene and aqueous $KHCO_3$ or K_2CO_3 has been reported as an effective and inexpensive substitute for 3-CPBA for the oxidation of 2-sulfonyl- and 2-sulfamylimines to their corresponding oxaziridines[92] as shown in Scheme 2.3 and Table 2.2.

Scheme 2.2. Oxidation of 2-sulfonyl- and 2-sulfamylimines to their corresponding oxaziridines.

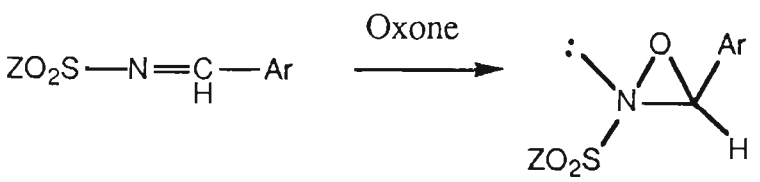


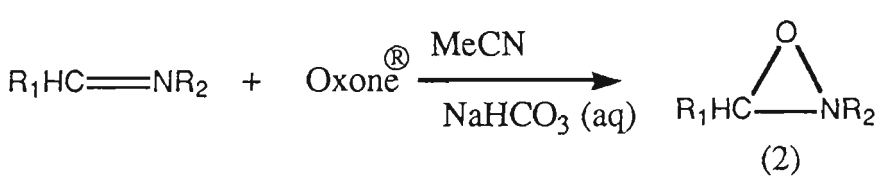
Table 2.2. Biphasic preparation of 2-sulfonyl and 2-sulfamyloxaziridines in toluene using buffered oxone.

entry	Z	Ar	oxone, equiv (buffer)	time (h)	yield (%)
1	Ph	Ph	1.2 ($KHCO_3$)	2	>95
2	Ph	Ph	1.2 (K_2CO_3)	15 min.	>95
3	Ph	2-O_2NPh	1.2 ($KHCO_3$)	2	>95
4	Ph	2-O_2NPh	1.2 (K_2CO_3)	15 min.	>95
5	Ph	3-O_2NPh	1.2 (K_2CO_3)	15 min.	>95
6	Ph	4-O_2NPh	1.2 (K_2CO_3)	15 min.	>95
7	Ph	2-Cl,5-O_2NPh	1.2 (K_2CO_3)	15 min.	>95
8	$(PhCH_2)_2N$	2-Cl,5-O_2NPh	3.0 (K_2CO_3)	15 min.	>95
9	$(PhCH_2)_2N$	2-Cl,5-O_2NPh	6.0 (K_2CO_3)	2	70

In our hands this procedure proved extremely sluggish for the oxidation of *N*-alkyl imines and completely ineffective for the

oxidation of diaryl imines ($Ar_1CH=NAr_2$). We have found that, by conducting these reactions in aqueous $NaHCO_3$ /acetonitrile or acetone, then the oxidation is extremely rapid (30 min. in acetonitrile and 15 min. in acetone) and almost quantitative (Table 2.3).[88] Furthermore, in the case of dialkyl or monoaryl imines, only the oxaziridine product and none of the corresponding nitrone could be detected from ^1H NMR spectroscopic analysis. In the case of diaryl imines (Table 2.3, entries 9 and 10) only the corresponding nitrones were formed under the above reaction conditions. In all cases, the crude product was judged to be of 95% purity based on ^1H NMR spectral and TLC analysis. The yields of oxaziridine products (Scheme 2.3) and (Table 2.3) were high and essentially the same when either acetone or acetonitrile was employed as solvent.[88]

Scheme 2.3. Oxidation of imine to compound (2) with Oxone.



(2)

a; R_1=Ph R_2=Me

b; R_1=Ph R_2=*i*-Pr

c; R_1=Ph R_2=*t*-Bu

d; R_1=3-HOC_6H_4 R_2=*t*-Bu

e; R_1=4-$MeOC_6H_4$ R_2=*t*-Bu

f; R_1=3,4-$(MeO)_2C_6H_3$ R_2=3,4-$(MeO)_2C_6H_3CH_2CH_2$

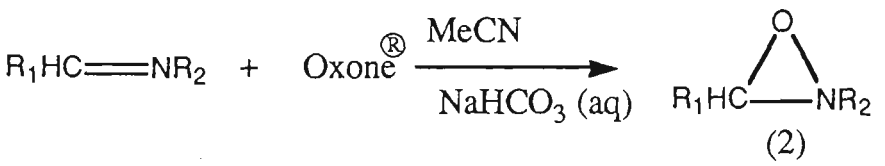
g; R_1=*t*-Bu R_2=*t*-Bu

h; R_1=*i*-Pr R_2=*t*-Bu

i; R_1=Ph R_2=Ph

j; R_1=2-furanyl R_2=Ph

Table 2.3. Oxidation of imine to compound (2) with Oxone.[88]



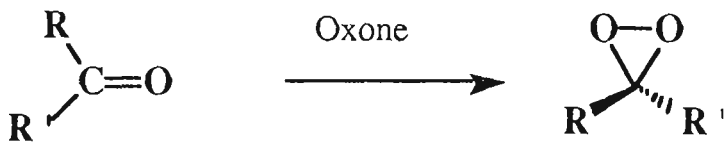
(2)

Entry	R1	R2	yield %	^{1}H NMR ($CDCl_3$)
1	Ph	Me	96	4.43 (s, 1H)
2	Ph	*i*-Pr	96	4.48 (s, 1H)
3	Ph	*t*-Bu	98	4.74 (s, 1H)
4	3-HOC_6H_4	*t*-Bu	98	4.67 (s, 1H)
5	4-$MeOC_6H_4$	*t*-Bu	98	4.62 (s, 1H)
6	3,4-$(MeO)_2C_6H_3$	3,4-$(MeO)_2$ $C_6H_3CH_2CH_2$-	95	4.23 (s, 1H)
7	*t*-Bu	*t*-Bu	95	3.62 (s, 1H)
8	*i*-Pr	*t*-Bu	95	3.69 (s, 1H)
9	Ph	Ph	98	8.45 (s, 1H) , nitrone (m.p. 112-113 °C)[a]
10	2-furanyl	Ph	98	8.23 (s, 1H) nitrone (m.p. 78-80 °C)

[a] Literature 114° C; Wheeler, O. H.; Gore, P. H. *J. Am. Chem. Soc.* **1956**, *78*, 3363.

88. S.G. Pyne, and A.R. Hajipour, *J. Chem. Research(S)*, 388 (1992).

Oxone in acetone gives dimethyldioxirane which can be isolated by distillation[91] as shown below.



a, R=R'=H

b, R=R'=CF_3

c, R=CF_3, R'=CF_2Cl

d, R=R'=CH_3

e, R=CH_3, R'=CH_3CH_2

f, R=CH_3, R'=$CH_3CH_2CH_2$

g, R=CH_3, R'=$CH_3CH_2CH_2CH_2$

h, R=R'=CH_3CH_2

This reagent has been used to convert imines to nitrones.[89] It is very likely that in our reactions, with acetone as solvent, that dimethyldioxirane is formed *in situ* and this is the oxidising species. The preference for the formation of oxaziridines over nitrones in this present study is not clear. When acetonitrile is used as a solvent it is possible that the active oxidising species is a peroxyimidic acid (MeC(OOH)=NH). Such a species is formed from the reaction of acetonitrile and hydrogen peroxide and has been demonstrated to be a useful reagent for the epoxidation of alkenes.[94]

Figure 2.1 shows a copy of the ^1H NMR spectrum of the crude reaction mixture of (2g) from the reaction of *t*-Bu-CH=N-*t*-Bu with Oxone at room temperature in acetone. As was mentioned before in

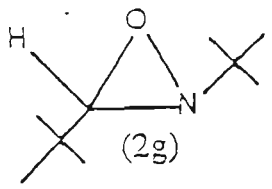
this oxidation (alkyl alkyl imine) only the oxaziridine is produced and none of the nitrone can be seen, the CH proton is clearly evident as a singlet at δ 3.62 (1 H) and the CH_3 and the *t*-Bu groups are clearly evident as singlets at δ 1.08 (9H) and δ 0.92 (9H), no protons for the nitrone can be seen in this spectrum.

Figure 2.2 shows a copy of the ^1H NMR spectrum of the crude reaction mixture of (2f) from the oxidation of *N*-(3,4-dimethoxyphenyethyl)-3',4'-dimethoxybenzylidene (alkyl aryl imine) with Oxone in acetone. Here again only the oxaziridine is produced and no nitrone can be seen. The CH of the oxaziridine is clearly evident at δ 4.23, the OMe groups are seen at δ 3.86 (s, 9H) and δ 3.75 (s, 3H). No nitrone can be seen in this ^1H NMR spectrum.

Figure 2.3 shows a copy of the ^1H NMR spectrum of the crude reaction mixture from the oxidation of Ph-CH=N-Ph (diaryl imine) with Oxone. As was mention before in this kind of reaction (diaryl imine) only the nitrone is produced and no oxaziridine can be detected. The signal due to the proton of the nitrone is clearly evident at δ 8.45 and no proton of the oxaziridine can be seen in the crude reaction mixture.

In conclusion, we have developed an efficient, rapid and inexpensive method for the synthesis of oxaziridines and diaryl nitrones that is superior to previously reported methods in terms of yields and purity of products.

Figure 2.1. ^1H NMR ($CDCl_3$) spectrum of the crude oxaziridine (2g).



(2g)

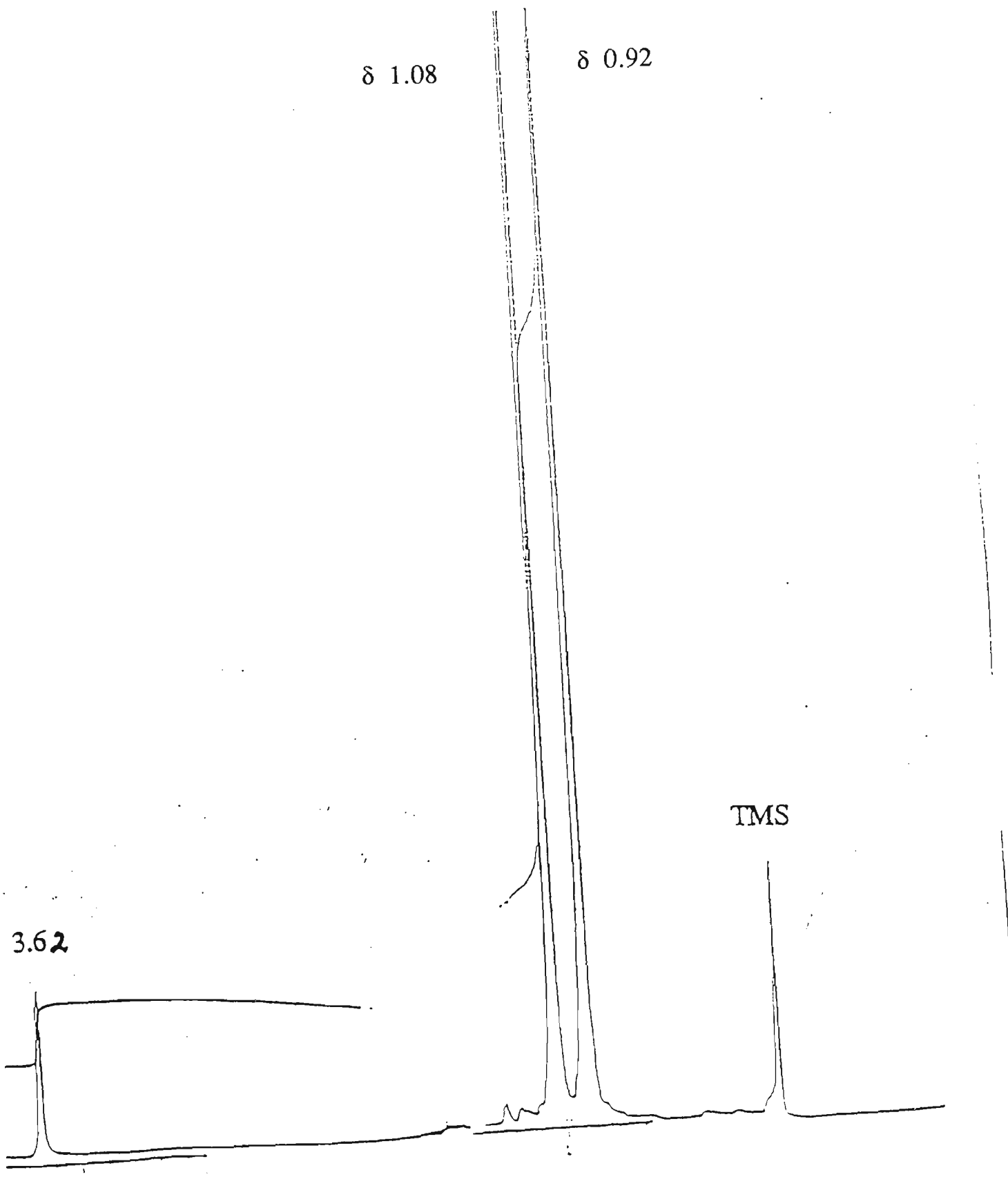
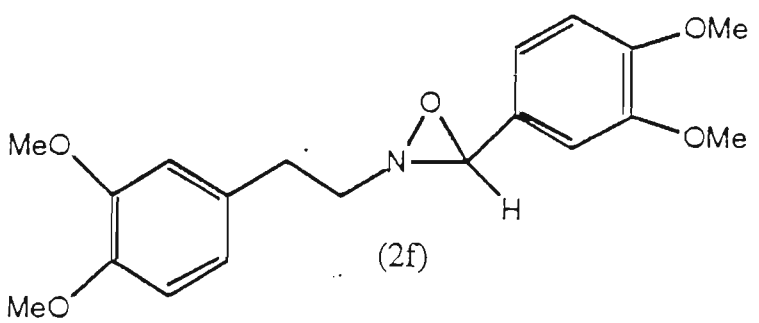


Figure 2.2. ^{1}H NMR ($CDCl_3$) spectrum of the crude oxaziridine (2f).



(2f)

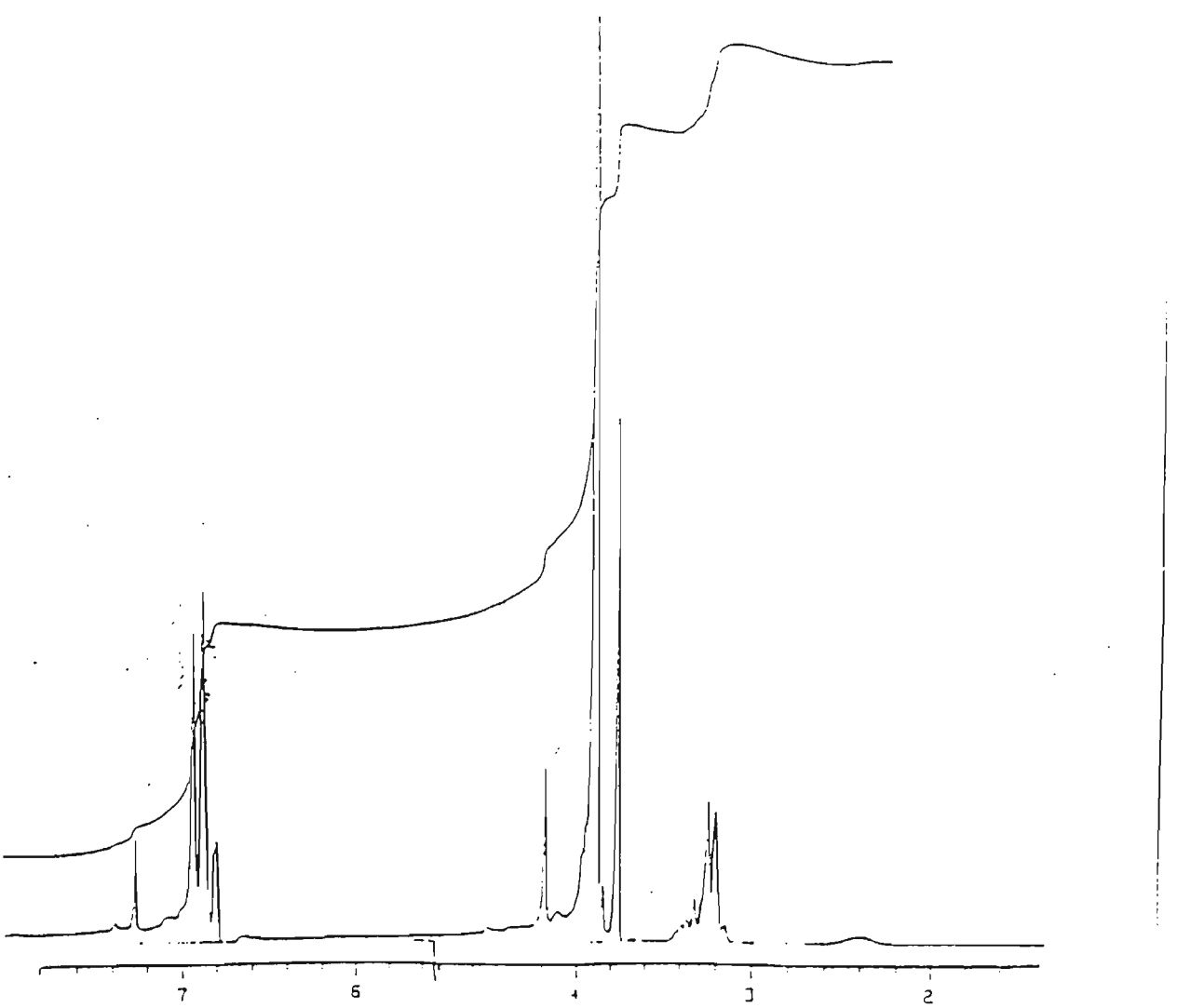
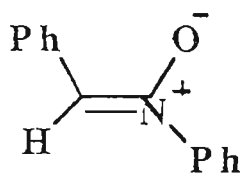
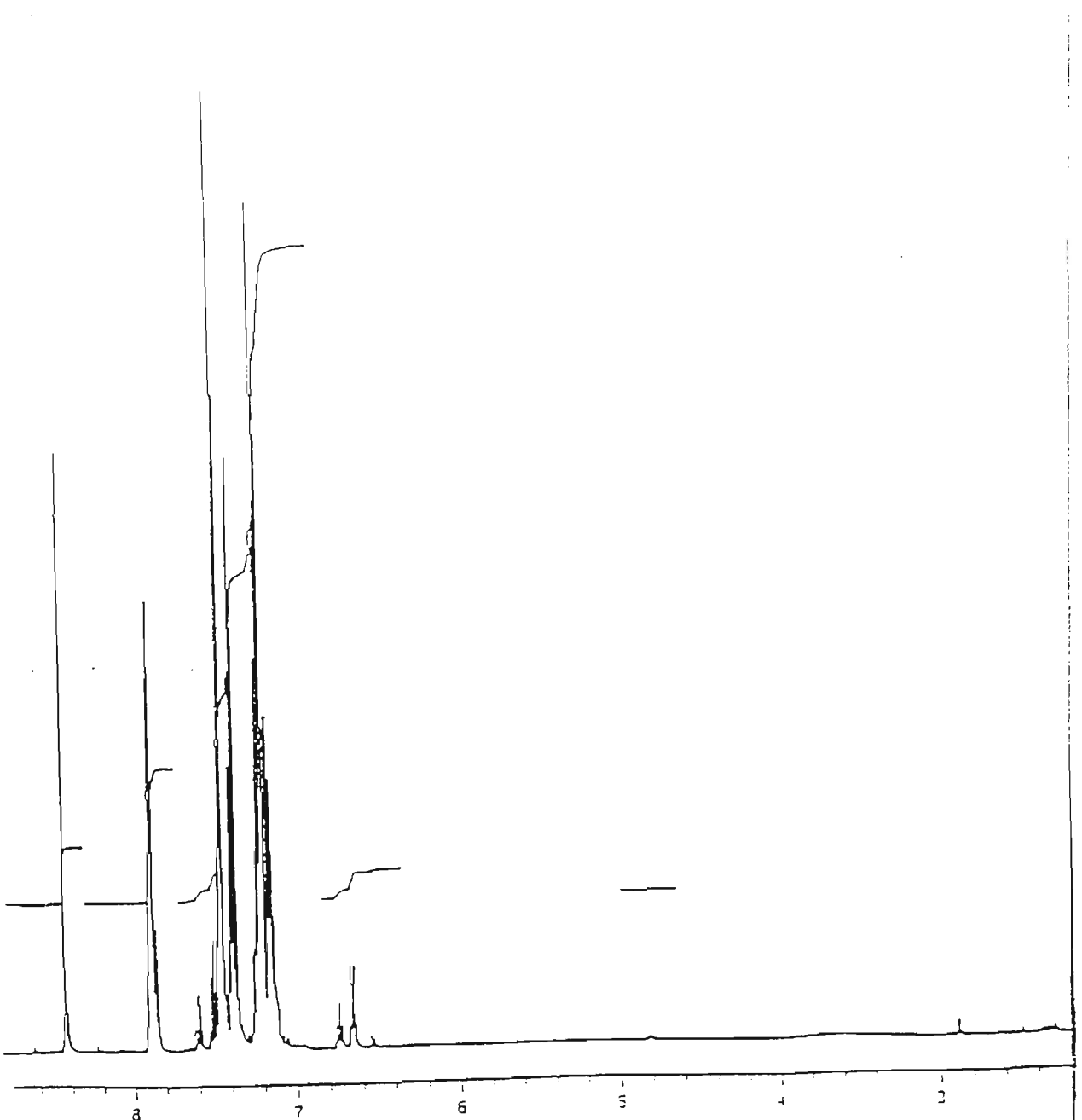


Figure 2.3. ^1H NMR ($CDCl_3$) spectrum of the crude nitrone from the oxidation of PhCH=NPh with oxone in acetone.

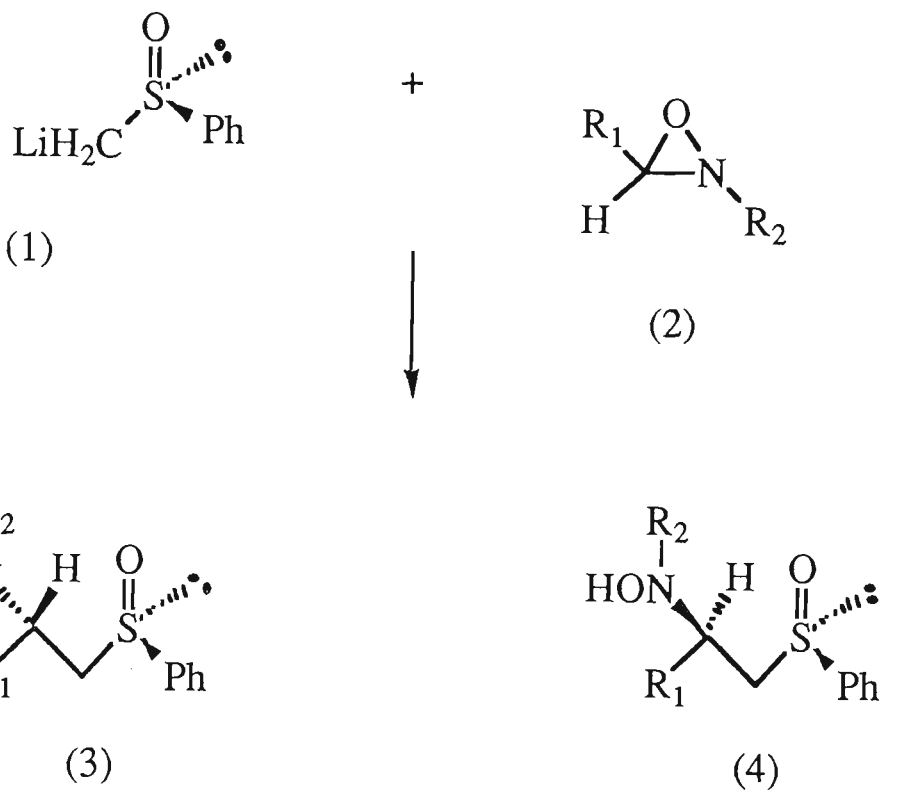




Diastereoselective additions of lithiated methyl phenyl sulfoxide (1) to oxaziridines (2)

Addition of a solution of the racemic oxaziridine (2) (2 equiv.) to a solution of 1 equiv. of lithiated racemic methyl phenyl sulfoxide (1) at -78° C in THF for 1 h afforded a mixture of the racemic diastereomeric β-hydroxylamine sulfoxides (3) and (4), in good yields, after purification by simple column chromatography (Table 2.4). The diastereoselectivity of the products, as determined by ^1H NMR spectral analysis on the crude reaction products, ranged from 67:33-75:25 as shown in Scheme 2.3 and Table 2.4. While the products (3) and (4) are racemic only one enantiomer is shown to simplify the discussion. The major and minor diastereoisomers, (3a) and (4a), were identical to those obtained from the addition of (1a) to PhCH=N(O)Me that was reported in Chapter 1. Hence we assume that (3c) and (3f) prepared according to Scheme 2.3 also have the relative $(1S^*, Rs^*)$ stereochemistry. We used two equivalents of oxaziridine because like lithiated methyl phenyl sulfoxide (1), oxaziridine (2) is also chiral and under normal conditions the reaction of lithiated (1) and (2) would be expected to give a 1:1 mixture of the diastereoisomers (3) and (4). However under the above conditions some amount of kinetic resolution has occurred and these reactions were diastereoselective, although the diastereoselectivity was only modest.

Scheme 2.3. Addition of lithiated methyl phenyl sulfoxide (1) to oxaziridines (2a), (2c) and (2f).



(a): R_1=Ph R_2=Me

(c): R_1=Ph R_2=*t*-Bu

(f):

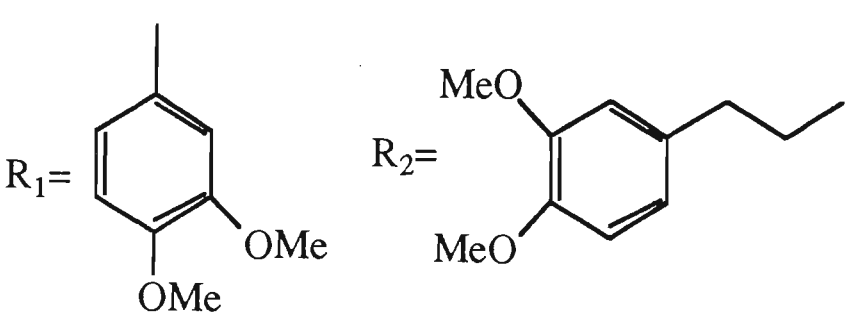
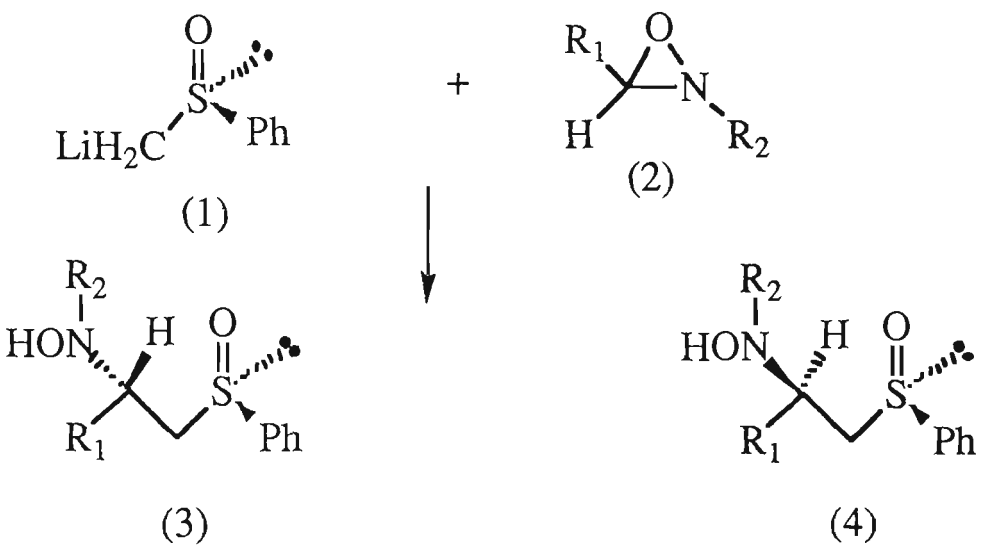


Table 2.4. Addition of lithiated methyl phenyl sulfoxide (1) to oxaziridines (2a), (2c) and (2f) at -78° C in THF.



entry	R_1	R_2	yield (%) (3)+(4)	diastereo selection (3):(4)
1	Ph	Me	83 %	67:33
2	Ph	*t*-Bu	63 %	75:25
3	Ar-	Ar-CH_2-CH_2-	61 %	68:32

Ar=

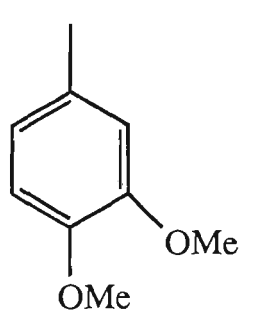
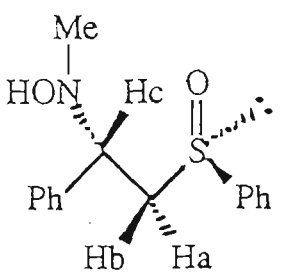


Figure 2.4 shows a copy of the ^1H NMR spectrum of the crude reaction mixture resulting from the reaction of lithiated sulfoxide (1) and oxaziridine (2a). This ^1H NMR spectrum shows the methyl group of both diastereoisomers (3a) and (4a) clearly as singlets at δ 2.55 and δ 2.51 . Integration of these signals indicated that the diastereoisomer ratio of the major and minor diastereoisomers, (3a) and (4a), was 67:33.

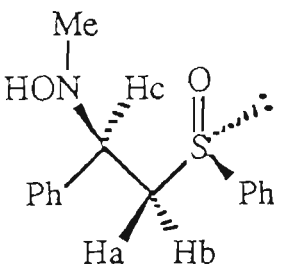
Figure 2.5 shows the copy of the ^1H NMR spectrum of the crude reaction mixture from the reaction of (1) and (2f). The protons Hc of both diastereoisomers, (3f) and (4f), are clearly shown as a doublet of doublets at δ 5.32 (J=2.8, 10 Hz) and δ 5.14 (J=2, 10 Hz) respectively. Integration of these signals indicated that the diastereoisomer ratio of the major to minor diastereoisomers was 68:32.

In conclusion, the diastereoselectivities of the reactions of (1) and oxaziridines (2) were in general similar to those of the analogous reactions of (1) with imines and nitrones.[28,82] However in contrast to the addition of lithiated sulfoxide (1) to aryl alkyl imines the yield of addition products from the reaction of lithiated sulfoxide (1) to aryl alkyl oxaziridines is good to excellent. The diastereoselectivity, however, is only modest. Clearly some kind of kinetic resolution is operating in these addition reactions, however the extent of the resolution is not sufficiently high for our synthetic purposes.

Figure 2.4. ^1H NMR ($CDCl_3$) spectrum of the crude reaction mixture of (3a) and (4a) from the reaction of lithiated sulfoxide (1) and oxaziridine (2a), showing the *N*-methyl resonances.



(3a)



(4a)

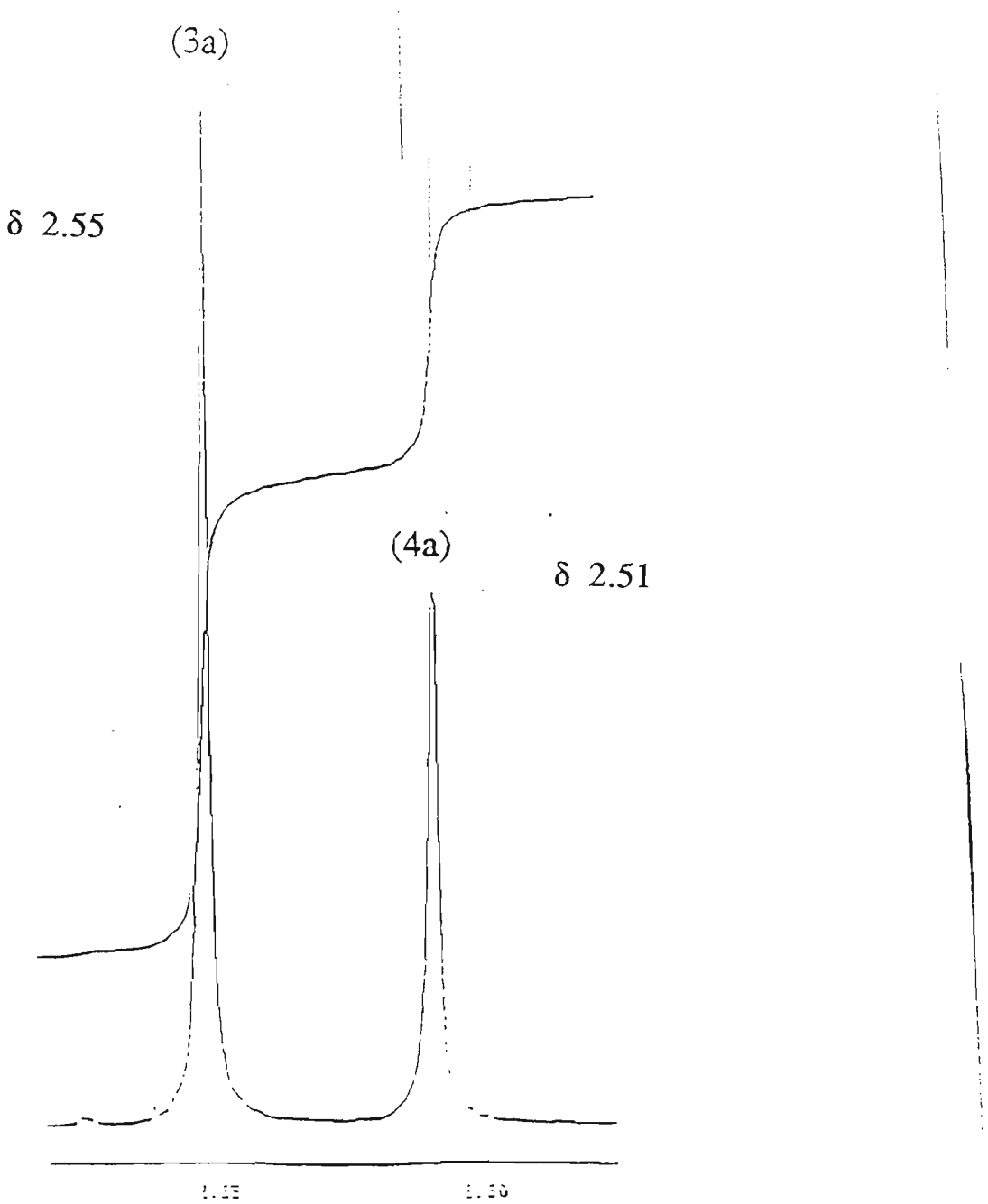
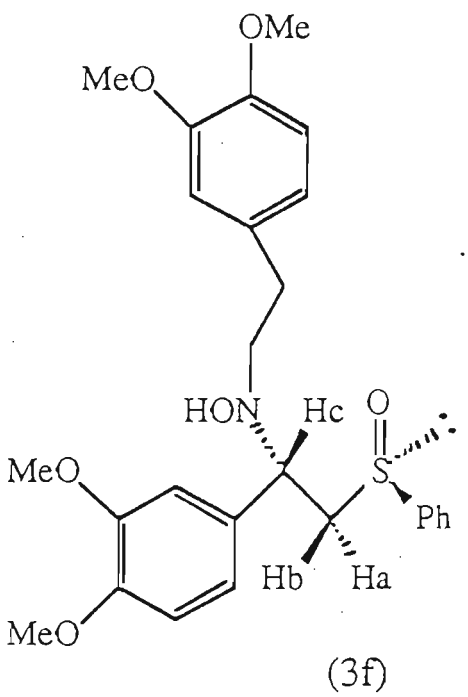
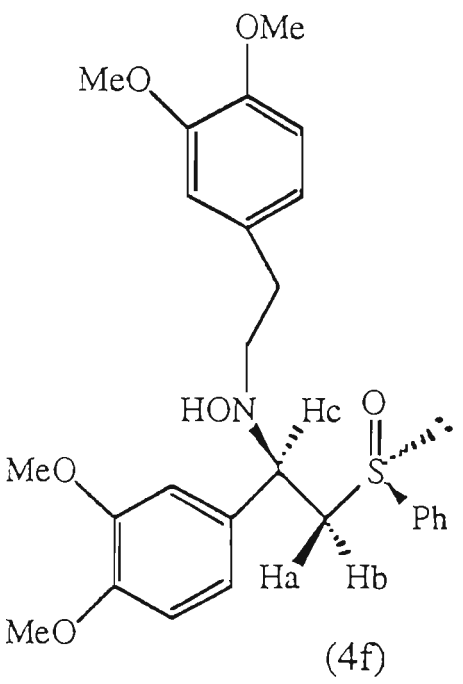


Figure 2.5 ^1H NMR ($CDCl_3$) spectrum of the crude reaction mixture of (3f) and (4f) from the reaction of lithiated sulfoxide (1) and oxaziridine (2f).

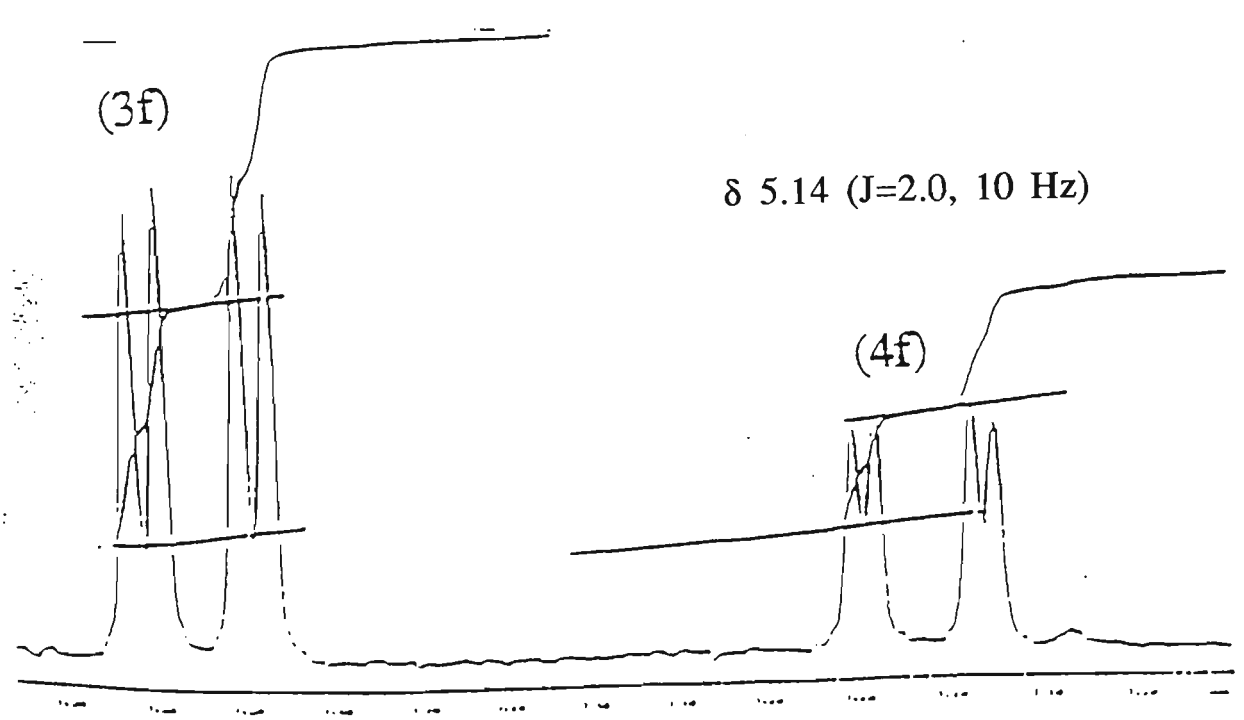


(3f)



(4f)

δ 5.32 (J=2.8, 10 Hz)



Experimental

General method for the preparation of oxaziridines.

To a 250 mL flask containing a magnetic stirrer bar, was added 8.2 mmol of the appropriate imine[95] in CH_3CN (50 mL) or acetone and $KHCO_3$ (6.89 g, 3.5 equivalent based on oxone) in water (50 mL). The reaction was stirred vigorously and a solution of Oxone® (6.0 g, 9.8 mmol) in water (50 mL) was added in one portion. After stirring for 15 min. (acetone reaction) or 30 min. (acetonitrile reaction) the reaction mixture was extracted with dichloromethane (3x50 mL), dried ($MgSO_4$) and the solvent was evaporated. The product was >95% pure by TLC and ^1H NMR analysis. The product could be further purified by short path distillation or column chromatography.

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2-Methyl-3-phenyloxaziridine (2a)

Colourless oil, b.p. 58-60 °C/0.1 mm Hg (lit.[96] 45 °C/0.07 mm Hg). ^1H NMR δ 2.93 (s, 3 H, CH_3), 4.43 (s, 1 H, CH), 6.7-7.45 (m, 5 H, aromatic).

2-Isopropyl-3-phenyloxaziridine (2b).

Yellow oil, b.p. 67-69 °C/0.38 mm Hg (lit.[96] 81-82 °C/0.45 mm Hg). ^1H NMR δ 0.92 (d, 3H), 1.1 (d, 3 H), 1.42 (m, 1 H), 4.48 (s, 1 H, CH), 6.85-7.1 (m, 5 H, aromatic).

2-*tert*-Butyl-3-phenyloxaziridine (2c)

Oil, b.p, 58-60 °C/0.3 mm Hg (lit.[96] 51-52 °C/2.8 mm Hg). ^{1}H NMR 1.24 (s, 9 H, *t*-Bu), 4.74 (s, 1 H, CH), 7.43 (m, 5 H).

2-*tert*-Butyl-3-(3'-hydroxyphenyl)oxaziridine (2d)

White crystals, m.p. 85-86 °C (lit.[97] m.p. 85-86 °C). ^{1}H NMR δ 1.16 (s, 9 H, *t*-Bu), 4.67 (s, 1 H, CH), 6.74-7.23 (m, 4 H, aromatic).

2-*tert*-Butyl-3-(4'-methoxyphenyl)oxaziridine (2e).

Oil, b.p. 90-93 °C/0.2 mm Hg (lit.[97]102-103 °C/0.25 mm Hg). ^{1}H NMR δ 1.14 (s, 9 H, Bu^t), 3.75 (s, 3 H, OMe), 4.62 (s, 1 H, CH), 6.7-7.4 (m, 4H, aromatic).

2-(3',4'-Dimethoxyphenylethyl)-3-(3',4'-dimethoxyphenyl)oxaziridine (2f).

M.p. 78-79 °C. ^{1}H NMR δ 2.85 (t, 4H, CH_2), 3.75 (s, 9 H, OMe), 3.86 (s, 3 H, OMe), 4.23 (s, 1 H, CH), 6.8-7.24 (m, 6H).

2,3-di-*tert*-Butyloxaziridine (2g)

Oil, b.p. 60 °C/25 mm Hg (lit.[98] 65 °C/0.3 mm Hg). ^{1}H NMR δ 0.92 (s, 9 H, *t*-Bu), 1.08 (s, 9 H, *t*-Bu), 3.62 (s, 1 H, CH).

2-*tert*-Butyl-3-isopropyloxaziridine (2h).

Oil, b.p. 77-79 °C/.05 mm Hg (lit.[99] 100-101 °C/0.1 mm Hg). ^{1}H NMR δ 3.69 (d, 1 H, CH), 3.55 (m, (CH3)CH, 1 H) , 1.25 (s, 9 H, Bu^t), 1.7 (d, 3 H, CH_3), 1.16 (d, 3 H, CH_3).

***C*-Phenyl-*N*-phenyl nitrone.**

M.p. 78-79 °C, (lit.[99] m.p. 77 °C). ^{1}H NMR δ 8.0-6.99 (m, 10 H, aromatic), 8.45 (s, 1 H, CH).

***C*-(2'-Furanyl)-*N*-phenyl nitrone.**

M.p. 78-80° C. ^{1}H NMR δ 8.23 (s, 1 H), 7.8-6.1 (m, 8 H). MS m/z 188.2 (100 %, M^+H^+). Anal calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.50 %. Found: C, 70.62; H, 4.81; N. 7.72 %.

Reaction of lithiated methyl phenyl sulfoxide (1) with oxaziridine (2);

A General Procedure:

Methyl phenyl sulfoxide (2.0 mmol) in anhydrous tetrahydrofuran (5 mL) was added dropwise to a cooled (-78°C), stirred solution of LDA, prepared from diisopropylamine (0.35 mL, 2.2 mmol) and n-butyllithium (2.4 mmol, 1.47 mL of 1.6 M solution in hexane) in THF (5 mL)). The mixture was allowed to reach -20°C, and was then cooled again to -78°C, and treated with a solution of the oxaziridine (4 mmol) in THF (15 mL). The mixture was stirred for 30 min. at -78°C and then

quenched with NH_4Cl. The mixture was warmed to room temperature and then extracted with CH_2Cl_2 (2 x 20 mL). The combined extracts were washed with water, dried ($MgSO_4$) and then evaporated to dryness. The crude product was then purified by column chromatography on silica gel using ethyl acetate/hexane (1:1) as the eluent. The diastereoselection of these reactions were determined by ^1H NMR (400 MHz) spectroscopic analysis of the crude reaction product.

(R_S^*,1*S)-*N*-Methyl-*N*-(1-phenyl-2-phenylsulfinyl)ethylhydroxylamine (3a).**

Oil. IR (film) 3600-3200(br), 3300 (sharp), 1035 cm^{-1}. ^1H NMR δ 7.52 (d, J = 8.2 Hz, 2H), 7.27 (dd, J = 4, 6.4 Hz, 1H), 4.11 (dd, J = 6.8, 9.6 Hz, 1H), 3.72 (dd, J = 9.6, 13.6 Hz, 1H), 3.05 (dd, J = 6.8, 13.6 Hz, 1H); 2.55(s, Me, 3H). ^{13}C NMR δ 141.2, 140.9, 140.6, 129.6, 128.3, 127.2, 126.6, 123.6, 65.0, 59.1, 33.8, 20.9. MS(CI) m/z 276 (100, $M+H^+$), 229 (32, $M+H^+$- NMeOH), 136 (75), 125 (100).

(R_S^*,1R^*)-*N*-Methyl-*N*-(1-phenyl-2-phenylsulfinyl)ethylhydroxylamine (4a).

^1H NMR (in part) δ 3.92 (dd J = 4, 6 Hz, 1H); 3.45 (dd, J = 4, 13 Hz, 1H), 3.25 (dd, J = 6, 13 Hz, 1H); 2.51(s, Me, 3H).

(R^*_S,1S*)-*N*-*tert*-Butyl-*N*-(1-phenyl-2-phenylsulfinyl)ethylhydroxylamine (3c).

M.p. 144-146 °C. IR (nujol) 3520, 3330, 1030 cm-1. ^{1}H NMR δ 8.2 (m, 1H), 7.2-7.8 (m, 9H), 4.55 (dd, J = 4.0, 11 Hz, 1H), 3.58 (dd, J = 11, 13.2 Hz, 1H), 2.94 (dd, J = 4.0, 13.2 Hz, 1H), 0.981 (s, 9H). ^{13}C NMR δ 144.6, 130.5, 129.5, 128.5, 127.3, 126.9, 126, 125, 69.3, 63.7, 28.8, 26.8. MS (CI) m/z 318 (75, M+H$^+$), 302 (20), 262 (25). Anal calcd for $C_{18}H_{23}NO_2S$: C, 68.1; H, 7.3; N, 4.4%. Found: C, 68.2; H, 7.4; N, 4.4%.

(R^*_S,1R^*)-*N*-*tert*-Butyl-*N*-(1-phenyl-2-phenylsulfinyl)ethylhydroxylamine (4c).

^{1}H NMR (in part) δ 3.64 (dd, J = 10.8, 13.6 Hz, 1H), 3.01 (dd, J = 6.4, 13.6 Hz, 1H), 1.021 (s, 9H).

(R^*_S,1S*)-*N*-(2-(3',4'-Dimethoxyphenyl)ethyl)-*N*-(1-(3',4'-dimethoxyphenyl)-2-phenylsulfinyl)ethylhydroxylamine (3f).

M.p. 132-133 °C. IR (nujol) 3502, 3320, 1030 cm^{-1}. ^{1}H NMR δ 8.99-6.5 (m, 11H), 5.32 (dd, J = 2.8, 10.0 Hz, 1H), 3.8 (4xs, 12 H), 3.35 (dd, J = 10, 13.2 Hz, 1H), 3.1 (dd, J = 2.8, 13.2 Hz, 1H). ^{13}C NMR δ 183.3, 178.23, 170.54, 168.65, 160.24,.155.4, 148.3, 144.8, 141.6, 132.2, 126.8, 126.3, 124.5, 119.7, 117.3, 112.6, 60.2, 58.4, 57.8, 56.2, 55.6, 46.4, 34.7. MS m/z 485.6 (100, M$^+$), 468, 343, 339, 202, 185, . Anal calcd for $C_{26}H_{31}NO_6S$: C, 64.31; H, 6.43; N, 2.88 %. Found: C, 64.29; H, 6.48; N, 2.85%.

(R^*_S,1R^*)-*N*-(2-(3',4'-Dimethoxyphenyl)ethyl)-*N*-(1-(3',4'-dimethoxyphenyl)-2-phenylsulfinyl)ethylhydroxylamine (4c)

^{1}H NMR (in part) δ 5.14 (dd, J=2, 10.0 Hz, 1H), 3.32 (dd, J=10.0, 7 Hz, 1H), 2.99 (dd, J=7, 10.0 Hz, 1H).

CHAPTER 3

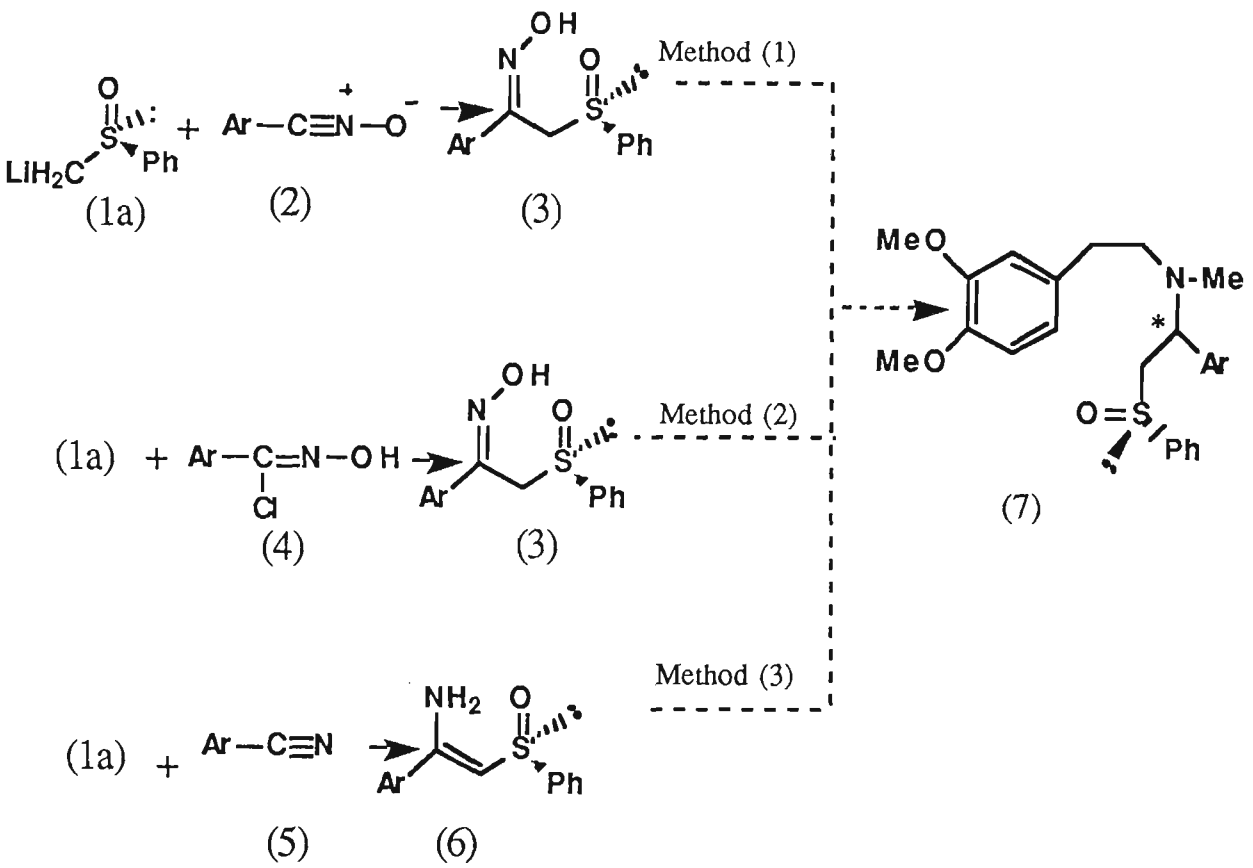
Chapter 3

Preparation and Reduction of α-Sulfinyl Oximes and β-Enamino Sulfoxides

The aim of this study was to evaluate the potential of Methods (1-3) in Scheme 3.1 for preparing chiral β-amino sulfoxide (7).

We planned to prepare β-amino sulfoxide (7) from either α-sulfinyl oxime (3) or β-enamino sulfoxide (6) by a diastereoselective reduction of the imino or enamino group followed by elaboration of the nitrogen functionality as shown in Scheme 3.1. Compound (3) was prepared from either the addition of 1 equiv. of the lithiated sulfoxide (1a) to benzenenitrile oxide (2) or the reaction of 1 equiv. of lithiated sulfoxide (1a) and 1 equiv. of LDA with hydroximinoyl chloride (4). In the latter reaction (2) is formed *in situ*. Reaction of lithiated sulfoxide (1a) with nitrile (5) should give compound (6) as shown in Scheme 1.3.[38]

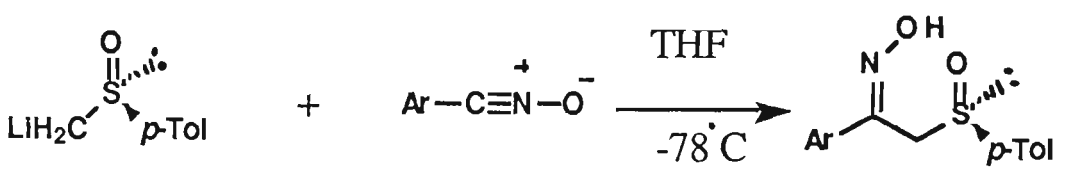
Scheme 3.1. Methods for the preparation of β-aminosulfoxide (7)



In 1983 Annunziata and Cinquini[38] reported the addition of (*R*)-(1b) to aryl nitrile oxides and readily available hydroximinoyl chlorides gave α-sulfinyl oximes as outlined in Scheme 3.2 and Table 3.1.

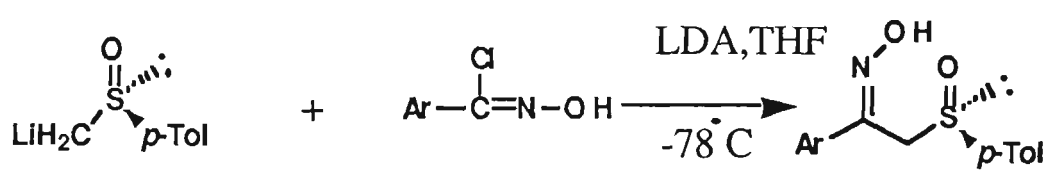
Scheme 3.2. Addition of (*R*)-(1b) to compounds (2) and (4).

Method 1



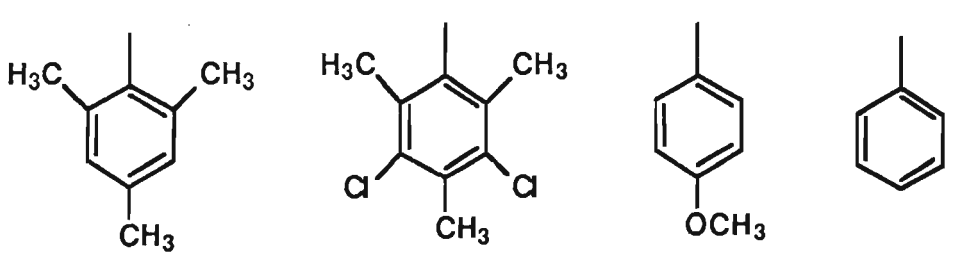
(*R*)-(1b) (2) (3)

Method 2



(*R*)-(1b) (4) (3)

Ar=



(a) (b) (c) (d)

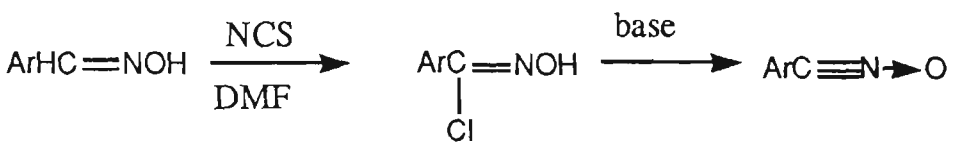
Table 3.1. Synthesis of optically active (+)-(*R*)-α-sulfinyl oximes (3).

product	method	yield (%)	m.p.(°C)	$[\alpha]_D^{25}$ (c 1, $CHCl_3$)
(3a)	(1)	78	144	+301.0
(3a)	(2)	71	144	+303.0
(3b)	(1)	55	172	+273.0
(3c)	(1)	78	135	+53.8
(3c)	(2)	71	135	+55.8
(3d)	(2)	80	116	+46.0

Preparation of hydroximinoyl chlorides and nitrile oxides.

The most widely employed method for preparation of hydroximinoyl chlorides (4), which are especially useful storable precursors of the relatively unstable nitrile oxides (2), that tend to dimerize within a few minute to several days, is chlorination of oximes with chlorine. Chlorine gas, however is hazardous and ring chlorination occurs with benzaldehyde oximes that contain electron donating substituents.[100] *N*-Chlorosuccinimide (NCS) in DMF have been found to provide a particularly selective and most convenient method for the preparation of these compounds as shown in Table 3.2.[101a]

Table 3.2. Preparation of hydroximinoyl chlorides (4) with NCS/DMF.



(4) (2)

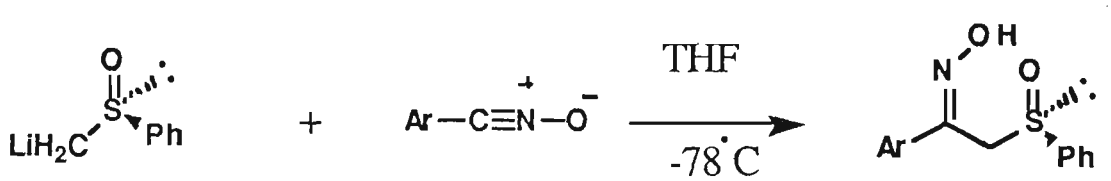
	crude product		purified product	
Ar	yield (%)	m.p.(°C)	yield (%)	m.p.(°C)
2,4,6-$(CH_3)_3C_6H_2$	92	61-69		
2-$CH_3OC_6H_4$	92	105-108	57	112-112.5
3-$C_6H_5OC_6H_4$	92	84-85		
2-$CH_3C_6H_4$	84	oil		
4-$C_6H_5C_6H_4$	89	148-164 dec	62	150-156 dec
3-ClC_6H_4	96	58-61	70	65-67
4-ClC_6H_4	75	87.5-89.0		
2-$CF_3C_6H_4$	99	70-81	68	78-82
4-$CF_3C_6H_4$	85	89.5-91.5		
3-$O_2NC_6H_4$	96	94.0-96.5		
3-NCC_6H_4	80	133.5-135.0		

Hydroximinoyl chlorides (4) can be easily converted to benzenenitrile oxides (2) *in situ* by base as outlined below.[101]

Addition of lithiated methyl phenyl sulfoxide (1a) to nitrile oxide (2) and hydroximinoyl chloride (4).

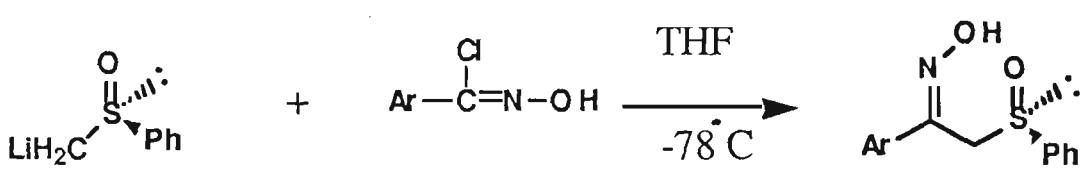
We have examined the addition of lithiated methyl phenyl sulfoxide (1a) to nitrile oxides (2a) and (2b) and hydroximinoyl chlorides (4a) and (4b) as shown in Method 1 and Method 2.

Method 1

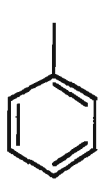
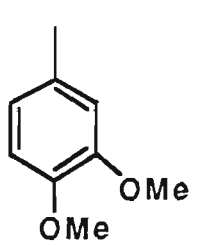


(1a) (2) (3)

Method 2



(1a) (4) (3)

			Method 1	Method 2
Ar=	(a);		yield 63 %	yield 56 %
	(b);		yield 60 %	yield 54 %

In our hands the yields for the addition of sulfoxide (1a) to nitrile oxide (2) and hydroximinoyl chloride (4) were good (Table 3.3). The ^1H NMR spectrum of the products (3a) and (3b) indicated that they had the oxime rather than the enamine structure. The ^1H

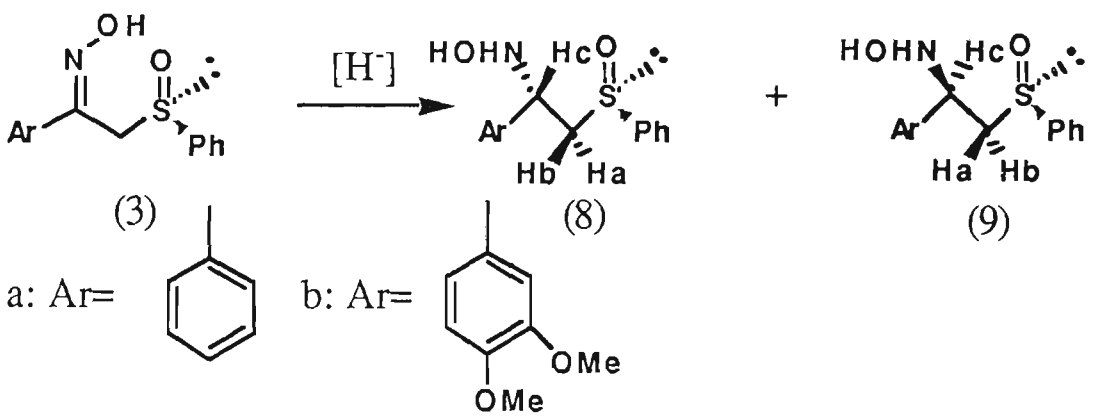
NMR spectrum of (3a) showed a typical AB quartet at δ 4.50 (d, J_{AB}= 13.2 Hz, 1 H) and 4.68 (d, J_{AB}=13.2 Hz, 1 H) for the two diastereotopic methylene protons α to the sulfoxide group.

Table 3.3. Synthesis of α-sulfinyl oximes (3) from addition of sulfoxide (1a) to nitrile oxides (2a-b) and hydroximinoyl chlorides (4a-b).

entry	nitrile oxide (2) or hydroximinoyl chloride (4)	product (3)	yield (%)	m.p.(°C)
1	(2a)	(3a)	63	89-91
2	(2b)	(3b)	60	oil
3	(4a)	(3a)	56	89-91
4	(4b)	(3b)	54	oil

The yield for the reduction of α-sulfinyl oximes (3) to β-hydroxyamino sulfoxides (8) and (9), however was low using either $Na(OAc)_3BH$ or $NaCNBH_3$ as the reducing agent, and the diastereoselectivity was poor. Some improvement in the diastereoselectivity was obtained when these reduction were initiated at -78° C as shown in Table 3.4.

Table 3.4. Reduction of α-sulfinyl oxime (3) to a mixture of β-hydroxyamino sulfoxides (8) and (9) with Na(OAc)3BH or NaCNBH3 .



(3) (8) (9)

a: Ar= b: Ar=

entry	method	yield (%)	d.r. (8):(9)
1	a	56	50:50
2	a	54	50:50
3	b	52	50:50
4	b	52	50:50
5	c	51	55:45
6	c	48	55:45
7	d	45	64:36
8	d	42	64:36

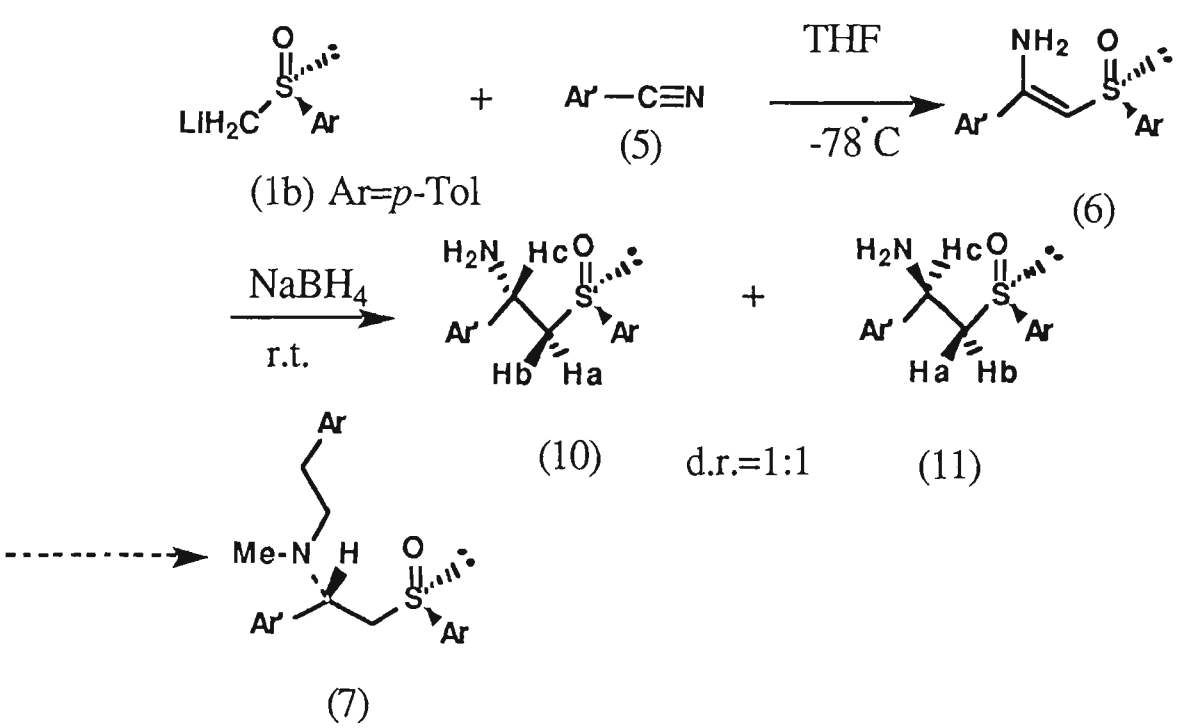
method a : Na(OAc)3BH/DCM (R.T., 2 h)
method b: NaCNBH3/MeOH (R.T., 2 h)
method c: Na(OAc)3BH/DCM (-25 °C-> R.T., 4 h)
method d: Na(OAc)3BH/DCM (-78 °C->0 °C, 6 h)

The stereochemistry of the diastereoisomers (8) and (9) will be discussed later in this chapter.

As the yield and diastereoselection of these reactions were low, none of them was fit for our purpose, so we next examined the addition of sulfoxide (1a) to nitriles.

Diastereoselective addition of lithiated sulfoxide (1a) to nitriles (5).

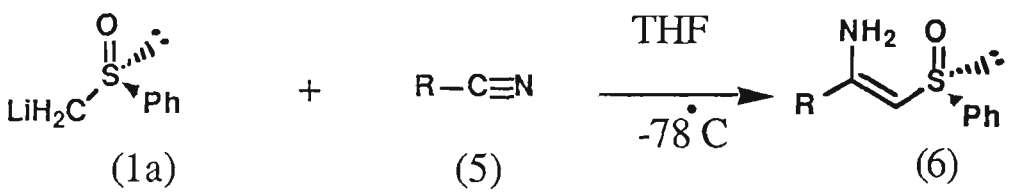
In 1973, G-I.Tsuchihashi[27] and co-workers reported that the addition of (*R*)-(1b) to nitrile (5) gave β-enamino sulfoxide (6) which upon reduction at room temperature in methanol with sodium borohydride gave the β-amino sulfoxides (10) and (11). The diastereoselectivity of the latter reaction however, was poor (d.r.=1:1). This method may also be used for preparing of β-amino sulfoxide (7) as outlined below, if a method for improving the diastereoselectivity of the reduction step could be developed.



(7)

In my hands reaction of sulfinyl carbanion (1a) with nitriles (5a-c) gave the β-enamino sulfoxides (6a-c) almost quantitatively as shown in Scheme 3.4 and Table 3.5.

Scheme 3.4. Reaction of lithiated sulfoxide (1a) with nitriles (5a-e) at -78° C in THF.



(1a) (5) (6)

a; R=Me b; R=Ph c; R=3,4-dimethoxyphenyl

d; R=Ph-CH_2 e; R=3,4-dimethoxybenzyl

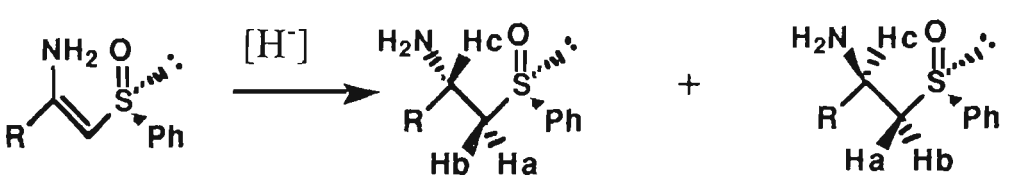
Table 3.5. Reaction of lithiated sulfoxide (1a) with nitriles (5) at -78° C in THF.

entry	nitrile (R)	product	yield (%)
1	Me	(6a)	92
2	Ph	(6b)	97
3	3,4-dimethoxyphenyl	(6c)	95
4	Ph-CH_2	no reaction	
5	3,4-dimethoxybenzyl	no reaction	

These reactions worked well when R of the nitrile was aryl or methyl, whereas phenylacetonitrile or 3,4-dimethoxybenzylnitrile did not give a satisfactory result (Table 3.5, entry 4 and 5), probably due to the high acidity of their methylene protons as shown in Scheme 3.4. The ^1H NMR spectrum of (6a-c) showed that these compounds were in the enamine form ((6a): δ 4.12, (6b): δ 4.24, and (6c): δ 4.28, each of these signals were a singlet that integrated for 1 H)).

As the β-enamino sulfoxide (6) was unstable at room temperature, it was immediately reduced with $NaBH_4$ or $NaCNBH_3$ at different temperatures in methanol to give a diastereomeric mixture of the β-amino sulfoxides (10) and (11) in moderate to good yield but with poor diastereoselectivity as shown in Scheme 3.5 and Table 3.6. The diastereoisomer ratio was measured by ^1H NMR (400 MHz) spectroscopy.

Scheme 3.5.



(6) (10) (11)

a: R=Me b: R=Ph c: R=3,4-dimethoxyphenyl

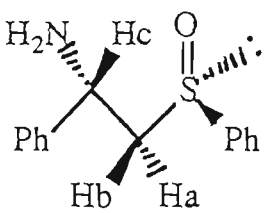
Table 3.6. Reduction of β-enamino sulfoxide (6) to β-amino sulfoxides (10) and (11) with different reducing reagents and at different temperatures.

entry	compound (6)	method	yield (%) (10)+(11)	d.r. (10):(11)
1	(6a)	(a)	71	50:50
2	(6b)	(a)	68	50:50
3	(6c)	(a)	62	50:50
4	(6a)	(b)	59	55:45
5	(6b)	(b)	54	55:45
6	(6c)	(b)	51	55:45
7	(6a)	(c)	56	67:33
8	(6b)	(c)	53	67:33
9	(6c)	(c)	48	67:33

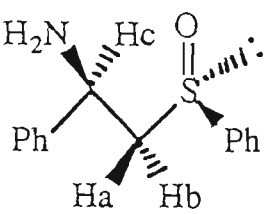
method a: $NaBH_4$; R.T.(2h).
method b: $NaCNBH_3$; R.T. (2h).
method c: $NaBH_4$, -78° C->R.T.(6h).

Figure 3.1 shows a copy of the ^1H NMR spectrum of the crude reaction mixture from the reduction of (6b). The protons H_a of both diastereoisomers, (10b) and (11b) are clearly evident as a doublet of doublets at δ 3.34 (dd, J=6.7, 13.4Hz) and 3.23 (dd, J=4.4, 13.2 Hz) respectively. Integration of these signals indicated that the diastereoisomer ratio was 67:33.

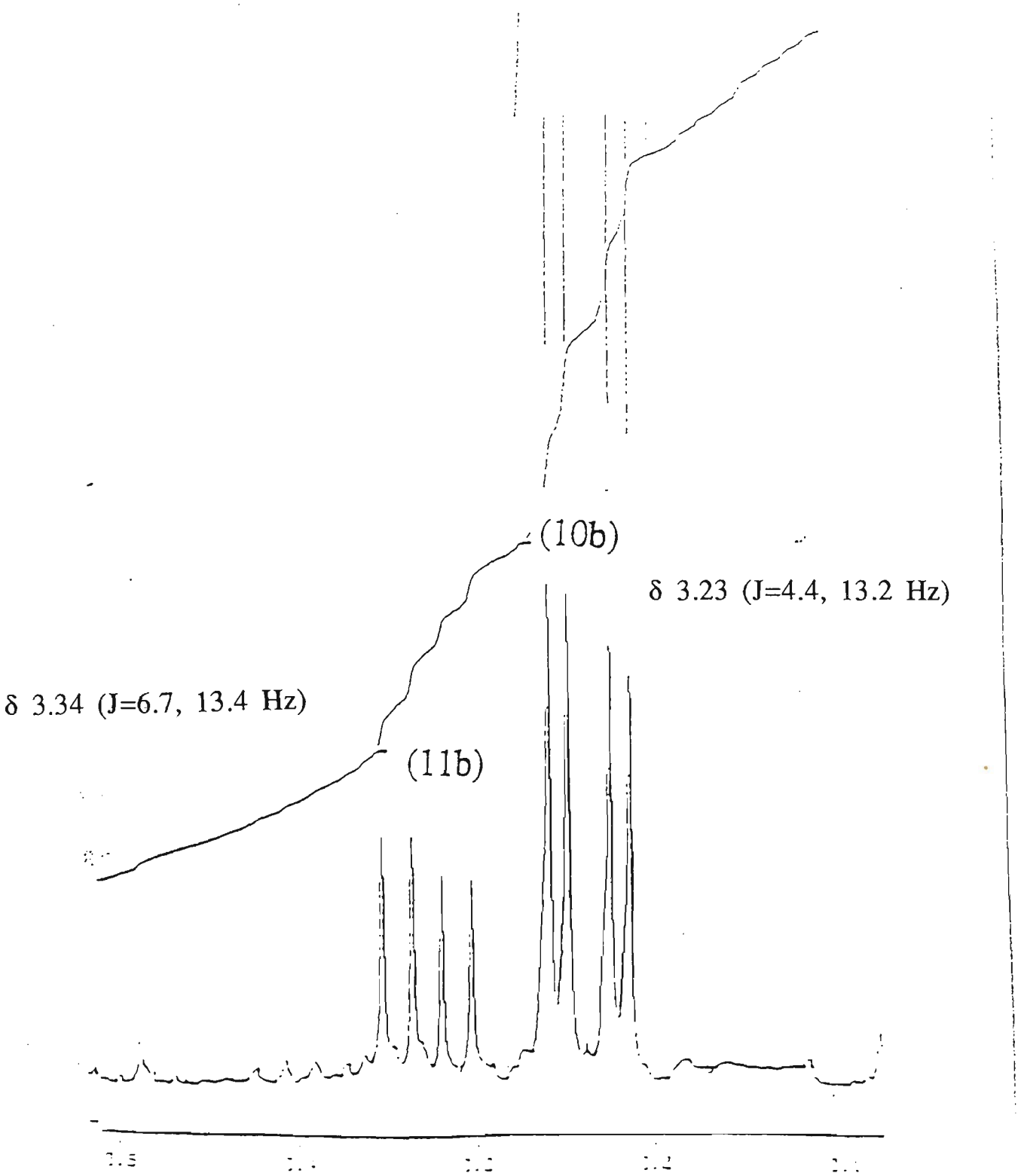
Figure 3.1. ^1H NMR ($CDCl_3$) spectrum of the crude reaction mixture of (10b) and (11b) from the reduction of (6b) with $NaBH_4$ in methanol at -78 °C.



(10b)



(11b)



Proof of stereochemistry of compounds (8), (9), (10) and (11).

The relative *(1S*,Rs*)* stereochemistry was assigned to the major diastereomeric products (8a) and (8b) based on the similarity of their ^{1}H NMR spectra to that of (5a) and (5b) respectively in Chapter 1, that were obtained from the addition of lithiated methyl phenyl sulfoxide (1a) to nitrones (4a) and (4b).[82] The ^{1}H NMR spectral data of (8a,b) and (9a,b) are summarised in Table 3.7.

The relative (*1S*,Rs**) stereochemistry assigned to the major diastereomeric products (10a), (10b) and (10c) based on the similarity of their ^{1}H NMR spectra to that of (7a) and (7b) in Chapter 1, that were obtained from the addition of lithiated methyl phenyl sulfoxide to imines (2a) and (2b).[28] The ^{1}H NMR spectral data for compounds (10a,b,c) and (11a,b,c) are summarised in Table 3.7. In each case H_c for the major diastereoisomer (8) or (10) comes downfield from its corresponding diastereoisomer (9) or (11) respectively as shown in Table 3.7. In the case of (8) and (10), J_{ac} and J_{bc} are also consistent with these compounds having the relative (*1S*,Rs**) stereochemistry (refer to Chapter 1 for a discussion of the ^{1}H NMR spectra of related compounds).

Table 3.7. ^1H NMR ($CDCl_3$) chemical shifts and coupling constants (Hz) for compounds (8a-b), (9a-b), (10a-c) and (11a-c).

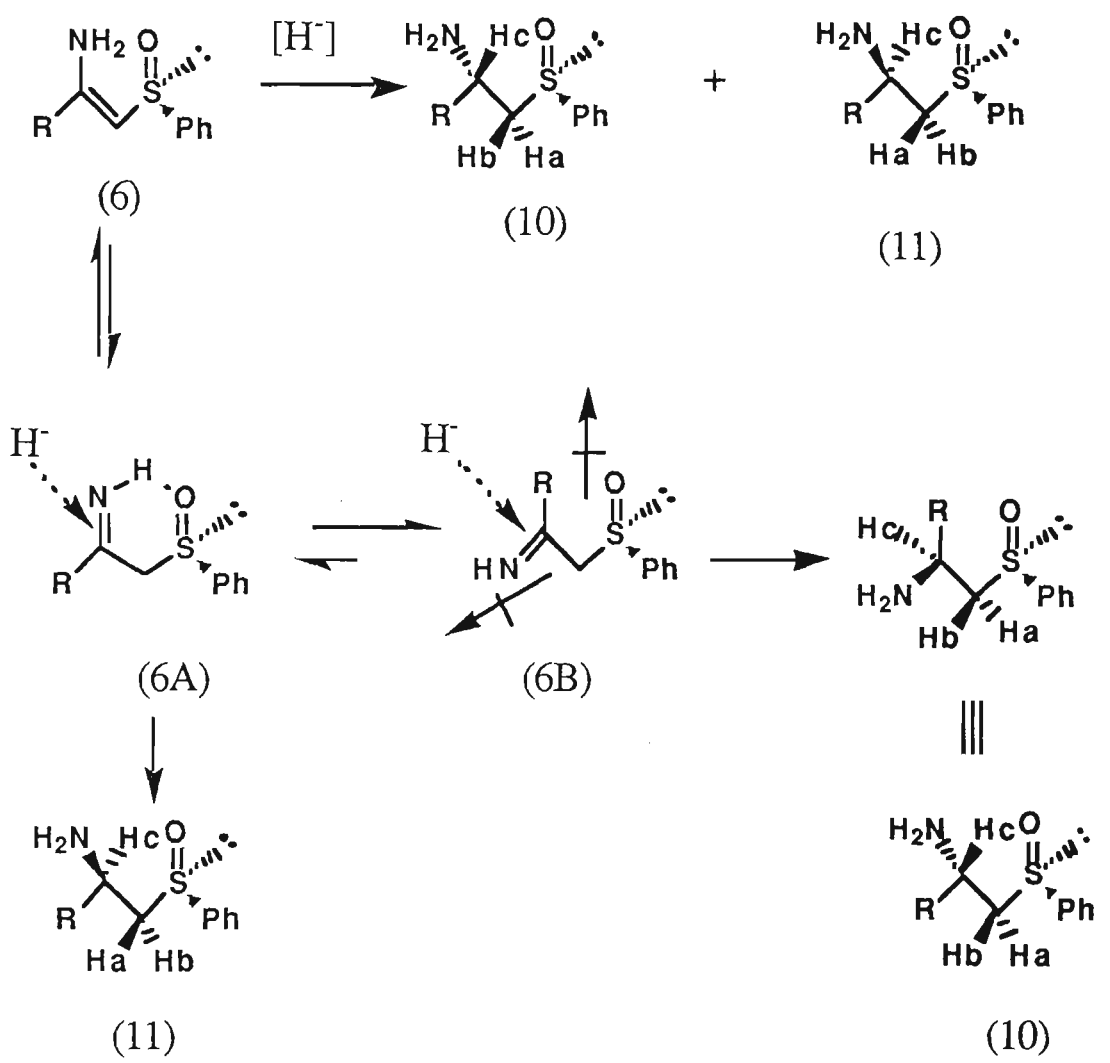
Compound	chemical shifts (ppm)			coupling constants (Hz)		
	H_a	H_b	H_c	J_{ac}	J_{bc}	J_{ab}
(8a)	3.32	3.20	4.60	10.2	6.2	13.6
(9a)	*a*	*a*	4.48	11.8	8.6	-
(8b)	3.48	3.22	4.56	10.4	6.0	13.2
(9b)	3.54	3.12	4.42	12	8.4	13.6
(10a)	2.99	2.76	3.99	10.2	3.2	13.6
(11a)	3.08	*a*	3.88	8.6	6.6	13.2
(10b)	3.23	3.12	5.22	10.0	4.4	13.2
(11b)	3.34	2.98	5.14	8.2	6.7	13.4
(10c)	3.28	3.14	5.18	10.8	4.8	13.6
(11c)	3.38	3.08	5.03	8.6	6.8	13.2

[a] obscured by other peaks in the ^1H NMR spectrum.

In the reduction of (6), the addition of hydride was thought to occur via attack of hydride on the imine forms (6A) and (6B) via the conformations shown in Scheme 3.5. Conformation (6A) is internally H-bonded while conformation (6B) is the one in which dipole-dipole interactions between the C=NH and the S=O groups are minimized. Addition should occur from the least hindered face of the imine double bond, that is the face that is *anti* to the S-Ph in (6A) and (6B) to give (11) and (10) respectively. At low temperatures there is a slight preference for attack on conformation (6B), giving product (10) as the

major diastereomeric product. A similar rationale can be used to explain the stereochemical outcome of the reduction of α-sulfinyl oximes (3).

Scheme 3.5. Reduction of β-imino sulfoxide (6) to β-amino sulfoxide (10) and (11).



a: R=Me b: R=Ph c: R=3,4-dimethoxyphenyl

In conclusion, we have developed a useful method for preparing β-hydroxyamino sulfoxides (8) and (9) in modest diastereomeric purity from the reduction of α-sulfinyl oximes (3) using either $Na(OAc)_3BH$ or $NaCNBH_3$ as the reducing agent. Some improvement in the diastereoselectivity was obtained when these reduction were initiated at -78° C as shown in Table 3.4. We have also developed a useful method for preparing β-amino sulfoxides (10) and (11) in modest diastereomeric purity based on the reduction of the β-enamino sulfoxide (6) with $NaBH_4$ or $NaCNBH_3$ at different temperatures in methanol. The diastereoselectivity of the reductions of (3) and (6) were poor and alternative methods were sought for the synthesis of β- amino sulfoxides (7).

EXPERIMENTAL

General procedure for *syn* oxime preparation.[101a]

To a mixture of 0.5 mol of aldehyde in 125 mL of water, 125 mL of ethanol and 215 mL of ice was added 0.55 mol of hydroxylamine hydrochloride. Then 100 mL of 50 % NaOH was added with stirring. Enough ice to keep the temperature at 25-30 °C was added. The mixture was stirred for 1 h, extracted with 500 mL of ether to remove neutral impurities, acidified with concentrated hydrochloric acid to pH 6 (ice was added to keep the temperature at 20-30 °C), and extracted with two 500 mL portions of ether or dichloromethane. These two extracts were combined, dried ($CaSO_4$), and concentrated under vacuum to give the solid oxime. Oximes prepared in this manner did not require further purification for conversion to the hydroximinoyl chloride. Small samples of crude oximes were recrystallized for comparison of melting points with literature values.

General procedure for *anti* oximes preparation.[102]

In a hood, anhydrous hydrogen chloride is passed through a stirred ether solution of 0.02 moles of *syn* oximes for 15 min. The less soluble hydrochloride salt of the *anti* isomer precipitated. After filtration of the product and washing with ether, the intermediate is dissolved in water. The solution was treated with a 2 N solution of sodium hydroxide until the mixture reached pH 9. The precipitated product was collected by filtration and washed with cold water to afford the *anti* oximes.

Benzaldehyde oxime

Prepared in 76 % yield, m.p. 36 °C for *syn*, 132.5 °C for *anti* (lit. [102] 35 °C and 133 °C for *syn* and *anti* respectively).

3,4-Dimethoxybenzaldehyde oxime

Prepared in 85 % yield, m.p. *syn* 92 °C and *anti* 119.5 °C (lit.[102] 92-94 °C and 119 °C for *syn* and *anti* respectively).

General procedure for hydroximinoyl chloride preparation.[101a]

Reaction of N-Chlorosuccinimide (NCS) with benzaldoximes in DMF exhibits an induction period and can become fairly exothermic for most substrates if the reaction initiates after a considerable portion of the NCS has been added. It has been found it desirable to initiate the reaction prior to addition of more than one-fifth of the NCS. This is accomplished by addition of HCl gas and for deactivated benzaldoximes by application of heat.

To a stirred solution of the *anti* benzladoxime (0.30 mol) in DMF (250 mL) at 25-30 ° C was added about one-tenth to one-fifth of 0.30 mol of solid NCS. The initial NCS addition resulted in a slight temperature decrease (negative heat of solution). If the reaction failed to self-initiate within 10 min, as indicated by a slight temperature rise (at first), 20 mL of gas from the head space of a concentrated hydrochloric acid reagent bottle was collected in a syringe and then bubbled into the

DMF solution. The reaction normally initiated within another 10-15 min. Once the reaction began, the temperature was kept below 35 °C by the rate of addition of the rest of the NCS and by intermittent cooling (dry ice-acetone bath). Completion of the reaction was indicated by cessation of the exotherm. The solution was poured into four volumes of ice water. The mixture was extracted twice with ether. The combined ether extracts were washed three times with water, dried ($CaSO_4$), and concentrated under vacuum to give the hydroximinoyl chloride product.

Phenylhydroximinoyl chloride

M.p. 48 °C (lit. [101b] m.p 45 °C) , yield 94 %. ^1H NMR δ 9.25 (br s, 1 H, NOH) 7.7-6.83 (m, 5 H). MS m/z, 156(100 %, M^+).

3,4-Dimethoxyphenylhydroximinoyl chloride

M.p. 114 °C, yield 92 %. ^1H NMR δ 9.95 (br s, 1 H, NOH) 7.7-6.83 (m, 3 H), 3.95 (s, 3 H OMe) 3.85(s, 3 H, OMe). MS m/z, 216 (100 %, M^+).

Preparation of β-imino sulfoxide (3); typical procedures:

Method 1.

A solution of phenyl methyl sulfoxide (0.28 g, 2 mmol) in anhydrous tetrahydrofuran (5mL) was added dropwise to a cooled (-78° C), stirred solution of lithium diisopropylamide, prepared from diisopropylamine(0.58 mL, 4.0 mmol) and n-butyllithium (2.66 mL of a 1.6 normal solution in hexane, 4.0 mmol) in THF (5 mL). The mixture

was then allowed to reach -20 °C, cooled again to -78 °C, and then treated with the hydroximinoyl chloride (4) (2.0 mmol) in THF (10 mL). After 30 min. stirring at -78° C, the reaction mixture was quenched with saturated ammonium chloride solution (5 mL) and the mixture was warmed to room temperature. The organic phase was separated, dried over $MgSO_4$, filtered, and evaporated. The crude material was then chromatographed (silica gel: ether:hexane 7:3) to give the product (3).

Method 2.

A solution of phenyl methyl sulfoxide (0.28 g, 2 mmol) in anhydrous tetrahydrofuran (5mL) was added dropwise to a cooled (-78° C), stirred solution of lithium diisopropylamide, prepared from diisopropylamine (0.58 mL, 4.0 mmol) and n-butyllithium (2.66 mL of a 1.6 normal solution in hexane, 4.0 mmol) in THF (5 mL). The mixture was then allowed to reach -20 °C, cooled again to -78 °C, and was treated with nitrile oxide (2). Nitrile oxide (2) was prepared *in situ* from hydroximinoyl chloride (4), (2.0 mmol) in THF (10 mL) by treatment with lithium diisopropylamide, (prepared from diisopropylamine (0.15 mL, 1.0 mmol) and n-butyllithium (0.67 mL of a 1.6 normal solution in hexane, 1.0 mmol) in THF (5 mL)) at -20°C for 20 min. After 30 min. stirring at -78° C, the reaction mixture was quenched with saturated ammonium chloride solution (5 mL) and the mixture was warmed to room temperature. The organic phase was separated and dried over $MgSO_4$, filtered, and evaporated. The crude material was then chromatographed (silica gel: ether:hexane 7:3) to give the product (3).

2-(Phenylsulfinyl)-acetophenone oxime (3a)

M.p. 89-91°C, 63 % yield. ^{1}H NMR δ 9.25 (br, N-OH, 1 H), 7.88-6.76 (m, 10 H), 4.50, 4.68 (d, J_{AB}=13.2, 2H). MS, m/z 260 (100 %, M^+). Anal calcd for $C_{14}H_{13}NO_2S$: C, 64.84; H, 5.05; N, 5.40 %. Found: C, 64.89 ; H, 5.11; N, 5.35 %.

2-(Phenylsulfinyl)-3',4'-dimethoxyacetophenone oxime (3b)

Oil, 60 % yield. ^{1}H NMR δ 9.87 (br, N-OH, 1 H), 7.88-6.68 (m, 8 H), 4.58, 4.65 (d, J_{AB}=13.6, 2H), 3.98 (s, 3 H, OMe), 3.88 (s, 3 H, OMe). MS m/z 319 (100 %, M^+). Anal calcd for $C_{16}H_{17}NO_4S$: C, 60.17; H, 5.37; N , 4.39 %. Found: C, 60.12; H, 5.39; N, 4.42 %.

Reduction of (3) to (8) and (9).

General procedure:

Method A:

To 2 mmol of compound (3) in dry CH_2Cl_2 (20 mL) was added $Na(OAc)_3BH$ (6 mmol, 1.28 g) in small portions over 15 min. at room temperature. The reaction was stirred for 2 h at this temperature, and then water (50 mL) was added and the mixture was extracted with dichloromethane (2x25 mL). The extract was dried over $MgSO_4$, evaporated and the crude product was chromatographed (silica gel, hexane/ethyl acetate 8:2) to give a mixture of (8) and (9), the d.r. was 50:50.

Method B:

The same procedure as described in method A was employed, except using $NaCNBH_3$ (6 mmol, 0.38 g) in methanol (20 mL). The mixture was stirred at room temperature for 2 h, the solvent was evaporated and the crude product was dissolved in water (20 mL) and extracted with dichloromethane (2x25 mL). The extract was dried over $MgSO_4$ and evaporated. The crude product was chromatographed (silica gel, hexane/ethyl acetate 8:2) to give compound (8), the d.r. was 50:50.

Method C:

The same procedure as described in method A was employed, except the reaction was stirred at -25 °C and then was allowed to warm to R.T. over 4 h. The d.r. of the product (8) was 55:45.

Method D:

The same procedure as described in method A was employed except the reaction was stirred at -78 °C and then allowed to warm to R.T. over 6 h. The d.r. of the product (8) was 64:36.

(R_S^*,1S*)-1-Phenyl-2-(phenysulfinyl)ethylhydroxylamine (8a)

Oil. ^1H NMR δ 7.88-6.76 (m, 10 H), 4.60 (dd, J= 6.2, 10.2 Hz, 1H), 3.32 (dd, J =10.2, 13.6. Hz, 1 H), 3.20 (dd, J= 6.2,13.6 Hz, 1 H). MS m/z 262 (100 %, M^+). Anal calcd for $C_{14}H_{15}NO_2S$: C, 64.34; H, 5.79; N, 5.36 %. Found: C, 64.39; H, 5.75; N, 5.35 % .

(R_S^*,1R^*)-1-Phenyl-2-(phenysulfinyl)ethylhydroxylamine (9a).

^{1}H NMR (in part) δ 4.48 (dd, J=8.6, 11.8 Hz, 1H).

(R_S^*,1S^*)-1-(3,4-Dimethoxyphenyl)-2-(phenylsulfinyl) ethylhydroxylamine (8b)

Oil. ^{1}H NMR δ 7.88-6.68 (m, 8 H), 4.56(dd, J=6.0 , 10.4 Hz,1H), 3.48 (dd, J=10.4 , 13.2 Hz, 1 H) 3.98 (s, 3 H, OMe), 3.88(s, 3 H, OMe), 3.22 (dd, J=6.0, 13.2 Hz, 1 H). MS m/z 321 (100 %, M^+). Anal calcd for $C_{16}H_{19}NO_4S$: C, 59.80; H, 5.96; N, 4.36 %. Found: C, 59.76; H, 5.93; N, 4.42 %.

(R_S^*,1R^*)-1-(3,4-Dimethoxyphenyl)-2-(phenylsulfinyl)-ethylhydroxylamine (9b)

^{1}H NMR (in part) δ 4.42 (dd, J=8.4, 12.0 Hz, 1H), 3.54 (dd, J=12.0, 13.6.Hz, 1 H), 3.12 (dd, J=8.4, 13.6 Hz, 1 H).

Method 3:

Reaction of sulfoxide (1a) with nitriles (5) to prepare (6)

Phenyl methyl sulfoxide (0.28 g, 2 mmol) in a solution of anhydrous tetrahydrofuran (5 mL) was added dropwise to a cooled (-78° C), stirred solution of lithium diisopropylamide, prepared from

diisopropylamine (0.58 mL, 4.0 mmol) and n-butyllithium (2.66 mL of a 1.6 normal solution in hexane, 4.0 mmol) in THF (5 mL). The mixture was allowed to reach -20 °C, cooled again to -78 °C, and treated with the nitrile (2.0 mmol) in THF (5 mL). After 30 min. stirring at -78 °C, the reaction mixture was quenched with saturated ammonium chloride solution (5 mL) and the mixture was warmed to room temperature. The organic phase was separated, dried over $MgSO_4$, filtered, and evaporated. As the crude material was unstable it was directly reduced, without further purification. ^1H NMR δ for (6b), 6.8-7.8 (m, 10 H), 4.24 (s, 1 H).

Reduction of (6) to β-amino sulfoxides (10) and (11).

General procedure:

Method A:

To 2 mmol of compound (6) in methanol (20 mL) was added $NaCNBH_3$ (6 mmol, 0.38 g) in small portions over 15 min. at room temperature. The reaction was stirred for 4 h at this temperature, and then the methanol was evaporated at reduced pressure. Water (50 mL) was then added to the residue which was extracted with DCM (2x25 mL). The combined extracts were dried over $MgSO_4$. Evaporated of the solvent, and chromatographic purification (silica gel, hexane/ethyl acetate 8:2) gave a mixture of (10) and (11).

Method B:

The same procedure as described in method A was employed, except $NaBH_4$ (6 mmol, 0.23 g) was used and the reaction was stirred at room temperature for 2 h.

Method C:

The same procedure as described in method B was employed, using $NaBH_4$ (6 mmol, 0.23 g) except that the reaction was stirred initially at -78 °C and was then allowed to warm to r.t. over 6 h. The d.r. of the product (8) in method A and B was 1:1 but in method C it was 2:1.

(R_S^*,1S*)-1-Phenylsulfinyl-2-propylamine (10a).

Oil. IR (film) 3600-3200(br), 3300 (sharp), 1035 cm^{-1}. ^1H NMR δ 7.52 -7.27(m, 5H), 3.99 (m, J =3.2, 10.2 Hz, 1H), 2.99 (dd, J = 10.2, 13.6 Hz, 1H), 2.76 (dd, J = 3.2, 13.6 Hz, 1H), 1.42 (d, 3 H, CH_3). ^{13}C NMR δ 141.2, 140.9, 140.6, 129.6, 128.3, 127.2, 126.6, 123.6, 65.0, 59.1, 33.8. MS (CI) m/z 183 (100, M^+).

(R_S^*,1R*)-1-phenylsulfinyl-2-propylamine (11a).

^1H NMR (in part) δ 3.88. (m, J = 6.6, 9.6 Hz, 1H); 3.08 (dd, J = 6.6, 13.2 Hz, 1H), 1.16 (d, 3 H, CH_3).

(R_S^*,1S*)-1-Phenyl-2-(phenysulfinyl)ethylamine (10b)

Oil. ^{1}H NMR δ 7.88-6.76 (m, 10 H), 5.22 (dd, J= 4.4, 10.0 Hz, 1H), 3.23 (dd, J=10.0, 13.2 Hz, 1 H), 3.12 (dd, J= 4.4, 13.2 Hz, 1 H). MS m/z, 248 (100 %, M^+). Anal calcd. for $C_{14}H_{15}NOS$: C, 68.54; H, 6.16; N, 5.71 %. Found: C, 68.51; H, 6.13; N, 5.67 %.

(R_S^*,1R^*)-1-Phenyl-2-(phenysulfinyl)ethylamine (11b)

^{1}H NMR (in part) δ 5.14 (dd, J=6.7, 8.2 Hz, 1H), 3.34 (dd, J=8.2, 13.4 Hz, 1H), 2.98 (dd, J=6.7, 13.4, 1H).

(R_S^*,1S*)-2-Phenylsulfinyl-1-(3,4-dimethoxyphenyl)-2 ethylamine (10c)

Oil. ^{1}H NMR δ 7.88-6.68 (m, 8 H), 5.18(dd, J=4.8, 10.8 Hz,1H), 3.95 (s, 3H, OMe), 3.91 (s, 3 H, OMe), 3.28 (dd, J=10.8, 13.6 Hz, 1 H) 3.14 (dd, J=4.8, 13.6 Hz, 1 H). MS, m/z, 305 (100 %, M^+).

(R_S^*,1R^*)-2-Phenylsulfinyl-1-(3,4-dimethoxyphenyl)-2 ethylamine (11c)

^{1}H NMR (in part) δ 5.03 (dd, J=6.8, 8.6 Hz, 1H), 3.38 (dd, J=8.6, 13.2 Hz, 1H), 3.08 (dd, J=6.8, 13.2 Hz, 1H).

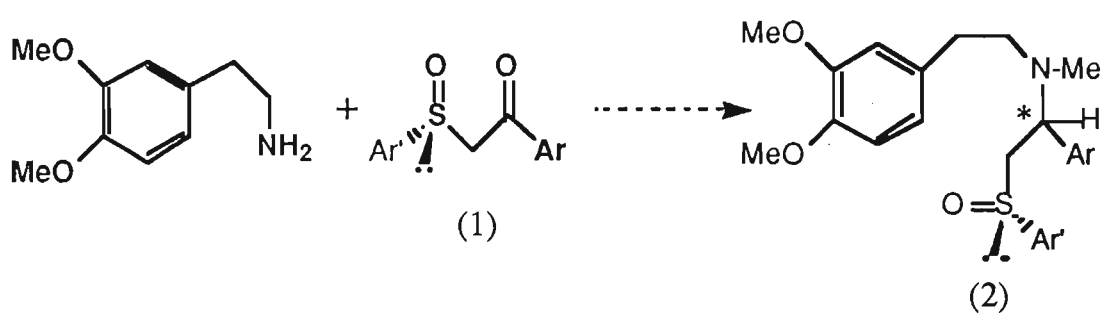
CHAPTER 4

Chapter 4

Preparation and Reduction of β-Sulfinyl Enamines and Pummerer Reaction of β-Amino Sulfoxide (2)

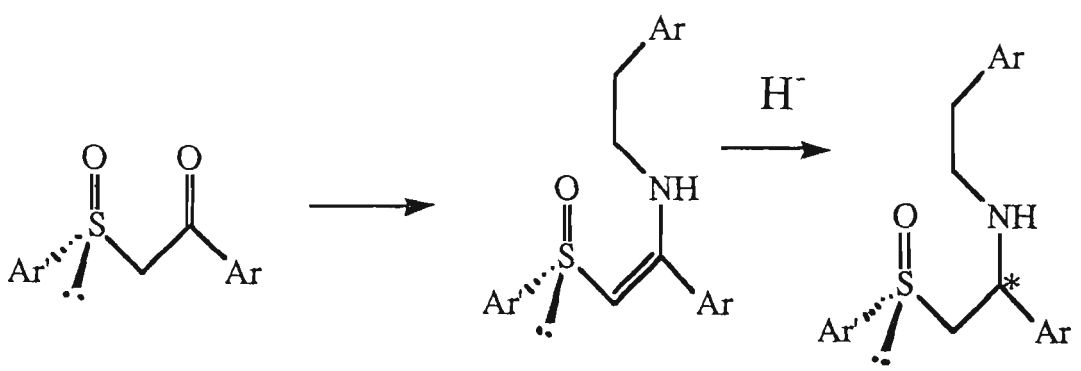
As was described in the Introduction (path c) Scheme 23, one of the methods that can be used for the preparation of β-amino sulfoxide (2) is from the β-keto sulfoxide (1) as outlined in Scheme 4.1

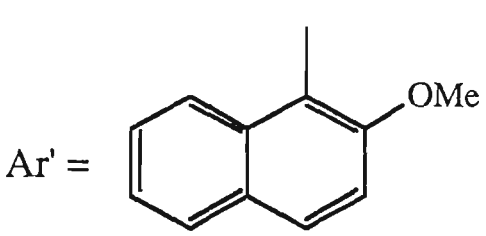
Scheme 4.1. Preparation of β-amino sulfoxide (2) from β-keto sulfoxide (1).

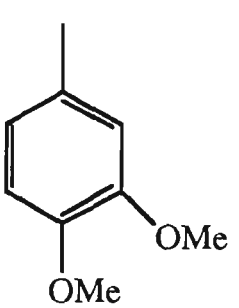


When we started this project the chemistry outlined in path (c) (Introduction, Scheme 23) had no literature precedent. During the course of this project both Hua[30a] and Carreno[30b] reported the diastereoselective reduction of cyclic β-sulfinyl enamines. After these publications the reduction of acyclic β-sulfinyl enamines with L-Selectride and DIBAL was also reported.[31a,b] It is proposed that readily available β-keto sulfoxide (1)[34,36] can be converted to its corresponding enamine (3), which upon diastereoselective reduction should afford the desired chiral β-amino sulfoxide (4) as shown in Scheme 4.2

Scheme 4.2. Reduction of β-sulfinyl enamine (3) to β-amino sulfoxide (4).







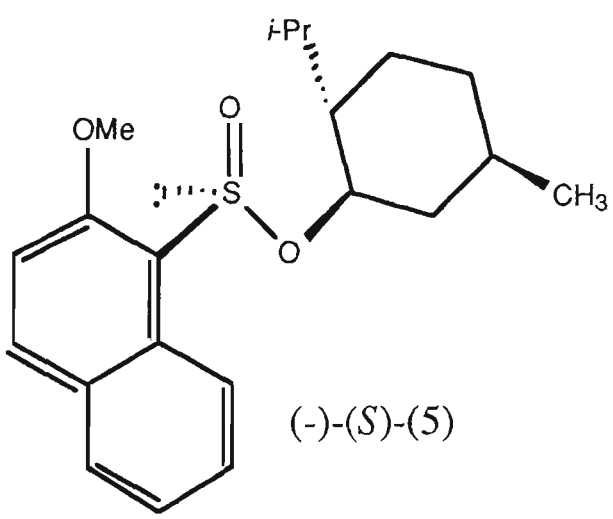
(b) Ar=Ph

Preparation of β–keto sulfoxide (1)

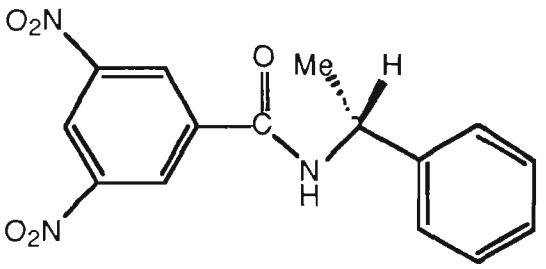
We examined three different methods to synthesise the starting material (+)-*(R)*-(1).

In Method A, *(R)*-(8) was prepared from (-)-(*S*)-(5) and α-lithiated *N,N*-dimethylhydrazone (7).[35] Cupric ion catalysed hydrolysis of *(R)*-(8) gave β-oxosulfoxides (+)-*(R)*-(1a) in 43 % overall yield. The enantiomeric purity of this compound was determined to be 80% from ^{1}H NMR studies using (-)-*(R)*-*N*-(3,5-dinitrobenzoyl)-α-phenylethylamine (6) as a chiral shift reagent. Clearly some racemization at the sulfur centre has occurred

occurred either in the first step or during the cupric ion hydrolysis step. The 400 MHz ^1H NMR study of β–keto sulfoxide (1a) showed an AB quartet at δ 5.02 (d, J_{AB}=13.2 Hz, 1 H) and δ 4.85 (d, J_{AB}=13.2 Hz, 1 H), for the two diastereotopic methylene protons of (1a). The three methoxy groups were evident at δ 4.00 (s, 3 H, OMe), 3.95 (s, 3 H, OMe), and 3.80 (s, 3 H, OMe), (Figure 4.1). After adding 1 equiv. of (-)-*(R)*-*N*-(3,5-dinitrobenzoyl)-α-phenylethylamine (6) as a chiral shift reagent the AB quartet of the CH_2 group split into two different AB quartets at δ 5.06 (d, J_{AB}=13.2 Hz), 4.82 (d, 13.6 Hz) and δ 5.04 (d, 13.6 Hz), 4.70 (d, 13.6 Hz) for the major and minor enantiomers respectively. Integration of these peaks showed the enantiomeric ratio was 90:10 (e.e. 80 %). In the original report on this reaction the analogous *(S)*-*p*-tolyl β-keto sulfoxide was obtained in 85 % e.e. Racemization was thought to have occurred during the hydrolysis step.[35]

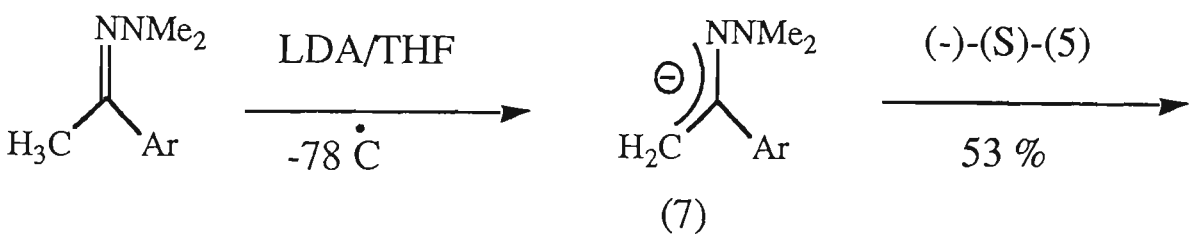


(-)-(*S*)-(5)

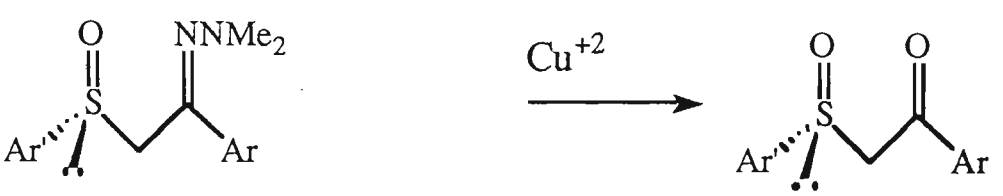


(6)

Method A.

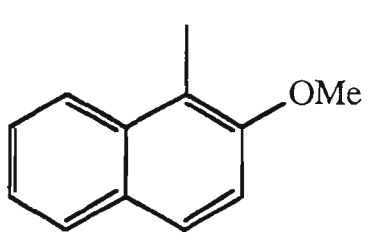


(7)



(*R*)-(8)

(+)-(R)-(1a)
e.e. 80 %

Ar'= 

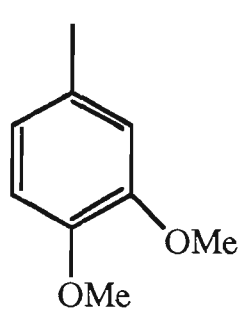
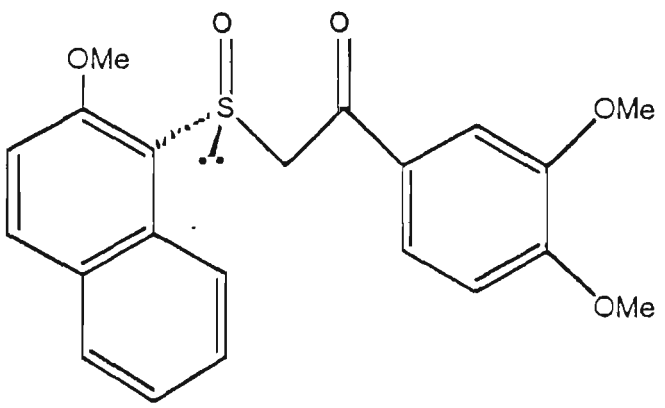
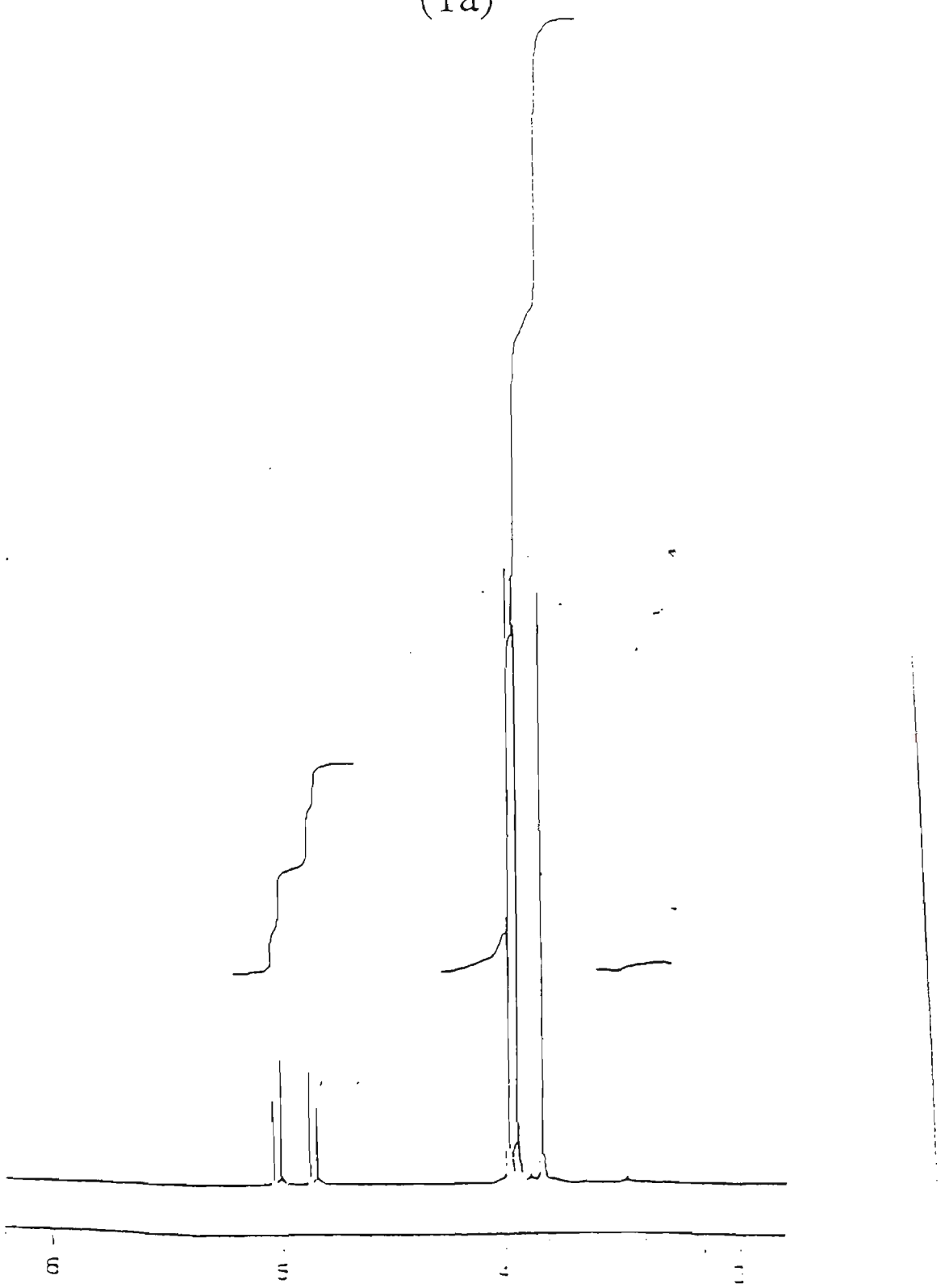
Ar= 

Figure 4.1 ^{1}H NMR ($CDCl_3$) of β-keto sulfoxide (1a)

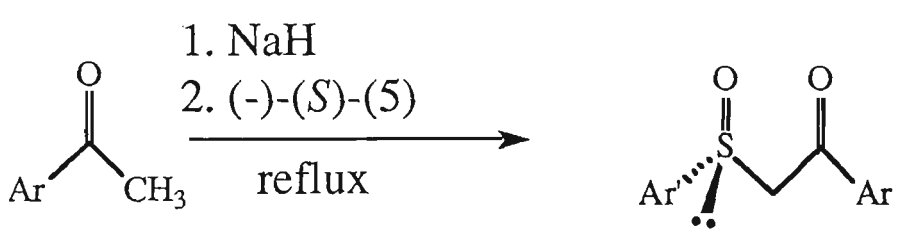


(1a)

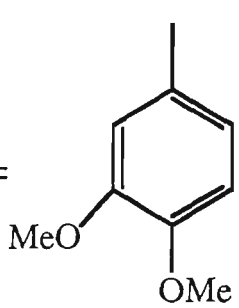


In Method B, (+)–*(R)*-(1a) and (1b) were prepared from (-)-*(S)*-(5) and acetophenone or 3,4-dimethoxyacetophenone using sodium hydride as base, according to the literature.[34,36] The reaction was quenched with saturated NH_4Cl rather than aqueous HCl as in the original procedure for the condensation of ketones with racemic methyl *p*-tolyl sulfoxide.[34,36] The enantiomeric purity of compounds (1a) and (1b) was determined to be 60% and 80 % respectively from ^1H NMR shift studies using (-)-*(R)-N*-(3,5-dinitrobenzoyl)-α-phenylethylamine (6), as a chiral shift reagent (Figure 4.2). The chemical yields were 91 % and 80 % respectively as outlined below.

Method B.



(+)-(*R*)-(1)

(a): Ar=  yield=91 %
e.e. 60 %

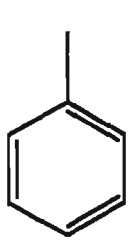
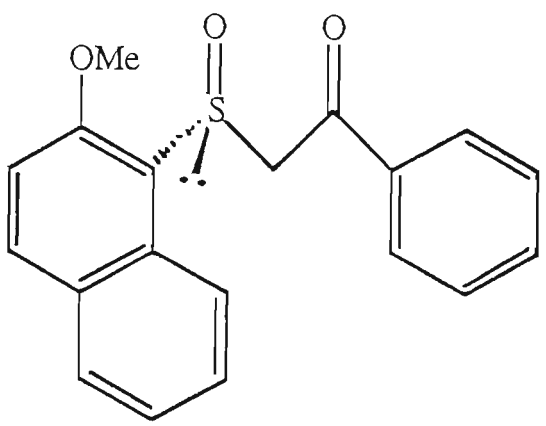
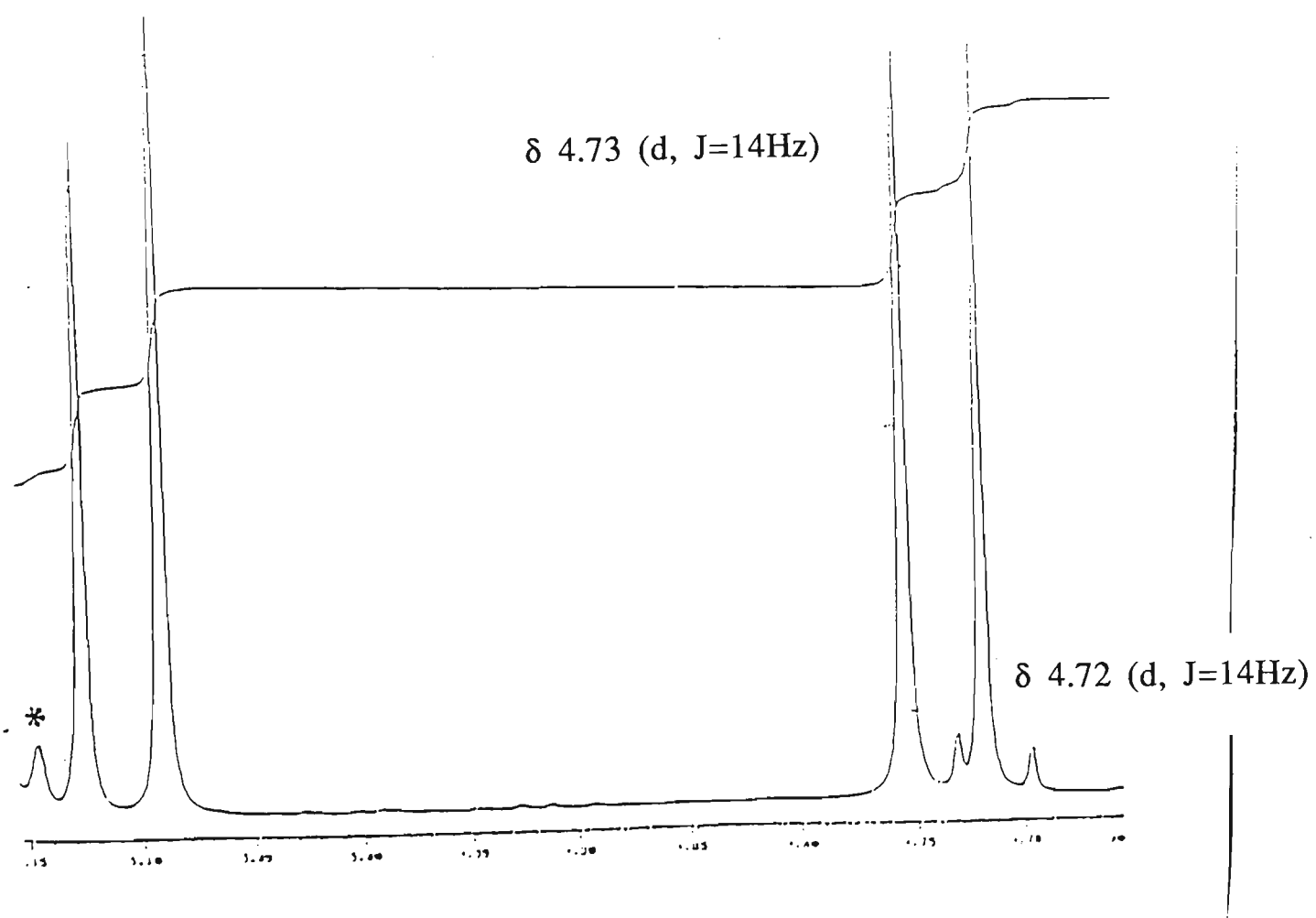
(b): Ar=  Yield=80 %
e.e. 80 %

Figure 4.2. ^1H NMR shift studies of (+)-(*R*)-β-keto sulfoxide (1b) using (-)-(*R*)-*N*-(3,5-dinitrobenzoyl)-α-phenylethylamine (6) as a chiral shift reagent.



(+)-(*R*)-(1b)



* signal from (6)

Figure 4.2 shows a copy of the ^1H NMR spectrum of (1b) that was determined to be 80 % enatiomerically pure from ^1H NMR shift studies using (-)-*(R)*-*N*-(3,5-dinitrobenzoyl)-α-phenylethylamine (6) as a chiral shift reagent. Peaks from the major and minor enantiomers can be seen at δ 4.73 (d, J=14 Hz), and δ 4.72 (d, J=14 Hz) respectively. The ratio of these peaks is 90:10 (e.e. 80 %).

In the literature, it has been reported that preparation of β-keto sulfoxide (1) by this method (method B), gives racemic product[34,36] in our hands we prepared β-keto sulfoxide (1b) in high enantiomeric purity (e.e. 80 %) by a modification of the reported procedure.[34,36] Clearly the strong acid used in the original published procedure is responsible for the racemization of the β-keto sulfoxide. The reason for the difference in the enantiomeric purity of (1a) and (1b) is unclear.

In Method C, (+)–*(R)*-(1a) was prepared from α-lithiated-(+)-methyl 2-methoxy-1-naphthyl sulfoxide (9) and methyl 3,4-dimethoxybenzoate, according to the method of Solladie using 2 equiv. of sulfoxide anion.[33] The enantiomeric purity of this compound was determined to be 98 % from ^1H NMR chiral shift studies using (-)-*(R)*-*N*-(3,5-dinitrobenzoyl)-α-phenylethylamine (6) as a chiral shift reagent, but the yield of this reaction was very low (25 %), the reaction is shown below.

Method C.

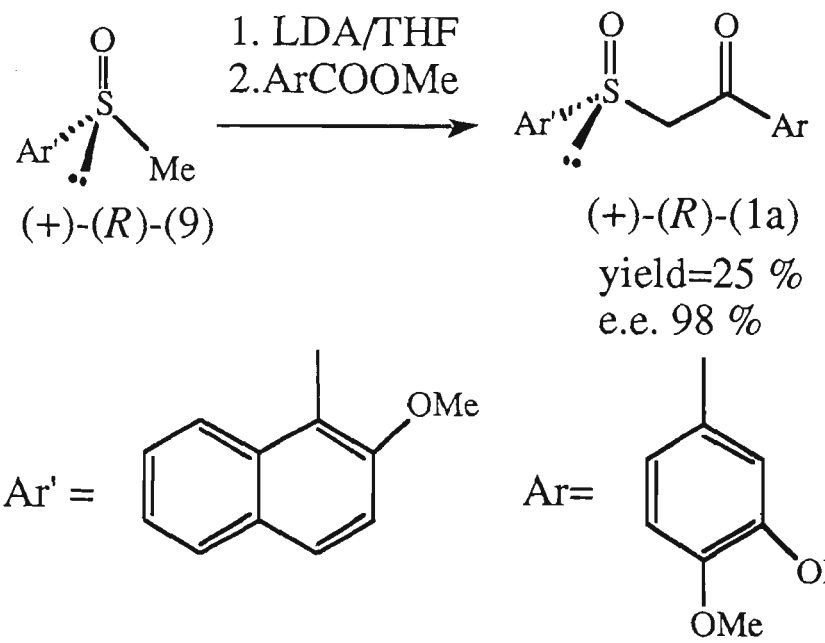


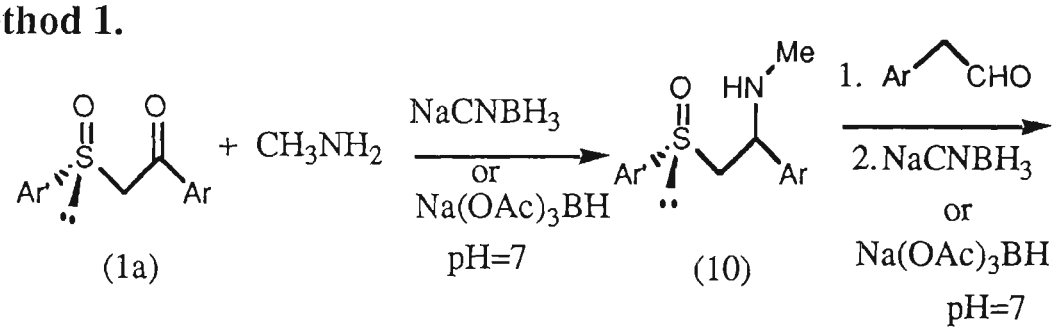
Table 4.1. ^{1}H NMR chemical shifts and coupling constants (Hz) for compounds (1a) and (1b).

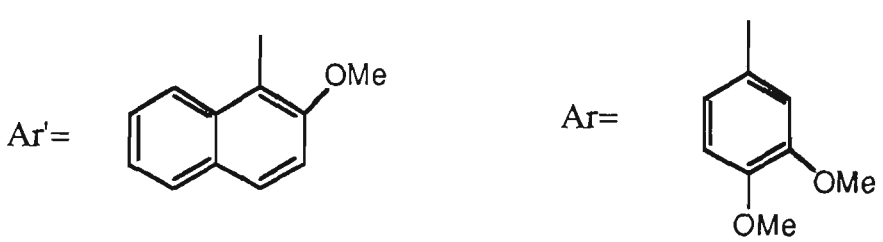
Compound	Chemical Shift (ppm)*		Coupling Constant (Hz)
	Ha	Hb	Jab
(1a)	5.02	4.85	13.2
(1b)	5.05	4.82	13.2
(1a)+(6) major	5.06	4.72	13.6
(1a)+(6) minor	5.04	4.70	13.6
(1b)+(6) major	5.10	4.73	14.0
(1b)+(6) minor	5.09	4.72	14.0

* The assignments of protons Ha and Hb may be reversed.

To prepare compound (2) from β-keto sulfoxide (1a) we have employed four different methods. In Method 1, reductive alkylation of β-keto sulfoxide (1a) with methylamine and either $NaCNBH_3$ or $Na(OAc)_3BH$ as reducing agent gave β-amino sulfoxide (10) in 56 % and 58 % yield respectively. Further reductive alkylation of (10) with 3,4-dimethoxyphenyl acetaldehyde and either $NaCNBH_3$ or $Na(OAc)_3BH$ as reducing agent gave β–amino sulfoxide (2) in 34 % overall yield with a d.r. of 75:25. The reaction is outlined below.

Method 1.

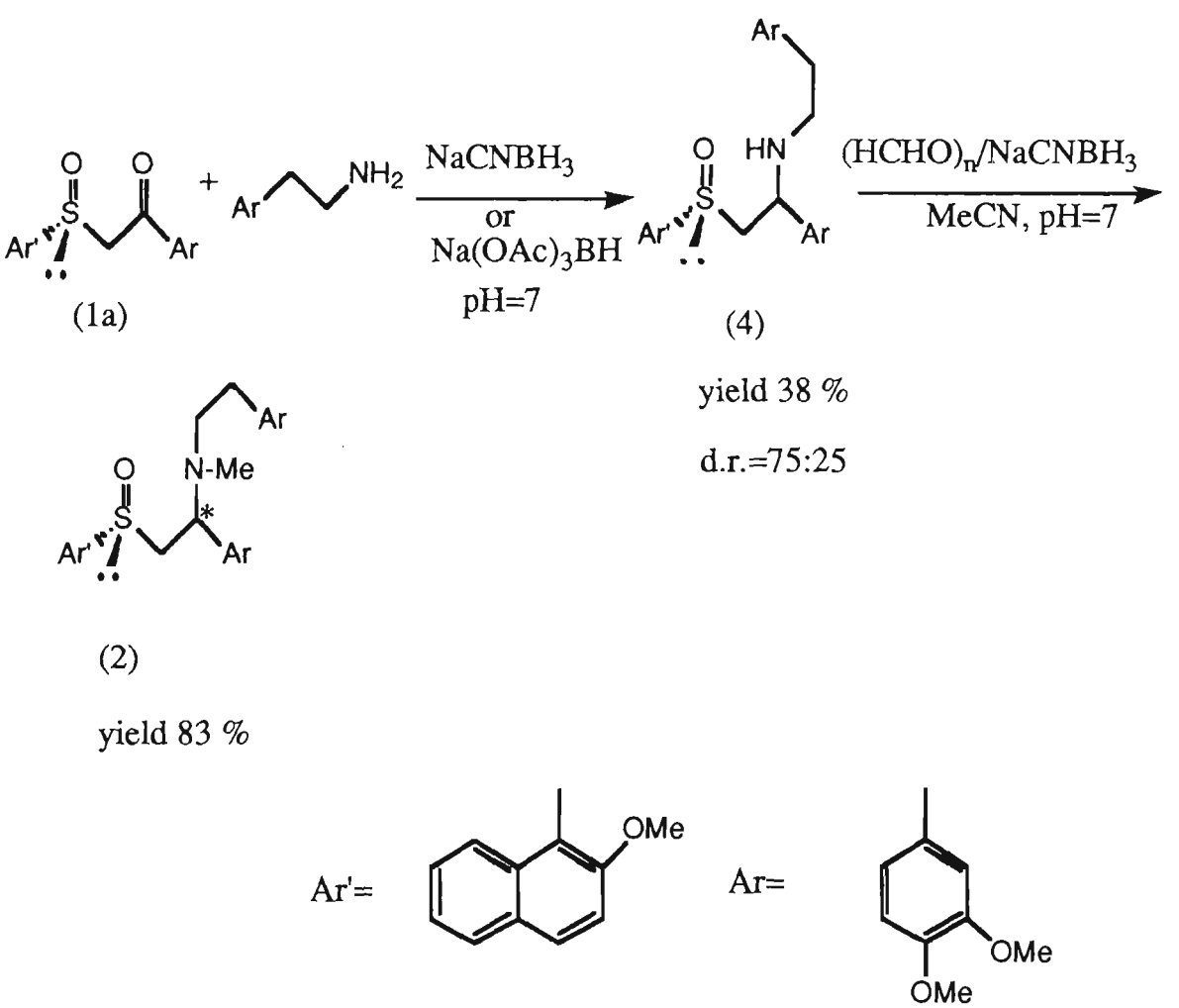




In Method 2, reductive alkylation of β-keto sulfoxide (1a) in the presence of 2-(3,4-dimethoxyphenyl)ethylamine gave the β-amino sulfoxide

(4) in 38 % yield. The diastereoselection was determined to be 75:25 from ^{1}H NMR spectral analysis. Reductive methylation of β–amino sulfoxide (4) with formaldehyde gave the β–amino sulfoxide (2) in 83% yield. The reaction is outlined below.

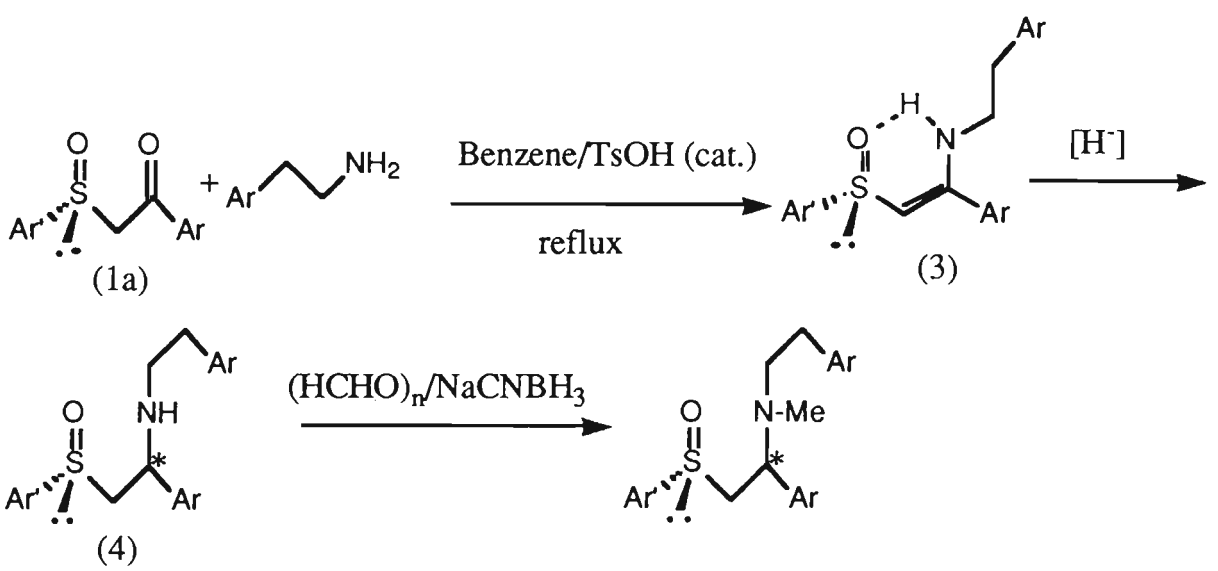
Method 2.



In Method 3, we prepared β-enamino sulfoxide (3) in 86 % yield from the reaction of (1a) and 2-(3,4-dimethoxyphenyl) ethylamine at reflux with the removal of water employing a Dean-Stark apparatus. The ^{1}H NMR spectrum of (3) indicated that this compound was completely in the enamine form (^{1}H NMR δ 4.60, 1 H, CH=C). We assume that the molecule has the

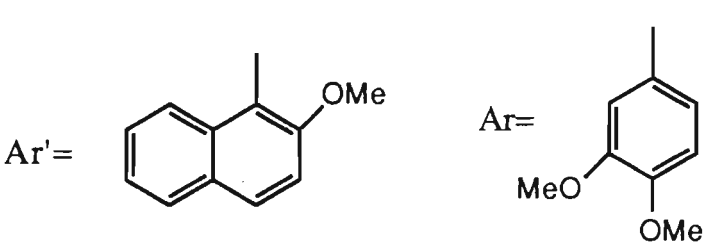
(Z) geometry shown in (3) due to a favourable H-bonding between the amino NH and the sulfoxide oxygen.[35a] Reduction of β-enamino sulfoxide (3) with $NaBH_4$ in a mixture of methanol and ammonia (9:1)[35b] at room temperature gave β-amino sulfoxide (4) in 95 % yield and the d.r. was 78:22.

Method 3.



overall yield 83 %

d.r.=78:22



Reductive methylation of β-amino sulfoxide (4) gave β-amino sulfoxide (2) in 83 % overall yield. The two diastereoisomers of (2) were separated easily by simple column chromatography. The ^{1}H NMR spectrum of the major diastereoisomer is shown in Figure 4.4. The major and minor diastereoisomers of (2) were the same for the synthesis of (2) from either methods 1, 2 or 3. The structure and diastereoisomer ratio of compounds (10), (4) and (2) were studied by ^{1}H, ^{13}C and DEPT NMR spectroscopic techniques (Figure. 4.3, 4.4, and 4.5).

Figure 4.3 shows a copy of part of the ^{1}H NMR spectrum of the crude reaction mixture from the reduction of (3) to the β-amino sulfoxide (4) by $NaBH_4$ in methanol and ammonia (9:1) at room temperature for 2 h. The proton Ha of the major and minor diastereoisomers of β-amino sulfoxide (4) are clearly shown as doublet of doublets at δ 3.18 (dd, J=10.4,13.2 Hz) and 3.25 (dd, J=5.6, 13.2 Hz) respectively, the ratio of the major and minor diastereoisomers is 78:22.

Figure 4.4 shows a copy of part of the ^{1}H NMR spectrum of the major diastereoisomer (2) from the reduction of (3) by $NaBH_4$ in methanol and ammonia at room temperature for 2 h and then reductive methylation of the resulting β-amino sulfoxide (4). The proton Hc of the major diastereoisomer of β-amino sulfoxide (2) is clearly shown as a doublet of doublets at δ 4.32 (dd, J=3.2 and 10.4 Hz).

Figure 4.5 shows a copy of the ^{13}C NMR spectrum for the β–amino sulfoxide (2), signals for C1 and C2 of this compound can be seen at δ 61.9 and 54.0 respectively.

Finally, in Method 4, we synthesised β-sulfinyl enamine (3) directly in 65 % yield by condensation of the anion of imine (11) with optically pure

(-)-(*S*)-(5). Reduction of the enamine (3) with various reducing reagents gave β-amino sulfoxide (4). Reductive methylation of β-amino sulfoxide (4) gave β-amino sulfoxide (2) as outline below.

Method 4.

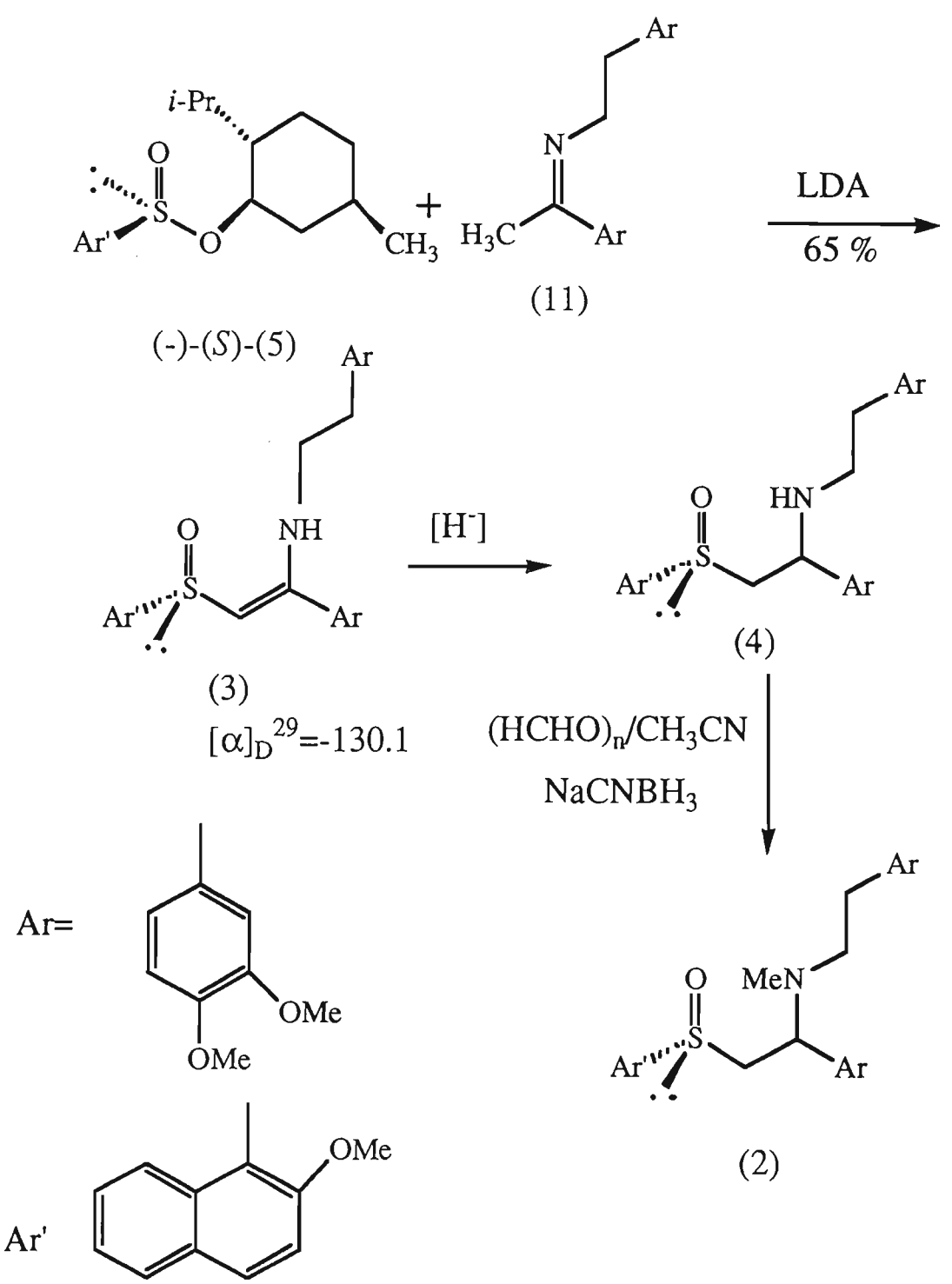
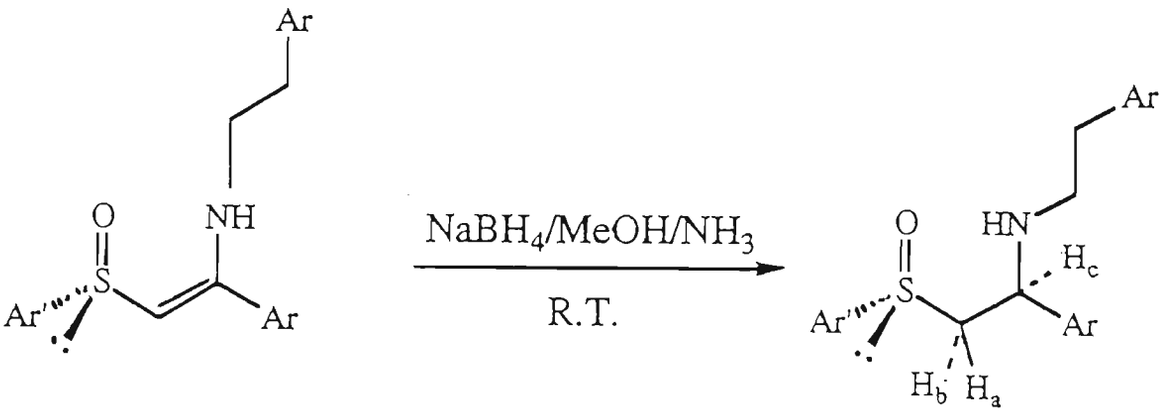
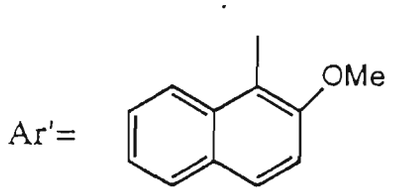
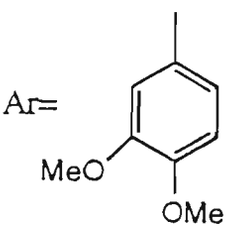


Figure 4.3. ^1H NMR spectrum ($CDCl_3$) of the crude reaction mixture from the reduction of β-enamino sulfoxide (3) by $NaBH_4$ in $MeOH/NH_3$ at room temperature to give β-amino sulfoxide (4).



(3) (4)





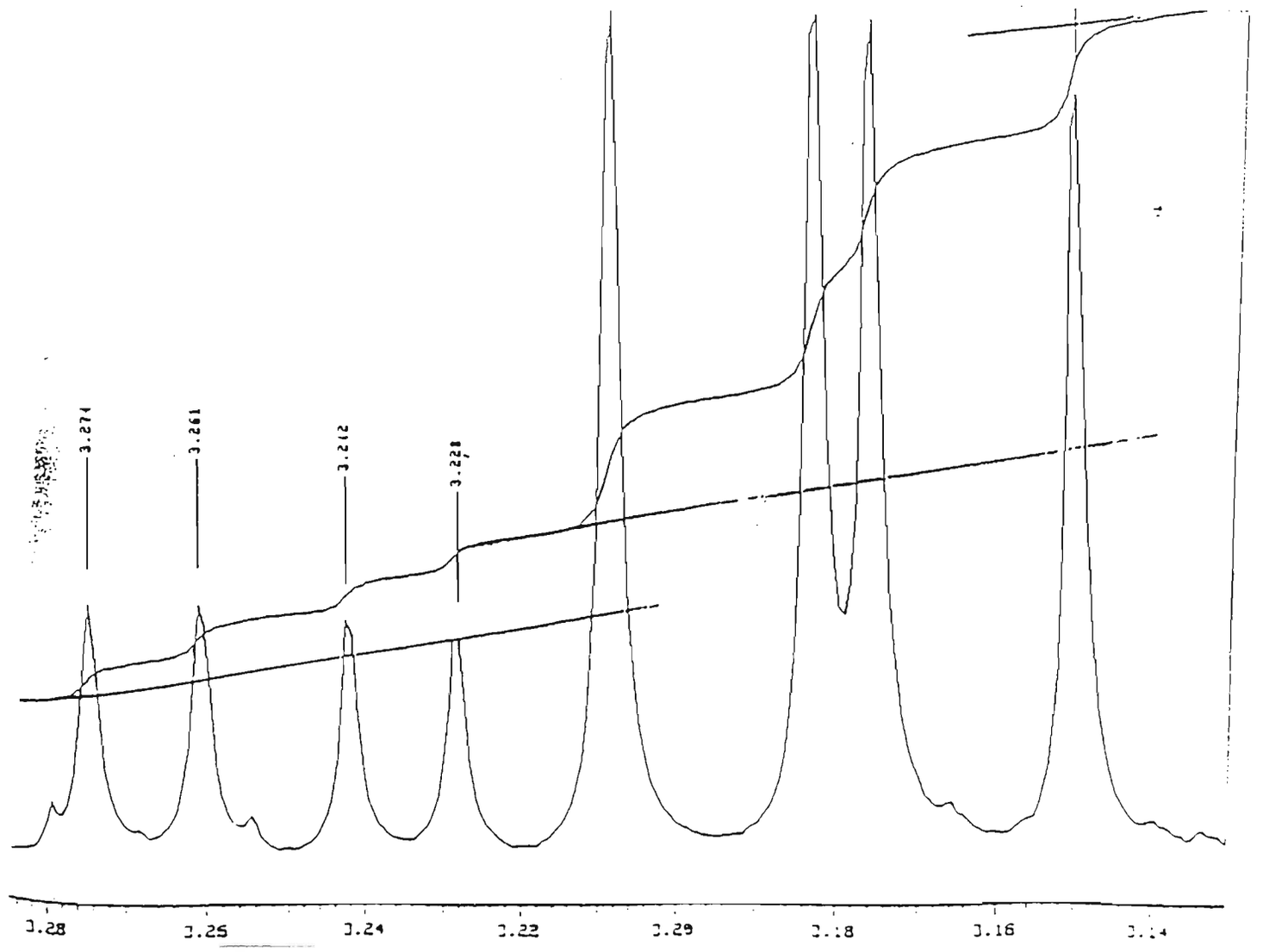
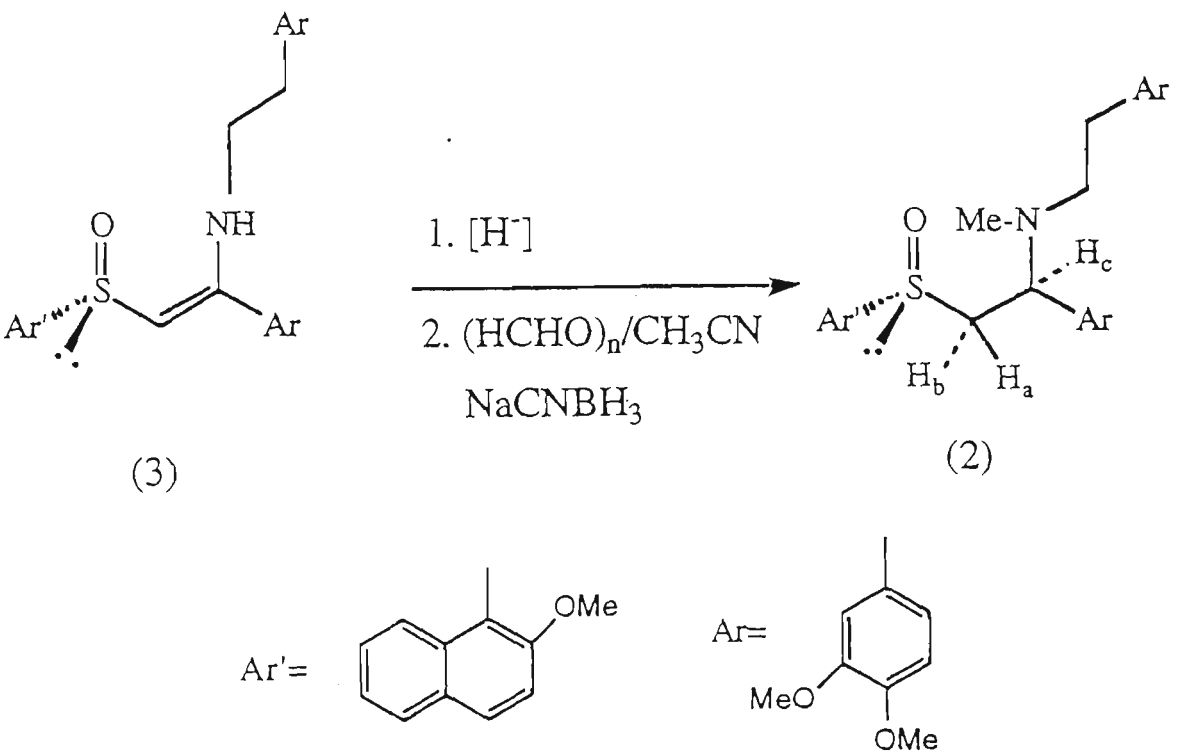


Figure 4.4. ^1H NMR spectrum ($CDCl_3$) of the major diastereoisomer of β-amino sulfoxide (2).



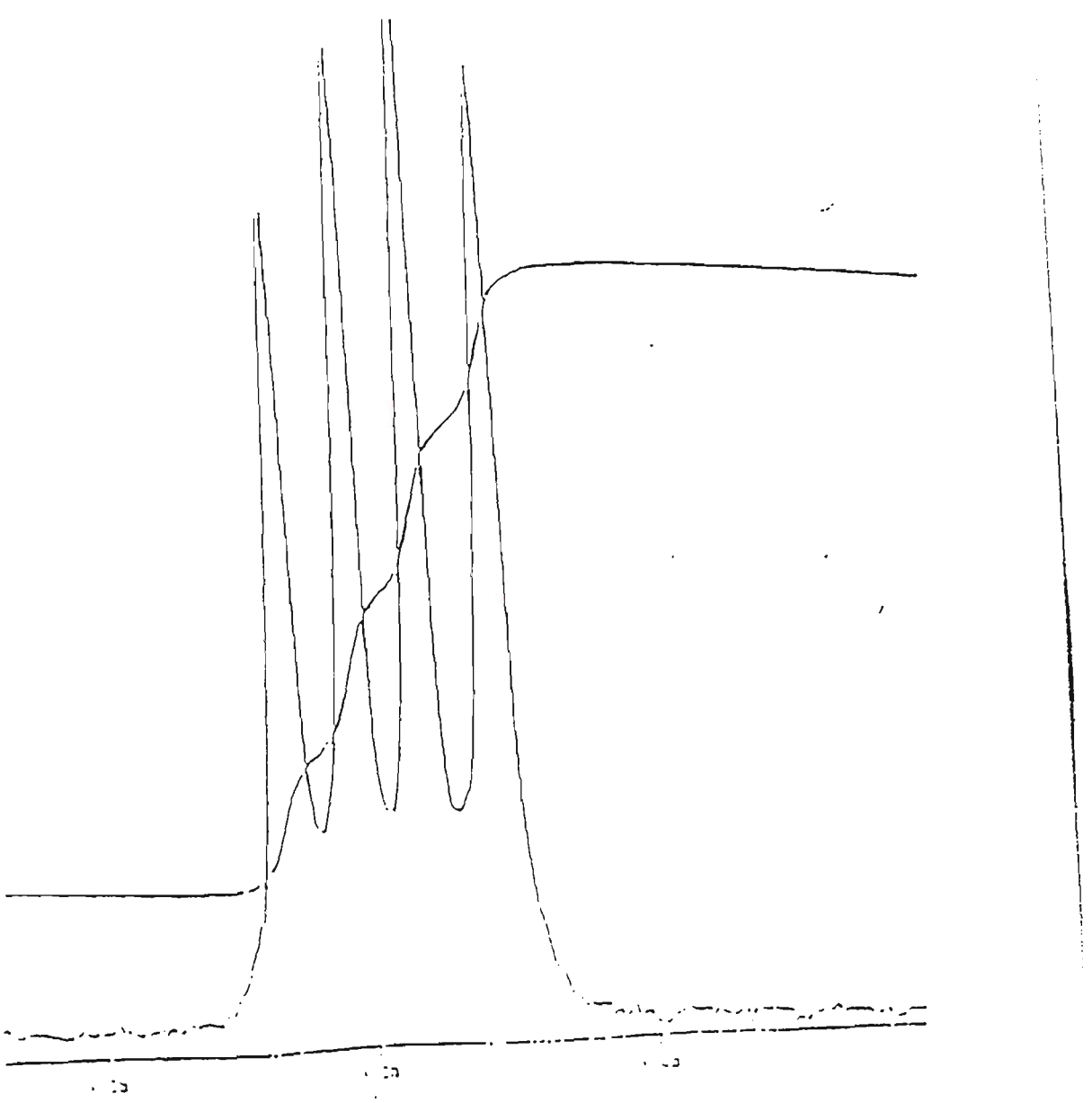
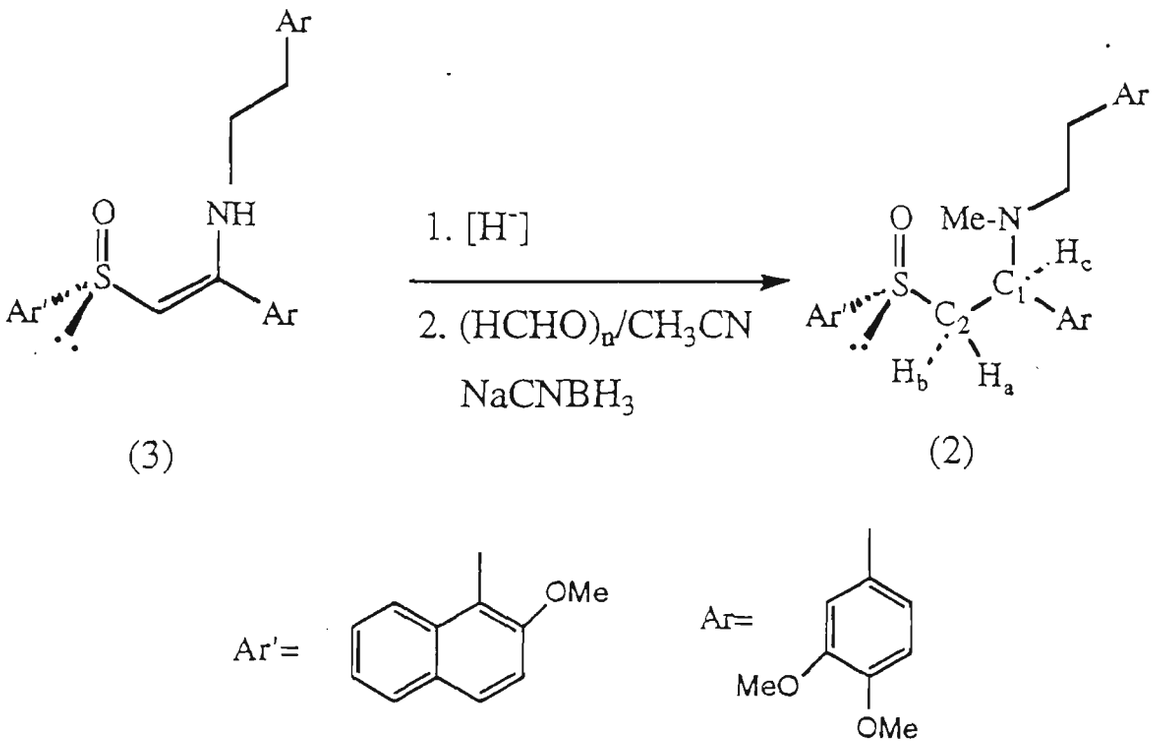
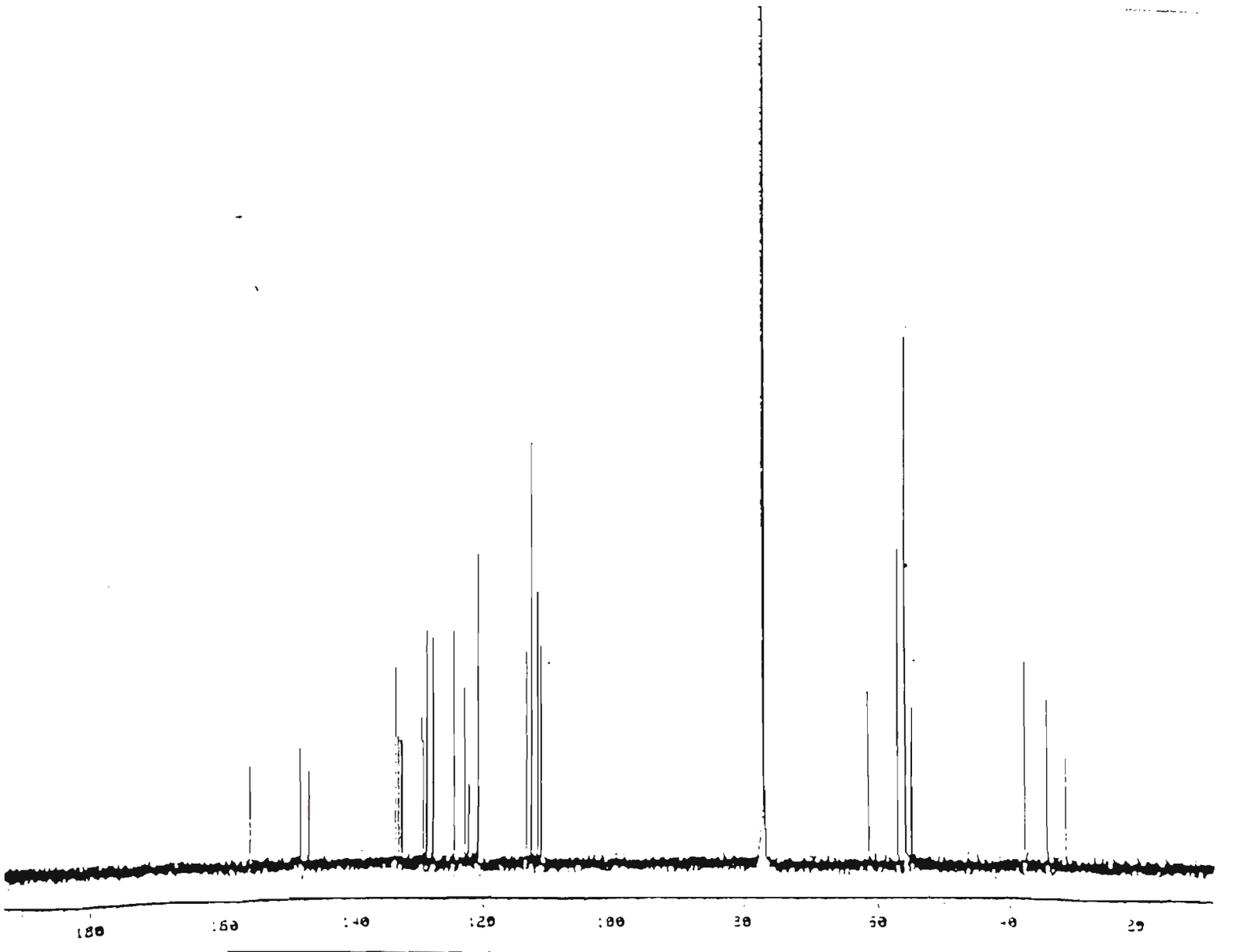
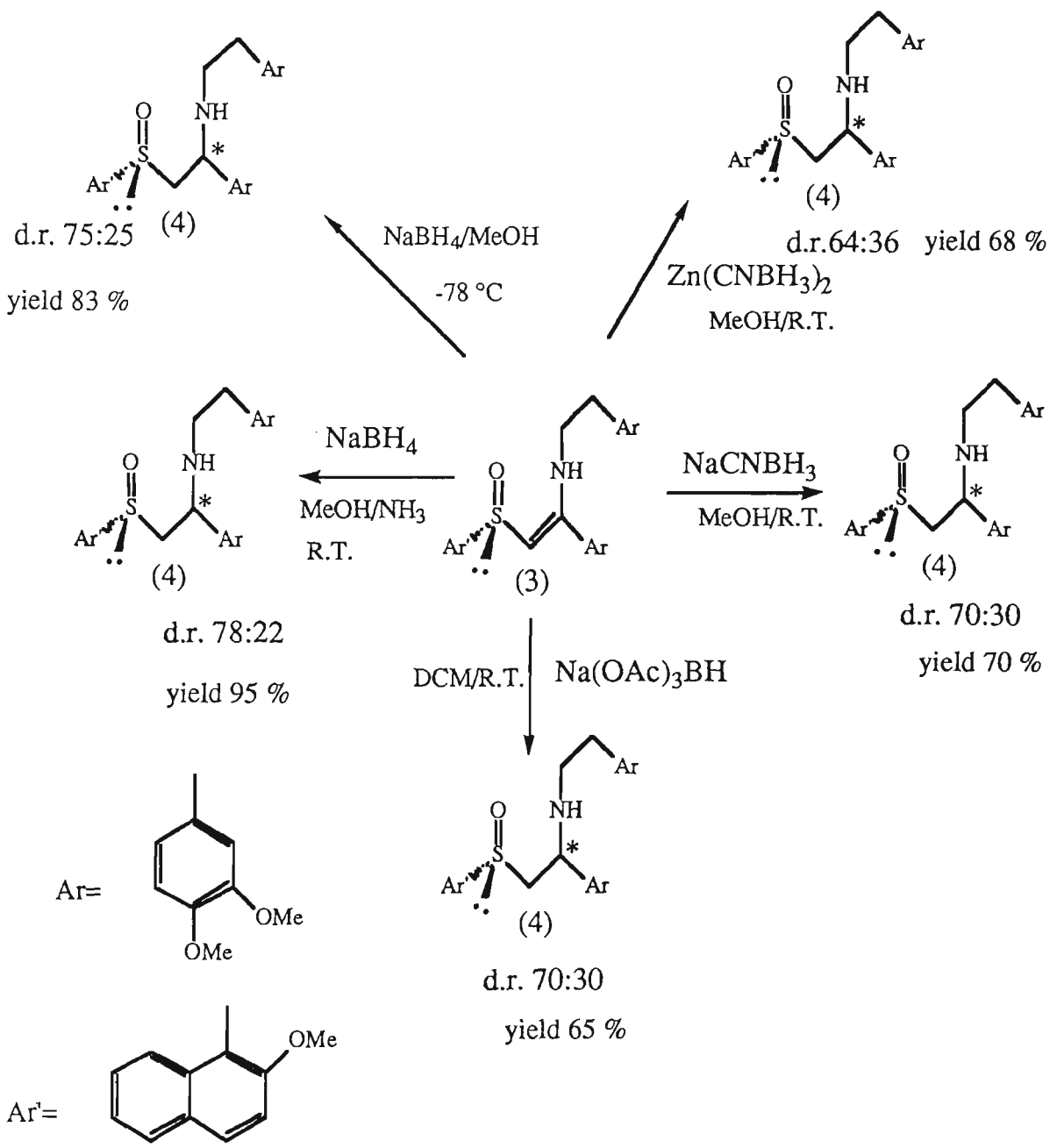


Figure 4.5. ^{13}C NMR spectrum ($CDCl_3$) of the β-amino sulfoxide (2).





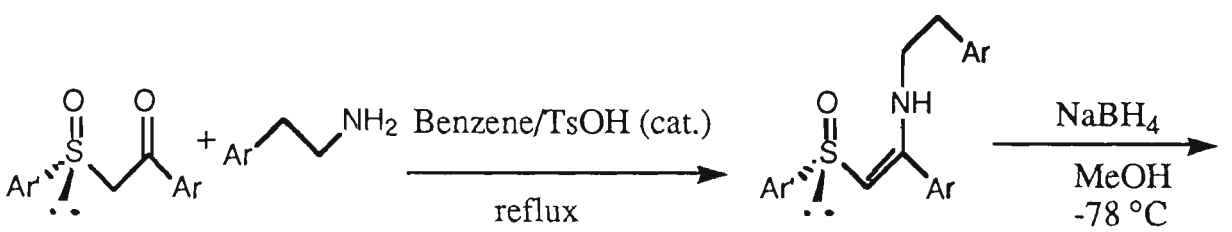
To find optimal conditions for preparing the β-amino sulfoxide (4) we tried different reducing reagents ($NaCNBH_3$, $Zn(CNBH_3)_2$, $Na(OAc)_3BH$ and $NaBH_4$) to reduce β–sulfinyl enamine (3). The yields and d.r. of these reduction reactions are shown below. Clearly the reduction with $NaBH_4$ in a mixture of $MeOH/NH_3$ (9:1) at room temperature proceeds with the highest diastereoselection.



To study the effect of the steric demand of the sulfoxide aryl substitutent on the diastereoselectivity of these reduction, the β-enamino sulfoxides (3) and (13) were reduced under identical conditions. Treatment

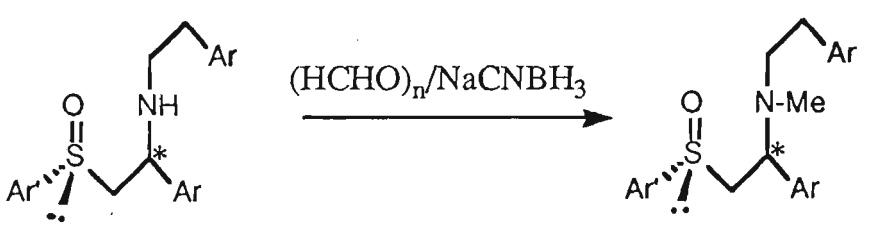
of β-enamino sulfoxides (3) and (13) with $NaBH_4$ at -78 °C in methanol gave β-amino sulfoxides (4) and (14) respectively. Reductive methylation of β-amino sulfoxides (4) and (14) with $NaCNBH_3$ and formaldehyde gave β-amino sulfoxides (2) and (15) in 83 % yield (d.r. 75:25) and 80 % yield (d.r. 57:43) respectively (Scheme 4.3). The d.r. of the β-amino sulfoxides (2) and (15) were determined from ^1H NMR (400 MHz) spectral analysis.

Scheme 4.3. Synthesis of (2) and (15).



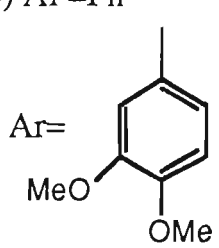
(1) Ar'=2-MeO-1-naphthyl
(12) Ar'=Ph

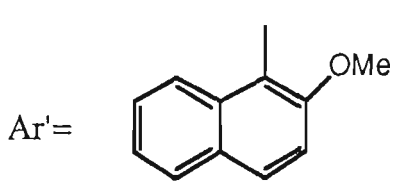
(3) Ar'=2-MeO-1-naphthyl
(13) Ar'=Ph



(4) Ar'=2-MeO-1-naphthyl
(14) Ar'=Ph

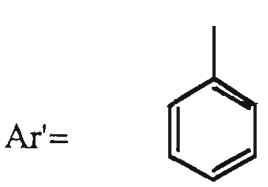
(2) Ar'=2-MeO-1-naphthyl
(15) Ar'=Ph





overall yield 83 %

d.r. 75:25



Overall yield 80%

d.r. 57:43

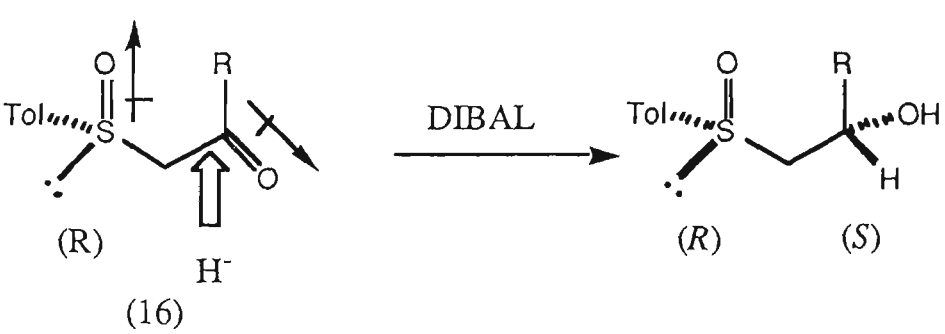
Proof of stereochemistry of compounds (2), (4) and (10)

Table 4.3 summarises the ^1H NMR spectral data for H_a, H_b and H_c for the major diastereoisomer (10a) of (10) and the major (4a) and minor (4b) diastereoisomers of (4). The analogous data for compounds (A) and (B) that are reported to have the (*Rs*, 1*S*) and (*Rs*,1*R*) stereochemistry respectively[28] are also included in Table 4.3. From a comparison of the coupling constants J_{ac} and J_{bc} for (10a) and (4a) with those of (A) and (B) it is clear that (10a) and (4a) have the *(Rs, 1S)* stereochemistry.

A major difference between the ^1H NMR spectral data of (A) and (B) and (10a), (4a) and (4b) is the chemical shift of Ha and Hc which are slighly deshielded in the latter three compounds. This effect may be a consequence of the 2-methoxy-1-naphthyl group.

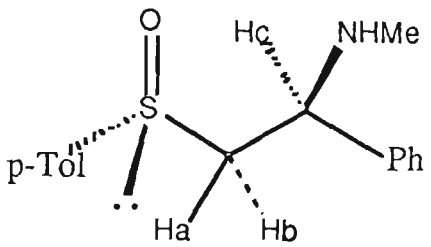
Solladie and co-workers[103] reported that the stereochemistry of the major diastereomeric product from the reduction of *(R)*-β-keto sulfoxides with DIBAL had the (*Rs*, 1*S*) stereochemistry while that from the reduction with DIBAL/$ZnCl_2$ had the (*Rs*, 1*R*) stereochemistry as shown below.

In the DIBAL reduction addition of hydride was thought to occur via attack of hydride on the conformation (16) in which dipole-dipole interactions between the C=O and the S=O groups are minimized.

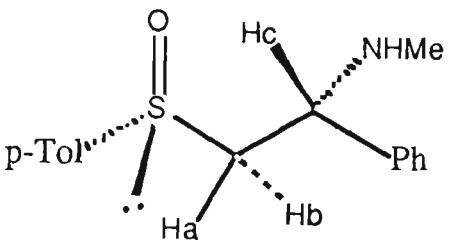


(16)

Table 4.3. ^1H NMR ($CDCl_3$) data of the major and minor diastereoisomers of (10) and (4).



(*1S, Rs*)-(A)

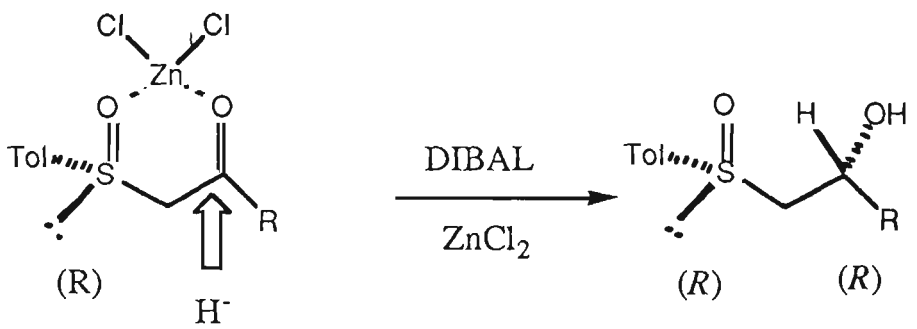


(1*R, Rs*)-(B)

Compound	Configu ration	Chemical shift (ppm) Ha	Hb	Hc	Coupling constants (Hz) Jac	Jbc	Jab
A[a]	*(1S, Rs)*	3.00	2.93	4.06	10.2	3.4	13.4
B[a]	*(1R, Rs)*	3.22	2.81	b	8.4	5.5	13.1
(10a)	*(1S, Rs)*	3.19	c	4.24	10.4	3.6	13.2
(4a)	*(1S, Rs)*	3.18	c	4.32	10.4	3.2	13.2
(4b)	*(1R, Rs)*	3.25	c	4.15	8.4	5.6	13.1

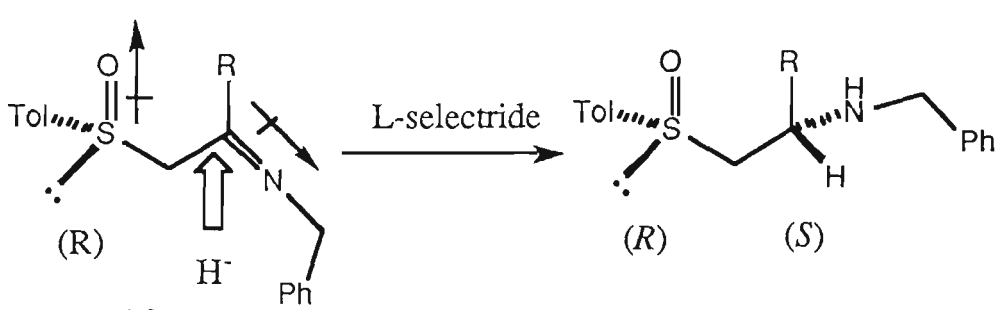
a: from reference 28.
b: signal not reported.
c: signals obscured by MeO resonances.

Addition of hydride to the zinc chelated form (17) from the least sterically demanding face (i.e. *anti* to the *S*-tolyl group) of the ketone accounted for the stereochemical outcome of the DIBAL/$ZnCl_2$ reduction of these compounds.

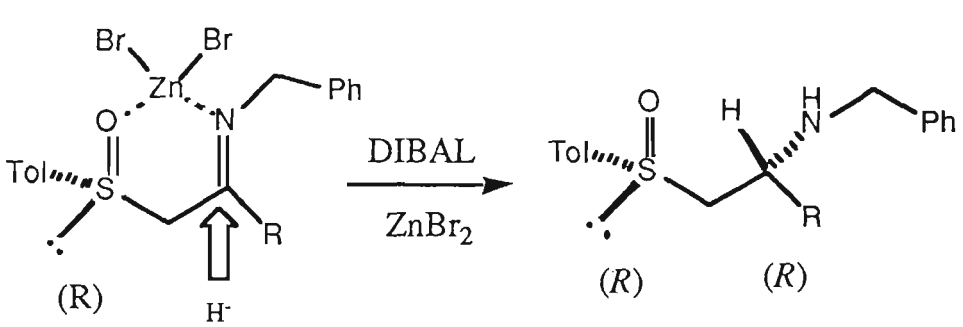


(17)

Carreno and co-workers[30b] reported the stereochemistry of the major diastereomeric product of the reduction of β-imino sulfoxide (18) with L-Selectride had the (*Rs*, 1*S*) stereochemistry while that from the reduction with $ZnBr_2$/DIBAL had the (*Rs*, 1*R*) stereochemistry as outline below. The chelated intermediate (19) has been invoked to explain the stereochemical outcome of this reduction.

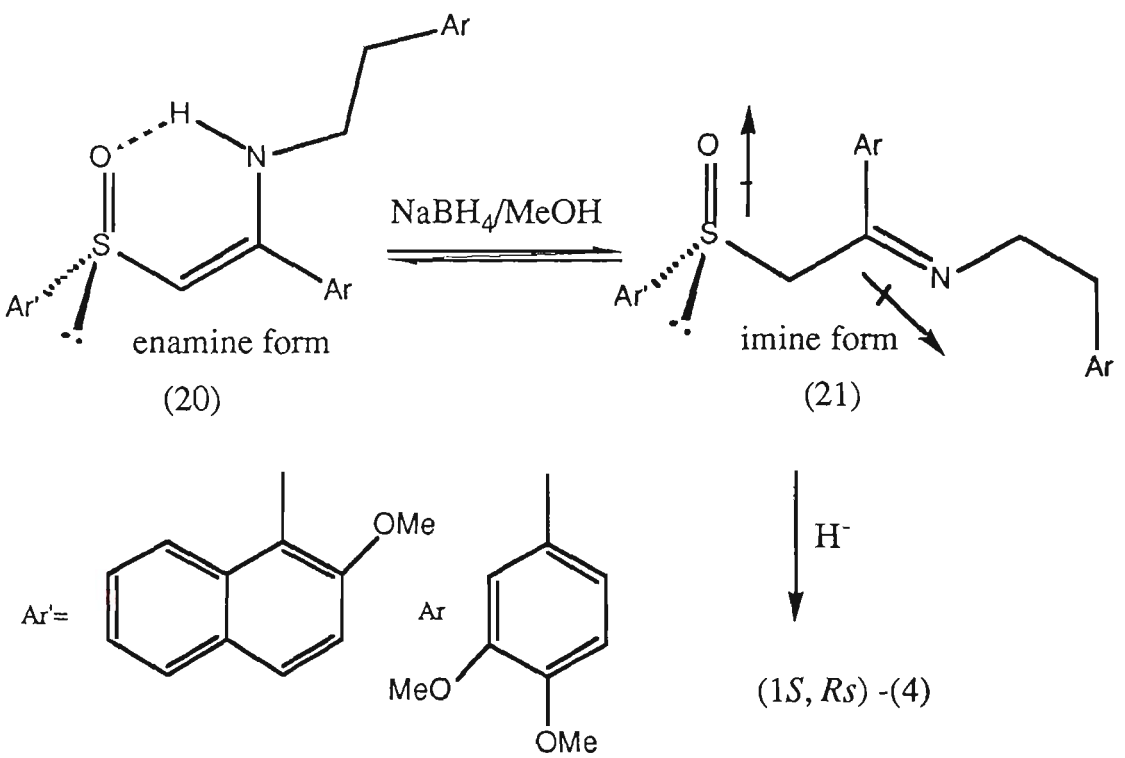


(18)



(19)

In our reductions of (3) with NaBH4 in methanol we assume that reduction occurs via the imine form (21) which is in equilibrium with the observed enamine form (20). By analogy with the reduction of β-keto sulfoxides in the absence of a chelating Lewis acid, reduction should occur on (21) to give the (*Rs*, 1*S*) product.

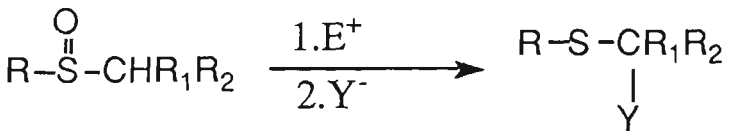


Our attempts to reduce (3) with L-Selectride or DIBAL in THF failed and only unreduced starting material was isolated. We assume that in THF the above equilibrium favours only the enamine form (20) which can not undergo reduction.

ATTEMPTED PUMMERER TYPE CYCLIZATION OF β-AMINO SULFOXIDE (2).

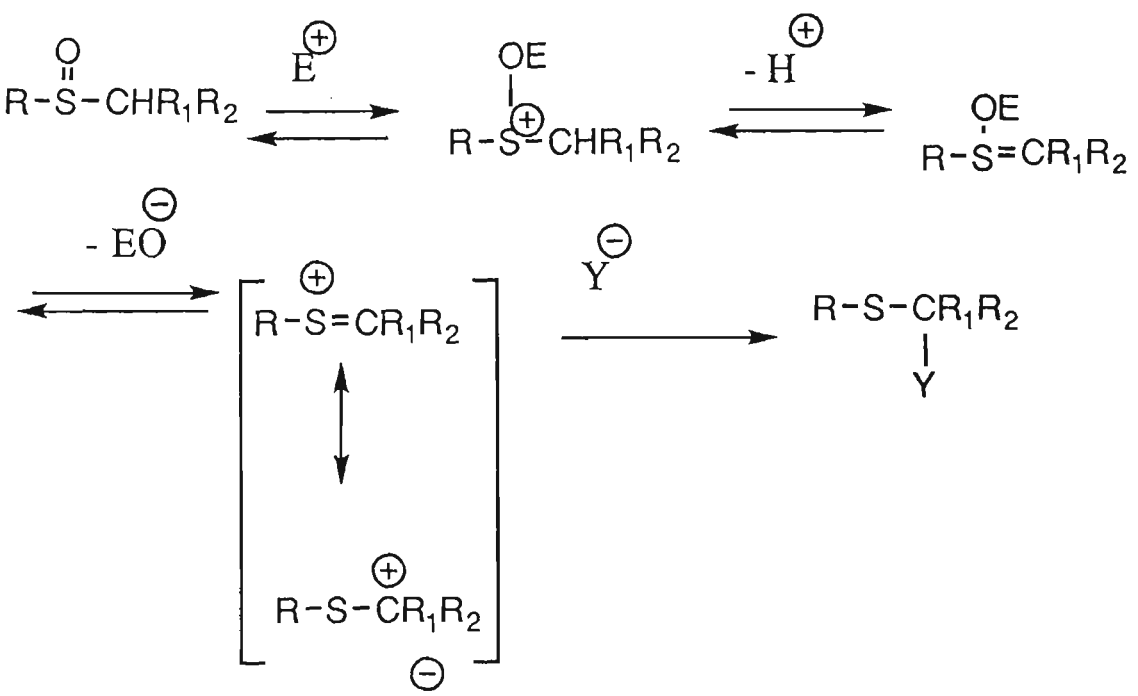
As was mentioned in the Introduction, the Pummerer reaction involves the formation of an α-functionalised sulfide from a sulfoxide bearing at least one α–hydrogen atom. The reaction can also be described as

an internal redox process where the S=O group is reduced and the α-carbon is oxidised.



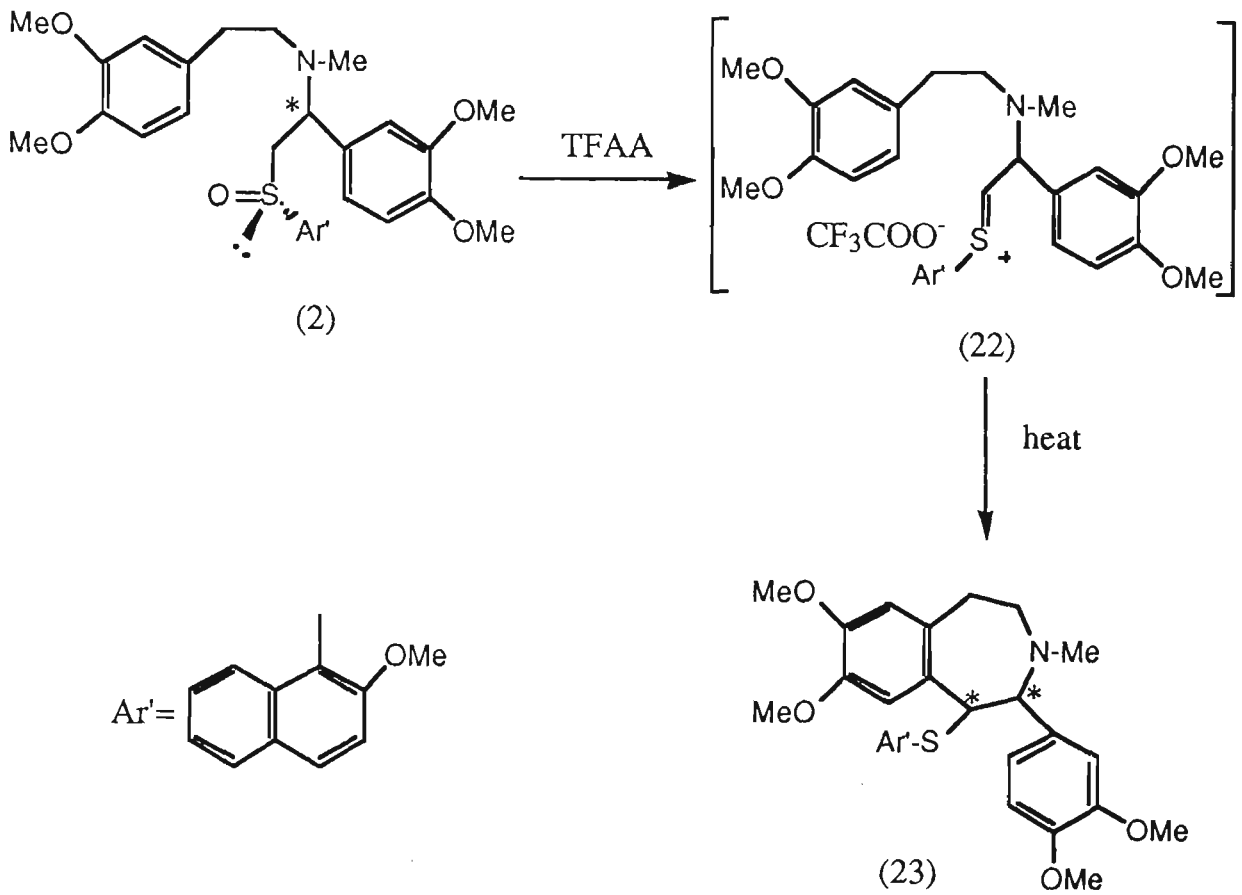
Y=OH ,OOCR , Halogen , OR , SR , NR_2 .

A generalised mechanism for the Pummerer reaction has been reported as shown below.[18]



Several methods were employed during this study in an attempt to prepare the benzazepine (23), via the Pummerer cyclization of (2), via the reaction intermediate (22) as shown in Scheme 4.4.

Scheme 4.4. Proposed Pummerer cyclization reaction.

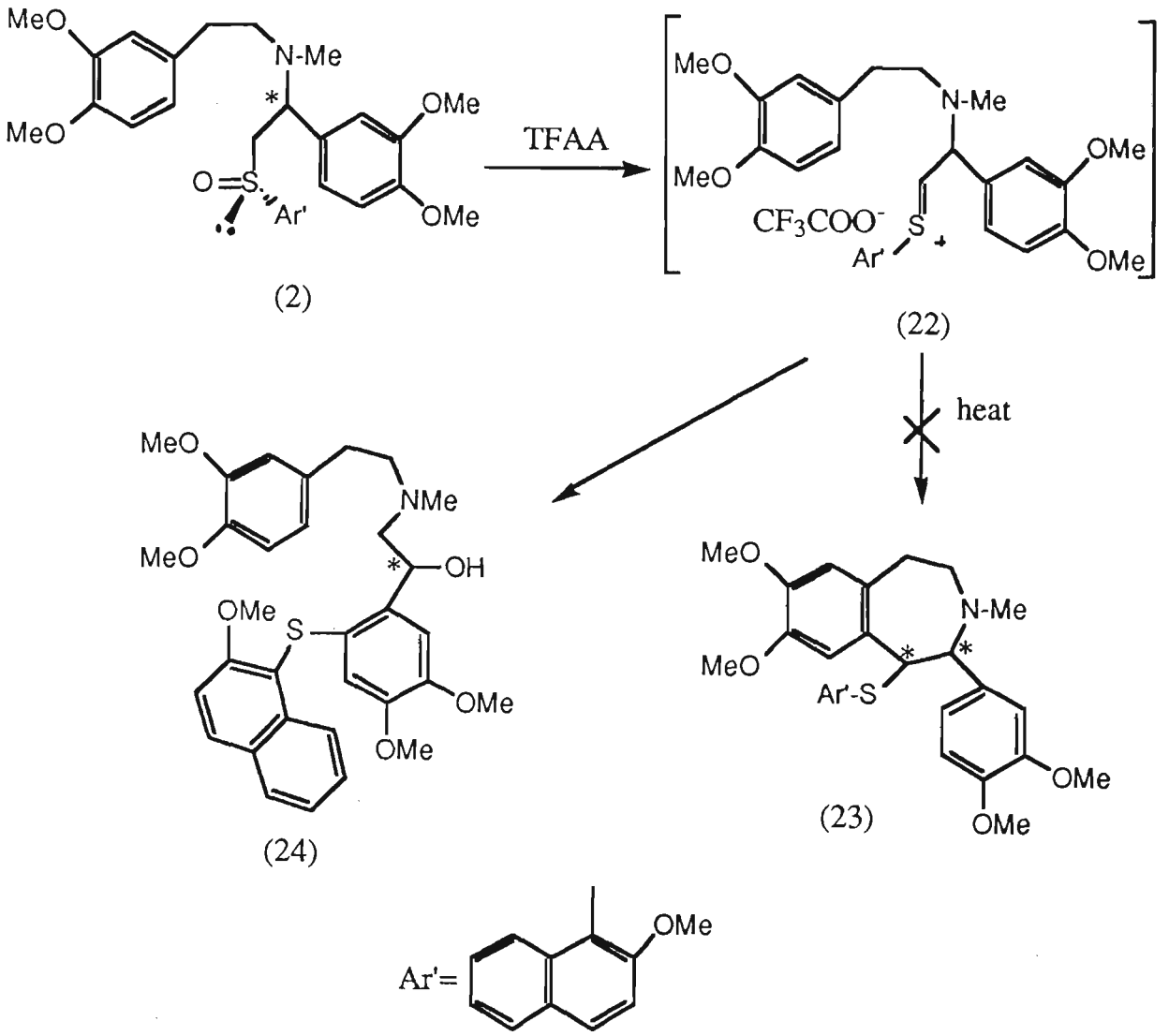


Treatment of (2) under standard Pummerer cyclization condition, i.e. with TFAA at 0 °C and then at 80 °C,[21] or with TsOH at reflux,[23] or with TFAA and $SnCl_4$ at 0 °C and then at room temperature,[104] gave a complex mixture of reaction products.

We also tried the chlorination of compound (2), with NCS to give the corresponding α-chloro sulfoxide. Lewis acid catalysed Friedel-Crafts type alkylation of α-chloro sulfoxides is known,[105] however the chlorination of (2) gave a complex mixture of products.

Treatment of (2) in DCM with 1.2 equiv. of TFAA and 3 equiv. of TFA at 0 °C for 15 min. in a sealed tube under argon and then heating at 90 °C for 2 h gave, after an aqueous work up only the alcohol (24) in 86 % yield. None of the benzazepine compound (23) could be found from this reaction (Scheme 4.5).

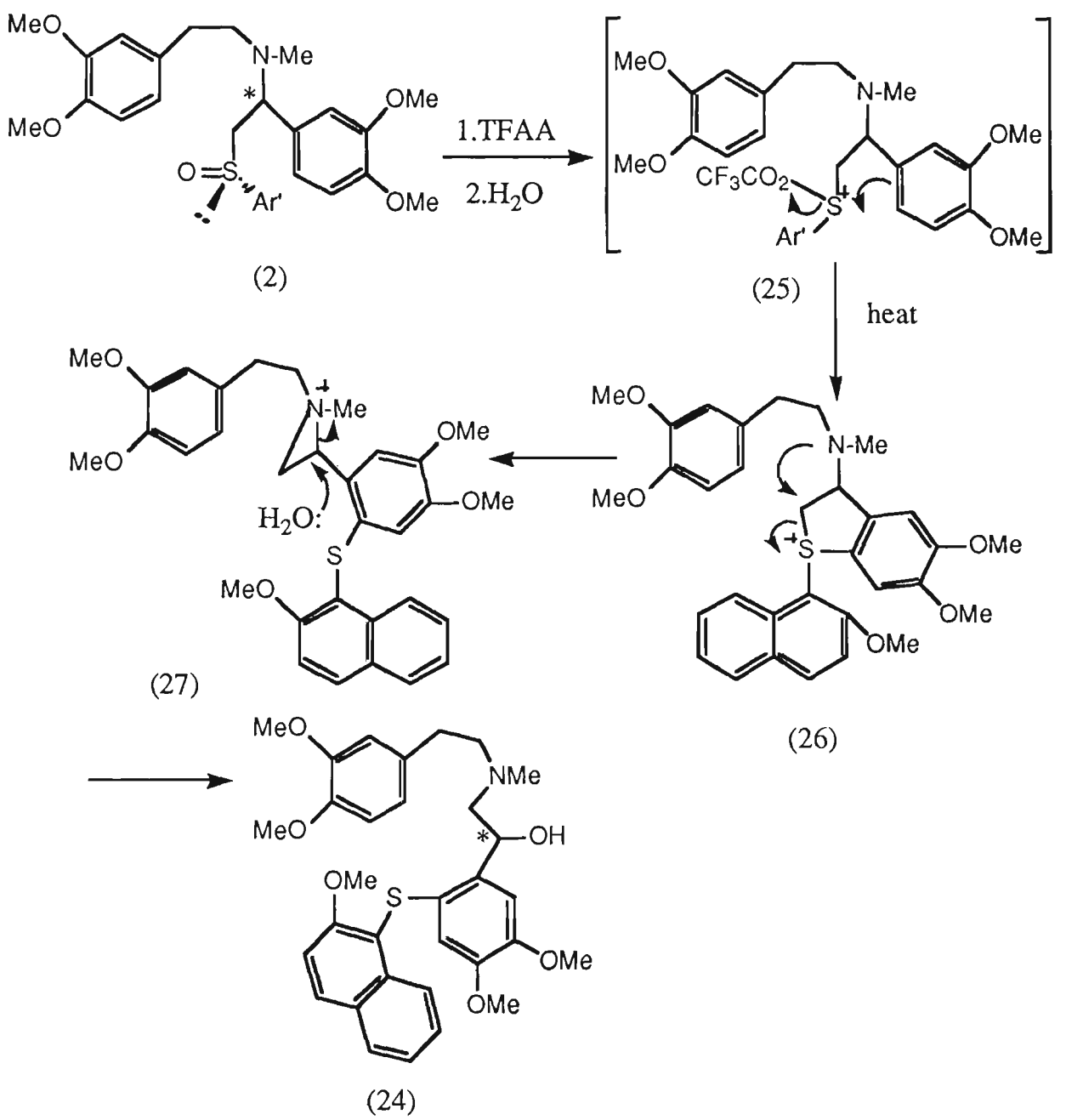
Scheme 4.5. Pummerer reaction of (2).



We believe the formation of alcohol (24) occurs via the mechanism outlined in Scheme 4.6. At first, after addition of trifluoroacetic anhydride, the intermediate (25) is produced in the reaction mixture. Electrophilic aromatic substitution of (25) will give the five member ring sulfonium salt (26). Addition of the lone pair of nitrogen produces the aziridinium salt (27), and finally, after addition of water to the three member ring of (27) the alcohol (24) is produced. This latter reaction most likely occurs during the aqueous work up of this reaction. Attempts to convert the intermediate (25) to the desired (22) by the addition of base (diisopropylethylamine)[106]

prior to heating the reaction mixture gave no identifiable products. The alcohol (24) had no optical rotation and was therefore most likely racemic. This result suggests that ring opening and ring closure of the aziridine ring of (27) must have occurred to give a racemic aziridinium ion.

Scheme 4.6. Proposed mechanism for the formation of (24).



The structure of compound (24) was confirmed by ^{1}H, ^{13}C, DEPT, COSY, HMBQ (heteronuclear multiple quantum coherence) and HMBC

(heteronuclear multiple bond correlation) NMR spectroscopy (Figure. 4.5, 4.6, 4.7, 4.8 and 4.9).

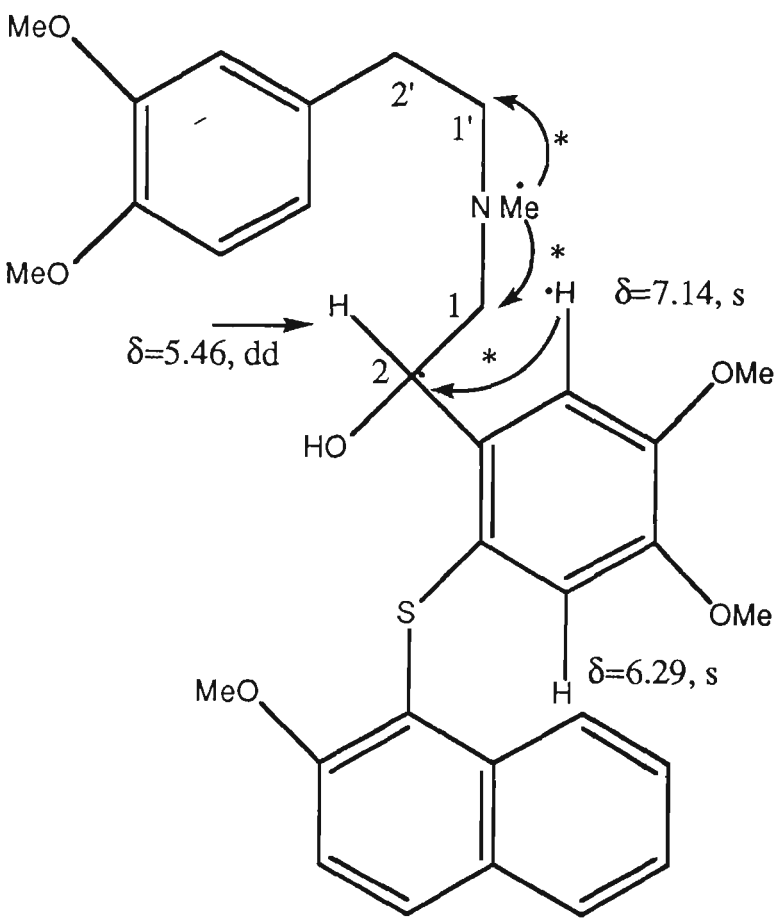
The ^1H NMR spectrum of (24) showed two Ar<u>H</u> singlets at δ 6.29 and δ 7.14 which indicated that substitution had occurred at one of the phenyl rings to give a 1,2,4,5 tetrasubstituted benzene. The ^1H NMR spectrum showed a doublet of doublets at δ 5.46, consistent with H_c in the system Ar-CH_c(OH)CH_aH_b-NMe-, H_a and H_b were located at δ 2.60 and δ 2.70 from COSY and HMQC NMR spectral analysis. (Figure 4.9)

The DEPT NMR spectrum showed three CH_2 groups, consistent with, -CH_2-CH_2N(Me)CH_2-, twelve CH groups (1 aliphatic and 11 aromatic CH groups) and six CH_3 groups (one *N*-Me and five OMe groups).

Figure 4.5 A summary of the NMR data of compound (24).

DEPT: 3 CH_2 (aliphatic)

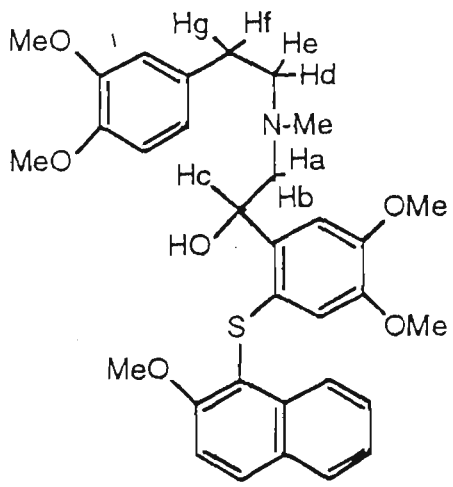
12 CH



* From HMBC

The HMBC NMR spectrum showed a cross peak between C2 and the aromatic proton at δ 7.14 indicating that C2 was attached to the aromatic ring. Other cross peaks in the HMBC NMR spectrum of (24), that were consistent with its structure, were those between the NMe protons and C1 and C1' as shown in Figure 4.5.

Figure 4.6. The COSY spectrum of the alcohol (24).



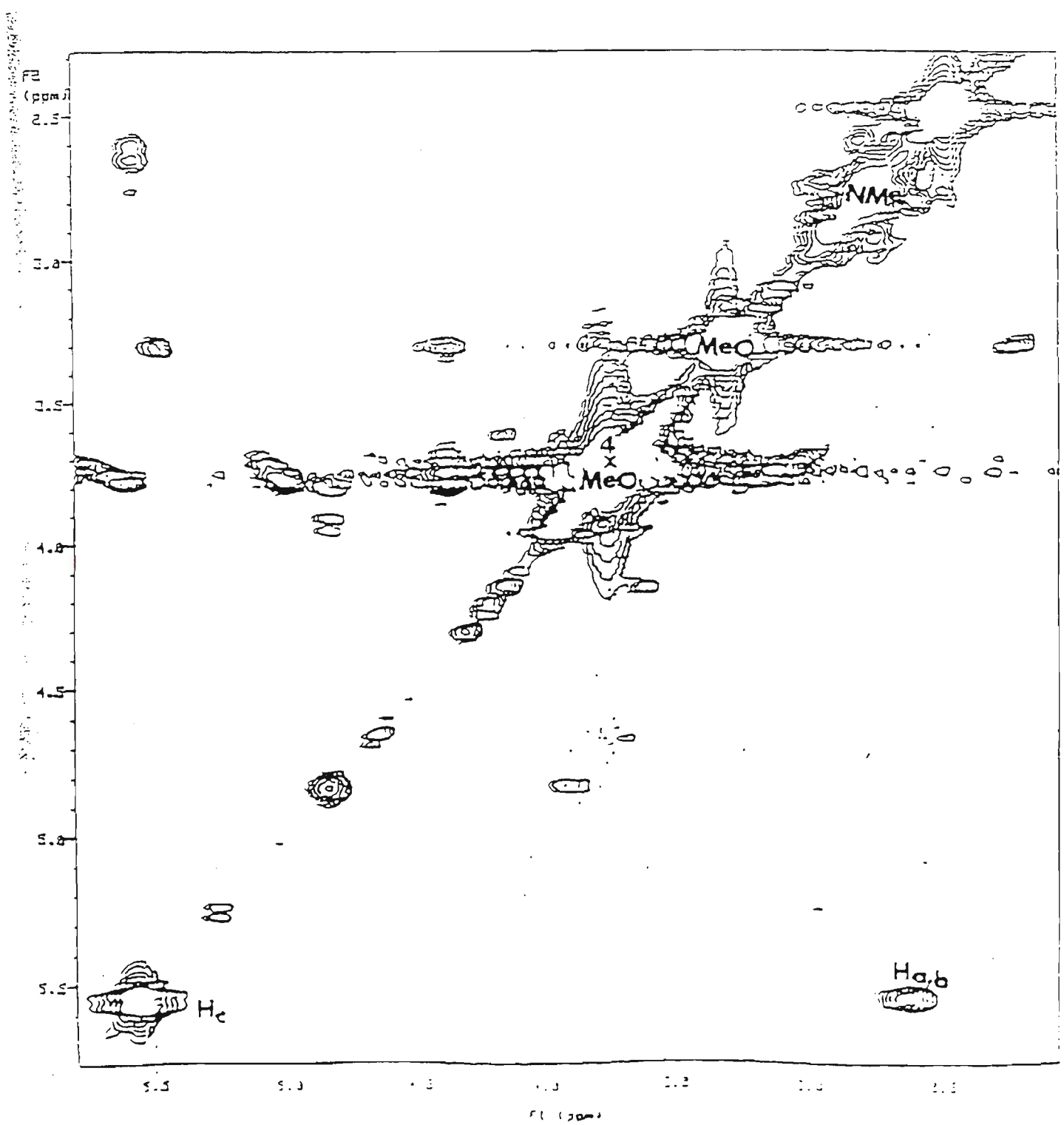


Figure 4.7. ^{13}C NMR assignments of the alcohol (24)

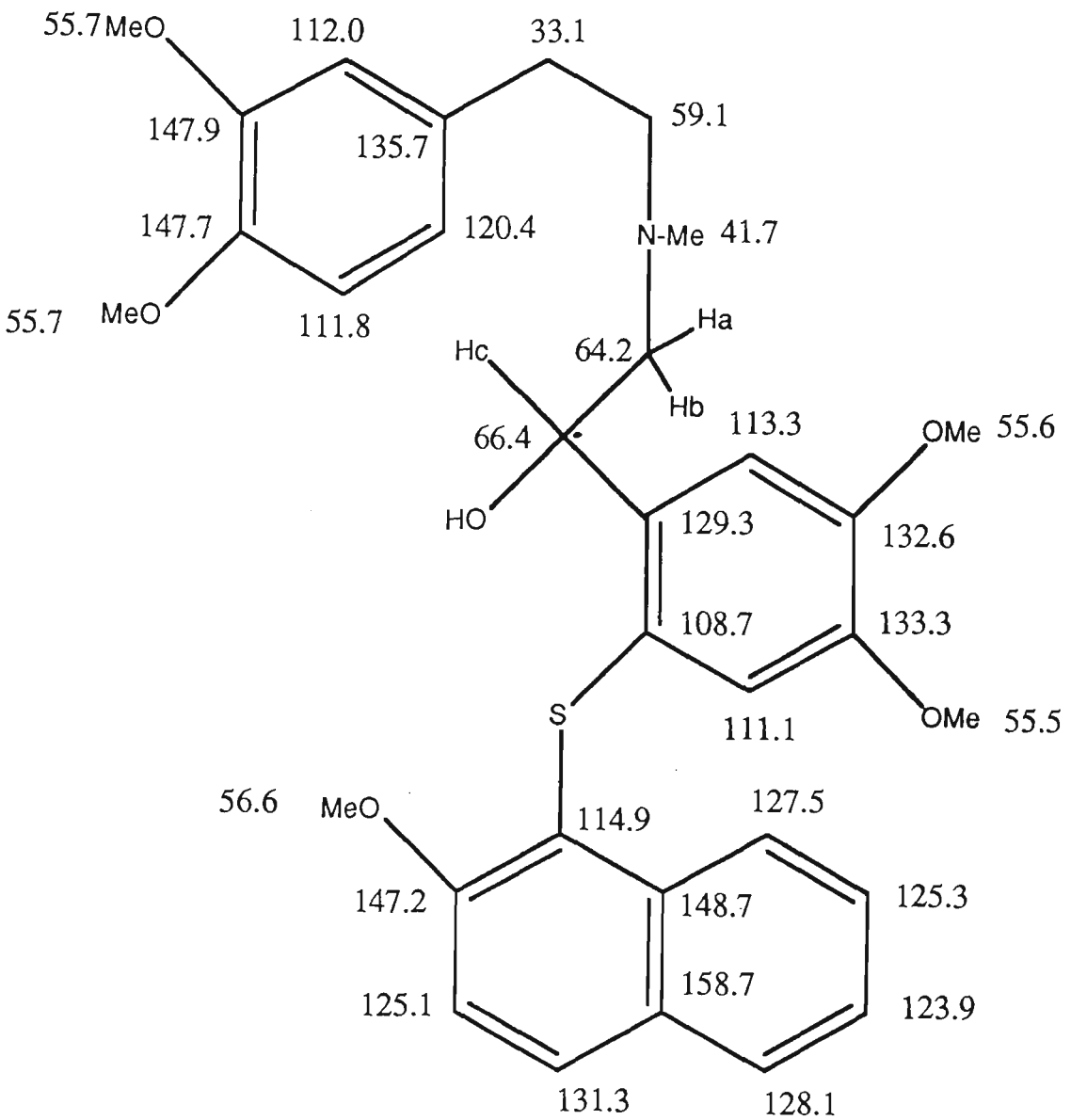
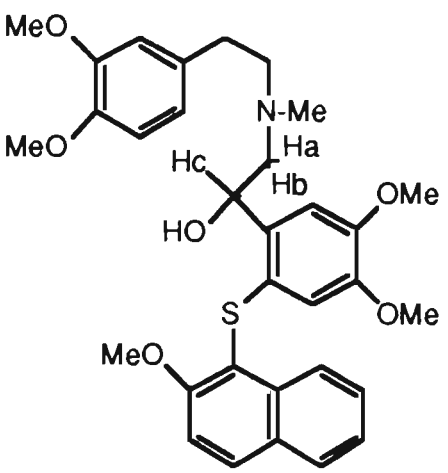


Figure 4.8. The DEPT NMR spectrum of alcohol (24)



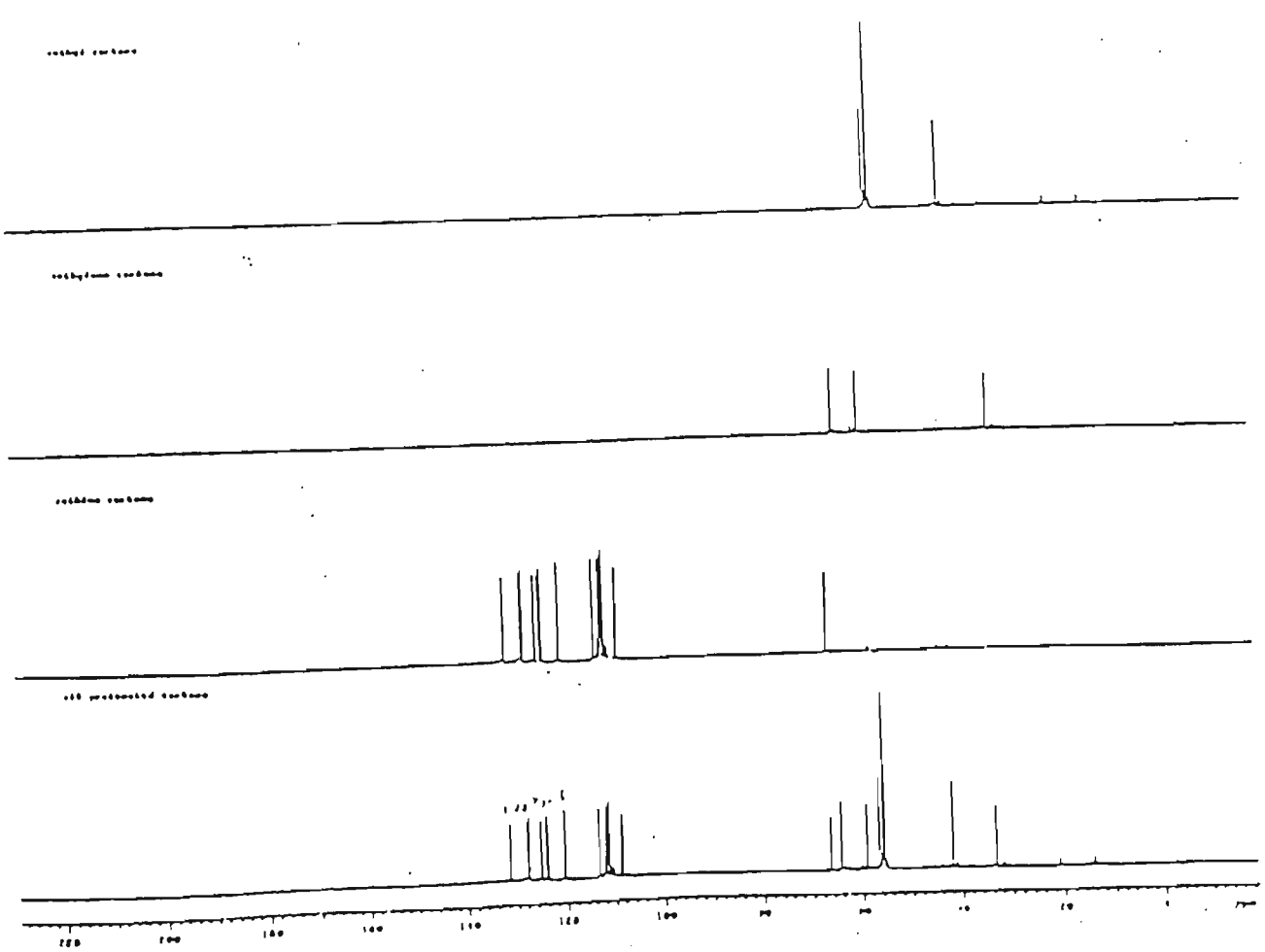
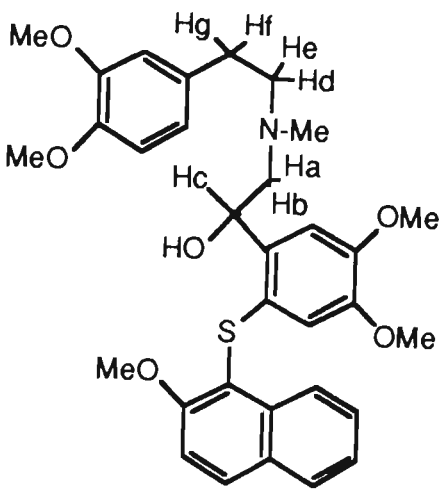
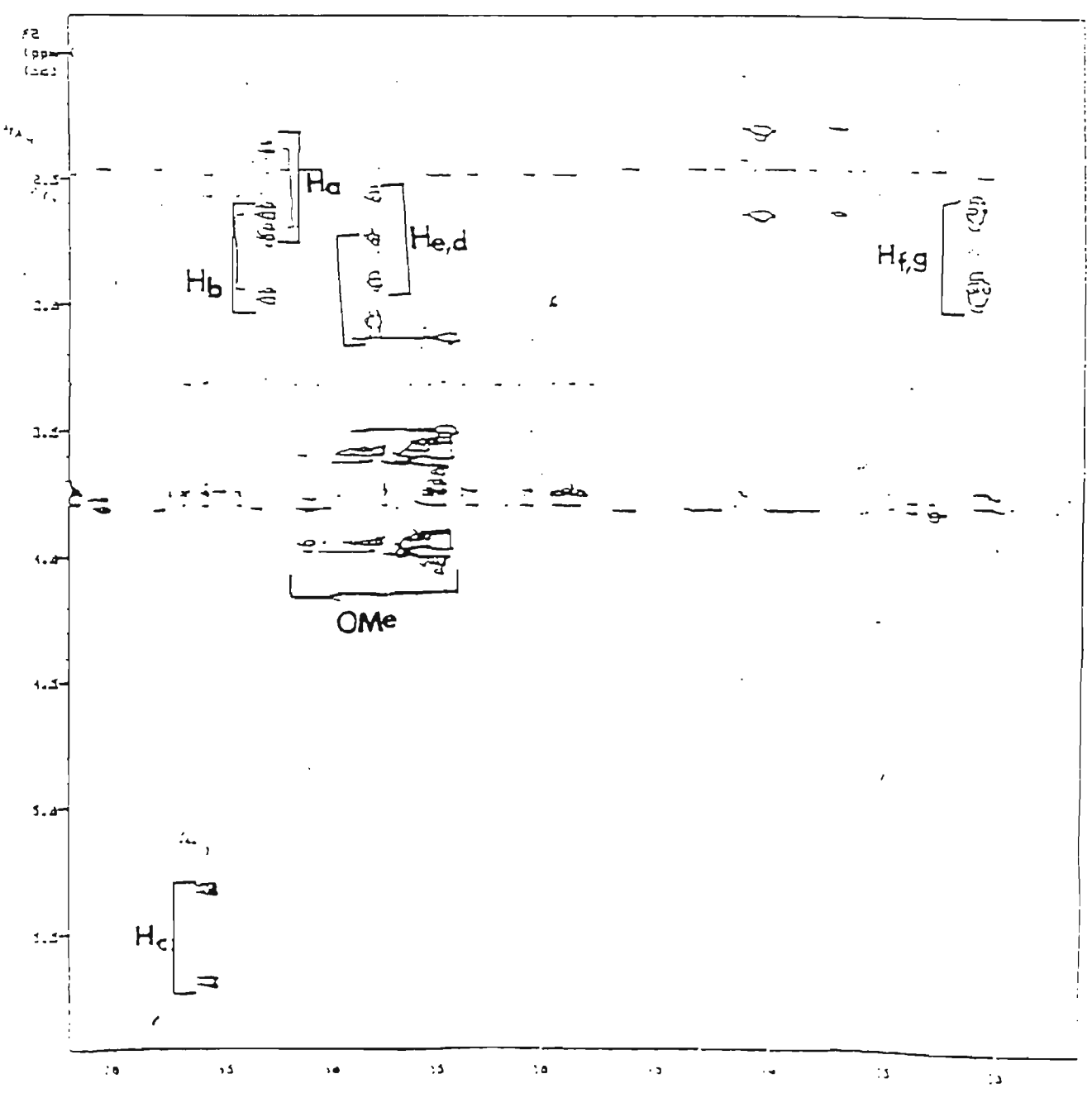


Figure 4.9. HMQC NMR spectrum of the alcohol (24).





In conclusion we have discovered a useful method for preparing β-amino sulfoxides in good diastereomeric purity based on the reduction of β-(2-methoxy-1-naphthylsulfinyl)-enamines with $NaBH_4$. Unfortunately compound (2) was not useful for the synthesis of benzazepine alkaloids since the Pummerer reaction of (2) did not proceed as proposed in the Introduction (Scheme 14). Instead of obtaining the expected 7-membered ring cyclization product, electrophilic attack at sulfur to give a 5-membered ring intermediate (26) was favoured. Further reaction of (26) lead to the unexpected alcohol (24).

EXPERIMENTAL

Synthesis of *(R)*-2-(2'-Methoxynaphthyl-1'-sulfinyl) -3,4-dimethoxyacetophenone (1a).

Method A:

(+)-*(R)*-2-(2'-Methoxynaphthyl-1'-sulfinyl)-3,4-dimethoxy acetophenone *N,N*-dimethylhydrazone (8).

To a stirred suspension of α-lithio-3,4-dimethoxyacetophenone-*N*-*N*-dimethylhydrazone[35] (15.24 mmol), [(prepared from diisopropyamine (5.78 mL, 15.24 mmol) and n-butyllithium (15.24 mmol, 24.40 mL of 1.6 M solution in hexane in THF (50 mL), and 3,4-dimethoxyacetophenone-*N*-*N*-dimethylhydrazone[35] (15.24 mmol, 2.9 g)] in THF (25 mL)), at -78 °C was added dropwise a solution of (-)-*(S)*-menthyl 2-methoxynaphthyl-1-sulfinate (2.78 g, 7.62 mmol) in THF (35 mL) over 20 min. After a further 30 min. at -78 °C, the pale yellow, clear solution was quenched with saturated ammonium chloride solution (10 mL), and extracted with dichloromethane (3x25 mL). The organic extract was dried over MgSO4, and evaporated in vacuo. The crude product was purified by column chromatography using ethyl acetate containing 3 % triethylamine as eluent to give compound (8) as yellow crystals (m.p 112-113 °C) in 53 % yield. ^{1}H NMR δ 8.95 (s, 1 H), 6.8-8 (m, 7 H), 4.38 and 4.31 (AB quartet system, J=12 Hz, 2 H), 4.0 (s, 3 H, OMe), 3.95 (s, 3 H, OMe), 3.80 (s, 3 H, OMe), 2.34 (s, 6 H, N(CH3)2).

Hydrolysis of α-sulfinyl hydazone (8) to β-keto sulfoxide (1a).

To a solution of α-sulfinyl hydazone (8), (1 mmol, 0.395 g), in THF (20 mL), was added copper(II) chloride (0.188 g, 1.1 mmol) in phosphate buffer (8 mL, pH 7). The mixture was stirred at room temperature for 3 h, and 50 mL of distilled water was added and the mixture was extracted with dichloromethane (3x25 mL). The crude product was purified by column chromatography on silica gel using ethyl acetate as eluent to give β-keto sulfoxide (1a), m.p. 119-121 °C in 63 % yield. ^{1}H NMR δ 8.95 (d, 1 H), 6.8-8 (m, 7 H), 5.02, and 4.85 (AB quartet system, J=13.2 Hz, 2 H), 4.00 (s, 3 H, OMe), 3.95 (s, 3 H, OMe), 3.80 (s, 3 H, OMe). MS m/z, 385.1(50 %, M^+), 288.3 (25 %), 205 (100 %). Anal calcd for $C_{21}H_{20}O_5S$: C, 65.61; H, 5.24 %. Found: C, 65.70; H, 5.38 %, $[\alpha]_D^{28}$ +90.8, (c 1.3, DCM).

Method B.

3,4-Dimethoxyacetophenone (5 g, 28 mmol) in anhydrous THF (50 mL) was added over 10 min. period to a stirred refluxing suspension of oil free sodium hydride (1.1 g, 42 mmol) in THF (50 mL) containing 2-methoxynaphthalene-1-sulfinate (5), (10.22 g, 28 mmol), under a nitrogen atmosphere. The mixture was heated at reflux overnight, then cooled and treated with saturated NH_4Cl (30 mL), and finally extracted with DCM (3x100 mL). The DCM extracts were combined and then washed with saturated sodium hydrogen carbonate (2x50 mL), dried over $MgSO_4$, and evaporated at reduced pressure to give very thick oil. Crystallisation from DCM/hexane gave 9.79 g (91 %) of (+)-*(R)*-(1a), 119-120 °C $[\alpha]_D^{25}$ +81.3, (c 1.1, DCM).

(+)-*(R)*-2-(2'-Methoxynaphthyl-1'-sulfinyl)-acetophenone (1b).

Acetophenone (3.36 g, 28 mmol) in anhydrous THF (50 mL) was added over a 10 min. period to a stirred refluxing suspension of oil free sodium hydride (1.1 g, 42 mmol) in THF (50 mL) containing (-)-(S)-menthyl 2-methoxynaphthalene-1-sulfinate (10.22 g, 28 mmol), under a nitrogen atmosphere. The mixture was heated at reflux overnight, then cooled and treated with saturated NH_4Cl (30 mL), and finally extracted with DCM (3x100 mL). The DCM extracts were combined, washed with saturated sodium hydrogen carbonate (2x50 mL), dried over $MgSO_4$, and evaporated at reduced pressure to give a very thick oil. Crystallisation from DCM/hexane gave 7.23 g (80 %) of (+)-*(R)*-(1b) as white crystals, m.p. 89-90 °C. ^1H NMR δ 8.92 (d, 1H), 7.1-7.9 (m, 10H), 5.05, and 4.82 (AB quartet system, J=13.2 Hz, 2 H), 3.90 (s, 3H, OMe). MS m/z, 325.5 (80 %. M^+), 226.3 (25 %), 141 (100 %). Anal calcd for $C_{19}H_{16}O_3S$: C, 70.35; H, 4.97 %. Found: C, 70.41; H, 4.88 %. $[\alpha]_D^{28}$ +97.5, (c 1.2, DCM)

Method C.

Menthyl 2-methoxynaphthalene-1-sulfoxide (4.0 mmol, 0.88 g) in anhydrous THF (5 mL) was added dropwise to a cooled (-78° C), stirred solution of LDA ((prepared from diisopropyamine (0.58 mL, 4 mmol) and n-butyllithium (4 mmol, 2.45 mL of 1.6 M solution in hexane in THF (5 mL)). The mixture was allowed to reach -20 °C, and was then cooled again to -78 °C, and treated with a solution of the methyl 3,4-dimethoxybenzoate (2 mmol) in THF (15 mL). The mixture was stirred for 30 min. at -78 °C and then warmed to room temperature and stirred at this temperature overnight. The mixture was quenched with NH_4Cl and then extracted with

DCM (2x20 mL). The combined extracts were washed with water, dried ($MgSO_4$) and then evaporated to dryness. The crude product was then purified by column chromatography on silica gel using ethyl acetate/hexane (1:1) as the eluent to give (+)-*(R)*-(1a) 25 % yield, e.e.=98 %, $[\alpha]_D^{28}$ +90.4.(c 1.2, DCM).

_N_-Methyl-_N_-[1-(3,4-dimethoxyphenyl)-2-(2'-methoxy-1'-naphthylsulfinyl]ethyl-_N_-(3',4'-dimethoxyphenyl)ethylamine (2)

Four different methods were employed to prepare (2).

Method 1

Preparation of _N_-methyl-_N_-[1-(3,4-dimethoxyphenyl)-2-(2'-methoxynaphthyl-1'-sulfinyl)]ethylamine (10)

To a solution of (1a) (6 mmol, 2.3 g) and methylammonium chloride (0.62 g, 9 mmol) in acetonitrile (4 mL) was added sodium cyanoborohydride (50 mg, 0.8 mmol). After 20 min. the pH of the solution was adjusted to neutral on wet pH paper by the addition of glacial acetic acid. After 24 h the mixture was concentrated by evaporation, treated with 2 M KOH (2 mL) and then extracted with chloroform. The combined extracts were dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography on silica gel using ethyl acetate/methanol (95:5) as eluent, to give compound (10) in 56 % yield (1.34 g).

(*Rs,1S*) *N*-Methyl *N*-[1-(3',4'-dimethoxyphenyl)-2-(2'-methoxynaphthyl-1'-sulfinyl)]ethylamine (10a)

Oil. ^{1}H NMR δ 9.02 (d, J=8.8, 1 H), 7.2-8 (m, 10 H, aromatic), 4.24 (dd, 1 H, J=3.6, 10.4 Hz), 3.19 (dd, 1 H, J=10.4, 13.2 Hz) 3.88-3.95 (3xs, 9 H, OMe), 2.35 (s, 3 H, Me). MS m/z, 399 (80 %, M^+H^+), d.r.=3:1.

(*Rs,1R*) *N*-Methyl *N*-[1-(3',4'-dimethoxyphenyl)-2-(2'-methoxynaphthyl-1'-sulfinyl)]ethylamine (10b)

^{1}H NMR (in part) δ 8.97 (d, J=8.4 Hz, 1 H) 4.08 (dd, 1 H, J=4.0, 10.0 Hz, 1 H), 2.27 (s, 3 H, Me).

***N*-Methyl-*N*-[1-(3',4'-dimethoxyphenyl)-2-(2'-methoxynaphthyl-1'-sulfinyl)ethyl-*N*-(3',4'-dimethoxyphenylethyl)]amine (2) from *N*-methyl-*N*-[1-(3,4-dimethoxyphenyl)-2-(2'-methoxynaphthyl-1'-sulfinyl)]ethylamine (10)**

To a solution of crude (10) (3.4 mmol, 1.35 g) in acetonitrile (4 mL) and 3,4-dimethoxyphenylacetalaldehyde (5 mmol, 0.92 g) was added sodium cyanoborohydride (315 mg, 5mmol). After 20 min. the pH of the solution was adjusted to neutral on wet pH paper by the addition of glacial acetic acid. After 24 hr the mixture was concentrated by evaporation, treated with 2 M KOH (2 mL) and then extracted with chloroform (3x50 mL). The combined extracts were dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography on silica gel using ethyl acetate/methanol (95:5) as eluent, to give compound (2) as a semi-solid compound in 34 % overall yield (651 mg), the d.r. was (3:1).

(*Rs*, 1*S*) *N*-Methyl-*N*-[1-(3,4-dimethoxyphenyl)-2-(2'-methoxy-1'-naphthylsulfinyl)]ethyl-*N*-(3',4'-dimethoxyphenyl)ethylamine (2a)

^{1}H NMR δ 8.87 (d, J=8.8, 1 H), 6.6-8 (m, 11 H, aromatic), 4.31 (dd, 1 H, J=5.3 and 10.4), 3.99 (s, 3 H, OMe), 3.95 (s, 6 H, OMe), 3.91 (s, 3 H, OMe), 3.89 (s, 3 H, OMe), 3.88 (dd, J=3.2, 14 Hz, 1 H), 2.70 (m, 5 H), 2.30 (s, 3 H, Me). ^{13}C NMR δ 30.92 (CH_2), 34.10 (CH_2), 37.59 (N-Me), 54.80, 56.10 (3OMe), 57.04 (2OMe), 61.90, 110.58, 111.144, 113.05, 120.51, 120.78, 132.74, 124.44, 127.69, 128.64, 129.206, 129.46, 132.67, 133.16, 133.79, 147.23, 148.44, 148.72, 156.24. DEPT, 12 CH, 3 CH_2, 6 CH_3. MS m/z, 564.3 (100 %, M+H$^+$). Anal. calcd. for $C_{32}H_{37}NO_6S$: C, 68.18; H, 6.62; N, 2.48 %, Found: C, 64.22 ; H, 6.68; N, 2.50 %.

(*Rs*, 1*R*) *N*-Methyl-*N*-[1-(3',4'-dimethoxyphenyl)-2-(2'-methoxy-1'-naphthylsulfinyl)]ethyl-*N*-(3',4'-dimethoxyphenyl)ethylamine (2b)

^{1}H NMR (in part) δ 8.84 (d, J=8.4 Hz, 1 H),3.87 (s, 3 H, OMe), 3.83 (s, 3 H, OMe), 3.82 (s, 3 H, OMe), 3.76 (s, 3 H, OMe), 3.72 (dd, J=3.6, 12.4 Hz 1 H), 2.23 (s, 3 H, N-Me).

Method 2: Preparation of *N*-methyl-*N*-[1-(3',4'-dimethoxyphenyl)-2-(2'-methoxynaphthyl-1'-sulfinyl)]ethyl-*N*-(3',4'-dimethoxyphenyl)ethylamine (2) from *N*-[1-(3',4'-dimethoxyphenyl)-2-(2'-methoxynaphthyl-1'-sulfinyl)]ethyl-*N*-(3',4'-dimethoxyphenyl)ethylamine (4).

To a solution of (1a) (0.6 mmol, 0.23 g), in acetonitrile (4 mL) and 3,4-dimethoxyphenylethylamine (0.9 mmol, 164 mg) was added sodium cyanoborohydride (50 mg, 0.8 mmol). After 20 min. the pH of the solution was adjusted to neutral on wet pH paper by the addition of glacial acetic acid. After 24 h the mixture was concentrated by evaporation, treated with 2 M KOH (2 mL) and then extracted with chloroform (3x15 mL). The combined extracts were dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography on silica gel using ethyl acetate/methanol (95:5) as eluent, to give compound (4) as a semi-solid in 38 % yield (125 mg), the d.r. was (3:1).

(*Rs*, 1*S*) *N*-[1-(3,4-Dimethoxyphenyl)-2-(2'-methoxynaphthyl-1'-sulfinyl)]ethyl-*N*-(3',4'-dimethoxyphenyl)ethylamine (4a).

Semi-solid. ^1H NMR δ 8.93 (d, J=8.8 Hz, 1 H), 6.6-8 (m, 11 H, aromatic), 4.32 (dd, 1 H, J=3.2 and 10.4), 3.98 (s, 3 H, OMe), 3.86 (s, 3 H, OMe), 3.85 (s, 3 H, OMe), 3.84 (s, 3 H, OMe), 3.80 (s, 3H, OMe), 3.18 (dd, J=10.2, 13.2 Hz, 1 H), 2.80 (t, 4 H). ^{13}C NMR δ 35.76 (CH_2), 37.59 (CH_2), 54.83 (OMe), 55.65 (OMe), 55.84 (OMe), 55.90 (OMe), 56.99 (OMe), 63.43 (Ar-CH-NH-Ar, 66.3 (-CH-CH2-S(O)), 110.58, 111.14, 113.05, 120.51, 120.78, 132.74, 124.44, 127.69, 128.64, 129.21, 129.46, 132.67, 133.16, 133.79, 147.23, 148.44, 148.72, 156.24. DEPT, 12 CH, 3

CH_2, 5 CH_3. MS m/z, 550.3 (100 %, $M+H^+$). Anal. calcd. for $C_{31}H_{35}NO_6S$: C, 67.74; H, 6.42; N, 2.55 %. Found: C, 67.85; H, 6.48; N, 2.50 %.

(*Rs*, 1*R*) *N*-[1-(3,4-Dimethoxyphenyl)-2-(2'-methoxynaphthyl-1'-sulfinyl)]ethyl-*N*-(3',4'-dimethoxyphenyl)ethylamine (4b).

^1H NMR (in part), δ 8.95, (d, J=8.8, 1 H), 4.15 (dd, J=5.6, 8.4 Hz. 1 H), 3.94 (s,3 H, OMe), 3.87 (s, 3 H, OMe), 3.85 (s, 3 H, OMe), 3.84 (s, 3 H, OMe), 3.78 (s, 3 H, OMe), 3.25 (dd, J=5.6,13.2 Hz, 1 H).

***N*-Methyl-*N*-[1-(3,4-dimethoxyphenyl)-2-(2'-methoxynaphthyl-1'-sulfinyl)]ethyl-*N*-(3',4'-dimethoxyphenyl)ethylamine (2)**

To a solution of the crude compound (4) (128 mg, 0.22 mmol) in acetonitrile (4 mL) and aqueous formaldehyde (37 %, 0.5 mL) was added sodium cyanoborohydride (50 mg, 0.8 mmol). After 20 min. the pH of the solution was adjusted to neutral on wet pH paper by the addition of glacial acetic acid. After 6 h the mixture was concentrated by evaporation, treated with 2 M KOH (2 mL) and then extracted with chloroform (3x15 mL). The combined extracts were dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography on silica gel using ethyl acetate/methanol (95:5) as eluent, to give compound (2) as a semi-solid in 83 % yield (110 mg), the d.r. was (3:1).

Method 3

Preparation of *N*-methyl-*N*-[1-(3,4-dimethoxyphenyl)-2-(2'-methoxynaphthyl-1'-sulfinyl)]ethyl-N-(3',4'-dimethoxyphenyl)ethylamine (2) from *(R)*-*N*-(2-(2'-methoxy-1'-naphthylsulfinyl)-1-(3',4'-dimethoxyphenyl)ethenyl-*N*-(2-(3',4'-dimethoxyphenyl)ethylamine (3)

To a solution of the β-keto sulfoxide (1a) (0.6 mmol, 0.23 g) in benzene (10 mL) and 3,4-dimethoxyphenylethylamine (0.9 mmol, 164 mg) was added *p*-toluenesulfonic acid (3 mg). The mixture was heated to reflux using a Dean-Stark apparatus to separate the theoretical amount of water. After 20 h refluxing the mixture was concentrated by evaporation and then treated with 2 M KOH (2 mL) and then extracted with chloroform (3x15 mL). The combined extracts were dried ($MgSO_4$) and evaporated. The crude product was purified by crystalization from DCM/hexane (4:1) to give compound (3) as yellow pale crystals, m.p 68-69 °C in 86 % yield (281 mg). ^1H NMR δ 8.65 (d, J=8.4, 1 H), 6.6-8 (m, 11 H, aromatic), 4.60 (s, 1 H, CH=C-N), 3.99 (s, 3 H, OMe), 3.88 (s, 3 H, OMe), 3.78 (s, 6 H, OMe), 3.72 (s, 3 H, OMe), 2.80 (t, 4 H). ^{13}C NMR δ 35.63, 38.85, 54.93, 55.65, 55.87, 55.99, 58.22, 68.53 110.98, 112.19, 113.85, 120.51, 120.78, 132.74, 124.44, 127.69, 128.64, 129.206, 129.46, 132.67, 133.16, 133.79, 147.23, 148.44, 148.72, 156.24. MS m/z 547 (100 %, M^+). Anal. calcd. for $C_{31}H_{33}NO_6S$: C, 67.99; H, 6.07; N, 2.56 %, Found: C, 68.26; H, 5.98; N, 2.62 %. $[\alpha]_D^{29}$ -130.1 (c 1.1, DCM).

Reduction of (3) to *N*-[1-(3',4'-dimethoxyphenyl)-2-(2'-methoxynaphthyl-1'-sulfinyl)]ethyl-*N*-(3',4'-dimethoxyphenyl)ethylamine (4).

Method A:

To a solution of (3), (0.6 mmol, 0.33 g), in methanol (6 mL) was added $NaCNBH_3$ (0.38 g, 0.8 mmol). After 20 min. the pH of the solution was adjusted to neutral on wet pH paper by the addition of glacial acetic acid. After 10 h the mixture was concentrated by evaporation and then was treated with 2 M KOH (2 mL) and then extracted with chloroform (3x15 mL). The combined extracts were dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography on silica gel using ethyl acetate/methanol (95:5) as eluent, to give compound (4) as a semi-solid in 98 % yield (323 mg), the d.r. was 70:30 by this method.

Method B:

The same procedure as described above in Method A, except that $Na(OAc)_3BH$ (1.2 mmol, 0.20 g) in DCM (6 mL) was used. The reaction was stirred at room temperature for 2 h, and then worked up as described above in Method A. The d.r. was 70:30.

Method C:

The same procedure as described above in Method A, except that $Zn(CNBH_3)_2$ (1.2 mmol, 0.18 g) was used, which was prepared from $NaCNBH_3$ (0.44 g, 2.4 mmol) and $ZnCl_2$, (0.16 g, 1.2 mmol) in methanol .

The mixture was stirred at room temperature for 1 h and then added dropwise over 10 min. to a solution of (3) (0.6 mmol, 0.33g) in methanol (6 mL). The mixture was stirred at room temperature for 2 h, and then worked up as described in Method A was d.r. 64:36.

Method D:

To a solution of (3) (0.6 mmol, 0.33 g), in a mixture of methanol and ammonia (10 mL, 9:1) at room temperature was added $NaBH_4$ (1.2 mmol , 0.046 g). The reaction mixture was stirred at room temperature over 2 h and then the methanol was evaporated. The residue was treated with 2 M KOH (2 mL) and then extracted with chloroform (3x15 mL). The combined extracts were dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography on silica gel using ethyl acetate/methanol (95:5) as eluent, to give compound (4) as a semi-solid in 95 % yield . The d.r. was 78:22 by this method.

Method 4

Preparation of (2) via addition of lithiated imine (11) to (-)-*(S)*-(5).

Preparation of imine (11)

To a solution of 3,4-dimethoxyacetophenone (18.0 g, 0.1 mol) in benzene (150 mL) was added 3,4-dimethoxyphenylethylamine (27.3 g, 0.15 mol) in one portion and 0.01 g of *p*-toluenesulfonic acid. The mixture was heated to reflux and a Dean-Stark apparatus was used to separate the

theoretical amount of water. Evaporation of the solvent, and crystallisation of the residue from ethanol gave compound (11) in 75 % yield (25.9 g), m.p 86-87 °C, ^{1}H NMR δ 2.05 (s, 3 H), 3.01 (t, 4 H), 3.79(2xs, 6H), 6.8-7.4 (m, 6 H).

Synthesis of *N*-[1-(3',4'-dimethoxyphenyl)-2-(2'-methoxynaphthyl-1'-sulfinyl)]ethyl-N-(3',4'-dimethoxyphenyl)ethylamine(3) from the addition of imine (11) to (-)-(*S*)-(5).

n-Butyllithium (5 mL, 8 mmol, 1.6 M in hexane), was added dropwise to a stirred solution of di-isopropylamine (0.62 mL, 8 mmol), in THF (20 mL). The mixture was kept at -10 °C for 30 min., cooled to -40 °C and the imine (11) (8 mmol, 2.76 g), in anhydrous THF (12 mL) was added dropwise over 30 min. via a syringe under nitrogen. The mixture was kept at -10 °C for 1 h and then cooled to -78 °C. A solution of (-)-(*S*)-(5), (1.45 g, 4 mmol) in THF (10 mL) was then added over 10 min. dropwise. After stirring for 2 h at -78 °C, the reaction mixture was quenched with 5 mL methanol. The mixture was then brought to room temperature and the solvents were evaporated under reduced pressure. The residue was dissolved in DCM (50 mL) and the organic phase was washed with water and then dried ($MgSO_4$). The solvent was evaporated under reduced pressure at room temperature and the residue was crystallised from DCM and hexane (5:1) to give compound (3) as yellow pale crystals, m.p 68-69 °C, 1.34 g (65 % yield).

Pummerer rearrangement

Synthesis of 1-[2-(2'-Methoxy-1'-naphthyl)thio-4,5-dimethoxy]phenyl-2-[*N*-methyl-2-(3,4-dimethoxy)phenyl]ethylaminoethanol (24)

To a solution of β-amino sulfoxide (2) (0.563 g, 1 mmol) in DCM (2 mL), and TFA (1 mL), in a sealed tube under argon at 0 °C was added TFAA (1.2 eq., 0.23 g) in one portion and then the reaction was heated at 90 °C for 30 min. The reaction mixture was cooled and then basified with 10 % aqueous KOH (10 mL). The reaction mixture was extracted with chloroform (3x20 mL) and the extracts were dried over K_2CO_3. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (silica gel, ethyl acetate). The last fraction was collected as a semi-solid to give (24), (0.470 g, 86 % yield). ^1H NMR δ 8.45 (d, J=8.8 Hz, 1 H), 6.8-8 (m, 9 H, aromatic), 7.14 (s, 1 H), 6.29 (s,1 H), 5.46 (dd, 1 H, J=2 , 10.8 Hz), 3.99 (s, 3 H, OMe), 3.88 (s, 3 H, OMe), 3.78 (s, 6 H, OMe), 3.72 (s, 3 H, OMe), 3.4(s, 3 H, OMe) 2.95 (dd, J=10.2, 14 Hz, 1 H), 2.80 (t, 4 H), 2.75 (dd, 1 H, J=2, 14 Hz) 2.35 (s, 3 H, Me). ^{13}C NMR δ 33.1, 41.7, 55.5, 55.6, 55.7, 55.7, 56.6, 59.1, 64.2, 66.4, 108.7, 111.1, 111.8, 112.0, 113.3, 114.9, 120.4, 123.9, 125.1, 125.3, 127.5, 128.1, 129.3, 131.3, 132.6, 133.3, 135.7, 147.2, 147.7, 147.9, 148.7, 158.7. DEPT NMR, 12 CH, 3 CH_2, 6 CH_3. MS m/z 564.3 (100 %, M^+). Anal. calcd. for $C_{32}H_{37}NO_6S$: C, 68.18; H, 6.62; N,2.48 %, Found: C. 68.22; H, 6.68; N, 2.50 %.

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