ASYMMETRIC FUNCTIONALIZATION OF a -KETO CARBOXYLIC ACIDS

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CHEMISTRY

BY

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PUNE 411 008

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled **"Asymmetric Functionalization of** a **-Keto Carboxylic Acids"** submitted by Mr. Rajendra P. Jain was carried out by him under my supervision at the National Chemical Laboratory, Pune. Material that has been obtained from other sources is duly acknowledged in the thesis.

Dr. S. V. Pansare

Date: 29-5-2000 Research Guide

DECLARATION

I hereby declare that the work incorporated in the thesis entitled **"Asymmetric Functionalization of** a **-Keto Carboxylic Acids"**, submitted for the degree of Doctor of Philosophy to the University of Pune, has been carried out by me at the National Chemical Laboratory, Pune under the supervision of Dr. S. V. Pansare. The work is original and has not been sub mitted in part or full by me for any other degree or diploma to this or any other University.

Date: Rajendra P. Jain

TO

MY PARENTS

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List of Abbreviations:

aq.	aqueous
Cbz	benzyloxycarbonyl
de	diastereomeric excess
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
ds	diastereoselectivty
ee	enantiomeric excess
Et	ethyl
equiv.	equivalent
FAB	fast-atom bombardment
g	gram
GC	gas chromatography
h	hour
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrum
IR	Infrared
M	molar
M^+	molecular ion
Me	methyl
min	minute
ml	milliliter
mmol	millimole
mp	melting point
MS	mass spectrum
MTPA	α-methoxy-α-(trifluoromethyl)phenylacetic acid
nm	nano meter
NMR	nuclear magnetic resonance
Ph	phenyl
Pr	propyl
*i*Pr	isopropyl
s	second
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
Ts	tosyl

ABSTRACT

The thesis entitled **"Asymmetric Functionalization of** a **-Keto Carboxylic Acids"** is divided into five chapters.

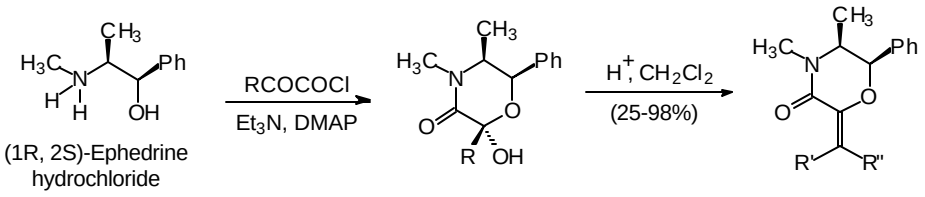
CHAPTER I

Asymmetric Synthesis of a **-H,** a **-Hydroxy Carboxylic Acids:**

Enantiomerically pure α-H, α-hydroxy carboxylic acids are an important class of organic compounds because of their use as building blocks for the asymmetric synthesis of natural products and biologically active molecules. The objective of this investigation was to develop a new route to α-H, α-hydroxy carboxylic acids by asymmetric functionalization of α-keto carboxylic acids using 1*R*,2*S*-ephedrine as a chiral controller.

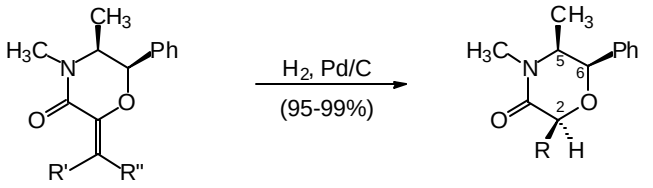
The diastereomerically pure hemiacetals **1a-d** which are readily available from the acylation of 1*R*, 2*S*-ephedrine hydrochloride with aliphatic α-keto acid chlorides served as starting materials for this study. Acid catalyzed dehydration of **1a-d** affords the alkylidene morpholinones **2a-d** in 25-98 % yield (Scheme 1).

Scheme 1.



The alkylidene morpholinones **2b** and **2c** have been assigned the *Z* geometry by comparison of ^{1}H NMR of **2b** with the *E* isomer obtained by irradiation of **2b** at 254 nm. Hydrogenation of **2a-d** (H_2, Pd/C, 50 psi) generates **3a-d** as single diastereomers in quantitative yield (Scheme 2).

Scheme 2.

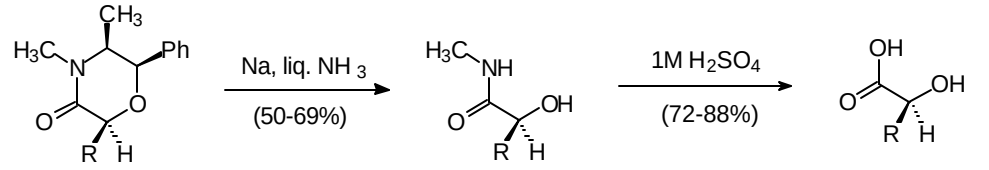


	2a	**2b**	**2c**	**2d**
R'	H	H	H	Me
R"	H	Me	Et	Me

	3a	**3b**	**3c**	**3d**
R	Me	Et	Pr	*i*Pr

The stereochemistry of the new stereocenter in **3** is assigned as *'S'* by NOE measurements on **3d** which indicate a *cis* relationship of the hydrogens at C2, C5 and C6 in the morpholinone ring and by anology in the ^{1}H NMR spectrum of **3a-d**. Dissolving metal reduction (Na/NH_3, 20 sec.) of morpholinones **3** yields the α-hydroxy amides **4** (50-69%). Hydrolysis of **4b-d** (1M H_2SO_4, reflux) generates the α-hydroxy acids **5b-d** (Scheme 3, 72-88% yield, 92-96% ee by ^{1}H NMR or HPLC analysis of Mosher derivatives of the methyl esters) with *'S'* configuration which confirms the stereochemistry of **3**.

Scheme 3.



	3a	**3b**	**3c**	**3d**
R	Me	Et	Pr	*i*Pr

	4a	**4b**	**4c**	**4d**
R	Me	Et	Pr	*i*Pr

	5b	**5c**	**5d**
R	Et	Pr	*i*Pr

The overall conversion of the hemiacetals **1** to the α-H, α-hydroxy acids **5** constitutes a new approach to these important molecules that involves asymmetric functionalization of readily available α-keto carboxylic acids as the key step.

CHAPTER II

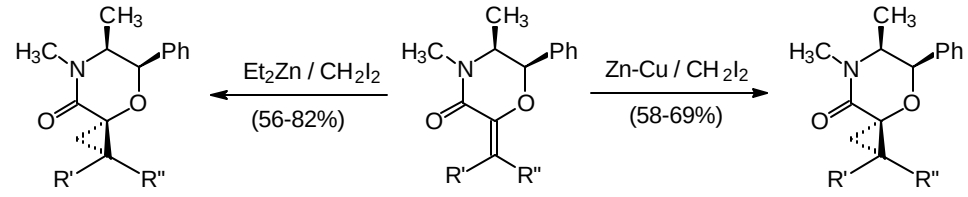
Asymmetric Synthesis of α-Hydroxycyclopropanecarboxylic Acids:

α-Hydroxycyclopropanecarboxylic acids constitute a unique class of hydroxy acids due not only to their structural novelty but also their applications in the synthesis

of five and six membered ring systems, as enzyme inhibitors, and as components of fungicides and agricultural microbicides. The objective of this investigation was to develop a new route to these molecules by asymmetric functioanalization of α-keto carboxylic acids using 1*R*,2*S*-ephedrine as a chiral controller.

The alkylidene morpholinones **2b-d** served as starting materials for this study. Initial studies were conducted on acrylamide **2b**. Simmons-Smith cyclopropanation of **2b** employing Zn-Cu/CH_2I_2 in refluxing DME afforded the cyclopropyl morpholinone **6b** in 62% yield as a 4/1 mixture of diastereomers (Scheme 4). Lower reaction temperatures are beneficial and cyclopropanation with the Et_2Zn/CH_2I_2 derived reagent at ambient temperature generates **6b** with 16/1 diastereoselectivity.

Scheme 4.



	6b	**6c**	**6d**
R'	H	H	Me
R"	Me	Et	Me

ds = 16 - 19/ 1

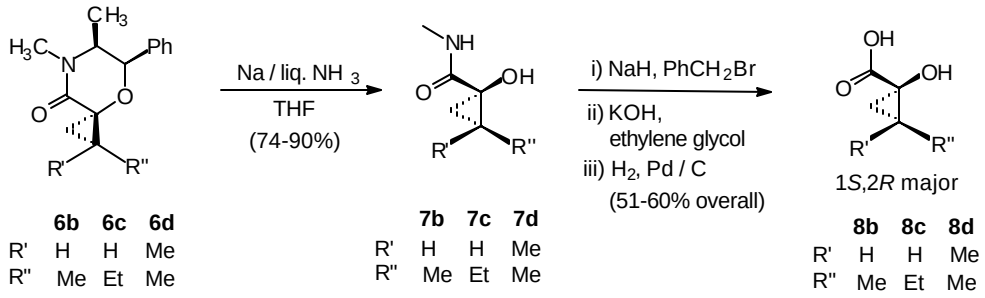
	2b	**2c**	**2d**
R'	H	H	Me
R"	Me	Et	Me

	6b	**6c**	**6d**
R'	H	H	Me
R"	Me	Et	Me

ds = 4 - 15/ 1

The absolute configuration of the major diastereomer in **6b** was determined by conversion of **6b** to the known α-hydroxycyclopropanecarboxylic acid **8b**. Dissolving metal reduction of **6b** (Na/liq. NH_3 in THF) generates the hydroxy amide **7b** (74%). Hydrolysis of the amide was achieved by protection of the free hydroxyl group as a benzyl ether (NaH, $PhCH_2Br$, 63%) followed by treatment with KOH in ethylene glycol (120 °C, 87%). Debenzylation by hydrogenolysis (1 atm. H_2, Pd/C, 93%) afforded **8b** with the 1*S*,2*R* configuration (Scheme 5) in an overall yield of 51% from **7b**.

Scheme 5.



	6b	6c	6d
R'	H	H	Me
R"	Me	Et	Me

	7b	7c	7d
R'	H	H	Me
R"	Me	Et	Me

	8b	8c	8d
R'	H	H	Me
R"	Me	Et	Me

Acrylamides **2c** and **2d** were also readily cyclopropanated with good stereoselectivity employing the the Et_2Zn/CH_2I_2 derived reagent to give morpholinones **6c** (19/1) and **6d** (19/1) respectively. The cyclopropyl morpholinones **6c,d** (obtained from the Zn-Cu/CH_2I_2 cyclopropanation) were converted to the free hydroxy acids **8c** and **8d** *via* the hydroxy amides **7c,d** as described for **6b**. The configuration of **8c** (1*S*,2*R*) and **8d** (1*S*) is assigned by analogy to **8b**.

The above reaction sequence constitutes a new, stereoselective route to α-hydroxycyclopropanecarboxylic acids.

CHAPTER III

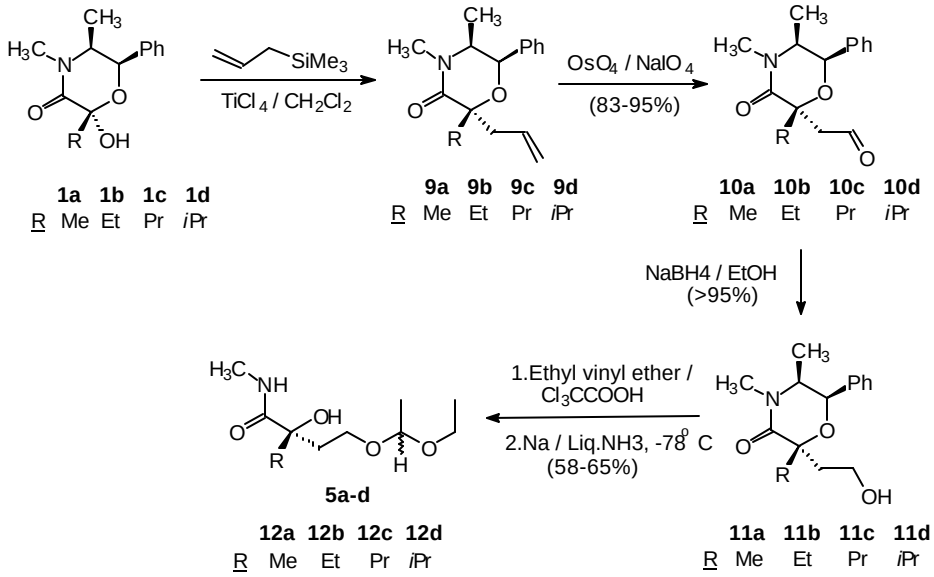
Asymmetric Synthesis of a-Alkyl-a-Hydroxy-g-Butyrolactones:

Enantiomerically pure α-alkyl-α-hydroxy-γ-butyrolactones with alkyl substituents in the ring are an important class of compounds due to their utility as intermediates and as chiral building blocks for the synthesis of natural products and biologically active molecules. The objective of this investigation was to develop a new route to these lactones by asymmetric functionalization of α-keto carboxylic acids.

Hemiacetals **1a-d** (Chapter 1) can be readily converted to the diastereomerically pure allyl morpholinones **9a-d** by reaction with allyltrimethylsilane/$TiCl_4$ (Scheme 6). Oxidative cleavage of the allylic double bond in **9a-d** with $OsO_4/NaIO_4$ cleanly generates the aldehydes **10a-d** (83-95% yield). These are quantitatively converted to the corresponding alcohols **11a-d** by reduction with $NaBH_4$ in ethanol. Conversion of **11** to the ethoxyethyl ether followed by dissolving metal reduction generated the α-hydroxy amides **12a-d** in

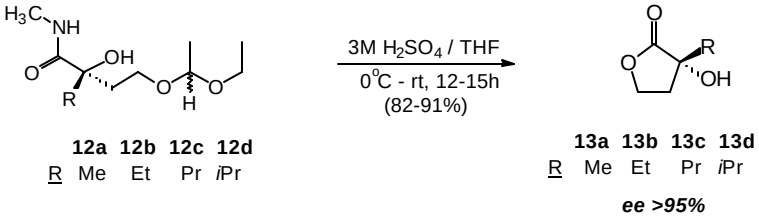
58-65% yield over two steps (Scheme 6).

Scheme 6.



Conversion of the α-hydroxy amides **12** to the target lactones **13** was achieved by unmasking of the primary alcohol in **12** by treatment with 3M H_2SO_4/THF which proceeds with concomitant lactonization to generate the desired α-alkyl-α-hydroxy-γ-butyrolactones **13a-d** in 82-91% yield (Scheme 7).

Scheme 7.



The overall conversion of the allyl morpholinones **9** to the lactones **13** constitutes a new approach to these important intermediates.

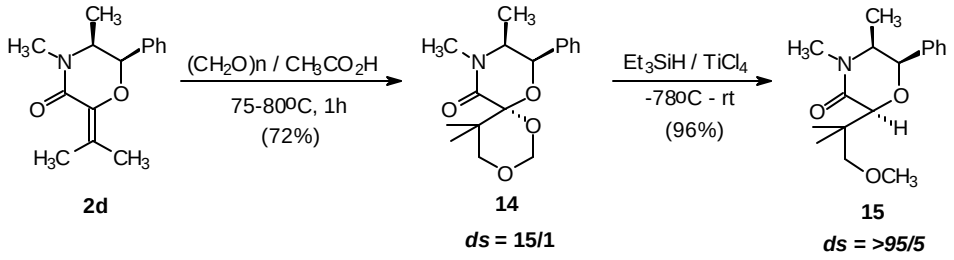
CHAPTER IV

Enantioselective Synthesis of *S*-(+)-Pantolctone:

An enantioselective synthesis of *S*-(+) pantoactone was developed. Pantolactone is of interest due to its utility as a building block in the synthesis of natural products and their analogues, the biological activity of derivatives and it's application as a chiral auxiliary in asymmetric synthesis.

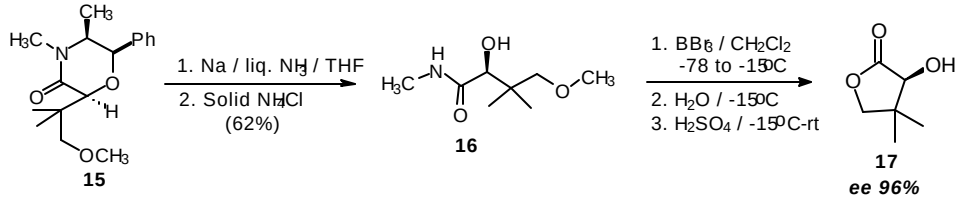
The α-alkoxy acrylamide **2d** served as a starting material for the asymmetric synthesis of (*S*)-(+)-pantolactone. The Prins reaction of acrylamide **2d** with $(CH_2O)n/conc.H_2SO_4$ in CH_3COOH (75-80°C/1h) gave the desired spiro bis-acetal **14** in 72% yield as a single diastereomer. Reduction of **14** proceeds smoothly with $Et_3SiH/TiCl_4$ (-78°C- rt/24h) to give the desired morpholinone **15** as a single diastereomer in excellent yield (Scheme 8).

Scheme 8.



Dissolving metal reduction of **15** (Na/liq. NH_3 in THF) generates the α-hydroxy-γ-methoxybutyramide **16** in 62% yield. Demethylation of **16** (BBr_3/CH_2Cl_2/-78°C to -15°C) followed by concomitant acid catalyzed hydrolysis was achieved in one pot to give the desired (*S*)-pantolactone **17** in 68% yield and 96% enantiomeric excess (Scheme 9).

Scheme 9.



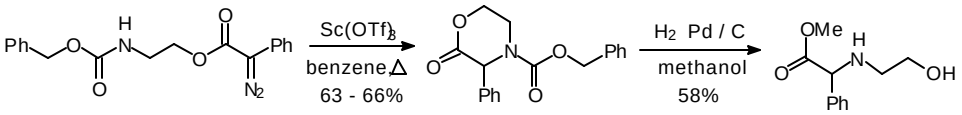
CHAPTER V

Asymmetric Diazocarbonyl Insertion Reactions into Heteroatom-Hydrogen Bonds:

The objective of this investigation was to develop a new approach to α-amino acids by asymmetric N-H insertion reaction of α-diazoesters as the key step. Asymmetric diazocarbonyl O-H insertion reactions were also investigated using $Sc(OTf)_3$ as a new insertion catalyst.

The diazoester **18** was studied as a model compound for the intramolecular N-H insertion reactions. When a benzene solution of **18** was heated in the presence of $Rh_2(OAc)_4$ (1 mol%), 3-phenyl-4-benzyloxycarbonyl morpholin-2-one **19**, the product of intramolecular N-H insertion, was obtained in only 10% yield. Our search for alternative catalysts led us to investigate the use of $Sc(OTf)_3$. Remarkably, when $Sc(OTf)_3$ (1 mol%) was employed under identical conditions, **19** was obtained in 63-66% yield. The observation that no **19** is formed in the absence of any catalyst confirms the catalytic effect of $Sc(OTf)_3$ in the N-H insertion reaction. Hydrogenation of **19** in methanol proceeds with concomitant methanolysis to generate the phenylglycine derivative **20** (58%, unoptimized, Scheme 10).

Scheme 10.

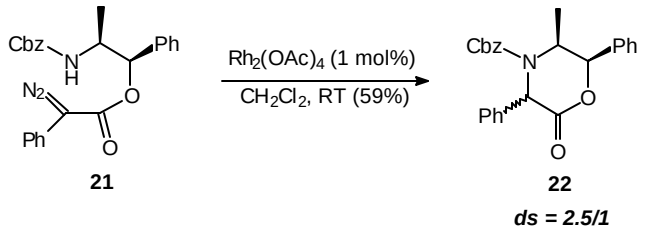


18 **19** **20**

The overall conversion of **18** to **20** constitutes a new approach to α-amino acids, based on intramolecular N-H insertion that proceeds with the creation of a stereogenic center.

An asymmetric version of the methodology was investigated using **21** as the substrate (ethanolamine in **18** replaced with 1*R*,2*S*-norephedrine). Although intramolecular NH insertion of the diazoester **21** could not be achieved with $Sc(OTf)_3$ (1 mol%) in refluxing benzene, the $Rh_2(OAc)_4$ catalyzed N-H insertion proceeds at ambient temperature in dichloromethane to generate the morpholinone **22** in 46% yield and with 2.5/1 diastereoselectivity (Scheme 11).

Scheme 11.

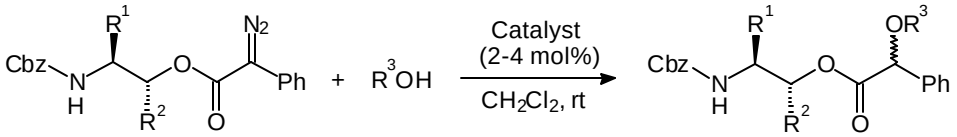


21 **22**

ds = 2.5/1

The asymmetric intermolecular O-H insertion reaction of chiral diazoesters **21** and **23** with achiral alcohols was also examined. Reaction of **21** and **23** with isopropyl alcohol and benzhydrol in the presence of $Rh_2(OAc)_4$ as well as $Sc(OTf)_3$ in dichloromethane at ambient temperature generates the α-alkoxy esters **24** in excellent yields but with low diastereoselectivity (ds = 1-1.5/1, Scheme 12).

Scheme 12.



21: $R^1 = CH_3$, $R^2 = Ph$

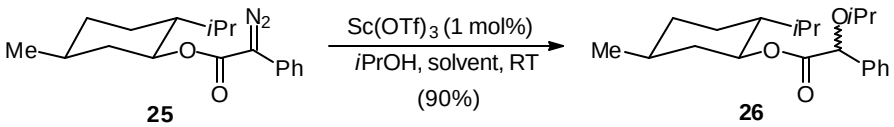
23: $R^1 = CH_2Ph$, $R^2 = H$

24

ds 1-1.5 / 1

The asymmetric intermolecular O-H insertion reaction of the menthol derived chiral diazoester **25** was also examined. Reaction of **25** with isopropyl alcohol in the presence of $Sc(OTf)_3$ (1 mol%) in a variety of solvents at ambient temperature generates the α-isopropoxy ester **26** in excellent yield but with low diastereoselectivity (ds = 1.2/1, Scheme 13).

Scheme 13.



25 **26**

ds = 1.2/1

CHAPTER I

ASYMMETRIC SYNTHESIS OF a -H, a -HYDROXY CARBOXYLIC ACIDS

1. INTRODUCTION

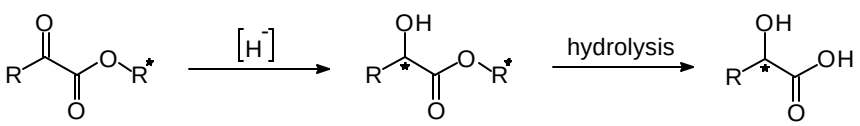
Enantiomerically pure α-hydroxy acids are an important class of organic compounds because of their use as building blocks for the asymmetric synthesis of natural products and biologically active molecules[1]. They are of great value as constituents of antineoplastic agents,[2] components of stationary phases in chiral chromatographic columns,[3] and potential precursors of chiral vicinal glycol systems which appear in many natural products. A recent development is their use as ingredients of lotions and skin creams to increase dermal moisture content and also facilitate the shedding of dead skin cells,[4] thereby benefiting wrinkled and damaged skin. The stereoselective synthesis of α-hydroxy acids has therefore attracted considerable interest and has been intensely investigated in recent years. Numerous methods have been described and a summary of these methods, based on key synthetic transformations, follows. It should be emphasized that historically important methods and also those providing α-hydroxy acids with moderate to good enantioselectivity have been included.

Stereoselective syntheses of α-hydroxy acids based on chiral α-keto acid and derivatives

Stereoselective reduction of chiral α-keto esters

The simplest approach to the synthesis of enantiomerically pure α-hydroxy acid derivatives is reduction of chiral α-keto esters (Figure 1).

Figure 1. Reduction of chiral α-keto esters

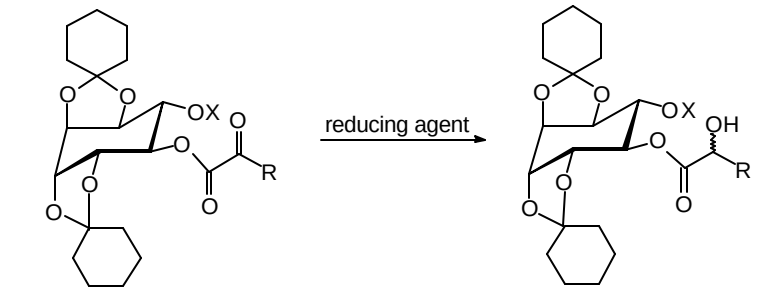


The first attempt at an asymmetric synthesis by the general process of creating a new chiral center in the acid moiety of an ester derived from an optically active alcohol by Kipping[5] (reduction of the (-)-bornyl esters of the α-keto acids) and Cohen and Whiteley[6] (reduction of menthyl pyruvate) in 1900 failed for practical reasons (racemisation during hydrolysis in the case of mandelic acid and problems with isolation of lactic acid). Four years later McKenzie[7] repeated the same reactions, and also successfully applied the then recently discovered Grignard reactions to the same system, thereby circumventing the racemization problem. This development transformed the α-keto ester asymmetric synthesis to a practical system for extensive study and has become a classical model for many asymmetric syntheses. It was further developed by Prelog[8] into a valuable procedure for the configurational correlation of secondary alcohols. In spite of these extensive studies, the stereoselectivities of reduction of chiral α-keto esters remained only poor to moderate (Figure 1, R^* = (-)-menthyl (maximum 41% e.e.)[9], 1,2:5,6 di-*O*- cyclohexylidine D-glucofuranose (maximum 45% e.e.)[10], (+)-bornyl (3%e.e.)[11], (+)-phenyldihydrothebainyl (maximum 69% e.e.)[12], α-amyrinyl (6 % e.e.)[11], cholesteryl (maximum 4% e.e.)[9b,c], (-)-1-phenyl ethanol (maximum 7% e.e.)[13]).

Interest in the asymmetric reductions of chiral α-keto esters has reemerged only recently and a significant improvement in reduction diastereoselectivity has been achieved, although only in a few cases. Synthesis of α-hydroxy esters (22-70% de) by the diastereoselective reduction of α-keto esters derived from cholic acid[14] has been reported recently. Ozaki[15] *et.al.* have reported synthesis of α-hydroxy esters by the reduction of α-keto esters derived from chiro-inositol for which reduction with

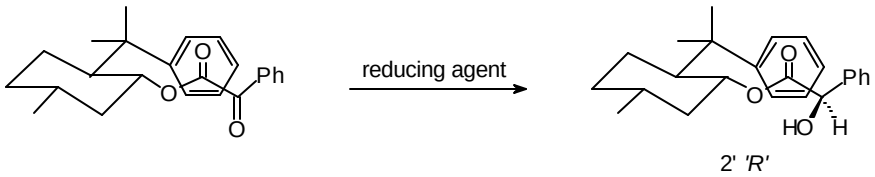
selectride reducing agents proceeds with high diastereoselectivity (maximum 94% d.e.) to afford the *'S'* isomer of the hydroxy acid. The selectivity was reversed when 18-crown-6 was used as additive (*'R'* isomer, maximum 92% e.e. (Scheme 1)).

Scheme 1.



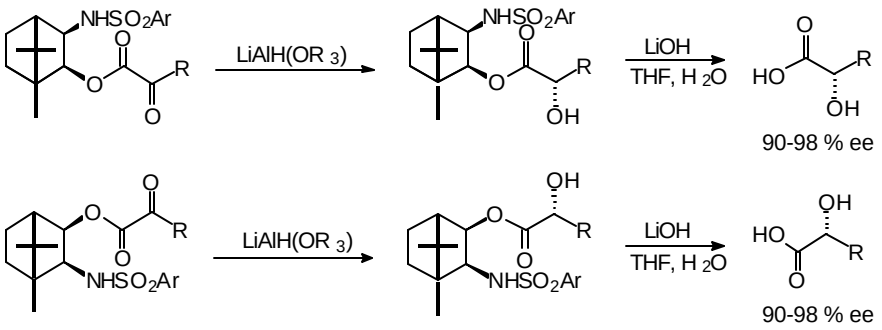
In another approach[16], 8-phenylmenthol was used as the chiral auxiliary. Diastereoselectivities of maximum 94% could be obtained in the reduction of phenylglyoxylate esters (Scheme 2).

Scheme 2.



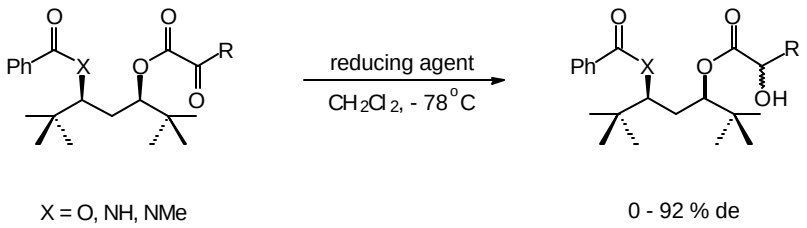
Very high diastereoselectivies (90-98% e.e.) have been reported by Xiang[17] *et. al.* in the reduction of chiral α-keto esters derived from α-(arylsulfonamido) borneols with modified lithium aluminium hydride reagents (Scheme 3).

Scheme 3.



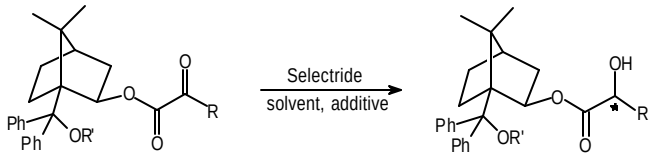
Very recently, new acyclic amino alcohol and diol auxiliaries were reported[18] by Yamamoto and coworkers. Chiral α-keto esters derived from these auxiliaries can be reduced with a variety of reducing agents to provide the α-hydroxy esters. The diastereoselectivity (20-92% d.e., Scheme 4) is highly dependant on the reducing agent and DIBAL gave the best results.

Scheme 4.



Chen[19] and coworkers have introduced exo-10,10-diphenyl-2,10-camphanediol and exo-10,10-diphenyl-10-methoxy-2-camphanol as chiral auxiliaries for the asymmetric reduction of α-keto esters (6-99% de). The influence of solvents and additives on the reaction course has been investigated. Thus, both diastereomers of α-hydroxy esters have been obtained from a single chiral auxiliary with excellent optical purity by the appropriate choice of reaction conditions (Scheme 5).

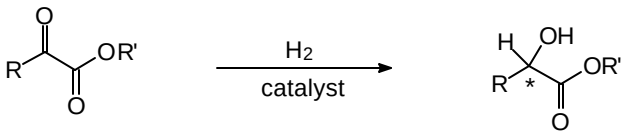
Scheme 5



Asymmetric hydrogenation of a **-keto esters**

The stereoselective hydrogenation of α-keto esters has also been extensively investigated. Most of the chiral substrates in the reduction studies employing hydride reducing agents have also been reduced by catalytic hydrogenation. In addition, achiral esters have been hydrogenated over asymmetrically modified catalysts.

Figure 2. Asymmetric hydrogenation of α-keto esters.



chiral ester / achiral catalyst
achiral ester / chiral catalyst

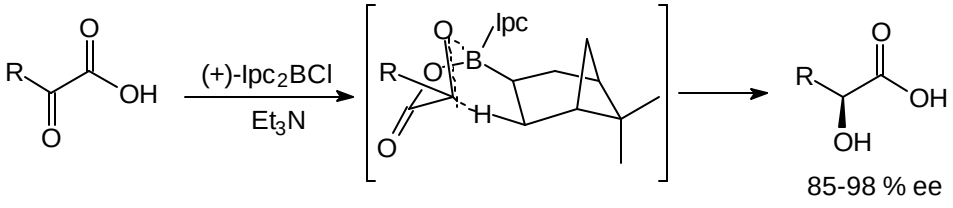
Extensive studies on catalytic hydrogenation of α-keto esters derived from (-)-menthol, (+)-borneol, and various sugars employing PtO_2, Raney Ni, Pd/C, $Pd/CaCO_3$, $Pd/BaSO_4$ etc. as catalysts have been reported in the literature.[9c,13,20] Relatively high enantioselectivity was reported by Harada[21] *et. al.* in the hydrogenation of chiral amides of optically active benzylic amines with palladium. Recently Noyori *et. al.* have reported[22] Binap-Ru catalysed hydrogenation of methyl pyruvate which generates *'R'* lactic acid with 83% e.e. Blaser *et. al.* have studied[23] the enantioselective hydrogenation of ethyl pyruvate to ethyl lactate (maximum 90% e.e.) catalysed by Cinchona-modified Pt/Al_2O_3. A general method[24] for synthesizing heterogeneous

catalysts for the asymmetric hydrogenation reaction with chiral, quaternary nitrogen containing groups (cinchonine, quinine, *N*-methylephedrine) on a polystyrene-support was reported by Bhaduri and coworkers, but the enantioselectivities for pyruvate reduction were found to be low (37% e.e.). Baiker and coworkers have reported[25] the enantioselective hydrogenation of ethyl pyruvate over Pt/Al_2O_3 modified with simple chiral amino alcohols and have demonstrated that chiral amino alcohols such as 2-(1-pyrrolidinyl)-1-(naphthyl)ethanol can induce enantioselectivities up to 75%. Agbossou and coworkers have synthesized new chiral ruthenium complexes from chiral bidentate amino(amido)phosphinephosphinite bisphosphines and demonstrated that these complexes act as efficient catalysts for the homogeneous asymmetric hydrogenation of α-ketoesters with a maximum of 79% enantiomeric excess.[26]

Stereoselective reduction of a **-keto carboxylic acids**

Wang[27] *et. al.* have synthesized enantiomerically enriched α-hydroxy acids by reduction of the corresponding α-keto carboxylic acids using B-chlorodiisopinocampheylborane. The α-carboxylic substituent has been shown to exert a remarkable neighbouring group effect on the reduction (Scheme 6).

Scheme 6.

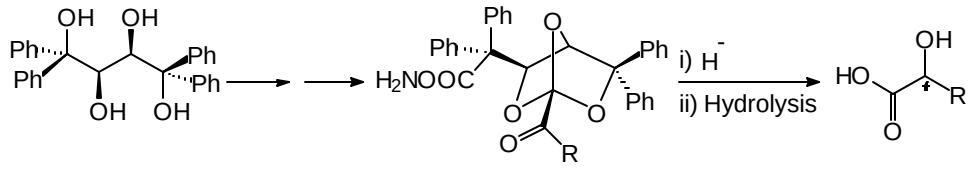


Stereoselective reduction of chiral orthoesters

The use of chiral orthoesters[28] of α-keto acids for the synthesis of α-hydroxy acids has been recently reported by Dubé. Reduction of these chiral

orthoesters proceeds with very high selectivity (>99% d.e.). Hydrolysis affords enantiomerically enriched α-hydroxy acids with *'R'* configuration (Scheme 7).

Scheme 7.



Stereoselective alkylation of chiral glyoxylate esters

Excellent asymmetric induction has been achieved by Whitesell in the addition of Grignard reagents to a chiral glyoxylate ester of 8-phenyl menthol. The desired α-hydroxy esters are obtained with *'S'* configuration[29] and in high chemical yield and excellent levels of asymmetric induction (98-99% e.e., Scheme 8). The stereoselectivity is due to effective shielding of one face of the aldehyde carbonyl by the phenyl group in the auxiliary. It has also been shown that the diastereomer with *'R'* configuration at the newly generated stereocenter (d.e.>90%) can be obtained by the hydride reduction of the α-ketoesters of 8-phenylmenthol.[30]

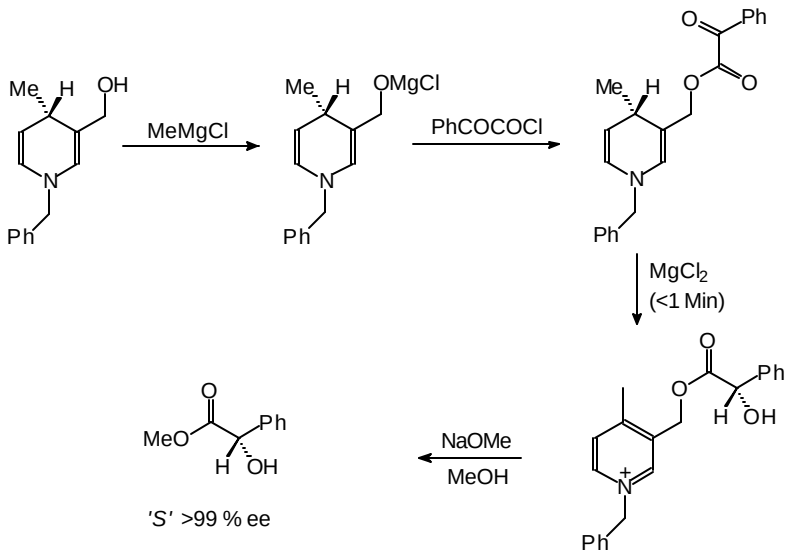
Scheme 8.

2' *'S'*

Intramolecular reduction of a **-keto esters**

Meyers[31] has reported one example of intramolecular reduction of an α-keto acid derivative. The method employs a chiral NADH analog which forms the chiral ester portion in the α-keto ester (Scheme 9).

Scheme 9.



Self-immolative chirality transfer in the reduction of a benzoylformic ester of '*S*'-*N*-benzyl-3-(hydroxymethyl)-4-methyl-1,4-dihydropyridine is mediated by magnesium ion and proceeds with >99% stereoselectivity. The reaction is complete in a few seconds

In some of the above studies, the difficulty in obtaining good stereoselectivities may be due to the inherent conformational flexibility of the ester linkage. Most of the recent studies have focused on chiral amides of α-keto acids and these approaches have been discussed below.

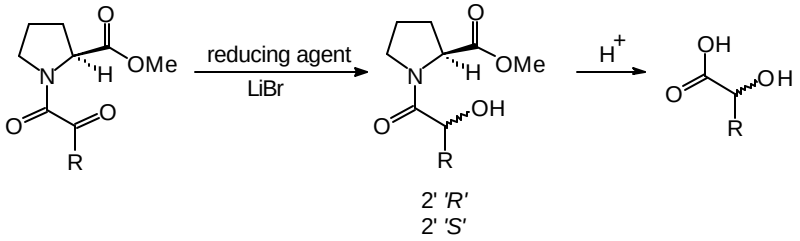
Stereoselective reduction of chiral a **-keto amides**

The use of chiral α-keto amides has been actively investigated in recent years, and reductions of α-keto amides derived from chiral amine and amino acid based auxiliaries have been reported.

Asymmetric synthesis of the both enantiomers of α-hydroxy acids by the

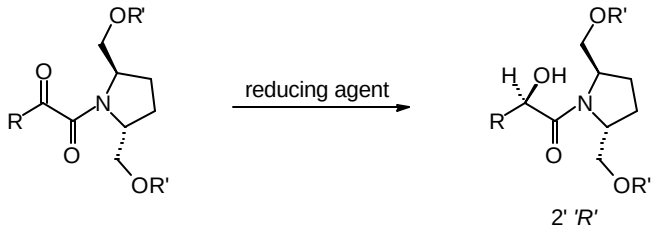
diastereoselective reduction of a chiral α-keto amide derived from *'S'* methyl prolinate has been reported by Soai.[32] Reduction with lithium borohydride afforded *'S'* α-hydroxy acids (80% e.e.), whereas diisobutylaluminum hydride afforded *'R'* α-hydroxy acids (66% e.e.) (Scheme 10).

Scheme 10.



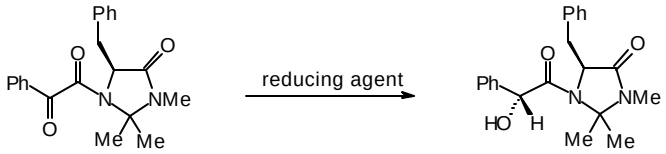
In related work, Kawanami[33] *et. al.* have showed that α-keto amides derived from a C_2 symmetric pyrrolidine are more beneficial, and the diastereoselectivity of reduction may be improved to 98% (Scheme 11).

Scheme 11.



Reduction of a chiral α-keto amide derived from 5*'S'*-5-benzyl-2,2,3-trimethyl imidazolidin-4-one, reported by Solodin[34] proceeds with 90-100% diastereoselectivity and the newly formed stereocenter was found to have *'R'* configuration (Scheme 12).

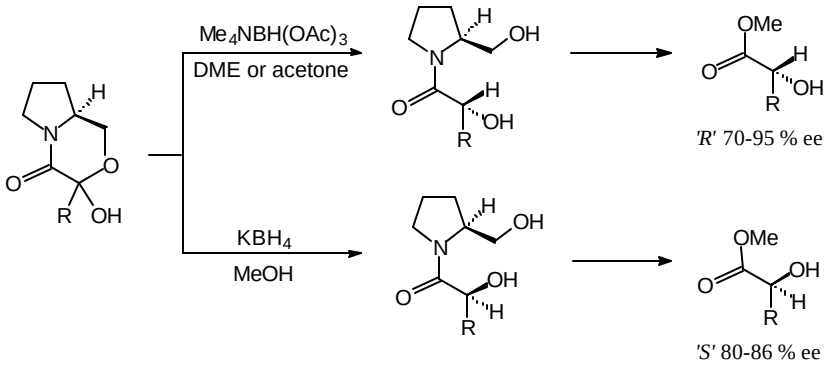
Scheme 12.



2' *'R'*

Recent work from our group has demonstrated a stereodivergent approach to the synthesis of either enantiomer of α-hydroxy esters with good enantiomeric excess.[35] Substrate directed reduction of '*S*'-2-hydroxymethyl pyrrolidine derived α-keto amides with tetramethyl ammonium triacetoxy borohydride proceeds with good stereoselectivity at room temperature. A reversal of stereochemistry is observed in reductions with conventional borohydride reducing agents in protic solvents (Scheme 13). The advantages of this method are: a) good stereoselectivity at ambient temperature and b) reagent control of diastereoselectivity.

Scheme 13.



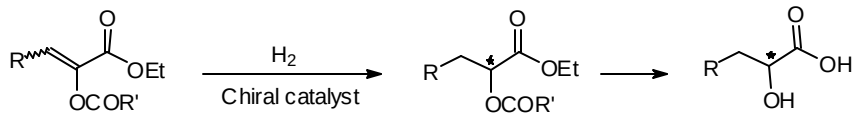
Stereoselective syntheses of α**-hydroxy acids from substrates other than** α**-keto acid derivatives**

Several syntheses of α-hydroxy acids employing achiral substrates other than α-keto acid derivatives are known in the literature. A brief discussion follows.

Catalytic asymmetric hydrogenation of a **-acyloxy acrylates**

A few studies on catalytic asymmetric hydrogenation of α-acyloxy acrylates employing chiral rhodium or ruthenium catalysts have been reported in the literature.

Figure 3. Asymmetric hydrogenation of α-alkoxy acrylates



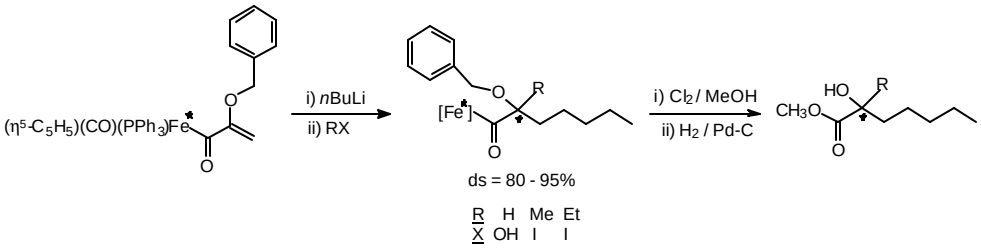
R = H, Alkyl, Aryl
R' = CH_3CO, $(CH_3)_3CCO$

Bosnich and coworkers have studied the hydrogenation of ethyl-α-acetoxy acrylate by using rhodium(I) complex of (*R*)-1,2-*bis*(diphenylphosphino) propane as an asymmetric hydrogenation catalyst to obtain to the (*S*)-lactate with 81% e.e. The enantoselectivity was improved to 89% by using (*R,R*)-DiPAMP as a chiral ligand (Koenig[37] *et. al.*). Schmidt[38] *et. al.* have used Rh-DiPAMP and Ru-BINAP catalysts to hydrogenate a variety of α-acyloxy acrylates and the corresponding α-acyloxy carboxylates were obtained with 82-98% e.e. The use of Rh(I)DuPHOS comlexes produced the α-acyloxy carboxylates with 93-99% e.e. (Burk[39] *et. al.*).

Michael addition on a **-alkoxy acryl moiety**

Tamm[40] and coworkers have synthesized α-hydroxy acids using chiral organoiron(II)complex. A Michael addition of *n*-BuLi to enantiomerically pure α-benzyloxyacryliron(II) complex followed by stereospecific protonation (with water) or alkylation (with alkyl halides) of the intermediate enolate leads to α-hydroxy carbonyl derivatives with 80-95% *ds*. Oxidative cleavage of the Fe-complex fragment and hydrogenolysis of the *O*-benzyl function yields the α-hydroxy esters (Scheme 14).

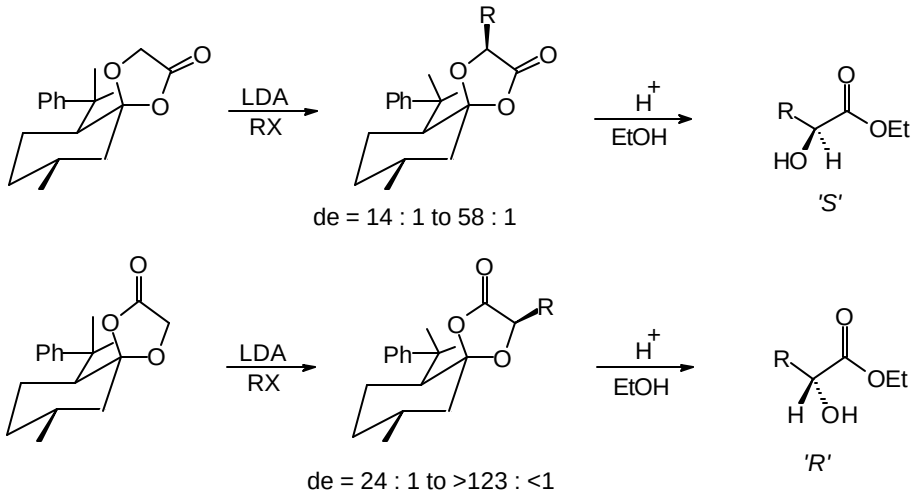
Scheme 14.



Stereoselective alkylation of chiral dioxolanes

Highly diastereoselective alkylation of chiral glycolate enolates derived from menthone and 8-phenylmenthone has been reported by Pearson (Scheme 15). Acid hydrolysis of the alkylated dioxolanes provides the requisite α-hydroxy acids.[41]

Scheme 15.

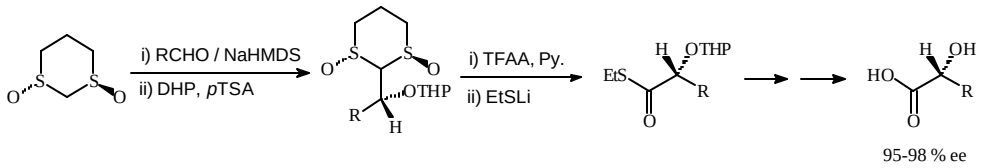


Pummer reaction of chiral 1,3-dithiane-1,3-dioxide:

Recently, Aggarwal[42] *et. al.* have demonstrated the use of *trans*-1,3-dithiane-1,3-dioxide as an acyl anion equivalent in the asymmetric synthesis of α-hydroxy acids and derivatives. The adducts obtained by the reaction with aldehydes were subjected to Pummerer reaction. Subsequent trans esterification with EtSLi provides the

thioesters which were readily converted into α-hydroxy acids with 95-98% ee (Scheme 16).

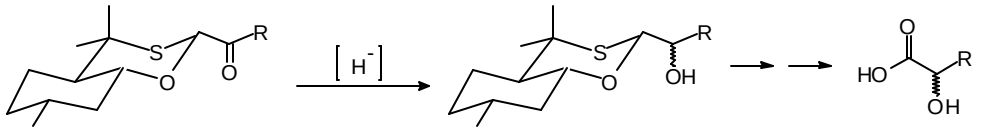
Scheme 16.



Reduction of chiral 2-acyl-1,3-oxathianes

Reduction of 2-acyl-1,3-oxathianes[43] (derived from (+) pulegone) with moderate diastereoselectivity (60-80% d.e.), has been reported by Eliel. The resulting alcohols can be converted to the free α-hydroxy acids without racemization (Scheme 17).

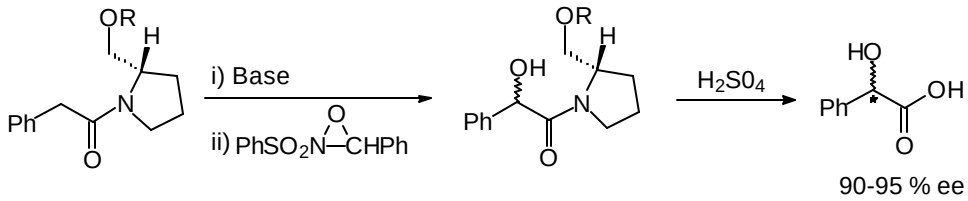
Scheme 17.



Oxidation of chiral amide enolates

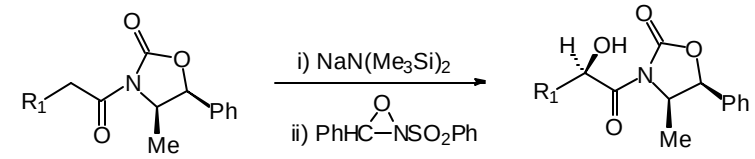
The direct oxidation of chiral enolates also provides an efficient approach to α-hydroxyacids. Oxidation of a chiral amide enolate derived from phenylacetic acid and *'S'*-2-pyrrolidinemethanol using 2-sulfonyloxaziridines as oxygen transfer agents has been reported by Davis.[44] The method generates mandelic acid with 90->95% e.e. The stereoselectivity is highly dependant on the counterion used and by changing the metal ion, both the enantiomers of mandelic acid can be obtained. Lithioenolates afford *'S'* mandelic acid, whereas sodioenolates afford *'R'* mandelic acid (Scheme 18).

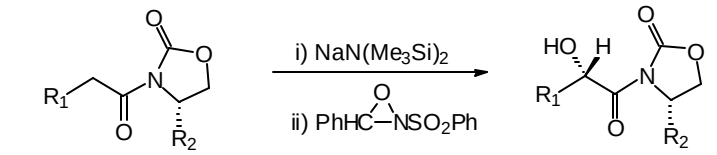
Scheme 18.



Good stereoselectivity has been achieved in the synthesis of α-hydroxy acid precursors by Evans[45] from oxazolidinone derived chiral amide enolates. '*Z*' sodium enolates could be oxidized with a slight excess of oxaziridine to furnish the α-hydroxy amides with maximum 98% diastereoselectivity (Scheme 19).

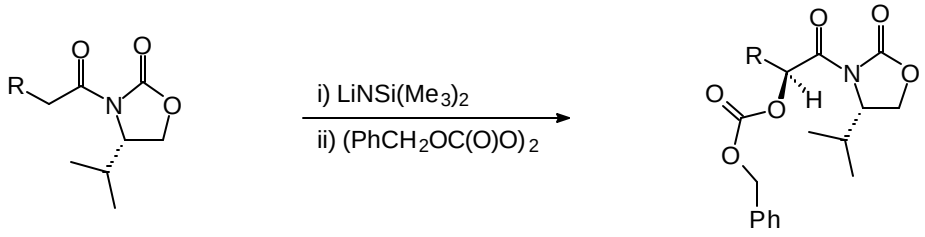
Scheme 19.





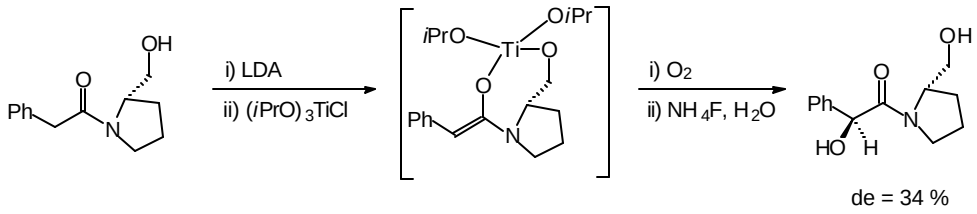
Oxidation of oxazolidinone based enolates using dibenzyl peroxydicarbonate as the oxidizing agent has been reported by Vederas[46] (Scheme 20). The advantage of this method is the direct obtainment of '*O*'-protected α-hydroxy carbonyl compounds with more than 98% diastereoselectivity. The procedure is also applicable to the oxidation of other carbon nucleophiles.

Scheme 20.



Recently, a synthesis of α-hydroxy amides and esters by direct oxidation of their titanium enolates was reported[47] by Adam et. al. (Scheme 21). However, the diastereoselectivity of this procedure is low (34% d.e. of the hydroxyamide).

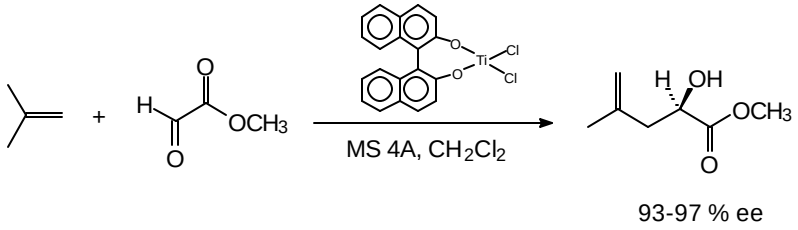
Scheme 21.



Syntheses employing chiral catalysts

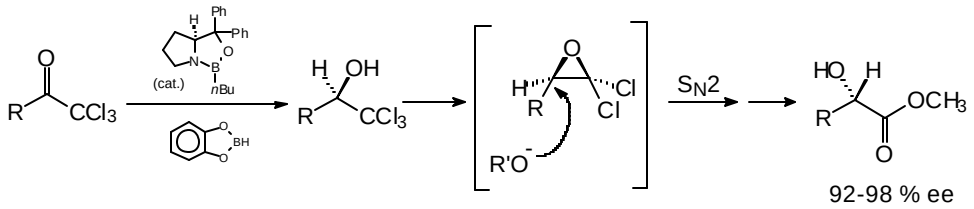
An efficient, asymmetric glyoxylate-ene reaction catalysed by a binaphthol derived titanium complex for the synthesis of optically pure α-hydroxy acids in high enantiomeric excess was developed by Mikami.[48] The method provides a useful route to functionalised *'R'* α-hydroxy esters (Scheme 22).

Scheme 22.



Corey has reported[49] a highly enantioselective reduction of trichloromethyl ketones by catecholborane in the presence of an oxazaborolidine catalyst. The product trichloromethyl carbinols, obtained in 92-98% e.e., can be readily converted to α-hydroxy acids with inversion of configuration (Scheme 23).

Scheme 23.



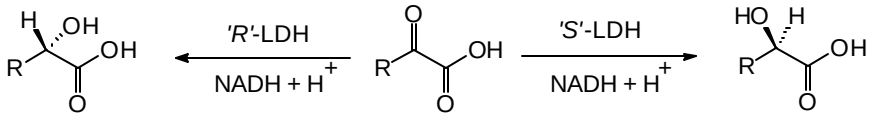
Other stereoselective syntheses of α-hydroxy acids

Other stereoselective syntheses of α-hydroxy acids and derivatives include asymmetric reduction of propargyl ketones (74-100% e.e.) followed by oxidation of the acetylene to the carboxylic acid,[50] regioselective ring opening of chiral 2,3-epoxyalcohols (readily prepared by Sharpless epoxidation) followed by ruthenium dioxide oxidation,[51] diastereoselective O-H insertion of rhodium carbenoids derived from chiral phenyldiazoacetates[52] and nucleophilic substitution in chiral α-bromo amides.[53]

Enzymatic syntheses of α-hydroxy acids

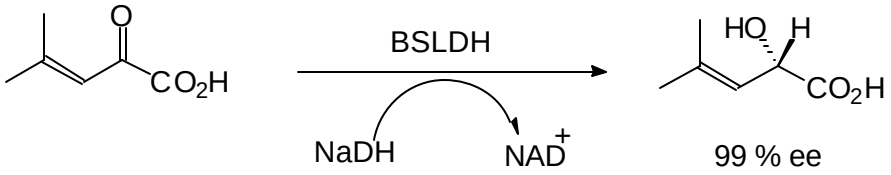
The use of enzymes has been particularly useful for the synthesis of enantioenriched α-hydroxy acids. The application of the enzyme lactase dehydrogenase (LDH) as a catalyst for the stereospecific reduction of α-keto acids has been established as a useful method for the preparation of both the enantiomers of α-hydroxy acids[54] (Scheme 24).

Scheme 24.



Casy et. al. have synthesized β,γ-uasaturated α-hydroxy acids in very high enantiomeric excess (97-99%) by the enantioselective reduction of the corresponding α-keto acids using *Bacillus stearothermophilus* lactase dehydrogenase (BSLDH) [55] (Scheme 25).

Scheme 25.



Lipase catalysed enantioselective esterification (maximum 100% e.e.) of α-hydroxy acids in anhydrous organic solvents with primary alcohols has been reported[56] by Dordic. Enantioselective oxidation of 1,2-diols to α-hydroxy aldehydes using alcohol dehydrogenase (ADH), followed by the oxidation to the α-hydroxy acids using aldehyde dehydrogenase (AldDH) as catalysts has also been reported.[57] Reduction of α-keto esters with baker's yeast provides the *'S'* α-hydroxy acid (94% e.e.).[58] Enantioselective α-hydroxylation of carboxylic acids with molecular oxygen catalyzed by the α-oxidation enzyme system of young pea leaves (*pisum sativum*) provides enantiomerically pure *'R'* α-hydroxy acids (>99% e.e.).[59]

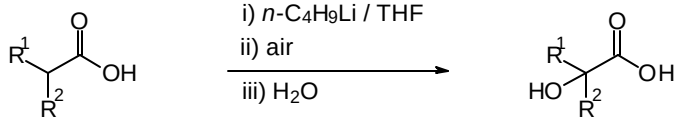
The microbial transformation[60] of α-keto esters to the corresponding α-hydroxy acids with up to 100% enantioselectivity using the fungus Geotrichum *sp*. G38

reported by Qiang also provides a useful method for the synthesis of optically pure α-hydroxy acids.

General synthesis of racemic a -hydroxy acids

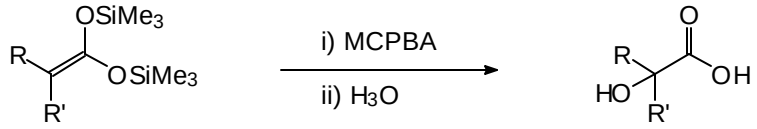
Several methods are available for the preparation of α-hydroxy acids in racemic form. For example, Pummerer reaction of β-keto sulfoxides with acetic anhydride in the presence of sodium acetate yields α-acetoxy acid thioesters which are transformed into various types of α-hydroxy acid derivatives.[61] Aeration of lithiated carboxylic acids in tetrahydrofuran solution is a very simple and effective route to the α-hydroxy acids[62] (Scheme 26).

Scheme 26.



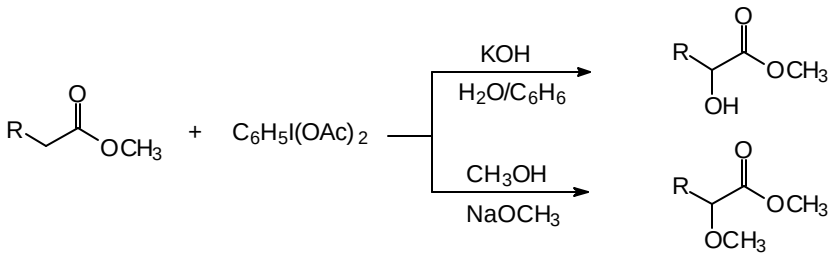
Similarly, oxidation of ketene bis(trimethylsilyl) acetals with *m*-chloroperbenzoic acid followed by mild acid hydrolysis is a general, high yielding method for the preparation of α-hydroxy acids[63] (Scheme 27).

Scheme 27.



Aryl and alkylcarboxylate esters are converted into the corresponding α-hydroxy acids or α-alkoxy esters upon treatment with hypervalent iodine compounds such as $C_6H_5I(OAc)_2$ and base in an appropriate solvent[64] (Scheme 28).

Scheme 28.

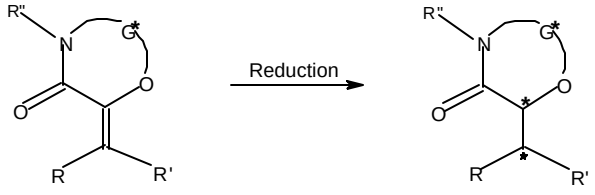


It may be noted that almost all of these methods are amenable to asymmetric modification and thus provide avenues for future work in the stereoselective synthesis of α-hydroxy acids.

2. OBJECTIVES

The objective of this undertaking was to develop a highly stereoselective synthesis of α-H-α-hydroxy acids by asymmetric reduction of α-alkoxy acrylic acid derivatives. Specifically, we chose to investigate the utility of α-alkoxy alkylidene amides derived from chiral aminoalcohols. As a primary objective, we decided to investigate the possibility of carrying out asymmetric reductions of substituted, chiral α-alkoxyacrylamides (Figure 4).

Figure 4.

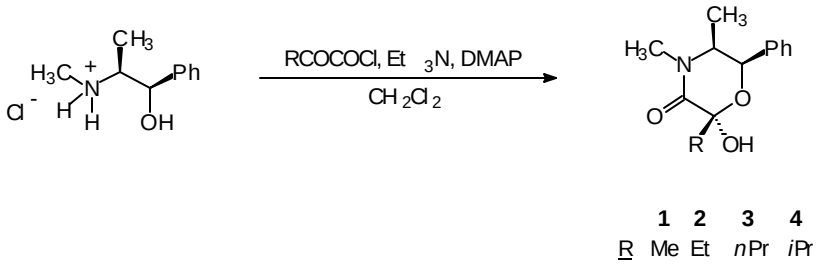


3. RESULTS AND DISCUSSION

Among the several chiral amino alcohols available[65] we chose to employ 1*R*, 2*S*-ephedrine due to its commercial availability and more importantly, the presence of a hydrogenolyzable carbon-oxygen bond. It is worthy of mention that relatively few reports in the literature describe the use of ephedrine as a chiral auxiliary/controlling group.[66-71]

Acylation of 1*R*, 2*S*-ephedrine hydrochloride with aliphatic α-keto acid chlorides generates, the corresponding hemiacetals **1-4** in 65-71% yield with 'S' configuration of the hemiacetal stereocenter (Scheme 29).[72] These served as starting materials for this study.

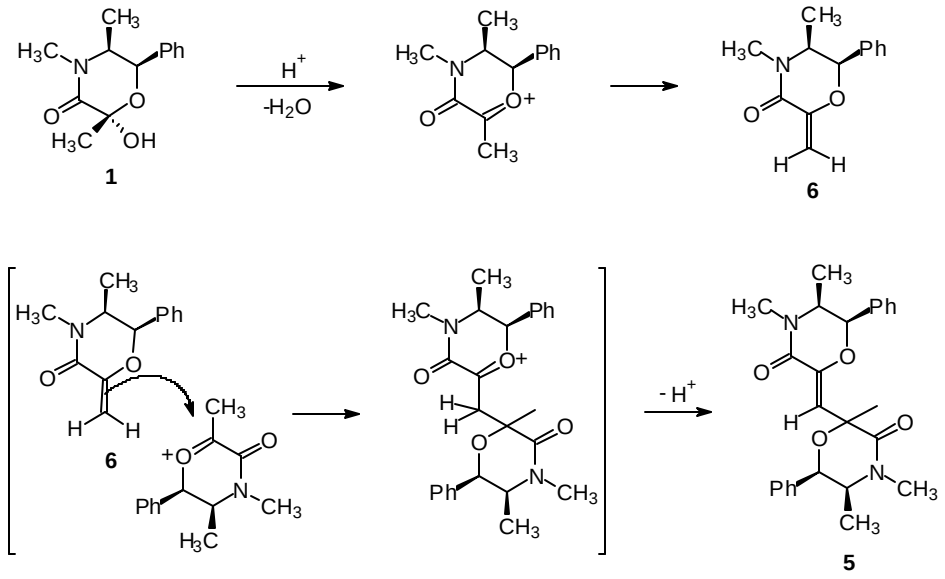
Scheme 29.



	1	2	3	4
R	Me	Et	*n*Pr	*i*Pr

Initial experiments were conducted with hemiacetal **1**. The attempted dehydration of **1** to the corresponding alkylidine morpholinone **6** was found either unsuccessful or low yielding under a variety of acid catalysed conditions. Thus the reaction of **1** with catalytic *p*-toluenesulfonic acid in refluxing benzene and with catalytic trifluoroacetic acid in refluxing CH_2Cl_2 could not provide any dehydration product **6**. The reaction of **1** either with excess $TiCl_4$ (CH_2Cl_2, -78°C-rt) or with catalytic conc. H_2SO_4 in refluxing CH_2Cl_2 lead to the exclusive formation of a dimeric product **5**. Compound **5** probably arises by reaction of the required alkylidene morpholinone **6** with its oxocarbenium ion precursor (Scheme 30).

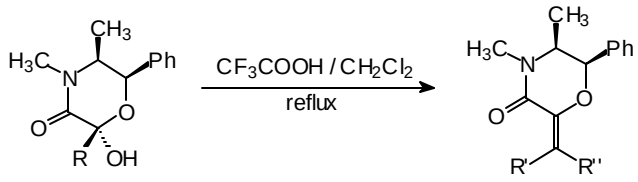
Scheme 30.



The reaction of **1** either with catalytic TFA in benzene at 40-45 °C or with amberlyst-15 in refluxing CH_2Cl_2 was low yielding and gave the desired dehydration product **6** in <20% yield. The yield was improved to 25% (34% recovery of the starting material) by treatment of **1** with conc. H_2SO_4 in CH_2Cl_2 at 0 °C for 20 min. Extended reaction times lead to the exclusive formation of the dimeric product **5**.

In contrast, hemiacetals **2-4** could easily be dehydrated to the corresponding alkylidene morpholinones **7-9** in quantitative yields by treatment of TFA in refluxing CH_2Cl_2 (Scheme 31).

Scheme 31.

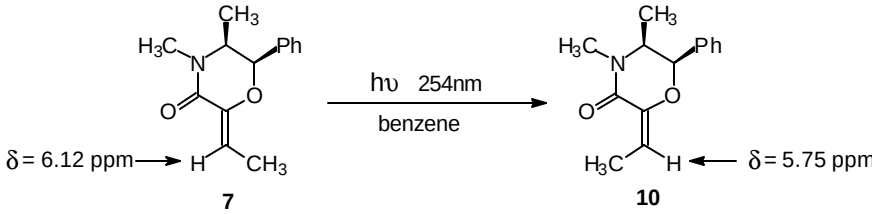


	2	3	4
R	Et	*n*Pr	*i*Pr

	7	8	9
R'	H	H	Me
R"	Me	Et	Me

The olefins **7** and **8** have been assigned the *Z* geometry on the basis of the chemical shift of the olefinic methine proton (δ 6.12 in **7**) as compared to the upfield shift in the *E* isomer **10** (δ 5.75). Compound **10** was obtained as a mixture with **7** by irradiation of **7** in benzene at 254 nm (Scheme 32). This stereochemical assignment is based on the reported trend in chemical shifts for the olefinic methine protons in *E* and *Z* benzylidene camphor derivatives.[73]

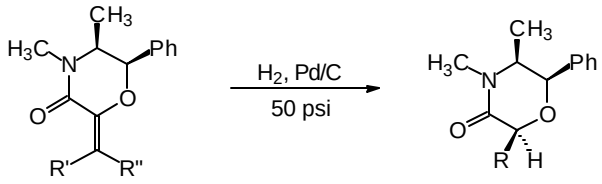
Scheme 32



7 **10**

With the requisite alkylidene morpholinones in hand, we examined their diastereoselective reduction. Hydrogenation of the alkylidene morpholinones **6-9** (H_2, Pd/C, 50 psi) in ethyl acetate cleanly generated the reduced products **11-14** in quantitative yields and as single diastereomers as determined by ^{1}H and ^{13}C NMR spectroscopy (Scheme 33).

Scheme 33.

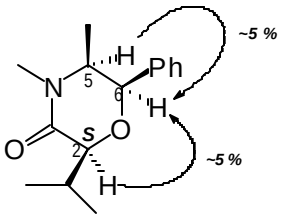


	6	7	8	9
R'	H	H	H	Me
R"	H	Me	Et	Me

	11	12	13	14
R	Me	Et	*n*Pr	iPr

The stereochemistry of the new stereocenter in **11-14** is assigned as *'S'* by NOE measurements on **14** which indicated a *cis* relationship of the hydrogens at C2, C5 and C6 in the morpholinone ring, and by anology in the ^{1}H NMR spectrum of **11-14** (Figure 5).

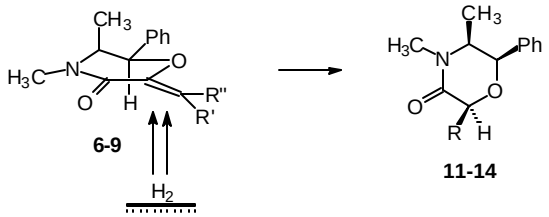
Figure 5.



14

The sense of asymmetric induction in the reduction step can be explained by adsorption on the catalyst surface and subsequent hydrogenation of the double bond from the sterically less hindered face in the molecule (Figure 6). The high stereoselectivity for hydrogenation emphasizes the strong, intrinsic stereochemical bias for reagent approach in the ephedrine derived template.

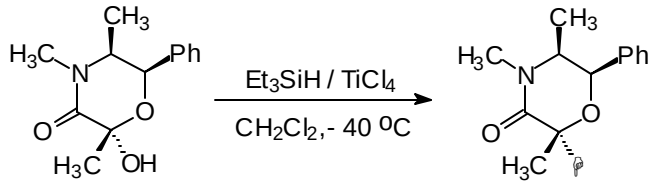
Figure 6.



6-9 **11-14**

Alternately, **1** can directly be reduced to **11** ($TiCl_4$, Et_3SiH, CH_2Cl_2, -40 °C),[74] but with low stereoselectivity (88% yield of **11**, ds = 5/1) (Scheme 34).

Scheme 34



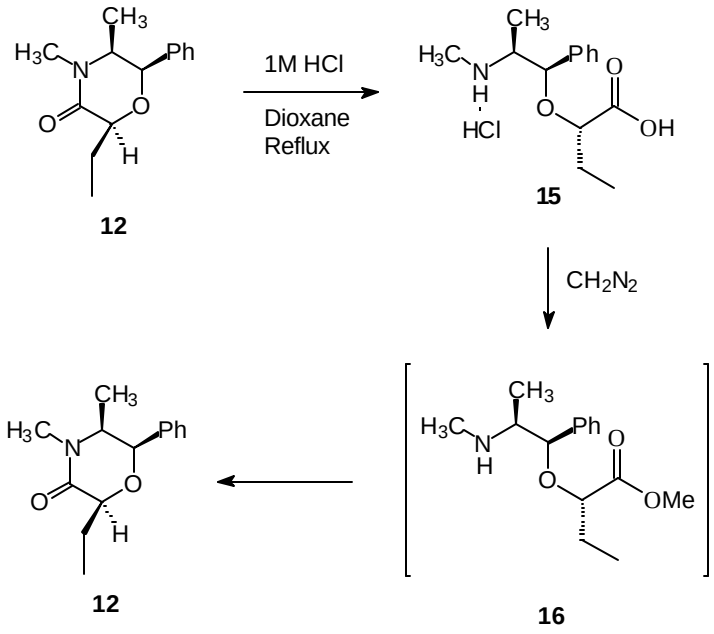
1 **11**

ds = 5/1

Liberation of the free hydroxy acids from the ephedrine template in **11-14** proved to be challenging. It may be noted, that the alkylation of an ephedrine derived glycolic acid derivative has been briefly described, but removal of the ephedrine portion was not investigated due to potential difficulties.[67] The benzylic C-O bond is resistant to cleavage under a variety of hydrogenolytic conditions and is also inert under mild ether cleavage conditions such as TMSI[75] or NBS/CCl_4, followed by NaOH.[76]

As an alternative, we examined the possibility of removal of the ephedrine portion by initial amide hydrolysis followed by reductive cleavage of the benzylic C-O bond. The acid catalyzed hydrolysis of **12** (1M HCl, reflux) gave the requisite acid **15** as the hydrochloride salt. No epimerization was detected (^{1}H NMR). Attempted cleavage of the benzylic C-O bond in the hydrochloride salt **15** was unsuccessful under a variety of hydrogenolytic conditions. Treatment of **15** with TMSI led to decomposition.

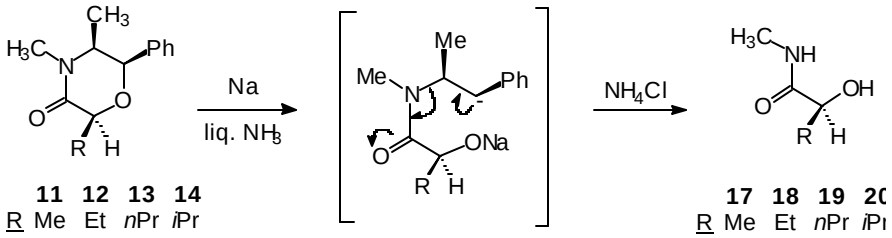
Scheme 35.



Esterification of **15** (in order to facilitate isolation of the hydroxy acid as its methyl ester) with diazomethane did not yield the desired methyl ester **16** and **12** was isolated as the only product. Presumably, excess diazomethane also neutralizes the hydrochloride salt to the amine and the resulting amino ester **16** undergoes a facile intramolecular cyclization under the reaction conditions to give **12** (Scheme 35).

Gratifyingly, dissolving metal reduction of **11-14** with Na in liq. NH_3 at -78°C (20 s) generates the hydroxy amides **17-20**[77] in 51-68% yield. Presumably, the intermediate benzylic anion derived from **11-14** undergoes facile β-elimination of the *N*-acyl moiety at low temperature (Scheme 36). It is noteworthy that this reduction is extremely rapid at -78 °C and prolonged reaction times (>30 sec.) result in significantly lower yields of **17-20**.

Scheme 36.

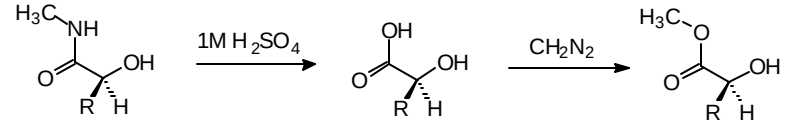


11 12 13 14
R Me Et *n*Pr *i*Pr

17 18 19 20
R Me Et *n*Pr *i*Pr

Hydrolysis of **18-20** (1M H_2SO_4, reflux) generates the α-hydroxy acids **21-23**[78-80] in good yield (72-88%). Hydrolysis of **17** was not examined due to possible difficulties in the isolation of lactic acid which is water soluble. Thus the acids **21-23** were obtained with *'S'* configuration which was assigned by comparison of the sign of optical rotation of the acids or their methyl esters with the literature values.[78-80] This also confirms the stereochemistry of **11-14**. The enantiomeric excess of the acids was determined as 92-96% by the ^{1}H NMR and/or HPLC analysis of their Mosher derivatives. The acids **21-23** were esterified with diazomethane in ether to the corresponding methyl esters **24-26** (Scheme 37). The esters **24-26** were derivatised with either *'R'*-(-)- or *'S'*-(+)-methoxytrifluoromethylphenylacetic acid and the MTPA esters[81] thus obtained were used for determination of the enantiomeric excess.

Scheme 37.



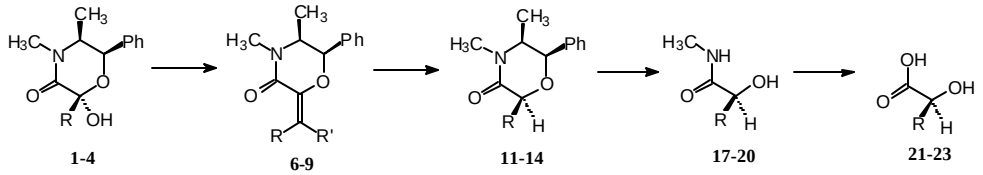
18 19 20
R Et *n*Pr *i*Pr

21 22 23
R Et *n*Pr *i*Pr

24 25 26
R Et *n*Pr *i*Pr

The results of dehydration of **1-4**, hydrogenation of **6-9**, dissolving metal reduction of **11-14** and subsequent hydrolysis to α-H-α-hydroxy acids **21-23** have been summarized in Table 1.

Table 1: Conversion of hemiacetals 1-4 to the a **-hydroxy acids 21-23**



Substrate	**Alkylidene morpholinone** (% yield)	**Hydrogenation product** (% yield)	**Hydroxy amide** (% yield)	a - **Hydroxy acid**	% yield	% ee
1	**6** (25)	**11** (96)	**17** (50)	-	-	-
2	**7** (96)	**12** (95)	**18** (68)	**21**	87	92
3	**8** (92)	**13** (99)	**19** (59)	**22**	88	92
4	**9** (98)	**14** (99)	**20** (51)	**23**	72	96

4. CONCLUSIONS

In conclusion, we have demonstrated high stereoselectivity in asymmetric C-H bond construction by hydrogenation of chiral alkylidene morpholinones derived from α-keto acids and ephedrine. The methodology has been applied to a highly stereoselective synthesis of several α-H-α-hydroxy amides and α-H-α-hydroxy acids.

5. EXPERIMENTAL

General: All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven-dried glassware (120 °C) which was cooled under argon. THF was distilled from sodium benzophenone ketyl and dichloromethane, triethylamine were distilled from CaH_2. Commercially available titanium tetrachloride ($TiCl_4$) was used as such. Petroleum ether refers to the fraction boiling in the range 60-80 °C. Commercial, precoated silica gel (Merck 60F-254) plates were used for TLC. Silica gel for column chromatography was 60-120 mesh or 230-400 mesh. All melting points are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker MSL-300 or Bruker AC-200 instruments. Optical rotations were measured at the sodium D line on a JASCO-181 digital polarimeter at ambient temperature. Elemental analyses were performed by the Microanalysis facility at NCL, Pune.

General procedure for the preparation of hemiacetals 1-4:[72]

To a suspension of the sodium salt of the α-keto acid in CH_2Cl_2 or to the neat α-keto acid was added Cl_2CHOMe at ambient temperature and the mixture was stirred for 20 minutes. The resulting suspension or solution was heated at 50-55 °C for 60-90 minutes after which it was cooled to ambient temperature, diluted with anhydrous CH_2Cl_2 and the solution was added to a suspension of 1*R*,2*S*-ephedrine hydrochloride, triethylamine and DMAP in anhydrous CH_2Cl_2 dropwise with cooling (ice bath). The mixture was then stirred at ambient temperature for 6 h. The reaction mixture was diluted with CH_2Cl_2, washed with 5% HCl, saturated sodium bicarbonate,

brine, dried (Na_2SO_4) and concentrated to provide the crude product which was purified by flash chromatography on silica gel using petroleum ether/ethyl acetate.

2*S*,5*S*,6*R*-2,4,5-Trimethyl-2-hydroxy-6-phenyl morpholin-3-one (1):

Reaction of pyruvoyl chloride (prepared from pyruvic acid (2.06 mL, 30 mmol) and Cl_2CHOCH_3 (3.2 mL, 35 mmol)) and 1*R*,2*S*-ephedrine hydrochloride (3 g, 15 mmol) in the presence of triethylamine (8.4 mL, 60 mmol) and DMAP (183 mg, 1.5 mmol) in CH_2Cl_2 (45 mL) afforded 4.03 g of crude product which on purification by flash chromatography on silica gel (3/7 petroleum ether/ethyl acetate) furnished 2.48 g (71%) of **1**. An analytical sample was obtained by crystallization from ethyl acetate.

mp: 110 °C

^{1}H NMR (300 MHz, $CDCl_3$):

δ 7.36-7.23 (m, 5H, Ar*H*), 5.47 (d, 1H, *J* = 2.9, PhC*H*), 4.4 (br s, 1H, O*H*), 3.43 (dq, 1H, *J* = 2.9, 6.5, C*H*CH$_3$), 2.99 (s, 3H, NC*H*$_3$), 1.69 (s, 3H, C*H*$_3$COH), 0.93 (d, 3H, *J* = 6.5, CHC*H*$_3$).

^{13}C NMR (50 MHz, $CDCl_3$):

δ 168.7 (N*C*=O), 137.4 (Ar*Cipso*) , 128.1 (Ar*C*H), 127.4 (Ar*C*H), 125.6 (Ar*C*H), 95.9 (CH$_3$*C*OH), 71.2 (Ph*C*H), 59.2 (N*C*H), 33.5 (N*C*H$_3$), 26.3 (C*C*H$_3$), 11.9 (CH*C*H$_3$).

IR ($CHCl_3$):

3340, 3000, 2940, 1635, 1490, 1450, 1380, 1220, 1130, 1010, 940, 890, 750 cm^{-1}.

MS (70 eV):

m/z 58 (100), 77 (12), 91 (8), 100 (28), 105 (71), 118 (32), 146 (2), 235 (<1, M^+).

[a]$^{25}_{D}$ = -107.4 (c 1.1, $CHCl_3$).

Analysis for $C_{13}H_{17}NO_3$:

Calcd: C, 66.36; H, 7.28; N, 5.95

Found: C, 66.39; H, 7.43; N, 5.99.

2*S*,5*S*,6*R*-2-Ethyl-4,5-dimethyl-2-hydroxy-6-phenyl morpholin-3-one (2):

Reaction of 2-oxo butyryl chloride (prepared from 2-oxobutyric acid (0.51 g, 5 mmol) and Cl_2CHOCH_3 (0.53 mL, 6 mmol)) and 1*R*,2*S*-ephedrine hydrochloride (0.5 g, 2.5 mmol) in the presence of triethylamine (1.7 mL, 12.5 mmol) and DMAP (0.12 g, 1 mmol) in CH_2Cl_2 (16 mL) afforded 0.88 g of a gum which on purification by flash chromatography on silica gel (35/65 petroleum ether/ethyl acetate) furnished 0.41 g (66%) of **2** as a solid.

mp: 88-89 °C

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.45-7.20 (m, 5H, Ar*H*), 5.52 (d, 1H, *J* = 3.0, PhC*H*) 3.70 (br s, 1H, O*H*), 3.46 (dq, 1H, *J* = 6.5, 3.0, CH_3CH), 3.03 (s, 3H, NCH_3), 2.26-2.08 (m, 1H, CH_3CH_2), 2.02-1.84 (m, 1H, CH_3CH_2), 1.06 (t, 3H, *J* = 7.0, CH_3CH_2), 0.97 (d, 3H, *J* = 6.5, $CHCH_3$).

^{13}C NMR (50.3 MHz, $CDCl_3$):

δ 168.2 (N*C*=O), 137.4 (Ar*Cipso*), 127.8 (Ar*C*H), 127.0 (Ar*C*H), 125.3

(Ar*C*H), 97.8 (*C*OH), 70.3 (Ph*C*H), 58.7 (CH_3*C*H), 33.2 (N*C*H_3), 31.8 (*C*H_2), 12.1 (*C*H_3), 7.8 (*C*H_3).

IR ($CHCl_3$):

3340, 3120, 1640, 1450, 1452, 1220, 1214, 1140, 1020, 750 cm^{-1}.

MS (70 eV):

m/z 57 (43), 77 (15), 86 (35), 91 (15), 105 (8), 118 (100), 143 (7), 174 (2), 232 (2).

[a **]$^{25}_{D}$** = - 110 (c 2.3, $CHCl_3$)

Analysis for $C_{14}H_{19}NO_3$:

Calcd: C, 67.45; H, 7.68; N, 5.62

Found: C, 67.21; H, 7.75; N, 5.54

2*S*,5*S*,6*R*-4,5-Dimethyl-2-hydroxy-6-phenyl-2-propyl morpholin-3-one (3):

Reaction of 2-oxopentanoyl chloride prepared from (2-oxopentanoic acid sodium salt (0.7 g, 5 mmol) and Cl_2CHOCH_3 (0.53 mL, 6 mmol)) and 1*R*,2*S*-ephedrine hydrochloride (1 g, 5 mmol) in the presence of triethylamine (1.67 mL, 12 mmol), DMAP (0.12 g, 1 mmol) in CH_2Cl_2 (20 mL) afforded 1.2 g of a gum which on purification by flash chromatography on silica gel (35/65 petroleum ether/ethyl acetate) furnished 0.85 g (65%) of **3** as a solid.

mp: 132-133 °C

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.41-7.24 (m, 5H, Ar*H*), 5.5 (d, 1H, *J* = 3.0, PhC*H*), 3.85 (br s, 1H, O*H*), 3.45 (dq, 1H, *J* = 6.8, 3.0, CH_3C*H*), 3.0 (s, 3H, NC*H*$_3$), 2.11 (ddd, 1H, *J* =

13.4, 11.6, 4.8, $CH_3CH_2CH_2$), 1.88 (ddd, 1H, *J* = 13.4, 11.6, 4.8, $CH_3CH_2CH_2$), 1.69-1.56 (m, 1H, $CH_3CH_2CH_2$), 1.45-1.29(m,1H, $CH_3CH_2CH_2$), 0.97 (t, 3H, *J* = 7.4, $CH_3CH_2CH_2$), 0.95 (d, 3H, *J* = 6.8, CH_3CH).

^{13}C NMR ($CDCl_3$):

δ 168.3 (N*C*=O), 137.5 (Ar*Cipso*), 127.9 (Ar*C*H), 127.1 (Ar*C*H), 125.4 (Ar*C*H), 97.5 (*C*OH), 70.5 (Ph*C*H), 58.8 (CH_3CH), 41.1 (CCH_2), 33.2 (NCH_3), 16.8 (CH_3CH_2), 13.8 (CH_3), 12.2 (CH_3).

IR ($CHCl_3$):

3340, 2963, 2874, 1642, 1498, 1452, 1342, 1282, 1257, 1239, 1214, 1148, 1120, 1102, 1064, 1049, 1024, 1005, 991, 927, 907, 893, 862, 773 cm^{-1}.

MS (70 eV)

m/z 57 (100), 71 (44), 77 (19), 96 (2), 105 (11), 118 (83), 128 (62), 132 (57), 142 (38), 146 (100), 157 (81), 164 (30), 174 (16), 186 (3), 192 (6), 220 (14), 235 (7), 246 (7), 263 (1, M^+).

[a]$^{25}_D$ = - 102 (c 1.9, $CHCl_3$)

Analysis for $C_{15}H_{21}NO_3$:

Calcd: C, 68.42; H, 8.04; N, 5.32

Found: C, 68.10; H, 8.35; N, 5.24.

2*S*,5*S*,6*R*-4,5-Dimethyl-2-hydroxy-6-phenyl-2-(2-propyl)morpholin-3-one (4):

Reaction of 3-methyl-2-oxobutyryl chloride prepared from (3-methyl-2-oxo butyric acid sodium salt (0.7 g, 5 mmol) and Cl_2CHOCH_3 (0.53 mL, 6 mmol)) and

1*R*,2*S*-ephedrine hydrochloride (1 g, 5 mmol) in the presence of triethylamine (1.67 mL, 12 mmol), DMAP (0.12 g, 1 mmol) in CH_2Cl_2 (20 mL) afforded 1.4 g gum which on purification by flash chromatography on silica gel (35/65 petroleum ether/ethyl acetate) furnished 1 g (65%) of **4** as a solid.

mp: 100-102 °C

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.45-7.20 (m, 5H, Ar*H*), 5.5 (d, 1H, *J* = 3.0, PhC*H*), 3.7 (br s, 1H, O*H*), 3.48 (dq,1H, *J* = 6.7, 3, CH_3CH), 3.03 (s, 3H, NCH_3), 2.55-2.35 (m, 1H, $CH(CH_3)_2$), 1.14 (d, 3H *J* = 6.9, $CH(CH_3)_2$), 0.99 (d, 3H, *J* = 6.9, $CH(CH_3)_2$), 0.96 (d, 3H, *J* = 6.7, $CH(CH_3)_2$).

^{13}C NMR (50.3 MHz, $CDCl_3$):

δ 168.9 (N*C*=O), 137.6 (Ar*Cipso*), 127.9 (Ar*C*H), 127.1 (Ar*C*H), 125.3 (Ar*C*H), 98.7 (*C*OH), 70.2 (Ph*C*H), 58.7 (CH_3CH), 35.3 ($CH(CH_3)_2$), 33.2 (NCH_3), 17.7 (CH_3), 14.2 (CH_3), 12.2 (CH_3).

IR ($CHCl_3$):

3400, 3018, 1651, 1639, 1561, 1499, 1451, 1405, 1381, 1142, 1098, 1073, 1039, 1028, 930, 701 cm^{-1}.

MS (70 eV):

m/z 58 (76), 77 (12), 91 (23), 105 (7), 118 (100), 146 (7), 157 (4), 174 (3), 220 (4), 246 (2).

$[\alpha]^{23}_D$ = - 146.5 (c 2, $CHCl_3$)

Analysis for $C_{15}H_{21}NO_3$:

Calcd: C, 68.42; H, 8.04; N, 5.32

Found: C, 68.42; H, 7.74; N, 5.28

5*S*,6*R*-2-Methylidene -4,5-dimethyl-6-phenyl morpholin-3-one (6):

A solution of the hemiacetal **1** (225 mg, 0.96 mmol) in dichloromethane (14 ml) was treated with concentrated sulfuric acid (0.5 ml) at 0 °C and the mixture was stirred vigorously at 0 °C for 20 minutes. The mixture was then neutralized with excess of saturated aqueous sodium bicarbonate. The organic layer was separated and dried over anhydrous sodium sulfate. Concentration of the organic phase under reduced pressure gave crude product which on purification by flash chromatography on silica gel gave 53 mg (25%) of **6** as a colourless oil and unreacted **1** (81mg, 34%). The purified product decomposes gradually at room temperature. Storage at -20 °C under Ar is beneficial. However, **6** is stable in solution in common organic solvents at ambient temperature.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.5-7.3 (m, 5H, Ar*H*), 5.57 (s, 1H, C(CH_2)), 5.27 (d, *J* = 2.5, 1H, C*H*Ph), 4.92 (s, 1H, C(CH_2)), 3.55 (dq, *J* = 2.5, 7, 1H, CH_3C*H*), 3.1 (s, 3H, NCH_3), 1.00 (d, *J* = 7, 3H, CH_3CH).

^{13}C NMR (50.3 MHz, $CDCl_3$):

δ 158.9 (N*C*=O), 150.6 (*C*=CH_2), 136.5 (Ar*Cipso*), 128.4 (Ar*C*H), 128.0 (Ar*C*H), 125.5 (Ar*C*H), 98.7 (*C*H_2), 77.2 (Ph*C*H), 58.7 (CH_3*C*H), 33.4 (N*C*H_3), 11.6 (CH*C*H_3).

IR (neat):

2930, 1665, 1623, 1401, 1306, 1221, 1144, 1021, 870, 761 cm^{-1}.

MS (70 eV):

m/z 56 (100), 68 (16), 77 (19), 82 (47), 91 (24), 105 (14), 117 (27), 126 (6), 131 (8), 146 (7), 200 (19), 217 (M^+, 56).

General procedure for dehydration of hemiacetals 2-4 to alkylidene morpholinones 7-9:

A solution of the hemiacetals **2-4** in dichloromethane and trifluoroacetic acid was heated to reflux for 78 h. The reaction mixture was cooled to ambient temperature and then washed with saturated aqueous sodium bicarbonate solution followed by brine. The organic layer was separated, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude product which was purified by column chromatography over flash silica gel using a mixture of petroleum ether/ethyl acetate. The purified products decompose gradually at room temperature. Storage at -20 ^oC under Ar is beneficial. However, solutions in common organic solvents are stable at ambient temperature.

(2,1')*Z*,5*S*,6*R*-2-Ethylidene-4,5-dimethyl-6-phenyl morpholin-3-one (7):

Prepared from hemiacetal **2** (470 mg, 1.88 mmol), trifluoroacetic acid (1 ml) in anhydrous dichloromethane (20 ml). Purification of the crude product by flash chromatography on silica gel gave 418 mg (96%) of **7** as a pale yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.5-7.3 (m, 5H, Ar*H*), 6.12 (q, *J* = 7, 1H, olefinic C*H*CH$_3$), 5.22 (d, *J* = 2.5 1H, C*H*Ph), 3.55 (dq, *J* = 2.5, 7, 1H, CH$_3$C*H*), 3.07 (s, 3H, NC*H*$_3$), 1.77 (d, *J* = 7, 3H, olefinic CHC*H*$_3$), 0.97 (d, *J* = 7, 3H, C*H*$_3$CH).

^{13}C NMR (50.3 MHz, $CDCl_3$):

δ 159.0 (N*C*=O), 144.3 (*C*=CHCH$_3$), 136.7 (Ar*Cipso*), 127.9 (Ar*C*H), 127.4 (Ar*C*H), 125.0 (Ar*C*H), 110.6 (C=*C*HCH$_3$), 76.5 (Ph*C*H), 58.0 (CH$_3$*C*H), 32.9 (N*C*H$_3$), 29.8 (*C*H$_3$), 11.2 (*C*H$_3$).

IR (neat):

2980, 2933, 2917, 1676, 1632, 1480, 1449, 1401, 1380, 1316, 1258, 1212, 1177, 1146, 1042, 1022, 738, 701 cm^{-1}.

MS (70 eV):

m/z 56 (52), 68 (17), 77 (10), 83 (100), 91 (27), 105 (15), 118 (100), 131 (8), 140 (14), 146 (16), 214 (26), 231 (M^+, 100).

[a **]$^{25}_{D}$**= -197.9 (c 2.3, $CHCl_3$)

UV λ_{max} = 245 nm.

(2,1')*Z*,5*S*,6*R*-2-(1-Propylidene)-4,5-dimethyl-6-phenyl morpholin-3-one (8):

Prepared from hemiacetal **3** (131 mg, 0.49 mmol), trifluoroacetic acid (0.25 ml) in anhydrous dichloromethane (10 ml). Purification of the crude product by flash chromatography on silica gel gave 113mg (92%) of **8** as a pale yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.5-7.3 (m, 5H, Ar*H*), 6.07 (t, *J* = 7, 1H, olefinic C*H*CH$_2$), 5.22 (d, *J* = 2.5, 1H, PhC*H*), 3.55 (dq, *J* = 2.5, 7, 1H, CH$_3$C*H*), 3.1 (s, 3H, NC*H*$_3$), 2.27

(quin., J = 7, 2H, CH_2), 1.05 (t, J = 7, 3H, CH_2CH_3), 1.00 (d, J = 7, 3H, $CHCH_3$).

^{13}C NMR (50 MHz, $CDCl_3$):

δ 159.1 (N*C*=O), 143.1 (*C*=CHCH$_2$), 136.6 (Ar*Cipso*), 127.9 (Ar*C*H), 127.3 (Ar*C*H), 124.9 (Ar*C*H), 117.5 (C=*C*HCH$_2$), 76.4 (Ph*C*H), 57.9 (CH$_3$*C*H), 32.9 (N*C*H$_3$), 17.7 (*C*H$_2$), 12.9 (*C*H$_3$), 11.1 (*C*H$_3$).

IR (neat):

2969, 2934, 2874, 1671, 1631, 1481, 1451, 1401, 1380, 1335, 1301, 1211, 1177, 1148, 1045, 701 cm^{-1}.

MS (70 eV):

m/z 56 (22), 69 (14), 77 (6), 91 (18), 105 (10), 118 (100), 128 (8), 146 (8), 148 (11), 154 (4), 228 (6), 245 (M^+, 50).

$[\alpha]^{23}_D$ = -186.4 (c 2.3, $CHCl_3$)

5*S*,6*R*-2-(2-Propylidene)-4,5-dimethyl-6-phenylmorpholin-3-one (9):

Prepared from hemiacetal **4** (108 mg, 0.41 mmol), trifluoroacetic acid (0.5 mL) in anhydrous dichloromethane (8 mL). Purification of the crude product by flash chromatography on silica gel (7/3 petroleum ether/ethyl acetate) gave 99 mg (98%) of **9** as a pale yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.5-7.3 (m, 5H, Ar*H*), 5.12 (d, *J* = 2.5, 1H, PhC*H*), 3.55 (dq, *J* = 2.5, 7, 1H, CH_3CH), 3.05 (s, 3H, NCH_3), 2.25 (s, 3H, CCH_3), 1.9 (s, 3H, CCH_3), 0.95 (d, *J* = 7, 3H, $CHCH_3$).

^{13}C NMR (50.3 MHz, $CDCl_3$):

δ 160.4 (N*C*=O), 138.2 (*C*=$C(CH_3)_2$), 137.3 (Ar*Cipso*), 128.1 (Ar*C*H), 127.4 (Ar*C*H), 126.3 (C=*C*$(CH_3)_2$), 125.1 (Ar*C*H), 76.5 (Ph*C*H), 58.5 (CH_3CH), 33.0 (NCH_3), 19.8 (CH_3), 11.6 (CH_3).

IR (neat):

2922, 1660, 1626, 1449, 1378, 1291, 1174, 1067, 757 cm^{-1}.

MS (70 eV):

m/z 56 (43), 67 (33), 77 (24), 82 (40), 91 (47), 96 22), 105 (19), 110 (7), 118 (100), 128 (21), 140 (6), 146 (25), 154 (15), 228 (16), 245 (M^+, 67).

[a **]$^{23}_{D}$** = -177.1 (c 0.7, $CHCl_3$).

General procedure for reduction of alkylidene morpholinones 6-9 to morpholinones 11-14:

A solution of alkylidene morpholinones **6-9** in ethyl acetate was shaken with 5% Pd/C in a Parr hydrogenator under 50 psi of hydrogen at ambient temperature for 1.5-2.5 h. The catalyst was filtered off and the filtrate was concentrated *in vacuo* to give pure morpholinones **11-14** as colourless oils.

2*S*,5*S*,6*R*-2,4,5-trimethyl-6-phenyl morpholin-3-one (11):

Prepared from **6** (140 mg, 0.64 mmol) in ethyl acetate (14 ml) and Pd/C (5%, 28 mg). Reaction time: 1.5h. Yield: 136 mg (96%).

^{1}H NMR (200MHz, $CDCl_3$):

δ 7.43-7.29 (m, 5H, Ar*H*), 5.01 (d, *J* = 2.8, 1H, PhC*H*), 4.42 (q, *J* = 6.8, 1H, CH_3CH-O), 3.48 (dq, *J* = 2.8, 6.4, 1H, CH_3CH-N), 3.03 (s, 3H, NCH_3), 1.58 (d, *J* = 6.8, 3H, CH_3CH-O), 0.98 (d, *J* = 6.4, 3H, CH_3CH-N).

^{13}C NMR (50MHz, $CDCl_3$):

δ 169.3 (N*C*=O), 137.4 (Ar*Cipso*), 127.8 (Ar*C*H), 127.1 (Ar*C*H), 125.0 (Ar*C*H), 76.1 (*C*H), 74.2 (*C*H), 58.3 (CH_3CH), 33.0 (NCH_3), 18.2 (CH_3), 12.5 (CH_3).

IR (neat):

2979, 2936, 2855, 1657, 1451, 1379, 1281, 1148, 1112, 1038, 753, 703 cm^{-1}.

MS (70eV):

m/z: 58 (100), 70 (13), 77 (15), 85 (71), 91 (21), 113 (83), 117 (38), 133 (8), 219 (M^+, 11).

HRMS for $C_{13}H_{17}NO_2$

Calcd: 219.1260

Found: 219.1282

[a]$^{25}_D$ = -120.1 (c 0.8, $CHCl_3$).

2*S*,5*S*,6*R*-2-Ethyl-4,5-dimethyl-6-phenyl morpholin-3-one (12):

Prepared from **7** (145 mg, 0.62 mmol) in ethyl acetate(14 ml) and Pd/C (5%, 29 mg). Reaction time: 1.5h. Yield: 139 mg (95%). Solidified slowly into a white wax when stored under refrigeration.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.45-7.25 (m, 5H, Ar*H*), 5.00 (d, *J*=2.8, 1H, PhC*H*), 4.30 (dd, *J*=3.8, 6.6, 1H, CH_2CH), 3.49 (dq, *J*=2.8, 6.4, 1H, CH_3CH), 3.03 (s, 3H, NCH_3), 1.85-2.2 (m, 2H, CH_2), 1.09 (t, *J*=7.3, 3H, CH_2CH_3), 0.98 (d, *J*=6.4, 3H, $CHCH_3$).

^{13}C NMR (50MHz, $CDCl_3$):

δ 168.9 (N*C*=O), 137.8 (Ar*Cipso*), 128.0 (Ar*C*H), 127.2 (Ar*C*H), 125.2 (Ar*C*H), 78.7 (*C*H), 76.0 (*C*H), 58.4 (CH_3CH), 33.1 (NCH_3), 25.5 (CH_2), 12.7 (CH_3), 9.3 (CH_3).

IR (neat):

2977, 2934, 1650, 1451, 1401, 1380, 1148, 1016, 703 cm^{-1}.

MS (70eV):

m/z: 58 (100), 65 (7), 70 (14), 77 (19), 84 (35), 91 (27), 99 (89), 105 (15), 117 (40), 127 (94), 146 (4), 233 (M^+, 7).

HRMS for $C_{14}H_{19}NO_2$

Calcd: 233.1416

Found: 233.1408

[a]$^{24}_{D}$ = -163 (c 2.3, $CHCl_3$)

2*S*,5*S*,6*R*-2-Propyl-4,5-dimethyl-6-phenyl morpholin-3-one (13):

Prepared from **8** (182 mg, 0.74 mmol) in ethyl acetate (18 ml) and Pd/C (5%, 36 mg). Reaction time: 1.5h. Yield: 182 mg (99%).

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.45-7.25 (m, 5H, Ar*H*), 4.98 (d, *J* = 2.8, 1H, PhC*H*), 4.32 (dd, *J* = 3.7, 7.3, 1H, CH_2CH), 3.48 (dq, *J* = 2.8, 6.4, 1H, CH_3CH), 3.02 (s, 3H, NCH_3), 2.07-1.79 (m, 2H, CH_2), 1.67-1.48 (m, 2H, CH_2), 0.99 (t, *J* = 7.2, 3H, CH_2CH_3), 0.96 (d, *J* = 6.4, 3H, $CHCH_3$).

^{13}C NMR (50MHz, $CDCl_3$):

δ 169.0 (N*C*=O), 137.7 (Ar*Cipso*), 127.9 (Ar*C*H), 127.1 (Ar*C*H), 125.1 (Ar*C*H), 77.6 (*C*H), 76.0 (*C*H), 58.3 (CH_3CH), 34.3 ($CHCH_2$), 33.0 (NCH_3), 18.2 (CH_3CH_2), 13.6 (CH_3), 12.6 (CH_3).

IR (neat):

2961, 2872, 1650, 1452, 1401, 1151, 758, 703 cm^{-1}.

MS (70eV):

m/z: 58 (100), 77 (19), 84 (25), 91 (22), 98 (23), 105 (20), 113 (64), 117 (47), 141 (64), 205 (24), 247 (M^+, 6).

$[\alpha]^{23}_D$ = -154.7 (c 3.1, $CHCl_3$)

2*S*,5*S*,6*R*-2-(2-Propyl)-4,5-dimethyl-6-phenyl morpholin-3-one (14):

Prepared from **9** (150 mg, 0.61 mmol) in ethyl acetate (15 mL) and Pd/C (5%, 30 mg). Reaction time: 2.5h. Yield: 150 mg (99%).

^{1}H NMR (300MHz, $CDCl_3$):

δ 7.37-7.24 (m, 5H, Ar*H*), 4.93 (d, *J* = 2.8, 1H, PhC*H*), 4.16 (d, *J* = 2.4, 1H, CHC*H*-O), 3.45 (dq, *J* = 2.8, 6.4, 1H, CH_3CH), 3.00 (s, 3H, NCH_3), 2.52 (dsepte t, *J* = 6.9, 2.4, 1H, $CH(CH_3)_2$), 1.12 (d, *J* = 6.9, 3H, CH_3), 0.96 (d, *J* = 6.9, 3H, CH_3), 0.92 (d, *J* = 6.4, 3H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$):

δ 168.7 (N*C*=O), 137.9 (Ar*Cipso*), 128 (Ar*C*H), 127.2 (Ar*C*H), 125.1 (Ar*C*H), 82.0 (*C*H), 75.7 (*C*H), 58.3 (CH_3CH), 33.0 (NCH_3), 30.4 ($CH(CH_3)_2$), 19 (CH_3), 16.3 (CH_3), 12.8 (CH_3).

IR (neat):

2966, 1735, 1648, 1451, 1253, 1151, 1042, 705 cm^{-1}.

MS (70 eV):

m/z 58 (92), 69 (43), 77 (24), 84 (20), 91 (34), 98 (31), 105 (22), 113 (71), 118 (100), 126 (21), 141 (86), 148 (12), 205 (11), 247 (M^+, 29).

HRMS for $C_{15}H_{21}NO_2$

Calcd: 247.1573

Found: 247.1565

[a]$^{24}_D$ = -158.7 (c 1.8, $CHCl_3$).

General procedure for dissolving metal reduction of morpholinones 11-14 to amides 17-20:

To anhydrous liquid ammonia (distilled over sodium) was added Na (10 eq.) at -78 °C and the mixture stirred for 15 minutes. To the resulting blue solution was added a solution of **11-14** (1 eq.) in anhydrous THF and the mixture was stirred for 15-20

sec. Anhydrous ammonium chloride (20 eq.) was added and the mixture was warmed up to ambient temperature to remove ammonia. The resulting solid mass was directly purified by flash chromatography on silica gel.

'*S*'-2-Hydroxypropanoic acid *N*-methyl amide (17):[77]

Prepared from **11** (0.09 g, 0.41 mmol) in THF (0.5 ml) and Na (0.1g, 4.34 mmol) in ammonia (8 mL). Purification by flash chromatography on silica gel (ethyl acetate) furnished 0.021g (50%) of **17** as a clear, colourless gum.

^{1}H NMR (300 MHz, $CDCl_3$):

δ 6.77 (bs, 1H, N*H*), 4.18 (q, *J* = 6.7, 1H, C*H*OH), 3.59 (bs, 1H, O*H*), 2.83 (d, *J* = 4.9, 3H, CH_3N), 1.41 (d, *J* = 6.7, 3H, CH_3C).

IR (neat):

3370, 2978, 1649, 1550, 1412, 1282, 1122, 1011, 911, 848, 614 cm^{-1}.

MS (70eV):

m/z: 58 (100), 59 (33), 60 (60), 88 (4), 103 (M^+,6).

[a]$^{25}_D$ = - 22.6 (c 3.6, EtOH).

'*S*'-2-Hydroxybutanoic acid *N*-methyl amide (18):[77]

Prepared from **12** (0.186 g, 0.80 mmol) in THF (1.5 ml) and Na (0.215 g, 9.34 mmol) in ammonia (20 mL). Purification by flash chromatography on silica gel (ethyl acetate) furnished 0.064g (68%) of **18** as a clear, colourless gum.

^{1}H NMR (300 MHz, $CDCl_3$):

δ 6.68 (bs, 1H, N*H*), 4.06 (b, 1H, C*H*OH), 3.28 (bs, 1H, O*H*), 2.84 (d, *J* = 4.9, 3H, CH_3N), 1.91-1.82 and 1.72-1.59 (m, 2H, CH_3CH_2), 0.96 (t, *J* =7.5, 3H, CH_3C).

IR (neat):

3359, 2968, 1646, 1551, 1461, 1413, 1316, 1127, 1048, 986, 590cm^{-1}.

MS (70eV):

m/z: 58 (60), 59 (87), 60 (47), 88 (62), 89 (100), 99 (7), 117 (M^+,33).

$[a]^{25}_D$ = - 48.7 (c 1.2, $CHCl_3$)

'*S*'-2-Hydroxy pentanoic acid *N*-methyl amide (19):[77]

Prepared from **13** (0.333g, 1.35 mmol) in THF (1 ml) and Na (0.31 g, 13.5 mmol) in ammonia (10 mL). Purification by flash chromatography on silica gel (ethyl acetate) furnished 0.104g (59%) of **19** as white solid.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 6.75 (bs, 1H, NH), 4.1 (m, 1H, C*H*OH), 3.50 (bs, 1H, OH), 2.85 (d, *J* = 4.9, 3H, CH_3N), 1.35-1.9 (m, 4H, CH_2CH_2), 0.95 (t, *J* = 7.5, 3H, CH_3C).

IR ($CHCl_3$):

3340, 2959, 1648, 1548, 1411, 1286, 1131, 757cm^{-1}.

MS (70eV):

m/z: 55 (44), 58 (73), 73 (29), 89 (100), 113 (2), 132 (M+1, 9).

[$a]^{25}_D$ = - 48.4(c 1.4, $CHCl_3$)

'*S*'-2-Hydroxy 3-methyl butanoic acid *N*-methyl amide (20)[77]**:** Prepared from **14** (0.488 g, 1.98 mmol) in THF (2ml) and Na (0.453 g, 19.7 mmol) in ammonia (40 mL). Purification by flash chromatography on silica gel (ethyl acetate) furnished 0.132g (51%) of **20** as white solid.

^{1}H NMR (200MHz, $CDCl_3$):

δ 6.59 (bs, 1H, N*H*), 3.98 (bs, 1H, C*H*OH), 2.96 (bs, 1H, O*H*), 2.85 (d, *J* = 4.9, 3H, NHCH_3), 2.17 (dsept, *J* = 3.1, 6.9, 1H, C*H*$(CH_3)_2$), 1.02 (d, *J* = 6.9, 3H, CH_3), 0.84 (d, *J* = 6.9, 3H, CH_3).

IR ($CHCl_3$):

3365, 2958, 1632, 1577, 1409, 1021, 616 cm^{-1}.

MS (70 eV):

m/z 55 (87), 58 (74), 60 (64), 73 (86), 83 (17), 89 (100), 98(3), 113 (11), 131(M^+, 5).

[a]$^{25}_D$ = - 57.0 (c 2.6, $CHCl_3$).

General procedure for the hydrolysis of the amides 18-20:

The hydroxy amides **18-20** were suspended in 1M H_2SO_4 and the mixture was heated to reflux till hydrolysis was complete. After cooling to 0 ^oC, the solution was neutralized with solid $NaHCO_3$ and the mixture was extracted with ether. The aqueous layer was acidified with conc. H_2SO_4 and the α-hydroxy acid was extracted repeatedly with ether. The combined extracts were dried over anhydrous Na_2SO_4 and concentrated to furnish the acids **21-23**. The acids were converted to the methyl esters **24-26** by treatment with diazomethane in ether.

Synthesis of MTPA derivatives of the a **-hydroxy methyl esters 24-26:**

'S' or *'R'*-Methoxytrifluromethylphenylacetyl chloride was prepared according to the literature procedure[81] by refluxing the corresponding methoxytrifluoromethylphenylacetic acid (1.0 g) and NaCl (0.01 g) in thionyl chloride (6 mL) for 50 h. The excess thionyl chloride was removed by distillation. Kugelrohr distillation of the residue furnished 0.85-0.90 g of the pure acid chloride as a colourless oil. A stock solution of the MTPA chloride was prepared in dichloroethane and stored in the refrigerator under argon. It was used when necessary. The MTPA esters were prepared by mixing the α-hydroxy ester, MTPA chloride (1.2-1.5 eq.) and 10 drops of pyridine. The reaction was complete at ambient temperature in 18-24 h.. The reaction mixture was diluted with $CHCl_3$ and washed with 5% HCl, saturated $NaHCO_3$, brine, dried (Na_2SO_4) and concentrated to furnish the crude MTPA ester which was purified minimally by filtration through a small pad of silica gel. The MTPA esters thus obtained were analysed for diastereomeric content by ^1H NMR and/or HPLC.

2*S*-2-Hydroxybutanoic acid (21):[80]

18 (40 mg, 0.34 mmol) in 1M H_2SO_4 (3 ml) was heated to reflux for 4 h to yield, after work up, 31 mg (87%) of **21** as colourless needles.

$[\alpha]^{25}_D$ = +5.5 (c 0.66, $CHCl_3$)

The acid was immediately converted to the methyl ester in order to prevent dimerisation.

2*S*-Methyl-2-Hydroxybutanoate (24):

^{1}H NMR (200 MHz, $CDCl_3$):

δ 4.2 (q, *J* = 7, 1H, C*H*), 3.8 (s, 3H, OCH_3), 2.75 (d, *J* = 7, 1H, O*H*), 1.95-1.55 (m, 2H, CH_2), 0.95 (t, *J* = 7, 3H, CH_2CH_3).

Enantiomeric excess:

92% by ^{1}H NMR analysis of the Mosher derivative of **24** with '*R*'-methoxytrifluoromethylphenylacetyl chloride.

2*S*-2-Hydroxypentanoic acid (22):[78]

19 (96 mg, 0.73 mmol) in 1M H_2SO_4 (6 ml) was heated to reflux for 8 h to yield, after work up, 76 mg (88%) of **22** as pale yellow solid.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 5.8-5.1 (bs, 2H, O*H*, CO_2H), 4.35-4.25 (m, 1H, C*H*), 1.95-1.65 (m, 2H, CHCH_2), 1.65-1.40 (m, 2H, CH_3CH_2), 1.00 (t, J = 7, 3H, CH_3).

IR ($CHCl_3$):

3420, 2960, 2360, 1725, 1227, 1131cm^{-1}.

MS (70eV):

m/z: 55 (100), 73 (80), 76 (28), 119 (M+1, 1).

2*S*-Methyl-2-Hydroxypentanoate (25):

IR (neat):

4258, 3833, 3398, 2926, 2342, 1750, 1641, 1563, 1451, 1093, 678 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 4.25-4.15 (m, 1H, C*H*), 3.8 (s, 3H, OCH_3), 2.7 (d, *J* = 7, 1H, O*H*), 1.9-1.3 (m, 4H, CH_2CH_2), 0.95 (t, *J* = 7, 3H, CH_2CH_3).

$[\alpha]^{25}_D$ = +9.9 (c 0.48, $CHCl_3$)

Enantiomeric excess:

92% by ^{1}H NMR analysis of the Mosher derivative of **25** with '*S*'-methoxytrifluoromethylphenylacetyl chloride.

2*S*-2-Hydroxy-3-methylbutanoic acid (23):[79]

20 (130 mg, 0.99 mmol) in 1M H_2SO_4 (18 ml) was heated to reflux for 36 h to yield, after work up, 85 mg (72%) of **23** as white solid.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 5.8 (bs, 2H, O*H*, CO_2H), 4.16 (d, *J* = 3.4, 1H, C*H*OH), 2.30-2.05 (m, 1H, C$H(CH_3)_2$), 1.07 (d, *J* = 6.9, 3H, CH_3), 0.93 (d, *J* = 6.9, 3H, CH_3).

IR ($CHCl_3$):

2967, 1728, 1467, 1215, 1136, 1028, 895, 759 cm^{-1}.

MS (70 eV):

m/z 55 (53), 58 (38), 73 (85), 76 (100), 87 (5), 102 (5), 118 (M^+, 2).

[a $]^{25}_D$ = +13.8 (c 1.5, $CHCl_3$)

2*S*-Methyl-2-Hydroxy-3-methylbutanoate (26):

^{1}H NMR (200 MHz, $CDCl_3$):

δ 4.04 (m, 1H, C*H*OH), 3.77 (s, 3H, OCH_3), 2.72 (d, J = 6, 1H, O*H*), 2.08-1.97 (m, 1H, C*H*$(CH_3)_2$), 0.98 (d, J = 7, 3H, CH(CH_3)$_2$), 0.83 (d, J = 7, 3H, CH(CH_3)$_2$).

Enantiomeric excess: 96% (HPLC analysis of the Mosher derivative of **26** with '*S*'-methoxytrifluoromethylphenylacetyl chloride; Macherey-Nagel Nucleosil®5 C_8 (reversed phase) column, 250 x 4 mm, acetonitrile/water 6/4, flow rate 1.2 ml/min. t_R (major): 3.81 min.; t_R (minor): 5.11 min).

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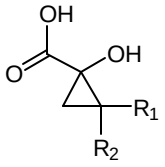
CHAPTER II

ASYMMETRIC SYNTHESIS OF a -HYDROXYCYCLOPROPANECARBOXYLIC ACIDS

1. INTRODUCTION

α-Hydroxycyclopropanecarboxylic acids constitute a unique class of hydroxy acids due to their structural novelty as well as their applications in the synthesis of five and six membered ring systems,[1] as enzyme inhibitors (**I**, Figure 1),[2] and components of fungicides and agricultural microbicides (**II**, Figure 1).[3,4]

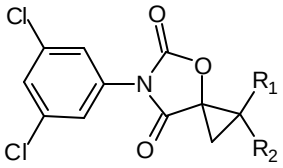
Figure 1.



I

R_1	H	Me	Me
R_2	H	Me	Et

Inhibitors of dihydroxyacid dehydratase from yeast and *E. coli*.



II

Fungicide ($R_1 = R_2 = H$)

Agricultural microbicide ($R_1 = R_2 = Me$)

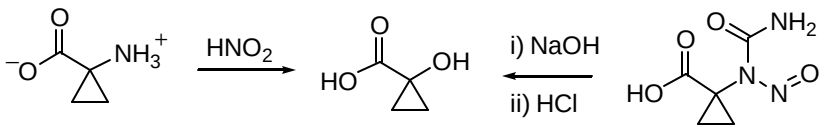
Synthesis of α-hydroxycyclopropanecarboxylic acids

Two approaches to α-hydroxycyclopropanecarboxylic acids have been reported in the literature.

Diazotization of α-aminocyclopropanecarboxylic acids

The first synthesis of the parent, achiral α-hydroxycyclopropanecarboxylic acid was reported by Ingold[5]. The approach involved conversion of α-amino- or α-(nitroso-ureido)-cyclopropanecarboxylic acid to the α-hydroxy analogue (Scheme 1).

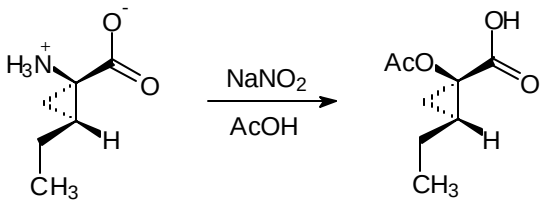
Scheme 1.



A diastereoselective version[6] of this methodology has also been demonstrated on racemic, diastereomerically pure 2-ethyl-1-aminocyclopropane-1-carboxylic acids.

The procedure involves diazotization of the α-amino acid with sodium nitrite in acetic acid to yield the corresponding α-acetoxy acids with retention of stereochemistry (Scheme 2).

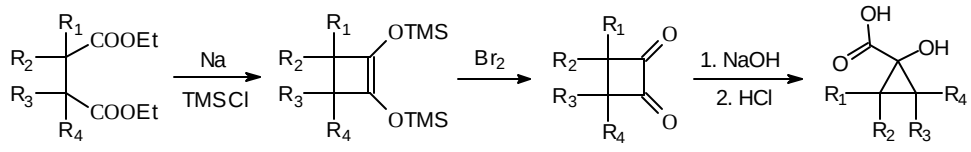
Scheme 2.



Stereoselective ring contraction of cyclobutane-1,2-diones

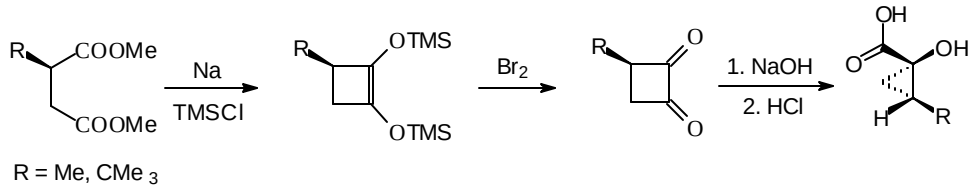
Heine[7,8] has synthesized α-hydroxycyclopropane carboxylic acids by stereoselective ring contraction of cyclobutane-1,2-diones prepared from the corresponding diethylsuccinates. The stereochemical course of the ring contraction process is governed by the preexisting stereocenter at in the cyclobutanedione to obtain α-hydroxycyclopropanecarboxylic acids in which the carboxylic acid group is *trans* with respect to the C2 substituent in the cyclopropane ring (Scheme 3).

Scheme 3.



This reaction has also been employed by Salaün[1,9] *et. al.* in an asymmetric approach to α-hydroxycyclopropanecarboxylic acids from enantiomerically enriched diethylsuccinates (Scheme 4).

Scheme 4.



R = Me, CMe_3

2. OBJECTIVES

The cyclobutanedione based synthesis[1,9] is the only procedure presently available for the preparation of enantiomerically enriched α-hydroxycyclopropanecarboxylic acids. The objective of this undertaking was to develop a general, asymmetric synthesis of α-hydroxycyclopropanecarboxylic acids that involves stereoselective cyclopropanation of chiral, α-alkoxy acrylamides derived from α-keto carboxylic acids. These acrylamides have been described in Chapter 1.

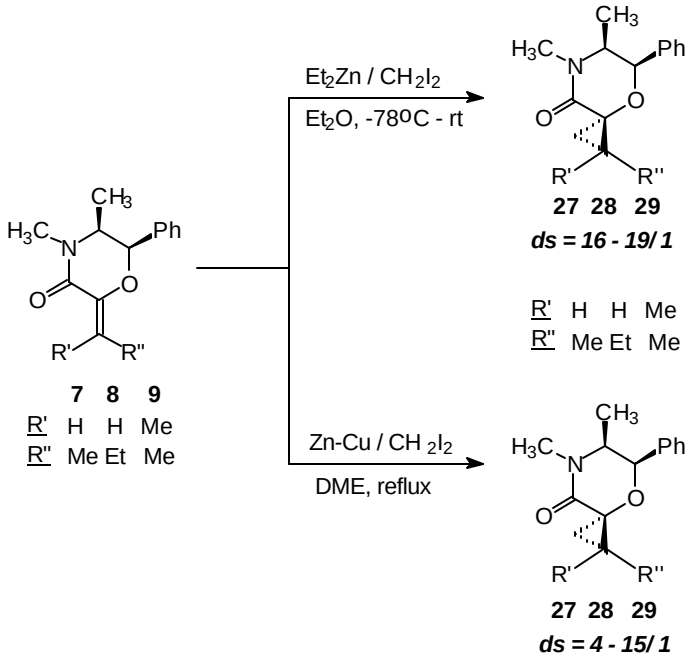
3. RESULTS AND DISCUSSION

Initial studies were conducted on α-alkoxy acrylamide **7**. Somewhat unexpectedly, cyclopropanation of **7** could not be achieved with CH_2N_2[11] and unreacted starting material was recovered from this reaction. The addition of a catalytic amount of $Pd(OAc)_2$[12] had no effect on the reaction. However, Simmons-Smith cyclopropanation[13] of **7** employing Zn-Cu[14]/CH_2I_2 in ether was successful and afforded the cyclopropyl morpholinone **27** in 62% yield (Scheme 5). The reaction proceeded only at the solvent reflux temperature and stereoselectivity was moderate.

Thus, in diethyl ether, **27** was obtained as a 3/1 mixture of diastereomers (^{1}H NMR). The use of DME or THF as a solvent marginally increased the selectivity to 4/1 (62% yield in refluxing DME). The α-alkoxy acrylamides **8** and **9** were also

cyclopropanated to the corresponding cyclopropyl morpholinones **28** (58% yield, *ds* = 4/1) and **29** (69% yield, *ds* = 15/1) in refluxing DME. Although the diastereoselectivity for **28** (4/1) was the same as that for **27**, the dimethyl compound **29** is obtained from **9** with good diastereoselectivity (15/1) at the DME reflux temperature (Scheme 5). The large increase in selectivity may be attributed to the increased steric demands of the substrate (tetrasubstituted double bond in **9**).

Scheme 5.



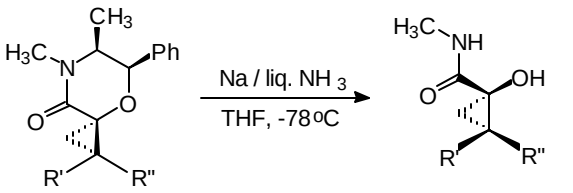
Cyclopropanation of **7-9** was also investigated by employing other reagents reported in the literature. Thus, the reaction of **7-9** with the Me_3Al/CH_2I_2[15] derived reagent could not produce any cyclopropanation product and only the starting material was recovered. However, the reaction with Et_2Zn[16]/CH_2I_2 derived reagent[17] at ambient temperature successfully generated the corresponding cyclopropyl morpholinones **27** (*ds* = 16/1), **28** (*ds* = 19/1) and **29** (*ds* = 19/1) with 56-82% yield (Scheme 5). The diastereomer ratio in **27-29** was readily determined by ^{1}H NMR spectroscopy of the

crude product and is based on the integration of the characteristic benzylic methine resonance (doublet in the 5 ppm region) due to the ephedrine portion of the molecule.

The absolute configuration of the major diastereomer in **27-29** was determined by their conversion to the corresponding α-hydroxy cyclopropane carboxylic acids and is described below.

Dissolving metal reduction of **27-29** with sodium in liq. ammonia at −78 °C generated the hydroxy amides **30-32** in 74-90% yield (Scheme 6).

Scheme 6.



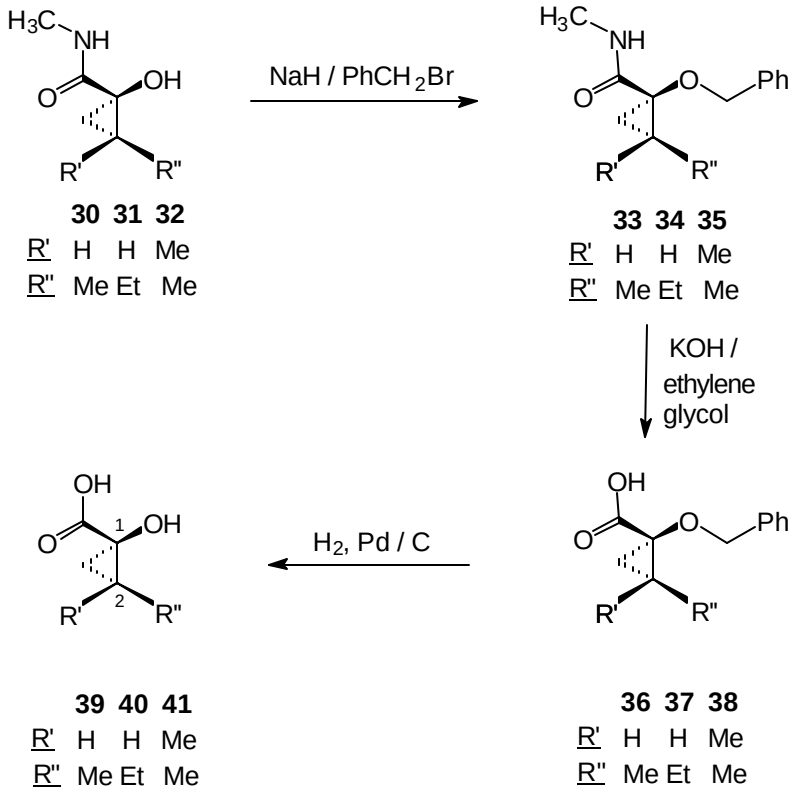
	27	**28**	**29**
R'	H	H	Me
R"	Me	Et	Me

	30	**31**	**32**
R'	H	H	Me
R"	Me	Et	Me

Hydrolysis of the amides **30-32** was problematic under acidic (6N HCl, 80 °C) as well basic (KOH, ethylene glycol, reflux) conditions and resulted in a complex mixture, presumably due to cleavage of the cyclopropane ring under the reaction conditions. Protection of hydroxyl group in **30-32** had a significant effect. Thus, reaction of **30-32** with NaH / $PhCH_2Br$ in anhydrous THF furnished the corresponding *O*-benzyl amides **33-35** in 66-81% yield (Scheme 7). Hydrolysis of **33-35** could not be achieved under acidic conditions (refluxing 1N HCl or refluxing 3M H_2SO_4) and resulted in a complex mixture. However, the treatment of **33-35** with KOH in ethylene glycol[18] (120 °C or 180 °C) cleanly generated the desired *O*-benzyl carboxylic acids **36-38** in 71-93% yield. Debenzylation of **36-38** by hydrogenolysis (H_2 (1 atm.), Pd/C,

EtOH) afforded the desired α-hydroxycyclopropanecarboxylic acids **39-41** in 82-94% yield. The overall transformation is shown in Scheme 7.

Scheme 7.



30 31 32
R' H H Me
R" Me Et Me

33 34 35
R' H H Me
R" Me Et Me

39 40 41
R' H H Me
R" Me Et Me

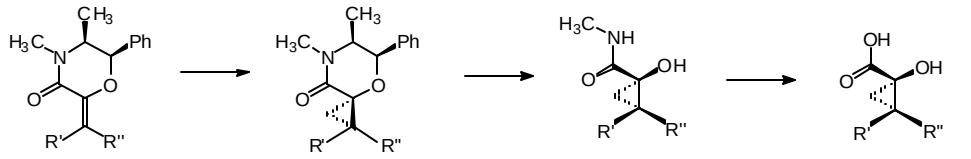
36 37 38
R' H H Me
R" Me Et Me

The absolute configuration of **39-41** was determined by comparision of the sign of the optical rotation of **39** with the literature value ($[\alpha]_D$ = -32.4 (c 1.6, $CHCl_3$) for **39** (Scheme 7); lit.[1] $[\alpha]_D$ = -57 (c 1.6, $CHCl_3$) for 1*S*,2*R* **39**) and by analogy in the ^1H NMR spectra of the precursors **27-29**. Thus, **39** and **40** have been assigned the 1*S*,2*R*, and the configuration of **41** is also 1*S* at C1.

The enantiomeric excess of the α-hydroxycyclopropanecarboxylic acids is based on the diastereomeric excess of the precursors **27-29** since epimerization of the newly generated stereo centers during conversion of **27-29** to **30-32** and **30-32** to

39-41 is unlikely. It should be noted that **7-9** obtained by the $Zn\text{-}Cu/CH_2I_2$ procedure were employed in the above sequence since they were available in larger quantities. The Et_2Zn/CH_2I_2 procedure is superior, since the stereoselectivity of cyclopropanation (and consequently the enantiomeric excess of the α-hydroxycyclopropanecarboxylic acids) is much higher. The results are summarized in Table 1.

Table 1: Stereoselective cyclopropanation of acrylamides **7-9** and their conversion to α-hydroxycyclopropanecarboxylic acids **39-41.**



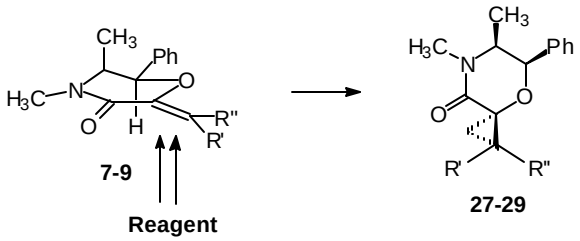
7-9 **27-29** **30-32** **39-41**

Substrate	**Reagent**	**Cyclopropyl morpholinone** (% yield)	**ds**[a]	**Hydroxy amide** (%yield)	**Hydroxy acid** (%yield)[b]	**er**[c]
7	$Zn\text{-}Cu/CH_2I_2$	**27** (62)	4/1	**30** (74)	**39** (51)	4/1
	Et_2Zn/CH_2I_2	**27** (56)[d]	16/1			
8	$Zn\text{-}Cu/CH_2I_2$	**28** (58)	4/1	**31** (85)	**40** (60)	4/1
	Et_2Zn/CH_2I_2	**28** (59)	19/1			
9	$Zn\text{-}Cu/CH_2I_2$	**29** (69)	15/1	**32** (90)	**41** (58)	15/1
	Et_2Zn/CH_2I_2	**29** (82)[d]	19/1			

a: determined by ^1H NMR spectroscopy b: overall yield for three steps c: based on the ds for precursors **27-29** d: based on recovered starting material.

The facial selectivity for cyclopropanation of **7-9** may be explained by considering a transition state conformation for **7-9** in which the phenyl group is *quasi* equatorial. An axial approach of the cyclopropanating species would result in the observed stereoselectivity (Figure 1).

Figure 1.



4. CONCLUSIONS

An asymmetric synthesis of α-hydroxycyclopropanecarboxylic acids has been achieved by cyclopropanation of chiral α-alkoxy acrylamides. It is noteworthy that enantiomerically enriched hydroxy acids such as **41**, which are symmetrically disubstituted on C2, may not be readily available by ring contraction of the corresponding cyclobutane-1,2-dione[9] since it is achiral. The present method thus offers a distinct advantage.

5. EXPERIMENTAL

General experimental techniques which have been described in the experimental section of Chapter 1 were followed.

Preparation of the zinc-copper couple:[14]

In a 250 mL round-bottomed flask fitted with magnetic stirrer were placed zinc powder (49.2 g, 0.75 g atom) and 40 mL aqueous hydrochloric acid (3%). The mixture was stirred rapidly for 1 min., the zinc was allowed to settle, and the supernatant liquid was decanted. The residual zinc powder was then washed successively with three additional 40 mL portions of hydrochloric acid (3%), five 100 mL portions of distilled water, two 75 mL portions of aqueous copper sulfate (2%), five 100 mL portions of distilled water, four 100 mL portions of absolute ethanol and five 100 mL portions of absolute ether. The resulting Zn-Cu couple was transferred to a Buchner funnel, washed with anhydrous ether and dried with suction. It was stored in a vacuum dessicator over phosphorous pentoxide and used when required.

General procedure for the Simmons-Smith cyclopropanation of α-alkoxy acrylamides 7-9:[13]

To α-alkoxy acrylamides **7-9** (1eq.) and Zn-Cu couple (10 eq.) in DME was added a crystal of iodene. To this stirred suspention was added di-iodomethane (10 eq.) dropwise. A vigorous reaction commences and the reaction mixture starts refluxing. The reflux was maintained for 6h (oil bath, 110 ^{o}C) at which point additional Zn-Cu couple (10 eq.) and diiodomethane (10 eq.) were added and the reflux was

continued for another 6h. The reaction mixture was cooled to ambient temperature and the solvent was removed under reduced pressure. The residue was taken up in ethyl acetate and washed with ice cold 2N HCl followed by water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The crude product obtained was purified by flash chromatography on silica gel using petroleum ether/ethyl acetate mixtures as eluant.

(*1R, 3S, 5R, 6S*)-1,6,7-Trimethyl-4-oxa-5-phenyl-7-aza-spiro[2.5]octan-8-one (27):

Prepared from **7** (0.69 g, 2.98 mmol) in anhydrous 1,2-dimethoxyethane (30 mL), Zn-Cu couple (3.8 g, 58.46 mmol), iodine (0.005 g) and di-iodomethane (4.82 mL, 59.83 mmol) to furnish 0.82 g of crude product (*ds* = 4/1 by ^{1}H NMR) which on purification by flash chromatography on silica gel (6/4 petroleum ether/ethyl acetate) furnished 0.46 g (62%) of **27** as clear, colourless gum.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.45-7.25 (m, 5H, Ar*H*), 5.20 (d, 1H, *J* = 2.4, PhC*H*), 3.65 (dq, 1H, *J* = 2.4, 6.4, NC*H*), 3.05 (s, 3H, NCH_3), 2.0-1.8 (m, 1H, CH_2C*H*), 1.40 (dd, 1H, *J* = 4.4, 9.7, CH_2) 1.30 (d, 3H, *J* = 6.3, CH_2CHCH_3), 1.00 (d, 3H, *J* = 6.4, NCHCH_3), 0.60 (dd, 1H, *J* = 4.4, 7.3, CH_2).

Visible peaks for the other diastereomer: δ 5.05 (d, 1H, PhC*H*), 1.15 (d, 3H, CHCH_3), 1.05 (d, 3H, CHCH_3), 0.80 (dd, 1H, CH_2).

^{13}C NMR (50 MHz, $CDCl_3$):

δ 169.6 (N*C*=O), 138.0 (Ar*Cipso*), 128.2 (Ar*C*H), 127.4 (Ar*C*H), 125.3 (Ar*C*H), 76.6 (Ph*C*H), 63.1 (*C*-O), 59.2 (N*C*H), 33.3 (N*C*H_3), 23.0 (*C*H_2), 20.0 (CH_2*C*H), 12.5 (*C*H_3), 11.7 (*C*H_3).

Visible peaks for the other diastereomer: δ 137.0 (Ar*Cipso*), 77.0 (Ph*C*H), 64.0 (*C*-O), 22.0 (CH_2*C*H), 21.0 (*C*H_2), 11.0 (*C*H_3).

IR (neat):

2978, 2932, 2874, 1651, 1605, 1450, 1400, 1379, 1340, 1296, 1258, 1213, 1198, 1141, 1094, 1070, 1042, 1015, 988, 918, 885 cm^{-1}.

MS (70 eV):

m/z 58 (4), 91 (16), 118 (100), 128 (85), 148 (2), 204 (1), 245 (M^+, 2).

$[a]^{25}_D$ = -117.8 (*c* 1 , $CHCl_3$)

(*1R, 3S, 5R, 6S*)-1-Ethyl-4-oxa-5-phenyl-6,7-dimethyl-7-aza-spiro[2.5]octane-8-one (28):

Prepared from **8** (0.7 g, 2.85 mmol) in anhydrous 1,2-dimethoxyethane (40 mL), Zn-Cu couple (3.6 g, 55.38 mmol), iodine (0.005g), di-iodomethane (4.6 mL, 57.1 mmol) to furnish 0.89 g of crude product (*ds* = 4/1 by ^{1}H NMR) which on purification by flash chromatography on silica gel (7/3 petroleum ether/ethyl acetate) furnished 0.431 g (58%) of **28** as clear, colourless gum.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.45-7.25 (m, 5H, Ar*H*), 5.20 (d, 1H, *J* = 2.7, PhC*H*), 3.60 (dq, 1H, *J* = 2.7, 6.5 NC*H*), 3.05 (s, 3H, NCH_3), 1.90-1.60 (m, 3H, CH_3CH_2CH),

1.35 (dd, 1H, J = 4.5, 9.0, CCH_2), 1.10 (t, 3H, J = 7.0, CH_2CH_3), 1.00 (d, 3H, J = 6.5, CHCH_3), 0.60 (dd, 1H, J = 4.5, 6.8, CCH_2).

Visible peaks for the other diastereomer: δ 5.05 (d, 1H, PhC*H*), 0.85 (dd, 1H, CCH_2).

^{13}C NMR (50 MHz, $CDCl_3$):

δ 169.1 (N*C*=O), 137.7 (Ar*Cipso*), 127.8 (Ar*C*H), 127.0 (Ar*C*H), 124.9 (Ar*C*H), 76.3 (Ph*C*H), 62.8 (*C*-O), 58.8 (N*C*H), 32.9 (N*C*H_3), 27.0 (CH_2*C*H), 21.7 (*C*H_2), 20.4 (*C*H_2), 13.3 (*C*H_3), 12.1 (*C*H_3)

Visible peaks for the other diastereomer: δ 137.0 (Ar*Cipso*), 77.0 (Ph*C*H), 64.0 (*C*-O), 29.0 (CH_2*C*H), 19.4 (*C*H_2), 19.0 (*C*H_2).

IR (Neat):

3475, 3064, 2962, 2931, 2872, 2361, 2238, 1647, 1451, 1400, 1379, 1340, 1299, 1264, 1198, 1142, 1097, 1069, 1046, 1006, 969, 943, 917, 888, 802 cm^{-1}.

MS (70 eV):

m/z 56 (3), 68 (2), 77 (6), 83 (8), 91 (12), 96 (1), 103 (8), 118 (100), 131 (4), 142 (45), 148 (8), 259 (M^+, 1).

$[\alpha]^{25}_D$ = -107.2 (*c* 5, $CHCl_3$)

(*3S, 5R, 6S*)-1,1,6,7-Tetramethyl-4-oxa-5-phenyl-7-aza-spiro[2.5]octane-8-one (29):

Prepared from **9** (0.65 g, 2.65 mmol) in anhydrous 1,2-dimethoxyethane (25 mL), Zn-Cu couple (3.36 g, 51.69 mmol), iodine (0.005 g), diiodomethane (4.26 mL,

52.8 mmol) to furnish 0.89 g of crude product (*ds* = 15/1 by ^{1}H NMR) which on purification by flash chromatography on silica gel (8/2 petroleum ether/ethyl acetate) furnished 0.48 g (69%) of **29** as white solid.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.50-7.20 (m, 5H, Ar*H*), 5.10 (d, 1H, *J* = 2.7, PhC*H*), 3.55 (dq, 1H, *J* = 2.7, 6.5, NC*H*), 3.05 (s, 3H, NCH_3), 1.45 (s, 3H, C(CH_3)$_2$), 1.40 (s, 3H, C(CH_3)$_2$), 1.35 (d, 1H, *J* = 4.5, CH_2), 1.00 (d, 3H, *J* = 6.5, CHCH_3), 0.80 (d, 1H, *J* = 4.5, CH_2).

Visible peaks for the other diastereomer: 1.55 (s, 3H, C(CH_3)$_2$), 1.50 (s, 3H, C(CH_3)$_2$).

^{13}C NMR (50 MHz, $CDCl_3$):

δ 168.6 (N*C*=O), 138.1 (Ar*Cipso*), 128.0 (Ar*C*H), 127.2 (Ar*C*H), 125.2 (Ar*C*H), 76.0 (Ph*C*H), 66.1 (*C*-O), 59.2 (N*C*H), 33.5 (N*C*H$_3$), 28.8 (*C*H$_2$), 27.0 (*C*(CH$_3$)$_2$), 21.4 (*C*H$_3$), 19.9 (*C*H$_3$), 12.3 (*C*H$_3$).

IR ($CHCl_3$):

3471, 2979, 2927, 1652, 1448, 1398, 1377, 1339, 1295, 1254, 1207, 1180, 1097, 1070, 1026, 968, 885 cm^{-1}.

MS (70 eV):

m/z 78 (2), 83 (11), 91 (8), 105 (3), 117 (100), 131 (1), 142 (63), 148 (3), 189 (1), 204 (1), 259 (M^+, 1).

Analysis for $C_{16}H_{21}NO_2$:

Calcd: C, 74.09; H, 8.16; N, 5.40

Found: C, 73.96; H, 8.29; N, 5.41

$[\alpha]^{25}_{D}$ = -167.4 (*c* 1, $CHCl_3$)

Preparation of diethylzinc:[16]

To a solution of zinc chloride (2.73 g, 20 mmol) in 30 mL anhydrous ether was added 40 mmol ethylmagnesium iodide (2.2 M in ether). The resulting suspension was stirred at for 2 h at ambient temperature and then treated with 12 mL of anhydrous 1,4-dioxane. The mixture was stirred for an additional 45 min. to ensure complete precipitation of the magnesium salts. The mixture was then filtered under an inert gas atmosphere using a Schlenk filter to give a clear solution of diethylzinc in ether.

General procedure for the cyclopropanation of 7-9 with Et_2Zn/CH_2I_2:[17]

To a solution of **7-9** (1eq.) in anhydrous ether (1 mL) at -78 °C was added diethylzinc (1M solution in ether, 10 eq.) followed by di-iodomethane (10 eq.). After 5 min. the reaction mixture was warmed to ambient temperature and stirred for 12 h after which it was cooled to -78 °C, additional Et_2Zn and CH_2I_2 were added (10 eq. each) and the reaction was continued for 12 h at ambient temperature. The mixture was diluted with ether and the solution was washed with 2N HCl follwed by water. The ether solution was dried over anhydrous Na_2SO_4 and concentrated to give the crude product which was purified by flash chromatography on silica gel using petroleum ether/ethyl acetate mixtures as eluant.

(*1R, 3S, 5R, 6S*)-1,6,7-Trimethyl-4-oxa-5-phenyl-7-aza-spiro[2.5]octan-8-one (27):

Prepared from **7** (0.09 g, 0.38 mmol) in ether (1 mL), Et_2Zn (1M solution in ether, 7.6 mL, 7.6 mmol), di-iodomethane (0.6 mL, 7.44 mmol) to furnish 0.14 g of crude product (ds = 16/1 by ^1H NMR) which on purification by flash chromatography on silica gel (65/35 petroleum ether/ethyl acetate) furnished 0.042 g (44%, 56% based on recovered **7**) of **27** as clear colourless gum.

$[\alpha]^{25}_D$ = -170.2 (*c* 1.1, CHCl3)

(*1R, 3S, 5R, 6S*)-1-ethyl-4-oxa-5-Phenyl-6,7-dimethyl-7-aza-spiro[2.5]octane-8-one (28):

Prepared from **8** (0.038 g, 0.15 mmol) in ether (1 mL), Et_2Zn (1M solution in ether, 1.5 mL, 1.5 mmol), di-iodomethane (0.12 mL, 1.48 mmol) to furnish 0.097 g of crude product (ds = 19/1 by ^1H NMR) which on purification by flash chromatography on silica gel (65/35 petroleum ether/ethyl acetate) furnished 0.024 g (59%) of **28** as clear colourless gum.

$[\alpha]^{25}_D$ = -163.3 (*c* 2.4, $CHCl_3$)

(*3S, 5R, 6S*)-1,1,6,7-tetramethyl-4-oxa-5-Phenyl-7-aza-spiro[2.5]octane-8-one (29):

Prepared from **9** (0.047 g, 0.19 mmol) in ether (1 mL), Et_2Zn (1M solution in ether, 4 mL, 4 mmol), di-iodomethane (0.32 mL, 3.97 mmol) to furnish 0.064 g of crude product (ds = 19/1 by ^1H NMR) which on purification by flash chromatography on silica gel (8/2 petroleum ether/ethyl acetate) furnished 0.034 g (69%, 82% based on recovered **9**) of **29** as white solid.

$[\alpha]^{25}_{D}$ = -170.8 (*c* 2, $CHCl_3$)

General procedure for dissolving metal reduction of 4-oxa-7-azaspiro[2.5]octane-8-ones 27-29:

To anhydrous liquid ammonia (distilled over sodium) was added Na (10 eq.) at -78 °C and the mixture was stirred for 15 minutes. To the resulting blue solution was added a solution of **27-29** (1 eq.) in anhydrous THF and the mixture was stirred for 2-3 minutes. Methanol was added followed by water, the mixture was warmed to ambient temperature and extracted with ethyl acetate after the removal of ammonia. The combined extracts were dried over Na_2SO_4 and concentrated to provide the crude product which was purified by flash chromatography on silica gel.

(*1S, 2R*)-2-Methyl-1-hydroxycyclopropane-1-carboxylic acid *N*-methyl amide (30):

Prepared from **27** (0.8 g, 3.26 mmol) in THF (2 mL) and Na (0.75 g, 32.6 mmol) in ammonia (25 mL) to furnish 0.38 g of crude product which on purification by flash chromatography on silica gel (2/8 petroleum ether/ethyl acetate) furnished 0.312 g (74%) of **30** as white solid.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.10 (br s, 1H, N*H*), 4.45 (br s, 1H, O*H*), 2.8 (d, 3H, *J* = 5.5, NHCH_3), 1.60-1.35 (m, 2H, CH_2, CH_3C*H*), 1.15 (d, 3H, *J* = 7.0, CHCH_3), 0.60 (m, 1H, CH_2).

^{13}C NMR (50 MHz, $CDCl_3$):

δ 175.7 (N*C*=O), 58.6 (*C*-OH), 26.1 (NH*C*H_3), 22.5 (*C*H_2), 20.6 (*C*H), 11.7 (CH*C*H_3).

IR ($CHCl_3$):

3434, 3345, 3017, 2975, 2963, 2932, 1641, 1544, 1415, 1280, 1255, 1216, 1191 cm^{-1}.

MS (70eV):

m/z 58 (17), 71 (64), 82 (5), 86 (19), 96 (4), 102 (8), 114 (34), 129 (M^+, 100).

Analysis for $C_6H_{11}NO_2$:

Calcd: C, 55.79; H, 8.58; N, 10.84

Found: C, 55.67; H, 9.01; N, 10.46

[a **]$^{25}_D$** = -46.7 (*c* 1.5, $CHCl_3$)

(*1S, 2R*)-2-Ethyl-1-hydroxycyclopropane-1-carboxylic acid *N*-methyl amide (31):

Prepared from **28** (0.23 g, 0.88 mmol) in THF (2 mL) and Na (0.204 g, 8.86 mmol) in ammonia (15 mL) to furnish 0.32 g of crude product which on purification by flash chromatography on silica gel (2/8 petroleum ether/ethyl acetate) furnished 0.108 g (85%) of **31** as white solid.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 6.95 (br s, 1H, N*H*), 3.45 (br s, 1H, O*H*), 2.85 (d, 3H, *J* = 5.5, NHCH_3), 1.60-1.40 (m, 4H, CH_3CH_2CH, CCH_2), 1.00 (t, 3H, *J* = 7.0, CH_2CH_3), 0.65 (m, 1H, CCH_2).

^{13}C NMR (75.5 MHz, $CDCl_3$):

δ 176.0 (N*C*=O), 58.6 (*C*-OH), 28.2 (NH*C*H_3), 26.1 (*C*H), 21.2 (*C*H_2), 20.5 (*C*H_2), 13.6 (CH_2*C*H_3).

IR ($CHCl_3$):

3374, 2962, 1644, 1548, 1413, 1258, 1193, 1104, 1043, 943, 885 cm^{-1}.

MS (70eV):

m/z 58 (19), 69 (11), 85 (100), 89 (24), 96 (5), 110 (5), 114 (15), 128 (5), 143 (M^+, 28).

[a **]$^{25}_D$** = -34.7 (*c* 1.5 , $CHCl_3$)

***1S*-2,2-Dimethyl-1-hydroxycyclopropane-1-carboxylic acid *N*-methyl amide (32):**

Prepared from **29** (0.275 g, 1.06 mmol) in THF (1 mL) and Na (0.245 g, 10.65 mmol) in ammonia (10 mL) to furnish 0.209 g of crude product which on purification by flash chromatography on silica gel (2/8 petroleum ether/ethyl acetate) furnished 0.138 g (90%) of **32** as white solid.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.10 (br s, 1H, N*H*), 4.55 (br s, 1H, O*H*), 2.80 (d, 3H, *J* = 5.0, NHCH_3), 1.35 (d, 1H, *J* = 5.2, CH_2), 1.25 (s, 3H, C(CH_3)$_2$), 1.15 (s, 3H, C(CH_3)$_2$), 0.70 (d, 1H, *J* = 5.2, CH_2).

^{13}C NMR (50 MHz, $CDCl_3$):

δ 174.2 (N*C*=O), 62.6 (*C*-OH), 27.1 (NH*C*H3), 26.1, 26.0 (*C*H_2,*C*(CH_3)$_2$), 20.9 (C*C*H_3), 19.3 (C*C*H_3).

IR ($CHCl_3$):

3354, 2924, 1641, 1544, 1412, 1187, 1019, 905 cm^{-1}.

MS (70eV):

m/z 59 (38), 69 (10), 73 (5), 85 (100), 103 (39), 116 (2), 128 (1), 143 (M^+, 4).

Analysis for $C_7H_{13}NO_2$:

Calcd: C, 58.72; H, 9.15; N, 9.78

Found: C, 58.78; H, 9.41; N, 9.56

$[a]^{25}_D$ = -58.2 (*c* 3, $CHCl_3$)

General procedure for *O*-benzylation of 1-hydroxycyclopropane-1-carboxylic acid *N*-methyl amides 30-32:

To a stirred suspension of NaH (2.8 eq. (washed with anhydrous petroleum ether)) in THF at -10 ^oC (ice-salt bath) was added drop wise a solution of **30-32** in THF. Benzyl bromide was added after 30 min. and the reaction mixture was slowly warmed up to and stirred at ambient temperature for 4h. Methanol was added followed by water and the reaction mixture was extracted with ethyl acetate. The combined extracts were dried over Na_2SO_4 and concentrated to provide the crude product which was purified by flash chromatography on silica gel.

(*1S, 2R*)-2-Methyl-1-*O*-benzylcyclopropane-1-carboxylic acid *N*-methyl amide (33):

Prepared from **30** (0.26 g, 2.01 mmol) in THF (2 mL), NaH (0.48 g, 28% dispersion in mineral oil, 5.6 mmol) in THF (4 mL) and benzyl bromide (0.28 mL, 2.35 mmol) to furnish 0.39 g of crude product which on purification by flash chromatography on silica gel (7/3 petroleum ether/ethyl acetate) furnished 0.273 g (62%) of **33** as white solid.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.45-7.25 (m, 5H, Ar*H*), 6.65 (br s, 1H, N*H*), 4.60 (d, 1H, *J* = 11.6, OCH_2), 4.50 (d, 1H, *J* = 11.6, OCH_2), 2.80 (d, 3H, *J* = 4.9, NHCH_3), 1.65-1.45 (m, 2H, CCH_2, CH_3C*H*), 1.20 (d, 3H, *J* = 6.0, CHCH_3), 0.75 (dd, 1H, *J* = 3.9, 5.8, CCH_2).

^{13}C NMR (50 MHz, $CDCl_3$):

δ 173.2 (N*C*=O), 137.4 (Ar*Cipso*), 128.5 (Ar*C*H), 127.8 (Ar*C*H), 127.3 Ar*C*H), 72.0 (O*C*H_2), 65.9 (*C*-O), 26.0 (NH*C*H_3), 22.5 (*C*H), 18.8 (C*C*H_2), 12.4 (CH*C*H_3).

IR ($CHCl_3$):

3442, 3348, 3064, 3030, 2932, 2872, 1666, 1522, 1454, 1410, 1288, 1258, 1188, 1106, 1082, 1048, 1028, 910, 818 cm^{-1}.

MS (70eV):

m/z 58 (21), 65 (9), 69 (17), 91 (100), 105 (1), 118 (13), 128 (61), 143 (1), 161 (5), 220 (M+1, 1).

Analysis for $C_{13}H_{17}NO_2$:

Calcd: C, 71.20; H, 7.81; N, 6.38

Found: C, 71.26; H, 7.81; N, 6.02

$[\alpha]^{25}_{D}$ = -9.83 (*c* 1.1, $CHCl_3$)

(*1S*, *2R*)-2-Ethyl-1-*O*-benzylcyclopropane-1-carboxylic acid *N*-methyl amide (34):

Prepared from **31** (0.072 g, 0.5 mmol) in THF (1 mL), NaH (0.12 g, 28% dispersion in mineral oil, 1.4 mmol) in THF (2 mL) and benzyl bromide (0.07 mL, 0.58 mmol) to furnish 0.102 g of crude product which on purification by flash chromatography on silica gel (85/15 petroleum ether/ethyl acetate) furnished 0.081 g (69%) of **34** as white solid.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.45-7.20(m, 5H, Ar*H*), 6.65 (br s, 1H, N*H*), 4.60 (d, 1H, *J* = 10.0, OCH_2), 4.45 (d, 1H, *J* = 10.0, OCH_2), 2.80 (d, 3H, *J* = 5.0, NHCH_3), 1.65-1.35 (m, 4H, CH_3CH_2CH, CCH_2), 1.05 (t, 3H, *J* = 7.0, CH_2CH_3), 0.80 (m, 1H, CCH_2).

^{13}C NMR (50 MHz, $CDCl_3$):

δ 173.3 (N*C*=O), 137.5 (Ar*Cipso*), 128.5 (Ar*C*H), 127.8 (Ar*C*H), 127.3 (Ar*C*H), 72.1 (O*C*H_2), 66.2 (*C*-O), 30.1 (NH*C*H_3), 26.0 (*C*H), 21.3 (*C*H_2), 17.6 (*C*H_2), 13.5 (CH_2*C*H_3).

IR ($CHCl_3$):

3276, 2928, 2440, 1640, 1528, 1406, 1256, 1192, 1060, 914 cm^{-1}.

MS (70eV):

m/z 58 (12), 65 (4), 83 (28), 91 (100), 105 (3), 132 (10), 142 (94), 149 (3), 175 (3), 234 (M+1, 1).

Analysis for $C_{14}H_{19}NO_2$:

Calcd: C, 72.07; H, 8.20; N, 6.00

Found: C, 71.95; H, 8.34; N, 5.84

[a **]**$^{25}_{D}$ = -2.5 (*c* 1.5, $CHCl_3$)

***1S*-2,2-Dimethyl-1-*O*-benzylcyclopropane-1-carboxylic acid *N*-methyl amide (35):**

Prepared from **32** (0.12 g, 0.83 mmol) in THF (2 mL), NaH (0.201 g, 28% dispersion in mineral oil, 2.34 mmol) in THF (6 mL) and benzyl bromide (0.1 mL, 0.84 mmol) to furnish 0.198 g of crude product which on purification by flash chromatography on silica gel (88/12 petroleum ether/ethyl acetate) furnished 0.16 g (81%) of **35** as white solid.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.50-7.20 (m, 5H, Ar*H*), 6.60 (br s, 1H, N*H*), 4.45 (s, 2H, OCH_2), 2.85 (d, 3H, *J* = 5.0, NHCH_3), 1.50 (d, 1H, *J* = 5.5, CCH_2), 1.30 (s, 3H, C(CH_3)$_2$), 1.15 (s, 3H, C(CH_3)$_2$), 0.85 (d, 1H, *J* = 5.5, CCH_2).

^{13}C NMR (50 MHz, $CDCl_3$):

δ 171.2 (N*C*=O), 137.6 (Ar*Cipso*), 128.4 (Ar*C*H), 127.8 (Ar*C*H), 127.5 (Ar*C*H), 71.4 (O*C*H$_2$), 70.6 (*C*-O), 26.8 (NH*C*H$_3$), 26.0 (*C*(CH$_3$)$_2$), 22.8 (C*C*H$_2$), 21.1 (C*C*H$_3$), 19.4 (C*C*H$_3$).

IR ($CHCl_3$):

3444, 3350, 3064, 3030, 2994, 2946, 2872, 1670, 1522, 1498, 1454, 1410, 1384, 1296, 1252, 1180, 1120, 1080, 10s40, 1026, 1002, 914, 840 cm^{-1}.

MS (70eV):

m/z 58 (12), 64 (3), 83 (89), 91 (65), 105 (2), 120 (1), 142 (100), 234 (M+1, 1).

$[a]^{25}_{D}$ = -23.7 (c1, $CHCl_3$)

General procedure for hydrolysis of 1-*O*-benzylcyclopropane-1-carboxylic acid *N*-methyl amides 33-35:

To **33-35** (1eq.) in ethylene glycol was added KOH (10 eq.) and the reaction mixture was heated at an oil bath temperature of 120°C or 180°C for 48-60 h. The reaction mixture was acidified with conc. HCl and extracted with CH_2Cl_2. The combined organic phase was extracted with saturated aq. $NaHCO_3$. The $NaHCO_3$ layer was acidified with conc. HCl and extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated to provide carboxylic acids **36-38** which were pure by ^{1}H NMR.

(*1S, 2R*)-2-Methyl-1-*O*-benzylcyclopropane -1-carboxylic acid (36):

Prepared from **33** (0.05 g, 0.22 mmol) in ethylene glycol (2 mL) and KOH (0.128 g, 2.28 mmol) at an oil bath temperature of 120°C (48 h) to furnish 0.041 g (87%) of **36** as pale yellow gum.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 10.25 (br s, 1H, CO_2H), 7.55-7.30 (m, 5H, Ar*H*), 4.90 (d, 1H, *J* = 10.8, OCH_2), 4.65 (d, 1H, *J* = 10.8, OCH_2), 1.95-1.75 (m, 1H, C*H*), 1.60 (dd, 1H, *J* = 4.8, 9.6, CCH_2), 1.35 (d, 3H, *J* = 6.0, $CHCH_3$), 0.95 (dd, 1H, *J* = 4.8, 7.4, CCH_2).

^{13}C NMR (50 MHz, $CDCl_3$):

δ 180.0 (*C*=O), 137.9 (Ar*Cipso*), 128.3 (Ar*C*H), 127.8 (Ar*C*H), 127.7 (Ar*C*H), 72.3 (OCH_2), 63.0 (*C*-O), 24.7 (*C*H), 22.7 (C*C*H2), 12.5 (*C*H3).

IR (neat):

3750, 3648, 3032, 2932, 2360, 1694, 1497, 1455, 1302, 1256, 1181, 1106, 1082, 1047, 1028, 995, 904, 836 cm^{-1}.

MS (70eV):

m/z 65 (13), 69 (4), 77 (4), 91 (100), 105 (3), 118 (19), 161 (4).

$[a]^{25}_D$ = -30.1 (*c* 3.3, $CHCl_3$)

(*1S, 2R*)-2-Ethyl-1-*O*-benzylcyclopropane -1-carboxylic acid (37):

Prepared from **34** (0.138 g, 0.59 mmol) in ethylene glycol (4 mL) and KOH (0.331 g, 5.91 mmol) at an oil bath temperature of 120ºC (48 h) to furnish 0.122 g (93%) of **37** as pale yellow gum.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.45-7.25 (m, 5H, Ar*H*), 4.85 (d, 1H, *J* = 11.0, OCH_2), 4.55 (d, 1H, *J* = 11.0, OCH_2), 1.85-1.45 (m, 4H, CH_3CH_2CH, CCH_2), 1.10 (t, 3H, *J* = 7.0, CH_2CH_3), 0.95 (dd, 1H, *J* = 4.9, 6.3, CCH_2).

^{13}C NMR (50 MHz, $CDCl_3$):

δ 180.4 (*C*=O), 137.9 (Ar*Cipso*), 128.3 (Ar*C*H), 127.6 (Ar*C*H), 72.2 (O*C*H_2), 63.1 (*C*-O), 32.2 (*C*H) , 21.3 (*C*H_2), 21.2 (*C*H_2), 13.5 (*C*H_3).

IR (neat):

3854, 3650, 2963, 2923, 2873, 2363, 1697, 1497, 1455, 1305, 1262, 1181, 1106, 1059, 940 cm^{-1}.

MS (70eV):

m/z 65 (4), 83 (4), 91 (100), 105 (1), 132 (5), 175 (1).

$[a]^{25}_{D}$ = -23.4 (c1.1, $CHCl_3$)

***1S*-2,2-Dimethyl-1-*O*-benzylcyclopropane -1-carboxylic acid (38):**

Prepared from **35** (0.15 g, 0.64 mmol) in ethylene glycol (8 mL) and KOH (0.36 g, 6.42 mmol) at an oil bath temperature of 180°C (60 h) to furnish 0.112 g (79%) of **38** as pale yellow gum.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.55-7.30 (m, 5H, Ar*H*), 4.75 (d, 1H, *J* = 10.8, OCH_2), 4.50 (d, 1H, *J* = 10.8, OCH_2), 1.50 (d, 1H, *J* = 5.3, CCH_2), 1.40 (s, 3H, C(CH_3)$_2$), 1.30 (s, 3H, C(CH_3)$_2$), 1.10 (d, 1H, *J* = 5.3, CCH_2).

^{13}C NMR (50 MHz, $CDCl_3$):

δ 177.6 (*C*=O), 137.4 (Ar*Cipso*), 128.4 (Ar*C*H), 127.9 (Ar*C*H), 71.9 (O*C*H_2), 68.1 (*C*-O), 29.9 (*C*(CH_3)$_2$), 26.6 (C*C*H_2), 21.4 (*C*H3), 19.9 (*C*H3).

IR (neat):

3854, 3840, 3822, 3805, 3752, 3736, 3712, 3691, 3677, 3650, 2925, 1695, 1497, 1455, 1425, 1386, 1302, 1262, 1183, 1115, 1042, 925, 832 cm^{-1}.

MS (70eV):

m/z 55(14), 65 (23), 83 (58), 91 (100), 101 (3), 129 (12).

$[\alpha]^{25}_{D}$ = -41.4 (*c*2.9 , $CHCl_3$)

General procedure for the hydrogenolysis of 1-*O*-benzylcyclopropane-1-carboxylic acids 36-38:

The solution of **36-38** in ethanol was hydrogenated over 10% Pd/C (20% by weight) at ambient temperature and atmospheric pressure for 6-8 h. The catalyst was removed by filtration through celite. The filtrate upon concentration furnished the hydroxy acids **39-41** which were pure by ^{1}H NMR.

(*1S, 2R*)-2-Methyl-1-hydroxycyclopropane-1-carboxylic acid (39):[1]

Prepared from **36** (0.15 g, 0.72 mmol) in ethanol (20 mL) and 10% Pd/C (0.03 g) to furnish 0.079 g (93%) of **39** as white solid.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 4.35 (br s, 2H, O*H*, CO_2H), 1.75-1.50 (m, 2H, CCH_2, C*H*), 1.25 (d, 3H, *J* = 7.0, $CHCH_3$), 0.95-0.80 (m, 1H, CCH_2).

^{13}C NMR (50 MHz, $CDCl_3$):

δ 180.7 (*C*=O), 57.0 (*C*-OH), 23.6 (CH_2), 23.1 (*C*H), 11.8 (CH_3).

IR ($CHCl_3$):

3404, 1710, 1165 cm^{-1}.

MS (70eV):

m/z 55 (94), 60 (21), 70 (100), 86 (4), 89 (10), 116 (M^+, 20).

[a]$^{25}_{D}$ = -32.4 (c 1.6, $CHCl_3$, lit.[1] **[a]$^{25}_{D}$** = -57 (c 1.6, $CHCl_3$) for *1S,2R* **39**).

(*1S, 2R*)-2-Ethyl-1-hydroxycyclopropane -1-carboxylic acid (40):

Prepared from **37** (0.1 g, 0.45 mmol) in ethanol (10 mL)and 10% Pd/C (0.02 g) to furnish 0.056 g (94%) of **40** as white solid.

^{1}H NMR (200 MHz, DMSO-d_6):

δ 1.50-1.35 (m, 2H, C*H*, CCH_2), 1.35-1.10 (m, 2H, CH_3CH_2), 0.90 (t, 3H, *J* = 7.0, CH_2CH_3), 0.60-0.45 (m, 1H, CCH_2).

^{13}C NMR (50 MHz, $CDCl_3$):

δ 181.4 (*C*=O), 57.5 (*C*-OH), 30.5 (*C*H), 22.5 (CH_2), 20.6 (CH_2), 13.7 (CH_3).

IR ($CHCl_3$):

3897, 3848, 3833, 3814, 3795, 3379, 2923, 2356, 1694, 1450, 1309, 1243, 1174, 1104, 1065, 1041, 997, 916, 873, 818 cm^{-1}.

MS (70 eV):

m/z 55 (48), 60 (18), 71 (39), 74 (67), 84 (100), 88 (99), 97 (11), 101 (17), 112 (35), 130 (M^+, 33).

[a]$^{25}_{D}$ = -9.0 (c 2.7, $CHCl_3$).

***1S*-2,2-Dimethyl-1-hydroxycyclopropane -1-carboxylic acid (41):**

Prepared from **38** (0.08 g, 0.36 mmol) in ethanol (10 mL) and 10% Pd/C (0.016 g) to furnish 0.043 g (91%) of **41** as white solid.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.40 (br s, 2H, O*H*, CO_2H), 1.40 (d, 1H, *J* = 5.2, CCH_2), 1.30 (s, 3H, $C(CH_3)_2$), 1.25 (s, 3H, $C(CH_3)_2$), 1.00 (d, 1H, *J* = 5.2, CCH_2).

^{13}C NMR (50 MHz, $CDCl_3$):

δ 179.0 (*C*=O), 62.0 (*C*-OH), 28.6, 28.4 (CH_2, $C(CH_3)_2$), 20.7 (CH_3), 19.9 (CH_3).

IR ($CHCl_3$):

3904, 3871, 3854, 3839, 3821, 3806, 3750, 3735, 3711, 3382, 2932, 2364, 1992, 1694, 1463, 1379, 1305, 1253, 1178, 1114, 1044, 1021, 984, 922, 873 cm^{-1}.

MS (70 eV):

m/z 56 (30), 59 (67), 69 (100), 85 (70), 97 (4), 103 (24), 115 (4), 130 (M^+, 15).

[a]$^{25}_{D}$ = -13.9 (c 2.4, $CHCl_3$).

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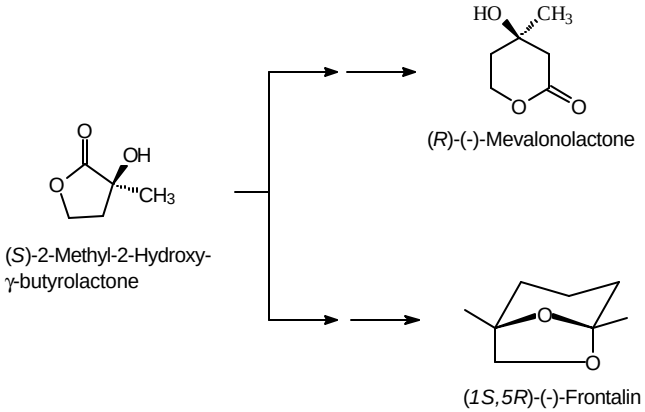
CHAPTER III

ASYMMETRIC SYNTHESIS OF α-ALKYL-α-HYDROXY-γ-BUTYROLACTONES

1. INTRODUCTION

Enantiomerically pure α-hydroxy-γ-butyrolactones constitute an important class of compounds due to their utility as intermediates for the synthesis of natural products and biologically active molecules.[1-7] α-Alkyl-α-hydroxy-γ-butyrolactones are important members of this class as exemplified by α-methyl α-hydroxy γ-butyrolactone which is a key intermediates in the synthesis of (1*S*,2*R*)-(-)-frontalin (pheromone) and (*R*)-(-)-mevalonolactone (Figure 1).[8]

Figure 1.

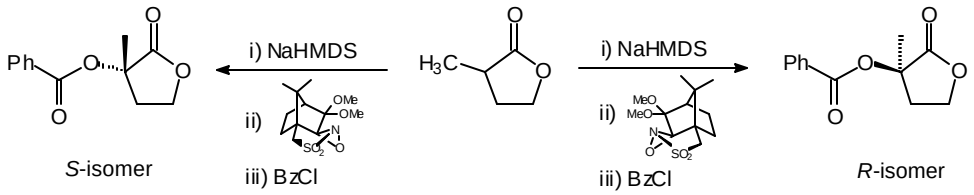


Despite their synthetic utility, only two approaches to α-alkyl-α-hydroxy-γ-butyrolactones have been reported in the literature.

Asymmetric enolate oxidation protocol

Davis[8] and co-workers have reported enantioselective hydroxylation of the sodium enolate of 2-methyl-γ-butyrolactone using optically pure 2-sulfonyloxaziridines as oxygen transfer reagents. Both enantiomers of 2-methyl-2-hydroxy-γ-butyrolactone have been obtained (isolated as their benzoate derivatives) with 84% e.e. by employing [(8,8-dimethoxycamphoryl)sulfonyl]oxaziridine (Scheme 1).

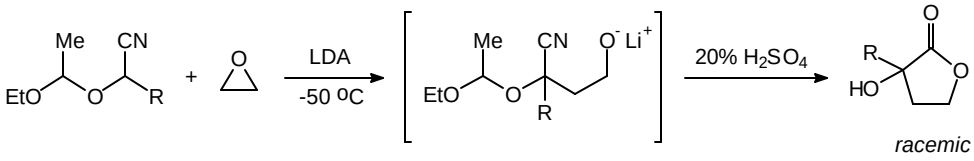
Scheme 1.



Condensation of cyanohydrins with epoxides

Muñoz *et. al.*[9] have reported synthesis of racemic α-alkyl-α-hydroxy-γ-butyrolactones by condensation of the lithium anion of ethoxyethyl-protected cyanohydrins with ethylene oxide, followed by treatment of the substituted nitrile with acid (Scheme 2).

Scheme 2.



These *racemic* α-alkyl-α-hydroxy-γ-butyrolactones serve as starting materials in the preparation of α,β-butenolides, α-alkylidene-γ-lactones and furans.[9]

2. OBJECTIVE

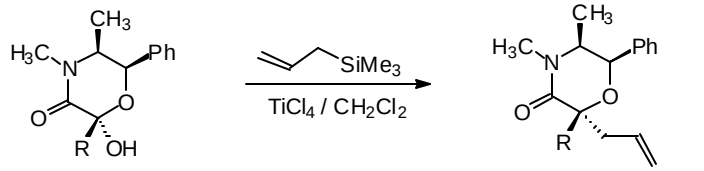
The objective of this study was to develop a stereoselective synthesis of α-alkyl-α-hydroxy-γ-butyrolactones from chiral allyl morpholinones which are readily prepared from α-keto acids.

3. RESULTS AND DISCUSSION

The allylation of chiral hemiacetals **1-4** (prepared from α-keto acids and 1*R*,2*S* ephedrine as described in Chapter 1) with allyltrimethylsilane/$TiCl_4$ proceeds with

excellent diastereoselectivity (>95/5) at - 40 °C, to generate the 2-alkyl-2-allyl-morpholinones **42-45** in good yield (75-92%)[10] (Scheme 3). These morpholinones served as starting materials for this study.

Scheme 3.

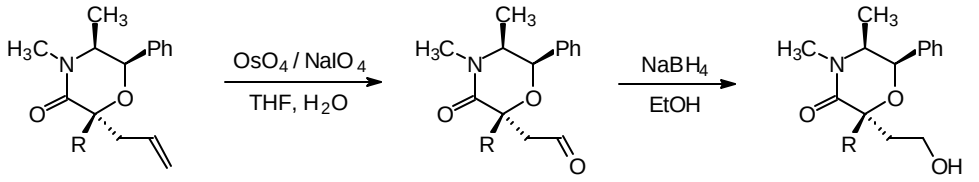


1 **2** **3** **4**
R Me Et Pr *i*Pr

42 **43** **44** **45**
R Me Et Pr *i*Pr
ds >95 / 5

Oxidative cleavage of the allylic double bond in **42-45** with $OsO_4/NaIO_4$[11] in THF/water at ambient temperature cleanly generates the aldehydes **46-49** (83-95% yield) which are quantitatively converted to the corresponding alcohols **50-53** by reduction with sodium borohydride in ethanol (Scheme 4).

Scheme 4.



42 **43** **44** **45**
R Me Et Pr *i*Pr

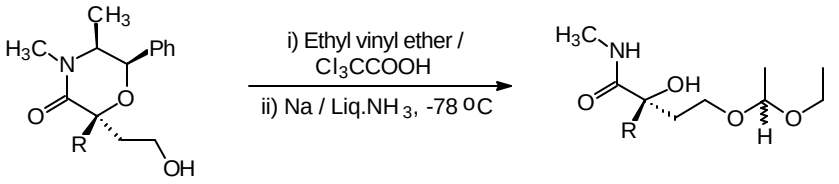
46 **47** **48** **49**
R Me Et Pr *i*Pr

50 **51** **52** **53**
R Me Et Pr *i*Pr

Removal of the ephedrine portion in **50** by dissolving metal reduction (Na, liq. NH_3, -78 °C) was problematic and resulted in a complex mixture, presumably due to the presence of the free hydroxyl group. Conversion of **50-53** to the corresponding ethoxyethyl ethers (mixture of diastereomers, obtained by treatment with ethyl vinyl ether/trichloroacetic acid) was beneficial and dissolving metal reduction of protected

50-53 proceeded smoothly at -78 °C to generate the α-hydroxy amides **54-57** in 60-65% yield over two steps (Scheme 5).

Scheme 5.



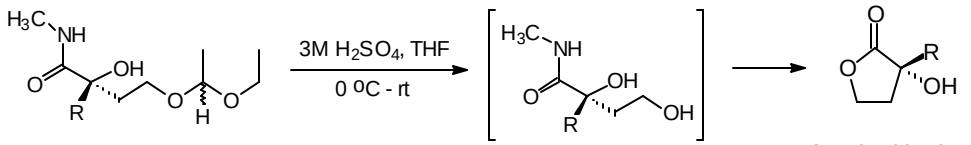
50 51 52 53
R Me Et Pr *i*Pr

54 55 56 57
R Me Et Pr *i*Pr

It is noteworthy that the crude alcohols **50-53** and the corresponding ethoxy ethyl ethers can be used in the Na/liq.NH_3 reduction step without any purification. This significantly enhances the utility of the procedure.

The conversion of the α-hydroxy amides **54-57** to the target lactones **58-61** was achieved under remarkably mild conditions. Unmasking of the primary alcohol in **54-57** is readily achieved by treatment with 3M H_2SO_4/THF at ambient temperature and proceeds with concomitant lactonization, presumably due to a very facile intramolecular acyl transfer from nitrogen to oxygen[12] to generate the desired α-alkyl-α-hydroxy-γ-butyrolactones **58-61** in 82-91% yield (Scheme 6).

Scheme 6.



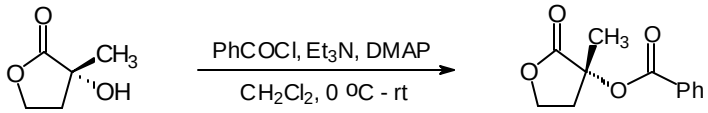
54 55 56 57
R Me Et Pr *i*Pr

58 59 60 61
R Me Et Pr *i*Pr

The absolute configuration and enantiomeric excess of **58-61** are based on those of the precursors **42-45** since epimerization of the newly generated stereocenter

in **42-45** during their conversion to the target α-alkyl-α-hydroxy-γ-butyrolactones **58-61** is unlikely. Thus, lactones **58-60** are assigned *R* configuration and **61** the *S* configuration. The configurational assignment was further confirmed by conversion of **58** (R = CH_3) to its benzoate derivative **62** (PhCOCl, Et_3N, DMAP,CH_2Cl_2, 89%) (Scheme 7) and comparison of the sign of the optical rotation of the benzoate with the literature value ($[\alpha]_D$ = +17.6 (*c* 1, $CHCl_3$); lit.[8] $[\alpha]_D$ = +18.9 (*c* 3.8, $CHCl_3$)).

Scheme 7.

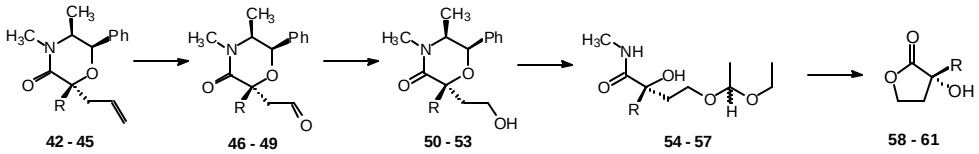


58 **62**

The overall conversion of the allyl morpholinones **42-45** to the lactones **58-61** constitutes a new approach to these important intermediates that involves asymmetric functionalization of readily available α-keto carboxylic acids as the key step. The results are summarized in Table 1.

Table 1.

Conversion of allyl morpholinones **42-45** to α-alkyl-α-hydroxy-γ-butyrolactones **58-61.**



42 - 45 **46 - 49** **50 - 53** **54 - 57** **58 - 61**

Substrate	**Aldehyde** (% yield)	**Alcohol** (% yield)[a]	**Hydroxyamide** (% yield)[b]	**Butyrolactone**	% yield	% e.e.[c]	Config.[d]
42	**46** (95)	**50** (96)	**54** (64)	**58**	91[a]	>95	*R*
43	**47** (85)	**51** (95)	**55** (60)	**59**	80	>95	*R*
44	**48** (84)	**52** (97)	**56** (65)	**60**	82	>95	*R*
45	**49** (83)	**53** (97)	**57** (62)	**61**	82	>95	*S*

a: yield of crude product which was pure by ^{1}H NMR b: from crude alcohols **50-53** over two steps c: based on d.e. of **42-45** d: based on the absolute configuration of **42-45**.

4. CONCLUSION

An asymmetric synthesis of α-alkyl-α-hydroxy-γ-butyrolactones has been achieved from (1*R*,2*S*)-ephedrine-derived allyl morpholinones. The methodology developed has been successfully applied to the synthesis of 2-methyl-2-hydroxy-γ-butyrolactone which serves as a key precursor in the synthesis of (1*S*,2*R*)-(-)-frontalin and (*R*)-(-)-mevalonolactone. Since (1*S*,2*R*)-ephedrine is also commercially available, the enantiomeric series of α-alkyl-α-hydroxy-γ-butyrolactones should also be readily available by this methodology.

5. EXPERIMENTAL

General experimental techniques which have been described in the experimental section of Chapter 1 were followed.

General procedure for the allylation of hemiacetals 1-4 to morpholinones 42-45:[10]

To a solution of **1-4** in CH_2Cl_2 was added allyltrimethylsilane at -40 °C followed by $TiCl_4$ and the solution was stirred for 6-10 h at -40 °C. Saturated NH_4Cl was added to the reaction mixture and it was warmed up to ambient temperature. The precipitated solids were dissolved with water and the solution was extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried (Na_2SO_4) and concentrated to furnish the crude product which was purified by flash chromatography on silica gel using petroleum ether/ethyl acetate as the eluant.

2*R*,5*S*,6*R*-2,4,5-Trimethyl-6-phenyl-2-(1-propenyl) morpholin-3-one (42):

Reaction of **1** (0.29 g, 1.23 mmol) and allyltrimethylsilane (1 mL, 6.3 mmol) in the presence of $TiCl_4$ (0.68 mL, 6.2 mmol) in CH_2Cl_2 (10 mL) afforded 0.32 g of a gum which on purification by flash chromatography on silica gel (7/3 petroleum ether/ethyl acetate) furnished 0.24 g (75%) of **42** as a gum.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.45-7.20 (m, 5H, Ar*H*), 5.98-5.75 (m, 1H, CH_2=C*H*), 5.2 (d, 1H, *J* = 2.7, PhC*H*), 5.18-5.03 (m, 2H, C*H*$_2$=CH), 3.5 (dq, 1H, *J* = 6.5, 2.7, CH_3C*H*), 3.04 (s, 3H, NC*H*$_3$), 2.83 (dd, 1H, *J* = 14.4, 5.9, CHC*H*$_2$), 2.53

(dd, 1H, J = 14.4, 8.7, CHCH_2), 1.50 (s, 3H, CCH_3), 0.98 (d, 3H, J = 6.5, CH_3CH).

^{13}C NMR ($CDCl_3$):

δ 171.4 (N*C*O), 137.7 (Ar*Cipso*), 132.6 (Ar*C*), 127.8 (Ar*C*), 127.0 (Ar*C*) 125.1 (*C*H=CH_2), 117.6 (CH=*C*H_2) , 78.8 (*C*CH_3), 71.7 (Ph*C*H), 58.7 (CH_3*C*H), 40.2 (*C*H_2), 33.2 (N*C*H_3), 24.8 (C*C*H_3), 12.1 (CH*C*H_3).

IR ($CHCl_3$):

3000, 1630, 1430, 1210, 750 cm $^{-1}$.

MS (70 eV):

m/z 58 (53), 67 (22), 77 (19), 91 (27), 105 (18), 117 (40), 148 (100), 174 (6), 190 (27), 218 (69), 259 (8, M^+).

HRMS (FAB+) for $C_{16}H_{22}NO_2$ (M+H):

Calcd: 260.1651

Found: 260.1645

[a **]$_D$** = - 67.1 (c 2.1, $CHCl_3$)

2*R*,5*S*,6*R*-4,5-Dimethyl-2-ethyl-6-phenyl-2-(1-propenyl) morpholin-3-one (43):

Reaction of **2** (0.27 g, 1.08 mmol) and allyltrimethyl silane (0.87 mL, 5.47 mmol) in the presence of $TiCl_4$ (0.6 mL, 5.47 mmol) in CH_2Cl_2 (8 mL) afforded 0.3 g of a gum which on purification by flash chromatography on silica gel (7/3 petroleum ether/ethyl acetate) furnished 0.24 g (81%) of **43** as a gum.

^{1}H NMR ($CDCl_3$):

δ 7.45-7.20 (m, 5H, Ar*H*), 5.95-5.74 (m, 1H, C*H*=CH$_2$), 5.25(d, 1H, *J* = 3.0, PhC*H*), 5.15-5.02 (m, 2H, C*H*$_2$=CH), 3.54 (dq, 1H, *J* = 6.5, 3.0, CH$_3$C*H*), 3.05 (s, 3H, NC*H*$_3$), 2.85 (tdd, 1H, *J* = 16.1, 5.8, 1.3, CHC*H*$_2$), 2.55 (dd, 1H, *J* = 14.6, 8.5, CHC*H*$_2$), 2.08-1.75 (m, 1H, CH$_3$C*H*$_2$), 1.35-1.10 (m, 1H, CH$_3$C*H*$_2$), 1.02 (t, 3H, *J* = 6.6, C*H*$_3$CH$_2$), 0.98 (d, 3H, *J* = 7.8, C*H*$_3$CH).

^{13}C NMR (75 MHz, CDCl$_3$):

δ 171.2 (N*C*O), 138.1 (Ar*Cipso*), 133.0 (Ar*C*), 128.1 (Ar*C*), 127.3 (Ar*C*), 125.5 (*C*H=CH$_2$), 117.9 (CH=*C*H$_2$), 82.3 (C*C*H$_3$), 71.4 (Ph*C*H), 59.1 (CH$_3$*C*H), 40.1 (CH$_2$=CH*C*H$_2$), 33.5 (N*C*H$_3$), 30.9 (CH$_3$*C*H$_2$), 12.9 (*C*H$_3$), 8.7 (*C*H$_3$).

IR (CHCl$_3$):

3010, 1625, 1440, 1215, 1140, 1030, 750 cm $^{-1}$.

MS (70 eV):

m/z 58 (100), 67 (23), 77 (21), 91 (31), 105 (12), 117 (39), 148 (90), 204 (35), 232 (78), 245 (1), 273 (6, M$^+$)

HRMS (FAB+) for C$_{17}$H$_{24}$NO$_2$ (M+H):

Calcd: 274.1807

Found: 274.1812

[a]$_D$ = - 60 (c = 1.8, CHCl$_3$)

2*R*,5*S*,6*R*-4,5-Dimethyl-6-phenyl-2-(1-propenyl)-2-propyl morpholin-3-one (44):

Reaction of **3** (0.3 g, 1.14 mmol) and allyltrimethyl silane (0.9 mL, 5.7 mmol) in the presence of $TiCl_4$ (0.62 mL, 5.7 mmol) in CH_2Cl_2 (9 mL) afforded 0.35 g of a gum which on purification by flash chromatography on silica gel (7/3 petroleum ether/ethyl acetate) furnished 0.27 g (82%) of **44** as a gum.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.4-7.2 (m, 5H, Ar*H*), 5.95-5.74 (m, 1H, C*H*=CH_2), 5.24 (d, 1H, *J* = 3.0, PhC*H*), 5.13-4.98 (m, 2H, CH_2=CH), 3.50 (dq, 1H, *J* = 6.5, 3.0, CH_3CH), 3.0 (s, 3H, NCH_3), 2.82 (tdd, 1H, *J* = 15, 5.8, 1.3, CHCH_2), 2.53 (dd, 1H, *J* = 14.6, 8.5, CHCH_2), 1.98-1.55 (m, 3H, $CH_3CH_2CH_2$), 1.4-1.1 (m, 1H, $CH_3CH_2CH_2$), 0.96 (d, 3H *J* = 6.5, CH_3CH), 0.94 (t, 3H *J* = 7.6, C$H_3CH_2CH_2$).

^{13}C NMR (75 MHz, $CDCl_3$):

δ 171.3 (N*C*O), 138.1 (Ar*Cipso*), 133.0 (Ar*C*), 128.1 (Ar*C*), 127.3 (Ar*C*), 125.4 (*C*H=CH_2), 117.9 (CH=*C*H_2), 81.9 (*C*CH_3), 71.3 (Ph*C*H), 59.1 (CH_3*C*H), 40.2 (CH=CH_2*C*H_2, *C*$H_2CH_2CH_3$), 33.6 (N*C*H_3), 17.5 (CH_2*C*H_2CH_3), 14.3 (*C*H_3), 12.9 (*C*H_3).

IR ($CHCl_3$):

3010, 1620, 1215, 1145, 1050, 755 cm $^{-1}$.

MS (70 eV):

m/z 58 (40), 71 (50), 77 (32), 84 (49), 91 (19), 105 (52), 118 (49), 148 (100), 218 (20), 246 (57), 281 (2), 287 (2, M^+)

[a]$_D$ = - 56.4 (c = 1.8, $CHCl_3$)

2*S*,5*S*,6*R*-4,5-Dimethyl-6-phenyl-2-(1-propenyl)-2-(2-Propyl) morpholin-3-one (45):

Reaction of **4** (0.09 g, 0.34 mmol) and allyltrimethyl silane (0.27 mL, 1.69 mmol) in the presence of $TiCl_4$ (0.19 mL, 1.73 mmol) in CH_2Cl_2 (3 mL) afforded 0.11 g of a gum which on purification by flash chromatography on silica gel (7/3 petroleum ether/ethyl acetate) furnished 0.09 g (91%) of **45** as a gum.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.50-7.20 (m, 5H, Ar*H*), 6.10-5.89 (m, 1H, C*H*=CH_2), 5.34 (d, 1H, *J* = 3, PhC*H*), 5.15-4.95 (m, 2H, CH_2=CH), 3.5 (dq, 1H, *J* = 6.5, 3, CH_3C*H*), 3.03 (s, 3H, NCH_3), 2.85-2.58 (m, 2H, CHCH_2), 2.4-2.15 (m, 1H, C*H*$(CH_3)_2$), 1.09 (d, 3H, *J* = 6.9, CH_3CHCH_3), 1.04 (d, 3H, *J* = 6.9, CH_3CHCH_3), 0.95 (d, 3H *J* = 6.5, CH_3CH).

^{13}C NMR (75 MHz, $CDCl_3$):

δ 171.2 (N*C*O), 138.3 (Ar*Cipso*), 134.3 (Ar*C*), 128.1 (Ar*C*), 127.2 (Ar*C*), 125.4 (*C*H=CH_2), 117.1 (CH=*C*H_2), 83.2 (*C*CH_3), 71.2 (Ph*C*H), 58.9 (CH_3*C*H), 40.1 (CH_2=CH*C*H_2), 35.3 (CH_3*C*HCH_3), 33.5 (N*C*H_3), 18.7 (*C*H_3), 16.0 (*C*H_3), 12.9 (*C*H_3).

IR ($CHCl_3$):

2970, 2940, 1625, 1440, 1375, 1280, 1140, 1030, 915, 750, 710 cm $^{-1}$;

MS (70 eV):

m/z 57 (39), 71 (76), 77 (37), 91 (40), 105 (34), 118 (100), 148 (93), 218 (41), 246 (97), 287 (12, M^+)

HRMS (FAB+) for $C_{18}H_{26}NO_2$ (M+H):

Calcd: 288.1964

Found: 288.1969

$[\alpha]_D$ = - 90.9 (*c* 1.6, $CHCl_3$)

General procedure for the oxidative cleavage of allylmorpholinones 42-45 with $OsO_4/NaIO_4$:[11]

To the stirred solution of **42-45** (1 eq.) in THF/H_2O (3:1) at 25 °C was added OsO_4 (0.5 M in toluene, 0.01 eq.). To this was added solid $NaIO_4$ (2.4 eq.) in portions over 20-30 min and the reaction mixture was stirred for 4 h. Brine was added and the solution was extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product obtained was purified by flash chromatography on silica gel under Ar gas using petroleum ether/ethyl acetate mixtures as eluant.

***2R,5S,6R*-2-(2-Oxoethyl)-2,4,5-trimethyl-6-phenylmorpholin-3-one (46):**

Prepared from **42** (0.8 g, 3.08 mmol) in THF (12 mL) and H_2O (4 mL), OsO_4 (0.5 M in toluene, 0.06 mL, 0.03 mmol) and $NaIO_4$ (1.58 g, 7.38 mmol) to furnish 932 mg of the crude aldehyde. Purification by flash chromatography on silica gel (3/2 petroleum ether/ethyl acetate) under Ar gas furnished 768 g (95%) of **46** as clear, colourless gum.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 9.85 (t, 1H, *J* = 3.0, C*H*O), 7.50-7.20 (m, 5H, Ar*H*), 5.20 (d, 1H, *J* = 2.5, PhC*H*), 3.50 (dq, 1H, *J* = 2.5, 6.8, CH_3CH), 3.05 (s, 3H, NCH_3), 2.9 (m, 2H, CH_2), 1.70 (s, 3H, CCH_3), 1.00 (d, 3H, *J* = 6.8, $CHCH_3$).

^{13}C NMR ($CDCl_3$):

δ 199.2 (*C*HO), 170.3 (N-*C*=O), 137.4 (Ar*Cipso*), 128.3 (Ar*C*H), 127.6 (Ar*C*H), 125.5 (Ar*C*H), 77.7 (*C*-O), 72.9 (Ph*C*H), 59.2 (CH_3CH), 50.2 (CH_2), 33.7 (NCH_3), 26.4 (CCH_3), 12.4 ($CHCH_3$).

IR ($CHCl_3$):

2980, 2934, 1716, 1646, 1496, 1450, 1402, 1378, 1142, 1098, 1018 cm^{-1}.

MS (70 eV):

m/z 69 (62), 77 (31), 91 (22), 98 (12), 105 (18), 117 (40), 126 (15), 133 (6), 148 (7), 156 (30), 190 (2), 232 (8), 261 (M+, 13).

[a]$^{25}_D$ = - 92.3 (*c* 1, $CHCl_3$).

***2R,5S,6R*-2-Ethyl-2-(2-oxoethyl)-4,5-dimethyl-6-phenylmorpholin-3-one (47):**

Prepared from **43** (0.84 g, 3.1 mmol) in THF (9 mL) and H_2O (3 mL), OsO_4 (0.5 M in toluene, 60 μL, 0.03 mmol) and $NaIO_4$ (1.57 g, 7.4 mmol) to furnish 0.89 g of the crude aldehyde. Purification by flash chromatography on silica gel (3/2 petroleum ether/ethyl acetate) under Ar gas furnished 722 mg (85%) of **47** as a white solid.

^{1}H NMR ($CDCl_3$):

δ 9.80 (t, 1H, *J* = 2.9, C*H*O), 7.50-7.20 (m, 5H, Ar*H*), 5.20 (d, 1H, *J* = 3.0, PhC*H*), 3.55 (dq, 1H, *J* = 3.0, 6.4, CH_3CH), 3.05 (s, 3H, NCH_3), 2. 85 (m,

2H, CH_2CHO), 2.30-1.85 (m, 2H, CH_3CH_2), 1.10 (t, 3H, *J* = 7.3, CH_2CH_3), 1.00 (d, 3H, *J* = 6.4, CHCH_3).

^{13}C NMR (50 MHz, $CDCl_3$):

δ 198.9 (*C*HO), 169.2 (N-*C*=O), 137.2 (Ar*Cipso*), 127.9 (Ar*C*H), 127.2 (Ar*C*H), 125.2 (Ar*C*H), 80.3 (*C*-O), 71.8 (Ph*C*H), 58.6 (CH_3CH), 48.7 (*C*H_2CHO), 33.1 (N*C*H_3), 31.9 (CH_3CH_2), 12.5 (*C*H_3), 8.1 (*C*H_3).

IR ($CHCl_3$):

2982, 2937, 2880, 1717, 1643, 1497, 1452, 1402, 1381, 1321, 1279, 1250, 1232, 1207, 1146, 1099, 1070, 1030 cm^{-1}.

MS (70 eV):

m/z 57 (25), 77 (24), 83 (79), 91 (52), 105 (43), 118 (100), 133 (12), 148 (24), 162 (5), 170 (53), 190 (4), 218 (2), 246 (12), 275 (M^+, 22).

HRMS (FAB+) for $C_{16}H_{22}NO_3$ (M+H):

Calcd: 276.1600

Found: 276.1607

[a **]$^{25}_D$** = - 76.5 (*c* 2.5, $CHCl_3$).

***2R,5S,6R*-2-(2-Oxoethyl)-2-propyl-4,5-dimethyl-6-phenylmorpholin-3-one (48):**

Prepared from **44** (0.66 g, 2.3 mmol) in THF (9 mL) and H_2O (3 mL), OsO_4 (0.5 M in toluene, 50 μL, 0.025 mmol) and $NaIO_4$ (1.17 g, 5.5 mmol) to furnish 0.72 g of the crude aldehyde. Purification by flash chromatography on silica gel (3/2 petroleum ether/ethyl acetate) under Ar gas furnished 562 mg (84%) of **48** as a white solid.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 9.80 (t, 1H, *J* = 3.0, C*H*O), 7.50-7.20 (m, 5H, Ar*H*), 5.20 (d, 1H, *J* = 2.9, PhC*H*), 3.55 (dq, 1H, *J* = 2.9, 6.4, CH_3CH), 3.05 (s, 3H, NCH_3), 2. 85 (m, 2H, CH_2CHO), 2.20-1.85 (m, 2H, $CH_3CH_2CH_2$), 1.85-1.60 (m, 1H, $CH_3CH_2CH_2$), 1.50-1.20 (m, 1H, $CH_3CH_2CH_2$), 1.00 (t, 3H, *J* = 7.3, CH_2CH_3), 1.00 (d, 3H, *J* = 6.4, $CHCH_3$).

^{13}C NMR (50 MHz, $CDCl_3$):

δ 199.3 (*C*HO), 169.6 (N-*C*=O), 137.4 (Ar*Cipso*), 128.1 (Ar*C*H), 127.5 (Ar*C*H), 125.3 (Ar*C*H), 80.4 (*C*-O), 72.1 (Ph*C*H), 58.9 (CH_3CH), 49.2 (CH_2CHO), 41.4 ($CH_3CH_2CH_2$), 33.4 (NCH_3), 17.2 ($CH_3CH_2CH_2$), 14.0 (CH_3)12.7 (CH_3).

IR ($CHCl_3$):

1719, 1643, 1452, 1404, 1381, 1215, 1146, 1038 cm^{-1}.

MS (70 eV):

m/z 58 (23), 69 (6), 77 (10), 91 (25), 97 (60), 105 (43), 118 (100), 126 (11), 148 (25), 154 (8), 162 (3), 184 (13), 260 (1), 289 (M^+, 2).

[a]$^{25}_D$ = - 73.6 (*c* 1.9, $CHCl_3$).

***2S,5S,6R*-2-(1-Methylethyl)-2-(2-oxoethyl)-4,5-dimethyl-6-phenylmorpholin-3-one (49):**

Prepared from **45** (0.92 g, 3.2 mmol) in THF (12 mL) and H_2O (4 mL), OsO_4 (0.5 M in toluene, 0.07 mL, 0.035 mmol) and $NaIO_4$ (1.64 g, 7.7 mmol) to furnish 0.99 g of the crude aldehyde. Purification by flash chromatography on silica gel (6/4

petroleum ether/ethyl acetate) under Ar gas furnished 774 mg (83%) of **49** as a white solid.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 9.85 (dd, 1H, *J* = 2.5, 3.4, C*H*O), 7.5-7.1 (m, 5H, Ar*H*), 5.15 (d, 1H, *J* = 3.4, C*H*Ph), 3.54 (dq, 1H, *J* = 3.4, 6.8, CH_3CH), 3.05 (s, 3H, NCH_3), 2.95 (dd, 1H, *J* = 3.4, 15.1, CH_2CHO), 2.80 (dd, 1H, *J* = 2.5, 15.1, CH_2CHO), 2.44 (sept., 1H, *J* = 6.8, Me_2CH), 1.16 (d, 3H, *J* = 6.8, $(CH_3)_2CH$), 1.06 (d, 3H, *J* = 6.8, $(CH_3)_2CH$), 0.98 (d, 3H, *J* = 6.8, $CHCH_3$).

^{13}C NMR (50 MHz, $CDCl_3$):

δ 199.5 (*C*HO), 170.1 (N-*C*=O), 137.6 (Ar*Cipso*), 128.2 (Ar*C*H), 127.5 (Ar*C*H), 125.4 (Ar*C*H), 82.0 (*C*-O), 72.6 (Ph*C*H), 58.8 (CH_3CH), 48.2 (CH_2CHO), 35.5 (CH_3CHCH_3)33.4 (NCH_3), 18.4 (CH_3), 15.6 (*C*H3), 12.8 (CH_3).

IR ($CHCl_3$):

2972, 2877, 1715, 1636, 1452, 1401, 1383, 1338, 1316, 1289, 1206, 1180, 1143, 1098, 1070, 1038 cm^{-1}.

MS (70eV):

m/z 58 (51), 69 (11), 77 (11), 91 (29), 97 (32), 105 (14), 118 (100), 125 (6), 133 (8), 148 (33), 156 (4), 184 (39), 218 (6), 246 (6), 260 (11), 289 (M^+, 30).

HRMS (FAB+) for $C_{17}H_{24}NO_3$ (M+H):

Calcd: 290.1756

Found: 290.1760

$[\alpha]^{25}_{D}$ = - 132.0 (*c* 1, $CHCl_3$)

General procedure for reduction of aldehydes 46-49 with $NaBH_4$:

To a solution of the aldehyde **(46-49)** in ethanol at ambient temperature was added sodium borohydride in small portions and the solution was stirred for 2 h. HCl (0.5 M) was added and the mixture was stirred for 10 min. The ethanol was removed under reduced pressure and the residue was taken up in water. The mixture was saturated with NaCl and extracted with ethyl acetate. The combined extracts were dried (Na_2SO_4) and concentrated to furnish the crude alcohols **50-54.** These were pure by ^{1}H NMR.

***2R,5S,6R*-2-(2-Hydroxyethyl)-2,4,5-trimethyl-6-phenylmorpholin-3-one (50):**

Prepared from **46** (0.22 g, 0.84 mmol) in ethanol (5 mL) and $NaBH_4$ (35 mg, 0.92 mmol) to furnish 0.213 g (96%) of crude **50** as a clear, colourless oil which was pure by ^{1}H NMR.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.50-7.20 (m, 5H, Ar*H*), 5.20 (d, 1H, *J* = 2.4, PhC*H*), 3.95-3.75 (m, 2H, CH_2OH), 3.45 (dq, 1H, *J* = 2.4, 6.8, CH_3C*H*), 3.05 (s, 3H, NCH_3), 2.35-2.00 (m, 2H, CH_2CH_2OH), 1.60 (s, 3H, CCH_3), 1.00 (d, 3H, *J* = 6.8, CHCH_3).

^{13}C NMR (50 MHz, $CDCl_3$):

δ 172.4 (N-*C*=O), 137.5 (Ar*Cipso*), 128.0 (Ar*C*H), 127.3 (Ar*C*H), 125.3 (Ar*C*H), 79.0 (*C*-O), 72.0 (Ph*C*H), 59.0 (CH_3CH), 58.2 (CH_2CH_2OH), 38.5 (CH_2CH_2OH), 33.6 (NCH_3), 25.0 (CCH_3), 12.2 ($CHCH_3$).

IR ($CHCl_3$):

3424, 2978, 2934, 1632, 1496, 1450, 1402, 1378, 1144, 1100, 1068, 1052, 1026 cm^{-1}.

MS (70 eV):

m/z 58 (100), 69 (30), 77 (14), 91 (19), 105 (9), 118 (55), 130 (5), 148 (13), 157 (9), 163 (5), 190 (8), 219 (17), 232 (2), 263 (M^+, 6).

[a]$^{25}_D$ = - 62.3 (*c* 3, $CHCl_3$)

***2R,5S,6R*-2-Ethyl-2-(2-hydroxyethyl)-4,5-dimethyl-6-phenylmorpholin-3-one (51):**

Prepared from **47** (0.14 g, 0.50 mmol) in ethanol (3 mL) and $NaBH_4$ (22 mg, 0.58 mmol) to furnish 0.132 g (93%) of crude **51** as a white solid which was pure by ^{1}H NMR.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.50-7.15 (m, 5H, Ar*H*), 5.25 (d, 1H, *J* = 2.9, PhC*H*), 3.95-3.65 (m, 2H, CH_2OH), 3.50 (dq, 1H, *J* = 2.9, 6.3, CH_3CH), 3.40 (b, 1H, O*H*), 3.05 (s, 3H, NCH_3), 2.35-1.75 (m, 4H, CH_3CH_2, CH_2CH_2OH), 1.05 (t, 3H, *J* = 7.3, CH_2CH_3), 1.00 (d, 3H, *J* = 6.3, $CHCH_3$).

^{13}C NMR (50 MHz, $CDCl_3$):

δ 171.9 (N-*C*=O), 137.8 (Ar*Cipso*), 128.0 (Ar*C*H), 127.3 (Ar*C*H), 125.3 (Ar*C*H), 81.9 (*C*-O), 71.4 (Ph*C*H), 59.0 (CH_3CH), 58.2 (CH_2CH_2OH), 38.0 (CH_2CH_2OH), 33.5 (NCH_3), 30.7 (CH_3CH_2), 12.6 (CH_3), 8.4 (CH_3).

IR ($CHCl_3$):

3418, 2880, 1634, 1450, 1402, 1381, 1205, 1148, 1099, 1032 cm^{-1}.

MS (70 eV):

58 (43), 77 (16), 83 (19), 91 (26), 105 (7), 117 (100), 131 (3), 148 (11), 163 (4), 190 (1), 233 (7), 277 (M^+, 1).

$[\alpha]^{25}_D$ = - 65.7 (*c* 1.8, $CHCl_3$).

***2R,5S,6R*-2-(2-Hydroxyethyl)-2-propyl-4,5-dimethyl-6-phenylmorpholin-3-one (52):**

Prepared from **48** (0.253 g, 0.87 mmol) in ethanol (5 mL) and $NaBH_4$ (37 mg, 0.97 mmol) to furnish 0.247 g (97%) of crude **52** as a white solid which was pure by ^1H NMR.

^1H NMR (200 MHz, $CDCl_3$):

δ 7.50-7.15 (m, 5H, Ar*H*), 5.25 (d, 1H, *J* = 3.0, PhC*H*), 4.00-3.65 (m, 2H, CH_2OH), 3.50 (dq, 1H, *J* = 3.0, 6.8, CH_3CH), 3.45 (b, 1H, O*H*), 3.05 (s, 3H, NCH_3), 2.35-1.50 (m, 5H, $CH3CH_2CH_2$, CH_2CH_2OH), 1.45-1.15 (m, 1H, $CH_3CH_2CH_2$), 1.10-0.90 (m, 6H, CH_2CH_3, $CHCH_3$).

^{13}C NMR (50 MHz, $CDCl_3$):

δ 172.2 (N-*C*=O), 137.7 (Ar*Cipso*), 128.2 (Ar*C*H), 127.5 (Ar*C*H), 125.4 (Ar*C*H), 81.8 (*C*-O), 71.4 (Ph*C*H), 59.1 (CH_3CH), 58.4 (CH_2CH_2OH), 39.9

(CH_2CH_2OH), 38.1 ($CH_3CH_2CH_2$) 33.7 (NCH_3), 17.4 ($CH_3CH_2CH_2$), 14.2 (CH_3), 12.8 (CH_3).

IR ($CHCl_3$):

3018, 2964, 2876, 1628, 1452, 1402, 1215, 1136, 1070, 1036 cm^{-1}.

MS (70 eV):

m/z 58 (8), 69 (16), 77 (11), 83 (32), 91 (25), 97 (32), 105 (22), 118 (100), 129 (7), 148 (25), 163 (8), 190 (7), 218 (5), 247 (25), 256 (4), 291 (M^+, 7).

$[\alpha]^{25}_D$ = - 63.9 (*c* 1, $CHCl_3$)

***2S,5S,6R*-2-(2-Hydroxyethyl)-2-(1-methylethyl)-4,5-dimethyl-6-phenyl-morpholin-3-one (53):**

Prepared from **49** (0.18 g, 0.62 mmol) in ethanol (3 mL) and $NaBH_4$ (26 mg, 0.68 mmol) to furnish 0.176 g (97%) of crude **53** as a white solid which was pure by ^1H NMR.

^1H NMR (200 MHz, $CDCl_3$):

δ 7.50-7.15 (m, 5H, Ar*H*), 5.25 (d, 1H, *J* = 3.0, PhC*H*), 4.30 (b, 1H, O*H*), 4.05-3.85 (m, 1H, C*H*$_2$OH), 3.80-3.60 (m, 1H, C*H*$_2$OH), 3.50 (dq, 1H, *J* = 3.0, 6.3, CH_3CH), 3.05 (s, 3H, NC*H*$_3$), 2.65-2.30 (m, 2H, C*H*$_2$CH$_2$OH, $(CH_3)_2CH$), 1.90 (ddd, 1H, *J* = 2.4, 5.4, 14.6, C*H*$_2$CH$_2$OH), 1.05 (d, 3H, *J* = 6.8, $(CH_3)_2CH$), 1.00 (d, 3H, *J* = 6.8, $(CH_3)_2CH$), 0.95 (d, 3H, *J* = 6.3, CHC*H*$_3$).

^{13}C NMR (50 MHz, $CDCl_3$):

δ 173.2 (N-*C*=O), 137.9 (Ar*Cipso*), 128.0 (Ar*C*H), 127.3 (Ar*C*H), 125.2 (Ar*C*H), 82.6 (*C*-O), 70.5 (Ph*C*H), 58.8 (CH_3CH), 58.5 (CH_2CH_2OH), 36.5 (CH_2CH_2OH), 33.6 (CH_3CHCH_3), 33.0 (NCH_3), 18.3 (CH_3), 15.6 (CH_3), 12.6 (CH_3).

IR ($CHCl_3$):

3403, 3064, 2974, 2937, 2878, 1953, 1631, 1452, 1401, 1382, 1339, 1315, 1289, 1216, 1181, 1144, 1099, 1071, 1038 cm^{-1}.

MS (70 eV):

m/z 58 (61), 69 (15), 77 (16), 83 (3), 91 (33), 97 (12), 105 (15), 118 (100), 132 (4), 148 (29), 163 (11), 190 (2), 202 (2), 218 (3), 247 (10), 291 (M^+, 1).

HRMS (FAB+) for $C_{17}H_{26}NO_3$ (M+H):

Calcd: 292.1913

Found: 292.1922

[a]$^{25}_D$ = -96.8 (*c* 1, $CHCl_3$)

General procedure for the conversion of alcohols 50-53 to the hydroxyamides 54-57:

To the solution of alcohol **(50-53)** (1 eq.) in anhydrous $CHCl_3$ was added ethyl vinyl ether (4-6 eq.) and a catalytic amount of trichloroacetic acid. The mixture was stirred at ambient temperature for 12 h. Saturated aqueous $NaHCO_3$ was added, the organic layer was seperated and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced

pressure to furnish the crude ethoxyethyl ether. This was dissolved in anhydrous THF and added to a mixture of anhydrous liquid ammonia (distilled over sodium) and Na (10 eq.) at -78 °C and the mixture was stirred for 3 minutes. Methanol was added and the mixture was warmed up to ambient temperature to remove ammonia. The methanol was removed under reduced pressure and the residue was taken up in water. The mixture was saturated with NaCl, extracted with ethyl acetate and the combined extracts were dried (Na_2SO_4) and concentrated to furnish the crude product which was purified by flash chromatography on silica gel using petroleum ether/ethyl acetate as the eluant.

2*R*-2-Methyl-4(1-ethoxy-ethoxy) butanoic acid *N*-methyl amide (54):

Prepared from alcohol **50** (60 mg, 0.22 mmol), ethyl vinyl ether (0.12 mL, 1.25 mmol) and trichloroacetic acid (2 mg, 0.012 mmol) in $CHCl_3$ (2 mL) to furnish 97 mg of the crude ethoxyethyl ether. This was dissolved in anhydrous THF (1 mL) and treated with Na (50 mg, 2.17 mmol) in anhydrous liq. ammonia (5 mL) to furnish 42 mg of the crude product. Purification by flash chromatography on silica gel (3/7 petroleum ether/ethyl acetate) furnished 32 mg of **54** as a clear, colourless gum (64% from **50** over two steps).

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.15 (b, 1H, N*H*), 4.80-4.50 (m, 2H, C*H*, O*H*), 3.90-3.35 (m, 4H, CH_3CH_2O, CH_2CH_2O), 2.85 (d, 3H, J = 4.9, CH_3NH), 2.40-2.10 (m, 1H, CH_2CH_2O), 2.05-1.80 (m, 1H, CH_2CH_2O), 1.40 (s, 3H, CCH_3), 1.30 (d, 3H, J = 5.4, $CHCH_3$), 1.20 (t, 3H, J = 7.3, OCH_2CH_3).

^{13}C NMR (50 MHz, $CDCl_3$):

δ 176.5 (N*C*O), 99.9 (O*C*HO), 76.4 (*C*-OH), 62.7 (O*C*H_2), 61.4 (O*C*H_2), 37.7 (N*C*H_3), 26.4 (C*C*H_2), 25.6 (*C*H_3), 19.6 (*C*H_3), 15.0 (*C*H_3).

IR (neat):

3424, 2978, 2934, 2884, 1654, 1542, 1410, 1380, 1134, 1088, 1056 cm^{-1}.

MS (70 eV):

m/z 58 (75), 73 (100), 87 (42), 103 (12), 115 (61), 130 (69), 146 (8), 174 (6), 220 (M+1, 1).

2*R*-2-Ethyl 4-(1-ethoxy-ethoxy) butanoic acid *N*-methyl amide (55):

Alcohol **51** (0.21 g, 0.75 mmol), ethyl vinyl ether (2 mL, 2.09 mmol) and trichloroacetic acid (5 mg, 0.03 mmol) in $CHCl_3$ (3 mL), to afforded 0.3 g of the crude product. Purification by flash chromatography on silica gel (1/1 petroleum ether/ethyl acetate) furnished 0.182 g (68%), of *O*-protected **51** as a clear, colourless gum.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.50-7.15 (m, 5H, Ar*H*), 5.20 (s, 1H, PhC*H*), 4.70-4.50 (m, 1H, OC*H*-O), 3.85-3.25 (m, 5H, NC*H*, OCH_2CH_2, OCH_2CH_3), 3.00 (s, 3H, NCH_3), 2.40-1.75 (m, 4H, CH_2CH_2O, CH_3CH_2C), 1.30-0.90 (m, 12H, OCH_2CH_3, OCHCH_3, CCH_2CH_3, NCHCH_3).

^{13}C NMR (50 MHz, $CDCl_3$):

δ 171.0 (N*C*O_2), 138.0 (Ar*Cipso*), 128.0 (Ar*C*H), 127.2 (Ar*C*H), 125.3 (Ar*C*H), 99.3 (O*C*H-O), 81.4 (*C*-O), 71.2 (Ph*C*H), 60.7, 60.5 (O*C*H_2),

60.2, 60.1 (O*C*H_2), 58.9 (N*C*H), 35.1 (C*C*H_2), 33.4 (N*C*H_3), 30.9 (C*C*H_2), 19.6, 19.5 (*C*H_3), 15.0 (*C*H_3), 12.8 (*C*H_3), 8.8 (*C*H_3).

IR (neat):

2980, 2936, 2880, 1651, 1497, 1481, 1450, 1400, 1379, 1342, 1312, 1281, 1250, 1207, 1148, 1099, 1070, 1059, 1042, 928 cm^{-1}.

The above ethoxyethyl ether (0.175 g, 0.5 mmol) was dissolved in anhydrous THF (1.5 mL) and treated with Na (0.115 g, 5 mmol) in anhydrous liq. NH_3 (8 mL) to afford 0.124 g of the crude product. Purification by flash chromatography on silica gel (1/4 petroleum ether/ethyl acetate) furnished 0.104 g of **55** as a clear, colourless gum (89%, 60% from **51** over two steps).

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.10 (b, 1H, N*H*), 4.70-4.60 (m, 1H, CH_3CH), 4.50, 4.45 (s, 1H, O*H*), 3.90-3.40 (m, 4H, CH_3CH_2O, CH_2CH_2O), 2.85 (d, 3H, *J* = 5.1, CH_3NH), 2.25-1.55 (m, 4H, CH_2CH_2O, CH_3CH_2C), 1.30 (d, 3H, *J* = 5.1, $CHCH_3$), 1.20 (t, 3H, *J* = 7.3, OCH_2CH_3), 0.85 (t, 3H, *J* = 7.3, CH_3CH_2C).

^{13}C NMR (50 MHz, $CDCl_3$):

δ175.6 (N*C*O_2), 99.8, 99.6 (O*C*H-O), 79.1, 79.0 (*C*-OH), 62.8, 62.6 (O*C*H_2), 61.2 (O*C*H_2), 36.6 (N*C*H_3), 32.2 (C*C*H_2), 25.4 (C*C*H_2), 19.4 (*C*H_3), 14.9 (*C*H_3), 7.2 (*C*H_3).

IR (neat):

3421, 3367, 2974, 2935, 2881, 1655, 1647, 1541, 1456, 1410, 1379, 1340, 1134, 1087, 1055, 949 cm^{-1}.

MS (70 eV):

m/z 57 (29), 73 (100), 85 (31), 129 (23), 144 (17), 160 (1), 175 (1), 188 (1).

2*R*-2-Propyl-4-(1-ethoxy-ethoxy) butanoic acid *N*-methyl amide (56):

Prepared from alcohol **52** (0.29 g, 1 mmol), ethyl vinyl ether (0.57 mL, 6.0 mmol) and trichloroacetic acid (8 mg, 0.048 mmol)in $CHCl_3$ (3 mL) to furnish 0.298 g of the crude ethoxyethyl ether. This was dissolved in anhydrous THF (1.5 mL) and treated with Na (0.19 g, 8.26 mmol) in anhydrous liq. ammonia (10 mL) to furnish 0.188 g of the crude product. Purification by flash chromatography on silica gel (3/7 petroleum ether/ethyl acetate) furnished 0.163 g of **56** as a clear, colourless gum (65% from **52** over two steps).

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.10 (b, 1H, N*H*), 4.70-4.55 (m, 1H, CH_3CH), 4.50 (b, 1H, O*H*), 3.80-3.35 (m, 4H, CH_3CH_2O, CH_2CH_2O), 2.85 (d, 3H, *J* = 4.9, CH_3NH), 2.25-2.10 (m, 1H, CH_2CH_2O), 2.05-1.35 (m, 5H, CH_2CH_2O, $CH_2CH_2CH_3$), 1.30 (d, 3H, *J* = 5.4, $CHCH_3$), 1.20 (t, 3H, *J* = 7.1, OCH_2CH_3), 0.90 (t, 3H, *J* = 7.1, $CH_2CH_2CH_3$)

IR (neat):

3429, 2963, 1657, 1535 cm^{-1}.

MS (70 eV):

m/z 58 (10), 73 (100), 83 (9), 87 (14), 99 (25), 117 (4), 143 (38), 158 (19), 174 (1), 189 (1), 202 (1).

2*S*-2-(1-methylethyl)-4-(1-ethoxy-ethoxy) butanoic acid *N*-methyl amide (57):

Prepared from alcohol **53** (0.365 g, 1.25 mmol), ethyl vinyl ether (0.71 mL, 7.4 mmol) and trichloroacetic acid (10 mg, 0.06 mmol) in $CHCl_3$ (4 mL) to furnish 0.36 g crude ethoxyethyl ether. It was dissolved in anhydrous THF (2 mL) and treated with Na (0.21 g, 9.13 mmol) in anhydrous liq. ammonia (15 mL) to furnish 0.207 g crude product. Purification by flash chromatography on silica gel (3/7 petroleum ether/ethyl acetate) furnished 0.194 g of **57** as white solid (62% from **53** over two steps).

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.10 (b, 1H, N*H*), 4.70-4.55 (m, 1H, CH_3CH), 4.35 (d, 1H, J = 6.4, O*H*), 3.85-3.35 (m, 4H, CH_3CH_2O, CH_2CH_2O), 2.85 (d, 3H, J = 4.8, CH_3NH), 2.20-1.90 (m, 3H, CH_2CH_2O, $(CH_3)_2CH$), 1.30 (d, 3H, J = 5.9, $CHCH_3$), 1.20 (t, 3H, J = 7.0, OCH_2CH_3), 0.95 (d, 3H, J = 6.8, $(CH_3)_2CH$), 0.85 (d, 3H, J = 6.8, $(CH_3)_2CH$).

IR ($CHCl_3$):

3425, 3369, 2976, 2936, 2882, 1651, 1539, 1410, 1381, 1173, 1134, 1101, 1088, 1055 cm^{-1}.

MS (70 eV):

m/z 58 (11), 73 (100), 87 (15), 99 (28), 114 (5), 143 (27), 158 (14), 174 (1), 189 (1), 202 (1).

a-Alkyl-a-hydroxy-g-butyrolactones 58-61:

To the stirred solution of **54-57** in THF at 0°C was added 3M H_2SO_4 dropwise over 3 min. The resulting solution was warmed to and stirred at ambient

temperature for 12-15 h. It was then diluted with ether and neutralized with excess solid $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product obtained was purified by flash chromatography on silica gel using petroleum ether/ethyl acetate as the eluant.

***R*-3-Hydroxy-3-methyl-dihydro-2(3*H*)-furanone (58):**[8,9]

Prepared from **54** (0.035 g, 0.15 mmol) in THF (1 mL) and 3M H_2SO_4 (1 mL) to furnish 0.017 g (91%) of crude **58** as clear colourless oil which was pure by ^{1}H NMR.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 4.50-4.35 (m, 1H, OC*H*$_2$), 4.30-4.15 (m, 1H, OC*H*$_2$), 3.2 (b, 1H, O*H*), 2.55-2.35 (m, 1H, C*H*$_2$CH$_2$O), 2.35-2.15 (m, 1H, C*H*$_2$CH$_2$O), 1.50 (s, 3H, C*H*$_3$).

***R*-3-Benzoyloxy-3-methyl- dihydro-2(3*H*)-furanone (62):**[8]

Benzoyl chloride (50 μL, 0.43 mmol) was added drop wise to a stirred solution of **58** (0.017 g, 0.14 mmol), triethylamine (50 μL, 0.35 mmol) and DMAP (0.005 g, 0.04 mmol) in anhydrous CH_2Cl_2 at 0 °C. The reaction mixture was stirred at ambient temperature for 20 h after which it was diluted with CH_2Cl_2, washed with 5% HCl, saturated aq. $NaHCO_3$, brine and dried (Na_2SO_4). Concentration under reduced pressure furnished 46 mg of crude product which on purification by flash

chromatography on silica gel (4/1 petroleum ether/ethyl acetate) furnished 29 mg (89%) of **62** as a white solid.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 8.05 (d, 2H, *J* = 6.9, ArCH), 7.70-7.55 (m, 1H, ArH), 7.55-7.35 (m, 2H, ArH), 4.70-4.55 (m, 1H, OCH_2), 4.45-4.25 (m, 1H, OCH_2), 3.00-2.80 (m, 1H, CH_2CH_2O), 2.50-2.30 (m, 1H, CH_2CH_2O), 1.75 (s, 3H, CH_3).

IR ($CHCl_3$):

3020, 1785, 1720, 1286, 1216, 1149, 1101, 1028 cm^{-1}.

MS (70 eV):

m/z 69 (1), 77 (33), 105 (100), 122 (1), 220 (M^+, 1).

[a]$^{25}_D$ = +17.6 (*c* 1, $CHCl_3$).

***R*-3-Hydroxy-3-ethyl- dihydro-2(3*H*)-furanone (59):**[9]

Prepared from **55** (0.19 g, 0.81 mmol) in THF (4 mL) and 3M H_2SO_4 (4 mL) to furnish 94 mg of the crude lactone. Purification by flash chromatography on silica gel (petroleum ether/ethyl acetate 7/3) furnished 85 mg (80%) of **59** as clear, colourless oil.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 4.50-4.35 (m, 1H, OCH_2), 4.30-4.15 (m, 1H, OCH_2), 2.65 (s, 1H, O*H*), 2.45-2.20 (m, 2H, CH_2CH_2O), 1.95-1.60 (m, 2H, CH_2CH_3), 1.05 (t, 3H, *J* = 7.3, CH_2CH_3).

13C NMR ($CDCl_3$):

δ 178.9 (*C*=O), 75.0 (*C*-OH), 65.2 (O*C*H_2), 34.0 (CH_3*C*H_2), 29.5 (*C*$H_2$$CH_2$O), 7.2 (*C*$H_3$$CH_2$).

IR ($CHCl_3$):

3437, 3021, 2975, 1774, 1217 cm^{-1}.

MS (70eV):

m/z 57 (100), 67 (7), 72 (41), 86 (50), 101 (21), 112 (1), 130 (M^+, 3).

HRMS for $C_6H_{10}O_3$:

Calcd: 130.0630

Found: 130.0624

[a **]$^{25}_D$** = + 59.0 (*c* 1.7, $CHCl_3$).

***R*-3-Hydroxy-3-propyl- dihydro-2(3*H*)-furanone (60):**[9]

Prepared from **56** (0.14 g, 0.56 mmol) in THF (3.5 mL) and 3M H_2SO_4 (3.5 mL) to furnish 87 mg of the crude lactone. Purification by flash chromatography on silica gel (petroleum ether/ethyl acetate 7/3) furnished 67 mg (82%) of **60** as a clear, colourless oil.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 4.50-4.35 (m, 1H, OC*H*$_2$), 4.30-4.15 (m, 1H, OC*H*$_2$), 2.70 (s, 1H, O*H*), 2.45-2.20 (m, 2H, C*H*$_2$$CH_2$O), 1.90-1.25 (m, 4H, C*H*$_2$C*H*$_2$$CH_3$), 1.00 (t, 3H, *J* = 7.0, CH_2C*H*$_3$).

IR (neat):

3445, 2936, 2876, 1771, 1456, 1379, 1113, 1020, 976, 947 cm^{-1}.

MS (70eV):

m/z 57 (73), 71 (100), 85 (19), 102 (50).

[a **]$^{25}_{D}$** = + 50.7 (*c* 3.4, $CHCl_3$).

_S_-3-Hydroxy-3-(1-methylethyl)- dihydro-2(3*H*)-furanone (61):[9]

Prepared from **57** (0.1 g, 0.4 mmol) in THF (2.5 mL) and 3M H_2SO_4 (2.5 mL) to furnish 53 mg of the crude lactone. Purification by flash chromatography on silica gel (ethyl acetate/petroleum ether, 3/7) furnished 48 mg (82%) of **61** as clear, colourless oil.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 4.5-4.3 (m, 1H, CH_2O), 4.3-4.15 (m, 1H, CH_2O), 2.8-2.45 (b, 1H, O*H*), 2.45-2.10 (m, 2H, CH_2), 2.05 (sept, 1H, *J* = 6.8, Me_2C*H*), 1.05 (d, 3H, *J* = 6.8, CHCH_3), 0.95 (d, 3H, *J* = 6.8, CHCH_3).

^{13}C NMR (75 MHz, $CDCl_3$):

δ 178.7 (*C*=O), 78.0 (*C*-OH), 65.4 (CH_2-O), 33.8 (*C*H), 30.8 (CH_2-C), 17.2 (CH_3), 15.8 (CH_3).

IR (neat):

3445, 2968, 2924, 2880, 1759, 1472, 1373, 1300, 1136, 1107, 1013, 984, 961, 943 cm^{-1}.

MS (70eV):

m/z 57 (65), 67 (26), 71 (100), 85 (99), 102 (82), 126 (1), 144 (M^+, 1).

HRMS (FAB+) for $C_7H_{13}O_3$ (M+H):

Calcd: 145.0865

Found: 145.0866

$[\alpha]_D^{25}$ = + 75.6 (*c* 3.2, $CHCl_3$).

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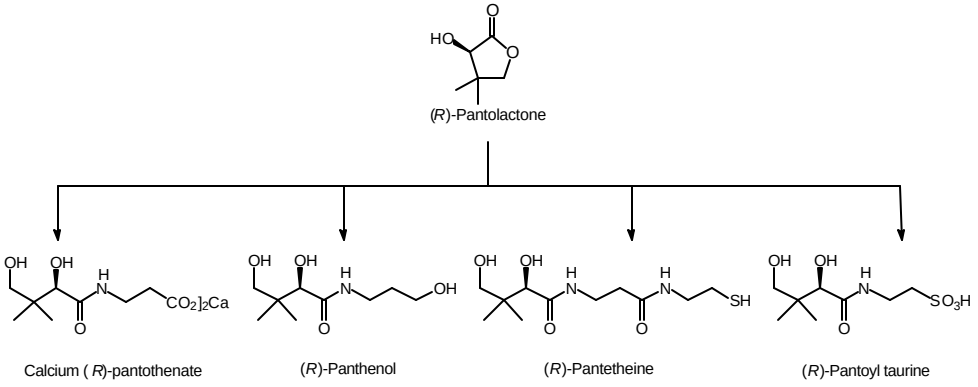
CHAPTER IV

ENANTIOSELECTIVE SYNTHESIS OF (*S*)-(+)-PANTOLACTONE

1. INTRODUCTION

The asymmetric synthesis of pantolactone (β,β-dimethyl-α-hydroxy-γ-butyrolactone) continues to be an area of active interest due to its utility as a building block in the asymmetric synthesis of natural products and their analogues. Pantolactone is an important starting compound for pantothenic acid (a member of the B complex vtamins),[1] calcium pantothenate (enzyme co-factor vitamin),[2] (R)-panthenol (bactericide),[3] (R)-pantetheine (growth factor),[4] and (R)-pantoyl taurine (bacterial growth inhibitor,[5] Figure 1) In addition, pantolactone has found application as a chiral auxiliary in the asymmetric synthesis.[6]

Figure 1.



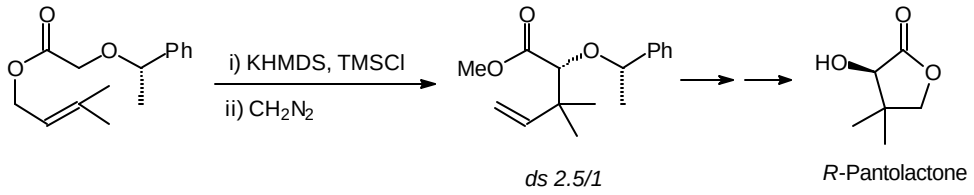
Enantiomerically enriched pantolactone has been obtained by several procedures. These include asymmetric functionalization of linear or cyclic precursors, asymmetric reduction of 3,3-dimethyl-2-oxobutyrolactone (ketopantolactone) and resolution of racemic pantolactone. Some of these approaches are described below.

Asymmetric functionalization of linear or cyclic precursors

Kallmerten[7] has developed a synthesis of *R*-pantolactone that employs an asymmetric Claisen rearrangement of a chiral glycolate ester as the key step. The

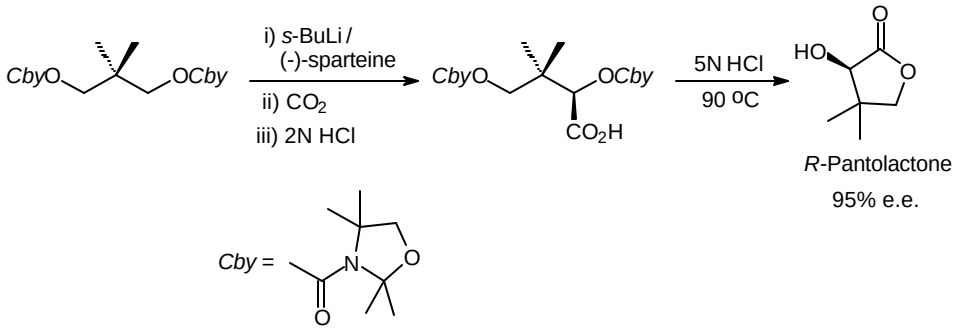
stereochemical course of the reaction is controlled by the chiral substituent appended to the hydroxyl group of the glycolic acid (Scheme 1).

Scheme 1.



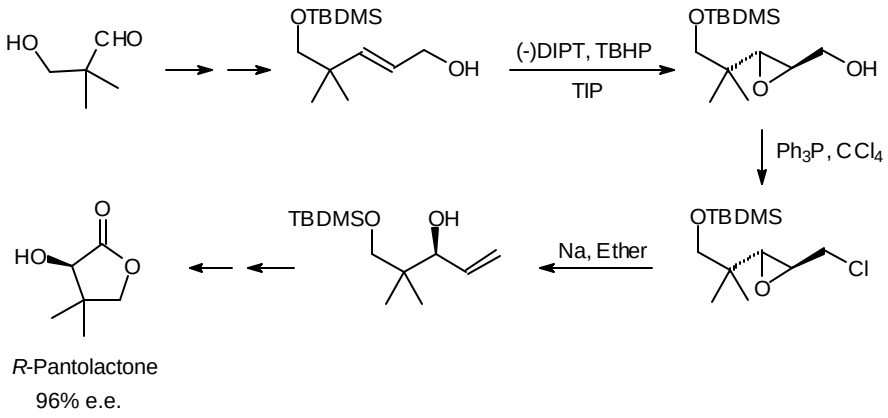
An efficient synthesis of *R*-pantolactone (e.e $\geq$ 95%) has been achieved by asymmetric carboxylation of the carbanion of a 1,3-propanediol dicarbamate. An asymmetric deprotonation employing a combination of *sec*-butyllithium and (-)-sparteine is the key step (Scheme 2).[8]

Scheme 2.



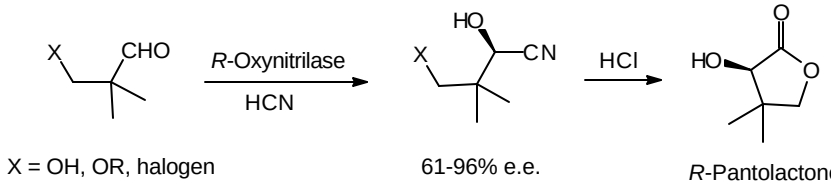
Rao *et al.*[9] have reported a synthesis of *R*-pantolactone that employs the Sharpless asymmetric epoxidation reaction as the key step in the construction of the lactone precursor. The synthesis begins with 3-hydroxy-2,2-dimethyl propanal which is functionalised as shown in Scheme 3.

Scheme 3.



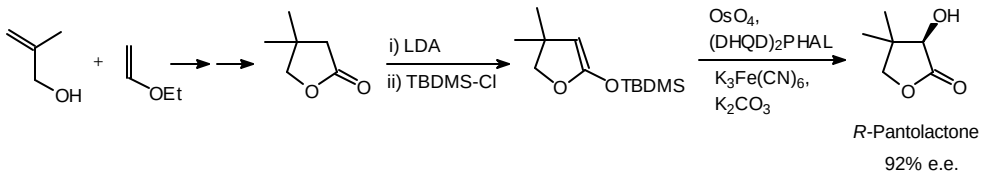
Effenberger[10] has examined the enzyme-catalyzed addition of hydrocyanic acid to substituted pivalaldehydes. The use of *R*-oxynitrilase in the presence of HCN affords the corresponding cyanohydrins in 61-96% e.e. These are converted to *R*-pantolactone by acid catalysed hydrolysis of the nitrile that proceeds with concomitant lactonization (Scheme 4).

Scheme 4.



A recent synthesis of *R*-pantolactone[11] utilizes the Sharpless asymmetric dihydroxylation reaction as the key step. The silyl enol ether of 3,3-dimethyl-γ-butyrolactone is subjected to the asymmetric dihydroxylation reaction to generate *R*-pantolactone with 92% e.e. (Scheme 5).

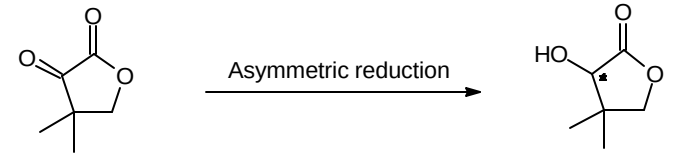
Scheme 5.



Asymmetric reduction of 3,3-dimethyl-2-oxo-butyrolactone (ketopantolactone)

The asymmetric reduction of ketopantolactone employing chemical or microbial catalysis has been extensively investigated as a general route to *R*- and *S*-pantolactones (Figure 2).

Figure 2.



Ketopantolactone Pantolactone

The catalytic asymmetric reduction of ketopantolactone with rhodium complexes containing chiral ligands provides high enantiomeric excess of pantolactone with excellent chemical yields. Ojima[12] has reported the reduction of ketopantolactone with BPPM-Rh (I) complex (86% e.e. of *R*-pantolactone), Achiwa[13] has used *4R,5R*-DIOCP-Rh (I) complex (75% e.e. of *R*-pantolactone), Tani[14] has reported reduction with (-)-*i*PrDIOP-Rh (I) complex (54% e.e. of *R*-pantolactone) and (-)-*t*Bu-CYCAPP-Rh (I) complex (66% e.e. of *S*-pantolactone), while Agbossou[15] has reported AMPP-Rh complex (98% e.e. of *R*-pantolactone) and BAMP-Rh (I) complex (87% e.e. of *S*-pantolactone). The reduction of ketopantolactone has also been achieved with CrO_3-complexed AMPP ligands (99% e.e. *S*-of pantolactone).[16]

Microbial reduction of ketopantolactone has also been examined. Nakamura *et. al.*[17] have reduced ketopantolactone using Baker's yeast to obtain *R*-pantolactone

with 73% e.e. Addition of β-dextrin increased the enantiomeric excess to 93%. Reduction of ketopantolactone with the ascomycete, *Byssochlamys fulva* provides *R*-pantolactone with 99% e.e.[18]

Resolution of racemic pantolactone

Since racemic pantolactone is readily accessible in a one-pot reaction from hydroxypivalaldehyde, sodium cyanide, hydrochloric acid and calcium chloride,[19] general racemate resolution techniques have been applied to obtain enantiomerically pure *R*-pantolactone. The racemic pantolactone has been resolved by conversion to diastereomeric amides with D-galactamine[20] and 1*R*-3-*endo*-aminoborneol.[21] An alternative approach involves resolution of the parent α,γ-dihydroxy-β,β-dimethylbutyric acid with chiral amines such as quinine[22] and (+)-3-aminomethylpinane.[23] The lactone may also be resolved by complexation with brucine or by acylation with diacetyl-*d*-tartaric anhydride followed by separation of diastereomers.[24] Racemic pantolactone has also been resolved by hydrolysis with NaOH followed by partial neutralization with 1*S*-(+)-10-camphorsulfonic acid.[25] Enzymatic resolution of racemic pantolactone has also been examined. Lipase catalysed enantioselective esterification of the racemate with vinyl acetate provides *R*-pantolactone in 88% e.e.[26] Lipase catalysed transesterification of racemic pantolactone acetate in *t*-butanol gives *R*-pantolactone with 70% e.e.[27]

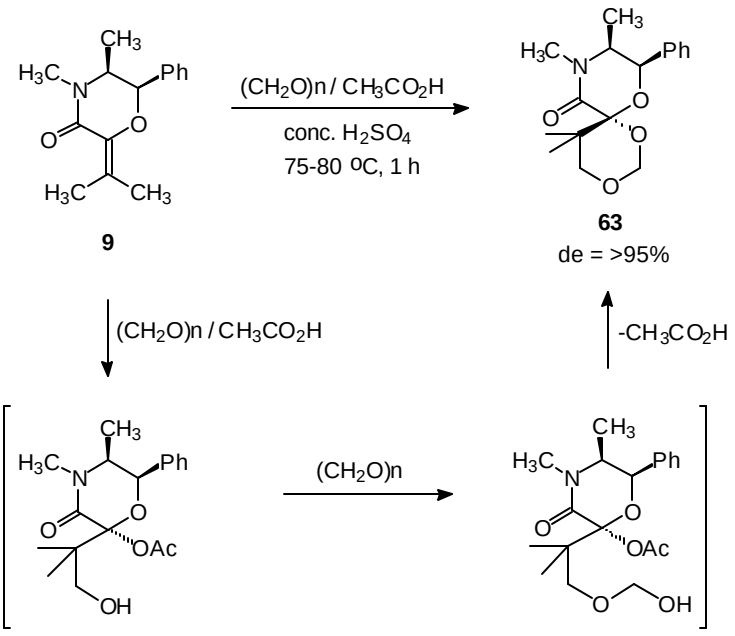
2. OBJECTIVE

The objective of this undertaking was to develop a new, enantioselective route to (*S*)-(+)-pantolactone by asymmetric functionalization of an α-keto acid derived, chiral alkylidene morpholinone.

3. RESULTS AND DISCUSSION

The alkylidene morpholinone **9** (prepared from 3-methyl-2-oxobutanoic acid and 1*R*,2*S* ephedrine as described in Chapter 1) served as a substrate for the enantioselective synthesis of (*S*)-(+)-pantolactone. Initial investigations on the Prins reaction of **9** were conducted with aqueous formaldehyde as an electrophile.[28] Sulfuric acid catalysed reaction of **9** with aqueous formaldehyde in 1,4-dioxane at 80-85 °C generated the spiro bis-acetal **63** as a single diastereomer in 41% yield. However, this reaction was capricious and frequently generated unwanted products in significant amounts or failed to give **63**. Changing the solvent to acetic acid was beneficial and the Prins reaction of **9** with paraformaldehyde in acetic acid at 75-80 °C in the presence of a catalytic amount of conc. sulfuric acid[29] consistently generated **63** in 70-72% yield (Scheme 6).

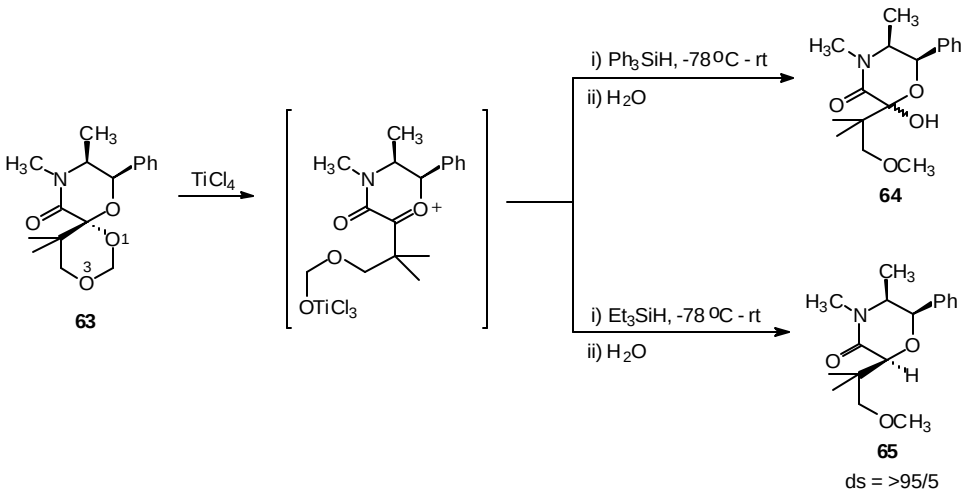
Scheme 6.



The stereochemistry at spiro acetal stereocenter is assigned by analogy to other reactions of the oxacarbenium ion intermediate in the ephedrine-derived template (chapter 1 and chapter 2).

Treatment of **63** with $Ph_3SiH/TiCl_4$[30] in CH_2Cl_2 (-78 °C-rt) followed by an aqueous work up generated the hemiacetal **64** as a mixture of diastereomers. Presumably, $TiCl_4$ coordinates with the exocyclic oxygen (O1, Scheme 7) in the spiro-acetal **63** to generate an endocyclic oxocarbenium ion which is inaccessible for reduction by Ph_3SiH due to steric reasons. Facile reduction of the resulting methylenedioxy functionality followed by reaction with water generates **64**. Replacement of Ph_3SiH by sterically less demanding Et_3SiH[30] resulted in facile reduction of the endocyclic oxocarbenium ion to furnish **65** in 96% yield and excellent diastereoselectivity (ds >95/5).

Scheme 7.

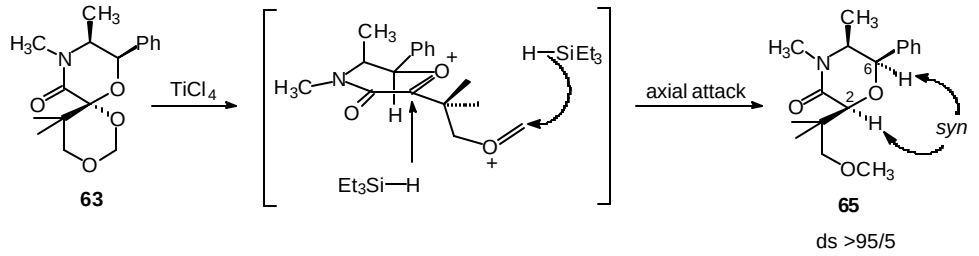


It should be noted that an excess of Et_3SiH (20 eq.) is essential for the conversion of **63** to **65**. Use of lesser amounts of Et_3SiH results in the formation of **9** which is generated by a competing retro-Prins reaction of the intermediate oxocarbenium ion (5% of **9** was formed when 10 eq. Et_3SiH was used).

Lewis acid coordination to O3 in **63** (Scheme 7) followed by acetal cleavage, would generate a free hydroxymethyl group in the product. However, this reaction path was not observed since there was no evidence of the corresponding product. Reasons for the regioselective Lewis acid coordination and acetal cleavage in **63** are unclear. It is plausible that the reaction is governed by the stability of the more substituted endocyclic oxocarbenium ion. The opposing dipole of the amide carbonyl may also be a stabilizing factor.

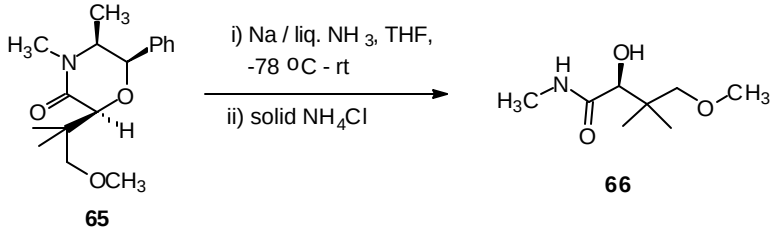
The stereochemistry of the newly generated chiral center in **65** was asigned '*S*' from a *NOESY* experiment that indicated a *syn* orientation of the hydrogens on C2 and C6 in morpholinone **65**. The stereochemistry is an outcome of a stereoelectronically controlled axial reduction of the intermediate oxocarbenium ion (Figure 3).

Figure 3.



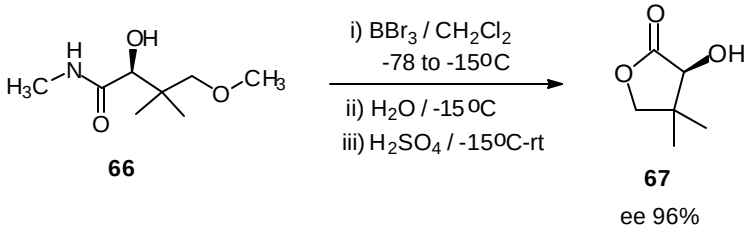
Morpholinone **65** is a protected version of the requisite α,γ-dihydroxy butyric acid precursor to pantolactone. Dissolving metal reduction of **65** (Na/liq. NH_3 in THF) proceeds rapidly (10-15 s) at -78°C to generate the α-hydroxy γ-methoxy butyramide **66** in 62% yield (Scheme 8).

Scheme 8.



Conversion of **66** to (*S*)-pantolactone **67** was achieved by a one-pot reaction sequence. The primary hydroxyl group in **66** was liberated by demethylation with BBr_3 in CH_2Cl_2 (–78°C to –15 °C). Subsequent acid catalysed lactonization (–15 °C to rt), which presumably involves a very facile intramolecular acyl transfer from nitrogen to oxygen,[31] furnished (*S*)-(+)-pantolactone **67** in 96% e.e. (68% yield and from **66** over two steps) (Scheme 9). $[\alpha]_D^{25}$ = +51.6 (*c* 2, H_2O); lit.[22] $[\alpha]_D^{25}$ = +50.1 (*c*2, H_2O).

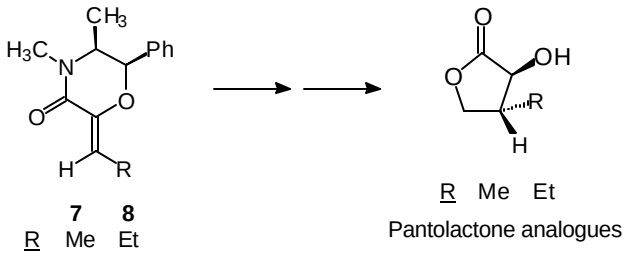
Scheme 9.



The enantiomeric excess (96%) of (*S*)-pantolactone **67** was determined by GC analysis of its Mosher derivative with *R*-MTPA.

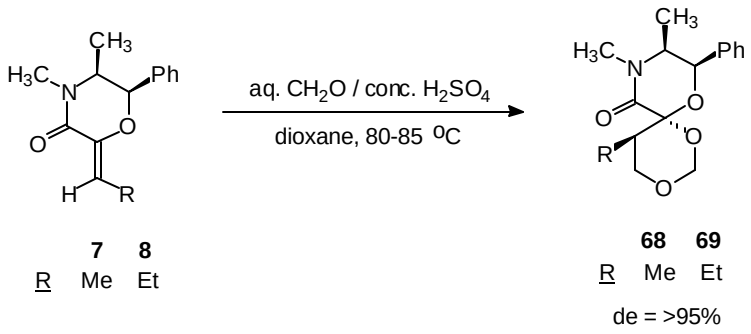
The synthesis of analogues of pantolactone was also investigated. The α-alkoxy acrylamides **7** and **8** (described in Chapter 1) are potential precursors of pantolactone analogues (Figure 4).

Figure 4.



The sulfuric acid catalysed Prins reaction of **7** and **8** with aqueous formaldehyde[28] in 1,4-dioxane at 80-85 °C (36-42 h) generated the corresponding spiro bis-acetals **68** (48%) and **69** (54%) as single diastereomers (Scheme 10), albeit in modest yield.

Scheme 10.

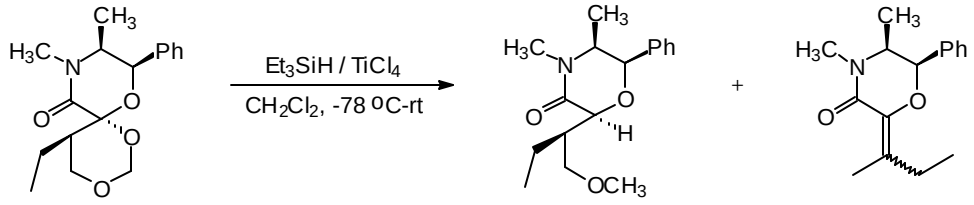


7 **8**
R Me Et

68 **69**
R Me Et
de = >95%

Reductive cleavage of the bis-acetal **69** with $Et_3SiH/TiCl_4$ (-78 °C-rt, 12 h) in CH_2Cl_2 generated the desired morpholinone **70** as a mixture of diastereomers (52%, *ds* = 3.5/1) along with the elimination product **71** as a mixture of *E*- and *Z*-isomers (22%, *ds* = 7.5/1, Scheme 11). Traces of acrylamide **8** (<5%) were also formed due to the retro-Prins reaction.

Scheme 11.



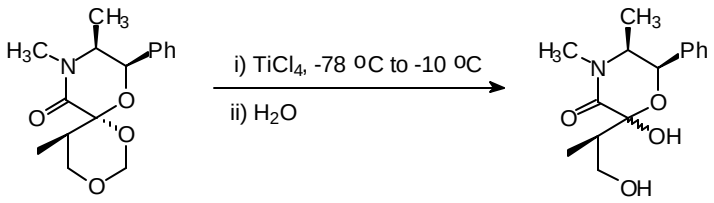
69

70
ds = 3.5 / 1

71
ds = 7.5 / 1

One of several attempts to improve the reduction stereoselectivity involved the reaction of a modified substrate that was derived from **68**. The bis-acetal **68** was converted to the hemiacetal **72** by reaction with $TiCl_4$ (-78 °C to – 10 °C, 60 h) followed by quenching with water (28% yield, Scheme 12).

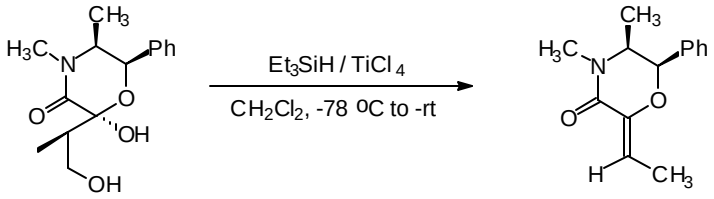
Scheme 12.



68 **72**

The reaction of hemiacetal **72** with $Et_3SiH/TiCl_4$ in CH_2Cl_2 (- 78 °C to rt, 24 h) did not generate any of the required reduction product but resulted in the exclusive formation the alkylidene morpholinone **7** (^1H NMR of the crude product, Scheme 13).

Scheme 13.



72 **7**

The reasons for the low stereoselectivity in the reduction of **68** and **69** are not clear at present and alternative reduction conditions are being explored.

4. CONCLUSION

An asymmetric synthesis of (*S*)-(+)-pantolactone has been achieved by employing a chiral, alkylidene morpholinone derived from *1R,2S*-ephedrine and 3-methyl-2-oxo-butyric acid. The salient features of the synthesis involve a Prins reaction followed by an asymmetric, regioselective reduction of the Prins product. Since 1*S*,2*R*-

ephedrine is also commercially available (*R*)-(-)-pantolactone should also be readily available by this methodology.

5. EXPERIMENTAL

General experimental techniques that have been described in the experimental section of Chapter 1 were followed.

6*R*,8*R*,9*S*-5,5,9,10-Tetramethyl-8-phenyl-1,3,7-trioxa-10-aza-spiro[5,5]undecan-11-one (63):

Prins reaction of 9 with $(CH_2O)_n/H_2SO_4$ in CH_3COOH:[29]

Conc. H_2SO_4 (0.25 g, 2.55 mmol) was added to a mixture of the alkylidene morpholinone **9** (1.2 g, 4.9 mmol) and paraformaldehyde (0.735 g, 24.5 mmol) in glacial acetic acid (20 mL) and the reaction mixture was heated at an oil bath tempereture of 75-80°C for 1 h. It was neutralized with saturated aq. $NaHCO_3$ and extracted with ether. The ether layer was washed with water, 2N HCl followed by water and dried over Na_2SO_4. Removal of the solvent under reduced pressure furnished 1.234 g of the crude product as clear colourless gum (single diastereomer by ^{1}H NMR). Purification by flash chromatography over silica gel (petroleum ether/ethyl acetate 7/3) furnished 1.086 g (72%) of the spiro acetal **63** as a white solid.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.5-7.2 (m, 5H, Ar*H*), 5.4 (d, 1H, *J* = 3.4, PhC*H*), 5.1 (d, 1H, *J* = 5.9, OCH_2O), 5.0 (d, 1H, *J* = 5.9, OCH_2O), 3.85 (s, 2H, OCH_2C), 3.45 (dq, 1H, *J* = 3.4, 6..3, CH_3C*H*), 3.00 (s, 3H, NCH_3), 1.30 (s, 3H, CCH_3), 1.1 (s, 3H, CCH_3), 0.95 (d, 3H, *J* = 6.3, CHCH_3).

^{13}C NMR (75 MHz, $CDCl_3$):

δ 165.0 (*C*=O), 137.2 (Ar*C*), 128.4 (Ar*C*H), 127.6 (Ar*C*H), 125.4 (Ar*C*H), 99.4 (O*C*O (quat)), 88.3 (O-*C*H_2-O), 74.5 (C*C*H_2O), 70.7 (Ph*C*H), 58.9 (CH_3*C*H), 38.0 ((CH_3)$_2$*C*), 33.5 (N*C*H_3), 22.0 (C*C*H3), 21.3 (C*C*H_3), 12.4 (CH*C*H_3).

IR ($CHCl_3$):

3017, 2982, 1655, 1479, 1215, 1178, 1150, 1132, 1097, 1036, 1013, 976 cm^{-1}.

MS (70 eV):

m/z 91 (8), 105 (3), 118 (100), 146 (4), 220 (3), 305 (M^+, 3).

HRMS (CI, NH_3) for $C_{17}H_{24}NO_4$ (M+H):

Calcd: 306.1706

Found: 306.1707.

[a **]$^{25}_D$** = -117.3 (*c* 1.1, $CHCl_3$).

2*S*,5*S*,6*R*-4,5-Dimethyl-6-phenyl-2-hydroxy-2-(1,1-dimethyl-2-methoxyethyl) morpholin-3-one (64):

Reductive cleavage of spiro acetal 63 with $TiCl_4$/Ph_3SiH:

To a solution of **63** (0.036 g, 0.12 mmol) in dichloromethane (2 mL) at -78°C was added Ph_3SiH (0.2 g, 0.77 mmol) followed by $TiCl_4$ (0.07 mL, 0.66 mmol) and the reaction mixture was slowly warmed to and stirred at ambient temperature for 12 h. It was then cooled to 0 °C, saturated aqueous NH_4Cl was added and the mixture was warmed up to ambient temperature. Water was added to dissolve precipitated solids and the solution was extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were

dried (Na_2SO_4) and concentrated to furnish 0.23 g of a mixture of **64** and triphenylsilane.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.70-7.2 (m, 5H, Ar*H*), 5.55 (br s, 1H, PhC*H*), 3.75 (d, 1H, *J* = 8.3, CH_2), 3.55 (d, 1H, *J* = 8.3, CH_2), 3.45 (dq, 1H, *J* = 3.4, 6.3, MeC*H*), 3.35 (s, 3H, OCH_3), 2.95 (s, 3H, NCH_3), 1.30 (s, 3H, C(CH_3)$_2$), 1.05 (s, 3H, C(CH_3)$_2$), 0.90 (d, 3H, *J* = 6.3, CHCH_3).

Visible peaks for the other diastereomer:

δ 5.65 (br s, 1H, PhC*H*), 3.30 (s, 3H, OCH_3).

2*S*,5*S*,6*R*-4,5-Dimethyl-6-phenyl-2-(1,1-dimethyl-2-methoxyethyl) morpholin-3-one (65):

Reductive cleavage of spiro acetal 63 with $TiCl_4$/Et_3SiH:

To a solution of **63** (1.08 g, 3.54 mmol) in dichloromethane (30 mL) at -78°C was added Et_3SiH (11.3 mL, 70.8 mmol) followed by $TiCl_4$ (4.65 mL, 42.48 mmol) and the reaction mixture was slowly warmed to and stirred at ambient temperature for 24 h. It was then cooled to 0 °C, saturated aqueous NH_4Cl was added and the mixture was warmed up to ambient temperature. Water was added to dissolve precipitated solids and the solution was extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were dried (Na_2SO_4) and concentrated to furnish 1.22 g of crude product (single diastereomer by 1H NMR) which on purification by flash chromatography on silica gel (7/3 petroleum ether/ethyl acetate) furnished 0.99 g (96%) of **65** as clear colourless gum.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.5-7.2 (m, 5H, Ar*H*), 4.9 (d, 1H, *J* = 2.9, PhC*H*), 4.25 (s, 1H, C*H*-O), 3.55 (d, 1H, *J* = 8.8, CH_2), 3.45 (d, 1H, *J* = 8.8, CH_2), 3.48 (dq, 1H, *J* = 2.9, 6.6, MeC*H*), 3.35 (s, 3H, OCH_3), 3.0 (s, 3H, NCH_3), 1.15 (s, 6H, C(CH_3)$_2$), 0.95 (d, 3H, *J* = 6.6, CHCH_3).

^{13}C NMR (22.5 MHz, $CDCl_3$):

δ 168.3 (*C*=O), 138.0 (Ar*C*), 127.9, 127.1, 125.1 (Ar*C*H),81.3 (*C*H-O), 79.4 (*C*H_2O), 76 (Ph*C*H), 58.7, 58.4 (O*C*H_3, *C*H_3CH), 39.8 (N*C*H_3), 33 (*C*(CH$_3$)$_2$), 21.7 (C(*C*H$_3$)$_2$), 12.7 (*C*H$_3$CH).

IR (neat):

2976, 2932, 2874, 1651, 1477, 1452, 1396, 1379, 1308, 1252, 1150, 1111, 1063 cm^{-1}.

MS (70eV):

m/z 58 (7), 84 (33), 118 (100), 140 (15), 148 (7), 205 (70), 276 (1), 291 (M^+, 1).

HRMS (CI, NH_3) for $C_{17}H_{26}NO_3$ (M+H):

Calcd: 292.1913

Found: 292.1913.

[a **]$^{25}_{D}$** = -193.4 (*c* 3, $CHCl_3$).

2*S*-3,3-Dimethyl-2-hydroxy-4-methoxybutanoic acid *N*-methyl amide (66):

Dissolving metal reduction of 65:

To anhydrous liquid ammonia (25 mL, distilled over sodium) was added Na metal (0.8 g, 34.7 mmol) at -78 ^oC and the mixture stirred for 15 minutes. To the resulting blue solution was added a solution of **65** (0.98 g, 3.36 mmol) in anhydrous THF (2 mL) and the mixture was stirred for 10-15 sec. Anhydrous ammonium chloride (6 g) was added and the mixture was warmed to ambient temperature to remove ammonia. The resulting solid mass was extracted with hot ethyl acetate to furnish 0.8 g of the crude product. Purification by flash chromatography on silica gel (petroleum ether/ethyl acetate 2/8 furnished 0.369 g

(62%) of **66** as clear colourless gum.

^{1}H NMR (300 MHz, $CDCl_3$):

δ 6.8 (br s, 1H, N*H*), 4.45 (d, 1H, J = 3.6, O*H*), 4.00 (d, 1H, *J* = 3.6, C*H*), 3.35 (s, 3H, OCH_3), 3.35 (d, 1H, *J* = 9.2, CH_2), 3.25 (d, 1H, *J* = 9.2, CH_2), 2.85 (d, *J* = 5.1, 3H, NCH_3), 1.00 (s, 6H, C(CH_3)$_2$).

^{13}CNMR (22.5 MHz, $CDCl_3$):

δ 172.9 (*C*=O), 81.7 (*C*HOH), 77.9 (O*C*H$_2$), 59.1 (O*C*H$_3$), 38.4 (*C*(CH$_3$)$_2$), 25.0, 25.3 (N*C*H$_3$), 21.6 (C(*C*H$_3$)$_2$), 20.2 (C(*C*H$_3$)$_2$).

IR ($CHCl_3$):

3431, 2964, 2936, 2880, 2251, 1666, 1541, 1477, 1414, 1101, 1074, 908 cm^{-1}.

HRMS (CI, NH_3) for $C_8H_{18}NO_3$ (M+H):

Calcd: 176.1287

Found: 176.1288.

***S*-(+)-3-Hydroxy-4,4-dimethyl-dihydro-2(3*H*)-furanone (Pantolactone) (67):**

To a solution of **66** (0.1 g, 0.57 mmol) in CH_2Cl_2 (4 mL) was added at -78°C BBr_3 (2M in CH_2Cl_2, 2.5 mL) and the resulting mixture was slowly warmed to and stirred at -15°C for 2h. Water (2 mL) was added and the reaction mixture was stirred for an additional 10 min after which 2 mL of ice cold 6M H_2SO_4 was added dropwise and the reaction mixture was slowly warmed to and stirred at ambient temperature for 12 h. It was cooled (ice bath) and neutralized by addition of small portions of solid $NaHCO_3$. The resulting semi-solid residue was extracted with hot CH_2Cl_2 to furnish 72 mg of the crude lactone as clear colorless oil. Purification by flash chromatography on silica gel (6/4 petroleum ether/ethyl

acetate) furnished 0.051 g (68%) of *S*-(+)-pantolactone **67** as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$):

δ 4.1 (d, 1H, J = 3.7, C*H*OH), 4.03 (d, 1H, *J* = 9.2, CH_2), 3.95 (d, 1H, *J* = 9.2, CH_2), 2.82 (d, 1H, *J* = 3.7, O*H*), 1.24 (s, 3H, CH_3), 1.08 (s, 3H, CH_3).

IR ($CHCl_3$):

3445, 1782, 1113, 1007 cm^{-1}.

MS (70eV):

m/z 57 (19), 68 (15), 71 (100), 85 (2), 130 (M^+, 1).

[a **]$_D^{25}$** = +51.6 (*c* 2, H_2O, lit.[20] **[**a **]$_D^{25}$** = +50.1 (*c* 2, H_2O) for *S*-**67**).

Enantiomeric excess: 96% (GC analysis of the Mosher derivative of **67** with '*R*'-methoxytrifluoromethylphenylacetyl chloride; column: BP1 (non-polar) 100% dimethylpolysiloxane; 0.53 mm id; nitrogen as carrier gas (3.8 mL/min); injection temperature 280 °C; column temperature 140-280 °C at 10 °C/min; t_R(minor) 9.54 min, t_R(major) 9.87 min.

General procedure for the Prins reaction of acrylamides 7 and 8 with aq. CH_2O/H_2SO_4 in dioxane:[28]

Conc. H_2SO_4 was added to a mixture of the alkylidene morpholinone **7** or **8** (1 eq.) and aqueous formaldehyde (37% w/v, 4 eq.) in dioxane and the reaction mixture was heated at an oil bath tempereture of 80-85 °C for 36-42 h. The solvent was removed under reduced pressure, water was added and the mixture was extracted with ether. The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to furnish the crude product that was purified by flash

chromatography on silica gel using a mixture of petroleum ether/ethyl acetate as the eluant.

5*R*,6*R*,8*R*,9*S*-8-Phenyl-5,9,10-Trimethyl-1,3,7-trioxa-10-aza spiro[5,5]undecan-11-one (68):

Prins reaction of 7 with aq. CH_2O/H_2SO_4 in dioxane:

Prepared from **7** (0.45 g, 1.94 mmol), aqueous formaldehyde (37% w/v, 0.64 mL, 7.96 mmol) and conc. H_2SO_4 (0.2 mL) in dioxane (12 mL) to furnish 0.438 g of the crude product (single diastereomer by ^{1}H NMR) which on purification by flash chromatography on silica gel (7/3 petroleum ether/ethyl acetate) furnished 0.272 g (48%) of **68** as a white solid.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.60-7.20 (m, 5H, Ar*H*), 5.50 (d, 1H, *J* = 3.0, PhC*H*), 5.05 (d, 1H, *J* = 5.9, OCH_2O), 4.80 (d, 1H, *J* = 5.9, OCH_2O), 3.95-3.70 (m, 2H, OCH_2CH), 3.55 (dq, 1H, *J* = 3.0, 6.8, NC*H*), 3.05 (s, 3H, NCH_3), 3.10-2.90 (m, 1H, OCH_2C*H*), 1.00 (d, 3H, *J* = 6.8, CHCH_3), 0.90 (d, 3H, *J* = 6.8, CHCH_3).

^{13}C NMR (50 MHz, $CDCl_3$):

δ 164.0 (*C*=O), 136.8 (Ar*C*), 128.1 (Ar*C*H), 127.3 (Ar*C*H), 124.9 (Ar*C*H), 98.2 (O*C*O (quat)), 86.0 (O-$C$$H_2$-O), 69.8 (Ph*C*H), 67.3 (O*C*H_2CH) 58.3 (N*C*H), 34.1 (OCH_2*C*H), 33.2 (N*C*H_3), 12.2 (CH*C*H3), 10.9 (CH*C*H_3).

IR ($CHCl_3$):

3040, 1670, 1420, 1390, 1300, 1230, 1180, 1050, 990, 950 cm^{-1}.

MS (70 eV):

m/z 56 (7), 77 (4), 91 (6), 105 (8), 118 (100), 148 (7), 291 (M^+, 5).

5*R*,6*R*,8*R*,9*S*-9,10-Dimethyl-5-ethyl-8-phenyl-1,3,7-trioxa-10-aza-spiro[5,5]undecan-11-one (69):

Prins reaction of 8 with aq. CH_2O/H_2SO_4 in dioxane:

Prepared from **8** (0.4 g, 1.63 mmol), aqueous formaldehyde (37% w/v, 0.6 mL, 7.46 mmol) and conc. H_2SO_4 (0.1 mL) in dioxane (10 mL) to furnish 0.403 g of the crude product (single diastereomer by ^{1}H NMR) which on purification by flash chromatography on silica gel (7/3 petroleum rther/ethyl acetate) furnished 0.27 g (54%) of **69** as a white solid.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.50-7.20 (m, 5H, Ar*H*), 5.50 (d, 1H, *J* = 2.9, PhC*H*), 5.00 (d, 1H, *J* = 5.9, OCH_2O), 4.80 (d, 1H, *J* = 5.9, OCH_2O), 4.05 (dd, 1H, *J* = 4.9, 11.0, OCH_2CH), 3.80 (t, 1H, *J* = 11.0, OCH_2CH), 3.50 (dq, 1H, *J* = 2.9, 6.4, NC*H*), 3.05 (s, 3H, NCH_3), 2.90-2.70 (m, 1H, OCH_2C*H*), 1.45-1.20 (m, 2H, CH_3CH_2), 1.00 (d, 3H, *J* = 6.4, CHCH_3), 0.90 (t, 3H, *J* = 7.4, CH_2CH_3).

^{13}C NMR (75 MHz, $CDCl_3$):

δ 164.2 (*C*=O), 136.8 (Ar*C*), 128.1 (Ar*C*H), 127.4 (Ar*C*H), 125.0 (Ar*C*H), 98.2 (O*C*O (quat)), 86.1 (O-*C*H_2-O), 69.8 (Ph*C*H), 65.9 (O*C*H_2CH) 58.4 (N*C*H), 40.5 (OCH_2*C*H), 33.3 (N*C*H_3), 19.6 (CH_3*C*H_2), 12.2 (*C*H_3), 10.8 (*C*H_3).

MS (70 eV):

m/z 56 (21), 77 (5), 91 (10), 106 (4), 118 (100), 131 (3), 148 (7), 174 (1), 247 (1), 258 (1), 305 (M^+, 2).

2*S*,2(1*R*),5*S*,6*R*-4,5-Dimethyl-6-phenyl-2-(1-methoxymethylpropyl) morpholin-3-one (70):

Reductive cleavage of spiro acetal 69 with $TiCl_4$/Et_3SiH:

To a solution of **69** (0.337 g, 1.1 mmol) in dichloromethane (10 mL) at -78°C was added Et_3SiH (2.1 mL, 13.1 mmol) followed by $TiCl_4$ (1.2 mL, 10.9 mmol) and the reaction mixture was slowly warmed to and stirred at ambient temperature for 12 h. It was then cooled to 0 °C, saturated aqueous NH_4Cl was added and the mixture was warmed up to ambient temperature. Water was added to dissolve precipitated solids and the solution was extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were dried (Na_2SO_4) and concentrated to 0.4 g of the crude product that was a mixture of **70** (*ds* = 3.5/1 by ^{1}H NMR) and **71** (*ds* = 7.5/1 by ^{1}H NMR). Purification by flash chromatography on silica gel (3/2 petroleum ether/ethyl acetate) furnished 0.168 g (52%) of **70** as clear, colourless gum and 0.064 g (22%) of **71** as clear colourless gum.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.50-7.20 (m, 5H, Ar*H*), 5.00 (d, 1H, *J* = 3.0, PhC*H*), 4.50 (d, 1H, *J* = 2.5, C*H*-O), 3.65-3.40 (m, 3H, OCH_2, NC*H*), 3.35 (s, 3H, OCH_3), 3.05 (s, 3H, NCH_3), 2.65-2.40 (m, 1H, CH_2C*H*), 1.65-1.35 (m, 2H, CH_3CH_2), 1.10-0.80 (apparent m, 6H, CH_2CH_3, CHCH_3).

Visible peaks for the other diastereomer:

δ 5.15 (d, 1H, *J* = 3.0, PhC*H*), 4.40 (d, 1H, *J* = 2.5, C*H*-O), 3.25 (s, 3H, OCH_3).

MS (70 eV)

58 (74), 71 (6), 83 (47), 91 (17), 98 (11), 105 (10), 118 (100), 128 (14), 140 (33), 148 (8), 159 (5), 174 (1), 186 (2), 205 (83), 246 (7), 260 (1), 276 (1), 291 (M^+, 16).

5*S*,6*R*-2-(2-Butylidene)-4,5-dimethyl-6-phenyl morpholin-3-one (71):

Formed as a mixture of *E*- and *Z*-isomers (*ds* = 7.5/1) during the reductive cleavage of spiro-acetal **69** with $TiCl_4/Et_3SiH$.

^{1}H NMR (200 MHz, $CDCl_3$):

Major diastereomer:

δ 7.50-7.20 (m, 5H, Ar*H*), 5.10 (d, 1H, *J* = 2.9, PhC*H*), 3.55 (dq, 1H, *J* = 2.9, 6.4, NC*H*), 3.05 (s, 3H, NCH_3), 2.40-2.20 (m, 2H, CH_2), 2.25 (s, 3H, olefinic CH_3), 1.05 (t, 3H, *J* = 7.4, CH_2CH_3), 0.95 (d, 3H, *J* = 6.4, CHCH_3).

Visible peaks for the other diastereomer:

δ 5.00 (d, 1H, *J* = 2.9, PhC*H*).

2*S*,2(1*R*),5*S*,6*R*-4,5-Dimethyl-6-Phenyl-2-hydroxy-2-(1-hydroxymethylethyl)morpholin-3-one (72):

Conversion of spiro-acetal 68 to hemiacetal 72:

To a solution of **68** (0.52 g, 1.78 mmol) in anhydrous CH_2Cl_2 (25 mL) was added $TiCl_4$ (2 mL, 18 mmol) at −78 °C after which the mixture was warmed to and

stirred at −10 °C for 60 h. It was quenched by ice and extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were dried (Na_2SO_4) and concentrated to furnish 0.49 g of crude product. Purification by flash chromatography on silica gel (1/4 petroleum ether/ethyl acetate) furnished 0.142 g (28%) of **72** as a wax.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.5-7.2 (m, 5H, Ar*H*), 6.15 (s, 1H, O*H*), 5.65 (d, 1H, *J* = 3.0, PhC*H*), 4.30-4.05 (m, 1H, C*H*$_2$OH), 3.90 (dd, 1H, *J* = 3.9, 10.7, C*H*$_2$OH), 3.50 (dq, 1H, *J* = 3.0, 6.4, NC*H*), 3.20-2.95 (b, 1H, O*H*), 3.05 (s, 3H, NC*H*$_3$), 2.95-2.70 (m, 1H, CH$_2$C*H*), 1.00 (d, 3H, *J* = 6.4, CHC*H*$_3$), 0.90 (d, 3H, *J* = 6.9, CHC*H*$_3$).

Visible peaks for the other diastereomer:

δ 5.60 (d, 1H, PhC*H*), 3.10 (s, 3H, NC*H*$_3$).

^{13}C NMR (50 MHz, $CDCl_3$):

δ 167.6 (*C*=O), 138.0 (Ar*C*), 128.1 (Ar*C*H), 127.3 (Ar*C*H), 125.6 (Ar*C*H), 100.2 (*C*-OH), 70.1 (Ph*C*H), 64.4 (*C*H$_2$OH), 58.9 (N*C*H), 40.4 (CH$_2$*C*H), 33.4 (N*C*H$_3$), 12.5 (CH*C*H$_3$), 12.4 (CH*C*H$_3$).

Visible peaks for the other diastereomer:

δ 128.4 (Ar*C*H), 125.2 (Ar*C*H), 73.3 (Ph*C*H), 57.9 (N*C*H), 42.9 (CH$_2$*C*H), 34.1 (N*C*H$_3$), 13.0 (CH*C*H$_3$), 12.7 (CH*C*H$_3$).

IR ($CHCl_3$):

3400, 3040, 1660, 1510, 1480, 1470, 1435, 1420, 1400, 1230, 1040 cm^{-1}.

MS (70eV):

m/z 58 (62), 68 (4), 77 (8), 86 (6), 91 (14), 105 (7), 118 (100), 132 (2), 146 (7), 155 (1), 173 (3), 183 (1), 214 (1), 220 (3), 231 (5), 257 (1), 279 (M^+, 1).

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CHAPTER V

ASYMMETRIC, DIAZOCARBONYL INSERTION REACTIONS INTO HETEROATOM-HYDROGEN BONDS

1. INTRODUCTION

α-Diazocarbonyl compounds constitute a class of compounds that have exceptional flexibility in organic synthesis. Their most significant reactions are those that proceed with loss of nitrogen which can be brought about thermally,[1] photochemically[2] or catalytically.[3] These compounds react stoichiometrically with many Brönsted acids and electrophiles, and catalytically with numerous transition metals and their salts.

The reactions of diazo compounds that are catalysed by transition metal complexes primarily fall into two catagories: a) cyclopropanation and b) insertion into carbon-hydrogen and heteroatom-hydrogen bonds.

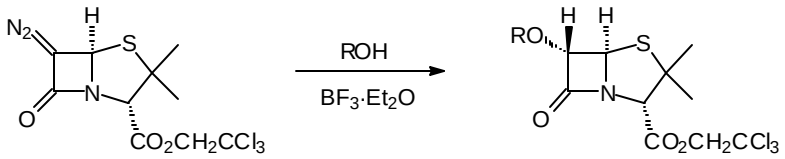
The transition metal catalysed heteroatom-H bond insertion reactions of α-diazocarbonyl compounds have been the focus of several recent investigations. In particular, the diazocarbonyl/OH as well as the diazocarbonyl/NH insertion reactions have been extensively studied. A brief discussion follows.

Diazocarbonyl insertion reactions into O-H bonds:

There have been several imaginative uses of diazocarbonyl/OH insertion reactions involving alcohols and water as the heteroatom donors.

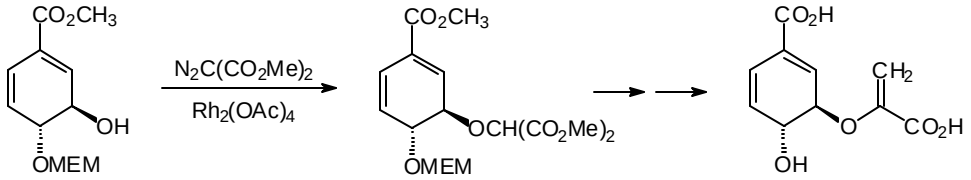
Thomas and coworkers[4] have reported the borontrifluoride catalysed addition of alcohols to 6-diazopenicillanate as a direct route to 6-oxypenicillanate derivatives (Scheme 1).

Scheme 1.



In a synthesis of chorismic acid, Ganem and coworkers[5] have introduced the enol pyruvate side chain by employing a rhodium (II) acetate catalysed O-H insertion reaction with diazomalonate as the key step (Scheme 2).

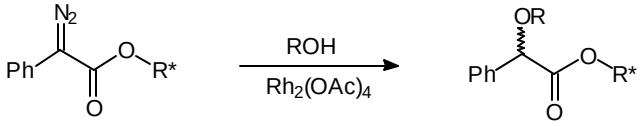
Scheme 2.



Berchtold[6] and Bartlett[7] have also used this approach to the introduction of the enol pyruvate side chain in shikimate-derived metabolites.

An asymmetric version of the intermolecular diazocarbonyl/OH insertion reaction has been studied by Moody[8] by employing phenyldiazoacetate esters of (-)-borneol, (+)-menthol, (-)-menthol, (-)-8-phenylmenthol, (-)-*trans*-2-phenylcyclohexanol, (+)-*trans*-2-phenylcyclohexanol, and (-)-10-(dicyclohexylsulfamoyl)-D-isoborneol. The diastereoselectivity of the insertion was very dependent on the size of the alcohol and the nature of the chiral auxiliary. The combination of *tert*-butanol as the donor and an 8-phenylmenthol as the auxiliary gives the highest d.e. (53%, Scheme 3).

Scheme 3.

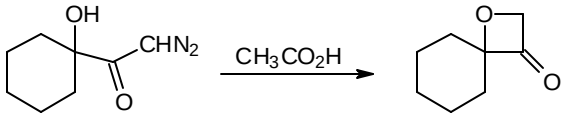


1-53% d.e.

Several aspects of the intramolecular version of the OH insertion of alcohols into diazocarbonyl substrates have been studied, the earliest example being that of Marshall[9] who observed the cyclisation of an α-hydroxy diazoketone

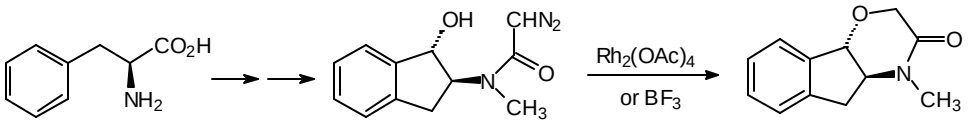
in glacial acetic acid to form an oxetanone derivative (Scheme 4).

Scheme 4.



McClure[10] and coworkers have developed a stereoselective synthesis of a 1,4-oxazinone by employing an intramolecular O-H insertion reaction as the key step. Treatment of the phenylalanine derived β-hydroxy diazoacetamide derivative with rhodium acetate ($Rh_2(OAc)_4$) or borontrifluoride etherate furnishes the required product (Scheme 5).

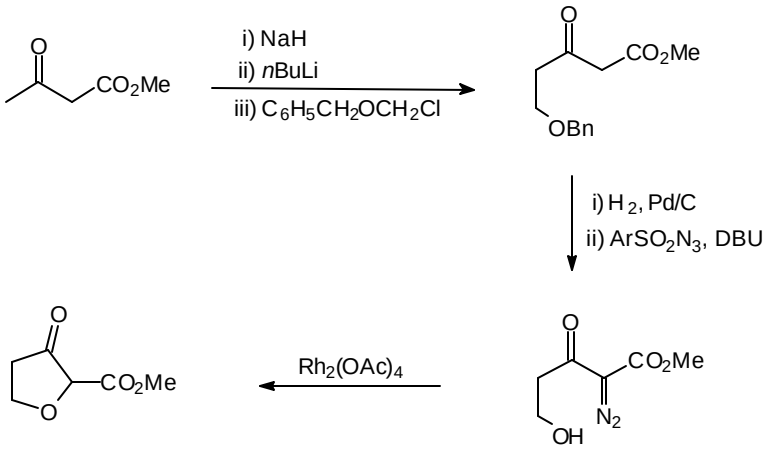
Scheme 5.



There are several reports on the use of Rh(II) catalysed intramolecular diazocarbonyl/OH insertion reactions for the construction of five, six, seven, and eight membered cyclic ethers.

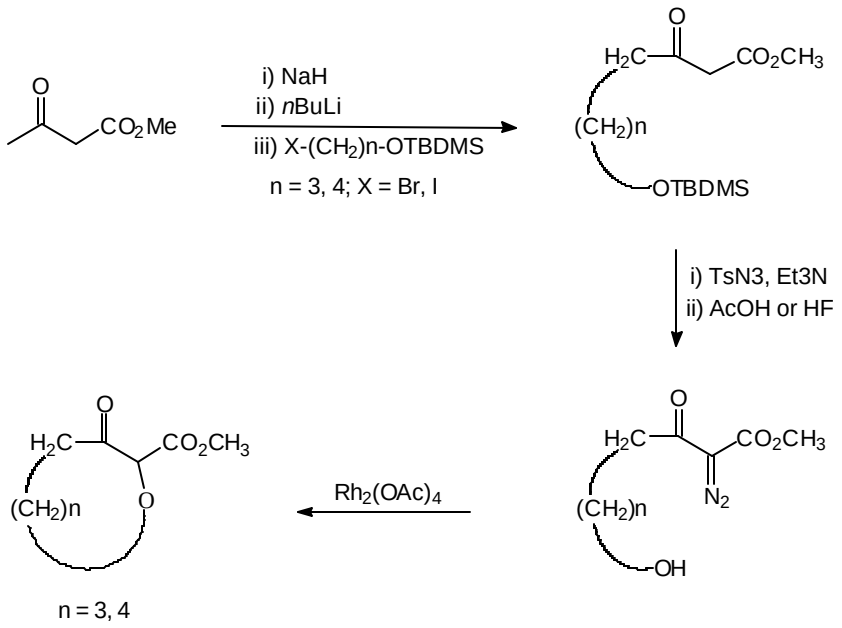
Rapoport[11] has reported the synthesis of a 3-oxo-tetrahydrofuran derivative in quantitative yield by the Rh(II) acetate catalysed intramolecular O-H insertion reaction of the corresponding α-diazoester which was prepared as shown in Scheme 6.

Scheme 6.



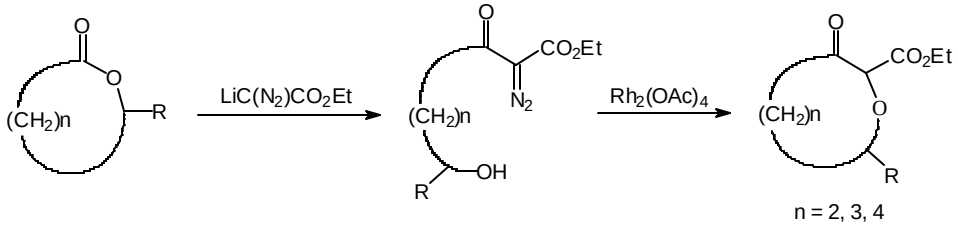
A similar approach has been used by Moody[12] for the preparation of seven- and eight-membered cyclic ethers (Scheme 7).

Scheme 7.



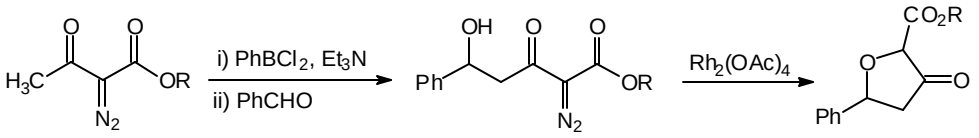
In another intramolecular O-H insertion approach to the synthesis cyclic ethers, Moody has synthesized the requisite acyclic diazocarbonyl precursors by a ring opening reaction of the appropriate lactone with lithio diazoacetate (Scheme 8).[13]

Scheme 8.



In yet another approach, Calter[14] has demonstrated a two step reaction sequence for the synthesis of substituted tetrahydrofurans. In this case, the starting material is prepared by an aldol reaction of an α-diazo-β-ketoester. Subsequent Rh(II) catalysed intramolecular O-H insertion furnishes the required product (Scheme 9).

Scheme 9.



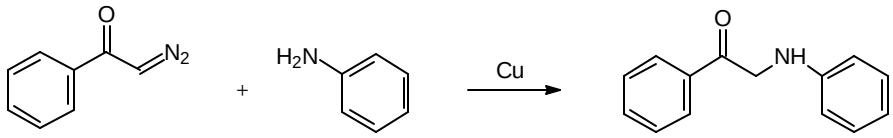
Diazocarbonyl insertion reactions into N-H bonds:

The insertion of α-diazocarbonyl compounds into N-H bonds had attracted little attention as a synthetic route to α-amino ketones or esters until 1978 when its use in bicyclic β-lactam synthesis was reported by a Merck group.[15] Since then there have been numerous examples of the utility of this reaction.

The diazocarbonyl insertion into N-H bonds of a variety of nitrogen containing compounds (amines, amides, carbamates or lactams) is a facile reaction and both intermolecuar and intramolecular versions of the reaction have been investigated.

The earliest example of an intermolecular N-H insertion reaction was reported by Yates[16] who examined the copper catalysed reaction of an α-diazoester and aniline to generate the α-anilino ester (Scheme 10).

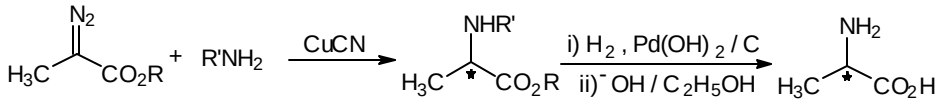
Scheme 10.



Cuprous cyanide or chloride were later used as catalysts for the insertion of ethyldiazoacetate into the N-H bonds of piperidine, morpholine, and butylamine.[17]

Kagan[18] has used cuprous cyanide as a catalyst for the N-H insertion reaction of diazopropionates with chiral benzylamines in an asymmetric synthesis of alanine. Although the insertion reaction was successful, the enantioselection in the creation of the new stereogenic center was low (15-26% e. e., Scheme 11).

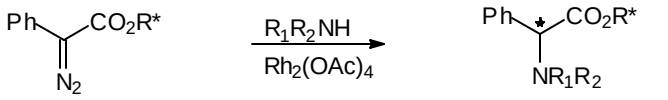
Scheme 11.



R = C_6H_{11} or L-menthyl
R' = (*S*)-phenylethylamine
(*R*)-phenylethylamine
(*S*)-(-)-1-(1-naphthyl)ethylamine
(*R*)-(+)-1-(1-naphthyl)ethylamine

In another asymmetric approach to α-amino acid derivatives, Moody[19] has studied Rh(II) acetate catalysed insertion reactions of α-diazo phenylacetate esters of (-)-borneol, (+)-menthol and (-)-8-phenylmenthol with diethylamine, acetamide and methylcarbamate. The α-aminoesters were obtained in moderate yields (37-71%) and with low diastereoselectivity (maximum 13% de, Scheme 12).

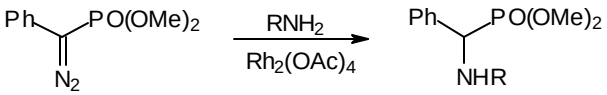
Scheme 12.



maximum 13% d.e.

The intermolecular N-H insertion reactions of diazophosphonates with amines, amides and carbamates have also been reported (Scheme 13).[19]

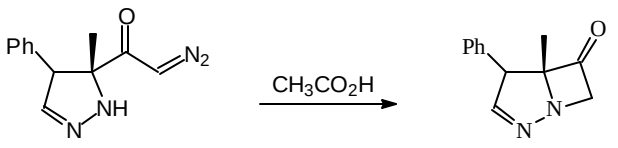
Scheme 13.



By far, the most successful N-H insertions have been the intramolecular reactions leading to small ring heterocycles.

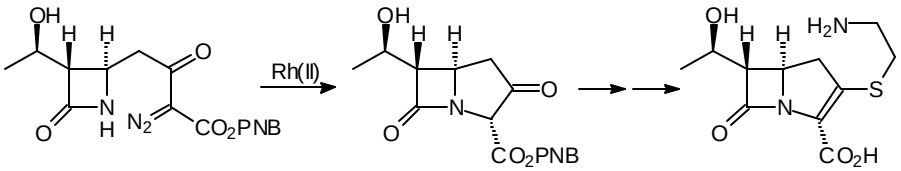
The earliest example of intramolecular diazocarbonyl/NH insertion was reported by Moore[20] in the synthesis of an azacyclobutane derivative as shown in Scheme 14.

Scheme 14.



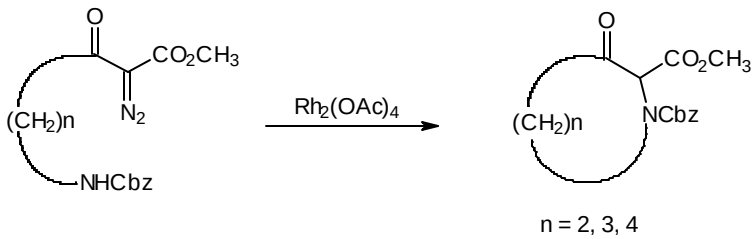
Cama[15] has reported the synthesis of a penicillin analogue via a Rh(II) catalysed intramolecular insertion of an α-keto carbenoid into the N-H bond of the β-lactam. This method is the key step in the Merck synthesis of the antibiotic thienamycin (Scheme 15).[21]

Scheme 15.



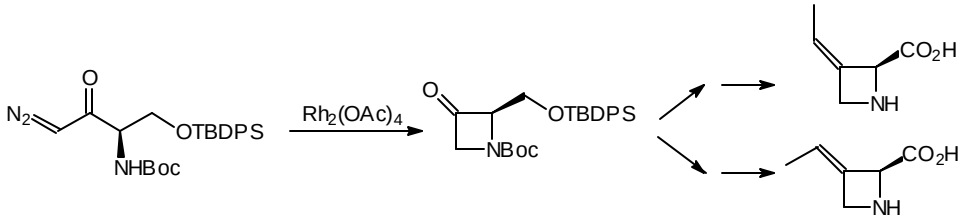
The intramolecular carbenoid/NH insertion reaction has also been demonstrated to be a mild, efficient and regiospecific method for the construction of a variety of nitrogen containing rings (Scheme 16).[11]

Scheme 16.



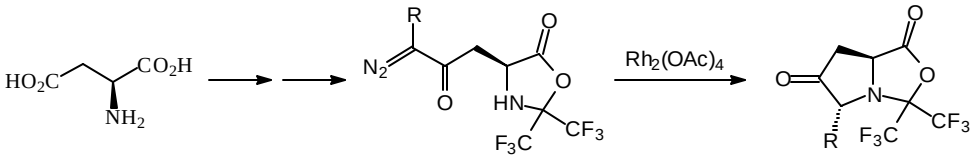
A chiral 3-azetidinone, obtained from a *N*-and *O*-protected *R*-serine-derived diazoketone, has been transformed into optically active *cis*- and *trans*-polyoximic acid (Scheme 17).[22]

Scheme 17.



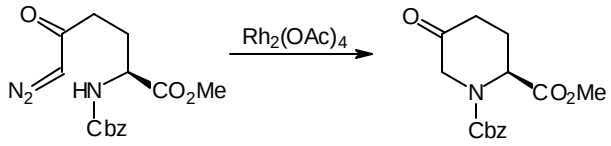
Burger[23] has reported the synthesis of 4-oxo-L-proline derivative from L-aspartic acid using the intramolecular NH insertion as a key step (Scheme 18).

Scheme 18.



Ko[24] has reported a convenient synthesis of a 5-oxo-pipecolic acid derivative by the rhodium(II) acetate catalysed intramolecular N-H insertion reaction of a *S*-glutamic acid derived diazoketone as shown in Scheme 19.

Scheme 19.



2. OBJECTIVE

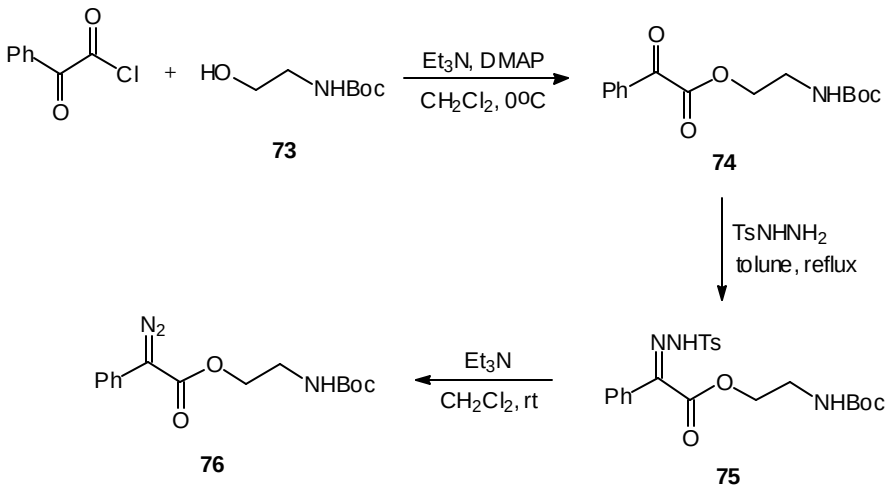
The objective of this undertaking was to synthesize benzoyldiazoformate esters of achiral and chiral amino alcohols and to investigate their asymmetric intramolecular N-H insertion reactions and asymmetric intermolecular O-H insertion reactions as routes to α-amino and α-hydroxy acid derivatives. Although diazocarbonyl insertion reactions into O-H and N-H bonds have been extensively investigated in literature, relatively few reports have examined their asymmetric version that proceeds with the creation of a new stereogenic center.

3. RESULTS AND DISCUSSION

Intramolecular diazocarbonyl / NH insertion reactions

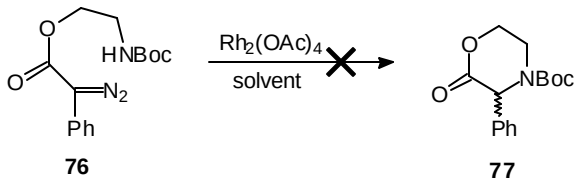
Initial investigations were conducted with *N*-Boc-ethanolamine **73**.[25] Acylation of *N*-Boc-ethanolamine with benzoyl formyl chloride generated the corresponding α-keto ester **74** in 86% yield. Reaction of **74** with tosylhydrazide in refluxing toluene[8] gave hydrazone **75** (69% yield) which was readily converted into diazo ester **76** (89% yield) by treatment with triethylamine in dichloromethane at ambient temperature[8] (Scheme 20).

Scheme 20.



The rhodium(II) acetate catalysed intramolecular N-H insertion reaction of **76** was studied under a variety of conditions (CH_2Cl_2, $CHCl_3$ or benzene at ambient temperature or reflux) but the desired morpholin-2-one derivative **77** could not be obtained (Scheme 21).

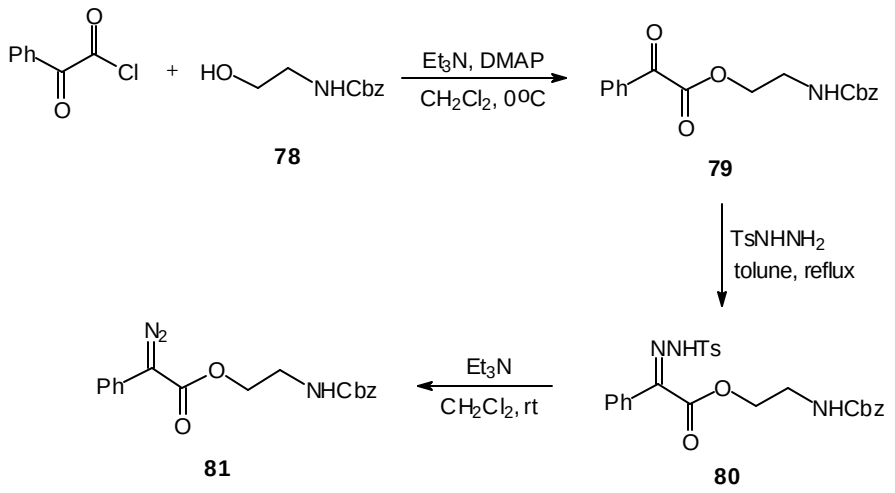
Scheme 21.



It is plausible that steric hindrance in **76**, due the bulky *N*-Boc protecting group, in the vicinity of the reaction site (N-H bond) inhibits the insertion reaction. This led us to investigate the reactivity of the *N*-Cbz analogue.

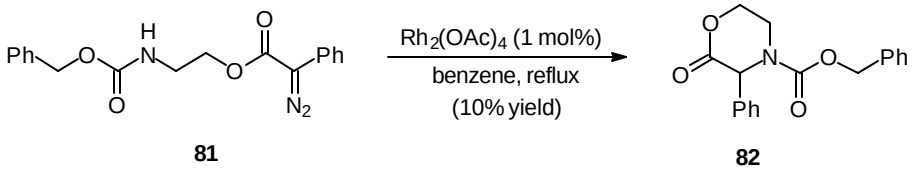
Thus, Cbz-ethanolamine **78**[26] was converted into the corresponding diazoester **81** (51% overall yield) by following the same reaction sequence as employed for the preparation of **76** (Scheme 22).

Scheme 22.



The rhodium(II) acetate catalysed intramolecular diazocarbonyl insertion reaction of **81** into the carbamate N-H bond was studied under a variety of conditions. When a benzene solution of **81** was heated in the presence of $Rh_2(OAc)_4$ (1 mol%), 3-phenyl-4-benzyloxycarbonyl morpholin-2-one **82**, the product of intramolecular N-H insertion, was obtained in only 10% yield (Scheme 23).

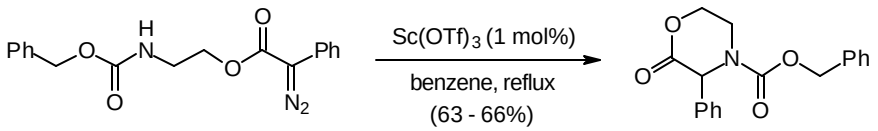
Scheme 23.



The conversion of **81** to **82** could not be achieved in CH_2Cl_2, $CHCl_3$ or benzene at ambient temperature and in refluxing CH_2Cl_2 or $CHCl_3$.

Our search for an alternative, more effective catalyst for the insertion reaction led us to investigate the use of $Sc(OTf)_3$. Remarkably, when $Sc(OTf)_3$ (1 mol%) was employed under the reactions conditions employed for $Rh_2(OAc)_4$, **82** was obtained in 63-66% yield. The observation that no **82** is formed in the absence of any catalyst confirms the catalytic effect of $Sc(OTf)_3$ in the N-H insertion reaction (Scheme 24).

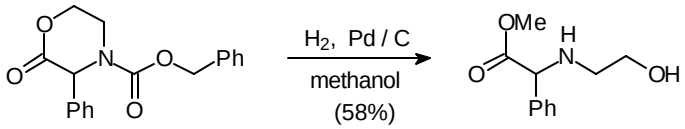
Scheme 24.



81 **82**

Hydrogenolysis of **82** (Pd/C, H_2, 1atm. MeOH) proceeds with concomitant methanolysis to generate the phenylglycine derivative **83** in 58% yield (Scheme 25).

Scheme 25.



82 **83**

The overall conversion of **81** to **83** constitutes a new approach to α-amino acids, based on intramolecular N-H insertion that proceeds with the creation of a stereogenic center.

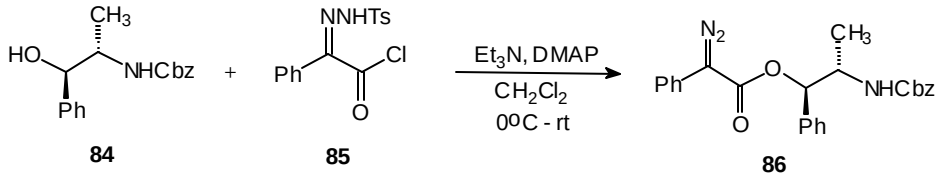
Under identical reaction conditions, the Boc-protected diazoester **76** could not furnish any intramolecular N-H insertion product.

The success in the intramolecular N-H insertion reaction of the Cbz-ethanolamine derived diazoester **81** encouraged us to examine the asymmmetric version of the transformation. Benzoyldiazoformate esters prepared from chiral amino alcohols were therefore examined as substrates.

The reaction of *(1R,2S)*-Cbz-norephedrine **84**[27] (prepared from 1*R*,2*S*-norephedrine and carbobenzyloxy chloride in the presence of Et_3N and DMAP in CH_2Cl_2) with 2-oxophenylacetyl chloride tosylhydrazone **85**[28] in the presence of excess

triethylamine directly provides the corresponding diazoester **86** in 58% yield (Scheme 26).

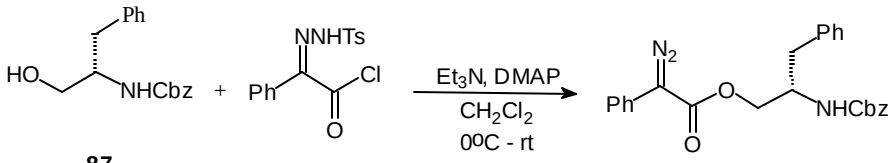
Scheme 26.



84 **85** **86**

(S)-Cbz-phenylalaninol **87**[29] was similarly converted to the diazoester **88** in 52% yield (Scheme 27).

Scheme 27.

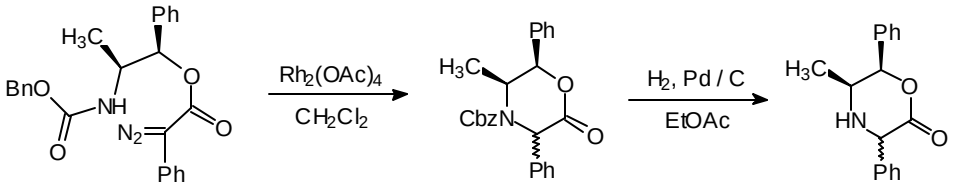


87 **85** **88**

The chiral diazoesters **86** and **88** were examined for the intramolecular N-H insertion in refluxing benzene using $Sc(OTf)_3$ as the insertion catalyst. Contrary to expectations, reaction of **86** and **88** with catalytic scandium triflate in refluxing benzene could not provide the desired intramolecular N-H insertion product. However, the rhodium(II) acetate catalyzed insertion reaction of **86** in CH_2Cl_2 at ambient temperature generated the desired morpholinone **89** in 46% yield with the creation of a new stereogenic center (Scheme 28). The diastereoselectivity of the insertion step was determined as 2.5/1 by conversion of **89** to the corresponding morpholinone **90** (H_2, Pd/C, EtOAc). The diastereomer ratio in **90** was readily determined by ^1H NMR spectroscopy and is based on the integration of the characteristic benzylic methine

resonance (doublet in the 5-6 ppm region) due to the ephedrine portion of the molecule.

Scheme 28.



86 **89** **90**

***ds* = 2.5 / 1**

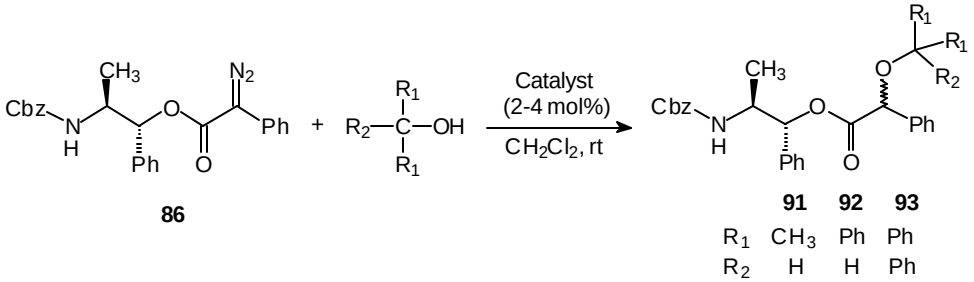
The rhodium(II) acetate catalysed reaction of diazoester **88** was capricious and did not give reproducible results for the intramolecular diazocarbonyl/N-H insertion reaction.

Intermolecular diazocarbonyl / OH insertion reactions

Asymmetric, intermolecular O-H insertion reactions of the chiral diazoesters **86** and **88** were also investigated by employing achiral alcohols under rhodium(II) acetate and $Sc(OTf)_3$ catalysis. Thus, the reaction of **86** or **88** with isopropyl alcohol and benzhydrol in the presence of catalytic rhodium(II) acetate or $Sc(OTf)_3$ (2-4 mol%) in CH_2Cl_2 at ambient temperature generated the desired intermolecular O-H insertion products in quantitative yields but with low diastereoselectivity (*ds* = 1.5/1 for **86** and 1.2/1 for **88**). It is noteworthy that the intermolecular O-H insertion proceeds effeciently in the presence of a carbamate N-H bond and no N-H insertion product is observed. The scandium triflate catalysed reaction of **86** and **88** with triphenylmethanol in CH_2Cl_2 at ambient temperature could not provide any insertion product (recovery of the starting material) while the rhodium(II) acetate catalysis of the reaction produced a

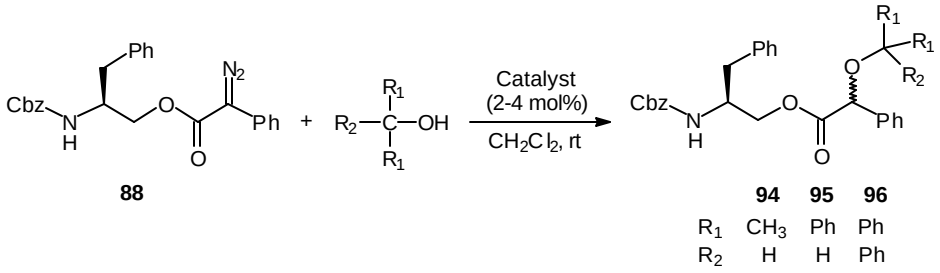
complex mixture under the identical conditions. These results are summerized in table 1 and 2.

Table 1. Intermolecular O-H insertion reactions of **86**



Entry	Alcohol	Catalyst	Product	Yield	ds
1	2-Propanol	$Rh_2(OAc)_4$	**91**	98%	1.5/1
		$Sc(OTf)_3$	**91**	97%	1/1
2	Benzhydrol	$Rh_2(OAc)_4$	**92**	95%	1.5/1
		$Sc(OTf)_3$	**92**	93%	1.5/1
3	Triphenylmethanol	$Rh_2(OAc)_4$	**93**	--	--
		$Sc(OTf)_3$	**93**	--	--

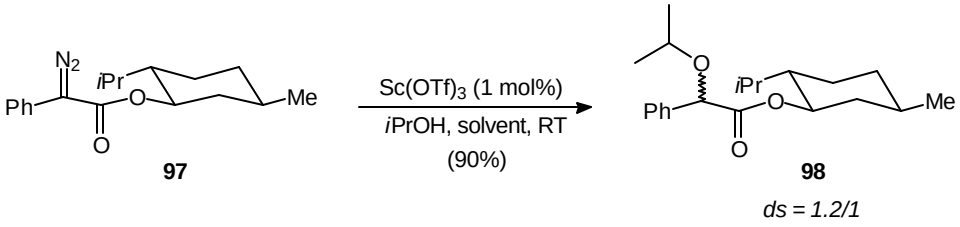
Table 2: Intermolecular O-H insertion reactions of **88**



Entry	Alcohol	**Catalyst**	Product	Yield	ds
1	2-Propanol	$Rh_2(OAc)_4$	**94**	97%	1/1
		$Sc(OTf)_3$	**94**	96%	1/1
2	Benzhydrol	$Rh_2(OAc)_4$	**95**	95%	1.2/1
		$Sc(OTf)_3$	**95**	94%	1.2/1
3	Triphenylmethanol	$Rh_2(OAc)_4$	**96**	--	--
		$Sc(OTf)_3$	**96**	--	--

The intermolecular O-H insertion reaction of the menthol derived diazoester **97**[8] was also examined by using $Sc(OTf)_3$ as the insertion catalyst. Reaction of **97** with isopropyl alcohol in the presence of $Sc(OTf)_3$ (1 mol%) was very facile in a variety of solvents and generated the α-isopropoxy ester **98** in excellent yield (90%) but with low diastereoselectivity at ambient temperature (*ds* 1.2/1, Scheme 29).

Scheme 29.



97 **98**

ds = 1.2/1

4. CONCLUSION

$Sc(OTf)_3$ has been demonstrated to be a useful catalyst for diazoester derived carbenoid/heteroatom-hydrogen bond insertion reactions. α-Diazoesters of chiral amino alcohols have been synthesized and their utility towards the asymmetric synthesis of α-hydroxy and α-amino acid derivatives has been examined. Although these reactions are quite efficient, they are not very diastereoselective.

5. EXPERIMENTAL

General experimental techniques which have been described in the experimental section of Chapter 1 were followed.

2-(Carbobenzyloxyamino)-1-ethanol (78):[26]

A 250 mL round bottomed flask equipped with a stirring bar was charged with 2-aminoethanol (3.6 mL, 60 mmol), sodium bicarbonate (5.55 g, 66 mmol), and dioxane:water (1:1, 100 mL). The resulting solution was cooled to 0 ^{o}C. Benzyl chloroformate (9.4 mL, 66 mmol) in dioxane:water (1:1, 20 mL)was added over 20 min. The mixture was allowed to warm to ambient temperature over 1 h and was stirred for additional 4 h. It was then transferred to a separatory funnel and partitioning between EtOAc (100 mL) and water (100 mL) were added. The organic phase was separated and washed with 1N HCl (3 x 50 mL), 5% $NaHCO_3$ (3 x 50 mL), brine (1 x 100 mL) and dried (Na_2SO_4) and concentrated under reduced pressure to give a yellow solid. Recrystallization from CH_2Cl_2-pentane afforded **78** as white needles.

mp: 62 ^{o}C (Lit.[26] mp: 62-63 ^{o}C)

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.35 (s, 5H, Ar*H*), 5.35 (b, 1H, N*H*), 5.1 (s, 2H, PhCH_2), 3.7 (t, 2H, *J* = 5.5, OCH_2), 3.35 (q, 2H, *J* = 5.5, NCH_2), 2.70 (b, 1H, O*H*).

(2-Carbobenzyloxyamino-ethyl)-oxophenylacetate (79):

A solution of benzoylformylchloride (prepared from benzoylformic acid (0.574 g, 3.82 mmol) and oxalyl chloride (1.5 mL, 17.2 mmol), reflux, 2 h) in anhydrous CH_2Cl_2 (10 mL) was added to a solution of **78** (0.56 g, 2.9 mmol), triethylamine (1.3

mL, 9.5 mmol), and DMAP (36 mg, 0.3 mmol) in CH_2Cl_2 (20 mL) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 2 h after which it was diluted with CH_2Cl_2, washed with 5% HCl, saturated aqueous sodium bicarbonate, brine, dried (Na_2SO_4), and concentrated to furnish 1.05 g of the crude product which on purification by flash chromatography on silica gel (7/3 petroleum ether/ethyl acetate) furnished 839 mg (89%) of **79** as a pale yellow gum.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 8.0 (d, 2H, J = 7.0, Ar*H*), 7.65 (t, 1H, J = 7.0, Ar*H*), 7.50 (t, 2H, J = 7.0, Ar*H*), 7.35 (s, 5H, Ar*H*), 5.20 (br, 1H, N*H*), 5.10 (s, 2H, PhCH_2), 4.45 (t, 2H, J = 5.4, OCH_2CH_2), 3.60 (q, 2H, J = 5.4, NCH_2).

^{13}C NMR (50 MHz, $CDCl_3$):

δ 185.6 (Ph*C*=O), 163.3 (*C*O_2CH_2), 156.3 (N*C*O_2), 136.3 (Ar*C*), 134.7 (Ar*C*), 132.2 (Ar*C*), 129.8 (Ar*C*), 128.7 (Ar*C*), 128.3 (Ar*C*), 127.8 (Ar*C*), 66.7 (O*C*H_2), 64.7 (O*C*H_2), 39.8 (N*C*H_2).

IR (neat):

3400, 3342, 3065, 3034, 2957, 1732, 1715, 1693, 1597, 1580, 1537, 1520, 1452, 1393, 1367, 1321, 1258, 1198, 1177, 1159, 1124, 1099, 1080, 1028, 1018, 1003, 986, 910 cm^{-1}.

MS (70 eV):

m/z 77 (40), 91 (33), 105 (100), 117 (4), 122 (53), 131 (2), 151 (1), 221 (1).

(2-Carbobenzyloxyamino-ethyl)-((4-methylphenylsulfonyl)hydrazono)-phenylacetate (80):

A mixture of **79** (0.8 g, 2.44 mmol) and tosylhydrazide (0.445 g, 2.44

mmol) in anhydrous toluene was heated under reflux with azeotropic removal of water for 18 h after which time the solvent was removed under reduced pressure to obtain 1.3 g of a pale yellow solid. Purification by flash chromatography on silica gel (7/3 petroleum ether/ethyl acetate) furnished 0.749 g (61%) of **80** as a pale yellow solid.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.90 (d, 2H, *J* = 7.0, Ar*H*), 7.60-7.20 (m, 12H, Ar*H*), 5.10 (s, 2H, PhCH_2), 5.00 (b, 1H, N*H*), 4.40 (t, 2H, *J* = 5.5, OCH_2CH$_2$), 3.50 (q, 2H, *J* = 5.5, NCH_2), 2.40 (s, 3H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$):

δ 161.7 (*C*O$_2$), 156.4 (N*C*O$_2$), 144.3 (*C*=N), 138.4 ((Ar*Cipso*), 136.1 (Ar*Cipso*), 135.2 (Ar*Cipso*), 133.6 (Ar*Cipso*), 129.5 (Ar*C*H), 129.3 (Ar*C*H), 128.3 (Ar*C*H), 128.1 (Ar*C*H), 127.9 (Ar*C*H), 127.8 (Ar*C*H), 66.7 (O*C*H$_2$), 64.9 (O*C*H$_2$), 39.5 (N*C*H$_2$), 21.4 (*C*H$_3$).

IR ($CHCl_3$):

2980, 2360, 1685, 1480, 1350, 1190, 1150, 1045 cm^{-1}.

Analysis for $C_{25}H_{25}N_3O_6S$:

Calcd: C, 60.59; H, 5.08; N, 8.48

Found: C, 60.80; H, 5.32; N, 8.58

(2-Carbobenzyloxyamino-ethyl)-diazophenylacetate (81):

Triethylamine (0.2 mL, 1.43 mmol) was added dropwise to a stirred solution of **80** (0.57 g, 1.15 mmol) in anhydrous CH_2Cl_2 (30 mL) at ambient temperature and the mixture was stirred at ambient temperature for 16 h after which the solvent was

removed under reduced pressure to obtain the crude diazoester which on purification by chromatography on silica gel (60-120 mesh, 3/1 petroleum ether/ethyl acetate) furnished 0.369 g (94%) of **81** as yellow solid.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.60-7.20 (m, 10H, Ar*H*), 5.15 (s, 3H, PhCH_2, N*H*), 4.40 (t, 2H, *J* = 5.5, OCH_2CH_2), 3.60 (q, 2H, *J* = 5.5, NCH_2).

^{13}C NMR (50 MHz, $CDCl_3$):

δ 164.6 (*C*O_2), 156.2 (N*C*O_2), 136.2 (Ar*Cipso*), 128.6 (Ar*C*H), 128.1 (Ar*C*H), 127.7 (Ar*C*H), 125.5 (Ar*C*H), 124.9 (Ar*Cipso*), 123.6 (Ar*C*H), 66.4 (O*C*H_2), 63.4 (O*C*H_2), 63.0 (*C*N_2), 40.0 (N*C*H_2).

IR ($CHCl_3$):

2980, 2060, 1690, 1500, 1320, 1230, 1200, 1140, 1030 cm^{-1}.

MS (70eV):

65 (10), 77 (25), 91 (100), 98 (3), 105 (85), 118 (12), 132 (5), 148 (8), 160 (2), 171 (1), 176 (10), 183 (2), 220 (3), 339 (M^+, 1).

Analysis for $C_{18}H_{17}N_3O_4$:

Calcd: C, 63.71; H, 5.05; N, 12.38

Found: C, 63.88; H, 5.15; N, 12.32

3-Phenyl-4-benzyloxycarbonyl morpholin-2-one (82):

To refluxing suspension of $Sc(OTf)_3$ (1.5 mg, 0.003 mmol, 1 mol%) in benzene (0.5 mL) was added dropwise a solution of diazoester **81** (0.1 g, 0.3 mmol) in benzene

(1 mL). The mixture was heated to reflux for 1 h after which it was concentrated. The residue was purified by flash chromatography on silica gel

(3/1 petroleum ether/EtOAc) to give 0.061 g (66%) of **82** as a colourless gum.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.6-7 (m, 10H, Ar*H*), 6.2-5.75 (br, 1H, PhC*H*), 5.4-4.95 (br, 2H, PhCH_2), 4.5-4.1 (br, 2H, OCH_2CH_2), 3.95-3.60 (m, 2H, NCH_2).

^{13}C NMR (50.3 MHz, $CDCl_3$):

δ 166.8 (*C*O_2), 154.8 (N*C*O_2), 135.8, 135.3 (Ar*C*ipso), 129.0, 128.5, 128.3, 127.9, 125.7 (Ar*C*H), 68.0, 64.9 (O*C*H_2), 59.6 (Ph*C*H), 40.7 (N*C*H_2).

IR (neat):

3080, 3040, 2960, 2900, 1770, 1720, 1610, 1600, 1500, 1460, 1430, 1300, 1220, 1130, 1070, 1040, 1010, 980, 920, 860 cm^{-1}.

MS (70 eV):

m/z 65 (21), 77 (19), 91 (100), 105 (33), 118 (15), 132 (10), 148 (5), 176 (13), 220 (25), 311 (M^+, 1).

Methyl (2-(2-hydroxyethyl)-amino)phenylacetate (83):

A mixture of **82** (45 mg, 0.13 mmol) and 5% Pd/C (9 mg, 20% w/w) in MeOH (10 mL) was hydrogenated at 1 atm. H_2 at ambient temperature for 4 h after which the mixture was filtered through celite and concentrated to obtain 27 mg of the crude product. Purification by flash chromatography on silica gel (EtOAc) furnished 24 mg (58%) of **83** as clear colourless gum.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.50-7.15 (m, 5H, Ar*H*), 4.40 (s, 1H, PhC*H*), 3.70 (s, 3H, OCH_3), 3.60 (t, 2H, *J* = 5.0, CH_2O), 2.75 (m, 2H, NCH_2), 2.20 (br, 2H, O*H*, N*H*).

^{13}C NMR (75 MHz, $CDCl_3$):

δ 173.5 (*C*O_2), 138.2 (Ar*Cipso*), 128.8 (Ar*C*H), 128.2 (Ar*C*H), 127.5 (Ar*C*H), 65.3 (Ph*C*H), 61.2 (*C*H2OH), 52.2 (O*C*H3), 49.2 (N*C*H_2).

IR ($CHCl_3$):

3448, 3088, 3067, 3018, 2955, 2907, 2887, 2851, 2800, 1736, 1495, 1468, 1454, 1437, 1406, 1367, 1292, 1215, 1175, 1153, 1067, 1030, 1020, 1005, 995 cm^{-1}.

MS (70 eV):

m/z 59 (11), 65 (25), 77 (61), 91 (73), 105 (48), 118 (100), 132 (61), 150 (43), 162 (71), 179 (1), 192 (1).

***1R,2S*-2-(Carbobenzyloxyamino)-1-phenyl-1-propanol (84):**[27]

Benzyl chloroformate (0.17 mL, 1.2 mmol) was added dropwise to a solution of 1*R*,2*S*-norephedrine (0.151 g, 1 mmol), triethylamine (0.17 mL, 1.2 mmol), and DMAP (6 mg, 0.05 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The reaction mixture was warmed to and stirred at ambient temperature for 18 h after which it was diluted with CH_2Cl_2, washed with 5% HCl, saturated sodium bicarbonate, brine, dried (Na_2SO_4), and concentrated under reduced pressure to afford 292 mg of the crude product which on purification by flash chromatography on silica gel (3/1 petroleum ether/ethyl acetate) furnished 218 mg (76%) of 84 as a white solid.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.55-7.20 (m, 10H, Ar*H*), 5.10 (s, 2H, CH_2), 4.95 (d, 1H, *J* = 7.8, N*H*), 4.85 (br, 1H, PhC*H*), 4.15-3.90 (m, 1H, CH_3C*H*), 2.90 (d, 1H, *J* = 2.4, O*H*), 1.00 (d, 3H, *J* = 7.4, CH_3).

2-((4-Methylphenylsulfonyl)-hydrazono)-phenylacetylchloride (85):[28]

To a solution of benzoylformic acid (3.2 g, 21 mmol) in anhydrous methanol (4 mL) was added in one portion, a hot solution of *p*-toluenesulfonhydrazide (4 g, 21 mmol) in methanol (15 mL) containing 1 drop of conc. HCl. The reaction mixture was then warmed for 5 min and stored at −20 °C for 12 h at which point 5 mL of water was added and flask stored for an additional 12 h. The reaction mixture was concentrated under reduced pressure to furnish 6.7 g of the crude 2-oxophenylacetic acid tosylhydrazone as a white solid. This was taken up in anhydrous benzene (25 mL) and heated to reflux with thionyl chloride (4 mL, 54.8 mmol) for 2.5 h after which it was concentrated under reduced pressure to obtain crude 85 as a yellow solid which upon recrystallization from anhydrous benzene/anhydrous petroleum ether furnished 4.9 g (69%) of pure 85 as a yellow solid.

mp: 136 °C.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 8.60 (s, 1H, N*H*), 7.90 (d, 2H, J = 8.0, Ar*H*), 7.60-7.10 (m, 7H, Ar*H*), 2.45 (s, 3H, CH_3).

IR (nujol):

3190, 1740, 1590, 1560, 1440, 1380, 1350, 1270, 1190, 1160, 1070, 1020, 870, 820 cm^{-1}.

1*R*,2*S*-((1-Phenyl-2-carbobenzyloxyamino)propyl)-diazophenylacetate (86):

Triethylamine (0.26 mL, 1.86 mmol) was added dropwise to a solution of **84** (0.183 g, 0.64 mmol) and 2-oxophenylacetyl chloride tosylhydrazone **85** (0.217 g, 0.64 mmol) in anhydrous CH_2Cl_2 (2 mL) at 0 °C after which the mixture was slowly warmed to and stirred at ambient temperature for 18 h. Solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (9/1 petroleum ether/EtOAc) to furnish 0.161 g (58%) of **86** as a yellow solid.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.55-7.10 (m, 15H, Ar*H*), 6.05 (d, 1H, *J* = 3.4, PhC*H*), 5.10 (s, 2H, CH_2), 4.80 (d, 1H, *J* = 9.3, N*H*), 4.25 (m, 1H, C*H*CH_3), 1.10 (d, 3H, *J* = 6.8, CHCH_3).

^{13}C NMR (50 MHz, $CDCl_3$):

δ 163.9, 159.5 (*C*O_2), 155.5 (N*C*O_2), 136.6, 136.3, 128.8, 128.4, 128.0, 127.9, 126.3, 125.8, 125.0, 123.8 (Ar*C*), 66.6, 63.5 (O*C*H, O*C*H_2), 50.5 (N*C*H), 15.3 (*C*H_3), (*C*=N_2 not observed).

IR ($CHCl_3$):

3450, 3018, 2089, 1713, 1508, 1499, 1244, 1217, 1153 cm^{-1}.

Analysis for $C_{25}H_{23}N_3O_4$:

Calcd: C, 69.92; H, 5.40; N, 9.78

Found: C, 70.16; H, 5.70; N, 9.66

***S*-2-(Carbobenzyloxyamino)-3-phenyl-1-propanol (87):**[29]

Benzyl chloroformate (1.71 mL, 12 mmol) was added dropwise to a solution of *S*-phenylalaninol (1.51 g, 10 mmol), triethylamine (1.67 mL, 12 mmol), and DMAP (61 mg, 0.5 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The reaction mixture was warmed to and stirred at ambient temperature for 18 h after which it was diluted with CH_2Cl_2, washed with 5% HCl, saturated aqueous sodium bicarbonate, brine, dried (Na_2SO_4), and concentrated under reduced pressure to afford 2.81 g of the crude product which on purification by flash chromatography on silica gel (3/2 petroleum ether/ethyl acetate) furnished 2.21 g (77%) of 87 as a white solid.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.50-7.10 (m, 10H, Ar*H*), 5.15 (br, 1H, N*H*), 5.05 (s, 2H, PhCH_2O), 4.00-3.80 (m, 1H, NC*H*), 3.70-3.40 (m, 2H, CH_2OH), 2.85 (d, 2H, *J* = 6.8, PhCH_2CH), 2.65 (br, 1H, O*H*).

(*S*-((2-(Carbobenzyloxyamino)-3-phenyl)propyl)-diazophenylacetate (88):

Triethylamine (2.11 mL, 15.15 mmol) was added dropwise to a solution of **87** (1.44 g, 5.05 mmol) and 2-oxophenylacetyl chloride tosylhydrazone **85** (1.7 g, 5.05 mmol) in anhydrous CH_2Cl_2 (20 mL) at 0 °C after which the mixture was slowly warmed to and stirred at ambient temperature for 18 h. Solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (9/1 petroleum ether/EtOAc) to furnish 1.124 g (52%) of **88** as a yellow solid.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.50-7.10 (m, 15H, Ar*H*), 5.05 (s, 2H, OCH_2Ph), 4.90 (d, 1H, *J* = 5.8, N*H*), 4.40-4.10 (m, 3H, OCH_2C*H*), 3.0-2.75 (m, 2H, PhCH_2CH).

^{13}C NMR (125 MHz, $CDCl_3$):

δ 164.8 (*C*O_2), 155.7 (N*C*O_2), 136.7, 136.3, 129.1, 128.9, 128.6, 128.4, 128.1, 128.0, 126.8, 126.0, 125.1, 124.0 (Ar*C*), 66.7, 65.2 (O*C*H_2), 51.4 (N*C*H), 37.7 (Ph*C*H_2CH), (*C*=N_2 not observed).

IR ($CHCl_3$):

3018, 2091, 1717, 1705, 1506, 1499, 1244, 1215, 1155 cm^{-1}.

MS (70 eV):

m/z 65 (14), 77 (9), 91 (100), 105 (9), 117 (5), 130 (2), 150 (1), 266 (9), 311 (1).

Analysis for $C_{25}H_{23}N_3O_4$

Calcd: C, 69.92; H, 5.40; N, 9.78

Found: C, 70.03; H, 5.53; N, 9.76

5*S*,6*R*-3,6-Diphenyl-4-benzyloxycarbonyl-5-methylmorpholin-2-one (89):

A solution of **86** (0.17 g, 0.39 mmol) in anhydrous CH_2Cl_2 (0.8 mL) was added dropwise to a stirred suspension of $Rh_2(OAc)_4$ (2 mg, 0.004 mmol) in CH_2Cl_2 (0.5 mL) at ambient temperature over a period of 2 h. The mixture was stirred at ambient temperature for another 2 h after which it was concentrated and purified by flash chromatography on silica gel (8/2 petroleum ether/EtOAc) to furnish 74 mg (46%) of **89** as white foam.

^{1}H NMR (200 MHz, $CDCl_3$) **(mixture of diastereomers):**

δ 7.55-6.70 (m, 15H, Ar*H*), 5.80-5.60 (m, 2H, PhC*H*-N, C*H*-O), 5.25-4.75 (m, 3H, CH_2, C*H*CH_3), 1.10 (d, 3H, *J* = 6.9, CH_3).

^{13}C NMR ($CDCl_3$) **(mixture of diastereomers):**

δ 167.0, 162.8 (*C*O_2), 155.5, 154.5 (N*C*O_2), 137.6, 136.0, 135.5, 135.3, 134.8, 132.3, 129.9, 128.8, 128.6, 128.5, 128.3, 128.2, 128.0, 127.9, 127.7, 127.4, 126.3, 125.3 (Ar*C*), 82.1, 79.0 (O*C*H), 67.9, 66.7 (*C*H_2), 58.6 (Ph*C*H-N), 50.9 (*C*HCH_3), 14.8, 12.4 (*C*H_3).

5*S*,6*R*-3,6-Diphenyl-5-methylmorpholin-2-one (90):

A mixture of crude **89** (prepared from **86** (0.6 g, 1.39 mmol) and $Rh_2(OAc)_4$ (6 mg, 0.013 mmol)) and 10% Pd/C (0.12 g) in EtOAc (30 mL) was hydrogenated at 1 atm. H_2 at ambient temperature for 18 h after which the mixture was filtered through celite. The filtrate was concentrated to obtain 0.382 g of the crude product as a pale yellow gum (*ds* = 2.5/1 by ^{1}H NMR). Purification by flash chromatography on silica gel (7/3 petroleum ether/ethyl acetate) furnished 168 mg of **90** as clear, colourless gum (45% from **86** over two steps).

^{1}H NMR (200 MHz, $CDCl_3$):

Major diastereomer: δ 7.70-7.20 (m, 10H, Ar*H*), 5.50 (d, 1H, *J* = 3.4, OC*H*), 4.95 (s, 1H, PhC*H*N), 3.95-3.70 (m, 1H, C*H*CH_3), 1.00 (d, 3H, *J* = 6.8, CH_3).

Minor diastereomer: δ 7.70-7.20 (m, 10H, Ar*H*), 5.65 (d, 1H, *J* = 3.5, OC*H*), 5.00 (s, 1H, PhC*H*N), 3.95-3.70 (m, 1H, C*H*CH_3), 1.00 (d, 3H, *J* = 6.8, CH_3).

IR (neat):

3323, 3063, 3032, 2974, 2932, 1747, 1732, 1589, 1497, 1454, 1435, 1371, 1331, 1254, 1202, 1165, 1140, 1028, 1003 cm^{-1}.

MS (70 eV):

65 (30), 77 (35), 84 (17), 91 (100), 105 (25), 118 (16), 136 (25), 223 (1), 267 (M^+, 1).

General procedure for the intermolecular O-H insertion reactions of diazoesters 86 and 88 with alcohols:

To a stirred solution of the diazo ester and alcohol in anhydrous CH_2Cl_2 was added ($Rh_2(OAc)_4$ or $Sc(OTf)_3$ (2-4 mol% with respect to the diazo ester) and the mixture was stirred at ambient temperature for 2-4 h after which it was concentrated under reduced pressure to furnish the crude product. Removal of the catalyst by filtration through a pad of silica gel (EtOAc) furnished the pure product in quantitative yield.

(1*R*,2*S*-(1-Phenyl-2-carbobenzyloxyamino)propyl)-2-(2-propoxy)- phenylacetate (91):

Rhodium acetate catalysed O-H insertion of 86 with 2-propanol:

A mixture of **86** (0.11 g, 0.25 mmol) and 2-propanol (1 mL) was treated with $Rh_2(OAc)_4$ (2 mg, 0.004 mmol) for 2 h to furnish 0.116 g (98%) of **91** as a gum (*ds* 1.5/1 by ^1H NMR of crude product).

^1H NMR (200 MHz, $CDCl_3$):

Major diastereomer: δ 7.70-6.85 (m, 15H, Ar*H*), 5.95 (d, 1H, J = 3.0, PhC*H*CH), 5.20-4.95 (m, 3H, PhCH_2, COC*H*Ph), 4.20 (d, 1H, *J* = 8.7, N*H*), 4.05-3.90 (m, 1H, NC*H*), 3.80-3.60 (m, 1H, C*H*$(CH_3)_2$), 1.20 (d, 6H, *J* = 5.9, CH(CH_3)$_2$), 0.80 (d, 3H, *J* = 7.3, CH_3CH).

Minor diastereomer: δ 7.70-6.85 (m, 15H, Ar*H*), 5.85 (d, 1H, *J* = 3.0, PhC*H*-OCO), 5.20-4.95 (m, 3H, PhCH_2, COC*H*Ph), 4.55 (d, 1H, *J* =8.7 , N*H*), 4.15-4.05 (m, 1H, NC*H*), 3.80-3.60 (m, 1H, C*H*$(CH_3)_2$), 1.25 (d, 6H, *J* = 5.9, CH(*C*H$_3$)$_2$), 0.95 (d, 3H, *J* = 7.3, CH_3CH).

^{13}C NMR (50 MHz, $CDCl_3$) **(mixture of diastereomers):**

δ 170.1 (*C*O$_2$), 155.4, 155.2 (N*C*O$_2$), 137.5, 137.2, 137.0, 136.4, 128.4, 128.2, 128.0, 127.7, 127.3, 127.0, 126.4, 126.2, 125.9 (Ar*C*), 78.5, 77.6, 70.9 (O*C*H), 66.4 (O*C*H$_2$), 50.9, 50.7 (N*C*H), 22.0, 21.8 (CH(*C*H$_3$)$_2$), 15.0, 14.4 (CH*C*H$_3$).

IR ($CHCl_3$):

3413, 3345, 3089, 3065, 3031, 2974, 2933, 1753, 1722, 1714, 1604, 1586, 1510, 1453, 1402, 1381, 1334, 1227, 1170, 1110, 1060, 1029, 989, 925, 830 cm^{-1}.

Scandium triflate catalysed O-H insertion of 86 with 2-propanol:

A mixture of **86** (0.125 g, 0.29 mmol) and 2-propanol (40 μL, 0.52 mmol) in CH_2Cl_2 (1 mL) was treated with Sc(OTf)$_3$ (7 mg, 0.014 mmol) for 4 h to furnish 0.131 g (97%) of **91** as a gum (*ds* 1/1 by ^{1}H NMR of the crude product).

(1*R*,2*S*-(1-Phenyl-2-carbobenzyloxyamino)propyl)-2-(diphenylmethoxy)-phenylacetate (92):

Rhodium acetate catalysed O-H insertion of 86 with 1,1-diphenylmethanol:

A mixture of **86** (0.1 g, 0.23 mmol) and benzhydrol (44 mg, 0.23 mmol) in CH_2Cl_2 (1 mL) was treated with $Rh_2(OAc)_4$ (2 mg, 0.004 mmol) for 2 h to furnish 0.13 g (95%) of **92** as a gum (*ds* 1.5/1 by ^{1}H NMR of the crude product).

^{1}H NMR (200 MHz, CDCl3):

Major diastereomer:

δ 7.50-6.85 (m, 25H, Ar*H*), 6.00 (d, 1H, *J* = 3.0, PhC*H*O), 5.50 (s, 1H, COC*H*Ph), 5.05 (s, 1H, Ph_2CH), 5.00 (s, 2H, PhCH_2), 4.15 (d, 1H, *J* = 8, N*H*), 4.10-3.90 (m, 1H, CH_3CH), 0.75 (d, 3H, *J* = 6.9, CH_3).

Minor diastereomer:

δ 7.50-6.85 (m, 25H, Ar*H*), 5.85 (d, 1H, *J* = 3.0, PhC*H*-OCO), 5.55 (s, 1H, COC*H*Ph), 5.05 (s, 1H, Ph_2CH), 5.00 (s, 2H, PhCH_2),4.50 (d, 1H, *J* = 8, N*H*), 4.10-3.90 (m, 1H, CH_3CH), 0.90 (d, 3H, *J* = 6.8, CH_3).

^{13}C NMR ($CDCl_3$) **(mixture of diastereomers)**

δ 169.7, 169.6 (*C*O_2), 155.4, 155.2 (N*C*O_2), 144.0, 141.3, 141.2, 141.0, 140.9, 136.9, 136.6, 136.4, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.7, 127.6, 127.3, 127.1, 126.4, 126.0, 125.8, 125.3 (Ar*C*), 81.5, 78.1, 77.8, 77.5, 75.9 (O*C*H), 66.6 (O*C*H_2), 50.9, 50.5 (*C*HCH_3), 14.9, 14.1 (*C*H_3CH).

IR ($CHCl_3$):

3410, 3062, 3029, 1750, 1719, 1708, 1600, 1495, 1452, 1403, 1333, 1229, 1170, 1095, 1067, 1028 cm^{-1}.

Scandium triflate catalysed O-H insertion of 86 with 1,1-diphenylmethanol:

A mixture of **86** (22 mg, 0.05 mmol) and benzhydrol (10 mg, 0.05 mmol) in CH_2Cl_2 (0.3 mL) was treated with $Sc(OTf)_3$ (1 mg, 0.002 mmol) for 4 h to furnish 28 mg (93%) of **92** as a gum (*ds* 1.5/1 by ^1H NMR of crude product).

(*S*-((2-(Carbobenzyloxyamino)-3-phenyl)propyl)-2-(2-propoxy)-phenylacetate (94):

Rhodium acetate catalysed O-H insertion of 88 with 2-propanol:

The mixture of **88** (0.11 g, 0.25 mmol) and 2-propanol (2 mL) was treated with $Rh_2(OAc)_4$ (2 mg, 0.004 mmol) for 2 h to furnish 0.115 g (97%) of **94** as a gum (*ds* 1/1 by ^1H NMR of crude product).

^1H NMR (200 MHz, $CDCl_3$) **(mixture of diastereomers):**

δ 7.70-6.75 (m, 15H, Ar*H*), 5.20-4.95 (m, 3H, OCH_2Ph, PhC*H*), 4.80 and 4.65 (d, 1H, *J* = 8, N*H*), 4.20-3.90 (m, 3H, OCH_2C*H*), 3.80-3.60 (m, 1H, C*H*$(CH_3)_2$), 2.80-2.40 (m, 2H, PhCH_2CH), 1.35-1.10 (m, 6H, CH(CH_3)$_2$).

^{13}C NMR (50 MHz, $CDCl_3$) **(mixture of diastereomers):**

δ 171.0 (*C*O_2), 155.5 (N*C*O_2), 137.3, 136.7, 136.4, 129.0, 128.4, 127.8, 127.3, 126.9, 126.5 (Ar*C*), 78.4, 70.9 (O*C*H), 66.6, 64.8 (O*C*H_2), 51.4 (N*C*H), 37.4 (Ph*C*H_2CH), 21.9 ((*C*H_3)$_2$CH).

IR ($CHCl_3$):

3343, 3063, 3030, 2971, 2929, 1951, 1750, 1728, 1712, 1698, 1588, 1535, 1453, 1382, 1327, 1237, 1171, 1113, 1065, 1028, 926, 832 cm^{-1}.

Scandium triflate catalysed O-H insertion of 88 with 2-propanol:

A mixture of **88** (0.125 g, 0.29 mmol) and 2-propanol (40 μL, 0.52 mmol) in CH_2Cl_2 (1 mL) was trated with $Sc(OTf)_3$ (7 mg, 0.014 mmol) for 4 h to furnish 0.13 g (96%) of **94** as a gum (*ds* 1/1 by ^1H NMR of crude product).

(*S*-((2-(Carbobenzyloxyamino)-3-phenyl)propyl)-2-(diphenylmethoxy)-phenylacetate (95):

Rhodium acetate catalysed O-H insertion of 88 with 1,1diphenylmethanol:

A mixture of **88** (0.125 g, 0.29 mmol) and benzhydrol (55 mg, 0.29 mmol) in CH_2Cl_2 was treated with $Rh_2(OAc)_4$ (2.6 mg, 0.005 mmol) for 2 h to furnish 0.162 g (95%) of **95** as a gum (*ds* 1.2/1 by ^1H NMR of crude product).

^{1}H NMR (200 MHz, $CDCl_3$):

Major diastereomer:

δ 7.50-6.75 (m, 25H, ArH), 5.50 (s, 1H, PhC*H*O), 5.02 (s, 2H, OCH_2Ph), 4.96 (s, 1H, Ph_2CH), 4.55 (d, 1H, *J* = 7.3, N*H*), 4.20-3.85 (m, 3H, OCH_2C*H*), 2.80-2.40 (m, 2H, PhCH_2CH).

Minor diastereomer:

δ 7.50-6.75 (m, 25H, ArH), 5.51 (s, 1H, PhC*H*O), 5.03 (s, 2H, OCH_2Ph), 4.95 (s, 1H, Ph_2CH), 4.75 (d, 1H, *J* = 7.3, N*H*), 4.20-3.85 (m, 3H, OCH_2C*H*), 2.80-2.40 (m, 2H, PhCH_2CH).

^{13}C NMR (50 MHz, $CDCl_3$) **(mixture of diastereomers):**

δ 170.6, 170.5 (CO_2), 155.5 (NCO_2), 141.2, 141.0, 136.7, 136.5, 136.3, 129.1, 129.0, 128.7, 128.4, 128.0, 127.8, 127.4, 127.2, 126.6, 126.5 (Ar*C*), 81.7, 81.6, 78.2, 78.0 (O*C*H), 66.7, 64.9 (OCH_2), 51.3 (N*C*H), 37.5 ($PhCH_2CH$).

Scandium triflate catalysed O-H insertion of 88 with 1,1-diphenylmethanol:

The mixture of **88** (0.15 g, 0.34 mmol) and benzhydrol (63 mg, 0.34 mmol) in CH_2Cl_2 (2 mL) was treated with $Sc(OTf)_3$ (7 mg, 0.014 mmol) for 4 h to furnish 0.193 g (94%) of **95** as a gum (*ds* 1.2/1 by ^{1}H NMR of crude product).

(1*R*,2*S*,5*R*-(2-(2-propyl)-5-methyl-cyclohexyl)-diazophenylacetate (97):[8]

A solution of menthol (0.156 g, 1 mmol) in toluene (2 mL) was added dropwise to a stirred suspension of NaH (28% dispersion in mineral oil, 0.343 g, 4 mmol) in toluene (2 mL) at 0 ^{o}C and the mixture was stirred for 30 min. A solution of 2-oxophenylacetyl chloride tosylhydrazone **85** (0.336 g, 1 mmol) in toluene (4 mL) was then added dropwise and the mixture was warmed to and stirred at ambient temperature for 12 h. Water was added and the mixture was extracted with EtOAc. The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure to furnish the crude product which on purification by flash chromatography on silica gel (99/1 petroleum ether/ethyl acetate) furnished 0.128 g (42%) of **97** as an orange gum.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.60-7.10 (m, 5H, Ar*H*), 4.90 (dt, 1H, *J* = 4.4, 10.7, C*H*-O), 2.25-0.75 (m, 9H, 3xCH_2, 3xC*H*), 0.92 (d, 3H, *J* = 7.0, CH_3), 0.91 (d, 3H, *J* = 7.0, CH_3), 0.80 (d, 3H, *J* = 7.0, CH_3).

(1*R*,2*S*,5*R*-(2-(2-propyl)-5-methyl-cyclohexyl)-2-(2-propoxy)-phenylacetate (98):

Scandium triflate catalysed O-H insertion of 97 with 2-propanol:

To a solution of **97** (12 mg, 0.04 mmol) and 2-propanol (10 μL, 0.13 mmol) in CH_2Cl_2 (0.4 mL) was added $Sc(OTf)_3$ (2 mg, 0.004 mmol) and the reaction mixture was stirred at room temperature for 42 h after which it was diluted with CH_2Cl_2. The solution was washed with water, dried (Na_2SO_4) and concentrated to furnish 12 mg (90%) of crude **98** as a clear, colourless gum which was pure by ^{1}H NMR (*ds* = 1.2/1).

^{1}H NMR (200 MHz, $CDCl_3$):

Major diastereomer:

δ 7.50-7.25 (m, 5H, Ar*H*), 4.93 (s, 1H, PhC*H*), 4.80-4.55 (m, 1H, C*H*-OCO), 3.70 (sept, 1H, $(CH_3)_2$C*H*O), 2.10-0.40 (m, 24H, C*H*, CH_2, CH_3).

Visible peaks for the other diastereomer:

δ 4.97 (s, 1H, PhC*H*).

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List of publications:

1. Asymmetric Allylation and Reduction on an Ephedrine Derived Template: Stereoselective Synthesis of α-Hydroxy acids and Derivatives. Pansare, S. V.; Ravi, R. G.; **Jain, R. P.** *J. Org. Chem.* **1998,** *63,* 4120.

2. Stereoselective Synthesis of α-Hydroxycyclopropanecarboxylic Acids. Pansare, S. V.; **Jain, R. P.** *Tetrahedron Lett.* **1999**, *40*, 2625.

3. Scandium Triflate Catalyzed Diazocarbonyl Insertions into Heteroatom-Hydrogen Bonds.
   Pansare, S. V.; **Jain, R. P.**; Bhattacharyya, A. *Tetrahedron Lett.* **1999**, *40*, 5255.

4. Asymmetric Synthesis of α-Alkyl-α-Hydroxy-γ-Butyrolactones. Pansare, S. V.; **Jain, R. P.**; Ravi, R. G. *Tetrahedron: Asymmetry* **1999**, *10*, 3103.

5. Enantioselective Synthesis of (*S*)-(+)-Pantolactone.
   Pansare, S. V.; **Jain, R. P.** *Org. Lett.* **2000**, *2*, 175.

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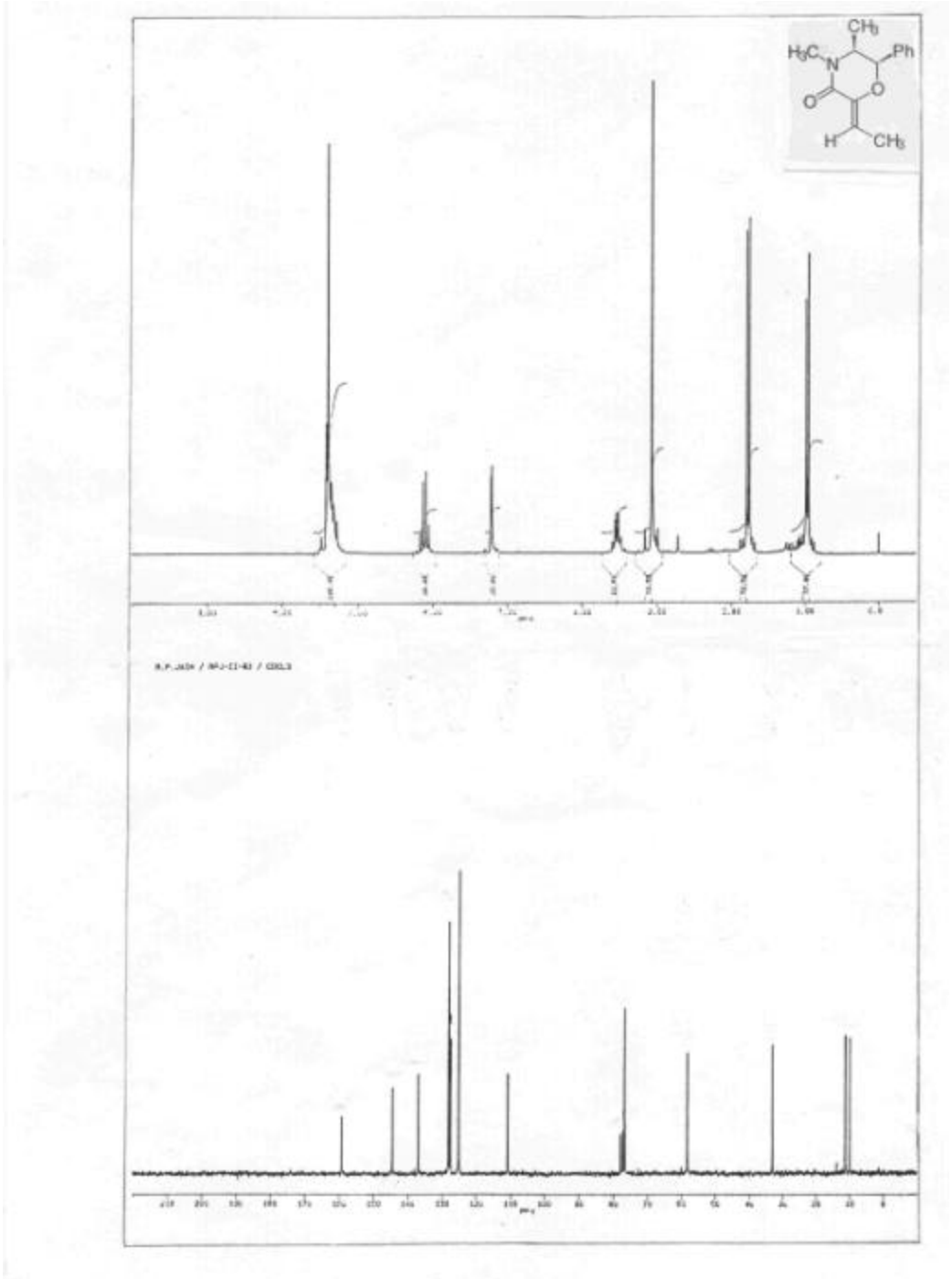

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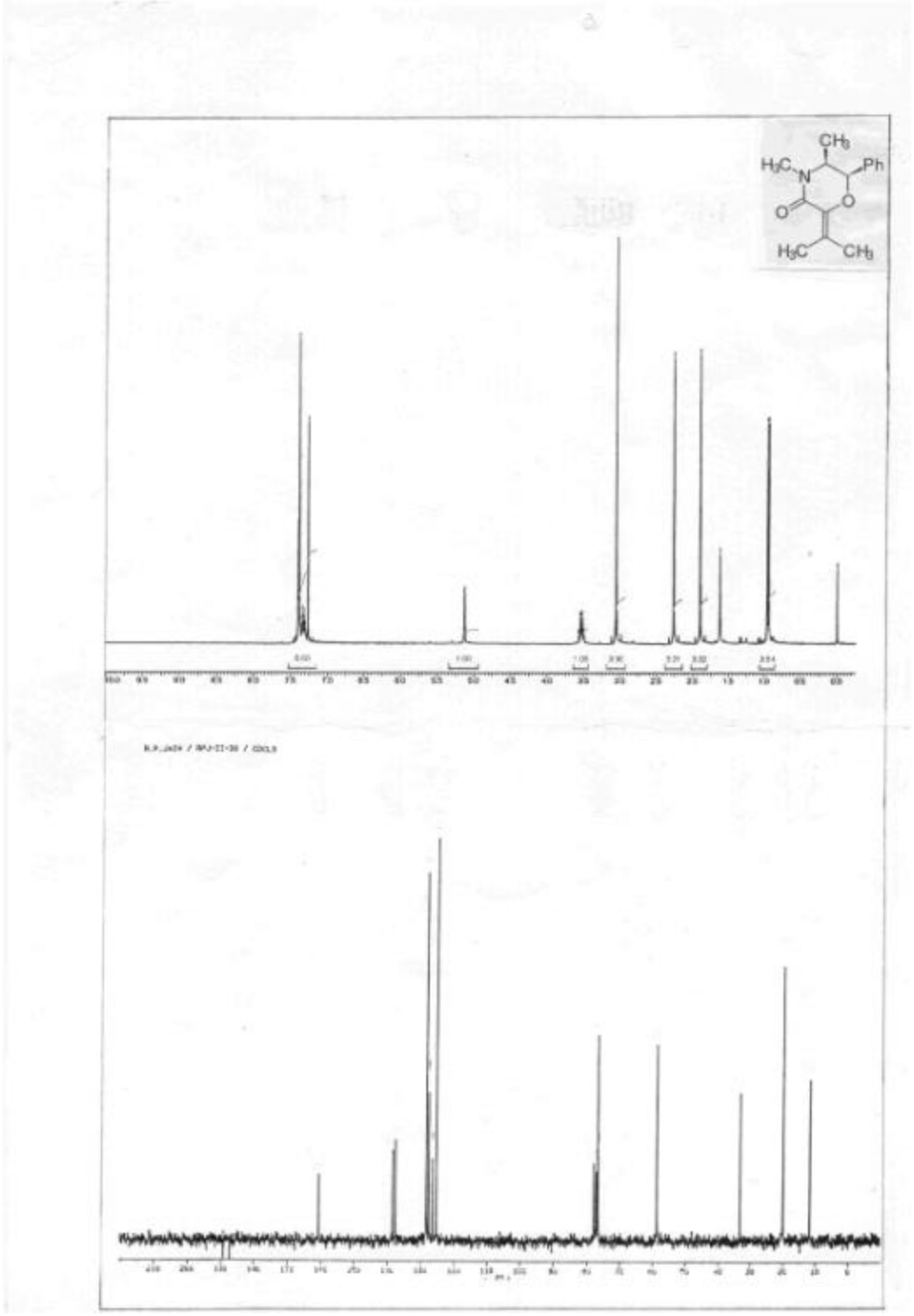

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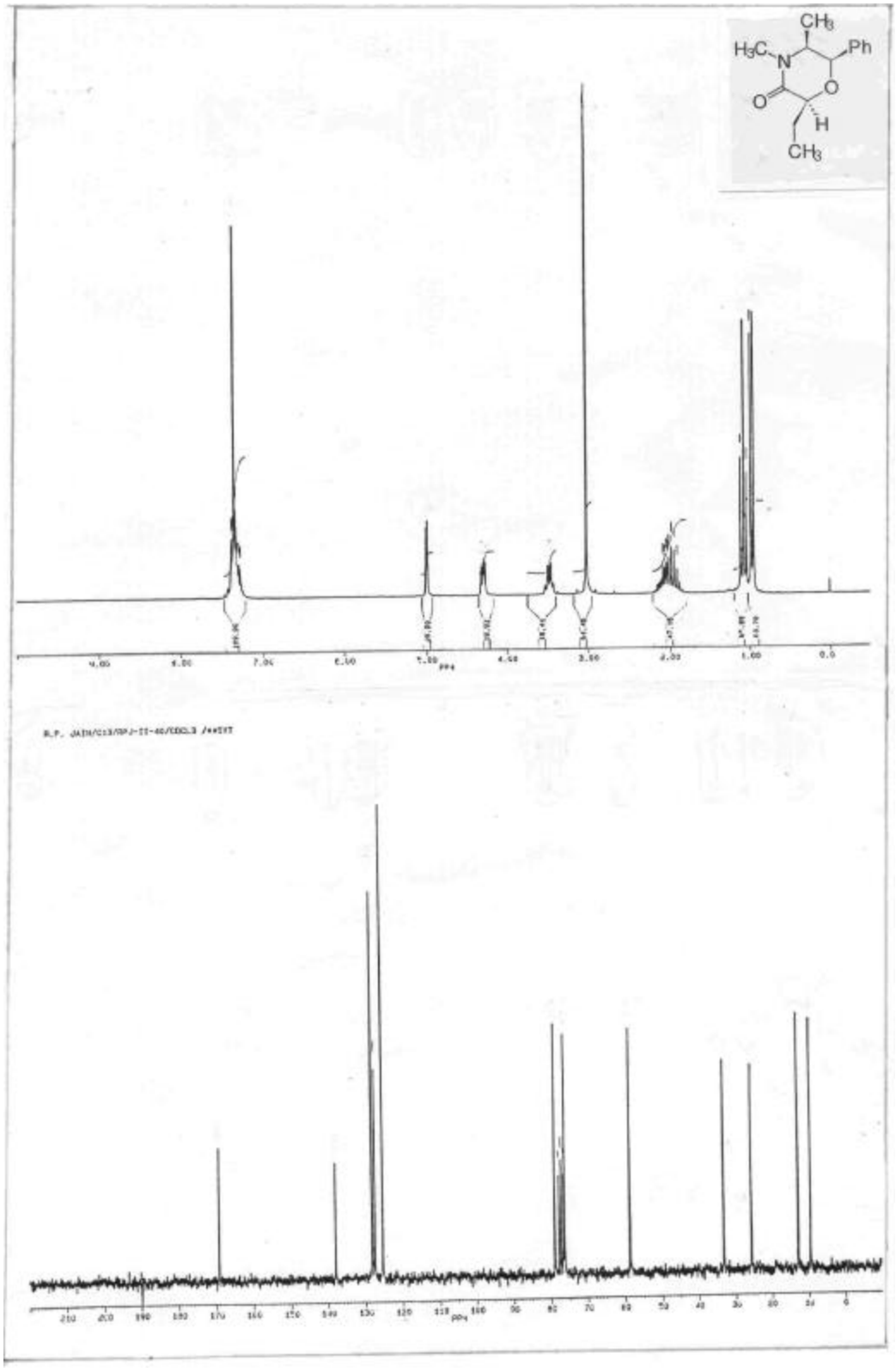

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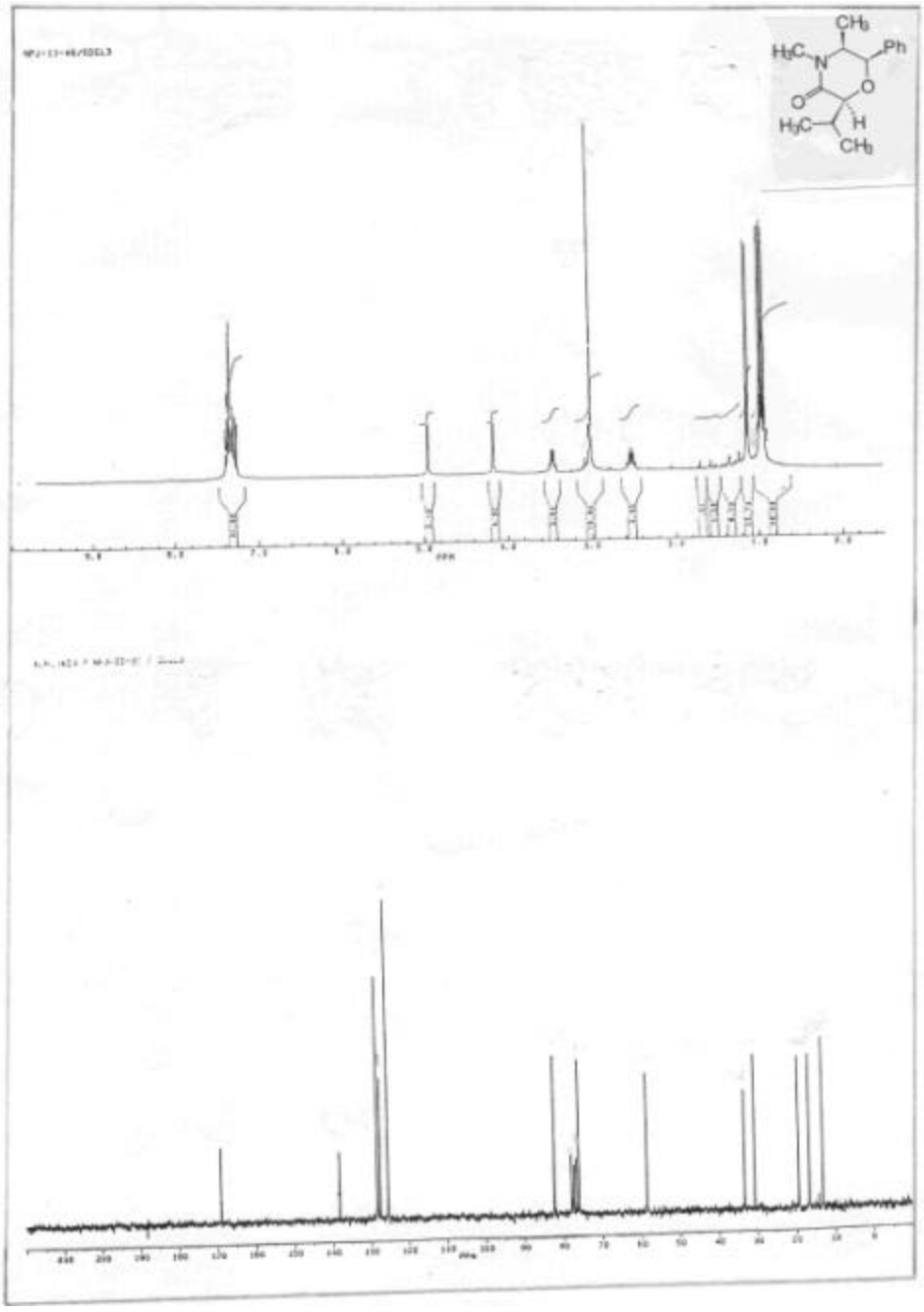

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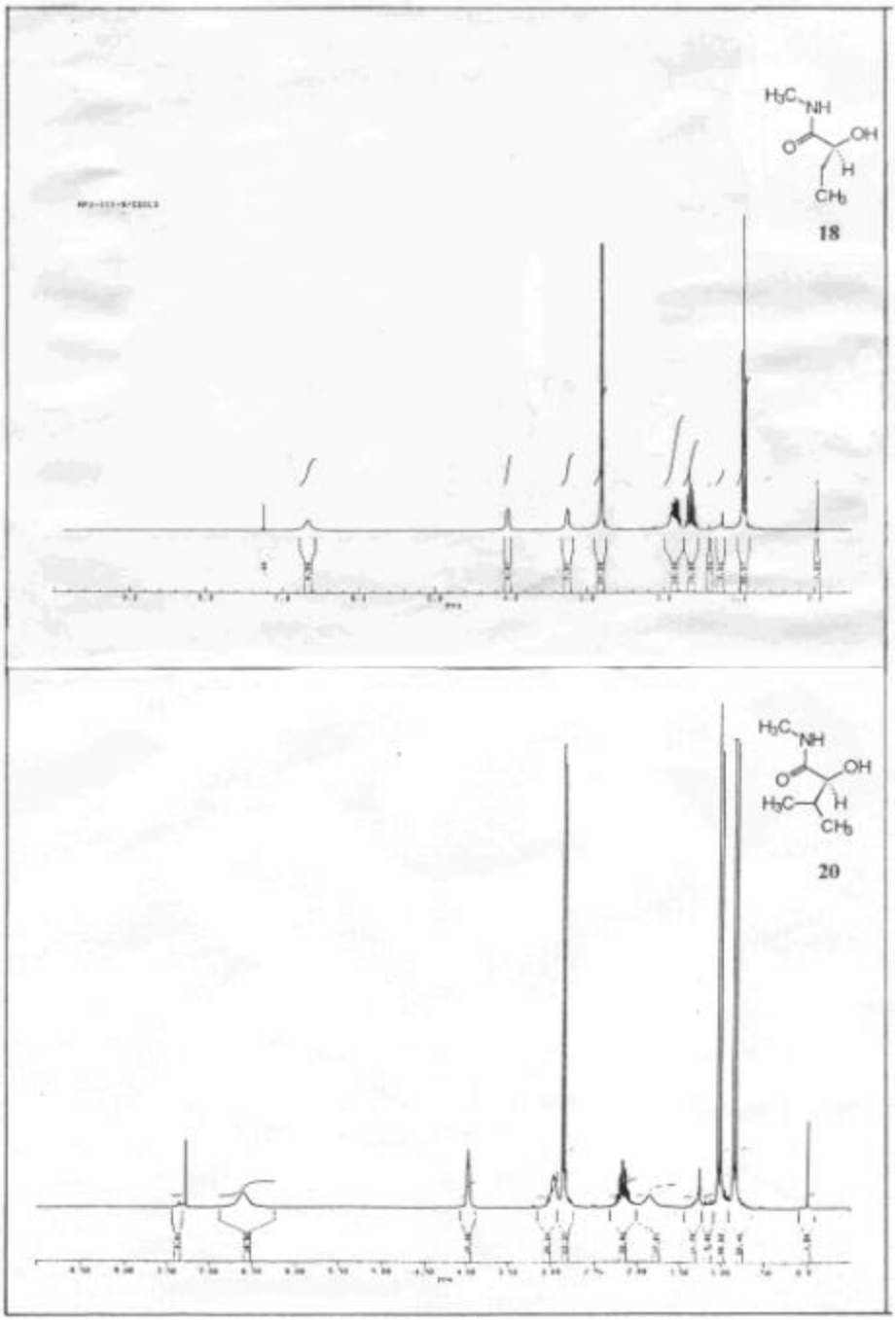

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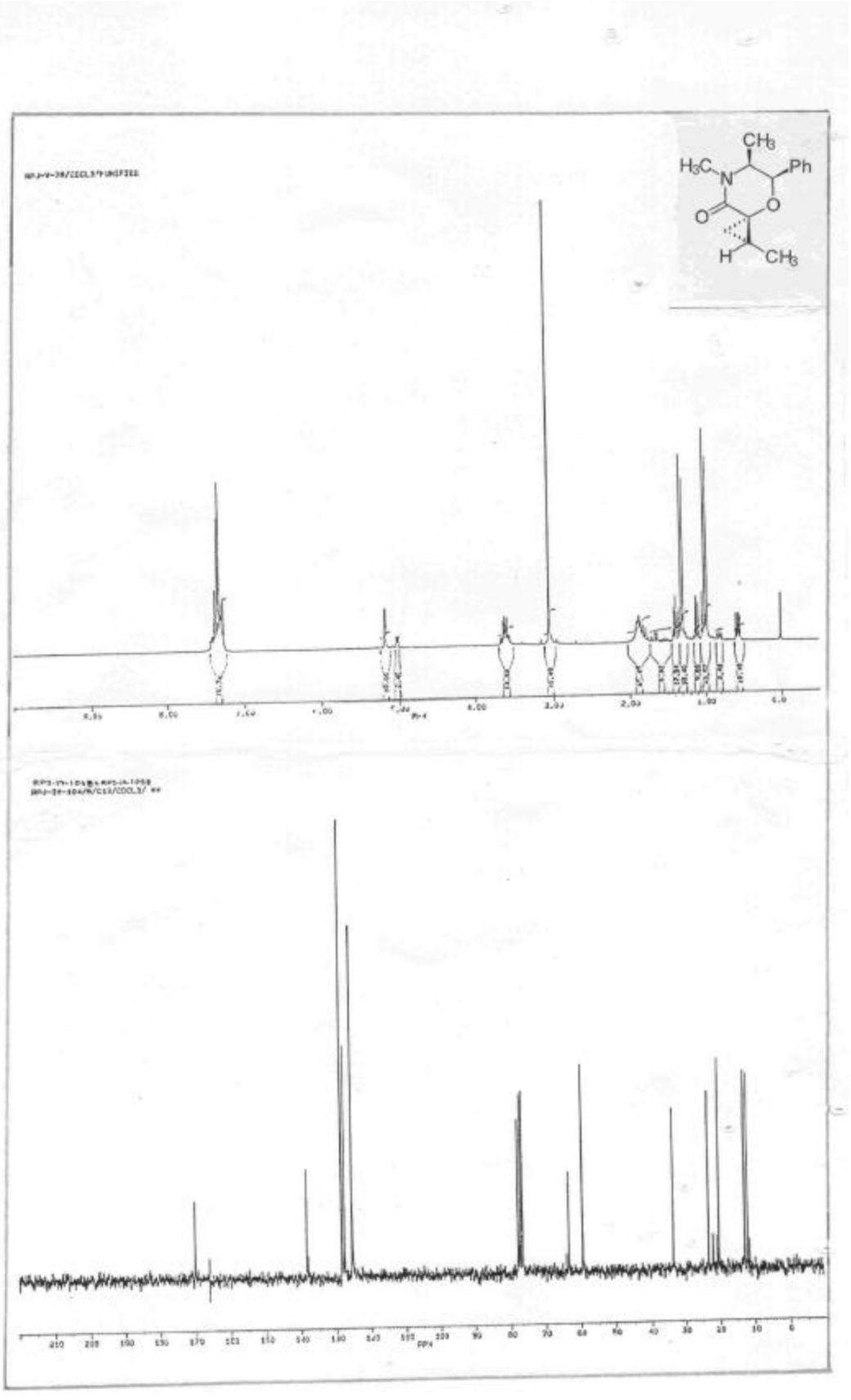

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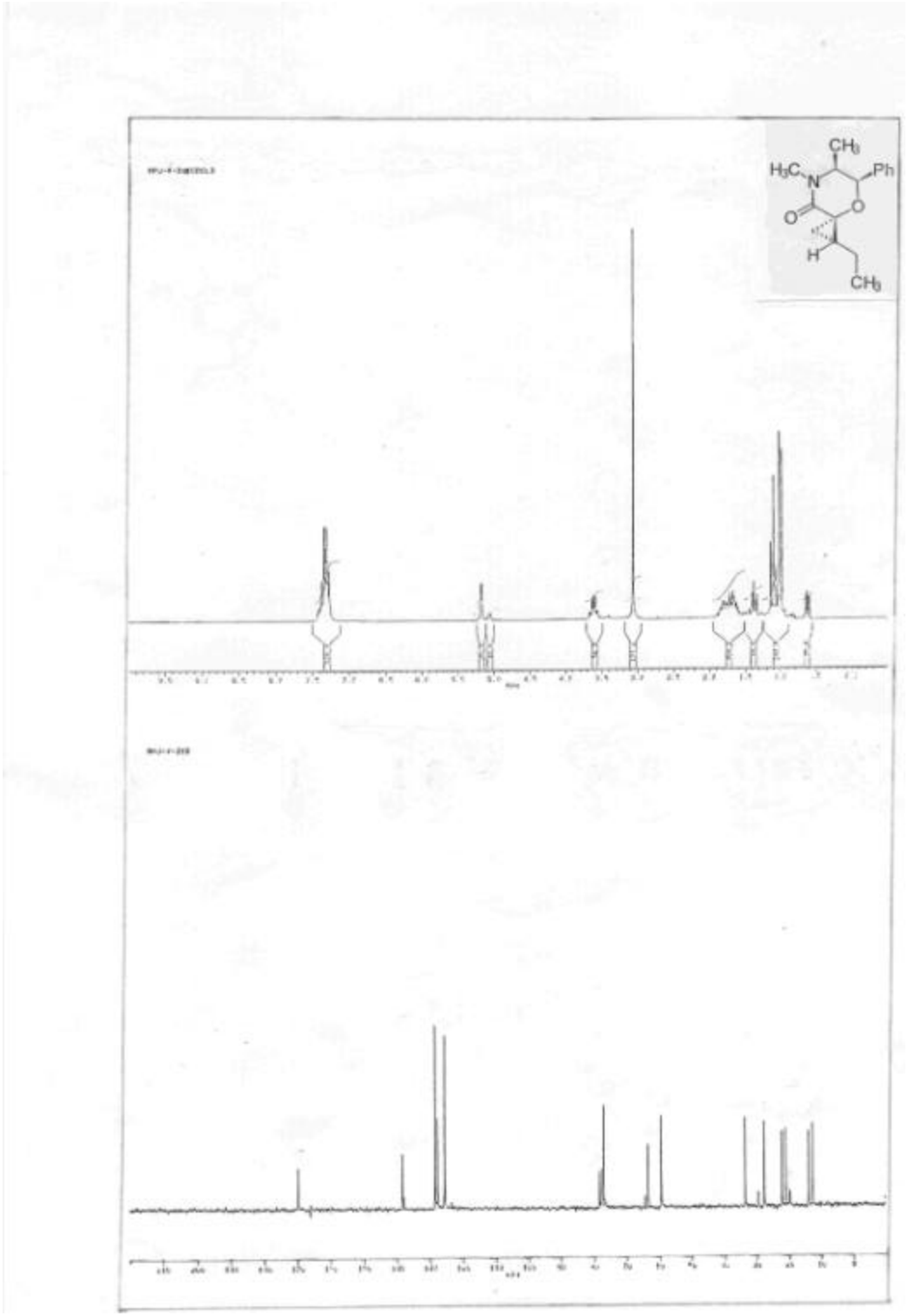

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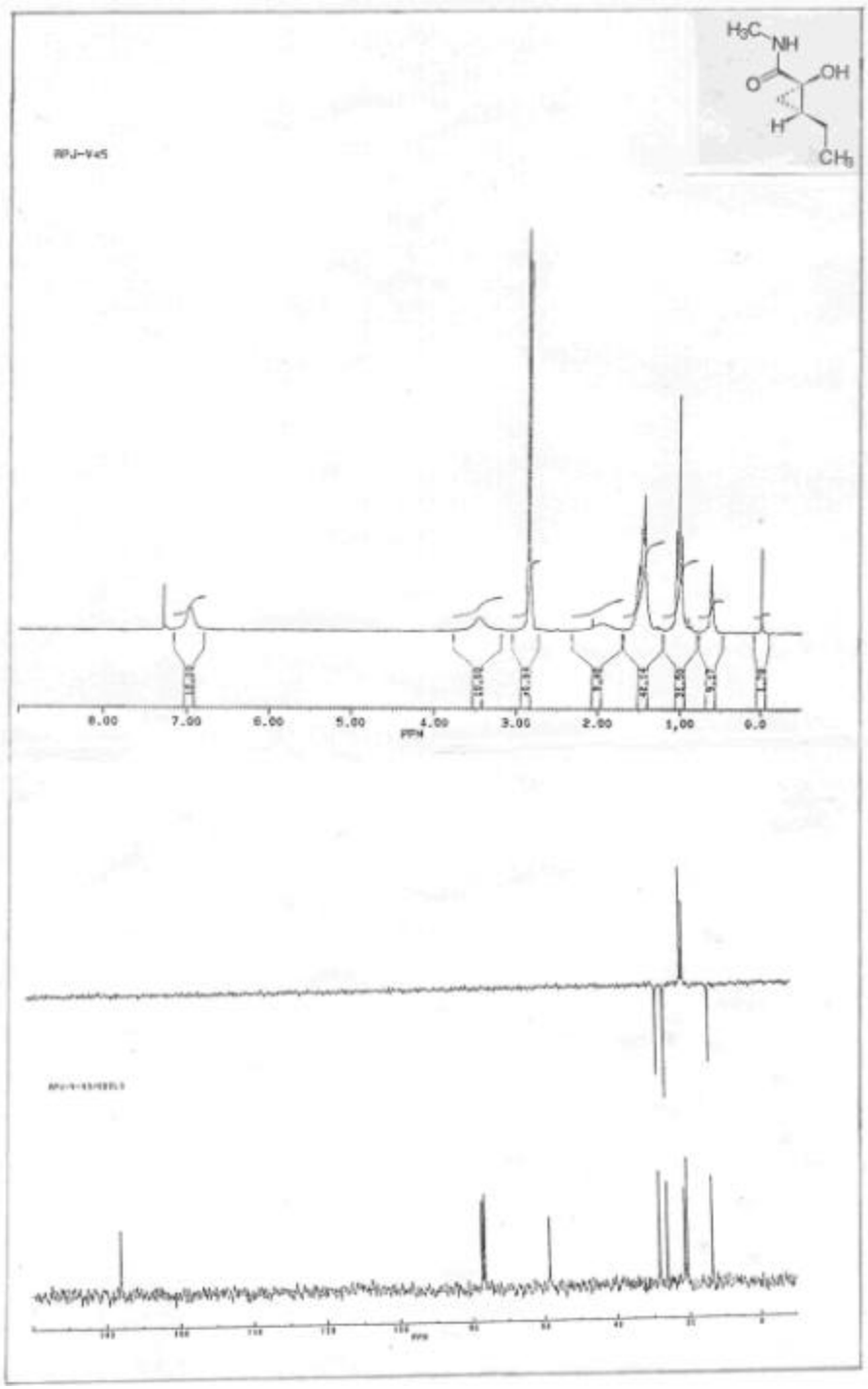

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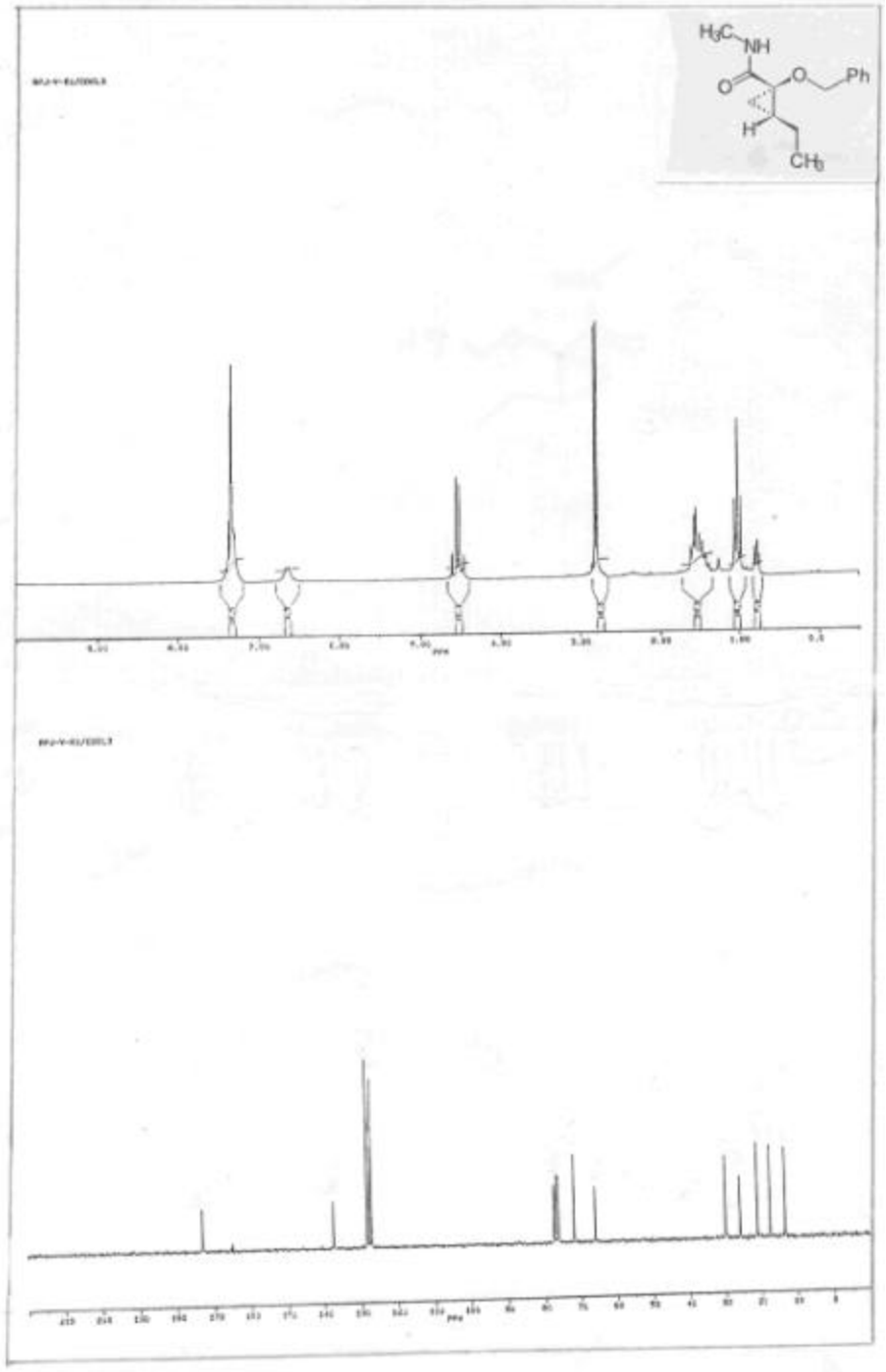

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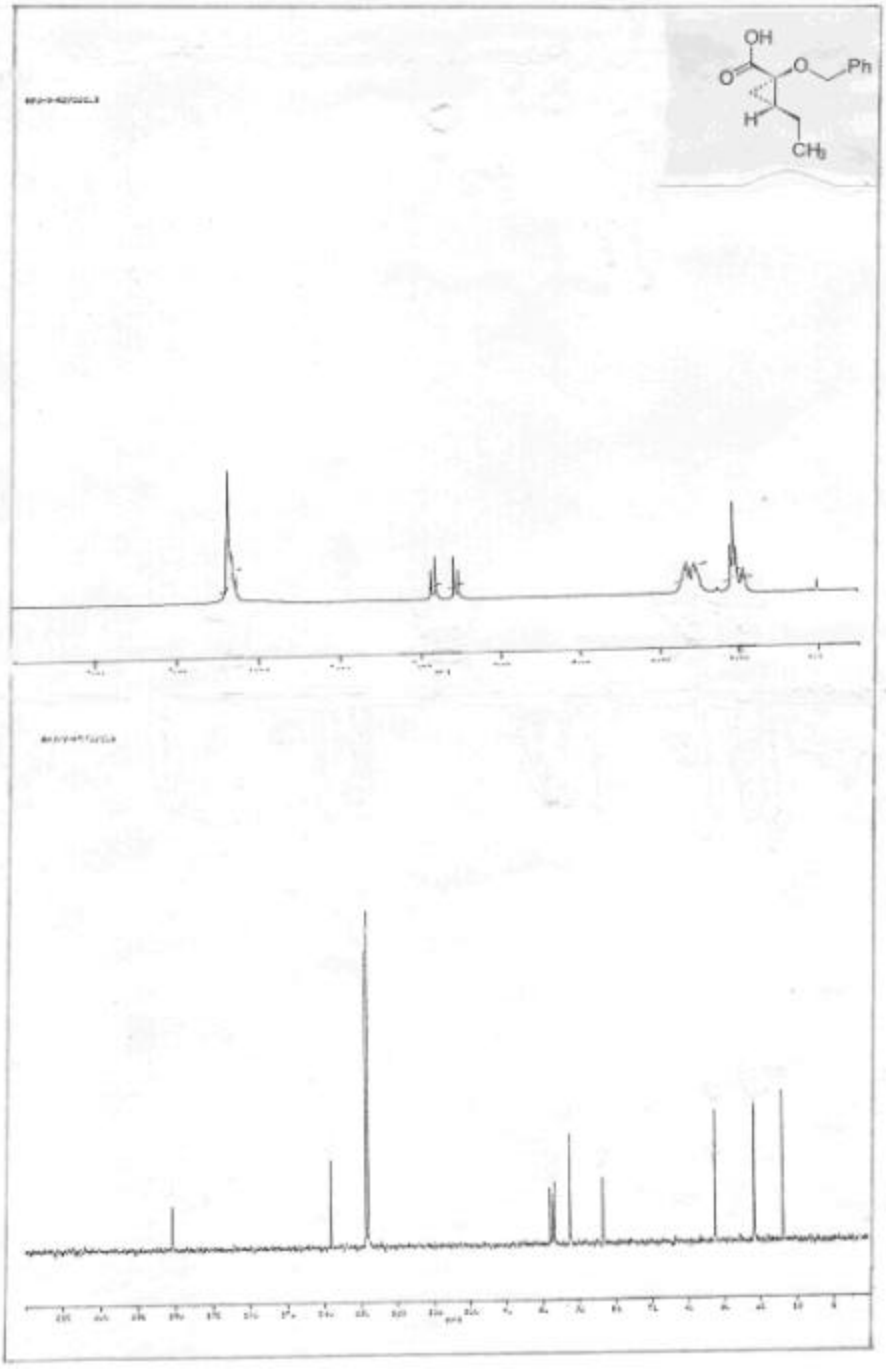

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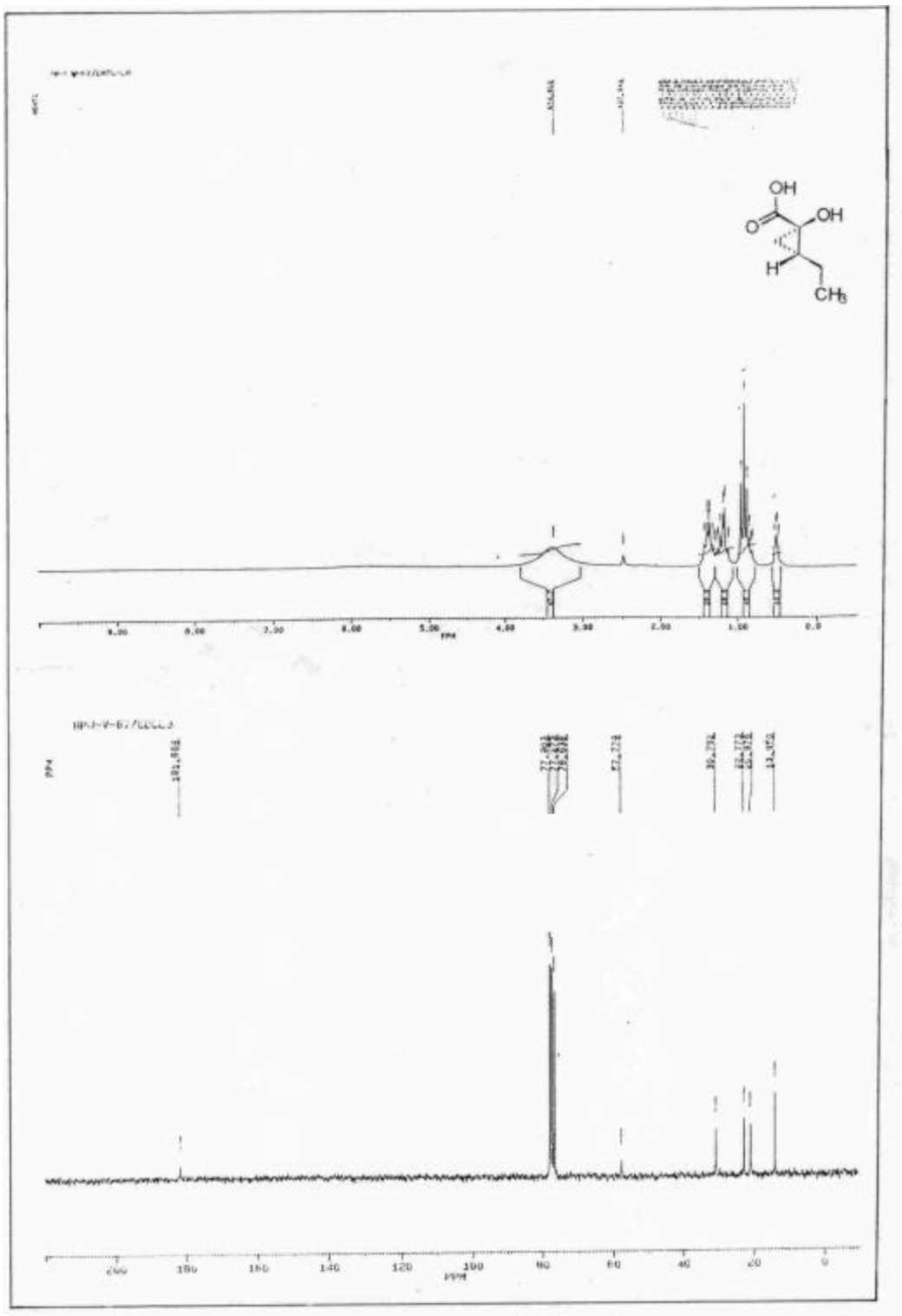

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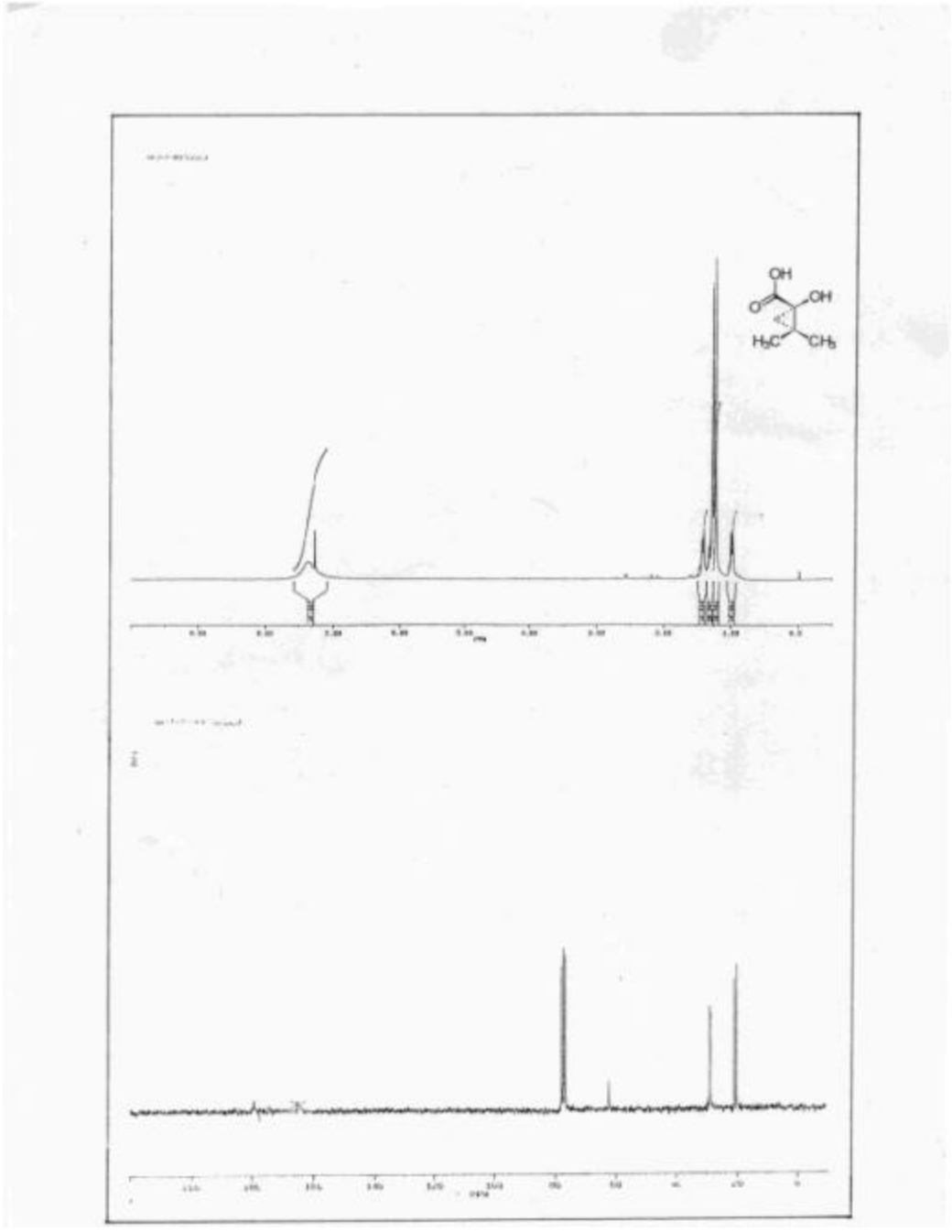

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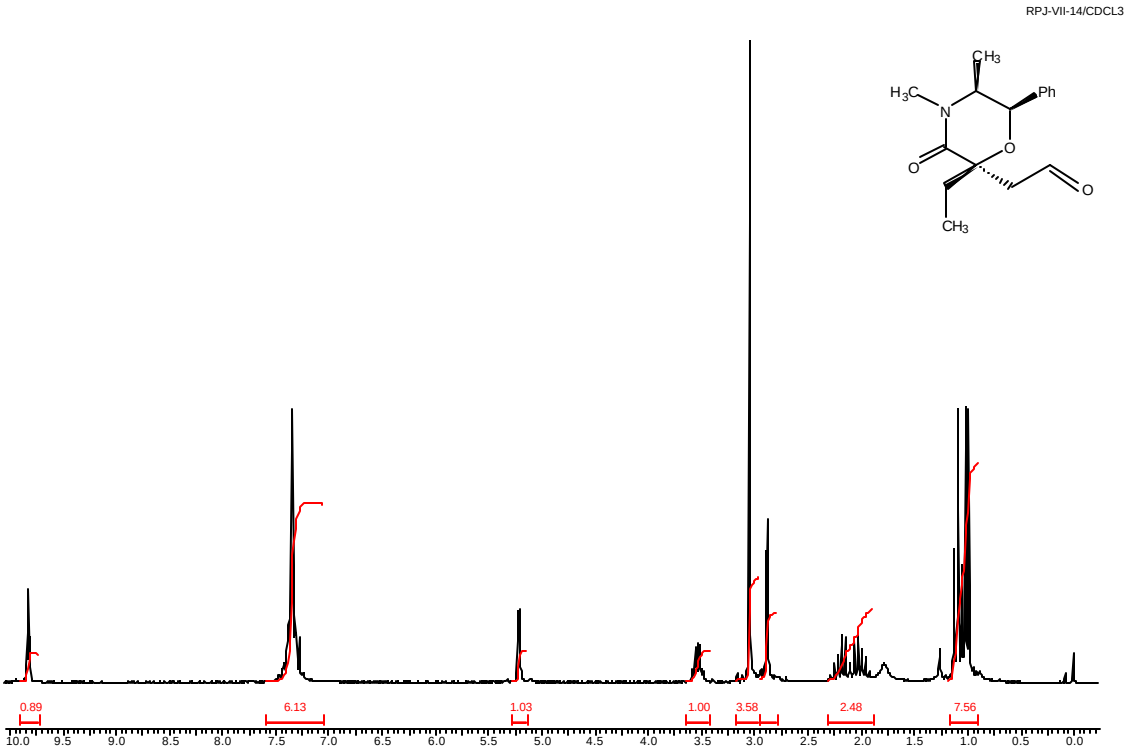
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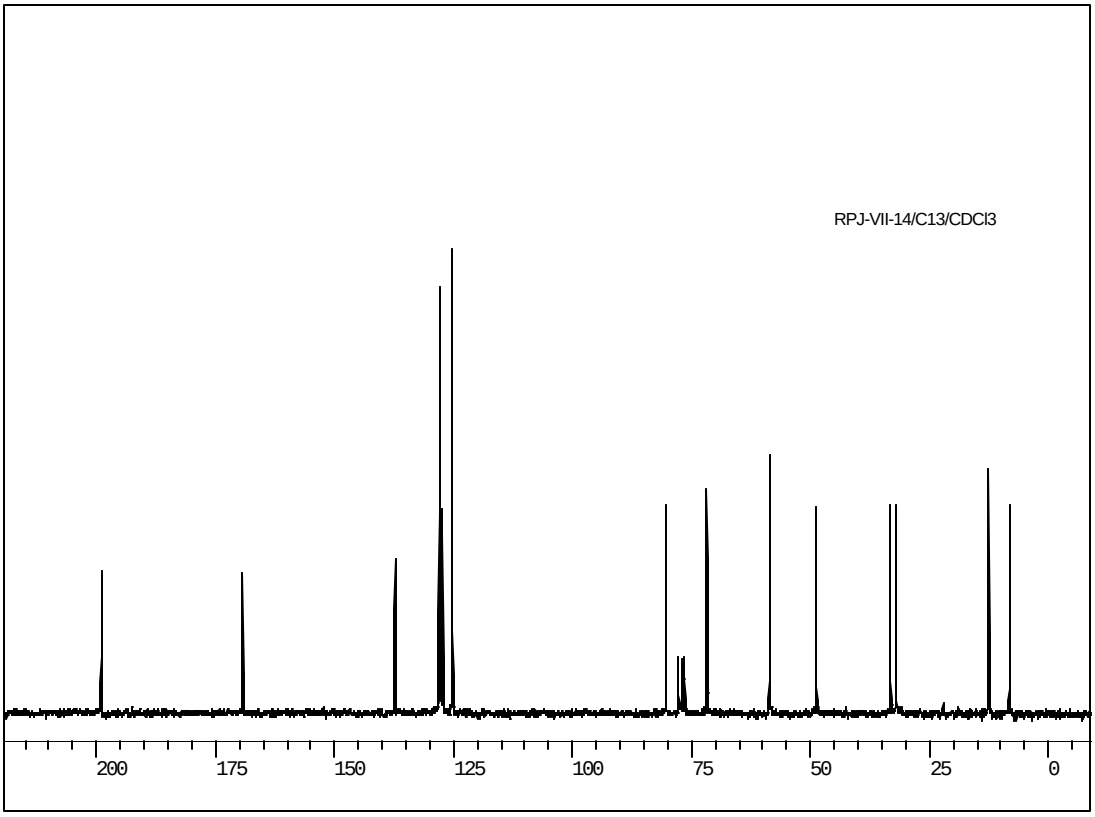
H3C
N
Ph
O
O
O
CH3
0.89
6.13
1.03
1.00
3.58
2.48
7.56
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0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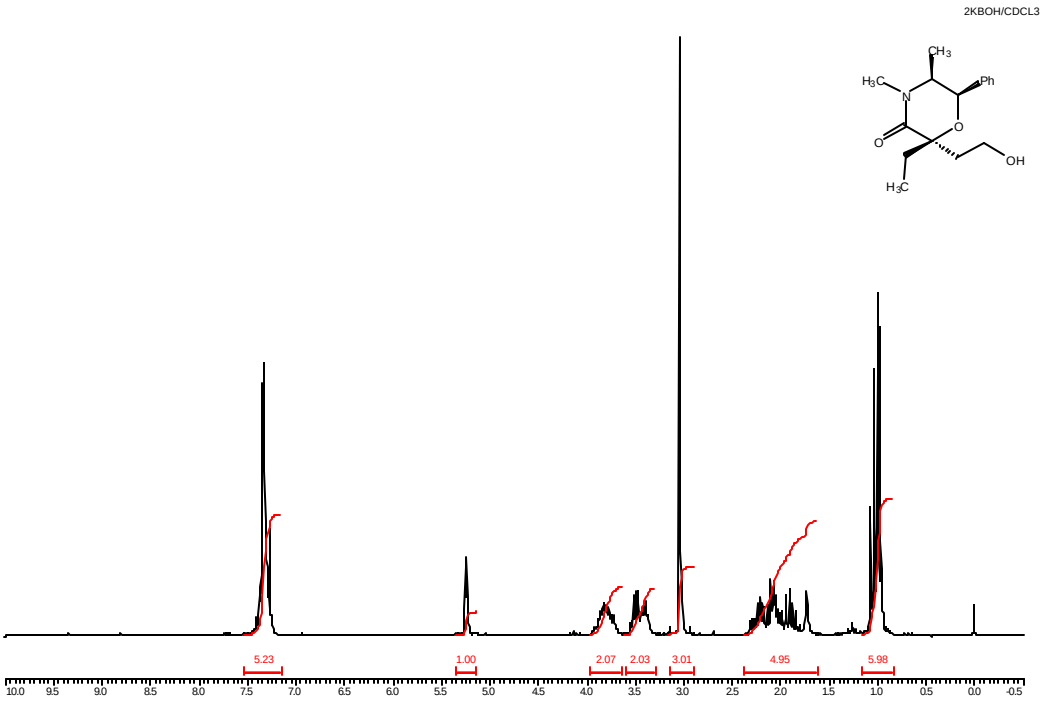
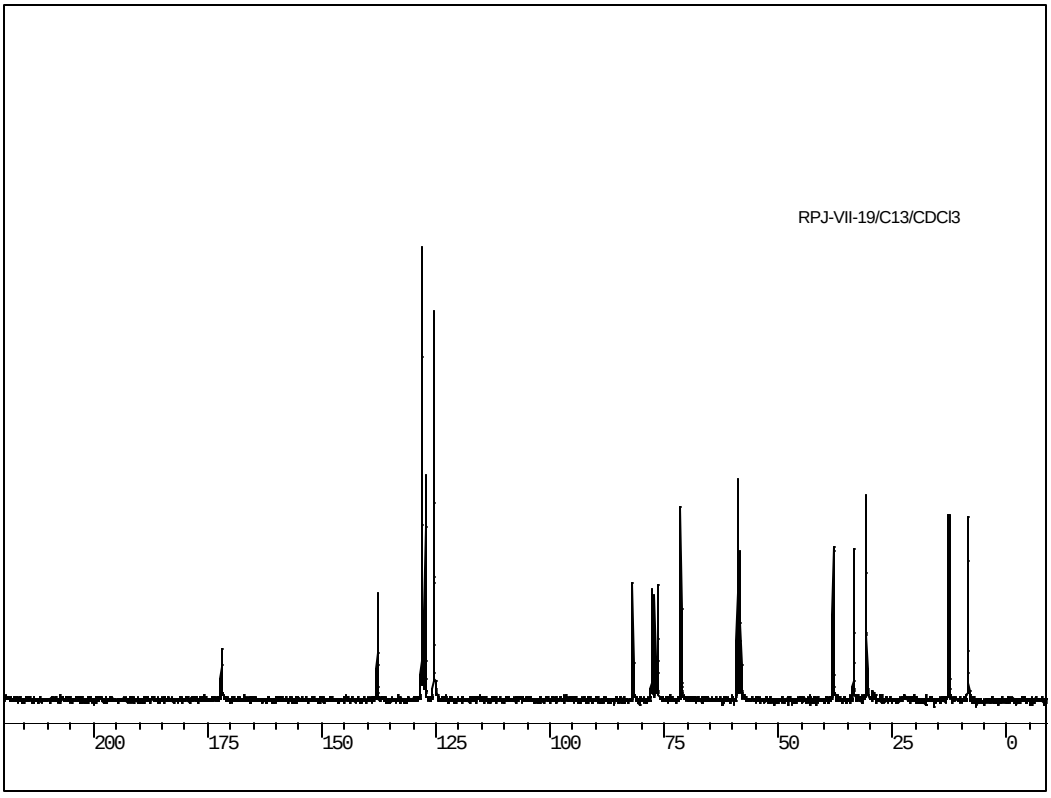
200
175
150
125
100
75
50
25
0

COMPOUND NO. 51





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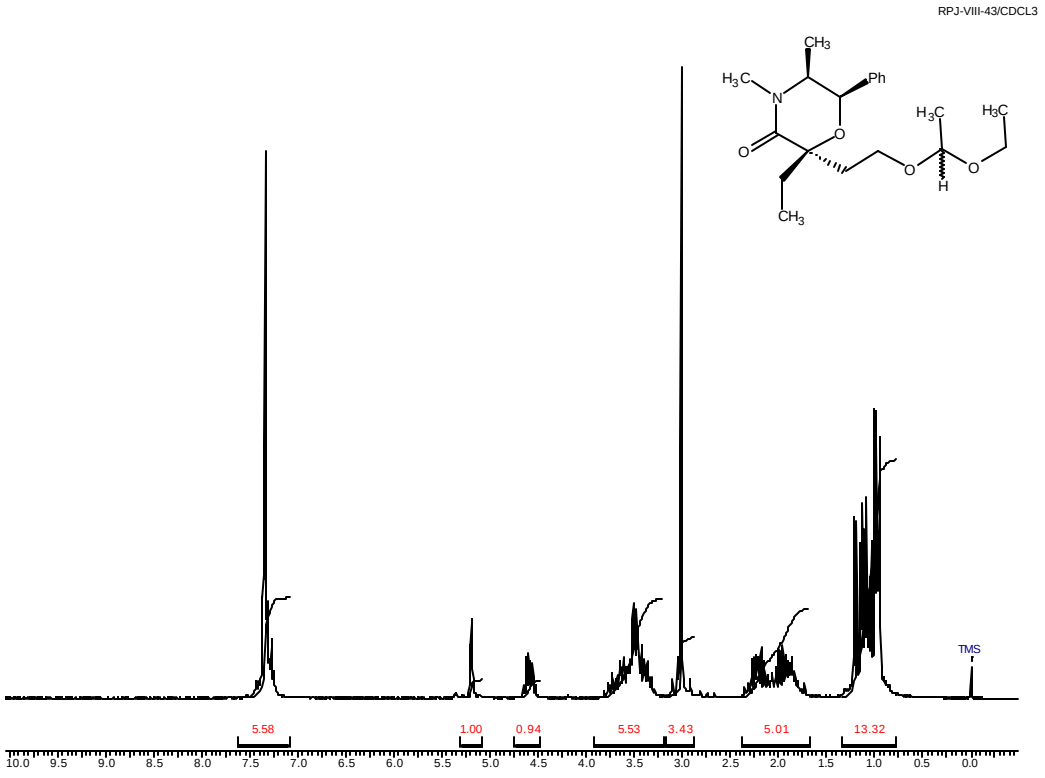

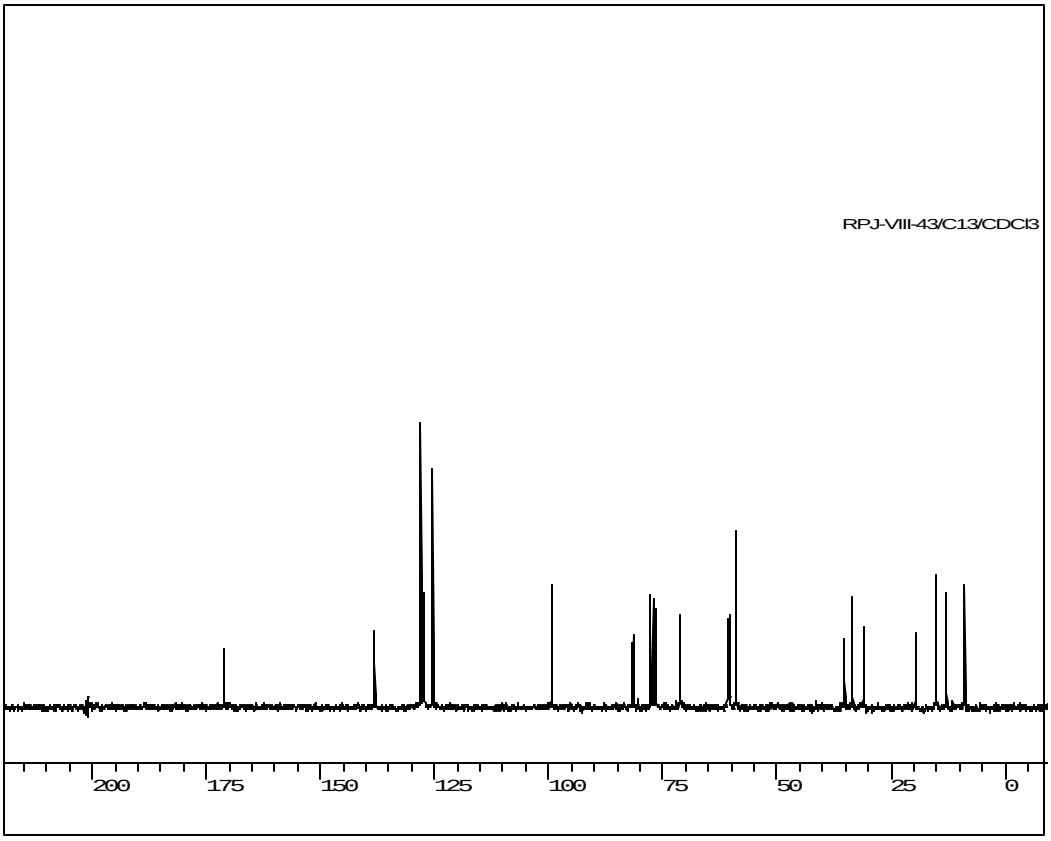

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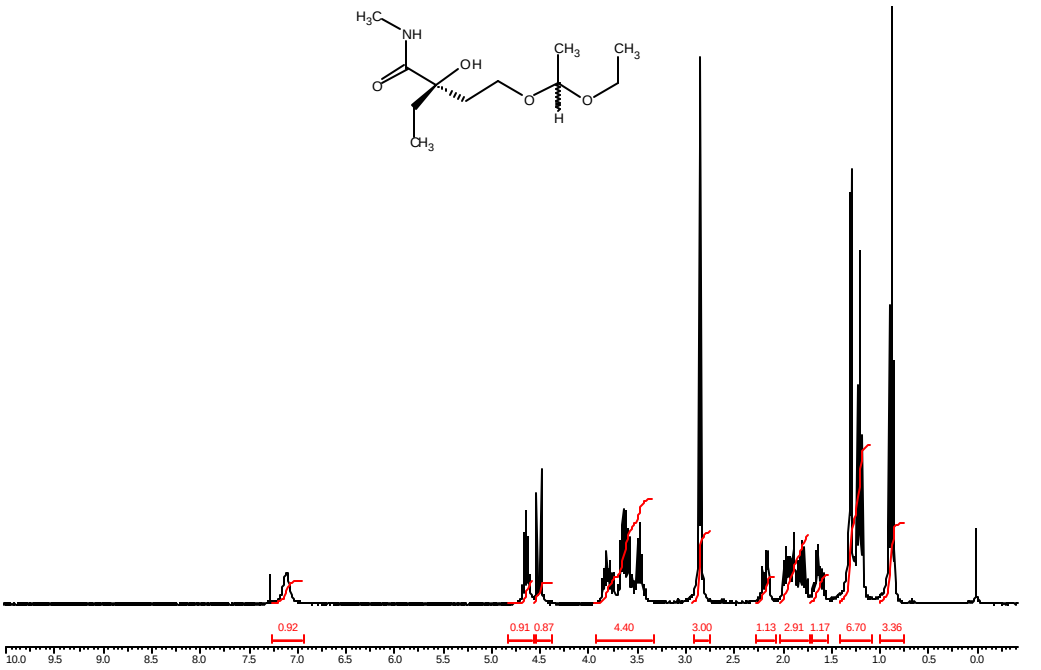

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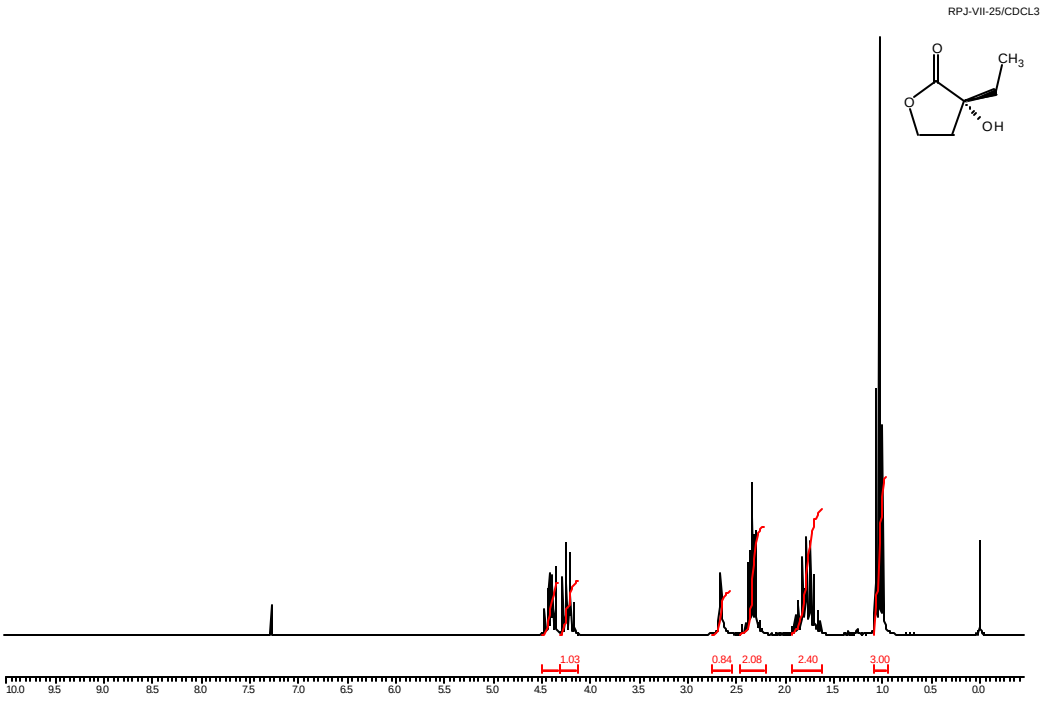

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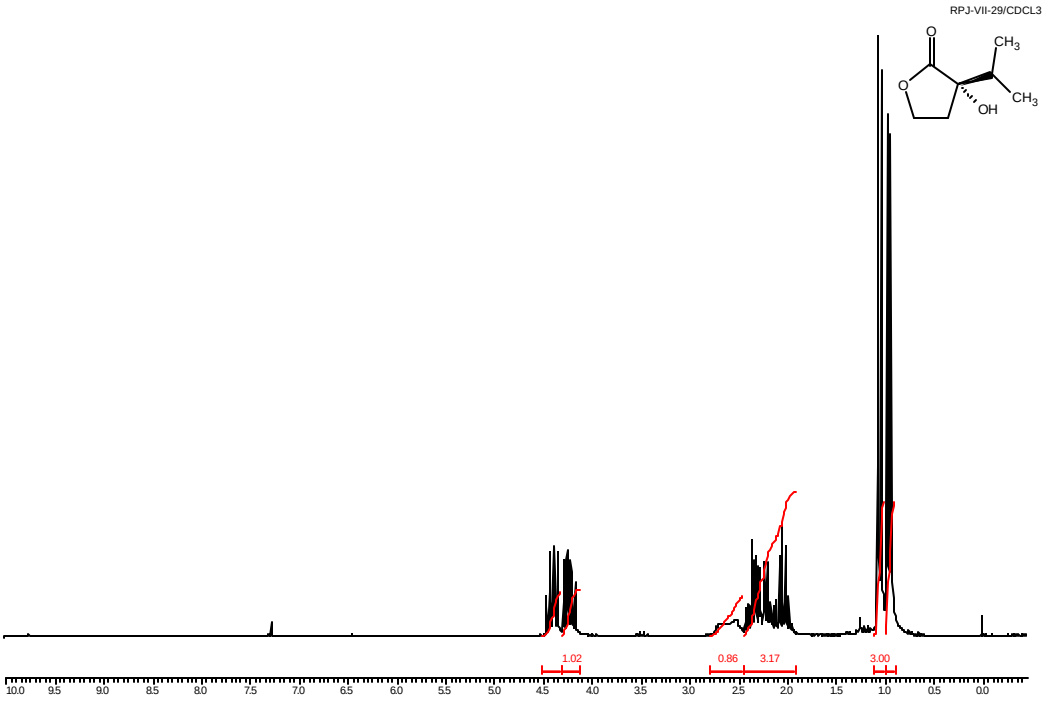

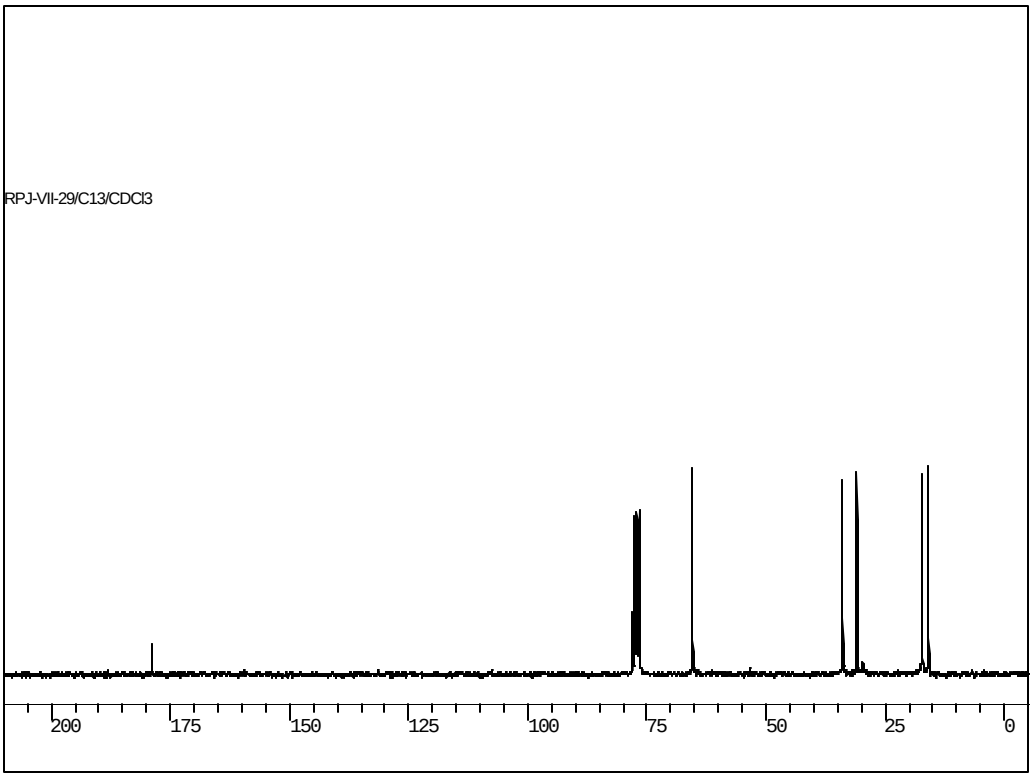

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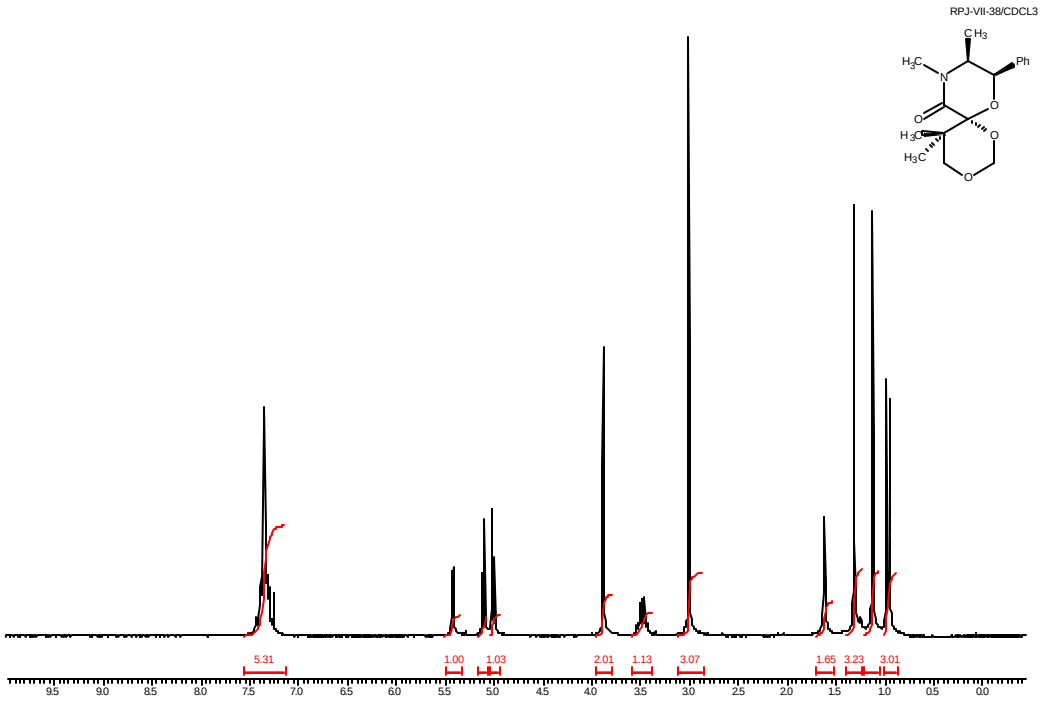

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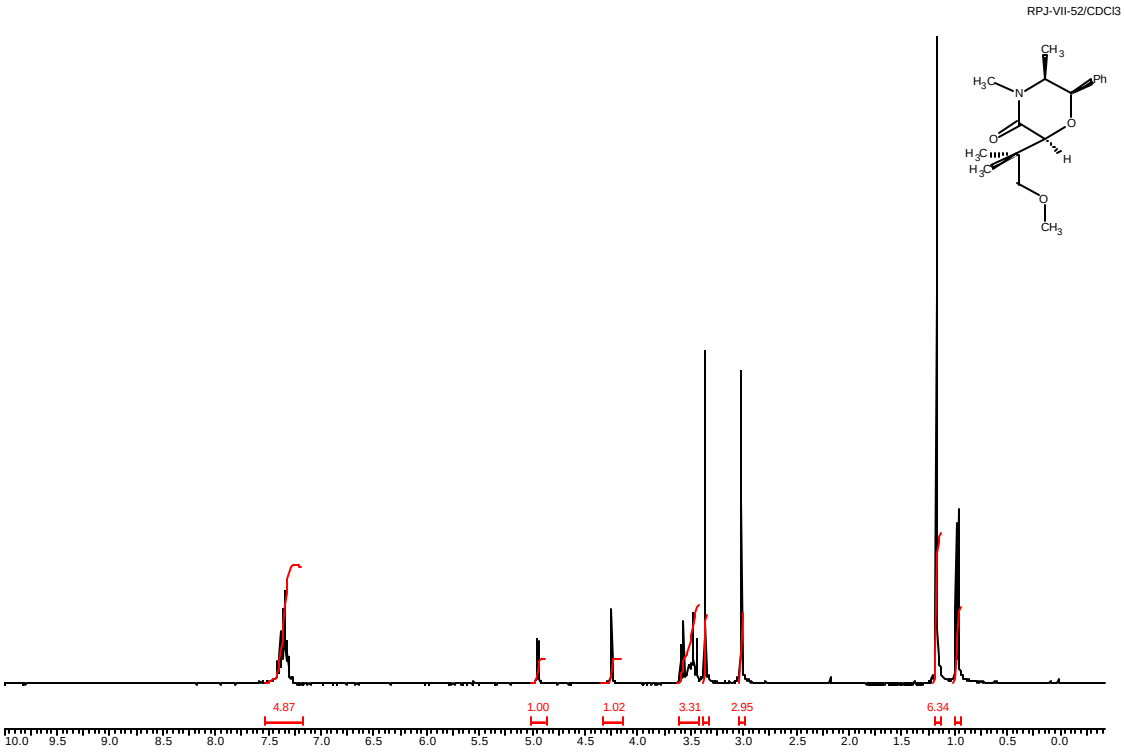

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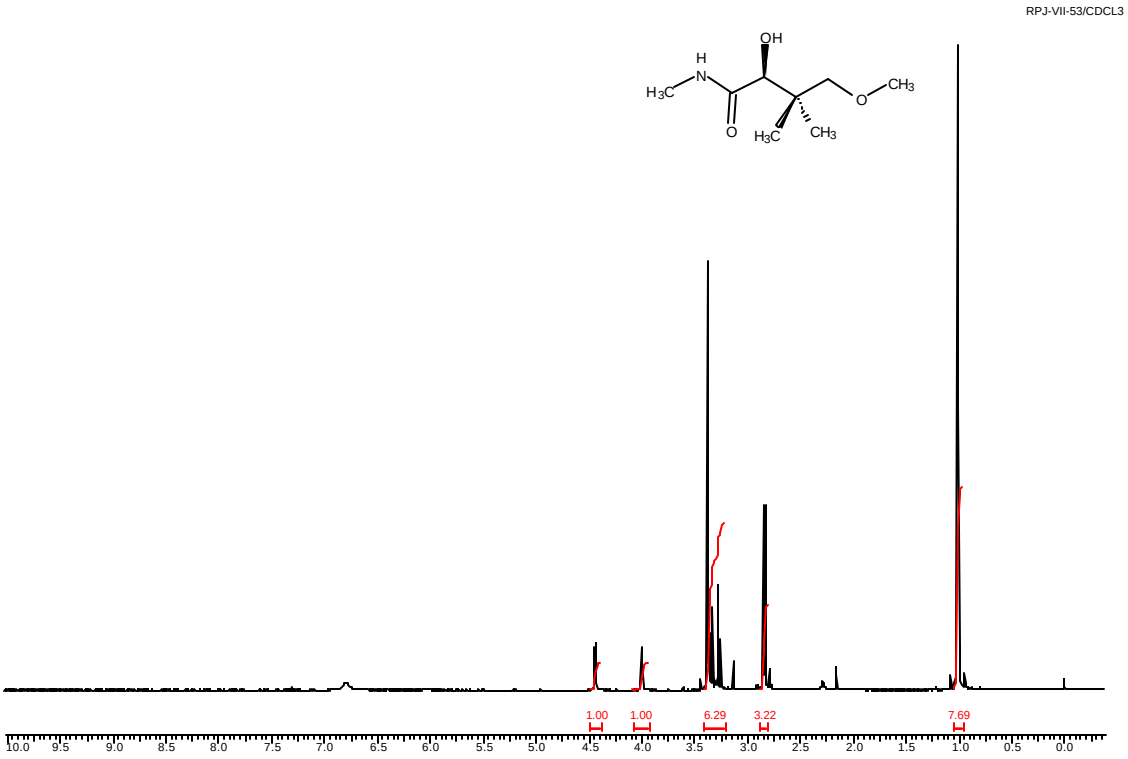

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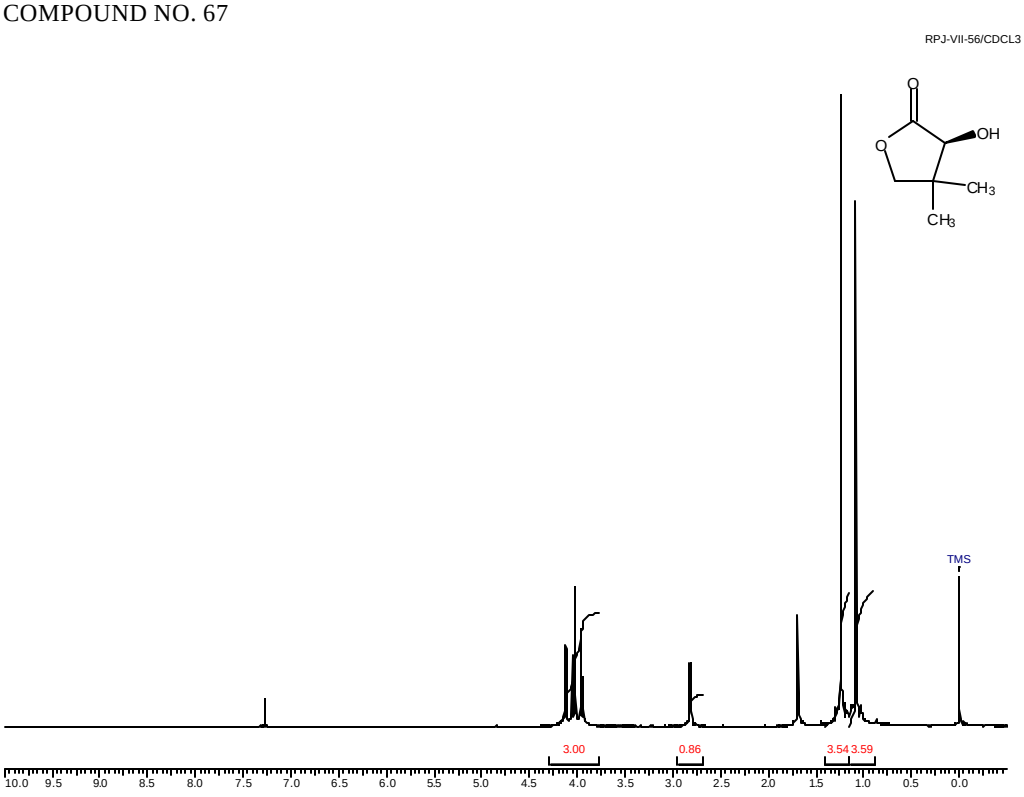
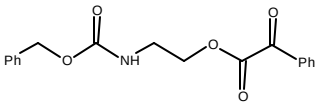
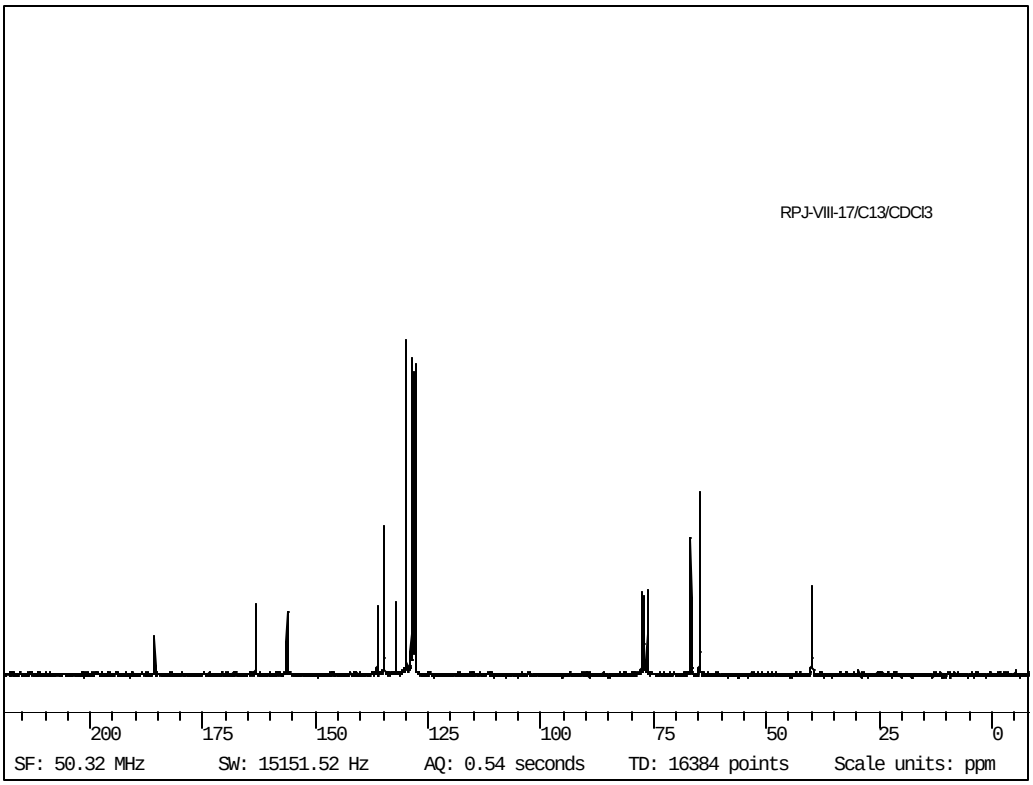


COMPOUND NO. 79

R. P. JAIN/ RPJ-VIII-17/ CDCL3





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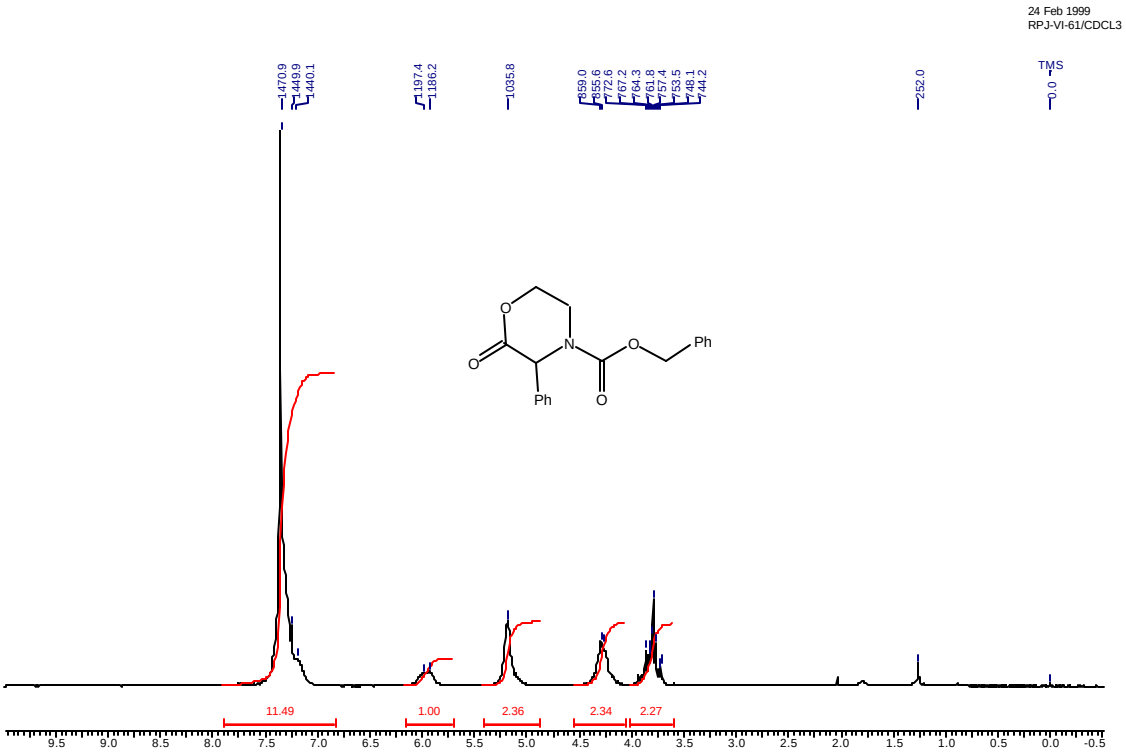

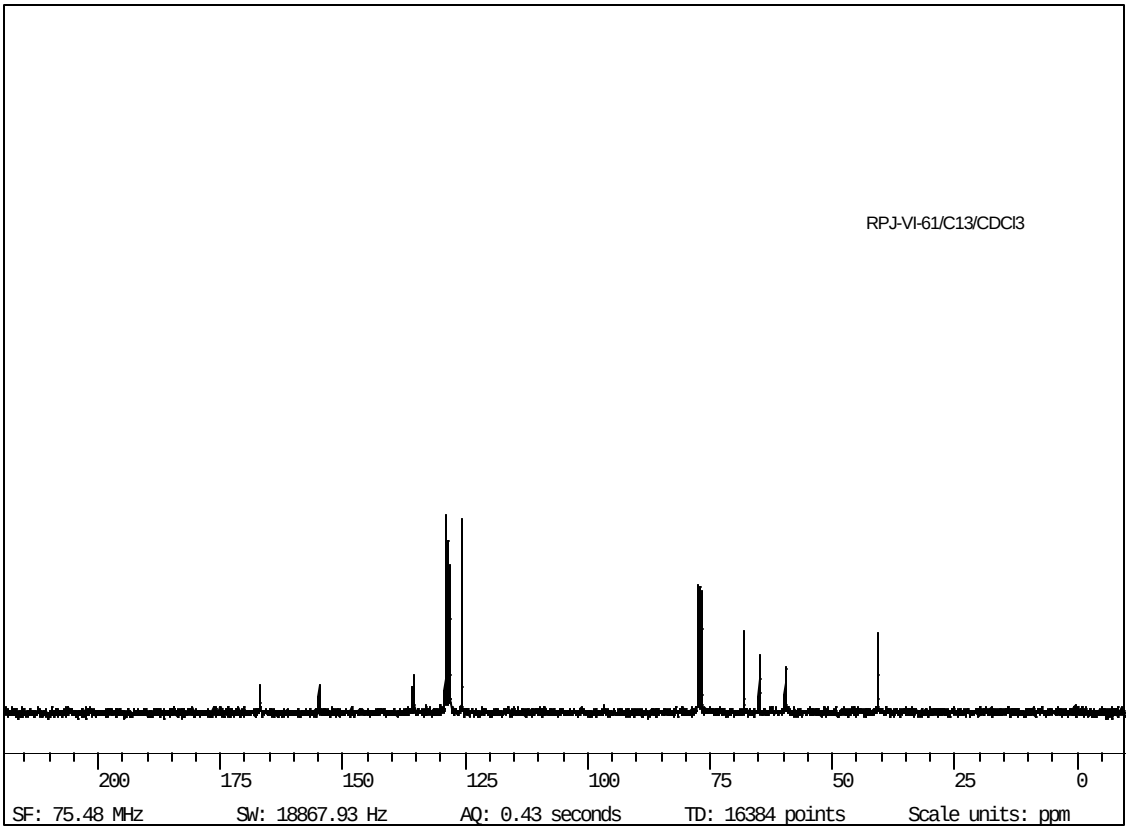

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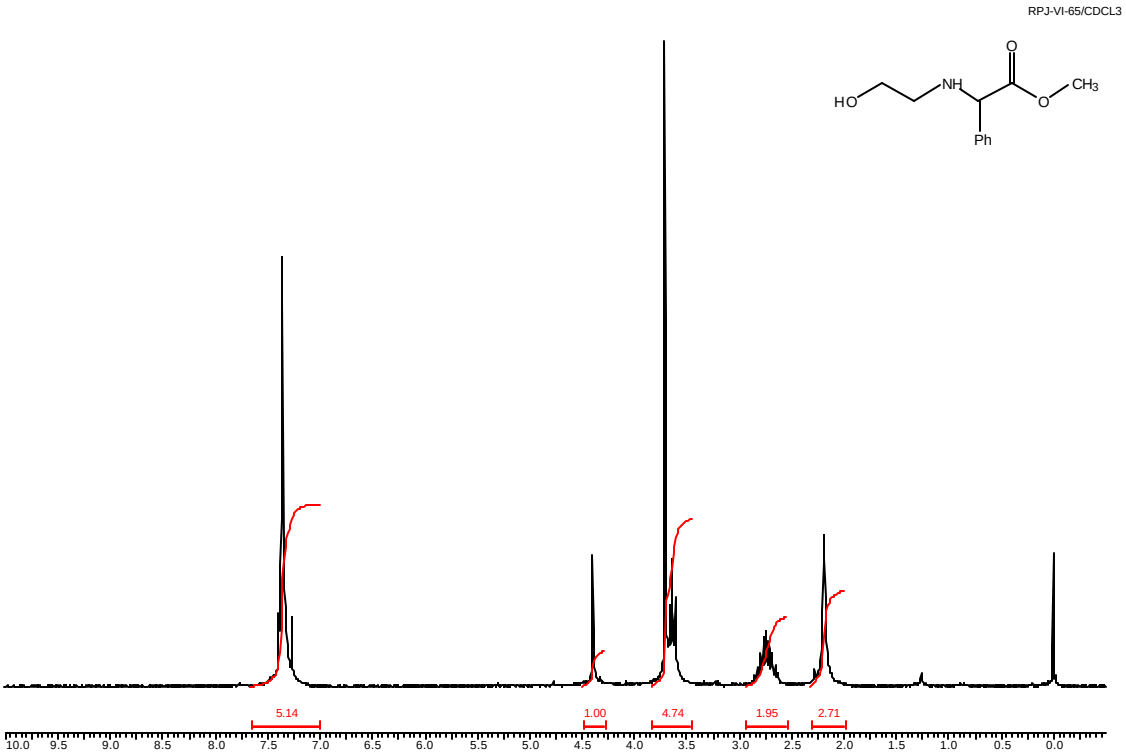

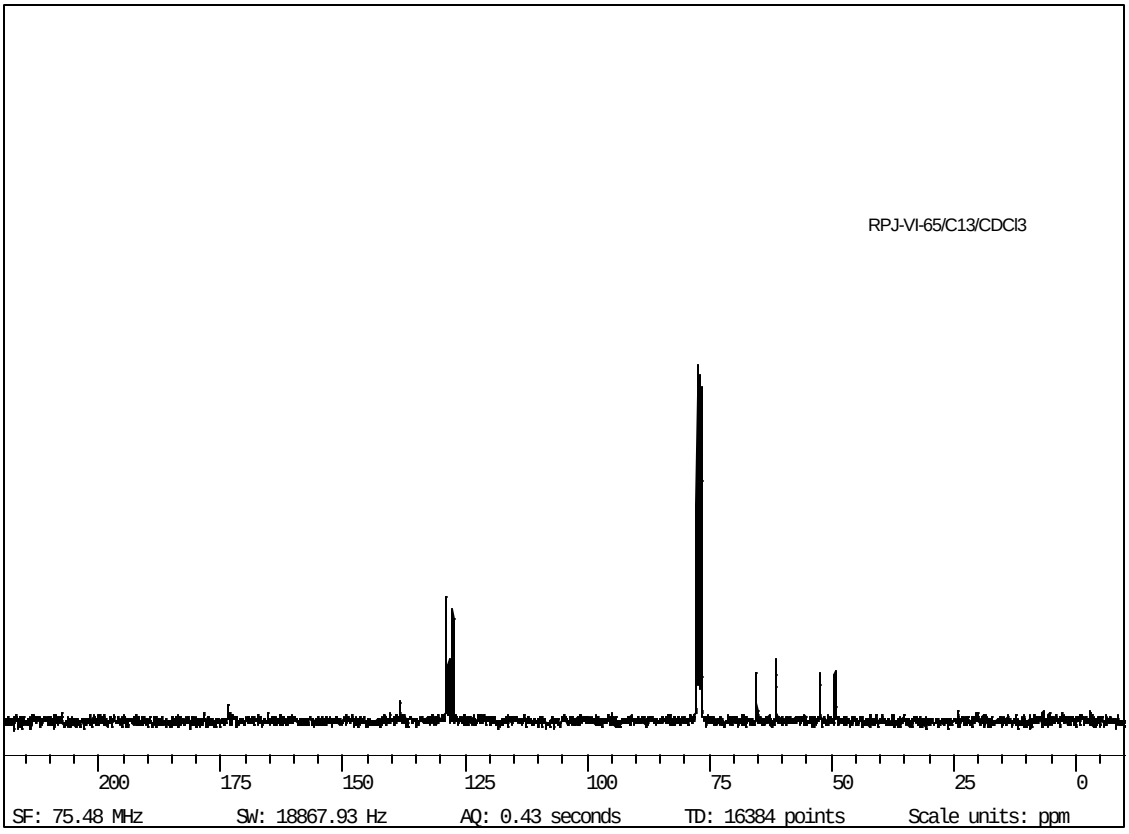

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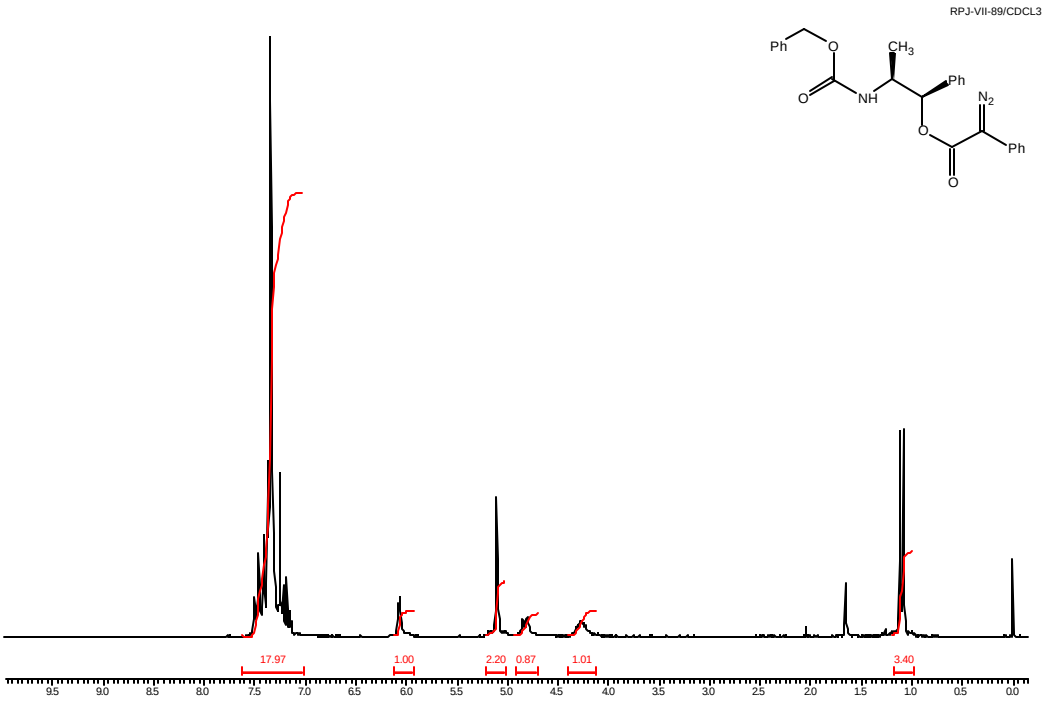

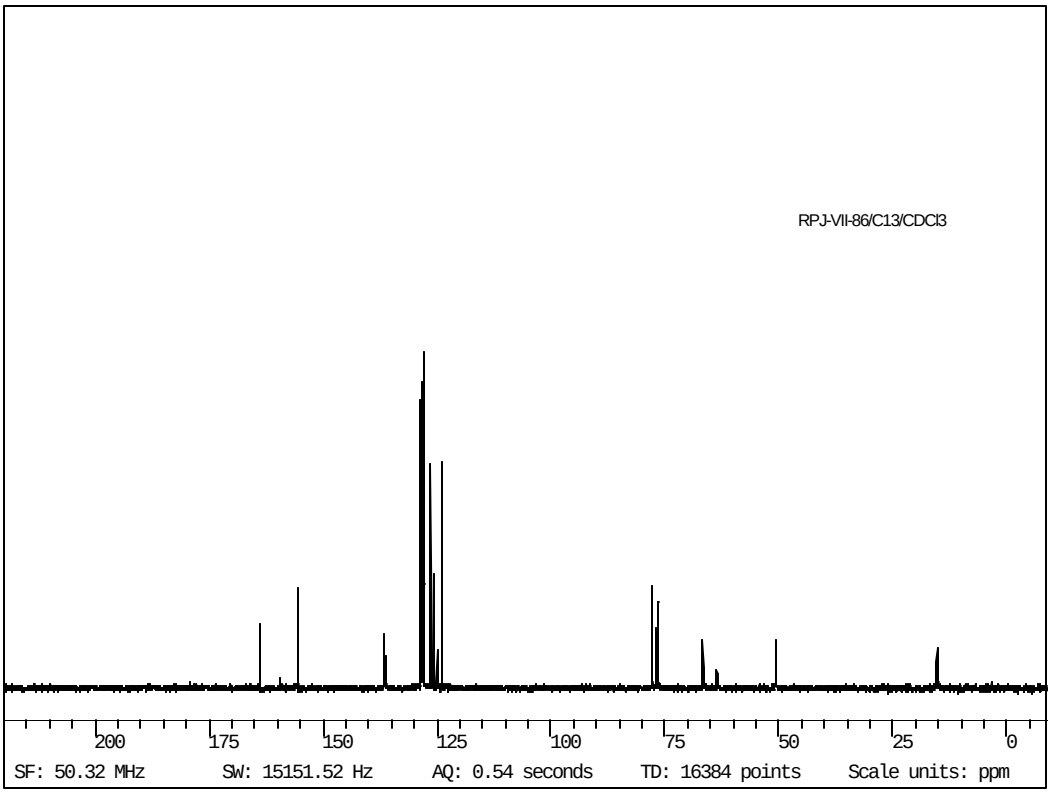

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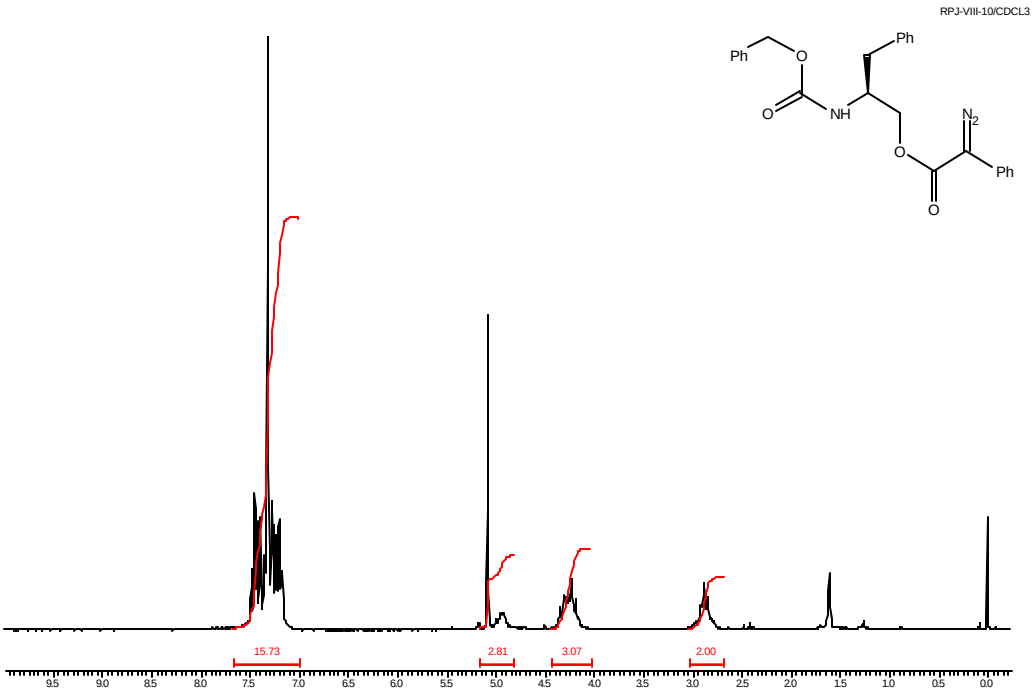

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